



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Editorial

COVID-19 vaccination and frailty in older adults



ARTICLE INFO

Keywords

COVID-19
disability
frailty
vaccination

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

<https://doi.org/10.1016/j.archger.2021.104487>

Available online 14 July 2021

0167-4943/© 2021 Elsevier B.V. All rights reserved.

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.

References

- Antonelli Incalzi, R., Trevisan, C., Del Signore, S., Volpato, S., Fumagalli, S., Monzani, F., Bellelli, G., Gareri, P., Mossello, E., Malara, A., Coin, A., Zia, G., & Ranhoff, A. H. (2021). Are vaccines against COVID-19 tailored to the most vulnerable people? *Vaccine*, 39(17), 2325–2327.
- Baden, L. R., Sahly, H. H., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Roupael, N., Creech, C. B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., & COVE Study Group. (2021). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *The New England journal of medicine*, 384(5), 403–416.
- Berry, S. D., Johnson, K. S., Myles, L., Herndon, L., Montoya, A., Fashaw, S., & Gifford, D. (2021). Lessons learned from frontline skilled nursing facility staff regarding COVID-19 vaccine hesitancy. *Journal of the American Geriatrics Society*, 69(5), 1140–1146. <https://doi.org/10.1111/jgs.17136>
- Covino, M., De Matteis, G., Polla, D., Santoro, M., Burzo, M. L., Torelli, E., Simeoni, B., Russo, A., Sandroni, C., Gasbarrini, A., & Franceschi, F. (2021). Predictors of in-hospital mortality AND death RISK STRATIFICATION among COVID-19 PATIENTS aged ≥ 80 YEARS OLD. *Archives of gerontology and geriatrics*, 95, Article 104383. <https://doi.org/10.1016/j.archger.2021.104383>
- Domi, M., Leitson, M., Gifford, D., Nicolau, A., Sreenivas, K., & Bishnoi, C. (2021). The BNT162b2 vaccine is associated with lower new COVID-19 cases in nursing home residents and staff. *Journal of the American Geriatrics Society*. <https://doi.org/10.1111/jgs.17224>. Advance online publication. 10.1111/jgs.17224.
- Duim, E., & Lima Passos, V. (2020). Highways to Ageing - Linking life course SEP to multivariate trajectories of health outcomes in older adults. *Archives of gerontology and geriatrics*, 91, Article 104193. <https://doi.org/10.1016/j.archger.2020.104193>. Advance online publication.
- Dumitrascu, F., Branje, K. E., Hladkovic, E. S., Lalu, M., & McIsaac, D. I. (2021). Association of frailty with outcomes in individuals with COVID-19: A living review and meta-analysis. *Journal of the American Geriatrics Society*. <https://doi.org/10.1111/jgs.17299>. Advance online publication. 10.1111/jgs.17299.
- Hajek, A., & König, H. H. (2020). Feeling too old? Consequences for subjective well-being. Longitudinal findings from the German Ageing Survey. *Archives of gerontology and geriatrics*, 90, Article 104127. <https://doi.org/10.1016/j.archger.2020.104127>
- Harrison, J., Berry, S., Mor, V., & Gifford, D. (2021). "Somebody Like Me": Understanding COVID-19 Vaccine Hesitancy among Staff in Skilled Nursing Facilities. *Journal of the American Medical Directors Association*, 22(6), 1133–1137. <https://doi.org/10.1016/j.jamda.2021.03.012>
- Hsu, C. C., Yu, P. C., Lin, M. H., Peng, L. N., & Chen, L. K. (2021). Early geriatric evaluation and management services reduced in-hospital mortality risk among frail oldest-old patients. *Ageing Medicine and Healthcare*, 12(1), 53–61.
- Jeon, H. O. (2020). Correlation of physical, psychological, and functional factors with independent medication adherence in Korean older adults with chronic illness: Using the 2017 national survey of older Koreans. *Archives of gerontology and geriatrics*, 90, Article 104130.
- Jiang, J. S. E., Han, A. Y. Y., Tan, X. L., Goh, J., & Tan, B. Y. (2020). Frailty in a community hospital in Singapore: Prevalence and contributing factors. *Ageing Medicine and Health Care*, 11, 39–46.
- Kahn, R., Holmdahl, I., Reddy, S., Jernigan, J., Mina, M. J., & Slayton, R. B. (2021). Mathematical modeling to inform vaccination strategies and testing approaches for COVID-19 in nursing homes. *Clinical infectious disease: an official publication of the Infectious Diseases Society of America* (p. ciab517). <https://doi.org/10.1093/cid/ciab517>. Advance online publication.
- Karlsson, L. K., Jakobsen, L. H., Hollensberg, L., Ryg, J., Midttun, M., Frederiksen, H., Glenthøj, A., Kodahl, A. R., Secher-Johnsen, J., Nielsen, L. K., Boffill, N. G., Knudtzen, F. C., & Lund, C. M. (2021). Clinical presentation and mortality in hospitalized patients aged 80+ years with COVID-19-A retrospective cohort study. *Archives of gerontology and geriatrics*, 94, Article 104335. <https://doi.org/10.1016/j.archger.2020.104335>
- Lee, W. J., Peng, L. N., & Chen, L. K. (2020). Metabolic syndrome and its components are associated with frailty: a nationwide population-based study in Taiwan. *Ageing Medicine and Health Care*, 11, 47–52.
- Lee, W. J., Peng, L. N., Lin, M. H., Loh, C. H., & Chen, L. K. (2020). Determinants and indicators of successful ageing associated with mortality: a 4-year population-based study. *Ageing*, 12(3), 2670–2679. <https://doi.org/10.18632/aging.102769>
- Li, H. W., Lee, W. J., Lin, M. H., Peng, L. N., Loh, C. H., Chen, L. K., & Lu, C. C. (2021). Quality of Life among Community-Dwelling Middle-Aged and Older Adults: Function Matters More than Multimorbidity. *Archives of gerontology and geriatrics*, 95, Article 104423. <https://doi.org/10.1016/j.archger.2021.104423>

