

Predictive Profiling of Post-Booster Reactogenicity: Identifying Factors Associated with Adverse Events Following COVID-19 Vaccination

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Abstract

COVID-19 booster vaccination remains central to protecting older adults against severe disease; however, the occurrence and severity of post-booster adverse events vary considerably between individuals. This prospective observational cohort study evaluated factors associated with post-booster reactogenicity among adults aged ≥ 60 years receiving a COVID-19 booster dose. Local and systemic adverse events were recorded using a structured follow-up form and combined into a composite adverse-event score as the primary outcome. Candidate predictors, including age, sex, previous COVID-19 infection, previous significant vaccine reaction, booster-dose interval, diabetes mellitus, and hypertension, were evaluated using univariable analysis and multivariable linear regression. Independent predictors were incorporated into a simplified point-based score, and model performance was assessed by internal validation. Among 500 enrolled participants, 472 (94.4%) completed follow-up. Injection-site pain was the most frequently reported adverse event (60.6%), followed by fatigue (51.1%) and headache (41.9%). Female sex, previous COVID-19 infection, previous significant vaccine reaction, and a shorter booster-dose interval (< 6 months) were independently associated with higher adverse-event scores. Previous significant vaccine reaction showed the strongest association ($\beta = 0.68$; standardized $\beta = 0.25$), whereas age, diabetes mellitus, and hypertension were not independent predictors. The multivariable model explained 34% of the variance in adverse-event scores (RMSE = 1.12), with 31% explained on internal validation (RMSE = 1.18). A simplified 0–5 point score classified participants into low-, moderate-, and high-risk categories, with mean predicted scores of 1.2, 2.8, and 4.3, respectively. These findings indicate that sex, previous infection, prior vaccine-reaction history, and booster-dose interval are associated with individual differences in post-booster reactogenicity among older adults. Although the proposed score may support individualized counselling and post-vaccination monitoring, it should be considered exploratory and requires external validation in larger, independent cohorts before clinical application.

1. INTRODUCTION

COVID-19 vaccines have been deployed worldwide to reduce the risk of severe disease, hospitalisation and death from SARS-CoV-2 infection. The emergence of new viral variants

and the waning of immunity in the months after the primary series have made booster doses necessary to sustain protection, particularly in older adults and people with underlying health

conditions [1, 2]. Booster vaccination has consequently become an integral part of long-term COVID-19 prevention. Booster doses are generally well tolerated, but adverse events following immunisation (AEFIs), notably injection-site pain, fatigue, headache, myalgia, fever and malaise, continue to be reported frequently [3, 4].

The incidence and severity of these events differ considerably between individuals. This variation has been attributed, in part, to demographic characteristics, previous SARS-CoV-2 infection, vaccination history, comorbidities and differences in immune responsiveness [3–5]. Age is one such characteristic: older adults have been reported to show reactogenicity profiles different from those of younger people [2, 5]. Prior infection or earlier mRNA vaccine doses may also modify the immune response and, with it, reactogenicity [4, 7]. Understanding these differences matters for vaccine counselling, clinical monitoring and personalised risk communication.

Most COVID-19 vaccine safety studies have reported the frequency, incidence or severity of individual adverse events [3, 4, 6]. Such analyses are valuable, but they do not capture each person's overall experience after vaccination, since one individual may have several mild symptoms while another has a single severe one. A composite measure of adverse-event burden, analysed as a continuous outcome, offers a complementary view and allows the factors associated with higher or lower burden to be quantified directly.

Predictive modelling provides a formal way of turning individual clinical and epidemiological characteristics into an estimate of expected

adverse-event burden. Both statistical and machine-learning approaches have been used to detect and categorise adverse effects of COVID-19 vaccines [6, 7]. A valid prediction model could help identify people likely to experience a greater burden after a booster and so support tailored counselling and follow-up. This is especially relevant in older populations, in whom prior infection, vaccination history and immune senescence may each contribute to between-person differences in reactogenicity [2, 4, 5].

Although the safety profile of COVID-19 vaccines is well documented, prediction of post-booster adverse-event burden has received far less attention. Few studies have developed and internally validated a practical tool that combines several demographic, clinical and vaccination-related variables to estimate the overall reactogenicity of a booster dose [3, 4, 6]. Addressing this gap may improve understanding of the drivers of heterogeneous responses to vaccination and provide a clinically intuitive framework for risk stratification.

We therefore conducted a prospective cohort study in adults aged ≥ 60 years to (i) describe the frequency of local and systemic adverse events after a COVID-19 booster; (ii) identify demographic, clinical, infection-related and vaccination-related factors independently associated with a composite adverse-event score; and (iii) derive and internally validate a simplified point-based score for stratifying older adults by expected post-booster adverse-event burden.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This was an open-label, prospective observational cohort study of adults aged ≥ 60 years who received a COVID-19 booster vaccine. Participants were recruited before or at the time of booster vaccination and followed prospectively over a predefined post-vaccination observation period [8, 11]. The study aimed to evaluate demographic, clinical, infection-related and vaccination-related factors associated with post-booster adverse-event burden and to develop an exploratory prediction model. Model development, validation and reporting followed contemporary recommendations for clinical prediction models [20–22].

