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SARS-CoV-2

Infection, Transmission, and Prevention

Edited by
Eduardo Araújo Oliveira and Ana Cristina Simões E Silva

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Guest Editors

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About the Editors

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Article

Temporal Dynamics of Vaccine Uptake: Perceptual and Social Drivers of Adoption Speed Across Innovation Diffusion Curve

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Abstract

The effectiveness of infection prevention depends on not only uptake but also the timing of adoption. Vaccination studies typically treat uptake as binary, overlooking *when* while investigating *why* individuals get vaccinated. Using the novel mRNA COVID-19 vaccines as a case study, the influences of risk perceptions and social norms on vaccination timing were examined through an Innovation Diffusion framework. An online survey was conducted in November 2021 to assess vaccination behaviors, attitudes, and peer expectations of 1710 U.S. residents (51.64% females, 31.23% minorities, with a relatively balanced distribution across age and income brackets). Participants were classified by vaccination timing and intentions as early adopters, early majority, late majority, or laggards for comparative analyses. One year after vaccine rollout, 64.3% had received at least one dose; 20.1% reported no intention to vaccinate, and this resistance persisted through May 2023 when the pandemic ended. Vaccine confidence and prior behavior (e.g., influenza vaccination) demonstrated strong gradients across adoption timing. Earlier uptake was associated with higher perceived vaccine importance, infection risk, and peer uptake, whereas age and education effects diminished over time. Perceived illness severity and disease knowledge showed inconsistent influences. Later adopters anticipated higher post-vaccination infection risk and greater peer non-vaccination, reinforcing hesitancy. Social norms (but not risk perception) mediated the relationship between confidence and timing; earlier adoption further predicted booster acceptance. These findings highlight the importance of trust, correcting efficacy misperceptions, and leveraging positive peer norms to promote timely vaccination and inform strategies for other infectious diseases.

Keywords: public health; SARS-CoV-2; vaccine hesitancy; risk perception; innovation adoption; social influence; norm; health behavior; decision-making; mediator

1. Introduction

The effectiveness of a scientific invention or medical breakthrough, be it an infection preventive procedure or novel treatment, largely depends on whether the intended population is willing and able to accept the new measure and obtain it in time. Despite the availability of numerous safe and effective vaccines, many individuals delay or refuse vaccination—a phenomenon known as vaccine hesitancy that impedes progress toward herd immunity against infectious diseases [1–3]. This challenge is especially pronounced

and concerning during regional or global outbreaks, as seen during the COVID-19 pandemic, when prompt and mass uptake was essential to curb transmission and support economic recovery [4].

The Centers for Disease Control and Prevention's (CDC) Immunization Services Division distributed the COVID-19 vaccine to each of the CDC's 64 jurisdictions (50 states, the District of Columbia, five cities and eight territories). Census data and vaccine availability projections were used to determine jurisdictional vaccine allocations; each jurisdiction developed its own COVID-19 allocation framework using general guidance from the CDC and available data on critical and vulnerable populations. Although the plans were provided to the CDC, state and local health departments determined how many doses to distribute to the enrolled providers in their jurisdiction [5,6].

Even when the new mRNA vaccine was provided free to the public, with costs covered by the U.S. government, only 61.43% of the American population were fully vaccinated by the end of 2021, one year after the launch of the vaccine (compared to 74.91% in France, 69.54% in the United Kingdom (UK), and 79.77% in Japan) [7]. Likewise, for the seasonal flu shot, recommended for people six months and older but not required (except for certain professions like military and healthcare) and fully covered by both public and private insurance in the U.S., the vaccination rates have hovered around 41–63%, varying by state and declining since the pandemic [8,9].

To understand vaccine decision-making, researchers have drawn on behavioral models such as the Health Belief Model (HBM) [10–12], Theory of Planned Behavior (TPB) [12–14], and Precaution Adoption Process Model (PAPM) [15,16]. The PAPM emphasizes how knowledge, provider reassurance, and social norms influence Human Papillomavirus (HPV) vaccine acceptance [16]. Similarly, the HBM links acceptance to perceived efficacy, risk, and provider recommendation, and identifies barriers such as cost and concerns that vaccinating against a common sexually transmitted infection (STI) like HPV may be seen as implicitly promoting adolescent sexual activity [12,17]. Though these models provide a cognitive, individual-level explanation of behavior, they often investigate vaccination as a dichotomy and fall short of accounting for or predicting the timing or speed of adoption and the ratio of unprotected population across broader social systems at a particular phase. These dynamics could determine the length of an outbreak and the risk of it turning into an epidemic.

The Diffusion of Innovations (DOI) theory, developed by Everett Rogers with origins in sociology and communication [18], addresses this gap by examining how new ideas and technologies are spread within populations. It categorizes individuals into five groups based on adoption timing: innovators, early adopters, early majority, late majority, and laggards [19]. The categorization reflects differences in response to new information, uncertainty, and social influence. DOI also identifies five innovation characteristics that shape adoption: relative advantage, compatibility, complexity, trialability, and observability [19]. The theory has been applied globally in healthcare [20,21], technology (e.g., e-health [22] and patient portals [23]), and public policy [24,25]. For instance, the DOI theory was used to successfully predict healthcare workers' readiness to adopt E-Health platforms in a Mauritian hospital setting, with early adopters serving as key leaders in driving diffusion across adopter categories [22]. Preventive innovations like vaccines often diffuse slowly, as their benefits are less immediately visible and their value may be difficult to comprehend or assess [26].

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In influenza and HPV vaccination studies, DOI has helped demonstrate how factors like alignment with individual beliefs, access, and trusted messengers (e.g., school nurses [27]) motivated uptake over time [27–29]. However, peer-to-peer influence, despite its central role in the theory, has largely been overlooked. Many studies have focused on trusted sources like healthcare providers or pastors [30,31], but people also take cues from friends, coworkers, and others in their social circles [32]. Recognizing the potential sway of these personal networks, or "observability" as the DOI describes, can bring deeper insight into the social drivers of vaccination behavior. Further, many studies inquired about intentions or hypothetical responses rather than the action of actual uptake [16,33–36], which may not fully represent the behavior or capture changes in perceptions and contextual factors at the time of decision.

The COVID-19 vaccine offers a unique and compelling case for applying DOI theory in studying real-time adoption behavior: it was the first mRNA vaccine with FDA approval [37], beneficial to populations worldwide yet unfamiliar to the public. Some obtained the vaccine as soon as it became available, and others stalled for months or longer—or never accepted it [38,39]—despite widespread access, vast promotion, and amidst increasing confirmed cases nationally and worldwide [40]. In September 2020, two regional polls in North Carolina and Iowa, respectively, found 20.6% and 28.0% respondents said they would take the shot as soon as they could, while 51.0% and 45% chose to wait until others have taken it [41,42]. DOI's core premise that adoption depends on perceived risk, benefit, and trust provides a temporal framework to examine the progression of uptake. A few COVID-19 studies referenced DOI, but not all applied the full model in comparing the timing of adoption or considered the influence of social perception. For instance, a study in Cacao, China, examined COVID-19 vaccination timing among tourism workers, integrating DOI with TPB and finding that vaccine attitude, perceived behavioral control, and prior influenza vaccination history predicted earlier uptake [43]. While this work demonstrates the value of a timing-based, DOI-informed approach in a non-Western context, it was limited to a single high-risk occupational group and did not explore peer-to-peer social influence.

Building on prior research, the objective of this study was to investigate the uptake progression via the DOI framework with a nationally representative sample in assessing not just who obtained vaccination but *when* and *why*. This approach aimed to overcome the shortfall of binary classification in most studies contrasting vaccinated vs. unvaccinated individuals, which oversimplifies the complex interplay of social, psychological, and contextual factors [1,16]. Specifically, actual adoption timing (or intention, for those not yet vaccinated) and the factors shaping it are analyzed, including common behavioral drivers like perceived infection risk and past vaccination behavior (e.g., annual flu shot) [39,44,45], as well as how self-perceived knowledge, external conditions, and peer influence affect vaccine decisions across adopter categories. The findings could help inform healthcare providers and policymakers in understanding and applying the differing effects of relevant factors that motivate vaccination adoption, encourage early action, or delay uptake.

2. Methods

2.1. Study Design and Participants

An online survey was conducted in November-December 2021, approximately one year after the launch of the first COVID-19 vaccine, to assess participants' and their peers' vaccination status, attitudes and experience relating to the COVID-19 pandemic and vaccine, along with demographic information (age, gender, race, education, and household income). To minimize selection bias, a stratified quota sampling approach

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was employed with the support of a professional panel company to strengthen the representativeness of the sample. Potential participants were only notified about the opening of the survey and not informed of the subject matter to avoid self-selection bias that may lead to oversampling people who had particularly strong opinions about the pandemic or vaccine. Unique to COVID-19 vaccination, most people remembered the month of their first dose at the time of the survey because of the widespread attention to the initial eligibility prioritization, the need to make and often wait for an appointment, and the required interval to receive the second dose or a booster (or they could check the date on their vaccination card), which reinforced memory.

The selection of indicators was based on theory, the literature review, and study objectives. The questionnaire was reviewed and advised by an expert panel and pilot tested with a small, diverse group resembling the intended sample before fielding. Because COVID-19 vaccines became available through emergency authorization in December 2020 for people aged 16 and older, the target population included U.S. residents aged 16+ (approximately 275 million) [46]. With a goal of achieving a 98% confidence level and 3% margin of error, the sample size was estimated to be at least 1509 [47]. Participants were recruited through a panel company to reach a nationally representative sample. The study protocol was approved by Duke University's Institutional Review Board. Each participant indicated their consent by clicking the "next" button at the end of the informed consent webpage to start the survey.

2.2. Measures

2.2.1. Vaccination Status and DOI Group Categorization

The primary outcome variable was vaccination timing. Participants reported their COVID-19 vaccine status with six answer options: 1—No, I do not plan to get it; 2—I am not sure whether to get it; 3—I will (or plan to) get it; 4—I received one dose of the Pfizer or Moderna vaccine, but I am not sure if I want to get the second dose; 5—I received one dose and will get the second dose soon; and 6—I am fully vaccinated. Those vaccinated (responded 4–6) then reported the month of their first dose.

Following Rogers' DOI theory [18], participants were initially grouped into five categories—innovators, early adopters, early majority, late majority, and laggards—based on the month (or absence) of their first COVID-19 vaccine dose. Due to the small number of innovators, as well as the initial vaccine shortage and limited eligibility that might have delayed some eager individuals from obtaining the vaccine, this group was merged with early adopters, resulting in four categories for statistical analysis.

Participants vaccinated between December 2020 and March 2021 were classified as *early adopters* (23%), April–July 2021 as *early majority* (30.6%), after July 2021 or those expressing intent or uncertainty about vaccination as *late majority* (26.4%), and those with no intention to get vaccinated as *laggards* (20.1%). This distribution aligns with CDC-reported national trends: by December 2021, 68.6% of the U.S. population had received at least one dose, rising to 78.43% by December 2022 [7]. The proportion of laggards in this study (20.1%) closely mirrors the ~20% who remained unvaccinated at the end of the pandemic (May 2023) [7].

2.2.2. Risk Perceptions, Attitudes, and Knowledge

Independent variables were selected based on prior literature on vaccine uptake and hesitancy. Risk-related measures included perceived risk of contracting COVID-19 (called "infection risk" hereafter), perceived risk of becoming seriously ill from COVID-19 ("severity risk"), perceived risk of infection despite vaccina-

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tion ("post-vaccination infection risk"), and perceived overall seriousness of the situation ("seriousness").

Attitudinal measures included confidence in the COVID-19 vaccines ("confidence"), belief in the importance of vaccination ("importance"), general support of vaccines ("support"), and past flu shot uptake ("past vaccination"). In addition, self-rated COVID-19 knowledge ("knowledge") and intention to receive a booster ("booster intention") were measured, all via Likert scales. Higher scores represented a higher inclination to vaccinate. "Prefer not to say" responses were coded as missing, and "Other" or "Unsure" responses were recoded or treated as missing as appropriate.

2.2.3. Social Influence

To assess social influence, participants were asked about the perceived vaccination status of peers. A distinction was made between frequent contacts (i.e., classmates or coworkers) and friends to investigate whether vaccination decisions were shaped more by proximity or personal connection and trust.

2.3. Data Analysis

Correlation analyses examined associations between vaccination timing and predictors, followed by Kruskal–Wallis tests to assess differences across DOI groups. Significant differences were assessed using post hoc comparisons. Mediation analyses tested whether perceived COVID-19 seriousness and peers' vaccination status influenced the effects of confidence and infection risk on speed to adoption (or vaccination timing). To extend beyond bivariate relationships and considering the nonlinearity of some of the relationships, a multinomial logistic regression (MNLR) was performed to examine predictor significance and the odds of each adoption group membership, designating laggards as the reference category. All theoretically relevant predictors were entered into the MNLR model to discover the relative influences of the indicators.

Predictors comprised categorical demographic variables (dummy-coded with reference groups: age $\geq$ 65, White, female) alongside continuous/ordinal covariates. Model assumptions were tested before interpretation, including independence of observations, mutual exclusivity and exhaustiveness of outcome categories, linearity in the logit for continuous predictors, absence of severe outliers or influential points, and multicollinearity evaluated using variance inflation factors (VIFs), with a conservative threshold of VIF < 3 indicating acceptable collinearity [48–51]. Significance was set at $p < 0.05$ for all analyses.

Analysis was performed via IBM SPSS Statistics (Version 31) [52] and the PROCESS macro extension (Version 4.3) [53] was used to conduct mediation analyses. Data visualization was conducted in Python (Version 3.14.3) using the Matplotlib library (Version 3.10.8) [54,55], with code developed in Visual Studio Code (Version 1.109).

3. Results

A total of 1710 individuals aged 16 years or older responded to the survey (participant characteristics presented in Table 1). Within one year of the COVID-19 vaccine rollout, 64.3% (n = 1100) had received at least one dose, with 1024 fully vaccinated. Among the 35.7% not yet vaccinated (610, presented in orange and red bars, Figure 1), 56.2% (343, or 20.1% of the sample) reported no intention to get vaccinated (red bar).

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Table 1. Participant self-reported demographic characteristics by adoption group, based on the timing of obtaining the first dose of COVID-19 vaccine (*N* = 1710).

	TOTAL % (*N*)	**Early Adopters % (*n*)**	**Early Majority % (*n*)**	**Late Majority % (*n*)**	**Laggard % (*n*)**
	100 (1710)	22.98 (393)	30.58 (523)	26.37 (451)	20.06 (343)
Age Group					
16–17	15.32 (262)	6.87 (18)	35.11 (92)	36.26 (95)	21.76 (57)
18–22	15.32 (262)	12.21 (32)	36.26 (95)	32.44 (85)	19.08 (50)
23–29	4.74 (81)	16.05 (13)	28.40 (23)	27.16 (22)	28.40 (23)
30–39	16.84 (288)	13.23 (52)	13.96 (73)	18.85 (85)	22.74 (78)
40–49	24.21 (414)	28.02 (116)	31.88 (132)	23.19 (96)	16.91 (70)
50–64	15.91 (272)	33.82 (92)	29.04 (79)	20.22 (55)	16.91 (46)
65+	7.66 (131)	53.44 (70)	22.14 (29)	9.92 (13)	14.50 (19)
Gender					
Male	46.55 (796)	28.52 (227)	31.16 (248)	22.49 (179)	17.84 (142)
Female	51.64 (883)	18.01 (159)	29.90 (264)	29.78 (263)	22.31 (197)
Other	1.81 (31)	22.58 (7)	35.49 (11)	29.03 (9)	12.90 (4)
Race					
Native American	1.64 (28)	10.71 (3)	17.86 (5)	35.71 (10)	35.71 (10)
Asian/Pacific Islander	5.73 (98)	17.35 (17)	53.06 (52)	20.41 (20)	9.18 (9)
Black/African American	12.40 (212)	9.91 (21)	26.89 (57)	41.04 (87)	22.17 (47)
Hispanic/Latino	8.36 (143)	17.48 (25)	35.66 (51)	36.36 (52)	10.49 (15)
White/Caucasian	68.77 (1176)	27.38 (322)	28.91 (340)	22.45 (264)	21.26 (250)
Other	3.10 (53)	9.44 (5)	33.96 (18)	33.96 (18)	22.64 (12)
Household Income *					
<$25,000	21.16 (251)	17.13 (43)	25.50 (64)	27.49 (69)	29.88 (75)
$25,000–$49,999	25.72 (305)	24.26 (74)	29.18 (89)	23.93 (73)	22.62 (69)
$50,000–$99,999	28.50 (338)	31.95 (108)	26.63 (90)	22.49 (76)	18.93 (64)
$100,000–$199,999	17.62 (209)	40.19 (84)	33.01 (69)	17.70 (37)	9.09 (19)
$200,000+	3.71 (44)	45.45 (20)	31.82 (14)	15.91 (7)	6.82 (3)
Prefer Not to Answer	3.29 (39)	35.90 (14)	25.64 (10)	23.08 (9)	15.38 (6)

* For reference, the median annual household income in the U.S. for 2024–2025 was $83,730. The average monthly cost of living is $2924 for a single person and $7101 for a family of four, with variation across states and cities.

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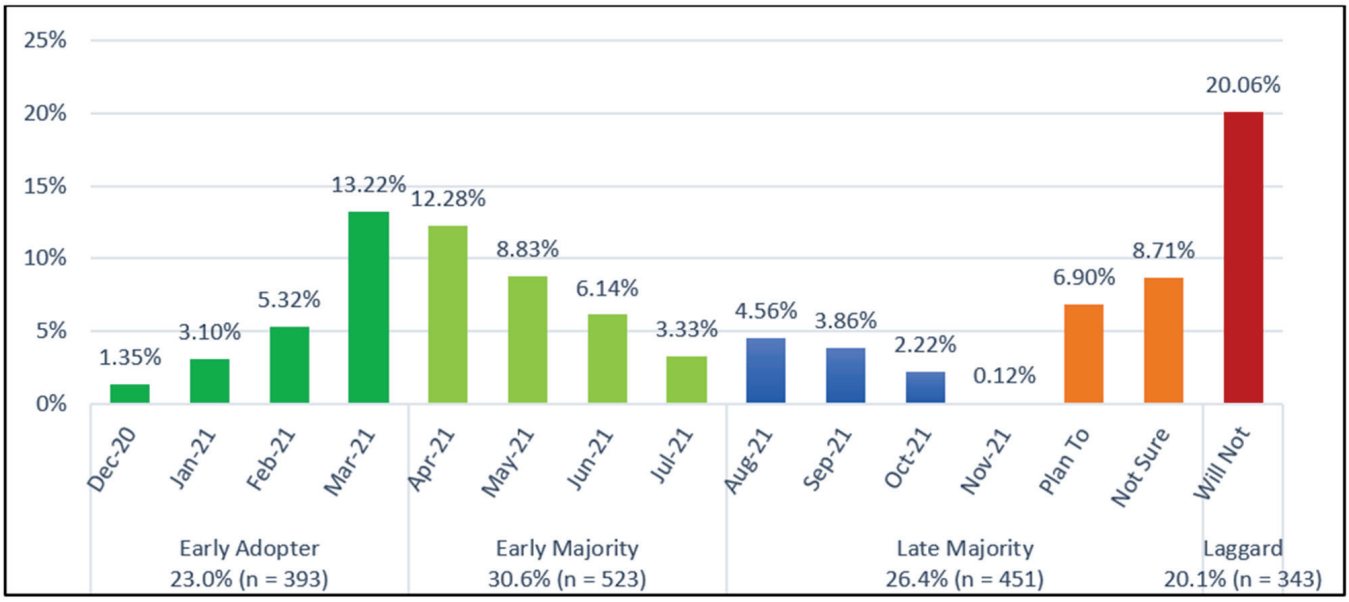

Figure 1. Timing of first COVID-19 vaccination and corresponding adoption groups in the U.S. (*N* = 1710). One year after vaccine rollout, 64.3% (1100) received at least one vaccine dose, and 35.7% (610; orange and red bars) were unvaccinated. Among the total sample, 20.1% (343; red bars only) expressed no intention to get vaccinated.

3.1. Demographic, Behavioral, and Attitudinal Factors

Vaccine adoption timing was significantly associated with multiple demographic and psychosocial factors (all $p < 0.001$). Among demographic variables, education exhibited the strongest positive correlation with earlier vaccination (r = 0.264), followed by income (r = 0.251) and age (r = 0.216), indicating that individuals who were older, had obtained more years of formal education, and were in the higher income groups (among the five levels presented in Table 1) tended to vaccinate earlier. Both past and future vaccination behavior were associated with earlier uptake, including the pattern of obtaining flu shots (r = 0.393) and booster intention (r = 0.234). On the other hand, self-reported COVID-19 knowledge showed a weak but statistically significant association (r = 0.093). Non-parametric analysis indicated that prior flu shot pattern differed across all four groups at each phase (H(3) = 310.82, $p < 0.001$). Knowledge also varied (H(3) = 13.69, $p = 0.003$) but the pattern was inconsistent; pairwise comparisons showed a significant difference only between early adopters and later adopter groups.

Relating to attitudes, belief in vaccine importance (r = 0.604; H(3) = 708.16, $p < 0.001$), vaccine confidence (r = 0.599; H(3) = 671.79, $p < 0.001$), and general support for vaccination (r = 0.562; H(3) = 592.38, $p < 0.001$) were associated with adoption speed. All showed variations across groups, with consistent pairwise differences except between early adopters and early majority (for importance and support). Later adopters, particularly laggards, reported more skepticism and lower perceived importance. Past vaccination behavior showed a clear gradient across adopter groups, with the proportion reporting "always or almost always" obtaining flu shots decreasing from 66.07% among early adopters to 11.21% among laggards (Figure 2).

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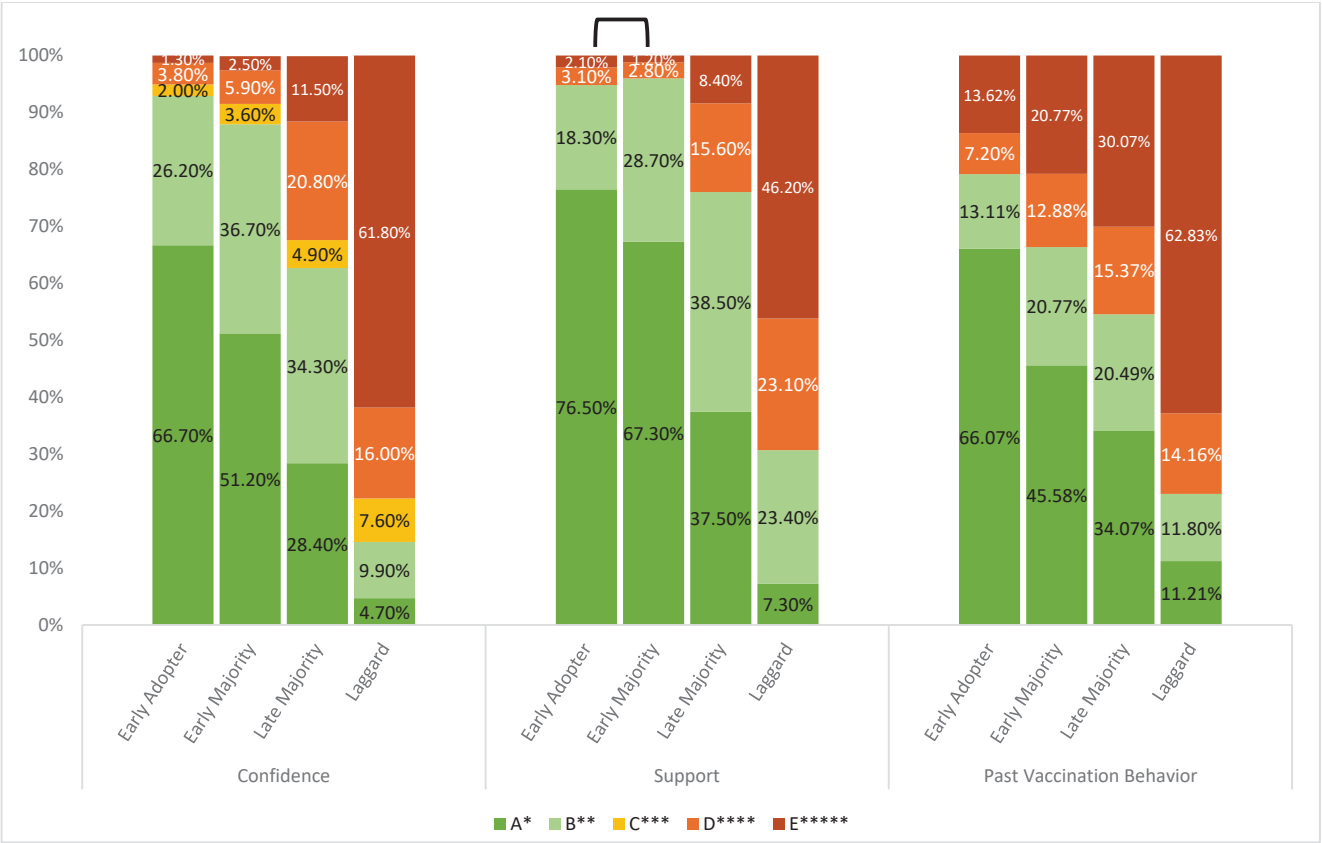

Figure 2. Portions of participants expressed levels of vaccine confidence, support, and past vaccination behavior across adoption groups (n = 1710). Ranges of response options (A to E) for confidence in the COVID-19 vaccine were as follows: very confident to very unconfident; general support of vaccines: strongly agree to strongly disagree; past-vaccination behavior (flu shot uptake): always or almost always to never. All three attitudes varied significantly across adoption groups (Kruskal–Wallis: H(3) = 671.79, 592.38, 310.82, respectively; all $p < 0.001$). The reversed U-shape on top of the bars indicates the pairs of groups that were insignificant from one another.

3.2. Perceived Infection, Severity, Post-Vaccination, and Situational Risks

Likewise, perceived infection risk (r = 0.415), seriousness of the situation (r = 0.279), and illness severity risk (r = 0.150) were associated with earlier uptake. On the other hand, those who believed that post-vaccination risk was likely tended to delay or refuse the vaccine (r = 0.330).

Significant differences were observed across the four adoption groups (all $p < 0.001$), yet each followed distinct patterns (Figure 3). Infection risk was highest among early adopters and declined across later groups, though pairwise comparisons showed that differences between the first two groups—early adopters and early majority—were insignificant. Severity risk showed little variation among the first three groups—early adopters, early majority, and late majority ($p > 0.05$); laggards deviated from them ($p < 0.001$), with 59.5% believing severe illness was somewhat/very unlikely. Post-vaccination infection risk revealed a reverse trend. Early adopters and early majority expressed stronger belief in vaccine protection, whereas over three-quarters of laggards believed infection after vaccination was still somewhat/very likely (Figure 3), citing it as a main reason for rejecting the vaccine.

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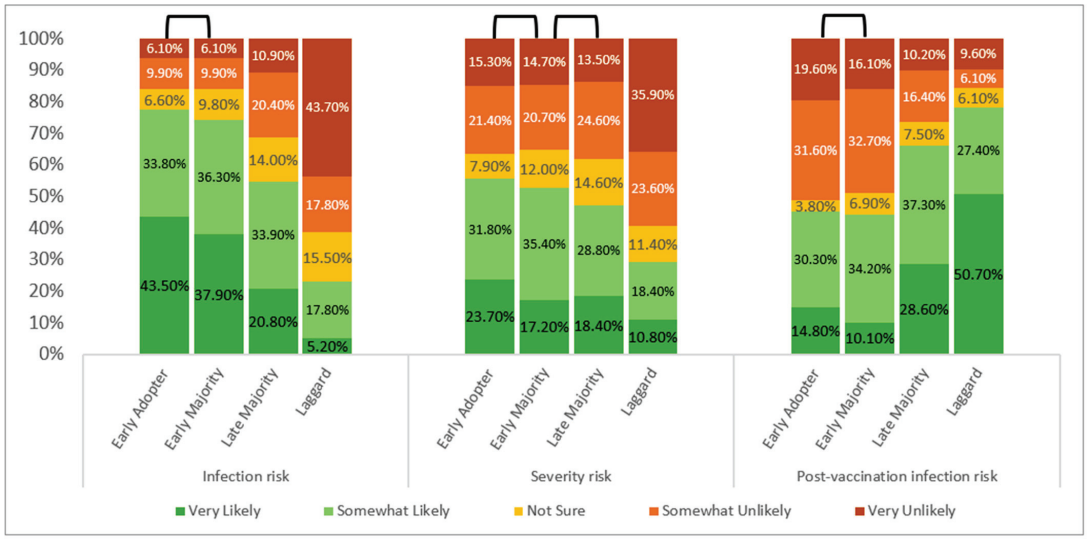

Figure 3. Levels of perceived COVID-19 infection risk, severe illness risk, and post-vaccination infection risk across adoption categories (N = 1710). Responses were 5-point Likert scales ranging from very likely to very unlikely. All three perceptions varied significantly across adoption groups (Kruskal–Wallis: H(3) = 353.73, 79.64, 204.04, respectively; all $p < 0.001$). The reversed U-shape on top of the bars indicates that the pairs of groups were insignificant from one another.

3.3. Social Influence on Vaccination Speed

Both social influence factors were significantly associated with adoption speed, with individuals who had more friends (r = 0.542) or peers (r = 0.496) who were already vaccinated also obtaining vaccination earlier. Reported vaccination levels among friends and peers were similar between early adopters and early majority but differed significantly with later groups (friends: H(3) = 452.102; peers: H(3) = 247.565; both $p < 0.001$). The percentages declined steadily from early adopters to laggards, while non-vaccinated rates increased across later groups (Figure 4). At the same time, a substantial share of participants reported uncertainty regarding their peers' vaccination status: 17.5% unsure about friends and 42.4% for coworkers or classmates. These responses were excluded from the primary analysis.

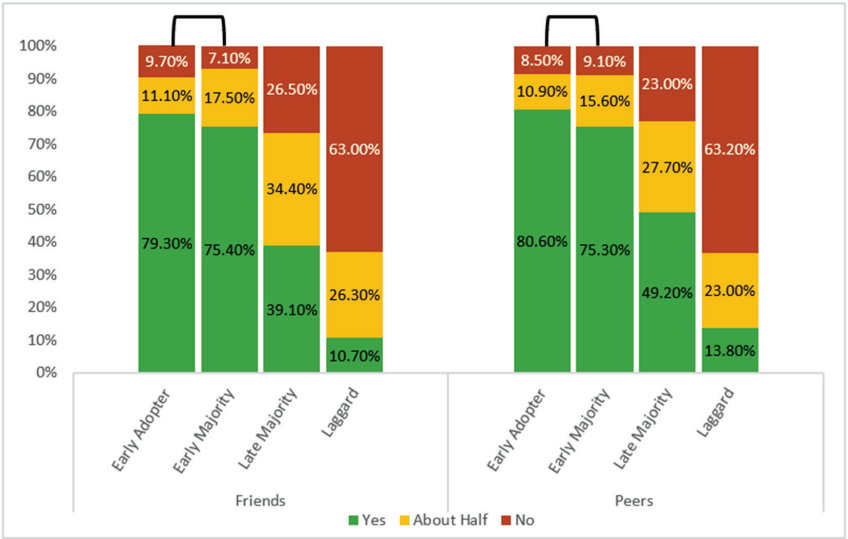

Figure 4. Perceived vaccination status of friends and peers across vaccine adoption groups (N = 1710). Participants indicated whether most friends and classmates/coworkers were vaccinated (Kruskal–Wallis: H(3) = 452.102 and 247.565, respectively; both $p < 0.001$). The reversed U-shape on top of the bars indicates the pairs of groups that were not significantly different from one another.

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3.4. Mediation Analysis and Multinomial Regression

Vaccine confidence (β = 0.58, SE = 0.10, $p < 0.001$) and perceived infection risk (β = 0.29, SE = 0.09, $p = 0.001$) were clear indicators of adoption timing. In exploring potential mediating effects, peer vaccination status was found to partially mediate the relationship between confidence and adoption timing (β = 0.04, BootSE = 0.02, 95% CI [0.01, 0.09]) but not with infection risk. Perceived seriousness did not mediate either relationship.

MNLR results are presented in Table 2, and the odds ratios (OR) of significant indicators are plotted in a coefplot (Figure 5), with laggards as the reference category. All model assumptions were assessed and met, as described in Section 2. The model showed acceptable fit and strong explanatory power: Nagelkerke $R^2 = 0.602$ (>0.4 indicates a strong relationship); likelihood-ratio test $p < 0.001$.

Table 2. Predicting COVID-19 vaccine adoption timing groups via multinomial logistic regression ($N = 1710$).

Adopter Group [a]	Parameter	B	Std. Error	Wald	df	Sig.	Odds Ratio (OR)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Early Adopter	Intercept	−11.681	0.980	142.013	1	0.000			
	Race (Factor Variable)								
	Native American	−1.471	1.035	2.019	1	0.155	0.230	0.030	1.747
	Asian/PI	0.267	0.637	0.176	1	0.675	1.306	0.375	4.555
	Black	−0.789	0.399	3.917	1	0.048	0.454	0.208	0.992
	Hispanic/Latino	0.590	0.501	1.386	1	0.239	1.804	0.676	4.815
	White	0 [b]			0				
	Covariate Variables								
	Flu shot history	0.747	0.105	50.527	1	0.000	2.111	1.718	2.594
	Infection risk	0.909	0.146	38.828	1	0.000	2.482	1.865	3.304
	Severity risk	−0.255	0.145	3.101	1	0.078	0.775	0.583	1.029
	Seriousness	0.325	0.162	4.016	1	0.045	1.384	1.007	1.902
	Confidence	1.496	0.161	85.886	1	0.000	4.465	3.254	6.127
	Support	0.975	0.163	35.657	1	0.000	2.651	1.925	3.651
	Knowledge	0.085	0.135	0.402	1	0.526	1.089	0.836	1.419
	Post-vac risk	0.384	0.139	7.608	1	0.006	1.468	1.117	1.928
Early Majority	Intercept	−10.385	0.913	129.483	1	0.000			
	Race (Factor Variable)								
	Native American	−0.695	0.831	0.700	1	0.403	0.499	0.098	2.544
	Asian/PI	1.153	0.587	3.857	1	0.050	3.168	1.002	10.015
	Black	0.013	0.332	0.001	1	0.970	1.013	0.529	1.940
	Hispanic/Latino	0.981	0.465	4.448	1	0.035	2.667	1.072	6.637
	White	0 [b]			0				
	Covariate Variables								
	Flu shot history	0.449	0.097	21.646	1	0.000	1.567	1.297	1.894
	Infection risk	0.920	0.135	46.070	1	0.000	2.508	1.923	3.271
	Severity risk	−0.171	0.136	1.581	1	0.209	0.843	0.645	1.100
	Seriousness	0.327	0.147	4.921	1	0.027	1.387	1.039	1.851
	Confidence	1.117	0.140	63.453	1	0.000	3.054	2.321	4.020
	Support	1.022	0.140	53.134	1	0.000	2.778	2.111	3.656
	Knowledge	−0.050	0.124	0.162	1	0.687	0.951	0.746	1.213
	Post-vac risk	0.494	0.131	14.232	1	0.000	1.640	1.268	2.120

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Table 2. *Cont.*

Adopter Group [a]	Parameter	B	Std. Error	Wald	df	Sig.	Odds Ratio (OR)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Late Majority	Intercept	−6.197	0.800	60.012	1	0.000			
	Race (Factor Variable)								
	Native American	0.189	0.659	0.082	1	0.774	1.208	0.332	4.395
	Asian/PI	0.255	0.587	0.189	1	0.664	1.290	0.409	4.075
	Black	0.498	0.290	2.939	1	0.086	1.645	0.931	2.905
	Hispanic/Latino	1.215	0.430	7.963	1	0.005	3.369	1.449	7.833
	White	0 [b]			0				
	Covariate Variables								
	Flu shot history	0.354	0.089	15.998	1	0.000	1.425	1.198	1.695
	Infection risk	0.540	0.122	19.517	1	0.000	1.715	1.350	2.179
	Severity risk	0.056	0.124	0.208	1	0.649	1.058	0.830	1.348
	Seriousness	0.183	0.128	2.025	1	0.155	1.200	0.933	1.544
	Confidence	0.873	0.121	51.999	1	0.000	2.393	1.888	3.034
	Support	0.448	0.112	15.891	1	0.000	1.565	1.256	1.951
	Knowledge	−0.002	0.109	0.000	1	0.985	0.998	0.806	1.236
	Post-vac risk	0.091	0.120	0.579	1	0.447	1.096	0.866	1.387

a. The reference category is laggard. b. White participants were designated as the reference group; this parameter is set to zero because it is redundant.

