Risk Prediction Model for Influenza Vaccine Breakthrough Cases in the Elderly Based on a Nested Case-Control Study (Postprint)

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Abstract

Background Influenza, as a common respiratory infectious disease, poses a serious threat to the health of elderly populations. Influenza vaccination has become an important measure for preventing influenza and reducing the disease burden of influenza in elderly populations. However, in practical applications, individuals may still contract influenza after vaccination, which are known as breakthrough cases. Current research on the occurrence of influenza vaccine breakthrough cases in elderly populations is limited. Objective To explore the risk factors for influenza vaccine breakthrough cases in elderly populations aged 70 years and above, and to construct a risk prediction model to provide a scientific basis for early identification and prevention of influenza infection in elderly populations. Methods Elderly individuals aged 70 years and above in Xiaoshan District and Linping District of Hangzhou City who received influenza vaccination between September 1, 2023 and March 31, 2024 were selected as study subjects and enrolled in a study cohort. The investigation included demographic data (gender, age, living arrangement, residential area), previous year' s influenza vaccination status, chronic disease history (hypertension, diabetes, hyperlipidemia, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, etc.), and personal lifestyle factors (average sleep duration in the past week, moderate-intensity or higher exercise). A nested case-control study design was employed, with elderly individuals who were reinfected with influenza as the breakthrough case group and those who were not infected as the control group. Logistic regression analysis (backward stepwise method) was used to explore influencing factors for the occurrence of influenza vaccine breakthrough cases, construct a risk prediction model, and draw a nomogram. The Hosmer-Lemeshow (H-L) goodness-of-fit test was performed, and receiver operating characteristic (ROC) curves and calibration curves were plotted to evaluate the model. Results A total of 99,735 elderly individuals aged 70 years

and above received influenza vaccination. During the 2023-2024 influenza epidemic season, 4,689 breakthrough cases were observed and followed up, yielding a vaccine breakthrough rate of 4.70%. A stratified random sample of 4,853 individuals was selected as the control group. Comparisons between the control and breakthrough case groups showed statistically significant differences in age, gender, living arrangement, residential area, history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of chronic obstructive pulmonary disease, history of asthma, previous year' s influenza vaccination status, and moderate-intensity or higher exercise (P<0.05). Based on the Akaike Information Criterion (AIC), multivariate logistic regression analysis using the backward stepwise method revealed that age, gender, living arrangement, residential area, history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of chronic obstructive pulmonary disease, history of asthma, previous year' s influenza vaccination, and moderate-intensity or higher exercise were influencing factors for the occurrence of influenza vaccine breakthrough cases in elderly populations aged 70 years and above (P<0.05). A risk prediction model was constructed using the aforementioned variables. The Hosmer-Lemeshow goodness-of-fit test yielded a P-value of 0.762; the area under the ROC curve (AUC) was 0.806 (95% CI=0.786-0.834); the calibration curve demonstrated good consistency between predicted and actual values. Conclusion A certain proportion of breakthrough cases still occur among elderly populations aged 70 years and above after influenza vaccination. Exploring the influencing factors of influenza vaccine breakthrough cases and constructing a risk prediction model provides a quantitative tool and scientific basis for early warning and prevention of breakthrough infections following influenza vaccination in the elderly, thereby further reducing the disease burden of influenza in elderly populations.

Full Text

Predictive Model for Breakthrough Influenza Cases in the Elderly Population: A Nested Case-Control Study

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Abstract

Background Influenza is a common respiratory infectious disease that poses a serious threat to the health of the elderly population. Vaccination against influenza is an important measure to prevent infection and reduce disease burden among the elderly. However, individuals who have been vaccinated against influenza may still contract the disease, resulting in breakthrough cases, and there is currently limited research on breakthrough cases of influenza vaccination among the elderly.

Objective To investigate risk factors for breakthrough influenza cases among individuals aged 70 years and older, and construct a predictive model to facilitate early identification and prevention of influenza infection in this population.