- Lim, J. P., Low, K., Lin, N., Lim, C., Ong, S., Tan, W., Tay, W. C., Tan, H. N., Young, B. E., Lye, D., & Lim, W. S. (2021). Predictors for development of critical illness amongst older adults with COVID-19: Beyond age to age-associated factors. *Archives of gerontology and geriatrics*, *94*, Article 104331. <https://doi.org/10.1016/j.archger.2020.104331>
- Lim, W. S., Liang, C. K., Assantachai, P., Auyeung, T. W., Kang, L., Lee, W. J., Lim, J. Y., Sugimoto, K., Akishita, M., Chia, S. L., Chou, M. Y., Ding, Y. Y., Iijima, K., Jang, H. C., Kawashima, S., Kim, M., Kojima, T., Kuzuya, M., Lee, J., Lee, S. Y., & Arai, H. (2020). COVID-19 and older people in Asia: Asian Working Group for Sarcopenia calls to actions. *Geriatrics & gerontology international*, *20*(6), 547–558. <https://doi.org/10.1111/ggi.13939>
- Liu, L. K., Chou, K. H., Hsu, C. H., Peng, L. N., Lee, W. J., Chen, W. T., Lin, C. P., Chung, C. P., Wang, P. N., & Chen, L. K. (2020). Cerebellar-limbic neurocircuit is the novel biosignature of physio-cognitive decline syndrome. *Aging*, *12*(24), 25319–25336. <https://doi.org/10.18632/aging.104135>
- Mostaza, J. M., García-Iglesias, F., González-Alegre, T., Blanco, F., Varas, M., Hernández-Blanco, C., Hontañón, V., Jaras-Hernández, M. J., Martínez-Prieto, M., Menéndez-Saldaña, A., Cachán, M. L., Estirado, E., Lahoz, C., & Carlos III COVID Working Group. (2020). Clinical course and prognostic factors of COVID-19 infection in an elderly hospitalized population. *Archives of gerontology and geriatrics*, *91*, Article 104204.
- Nace, D. A., Kip, K. E., Mellors, J. W., Peck Palmer, O. M., Shurin, M. R., Mulvey, K., Crandall, M., Sobolewski, M. D., Enick, P. N., McCormick, K. D., Jacobs, J. L., Kane, A. L., Lukanski, A., Kip, P. L., & Wells, A. (2021). Antibody Responses After mRNA-Based COVID-19 Vaccination in Residential Older Adults: Implications for Reopening. *Journal of the American Medical Directors Association*. <https://doi.org/10.1016/j.jamda.2021.06.006>. S1525-8610(21)00555-7. Advance online publication.
- Nilsson, L., Andersson, C., & Sjö Dahl, R. (2021). COVID-19 as the sole cause of death is uncommon in frail home healthcare individuals: a population-based study. *BMC geriatrics*, *21*(1), 262. <https://doi.org/10.1186/s12877-021-02176-z>
- Niu, S., Tian, S., Lou, J., Kang, X., Zhang, L., Lian, H., & Zhang, J. (2020). Clinical characteristics of older patients infected with COVID-19: A descriptive study. *Archives of gerontology and geriatrics*, *89*, Article 104058.
- Palermo, S. (2020). Covid-19 Pandemic: Maximizing Future Vaccination Treatments Considering Aging and Frailty. *Frontiers in medicine*, *7*, Article 558835. <https://doi.org/10.3389/fmed.2020.558835>
- Pivetta, N., Marincolo, J., Neri, A. L., Aprahamian, I., Yassuda, M. S., & Borim, F. (2020). Multimorbidity, frailty and functional disability in octogenarians: A structural equation analysis of relationship. *Archives of gerontology and geriatrics*, *86*, Article 103931. <https://doi.org/10.1016/j.archger.2019.103931>
- Rizzi, A., Mammarella, L., Necozone, S., Bocale, R., Grassi, D., Ferri, C., & Desideri, G. (2020). Looking at intra-hospital non COVID-19 mortality among elderly patients during COVID-19 pandemic. *Archives of gerontology and geriatrics*, *90*, Article 104173. <https://doi.org/10.1016/j.archger.2020.104173>