2.2 Study Population

Eligible participants were adults aged ≥ 60 years who were due to receive a COVID-19 booster dose. Inclusion criteria were: (i) completion of the recommended primary COVID-19 vaccine series; (ii) receipt of a booster dose during the study period; (iii) written informed consent; and (iv) willingness to complete follow-up assessments according to the schedule.

Individuals were excluded if they had incomplete vaccination records; an acute illness at enrolment that could interfere with the assessment of post-vaccination symptoms (for example, symptomatic SARS-CoV-2 infection); or if they were unable to complete the required follow-up or withdrew consent. Participants who did not complete follow-up were excluded from the analysis (complete-case analysis).

2.3 Sample size and recruitment

Five hundred older adults were screened against the inclusion and exclusion criteria and enrolled. The sample size was planned according to the anticipated prevalence of the main risk factors, the expected effect size of each predictor, the

number of candidate predictors and the requirements for developing and internally validating a multivariable prediction model [9, 10]. Seven candidate predictors were considered, giving approximately 67 analysed participants per candidate predictor (472/7). All participants were informed of the study objectives and procedures and gave written informed consent before enrolment.

2.4 Data collection and variables

Baseline information was collected with a structured case-record form from participant interviews, clinical records and vaccination documents where available. Previous COVID-19 infection and previous vaccine reactions were recorded as participant-reported history, supplemented by medical or vaccination records where possible. The following variables were recorded:

- **Demographic:** age and sex.
- **Clinical:** history of previous COVID-19 infection, diabetes mellitus, hypertension and other relevant comorbidities where available.
- **Vaccination-related:** number of previous COVID-19 vaccine doses (≥ 2 required), history of a significant reaction to a previous COVID-19 vaccine dose, and the interval between the last previous dose and the booster dose (categorised as < 6 months or ≥ 6 months).

The booster product was Covaxin (BBV152). Participants were assessed at predefined follow-up intervals (1, 3, 6 and 12 months) for the occurrence and severity of solicited local and systemic adverse events, consistent with

standard reactogenicity outcomes for COVID-19 vaccines [12–14, 24].

2.5 Outcome assessment

Local adverse events were injection-site pain, swelling and redness. Systemic adverse events were fatigue, headache, myalgia, fever, chills, arthralgia and nausea. A participant could report more than one event, and each event was recorded individually together with its severity according to predefined criteria. These domains correspond to those used in COVID-19 vaccine reactogenicity studies and systematic reviews [12–14, 24].

The primary outcome was a composite post-booster adverse-event score obtained by aggregating the individual event responses. Higher scores indicate a greater adverse-event burden. The composite score was summarized as mean $\pm$ standard deviation (SD), and was used for all subsequent statistical and predictive analyses

2.6 Statistical analysis

2.6.1 Descriptive analysis. The frequency of each adverse event was expressed as n (%), using the 472 participants who completed follow-up as the denominator. Because participants could report several events, percentages are calculated independently and do not sum to 100%. Frequencies are presented in a table and in a horizontal bar chart in descending order.

2.6.2 Comparison of scores

The composite score was compared by sex, previous COVID-19 infection (yes/no), previous significant vaccine reaction (yes/no), age group

(60–65, 66–70 and >70 or ≥ 71] years) and booster-dose interval (<6 vs ≥ 6 months). Two-group and three-group comparisons used the independent-samples t-test and one-way ANOVA, respectively, with appropriate non-parametric alternatives when parametric assumptions were not met. These exploratory comparisons preceded regression modelling.

2.6.3 Univariable analysis

Univariable linear regression was used to examine the association of the composite score with age, sex, previous SARS-CoV-2 infection, previous significant vaccine reaction, short booster-dose interval, diabetes mellitus and hypertension. For each variable we report the β coefficient, 95% confidence interval (CI) and p-value. Variables with $p < 0.05$ or clinical relevance were considered for the multivariable model.

2.6.4 Multivariable analysis

Because the outcome was a continuous composite score, multivariable linear regression was used to identify independent predictors after adjustment for the other variables. The model included age, sex, previous COVID-19 infection, previous significant vaccine reaction, booster-dose interval, diabetes mellitus and hypertension. We report β , standard error (SE), standardized β and p-values; $p < 0.05$ (two-sided) was considered statistically significant. Reporting follows the TRIPOD+AI recommendations, which cover regression-based clinical prediction models [8, 11, 20–22].

2.6.5 Model assumptions

Linearity, independence of observations, normality and homoscedasticity of residuals and multicollinearity were checked before the results

were interpreted. Multicollinearity was assessed with the variance inflation factor (VIF) and tolerance, and linearity, normality, homoscedasticity and overall model adequacy with residual and diagnostic plots. Checking assumptions and predictive performance is important to limit model instability and overfitting [18].

2.7 Construction of the prediction score and relative importance of predictors

A simplified point-based score was derived from the independent predictors in the multivariable model. Points were allocated in proportion to the size of the regression coefficients and summed to give a total score, with higher totals indicating a greater predicted adverse-event burden. Participants were then grouped into low-, moderate- and high-risk categories using predetermined score ranges. Because the modelled outcome is a continuous burden score, these categories describe predicted adverse-event burden and not the probability of a binary clinical event.