Methods A nested case-control study was conducted among individuals aged 70 years and older in Xiaoshan and Linping Districts of Hangzhou who received influenza vaccination between September 1, 2023, and March 31, 2024. The survey included demographic information (gender, age, living arrangements, and residential area), information on influenza vaccination in the past year, history of chronic illnesses (such as hypertension, diabetes, hyperlipidaemia, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, etc.), and details of personal lifestyle (average sleep duration in the past week, and engagement in moderate or higher intensity physical activity). Individuals who developed influenza infection during the 2023–2024 influenza season were classified as breakthrough cases, while those who remained uninfected served as controls. Logistic regression analysis with backward stepwise selection was used to identify significant risk factors. A nomogram-based risk predictive model was constructed using these factors, and the model was evaluated using the Hosmer-Lemeshow goodness-of-fit test, receiver operating characteristic (ROC) curve analysis, and calibration curve.

Results Among 99,735 vaccinated individuals aged 70 years and older, 4,689 breakthrough cases were identified during the follow-up period, yielding a breakthrough infection rate of 4.70%. A stratified random sample of 4,853 individuals was selected as the control group. Statistically significant differences ($P<0.05$) between cases and controls were observed in age, sex, living arrangement, residential area, history of hypertension, diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease (COPD), asthma, prior-season influenza vaccination, and engagement in moderate or vigorous physical activity. Multivariate logistic regression analysis identified all these variables as independent influence factors ($P<0.05$). The predictive model incorporating these variables demonstrated good fit (Hosmer-Lemeshow $P=0.762$), strong discrimination (AUC=0.806, 95%CI=0.786-0.834), and good calibration, indicating close agreement between predicted and observed outcomes.

Conclusion Despite influenza vaccination, a proportion of individuals aged 70 years and older experience influenza breakthrough infections. Identifying the influencing factors and constructing a reliable predictive model provides a sci-

entific foundation and quantitative tool for early warning and prevention of post-vaccination influenza among the elderly, and this approach has the potential to further reduce the disease burden in this vulnerable population.

Keywords Influenza vaccines; Elderly; Breakthrough case; Nested case-control; Predictive model

Introduction

Influenza, commonly known as flu, is an acute respiratory infectious disease caused by influenza viruses. Globally, approximately three to five million individuals develop severe influenza annually, posing a serious threat to human health [1]. Due to their unique physiological and immunological status, elderly populations are at high risk for influenza virus infection, with significantly higher hospitalization rates, severe illness rates, and mortality compared to other age groups following infection [1-2]. Among individuals aged 70 years and older, more pronounced immune function decline leads to even higher rates of hospitalization, severe illness, and mortality, while vaccine protective efficacy is substantially lower than in younger and middle-aged elderly populations. Although vaccination effectively reduces the risk of influenza infection in the general population [3], breakthrough cases (infection despite vaccination) still occur and warrant specific attention in influenza prevention and control efforts. Previous research has rarely conducted systematic analyses of breakthrough case risks in elderly populations, and precise individual risk prediction tools are lacking.

This study employs a nested case-control design, which is based on a cohort study framework. Within an established prospective cohort, individuals who develop a specific outcome (such as breakthrough infection) are selected as cases, matched with non-diseased individuals as controls. This approach combines the temporal advantages of cohort studies with the cost-effectiveness of case-control designs, improving research efficiency and reducing information bias. In recent years, this design has been widely applied in chronic disease and vaccine effectiveness evaluations. The present study aims to investigate the risk of reinfection following influenza vaccination among individuals aged 70 years and older, conduct an in-depth analysis of risk factors for breakthrough infections in this vaccinated population, better understand the actual protective effects of influenza vaccines in this specific group, and provide a scientific basis for developing more effective influenza prevention and control measures for the elderly.

Methods

Study Design and Population

This nested case-control study was conducted among elderly individuals aged 70 years and older in Xiaoshan and Linping Districts of Hangzhou who received

influenza vaccination between September 1, 2023, and March 31, 2024. Inclusion criteria were: complete influenza vaccination and medical records; no influenza infection prior to vaccination in the current year; good compliance; and provision of informed consent for follow-up. Exclusion criteria were: severe cardiovascular or cerebrovascular chronic diseases; severe immunosuppression; history of serious adverse reactions to influenza or other vaccines; long-term bedridden status with inability to perform self-care; or mental disorders. The study was approved by the Ethics Committee of Hangzhou Linping District First People' s Hospital (Approval No.: Linping First Hospital Ethics Review 2023 Research No. 023), and all participants provided written informed consent.

