Community Neutrophil-to-Lymphocyte Ratio Can Predict Future Cardiovascular and Cardiac-related Mortality after the First Hospitalized COPD Exacerbation

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ABSTRACT **Background:** Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of cardiovascular events, especially following acute exacerbation (AECOPD). However, there is insufficient data to identify high-risk subjects.

Objectives: To evaluate the association between neutrophil-to-lymphocyte ratio (NLR), a marker of inflammation, and the risk of cardiovascular events following exacerbation.

Methods: This retrospective cohort included patients with COPD who were hospitalized with AECOPD between January 2016 and December 2022. We took the reference NLR before index admission and evaluated the incidence of major adverse cardiovascular events (MACE) or cardiovascular death over the following year. Multivariate analysis and competing risk regression were used to assess hazard ratio (HR) and NLR threshold for increased cardiovascular risk.

Results: In total, 15,224 patients with AECOPD completed one 1-year follow-up session. The majority were male (54%) with a mean age of 69 ± 3 years. The risk for MACE of patients in the highest NLR quartile was higher over the first year following AECOPD; however, the magnitude of effect decreased over time. After adjustment to other confounders that may increase NLR, a value > 3.5 was found with the strongest predictive power

Conclusion: Community NLR can be used to identify patients at increased risk of cardiovascular events following AECOPD, together with other risk factors. Every effort should be made to reduce exacerbation risk, and target intervention to those patients at highest risk.

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KEY WORDS: biomarker, cardiovascular, chronic obstructive pulmonary disease (COPD), community neutrophil-to-lymphocyte ratio (cNLR), neutrophil-to-lymphocyte ratio (NLR)

Chronic obstructive pulmonary disease (COPD) is a significant health problem. It is ranked as the third leading cause of death worldwide. Acute exacerbations of COPD (AECOPD) are critical events in the natural history of the disease, associated with increased mortality and accelerated decline in lung function, and impaired quality of life [1].

AECOPD impacts the cardiovascular system. Cardiovascular diseases are common co-morbidities in patients with COPD. In addition to common risk factors such as age and smoking, patients with COPD have a higher prevalence of traditional cardiovascular risk factors like hypertension and diabetes compared to those without COPD [2-4].

AECOPD itself can bring acute cardiovascular events, including myocardial infarction, stroke, and arrhythmia. Recent studies have demonstrated that both moderate and severe COPD exacerbations are independent risk factors for adverse cardiovascular events. Patients with more severe COPD, as indicated by lower function at one year (FEV1) and higher dyspnea scores, have higher exacerbation rates [4]. Frequent exacerbators have a higher risk, as each exacerbation increases the odds of future cardiovascular events [5-7].

The relationship between COPD exacerbations and cardiovascular events is multifaceted and driven largely by systemic inflammation [7-9]. In addition, hypoxemia and hemodynamic stress, coupled with increased myocardial oxygen demand during AECOPD, further increase cardiovascular risk [10]. The highest cardiovascular risk occurs during the immediate post-exacerbation period and continues for the first month [6,7,10]. Increased risk for cardiovascular events may continue over the following months, up to a year [11,12], particularly for heart failure decompensation [3,4].

In recent years, there has been growing interest in identifying biomarkers that can stratify the risk of adverse outcomes in COPD patients, particularly following AECOPD.

The neutrophil-to-lymphocyte ratio (NLR) has emerged as a promising candidate [13-16]. NLR is a simple, cost-effective biomarker derived from the complete blood count, calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Increased NLR has been associated with poor outcomes in various acute and chronic conditions, including cardiovascular diseases [13-14].

Elevated NLR reflects a complex interaction between the innate and adaptive immune responses during stress or inflammation. Pro-inflammatory cytokines and stress hormones recruit neutrophils and increase their number in the peripheral blood. Conversely, reduced lymphocytes under stress conditions result from the redistribution of lymphocytes to lymphoid organs and increased apoptosis [16]. This reciprocal change in neutrophils and lymphocytes leads to an increased NLR, potentially representing the intensity of the inflammatory reaction and its systemic impacts.

Despite the established association between NLR and adverse outcomes in various medical conditions, including cardiovascular diseases and the increased risk of cardiovascular events following AECOPD, the relationship between NLR and cardiovascular outcomes after AECOPD is unknown.

