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Review Article

COVID-19 Vaccine Immunogenicity, Effectiveness and Safety in Frail Older Adults

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SUMMARY

The pandemic of coronavirus disease 2019 (COVID-19) posed a severe threat to the public health worldwide. We focus on frail elderly adults who are the most vulnerable population, especially residents of long-term care facilities or nursing homes. Studies have shown a strong correlation between frailty and COVID-19 mortality in the older population. Meanwhile, older adults possess various characteristics in immune responses, symptoms presentation, and disease outcomes. Frailty decreases resilience in older people and makes the situation more complex.

Moreover, frailty is a strong predictor of prognosis in COVID-19 infected patients. Vaccination is considered an excellent way to stop SARS-CoV-2 spreading. Frail elderly adults are the most vulnerable population, and vaccination programs are implemented first in this group. However, most clinical trials did not enroll frail elderly adults in studies of COVID-19 vaccine development. Real-world evidence of vaccination in older adults with frailty is scanty. We reviewed available data from long-term care facilities and nursing homes.

We focused on immune responses, vaccine effectiveness, and safety of the COVID-19 vaccine. Vaccination could elicit antibody titers and cellular T cells responses in frail elderly adults. SARS-CoV-2 infection, hospital admission, and mortality in residents and staff in long-term care facilities were decreased. COVID-19 vaccination was safe and could prevent disease outbreak in long-term care facilities. Nevertheless, doctors should evaluate frailest or terminal elderly adults carefully.

Frailty-based vaccination program could help to evaluate who should receive the COVID-19 vaccine.

1. Introduction

The pandemic of coronavirus disease 2019 (COVID-19) has had a substantial impact on the world. As of November 30, 2021, the death toll of COVID-19 infection-related was more than 5.20 million.[1] Currently, a cure for the COVID-19 pandemic is unavailable, and vaccines might be an excellent way to stop the disease from spreading. The vulnerable groups in the COVID-19 pandemic include acute kidney injury, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, cardiovascular disease (CVD), cancer, increased D-dimer, male gender, old age, current smoker, and obesity.[2]

Even though the old age is a risk factor for SARS-CoV-2 mortality, frailty rather than age or comorbidity is paramount to predicting mortality in this pandemic.[3]

Frailty has been defined as an extreme state of vulnerability to poor resolution of reserve capacity after endogenous or exogenous stressors, which causes adverse outcomes in elderly adults.[4] Several tools were developed to access frailty, and the two main models of frailty are the phenotype model and the cumulative deficit model. In 2001, Fried and colleagues[5] proposed the frailty phenotype, based on five variables: unintentional weight loss, frequent exhaustion, low energy expenditure, gait slowness, and weak muscle strength. Following this, the frailty index, an accumulated deficits model, was developed from a five-year prospective cohort study by Rockwood et al.[6] Based on a comprehensive geriatric assessment, up to 92 variables of symptoms, signs, laboratory data, diseases, and disabilities were calculated to define frailty. The more cumulative deficits people have, the more possibility they have frailty. However, frailty index evaluation is time-consuming and not feasible in clinical practice. The Clinical Frailty Scale (CFS), a rapid frailty assessment tool, was developed by Rockwood K et al. to meet the need in the real world.[7] The CFS is used to qualify the degree of disability from frailty. The score ranks 1 (very fit) to 9 (terminally ill).

The age alone is insufficient to define the health characteristics of older adults and frailty is a better predictor of mortality in long-term follow-up.[8] Alone with aging, frailty per se increases hospitalization and mortality in elderly adults during the COVID-19 pandemic.[9] A recent meta-analysis revealed frailty as a mortality predictor in elderly adults with COVID-19. A total of 924,520 patients were analyzed, and the result revealed higher rates of COVID-19-related mortality in frail elderly adults (OR [odds ratio]: 5.76; 95% confidence interval [95% CI]: 3.85–8.61, I2: 40.5%).[10] The clinical frailty scale, a rapid assessment tool, was widely used to predict COVID-19 mortality.[11,12] The impact of frailty was strongly associated with COVID-19 prognosis and mortality rather than age.