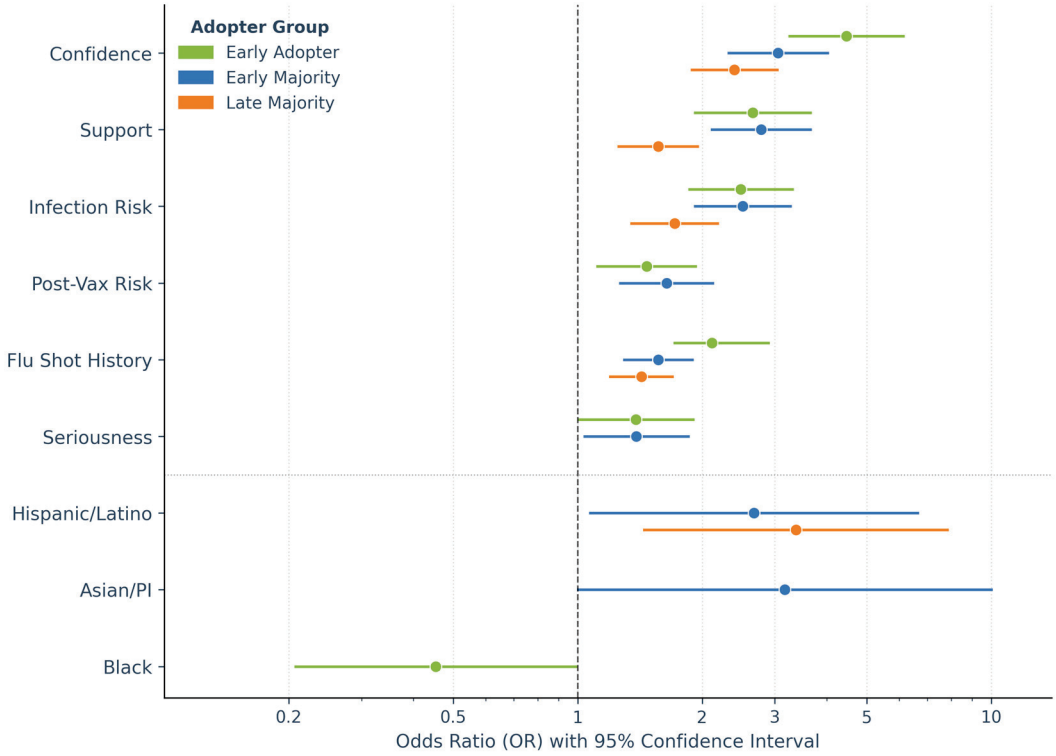

Figure 5. Significant predictors of vaccine adoption timing group membership. Odds ratios (ORs) from multinomial logistic regression are shown for statistically significant predictors ($p < 0.05$) across three adopter groups relative to the laggards group (reference category). Dots represent point estimates; respective accompanying horizontal lines indicate the 95% confidence intervals. The vertical dashed line at OR = 1 denotes no effect. Predictors below the dotted horizontal divider represent race/ethnicity variables; those above represent behavioral and attitudinal covariates.

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No significant gender differences were observed across groups. Compared with adults aged 65+, younger groups had lower odds of early adoption (all $p < 0.05$), while no significant age differences emerged for the two middle groups—early and late majorities. Black respondents were less likely to be in the initial group—early adopters (OR = 0.454, $p = 0.048$)—whereas Asian and Hispanic/Latino respondents had higher odds of being in the early or late majority groups.

Behavioral history and risk perceptions significantly differentiated adopter groups. Prior flu-shot history was associated with increased odds of being in the early adopter (OR = 2.111), early majority (OR = 1.567), and late majority group (OR = 1.425; all $p < 0.001$) relative to laggards. Higher perceived infection risk was similarly associated with increased odds of membership in all earlier adoption groups (all $p < 0.001$). Lower perceived post-vaccination infection risk, signaling stronger trust in the vaccine efficacy, was associated with higher odds of being an early adopter (OR = 1.468, $p = 0.006$) or early majority (OR = 1.640, $p < 0.001$). However, perceived severity was not significant across adopter groups.

Participants who reported greater pandemic seriousness were more likely to be an early adopter or early majority, but no significant differences were observed between the latter two groups. Those who expressed confidence in and support for the vaccine had very low odds of being laggards. Self-reported knowledge level was not associated with adopter group membership.

4. Discussion

This study examined vaccine behavior and perceptions by not only identifying *who* or *why* but also *how quickly* individuals would obtain vaccination. The temporal factor is critical in predicting and controlling the spread of disease. The pandemic provided a rare opportunity to investigate the progression of adopting a new vaccine at the population level, and the application of the DOI framework offered more nuanced insights into demographic, behavioral, and psychosocial factors. The findings provide additional evidence of the direct effects of confidence, risk perceptions, and social norms on adoption timing, as well as a mediating effect of peer vaccination status in the relationship between confidence and uptake.

Older adults were more likely to get vaccinated early, reflecting both their elevated COVID-19 infection risk and prioritization during the initial vaccine rollout—a strategy similarly adopted across countries globally and recommended by the World Health Organization (WHO) [56,57]. Due to the initial supply shortage [58] during the first few months in the U.S., frontline healthcare professionals and those who worked or lived in long-term care facilities were the first to obtain vaccination, followed by people aged 65 or older and front-line essential workers, stipulated by federal recommendation, with variation by states [59]. Such prioritization rendered higher vaccination rates among older adults worldwide (e.g., Germany and the UK observed 84% and 97% for adults over 65, respectively, compared to 78% in the U.S. [60]). Multinomial analyses confirmed that age exerted its strongest influence over the earliest phase, when limited availability and risk-focused messaging disproportionately favored older adults [61].

Higher education and income levels also predicted earlier acceptance, likely due to enhanced health literacy [39], trust in science [62,63], and better healthcare access [64,65]. Until spring 2021, COVID-19 vaccine demand had exceeded supply. Many individuals in the U.S., even when they became eligible according to their jurisdiction's allocation plan, waited days or weeks for an appointment; the shortage was particularly severe and persisted in lower-resourced nations [66–68]. However, the relationship between education

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and trust in science is not universal; across 142 countries, the positive association was weaker or nonexistent in highly corrupt countries, suggesting that institutional context moderates the role of education in vaccine-related decision-making [69]. Once vaccines became widely available, these demographic factors were no longer strong determinants of uptake timing. Such diminishing influences were often masked in prior binary studies that did not consider the progression of adoption over time, demonstrating the benefit of applying the DOI framework.

The different dimensions of risk perceptions exhibited varied effects and were further distinguished here. Extending the existing literature [39,70], infection risk, along with several attitudinal factors, was found to be positively associated with speed to vaccination. Research on coping responses indicated that higher perceived threat increased willingness to be vaccinated [71]; a similar association was reported in Australia and Slovenia [72,73]. The observed increase in uptake during August and September 2021 followed the surge in confirmed cases in late summer [7]. Nevertheless, this effect could be attenuated by anticipated severity risk: if the chance of getting very sick was low, then the urgency of avoiding infection seemed trivial. Evidenced by the indifference observed among the first three groups that diverged from laggard, severity risk may persuade the hesitant to get vaccinated but be insufficient to motivate earlier adoption.

Moreover, belief in lower post-vaccination infection risk was positively associated with uptake decision and timing. It aligned with documented hesitancy regarding the COVID-19 vaccine, which primarily stems from safety and efficacy concerns, e.g., the technology was too new, the vaccine was developed too quickly, or the approval process was too rushed [33,39,74,75]. The results revealed that over three-quarters of laggards believed infection after vaccination was still somewhat or very likely. While this belief is not entirely wrong—since no vaccine is 100% effective at preventing infection [76,77]—it suggests that laggards may over-emphasize this limitation, contributing to a misconception that vaccines are ineffective and thus not worth taking.

On the other hand, self-rated COVID-19 knowledge was only weakly associated with vaccination timing and showed no consistent pattern across adopter groups. Even among those who reported being well-informed, vaccine decisions may hinge on trust, values, and perceived risks. Research using Protection Motivation Theory (PMT) found that in Taiwan, perceived knowledge enhanced coping appraisals—individuals' positive perceptions of the COVID-19 vaccine as an effective prevention strategy—and led to uptake [78]. An American study of adolescents reported that perceived knowledge moderated the relationship between risk perception and vaccination among the low-knowledge group [79]. In the UK, however, knowledge was not predictive—likely due to misinformation and low institutional trust [80]. Consistent with this, MNLR did not identify self-rated knowledge as a significant predictor of earlier adoption, suggesting that information alone was insufficient to accelerate uptake. These findings underscore the need to communicate vaccine benefits more clearly to instill trust: they are intended to reduce hospitalization, morbidity, and mortality, not to completely eliminate infection [78]. Future studies could compare self-reported vs. objectively measured knowledge to help elucidate the discrepancy in the literature.

Attitudinal and behavioral factors, particularly belief in vaccine importance and confidence, consistently predicted earlier uptake, with confidence showing the clearest gradient across adopter groups. This mirrors findings from Australia, where use of trusted information sources such as government health websites and healthcare provider recommendations was among the strongest predictors of vaccine confidence and uptake [81]. Viewed through the DOI framework, these factors not only facilitated vaccination decisions

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but also could expedite adoption—key to disease prevention and epidemic control. In contrast, while perceived infection risk exerted a direct influence on uptake speed, severity did not independently predict adoption timing once confidence and infection risk were considered. Support for vaccines, including flu shot history, also contributed to earlier adoption, reflecting broader preventive health habits and compliance with public health recommendations among earlier groups. Understanding and applying the differing and interacting impacts of these facilitators are important, especially considering the continuously evolving SARS-CoV-2 virus and resurgence of several infectious diseases. Since the pandemic, the public has become vaccine-fatigued [82,83]. Messages and promotional strategies must be reevaluated to encourage adoption of subsequent boosters and timely vaccination.

While three in ten in the U.S. had not been vaccinated by the end of 2021, either still hesitated or refused (relatively high compared to 18.47% in Canada and 11.59% in China) [7], a notable subset of the population (20.1%) expressed no intention to get vaccinated, despite sufficient supply and continuously rising confirmed cases [84]. This rejection proportion remained stable through May 2023, when the last national cumulative data were reported, coinciding with the WHO's declaration of the end of the pandemic [85]. Similarly, the unvaccinated ratio was 26.66% in Asia and 35.37% globally at the time and plateaued [7]. This group represents entrenched resistance rather than temporary reluctance, indicating that access and information alone may be insufficient to shift attitudes. Given this, it would not be productive to endeavor to change their minds, as success is unlikely. Instead, public efforts should focus on those who are hesitant but still willing to consider vaccination and motivate them to adopt the vaccine earlier or faster. This points to the need to examine the differences in group drivers to tailor approaches to specific populations.

Social influence has been identified as a strong promoter of behavior, including vaccination [86,87]. Early adopters and early majority were shown to report having a much higher proportion of their network vaccinated (75–80% responded most of their friends or peers had already been vaccinated) than later groups. Similarly, among UK adolescents, vaccination decisions were primarily shaped by parents, healthcare providers, and peers rather than social media, underscoring the cross-national relevance of social influence on vaccine behavior [88]. Conversely, being surrounded by unvaccinated people may shape reluctance or stimulate refusal. The pronounced disparity in peer vaccination between early and later groups suggests the operational function of social norms in the diffusion process. As vaccination became more common within close social networks, uncertainty may have diminished, enabling hesitant adopters to move toward vaccination. A study applying Social Cognitive Theory similarly identified observational learning—waiting to see whether friends and family get vaccinated first—as a significant predictor of vaccine behavior [89].

Mediation analyses further elucidate the dual roles of social influence in vaccination decision-making. People with higher vaccine confidence were more likely to perceive higher vaccination uptake among their peers, and these perceived norms were associated with earlier vaccination. This suggests that confidence acts both at the individual level and through perceived social norms, which in turn facilitate earlier vaccination.

The results also revealed that many people actively discussed COVID-19 vaccination with others, more frequently with friends than with broader peer groups. While perception can influence behavior, it may not be factually accurate. Earlier studies showed that individuals often misjudge peer behaviors, which public health campaigns have leveraged by correcting misperceptions and promoting positive social norms [86]. Others highlighted the role of subjective norms, particularly perceived approval from

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peers and family, in sustaining vaccine behaviors [90]. Messaging that emphasizes widespread uptake (e.g., "most students your age are vaccinated") may help normalize vaccination and be particularly effective for younger, hesitant groups to move towards vaccination.

Limitations and Future Research

This study has several limitations. First, data were collected via a self-administered survey, relying on participants' recall and subjective perceptions, which may introduce bias or inaccuracies. For instance, knowledge was self-reported rather than objectively measured, which may explain part of the inconsistent effect on vaccine acceptance. Second, although actual uptake rather than intention alone was examined, the survey design cannot account for structural factors—such as access, mandates, or logistical barriers—that may have influenced vaccination behavior, especially during the early phase of rollout when there was a shortage. Finally, while the sample was relatively representative of the U.S. population and offered valuable insight into psychological and social drivers of vaccination timing, COVID-19 was a special case with rapid and widespread infection, high global mortality, daily news broadcasting, and a vaccine that employed a novel technology and was initially launched under emergency use authorization (EUA). These additional contextual factors may have intensified both the urgency to get vaccinated and, concurrently, hesitancy compared to other vaccines.

Future studies could examine the different influences between subjective and objective knowledge levels and their potential interaction effect. Similarly, given the strong role of social influence, it would be beneficial to further explore whether perceived norms and actual vaccination rate exert a similar impact on vaccination decision as well as timing.

5. Conclusions

Vaccine hesitancy studies have identified a range of factors influencing uptake decisions, primarily focusing on individual characteristics, including demographics, perceived risk, and attitudes (confidence in vaccine and authority or science, general support of such a preventive intervention). This study further distinguished various dimensions of risk perception, validated the influence of peer behavior, mapped actual vaccine adoption timing instead of hypothetical scenarios, and provided reference comparisons to other countries. In particular, the research examined these factors through the lens of the DOI framework, with the advantage of accounting for the progression of cumulated protection at the population level, expanding on and overcoming the deficiency of the more conventional dichotomized analysis of vaccinated vs. unvaccinated. Contextually, the pattern of uptake was also associated with availability, accessibility (both eligibility and ease of obtainment), and disease activity (levels of confirmed cases and mortality).

By identifying what separated early from late adopters, and what ultimately facilitated the hesitant to vaccinate, this study offers a more nuanced understanding of vaccination behavior and adds a critical temporal perspective that can inform and potentially improve future public health vaccination efforts. Using the DOI framework to focus on hesitant to vaccinate individuals and population groups using proven interventions to improve uptake, such as employing trusted community voices, clear provider communications, community-centered education and outreach, and the use of data to guide targeted outreach and vaccination programs has the potential to help individual providers, health departments, and health systems reverse the rising levels of vaccine hesitancy and declina-

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tion of vaccination seen in the U.S. and globally [91]. Improving vaccine confidence and trust among those who are hesitant to vaccinate may facilitate more effective approaches to addressing other infectious diseases and mitigating public health threats, especially in our most vulnerable communities.

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Article

Effectiveness of COVID-19 Vaccines Against Hospitalization and Severe Disease in Children with Diabetes Mellitus During Pandemic and Post-Pandemic Eras

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Abstract

Pediatric patients with SARS-CoV-2 infection are at an increased risk of severe disease and adverse outcomes. Nevertheless, comprehensive data on COVID-19 vaccine effectiveness (VE) in children with diabetes during the post-pandemic period remain limited. This study assessed the VE against severe COVID-19 outcomes during both the pandemic and post-pandemic phases in children with and without diabetes mellitus (DM). A cohort study based on population data was carried out, including all patients under 18 years of age with symptomatic SARS-CoV-2 infection as registered in the Brazilian national surveillance systems from February 2020 to June 2025. The main outcomes were hospitalization due to COVID-19 and severe illness, which included admission to the intensive care unit (ICU), need for invasive ventilation, and death. Utilizing a propensity score-matched cohort, we estimated the VE and the number needed to vaccinate (NNV) for a booster dose against these outcomes by comparing vaccinated and unvaccinated individuals, employing conditional logistic regression adjusted for confounding variables. The cohort comprised 3,730,007 pediatric patients with COVID-19, of whom 7675 (0.2%) had DM. At baseline, children with DM exhibited a significantly higher prevalence of hospitalization (11.2% vs. 2.0%), severe COVID-19 (6.4% vs. 0.6%), and mortality (1.9% vs. 0.1%) than those without DM (all $p < 0.001$). During the pandemic period, the adjusted VE was consistently higher in children with DM. Against severe disease, the VE was 72.8% (95% CI: 12.3–93.2) in the DM cohort compared with 45.7% (28.1–59.0) in the non-DM cohort. This increased effectiveness corresponded to a more favorable NNV; the NNV to prevent one severe case was 24 (95% CI: 12–232) for children with DM versus 243 (168–440) for those without DM. In the post-pandemic period, the VE remained significantly higher in the DM cohort. Against severe disease, the VE was 76.2% (11.5–93.5) for children with DM and 52.9% (32.7–67.1) for those without. The NNV to prevent one severe case was consistently lower in the DM

cohort (8 vs. 591). In conclusion, a complete vaccination regimen, including a booster dose, substantially mitigated severe COVID-19 outcomes in children with DM in the pandemic and post-pandemic periods.

Keywords: COVID-19; diabetes mellitus; children; vaccine effectiveness; post-pandemic

1. Introduction

During the COVID-19 pandemic, diabetes mellitus (DM) was established as a major risk factor for severe disease outcomes [1]. Research has established that SARS-CoV-2 infection markedly elevates the risk of severe illness, hospitalization, and mortality among adults with diabetes [2–4]. However, data on the outcomes of children with diabetes mellitus (DM) remain inconclusive. Generally, children with DM who contract SARS-CoV-2 tend to experience a mild course of COVID-19. For example, Nimri et al. [5] observed that young individuals with established type 1 diabetes (T1D) experienced mild COVID-19 infections, although factors such as elevated glucose levels during SARS-CoV-2 infection, advanced age, and comorbidities were associated with a prolonged disease course. Similarly, Demeterco-Berggren et al. [6] conducted a multicenter study involving patients with T1D and COVID-19 across 56 clinical centers in the United States. The study's findings indicated that older patients were at an increased risk for severe COVID-19, whereas children and younger adults experienced milder illness, with no fatalities reported in these age groups. However, SARS-CoV-2 infection may still cause severe disease in those pediatric patients with DM and underlying conditions [7,8]. For example, we previously showed a higher prevalence of severe outcomes in children and adolescents with DM. Compared with children and adolescents without DM, pediatric patients with DM had a higher prevalence of ICU admission (46.6% vs. 26%), invasive ventilation (16.9% vs. 10.3%), and death (15% vs. 7.6%) [9]. Additionally, evidence suggests that COVID-19 may be associated with new-onset diabetes in children and may lead to a higher likelihood of developing diabetic ketoacidosis in children with DM [10,11].

COVID-19 vaccines effectively reduce severe outcomes in individuals with DM, albeit with potentially modestly reduced immunogenicity, particularly in individuals with poor glycemic control [12,13]. Consequently, major health authorities recommend COVID-19 vaccination, including updated boosters, for all individuals with DM [14,15]. Following the WHO's declaration of the end of the public health emergency, SARS-CoV-2 has transitioned into an endemic state, which remains relatively understudied [16–19]. However, the virus continues to evolve and remains a relevant cause of morbidity and mortality due to acute respiratory infections [20,21]. For instance, we showed that children with a positive test for SARS-CoV-2 had a hazard of death three times higher than individuals with a negative test among children and adolescents hospitalized with severe acute respiratory infection from February 2020 to February 2023 in Brazil [22]. New variants continue to evolve to escape the neutralizing antibodies induced by both infection and vaccination, causing recurring, but generally less severe, waves of infection [23]. The highest burden of severe disease is now concentrated in specific high-risk groups: the elderly, immunocompromised individuals, and those with underlying chronic conditions including DM, cardiopulmonary disease, and obesity [24]. This ongoing evolution, coupled with an evolving immunological landscape, creates substantial uncertainty in the post-pandemic period. A key unresolved question is whether annual COVID-19 vaccine boosters continue to confer meaningful protection, underscoring the need for contemporary evidence on vaccine effectiveness (VE) to inform future public health policies [25].

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Nevertheless, data on the effectiveness of COVID-19 boosters in children during the post-pandemic period are limited. Using a nationwide Brazilian cohort, we retrospectively assessed the real-world vaccine effectiveness in preventing severe COVID-19 outcomes among children with DM, comparing the pandemic and post-pandemic eras.

2. Materials and Methods

Study design, participants, and data sources: We carried out a retrospective cohort study based on population data, utilizing information from two official Brazilian national COVID-19 surveillance systems supplied by the Ministry of Health: (1) e-SUS Notifica, which tracks non-hospitalized individuals, and (2) SIVEP-Gripe, which monitors those who are hospitalized. Our study included all individuals aged < 18 years with confirmed SARS-CoV-2 infection, as recorded in these systems from 20 February 2020 to 30 June 2025. SARS-CoV-2 infection was confirmed by a positive result from either quantitative reverse transcription PCR (RT-qPCR) or an antigen test. Comprehensive information regarding these systems is available at https://opendatasus.saude.gov.br/dataset (accessed on 30 June 2025). Complete information regarding database management and data handling is available elsewhere [26]. Figure 1 presents a flowchart illustrating the case-selection process used in our analysis.

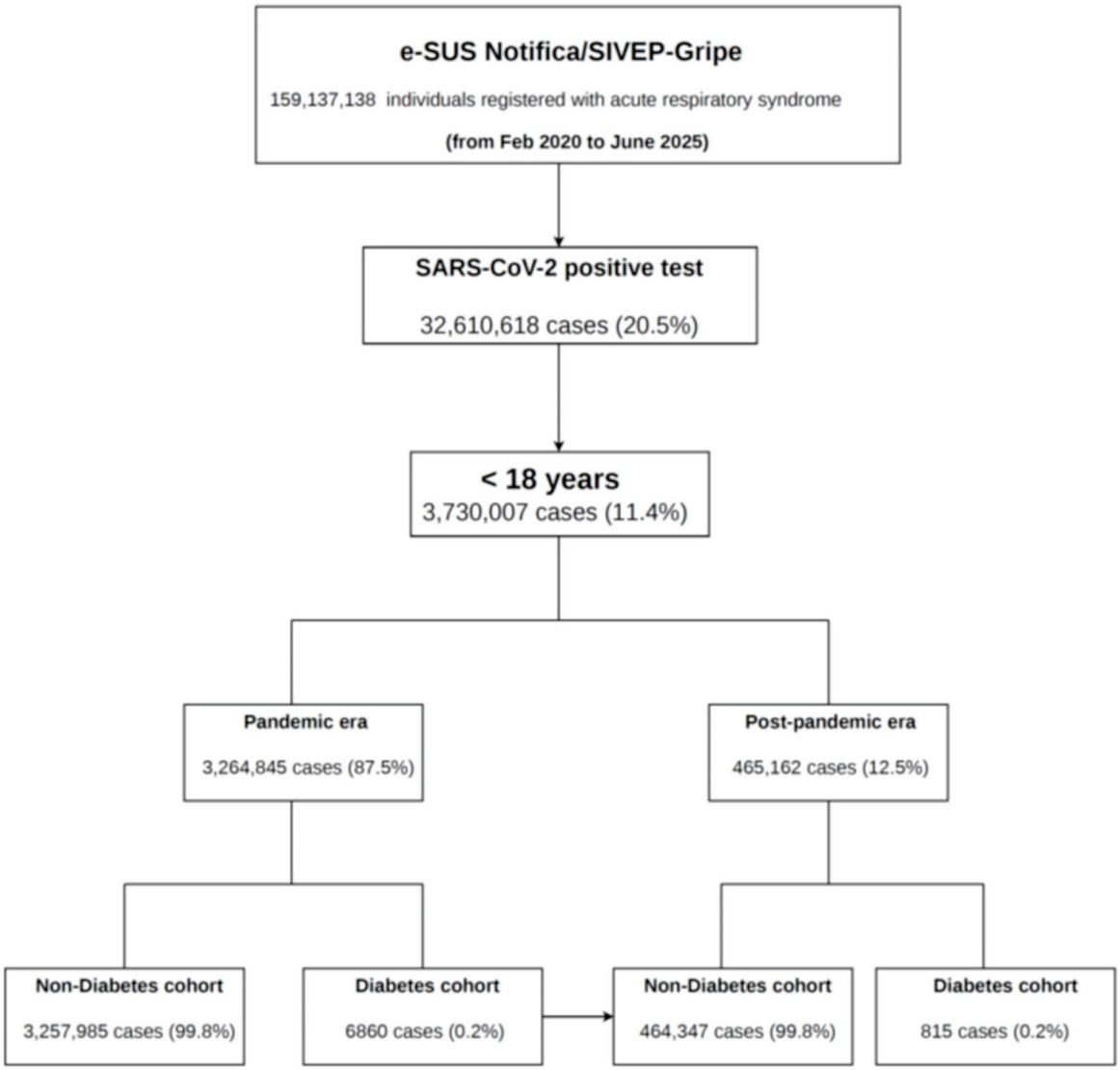

Figure 1. Flowchart of cohort selection.

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Exposure of interest: The main exposure of interest was DM. We identified the existence of DM and other related chronic health conditions using specific database fields for comorbidities in the datasets.

Covariates: Demographic data, including age, sex, ethnicity, and geographic region, were collected. Age was stratified into three categories: 0–4, 5–11, and 12–17 years. Ethnicity was classified according to the Brazilian Institute of Geography and Statistics (IBGE) system into five groups: White, Black, Pardo, Asian, and Indigenous. The geographic regions were categorized into five official Brazilian macro-regions, each characterized by distinct historical, socioeconomic, and healthcare system attributes [27,28]. The clinical data gathered encompassed the date of COVID-19 symptom onset, date of hospitalization, signs and symptoms at baseline, and the presence of chronic health conditions.

Comorbidities were identified in dedicated fields in both datasets, which assigned the presence or absence of chronic medical conditions such as asthma, obesity, immunodeficiency, malignancies, and heart, lung, kidney, nervous system, and blood diseases. For our analysis, we classified comorbidity status as a binary variable (either present or absent) and by the number of conditions (none, one, or two or more conditions). Considering the nature of the national surveillance databases, we addressed missing data in the comorbidity fields by assuming their absence [27,29].

The study period was empirically divided into two phases: the pandemic era (1 February 2020, to 31 December 2022) and the post-pandemic era (1 January 2023, to 30 June 2025), corresponding to the decline in the number of reported cases and COVID-19-related deaths in Brazil. For each case, the index date for era assignment was the date of symptom onset. In instances where this information was unavailable, the date of the SARS-CoV-2 test was used as the index date.

VaccinationStatus: Vaccination status was defined as the receipt of vaccine doses at least 14 days before symptom onset, as this period is necessary to elicit an immune response. Individuals were classified into four categories: (1) unvaccinated, (2) one dose, (3) two doses, and (4) three or more doses. Patients with unknown vaccination status were excluded from the primary analysis. Information regarding the vaccination program in Brazil is detailed elsewhere [30].

Outcomes: The primary outcomes were (i) hospitalization due to SARS-CoV-2 infection and (ii) severe COVID-19, a composite endpoint defined as admission to the ICU, the need for invasive mechanical ventilation, or mortality. The effectiveness of the vaccines against hospital admissions and severe COVID-19 was estimated separately for two time periods (pandemic and post-pandemic eras) and was stratified by the presence of DM.

Statistical analysis: Continuous data are expressed as the median (IQR) or mean (SD) based on their distribution. Categorical data are presented as proportions. Group comparisons were performed using the chi-square test for proportions and the Mann–Whitney U test for non-normally distributed continuous variables.

The effectiveness of the vaccines in preventing hospitalization and severe COVID-19 cases was assessed using multivariable logistic regression models. These models were created for the entire cohort and for subgroups divided by the presence or absence of DM and by time periods, specifically during and after the pandemic. In these models, clinical outcomes were assigned as dependent variables. Vaccination status was the primary independent variable, and the models were adjusted for the following confounders: age, sex, ethnicity, geographic macro-region, predominant viral strain, and year of diagnosis/admission. Unvaccinated individuals were used as the reference group.

To complement this analysis and provide a robust estimate of the most complete vaccination schedule, propensity score matching (PSM) was performed, focusing on individuals who received three or more doses versus those who were not vaccinated. Four separate

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PSM analyses were conducted for the subgroups of interest (patients with and without DM during the pandemic and post-pandemic eras). For each PSM, the vaccination status (three or more doses versus unvaccinated) was designated as the exposure variable. The groups were matched for age, sex, ethnicity, geographic region, viral lineage predominance, and admission year using 1:1 nearest-neighbor matching without replacement and a caliper width of 0.2 standard deviations [31,32]. Following matching on the estimated propensity score, the balance between the vaccinated and unvaccinated groups was assessed using standardized mean differences (SMD) and graphical density plots of the propensity scores [33]. To perform a more robust analysis that adjusted for any residual imbalance, conditional logistic regression was conducted on the matched datasets. The outcome was the dependent variable, and the vaccination status was the primary predictor, with adjustment for potential residual confounding factors. After PSM, we obtained the average treatment effect (ATE) from the matched dataset and calculated the number needed to vaccinate (NNV) to prevent one outcome of interest [34]. For all analyses, VE was calculated as (1—adjusted odds ratio) × 100% and reported with 95% confidence intervals (CI). Data analysis was conducted using R software (version 4.3.0, The R Foundation), employing the MatchIt package for propensity score matching, while STATA (version 19) was used to calculate the average treatment effects. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Clinical Characteristics and Outcomes

The cohort comprised 3,730,007 pediatric patients with COVID-19, including 7675 (0.2%) with DM. Table 1 displays the demographic and clinical characteristics of the patients. Overall, the cohort was evenly distributed between the 5–11 (39.1%) and 12–17 (39.1%) age groups, with a smaller proportion (21.9%) aged 0–4 years. The majority of patients were male (54.5%), resided in the Southeast (40.0%) or South (25.0%) regions, identified as White (55.6%), and had no recorded comorbidities (96.3%). The most common presenting symptoms were cough (43.3%) and fever (40.8%).

Table 1. Clinical and demographic features of children and adolescents with confirmed COVID-19 categorized by the presence of diabetes mellitus.

Covariates *	**Overall (%) 3,730,007 (100.0)**	**Non-DM Cohort (%) 3,722,332 (99.8)**	**DM Cohort (%) 7675 (0.2)**
Age (years)			
Median (IQR)	9.0 (5.0–14.0)	9.0 (5.0–14.0)	7.0 (1.0–14.0)
Mean (SD)	9.3 (5.2)	9.3 (5.2)	7.5 (6.5)
Age group (years)			
0–4	815,101 (21.9)	811,509 (21.8)	3592 (46.8)
5–11	1,458,324 (39.1)	1,457,094 (39.1)	1230 (16.0)
12–17	1,456,582 (39.1)	1,453,729 (39.1)	2853 (37.2)
Sex (n = 3,724,913)			
Male	2,031,465 (54.5)	2,028,219 (54.6)	3246 (42.4)
Female	1,693,448 (45.5)	1,689,033 (45.4)	4415 (57.6)
Region			
Southeast	1,491,076 (40.0)	1,487,314 (40.0)	3762 (49.0)
South	932,709 (25.0)	931,690 (25.0)	1019 (13.3)
Central-West	377,031 (10.1)	376,245 (10.1)	786 (10.2)
Northeast	636,856 (17.1)	635,268 (17.1)	1588 (20.7)
North	292,335 (7.8)	291,815 (7.8)	520 (6.8)

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Table 1. *Cont.*

Covariates *	Overall (%) 3,730,007 (100.0)	Non-DM Cohort (%) 3,722,332 (99.8)	DM Cohort (%) 7675 (0.2)
Ethnicity (n = 2,965,946)			
White	1,648,737 (55.6)	1,645,627 (55.6)	3110 (49.2)
Brown	1,177,553 (39.7)	1,174,788 (39.7)	2765 (43.7)
Black	77,658 (2.6)	77,340 (2.6)	318 (5.0)
Asian	61,288 (2.1)	61,156 (2.1)	132 (2.1)
Indigenous	710 (0.0)	709 (0.0)	1 (0.0)
Clinical presentation			
Fever	1,520,927 (40.8)	1,517,634 (40.8)	3293 (42.9)
Cough	1,616,742 (43.3)	1,612,356 (43.3)	4386 (57.1)
Dyspnea	236,071 (6.3)	234,494 (6.3)	1577 (20.5)
Odynophagia	1,035,656 (27.8)	1,032,888 (27.7)	2768 (36.1)
Number of Comorbidities			
None	3,593,339 (96.3)	3,593,339 (96.5)	0 (0.0)
1	129,500 (3.5)	123,816 (3.3)	5684 (74.1)
2	6266 (0.2)	4586 (0.1)	1680 (21.9)
3	902 (0.0)	591 (0.0)	311 (4.1)
Major comorbidities			
Pulmonary	58,735 (1.6)	58,355 (1.6)	380 (5.0)
Obesity	5956 (0.2)	5628 (0.2)	328 (4.3)
Cardiology	9405 (0.3)	8250 (0.2)	1155 (15.0)
Immunosuppression	6330 (0.2)	6185 (0.2)	145 (1.9)
Renal	1557 (0.0)	1520 (0.0)	37 (0.5)
SARS-CoV-2 strain			
Ancestral	609,332 (16.3)	607,708 (16.3)	1624 (21.2)
Gamma	1,087,021 (29.1)	1,084,529 (29.1)	2492 (32.5)
Delta	140,489 (3.8)	140,141 (3.8)	348 (4.5)
Omicron	1,893,165 (50.8)	1,889,954 (50.8)	3211 (41.8)
Admission Year #			
2020	590,014 (15.8)	588,449 (15.8)	1565 (20.4)
2021	1,252,910 (33.6)	1,250,003 (33.6)	2907 (37.9)
2022	1,421,921 (38.1)	1,419,533 (38.1)	2388 (31.1)
2023	329,655 (8.8)	329,107 (8.8)	548 (7.1)
2024	133,251 (3.6)	132,996 (3.6)	255 (3.3)
2025	2256 (0.1)	2244 (0.1)	12 (0.2)
Vaccine schedule (n = 3,437,430)			
None	2,759,411 (80.3)	2,754,055 (80.3)	5356 (74.6)
One	179,001 (5.2)	178,610 (5.2)	391 (5.4)
Two	421,044 (12.2)	419,914 (12.2)	1130 (15.7)
Three or more	77,974 (2.3)	77,670 (2.3)	304 (4.2)
Hospitalization			
No	3,654,309 (98.0)	3,647,492 (98.0)	6817 (88.8)
Yes	75,698 (2.0)	74,840 (2.0)	858 (11.2)
Severe COVID-19			
No	3,707,205 (99.4)	3,700,020 (99.4)	7185 (93.6)
Yes	22,802 (0.6)	22,312 (0.6)	490 (6.4)

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Table 1. *Cont.*

Covariates *	Overall (%) 3,730,007 (100.0)	Non-DM Cohort (%) 3,722,332 (99.8)	DM Cohort (%) 7675 (0.2)
Death (total)			
No	3,724,535 (99.9)	3,717,005 (99.9)	7530 (98.1)
Yes	5472 (0.1)	5327 (0.1)	145 (1.9)

* Data (n) in the first column represent the available data for those covariates with missing values (gender, ethnicity, and vaccine). All *p*-values < 0.001.

3.2. Vaccine Effectiveness (Pandemic vs. Post-Pandemic Eras)

Compared with the non-DM cohort, the DM cohort had a higher proportion of females (57.6%) and a different regional distribution, with more patients from the Southeast region (49.0%) ($p < 0.001$). This group also had a significantly younger age distribution, with 46.8% in the 0–4 age group, and a slightly lower proportion of White ethnicity (49.2%). Dyspnea at baseline was markedly more prevalent in the DM cohort (20.5% vs. 6.3%, $p < 0.001$). All major comorbidities, including cardiovascular disease, obesity, and hypertension, were significantly more prevalent in patients with DM. Notably, the DM cohort exhibited a higher prevalence of full vaccination than did the non-DM cohort (Figure 2).

In general, individuals with DM exhibited a greater incidence of severe COVID-19 outcomes than those without DM, as evidenced by hospital admission rates (11.2% vs. 2.0%), severe COVID-19 cases (6.4% vs. 0.6%), and mortality (1.9% vs. 0.1%) (all $p < 0.001$).

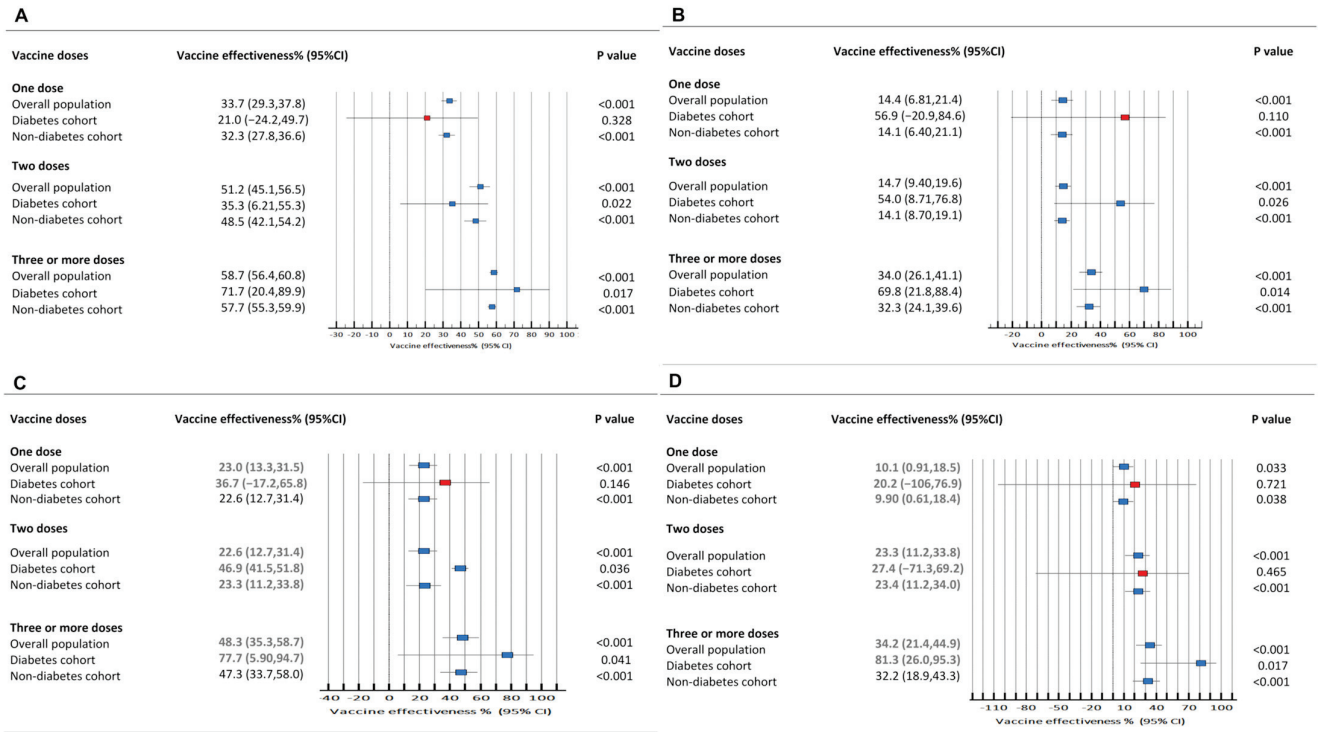

Figure 2. Estimated vaccine effectiveness against the outcomes of interest stratified by the pandemic and post-pandemic eras: hospitalization (Panel (**A**), pandemic; Panel (**B**), post-pandemic) and severe COVID-19 (Panel (**C**), pandemic; (**D**), post-pandemic). All models were adjusted for possible clinical and demographic confounders.

