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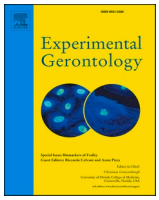

Sarcopenic patients "get even": The impact of COVID-19 vaccination on mortality

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ABSTRACT

Background: Coronavirus Disease-2019 (COVID-19), driven by the SARS-CoV-2 virus, has disproportionately affected the elderly, with comorbidities like sarcopenia worsening prognosis. Considering the significant impact of RNA vaccines on survival rates in this population, our objective is to investigate the impact of vaccination on the survival of hospitalized elderly patients with COVID-19, considering the presence or absence of sarcopenia.
Methods: Prospective study conducted on 159 patients aged>65 years from September 2021 to March 2022. Data about clinical and body composition, and mortality at 12-months after discharge were recorded. Sarcopenia was diagnosed according to the 2019 European Consensus criteria.
Results: At the twelfth month post-discharge, vaccinated sarcopenic individuals exhibited a mortality risk similar to vaccinated non-sarcopenic individuals, and lower than unvaccinated non-sarcopenic patients. Cox regression analysis, adjusted for age, gender, comorbidity, functional and vaccinal status, showed that the presence of sarcopenia did not significantly impact the risk of death within 12-months post-discharge.
Discussion: Vaccination emerges as a protective measure for sarcopenic patients, countering the potential adverse effects of sarcopenia on COVID-19 outcomes, underscoring the importance of immunization in the frail elderly with a call for meticulous monitoring of its benefits.
Conclusions: Our study represents the first attempt to analyze the vaccine's effect on survival in sarcopenic hospitalized older adults with COVID-19. The administration of vaccination to sarcopenic patients proves pivotal, as its omission could lead to notably unfavorable outcomes within this specific population.

1. Introduction

Coronavirus Disease-2019 (COVID-19) is an infectious condition caused by the SARS-CoV-2 virus, exhibiting a range of clinical manifestations, including the potential development of Severe Acute Respiratory Syndrome (WHO, 2021). As of December 2023, the global toll of COVID-19 has surpassed 6 million deaths, with over 770 million confirmed cases (WHO, 2021). From the start of the pandemic, the elderly population had the highest levels of morbidity - sometimes needing hospitalization in intensive care units - and of mortality. Contributing factors to increased risk among older adults include the presence of multiple comorbidities, advanced age, sarcopenia, and frailty, collectively accounting for a significant proportion of fatalities in this population (Pagano et al., 2022; Rockstrom et al., 2023).

Sarcopenia is defined as the structural and functional decline of skeletal muscle related to aging (Evans, 1997). Its prevalence is estimated to be in the range of 10–27 % in adults aged ≥60 years (Evans, 1997). The role of sarcopenia in increasing vulnerability to adverse outcomes, i.e. poorer quality of life, increased hospitalization, and mortality, is well known (Wang et al., 2023a). In older adults especially, COVID-19 was exacerbated by the harmful effects of sarcopenia, and on the other side sarcopenia worsened in presence of SARS-CoV-2 infection,

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triggering a vicious circle fueled by immobilization, malnutrition, inflammatory state, and comorbidities (Wang et al., 2023a; Piotrowicz et al., 2022; Siahaan et al., 2022).

Because of the negative effect of sarcopenia on SARS-CoV-2 infection, early detection of this geriatric syndrome, and insistence on prioritizing patients with sarcopenia for prime and booster SARS-CoV-2 vaccination is crucial (Wang et al., 2023a; Siahaan et al., 2022). Vaccines specific to SARS-CoV-2, based on mRNA, viral vectors, and inactivated viruses, have been globally employed. Although vaccine effectiveness has been confirmed in adults, debates have centered on the outcomes in the older people (Yang et al., 2023). Factors such as age, prior antigen exposure, vaccination schedule, and dose influence vaccine efficacy in this population (Yang et al., 2023). However, vaccine effectiveness in reducing mortality and adverse events in the old adults has been extensively demonstrated (Liu et al., 2023; Arbel et al., 2023; Johnson et al., 2023). A recent meta-analysis conducted on 26 studies (with a total of 8.968.085 participants aged 60 and above) reports that, compared to unvaccinated individuals, vaccinated individuals have in the following 60 days a reduced hospitalization, disease severity, and mortality increase with the number of vaccine doses administered, unaffected by factors such as age, gender, or comorbidities (Yang et al., 2023). Another recent meta-analysis focusing on adults aged 60 and above, based on 22 studies, confirmed the effectiveness of vaccines in preventing SARS-CoV-2 infection and reducing the number of COVID-19 related deaths in this population, with conflicting results regarding hospitalizations (Xu et al., 2023).