Standardized β coefficients are unitless, so they were compared by absolute magnitude to rank the independent predictors by their relative association with the outcome. Results are presented in a table and a horizontal bar chart (Figure 4).

2.8 Model performance and internal validation

Performance was assessed with R^2 , adjusted R^2 , root mean square error (RMSE) and mean

absolute error (MAE). R^2 is the proportion of outcome variance explained by the model (reported as a percentage of explained variability), adjusted R^2 accounts for the number of predictors, and RMSE and MAE measure prediction error, with lower values indicating better accuracy. Calibration was evaluated by comparing observed and predicted scores across the range of predictions. Internal validation used bootstrap resampling (10,000 resamples) to estimate optimism and the stability of the performance estimates [8–10, 18]. Performance in the development and validation datasets was compared as an indicator of overfitting, and the estimates are given in Table 6.

Agreement between observed and predicted scores was assessed graphically with a scatter plot and a 45° reference line indicating perfect agreement. Clustering of points around this line indicates good agreement. This graphical assessment complemented the quantitative measures of R^2 , RMSE, MAE and calibration [8, 20–22].

2.9 Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Human Ethics Committee of The Assam Royal Global University (Approval No. RGU/IEC/2026/006, dated 08/04/2026). Written informed consent was obtained from all participants before inclusion. Each participant was assigned a unique study code, personal identifiers were kept secure, and data were used only for research and analysed in coded or anonymised form.

3. Results

3.1 Participant flow and baseline characteristics

Of the 500 participants aged ≥ 60 years who were recruited, 28 did not complete the predefined

follow-up, leaving 472 (94.4%) for analysis (**Figure 1**). This high retention provided a sufficient sample for evaluating post-booster adverse events and their determinants.

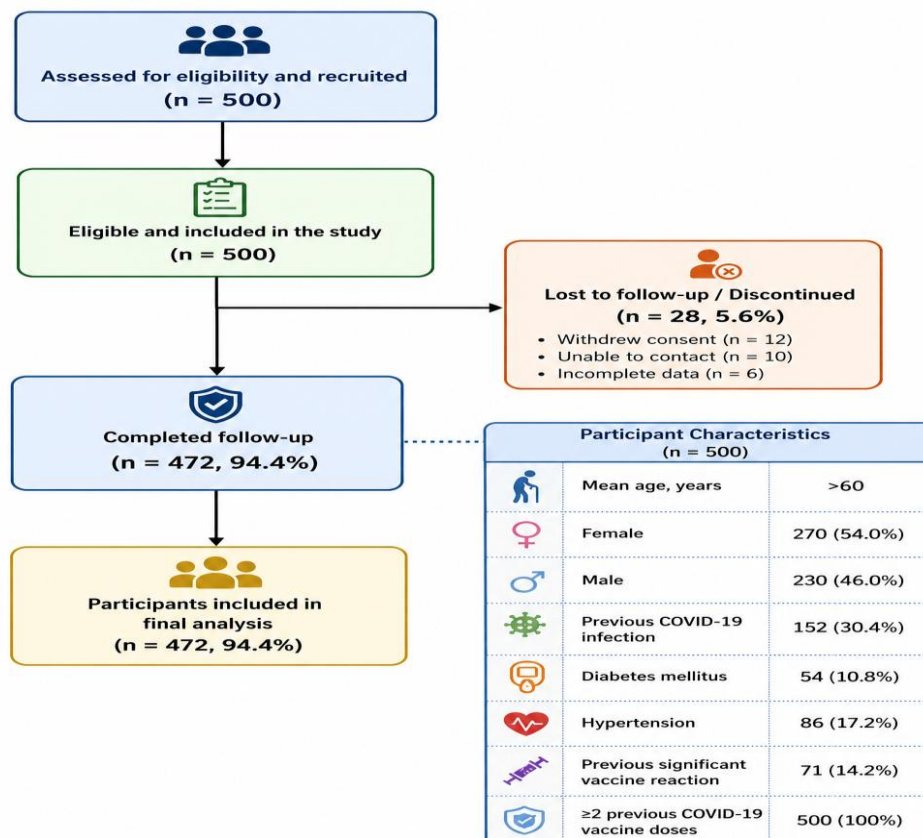


Figure 1. Participant recruitment and follow-up flow diagram

The cohort comprised 270 women (54.0%) and 230 men (46.0%). A previous COVID-19 infection was reported by 152 participants (30.4%), diabetes mellitus by 54 (10.8%), hypertension by 86 (17.2%) and a previous significant vaccine reaction by 71 (14.2%). All participants (100%) had received at least two

previous COVID-19 vaccine doses, as required for inclusion. Baseline characteristics are summarised in **Table 1**. The spread of these characteristics made it possible to examine their association with post-booster adverse-event burden in the regression analyses that follow.