We further evaluated the effectiveness of booster doses using propensity score matching (PSM). Overall, the PSM-adjusted estimates indicated a higher VE in children with diabetes. Post-matching, we compared vaccine effectiveness (VE) against specified outcomes and the number needed to vaccinate (NNV) during the pandemic and post-pandemic periods,

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stratified by DM status. As shown in Table 2, the estimated VE during the pandemic was consistently higher in children with DM. For instance, the VE against severe disease was 72.8% (95% CI, 12.3–93.2) in the DM cohort compared with 45.7% (95% CI, 28.1–59.0) in the non-DM cohort. This higher VE corresponded to a more favorable NNV; the NNV to prevent one severe case was 24 (95% CI, 12–322) for children with DM versus 243 (95% CI, 168–440) for those without.

Table 2. Propensity score matching. Estimated vaccine effectiveness (VE) and number needed to vaccinate (NNV) to prevent one outcome in children with and without diabetes mellitus.

Period	Outcomes	Odds Ratio (95% CI)	VE (%) (95% CI)	ATE (95% CI)	NNV (95% CI)
Pandemic era	Hospitalization			−0.068904 (−0.118433, −0.019375)	
	Diabetes cohort	0.309 (0.102–0.847)	69.1 (15.3–89.8)	−0.0015551 (−0.003048, −0.000735)	15 (8–52)
	Non-Diabetes cohort	0.756 (0.649–0.881)	24.4 (11.8–35.1)		643 (328–1360)
	Severe COVID-19			−0.0422418 (−0.081378, −0.003105)	
	Diabetes cohort	0.272 (0.068–0.877)	72.8 (12.3–93.2)		24 (12–322)
	Non-Diabetes cohort	0.543 (0.410–0.719)	45.7 (28.1–59.0)	−0.0041152 (−0.005952, −0.002272)	243 (168–440)
Post-pandemic era	Hospitalization				
	Diabetes cohort	0.110 (0.017–0.716)	89.0 (28.4–98.3)	−0.186813 (−0.289108, −0.084518)	5 (3–12)
	Non-Diabetes cohort	0.394 (0.296–0.523)	60.6 (47.7–70.4)	−0.0032506 (−0.004635, −0.001866)	307 (215–535)
	Severe COVID-19				
	Diabetes cohort	0.238 (0.064–0.885)	76.2 (11.5–93.5)		8 (5–33)
	Non-Diabetes cohort	0.471 (0.329–0.673)	52.9 (32.7.1)	−0.131868 (−0.208792, −0.054944)	591 (320–3800)
				−0.0016892 (−0.003117, −0.000261)	

VE, vaccine effectiveness; ATE (average treatment effect), NNV (number needed to vaccinate). All p-values < 0.01.

In the post-pandemic era, the estimated VE remained statistically significant and higher in the DM cohort. For example, the VE against hospitalization was 89.0% (95% CI, 28.4–98.3) for children with DM and 60.6% (95% CI, 47.7–70.4) for those without. The NNV to prevent one hospitalization or severe COVID-19 was also consistently much lower in the DM cohort (Table 2).

4. Discussion

Key points: In this large-scale, population-based cohort study of 3.7 million pediatric patients in Brazil, including 7675 children with DM, we evaluated the effectiveness of COVID-19 booster doses in preventing hospital admissions and severe disease in this high-risk group. Using robust methods, binary logistic regression, and propensity score matching, we estimated vaccine effectiveness (VE) across different phases of SARS-CoV-2 dissemination (pandemic vs. endemic). As expected, children with DM were at a greater

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initial risk of experiencing severe outcomes than those without DM. Consequently, the VE was consistently higher in children with DM for both outcomes, irrespective of the viral phase or statistical method. Notably, in the propensity score-matched analysis, the highest effectiveness was observed in the post-pandemic period following booster doses ($\geq$3 doses), with a VE of 89.0% (95% CI, 28.4–98.3) against hospital admission and 76.2% (95% CI, 11.5–93.5) against severe COVID-19. Our findings underscore that in the post-pandemic era, even within a changed immunological landscape, booster regimens maintained significant effectiveness in all pediatric patients, especially in children with DM. Finally, our results demonstrate that the NNV to prevent one severe outcome was highly favorable for children with DM, reinforcing the value of booster doses in this vulnerable population.

Comparative analysis: In contrast to the established elevated risk of severe COVID-19 in adults with DM, the risk in pediatric patients is debatable. Studies from high-income countries indicate that children with type 1 diabetes generally experience mild infections [5,6]. In contrast, our earlier research conducted in Brazil found that children with DM faced a greater risk of experiencing severe COVID-19 than those without diabetes. Confirming this, the current analysis, including a substantial cohort of hospitalized and non-hospitalized children, shows that patients with DM have a higher prevalence of severe disease and COVID-19-related mortality.

Regarding vaccination, it has been questioned whether individuals with DM can mount an effective immune response to COVID-19 vaccines, given that studies have suggested impaired cellular and humoral immunity in this population [35–38]. However, our findings highlight the substantial protective effect of full vaccination against hospitalization and severe outcomes in children with DM, which was sustained across both the pandemic and post-pandemic periods. The NNV to prevent one severe case was at least 34-fold lower in the DM cohort than in the non-DM cohort, indicating their higher initial risk and greater absolute benefit. When stratified by dose, the booster significantly increased VE, particularly in the post-pandemic period. This added benefit likely stems from the shorter interval between vaccination and exposure, which mitigates waning immunity, and from updated formulations targeting predominant variants.

Notably, vaccination significantly reduced the risk of severe disease in the DM cohort, with similar protection during the Delta (pandemic) and Omicron (post-pandemic) periods. While real-world data on VE in patients with DM post-pandemic are limited, our results align with those of a recent study by Sariol et al. [39], which found comparable immunogenicity after monovalent mRNA vaccination in children with and without DM. Although that study reported that boosters did not significantly increase neutralizing antibody titers against Omicron lineage variants, our real-world findings, consistent with other reports [40,41], confirm that primary vaccination provides effective protection against severe Omicron outcomes, with booster doses further enhancing VE.

Limitations and Strengths: This study was subject to several limitations. First, comorbidities in the official datasets were recorded only as binary variables (yes/no), lacking details on severity, control, or clinical history. This prevented the inclusion of critical features like DM phenotypes and glycemic parameters, potentially leading to an underestimation of VE [35,42]. Second, the generalizability of our findings may be limited, as the study was conducted in a middle-income country with a large vulnerable pediatric population [26], and VE is known to be context-dependent [43,44]. Third, vaccination dates for third or subsequent doses were unavailable. However, our sensitivity analysis revealed that misclassification predominantly affected individuals who received one or two doses, therefore exerting minimal influence on the VE estimates for those who received three or more doses. Fourth, the significant decrease in patients with DM during the post-pandemic period resulted in a small sample size, limiting our statistical power to analyze outcomes like

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mortality in this important subgroup. Finally, despite our diligent efforts, we were unable to identify other studies on the vaccination of children with diabetes in the post-pandemic period, which limited our ability to compare our findings with those of other populations.

Nevertheless, this study has some noteworthy features. Its overall large cohort size, including a substantial number of vaccinated children, enabled a comprehensive examination of outcomes and vaccine responses. Furthermore, this study was conducted among hospitalized and non-hospitalized patients with and without DM in Brazil during the pandemic and post-pandemic periods, providing valuable real-world evidence from a middle-income country.

Policy implications: Continuous review of the evidence is crucial for understanding the constantly changing epidemiological landscape and creating a solid foundation for medical guidelines and clinical decision-making. The findings of this study, based on a large population, can guide public health strategies and individual choices regarding COVID-19 vaccination in children with diabetes [45]. Specifically, we demonstrated that from a public health standpoint, the number of children who need to be vaccinated to prevent one severe COVID-19 outcome remains consistently low among children with DM. Considering the relatively low cost and established safety profile of the available vaccines, these findings support the consideration of annual booster schedules for high-risk groups, such as children with DM, as a highly efficient and cost-effective strategy.

5. Conclusions

During the pandemic phase, COVID booster vaccination was fundamental for preventing hospitalization and severe disease in all children. Importantly, this protective effect remained robust in all children in the post-pandemic context. During the pandemic period, the adjusted VE was consistently higher in children with DM. In the post-pandemic period, the VE remained significantly higher in the DM cohort. Furthermore, the NNV to prevent one hospitalization or severe case was consistently lower in children with DM, underscoring the efficiency and benefit of booster vaccination for this high-risk group. These findings provide strong evidence to support tailored booster vaccination strategies for children with DM.

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Institutional Review Board Statement: We accessed the data in SIVEP-Gripe, which is already de-identified and publicly available. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Federal of Minas Gerais (protocol code 6.127.414, date 19 June 2023).

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Informed Consent Statement: Patient consent was waived due to the retrospective design of the study.

Data Availability Statement: The original data presented in the study are openly available in https://opendatasus.saude.gov.br/dataset/ (accessed on 30 June 2025). Our analysis code is available upon request from the corresponding author (Eduardo A. Oliveira, eduolive812@gmail.com).

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

COVID-19	Coronavirus disease 2019
DM	Diabetes mellitus
WHO	World Health Organization
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIVEP-Gripe	Influenza Epidemiological Surveillance Information System
aOR	Adjusted odds ratio
CI	Confidence interval
NNV	Number Needed to Vaccinate
VE	Vaccine Effectiveness
ICU	Intensive Care Unit
ATE	Average treatment effect
SUS	Brazilian Public Health System

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Immunogenicity and Breakthrough Outcomes of mRNA Booster Strategies Among Healthcare Workers During the BA.1/BA.2 Omicron Surge

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Abstract: Throughout the 2019 coronavirus disease pandemic, various vaccine regimens were implemented. Real-world data comparing their effectiveness during the BA.1/BA.2 Omicron wave remain limited. We prospectively enrolled healthcare workers who had completed two doses of mRNA or ChAdOx1 (A) vaccine and received an mRNA vaccine booster (BNT162b2 (P) or mRNA-1273 (M)). Neutralizing antibody levels were measured 6 months after the primary vaccinations and 1 month post-booster vaccination using a surrogate virus neutralization assay. Breakthrough infections were identified through institutional surveillance and the national reporting system. Among 318 participants (P-P-P: 71; A-A-P: 205; A-P-P: 19; M-M-M: 23), pre-booster neutralizing activity was lowest in the ChAdOx1-primed groups. One month post-booster vaccination, the neutralizing activity exceeded 97% across all regimens. The cumulative incidence of breakthrough infection varied significantly from 43.7% (P-P-P) to 84.2% (A-P-P). In adjusted Cox models, A-P-P showed the highest infection risk (HR 2.99, 95% CI 1.65–5.42). In summary, mRNA boosters restored neutralizing activity, but during the early BA.1/BA.2 Omicron wave they were less effective in preventing infections regardless of disease severity. Therefore, antibody titers alone are insufficient for evaluating protection, underscoring the need for continuous monitoring to support timely policy decisions during epidemic surges.

Keywords: COVID-19; omicron variant; healthcare workers; heterologous booster; breakthrough infection

1. Introduction

During the 2019 coronavirus disease (COVID-19) pandemic, a pivotal challenge arose with the identification of the Omicron variant in late 2021 [1]. Omicron and its sublineages rapidly replaced Delta as the dominant circulating strain. During our study period in Republic of Korea, BA.1 and BA.2 were predominant, followed later by BA.4/5 and XBB.1.5 [2]. These variants carry more than 30 spike protein mutations. Their high transmissibility and immune escape capability led to widespread breakthrough infections, even among individuals who had completed the primary vaccination series [3,4]. Although booster immunization has been shown to restore neutralizing antibody responses against Omicron,

its real-world effectiveness in preventing infection remains suboptimal [5,6]. Neutralizing titers alone may not fully predict protection, as immune responses are also shaped by the nature of priming exposure. This phenomenon, referred to as immune imprinting, implies that adenoviral vector and mRNA vaccines can induce distinct recall responses upon boosting [7]. Beyond antibody quantity, differences in avidity, epitope specificity, and memory B and T cell formation may contribute to a potential disconnect between antibody titers and clinical outcomes [7–9].

In Republic of Korea, the COVID-19 vaccination program began in early 2021, with a phased rollout strategy based on occupational risk and age [10]. Healthcare workers (HCWs) received diverse regimens according to supply and policy shifts: some were primed with adenovirus-vectored ChAdOx1, while others received mRNA vaccines (BNT162b2 or mRNA-1273). This created a natural setting for comparing homologous and heterologous booster strategies within a relatively homogeneous occupational group [10,11].

Heterologous prime-boost strategies have been proposed for enhancing humoral and cellular immunity by stimulating various immunological pathways. Several immunogenicity studies have demonstrated that adenovirus-vectored priming, followed by mRNA boosting, can induce stronger or comparable neutralizing antibody responses to homologous regimens [12,13]. A recent systematic review suggested no consistent advantage of homologous over heterologous strategies in terms of breakthrough infection or severe disease, especially during the Omicron wave [14]. This distinction may reflect the different immunological correlates of protection: neutralizing antibodies are primarily associated with preventing infection, whereas T cell responses play a greater role in limiting severe outcomes [7,15].

However, most existing evidence is derived from controlled trials or meta-analyses across heterogeneous populations. Real-world cohort data for evaluating immune responses and clinical outcomes in occupationally homogeneous, vaccine-diverse settings are lacking. We hypothesized that while heterologous mRNA boosters could restore neutralizing antibody levels after adenovirus-vector priming, qualitative immune differences between vaccine platforms might still result in divergent risks of breakthrough infection. To address this gap, our goal was to assess whether heterologous mRNA vaccine boosters restored neutralizing antibody levels, and to determine whether neutralizing titers adequately predicted protection against breakthrough infection. We showed that heterologous mRNA vaccine boosters restored neutralizing antibody levels; however, neutralizing titers alone may be an insufficient predictor of protection.

2. Materials and Methods

2.1. Study Design

We conducted a prospective study of adult HCWs working at Hallym University Sacred Heart Hospital, a tertiary referral center with over 800 beds in Republic of Korea, from November 2021 to June 2022. Enrollment was open to all HCWs identified by the infection control office as due for a third (booster) dose 6 months after completion of their primary vaccination series. The primary vaccine regimen varied and included two mRNA vaccines and one vector vaccine (ChAdOx1, Vaxzervia, AstraZeneca AB, Södertälje, Sweden). They received a booster dose of one of two mRNA vaccines (BNT162b2, Comirnaty, Pfizer Inc., New York, NY, USA, P; or mRNA-1273, Spikevax, Moderna, Princeton, NJ, USA, M). Four types of regimens were used (P-P-P, M-M-M, A-A-P, and A-P-P). The distribution of vaccine regimens reflected national allocation policies and occupational risk rather than personal choice [10,11]. During the initial rollout in Republic of Korea, vaccine procurement and approval were staggered, resulting in age- and occupation-based allocation. Older individuals and high-risk staff were prioritized for adenovirus-vectored vaccines (ChAdOx1 or

single-dose of Ad26.COV2.S [Janssen Pharmaceuticals Companies of Johnson & Johnson, Titusville, NJ, USA]), while younger healthcare workers and the general population more frequently received mRNA vaccines (BNT162b2 or mRNA-1273). At our institution, these policies directly influenced vaccine assignment across occupational groups, leading to heterogeneous primary regimens in the workforce. For epidemiological data, national daily confirmed COVID-19 cases were obtained from the Korea Disease Control and Prevention Agency (KDCA; https://dportal.kdca.go.kr/pot/cv/trend/dmstc/selectMntrgSttus.do; accessed on 20 August 2025), and the study period was overlaid on the epidemic curve (Figure 1). This was because breakthrough infections were likely to have been strongly influenced by the magnitude of community outbreaks.

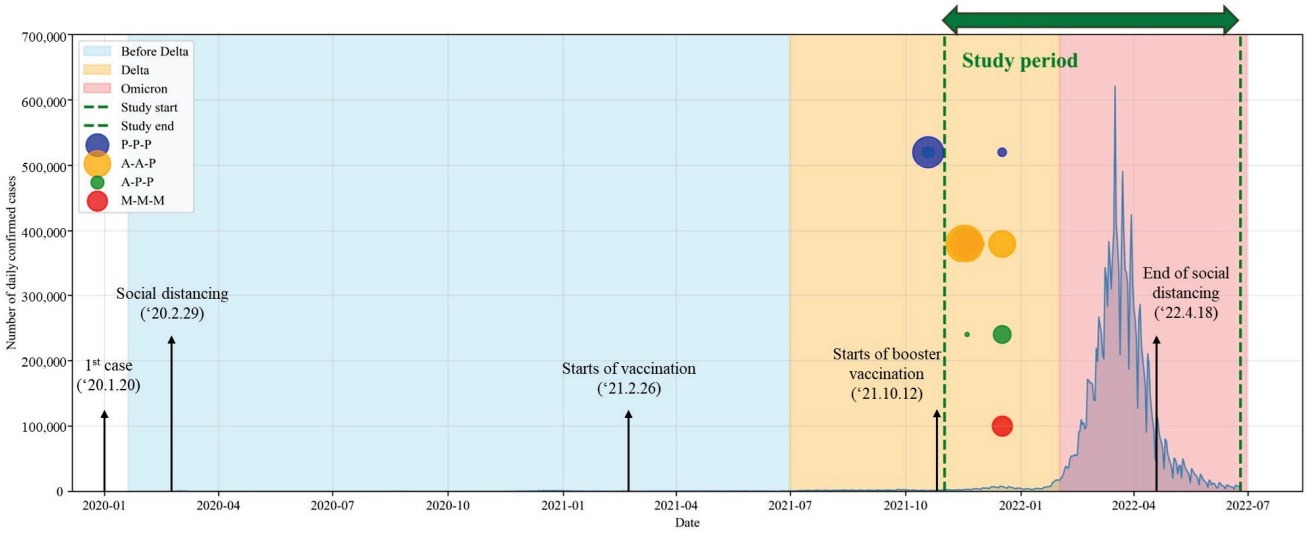

Figure 1. National daily confirmed 2019 coronavirus disease (COVID-19) cases in Republic of Korea with major variant periods and timing of booster vaccination among study participants. Daily case numbers were obtained from the KDCA (https://dportal.kdca.go.kr/pot/cv/trend/dmstc/selectMntrgSttus.do accessed on 20 August 2025). Shaded areas indicate Delta- and Omicron-dominant periods. Vertical dashed green lines represent the study observation period (1 November 2021–25 June 2022). Colored dots represent booster vaccination dates of study participants stratified by booster regimen (P-P-P, A-A-P, A-P-P, M-M-M), with dot size proportional to the number of participants vaccinated on that date.

2.2. Demographics and Serum Samples

We collected demographic data, including sex, age, and occupational information, classified according to whether they were in clinical roles (such as physicians, nurses, therapists) or non-clinical administrative/support roles (such as administrative staff, clerical workers, and support services). Sera from the HCWs were collected 6 months after the second dose of the severe acute respiratory syndrome-2 (SARS-CoV-2) vaccine and again 1 month after the third dose.

2.3. Immunogenicity Assessment

Serum samples were collected to assess humoral responses at two time points: immediately before the third (booster) dose (V1) and 1 month after the booster dose (V2). To assess the potential neutralizing capacity of the HCW sera, the cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript Biotech, Mainz, Germany) was used. This assay employs the spike receptor binding domain (RBD) of the ancestral Wuhan strain to measure inhibition of RBD- angiotensin-converting enzyme 2 interaction [16]. The samples were diluted tenfold according to the manufacturer's instructions. Sample values below the threshold of 30% were considered negative, and values at or above the cut-off

indicated the presence of SARS-CoV-2 neutralizing antibodies. At this cutoff, the negative and positive percentage agreements with the conventional plaque reduction neutralization test (PRNT) 50 and PRNT90 assays were approximately 100%. The manufacturer reported the sensitivity and specificity of the assay to be 93.8% and 99.4%, respectively. Inhibition (%) was calculated as (1 − OD value of sample/OD value of negative control) × 100. Seropositivity was defined as inhibition ≥30%. 'High responder' was defined a priori as inhibition ≥90%.

2.4. Breakthrough Infection Rate

The incidence of COVID-19 among participants was evaluated to assess vaccine effectiveness. Breakthrough infections were defined as laboratory-confirmed SARS-CoV-2 cases detected after booster vaccination. According to national policy during the study period, all symptomatic individuals and close contacts of confirmed cases were required to undergo PCR testing, while asymptomatic routine follow-up screening was not performed for vaccinated HCWs. At our institution, the infection control office actively monitored all in-hospital confirmed cases, conducted contact tracing, and required HCWs to promptly report any COVID-19 diagnosis, including those identified in the community.

To describe the temporal distribution of breakthrough infections, scatter plots were constructed by days since the booster. Histograms and rug plots were used to display the infection events across regimens, and these were overlaid with the national epidemic curve data obtained from the KDCA. For infection-free probability analyses, only the first breakthrough infection was considered, with follow-up censored at study end. Two time origins were prespecified: (i) the individual booster date and (ii) a common start date (17 December 2021).

2.5. Statistical Analysis

Descriptive statistics were used for demographic data. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), depending on the distribution. The Kruskal–Wallis test was used to compare continuous variables among the groups, and post hoc pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni correction. The chi-squared test or Fisher's (Fisher–Freeman–Halton for r × c table) exact test was used to compare categorical variables. Pre- and post-booster inhibition values were compared within groups using the Wilcoxon signed-rank test, and the Kruskal–Wallis test was used for between-group comparisons. Multiple testing correction was applied consistently to all post hoc pairwise comparisons of continuous outcomes (e.g., antibody inhibition levels and absolute changes between regimens), whereas infection-free probability analyses and Cox regression were treated as prespecified global or model-based analyses and were not adjusted. Kaplan–Meier survival curves illustrating infection-free probability were used to compare the probability of remaining free from breakthrough infection following the booster regimen, and differences were tested using the log-rank test. Cox proportional hazards models were fitted to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) after adjusting for age and sex. The proportional hazards assumption was evaluated using Schoenfeld residuals (Grambsch–Therneau test) and log(−log) infection-free probability plots (Figures S1–S3). Figures were generated using Python 3.10 (matplotlib, seaborn, and lifelines). Cox proportional hazards models estimated HRs with 95% CIs, using P-P-P as the reference category and adjusting for age and sex. In a sensitivity model, occupation (clinical vs. non-clinical) was additionally included. Immunogenicity plots (Figure 2) were generated using GraphPad Prism version 10.1.0 (GraphPad, San Diego, CA, USA). Differences were considered statistically significant at two-tailed p-values < 0.05.

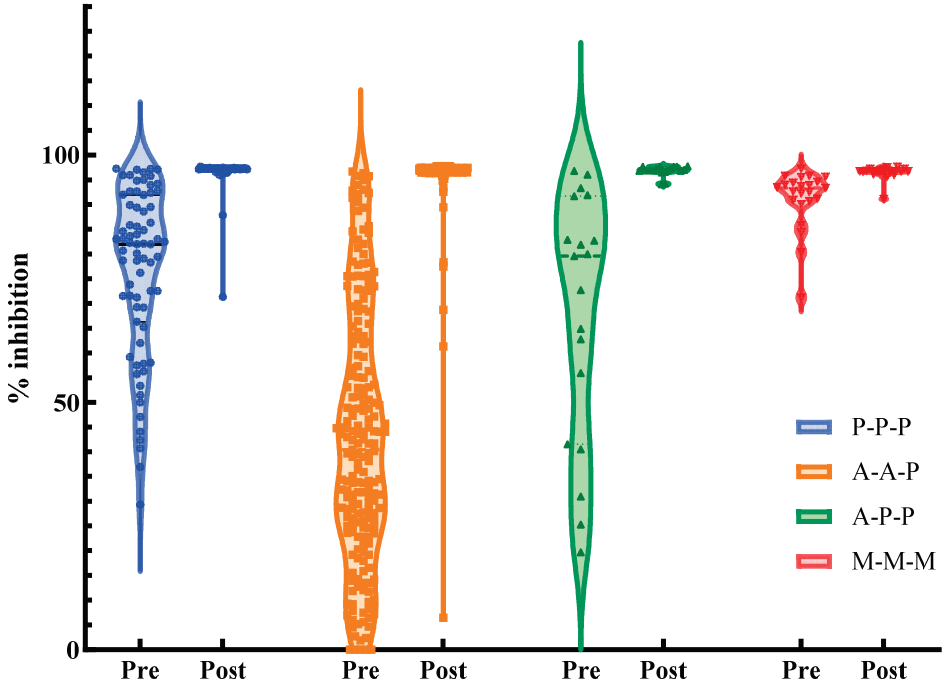

Figure 2. Violin plots of neutralizing antibody inhibition (%) at baseline (V1, pre-booster) and 1 month post-booster (V2) according to vaccine regimen. Each point represents an individual, and horizontal bars indicate the median and interquartile range (IQR). Vaccine regimens are denoted as follows: P-P-P = BNT162b2 (Pfizer-BioNTech) for all three doses; A-A-P = two doses of ChAdOx1 (AstraZeneca) followed by a BNT162b2 booster; A-P-P = one dose of ChAdOx1 and two subsequent doses of BNT162b2; M-M-M = mRNA-1273 (Moderna) for all three doses.

3. Results

3.1. Baseline Characteristics

Of 494 healthcare workers (HCWs) eligible for a booster dose 6 months after their primary vaccination, 318 (64.4%) consented to participate in this prospective cohort. The eligible population included P-P-P (n = 99), A-A-P (n = 255), A-P-P (n = 63), and M-M-M (n = 77). Among enrolled participants, 71 received P-P-P, 205 received A-A-P, 19 received A-P-P, and 23 received M-M-M. Baseline characteristics of the enrolled cohort are summarized in Table 1, with a median age of 32 years and 74.8% female. Age distribution differed significantly among the regimens ($p < 0.001$). The highest median age was observed in the A-P-P group (41 years, IQR: 34–44 years), followed by the A-A-P group (35 years, IQR: 27–49 years). The P-P-P (28; IQR, 26–37) and M-M-M (25; IQR, 23–31) groups included younger participants. Post hoc comparisons showed that A-P-P participants were significantly older than those in P-P-P and M-M-M, while no significant differences were found between A-P-P and A-A-P or between P-P-P and M-M-M (Table 1). This imbalance most likely reflects national allocation policies during the initial rollout, wherein higher-risk older adults were prioritized for vector-based priming, and mRNA-1273 was preferentially recommended to younger adults due to adverse-event concerns [17,18].

Clinical occupations, defined as patient-facing roles, such as physicians, nurses, and therapists, accounted for 73.6% of the total population. Seven participants (2.2%) had SARS-CoV-2 infection before the booster vaccination.

Table 1. Baseline characteristics of study participants according to booster vaccine group.

Characteristics	Total (*n* = 318)	P-P-P (*n* = 71)	A-A-P (*n* = 205)	A-P-P (*n* = 19)	M-M-M (*n* = 23)	*p*-Value
Age, years, median ± IQR	32 (27–44)	28 (26–37)	35 (27–49)	41 (34–44)	25 (23–31)	0.000
Sex: Female, n (%)	238 (74.8)	42 (59.2)	159 (77.6)	15 (78.9)	22 (95.7)	0.001
Occupation: Clinical, n (%)	234 (73.6)	59 (83.1)	152 (74.1)	5 (26.3)	18 (78.3)	0.000
Pre-booster infection, n (%)	7 (2.2)	1 (1.4)	3 (1.5)	2 (10.5)	1 (4.3)	0.068
Follow-up duration, days, median (IQR)	154 (110–220)	249 (147–277)	144 (113–220)	84 (81–94)	95 (80–190)	0.000

Clinical = patient-facing occupation (such as doctors, nurses, and direct patient care). Non-clinical = non-patient-facing occupation (such as administration, cleaning, and support staff).

The median follow-up duration also differed significantly across booster groups ($p < 0.001$). Post hoc analyses indicated longer follow-up in P-P-P than in A-A-P, A-P-P, and M-M-M (all adjusted $p < 0.001$). A-A-P differed from A-P-P and M-M-M (adjusted $p < 0.01$), whereas A-P-P and M-M-M did not differ. These findings indicate an imbalanced distribution of follow-up time (Table 1). Given these context-driven imbalances in age, occupation, and follow-up, we prespecified adjusted Cox models (age and sex; occupation in sensitivity analyses) and performed a common time-origin infection-free survival analysis aligned to the epidemic phase to mitigate confounding by calendar time and time-since-booster.

3.2. Immunogenicity After Booster Vaccination

Overall, booster vaccination substantially increased neutralizing antibody levels across all regimens (Table 2, Figure 2). Table 2 summarizes the immunogenicity results before and after booster vaccination. Before the booster vaccination, inhibition (%) differed significantly between groups, with post hoc analysis showing that it was significantly lower in the A-A-P group than in the P-P-P, M-M-M, and A-P-P groups. Seropositivity rates were substantially lower in the A-A-P group (64.9%) than in the other groups, exceeding 89%. The virus vector vaccine regimen showed lower antibody levels 6 months after the primary series. After 1 month, inhibition (%) increased sharply for all regimens (median values ~97), with P-P-P the highest, A-P-P the lowest, and A-A-P and M-M-M intermediates. Seropositivity rates exceeded 99% for all regimens after the booster vaccination. The absolute changes in antibody levels after booster vaccination (V2–V1) were calculated for each regimen (Table 2). The median (IQR) absolute change was 55 (34–71) in the A-A-P group, followed by the A-P-P, P-P-P, and M-M-M groups. In the M-M-M group, this smaller increment likely reflects a ceiling effect due to already high pre-booster levels. Post hoc pairwise comparisons with Bonferroni correction showed that A-A-P had significantly greater increases than A-P-P, M-M-M, and P-P-P (all $p < 0.01$), whereas A-P-P and P-P-P did not differ significantly ($p = 1.00$). The proportions of high responders ($\geq$90% inhibition) were 98.6%, 95.7%, 93.7%, and 73.7% in the P-P-P, M-M-M, A-A-P, and A-P-P groups, respectively. In addition, no significant difference in inhibition (%) at 1 month was observed between participants who subsequently experienced breakthrough infection and those who did not. Median post-booster values were nearly identical in both groups (e.g., P-P-P 97.2% vs. 97.2%; A-A-P 96.9% vs. 97.0%), indicating that similar antibody titers did not necessarily translate into equivalent protection.

Table 2. Neutralizing antibody inhibition (%) and seropositive rates before and after booster vaccination.

Outcome	P-P-P (*n* = 71)	A-A-P (*n* = 205)	A-P-P (*n* = 19)	M-M-M (*n* = 23)	*p*-Value
Before booster Inhibition (%), median (IQR)	82 (68–91)	40 (25–62)	80 (49–87)	93 (91–94)	0.000
Seropositive rate n (%)	70 (98.6)	132 (64.4)	17 (89.5)	23 (100.0)	0.000
1-month post-booster Inhibition %, median (IQR)	97 (97–97)	97 (97–97)	97 (97–97)	97 (97–97)	0.002
Δ Absolute change (V2–V1), median (IQR)	15 (5–30)	55 (34–71)	18 (10–47)	3 (2–6)	0.000
Seropositive rate, n (%)	71 (100.0)	204 (99.5)	19 (100.0)	23 (100.0)	0.907
High responder, n (%)	69 (97.2)	199 (97.1)	19 (100.0)	23 (100.0)	0.741
Breakthrough infection no event (%)	31 (43.7)	115 (56.1)	16 (84.2)	14 (60.9)	0.0137
Inhibition % (median) at post-booster, by infection status	97.2 vs. 97.2	96.9 vs. 97.0	97.0 vs. 96.9	96.7 vs. 96.6	NS

p-values were obtained using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. Post hoc pairwise comparisons were conducted, and significant differences are described in the Section 3. Seropositive is defined as inhibition ≥30%; High responder is defined as inhibition ≥90%: NS, no significant difference between infected and non-infected patients (Mann–Whitney U test). IQR, interquartile range.

3.3. Breakthrough Infections

During the follow-up period up to 25 June 2022, 175 breakthrough infections were documented, corresponding to an overall cumulative incidence of 55.0%. Most infections occurred during the Omicron wave, which was initially dominated by BA.1/1.1 and later by BA.2/2.3 sublineages. Figure 3 shows the temporal distribution of the breakthrough infections. In Figure 3A, infections are plotted by days since the booster, showing differences in timing across regimens. In contrast, the calendar date distribution of infections is shown in relation to national epidemic trends, highlighting the clustering of breakthrough infections during the peak of community transmission in Figure 3B. The cumulative incidence of breakthrough infection varied across the regimens, ranging from 43.7% in the P-P-P group to 84.2% in the A-P-P group, with the A-A-P and M-M-M groups showing intermediate rates (56.1% and 60.9%, respectively) (Table 2). The overall differences between the regimens were statistically significant ($p = 0.0137$), and the post hoc analysis indicated a significantly higher incidence in the A-P-P group than in the A-A-P and P-P-P groups. No significant differences were observed between the other groups.

3.4. Breakthrough Infections: Comparison Among Booster Regimens

The Kaplan–Meier infection-free survival curves for the booster regimen are shown in Figure 4. Using the booster date as the start of observation (Figure 4A), the P-P-P group had the highest infection-free probability without infection, whereas the A-P-P group demonstrated the steepest decline, and the A-A-P and M-M-M groups remained intermediate. Pairwise log-rank tests showed significant differences between P-P-P and A-P-P ($p < 0.001$), between P-P-P and A-A-P ($p = 0.017$), and between P-P-P and M-M-M ($p = 0.015$). In the Cox model adjusted for age and sex with P-P-P as the reference, the A-P-P regimen showed the highest risk of breakthrough infection (HR 5.82, 95% CI 2.61–12.94, $p < 0.001$). Both A-A-P (HR 1.57, 95% CI 1.09–2.27, $p = 0.016$) and M-M-M (HR 2.44, 95% CI 1.14–5.19, $p = 0.021$) also had significantly higher risks.

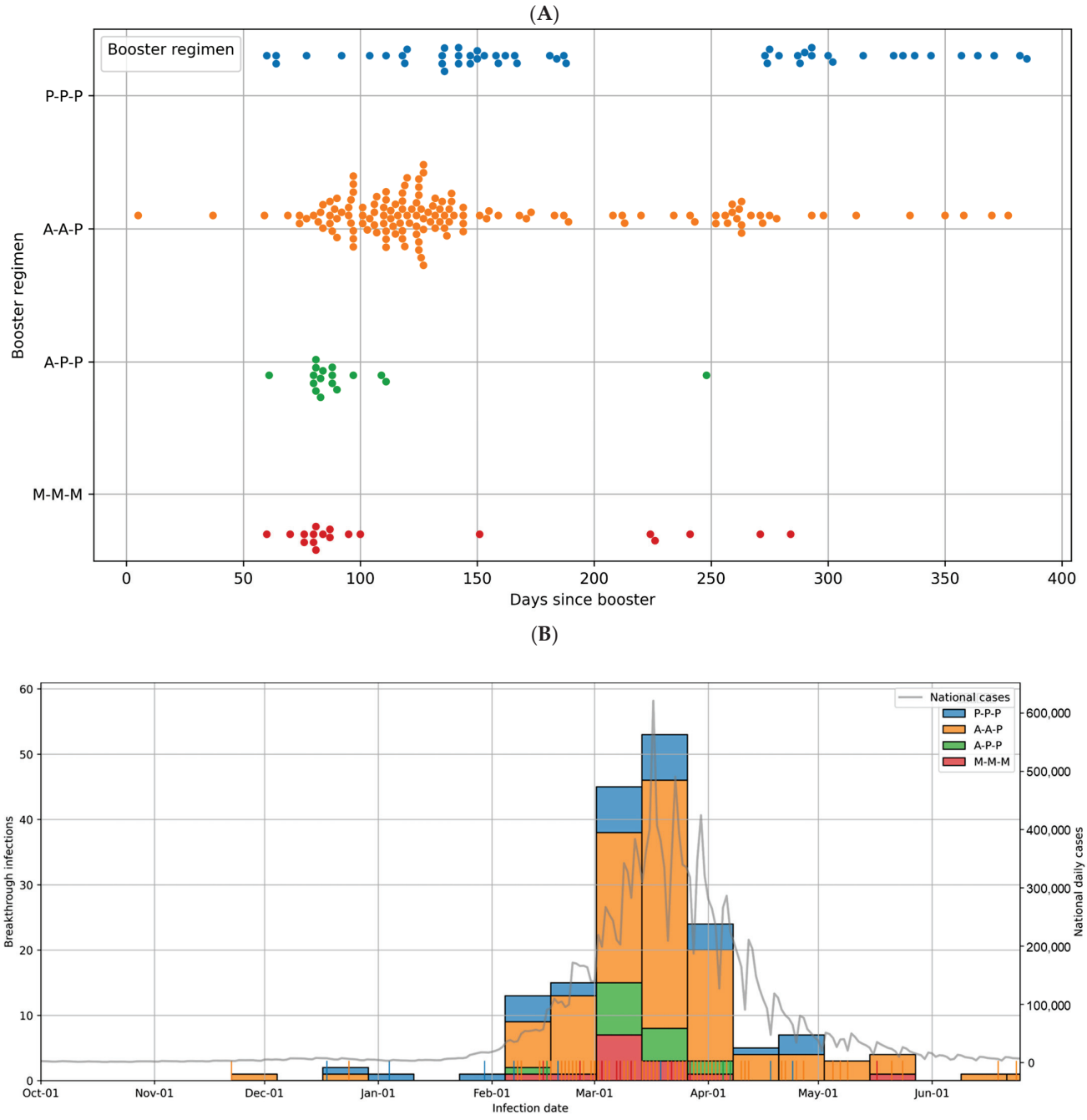

Figure 3. Breakthrough infection distribution by days since booster vaccination and by calendar date. (**A**) Distribution of breakthrough infections by days since booster vaccination. Histogram and rug plots showing the timing of breakthrough infections after booster vaccination across different booster regimens. Each dot represents an individual case, colored by regimen (P-P-P, A-A-P, A-P-P, M-M-M). (**B**) Distribution of breakthrough infections by calendar date during the study period. Daily distribution of breakthrough infections plotted against the national epidemic curve (gray line). Colored dots indicate individual breakthrough cases according to the booster regimen. Clustering of infections is observed during the peak of community transmission.