Given these premises, we might anticipate a favorable impact of vaccines on the survival of sarcopenic patients. However, as far as our current knowledge extends, there have been no studies to date exploring the potential influence of COVID-19 vaccinations on mortality rates among older adults with sarcopenia.

We hypothesized that vaccination can mitigate the severity of COVID-19 and improve survival in sarcopenic hospitalized older sarcopenic patients with COVID-19. Therefore, the study aims to assess the impact of vaccination on the survival of elderly patients hospitalized for COVID-19, 12 months post-discharge, and to determine whether the presence of sarcopenia may undermine the effectiveness of vaccination, negatively influencing patient outcomes.

2. Materials and methods

2.1. Study population

This prospective study was conducted with a consecutive series of Caucasian patients over 65 years of age recruited at the UOC Geriatria of the Azienda Ospedale - Università Padova from September 2021 to March 2022, regardless of their admission diagnosis. The inclusion criteria comprised individuals aged >60 years, who had been hospitalized within the preceding 12–24 h. Exclusion criteria encompassed patients presenting with fever, severe dehydration, or heart failure accompanied by significant body edema. Additionally, individuals with severe dementia rendering them incapable of following commands were not considered for inclusion.

The study protocol was conducted in accordance with good clinical practice guidelines and the ethical standards of the 1964 Declaration of Helsinki as revised in 2000, and was approved by the local Ethics Committee (Comitato Etico per la Sperimentazione Clinica della Provincia di Padova, protocol number 16412/AO/23). The study subjects were given a detailed explanation of the risks and benefits of participation, and all gave oral and written informed consent to publication of the data.

2.2. Data collection

The following information was obtained from each participant by trained physicians:

Patient characteristics: Clinical and pharmacological information, encompassing vaccination status, vaccine type, and the total number of vaccinations administered, were gathered through a medical interview conducted by experienced physicians. Comorbidities were assessed using the Cumulative Illness Rating Scale (CIRS) (Linn et al., 1968). In addition, the patients' functional autonomy was assessed with the Activities of Daily Living (ADL) (Katz, 1983), nutritional status with the Mini Nutritional Assessment (MNA) (Vellas et al., 1999), and cognitive performance with the Mini Mental State Examination (MMSE) (Folstein et al., 1975). Information on mortality was collected at 12 (T12) months after discharge.

COVID-19–Related Information: The campaign for COVID-19 vaccination in Italy started at the end of December 2020, and mRNA vaccines were mainly used (Moderna mRNA-1273 or Cominarty BNT162b2). National recommendations indicated administering only one vaccine dose in people with SARSCoV-2 infection in the previous 6 months; otherwise, a two-dose vaccination cycle was indicated. The third dose was a booster recommended for the continuation of the vaccination campaign, and especially for older people (over 60), for all those suffering from chronic pathologies, for healthcare workers and the armed forces (Piano nazionale di vaccinazione COVID-19, 2023). Date, type, and number of administered doses of SARS-CoV-2 vaccine were retrieved for each participant. Regarding COVID-19 symptoms, the following signs and symptoms have been recorded: presence of fever, headache, gastrointestinal symptoms, sore throat, delirium, cough, fatigue, loss of smell, hypogeusia, dyspnea, tachypnea, syncope upon admission to the hospital, need for oxygen upon hospital admission, presence of pneumonia upon hospital admission, requirement for transfer to the intensive care unit, and duration of hospital stay. Cases of asymptomatic COVID-19 have also been documented, where hospitalization was dependent on non-COVID-19-related conditions.

Anthropometry. Body weight was measured to the nearest 0.1 kg using a standard balance scale with individuals wearing light clothing and no shoes; a lift scale was used for those unable to walk. As most people were unable to maintain an upright position, body height was estimated using knee-heel length and Chumlea's formula (Chumlea et al., 1985). BMI was calculated as the ratio between weight (kg) and height squared (meters).

