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Risk factors associated with death due to the Omicron variant of COVID-19: retrospective analysis with elderly people in the Canary Islands.

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SUMMARY

Background and objective

Since the beginning of the COVID-19 pandemic, the elderly population has presented the highest rates of complications and mortality. The aim of this study was to determine the influence of different risk factors on deaths due to the Omicron variant in the Canary Islands.

Materials and methods

Retrospective observational study of 16,998 cases of COVID-19 over 40 years of age confirmed in the Canary Islands between August 1, 2022 and January 31, 2023. We extracted sociodemographic data (age, sex), clinical data (death, vaccination, hospital admission, previous pathologies and treatments).

Results

Among the deceased, there was a higher proportion of males, age over 70 years, diabetes, cardiovascular, renal, respiratory and systemic pathology, and residents of socio-health centers. Significant differences were also found in the number of vaccine doses. In the multiple regression model, male (OR [95% CI]=1.92 [1.42-2.58]), age (70-79 years, 9.11 [4.27-19.43]; 80-89 years, 21.72 [10.40-45.36]; 90-99 years, 66.24 [31.03-141.38]; 100 years or older, 69.22 [12.97-369.33]) and unvaccinated (6.96, [4.01-12.08]) or whose last dose was administered at least 12 months before diagnosis (2.38, [1.48-3.81]) showed a significant association with mortality.

Conclusions

Multiple possible factors may increase the risk of mortality due to COVID- 19 in the elderly population. In our study, only three predictors were found to increase the risk of COVID- 19 mortality in the elderly population.

can explain practically the same variability: older age, male sex, and not being vaccinated or last vaccination date prior to one year.

Key words: SARS-CoV-2, COVID-19, mortality, risk factors, aging, vaccination.

Risk factors for mortality from COVID-19 Omicron variant: retrospective analysis in elderly from the Canary Islands.

ABSTRACT
Background and aims
Since the beginning of the COVID-19 pandemic, the elderly population has had the highest rates of complications and mortality. This study aimed to determine the influence of different risk factors on deaths due to the Omicron variant in the Canary Islands.
Materials and methods
A retrospective observational study of 16,998 cases of COVID-19 over 40 years of age was conducted in the Canary Islands between August 1, 2022, and January 31, 2023. We extracted sociodemographic data (age and sex) and clinical data (death, vaccination history, hospital admission, previous diseases, and treatments).
Results
Among the deaths, there was a higher proportion of males aged over 70 years, with diabetes, cardiovascular, renal, respiratory, and systemic diseases, and nursing home residents. Significant differences were observed in the number of doses of the vaccine. The multiple regression model showed that male sex (OR [95% C.I.]=1.92 [1.42-2.58]), age (70-79 years, 9.11 [4.27-19.43]; 80-89 years, 21.72 [10.40-45.36]; 90-99 years, 66.24 [31.03-141.38]; 100 years or older, 69.22[12.97-369.33]), being unvaccinated (6.96, [4.01-12.08]), or having the last dose administered at least 12 months before the diagnosis (2.38, [1.48-3.81]) were significantly associated with mortality.
Conclusions
Multiple factors may increase the risk of mortality due to COVID-19 in the elderly population. In our study, we found that only three predictors can effectively explain the variability: older age, male sex, and not being vaccinated or last vaccination date prior to one year.

Keywords: SARS-CoV-2, COVID-19, mortality, risk factor, ageing, vaccination

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The present research has not received any specific grants from agencies in the public, commercial, or non-profit sectors.

Introduction

Since the beginning of the COVID-19 pandemic, the older population has presented the highest rates of complications and mortality from this disease.[1,2] As of January 27, 2023, 13,731,478 confirmed cases and 118,434 deaths had been reported through the National Epidemiological Surveillance Network (RENAVE) in Spain. Of these, 463,489 confirmed cases and 2,234 deaths corresponded to the Canary Islands.[3] The percentage of deaths in persons aged 60 years or more was 94.8% in the whole country and 90.5% in the Canary Islands.[4]