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Vaccines would be feasible to achieve herd immunity, and SARS-CoV-2 transmission is estimated to decrease when herd immunity reaches 70%.[13] After more than one year, several COVID-19 vaccines have been developed with clarification of high efficacy and effectiveness.[14,15] However, COVID-19 vaccine trials have generally excluded long-term care facility residents or frail elderly adults. For instance, in the phase III trial of ChAdOx1 nCoV-19, individuals over 65 only accounted for 22%.[15] The individuals over 55 years and older were 42.2% in the BNT162b2 mRNA Covid-19 Vaccine trial. The mRNA-1273 SARS-CoV-2 vaccine trial enrolled 24.8% of participants aged over 65 years. Even in the NVX-CoV2373 Covid-19 Vaccine, only 27.9% of participants were over age 65. A systemic review investigated the published and ongoing phase II-III studies and revealed that only a tiny fraction of the vulnerable elderly adults were included.[16] Given the safety concerns, the particular proportion of elderly adults included in clinical trials was in a relatively healthy status. Nevertheless, the frailest older adults were the first group to receive COVID-19 vaccination. About one-half of nursing homes and long-term care facilities residents are frail, and approximately 40% are in pre-frail condition.[17] The feasible data from the nursing home and long-term care facilities might provide evidence for referencing in frail elderly adults.

2. Immunogenicity

Effective vaccines are supposed to have protective immunity and maintenance of immunity against SARS-CoV-2. The immunity to SARS-CoV-2 infection is complex and is related to humoral antibodies, cellular immune responses, and the innate immune system.[18] For elderly frail adults, another consideration is “Immunosenescence”. “Immunosenescence” is defined as the declining function of the immune system in the elderly population with an increased vulnerability to diseased pathogens and poor response to vaccination.[19] Previously developed vaccines revealed poor immune response in elderly adults, including herpes zoster, influenza, and pneumococcal vaccine.[20] Therefore, we should consider immunosenescence when it comes to COVID-19 vaccine development.

The mRNA and viral vector vaccine continuously presented their safety and efficacy results, but most trials enrolled younger and healthy adults. Until this year, studies in long-term care facilities and nursing homes were conducted to confirm previous study results. Salmerón et al.[21] performed a small trial of the BNT162b2 vaccine, including 134 residents aged more than 65 years in long-term care facilities (Table 1). The result revealed that participants increased antibody levels after two doses of vaccination, and higher plasma antibody titers were noticed in the history of COVID-19 infection. Antibody titers were only related to previous COVID-19 infection status, regardless of frailty, disability, older age, or comorbidities. Torres et al.[22] evaluated humoral and cellular immunity of CD8+ and CD4+ T cells response after two doses of the BNT162b2 vaccine. The result reported that the BNT162b2 vaccine-elicited SARS-CoV-2 S antibody responses in nursing home residents and higher plasma antibody levels were observed in previously infected residents. Nevertheless, SARS-CoV-2 IFN-γ CD8+ and CD4+ T cells responses after vaccination were lower in nursing home residents, regardless of their SARS-CoV-2 infection status. T-cell response data was confounded and maybe a cross-reactive reaction of common cold coronaviruses. Tut et al.[23] focused on the immune response after a single dose of BNT162b2 or ChAdOx1 nCoV-19 vaccines in long-term care facilities. The trial enrolled 124 participants, with 89 (72%) younger staff and 35 (28%) elderly residents. The finding was that participants with previous COVID-19 infection had higher antibody titers after a single-dose vaccination. Nevertheless, for infection-naïve residents, delayed antibody responses to the first dose of vaccine were observed. Cellular responses were no specific difference between residents and staff. The presence of antibody titers and T-cell response is not equal to the immunity of SARS-CoV-2. Neutralizing antibodies against the SARS-CoV-2 challenge have been shown in rhesus macaques but not humans.[24] Even though the immune responses of SARS-CoV-2 are not clear, a combination of humoral antibodies and Th-1-based T cells’ immune responses will probably be optimal to against SARS-CoV-2 infection.[25]