Muscle strength measurement. Upper limb strength was evaluated with DynEx electronic hand dynamometers (MD Systems, Westerville, OH, USA) by trained medical personnel. Upper limb strength was assessed using the handgrip strength test, employing DynEx electronic hand dynamometers from Ohio, USA, administered by trained medical personnel. Three trials were conducted for each hand, and grip strength was determined by calculating the mean of the maximum performance for both the dominant and non-dominant hand (Sousa-Santos and Amaral, 2017).

Evaluation of body composition. Whole-body tetrapolar bioelectrical impedance analysis (BIA) was performed using a BIA 101 Anniversary analyzer (AKERN/RJL Systems, Florence, Italy) with an alternating sinusoidal electric current of 400 μA at a single operating frequency of 50 kHz. We previously described in detail the characteristics of BIA measures (Sergi et al., 2015). Estimate of appendicular skeletal muscle mass (ASMM) for our sample was calculated using the equation developed by Sergi et al. (Kyle et al., 2001; Kyle et al., 2003), i.e. ASMM = −3.964 + (0.227 * RI) + (0.095 * weight) + (1.384 * sex) + (0.064 * Xc), where men = 1 and women = 0. The ASMM index (ASMMI) was obtained by dividing the ASMM by the subject's height in meters squared.

2.3. Diagnosis of sarcopenia

Sarcopenia was diagnosed according to the 2019 European consensus criteria on the basis of muscle strength and mass values (Cruz-Jentoft et al., 2019). The cutoff values used to define sarcopenia were established as follows: lean muscle mass below 20 kg or 7.0 kg/m^2 in men and below 15 kg or 5.5 kg/m^2 in women, and handgrip strength

below 27 kg_f in men and 16 kg_f in women (Cruz-Jentoft et al., 2019). These criteria were applied to each participant, and sarcopenia was diagnosed if one or more of these cutoff values were exceeded.

2.4. Statistical analysis

The characteristics of the sample are expressed as means±standard deviations for the continuous quantitative variables with normal distributions, and as medians (interquartile range) for those with non-normal distributions. Normality of the distributions of the continuous quantitative variables was verified by the Shapiro-Wilk test. Categorical variables were expressed as counts and percentages. We divided patients into groups according to their vaccinal status and the presence of sarcopenia: unvaccinated non-sarcopenic ($n = 35$), unvaccinated sarcopenic ($n = 2$), vaccinated sarcopenic ($n = 32$) and vaccinated non-sarcopenic ($n = 90$). Given the small number of unvaccinated sarcopenic patients, they were excluded from the final sample, which therefore comprised 159 subjects. For this reason, the term "unvaccinated" henceforth refers exclusively to non-sarcopenic patients. The characteristics of the study participants were compared according to this classification using the Student's *t*-test or Chi-square test depending on the type of variable. For the survival analyses, Kaplan-Meier curves were calculated for all the categorical variables (unvaccinated, vaccinated sarcopenic, and vaccinated non-sarcopenic patients). Finally, a Cox regression model was employed to examine the independent variables correlated with mortality within 12 months post-discharge. We conducted three models. The first model was adjusted for gender, vaccination status, and age. The second model built upon the first by incorporating additional factors, including the comorbidity index, total number of drugs at discharge, functional status, and length of stay. Finally, the third model introduced the presence of sarcopenia as an additional variable. The statistical tests were considered significant at $p < 0.05$. All analyses were performed in IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

3. Results

Among 192 hospitalized patients, 159 met our inclusion criteria. A significant portion of the sample (81.6 %) had received at least one dose of an mRNA vaccine. Among those, 109 patients received a second vaccine dose, while only 32 completed the third dose. The patients identified as probable sarcopenic numbered 111 in total, comprising 17 unvaccinated and 94 vaccinated individuals (data not shown). Among the unvaccinated patients who were not probable sarcopenic, there was a trend towards younger age (76.69 ± 7.08 years) and lower comorbidity burden (CIRS-CI: 1.94 ± 1.29). Admissions unrelated to COVID-19 (asymptomatic positive patients) were more frequent among vaccinated patients, both probable sarcopenic and non-sarcopenic ($p = 0.01$). However, no statistically significant differences emerged regarding pneumonia rates and the frequency of transfers to the intensive care unit based on the vaccination status and the presence or absence of probable sarcopenia (data not shown). Table 1 outlines the baseline characteristics of our sample based on vaccination status. Sarcopenic patients who received the vaccine showed higher comorbidity levels and were on a greater number of medications upon admission, on average. However, there were no statistically significant differences in terms of COVID-19 severity between the groups.