Table 1. Baseline demographic and clinical characteristics

Variable	Participants, n (%)
Total recruited	500

Completed follow-up	472 (94.4)
Mean age, years	>60
Female	270 (54.0)
Male	230 (46.0)
Previous COVID-19 infection	152 (30.4)
Diabetes mellitus	54 (10.8)
Hypertension	86 (17.2)
Previous significant vaccine reaction	71 (14.2)
≥2 previous COVID-19 vaccine doses	500 (100)

3.2 Frequency of post-booster adverse events

Table 2 and **Figure 2** show the frequency of adverse events among the 472 participants who completed follow-up. Injection-site pain was the most common event ($n = 286$; 60.6%), followed by fatigue ($n = 241$; 51.1%) and headache ($n = 198$; 41.9%). Among the remaining systemic events, myalgia occurred in 176 participants (37.3%), fever in 128 (27.1%), chills in 96 (20.3%), arthralgia in 84 (17.8%) and nausea in 62 (13.1%). Local swelling ($n = 58$; 12.3%) and

redness ($n = 43$; 9.1%) were less frequent than local pain.

Overall, local pain and common systemic symptoms such as fatigue and headache accounted for most post-booster adverse events. These descriptive findings provide the basis for examining whether demographic characteristics, infection history, vaccine-reaction history, dose interval and comorbidities are associated with differences in overall adverse-event burden.

Table 2. Frequency of post-booster adverse events among participants completing follow-up ($n = 472$)

Adverse event	n	Percentage (%)
Injection-site pain	286	60.6
Fatigue	241	51.1
Headache	198	41.9
Myalgia	176	37.3
Fever	128	27.1
Chills	96	20.3
Arthralgia	84	17.8
Nausea	62	13.1
Injection-site swelling	58	12.3
Injection-site redness	43	9.1

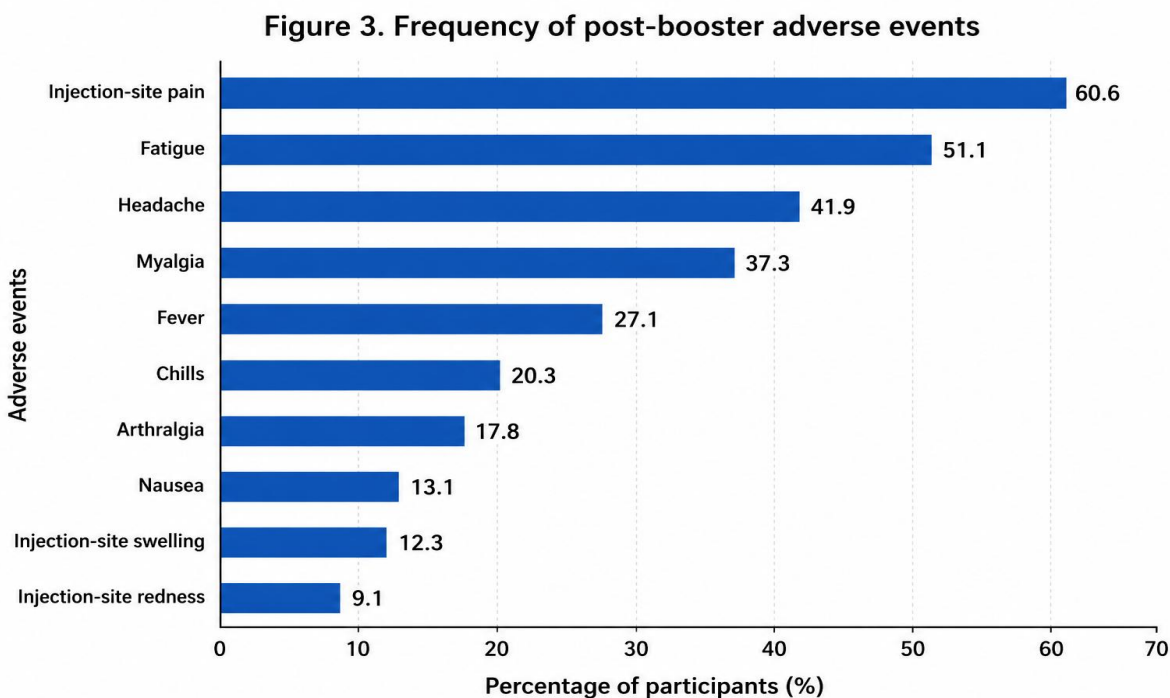


Figure 2. Frequency of post-booster adverse events (horizontal bars, descending order; n = 472).

3.3 Composite adverse-event score by risk factor

Mean composite scores differed across subgroups (**Table 3; Figure 3**). Women scored higher than men (4.01 ± 1.18 vs 3.42 ± 1.01 ; $p = 0.002$), as did participants with a previous COVID-19 infection compared with those without (4.02 ± 1.21 vs 3.51 ± 1.04 ; $p = 0.008$). The largest difference was seen for previous vaccine reaction: scores were higher in participants with a previous significant reaction than in those without (4.35 ± 1.28 vs 3.49 ± 1.03 ; $p < 0.001$), a difference of 0.86 points.

