



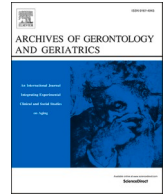
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Editorial

COVID-19 vaccination and frailty in older adults



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The COVID-19 pandemic strongly impacts the whole world in various dimensions (Wang, 2020), and studies have shown the high mortality risk of older patients with COVID-19 infections (Mostaza, et al., 2020; Niu, et al., 2020). Older age, geriatric syndromes, underlying chronic conditions and multimorbidity have been recognized as major determinants for adverse outcomes of older adults with various clinical conditions, and COVID-19 was no exception (Lim et al., 2020). Although the mortality risk of SARS-CoV-2 infections in older people has been reported, older people are not simply an age-defined entity with identical health characteristics (Hajek & König, et al., 2020; Lee, et al., 2020; Liu, et al., 2020). Instead, advancing age substantially increased the variation of health characteristics of older people in their late life (Duim & Lima Passos, 2020; Jeon, 2020). Studies have shown that functional impairment or disability was more important than multimorbidity in predicting their quality of life and mortality (Pivetta, et al., 2020; Li, et al., 2021), which may be applied to COVID-19 pandemic as well. Dumitrascu, et al., conducted a meta-analysis of 118,373 older COVID-19 patients and identified the importance of frailty in predicting mortality and delirium (Dumitrascu, et al., 2021), but not older age alone. Moreover, vulnerable populations like home-bound older persons were at greater mortality risk during the COVID-19 pandemic, but COVID-19 was not the sole cause (Nilsson, et al., 2021). The prevalence of geriatric syndromes and their impacts on disease severity and mortality of older patients with COVID-19 infections were similar across studies (Niu, et al., 2020; Covino, et al., 2021; Karlsson, et al., 2021). In hospital settings, frailty (defined by the Clinical Frailty Scale or frailty index) has been validated to predict adverse clinical outcomes in different perspectives, i.e., interval and rapid disease progression during hospital admissions (Lim, et al., 2021). Like the impacts of frailty on most clinical conditions, the diagnosis, treatment, and outcomes of COVID-19 was also strongly influenced by frailty, disability, and dementia that needs special attentions.

With the success of vaccine development, the strategies to respond to COVID-19 pandemic gradually shifted from border controls, quarantine, and lockdowns to vaccinations and specific therapeutic agents.

However, COVID-19 vaccination on frail older adults is challenging because they may be benefited and harmed by the newly developed vaccines. Overall, 24.8% of participants in the Moderna vaccine trial were people aged 65 years and older (Baden, et al., 2021), and the Oxford-AstraZeneca trial enrolled 5% participants aged over 70 years (Voysey, et al., 2021). Although these COVID-19 vaccine trials enrolled certain proportion of older adults, these trials only enrolled older adults with stable conditions. In the real world practice, the Norwegian government provided BNT162b2 mRNA vaccines for approximately 35,000 nursing home residents (mean age over 87 years), and received 100 reports of suspected fatal adverse events (Wyller, et al., 2021). After examinations of the expert groups, 10 probable and 26 possible vaccine-related fatal events were concluded, which approximately equaled to 1 potential vaccine-related fatality in 1,000 residents. Compared to healthy older adults receiving COVID-19 vaccines, nursing home residents showed higher vaccine-related fatality rate. The potential vaccine-related fatal events may be the existing frailty and disability, but not older age *per se*. Nevertheless, the post-vaccination deaths have attracted public attentions and concerns to COVID-19 vaccines of all brands. The focus group study indicated that the short development course with limited scales of testing was the major cause for the hesitancy of nursing home staff towards COVID-19 vaccines (Harrison, et al., 2021). The concerns about vaccine development were widespread in the frontline nursing home staff, (Berry, et al., 2021) not to mention the lay public.

The vulnerable groups needing vaccines are also the ones susceptible to adverse reactions. Antonelli, et al., have highlighted the lack of studies supporting the efficacy and safety of COVID-19 vaccines on older adults with frailty, disability, or living in long-term care facilities (Antonelli, et al., 2021). A recent study examined the immunogenicity and adverse reactions of BNT162b2 mRNA vaccines in older adults with frailty or living in long-term care facilities (Salmerón Ríos, et al., 2021), and showed favorable results, but the small sample size and inclusion criteria have caused some analytical concerns. In this study, 134 residents of 5 long-term care facilities were enrolled and over 40% of study