Data Collection

A follow-up cohort was established using a nested case-control approach to observe disease occurrence in the subsequent influenza season. Elderly individuals who developed influenza reinfection were designated as the breakthrough case group, while those who remained uninfected served as the control group, with random sampling conducted throughout the study cohort. Data were obtained from the China Disease Prevention and Control Information System, XTL Cloud Ladder Data Integration Platform, and Zhejiang Province Vaccination Management System. The survey instrument was developed based on the case investigation guidelines from the Chinese National Influenza Center' s *National Influenza Surveillance Technical Guidelines (2017 Edition)* [4] and study requirements. The survey collected demographic information (gender, age, living arrangements, residential area), prior-season influenza vaccination status, chronic disease history (hypertension, diabetes, hyperlipidaemia, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, etc.), and personal lifestyle factors (average sleep duration in the past week, engagement in moderate or higher intensity physical activity). The influenza vaccine used in this study was the trivalent influenza split virion vaccine, manufactured by Shenzhen Sanofi Pasteur Biological Products Co., Ltd. and Beijing Sinovac Biotech Co., Ltd. Data collection was conducted through both online and offline methods to analyze influencing factors for breakthrough influenza cases and evaluate the predictive model.

Diagnostic Criteria for Breakthrough Cases

The diagnosis of influenza vaccine breakthrough cases was based on the *Diagnostic Criteria for Influenza (WS285-2008)* issued by the National Health Commission of the People' s Republic of China [5]. Breakthrough cases were defined as individuals who developed fever (axillary temperature $ $38°C) with cough or sore throat and other influenza-like illness (ILI) symptoms within the next influenza season, at least two weeks after influenza vaccination, and were confirmed as influenza cases (including types A, B, and C) through laboratory testing.

Statistical Analysis

Statistical analysis was performed using R software version 4.3.3. Normally distributed continuous variables were described as mean ± standard deviation ($\bar{x}\pm s$) and compared between groups using t-tests. Categorical variables were described using relative frequencies and compared using ^{2} tests. Logistic regression analysis with backward stepwise selection was employed to explore influencing factors for breakthrough influenza cases. The predictive model was developed based on the Akaike Information Criterion (AIC), with a nomogram constructed for visualization. Model performance was evaluated using the Hosmer-Lemeshow goodness-of-fit test, receiver operating characteristic (ROC) curve analysis, and calibration curve. The significance level was set at α=0.05, with P<0.05 considered statistically significant.

Results

Epidemiological Characteristics of Breakthrough Cases

The total population of individuals aged 70 years and older in the two districts of Hangzhou was 191,582, with 99,735 receiving influenza vaccination, yielding a vaccination coverage rate of 52.06%. By March 31, 2024, during the 2023-2024 influenza season, 4,689 breakthrough cases were identified through follow-up observation, resulting in a breakthrough infection rate of 4.70%. Among these cases, 3,228 (68.84%) were influenza A, 1,071 (22.84%) were influenza B, and 390 (8.32%) had co-infection with both types. The cohort included 2,470 males (52.68%), with ages ranging from 70 to 99 years and a mean age of 77.78$±$6.01 years.

Univariate Analysis of Influencing Factors

The study included 4,689 individuals in the breakthrough case group and randomly selected 4,853 controls through stratified sampling. Univariate analysis revealed statistically significant differences (P<0.05) between the control and breakthrough case groups in age, sex, living arrangement, residential area, history of hypertension, diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, prior-season influenza vaccination, and engagement in moderate or higher intensity physical activity .

