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LETTER TO THE EDITOR

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The severity of the first 207 infections with the SARS-CoV-2 Omicron BA.2 variant, in Marseille, France, December 2021–February 2022

To the Editor,

In France, the Omicron variant (Pango lineage B.1.1.529) accounted for 99.3% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnoses at the country level in the last survey conducted on February 18 2022, with the BA.2 variant (B.1.1.529.2) accounting for 10.7% of cases which was a 2.4-fold increase as compared to the previous week.[1] The Omicron BA.2 variant has spread in other European countries and became predominant in Denmark.[2] The objective of this study is to describe the first 207 Omicron BA.2 cases diagnosed at the Institut Hospitalo-Universitaire Méditerranée Infection located in Marseille, France, which manages the vast majority of patients in the area, and to provide early information on its severity, in comparison with that of the Omicron BA.1 variant (B.1.1.529.1).

All available SARS-CoV-2 positive results obtained by our laboratory between December 27, 2021 (the date of the first identification of an Omicron BA.2 case) and February 14, 2022 led to genotyping using real-time reverse transcription-quantitative polymerase chain reaction (qPCR) and next-generation genome sequencing (NGS). Briefly, qPCR assays specific to variants included detection of spike mutations L452R, K417N, E484K, and/or P681H (Thermo Fisher Scientific), combined with the targeting of viral genes ORF1, N (nucleocapsid), and S (spike) with the TaqPath COVID-19 assay (Thermo Fisher Scientific). NGS used the Illumina CovidSeq or Artic combined with Oxford Nanopore Technologies procedures and genome assembly and analyses were done as previously described.[3] SARS-CoV-2 genome sequences have been deposited in the GISAID database (https://www.gisaid.org/).[4]

Demographics and clinical data were retrospectively obtained from electronic medical files and anonymized before analysis. Hospitalization, transfer to intensive care unit (ICU), and death rate were used for severity assessment. In case a patient had several conditions (being hospitalized, transferred later to ICU, and then dying), conditions were not mutually exclusive. Records with missing information on severity were excluded. This study project was validated by the ethics committee of the Méditerranée Infection Institute under reference 2022-001. Access to the patients' biological and registry data issued from the hospital information system was approved by the data protection committee of Assistance Publique-Hôpitaux de Marseille (AP-HM) and was recorded in the European General Data Protection Regulation Registry under number RGPD/AP-HM 2019-73.

As of February 14, 2022, 207 cases of the SARS-CoV-2 Omicron BA.2 variant were included and compared to 2793 cases of the SARS-CoV-2 Omicron BA.1 variant diagnosed during the same timeframe. Vaccination status against COVID-19 was available for 1573 patients (52.4%) infected with an Omicron variant, of whom 96.6% were vaccinated. The majority of vaccinated patients (89.8%) received at least two doses of vaccine and 12.9% of infections occurred during the first 21 days following the last dose. (Table 1). The median age of patients infected with Omicron BA.1 was 36 years and 55.8% were females. Their hospitalization rate was low (1.4%), only 3 patients (0.1%) were transferred to ICU and 10 (0.4%) died. Eight patients who died were older than 65 years old with comorbidities including cancer, chronic respiratory diseases, and diabetes. The two others suffered from leukemia and asthma. Five were unvaccinated, one patient received one dose of vaccine, one received two doses, and three received three doses. This pattern is consistent with that of the 1119 first patients diagnosed with the Omicron BA.1 variant between November 28 and December 31, 2021, at our institute.[5] The proportion of patients aged 65 years and more was higher in patients infected with Omicron BA.2 as compared to those infected with Omicron BA.1. Patients infected with the Omicron BA.2 variant were significantly more likely to be hospitalized (6.3%, $p < 10^{-2}$) (Table 1). None was transferred to ICU and three (1.5%) died. The three patients who died were aged 80, 97, and 99 years and two suffered from diabetes. Two (aged 80 and 97 years old) were vaccinated against COVID-19 (three doses). The median age of patients who died with Omicron BA.2 infection (97 years old, 100% ≥80 years old) was significantly higher than that of those who died with Omicron BA.1 infection (72.5 years, 30% ≥80 years old) (Table 2). In multivariate analysis, independent risk factors for hospitalization were older age and infection with the BA.2 variant while only older age was associated with death risk (Tables S1 and S2).

Our study has some limitations including its small number of patients and a lack of documentation of vaccination status in 47.6% of patients. Notwithstanding, severe infections with Omicron BA.2 were only observed in patients ≥80 years old. Given its increased transmissibility suggested by the UK and Danish data,[6,7] its close monitoring will be required in the near future.

TABLE 1 Characteristics of patients infected with SARS-CoV-2 the Omicron BA.1 and BA.2 variants from December 27, 2021 to February 14, 2022.