3. Effectiveness

Full FDA approval of a COVID-19 vaccine means the vaccine is safe and effective enough for most of the population. Given that the normal step of making a vaccine for the general population is time-consuming, Emergency Use Authorization (EUA) was applied for certain vaccines, which showed safety and effectiveness from limited data in small clinical trials. Vaccine effectiveness is the proportionate reduction in cases among vaccinated persons in a typical field condition (not a perfectly controlled).[26] All the approved vaccines are safe and effective in preventing disease infection or mortality in public. However, frail elderly adults were not enrolled in most trials. Domi et al.[27] investigated BNT162b2 vaccine effectiveness in 2,501 nursing homes. At six weeks, the adjusted incidence rate ratio (IRR) in resident cases and deaths were 0.64 (95% CI: 0.48–0.86) and 0.45 (95% CI: 0.31–0.65), respectively, after the first vaccination. Furthermore, fewer resident and staff cases were associated with fewer certified beds and high nurse staffing. VIVALDI study[28] was a prospective cohort study in a long-term care facility setting, which enrolled 10,412 care home residents aged 65 years and older to examine the vaccine effectiveness after the first dose of ChAdOx1 nCoV-19 and BNT162b2. The report showed that adjusted hazard ratios (HRs) for PCR-positive infection declined to 0.44 (95% CI: 0.24–0.81) at 28–34 days and 0.38 (95% CI: 0.19–0.77) at 35–48 days. A prospective cohort study of vaccine effectiveness was conducted on nursing home residents, staff, and healthcare workers in Spain. After excluding previous SARS-CoV-2 infection individuals, data of 28,456 nursing home residents, 26,170 nursing home staff, and 61,791 healthcare workers were analyzed in this study. They observed that the adjusted HRs of SARS-CoV-2 infection in nursing home residents, nursing home staff, and healthcare workers were 0.09 (95% CI: 0.08 to 0.11), 0.20 (95% CI: 0.17 to 0.24), and 0.13 (95% CI: 0.11 to 0.16) after two doses of vaccines. For nursing home residents, hospital admission and mortality decreased after two doses of vaccines.[29]

Monge et al.[30] conducted a study to differentiate the effectiveness between with and without previous SARS-CoV-2 infection. For residents with and without previous infection, vaccine effectiveness was 56.8% (95% CI: 47.1%–67.7%) and 81.8% (95% CI: 81.0%–82.7%) respectively. The risk of COVID-19 infection in non-vaccinated residents without previous infection decreased to 81.4% (95% CI: 73.3%–90.3%). This indirect vaccine protective effect might be associated with herd immunity. In brief, most vaccine effectiveness data are mostly based on the mRNA vaccine, and the results provide promising protective effects against SARS-CoV-2 infection. The governmental department made the policy of long-term care facilities’ testing requirements for staff and residents. The rule of routine testing of SARS-CoV-2 infection is not recommended unless symptomatic individuals are identified or an outbreak.[31] Post-vaccine infection rates are more likely to detect symptomatic residents than asymptomatic populations.

Table 1
COVID-19 vaccine immunogenicity, effectiveness and safety in frail elderly adults.