In this study, we evaluated the potential use of community NLR (cNLR) as a biomarker for increased cardiovascular complications following AECOPD. Integration of cNLR into risk-stratification strategies could guide targeted interventions for those at greatest risk.

PATIENTS AND METHODS

This retrospective study was performed on anonymized data, which was extracted from Clalit Health Services (CHS) medical records, using the MDclone platform. All members of CHS who were hospitalized for acute exacerbation of COPD between January 2016 and December 2022, were included, provided they had at least one blood count from the preceding year before index hospitalization. We excluded patients with active malignancy, neutropenia (neutrophils < 1500 cells/μl), lymphopenia (lymphocytes < 500 cells/μl), and cognitive impairment. Patients taking chronic anti-inflammatory medications or presenting with any end-stage disease expected to shorten life expectancy were also excluded.

cNLR was extracted from the closest blood count taken in the community before index hospitalization for COPD exacerbation. Since NLR is a dynamic value, we excluded results that might have been acutely impacted. Excluding parameters included any cause of hospitalization or medical intervention within the previous month, and treatment with antibiotics or anti-inflammatory medication (except for NSAIDs) within the bordering month. Also, patients with active malignancy were excluded. NLR was calculated as the neutrophil count divided by the lymphocyte count. The results were separated into four quartiles by cNLR results.

Endpoints of interest were all-cause mortality, cardiovascular mortality, and first acute cardiovascular event of any type, primarily inpatient diagnosis of major adverse cardiovascular events (MACE). Four-point MACE includes myocardial infarction, ischemic stroke, unstable angina hospitalization or revascularization, and decompensated heart failure. We did not include cardiovascular events within the index hospitalization because of the inability to classify the initial event as a COPD exacerbation. Mortality without cardiovascular events was defined as censoring criteria. All-cause mortality data were obtained from the Israeli National Insurance Institute (Bituach Leumi). Cardiovascular mortality was defined as death during hospitalization or 7 days post-discharge with primary diagnosis of myocardial or cerebrovascular disease as the cause of hospitalization.

Demographic data were extracted via MDclone. Socioeconomic status, for example, was automatically determined using a validated CHS index based on residential area-level income, education, employment, and welfare utilization, mapped to Israeli census data.

The institutional ethics committee approved the study (SOR 22-0200). Informed consent was waived, as all patient data were anonymized

DEFINITION OF CO-MORBIDITIES

COPD exacerbation was defined as either hospital admission of a patient older than 40 years with a primary diagnosis of COPD or emphysema (ICD-9 codes 490–492, 496) or respiratory complaint as primary diagnosis with prior COPD diagnosis and exclusion of competing diagnoses (e.g., heart failure, sepsis, pulmonary emboli). Treatment with at least one bronchodilator and respiratory antibiotic or systemic steroids was mandatory for both cases.

Of note, the diagnosis of COPD was based on clinical judgment rather than pulmonary function tests, as these data are unavailable from our electronic health records.

To reduce misclassification bias, a sensitivity analysis was performed on a subgroup of patients with a diagnosis of COPD given after a visit to a pulmonologist's office. This analysis assessed whether the observed pattern was held in a more stringently defined population. Cardiovascular outcomes were identified when COPD patients were admitted with a primary diagnosis of an acute coronary syndrome (ICD-9 codes 410–411, 413), heart failure (ICD-9 code 428), revascularization (ICD-9 codes 00.66, 36.01, 36.02, 36.05, 36.10–36.19), or stroke (ICD-9 codes 433-437.1). We used MACE as the primary outcome. We assessed the first MACE and specific cardiovascular events over the year following AECOPD. Baseline cardiovascular risk was defined as the risk of MACE in COPD patients from our cohort over the first year after hospital exacerbations.

STATISTICAL ANALYSIS

Descriptive statistics were employed to summarize the demographic and clinical attributes of the study population. Continuous variables are reported as means accompanied by standard deviations. Categorical variables are presented as frequencies and percentages. To investigate NLR as a biomarker, multivariable analysis was conducted using competing risk regression to assess the associations between NLR and survival when controlling for possible confounders such as sex, co-morbidities, and smoking status (assessed by ICD 9 diagnostic codes in electronic health records). The adjusted hazard ratio was reported with a 95% confidence interval. Obviously, mortality ends the risk of further flare-ups. We used competing risk analysis, the Fine Gray method, to evaluate the prognostic value of NLR in predicting the outcomes. We employed the Youden Index to determine an optimal threshold for mortality prediction. This index offers a balanced assessment of sensitivity and specificity, aiding in selecting the most effective cutoff point. Statistical analyses were performed using R Statistical Software, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall, 19,571 patients were admitted with AECOPD between January 2016 and December 2022. After applying exclusion criteria, there were 15,224 patients, 54% male, with a mean age of 67 ± 9 years. Most patients were ever-smokers with at least one additional cardiovascular risk factor. Patients in the highest NLR quartile were more likely to be male with a higher burden of systemic diseases. In