At the twelfth month post-discharge (T12), 46 deaths were recorded, constituting 28.9 % of the entire sample (95 % CI 21.7–36.1 %), with 17.6 % occurring among those who were not vaccinated (95 % CI 15.0–32.0 %, $p = 0.33$). Among exclusively vaccinated subjects, there was no significant difference in mortality risk between sarcopenic and non-sarcopenic individuals ($p = 0.19$) (Fig. 1). Additionally, the mortality risk in unvaccinated (non-sarcopenic) patients was higher than in

Table 1
Characteristics of the sample at baseline according to vaccinal status and presence of sarcopenia.

Variable	All (n = 159)	Not vaccinated (n = 35)	Vaccinated (n = 122)		p-value
			Sarcopenic patients (n = 32)	Non-sarcopenic patients (n = 90)	
Age [years]	82.82 ± 7.04	81.23 ± 7.82	85.19 ± 5.72	82.05 ± 6.89	0.05
Gender F	73 (47.1 %)	20 (57.1 %)	11 (34.4 %)	42 (46.7 %)	0.17
CIRS-CI	3.33 ± 1.87	2.49 ± 1.22	4.19 ± 1.79	3.51 ± 1.85	***<0.001***
No. of drugs at admission	5.81 ± 3.78	3.48 ± 2.83	7.25 ± 2.89	6.14 ± 3.59	***<0.001***
Smoking habits [%]					0.53
Active	10 (6.45 %)	1 (2.8 %)	3 (9.7 %)	6 (6.7 %)	
Previous	40 (25.8 %)	9 (26.5 %)	8 (25.8 %)	23 (25.6 %)	
COVID-19 severity					
O_2 at admission [L/min]	0.00 (0.00;4.00)	2.00 (0.00;6.00)	0.00 (0.00;6.00)	0.00 (0.00;5.50)	0.57
Pneumonia at admission [%]	79 (41.14 %)	22 (64.7 %)	22 (78.6 %)	41 (45.6 %)	***0.03***
Length of stay [days]	16.50 (11.00;25.00)	16.00 (10.00;24.00)	21.00 (12.00;29.50)	17.00 (12.00;23.00)	0.15
No. of antibiotics	2.09 ± 1.41	1.83 ± 1.34	2.17 ± 1.48	2.17 ± 1.40	0.58
Intensive Care [%]	9 (5.8 %)	1 (3.0 %)	3 (10 %)	5 (5.6 %)	0.53
Hospitalization unrelated to COVID [%]	52 (33.5 %)	7 (20.6 %)	11 (34.4 %)	34 (37.8 %)	0.10
Functional profile					
ADL	2.43 ± 2.25	2.34 ± 2.37	1.78 ± 2.04	2.58 ± 2.25	0.09
MNA	17.91 ± 4.36	18.17 ± 5.15	15.27 ± 3.85	18.52 ± 3.97	***<0.001***
MMSE	23.70 (18.15;27.70)	23.70 (20.70;28.40)	21.50 (14.00;24.40)	25.20 (18.40;27.70)	0.05
MPI	0.57 ± 0.19	0.55 ± 0.24	0.65 ± 0.15	0.56 ± 0.18	0.05
Body composition					
ASMMI [Kg/m^2]	6.65 ± 1.14	6.63 ± 1.21	5.83 ± 0.89	6.95 ± 1.07	***<0.001***
BMI [Kg/m^2]	27.19 ± 6.64	25.99 ± 6.46	25.17 ± 3.50	30.22 ± 5.84	***<0.001***
MHG [Kg_f]	17.80 (11.85;25.30)	16.80 (9.35;29.35)	16.75 (11.50;20.20)	18.50 (13.55;27.70)	0.12

Notes: Values are expressed as means ± standard deviation, medians (interquartile range) or counts (percentages %) as appropriate.
Abbreviations: F = females; CIRS-CI = Cumulative Illness Rating Scale - Comorbidity Index; O_2 = Oxygen; ADL = Activities of Daily Living; MNA = Mini Nutritional Assessment; MMSE = Mini Mental State Examination; MPI = Multidimensional Prognostic Index; ASMMI = Appendicular Muscle Mass Index; BMI = Body Mass Index; MHG = Maximum Handgrip Strength. P-values<0.05 are reported in bold.