Study	Country	Participants	Vaccine	Outcomes
Immunogenicity				
Salmerón Ríos, et al., 2021[21]	Spain	134 residents, mean age was 82.9 years (range 65–99), 96 (71.6%) were female, with different frailty and disability profiles in five LTCFs.	1st and 2nd doses of BNT162b2 vaccine	The mean antibody titers in residents with and without previous COVID-19 infection were 49,878 AU/ml and 15,274 AU/ml, respectively (mean difference 34,604; 95% CI: 27,699–41,509). Only pre-vaccination COVID-19 was an independent predictor of immunogenicity.
Torres, et al., 2021[22]	Spain	60 nursing-home residents, median age 87.5 years (range 53–100), 44 females, 10 had previously COVID-19 infection. 18 healthy controls, median age 48.5 years (range 27–54) 15 females.	1st and 2nd doses of BNT162b2 vaccine	SARS-CoV-2 IFN-γ $CD8^+$ and $CD4^+$ T-cell responses were documented in 88% (15/17) and all control subjects after vaccination, respectively, but only in 65.5% (38/58) and 22.4% (13/58) of nursing-home residents.
Tut, et al., 2021[23]	UK	124 participants from 14 LTCFs: 89 (72%) staff (median age 48 years [IQR 35.5–56]) and 35 (28%) residents, median age 87 years (range 77–90).	1st dose of BNT162b2 or ChAdOx1 nCoV-19 vaccines	SARS-CoV-2 (+): high antibody titers following vaccination. SARS-CoV-2 (-): titers were negatively correlated with age (r_s = -0·434, p < 0.0001) and were 8.2-times lower in residents than in staff. A kinetic delay antibody generation in older infection-naive participants (> 42 days).
Effectiveness				
Domi, et al., 2021[27]	USA	2,501 nursing homes Cohort 1: 840 facilities Cohort 2: 830 facilities Cohort 3: 831 facilities	1st BNT162b2 vaccine	At 5 and 6 weeks, resident cases (IRR: 0.68 [95% CI: 0.54–0.84], IRR: 0.64 [95% CI: 0.48–0.86], respectively); resident deaths (IRR: 0.59 [95% CI: 0.45–0.77], IRR: 0.45 [95% CI: 0.31–0.65], respectively).
Shrotri, et al., 2021[28]	UK	10,412 care home residents, median age 86 years (IQR 80–91), 7,247 (69.6%) females from 310 LTCFs. 1155 residents (11.1%) had previous SARS-CoV-2 infection	The 1st dose of ChAdOx1 nCoV-19 and BNT162b2 vaccines	Adjusted HRs for PCR-positive infection relative to unvaccinated residents declined from 28 days after the first vaccine dose to 0.44 (95% CI 0.24–0.81) at 28-34 days and 0.38 (0.19–0.77) at 35-48 days.
Cabezas, et al, 2021[29]	Spain	28,456 nursing home residents, 26,170 nursing home staff, and 61,791 healthcare.	1st and 2nd doses of BNT162b2 vaccine	The adjusted HRs for SARS-CoV-2 infection after 2nd doses: 0.09 (95% CI 0.08-0.11) for nursing home residents. Adjusted HRs for hospital admission and mortality after 2nd doses: 0.05 (0.04–0.07) and 0.03 (0.02–0.04), respectively, for nursing home residents.
Monge, et al., 2021[30]	Spain	299,209 residents in LTCFs, age ≥ 65 years. A previous SARS-CoV-2 infection was identified in 12.7% of vaccinated participants at the beginning of the reference period and 22.3% at the beginning of the study period.	99.0% had > 1st dose, 92.6% had 2nd doses 99.8% BNT162b2 vaccines	SARS-CoV-2 (-): VE was 81.8% (95% CI 81.0%–82.7%). SARS-CoV-2 (+): VE was 56.8% (95% CI 47.1%–67.7%). In nonvaccinated residents with no previous infection, risk decreased by up to 81.4% (95% CI 73.3%–90.3%).
Safety				
Wyller, et al., 2021[33]	Norway	35,000 nursing home residents.	1st BNT162b2 vaccine	100 reported deaths A casual like to the vaccine Probable: 10 cases Possible: 26 cases Unlikely: 59 cases Unclassifiable: 5 cases

CI: confidence interval, HRs: hazard ratios, IRR: incidence rate ratio, IQR: interquartile range, LTCFs: long-term care facilities, r_s: Spearman rank-order correlation coefficient, VE: vaccine effectiveness.

4. Safety

Since the beginning of the COVID-19 vaccination, post-vaccination deaths have been reported worldwide. According to the Centers for Disease Control and Prevention (CDC) in the United States, severe adverse events after the COVID-19 vaccine is rare but may occur. These severe adverse effects include anaphylaxis, thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré Syndrome (GBS), myocarditis, and pericarditis. Reports of death after COVID-19 vaccination are 8,390 (0.0021%).[32] Overall, this information is from the general population instead of frail individuals. Wyller et al.[33] performed a study in a nursing home in Norway to examine the causality between the COVID-19 vaccine and death. In the study period, 35,000 nursing home patients received the BNT162b2 vaccine, with 100 reports of suspected fatal reactions. The characteristics of 100 reported cases were age (87.7 years old) and moderate to severe frailty (CFS = 7.8). Four experts were assigned to assess the reported cases randomly. Among the 100 cases, the probable cases accounted for 10 (10%) with a sooner event time course after vaccination. Even in normal circumstances, elderly and frail residents in long-term care

facilities or nursing homes often have a higher mortality rate. Therefore, background rates of all-cause mortality among nursing home residents were investigated in Canna to inform COVID-19 vaccine safety. The study reported that the incidence rates of monthly mortality, hospitalization, and emergency department visits during vaccination were consistent with the pre-pandemic period.[34]