Older age groups, as well as some chronic diseases such as diabetes, hypertension or renal failure, have presented a higher risk of mortality.[5–7] On the other hand, polypharmacy, that is, the consumption of 5 or more drugs per day, has also been associated with greater morbidity and mortality among patients with COVID-19.[8–10] Considering that the elderly are a high-risk population, with a higher probability of presenting atypical symptoms, multimorbidity, greater severity and higher mortality in general, they became a priority for vaccination programs against COVID-19.[11] Vaccination with mRNA vaccines in Spain was shown to be highly effective in preventing SARS-CoV-2 infections and COVID-19 hospitalizations and deaths in residents of long-term care facilities for the elderly. [4,12] However, the protective effect of the vaccines has been different depending on the variants.[13] Since the beginning of 2020, there has been a progressive increase in the incidence of the Alpha variant in Spain, reaching 70%. From June 2021 onwards, it progressively decreased and was replaced by the Delta variant, which increased to 94-100%. Subsequently, Delta was replaced by Omicron, which as of week 47 of 2022 was between 99-100%.[14] Primary vaccination has shown a greater effect on hospitalization, severity and death associated with the Omicron variant, even months after the last dose.[15]

In order to update the existing evidence for the geriatric population with the Omicron variant, the aim of this study was to determine the influence of different risk factors on COVID-19 deaths in the population aged 40 years or older in the Canary Islands between August 1, 2022 and January 31, 2023.

Materials and methods

Sample

Data were extracted from all cases declared in the Canary Islands Epidemiological Surveillance Network (ReVECa), confirmed by microbiological testing (tests based on antigen detection and tests based on the detection of viral RNA by RT-PCR or an equivalent molecular technique),[16] who were users of the Canary Islands Health System (SCS) health card or, belonging to another Spanish public health system, had a history of medical care in the SCS during the last year. In addition, the cases had to meet the following inclusion criteria: having been diagnosed with SARS-CoV-2 infection between August 1, 2022 and January 31, 2023, and having been classified as cured or deceased at the end of follow-up. Patients in epidemiologic follow-up or without information at the end of follow-up were excluded. A total of 20,754 cases were found, of which 21 were excluded because they did not have information about their age. We also excluded 3,756 cases under 40 years of age, since there were no deaths under that age. Therefore, the final sample consisted of 16,998 cases aged 40 years or older, of which 188 were deaths.

Data

Through ReVECa, the files of patients who met the inclusion/exclusion criteria were identified, and the following data were extracted: outcome at the end of follow-up (cured or deceased), age in years, sex, date of diagnosis, vaccination data (number of doses and dates of these), data on hospital admissions for COVID-19 if any (date of admission and date of admission to the ICU). On the other hand, from the SCS Primary Care file number, we extracted all the available information on the previous pathologies of each patient, which were classified as: cardiovascular (ischemic heart, hypertensive and cerebrovascular diseases), diabetes, digestive, immunodeficiencies, solid organ neoplasms, hematological, renal, respiratory and systemic neoplasms (anemias, demyelinating diseases, extrapyramidal disorders, paralytic syndromes, systemic connective tissue disorders and metabolic disorders). To ensure the quality of the data on hospital admissions, it was verified that the admissions were the result of complications due to SARS-CoV-2 infection.

Age was categorized into decadal groups from 60 years of age onwards, and a reference group was created with cases aged 40 to 59 years. The date of the last vaccination and the days elapsed between that date and the date of diagnosis of COVID-19 were calculated.

The number of days between diagnosis and conventional or ICU admission, if any, was also calculated. The time elapsed between the last vaccination and diagnosis was categorized as: a) less than 3 months; b) between 3 and 6 months; c) between 6 and 12 months; d) more than 12 months; e) not vaccinated.[15] If the patient was vaccinated during the 13 days prior to diagnosis or after diagnosis, that vaccination date was discarded. Based on the number of active ingredients currently in the patient's history, cases of polypharmacy were identified in those records with five or more medications.[17]

Ethical considerations

Approval was obtained from the Ethics Committee for Research with Medicines of the Complejo Hospitalario Universitario de Canarias (approval code CHUC_2021_27). All procedures were carried out in accordance with the Declaration of Helsinki. Statistical analyses were performed with anonymized data to protect patient privacy and confidentiality. Therefore, individual informed consent was not required.