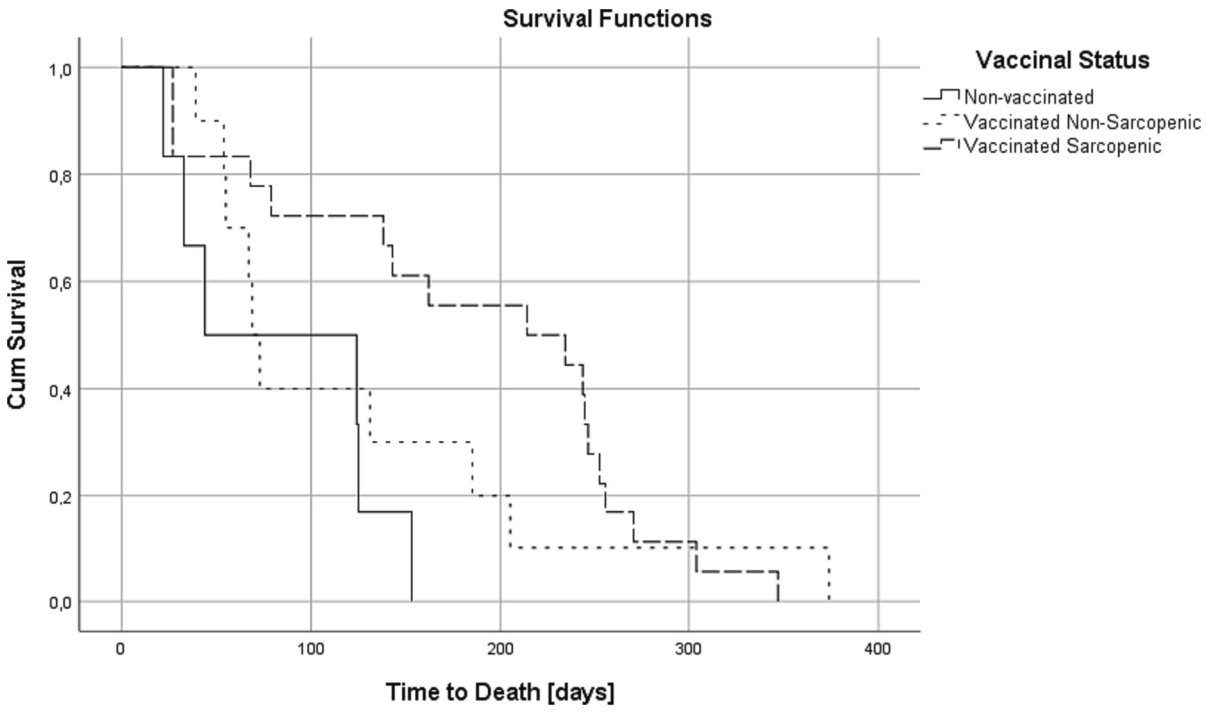

Fig. 1. Kaplan-Meyer survival curves: mortality at 12 months after discharge according to vaccinal status and presence of sarcopenia.

vaccinated sarcopenic patients, although this difference did not reach statistical significance. Considering solely the division between healthy individuals and those with probable sarcopenia, both among the vaccinated and non-vaccinated groups, the Kaplan-Meier survival curves appear very similar to those originally delineated based on the presence/absence of sarcopenia (please see Supplementary Fig. 1).

Cox regression analysis, adjusted for sample characteristics, is presented in Table 2. Vaccination status emerged as a protective factor against mortality in both Model 1 and Model 2 (HR 0.32, 95 % CI 1.19–0.85, $p = 0.03$ and 0.16, 95 % CI 0.10–0.56, $p = 0.004$, respectively). Conversely, when adjusting for the presence of sarcopenia, no significant risk factors were identified. In other words, holding all else constant, being sarcopenic did not influence the risk of death within 12 months post-discharge, compared to individuals with similar vaccination status. The same regression was conducted solely with respect to the presence of probable sarcopenia in relation to vaccination status. The results remain consistent, indicating that probable sarcopenia was not associated with an increased risk of 12-month mortality, even after adjusting for vaccination status. Notably, high values of ADL (OR 0.68, 95 % CI 0.48–0.98, $p = 0.04$), and a high number of medications at discharge (OR 1.24, 95 % CI 1.08–1.43, $p = 0.003$) achieved statistical significance (please see Supplementary Table 1).