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participants had their Barthel Index between 0-35. However, 58.2% of all participants had previous COVID-19 infections. The study concluded that the pre-vaccination COVID-19 status was the only factor associated with vaccine immunogenicity, but not age, frailty, disability, cognitive performance, multimorbidity, and depressive mood. Meanwhile, the study reported no severe adverse events during the study period. Authors concluded that BNT162b2 vaccinations for residents in long-term care facilities were not only safe, but also effective through the responses of immunogenicity. Notably, the immunogenicity among COVID-19 naïve residents was significantly lower than those with previous COVID-19 infections, and survivors of prior COVID-19 infections may possess certain immunity against another COVID-19 infection. Moreover, the small sample size with nearly 60% participants had pre-vaccination COVID-19 infections was unable to evaluate the adverse reactions of vaccines.

A recent review focused on the interrelationships between frailty and immunity in older adults showed that a well-functioning immune system prevented frailty and vice versa, and the adherence to immunization schedule not only prevented frailty but also maintained the immune homeostasis (Vetrano, et al., 2021). For vulnerable older adults with existing frailty and disability, recommendations for vaccination are always challenging due to several conditions: 1) infections of older adults with limited mobility are more commonly due to caregivers, 2) lower immunogenicity, especially the T-cell immune responses to vaccinations, limiting the clinical efficacy (Torres, et al., 2021), and 3) greater risk for adverse events to vaccines. Nace, et al., reported substantial variation in antibody responses among residents in assisted living, personal care, and independent living communities, so policies of vaccinations and reopening should differ in long-term care settings (Nace, et al., 2021). A large prospective cohort study based on over 10,000 care home residents indicated that COVID-19 vaccines (BNT162b2 and Oxford-AstraZeneca) significantly protected care home residents against COVID-19 infections, and reduced the SARS-CoV-2 transmission, but did not eliminate the infection risk (Shrotri, et al., 2021). However, a major confounder of related studies was the vaccination status of caregivers and the staff of long-term care facilities. Due to the lack of well-designed randomized controlled trials, the mathematical model demonstrated the importance of increasing vaccine coverage of the nursing home staff to reduce symptomatic cases of nursing home residents (Kahn, et al., 2021). A study of 2,501 nursing homes in the United States showed that the BNT162b2 vaccination strategies covering both residents and care staff reduced COVID-19 infections in both residents and nursing staff, especially the nursing home with fewer certified beds and higher nursing staff (Domi, et al., 2021). Although vaccinations did not entirely prevent postvaccination breakthrough COVID-19 infections, eventually, these breakthrough infections were mild or asymptomatic in nature (Teran, et al., 2021). Altogether, the vaccination strategies on frail older persons and nursing home residents should include both residents and staff of nursing homes, but safety and efficacy profiles of COVID-19 vaccines in long-term care settings still need further investigations.

In addition to residential care settings, the COVID-19 pandemic also brought special challenges to home care agencies that both caregivers and care recipients have experienced the risk of SARS-CoV-2 infections and transmission (Rowe, et al., 2020). However, millions of caregivers were absent from the development of policies and strategies of health care systems in responding to COVID-19 pandemic. Based on available evidences, more research efforts in vaccine development and vaccination strategies among older persons with frailty, disability, dementia, living in long-term care facilities, or home-bound status are needed (Palermo, 2020).

Not only the long-term care settings, even acute hospitals have experienced the indirect impacts of the COVID-19 pandemic because the hospital stay of non-COVID-19 patients were shortened and the mortality risk was increased during the pandemic (Rizzi, et al., 2020). It has been reported that delayed comprehensive geriatric assessment-based

care planning increased in-hospital mortality risk, (Hsu, et al., 2021) which may be extrapolated to the hospital care during COVID-19 pandemic. As a common condition in the communities and older hospital patients (Jiang, et al., 2020), modern health care systems should prioritize the assessment and management of frailty alone or with other conditions to improve quality of care for older people (Lee, et al., 2020). Despite vaccines successfully reduced SARS-CoV-2 infection and transmission in long-term care facilities, policy development targeted on frail older persons and nursing home residents deserve special attentions to optimize the best strategies for the vulnerable populations.

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Liang-Kung Chen^{a,b,c,*}^a Aging and Health Research Center, National Yang Ming Chiao Tung University Yangming Campus, Taipei, Taiwan^b Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan^c Taipei Municipal Dan-Dau Hospital, Taipei, Taiwan

* Corresponding author at: Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, No. 201, Sec 2 Shih-Pai Road, Taipei, Taiwan.

E-mail address: lkchen2@vghtpe.gov.tw.