Statistical analysis

To analyze the characteristics of the sample, frequencies and percentages were used for categorical variables, median and interquartile range (IQR) for age and days between the last vaccination and diagnosis, and minimum-maximum range for days between diagnosis and conventional or ICU admission. Differences between cured and deceased were tested using the chi-square test (χ^2) and the Wilcoxon signed-rank test.

After identifying statistically significant predictors in the previous step, bivariate logistic regression analyses were performed to estimate the effect size of each predictor on the probability of death, and presented as Odds Ratio with a 95% confidence interval (95% CI). Those predictors that were statistically significant in this step were included in a multiple logistic regression model, by which adjusted effect sizes ($_{\text{ORadjusted}}$) were obtained.

Only those predictors whose adjusted effects were statistically significant were included in the final model. For the interpretation of effect size, the values cited in the literature were taken as a reference: OR = 1.68, 3.47, and 6.71 for small, moderate, and large effects, respectively.[18]
The significance level was set at 0.05. All statistical analyses were performed using Stata 15.1 software (StataCorp, College Station, Texas, United States).

Results
A total of 16,998 confirmed cases of COVID-19 aged 40 years or more were studied. Of these, 16,810 were cured and 188 died. Table 1 presents the characteristics of the study patients.
Among the deceased patients in our sample, we found a higher proportion of males (54.3%) compared to cured patients (39.6%). They were also significantly older (median [RIC]: cured, 66 [56-77]; deceased, 85 [76- 90]). The number of hospitalizations and ICU admissions was higher among the deceased. As shown in Table 1, among preconditions, significantly higher proportions of diabetes, cardiovascular, renal, respiratory and systemic pathology were found. However, no differences were found in terms of digestive system pathology, immunodeficiencies, solid organ neoplasms or hematopoietic neoplasms. On the other hand, 75% of the deceased were on a polypharmacy regimen, while among the cured the percentage was significantly lower (51.6%).
Significant differences were found between cured and deceased in the number of doses of COVID-19 vaccine they had received. The median time elapsed between the last vaccine dose and COVID-19 diagnosis was 10 days shorter in the cured. Specifically, 16.5% of the deceased were found to have had no doses, compared with 4.2% of the cured. Finally, it was observed that the proportion of persons residing in socio-health centers was significantly higher among the deceased.
As shown in Table 2, it was observed that in the analysis of the crude effects of risk factors on death, only certain age groups showed large effects compared to the reference group (40 to 59 years). The group of unvaccinated patients, as well as those with cardiovascular or renal disease, and those on a polypharmacy medication regimen showed a moderate association with COVID-19 deaths. The rest of the risk factors showed small effect sizes.
In the multiple regression model, with an area under the ROC curve of 0.859, only men (in contrast to women), patients in age groups over 70 years and those not vaccinated or whose last dose was administered at least 12 months before diagnosis showed a significant association with the probability of death. In the final model, with an area under the ROC curve of 0.854, the effect size of male sex was estimated to be small ($OR_{adjustment}$ = 1.92, 95% C.I.: 1.42-2.58) compared to female sex, while ages above 70 years could have a large effect (70-79 years, $OR_{adjustment}$ = 9.11, C.I.: 1.42-2.58). 95%: 4.27-19.43; 80-89 years, $OR_{adjustment}$ = 21.72, C.I. 95%: 10.40-45.36; 90-99 years, $OR_{adjustment}$ = 66.24, 95% CI: 31.03-141.38; 100 years and older, $OR_{adjustment}$ = 69.22, 95% CI:
12.97-369.33) compared to patients aged 40-59 years. Additionally, moderate and large effects were also found for patients vaccinated with

more than 12 months prior to diagnosis ($OR_{adjustment}$ = 2.38, 95% CI: 1.48-3.81) and unvaccinated ($OR_{adjustment}$ = 6.96, 95% CI: 4.01-12.08) respectively.

Discussion

This retrospective study shows how, in the last wave of COVID-19 attributable to the Omicron variant in the Canary Islands,[14] patients in age groups over 70 years and those not vaccinated, or whose last dose was administered at least 12 months prior to diagnosis, showed a higher risk of mortality.