Table 1. Baseline characteristics of the study population

	Overall, n=15,224	NLR 1stQ, n=3806	NLR 2ndQ, n=3806	NLR 3rdQ, n=3814	NLR 4thQ, n=3798	*P*-value
NLR value	–	< 1.67	1.67-2.27	2.29-3.14	> 3.14	–
Age baseline	67 ± 9.2	65.9 ± 9.4	66.4 ± 9.4	67.4 ± 9.0	68.3 ± 8.6	< 0.001
Male	8246 (54)	1770 (47)	1981 (52)	2195 (58)	2300 (61)	< 0.001
BMI	29.4 ± 7.3	28.8 ± 7	29.7 ± 7.3	29.8 ± 7.3	29.3 ± 7.7	< 0.001
CCI	6.3 ± 3.1	5.6 ± 2.9	5.9 ± 3.1	6.4 ± 3.1	7.3 ± 3.2	< 0.001
Ever smokers	11,228 (74)	2721 (71)	2826 (74)	2837 (74)	2904 (76)	< 0.001
Low SES	3630 (24)	1009 (28)	890 (25)	909 (26)	822 (23)	< 0.001
IHD	7017 (46)	1497 (39)	1702 (45)	1822 (48)	1996 (53)	< 0.001
DM	7566 (50)	1637 (43)	1800 (47)	1985 (52)	2144 (56)	< 0.001
Obesity	8632 (57)	1996 (52)	2187 (57)	2241 (59)	2208 (58)	< 0.001
Hypertension	10,443 (69)	2302 (60)	2529 (66)	2731 (72)	2881 (76)	< 0.001
CRF	3517 (23)	542 (14)	681 (18)	972 (25)	1322 (35)	< 0.001
CVA	4189 (28)	952 (25)	1026 (27)	1090 (29)	1121(30)	< 0.001
Home O_2 therapy	759 (5.0)	114 (3.0)	153 (4.0)	218 (5.7)	274 (7.2)	< 0.001
ICS	10,532 (69)	2607 (69)	2631 (69)	2660 (70)	2634 (69)	0.71

Data are presented as median (IQR) or mean ± standard deviation as appropriate

BMI = body mass index, CCI = Charleston Comorbidity Index (scale 1–15), CRF = chronic renal failure, CVA = cerebrovascular accident, DM = diabetes mellitus, ICS = inhaled corticosteroids, IHD = ischemic heart disease, NLR = neutrophil-to-lymphocyte ratio SES = socioeconomic status (scale 1–3)

Table 2. Incidence of combined new major adverse cardiovascular events and cardiovascular mortality

	Overall, n=15,224	NLR 1stQ, n=3806	NLR 2ndQ, n=3806	NLR 3rdQ, n=3814	NLR 4thQ, n=3798	*P*-value
1-year follow-up	1243 (8.2)	264 (6.9)	295 (7.8)	330 (8.7)	354 (9.3)	< 0.001
30 days	619 (4.1)	96 (2.5)	116 (3.0)	159 (4.2)	248 (6.5)	< 0.001
90 days	1380 (9.1)	227 (6.0)	287 (7.5)	332 (8.7)	534 (14)	< 0.001
180 days	2071 (14)	361 (9.5)	434 (11)	498 (13)	778 (20)	< 0.001
365 days	3,162 (21)	571 (15)	705 (19)	757 (20)	1129 (30)	< 0.001