Scores also rose across age groups, from 3.62 ± 1.08 at 60–65 years to 3.88 ± 1.12 at 66–70

years and 4.16 ± 1.19 in the oldest group ($p < 0.001$). Participants who received the booster less than 6 months after their previous dose scored higher than those with an interval of ≥ 6 months (4.02 ± 1.20 vs 3.58 ± 1.05 ; $p = 0.015$). Because previous vaccine reaction showed the largest difference in mean score, it emerged as a leading candidate predictor for the regression analysis

Table 3. Comparison of composite adverse-event scores according to selected risk factors

Risk factor	Group	Mean outcome score $\pm$ SD	p-value
Sex	Male	3.42 ± 1.01	0.002
	Female	4.01 ± 1.18	

Previous COVID-19 infection	No	3.51 ± 1.04	0.008
	Yes	4.02 ± 1.21	
Previous vaccine reaction	No	3.49 ± 1.03	<0.001
	Yes	4.35 ± 1.28	
Age	60–65 years	3.62 ± 1.08	<0.001
	66–70 years	3.88 ± 1.12	
	≥ 70 years	4.16 ± 1.19	
Booster-dose interval	<6 months	4.02 ± 1.20	0.015
	≥ 6 months	3.58 ± 1.05	

Outcome variability according to major risk factors

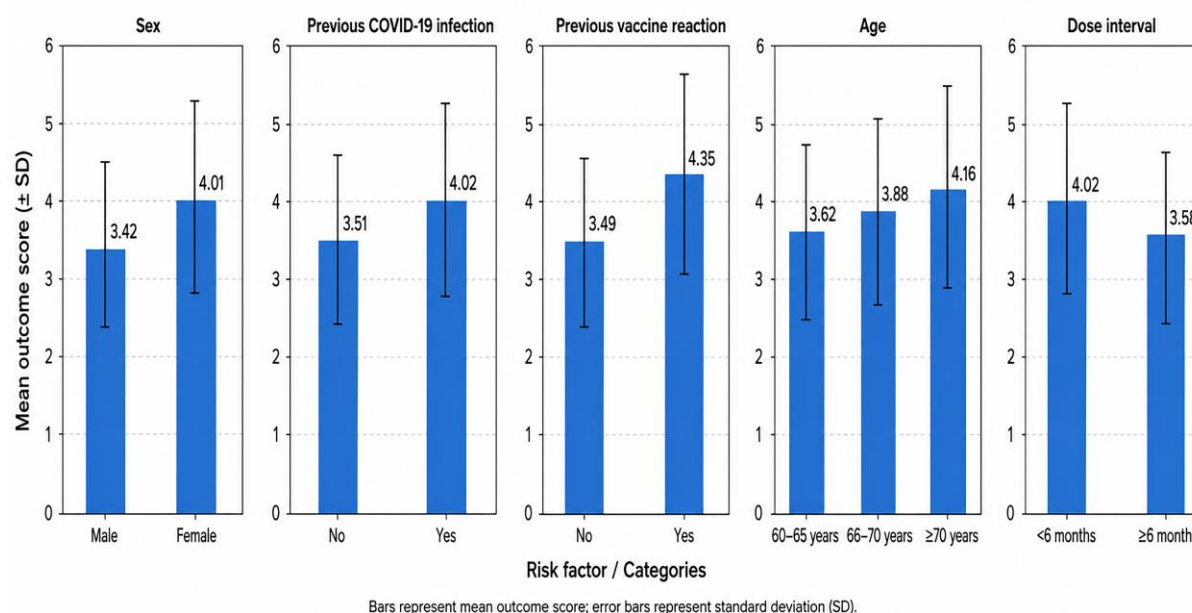


Figure 3. Mean composite adverse-event score ($\pm$ SD) by risk-factor group

3.4 Univariable analysis

In univariable linear regression (**Table 4**), female sex ($\beta = 0.24$; 95% CI 0.09–0.39; $p = 0.002$), previous COVID-19 infection ($\beta = 0.19$; 95% CI 0.05–0.33; $p = 0.008$), a shorter booster-dose interval ($\beta = 0.16$; 95% CI 0.03–0.29; $p = 0.015$) and previous significant vaccine reaction ($\beta = 0.31$; 95% CI 0.17–0.45; $p < 0.001$) were each associated with a higher composite score,

the last being the strongest. Age ($\beta = 0.00$; 95% CI -0.15 to 0.15 ; $p > 0.05$), diabetes mellitus ($\beta = 0.07$; 95% CI -0.04 to 0.18 ; $p = 0.214$) and hypertension ($\beta = 0.05$; 95% CI -0.04 to 0.14 ; $p = 0.301$) showed no significant association. Female sex, previous infection, previous vaccine reaction and shorter dose interval were therefore carried forward as candidate predictors and

tested in the multivariable model to determine whether their associations persisted after

adjustment.

Table 4. Univariable analysis of potential risk factors

Variable	β	95% CI	p-value	Interpretation
Age	0.00	-0.15 to 0.15	>0.05	Not significant
Female sex	0.24	0.09 to 0.39	0.002	Significant
Previous COVID-19 infection	0.19	0.05 to 0.33	0.008	Significant
Previous vaccine reaction	0.31	0.17 to 0.45	<0.001	Strongest association
Short booster-dose interval	0.16	0.03 to 0.29	0.015	Significant
Diabetes mellitus	0.07	-0.04 to 0.18	0.214	Not significant
Hypertension	0.05	-0.04 to 0.14	0.301	Not significant

***CI, confidence interval.

3.5 Multivariable analysis

In the multivariable model (Table 5), four factors were independently associated with a higher composite score. Previous significant vaccine reaction was the strongest ($\beta = 0.68$, SE = 0.16; standardized $\beta = 0.25$; $p < 0.001$), followed by female sex ($\beta = 0.42$, SE = 0.14; standardized $\beta = 0.18$; $p = 0.003$), previous COVID-19 infection ($\beta = 0.35$, SE = 0.13; standardized $\beta = 0.15$; $p = 0.008$) and a shorter booster-dose interval ($\beta = 0.29$, SE = 0.12; standardized $\beta = 0.12$; $p = 0.016$). Age ($\beta = 0.002$, SE = 0.018; $p = 0.912$), diabetes mellitus ($\beta = 0.11$, SE = 0.09; $p = 0.221$) and

hypertension ($\beta = 0.08$, SE = 0.08; $p = 0.318$) were not significant after adjustment.