In line with our work, different predictive models of mortality by COVID-19 have been previously developed, including variables such as age, sex, comorbidities or analytical values.[19,20] In the model presented by Banoei et al. for pre-Omicron variants, the presence of coronary artery disease, diabetes, altered mental status, age over 65 years and dementia were the most relevant predictors of mortality.[21] Liang et al. developed the COVID- GRAM risk score,[22] in which they identified 10 variables that were independent predictors, including age, number of comorbidities and history of cancer, in addition to other analytical variables. Although this score was designed in 2020, several authors have demonstrated its usefulness as a predictor of mortality at different times during the pandemic.[23–25] The 4C Mortality Score was developed to assess in-hospital mortality of patients with COVID-19 based on age, sex, number of comorbidities, in addition to vital signs and laboratory values.[26,27] However, Häger et al. did not find these new scores to be more useful than other pre-COVID era scores, such as NEWS, for predicting mortality. In this sense, the results of our study, based on cases with Omicron variant, also do not support the need to include a large number of predictors for COVID-19 mortality in the geriatric population.

With respect to how our results can be generalized to other geographical areas, it is worth reviewing the studies that have compared the case fatality rates between the different autonomous communities in different periods of the pandemic. For example, in reference to lethality by age, the Canary Islands were among the autonomous communities with a significantly lower number of deaths, especially in the first waves.[28] In the study by Alfaro-Martínez et al. it was shown that the incidence of COVID-19 in Spain in the first six waves occurred in the form of clusters that reproduced the division by autonomous communities.[29] These authors did not rule out that this was due to differences between autonomous communities when screening, diagnosing or reporting cases of COVID-19.

On the other hand, according to the study published by Kowall et al, the differences between countries in excess mortality are probably due to several factors, and may depend on the prevalence of chronic diseases in each country.[30] Among the risk factors that have been associated with mortality in the elderly population hospitalized by COVID-19 are some chronic pathologies such as ischemic heart disease/heart failure, hypertension or chronic kidney disease. Also among older patients, older age was associated with a higher risk of death.[5–7,31–33] In our study, we observed a higher proportion of patients with chronic cardiovascular, diabetic, renal, respiratory and systemic pathology among the deceased. However, no independent association was found between any chronic disease and increased risk of mortality. This association was only found with respect to sex (male), patients over 70 years of age and those who were not vaccinated. These results are not new, since they coincide with findings published by other authors. For example, in the 2021 meta-analysis by Pijls et al. on pre-Omicron variants and without data on vaccination, males and patients aged 70 years or older were shown to be at increased risk of COVID-19 infection, development of severe disease, ICU admission, and death.[34]

Regarding vaccine effect, some studies have shown how vaccine effectiveness against severe COVID-19 disease decreased slightly 6 months after full vaccination, although booster doses restored vaccine efficacy.[35,36] In our study, the median time elapsed between the last vaccine dose and COVID-19 diagnosis was 10 days shorter in those cured, and the percentage of cases without any vaccination dose was found to be higher in the deceased group. Those unvaccinated or whose last dose was administered at least 12 months prior to diagnosis showed a significant association with an increased risk of mortality. In the Higdon et al. study, the effectiveness of vaccination against symptomatic disease declined more rapidly with the Omicron variant than with the pre-Omicron variants, with the protective effect of primary vaccination disappearing after 4-6 months, and between 1-4 months after booster vaccination.[37] According to some authors, the rapid spread of Omicron is attributed to several factors, in particular its higher infectivity, transmissibility or immune evasion compared to earlier variants, including Delta. This would explain why the effect of primary vaccination on Omicron is less than the protection observed against Delta variant infection.[15] In this regard, according to Varea-Jiménez et al. unvaccinated persons infected with the Alpha or Omicron variants of SARS-CoV-2 were less likely to be hospitalized compared to the Delta variant. At the same time, it was also found that the probability of hospitalization was lower in fully vaccinated cases compared to unvaccinated cases for all variants.[13]

In our study, it was observed that the proportion of persons residing in socio-health centers was significantly higher among those who died. Regarding this population, the study by Van Ewijk et al. showed that the effectiveness of vaccination against mortality was moderate in elderly residents in long-stay centers. However, two weeks after the booster dose, no deaths occurred, despite the presence of susceptible residents. Other studies have also analyzed mortality due to COVID-19 in nursing homes, finding a higher percentage of mortality and hospital readmissions, since these are closed environments where there is interaction between young people with the possibility of asymptomatic infection and highly susceptible elderly people.[38–40] In the study by Visser et al.,[10] , those nursing home residents with a higher degree of polypharmacy and who were unvaccinated also had a higher 30-day COVID-related mortality.