4. Discussion

This is the first study that assessed the impact of COVID-19 vaccination on survival in a group of elderly individuals with sarcopenia. Our results show that, despite the widely recognized adverse effect of sarcopenia on mortality, the one-year mortality risk for vaccinated sarcopenic patients resembled that of vaccinated non-sarcopenic patients and remained unaffected by the presence of this condition. Administration of vaccination to sarcopenic patients emerges as crucial, as the absence of this intervention would likely result in significantly adverse outcomes for this specific population.

In March 2020, the World Health Organization (WHO) officially designated COVID-19 as a pandemic, attributing it to the SARS-CoV-2 virus. The intricacies associated with aging expose old individuals to

Table 2
Cox regression of covariate-adjusted mortality at T12.

Model	Outcome	Variable	HR	p-value	IC 95 %	
					Lower limit	Upper limit
1	Mortality per 1 point increase in variable or per specified category	Age [years]	0.99	0.69	0.95	1.03
		Gender F	1.11	0.75	0.57	2.16
		Being vaccinated	0.32	**0.02**	0.18	0.85
2	Mortality per 1 point increase in variable or per specified category	Age [years]	1.05	0.20	0.97	1.27
		Gender F	1.47	0.09	0.20	1.24
		Being vaccinated	0.16	**0.004**	0.05	0.56
		N.drugs at discharge	1.08	0.27	0.94	1.22
		CIRS-CI	1.87	0.17	0.94	1.22
		Poor ADL	1.06	0.72	0.78	1.42
		Short length of stay	0.98	0.24	0.95	1.01
3	Mortality per 1 point increase in variable or per specified category	Age [years]	1.05	0.40	0.93	1.18
		Gender F	1.65	0.55	0.16	2.66
		Being vaccinated	0.22	0.10	0.04	1.33
		N.drugs at discharge	1.41	0.19	0.93	1.39
		CIRS-CI	1.91	0.85	0.77	1.27
		Poor ADL	1.16	0.41	0.81	1.67
		Short length of stay	0.99	0.72	0.96	1.03
		Sarcopenia	3.89	0.06	0.95	5.40

Abbreviations: HR = Hazard Ratio; F = Female; CIRS-CI = Cumulative Illness Rating Scale - Comorbidity Index; ADL = Activities of Daily Living. Model 1 was adjusted for gender, vaccination status, and age. Model 2 was adjusted for gender, vaccination status, age, comorbidity index, total number of drugs at discharge, functional status, and length of stay. Model 3 was adjusted for gender, vaccination status, age, comorbidity index, total number of drugs at discharge, functional status, length of stay and sarcopenia. P-values<0.05 are reported in bold.