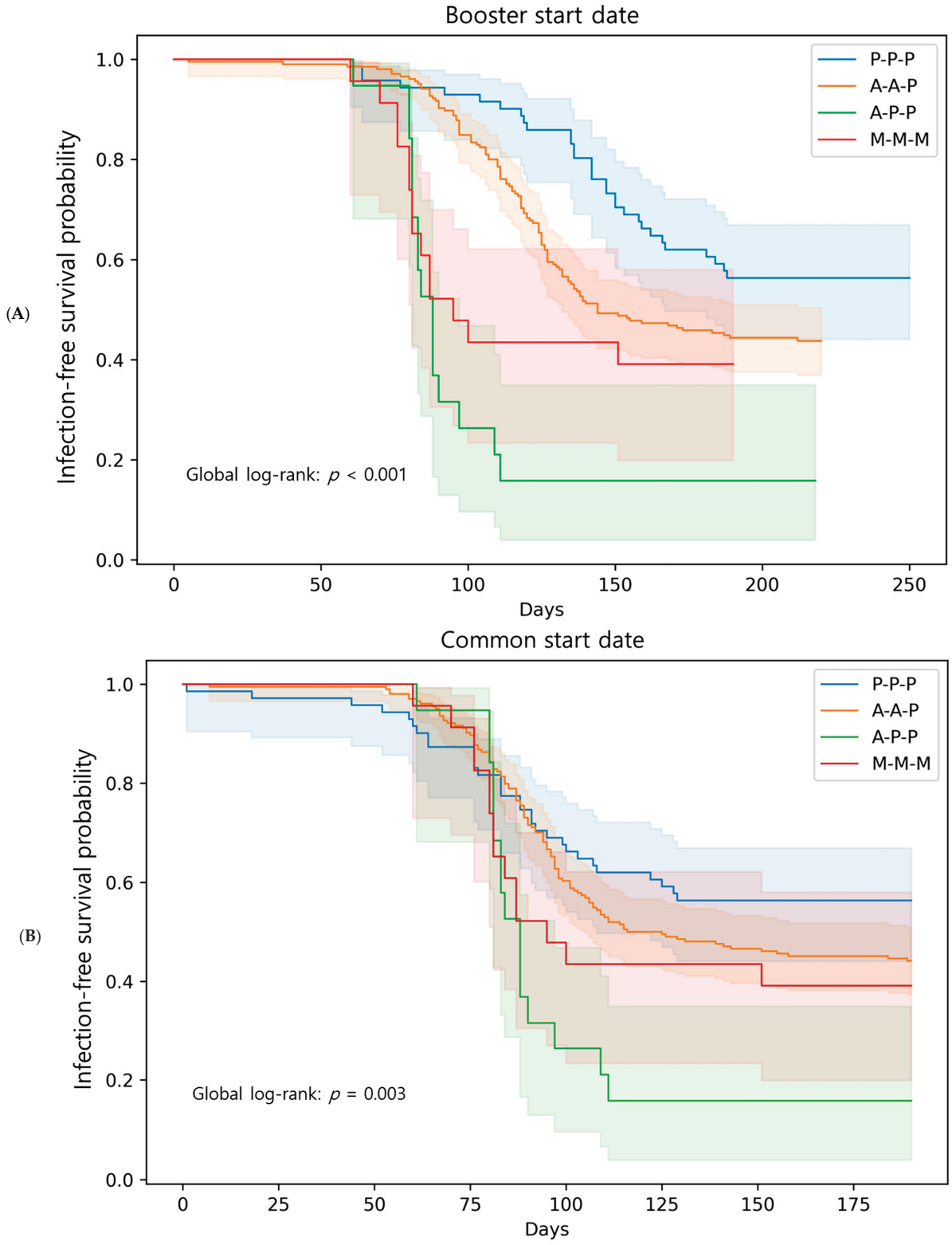

Figure 4. Kaplan–Meier infection-free survival curves for breakthrough infection according to booster regimen. (**A**) Infection-free survival curves with individual booster date as the start of follow-up. The P-P-P group showed the highest probability of remaining infection-free, while the A-P-P group demonstrated the steepest decline. Median follow-up durations were 249 days for P-P-P, 144 days for A-A-P, 84 days for A-P-P, and 95 days for M-M-M (Table 1) (**B**) Sensitivity analysis with 17 December 2021, when all participants had completed booster vaccination, as a common start date. In both analyses, the A-P-P group showed a significantly higher risk of breakthrough infection compared with other regimens.

Because the vaccination timing differed across groups, an infection-free survival analysis was also performed using a common observation start date (17 December 2021), when all booster vaccinations had been completed (Figure 4B). In this analysis, the infection-free survival curves showed that A-P-P had the lowest infection-free survival rate, whereas P-P-P remained the most favorable. The overall separation between the groups was attenuated; however, the log-rank comparisons remained significant for A-P-P versus P-P-P ($p < 0.001$), whereas other pairwise differences were not significant. The Cox model again showed that A-P-P was significantly associated with a higher risk (HR 2.99, 95% CI 1.65–5.42, $p = 0.0003$), while A-A-P and M-M-M were not significantly different from P-P-P. In the booster-date model, Schoenfeld residual tests indicated deviations for some regimen covariates (Figure S1), whereas no violations were observed in the common-date model (Figure S2). Log(−log) infection-free survival plots appeared approximately parallel across regimens, further supporting proportionality (Figure S3).

3.5. Occupation-Based Analysis

When stratified into clinical and non-clinical occupations, no significant difference was observed in the infection-free survival curves (log-rank $p = 0.43$) (Figure S4). In Cox regression adjusting for age, sex, and booster vaccination regimen, occupation was not significantly associated with infection risk (HR: 0.75, 95% CI: 0.52–1.10), suggesting that infection risk was driven primarily by community transmission rather than hospital exposure.

4. Discussion

This prospective cohort study of 318 HCWs during the BA.1/BA.2-dominant Omicron surge in Republic of Korea demonstrated that heterologous mRNA booster vaccination effectively restored neutralizing antibody levels, regardless of the primary vaccine regimen. While participants who received adenovirus-vectored primary vaccines (ChAdOx1) had significantly lower pre-booster antibody levels (6 months after the primary series) than those who received mRNA vaccines, all groups achieved comparable neutralizing activity 1 month after the mRNA vaccine booster dose. Despite this immunological restoration, our study found high breakthrough infection rates in all the vaccination groups, with a significantly higher incidence in the A-P-P group than in the A-A-P and P-P-P groups during the BA.1/BA.2 Omicron surge.

Heterologous prime-boost vaccination strategies have emerged as a critical approach for COVID-19 immunization, particularly driven by vaccine supply constraints and the need to optimize immune responses against emerging variants [19,20]. The scientific rationale for using heterologous vaccination regimens stems from the potential to stimulate different arms of the immune system, with adenovirus vector vaccines primarily inducing cellular immunity, and mRNA vaccines generating robust humoral responses [21,22].

Multiple studies have consistently demonstrated the superior immunogenicity of heterologous booster strategies compared with homologous regimens. A randomized clinical trial in HCWs showed that mRNA vaccines as boosters following ChAdOx1 priming resulted in substantial antibody increases; BNT162b2 boosters increased anti-spike IgG by 32.2-fold, while half- and full-dose mRNA-1273 boosters increased antibodies by 47.6-fold and 63.2-fold, respectively [23].

The immunological basis for enhanced heterologous responses likely involves the activation of different immunological pathways. Adenovirus vector vaccines induce strong CD4+ and CD8+ T cell responses through their ability to present antigens via major histocompatibility complex class I pathways, whereas mRNA vaccines excel at generating high-titer neutralizing antibodies through efficient antigen presentation and innate immune activation [24,25]. Such T cell-mediated immunity, which targets conserved epitopes largely

preserved against Omicron mutations [15], may provide benefits not fully reflected by serum IgG titers. Although the A-P-P regimen showed higher breakthrough infection rates, T cell responses could have contributed to attenuating the severity of these infections. Our study did not capture data on the clinical severity of breakthrough infections, so this possibility could not be directly evaluated. This complementary mechanism may explain why heterologous regimens often outperform homologous strategies in terms of breadth and magnitude of immune responses.

Moreover, immune imprinting may also influence these outcomes, as the nature of the initial priming—adenovirus-vectored versus mRNA platforms—can shape subsequent recall responses and potentially limit the breadth of neutralization against antigenically divergent Omicron sublineages [7]. Although neutralizing titers appeared comparable across regimens, qualitative features such as affinity maturation, Fc-mediated effector functions, and durability may differ by platform, thereby affecting protection beyond antibody levels alone [7,9]. Adenovirus-vectored priming has additionally been associated with trained innate immunity and enhanced T cell responses [8], yet such responses may not have been sufficient to overcome the rapid immune escape of Omicron.

These findings align with our results, where the heterologous A-A-P group showed the greatest increase in absolute antibody levels after booster vaccination, compared with smaller increases in homologous mRNA groups such as M-M-M and P-P-P. This larger absolute change in the A-A-P group likely reflects the lower baseline neutralizing antibody levels observed 6 months after the primary series with an adenoviral vector vaccine, providing a greater margin for recovery after boosting. In contrast, the P-P-P group showed a smaller absolute increase due to higher pre-booster antibody levels, yet maintained a relatively low risk of breakthrough infection during the BA.1/BA.2 Omicron surge. Taken together, the ability of the mRNA boosters used in this study to effectively restore neutralizing antibody levels regardless of the primary vaccine type demonstrates the potent immunogenicity of the mRNA vaccines. This suggests that, even when primary vaccination is performed using a regimen that induces weaker immunogenicity, an mRNA booster can effectively "rescue" the immune response, achieving comparable post-booster neutralizing activity across different primary regimens.

Despite the rescued immune status, breakthrough infections were more frequent in our cohort. The emergence of the BA.1/BA.2 Omicron variant poses major challenges to vaccine effectiveness owing to extensive mutations in the spike protein, which facilitate immune escape [26,27]. In this study, the overall cumulative breakthrough infection rate was 55%, reflecting the trend during the Omicron wave, when many boosted individuals were infected. Several large-scale studies have reported the reduced effectiveness of all vaccines against the Omicron variant. A Swedish nationwide cohort study showed that heterologous vaccination using ChAdOx1, followed by BNT162b2 or mRNA-1273, achieved 79% effectiveness against symptomatic COVID-19 infection during the delta-dominant period; however, this effectiveness dropped substantially during the Omicron wave [28]. Similarly, serological studies have consistently shown reduced neutralizing activity against the Omicron compared with the wild-type virus across all vaccine combinations [23,29].

Subsequent vaccination strategies have changed owing to issues with low efficacy against Omicron. The importance of adaptive vaccination strategies has been further demonstrated by the rapid development and deployment of variant-adapted vaccines in response to the evolving SARS-CoV-2 strains. Following the emergence of Omicron and its subvariants, regulatory agencies approved bivalent vaccines targeting both the original strain and Omicron variants. The Food and Drug Administration authorized Pfizer-BioNTech and Moderna bivalent vaccines in August 2022, specifically targeting the BA.4/BA.5 subvariants [30,31]. Subsequently, updated monovalent vaccines targeting the

XBB.1.5 variant were recommended for the 2023–2024 vaccination season, reflecting the continued evolution of the virus and the need for variant-specific immune responses [32,33]. Real-world effectiveness studies of these variant-adapted vaccines have demonstrated their superior performance against circulating strains compared with the original monovalent boosters. A large-scale study showed that bivalent boosters provided 30% additional protection against symptomatic infections with XBB/XBB.1.5 variants compared with monovalent boosters [34]. Similarly, the updated 2023–2024 vaccines showed enhanced neutralizing activity against emerging variants, including JN.1, which became dominant in late 2023 [35,36].

One of the key findings of our study was that equivalent neutralizing antibody responses did not translate into equivalent clinical protection. In addition, systemic neutralizing antibody titers may not adequately capture mucosal immunity, which is essential for blocking viral entry at the upper respiratory tract. Clinical studies have shown that intramuscular mRNA vaccination induces only limited mucosal IgA responses [37]. This suggests that serum antibody levels alone may not reliably predict protection against breakthrough infection. Beyond immune escape by viral variants, other immunological factors may also limit the reliability of neutralizing antibodies as correlates of protection. In particular, although the majority of participants were classified as high responders ($\geq$90% inhibition), their risk of breakthrough infection was not reduced compared with non-high responders, indicating that even very high neutralizing activity did not confer additional protection during the Omicron surge. A large Los Angeles cohort study of 859 participants found no association between receptor-binding domain antibody levels and breakthrough infection risk, with breakthrough rates of 19–23% regardless of antibody levels [38]. Similarly, Japanese HCWs showed no significant differences in pre-infection neutralizing antibody levels between breakthrough cases and controls among third-dose recipients [39]. This disconnect likely reflects the multifaceted nature of immune protection, which extends beyond circulating neutralizing antibodies to include cellular immunity, mucosal responses, antibody quality, and the kinetics of immune activation [40]. Our observation that the A-P-P regimen showed the highest breakthrough rates despite robust serological responses suggests fundamental differences in immune quality, rather than quantity. Vector-based vaccines may induce different patterns of memory B cell formation and T cell responses compared with mRNA platforms, potentially affecting the durability and breadth of protection [41]. The timing of the immune response development may also contribute to this paradox. While neutralizing antibodies were measured 1 month post-booster vaccination, the kinetics of immune activation and the establishment of protective immunity may differ between vaccine platforms. Studies have shown that breakthrough infections with Omicron variants primarily evoke immune responses targeting conserved epitopes rather than variant-specific sites, suggesting that initial immune imprinting from different vaccine platforms may influence subsequent protection patterns [42].

This study has some limitations. First, the number of participants and baseline characteristics, such as age, sex, and follow-up duration, were significantly different. This may have introduced bias in the comparison of breakthrough infection risks. Participation was voluntary, with 64.4% of eligible HCWs enrolled, so selection bias cannot be excluded. In addition, vaccine regimens were determined by national policy and occupational role, creating potential confounding between vaccine type and exposure risk. For example, an infection-free survival analysis using the booster date as the start of follow-up suggested superior infection-free survival in the P-P-P group (Figure 4A); however, this effect may have been overestimated because this group received boosters before the Omicron surge. To address this, we performed an additional analysis using a common start date after the completion of the booster vaccination (Figure 4B). Although the overall group differences

were attenuated, the A-P-P group showed the lowest infection-free survival, and the relative advantage of the P-P-P group remained. In this context, the apparently superior performance of P-P-P may have been underestimated in the common start date analysis because other groups were assessed at shorter intervals after boosting and likely had higher baseline antibody levels. Although the A-P-P group had a higher median age, this difference is unlikely to reflect a clinically meaningful impairment of immune function, as vaccine responses are generally preserved until later adulthood. Age and sex were adjusted for in our Cox model, and analysis by clinical versus non-clinical staff did not reveal significant differences (Supplementary Figure S4). Nevertheless, as community exposure was not captured and the A-P-P group was small, the apparent excess risk in this group should be interpreted with caution. Second, the single-center design limits the generalizability of our findings. Third, our dataset did not capture detailed information on the clinical severity of breakthrough infections, so the potential role of T cell responses in mitigating disease severity could not be evaluated. However, conducting the study in a homogeneous HCW population provided strengths in exposure assessment and case confirmation, as surveillance and infection control measures were consistently applied. The differences among the vaccine groups should also be interpreted in the context of rapidly evolving national vaccine policies rather than methodological shortcomings. Although not equivalent to randomized controlled trial conditions, these data represent a natural experiment that reflects real-world vaccination strategies during the dynamic transition period in Republic of Korea. In addition, neutralization was assessed using the cPass sVNT, which employs the ancestral Wuhan strain RBD. While this assay correlates well with PRNT, it does not capture non-RBD epitopes and may not fully reflect protection against Omicron subvariants carrying >30 spike mutations [3,43]. Thus, the correlation between post-booster sVNT levels and breakthrough infection risk should be interpreted with caution.

Despite these limitations, this study has several strengths. This prospective cohort captured a natural experiment during the Omicron surge in Republic of Korea, reflecting actual national vaccine allocation policies, direct comparison of four regimens in a homogeneous HCW population, with standardized exposure assessment and systematic surveillance. Although residual confounding by demographic factors and follow-up differences could not be fully controlled, randomized controlled trials under idealized conditions cannot fully predict vaccine performance in urgent, rapidly changing public health contexts. In contrast, real-world analyses such as ours provide valuable evidence of how vaccines perform under actual implementation conditions, complementing controlled trial data. The observed "rescue effect" of mRNA boosters, restoring neutralizing antibody levels irrespective of the primary regimen, supports flexible strategies adopted during the ChAdOx1 phase-out. Moreover, a systematic collection of immunogenicity and breakthrough outcomes offers baseline data that may inform preparedness for future pandemics. Real-world observations, including unexpected findings encountered during policy transitions, can provide important academic insights for guiding responses to emerging infectious diseases. Further studies should evaluate the durability of heterologous booster responses, optimal timing, and dosing intervals, and potential benefits of variant-specific boosters in mixed-platform regimens.

5. Conclusions

Heterologous mRNA boosters restored neutralizing antibody levels across all primary regimens. However, regimens including adenovirus-vectored vaccines, particularly the A-P-P combination, showed higher breakthrough infection rates during the BA.1/BA.2 Omicron surge, suggesting that neutralizing titers alone may not fully predict protection.

Vaccine development should therefore aim not only to maximize neutralizing antibodies but also to consider broader and potentially more durable immune responses, such as T cell-mediated immunity suggested in previous studies. Public health policy should likewise emphasize prospective monitoring of real-world effectiveness during booster rollouts, as immunological data alone may be misleading.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/microorganisms13102362/s1, Figure S1. Schoenfeld residual plots for booster-date Cox model. Scaled Schoenfeld residuals for each regimen covariate: (A) A-A-P, (B) A-P-P, (C) M-M-M. Figure S2. Schoenfeld residual plots for common-date Cox model. Scaled Schoenfeld residuals for each regimen covariate: (A) A-A-P, (B) A-P-P, (C) M-M-M. Figure S3. log(−log) infection-free survival plots for booster regimens. (A) Booster-date start, (B) Common-date start. Figure S4: Kaplan–Meier infection-free survival curves for breakthrough infection stratified by occupational category (clinical vs. non-clinical). There was no significant difference between the two groups (log-rank $p = 0.43$).

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Abbreviations

The following abbreviations are used in this manuscript:

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
HR	Hazard ratio
CI	Confidence interval
HCWs	Health care workers
IQR	Interquartile range
KDCA	Korea Disease Control and Prevention Agency

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Long-Term Safety of Anti-COVID-19 mRNA Vaccines in Patients with Systemic Lupus Erythematosus and Lupus-like Diseases with a Previous History of Myocarditis

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Abstract: Non-viral myocarditis is rare but relatively more frequent in patients with systemic autoimmune diseases (such as systemic lupus erythematosus, SLE, and allied conditions) than in the general population. In rare cases, mRNA-based vaccines can also trigger non-viral myocarditis. Limited data are available about the cardiac safety of mRNA vaccines in this subset of patients. Here, we report data from a third-level hospital on long-term safety, leveraging on a previously described cohort of 13 consecutive patients with SLE, Undifferentiated (UCTD) and Mixed Connective Tissue disease (MCTD), and a history of myocarditis, who had received anti-COVID-19 vaccination between April 2021 and January 2022. Demographics and clinical data (including validated clinometric for SLE) were collected at baseline, at the first available visit following the primary vaccination cycle, after an additional 12 months, and at the last available follow-up after at least 36 months. Twelve patients, seven females, ten with SLE, one MCTD, and one UCTD, had a median follow-up of 41 (35–45) months. One patient was lost at follow-up. No disease flare or sign of myocarditis recurrence were observed. At last visit, all patients were in a low disease activity state (LLDAS), and all but one were in remission, according to the Definition of Remission in SLE (DORIS) criteria. No significant variations in disease activity or damage accrual nor in markers of inflammation and myocardial injury were observed. Our data suggest that mRNA-based anti-COVID-19 vaccines in patients with previous autoimmune myocarditis in the context of SLE and allied conditions have a good long-term safety profile.

Keywords: anti SARS-CoV-2 vaccines; systemic lupus erythematosus; long term safety; myocarditis

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease (CTD) with a wide spectrum of clinical presentations, multi-organ involvement, and a relapsing–remitting course. It is widely acknowledged that viral triggers, such as severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may unmask latent autoimmune diseases, including SLE, and trigger disease flares [1–3]. Previous studies [4] suggest that up to 25% of SLE flares can be preceded by infections. Infection-related flares might exhibit distinct clinical and serological features and often present more severely compared to flares not related to infections [4]. Furthermore, patients with SLE have been reported to experience more severe clinical manifestations of SARS-CoV-2-related disease (COVID-19), with a higher mortality rate compared to the general population [5]. Thus, infection prevention via vaccination is a key objective for the management of patients with CTD [6].

The advent of mRNA-based and viral-vectored anti-COVID-19 vaccines enabled an effective and safe shielding of vulnerable subjects with immune-mediated disorders, including patients with SLE and allied conditions [7–9]. Nonetheless, concerns about vaccine safety were raised due to the exclusion of patients with pre-existing alterations of the immune response from vaccine registration trials and after reports of post-vaccine immune-mediated adverse events. Among them, myocarditis received enhanced attention due to its potential severity and its clinical/pathophysiological profile, lying at the crossroads among potential complications of viral infections, vaccine-related inflammatory adverse events, and autoimmunity [10]. Susceptible individuals might in fact develop uncontrolled cardiac injury, possibly triggered by viral infections and maintained and/or amplified by aberrant immune responses [11].

Compared to the baseline risk of myocarditis in the general population and to the risk of vaccine-related myocarditis, the chances of developing myocarditis are higher in patients with COVID-19, especially in the absence of previous vaccination [10,12]. Conversely, vaccine-related myocarditis is associated with a more favourable outcome, including a lower need for mechanical circulatory support and a reduced incidence of cardiogenic shock [11,13]. Vaccine-related myocarditis has predominantly been reported in young individuals between 12 and 39 years, with approximately 80.5% of cases occurring in males. It was most frequently linked to mRNA vaccines, particularly the Moderna vaccine [14]. Myocarditis constitutes an elusive, though clinically relevant, manifestation of SLE and other connective tissue disorders [15]. Epidemiological studies suggest that up to 10% of patients with SLE may develop myocarditis during the course of the disease [14,16]. Compared with other forms of autoimmune myocarditis, SLE-associated myocarditis is characterised by a higher prevalence of depressed left ventricular function and conduction abnormalities, despite potential subclinical presentations [10].

Short-term analyses conducted both in the general population [12,13,17] and in patients with rheumatic disorders [18] yielded reassuring results and consolidated existing knowledge on general vaccine safety in patients with a history of myocarditis, especially in the context of SLE and lupus-like CTDs [19–22]. To date, however, limited data are known about the long-term cardiac outcomes, data that could further support rheumatologists in the informed management of these patients. Here, building on a previously described, well-characterised cohort of subjects with SLE and lupus-like CTDs with a history of myocarditis, we propose to retrospectively explore possible adverse effects in terms of disease flare (both of myocarditis or of the underlying CTDs) and laboratory parameters over a period of more than three years after receiving the first mRNA-based anti-COVID-19 vaccine dose.

2. Materials and Methods

2.1. Study Design and Aim of This Study

This is a retrospective observational explorative study. We previously described a prospective observational cohort of 13 patients affected by SLE, MCTD, or UCTD, with a history of non-viral myocarditis [18], consecutively enrolled between April 2021 and

January 2022 during the anti-COVID-19 vaccination campaign. In the present study, we performed an exploratory analysis to assess the long-term safety of anti-COVID-19 vaccination, conducting a retrospective evaluation of patients from the same cohort who received at least three years of follow-up from the first vaccine dose. The long-term safety of anti-COVID-19 mRNA vaccines in patients with SLE and SLE allied conditions with a history of previous non-viral myocarditis was assessed considering (1) the occurrence of new episodes of myocarditis; (2) significant variation in underlying disease activity; (3) significant variation in myocardial and disease-specific biomarkers.

2.2. Patients

As previously reported [18], among a large population of patients regularly followed in the setting of the Lupus and Connective Tissue Diseases Clinic of San Raffaele University Hospital, a large, third level referral centre in Milan, Italy, we identified patients fulfilling the following criteria: (1) age $\geq$ 18 years; (2) diagnosis of (a) SLE according to the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) and/or the 2012 SLE International Collaborating Clinics (SLICC) classification criteria for SLE [23]; (b) UCTD as per the 1999 criteria [24]; or (c) MCTD as per Tanaka et al. [25]; (3) eligibility to receive mRNA-based anti-COVID-19 vaccination according to the national vaccination protocol [26]; (4) a history of virus-negative myocarditis proven by endomyocardial biopsy or typical features at magnetic resonance imaging (MRI) [27]. The only exclusion criteria were age < 18 years or refusal to sign informed consent. The enrolment took place between April 2021 and January 2022 during routine scheduled visits. Thus, 11/281 patients with SLE, 1/68 patients with UCTD, and 1/9 patients with MCTD were enrolled. No patients refused to be included in this study. As of April 2025, we retrospectively collected clinical information from the records of patients in the original cohort who had continued regular follow-up visits for at least three additional years after their first vaccine dose. Written informed consent was obtained from all participants under the Panimmuno Research protocol, conforming to the Declaration of Helsinki and approved on 8 March 2018 by the San Raffaele Institutional Review Board, with reference code 22/INT/2018.

2.3. Timepoints

Patients enrolled in this study were followed as per routine clinical practice and data were retrieved retrospectively from clinical charts redacted for the usual outpatient management of patients. In this setting, patients were seen on average every 3–6 months according to clinical needs. In addition, due to the lack of standardised procedures for monitoring cardiac function in anti-COVID-19 vaccinees, patients were prescribed to undergo extra laboratory tests ideally within three–five days from the first and second vaccine doses. These laboratory tests included blood cell counts, erythrocyte sedimentation rate, ESR, C-reactive protein, CRP, troponin T, and pro-brain natriuretic peptide, proBNP. The timing and content of these tests were agreed upon by consensus among experienced rheumatologists and cardiologists (GAR, GDL, SS, and GPe) based on available evidence at the time of enrolment, which showed that most vaccine-related adverse events occurred within less than one week from the receipt of a vaccine dose [28,29]. Patients showing abnormal cardiac marker values were invited to undergo tighter serial monitoring according to clinical judgement.

We defined the closest patient visit before the first dose of anti-COVID-19 vaccines as the baseline timepoint (Figure 1). The first visit after completion of a full cycle of the first two vaccine doses was categorised as a short-term evaluation timepoint. Assessment of patient status 12 months after the primary vaccination cycle was defined as a medium-term

evaluation timepoint. The long-term evaluation timepoint coincided with the last available visit and had to be performed at least 24 months after the short-term assessment.

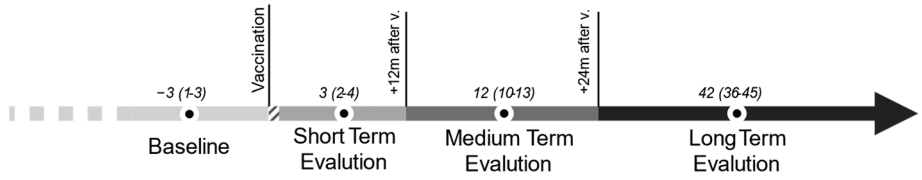

Figure 1. Timepoints of patients' evaluation. The median (interquartile range) times separating each timepoint from the first vaccination cycle are reported in italic font. v.—vaccination.

2.4. Connective Tissue Disease Clinical Features

Baseline clinical characteristics recorded in this study included demographics and CTD-related manifestations in patients' general history. Measures of disease activity, remission, and damage accrual were obtained at each timepoint (see Section 2.3), along with laboratory data and treatment changes. Disease activity was quantitated through the SLE disease activity index 2000 (SLEDAI-2K) and the British Isles Lupus Assessment Group (BILAG) 2004 scale [30]. Damage was estimated through the SLICC/ACR damage index (SDI) [31]. Remission was defined according to the Lupus Low Disease Activity Status (LLDAS) [32] and the Definition of Remission in SLE (DORIS) criteria [33]. We defined an SLE flare when relapse or new manifestations of the disease led to treatment escalation [34].

In addition to myocarditis-specific biomarkers, laboratory data included blood cell counts, markers of renal and liver function, complement C3 and C4, anti-double-stranded DNA antibody (ADNA) titres, CRP levels, and ESR.

Treatment information included the number of patients taking hydroxychloroquine, biotechnological immunomodulants (belimumab), and conventional or biotechnological immunosuppressants. We also recorded the number of patients taking corticosteroids and the dosage of corticosteroid treatments in prednisone equivalents.

2.5. Myocarditis Features

Myocardial activity was monitored by an assessment of clinical features, biomarkers, and imaging studies. Markers of cardiac injury and/or overload (troponin T, proBNP) were measured after each dose of the primary cycle of vaccination, at each following timepoint (see Section 2.3) and in the case of symptom exacerbation. Similarly, imaging was performed according to routine clinical indications and anticipated or repeated in the case of symptoms suggesting myocarditis recrudescence. Typical clinical symptoms encompassed chest pain or discomfort, fatigue, dyspnoea, palpitations, and/or syncope. Before vaccination, patients were instructed to report the potential occurrence of these symptoms after each vaccine dose. A myocarditis flare was defined as the occurrence of typical symptoms associated with elevated markers of myocardial necrosis and/or suggestive abnormalities on echocardiography or electrocardiogram (ECG) [28,35]. We also collected data on new cardiovascular events taking place during the follow-up period, including ischaemic heart disease and arrhythmic events.

2.6. Statistical Analysis

Statistical analyses were conducted with STATACORP Stata® version 18. The normal distribution of continuous variables was assessed with the Shapiro–Wilk normality test. Continuous variables were expressed as mean and standard deviation, or as the median and interquartile range (IQR) of 25th to 75th percentiles, depending on the distribution of data. Variations in quantitative variables over time were compared intra-individually through the Wilcoxon signed-rank test for repeated measurements. Categorical variables

were reported as numbers and percentages and were compared among groups by using Pearson's Chi-square test. A *p*-value was considered significant when $p < 0.050$, with confidence intervals set at 95%.

3. Results

3.1. Baseline Characteristics

Of the thirteen patients with baseline data, twelve (92%; seven women and five men) had a long-term follow-up (Table 1). One patient moved to another region and could not be investigated for long-term data. Ten (83%) patients had SLE, one (8%) had MCTD, and one (8%) had UCTD. The median age at the onset of CTD was 30 (25–45) years, and myocarditis occurred after a median of 4 (1–12) years from CTD diagnosis.

Table 1. Patients' specific disease and baseline characteristics.

Feature	Value
SLE | UCTD | MCTD, N (%)	10 (83) | 1 (8) | 1 (8)
Sex (female), N (%)	7 (58)
Age (years), median (IQR)	48 (44–52)
Disease Duration (year), median (IQR)	17 (4–22)
Constitutional, N (%)	11 (92)
Mucocutaneous, N (%)	8 (67)
Neuropsychiatric, N (%)	3 (25)
Musculoskeletal, N (%)	9 (75)
Cardiological, N (%)	12 (100)
Gastroenterological, N (%)	3 (25)
Ophthalmologic, N (%)	1 (8)
Renal, N (%)	5 (42)
Haematologic, N (%)	8 (67)
Anti DNA	8 (67)
Anti-Sm	4 (33)
Anti-Ro	2 (17)
Anti-La	1 (8)
Anti-RNP	2 (17)
Anti-Cardiolipine	5 (42)
Anti-β2GPI	4 (33)
Lupus anticoagulant	2 (17)
Anti-PS/PT	2 (17)

SLE—Systemic Lupus Erythematosus; UCTD—Undifferentiated Connective Tissue Disease; MCTD—Mixed Connective Tissue Disease; IQR—interquartile range; anti-β2GPI—anti-β2-glicoprotein; anti-PS/PT—anti-Phosphatidylserine/Prothrombin.

At baseline, the majority of patients were either in clinical remission or had low disease activity (Table 1). In SLE patients, 9/10 met LLDAS criteria. The median SLEDAI-2k was 2 (0–2), with only one patient with a score higher than 4. The other subjects were considered in remission by the attending physician. No patients had active myocarditis. The most frequent SLE disease domains according to the BILAG score were musculoskeletal (9; 75%), haematological (8; 66%), and mucocutaneous (8; 66%). Five (41%) had a history of renal involvement (Table 1). At the time of vaccination, two patients were taking low-dose corticosteroid therapy, six (50%) hydroxychloroquine, five (41%) mycophenolate mofetil, two (16%) subcutaneous belimumab, and one (8%) azathioprine. Only two patients were taking corticosteroids. The median daily prednisone dose was 3.1 (2.8–3.4) mg/day. As previously described, no patient underwent treatment changes during vaccination, and all patients received mRNA-based vaccines. Particularly, 11/12 patients received the Pfizer vaccine, and 1/12 received the Moderna vaccine. Two patients had developed a confirmed COVID-19 infection one year prior to vaccination, one 12 months prior to the

first dose, the another 7 months before the first dose. Both had a mild infection not requiring hospitalisation and both, according to the national protocol at the time, received a complete vaccination cycle.

3.2. Variations in Clinical and Laboratory Features over Time

The primary vaccination cycle occurred within 3 (1–3) months from baseline. Short-, intermediate-, and long-term evaluations were performed 3 (2–4), 12 (10–13), and 42 (36–45) months after the primary vaccination cycle, respectively.

3.2.1. Lupus Activity and Damage Accrual

As previously reported [18], no significant changes in disease activity or damage accrual were observed at short- and medium-term timepoints. At long-term evaluation, all patients were clinically stable and did not require treatment escalation. Considering patients classified with SLE, nine met the LLDAS and DORIS criteria for remission. One could not be attributed to DORIS remission due to mild thrombocytopenia. Consistent with this, the median SLEDAI-2k was 0 (0–2), and no patient had A- or B-grade activity in any BILAG domain. Three patients had C-grade activity in the haematological domain, in one case due to mild leukopenia, in one case due to lymphopenia, and in one case due to mild thrombocytopenia.

Longitudinally, SLEDAI-2k scores decreased significantly from the short- to the long-term evaluation [2 (0–4) to 0 (0–2); $p = 0.031$]. No other significant variations were observed in terms of measures of activity, damage, and remission across each distinct timepoint (Table 2). No increase in therapy was needed during follow-up. Of note, no patient was taking corticosteroids at the last visit, and two patients discontinued mycophenolate mofetil due to prolonged remission.

Table 2. SLE features across different timepoints.

SLE Patients (10)	Before Vaccination	After Vaccination		
		Short-Term	Medium-Term	Long-Term
Patients in LLDAS: n (%)	8 (80)	8 (80)	8 (80)	10 (100)
Patients in DORIS: n (%)	7 (70)	7 (70)	8 (80)	9 (90)
SLEDAI-2k: median (IQR)	2 (0–3)	2 (0–4)	1 (0–2)	0 (0–2) *
BILAG Constitutional: median (IQR)	0 (0–0)	0 (0–1) #	0 (0–0)	0 (0–0)
BILAG Mucocutaneous: median (IQR)	0 (0–1)	0 (0–0.75)	0 (0–0)	0 (0–0)
BILAG Neuropsychiatric: median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
BILAG Musculoskeletal: median (IQR)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)
BILAG Cardiological: median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
BILAG Gastroenterological: median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
BILAG Ophthalmologic: median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
BILAG RENAL: median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
BILAG Haematologic: median (IQR)	0 (0–1)	1 (0–1)	1 (0–1)	0 (0–1)
SLICC Damage Index: median (IQR)	1 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)

* $p < 0.05$ compared to after vaccination by signed-rank test. # $p < 0.05$ compared to pre-vaccination by the Wilcoxon signed-rank test.

Comparing baseline laboratory findings [18] with long-term evaluation, no significant variation in blood cell counts or serological markers was observed, except for a slight increase in complement fraction C4 [0.17 (0.13–0.20) vs. 0.23 (0.20–0.30) mg/L $p = 0.025$; Supplemental Table S1].

3.2.2. Clinical and Laboratory Markers of Myocardial Injury

No myocarditis relapse was observed in the short-, medium-, and long-term. In addition, no patient developed myocardial infarction or arrhythmia. Long-term heart ultrasonographic data were available for 9/12 patients, who were re-assessed 35 (29–41) months after the primary vaccination cycle. None of them had signs of active myocarditis or of additional damage compared to baseline evaluation. The median ejection fraction was 60 (55–65)%, and no significant worsening in myocardial function was reported. One patient underwent myocardial MRI, showing no active inflammation of the heart.

As previously reported [18], a transient and non-clinically significant rise in troponin T levels was observed following doses 1 and 2 of the primary vaccination cycle, mirrored by a statistically and clinically non-significant increase in proBNP levels. Both progressively showed a tendency towards normalisation. Long-term findings confirmed these trends. Specifically, the median troponin levels were 5.1 ng/mL (2–10.2) at baseline and 8.1 ng/mL (4.2–14) at long-term follow-up (p = 0.901), while proBNP levels were 119 pg/mL (53–167) at baseline and 66.5 pg/mL (43.3–232.3) at long-term follow-up (p = 0.250; Figure 2). Of note, only two patients (both with SLE) showed abnormal troponin T levels at long-term follow-up, in the context of already abnormal values at baseline. One patient with MCTD had transiently abnormal troponin T levels, which eventually returned within the normal range. With regard to other laboratory findings, we also observed a slight but significant decrease in CRP levels between the baseline and long-term evaluation [1.05 (0.93–3.88) vs. 0.90 (0.50–1.00) g/L, p = 0.023]. No difference in biomarker level was observed based on patients' autoantibody profiles.