Age deserves comment. Scores increased across age groups in the unadjusted comparison (Table 3), yet age modelled as a continuous variable was not associated with the outcome in either the univariable or the adjusted analysis. The age-group gradient was therefore not an independent effect in this cohort, which illustrates why multivariable modelling is needed to identify independent predictors. Previous vaccine reaction, sex, prior infection and dose interval were retained for the prediction score.

Table 5. Multivariable linear regression of the composite adverse-event score

Predictor	β	SE	Standardized β	p-value
Intercept	2.31	0.28	—	<0.001
Age	0.002	0.018	0.01	0.912
Female sex	0.42	0.14	0.18	0.003

Previous COVID-19 infection	0.35	0.13	0.15	0.008
Previous vaccine reaction	0.68	0.16	0.25	<0.001
Shorter booster-dose interval	0.29	0.12	0.12	0.016
Diabetes mellitus	0.11	0.09	0.06	0.221
Hypertension	0.08	0.08	0.05	0.318

β , regression coefficient; SE, standard error.

3.6 Relative importance of independent predictors

Ranked by standardized β (Table 6; Figure 4), previous significant vaccine reaction made the largest relative contribution (0.25), followed by female sex (0.18), previous COVID-19 infection (0.15) and shorter dose interval (0.12). Age contributed almost nothing (0.01). Chronological

age alone therefore added little once vaccination and infection history and sex were taken into account, despite the gradient seen in the unadjusted comparison. Standardized coefficients describe relative contributions within the model; they are not risk percentages or probabilities.

Table 6. Standardized β coefficients from the multivariable regression model

Predictor	Standardized β
Previous vaccine reaction	0.25
Female sex	0.18
Previous COVID-19 infection	0.15
Shorter dose interval	0.12
Age	0.01

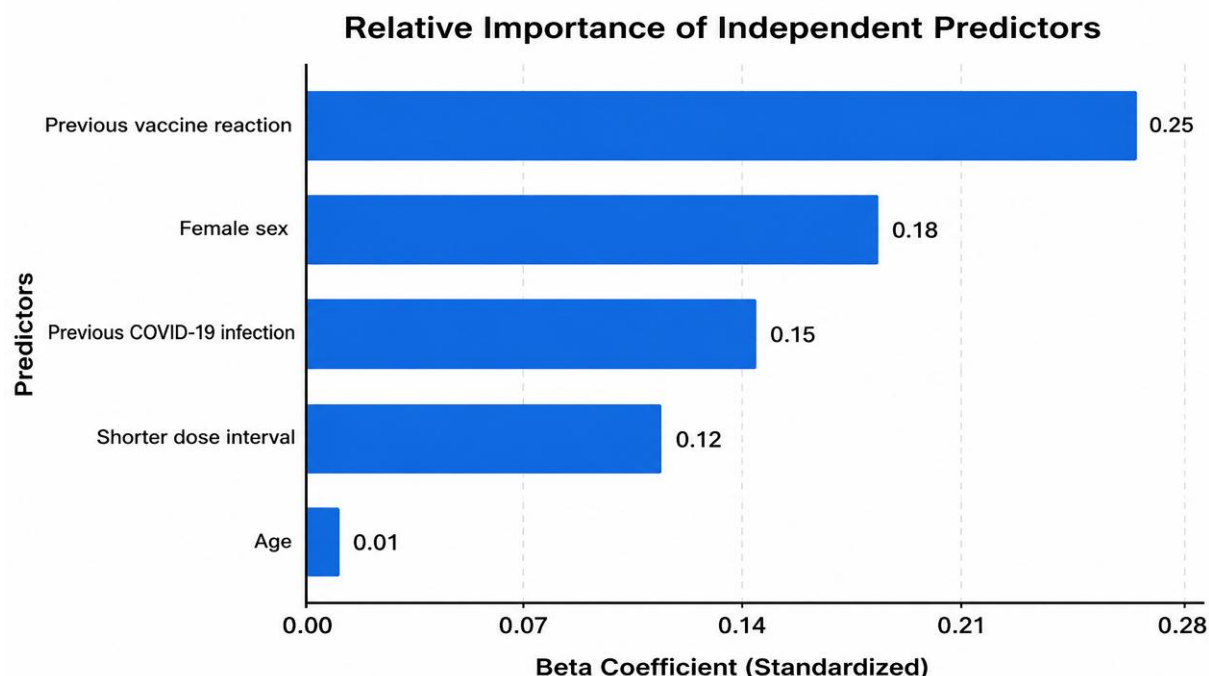


Figure 4. Relative importance of independent predictors

3.7 Model performance and internal validation

In the development cohort the model achieved an R^2 of 0.34 (adjusted R^2 0.32), meaning that the included predictors explained about 34% of the variability in the composite score (**Table 7**). The small gap between R^2 and adjusted R^2 indicates that the number of predictors did not materially inflate explanatory power. Prediction error was moderate (RMSE 1.12; MAE 0.86), i.e. predictions differed from observed scores by about 0.86 score units on average.