Our work is not without limitations. On the one hand, it is possible that fewer cases were reported during the study period, since the surveillance strategy during the present wave focuses on cases aged 60 years or older. However, this should not significantly affect the results, since our study has basically focused on this population. On the other hand, we have assumed that all reported cases of COVID-19 in the study period correspond to the Omicron variant. Although not all cases have been sequenced, according to the latest reports published by the Ministry of Health, between 99-100% of cases were for this variant. Nor has a differentiation been made between the Omicron sublineages, although according to the Organization

World Health Organization, subvariant BA. 5, which is the globally dominant and most contagious subvariant, is not considered more serious than the other Omicron subvariants.[41]
Finally, as this was a retrospective study based on information available in primary care medical records, some variables of interest that have been associated in some cases in the literature with a higher risk of severity or mortality, such as obesity, delirium, cognitive impairment, functional dependence or frailty,[32] were not available in all the records and could not be analyzed.

Conclusions

In summary, there are multiple possible factors that may increase the risk of COVID-19 mortality in the elderly population, ranging from some previous diseases (e.g. cardiovascular, diabetes, etc.) to living conditions (e.g. nursing homes). However, our study has found that, once adjusted for effects, only three predictors can explain practically the same variability: a large effect of older age, a small effect of men on women, and a large effect due to not being vaccinated, or a medium effect when the last vaccination date was before one year.
This could simplify pandemic management for public health authorities. However, given that the variants will continue to evolve in an a priori unpredictable manner, it is necessary to continue surveillance of the disease and update the evidence periodically in order to optimize intervention strategies.

Conflict of interest

The authors declare that there is no conflict of interest.

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Table 1. Characteristics of the sample.

Feature	Total	End of follow-up		p
		Curing	Deceased	
Number of cases	16.998	16.810	188	
Sex (male), n (%)	6.763 (39,8)	6.661 (39,6)	102 (54,3)	<0,001
Age (years), median (RIC)	66 (56-77)	66 (56-77)	85 (76-90)	<0,001
Hospitalization				
Conventional hospitalization, n (%)	592 (3,5)	439 (2,6)	153 (81,4)	<0,001
Days between diagnosis and admission, range	0-26	0-26	0-21	0,008
Admission to ICU, n (%)	54 (0,3)	31 (0,2)	23 (12,2)	<0,001
Days between diagnosis and admission to the ICU, range	0-28	0-28	0-10	0,034
Background				
Cardiovascular pathology, n (%)	11.353 (66,8)	11.193 (66,6)	160 (85,1)	<0,001
Diabetes, n (%)	4.726 (27,8)	4.643 (27,6)	83 (44,2)	<0,001
Digestive pathology, n (%)	469 (2,8)	464 (2,8)	5 (2,7)	0,933
Immunodeficiency n (%)	82 (0,5)	82 (0,5)	0 (0)	0,337
Solid organ neoplasm, n (%)	1.153 (6,8)	1.135 (6,8)	18 (9,6)	0,126
Hematopoietic neoplasm, n (%)	346 (2)	341 (2)	5 (2,7)	0,542
Renal pathology, n (%)	2.226 (13,1)	2.168 (12,9)	58 (30,9)	<0,001
Respiratory pathology, n (%)	4.617 (27,2)	4.548 (27,1)	69 (36,7)	0,003
Systemic diseases, n (%)	11.530 (67,8)	11.388 (67,8)	142 (75,5)	0,023
Polypharmacy, n (%)	8.817 (51,9)	8.676 (51,6)	141 (75)	<0,001
Vaccination				
Number of vaccine doses for COVID-19, n (%)				<0,001
0	738 (4,3)	707 (4,2)	31 (16,5)	
1	242 (1,4)	241 (1,4)	1 (0,5)	
2	2.290 (13,5)	2.269 (13,5)	21 (11,2)	
3	10.405 (61,2)	10.313 (61,4)	92 (48,9)	
4	3.323 (19,6)	3.280 (19,5)	43 (22,9)	
Days between last vaccination and diagnosis, median (RIC)	303 (267-366)	303 (267-366)	313 (258-394)	0,042
Time between vaccination and diagnosis, n (%)				<0,001
<3 months	1.980 (11,7)	1.954 (11,6)	26 (13,8)	
3-6 months	457 (2,7)	450 (2,7)	7 (3,7)	
6-12 months	9.720 (57,2)	9.658 (57,5)	62 (33)	
>12 months	4.099 (24,1)	4.037 (24)	62 (33)	
Never	742 (4,4)	711 (4,2)	31 (16,5)	
Socio-health center				
Resident, n (%)	719 (4,2)	705 (4,2)	14 (7,5)	<0,001