prolonged hospitalization and a higher risk of complications, including mortality. Consequently, various comorbidities predisposing individuals to severe SARS-CoV-2 infections were extensively studied for prevention and treatment, with a focus on improving survival rates, with particular emphasis on addressing sarcopenia (Siahaan et al., 2022). Sarcopenia is recognized as a geriatric syndrome primarily associated with aging. However, factors such as immobilization, malnutrition, and comorbidities can accelerate the depletion of lean mass (Cruz-Jentoft et al., 2019). In the context of COVID-19, some studies have coined the term 'acute sarcopenia' to describe rapid muscle wasting, aligning with the 'catabolic crisis' model. In this model, sarcopenia is not solely a gradual process but is expedited by intermittent periods of inactivity (Kirwan et al., 2020). Furthermore, sarcopenia is a recognized independent risk factor for numerous adverse outcomes, including prolongation of hospitalization during SARS-CoV-2 infection, and frequent and lengthy further hospitalizations (Kim et al., 2021; Carter et al., 2020; Bone et al., 2017). The main factors that may be involved in the relationship between lower muscle mass and poor respiratory outcomes are chronic inflammation, immune dysfunction, and respiratory muscle dysfunction (Wang et al., 2023a). In our study, the severity of infection in sarcopenic patients was comparable to that in non-sarcopenic patients. Interestingly, the overall disease course appeared milder in sarcopenic patients. We have also observed a noteworthy number of asymptomatic patients, both among vaccinated individuals (sarcopenic and non-sarcopenic) and among the non-vaccinated. Several studies have reported a broad range of proportions of asymptomatic patients (Bai et al., 2020; Kimball et al., 2020; Tong et al., 2020), with numbers often closely aligned with those observed in our sample. A meta-analysis on the subject has highlighted that over 17 % of individuals remain completely asymptomatic during the course of COVID-19 infection (Byambasuren et al., 2020). A hypothesis for asymptomatic COVID-19 infections suggests that the host may have a different immune response to the infection, such as the presence of circulating memory T cells, attributed to previous infections with other non-COVID coronaviruses or vaccinations (Tarke et al., 2021). In our study, although the difference did not reach statistical significance, unvaccinated patients seemed to have a lower frequency of asymptomatic infections, supporting this hypothesis. The presence of a substantial number of asymptomatic infections in our study aligns with the literature. Several studies have indeed recorded a higher incidence of asymptomatic infections in older or middle-aged individuals (Gao et al., 2021). Importantly, being asymptomatic does not necessarily imply lower infectivity, as asymptomatic individuals may have viral levels similar to symptomatic ones (Gunatilaka et al., 2022). No significant differences in viral levels emerged between asymptomatic and symptomatic individuals, as indicated in the study by Gunatilaka et al. (Gunatilaka et al., 2022). This suggests that the course of the disease in asymptomatic individuals may not substantially differ from those with mild symptoms. Furthermore, a study conducted by Piraee E and colleagues (Piraee et al., 2022) found that comorbidities and occupation did not significantly differ between asymptomatic and symptomatic patients, although there was a higher one-year mortality rate among symptomatic patients, partly attributable to a significant difference in average age between the two studies.

The effect of sarcopenia on mortality during the COVID-19 waves has been widely studied (Siahaan et al., 2022; Bone et al., 2017). The risk of mortality increases in the presence of a poor functional status before hospitalization (Stineman et al., 2012). In our study, we did not have access to details regarding the intensity and frequency of physical activity practiced by patients before hospitalization. However, we considered the functional aspect, measured by the ADL score. The absence of physical exercise significantly impacts ADLs (Wang et al., 2023b). In our study, although only marginally significant ($p = 0.09$), ADL scores were tendentially lower in sarcopenic patients, a result also confirmed by previous studies (Dai et al., 2023; Lee et al., 2024). This certainly increased their susceptibility to adverse events. While the studies published in scientific literature exhibit variability, a consistent finding is the elevated mortality observed in unvaccinated patients, particularly those with comorbidities and frailty (Fatima et al., 2022; Hardgrave et al., 2022). Surprisingly, our study found no significant difference in the risk of mortality between vaccinated individuals with sarcopenia and those without, particularly in the medium to long term. In a scenario where SARS-CoV-2 continues to exist, albeit with reduced threat, we can hypothesize that the vaccine provides a protective effect for sarcopenic patients, leading to improved long-term outcomes. Specifically, it seems that vaccination mitigates the potentially adverse impact of sarcopenia on the course of COVID-19. This is particularly noteworthy given that chronic inflammation and immunosenescence are associated with a variable immunological response to vaccination, especially in frail individuals (Ciarambino et al., 2023). Previous research suggests that the frailest patients may exhibit a reduced response to anti-SARS-CoV-2 vaccination, experiencing a significant decline in antibody titers within the first 6 months. This suggests a lower level of protection and an increased risk of severe forms of COVID-19, especially among men and seronegative older individuals (Lo Sasso et al., 2021; Lo Sasso et al., 2022). Some studies indicate the potential for maintaining high antibody titers with all three vaccine doses but underscore that frail patients exhibit a diminished response compared to their healthier counterparts (Ciarambino et al., 2023). Coupled with the rare but potentially severe local and systemic adverse events post-inoculation, these factors might contribute to vaccine hesitancy among the elderly globally, resulting in suboptimal adherence rates to vaccination campaigns. Contrary to these findings, our study suggests a different perspective, advocating for vaccination in frail elderly individuals. We emphasize the importance of closely monitoring the benefits of vaccination in this population (Xu et al., 2023; Widge et al., 2021).