- Rowe, T. A., Patel, M., O'Conor, R., McMackin, S., Hoak, V., & Lindquist, L. A. (2020). COVID-19 exposures and infection control among home care agencies. *Archives of gerontology and geriatrics*, *91*, Article 104214.
- Salmerón Ríos, S., Mas Romero, M., Cortés Zamora, E. B., Tabernero Sahuquillo, M. T., Romero Rízos, L., Sánchez-Jurado, P. M., Sánchez-Nievas, G., Señalada, J., García Nogueras, I., Estrella Cazalla, J. D., Andrés-Prete, F., Murillo Romero, A., Lauschke, V. M., Stebbing, J., & Abizanda, P. (2021). Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. *Journal of the American Geriatrics Society*, *69*(6), 1441–1447.
- Shrotri, M., Krutikov, M., Palmer, T., Giddings, R., Azmi, B., Subbarao, S., Fuller, C., Irwin-Singer, A., Davies, D., Tut, G., Lopez Bernal, J., Moss, P., Hayward, A., Copas, A., & Shallcross, L. (2021). Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. *The Lancet. Infectious diseases*. [https://doi.org/10.1016/S1473-3099\(21\)00289-9](https://doi.org/10.1016/S1473-3099(21)00289-9). S1473-3099(21)00289-9. Advance online publication.
- Teran, R. A., Walblay, K. A., Shane, E. L., Xydis, S., Gretsche, S., Gagner, A., Samala, U., Choi, H., Zelinski, C., & Black, S. R. (2021). Postvaccination SARS-CoV-2 Infections Among Skilled Nursing Facility Residents and Staff Members - Chicago, Illinois, December 2020-March 2021. *MMWR. Morbidity and mortality weekly report*, *70*(17), 632–638.
- Torres, I., Albert, E., Giménez, E., Alcaraz, M. J., Botija, P., Amat, P., Remigia, M. J., Beltrán, M. J., Rodado, C., Huntley, D., Olea, B., & Navarro, D. (2021). B and T cell immune responses elicited by the Comirnaty® COVID-19 vaccine in nursing home residents. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. <https://doi.org/10.1016/j.cmi.2021.06.013>. S1198-743X(21)00332-3. Advance online publication.
- Vetrano, D. L., Triolo, F., Maggi, S., Malley, R., Jackson, T. A., Poscia, A., Bernabei, R., Ferrucci, L., & Fratiglioni, L. (2021). Fostering healthy aging: The interdependency of infections, immunity and frailty. *Ageing research reviews*, *69*, Article 101351.
- Voysey, M., Clemens, S., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., Angus, B., Baillie, V. L., Barnabas, S. L., Bhorat, Q. E., Bibi, S., Briner, C., Cicconi, P., Collins, A. M., Colin-Jones, R., Cutland, C. L., Darton, T. C., Dheda, K., Duncan, C., Emary, K., & Oxford COVID Vaccine Trial Group. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*, *397* (10269), 99–111.
- Wang, C., Horby, P. W., Hayden, F. G., & Gao, G. F. (2020). A novel coronavirus outbreak of global health concern. *Lancet*, *395*(10223), 470–473. [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9)
- Wyller, T. B., Kittang, B. R., Ranhoff, A. H., Harg, P., & Myrstad, M. (2021). Nursing home deaths after COVID-19 vaccination. Dødsfall i sykehjem etter covid-19-vaksine. *Tidsskrift for den Norske lægeforening: tidsskrift for praktisk medicin, ny række*, *141*. <https://doi.org/10.4045/tidsskr.21.0383>, 10.4045/tidsskr.21.0383.

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.