IQR = interquartile range; range = minimum and maximum; *p* values represent differences between percentages using the chi-square test, and the Wilcoxon nonparametric test for the remainder.

Table 2. Bivariate and multivariate models for the association between risk factors and death

Risk factor, n (%)	Curing (n=16.910)	Deceased (n=188)	Simple		Multiple		Final model	
			ORI	.C. 95%.	OR adjusted I.	I.C. 95%.	OR adjusted I.	I.C. 95%.
Sex								
Female (reference)	10149 (60,4)	86 (45,7)	-		-		-	
Man	6661 (39,6)	102 (54,3)	1,81	1,35-2,41	1,85	1,37-2,51	1,92	1,42-2,58
Age group (years)								
from 40 to 59 (reference)	5529 (32,9)	8 (4,3)	-		-		-	
from 60 to 69	4293 (25,5)	11 (5,9)	1,77	0,71-4,41	2,08	0,82-5,24	1,97	0,79-4,91
from 70 to 79	3796 (22,6)	44 (23,4)	8,01	3,77-17,03	9,52	4,27-21,24	9,11	4,27-19,43
from 80 to 89	2495 (14,8)	71 (37,8)	19,67	9,45-40,91	22,24	9,99-49,52	21,72	10,40-45,36
from 90 to 99	679 (4,0)	52 (27,7)	52,93	25,04-111,89	68,47	30,11-155,71	66,24	31,03-141,38
of 100 or more	18 (0,1)	2 (1,1)	76,79	15,24-386,91	72,48	13,07-401,9	69,22	12,97-369,33
Vaccine-diagnostic time								
<3 months (reference)	1954 (11,6)	26 (13,8)	-		-		-	
3-6 months	450 (2,7)	7 (3,7)	1,17	0,50-2,71	1,22	0,52-2,89	1,17	0,50-2,73
6-12 months	9658 (57,5)	62 (33,0)	0,48	0,30-0,76	0,96	0,60-1,55	0,97	0,61-1,55
>12 months	4037 (24,0)	62 (33,0)	1,15	0,73-1,83	2,33	1,44-3,75	2,38	1,48-3,81
Never	711 (4,2)	31 (16,5)	3,28	1,93-5,56	6,87	3,92-12,05	6,96	4,01-12,08
Cardiovascular pathology	11193 (66,6)	160 (85,1)	2,87	1,92-4,29	0,67	0,41-1,09		
Diabetes	4643 (27,6)	83 (44,2)	2,07	1,55-2,77	1,09	0,80-1,50		
Renal pathology	2168 (12,9)	58 (30,9)	3,01	2,20-4,12	1,30	0,93-1,82		
Respiratory pathology	4548 (27,1)	69 (36,7)	1,56	1,16-2,11	1,21	0,88-1,66		
Systemic diseases	11388 (67,8)	142 (75,5)	1,47	1,05-2,05	0,86	0,6-1,24		
Polypharmacy	8676 (51,6)	141 (75,0)	2,81	2,02-3,92	1,28	0,86-1,9		

Resident in social-health center, n (%)	705 (4.2)	14 (7.5)	1,84	1,06-3,18	0,91	0,5-1,64

OR = Odds Ratio; adjusted OR = adjusted Odds Ratio; 95% CI = 95% confidence interval; statistically significant effects are indicated in bold; estimates of values were made using logistic regression equations.