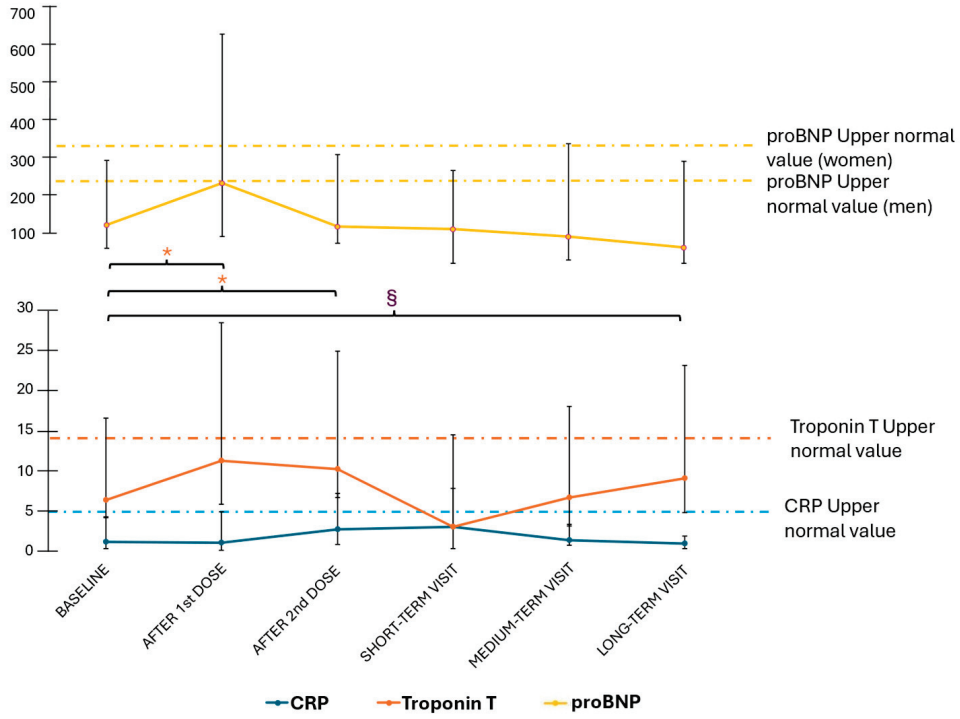

Figure 2. Variations in troponin T (ng/mL; orange), proBNP (pg/mL, yellow), and CRP (g/L; blue) levels at multiple timepoints. Dotted lines in the corresponding colour represent upper normal levels for each test. A statistically but not clinically significant transient increase in troponin T levels was recorded after the first and second dose, while long-term timepoint levels were consistent with baseline. CRP levels at long-term visit showed a slight but significant reduction compared with baseline. Significance levels for $p < 0.05$ are marked with * for troponin levels and § for CRP levels. CRP—C-reactive protein; proBNP—pro B natriuretic peptide.

4. Discussion

This study analysed the long-term clinical trajectories of a group of patients with a history of virus-negative myocarditis due to SLE and lupus-like CTDs after more than 2 years from exposure to a primary immunisation cycle with mRNA anti-COVID-19 vaccines. Adding to the preliminary safety data obtained in the short- and medium-term follow-up of these patients, our results show that the same patients remained clinically stable over time, with regard to both cardiac and non-cardiac manifestations. Imaging and laboratory data confirmed the absence of heart damage progression in the long term. Taken together, these results suggest that mRNA-based vaccines do not confer an increased risk of myocarditis and other cardiac events to patients with an autoimmune background and pre-existing defective immunological tolerance against the myocardium in the short and long term.

In line with our findings, growing evidence indicates that exposure to anti-COVID-19 vaccines is not associated with excess rates of short- and long-term morbidity in patients with immune-mediated diseases [36–38]. Conversely, disproportionate rates of autoimmune disease flares along with new-onset autoimmunity and accrual of general morbidity have been observed in association with COVID-19 [39–41]. Indeed, infections, in general, constitute an important source of morbidity and mortality in patients with autoimmune systemic diseases, both in terms of infection severity and of enhanced risk of disease flare [42,43].

To combat the additive risk of morbidity conferred by infections, prophylactic measures, including vaccines, are strongly encouraged and generally preferred over infection treatment [6,44] in the management of patients with autoimmune diseases. Furthermore, a higher number of boosts or the use of adjuvanted preparations are often needed to overcome coexisting inborn errors of immunity and/or the detrimental effects of immunosuppression [45–49]. However, vaccination rates in patients with autoimmune diseases remain suboptimal, often due to concerns about vaccination safety by both clinicians and patients [50,51]. The recent COVID-19 pandemic exacerbated this concern, possibly due to the coexistence of rising trends in a lack of trust towards academic institutions and state-driven programmes, defective shielding from fake news, and relatively limited data at the time of decision-making due to the emergency context [52–55].

Vaccine-related myocarditis constitutes a topic of particular interest in the rheumatological community, as virus-negative myocarditis is a shared, potentially life-threatening complication in multiple immune-mediated disorders [15,56,57]. Consistent with previous evidence in the literature [58], we found that the prevalence of clinically overt autoimmune myocarditis was relatively low in cohorts of SLE and lupus-like CTDs. Furthermore, no association was found between the risk of myocarditis relapse and exposure to mRNA anti-COVID-19 vaccines, both in the short [13,18,59,60] and long term. We also did not detect clear signals of cardiac complications other than myocarditis relapse in our cohort, further corroborating the concept of clinical safety associated with the use of mRNA vaccines in patients with previous myocarditis and autoimmune background and aligning with the existing literature, where relatively low risks of long-term cardiac sequelae are reported even in patients with confirmed vaccine-related myocarditis [61]. This evidence further supports existing position statements by cardiological societies, highlighting the higher risk of short- and long-term cardiac complications due to SARS-CoV-2 than to the anti-COVID-19 vaccine [62,63].

The stability of laboratory and imaging markers of cardiac injury in the long-term follow-up further consolidated our clinical findings. Nonetheless, statistically (but not clinically) significant alterations of troponin T were observed after the first vaccine dose compared to baseline. This evidence conforms with the few other studies reporting on

the serial monitoring of cardiac biomarkers. These studies suggest that transient, clinically non-relevant elevations in cardiac biomarkers can be observed after mRNA vaccine administrations both in healthy subjects and patients with pre-existing disorders, as observed in our cohort. One case of confirmed myopericarditis presenting with overt cardiac symptoms was reported in a study focusing on a demographically higher-risk group of 301 adolescents [64]. No additional clinically relevant events were recorded in independent cohorts of 777 [65], 324 [66], and 162 [67] subjects, despite 0.62–5% troponin elevation rates. Taken together, these data seem to indicate that the spectrum of transient clinical/pathological events ranging from the subclinical elevation of markers of cardiac injury after mRNA vaccine exposure to overt vaccine-related myocarditis might subtend unique pathogenic mechanisms, with only limited overlaps with virus-triggered and autoimmune myocarditis [68]. Enhanced susceptibility to oxidative stress (possibly exacerbated by disease-specific mechanisms in the setting of SLE and CTDs [67] and impaired regulation of IL-16/IL-18-biassed inflammatory responses [68,69] have been proposed as potential distinctive traits of vaccine-associated myocarditis and might account for troponin alterations uncoupled from clinically overt myocarditis relapses in the short- and long-term follow-up of patients receiving mRNA vaccines in the context of cardiac and non-cardiac autoimmunity. Confounders related to baseline systemic activity in these patients suggest the need for further translational studies in this setting.

Despite showing consistency with existing evidence in the literature, this work has some limitations that should be carefully considered for a correct interpretation of the data. First, the small size of our cohort prevents full generalisation of our findings, warranting further research in this field. Indeed, definite SLE-associated myocarditis is a rare condition [70], which inevitably reduces the ceiling of potential enrolment. Second, data collection was retrospective, which increases the risk of potentially missing minor clinical events that were not recorded in clinical charts. Third, the timing of laboratory data collection was not homogeneous, reflecting the complexity of real-life practice. Laboratory exams were also limited to routine testing. Therefore, serological response to vaccines was not assessed, and no conclusion about vaccine efficacy could be extrapolated. Furthermore, we could not ascertain whether the measurement of selected cytokines could have a role in patients with SLE and allied conditions to increase the sensitivity and specificity of myocarditis diagnosis.

Notwithstanding these limitations, our original findings add information concerning the long-term safety of SARS-CoV-2 vaccination in autoimmune patients with rare manifestations and can contribute to the management of these challenging cases.

5. Conclusions

Our work suggests that mRNA-based anti-COVID-19 vaccines are safe in patients with SLE and other lupus-like conditions with a history of myocarditis, both in the short and long term. Further studies and meta-analyses of aggregated data are needed to further validate our results.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/microorganisms13102266/s1, Table S1: Laboratory Exams at baseline and at long term evaluation.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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Article

COVID-19 Vaccination Still Makes Sense: Insights on Pneumonia Risk and Hospitalization from a Large-Scale Study at an Academic Tertiary Center in Italy

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Abstract: COVID-19 vaccines have revolutionized prevention and clinical management by reducing disease severity and mortality. However, their long-term impact on hospitalization is unclear. This retrospective study assessed whether vaccination status, timing, and number of vaccine doses influence the risk of hospitalization and COVID-19 pneumonia in a large cohort in Italy, several years after initial vaccine rollout. From 1 October 2023, to 2 February 2024, at Humanitas Research Hospital (Milan) and two affiliates, we recorded age, sex, comorbidities, vaccination status (number of doses and time since last dose), admission type (urgent vs. elective), and pneumonia diagnosis. Baseline health was quantified by the Charlson Comorbidity Index. Among 16,034 admissions (14,874 patients), vaccination data were available for 5743 cases: 40.8% were in the emergency setting and 59.2% were elective. Patients presented with pneumonia in 6.8% of cases. Laboratory results confirmed COVID-19 pneumonia occurred in 43.7% of pneumonia cases, with a 16.9% mortality. Patients with no vaccine dose had a higher proportion of COVID-19 pneumonia, while COVID-19 pneumonia rates were lower in individuals who had received more vaccine doses. There were no significant differences in COVID-19 pneumonia risk by timing of last vaccination. Moreover, hospitalized unvaccinated patients had overall more frequent emergency admissions (57.3%), while patients with three or more doses had about a ~40% emergency admission rate. COVID-19 positivity during hospitalization was highest in unvaccinated patients (90.7%) and declined with vaccination status. Vaccinated patients, especially those with multiple doses, had significantly lower COVID-19 pneumonia rates and emergency admissions. These findings suggest a possible protective effect of vaccination in modifying the clinical presentation and severity of illness among those who are hospitalized and support continued vaccination efforts for high-risk groups to reduce severe adverse outcomes.

Keywords: COVID-19; vaccination; pneumonia; vaccine hesitancy; hospitalization

1. Introduction

The diffusion of COVID-19 vaccines has significantly altered the approach to COVID-19 preventive management as well as its clinical course and management [1]. Although vaccines have shown substantial efficacy in decreasing serious illness and death in all age groups, their influence on specific outcomes such as pneumonia and hospitalization, especially in older populations, requires additional research [2–4].

Italy, similar to other countries, has implemented several types of COVID-19 vaccines, including mRNA-based vaccines and viral vector vaccines [2,3,5]. Some types of vaccine were subsequently withdrawn from the market, such as Vaxzevria from AstraZeneca, a viral vector vaccine, because of severe side effects, and in the last few years, mainly mRNA vaccines were employed in Italy [6]. While the mechanism of action of each vaccine type is distinct, and this can potentially lead to differences in immune response and protection against various manifestations of COVID-19 [7,8], a Cochrane review published in 2022 showed no difference between various types of vaccines and the development of side effects. Moreover, all the vaccines guaranteed a reduction in severe and critical disease [9].

Elderly patients represent a particularly vulnerable group, often with multiple comorbidities and age-related immune system decline. These factors may affect both the effectiveness of vaccination efficacy and susceptibility to pneumonia, whether caused by COVID-19 or other infections [10]. The relationship between vaccination status, vaccination type, and pneumonia risk in this population remains unclear.

Consequently, in elderly patients and in other high-risk populations, defining the best timing and number of vaccine doses is a critical factor. With the introduction of booster programs, it is essential to determine the optimal vaccination schedule to maintain protection, and continuous surveillance is necessary to monitor trends and adapt strategies to meet the evolving needs of the population based on their vaccination status [11].

We therefore conducted this study to evaluate whether the dose number and time of vaccination influence the risk of developing COVID-19 pneumonia and hospitalization in a large population of patients admitted to an academic tertiary center in Milan, Italy.

2. Materials and Methods

This retrospective observational study enrolled all consecutive patients admitted to Humanitas Research Hospital in Milan and two secondary hospitals from the same group in Italy, from 1 October 2023 to 2 February 2024.

All hospitalized patients with vaccination status were selected based on electronic health record data and anonymized before inclusion in the statistical analysis. This study received local IRB approval. We collected age, gender, comorbidities, vaccination status, number of doses, reason for admission, oxygen use, pneumonia data, clinical course, and outcomes.

COVID-19 positivity was defined according to the swab test results, using standardized terminology from laboratory and swab testing. Positive tests corresponded to standard RT-PCR detection of SARS-CoV-2 with high cycle threshold (Ct) values. Weakly positive tests included borderline RT-PCR positivity with low Ct values, and negative tests corresponded to undetectable viral RNA. In the study period, universal COVID-19 screening with swab testing was no longer routinely performed. Testing was reserved for high-risk patients and those presenting with respiratory symptoms, in accordance with regional health authority protocols.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical variables.

Categorical variables are reported as frequencies (percentages with 95% CIs) and continuous variables as means (with SDs) or medians (with interquartile ranges [IQRs] and 95% CIs) according to distribution. Groups were compared with Wilcoxon rank sum tests and with Pearson $\chi 2$ test (Fisher exact test where appropriate) for categorical variables.

The primary outcomes were the type of hospital admission (elective vs. emergency) and occurrence of pneumonia. COVID-19 infection status was categorized as positive, weakly positive, or negative based on swab test results. We used chi-square tests to assess associations between vaccination status and categorical outcomes (e.g., type of admission, COVID-19 test result, and pneumonia). Proportions and their 95% confidence intervals were estimated using binomial tests and visualized with bar plots and error bars.

Subgroup analyses were performed to explore pneumonia and COVID-19 pneumonia occurrence. Time since last vaccination was calculated and categorized in 180-day intervals, and its association with COVID-related pneumonia was evaluated using descriptive plots and chi-square tests. We analyzed data using R software, version 4.3 (R CoreTeam).

3. Results

From a total of 16,034 total hospital admissions out of 14,874 patients hospitalized over a period of 124 days from 1 October 2023 to 2 February 2024, we selected a total of 5743 patients presenting inclusion criteria.

A study flowchart is reported in Supplemental Material S1.

The 5743 patients with vaccination status data included 2348 (40.8%) emergency admissions and 3401 (59.2%) elective admissions. A total of 75 patients (1.3%) were not vaccinated, 70 (1.2%) had one dose of the vaccine, 520 (9.1%) had two doses, 3885 (67.7%) had three doses, 1026 (17.9%) had four doses, 155 (2.7%) had five doses, 16 (0.3%) had six doses, and 4 (0.06%) had more than six doses reported. Demographic characteristics and baseline data according to number of vaccine doses are reported in Table 1.

Table 1. Baseline characteristics according to number of vaccine doses.

	Overall	**0**	**1–2**	**3**	**≥4**	***P* for Difference**
N *	5749	75	590	1458	623	
Age (mean (SD))	66.52 (15.75)	70.32 (14.07)	58.83 (17.39)	69.17 (15.55)	73.70 (14.38)	<0.001
Sex = Male (*n*, %)	3289 (57.2)	33 (44.0)	319 (54.1)	863 (59.2)	358 (57.5)	0.764
CCI * (mean (SD))	1.84 (2.27)	2.75 (3.02)	1.62 (2.23)	2.46 (2.57)	2.40 (2.31)	0.881
Hypertension (*n*, %)	3007 (52.3)	45 (60.0)	213 (36.1)	836 (57.3)	408 (65.5)	<0.001
COVID-19 (*n*, %)						<0.001
Negative	1458 (68.9)	0 (0.0)	162 (78.6)	1458 (100.0)	0 (0.0)	
Positive	623 (29.5)	68 (90.7)	43 (20.9)	0 (0.0)	623 (100.0)	
Weak	34 (1.6)	7 (9.3)	1 (0.5)	0 (0.0)	0 (0.0)	
Pneumonia (*n*,%)	389 (6.8)	17 (22.7)	35 (5.9)	202 (13.9)	151 (24.2)	<0.001
COVID-19 Pneumonia (*n*, %)	157 (43.7)	17 (100.0)	10 (33.3)			

* N: total patients; CCI: Charlson Comorbidity Index.

Unvaccinated patients had an overall higher proportion of emergency admissions, not limited to cases related to COVID-19 (57.3% [95% CI 45.5–68.5%]) compared with those who received one dose (44.3% [95% CI 35.6–56.6%]), two doses (37.9% [95% CI 33.7–42.2%]), or three doses (40.8% [95% CI 39.3–42.4%]). For patients who received more than three doses (up to seven or more), the proportion of emergency admissions remained relatively stable, at approximately 40%. (Table 2).

Table 2. Type of hospitalization according to doses.

Vaccine Doses	Frequency	Emergency Admission (%)	95% CI Emergency Admission	Standard Admission (%)	95% CI Standard Admission
0	75	57.3	[45.4, 68.5]	42.7	[31.5, 54.6]
1	70	44.3	[32.6, 56.6]	55.7	[43.4, 67.4]
2	520	37.9	[33.7, 42.2]	62.1	[57.8, 66.3]
3	3885	40.8	[39.3, 42.4]	59.2	[57.6, 60.7]
4	1024	40.3	[37.3, 43.4]	59.7	[56.6, 62.7]
5	155	43.2	[35.4, 51.4]	56.8	[48.6, 64.6]
6	16	50	[28.0, 72.0]	50	[28.0, 72.0]
7+	4	50	[15.0, 85.0]	50	[15.0, 85.0]

This is mirrored by the progressive increase in the proportion of overall elective hospital admissions according to vaccination status, rising from 42.7% (95% CI 31.5–54.6%) in unvaccinated patients, to 55.7% (95% CI 43.4–67.4%) in patients with one vaccination and peaking at about 60% with two or more vaccinations.

In Figure 1, we plot the number of emergency hospital admissions by vaccination doses and compare different doses using a two-sample test for equality of proportions with continuity correction.

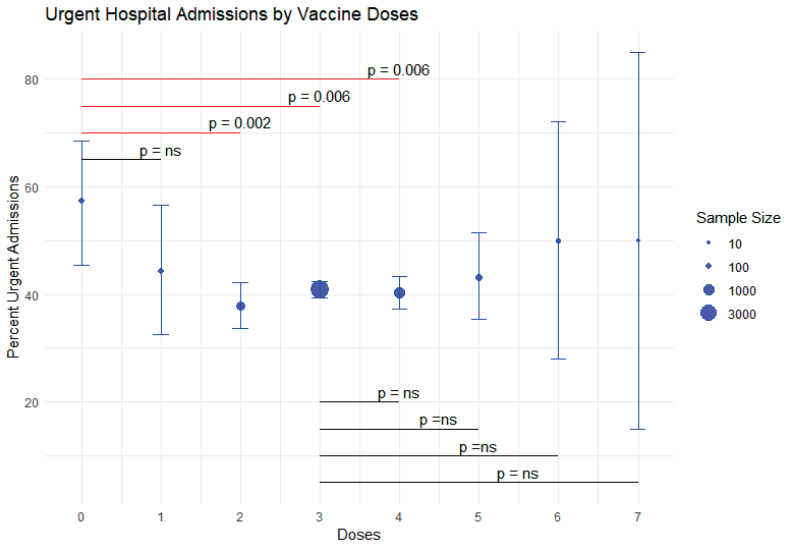

Figure 1. Overall emergency hospital admissions according to vaccination doses, with 95% CI. ns: Not significant.

COVID-19 Antigen Testing According to Vaccination Status

A total of 2115 (36.9%) were hospitalized with a recorded COVID-19 swab test, 1537 (72.7%) were emergency admissions, and 578 (27.3%) were ordinary admissions. Of these

patients, the large majority had a negative COVID-19 swab (68.9%), 29.5% had a positive COVID-19 swab, and 1.6% had a weak positive swab. Weakly positive swabs were clinically managed as positive patients and analyzed separately with positive tests because of the low occurrence. Figure 2 reports positive COVID-19 nasopharyngeal COVID-19 swabs according to vaccination status.

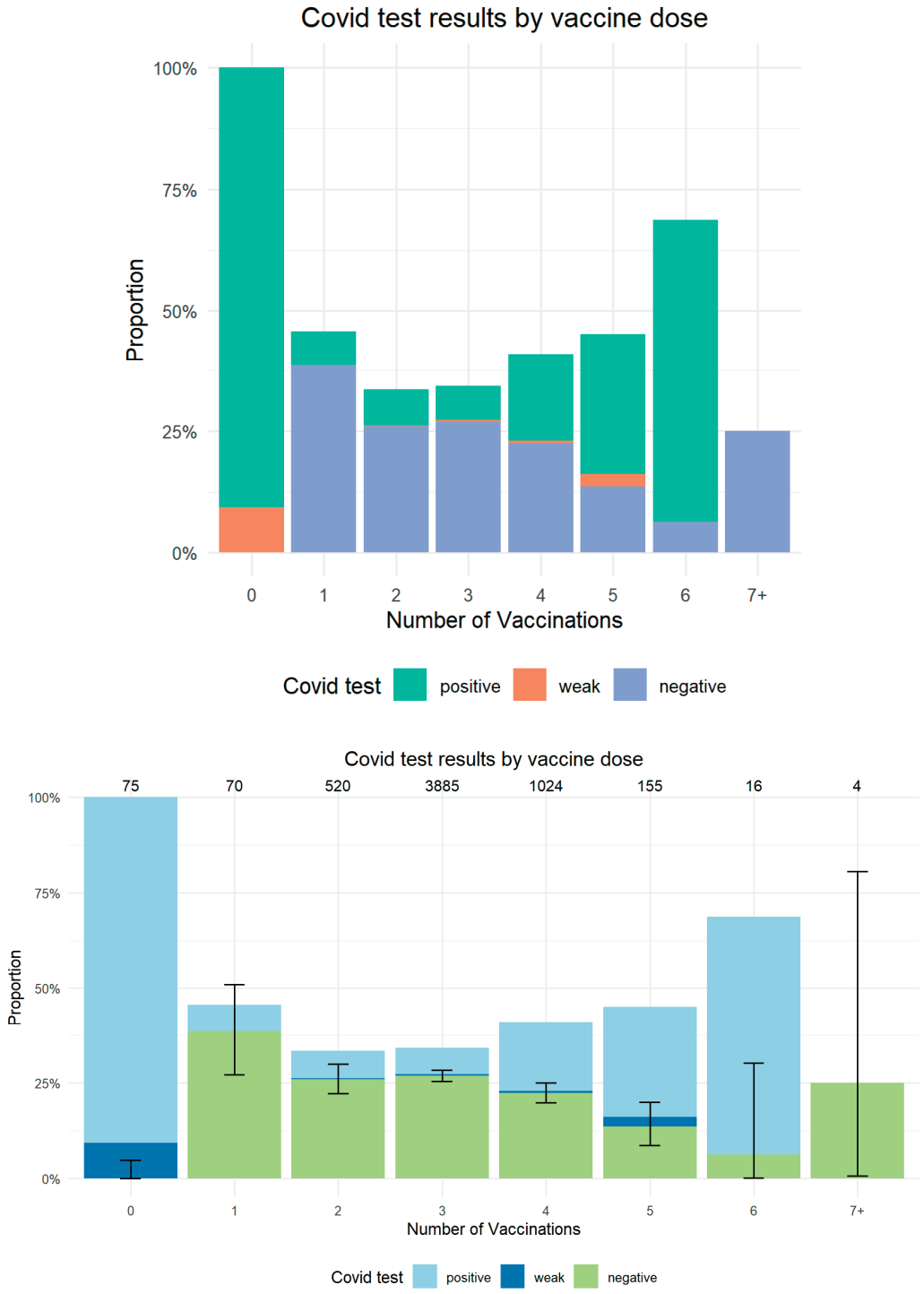

Figure 2. Positive COVID-19 nasopharyngeal swabs in hospitalized patients according to vaccination doses. Number of patients per group and 95% CI for negative swab results are reported.

When stratifying by vaccination status, unvaccinated patients undergoing COVID-19 swab testing had a positive result in 90.7% and a weak positive result in 9.3%. There

were no negative test results in unvaccinated patients. The percentage of positive tests dropped to 7.1% (95% CI 2.6–16.6%) in patients with one dose and 7.3% (95% CI 5.3–10.0%) in patients with two doses, progressing to 10.7% in patients with three or more doses. Among these, the proportion ranged from 6.9% (95% CI 6.2–7.8%) in patients with three doses and increased progressively to 62.5% (95% CI 35.9–83.7%) in patients with six doses (Figure 2). Unvaccinated patients had significantly more frequent positive COVID-19 tests than patients in all other categories ($p < 0.0001$).

There were 389 hospitalizations for COVID-19 and non-COVID-19 pneumonia (6.8% of 5749 admissions). In the whole population, COVID-19 pneumonia was diagnosed in 151 (38.8%) of pneumonia cases (2.6% of hospital admissions), leading to 26 deaths (16.9%). When considering COVID-19 pneumonia rates by vaccination status, unvaccinated hospitalized patients had COVID-19 pneumonia in 43.7% of cases vs. 6.9% of vaccinated patients with $\geq$3 doses. When assessing time since last vaccination and prevalence of COVID-19 pneumonia in this population, we did not find a statistically significant correlation ($p = 0.45$).

4. Discussion

We conducted a retrospective analysis of hospitalized patients according to their vaccination status for COVID-19 disease. We focused on a real-world population several years after the rollout of COVID-19 vaccines, allowing us to assess longer-term associations between vaccination status and hospital admissions. In general, we observed that unvaccinated individuals were more likely to require emergency hospital admission and had a significantly higher prevalence of positive or weakly positive COVID-19 test results compared with controls. Similarly, the proportion of hospitalized patients with COVID-19 pneumonia was significantly higher among unvaccinated individuals compared with those who had received vaccination.

As published in 2019 by the WHO, vaccination hesitancy is a serious problem all over the world; in particular, it is included among the ten threats to global health [12]. If this topic was relevant before the COVID-19 pandemic, it is now essential to face the problem to prevent or control the next pandemic.

During the different phases of the COVID-19 pandemic, there was a significant increase in vaccine hesitancy [13]. While the first dose of vaccine was generally considered as a necessary step to get over the most difficult period of the pandemic, skepticism grew around the effectiveness and safety of subsequent doses. Concerns about possible side effects led many individuals to decline additional vaccination [14].

The recommendation to re-vaccinate every 3–4 months, driven both by the rapid waning of neutralizing antibodies and by the continual emergence of immune-evasive variants (e.g., Omicron sub-lineages such as BA.2.86 and XBB), has added further concern. Unlike seasonal influenza—where a single annual shot is generally sufficient because antigenic drift is slower—SARS-CoV-2 currently demands a more frequent booster schedule, which many individuals perceive as burdensome and unnecessary.

Younger and more educated people showed greater trust in vaccines, especially for COVID-19, even if their confidence was reduced when they experienced side effects [15–17]. In addition, misinformation conveyed by the media, religion, and politics contributed to vaccination hesitancy among less educated people and those living in rural areas [18].

In our study, even if the percentage of unvaccinated patients is low, the difference in terms of hospitalization for COVID-19 pneumonia remains statistically significant. While it is difficult to assess how much COVID-19 vaccination can protect individuals from hospitalized patient data, the difference among the hospitalized population is evident. Moreover, some studies underlined the importance of COVID-19 vaccination to prevent

and reduce long COVID and to protect organs, in particular heart, kidneys, and brain, from developing chronic diseases caused by COVID-19, or at least to reduce the risk and the impact of COVID-19 on organ function [19–22].

Vaccine hesitancy is also a key issue among health workers [23]. Several studies demonstrated that health care workers' vaccination is helpful in preventing COVID-19 spread among patients, in particular in elderly and immunocompromised ones who are at particularly high risk [24–29]. Other studies underlined the importance of booster dose administration to maintain immune response [30–32]. In general, vaccine hesitancy can be a serious issue in future pandemics and could have a prominent impact on public health. The awareness of vaccine efficacy and safety among the general population should be developed and maintained to prevent a catastrophic impact on the public health system [13,33].

In this article, we have analyzed different aspects related to the impact of vaccination among hospitalized patients, focusing on elective vs. emergency admissions, risk of developing pneumonia, and vaccination timing. These are summarized in the following highlights and discussed below:

- Vaccination status is associated with the type of hospital admission required, with emergency hospital admission being more frequent in unvaccinated patients.
- Positive or weakly positive COVID-19 swabs were considerably more prevalent in unvaccinated patients requiring hospitalization.
- The proportion of COVID-19 pneumonia and overall pneumonia is higher in hospitalized patients with no COVID-19 vaccination compared with vaccinated individuals, with no influence of timing since last vaccination dose.

4.1. Vaccination Status and Hospital Admission Type

Our results show a significant association between vaccination status and the type of hospital admission. Unvaccinated patients had a higher frequency of emergency admissions compared with vaccinated individuals. This difference is likely not attributable solely to COVID-19 infection but may also reflect reduced access to—or lower utilization of—healthcare services among the unvaccinated population. This interpretation is further supported by the higher prevalence of hospitalizations for COVID-19-related pneumonia among unvaccinated patients, even when considering all causes of admission. This is consistent with the substantial body of literature that highlights the role of vaccination in reducing the severity of COVID-19 and consequently the need for emergency medical intervention [1,2,34–36].

Previous publications underlined the importance of booster dose administration to maintain immune response [29–31]. Booster vaccinations function to re-stimulate the immune system, elevating both antibody titers and memory B and T cell responses [37–39].

This is confirmed by our data, as shown in Supplementary Table S1, where prevalence of COVID-19 pneumonia in hospitalized patients reduces significantly after one dose, and this positive effect was maintained and even increased after the second and the booster dose of vaccine (considered as the third dose). While these findings on hospitalized patients cannot be translated to the whole population of vaccinated/unvaccinated individuals, they suggest that a booster dose may be useful to maintain long-term immunity, and support the notion that vaccination lowers the risk of severe disease, further highlighting its critical role in mitigating the public health impact [17,35].

4.2. Prevalence of Positive COVID-19 Testing

Our data also underscore the higher prevalence of positive or weakly positive COVID-19 test results in hospitalized patients with no previous vaccination compared with vac-

cinated patients. Previous studies show that patients who received at least two doses of vaccine had decreasing trends in COVID-19 case incidence [1].

While our data on hospitalized patients cannot directly confirm this, we demonstrated that when considering hospitalization, the unvaccinated patients exhibited a significantly higher proportion of positive test results, reinforcing the understanding that vaccination boosts immune protection, and this can have an effect on severe disease.

Recent studies underlined the positive impact of hybrid vaccination for both COVID-19 booster dose and influenza vaccine to prevent and reduce the risk of pneumonia and hospitalization for both the viruses [40] and underlined the efficacy of heterologous COVID-19 vaccination to prevent severe disease and to develop a stronger immunity against the virus ever more effectively than with the homologous vaccination [41].

For both the COVID-19 and influenza viruses, booster doses are mandatory to prevent infection and maintain immunity. Obviously, it is important to develop reformulated vaccines to target new subvariants to maintain strong protection [42,43]. Our findings, in conjunction with previous studies [9,44,45], emphasize the importance of vaccination as a strategy to control the spread of COVID-19, particularly among vulnerable populations such as the elderly and those with pre-existing health conditions.

4.3. Prevalence of COVID-19 and Non-COVID-19 Pneumonia

The proportion of hospitalization due to pneumonia, including COVID-19-related pneumonia, was notably higher among unvaccinated patients (Table 1), approximately six times higher than in vaccinated ones. Although the total number of pneumonia cases was relatively small, and the incidence of pneumonia in the overall population cannot be inferred from these data, our data confirm a trend towards higher hospitalization rates for pneumonia in unvaccinated individuals. This observation is consistent with the growing body of evidence that underscores the protective effects of COVID-19 vaccination in reducing the severity of infection and preventing complications such as pneumonia, which often lead to hospitalization [3,5].

Our data show a reduction in pneumonia in vaccinated people (even with only one dose). This is probably related to vaccines' ability to enhance immune responses, thereby preventing viral replication and severe respiratory complications. An interesting point is the concept that hybrid immunity, derived from both vaccination and prior infection, may provide superior and longer-lasting protection compared with vaccine-induced immunity alone, as shown in the literature [46]. Nonetheless, the relatively small sample size of pneumonia cases in our cohort limits the ability to draw definitive conclusions, and further research with larger cohorts is necessary to better understand the relationship between vaccination status and pneumonia risk.

The interval since the last vaccination was not associated with hospitalization for COVID-19 pneumonia in our population. This finding, as depicted in Figure 3, may seem in contrast with expectations that immunity might wane over time and that a longer interval since the last dose would lead to a higher risk of developing severe disease, including pneumonia. Nonetheless, a recent meta-analysis also suggested that the temporal decline in vaccine-induced antibodies after a full COVID-19 vaccination was moderate, maintaining protection against the development of COVID-19 pneumonia over time [47].

A possible explanation is that frail individuals—despite recent vaccination—may develop COVID-19 pneumonia because of a weaker immune response associated with age, comorbidities, or individual variability. As shown in other studies, vaccine effectiveness and immunogenicity tend to be lower and decline more rapidly in older adults [10,48–51]. Cancer, HIV, and comorbidities such as diabetes, hypertension, cardiovascular disease, and obesity also contribute to reduced vaccine efficacy [50,52,53]. Moreover, emerging variants

of the virus or changes in viral characteristics over time may also contribute to the observed pneumonia outcomes, highlighting the dynamic nature of the pandemic and the challenges in maintaining vaccine efficacy against new strains.

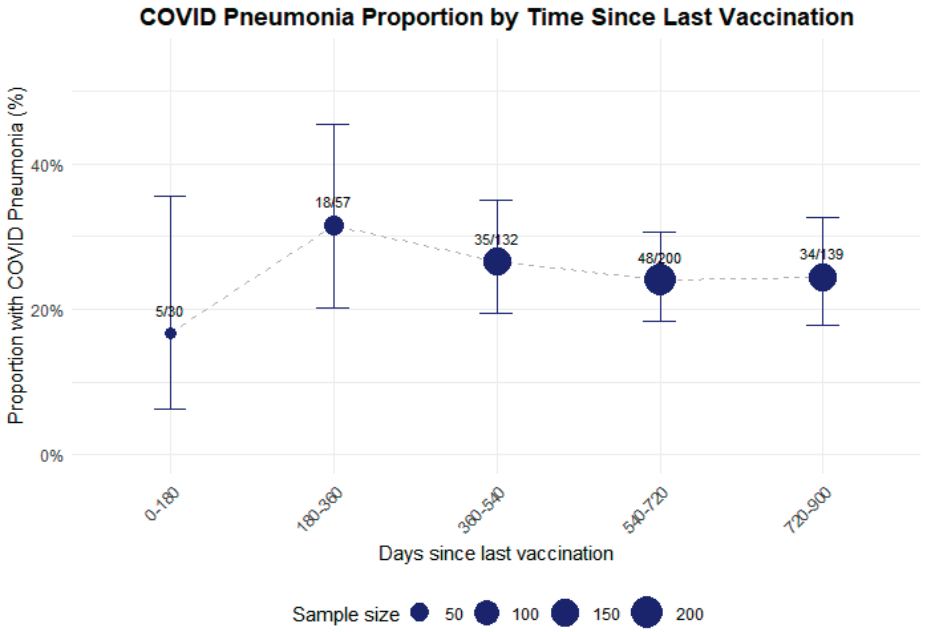

Figure 3. Proportion of patients with COVID-19 pneumonia according to vaccination timing (time since last vaccination).

In the Italian setting, people with ≥4 vaccine doses are not representative of the general ward population but of a policy-defined, exceptionally frail subgroup, as the Ministry of Health limits fourth and subsequent boosters to residents of long-term-care facilities, all adults ≥80 years, and 60–79-year-olds with major immunocompromised or other frailty conditions [54]. As a result, surveillance in November 2022 showed that—even with 65% second-booster coverage—people ≥ 80 years continued to post the highest national incidence of SARS-CoV-2 infection and hospitalization [55].

Our findings call for continued surveillance to monitor breakthrough infections and the evolving effectiveness of vaccines, especially in older adults and immunocompromised individuals.

4.4. Limitations

This study has several limitations. Despite the overall sample size being large, the distribution across categories was unbalanced, reflecting real-world prevalence. Consequently, patients with zero or more than four vaccine doses were underrepresented, which may have influenced statistical power for comparison involving these groups. We were also unable to perform multivariable regression analyses to adjust for potential confounders because of the highly unbalanced distribution of vaccination status and low event rates for certain outcomes. This limitation may affect the ability to isolate the independent effect of vaccination. Selective testing based on symptoms or risk profile may have introduced bias into the observed COVID-19 positivity rates across vaccination groups; nonetheless, this reflects the real-world scenario. Furthermore, unmeasured confounders such as frailty or prior infections may have influenced the results.

Due to the retrospective design of this study and the change in screening policy, detailed information about patients' vaccination status was not fully available for all patients, reflecting real-world practice. In fact, of the 16,034 hospitalized patients in this study period analyzed, only 5743 had complete information about vaccination status and

the number of doses. This can be related to different types of admissions. For instance, in the case of pneumonia or respiratory problems, it can be easier to find information about COVID-19 vaccinations. In other contexts, in which the cause of admission is different, such as neurologic diseases or trauma, these variables were more easily overlooked. Additionally, information on the type of vaccine administered was not available in our data, preventing vaccine-specific analysis.

5. Conclusions

In conclusion, our findings suggest that among hospitalized patients, COVID-19 vaccination is associated with a lower likelihood of emergency admission, confirmed COVID-19 diagnosis, and COVID-19 pneumonia. These results may reflect a protective role of vaccination in modifying the severity and clinical presentation of illness among those requiring hospitalization. While vaccination remains a cornerstone of public health strategies to mitigate the spread of COVID-19, the results also highlight the complexities of vaccine efficacy, particularly in high-risk populations and in the context of emerging variants.

Further research, particularly with larger sample sizes and longer follow-up periods, is needed to better understand these complex dynamics and optimize vaccination strategies to protect vulnerable populations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/microorganisms13081744/s1, Supplemental Material S1: Study flow chart; Supplementary Table S1: Percentage of positive COVID-19 swabs among vaccinated and unvaccinated patients.