Vaccination is an excellent way to prevent COVID-19 from spreading in nursing homes and long-term care facilities. Furthermore, mortality and admission rates decreased after vaccination. Therefore, most residents in these facilities are recommended to receive COVID-19 vaccines. However, we must think twice before implementing the COVID-19 vaccination program in frailest elderly adults. A previous case-control study revealed that vaccine effectiveness against influenza infection was different according to levels of frailty. Adjusted vaccine effectiveness in non-frail robust elderly adults is optimal (77.6%) and decreased to unrecognized effects in the frailest patients.[35] Frailty is a confounder when considering influenza vaccine effectiveness. It might be reasonable to consider frailty when evaluating COVID-19 vaccine effectiveness. For residents with a very short life expectancy or frailest status, vaccination may cause unnecessary discomforts and should be avoided.[36] Norwegian authorities investigated 23 deaths in frail elderly adults after BNT162b2 vaccination. The doctors concluded that common adverse effects may have led to fatal outcomes in some frail individuals.[37] The authority has recommended that doctors consider the benefits and risks of vaccination in frail elderly adults, such as 8 or 9 in the CFS ranking.[38]

Protective effects of the COVID-19 vaccine in frail older adults in community-dwelling are not well studied. In a systematic review, the prevalence of frailty in the community ranged from 4.0 to 59.1%, and the overall weighted prevalence was 10.7% (95% CI: 10.5–10.9; 21 studies; 61,500 participants).[39] A case-control study in the UK investigates risk factors of post-vaccination SARS-CoV-2 infection. One million two hundred forty thousand nine users of the COVID Symptom Study mobile phone app were analyzed.

The app users reported SARS-CoV-2 positive testing at least 14 days after the first vaccination or at least seven days after the second dose. The result revealed that frailty was related to post-vaccination infection in elderly adults aged more than 60 (odds ratio [OR]: 1.93, 95% CI: 1.50–2.48; $p < 0.0001$).[40] The putative reasons included frequent healthcare giver visiting and decreased immune responses to vaccination. Systematic frailty screening in community elderly adults might help develop frailty-based vaccination schedules.

5. Conclusion

Evaluating frailty in the COVID-19 vaccination program is essential for elderly adults. Frailty rather than age is crucial when predicting outcomes in the elderly population. Previous SARS-CoV-2 infection has an impact on humoral antibody responses after vaccination. Higher antibody titers were observed in SARS-CoV-2 infected individuals, while delayed antibody responses were noted in SARS-CoV-2 naïve population. In frail elderly adults, vaccination still could elicit immune responses. However, humoral antibody titers and cellular T cells responses cannot represent the immunity of SARS-CoV-2. Immune regulation is complex, and both humoral and cellular responses may play a role in the mechanism. Vaccine effectiveness in real-world data helps evaluate disease prevention. Large-scale vaccination programs in long-term care facilities and nursing homes revealed that the COVID-19 vaccine could prevent residents and staff from SARS-CoV-2 infection, hospital admission, and mortality. In addition, an indirect protective effect was found and might be related to herd immunity. Post-vaccination deaths were investigated in many countries. Generally, COVID-19 vaccination in frail elderly adults in long-term care facilities or nursing homes was safe and could prevent the disease from spreading effectively. However, in frailest or terminally ill older adults, doctors should evaluate when providing vaccination. Minor or common adverse effects might cause extreme discomforts or fatal outcomes. For community-dwelling frail adults, post-vaccination infection was a concern; therefore, preventive strategies and frailty screening were suggested.

It is promising that more studies involving elderly adults are ongoing, and hopefully, functional status and frailty will be measured. Overall, a frailty-based vaccination program is helpful and needs to be set up as soon as possible.

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Conflicts of interest

The authors declare that they have no competing interests.

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