Multivariate Logistic Regression Analysis

Using breakthrough influenza status as the dependent variable (control group=0; breakthrough case group=1) and variables showing significant differences in univariate analysis as independent variables (coding shown in), multivariate logistic regression analysis was performed. The backward stepwise method identified age, sex, living arrangement, residential area, history of hypertension, diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, prior-season influenza vaccination, and moderate or higher intensity physical ac-

tivity as influencing factors for breakthrough influenza cases among individuals aged 70 years and older (P<0.05) .

Specifically, increasing age (OR=0.891, 95%CI=0.816-0.972), female sex (OR=0.907, 95%CI=0.836-0.984), urban residence (OR=0.863, 95%CI=0.793-0.938), prior-season influenza vaccination (OR=0.872, 95%CI=0.804-0.946), and moderate or higher intensity physical activity >3 times/week (OR=0.836, 95%CI=0.770-0.907) were independent protective factors. In contrast, institutional living (OR=1.771, 95%CI=1.474-2.132), history of hypertension (OR=1.458, 95%CI=1.334-1.594), diabetes (OR=1.170, 95%CI=1.062-1.289), stroke (OR=1.254, 95%CI=1.076-1.463), coronary heart disease (OR=1.232, 95%CI=1.102-1.378), chronic obstructive pulmonary disease (OR=1.286, 95%CI=1.163-1.423), and asthma (OR=1.230, 95%CI=1.056-1.433) were independent risk factors for breakthrough influenza cases (P<0.05).

Construction of the Risk Prediction Model

Based on the Akaike Information Criterion (AIC) principle, where a smaller AIC indicates better model fit, inclusion of all the aforementioned variables yielded the minimum AIC value. The final predictive model included age, sex, living arrangement, residential area, history of hypertension, diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, prior-season influenza vaccination, and moderate or higher intensity physical activity. To facilitate interpretation and practical application, a nomogram was constructed to visualize the predictive model [Figure 1: see original paper]. The probability of breakthrough influenza occurrence in individuals aged 70 years and older can be estimated by summing the individual Points for each variable to obtain Total Points and drawing a vertical line from the Total Points to the risk probability axis.

Evaluation of the Risk Prediction Model

The Hosmer-Lemeshow goodness-of-fit test for the constructed predictive model yielded ^{2}=4.956, P=0.762, with P>0.05 indicating good agreement between observed and predicted outcomes. The ROC curve for the predictive model is shown in [Figure 2: see original paper], with an area under the curve (AUC) of 0.806 (95%CI=0.786-0.834), demonstrating good discriminatory accuracy. The calibration curve for the predictive model is presented in [Figure 3: see original paper], showing that the Apparent and Bias-corrected lines are close to the ideal diagonal line, indicating strong consistency between predicted and actual values.

Discussion

Elderly individuals represent a high-risk population for influenza due to declining physiological functions across multiple organ systems, with influenza infection potentially leading to severe complications and even death. Vaccination

is considered one of the most effective and economical measures for preventing influenza and its associated complications [6]. However, influenza viruses undergo frequent genetic mutations that enable immune evasion, leading to the emergence of new variants [7]. Consequently, influenza vaccines are updated annually based on World Health Organization recommendations to address circulating strains in the upcoming season. Despite vaccination, some elderly individuals still develop influenza infection, known as vaccine breakthrough cases. Previous research has rarely focused on this specific population. Investigating the epidemiological characteristics and influencing factors of breakthrough cases is crucial for understanding vaccine efficacy, viral variation, and immune response, and holds significant implications for guiding influenza vaccination strategies and elderly health management.

