Pattern of SARS-CoV-2 infection among dependant elderly residents living in retirement homes in Marseille, France, March-June 2020.

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Running title: dependant elderly residents and COVID-19

Abstract

Background. SARS-CoV-2 infection can cause significant mortality among dependant elderly residents living within medical retirements homes. We aimed to report the results of SARS-CoV-2 PCR-based screening campaigns conducted in dependent elderly resident in retirement homes in Marseille, France and the follow-up of positive cases.

Methods. Data of 1691 elderly residents and 1000 member staffs were retrospectively collected through interview of the medical team of 24 retirement homes and electronic health recording system of the hospital.

Results. Elderly residents were predominantly female (64.8%) with a mean age of 83.0 years old. SARS-CoV-2 detection in residents (226, 13.4%) was significantly higher than in staff members (87, 8.7%), with $p=4.10^{-4}$. Of 226 infected residents, 37 (16.4%) were detected on a case-by-case basis because of COVID-19 symptoms and 189 (83.6%) were detected through mass screening; 77.0% had possible COVID-19 symptoms, including respiratory symptoms and signs (44.5%) and fever (46.5%); 116 (51.4%) patients received a course of oral hydroxychloroquine and azithromycin (HCQ-AZ) for at least 3 days; and 47 (20.8%) died. In multivariate, death rate was positively associated with being male (30.7% vs. 14.0%, OR=3.64, p=0.005), being older than 85 years (26.1% vs. 15.6%, OR=2.46, p=0.042), and oxygen therapy (38.3% vs. 13.0%, OR=4.59, $p<10^{-4}$) and negatively associated with being diagnosed through mass screening (16.9%, vs. 40.6%, OR=0.20, p=0.001) and receiving HCQ-AZ treatment for at least 3 days (15.5% vs. 26.4%, OR=0.39, p=0.026).

Conclusion. Our data shows that early diagnosis and care of COVID-19 patients at retirement homes can be effective in saving lives.

Keywords: COVID-19; SARS-CoV-2; elderly resident; retirement home; mass testing; hydroxycloroquine.

Introduction

The treatment of COVID-19 has been the subject of terrible controversy, and in particular the use of hydroxychloroquine (HCQ) [1]. It appears to us that one of the elements of the controversy is both the heterogeneity of protocols using HCQ, with doses ranging from 800 mg to 1200 mg per day, the duration of treatment, the combination or not with azithromycin (AZ), and the stage of the disease at which patients were being treated. Indeed, we can consider that there is a purely viral phase with a more or less strong immune response, which can become predominant in what has been called the cytokine storm, followed in a number of cases, by necrotic lesions, linked to pulmonary infarctions [2]. Furthermore, mortality depends very significantly on age and thus in Europe almost all death were among persons aged 60 years or over with more than 50% in persons aged 85 years and over [3]. Under these conditions, it is very difficult to do comparative studies addressing the effect of HCQ on COVID-19-associated death. There are very few randomized studies and their interpretations have also led to heated debate. We believe, to aid the debate, one of the important elements may be to assess whether there is a clear reduction in mortality in the groups most at risk.

In France, as of June 2nd 2020, 10,350 elderly residents housed in retirement homes or medico-social establishments died from COVID-19 (27.6% lethality rate) accounting for 55.6% of French COVID-19 deaths [4]. Similar pictures have been also reported in many European countries [5]. The prevalence of chronic conditions such as cardiovascular diseases, hypertension and diabetes mellitus is high among elderly people living in retirement care facilities. Coronavirus disease (COVID-19) in this population may therefore have severe outcomes with high mortality rate [5, 6].

In Marseille, we had the opportunity for about two months to test and treat COVID-19 patients in retirement homes (Etablissement d'Hébergement pour Personnes Agées Dépendantes – EHPAD) with the combination of HCQ-AZ as we have described it on several occasions [2, 7-

9] and wanted to compare the lethality in patients treated in these EHPADs, the lethality of patients not treated in these EHPADs and the general lethality of patients in EHPADs in France.

Methods

Ethic statement

Ethical approvals were obtained from the Marseille Institutional Review Board and Ethics Committee (N° 2020-028).