Author Contributions: Conceptualization, E.A., B.L.P., A.V., A.D., M.B., S.A. and M.G.; methodology, E.A. and M.G.; validation, E.A. and M.G.; formal analysis, M.G.; investigation, B.L.P. and M.G.; resources, E.A. and B.L.P.; data curation, E.A. and M.G.; writing—original draft preparation, E.A.; writing—review and editing, E.A., B.L.P., A.D. and M.G.; supervision, E.A., A.V., M.B., S.A. and M.G.; project administration, E.A. and M.G. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CCI	Charlson Comorbidity Index
CI	Confidence interval
IQR	Interquartile ranges
SD	Standard deviation

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COVID-19 Vaccine Effectiveness and Risk Factors of Booster Failure in 480,000 Patients with Diabetes Mellitus: A Population-Based Cohort Study

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Abstract: To investigate the real-world effectiveness of COVID-19 vaccines in a large cohort of patients with diabetes mellitus (DM), we analyzed all >18-year-old patients with COVID-19 registered in a Brazilian nationwide surveillance database between February 2020 and February 2023. The primary outcome of interest was vaccine effectiveness against death, evaluated using multivariate logistic regression models. Among the 2,131,089 patients registered in the SIVEP-Gripe, 482,677 (22.6%) had DM. After adjusting for covariates, patients with DM had a higher risk of death than those without comorbidities (adjusted odds ratio [aOR] = 1.43, 95% CI, 1.39–1.47). For patients without comorbidities (72.7%, 95% CI, 70.5–74.7) and those with DM (73.4%, 95% CI, 68.2–76.7), vaccine effectiveness was similar after the booster dose. However, it was reduced in patients with DM associated with other comorbidities (60.5%; 95% CI, 57.5–63.2). The strongest factor associated with booster failure was the omicron variant (aOR = 27.8, 95% CI, 19.9–40.1). Our study revealed that COVID-19 vaccines provided robust protection against death in individuals with DM. However, our findings underscore the need to update vaccines and develop tailored strategies for individuals with diabetes, especially those with additional underlying conditions.

Keywords: COVID-19; diabetes mellitus; outcomes; vaccine; effectiveness

1. Introduction

Four years have passed since the World Health Organization (WHO) declared COVID-19 as a global pandemic on 11 March 2020. Early investigations revealed that the elderly and individuals with pre-existing chronic conditions were at significantly higher risk of severe COVID-19 illness and death due to SARS-CoV-2 infection [1–4].

Diabetes mellitus (DM) is a major public health concern affecting millions of people globally [5,6]. The COVID-19 pandemic has highlighted the vulnerability of individuals with DM, with studies reporting high rates of severe illness and mortality among this population [7–10]. A comprehensive study has shown that individuals with diabetes accounted for nearly 10% of severe cases and 17% of deaths worldwide [11]. Individuals with diabetes mellitus (DM) are at an elevated risk of severe COVID-19 owing to a confluence of factors, including immune dysfunction [12], chronic inflammation [13], and metabolic dysregulation [14]. Furthermore, DM exacerbates COVID-19-related morbidity and mortality, potentially extending the recovery duration [15,16]. Vaccines help mitigate these risks by inducing both humoral and cellular immune responses, which are essential for preventing severe disease [17]. As a result, many countries have prioritized patients with DM for COVID-19 vaccination [18]. However, research suggests that these individuals may have a weaker immune response to the vaccine than those without DM [19,20]. Furthermore, vaccine hesitancy has been observed among people with diabetes, often due to misinformation, lack of information, and mistrust [21].

Even after the pandemic control, SARS-CoV-2 may persist as an endemic seasonal pathogen for several years, evolving over time [22,23]. It remains uncertain how effective COVID-19 vaccinations have been in patients with potentially weakened immune systems due to pre-existing chronic conditions [24]. Although vaccination has been instrumental in mitigating the pandemic, real-world data on COVID-19 vaccine efficacy in people with DM remain limited [25]. The primary objective of this retrospective population-based cohort study was to investigate vaccine effectiveness (VE) against COVID-19-related death in a large group of patients with DM.

2. Materials and Methods

Data Source and Study Design. We conducted a population-based, retrospective cohort analysis, including all patients who were admitted to hospitals and registered in the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe). SIVEP-Gripe is a comprehensive national database in Brazil that tracks cases of severe acute respiratory infection (SARI) across the country [26,27]. The reporting of SARI is mandatory in Brazil and the database collects data from patients admitted to both public and private hospitals. The detailed information about the SIVEP-Gripe database, including the reporting form and data dictionary, coding, and de-identified data, is publicly available at https://opendatasus.saude.gov.br/dataset accessed on 20 February 2023. Additional information is provided in the Supplementary Materials (S1). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies [28].

Participants. The inclusion criterion was patients aged $\geq$ 18 years with laboratory-confirmed COVID-19 who were registered in the database between February 2020 and February 2023. All patients included had a positive quantitative reverse transcription polymerase chain reaction (RT-qPCR) test or antigen test results for SARS-CoV-2. The flowchart displays the complete information about the included and excluded cases (Figure 1).

Exposure of interest. The primary exposure of interest was DM. Patients with DM were identified in the SIVEP-Gripe database by retrieving data from specific fields concerning pre-existing chronic medical conditions. For analysis purposes, we divided the cohort into four groups, according to the presence of DM and other comorbidities: Group 1, patients without comorbidities; Group 2, patients with non-DM comorbidities; Group 3, patients with DM without other comorbidities; and Group 4, patients with DM associated with other comorbidities.

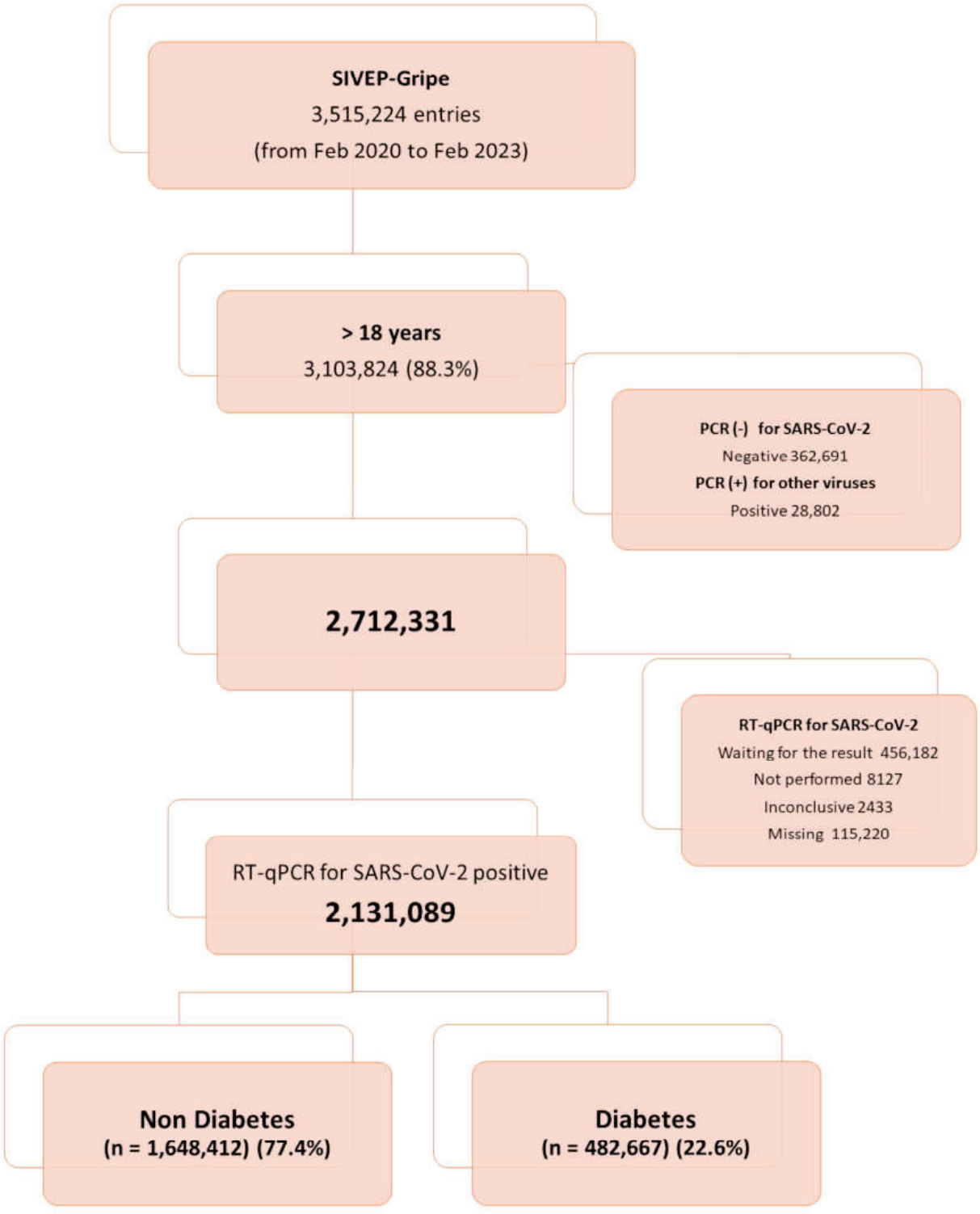

Figure 1. Flowchart of cohort selection.

Covariates. This study included a range of demographic and clinical covariates to account for potential confounding variables. Demographic data included age, sex, ethnicity, educational attainment, and geographic macro-region. Age was categorized into four strata: 19–29 years, 30–59 years, 60–79 years, and >80 years. Ethnicity data were based on the Brazilian Institute of Geography and Statistics (IBGE) classification system, encompassing White, Black, Brown, Asian, and Indigenous categories. Brazil's geopolitical macro-regions (north, northeast, central–west, southeast, and south) were included as covariates because of potential historical, social, economic, and healthcare system variations. Educational

attainment was categorized into five levels, based on the highest achieved school degree: illiterate, elementary school, middle school, high school, and college. Clinical covariates included the date of birth, symptom onset date, and admission date. Additionally, signs and symptoms at presentation (fever, cough, respiratory distress, gastrointestinal symptoms, and oxygen desaturation), nosocomial infections, and pre-existing comorbidities were documented. Oxygen saturation obtained at admission was classified as a dichotomous variable in the SIVEP-Gripe database (cut-off point of <95%). In addition to DM, the dataset provides data on other comorbidities including asthma, obesity, immune deficiencies; malignancies; and heart, lung, kidney, neurological, and hematological diseases. For analysis purposes, the presence of comorbidities was categorized into four levels based on the number of pre-existing conditions identified (none, one, two, and three or more).

Vaccination Status. Vaccination status was categorized at the time of the onset of the symptoms as unvaccinated, partially vaccinated (one dose), fully vaccinated (two doses) and boosted (three doses). In Brazil, the Ministry of Health (MS) is the only provider of COVID-19 vaccines. Four vaccine schedules of different platforms have been authorized in Brazil for the adult population: mRNA vaccine (Pfizer, BioNTech), inactivated virus vaccine (Sinovac; CoronaVac), and viral vector vaccines (ChAdOx1 nCoV-19, Astrazeneca, and Ad26.COV2.S, Johnson & Johnson's Janssen). Additional information on the Brazilian vaccination program and about the vaccination status of the individuals is provided in the Supplementary Materials (S2).

Outcomes. The primary outcome was VE against death. Additionally, this study assessed in-hospital mortality and healthcare resource utilization, including admission at intensive care unit (ICU) and the use of respiratory support among hospitalized patients. Respiratory support was categorized as none, non-invasive, and mechanical ventilation.

Statistical analysis. The analysis was performed in four steps. The first stage involved a comparative analysis of the demographic, clinical, and epidemiological characteristics of the four groups included in the analysis. Descriptive data for all eligible patients were presented as means and standard deviations, medians and interquartile ranges, or counts and proportions, as appropriate. For intergroup comparisons, Student's *t*-test and Pearson's chi-square test were used, where applicable. Second, to assess the effect of DM and other comorbidities on the survival of patients with COVID-19, we performed a binary logistic regression analysis. The model was controlled for age, sex, ethnicity, geographic macro-region, oxygen saturation at admission, nosocomial infection, epidemiological week of admission, viral strain, and number doses of vaccine. We also assessed the survival analyses by comparing the cumulative incidence function (CIF) of death among groups. Mortality was evaluated by competing risks analysis, using cumulative incidence function (CIF). Discharge was analyzed as a competing event by competing risks analysis. [29]. Third, we compared vaccine effectiveness against death conferred by the vaccines among the groups. For this analysis, we developed five models using the binary regression logistic method, including one overall model for the entire cohort and one model for each group included in the analysis. In the models, death was included as a dependent variable, and vaccination status, stratified according to the number of doses, was included as an independent variable. All models were adjusted for age, sex, ethnic group, geographic macro-regions, educational level, viral strain, and epidemiological week of admission. The results were expressed as VE (%) using the formula 100 × (1–adjusted odds ratio) and their 95% confidence intervals (CI). Finally, we evaluated potential factors associated with vaccine failure in this cohort. We defined vaccine failure as death after the patient received three doses of vaccine. For this analysis, we developed a binary regression logistic model with death as the dependent variable and clinical and epidemiological factors as the independent variables (age, sex, ethnicity, macro-regions, educational level, viral strain, and epidemiological week).

3. Results

3.1. Baseline Demographic and Clinical Characteristics

The cohort comprised 2,131,089 patients, including 482,677 patients with diabetes (22.6%). For the analysis, we divided the cohort into four groups: 911,270 (42.8%) patients without comorbidities, 737,142 (34.6%) patients with non-DM comorbidities, 381,828 (17.9%) patients with DM and other pre-existing conditions, and 100,849 (4.7%) patients with DM without associated comorbidities. The demographic and clinical characteristics of the cohort according to the four groups are shown in Table 1. In general, patients with DM were significantly older at presentation. Proportionally, patients with diabetes were more frequently from the south and southeast regions, of White ethnicity, and had a lower educational level than those without comorbidities. These patients also presented with a greater proportion of respiratory distress and oxygen saturation of <95% at baseline than patients without comorbidities. Cardiovascular disease (71.8%), hypertension (27.8%), obesity (15.7%), neurological disorders (8.6%), and kidney disorders (7.5%) were the most prevalent comorbidities.

Table 1. Demographic and clinical characteristics of hospitalized patients with laboratory-confirmed COVID-19, stratified according to the presence of diabetes mellitus (DM) and other comorbidities (*n* = 2,131,089).

Covariates [a]	**Group 1 (%) 911,270 (42.8)**	**Group 2 (%) 737,142 (34.6)**	**Group 3 (%) 100,849 (4.7)**	**Group 4 (%) 381,828 (17.9)**
Age (years)				
Median (IQR)	51.83 (40.1–65.25)	64.6 (51.66–76.91)	61.6 (51.58–71.83)	68.08 (58.83–76.91)
Mean (SD)	53.35 (17.28)	63.71 (17.1)	61.41 (14.76)	67.44 (13.23)
Age group (years)				
18–29.9	69,554 (7.6)	20,811 (2.8)	1945 (1.9)	1862 (0.5)
30–59.9	537,178 (58.9)	279,165 (37.9)	44,252 (43.9)	103,662 (27.1)
60–79.9	228,173 (25)	293,043 (39.8)	43,535 (43.2)	207,714 (54.4)
>80	76,365 (8.4)	144,123 (19.6)	11,117 (11.0)	68,590 (18.0)
Sex (*n* = 2,131,073)				
Male	533,422 (58.5)	393,956 (53.4)	56,109 (55.6)	189,280 (49.6)
Female	377,839 (41.5)	343,183 (46.6)	44,738 (44.4)	192,546 (50.4)
Region				
Southeast	433,950 (47.6)	374,041 (50.7)	50,569 (50.1)	193,660 (50.7)
South	144,818 (15.9)	138,439 (18.8)	13,710 (13.6)	66,197 (17.3)
Central-West	104,479 (11.5)	69,435 (9.4)	9303 (9.2)	32,642 (8.5)
Northeast	152,970 (16.8)	117,259 (15.9)	19,213 (19.1)	69,816 (18.3)
North	75,053 (8.2)	37,968 (5.2)	8054 (8)	19,513 (5.1)
Ethnicity (*n* = 1,739,886)				
White	363,718 (49.8)	334,908 (54.9)	41,753 (49.6)	167,992 (53.3)
Brown	323,001 (44.2)	233,366 (38.3)	36,268 (43.1)	122,952 (39.0)
Black	32,919 (4.5)	33,676 (5.5)	4671 (5.6)	19,673 (6.2)
Asian	9230 (1.3)	6910 (1.1)	1165 (1.4)	3869 (1.2)
Indigenous	2045 (0.3)	1009 (0.2)	244 (0.3)	517 (0.2)

Table 1. *Cont.*

Covariates [a]	**Group 1 (%) 911,270 (42.8)**	**Group 2 (%) 737,142 (34.6)**	**Group 3 (%) 100,849 (4.7)**	**Group 4 (%) 381,828 (17.9)**
Educational level (*n* = 754,185)				
Illiterate	14,574 (4.7)	20,962 (7.8)	2584 (7.0)	11,999 (8.7)
Elementary	63,500 (20.5)	81,871 (30.3)	11,268 (30.3)	47,969 (34.9)
Middle-School	53,693 (17.4)	51,813 (19.2)	7161 (19.3)	27,769 (20.2)
High-School	120,259 (38.9)	78,782 (29.2)	11,346 (30.5)	34,693 (25.2)
College	57,371 (18.5)	36,629 (13.6)	4793 (12.9)	15,149 (11.0)
Signs/symptoms at presentation				
Fever	525,529 (57.7)	398,280 (54.0)	56,592 (56.1)	198,376 (52.0)
Cough	625,239 (68.6)	499,164 (67.7)	71,337 (70.7)	259,120 (67.9)
Dyspnea	600,330 (65.9)	531,067 (72.0)	70,560 (70.0)	281,396 (73.7)
Odynophagia	186,518 (20.5)	112,622 (15.3)	18,360 (18.2)	56,415 (14.8)
Oxygen saturation <95% (*n* = 1,763,683)	508,688 (70.8)	490,602 (77.7)	63,647 (75.1)	263,152 (79.8)
Number of comorbidities				
None	911,270 (100)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	526,822 (71.5)	100,849 (100)	0 (0.0)
2	0 (0.0)	170,916 (23.2)	0 (0.0)	243,726 (63.8)
3	0 (0.0)	39,404 (5.3)	0 (0.0)	138,102 (36.2)
Major comorbidities				
Cardiology	0 (0.0)	408,461 (55.4)	0 (0.0)	274,329 (71.8)
Hypertension	0 (0.0)	169,165 (23.0)	0 (0.0)	106,296 (27.8)
Obesity	0 (0.0)	125,903 (17.1)	0 (0.0)	59,979 (15.7)
Neurologic	0 (0.0)	76,911 (10.4)	0 (0.0)	32,669 (8.6)
Pulmonary	0 (0.0)	62,110 (8.4)	0 (0.0)	23,492 (6.2)
Renal	0 (0.0)	41,944 (5.7)	0 (0.0)	28,498 (7.5)
Immunosuppression	0 (0.0)	37,762 (5.1)	0 (0.0)	11,088 (2.9)
Oncology	0 (0.0)	29,882 (4.1)	0 (0.0)	7130 (1.9)
Hematology	0 (0.0)	14,675 (2.0)	0 (0.0)	4737 (1.2)
Nosocomial				
No	899,664 (98.7)	718,522 (97.5)	99,327 (98.5)	372,195 (97.5)
Yes	11,606 (1.3)	18,620 (2.5)	1522 (1.5)	9633 (2.5)
SARS-CoV-2 strain				
Ancestral (predominant in 2020)	276,520 (30.3)	38,379 (38.1)	242,250 (32,9)	139,114 (36,4)
Gamma (more prevalent in 2021)	509,287 (55.9)	47,994 (47.6)	351,679 (47,7)	170,823 (44,7)
Delta (more prevalent in 2021)	45,467 (5.0)	4988 (4.9)	41,267 (5,6)	23,313 (6,1)
Omicron (predominant in 2022 and 2023)	79,996 (8.8)	9488 (9.4)	101,946 (13,8)	48,578 (12,7)
Admission Year				
2020	276,520 (30.3)	242,250 (32.9)	38,379 (38.1)	139,114 (36.4)
2021	559,932 (61.4)	397,527 (53.9)	53,695 (53.2)	196,728 (51.5)

Table 1. *Cont.*

Covariates [a]	Group 1 (%) 911,270 (42.8)	Group 2 (%) 737,142 (34.6)	Group 3 (%) 100,849 (4.7)	Group 4 (%) 381,828 (17.9)
2022/2023	74,818 (8.2)	97,365 (13.2)	8775 (8.7)	45,986 (12.0)
Vaccine doses (*n* = 1,887,890)				
None	664,759 (72.9)	490,768 (66.6)	72,370 (80.1)	251,177 (73.6)
One	38,292 (4.2)	38,930 (5.3)	5126 (5.7)	21,426 (6.3)
Two	64,008 (7.0)	81,028 (11.0)	8731 (9.7)	45,759 (13.4)
Three	32,684 (3.6)	45,788 (6.2)	4107 (4.5)	22,937 (6.7)
ICU (*n* = 1,836,099)				
No	518,821 (69.7)	386,078 (58.5)	56,054 (64.2)	185,766 (53.9)
Yes	225,110 (30.3)	274,360 (41.5)	31,235 (35.8)	158,675 (46.1)
Ventilatory support (*n* = 1,809,738)				
None	193,705 (26.5)	120,912 (18.5)	18,355 (21.3)	53,953 (15.9)
Non-invasive	426,169 (58.3)	381,401 (58.5)	50,857 (59.0)	194,575 (57.3)
Invasive	111,639 (15.3)	149,846 (23)	17,045 (19.8)	91,281 (26.9)
Mortality rate				
No	705,799 (77.5)	459,048 (62.3)	67,905 (67.3)	216,656 (56.7)
Yes	205,471 (22.5)	278,094 (37.7)	32,944 (32.7)	165,172 (43.3)

[a] Data (*n*) in the first column represent the available data for those variables with missing values. Legend: Group 1, patients without comorbidities; Group 2, patients with non-DM comorbidities; Group 3, patients with DM without other comorbidities; and Group 4, patients with DM associated with other comorbidities. For intergroup comparisons, Student's *t*-test and Pearson's chi-square test were used, where applicable. All comparisons among the groups were $p < 0.001$.

3.2. Outcomes

Regarding the overall clinical outcomes, 689,380/1,836,099 patients (37.5%) were admitted to the ICU; 1,053,002/1,809,738 (58.2%) required non-invasive oxygen support; and 369,811/1,809,738 (20.4%) required mechanical ventilation. The overall in-hospital mortality rate was 32% (681,681/2,131,089). The clinical outcomes according to group are shown in Table 1. The prevalence of DM was 27.5% among patients admitted in ICU, 29.3% in those requiring mechanical ventilation, and 29.1% among deceased patients. Patients with DM had a higher prevalence of ICU admission (44% vs. 35.6%), mechanical ventilation (25.4% vs. 18.9%), and death (41% vs. 29.3%) than those without comorbidities.

The estimated probabilities of fatal outcomes in the first 30 days of hospitalization were 30.3% and 40.7% for the non-diabetic and diabetic cohorts, respectively. The CIF of death according to the groups is shown in Figure 2. The estimated probabilities of fatal outcomes within the initial 30-day period of hospitalization were 23.6%, 33.6%, 38.3%, and 43.7% for patients without comorbidities, those with DM, those with other comorbidities excluding DM, and those with both DM and additional comorbidities, respectively.

The results of the univariate binary logistic regression analysis for the risk factors associated with mortality in the entire cohort indicated that all groups of patients with comorbidities were consistently associated with an increased risk of death compared with the groups without comorbidities (Supplementary Table S1). After adjusting for potential clinical and epidemiological confounders, all patient groups demonstrated a significantly higher risk of mortality than those without comorbidities: diabetes without other comorbidities (OR = 1.43, 95%CI, 1.39–1.47), other comorbidities without DM (OR = 1.87, 95%CI, 1.85–1.90), and DM with other comorbidities (OR = 2.18, 95%CI, 2.14–2.21) (Figure 3).

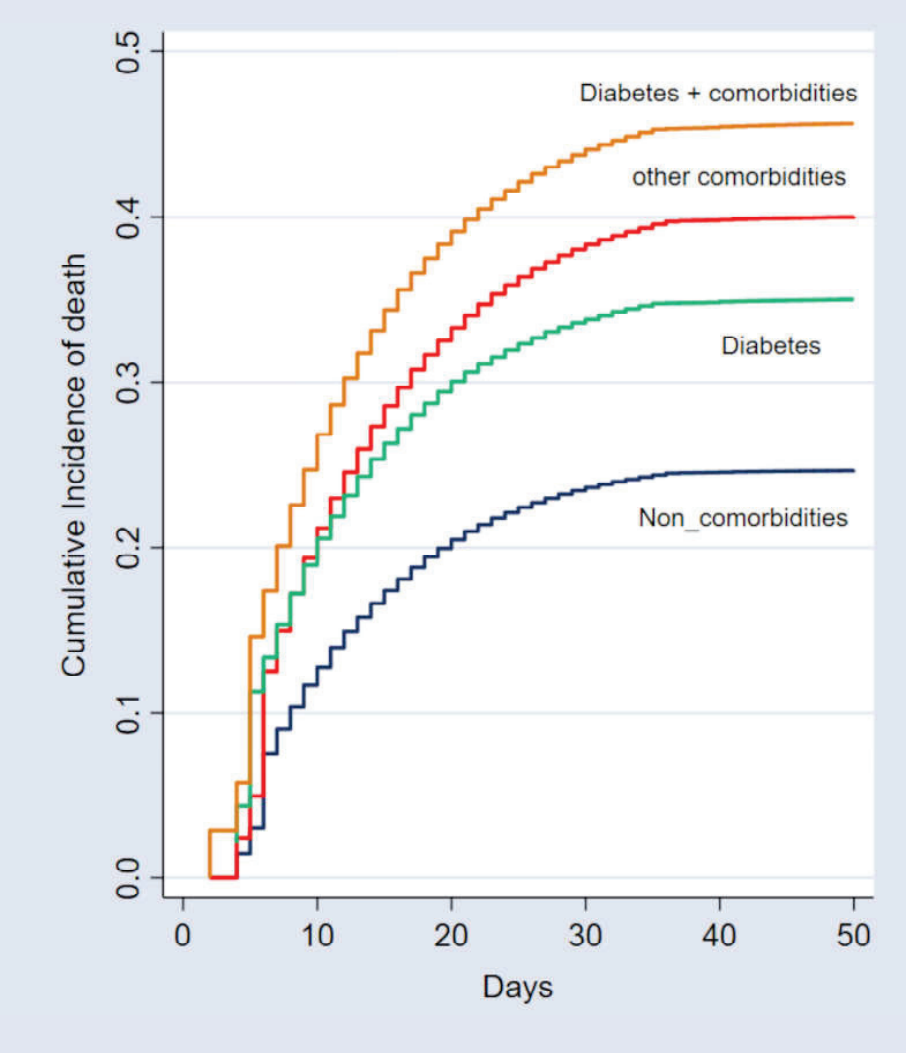

Figure 2. Cumulative incidence of death according to the presence of diabetes mellitus and comorbidities. Statistical test: competing-risk survival analysis. Reference category: individuals without comorbidities ($p < 0.001$).

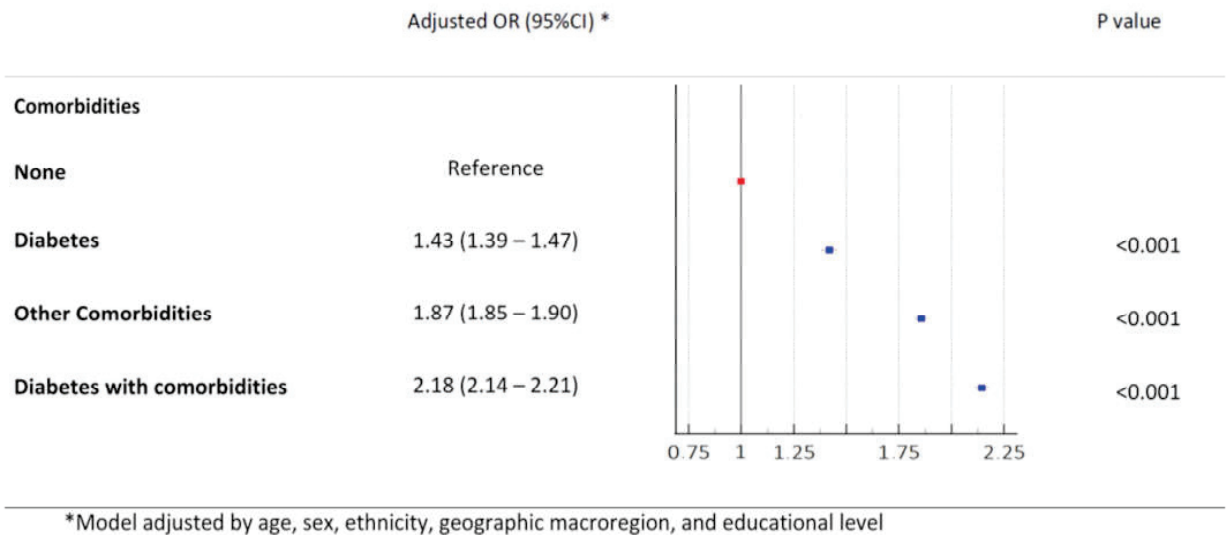

Figure 3. Adjusted odds ratio of death according to the presence diabetes mellitus and other comorbidities. Statistical test: binary logistic model. Reference category: individuals without comorbidities.

3.3. Vaccine Effectivennes

Among the 1,887,890 hospitalized patients with a known vaccination status, a significant majority (78.3%) were not fully vaccinated. This included 1,479,074 individuals who had received no doses, 103,774 who had received one dose, and 199,526 who had received two doses. Only 105,516 patients were fully vaccinated with all three doses at the time of data collection. Remarkably, 581,375 (96.1%) of the 605,164 patients who died in this cohort were not fully vaccinated. Similarly, among the 198,116 patients with DM who died, a similar proportion (96.5%) were not fully vaccinated.

Figure 4 shows the vaccine effectiveness (VE) against death for each group included in the analysis according to the number of received doses. Two or three doses of the vaccine conferred significant protection against death in all the groups. However, after the booster dose, there was a noticeable increase in vaccine protection in all the groups. Overall, VE against death was 67.2% (95% CI: 66.0–68.4) after the booster dose. Notably, after three doses, VE for patients without comorbidities (72.7%, 95%CI, 70.5–74.7) and patients with DM (73.4%, 95%CI, 68.2–76.7) were similar, with overlapping confidence intervals. Interestingly, VE against death was reduced for patients with other comorbidities (58.6%, 95%CI, 56.4–60.7) and patients with DM and other comorbidities (60.5%, 95%CI, 57.5–63.2) albeit still statistically significant. Again, there was an overlap between the confidence intervals for the former two groups.

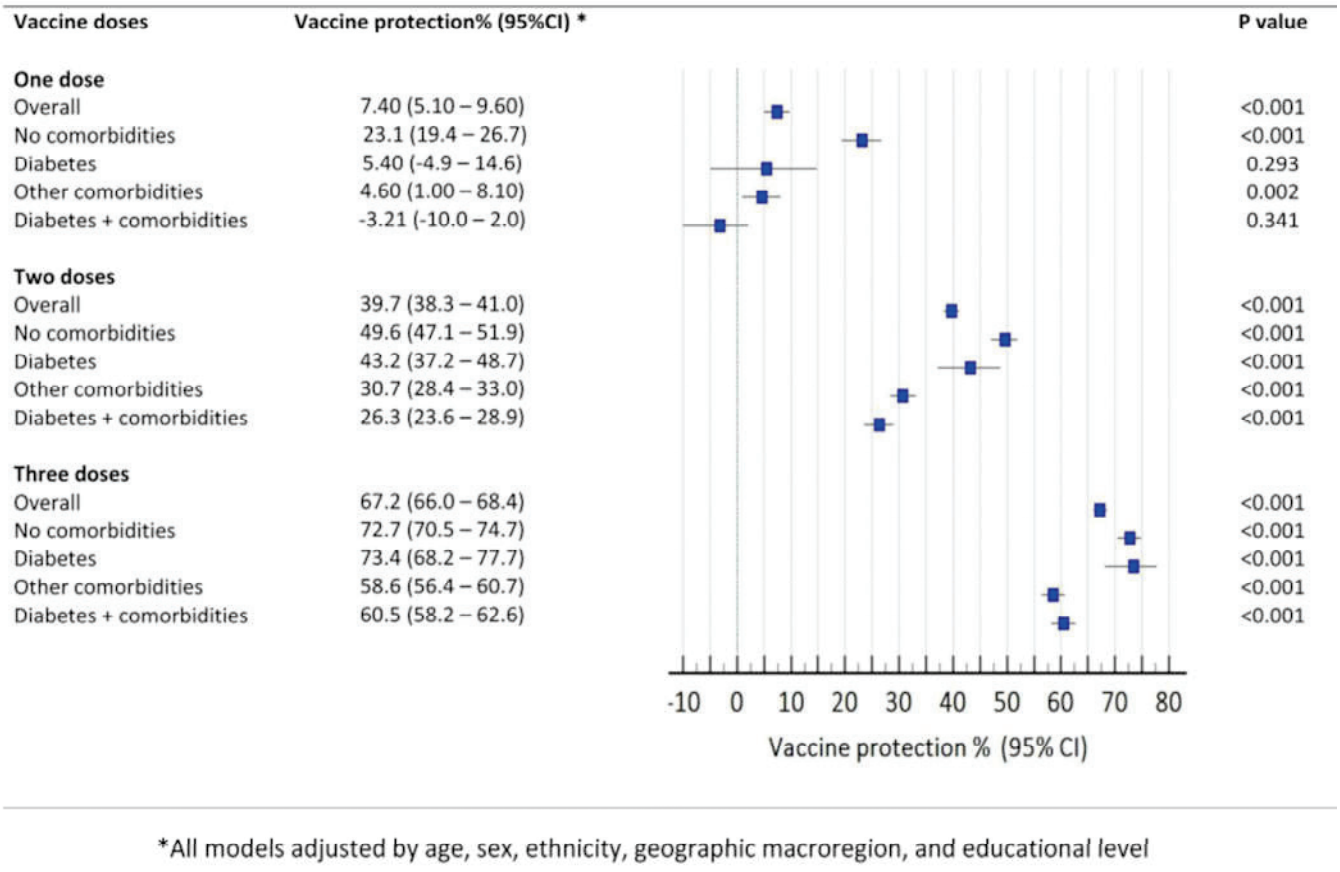

Figure 4. Effectiveness of the vaccine against COVID-19-related deaths according to the presence of diabetes mellitus and other comorbidities. Statistical test: binary logistic models. Reference category: individuals with no dose of the vaccines. All models were adjusted for age, sex, ethnicity, region, educational level, and epidemiological week of hospitalization.

3.4. Booster Failure

Among the 105,516 patients who received three doses of the vaccine, 23,789 (22.5%) had a fatal outcome. After adjustment for multivariate regression analysis, the following factors were significantly associated with booster failure in protection against death: diabetes associated with other comorbidities (but not in cases of diabetes without comorbidities), age (on an incrementally increasing gradient for older individuals), male sex, Brown or Black ethnicity, and low educational attainment (also in a stepped gradient) (Figure 5). However, the strongest factor associated with booster failure was the virus variants. Patients hospitalized during the delta (OR = 5.3, 95%CI, 3.8–7.3) and omicron (OR = 27.9, 95%CI, 16.9–45.8) waves had a remarkably increased risk of booster failure (Figure 5).

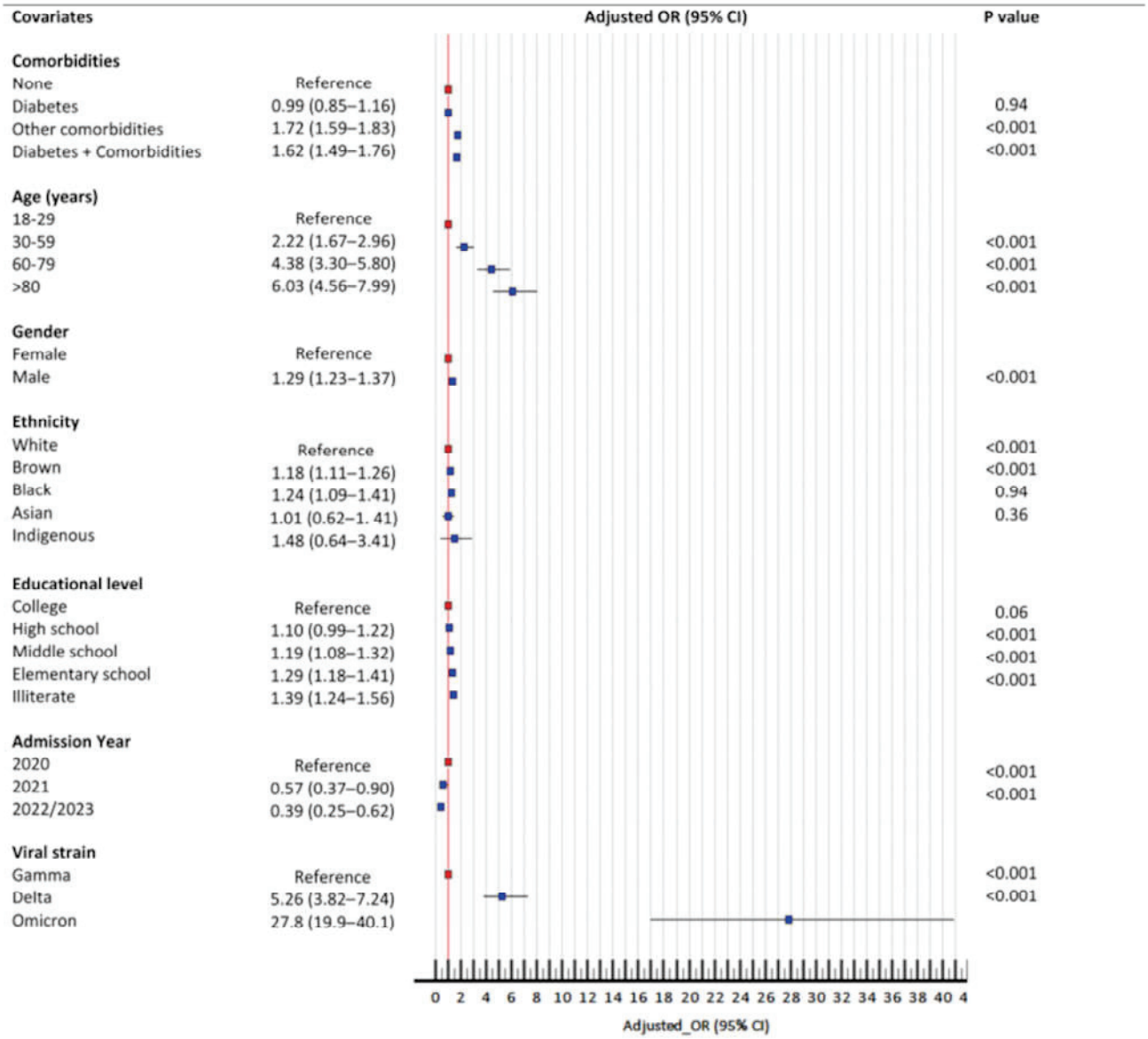

Figure 5. Risk factors of booster failure. Statistical test: binary logistic model.