On internal validation, R^2 fell slightly to 0.31 (31% explained variability), RMSE rose from 1.12 to 1.18 and MAE from 0.86 to 0.91. Calibration was acceptable in both datasets. The small deterioration suggests reasonable stability and limited overfitting. At the same time, roughly two-thirds of the variability in adverse-event scores remained unexplained, indicating that other demographic, biological, behavioural or vaccine-related factors also influence post-booster responses.

Table 7. Prediction-model performance

Parameter	Development cohort	Internal validation
R^2	0.34	0.31
Adjusted R^2	0.32	—
RMSE	1.12	1.18
MAE	0.86	0.91
Explained variability	34%	31%

Calibration	Acceptable	Acceptable
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***RMSE, root mean square error; MAE, mean absolute error.

3.8 Observed versus predicted scores

Observed and predicted composite scores were positively related, with higher observed scores tending to correspond to higher predicted scores (Figure 5). Points were reasonably distributed around the 45° line of perfect agreement,

although some deviations were evident. This is consistent with the quantitative metrics (R^2 0.34 and 0.31; RMSE 1.12 and 1.18; MAE 0.86 and 0.91 in the development and validation datasets, respectively), and indicates moderate predictive performance with imperfect prediction at the individual level.

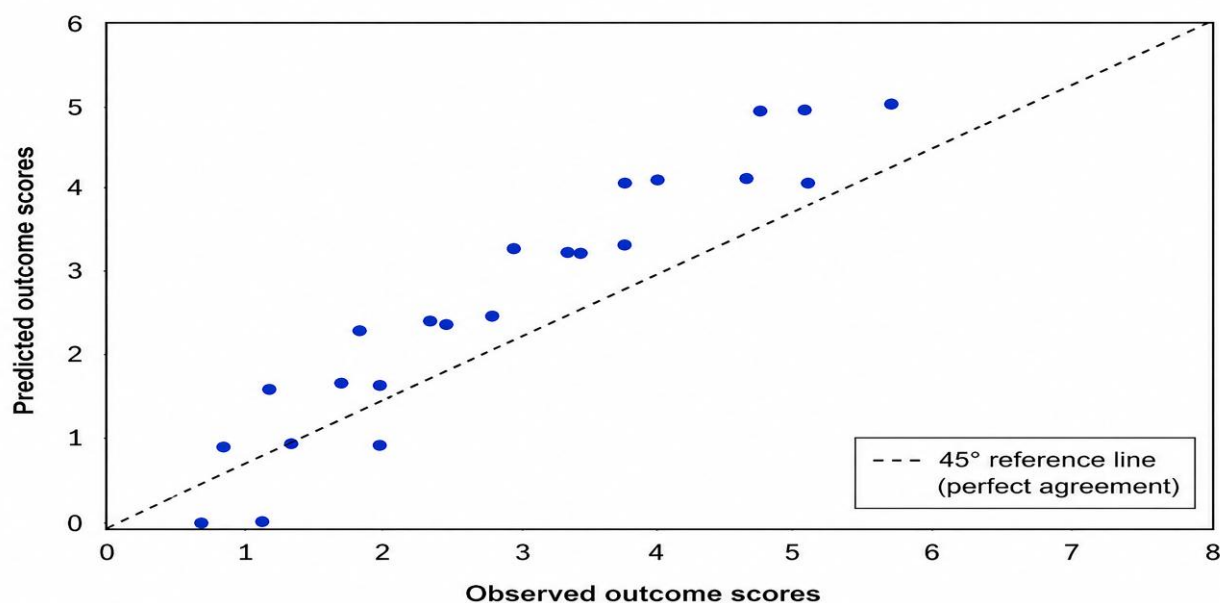


Figure 5. Observed versus predicted composite adverse-event scores with the 45° line of perfect agreement.

3.9 Development of the clinical prediction score

The independent predictors from the multivariable model were converted into a point-based score (Table 8). Previous significant vaccine reaction, which had the largest coefficient ($\beta = 0.68$, roughly twice that of the other predictors), was assigned 2 points. Female sex, previous COVID-19 infection and a

booster-dose interval <6 months were assigned 1 point each. Age was assigned 0 points because its independent contribution was negligible. The total score therefore ranges from 0 to 5, with higher scores indicating greater predicted adverse-event burden. The score is a simplified summary of the regression results intended for initial risk stratification.