Data are presented as a number (% percent)
NLR = neutrophil-to-lymphocyte ratio

Table 3. Hazard ratio of NLR quartiles after regression

Time from index, exacerbation	HR (95%CI)	*P*-value
30 days		
NLR 1stQ	–	
NLR 2ndQ	0.98 (0.69 – 1.39)	0.92
NLR 3rdQ	1.15 (0.82 – 1.60)	0.41
NLR 4thQ	1.46 (1.07 – 2.00)	0.018
90 days		
NLR 1stQ	–	
NLR 2ndQ	1.10 (0.89 – 1.36)	0.38
NLR 3rdQ	1.15 (0.94 – 1.42)	0.17
NLR 4thQ	1.52 (1.25–1.84)	< 0.001
180 days		
NLR 1stQ	–	
NLR 2ndQ	1.10 (0.93–1.30)	0.25
NLR 3rdQ	1.18 (1.01–1.39)	0.042
NLR 4thQ	1.48 (1.27–1.72)	< 0.001
365 days		
NLR 1stQ	–	
NLR 2ndQ	1.12 (0.99–1.28)	0.072
NLR 3rdQ	1.11 (0.98–1.26)	0.093
NLR 4thQ	1.38 (1.23–1.56)	< 0.001

addition, higher cNLR was associated with more cardiovascular risk factors before the index exacerbation. As for the severity of COPD, we did not have pulmonary function test (PFT) results, but patients in the highest NLR group had more O_2 prescriptions and moderate COPD exacerbations before enrollment, suggesting a more severe disease. Patient characteristics are presented in Table 1.

The risk of a significant cardiovascular event increased significantly following exacerbation. The incidence of severe cardiovascular events was significantly higher in the increased with higher cNLR [Table 2]. This correlation persisted throughout the follow-up period; however, the size effect was most pronounced 30 days after hospitalization and reduced over time. The result was lowest in the non-exacerbating group (i.e., those without an exacerbation in the preceding year).

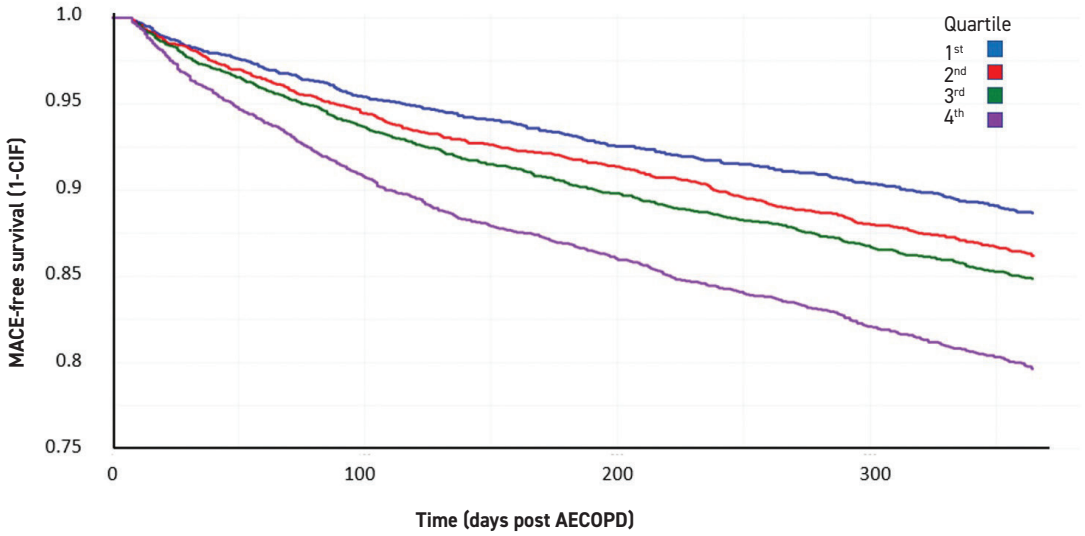
In a multivariate regression model, we adjusted the model to isolate the independent effect of NLR on cardiovascular risk. After adjustment to other confounders that might increase NLR, such as older age, smoking history, cardiovascular risk factors, and co-morbidities, the HR for cardiovascular was 1.38–1.52 compared to the lowest quartile NLR [Table 3].

To validate these findings, a sensitivity analysis was conducted on a more strictly defined subgroup of 8413 patients with COPD showed a similar pattern. In this group, the HRs remained elevated, ranging from 1.26 to 1.77. The trend of decreasing HRs over time was even more pronounced, where HR at 30 days was 1.77 and at 365 days at 1.26. Competing for risk analysis and receiver operation curve found a cNLR value ≥ 3.5 to have the strongest discriminatory power. Patients with cNLR above 3.5 were more likely to develop MACE or experience cardiac-related death. Interestingly, the cutting point to enter the top NLR quartile was 3.18, suggesting that less than 25% of AECOPD had an increased risk of developing MACE following AECOPD.