4. Discussion

Key points. This large cohort study examined COVID-19 outcomes and VE in a population of patients with DM hospitalized during the three-year pandemic period in Brazil. Our findings confirmed the heightened risk of severe COVID-19 and mortality among patients

with DM compared to those without comorbidities, even after adjusting for confounders. Importantly, we observed comparable protection against death from COVID-19 conferred by the three vaccine doses in both DM patients and those without comorbidities. However, VE was reduced in patients with DM associated with additional comorbidities, although significant protection against death persisted. Notably, we observed a high rate of vaccine failure in patients hospitalized during the omicron wave.

Comparative analysis: clinical outcomes. Our findings underscore the strong association between diabetes mellitus (DM) and severe COVID-19 outcomes, consistent with previous studies [1,30–34]. This alignment is further supported by two recent large-scale meta-analyses [11,35]. In our cohort of hospitalized COVID-19 patients, the prevalence of DM was substantial (22.6%), escalating to 27.3% in ICU admissions, 29.3% in those requiring mechanical ventilation, and 29.1% among deceased patients. These findings mirror those of the recent meta-analysis by Li et al. [11], which demonstrated a progressive increase in DM prevalence with increasing COVID-19 severity. Our adjusted analysis revealed a significantly higher risk of death for patients with DM (OR 1.43, 95% CI 1.39–1.47). This risk was amplified in DM patients with other comorbidities (OR 2.18, 95% CI 2.14–2.21). These results corroborate those of a meta-analysis by Li et al. [35], reporting a pooled adjusted risk ratio of 1.43 for DM-associated mortality. In addition, Schlesinger et al. [36] highlighted worsened COVID-19 prognosis in individuals with severe DM and other comorbidities.

In the second phase of our study, we identified the risk factors for COVID-19 mortality in individuals with DM. After adjusting for potential confounders, age (in a stepped gradient), male sex, Brown, Black, and Indigenous ethnicities, patients from the northern region, pre-existing comorbidities (also in an incremental stepped gradient), low oxygen saturation at admission, and nosocomial infection were associated with increased mortality risk. Conversely, higher education and COVID-19 vaccination (two or three doses) were protective factors. Our findings align with previous research, demonstrating that age, male sex, and comorbidities are general risk factors for COVID-19 mortality in patients with DM [37–40]. The finding of an increased risk of in-hospital mortality in patients with diabetes of non-White ethnicity in our cohort is consistent with previous studies of the general adult population hospitalized with COVID-19 in Brazil [41,42]. As in many countries, ethnicity in Brazil is also strongly linked to the social determinants of health, including socioeconomic disparities, housing, education, income, and access to quality healthcare [26,43].

Comparative analysis: vaccine effectiveness. Previous research has indicated that individuals with DM may have reduced vaccine efficacy, including seasonal influenza [44,45]. Consequently, the effectiveness of COVID-19 vaccines in this population has been questioned [46]. A recent systematic review provides an overview of the COVID-19 VE in individuals with and without DM [25]. Overall, for all outcomes (infection, symptomatic illness, hospitalization, or death), VE data were numerically lower for individuals with DM than for controls, but there were several overlapping CIs [25]. Nevertheless, the included studies were severely heterogeneous, precluding meta-analysis [25]. In an assessment of COVID-19 VE against acute symptomatic SARS-CoV-2 infection in patients with comorbidities in the UK, Whitaker et al. [47] reported a VE of 43.2% (95% CI, 26.0–56.3) after the first dose and 72.9% (95% CI, 25.8–90.1) after the second dose in individuals with DM [47]. Our findings show that COVID-19 vaccination significantly reduced the mortality risk in individuals with DM, with protection increasing from 43.2% after the second dose to 73.4% after the booster. Notably, DM patients without comorbidities responded similarly to non-DM patients hospitalized with COVID-19, whereas those with additional comorbidities had a reduced but still significant vaccine benefit. Limited real-world data exist regarding COVID-19 vaccine effectiveness (VE) in patients with DM. Our results are consistent with

those of a large Hungarian study by Molnár et al. [48], which reported similar VE in DM patients and controls, with higher effectiveness in older DM patients receiving mRNA vaccines. For non-mRNA vaccines, VE was comparable to our findings (approximately 50–70%) [48].

Finally, we assessed the risk factors for booster failure among individuals who received a third dose but subsequently died of COVID-19 during hospitalization. Consistent with the general population, older age and male sex were associated with an increased risk of death after booster vaccination. Although diabetes alone was not a risk factor, it significantly increased the risk of booster failure when combined with other comorbidities (61% increase in risk). Our study revealed a heightened risk of booster failure following the emergence of SARS-CoV-2 variants, particularly during the omicron period. This aligns with previous research demonstrating decreased vaccine effectiveness owing to waning immunity and the ability of the virus to evade immune responses [49–51]. In particular, the omicron variant significantly reduced the protection provided by the primary vaccine against severe disease compared to pre-omicron strains [52]. As a result, many countries have implemented booster programs to safeguard vulnerable populations, successfully increasing protection against severe omicron disease [53,54]. Nevertheless, SARS-CoV-2 continues to evolve, with omicron sub-lineages emerging, and some studies have shown that neutralizing antibody titers declined rapidly within three months of the third dose, particularly against sub-lineages BA.2.12.1 and BA.4/5 [55]. Taken together, these findings underscore the need for continued research and adaptive vaccination strategies, especially for high-risk individuals [53,54].

Limitations and Strengths. Our study has several limitations. First, the SIVEP-Gripe dataset's limited comorbidity information, restricted to binary (yes/no) responses without detailed clinical characteristics, hinders a more comprehensive analysis. Consequently, we were unable to incorporate crucial variables, such as diabetes phenotypes and glycemic parameters, limiting our ability to thoroughly investigate the risk factors for the studied outcomes. Furthermore, it is important to acknowledge that the administrative nature of the database used in this study precludes a more detailed analysis, such as the assessment of the initial lung injury or the determination of the clinical management of patients. Second, given the focus on hospitalized patients, our findings may not be generalizable to all individuals with DM and SARS-CoV-2 infections. Third, the lack of individual-level vaccination data, including the timing between doses, vaccine types, and antibody responses, has limited our capacity to investigate important issues such as waning immunity or vaccine-specific effectiveness. Nevertheless, the strength of this study lies in its large cohort size, enabling a comprehensive examination of clinical characteristics, risk factors, outcomes, and vaccine responses among hospitalized patients with diabetes and COVID-19 in Brazil during the pandemic.

Public Health Implications and Future Directions. From a public health perspective, our findings highlight the need for targeted vaccination strategies to ensure adequate protection for individuals with DM. Additionally, strategies to promote and maintain healthy lifestyles should be prioritized at the population level, as they may help reduce the burden of COVID-19 among patients with chronic diseases [56]. Further studies exploring innovative methodologies, such as machine learning techniques, are essential to improving risk stratification and developing tailored prevention strategies at the population level [57].

5. Conclusions

In summary, our analysis of a large national database of hospitalized patients with confirmed SARS-CoV-2 infection revealed that individuals with DM experienced a more severe COVID-19 illness and a higher mortality risk than those without DM. Our study

underscores the substantial protective effect of the COVID-19 booster dose against mortality in hospitalized patients with DM. Notably, VE in DM patients without comorbidities was comparable to that in healthy individuals. However, the reduced effectiveness in patients with multiple comorbidities suggests potential biological differences in the immune response, which warrant further investigation. Furthermore, we observed a concerning rate of booster failure in preventing death among patients hospitalized during the delta and omicron waves. The emergence of viral variants appears to be the most critical determinant of vaccine effectiveness. Given the heightened risks faced by individuals with DM, targeted vaccination strategies are crucial. Additional studies are needed to establish an optimal vaccination schedule for patients with DM and to determine the role of updated vaccines in years to come.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/microorganisms13050979/s1. Table S1: Univariate analysis of risk factors of death among patients hospitalized with laboratory-proven SARS-CoV-2 symptomatic infection Supplementary Material S1: Data source information; Supplementary Material S2: Vaccination program.

Author Contributions: Conceptualization, D.R.M.; data curation, D.R.M. and E.A.O.; formal analysis, E.A.C., F.E.S.d.O. and E.A.O.; funding acquisition, D.R.M. and E.A.O.; investigation, M.C.L.O., D.R.M., A.C.S.e.S., C.S.D., L.M.D., C.C.P., S.C.G., F.N.D., L.E.C., L.G.C., M.E.T.B., H.M.-J., F.E.S.d.O., R.H.M. and E.A.O.; methodology, M.C.L.O. and E.A.O.; project administration, D.R.M. and E.A.O.; resources, D.R.M. and E.A.O.; supervision, D.R.M. and E.A.O.; validation, L.M.D., E.A.C. and E.A.O.; writing—original draft, M.C.L.O., D.R.M., A.C.S.e.S. and E.A.O.; writing—review and editing, M.C.L.O., D.R.M., A.C.S.e.S., H.M.-J., R.H.M. and E.A.O. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: We accessed the data in SIVEP-Gripe; these data were already de-identified and are publicly available. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of UNIVERSITY FEDERAL OF MINAS GERAIS (protocol code 6.127.414, date 19 June 2023).

Informed Consent Statement: We accessed data in SIVEP-Gripe; these data were already de-identified and are publicly available. Following ethically agreed principles on open data, this analysis did not require ethical approval in Brazil.

Data Availability Statement: All SIVEP-Gripe data are publicly available at the following address https://opendatasus.saude.gov.br/dataset/. Dataset accessed on 20 February 2023. Our analysis code is available upon request from the corresponding author (Eduardo A. Oliveira, eduolive812@gmail.com).

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Abbreviations

The following abbreviations are used in this manuscript:

COVID-19	Coronavirus disease 2019
DM	Diabetes mellitus
WHO	World Health Organization
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIVEP-Gripe	Influenza Epidemiological Surveillance Information System
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
aOR	Adjusted odds ratio
CI	Confidence interval

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Risk Factors for Flares and New Lesions of Hidradenitis Suppurativa Following COVID-19 Disease: A Retrospective Cohort Study of 310 Patients in Greece

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Abstract: Background: COVID-19 disease has been associated with flares or new onsets of various autoinflammatory diseases such as psoriasis and atopic dermatitis. Our aim is to investigate the occurrence and risk factors of flares or new onsets of Hidradenitis Suppurativa (HS) following COVID-19 disease. Methods: A retrospective cohort study was performed including 310 patients with HS following COVID-19 disease. Data on the rate of HS flares, new lesions, time of flare onset, and flare duration were recorded. Demographics, clinical characteristics, and treatment parameters were compared between patients with and without HS flares. Results: HS flares developed in 69 (22.2%) patients, with 14 experiencing their first episode. The median period between COVID-19 and flare onset was 17 days, with a median flare duration of 14 days. For new HS onset, the median period was 9.5 days, and the median duration was 13 days. Biologic treatment was less common in patients with flares (7.2% vs. 23.2%, $p = 0.003$), and fewer patients with flares were vaccinated (81.1% vs. 99.1%, $p < 0.001$). Multivariable analysis showed lower risk for flares in those receiving biologics (aOR = 0.14, $p = 0.002$) and those who were vaccinated (aOR = 0.02, $p < 0.001$). Conclusions: COVID-19 may trigger HS flares and new onset, with biologic treatment and vaccination offering protection.

Keywords: hidradenitis suppurativa; epidemiology; infection; autoinflammatory disorders; immunology; cytokines; virology

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was spread rapidly throughout the world in 2019–2020, resulting in the Coronavirus Disease (COVID-19) pandemic [1]. Despite being mostly a respiratory disease, SARS-CoV-2 infection has been

involved in various pathogenetic mechanisms, including a cytokine storm that has been associated with a hyperinflammatory environment in multiple organs. New onset of several autoimmune and autoinflammatory conditions has been reported following SARS-CoV-2 infection, while also exacerbation of preexisting autoinflammatory diseases was also evident in various studies [2–5].

Hidradenitis Suppurativa (HS) is a chronic inflammatory skin condition primarily affecting the apocrine gland-bearing areas of the body, such as the axillae, inguinal, and anogenital regions [6–9]. Given the immunological dysregulation seen in HS, concerns have been raised regarding the impact of COVID-19 infection in patients with HS [10,11]. Concerns about potential exacerbation of HS symptoms, adverse events, and the impact on disease activity and treatment response have been reported in the literature [12–14]. Existing evidence suggests that COVID-19 disease may affect the course of HS and lead to temporary disease exacerbation [15]. Studies investigating trigger factors for HS deterioration during the SARS-CoV-2 pandemic showed that 20% of HS patients experienced a worsening of their condition compared to before the pandemic. Interestingly, reported dietary changes during the pandemic were also associated, among other trigger factors, with HS exacerbation [16]. Moreover, persistent immune dysregulation and endothelial dysfunction after SARS-CoV-2 infection contribute to a systemic inflammatory state. This is further supported by the increased incidence of hypercoagulability and cardiovascular events in long-COVID patients [17]. Additionally, treatments widely used for severe COVID-19 infection, such as corticosteroids and remdesivir, might have influenced the course of autoinflammatory diseases [18,19]. It is true that the underlying mechanisms through which COVID-19 infection may trigger or worsen HS remain unclear, while it is crucial to differentiate between infection-related reactions and natural disease progression [20].

Moreover, there are reports that COVID-19 vaccination may also trigger HS flares or new HS-related lesions [21]. It is well established that COVID-19 vaccination activates the immune system. This is also evident from post-COVID-19 lymphadenopathy in both typical and atypical sites, as shown in many studies, reflecting an inflammatory response to vaccination [22,23]. On the other hand, the immune dysregulation associated with HS, including altered cytokine profiles and impaired immune cell function, raises concerns about the potential impact of HS on vaccine response. However, preliminary studies suggest that patients with HS can mount an adequate immune response to COVID-19 vaccination, with comparable antibody levels to the general population.

The aim of this study was to investigate the occurrence and risk factors of flares or new onsets of HS following COVID-19 disease, using real-world data.

2. Materials and Methods

A retrospective cohort study was performed from March 2020 to March 2024 at the HS outpatient clinic of our hospital. Written consent was obtained from all patients, while the study was approved by the Institutional Review Board of the "Andreas Sygros" Hospital for Venereal and Cutaneous Diseases (Reference No. 321/8-7-2024). Eligible patients were considered those who were $\geq$18 years old with a history of HS for more than one year and experienced COVID-19 disease (typical symptoms, confirmed by a positive rapid test and/or PCR). Those who developed a first episode of HS following COVID-19 disease were also included. Exclusion criteria were COVID-19 vaccination within 30 days from COVID-19 infection, frequent HS flares ($\geq$1 flare/month) during the previous 12 months, severe or critical COVID-19 disease and chronic use of corticosteroids for other reasons, such as inflammatory bowel disease or rheumatoid arthritis. HS flare was defined as an episode of a new or substantial worsening of clinical signs or symptoms occurring within 30 days after the first symptoms of COVID-19 disease. The first day of "COVID-19

disease" was defined as the day when the first symptoms of the infection developed, even though confirmation (through rapid test and/or PCR) took place on a subsequent day. New HS-related lesions within 30 days following COVID-19 disease were diagnosed by specialized physicians based on widely used criteria. All patients experiencing HS flares had a positive response to the question: "Have you ever experienced a flare related to COVID-19-disease?". Severe COVID disease was defined, according to widely used criteria, as having an SpO2 <93% on room air at sea level, a respiratory rate >30 breaths/min, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, or lung infiltrates >50%. Critical COVID-19 disease was defined as having respiratory failure, multiple organ dysfunction, or septic shock [24].

Evaluation of patients was performed using the Hurley score, the International Hidradenitis Suppurativa 4 (IHS4) score, and the Dermatology Quality of Life Index (DLQI). Moreover, patients were asked to self-evaluate the severity of their symptoms, on a scale from 1 to 10, with 10 being the worst HS flare they had ever experienced (Supplement S1). Data regarding demographics (such as age, gender, Body Mass Index [BMI]), HS scores (Hurley score, IHS4, DLQI), and type of treatment were collected and compared between patients with and without HS flares. Additional data such as time of flare/onset following COVID-19 disease and total duration of flare were also collected. Finally, patients' self-reported score, Hurley score, IHS4, and DLQI were compared before and after COVID-19 disease.

Statistical Analysis

Data were presented as means ± standard deviations (SD), medians with interquartile ranges (IQR) for quantitative parameters, or as frequencies (percentages) for qualitative parameters. The chi-square test and the two-sample Wilcoxon rank-sum (Mann–Whitney) test were employed to compare demographic and clinical characteristics between independent groups. To compare clinical parameters in patients with flares before and after COVID-19 disease, the Wilcoxon matched-pairs signed-rank test was used. Additionally, to evaluate the impact of biologic treatment and prior COVID-19 vaccination on the risk of developing HS flares, a multivariable logistic regression analysis was conducted. In this model, flare development served as the dependent variable, while gender, age, BMI, smoking status, biologic treatment, and prior COVID-19 vaccination were included as independent variables. Two-tailed *p*-values less than 0.05 were considered statistically significant. All analyses were performed using Stata 15.0 software (Stata Corp., College Station, TX, USA).

3. Results

Overall, 338 HS patients were assessed for their eligibility to be included in the study. Among them, 12 with HS flare following COVID-19 disease were excluded because they had received a COVID-19 vaccine within 30 days prior to the onset of the flare; therefore, the flare could be associated to the vaccination and not to COVID-19 disease [24]. Moreover, four patients were excluded because they suffered critical or severe COVID-19 illness, seven patients with frequent flares (≥1 flare/month), and five patients who were receiving corticosteroids on a chronic basis for other autoimmune diseases such as rheumatoid arthritis. Finally, 310 HS patients who had COVID-19 disease were included (Figure 1). In all these patients, COVID-19 disease was confirmed by a positive rapid test and/or PCR.

In the study population (n = 310), 69 patients (22.2%) had experienced HS flares after COVID-19 disease, while the majority (n = 241; 77.8%) did not have any flare. Among those patients who experienced HS flares (n = 69), there were 14 patients in whom HS was newly diagnosed. Therefore, 296 patients of our study population had been diagnosed with HS

before COVID-19 disease. Patients with and without flares had comparable distributions of age (medians: 43 vs. 45 years; $p = 0.20$), BMI (medians: 28.6 vs. 30.3 kg/m^2; $p = 0.23$), gender (males: 47.8% vs. 53.5%; $p = 0.40$), and smoking status (56.5% vs. 59.7%; $p = 0.63$) (Table 1). However, biologic treatment (anti-TNF therapy) was less common among patients with flares compared to those without (7.2% vs. 23.2%; $p = 0.003$), while also a lower percentage of patients with flares had been previously vaccinated for COVID-19 (81.1% vs. 99.1%; $p < 0.001$). Among the 61 patients who were treated with ant-TNF, 58 (95%) patients were vaccinated. Finally, patients with and without flares had comparable baseline disease scores, including the Hurley score, IHS4 score, and DLQI ($p = 0.84$, $p = 0.79$, and $p = 0.28$, respectively; Table 1).

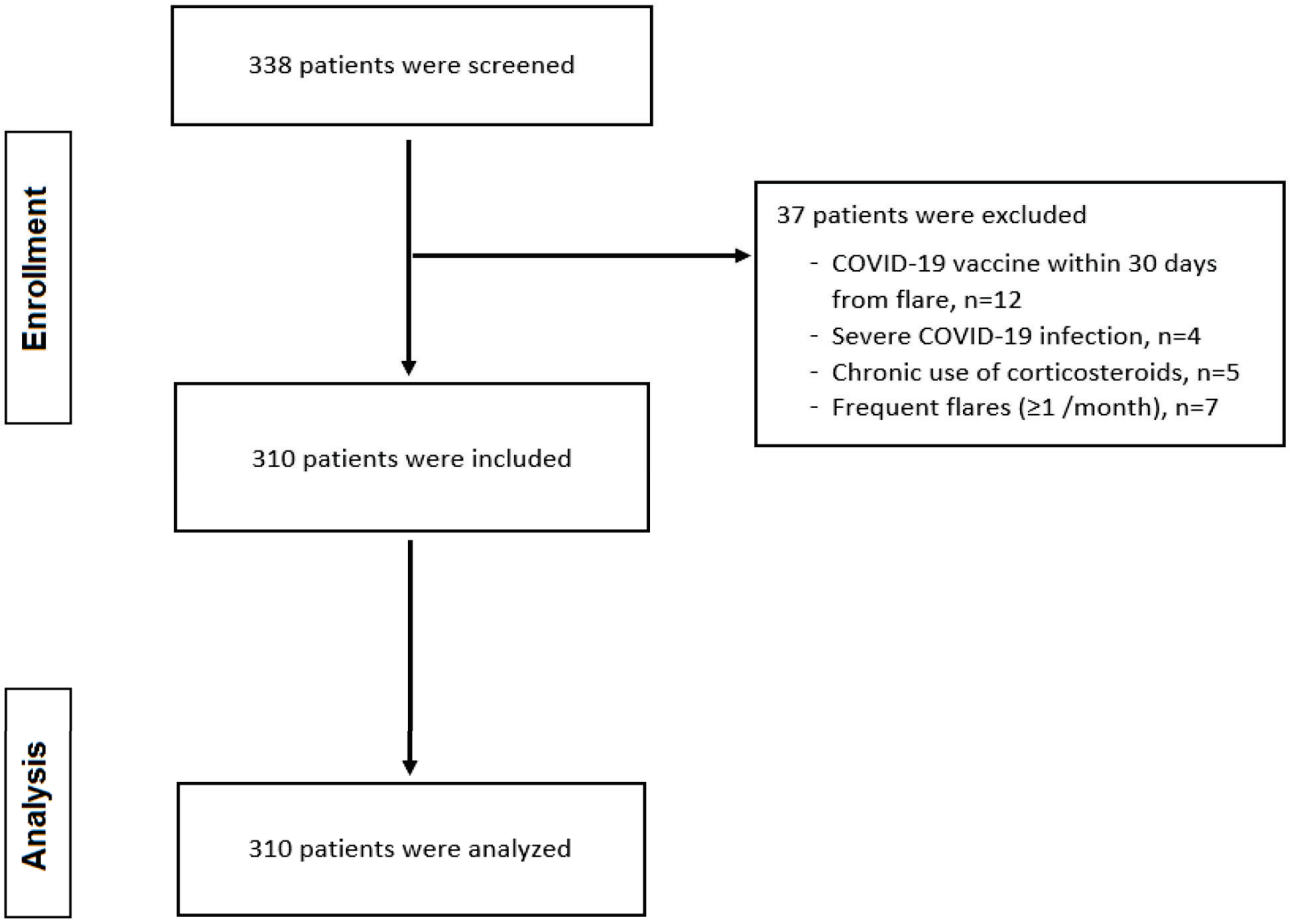

Figure 1. Flowchart of the study population.

Table 1. Characteristics of the study population (n = 310).

Parameters	Patients with Flares (n = 69)	Patients Without Flares (n = 241)	*p*–Value
Gender (male, %)	33 (47.8)	129 (53.5)	0.40
Age (years)	41.0 ± 11.6, 43.0 (31.0–49.0)	43.5 ± 12.6, 45.0 (37.0–52.0)	0.20
BMI (kg/m^2)	30.2 ± 8.0, 28.6 (23.5–35.0)	30.6 ± 6.6, 30.3 (26.1–33.6)	0.23
Smoking Status	39 (56.5)	144 (59.7)	0.63
Vaccination	56 (81.1)	239 (99.1)	**0.001**
Vaccine Type mRNA non–mRNA	 51 (73.9) 5 (7.2)	 200 (82.9) 39 (16.1)	0.16

Table 1. *Cont.*

Parameters	Patients with Flares (n = 69)	Patients Without Flares (n = 241)	*p*–Value
Baseline Hurley score			
I	15 (21.7)	54 (22.4)	0.84
II	29 (42.0)	92 (34.2)	
III	25 (36.2)	95 (35.3)	
Baseline IHS4 score	8.0 ± 7.2, 6 (3–11)	7.8 ± 6.5, 6 (3–12)	0.79
Baseline DLQI score	6.4 ± 5.0, 5 (3–9)	7.5 ± 5.8, 6 (3–11)	0.28
Biologic treatment (anti-TNF)	5 (7.2)	56 (23.2)	**0.003**

The data are presented as means ± standard deviations (SD), medians with interquartile ranges (IQR) for quantitative parameters, or as frequencies (percentages) for qualitative parameters. The Wilcoxon rank-sum and the chi-square tests were used for comparisons between the two groups. Abbreviations: BMI, Body Mass Index; DLQI, Dermatology Life Quality Index; IHS4, International Hidradenitis Suppurativa Severity Score System.

The median period between COVID-19 disease and flare onset was 17 days (Interquartile Range [IQR]: 12–21), while these flares lasted for a median period of 14 days (IQR: 13–18; Table 2). Moreover, for those patients with HS flares following COVID-19 disease, the severity of symptoms based on the subjective self-reported score increased after COVID-19 disease (medians: 7 vs. 11; $p < 0.001$), while also the DLQI and the IHS4 scores indicated worsening of symptoms following COVID-19 disease (medians: 5 vs. 14; $p < 0.001$, and 6 vs. 16; $p < 0.001$, respectively; Table 2). Finally, the stage of HS based on Hurley score was also worse following COVID-19 disease, since most patients (n = 29, 42%) were on stage II before COVID-19 disease, while after COVID-19 disease, most patients (n = 38, 55%; $p = 0.002$) were on stage III.

Table 2. Characteristics of HS patients with flares or new-onset disease following COVID-19 (n = 69).

Parameters	Before COVID-19	After COVID-19	*p*-Value
Time of onset of flare (days)	16.2 ± 5.9, 17 (12–21)		-
Duration of flares (days)	15.4 ± 4.3, 14 (13–18)		-
New locations	51 (20.4)		-
Patients' reported score	6.7 ± 1.7, 7 (6–8)	10.7 ± 1.7, 11 (10–12)	**<0.001**
Hurley score			
I	15 (21.4)	2 (2.9)	**0.002**
II	29 (42.0)	29 (42.0)	
III	25 (36.2)	38 (55.0)	
IHS4 score	8.0 ± 7.2, 6.0 (3–11)	17.4 ± 8.0, 16 (11–22)	**0.001**
DLQI score	6.4 ± 5.0, 5 (3–9)	15.8 ± 7.2, 14 (10–26)	**0.001**

The data are presented as means ± standard deviations (SD), medians with interquartile ranges (IQR) for quantitative parameters, or as frequencies (percentages) for qualitative parameters. The Wilcoxon signed-rank test was used for the comparison of scores before and after vaccination. Abbreviations: DLQI, Dermatology Life Quality Index; IHS4, International Hidradenitis Suppurativa Severity Score System.

The median time period between the COVID-19 disease and the onset of the first HS episode for the 14 patients with new HS onset was 9.5 days (IQR: 7–13 days), while the median duration of these first episodes was 13 days (IQR 11–18; Table 3).

The inverse association between biologic treatment (anti-TNF) and the risk of developing HS flares was further confirmed though the multivariable logistic regression analysis (adjusted odds ratio [aOR] = 0.14, 95% confidence interval [CI] 0.04–0.50; $p = 0.002$), indicating that biologic treatment may provide a protection against HS flares (Table 4). Similarly, prior COVID-19 vaccination was associated with a lower risk of HS flares following COVID-19 disease (aOR = 0.02, 95% CI 0.005–0.15; $p < 0.001$) (Table 4).

Table 3. Characteristics of the 14 patients with the new onset of HS disease.

Parameters	
Gender (male, %)	7 (50.0)
Age (years)	42.5 ± 14.2, 42 (30–53)
BMI (kg/m^2)	30.5 ± 7.0, 29.7 (25.1–34.1)
Smoking Status	7 (50.0)
Time of onset after disease (days)	10.0 ± 3.8, 9.5 (7–13)
Duration of first episode (days)	14.2 ± 4.9, 13 (11–18)
Vaccinated for COVID	12 (85.7)
Biologic treatment (anti-TNF)	5 (35.7)
Patients' reported score	10.2 ± 1.6, 10 (9–11.5)
Hurley score	
I	0 (0.0)
II	8 (57.1)
III	6 (42.9)
IHS4 score	14.0 ± 5.0, 13.5 (10–18)
DLQI score	10.3 ± 6.4, 9 (7–11)

The data are presented as means ± standard deviations (SD), medians with interquartile ranges (IQR) for quantitative parameters, or as frequencies (percentages) for qualitative parameters. Abbreviations: DLQI, Dermatology Life Quality Index; IHS4, International Hidradenitis Suppurativa Severity Score System.

Table 4. Multivariable logistic regression analysis: flare development served as the dependent variable, while gender, age, BMI, smoking status, biologic treatment, and prior COVID-19 vaccination were included as independent variables.

Variables	**Development of Flare**		
	aOR	**(95% CI)**	***p*-Value**
Gender (male)	0.69	(0.28–1.68)	0.42
Age (per 1-year increase)	0.99	(0.95–1.004)	0.11
BMI (per 1-unit increase)	1.01	(0.95–1.08)	0.57
Vaccination	0.02	(0.005–0.15)	**<0.001**
Biologic treatment (anti-TNF)	0.14	(0.04–0.50)	**0.002**
Smoking status	0.69	(0.34–1.39)	0.30

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

4. Discussion

There is some evidence indicating that COVID-19 infection is associated with flares of autoinflammatory diseases [12]. COVID-19 infection may cause a cytokine storm that can exacerbate diseases with inflammation-based pathophysiology. The aim of this study was to investigate the association between COVID-19 infection and exacerbations of HS. Our results indicate that COVID-19 infection may cause an HS exacerbation in almost 20% of patients. Moreover, new HS lesions were evident in some patients, suggesting that COVID-19 infection may also result in a new HS onset. The median periods between COVID-19 infection and HS flares, and between COVID-19 infection and HS new onset were 17 and 9.5 days, respectively, whereas the median durations of HS flares and first HS episodes were 14 and 13 days, respectively. Moreover, patients who were on biologic treatment (anti-TNF) for HS and those who were previously vaccinated for COVID-19 infection were less likely to develop HS flares following disease. These findings suggest

that COVID-19 vaccination and biologic treatment (anti-TNF) may have a protective role against HS flares. To our knowledge, this is the first cohort study investigating the impact of COVID-19 infection on the natural course of HS.

Our findings are in line with other studies indicating that COVID-19 infection is associated with various autoimmune diseases such as rheumatoid arthritis, immune mediated thrombocytopenia, multiple sclerosis, and vasculitis [25]. In a recent retrospective cohort study including 362 patients with psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis, 117 (32.3%) patients were affected by COVID-19 infection with 40 (34.2%) of them experiencing an inflammatory arthritis flare within one month of the infection, while 3 (7.5%) of them needed to switch to another type of therapy [26]. In our study, HS flares following COVID-19 infection were also developed within one month (median time: 17 days) after infection. In another recent study evaluating 1928 patients with rheumatoid arthritis following COVID-19 infection, it was shown that younger age, past history of tuberculosis, treatment with methotrexate, and poor global physical health were independent factors associated with disease flares in patients [27]. As opposed to the results of this study, gender, smoking, and BMI were similar between patients with or without HS flares in our study. Finally, the authors of the review article enrolling 3,335,084 individuals reported an increased incidence of inflammatory arthritis, including rheumatoid arthritis, after COVID-19 infection, with the greatest increase occurring during the first year following COVID-19 infection [28].

There are also several studies evaluating the association between flares and COVID-19 infection in patients with autoimmune skin disorders such as HS. In a recent meta-analysis including 185,000 psoriasis patients, it was found that patients who had not missed their scheduled biologic administration were experiencing milder COVID-19 symptoms. The authors of this meta-analysis reported that biologics may have a desirable effect on overcoming the hyperinflammation state caused by COVID-19 infection and recommended against withholding biologics due to COVID-19 infection [29]. Several studies enrolling large populations have also been conducted in order to assess the impact of COVID-19 infection on psoriasis course. One questionnaire-based study in the Netherlands assessed 1132 adult patients with atopic dermatitis and psoriasis and found that 26% of them experienced worsening of their condition during symptomatic infection with SARS-CoV-2 [30]. Indeed, atopic dermatitis is another inflammatory skin disease that has been reported to be affected after COVID-19 infection. In a study evaluating 21 adults with atopic dermatitis who had been infected with SARS-CoV-2, it was found that 43% of the patients experienced disease exacerbation, although it did not require systemic intervention. Moreover, patients with severe atopic dermatitis who were receiving immunosuppressive therapy had milder exacerbations [31].

The exact pathophysiology involved in the association between COVID-19 infection and flares of autoinflammatory diseases is still unknown. It has been reported that other viruses such as human papillomavirus, hepatitis B, and influenza can also contribute to the onset or worsening of autoimmune disorders through molecular mimicry. This refers to the resemblance between certain viral components and self-molecules, leading to the activation of the immune system against pathogenic antigens and the mistaken attack on similar proteins [32]. Other evidence suggests that viral-induced autoimmunity can be triggered by various mechanisms including bystander activation and immortalization of infected B cells [33]. The term "cytokine release syndrome" describes the uncontrolled secretion of pro-inflammatory cytokines induced by COVID-19 infection, mostly interleukins and tumor necrosis factor α, which disrupt human innate and acquired immune response [34,35]. Multiple autoantibodies have also been detected in patients with COVID-19 infection,

including anti-CCP antibodies (biomarkers for psoriasis/inflammatory arthritis) and anti-nuclear antibodies (biomarkers for Guillain–Barré syndrome) [34].

The management of biologic treatment in patients with COVID-19 infection has been a topic of debate, with concerns regarding the potential negative impact of biologic agents on the course of COVID-19 infection. COVID-19 infection is a multiphasic viral disease which commences with an antiviral response phase followed by a hyperinflammatory state. Many cytokines such as tumor necrosis factor-alpha (TNFa), interleukin (IL)-1, and IL-6 are related to the cytokine storm that influences the severity of COVID-19 infection [36]. The main cytokines that dominate the first (antiviral) phase differ from the cytokines which prevail during the hyperinflammatory phase [14]. Interleukin (IL)-15, interferon-α, interferon-β, and interferon-γ are the major cytokines responsible for viral clearance, whereas TNF-α, IL-17, IL-6, and granulocyte–monocyte colony stimulating factor preponderate during the hyperinflammatory phase [37,38]. Therefore, it seems reasonable not to discontinue anti-TNF-α and anti-IL-17 medications during the hyperinflammatory state of COVID-19, since these medications do not seem to affect the course of the antiviral phase. In phase 3 trials of adalimumab for HS, it was shown that there is a slightly escalated risk for total infections and nasopharyngitis by 2.5% but there was no significant difference between adalimumab and the placebo group in terms of upper respiratory tract infections [39]. The authors of a recent study showed that treatment of HS with the adalimumab does not increase the risk for COVID-19 infection [10]. This is in line with our findings, since this is the first study –to our knowledge- showing that post COVID-19 HS flares were more likely to occur in patients who were not receiving biologic agents, indicating a protective role of these medications against HS flares.

Following the launch of COVID-19 vaccination, cases of newly diagnosed autoimmune disorders had been reported, including autoimmune liver diseases, GBS, IgA nephropathy, and Hidradenitis Suppurativa, as potential side effects of COVID-19 vaccination [21,24]. It has been hypothesized that COVID-19 vaccination can activate autoimmune diseases through the production of autoantibodies (e.g., platelet factor 4 antibody-mediated platelet may lead to immune mediated thrombocytopenia). Moreover, vaccine adjuvants can enhance the immune response through activation of the NLR pyrin domain containing 3 (NLRP3) inflammasome, which is part of the innate and adaptive immune system and is linked to a range of autoimmunity. This is in line with a previous study from our group showing that COVID-19 vaccination may be associated with HS flares, since HS flares occurred in 19.2% of vaccinated patients. However, these post-vaccination flares were less severe (based on DLQI and ISH4 scores) compared to those that were observed in this study following COVID-19 infection. Moreover, another interesting finding of our study is that patients who were previously vaccinated against COVID-19 infection were less likely to develop flares. Therefore, based on these findings, COVID-19 vaccination should be strongly recommended in HS patients, not only because post-vaccination flares are less severe compared to post COVID-19 flares, but also because in the long-term, vaccination may have a protective role against future flares following COVID-19 infection.

Our study has some limitations that need to be mentioned. First, it was a single center study with no control group; therefore, comparison of flare rates between HS patients with and without COVID-19 infection could not be performed. Therefore, comparative studies with larger populations are required to validate our findings. Moreover, the relatively small number of patients poses a certain limitation, although this is the first study evaluating patients with HS flares following COVID-19 disease. Also, the definition of HS flare that was used in our study may lead to over- or under-estimation of the true incidence of HS flares due to COVID-19 infection. HS flares were defined as those that occurred within one month from the infection. However, a flare within one month could be attributed to

the natural history of the disease, while on the other hand, a flare caused by COVID-19 infection can also occur later than a month. Moreover, the questionnaire that was used to evaluate the severity of HS symptoms, although standard, has not been validated which limits its reliability. Another limitation is that the severity of the COVID-19 disease was not evaluated; therefore, an association between the severity of the infection and the risk of developing HS flares could not be investigated. Last, available data regarding other comorbidities or dermatological conditions that could also be associated with the risk of developing HS flares were not available for our study population.