Beyond the scope of COVID-19, there is significant interest in identifying individual factors that heighten susceptibility in individuals with compromised immune systems. On the other hand, sarcopenia and progressive functional decline are aspects not yet well understood in patients with COVID-19, for whom there is a lack of primary and rehabilitative action plans capable of promoting an increase in life expectancy in the post-infection phase (Ciarambino et al., 2023). Our findings provide a foundation for further exploration of the often-overlooked condition of sarcopenia, closely linked to malnutrition, which can, in turn, have significant negative consequences for immune system function. There is a close relationship between nutrition, sarcopenia, and chronic inflammatory status and infections further diminish nutrient absorption, perpetuating a vicious cycle (Ciarambino et al., 2023). Thus, our insights into the impact of vaccination on sarcopenic patients could play a crucial role in public health by emphasizing the importance of adequate vaccination for older individuals. Further studies are warranted to delve deeper into this issue, employing more specific analyses to elucidate the risk factors for mortality in elderly patients and the role of vaccination in this context. Considering the challenges related to time and instrumentation in assessing sarcopenia in clinical settings, future research should focus on developing new approaches for accurately estimating muscle mass. The analysis of radiation absorption by muscles can provide crucial insights into their composition and health, identifying early signs of issues such as myosteatosis, characterized by excessive accumulation of intramuscular fat. Myosteatosis represents an early change in muscle structure preceding a decline in strength and performance. Developing diagnostic criteria for low muscle attenuation and a systematic technique for quantifying myosteatosis would be advantageous for research in the field of sarcopenia and its implications. Basic myosteatosis could serve as an independent risk factor for shorter overall survival, potentially exerting a greater impact than basic sarcopenia (Findlay et al., 2020; Erul et al., 2023).

We acknowledge that, given the period during which this study was carried out, i.e. the fourth wave, comparison with previous studies is problematic. Another limitation is the small sample size, and in

particular the absence of the fourth control group of sarcopenic non-vaccinated patients. This exclusion results, foremost, in a loss of granularity and an undue simplification of the complexity inherent in the phenomenon under investigation. Furthermore, the absence of a direct comparison with unvaccinated sarcopenic patients represents a missed opportunity to enhance the depth of our conclusions concerning the vaccine's impact on the survival of sarcopenic patients. We also recognize that the absence of a third control group may compromise the statistical power of our analyses (a posteriori power analysis based on Cox regression results revealed that the sample achieved a power 0.44 at 0.05 significance level): future ad hoc researches are required to confirm our results. Moreover, in this study, data regarding the detailed physical activity pre-admission and vaccine side effects experienced by individuals were not collected. The symptoms recorded upon admission to the hospital were related to the diagnosis upon admission and may have, in some cases, masked potential adverse effects of the vaccine. On the other side, our strength lies in having included evaluation of body composition in our Comprehensive Geriatric Assessment. We believe that our study provides crucial insights into the prognosis of vaccinated sarcopenic patients. However, larger cohort studies will be necessary to confirm our findings.

5. Conclusions

Our study represents the first attempt to analyze the vaccine's effect on survival in elderly patients with sarcopenia. Despite the negative impact on vaccine response due to immunosenescence, our survival analysis revealed a higher mortality risk in unvaccinated patients and no significant difference between sarcopenic and non-sarcopenic individuals in the exclusively vaccinated group. We hope that these results not only encourage greater adherence to vaccination campaigns but also serve as a stimulus for further investigations in this direction.

Declarations

All authors declare that they meet all ICMJE criteria for authorship.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Padua (protocol number 16412/AO/23, February 2023).

Informed consent statement

Informed consent to participation was obtained from all subjects involved in the study. All participants gave written informed consent to the publication of this paper.

CRediT authorship contribution statement

Chiara Ceolin: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Marina De Rui:** Writing – review & editing, Conceptualization. **Cristina Simonato:** Data curation. **Margherita Vergadoro:** Data curation. **Sara Cazzavillan:** Data curation. **Vittorio Acunto:** Data curation. **Mario Virgilio Papa:** Data curation. **Giulia Salerno Trapella:** Data curation. **Bruno Micael Zanforlini:** Supervision. **Chiara Curreri:** Supervision. **Anna Bertocco:** Supervision, Conceptualization. **Maria Devita:** Supervision. **Alessandra Coin:** Writing – review & editing, Supervision. **Giuseppe Sergi:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

x All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

x This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

x The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

x The following authors have affiliations with organizations with direct or indirect financial interest in the subject matter discussed in the manuscript.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2024.112382.

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