Table 8. Proposed clinical prediction scoring system

Predictor	Criteria	Points
Age	≥ 60 years	0
Sex	Female	1

	Male	0
Previous COVID-19 infection	Yes	1
	No	0
Previous significant vaccine reaction	Yes	2
	No	0
Booster-dose interval	<6 months	1
	≥6 months	0
Maximum possible score		5

3.10 Risk stratification using the prediction score

Participants were classified by total score as low risk (0–1), moderate risk (2–3) or high risk (4–5) (Table 9). Mean predicted outcome scores rose stepwise across the categories, from 1.2 (low) to 2.8 (moderate) and 4.3 (high). This graded pattern supports the internal consistency of the

Table 9. Risk stratification by prediction score

Total score	Risk category	Mean predicted outcome score
0–1	Low	1.2
2–3	Moderate	2.8
4–5	High	4.3

scoring system and its potential as an initial risk-stratification tool. However, the cut-offs are exploratory because the score was derived and evaluated in the same population, and independent validation is needed before its clinical applicability can be judged.

4. Discussion

4.1 Principal findings

In this prospective cohort of 472 adults aged ≥60 years, local pain, fatigue and headache were the most frequent adverse events after a COVID-19 booster. Previous significant vaccine reaction, female sex, previous COVID-19 infection and a booster interval shorter than 6 months were each independently associated with a higher composite adverse-event score, whereas age, diabetes mellitus and hypertension were not. A simple 0–5 point score built from these four factors gave a graded separation of participants into low-, moderate- and high-risk categories, and the underlying model showed moderate performance (R^2 0.34) with only slight loss on internal validation (R^2 0.31).

4.2 Interpretation of the predictors

A previous significant reaction to a COVID-19 vaccine was the strongest predictor. This is plausible: people who reacted strongly once may carry a relatively stable tendency towards a pronounced innate or inflammatory response, and prior experience may also shape symptom perception and reporting. This is clinically useful because the information is simple to obtain at the point of vaccination.

Female sex was also independently associated with a higher score. Greater reactogenicity in women is a consistent observation in vaccine safety research and is commonly linked to sex differences in innate and adaptive immune

responses and, potentially, to differences in reporting. Our findings extend this observation to a population of older adults and to a composite measure of burden.

Previous SARS-CoV-2 infection was associated with a higher score, in line with the idea that prior antigen exposure primes the immune system so that a booster elicits a stronger response [4, 7]. A shorter interval between the previous dose and the booster was likewise associated with greater burden. One possible explanation is that a booster given while immunity from the earlier dose is still high provokes a more pronounced response, although we did not measure immune parameters and this remains speculative. If confirmed, the dose-interval finding is modifiable and may be relevant to scheduling.

Age showed a gradient in the unadjusted comparison, with higher scores in older groups, but no independent association with the score once the other variables were accounted for. The unadjusted gradient may therefore reflect differences in infection or vaccination history across age groups rather than an effect of age itself, though we did not formally test this. Previous reports have suggested that older adults experience less reactogenicity than younger adults [2, 5]; because our cohort comprised only people aged ≥ 60 years, the range of age was limited and our results cannot be compared directly with such findings. Diabetes mellitus and hypertension were not associated with the outcome, which is reassuring for these common comorbidities, although the study may have been underpowered to detect small effects.

4.3 Clinical implications

Most booster reactions in this cohort were common, expected local and systemic events. The score is not intended to discourage or withhold vaccination, which remains important for older adults. Its potential value lies in setting

expectations and tailoring counselling, for example by advising higher-scoring individuals about likely symptoms and when to seek help, and by targeting post-vaccination monitoring. The score uses four items that are easily collected, which favours its practical use, but this will need to be shown in an implementation setting.

4.4 Strengths and limitations

The strengths of this study include its prospective design, high follow-up (94.4%), a focus on older adults, a composite outcome that captures overall burden rather than single events, and development and internal validation of the model following established prediction-model recommendations [8–10, 18, 20–22]. Several limitations should be noted. First, internal validation addresses stability within the development population but does not establish generalisability; the score needs external validation, ideally in other settings and with different vaccine products. Second, the model explained about one-third of the variability in adverse-event scores, and the score has only six possible values, which limits individual-level prediction. Third, adverse events were collected through follow-up reports and may be affected by recall and reporting bias, and the composite score is a study-specific measure that has not been validated against an external standard. Fourth, previous infection and previous vaccine reactions were largely participant-reported. Fifth, the 28 participants who did not complete follow-up (5.6%) were excluded, which could introduce attrition bias if their characteristics or outcomes differed. Sixth, potentially relevant factors such as vaccine product, body mass index, concomitant medication, prior infection timing and immune measures were not included. Finally, the risk-category cut-offs are exploratory, and the observational design supports association but not causation.

4.5 Future research

Future work should validate the score in larger independent cohorts, assess calibration and discrimination of the categories against observed outcomes, and test whether additional variables such as vaccine product, immune markers or the timing of prior infection improve performance. Studies should also examine whether use of the score in counselling improves patient experience or monitoring.

5. Conclusion

In this prospective cohort of older adults, 472 of 500 participants (94.4%) completed follow-up. Injection-site pain, fatigue and headache were the most common post-booster adverse events. Previous significant vaccine reaction, female sex, previous COVID-19 infection and a booster interval shorter than 6 months were independent predictors of a higher adverse-event score, with previous vaccine reaction contributing most. A 0–5 point score built from these factors produced a graded separation of low-, moderate- and high-risk groups, and the model explained 34% of outcome variance in development and 31% on internal validation. The score may offer a practical basis for preliminary risk stratification and counselling, but it is exploratory and requires validation in larger external cohorts before it is used in clinical practice.

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