DISCUSSION

Our main finding was that higher stable phase cNLR has an independent prognostic value for future cardiovascular events following AECOPD. This effect lasts for at least 1 year, but the magnitude of the effect declines over time. The observation that cNLR is associated with increased all-cause mortality and overall cardiovascular risk over the year following the index hospitalization aligns with the growing body of evidence linking chronic systemic inflammation to long-term cardiovascular outcomes in COPD patients.

Figure 1. Estimated event free (cardiovascular) probability by NLR quartile during the 365 days post-AECOPD, divided into NLR quartiles
1-CIF = one minus the cumulative incidence function, or probability not having major cardiovascular event, AECOPD = acute exacerbation chronic obstructive pulmonary disease, NLR = neutrophil-to-lymphocyte ratio



While NLR is a well-established biomarker for cardiovascular risk in the general population, its clinical relevance in COPD patients deserves special attention due to the unique inflammatory milieu and co-morbidity burden characteristic of this population. COPD is marked by persistent low-grade systemic inflammation, frequent exacerbations, and a disproportionately high rate of cardiovascular morbidity and mortality. In this context, elevation in inflammatory markers such as NLR may reflect a heightened cardiovascular risk state. Importantly, the post-exacerbation period represents a particularly vulnerable phase during which cardiovascular events are more likely to occur. Our findings underscore that elevated cardiovascular risk following AECOPD is not evenly distributed between patients but rather concentrated in patients with high cNLR. We found that cNLR >3.5 is an independent marker of increased risk for cardiovascular events even after stratification for traditional risk factors. Therefore, NLR, measured in the stable phase, could serve as a practical and accessible biomarker for increased cardiovascular risk, especially in the post-AECOPD timeframe. This finding adds a new dimension to existing evidence by validating the prognostic value of stable-state NLR in a disease-specific, clinically meaningful context.

Interestingly, we could not demonstrate a similar effect of NLR taken in the emergency department after patient arrival (data not shown). We suspect that early initiation of steroids before admission, either by the patient or emergency services, might disrupt the NLR measurements.

Patients with COPD, especially those with exacerbation phenotype, might benefit from more aggressive cardiovascular risk reduction strategies [2,7]. For example, patients with elevated cNLR might benefit from intense control of cardiovascular risk factors, earlier initiation of cardioprotective medications, and adoption of lifestyle practices aimed at reducing inflammation.

A biomarker used in a stable phase of disease must be consistent and dependable.

While the association between increased NLR and COPD exacerbations and the heightened risk of cardiovascular sequel is well known, this is the first study, to the best of our knowledge, to demonstrate added risk in the subgroup of patients with elevated NLR

Several mechanisms might explain the association between cNLR and the long-term cardiovascular risk in COPD patients. Studies have shown that inflammatory markers, including IL-6, C-reactive protein, and fibrinogen in the blood, are significantly higher in COPD patients. High cNLR can imply low-grade ongoing inflammation, which elevates traditional cardiovascular risk factors like hypertension, diabetes, and dyslipidemia [4]. In addition, inflammation can trigger endothelial

dysfunction and arterial stiffness [17,18], important elements in the progression of atherosclerosis [19]. Furthermore, increased inflammation during AECOPD results in oxidative stress and a hypercoagulable state, which leads to plaque rupture and thrombus formation.

The use of cNLR has several advantages. Previous studies that evaluated the prognostic value of cNLR in predicting AECOPD demonstrated that NLR is repeatable and that a single NLR value is representative over time [20]. Blood counts are inexpensive and available for most COPD patients, since the eosinophil count is part of the routine assessment of COPD patients and used to guide inhaled corticosteroids treatment.

This study has several strengths, including its large sample size, long follow-up period, and the use of real-world data combining community and hospital data from representative national cohorts, making our findings generalizable and relevant to clinical practice.

There are a few limitations to consider. The retrospective nature of the study precludes the establishment of causal relationships. In addition, although the study was designed to ensure that blood counts were not taken during an acute event, unobserved confounders, such as concurrent infections or unreported use of anti-inflammatory medications, might have influenced both NLR and cardiovascular outcomes.