The COVID-19 pandemic has raised challenges in the management of chronic autoinflammatory diseases, such as HS. Physicians should be prepared to treat disease exacerbations following COVID-19 disease, since as indicated from our findings, about one out of five patients with HS may experience a flare following COVID-19 disease. However, HS flares were more likely to develop in patients who were not vaccinated, indicating that COVID-19 vaccination should be strongly encouraged in HS patients in order to reach an increased rate of immunity against SARS-CoV-2 virus. The biologic medications should also not be discontinued during COVID-19 infection, since based on our findings, they seem to have a protective role in post-COVID-19 HS flares. Although the worst has passed with the COVID-19 pandemic, our results regarding the association between COVID-19 disease and HS flares could be the basis for further research regarding flares of autoinflammatory diseases following viral infections, while they could aid physicians to be better prepared in case of upcoming challenges for global health with new infectious pathogens.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/microorganisms13030542/s1. Supplement S1. Questionnaire distributed to patients, asking about possible exacerbation or new lesions of Hidradenitis Suppurativa, following COVID-19 disease.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

COVID-19	Coronavirus Disease 2019
HS	Hidradenitis Suppurativa
BMI	Body Mass Index;
DLQI	Dermatology Life Quality Index;
IHS4	International Hidradenitis Suppurativa Severity Score System.
aOR	Adjusted odds ratio

CI Confidence interval

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MDPI

Review

Autoimmune Skin Diseases in the Era of COVID-19: Pathophysiological Insights and Clinical Implications

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Abstract: The COVID-19 pandemic has highlighted intricate associations between SARS-CoV-2 infection and autoimmune skin diseases (ASDs). This review examines the bidirectional relationship between COVID-19 and ASDs including hidradenitis suppurativa, psoriasis, atopic dermatitis, alopecia areata, autoimmune bullous diseases, cutaneous and systemic lupus erythematosus, systemic sclerosis, dermatomyositis, and lichen planus. Current evidence indicates that SARS-CoV-2 may precipitate or worsen ASDs via mechanisms such as molecular mimicry, dysregulated cytokine signaling, and enhanced Th1/Th17 immune responses, leading to loss of self-tolerance and autoantibody production. Epidemiological studies have identified increased incidence and flares of psoriasis, hidradenitis suppurativa, and other ASDs following both COVID-19 infection and vaccination, with mRNA vaccines associated with a higher risk of flare in hidradenitis suppurativa compared with non-mRNA vaccines. Notably, severe COVID-19 is associated with a greater risk of new-onset autoimmune disease, and patients with pre-existing inflammatory skin conditions may have increased susceptibility to SARS-CoV-2 infection but experience less severe COVID-19 courses. These findings underscore the need for ongoing surveillance and mechanistic studies to clarify the immunopathogenic links between SARS-CoV-2 and ASDs and inform management strategies for affected patients in the context of both infection and vaccination.

Keywords: COVID-19; SARS-CoV-2; autoimmune skin diseases; hidradenitis suppurativa; psoriasis

1. Introduction

From the start of the outbreak, several reports appeared on the autoimmune manifestations and autoimmune sequelae of Coronavirus Disease-2019 (COVID-19) infection [1]. The COVID-19 pandemic has brought unprecedented challenges to healthcare systems globally, not only due to the acute effects of SARS-CoV-2 infection, but also because of its broader immunological consequences. Increasing evidence suggests that COVID-19 can act as a trigger or modulator of autoimmune phenomena. Autoimmune skin diseases (ASDs), including psoriasis, hidradenitis suppurativa (HS), atopic dermatitis (AD), and alopecia areata, have shown variable responses during the pandemic, ranging from disease exacerbation to new-onset presentations. Potential mechanisms include direct viral effects, molecular mimicry, dysregulated cytokine responses, and psychological stress. Moreover, the widespread use of immunomodulatory therapies and the introduction of COVID-19 vaccines have raised questions about the safety, efficacy, and impact of these interventions in patients with preexisting or newly emerging ASDs [2]. Despite the growing body of literature, the relationship between COVID-19 and ASDs remains incompletely understood. Current reports are fragmented, and the findings are sometimes conflicting, particularly regarding the bidirectional effects of infection and treatment. A comprehensive synthesis is therefore needed to clarify the clinical patterns, pathophysiological mechanisms, and therapeutic implications. This review aims to summarize the available evidence on the interplay between COVID-19 and autoimmune skin diseases, highlight emerging pathophysiologic insights, and discuss implications for clinical management and vaccination strategies.

2. Hidradenitis Suppurativa

The COVID-19 pandemic has significantly impacted the management and progression of chronic inflammatory skin diseases, notably HS. HS is a chronic inflammatory skin disorder characterized by painful nodules, abscesses, and sinus tracts, primarily affecting intertriginous areas. The pathogenesis of HS involves immune dysregulation, with elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17) [3–5].

The relationship between COVID-19 infection and HS disease activity has been a subject of investigation. Although the exact mechanisms associated between COVID-19 and flares in autoimmune skin diseases remain unclear, viral infections can exacerbate autoimmunity through molecular mimicry, bystander activation, and persistent immune dysregulation. Cytokines such as TNF-α, IL-17, and IL-23 drive inflammation in HS patients, with COVID-19 infection potentially enhancing this response through increased IL-1β production, IL-17 activation, and inflammasome activation [6–8]. COVID-19-induced cytokine release syndrome, marked by excessive interleukin and TNF-α secretion, may disrupt immune homeostasis, triggering disease exacerbation [9–12]. Moreover, limited access to healthcare services during lockdowns led to delays in diagnosis and treatment, adversely affecting disease control. Additionally, lifestyle changes such as reduced physical activity and dietary alterations contributed to weight gain, potentially exacerbating HS severity. A study highlighted that decreased physical activity during lockdowns increased the obesity rates, a known exacerbating factor for HS [13]. Another study reported that while most HS patients infected with COVID-19 experienced no change in disease activity, approximately 18.8% noted a marked increase in pain and the development of new inflammatory lesions during infection. These findings suggest that COVID-19 may exacerbate HS in a subset of patients, potentially due to the systemic inflammatory response triggered by the virus [14].

The management of biologic treatments in patients with COVID-19 has been debated due to concerns about the potential negative effects on infection progression. COVID-19 follows a biphasic course, beginning with an antiviral phase and transitioning to a

hyperinflammatory state. Cytokines like TNF-α, IL-1, and IL-6 dominate the inflammatory phase, while IL-15, interferons, and other cytokines are crucial for viral clearance. These pathways suggest that anti-TNF-α and anti-IL-17 therapies may not directly impair antiviral responses. Clinical guidance on the continuation or discontinuation of biologics should be individualized and is supported by phase 3 trials showing no increased infection risk in HS patients treated with adalimumab [15–17].

Regarding COVID-19 susceptibility, the current evidence does not indicate that HS inherently increases the risk of contracting SARS-CoV-2. However, concerns have been raised regarding whether HS itself predisposes patients to more severe COVID-19 outcomes. A retrospective study compared HS patients who contracted COVID-19 with non-HS COVID-19 patients [18]. The study found that HS patients who contracted COVID-19 were significantly more likely to experience complications (35% vs. 7%; $p = 0.001$) and require COVID-19 treatment (37% vs. 7%; $p = 0.0001$) compared with non-HS COVID-19 patients. However, it is important to note that HS patients often have comorbidities such as obesity and cardiovascular disease, which are established risk factors for severe COVID-19. Therefore, the presence of these comorbidities, rather than HS itself, may contribute to increased risk.

Although the introduction of COVID-19 vaccines has been pivotal in controlling the pandemic, there have been reports of HS exacerbations following vaccination. Recent studies have investigated the impact of COVID-19 vaccination on HS, raising questions about safety and potential disease exacerbation. In a retrospective study of 250 vaccinated HS patients, mRNA vaccines were associated with a higher risk of post-vaccination flares compared with non-mRNA vaccines [19,20]. However, as this was a single-center study with a limited sample size, the findings should be interpreted with caution and require confirmation in larger cohorts. Notably, HS patients on biologic therapy were less likely to develop flares post-vaccination, suggesting a protective role of biologics. A small case series, including reports by Martora et al. and Alexander et al., described HS exacerbations post-vaccination. However, the authors of both studies concluded that these flares did not justify contraindicating further doses [21,22]. Larger studies, such as a multicenter retrospective cohort by Pakhchanian et al., found no significant increase in vaccine-related adverse events among HS patients, even those on systemic therapy. Clinicians should monitor patients for potential flares and optimize disease management pre- and post-vaccination. Further epidemiological and mechanistic studies are needed to clarify the relationship between COVID-19 vaccination and HS [23].

While data specific to HS are limited, extrapolation from other inflammatory conditions suggests that patients on biologic therapies can mount adequate immune responses to vaccines. Consultation with healthcare providers is essential to determine the optimal timing of vaccination, especially concerning ongoing immunosuppressive treatments. Ongoing research and patient registries, such as the Global HS COVID-19 Registry, are essential in deepening our understanding and guiding management strategies for HS patients during this unprecedented time [24–26].

3. Psoriasis

Psoriasis is a chronic autoimmune skin disorder characterized by the hyperproliferation of keratinocytes and systemic inflammation. The COVID-19 pandemic has introduced complexities in managing psoriatic patients, particularly concerning the interplay between the disease, its treatments, and SARS-CoV-2 infection [27–29].

Emerging evidence suggests that COVID-19 infection may act as a triggering factor for psoriasis exacerbations, likely through the dysregulation of immune pathways implicated in the disease. The relationship between psoriasis and COVID-19 is multifaceted. In

psoriasis, the Th17-driven inflammatory response, characterized by elevated levels of IL-23, IL-17, and TNF-α, is amplified during COVID-19 infection, triggering disease flares [30–32]. Psoriasis flares in the context of COVID-19 infection are primarily attributed to the virus-induced hyperinflammatory state, commonly referred to as a "cytokine storm". COVID-19 infection leads to the excessive production of pro-inflammatory cytokines, including ILs and TNF-α, which are pivotal in the pathogenesis of psoriasis. This overproduction can disrupt the delicate immune balance, potentially triggering or exacerbating psoriatic lesions. Additionally, the binding of the SARS-CoV-2 spike protein to the ACE2 receptor results in its downregulation, leading to increased levels of angiotensin II. Elevated angiotensin II can further promote inflammation, contributing to psoriatic flare-ups. Moreover, the systemic inflammation associated with COVID-19 may amplify the availability of self-antigens through mechanisms like antigen mimicry and epitope spreading, further fueling psoriatic disease activity. Moreover, the psychological impact of the pandemic on psoriatic patients has also been significant. Stress is a well-known trigger for psoriasis exacerbations, and the global crisis has undoubtedly heightened the stress levels among individuals [29,33,34]. Several case reports have documented post-COVID-19 flares of psoriasis including guttate, pustular, and severe plaque variants [35–39]. Although current data are limited to individual case observations, these findings underscore the need for heightened clinical awareness and further investigation into the immunological interplay between COVID-19 and chronic inflammatory dermatoses such as psoriasis [39].

The management of psoriasis during the pandemic has seen varied approaches. Notably, studies reported that teledermatology services effectively managed psoriasis patients, reducing the need for face-to-face consultations and thereby minimizing potential exposure to the virus. This approach not only ensured continuity of care, but also maintained high patient satisfaction and compliance. Teledermatology emerged as an important tool for psoriasis care, ensuring the continuity of treatment and minimizing exposure risks. Studies reported high patient satisfaction, improved treatment adherence, and reduced need for in-person visits [40–43]. However, limitations included uneven access to technology and challenges in assessing subtle clinical changes remotely. In many cases, the COVID-19 pandemic led to treatment disruptions due to concerns about immunosuppression, prompting some individuals to discontinue or delay biologic therapies, potentially leading to disease flares. While initial fears prompted treatment interruptions, accumulating evidence suggests that biologics targeting IL-17 and IL-23 do not increase COVID-19 severity. Observational studies and registry data have reported no higher rates of infection or adverse outcomes among psoriasis patients receiving biologics compared with those not on systemic therapy [40]. Nonetheless, the evidence is largely derived from observational cohorts, and randomized trial data remain lacking. Therefore, many patients and clinicians opted to continue biologic therapies, given the lack of definitive evidence linking these treatments to increased COVID-19 severity. Based on the current literature, the continuation of biological therapy under medical supervision is advised, balancing the benefits of disease control against potential infection risks [40].

Early in the pandemic, concerns arose regarding the susceptibility of psoriatic patients to COVID-19, especially those on immunomodulatory therapies. However, accumulating evidence suggests that psoriasis itself does not inherently increase the risk of contracting COVID-19. Instead, comorbidities frequently associated with psoriasis, such as obesity, diabetes, and cardiovascular diseases, have been identified as significant risk factors for severe COVID-19 outcomes [27,28]. A study indicated that among psoriasis patients infected with SARS-CoV-2, 5.8% required hospitalization, and 23.6% experienced psoriasis exacerbation due to the infection [29].

Vaccination against COVID-19 has been a pivotal strategy in controlling the pandemic. For psoriatic patients, concerns regarding vaccine efficacy and potential disease flares post-vaccination have been prevalent. Current evidence indicates that mRNA COVID-19 vaccines are safe for individuals with psoriasis including those on immunomodulatory therapies [44].

The psychological impact of the pandemic on psoriatic patients has also been significant. Stress is a well-known trigger for psoriasis exacerbations, and the global crisis has undoubtedly heightened stress levels among individuals. A study conducted in Denmark highlighted that individual with psoriasis experienced worsened mental well-being during the pandemic compared with healthy individuals, underscoring the need for holistic patient care that addresses both physical and psychological health [45].

4. Atopic Dermatitis

The relationship between COVID-19 infection and AD remains complex. AD is a chronic inflammatory condition resulting from a combination of skin barrier dysfunction and immune dysregulation. Two main theories explain its pathogenesis: the "outside-in" hypothesis, which suggests that environmental allergens initiate the disease by weakening the skin barrier and promoting IgE sensitization, and the "inside-out" hypothesis, which proposes that genetic factors—most notably mutations in the filaggrin (FLG) gene—lead to impaired barrier function and subsequent immune activation. During the COVID-19 pandemic, AD flares have been reported more frequently, likely due to enhanced type 2 cytokine activity (IL-4, IL-13, IL-31), increased psychological stress, and repetitive hand hygiene practices that further compromise the skin. Exacerbations may be managed with topical corticosteroids, while systemic treatments such as JAK inhibitors are considered for more severe or persistent disease [46,47]. Skin biopsies from AD patients also show a predominance of Th2-derived cytokines including IL-4 and IL-13, implicated in pathogenesis [48]. The Th2/Th1 imbalance observed in AD, which promotes IgE-mediated hypersensitivity, may be disrupted by COVID-19 infection, leading to AD exacerbations [49,50]. In an investigation conducted in the Netherlands, 26% of the participants with AD reported a deterioration in symptoms during active COVID-19 infection [51]. Another study revealed that 43% of AD patients experienced disease flare-ups post-COVID-19, with many requiring treatment adjustments. Interestingly, exacerbation in patients receiving immunosuppressives was less pronounced, possibly due to the protective benefits of these drugs against virus-induced inflammatory cascades [47,52–55]. Epidemiological evidence further supports a potential link between COVID-19 and new-onset AD. A retrospective study reported that individuals with a history of SARS-CoV-2 infection had a 33% higher likelihood of developing AD compared with matched controls [54]. However, this study relied on registry data and lacked long-term follow-up, so the findings should be interpreted with caution.

In conclusion, COVID-19 may exacerbate AD through several interrelated mechanisms, including heightened type 2 cytokine activity (IL-4, IL-13, IL-31), skin barrier impairment from repetitive hand hygiene practices, and increased psychological stress, all of which converge to disrupt immune homeostasis and promote disease flares.

5. Alopecia Areata

Recent research has explored the link between COVID-19 and alopecia areata (AA), revealing that the virus may act as a catalyst for the onset or exacerbation of the condition. The exact mechanisms linking COVID-19 to AA remain under investigation. The current mechanism of AA is not clear. From a biological perspective, SARS-CoV-2 infection may exacerbate or trigger AA through IFN-mediated antiviral responses that disrupt hair follicle

immune privilege, upregulate MHC class I expression, and activate pro-inflammatory cytokines such as IL-6 [56]. In parallel, psychological stress, which was pervasive during the pandemic, may act as an additional aggravating factor. Stress is known to influence immune responses and exacerbate autoimmune conditions and therefore may contribute independently or synergistically to AA flares during the COVID-19 era [57,58]. The systemic inflammatory response caused by the virus could also provide a potential and plausible explanation [59].

COVID-19 has been shown to affect AA recurrence, as higher relapse rates (44%) were noted among those who contracted SARS-CoV-2 compared with the control group (12%) [60]. Other data support that individuals developed AA 1 to 2 months after infection from COVID-19, suggesting an association between infection and disease emergence [61]. Epidemiological studies also support this association. For instance, large-scale research in South Korea found an increased incidence of AA among individuals who had recovered from COVID-19 [58]. Another large retrospective cohort highlighted that this correlation of disease incidence was also tightly interconnected to the severity of COVID-19 [62,63]. While these findings are compelling, the relationship between COVID-19 and AA remains complex, and for the most part unknown. It is important to note that the majority of available evidence consists of case reports and retrospective cohorts, which may be subject to publication bias. While emerging data suggest a possible link between COVID-19 and AA, this relationship remains complex and is not yet fully elucidated. Larger, prospective studies are needed to disentangle the biological effects of SARS-CoV-2 infection from psychological stressors and to minimize the influence of publication bias inherent in early reports. Unraveling this connection in the post-COVID-19 era, when our information and understanding of both entities increases, could significantly improve the management of AA in patients affected by COVID-19. The delineation of the relationship between COVID-19 and AA could provide insights into how viral infections impact autoimmune diseases.

6. Autoimmune Bullous Diseases

Autoimmune bullous diseases (AIBDs), such as pemphigus vulgaris and bullous pemphigoid, arise when autoantibodies target structural proteins in the skin, leading to blister formation. Emerging data suggest that SARS-CoV-2 infection can trigger or worsen AIBDs through immune dysregulation: viral-induced cytokine release and molecular mimicry between viral peptides and skin antigens—as evidenced by shared epitope sequences with bullous pemphigoid—may provoke autoantibody production [64]. Several case reports have reported that in patients with pre-existing pemphigus or bullous pemphigoid, the onset of COVID-19 has been associated with flare-ups or new cases [61,65]. The immune system's heightened inflammatory response during COVID-19 infection may contribute to the worsening of these conditions, as it can potentially activate autoimmune mechanisms, leading to the breakdown of skin structures that result in antigen shedding, immune activation, and ultimately blister formation and manifestation of the clinical entities of autoimmune bullous disease of the skin [66]. In addition to the above, the use of corticosteroids and other immunosuppressive medications (e.g., CD20-directed agents) commonly prescribed to manage severe pemphigus, and bullous pemphigoid may further complicate the management of COVID-19 infection [67]. B-cell depletion and subsequent humoral immunity impairment make patients highly susceptible to a broad range of infections, including COVID-19, and possibly influence the severity of the disease course [68]. Current expert guidance suggests that abrupt discontinuation of immunosuppressive therapy in patients with AIBDs should generally be avoided, as uncontrolled disease activity may itself increase morbidity. Instead, therapy should be tailored individually: patients on systemic corticosteroids may require careful dose adjustments, while those on B-cell–depleting

agents such as rituximab should be closely monitored, with the consideration of delaying treatment in stable disease during active SARS-CoV-2 infection [68]. This has been documented in clinical evidence supporting that patients on long-term immunosuppressive therapy for autoimmune blistering diseases may experience more severe COVID-19 infection [69]. It should be noted that the majority of current evidence derives from case reports and small retrospective studies, which are inherently subject to publication bias and limited generalizability. As a result, the association between COVID-19 and AIBDs should be interpreted with caution until supported by larger prospective studies.

7. Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) encompasses autoimmune skin disorders that can be influenced by various environmental factors including viral infections. Emerging evidence suggests a correlation between SARS-CoV-2 infection and the onset or exacerbation of CLE [70]. Although SARS-CoV-2 has been associated with the induction of autoantibodies such as ANA, lupus anticoagulant, and anti-Ro/SSA in some reports, these findings remain preliminary and do not establish a direct pathogenic link to lupus or systemic sclerosis. The proposed mechanisms should therefore be interpreted as speculative hypotheses rather than confirmed pathways [71,72].

A few case reports have described an association between COVID-19 and CLE. A 67-year-old woman with pre-existing CLE developed a Rowell syndrome-like flare approximately two weeks after contracting SARS-CoV-2 [73]. Another case report presented a patient with a rare variant of CLE, namely lupus panniculitis, as the primary manifestation of SLE stimulated by COVID-19 infection [74]. Although the clinical relevance of this evidence remains limited, the association between LE and COVID-19 is expected to be further delineated as our knowledge and experience with the virus expands. Overall, while case reports suggest a possible association between COVID-19 and lupus manifestations, the evidence remains anecdotal, and mechanistic explanations are speculative. More robust studies are needed to determine whether SARS-CoV-2 acts as a true disease trigger or whether the observed associations reflect coincidental findings.

8. Systemic Sclerosis

There have been reports of new-onset SSc following COVID-19 infection. SS, defined by progressive fibrosis and vascular dysfunction, parallels COVID-19-related endothelial injury and hyperinflammation [75,76]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could thus accelerate fibrotic processes, contributing to worsened outcomes in SSc patients [77]. Interestingly, a case report described a female patient who developed systemic sclerosis after COVID-19 infection, highlighting the potential for SARS-CoV-2 to trigger autoimmune responses leading to SSc development. Additionally, the SARS-CoV-2 spike protein has been found to accelerate systemic sclerosis by promoting fibrosis through the upregulation of pathways involved in inflammatory responses and autoantibody formation and secretion [78]. A major SSc complication is interstitial lung disease (ILD). Therefore, ILD could potentially predispose SSc patients to severe COVID-19 infection associated with poor outcomes [78]. Additionally, considering the concomitant use of immunosuppressive therapies in severe SSc, the risk could increase even more [75]. COVID-19 can cause severe pneumonia with radiological features of interstitial fibrosis, similar to ILD secondary to SSc, thereby complicating the clinical scenario by presenting a unique challenge in differential diagnosis between the two [79].

9. Dermatomyositis

Dermatomyositis (DM) is a systemic autoimmune disease characterized by skin manifestations and proximal muscle weakness, with COVID-19 increasingly reported as a potential trigger for both new-onset disease and flares of pre-existing DM. Evidence remains limited and largely anecdotal. For example, single case reports describe new-onset DM following SARS-CoV-2 infection and flare-ups in young patients after even mild COVID-19 illness [80,81]. While these reports suggest a possible association, the reliance on case-based data limits generalizability and may be influenced by publication bias.

Mechanistically, autoantibodies play a central role. Notably, *anti-melanoma differentiation-associated gene 5* (MDA5) antibodies, which are linked to severe forms of DM with interstitial lung disease, have also been associated with worse COVID-19 outcomes and increased mortality [82]. The management of DM during the COVID-19 pandemic requires balancing immunosuppression with infection risk. Data suggest that maintaining disease control is critical, as uncontrolled DM poses greater risks than potential viral complications. Corticosteroids should be used at the lowest effective dose, and steroid-sparing immunosuppressive agents (e.g., methotrexate, azathioprine, mycophenolate mofetil) may be considered [83]. B-cell depleting therapies and high-dose corticosteroids should be used with caution, particularly in patients at high risk for severe COVID-19. Vaccination and preventive measures remain essential adjuncts to care [83]. Further research is needed to provide more insights into the optimal management strategies for DM patients amidst the pandemic.

10. Lichen Planus

Lichen planus (LP) is a group of chronic inflammatory diseases that mainly affect middle-aged adults. While LP primarily includes skin and oral mucosa, other mucous membranes and skin appendages, such as nails and hair, can also be damaged [83–87]. LP is increasingly considered a T cell-mediated autoimmune condition in which cytotoxic CD8+ T cells induce basal keratinocyte apoptosis, producing the characteristic interface dermatitis [88–90]. Although the exact etiology remains unclear, both infectious triggers (e.g., herpes simplex, varicella zoster, HPV-16) and immune dysregulation have been implicated [90–92]. However, the precise relationship between viruses and LP remains an area of ongoing research.

In the context of COVID-19, several overlapping immunological pathways may contribute to LP pathogenesis. SARS-CoV-2 infection stimulates robust Th1 and Th17 immune responses and cytotoxic CD8+ T-cell activity, all of which can promote keratinocyte apoptosis, a hallmark of LP [93–98]. Molecular mimicry between SARS-CoV-2 antigens and epidermal self-antigens may further drive autoimmune cytotoxicity [92,99,100]. Additionally, ACE2 receptors expressed in keratinocytes and oral mucosal cells provide a potential portal for viral interaction, amplifying local inflammation [101–103]. Together, these mechanisms suggest that SARS-CoV-2 infection could act as a trigger for LP in genetically or immunologically predisposed individuals, though definitive causal links remain unproven. Another hypothesis is that molecular mimicry is responsible for triggering the autoimmune cytotoxic T cell (CTL) and Th1 responses that mediate LP in COVID-19 infection [92,100]. The SARS-CoV-2 antigen has demonstrated cross-reactivity with multiple endogenous human antigens including those found on the basal keratinocytes of the epidermis. Another important consideration is that the role of ACE2 receptors for host cell entry may be implicated, as these receptors are abundant in cells of the skin and oral mucosa. The binding of the SARS-CoV-2 spike protein to ACE2 receptors on epidermal cells may trigger Th1 recruitment and the subsequent autoimmune cascade responsible for LP pathogenesis in infection with SARS-CoV-2 [101–103].

Clinically, sporadic reports describe both new-onset and exacerbations of LP after COVID-19 infection [96]. Interestingly, more cases have been documented following COVID-19 vaccination, though these remain rare and are primarily limited to case reports and small series [97]. Given the scale of the global vaccination efforts, the absolute risk appears extremely low, and causality has not been established. Current evidence therefore does not alter existing vaccination recommendations, which remain strongly favorable for patients with chronic inflammatory diseases.

Finally, there are concerns that immunocompromising comorbidities, including hypertension, diabetes and vitamin D deficiency, are risk factors that may increase susceptibility to LP after COVID-19 infection. Diabetes and hypertension have been identified as risk factors for oral LP development and COVID-19 mortality, and vitamin D has been found to modulate Th1 cells and regulate *T*-cell-mediated immune activity [99]. However, further systematic studies are required to disentangle these associations from coincidental findings. The findings of autoimmune and chronic inflammatory skin diseases affected by COVID-19 infection are summarized in Table 1 and Figure 1.

Table 1. Autoimmune and chronic inflammatory skin diseases affected by COVID-19 infection.

Disease	Impact of COVID-19 Infection	Proposed Mechanisms	Notes
Psoriasis	New onset and exacerbation reported	IL-17, IL-23, TNF-a axis dysregulation; stress-induced immune dysregulation, ACE2 mediated inflammation	Exacerbations more common with prior history; may be influenced by treatments
Hidradenitis Suppurativa	Exacerbation common	IL-17, IL-23, TNF-a axis dysregulation, stress, cytokine storm	Disease flares may be related to COVID-induced cytokine storm
Atopic Dermatitis	New onset and flare-ups	Th2 dominance; impaired skin barrier, psychological stress	Severe flares reported in previously well-controlled cases
Alopecia Areata	New onset or exacerbation	Systemic inflammation, immune dysregulation, psychological stress	Onset often 1–2 months post-infection; relapse rate higher than controls
Pemphigus and Bullous Pemphigoid	Flare-ups or new onset	Hyperinflammatory immune activation, autoantigen exposure	Immunosuppressants may increase infection risk/severity
Cutaneous Lupus Erythematosus	Exacerbation or rare new onset	Viral-triggered immune activation	Limited to case reports
Systemic Sclerosis	New onset; possible ILD worsening	Spike-protein-induced fibrosis; autoantibody activation	ILD may mask or worsen COVID-related respiratory symptoms
Dermatomyositis	Disease onset and exacerbation	Autoimmune cascade activation	Flare-ups also after mild cases
Lichen Planus	Sporadic new onset	CD8+ T-cell activation, Th17 involvement, molecular mimicry	Vitamin D deficiency, HTN, diabetes may be co-factors

Abbreviations: HTN, hypertension, ILD, interstitial lung disease, IL, interleukin, TNF, tumor necrosis factor, ACE, angiotensin-converting enzyme.

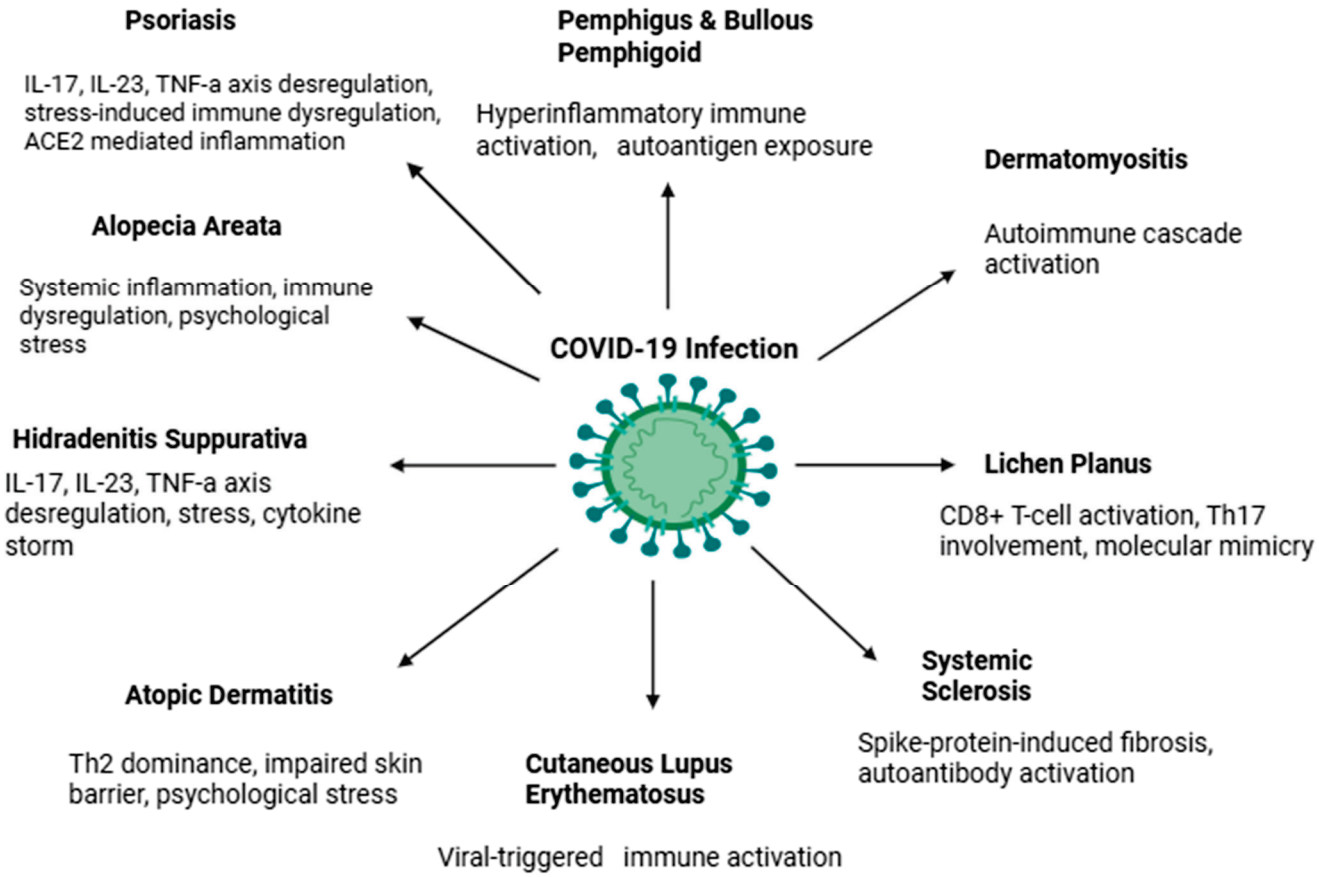

Figure 1. Potential mechanisms linking COVID-19 infection with the development or exacerbation of dermatologic autoimmune and inflammatory skin diseases.

11. COVID-19 and Vaccines

Emerging reports indicate cutaneous adverse events associated with COVID-19 vaccination including new-onset conditions and exacerbations of pre-existing dermatoses [104]. Both mRNA and adenoviral vector SARS-CoV-2 vaccines activate innate immune sensors through intrinsic adjuvant activity, leading to the production of IFNs and pro-inflammatory cytokines [105]. Adenoviral vectors activate Toll-like receptors (TLRs) 2 and 9, inducing cytokine expression through macrophage activation in the liver and spleen, while also eliciting robust CD4+ Th1 and humoral immune responses. In contrast, mRNA vaccines activate inflammation through TLRs 3, 7, and 8, with lipid nanoparticles (LNPs) exhibiting immunostimulatory properties even in the absence of mRNA cargo [106]. Essentially, both vaccine platforms predominantly induce a Th1-skewed immune response, characterized by the increased production of TNF-α, IFN-γ, and IL-2. In this context, this Th1-dominant environment necessitates the awareness of potential flares in immune-mediated skin conditions and connective tissue diseases, where Th1-mediated mechanisms are implicated in pathogenesis [107].

Additionally, the incidence of de novo or relapsing autoimmune skin diseases appears higher following mRNA-based vaccines, potentially due to their elevated immunogenicity compared with viral vector and inactivated vaccines [108]. In patients with hidradenitis suppurativa, a recent study has shown that those who received mRNA vaccines were 3.5 times as likely to develop flares following vaccination compared with patients who received non-mRNA vaccines, indicating that mRNA COVID-19 vaccines could be associated with hidradenitis suppurativa flares [109]. Moreover, a study by Jęśkowi-ak-Kossakowska et al. suggests that adenoviral vector vaccines may present fewer adverse effects, possibly due to the organism's faster adaptation to this technology [110]. On the other hand,

inactivated viral vaccines, while weaker inducers of CD8+ T cell responses compared with mRNA and adenoviral vector vaccines, may therefore present a lower theoretical risk of triggering Th1-driven autoimmunity. Indeed, observational data suggest that inactivated vaccines are generally well-tolerated in patients with autoimmune and chronic inflammatory conditions. However, their immunogenicity is influenced by the choice of adjuvant, and large-scale comparative data in dermatologic autoimmune diseases remain scarce. This underscores the need for future studies to clarify their precise safety and efficacy profile in this population [111].

Finally, a study by Sprow et al. found that most patients with autoimmune skin diseases effectively tolerated the COVID-19 vaccine. Although 14.8% of fully vaccinated participants reported exacerbations of autoimmune symptoms after vaccination, only 6.7% required an escalation in treatment, indicating that the overall safety and tolerability of the COVID-19 vaccine in this population remain high, despite the presence of underlying autoimmune conditions [108]. Importantly, despite reports of cutaneous flares, the overall safety and tolerability of COVID-19 vaccines in patients with autoimmune skin diseases remain high, as the vast majority of individuals tolerated vaccination without clinically significant worsening of disease activity. These findings are summarized in Table 2.

Table 2. Autoimmune skin diseases and COVID-19 vaccination.

Vaccine Platform	Mechanism of Immune Activation	Dominant Cytokines/Immune Responses	Cutaneous Adverse Events	Autoimmune Flare Risk
mRNA Vaccines	Activation of TLRs 3, 7, 8 via mRNA Intrinsic adjuvanticity of lipid nanoparticles Type I IFN production	Th1 polarization: ↑ TNF-α, ↑ IFN-γ, ↑ IL-2 Robust CD8+ T-cell activation	Higher prevalence of psoriasis, lichen planus, lupus flares Localized erythema	Elevated due to Th1 skewing Strong immunogenicity linked to higher autoimmune risk
Adenoviral Vector Vaccines	TLRs 2, 9 activation Macrophage activation in liver/spleen Stimulation of CD4+ Th1 and antibody production	Th1-dominant: ↑ TNF-α, ↑ IFN-γ, ↑ IL-2 Moderate CD8+ T-cell activation	Lower CAE incidence Dermatitis, mild urticaria	Reduced due to faster immune adaptation Milder flares compared to mRNA vaccines
Inactivated Virus Vaccines	Weak innate activation via adjuvants Dependent on antigen formulation	Limited Th1 polarization Weak CD8+ T-cell activation	Minimal CAEs Mild transient rashes	Lower risk due to weaker immune activation Rare autoimmune flare cases

Abbreviations: ASD, autoimmune skin diseases, TNF-α, tumor necrosis factor-a, IFN, interferon, TLR, Toll-like receptors, CAE, cutaneous adverse events. ↑, increase

12. Conclusions

Cutaneous manifestations of COVID-19 represent a heterogeneous spectrum, and their prognostic significance depends on the specific type of lesion rather than their mere presence. Early recognition of characteristic skin findings can enable dermatologists to contribute to timely COVID-19 diagnosis, particularly in patients with mild or asymptomatic infection. At present, the impact of pre-existing autoimmune skin diseases on COVID-19 severity and mortality remains uncertain, underscoring the importance of long-term monitoring to detect potential disease exacerbations or the development of new autoimmune connective tissue disorders. Vaccination with non-living platforms, including mRNA vaccines, is generally safe and effective in reducing severe outcomes, though a minority of patients may experience disease flares or new-onset autoimmune conditions. This highlights the need for individualized vaccination planning and close follow-up in patients with autoimmune skin diseases. Importantly, the lessons learned from the impact of COVID-19 on autoimmune skin disorders can serve as a framework for anticipating and

mitigating similar complications in future pandemics. Strengthening surveillance systems, fostering multidisciplinary collaboration, and ensuring early dermatologic recognition may reduce morbidity and improve outcomes in comparable global health crises.

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