	BA.1 N = 2793		BA.2 N = 207		
Variables	***n***	**%**	***n***	**%**	***p****
Age (years)					
Median	36	39			0.08
Interquartile	25–51	24–59			
Range	0–94	0–99			
Age group (years)					
<45	1803	64.5	126	60.9	0.002
45–64	745	26.7	50	24.1	
65–79	198	7.1	19	9.2	
>80	47	1.7	12	5.8	
Gender					
Female	1559	55.8	113	54.6	0.73
Male	1234	44.2	94	45.4	
COVID-19 vaccination status[1497, 76]					
Not vaccinated	51	3.4	2	2.6	1.0
Vaccinated	1446	96.6	74	97.4	
Number of vaccine injections among vaccinated patients[1446, 74]					
One dose	144	10.0	11	14.9	0.19
Two doses	905	62.3	38	51.3	
Three doses	395	27.3	25	33.8	
Four doses	2	0.1	0	0	
Number of vaccine injections (not vaccinated vs. two or three doses)[1351, 65]					
Not vaccinated	51	3.8	2	3.1	1.0
Vaccinated with two or three doses	1300	96.2	63	96.9	
The median time between the last vaccine injection and positive SARS-CoV-2 PCR (min, max) (days)[934, 53]	117 (0 – 375)	83 (9 – 208)			0.13
Time range between last vaccine injection and positive SARS-CoV-2 PCR (days)[922, 53]					
≤21	123	13.3	3	5.7	0.11
>21	799	86.7	50	94.3	
Hospitalization					
No	2755	98.6	194	93.7	<0.0001
Yes	38	1.4	13	6.3	
Transfer to the intensive care unit					
No	2737	98.0	207	92.3	1.0
Yes	3	0.1	0	0	

(Continues)

TABLE 1 (Continued)

Variables	BA.1 N = 2793 n	%	BA.2 N = 207 n	%	p*
Death					
No	2783	99.6	204	98.5	0.06
Yes	10	0.4	3	1.5	

Note: Superscript numbers indicate the number of patients for whom data were available.

Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*Statistical analyses were carried out using Stata version 16.0 (http://www.stata.com). The Pearson's χ^2 test and Fisher's exact test, as appropriate, were applied to analyze the categorical variables. The Student's *t*-test was used to compare the difference in the mean of quantitative variables. Qualitative variables were presented by percentage. The univariable and multivariable (logistic regression) was conducted to evaluate the association between multiple factors (age, gender, vaccination status, and Omicron variants) and clinical outcomes (hospitalization and death) of COVID-19 patients. We did not carry out an analysis of transfer to intensive care unit outcomes because of low effectiveness. The results were presented by odds ratio with a 95% confidence interval. $p < 0.05$ was considered statistically significant.

TABLE 2 Age of patients with severe infections according to Omicron variants.

	BA.1 n	%	BA.2 n	%	p
Hospitalized patients	N = 38		N = 13		
Median age in years (range)	66.5 (0–93)		63 (0–99)		0.41
Age ≥80 years old	11	29.0	4	30.8	0.74
Patients transferred to the intensive care unit	N = 3		N = 0		
Median age (range)	71 (55–84)		–		NA
Age ≥80 years old	1	33.3	0	0	NA
Patients who died	N = 10		N = 3		
Median age (range)	72.5 (15–84)		97 (80–99)		0.03
Age ≥80 years old	3	30.0	3	100	0.07

Abbreviation: NA, not applicable.

AUTHOR CONTRIBUTIONS

Philippe Gautret analyzed and wrote the first draft, Van T. Hoang performed the statistical analysis, Pierre E. Fournier and Philippe Colson provided virological data, and Marie T. Jimeno, Jean-Christophe Lagier, and Pascal Rossi provided clinical data. Didier Raoult supervised the work. All authors contributed significantly to this manuscript. All authors reviewed and approved the final submission.

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CONFLICTS OF INTEREST

Didier Raoult has a conflict of interest, having been a consultant for Hitachi High-Technologies Corporation, Tokyo, Japan, from 2018 to 2020. He is a scientific board member of Eurofins company and a founder of a microbial culture company (Culture Top). Other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article. Data are available on request to the corresponding author.

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REFERENCES

1. Santé Publique France. *COVID-19. Point epidémiologique. N°103*. Accessed February 17, 2022. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-17-fevrier-2022
2. Desingu PA, Nagarajan K. Omicron BA.2 lineage spreads in clusters and is concentrated in Denmark. *J Med Virol*. 2022. doi:10.1002/jmv.27659
3. Colson P, Delerce J, Beye M, et al. First cases of infection with the 21L/BA.2 Omicron variant in Marseille, France. *J Med Virol*. 2022. doi:10.1101/2022.02.08.22270495
4. Alm E, Broberg EK, Connor T, et al. Geographical and temporal distribution of SARS-CoV-2 clades in the WHO European Region, January to June 2020 separator. *Euro Surveill*. 2020;25(32):2001410. doi:10.2807/1560-7917.ES.2020.25.32.2001410
5. Houhamdi L, Gautret P, Hoang VT, Fournier PE, Colson P, Raoult D. Characteristics of the first 1119 SARS-CoV-2 omicron variant cases, in Marseille, France, November-December 2021. *J Med Virol*. 2022;94:2290-2295. doi:10.1002/jmv.27613
6. Mahase E. Covid-19: What do we know about omicron sublineages? *BMJ*. 2022;376:o358. doi:10.1136/bmj.o358
7. Lyngse FP, Kirkeby CT, Denwood M, et al. Transmission of SARS-CoV-2 omicron VOC subvariants BA.1 and BA.2: evidence from Danish households. *medRxiv*. 2022. doi:10.1101/2022.01.28.22270044

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