The use of MDclone for data extraction and anonymization prevented the integration of pulmonary function tests into our analysis, so the diagnosis of COPD cannot be assured. Nevertheless, the study population was extracted from patients who were admitted to the hospital, diagnosed, and treated as AECOPD by an internist, reducing the possibility of misclassification bias. Moreover, to address the final limitation, we conducted a sensitivity analysis in a more strictly defined subgroup of patients with COPD. Inclusion in this subgroup required a documented COPD diagnosis, a prescription for inhaled bronchodilators, and at least one recorded visit to a pulmonologist before the index AECOPD. Analysis of this subset yielded consistent findings and demonstrated similar patterns of declining cardiovascular risk over time following the exacerbation, as well as a comparable percentage of smokers (79% compared to 74% in the main group). These results support the robustness of our findings and mitigate concerns regarding the accuracy of COPD diagnosis in the cohort. They also reinforce the interpretation that the relatively low percentage of smokers compared to expectations for a COPD population is likely due to underreporting rather than misclassification in the primary study population.

CONCLUSIONS

Our study demonstrates the potential of cNLR as a valuable biomarker for cardiovascular risk stratification in COPD patients following AECOPD. We found that higher cNLR had an independent prognostic value for future cardiovascular events following AECOPD. These findings pave the way for more personalized risk assessment and management strategies in this high-risk population. Future prospective studies are warranted to validate these findings and to prospectively evaluate the impact of NLR-guided interventions on cardiovascular outcomes in COPD patients.

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Capsule

Global prevalence of self-reported non-coeliac gluten and wheat sensitivity

Shiha and colleagues conducted a systematic review and meta-analysis to estimate the global burden and clinical characteristics of self-reported Non-coeliac gluten/wheat sensitivity (NCGWS). Twenty-five studies comprising 49,476 participants from 16 countries were included in the analysis. The pooled prevalence of self-reported NCGWS was 10.3% (95% confidence interval [95%CI] 7.0–14.0%), with marked variations between countries. Among individuals reporting NCGWS, 40% (95%CI 25.2–55.0%) adhered to a gluten-free diet. The most common symptoms were bloating (71.0%; 95%CI 62.8%–79.1%), abdominal discomfort (46.0%; 95%CI 39.0–52.7%), abdominal pain (36.0%; 95%CI 28.6–43.2%), and fatigue (32.1%; 95%CI 25.3–39.0%). Self-reported NCGWS was significantly more common in females than in males (odds ratio [OR] 2.29; 95%CI 1.80–2.90; $P < 0.001$). Individuals who self-reported NCGWS were significantly more likely to report anxiety (OR 2.95; 95%CI 1.56–5.57; $P < 0.001$), depression (OR 2.42; 95%CI 1.80–3.24; $P < 0.001$), and irritable bowel syndrome (OR 4.78; 95%CI 3.48–6.57; $P < 0.001$) than controls.

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Capsule

An intranasal adjuvanted, recombinant influenza A/H5 vaccine primes against diverse H5N1 clades: a phase I trial

Deming et al. reported on a randomized, controlled phase I trial of a recombinant influenza A/H5 (A/Indonesia/05/2005, clade 2.1) hemagglutinin vaccine formulated with a nanoemulsion adjuvant (W805EC). The vaccine was administered intranasally in two doses 28 days apart at three antigen levels. Controls received unadjuvanted H5 or placebo. Six months later, participants received an intramuscular boost with unadjuvanted inactivated A/H5N1 (A/Vietnam/1203/2004, clade 1) vaccine. Primary outcomes were solicited and unsolicited adverse events (AEs), laboratory safety abnormalities, medically attended AEs, potential immune-mediated conditions, new-onset chronic conditions, and serious AEs. All vaccines were well tolerated. After the intranasal series, hemagglutination inhibition and microneutralization responses were minimal. However, adjuvanted H5 recipients showede significant increases in mucosal and serum IgG/IgA, surface plasmon resonance antibody binding, memory B and CD4 T cell activity, and antibody-dependent cell-mediated cytotoxicity. Following H5N1 boost, participants mounted robust responses across measurements and had microneutralization responses against diverse H5N1 clades (including circulating clade 2.3.4.4b). The findings demonstrated successful mucosal priming and broad cross-clade responses. This intranasal vaccine supports further exploration of mucosal immune biomarkers and may accelerate development of intranasal influenza vaccines.

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