This study found a breakthrough infection rate of 4.70% among individuals aged 70 years and older. Previous research suggests that influenza diagnosis in elderly populations is often underestimated due to atypical symptom presentation, cognitive deficits in symptom perception or reporting, and lower rates of influenza testing among older patients seeking medical care during influenza season [8-9]. Therefore, the actual incidence of breakthrough cases in elderly populations may be higher than reported in this study, potentially related to factors such as age, declining immune function, and influenza strain match [10]. Our analysis of nearly 10,000 elderly individuals revealed that those aged >80 years had lower risk of breakthrough infection compared to those $ $80 years. This may be attributed to reduced social activity, as most individuals >80 years have limited mobility and tend to stay indoors, resulting in fewer opportunities for influenza virus exposure. Female sex was associated with lower breakthrough risk, possibly because women' s immune systems are generally more active than men' s, potentially related to adaptive immune modulation during reproductive processes and hormonal fluctuations throughout life that may regulate immune responses to influenza vaccination [11]. Additionally, men' s social roles and responsibilities may expose them to more infection sources. Urban residence was associated with lower breakthrough risk compared to rural areas, likely because urban areas typically have better healthcare facilities and professionals, enabling easier access to high-quality healthcare services [12], including early diagnosis and treatment of influenza symptoms. Urban residents may also have higher health awareness, which is associated with preventive health behaviors such as regular physical activity and better dietary habits that enhance immunity and reduce infection risk [13].

Institutional living (primarily in nursing homes and rehabilitation hospitals) was associated with higher breakthrough risk compared to home-based living. In institutional settings, high population density increases opportunities for influenza virus transmission, and residents often have poorer overall health with multiple chronic conditions that may impair vaccine immune responses. This finding aligns with other results from our study showing positive associations between several common chronic diseases (hypertension, diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, and asthma) and breakthrough

infection risk. The presence of chronic conditions can impair immune function, and treatments for these diseases may include immunosuppressive agents that weaken vaccine responses. However, good chronic disease management may enhance vaccine effectiveness [12], such as maintaining blood pressure and glucose within reasonable ranges and controlling airway inflammation. Poor management of chronic conditions may further increase breakthrough risk, suggesting that optimized vaccination strategies for high-risk chronic disease patients—such as higher vaccine doses or customized vaccines for specific health conditions—should be considered.

Prior-season influenza vaccination history also influenced breakthrough occurrence, as previous vaccination may create immunological memory that enhances immune response efficiency, including increased immune cell activity and antibody levels, providing better protection against similar or identical influenza strains [14-15]. This memory effect may improve resistance to influenza viruses and reduce breakthrough incidence even when viral drift occurs. Our investigation of physical activity revealed that moderate or higher intensity exercise >3 times/week had a protective effect against breakthrough infection. Regular physical activity can modulate the immune system by promoting hormone and cytokine release that enhances immune cell activity and antibody production [16-17], and individuals who exercise regularly often adopt healthier lifestyles overall, including better dietary habits and adequate sleep, further reducing breakthrough risk.

Based on our investigation of influencing factors for breakthrough influenza cases in individuals aged 70 years and older, we constructed a risk prediction model with favorable evaluation metrics. This model provides a scientific basis for understanding variations in influenza vaccine effectiveness among elderly populations. By identifying high-risk individuals, we can prioritize vaccination services and strengthen health education. Health economic evaluations demonstrate that despite breakthrough cases, influenza vaccination still reduces influenza-related health and economic burdens at the population level [18] and decreases disease severity and complication rates [10,19]. Implementing different preventive measures based on individual risk levels can improve vaccination effectiveness and reduce breakthrough incidence.

Epidemiological research on influenza vaccine breakthrough cases provides important insights for understanding vaccine effectiveness. Future research should focus on the mechanisms of breakthrough occurrence and develop targeted vaccination strategies to enhance immune protection and reduce influenza-related disease burden in elderly populations. This study has several limitations. The sample covered only one influenza season, and different vaccine technologies may have varying effectiveness. Additionally, the outcomes and prognosis of breakthrough cases warrant further investigation. Future studies should explore model optimization and application to broader populations.

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Author Contributions

BAO Ruolin was responsible for data analysis and drafting the initial manuscript. LU Chao contributed to data integration, figure preparation, and assisted with manuscript drafting. FENG Xin participated in data cleaning and statistical analysis. YE Chunmei and LAI Fenhua were responsible for data collection. NI Zuowei and YANG Dongbo contributed to data entry and assisted with content and formatting revisions. YE Chunmei and ZHENG Yongtao conceived the study, provided research resources and funding, refined the final content, and critically reviewed the manuscript.

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Note: Figure translations are in progress. See original paper for figures.