Setting, study design and population

SARS-CoV-2 cross-sectional mass screening campaigns were conducted in residents and staff members from 24 retirement homes (EHPADs) in Marseille, from March 24th to June 2nd, 2020. In some centers, screening campaigns were conducted following the diagnosis of confirmed COVID-19 cases in symptomatic patients that were sampled on a case-by-case strategy. In other centers, screening campaigns were conducted systematically. In all cases, screening campaigns were conducted following a demand by the directors and medical staffs of the retirement homes. Nasopharyngeal samples were processed for SARS-CoV-2 PCR testing at the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection at Assistance Publique-Hôpitaux de Marseille (AP-HM), as previously described (Amrane, TMAID) or in private laboratories in Marseille, in some cases. Residents who tested positive were either i) managed at retirement homes by local medical staffs only or ii) managed at retirement homes in coordination with the AP-HM Home Hospitalization Unit (HHU) of or iii) admitted to the IHU (in day-care hospital or conventional units) or iv) transferred to AP-MH Intensive Care Units (ICU). For confirmed cases, demographics, chronic medical conditions, COVID-19 treatment and clinical data including fever, asthenia, anorexia and weight loss, respiratory symptoms and signs (cough, rhinorrhea, dyspnea, chest pain, acute respiratory distress syndrome) and death was collected retrospectively from the following sources: i) interview of the medical team of twenty-three retirement homes, ii) electronic health recording system of the AP-HM.

Statistical methods

Statistical procedures were performed using STATA 11.1. We used the Pearson's chi-square or Fisher's exact tests to compare differences between groups of patients where appropriate. A two-sided p-value of less than 0.05 was considered statistically significant. A separate logistic regression analysis was used to identify independent risk factors for SARS-CoV-2 death prevalence among all elderly residents testing positive for SARS-CoV-2. The results were presented by percentages and odd ratio (OR) with 95% confidence interval (95%CI). The initial model included variables presenting a p-value <0.2. The stepwise regression procedure and likelihood-ratio tests were applied to determine the final model.

Results

Over the study period, 1691 elderly residents and 1000 staff members were tested (Table 1). For residents, the sex ratio (male to female) was 1:1.8 and the mean age (± standard derivation [SD]) was 83.0 (±10.6) years (ranging from 50 to 106 years). For staff members, the sex ratio was 1:3.5 and the mean age (± SD) was 40.8 (±12.8) years (ranging from 18 to 87 years). Of note, two religious staff members at one retirement home were aged 75 and 87 years, respectively.

Overall, 313 participants (of 2691, 11.6%) were confirmed positive for SARS-CoV-2. The prevalence in residents (226 of 1691, 13.4%) was significantly higher than in staff members (87 of 1000, 8.7%), $p=4.10^{-4}$). With regard to the housing facilities, at least one individual was positive in 11/24 (45.8%) centres with prevalence of SARS-CoV-2 detection ranging from 0% to 57.6% among residents and from 0% to 24.1% among staff members (Table 1). The lethality rate among residents was 20.8% while no death occurred among staff members ($p<10^{-4}$).

Characteristic of 226 elderly residents testing positive for SARS-CoV-2 (Table 2 and 3)

Of 226 SARS-CoV-2-positive elderly residents, 37 were diagnosed on a case-by-case basis through selected sampling of patients with COVID-19 symptoms and 189 (83.4%) were detected through massive screening. Regarding co-morbidities, most frequent chronic condition was hypertension (39.9%), followed by other cardiovascular diseases (36.4%), dementia (28.0%) and other mental disorders (24.5%). Regarding clinical findings, 77.0% had possible COVID-19 symptoms, including respiratory symptoms and signs (44.5%), and fever (46.5%) (Table2).

Regarding therapeutic management, 62 (27.4%) patients were managed at retirement homes by local medical staff only, 117 (51.8%) were managed at retirement home in collaboration with the HHU, 16 (7.1%) were admitted to IHU and 31 (13.7%) were transferred to ICU. Overall, 116 (51.4%) patients received an oral HCQ (200 mg three times daily for ten days), and AZ (500 mg on day 1 followed by 250 mg daily for the next four days) for at least three days and were monitored as described in previous studies [7-9]. Among the 110 others (48.6%), 1 (0.4%) received a 2-day course of HCQ-AZ, 1 (0.4%) received HCQ alone, 37 (16.4%) received AZ alone, and 71 (31.4) did not receive either drugs. Other treatments are described in Table 2. A total of 179 patients survived (79.2%) and 47 (20.8%) died.

Table 3 shows lethality rates among elderly residents with COVID-19, according to demographics, chronic conditions, circumstance of diagnosis, type of medical management of patients and use of HCQ-AZ. In univariate analysis, death was significantly associated with male gender, age > 85 years, and suffering chronic lung diseases and cancer while patients suffering dementia were less likely to die from COVID-19. In addition, patients who were diagnosed on a case-by case basis because of COVID-19 symptoms were more likely to die (40.6%) than those diagnosed through systematic screening (16.9%). Finally, patients who received HCQ-AZ treatment for at least 3 days were less likely to die (15.5%) than those who did not received such a treatment (26.4%). In multivariate, death rate was positively associated with being male (30.7% vs. 14.0%, OR=3.64, p=0.005), being older than 85 years (26.1% vs. 15.6%, OR=2.46, p=0.042), and oxygen therapy (38.3% vs. 13.0%, OR=4.59, $p<10^{-4}$) and negatively associated

with being diagnosed through mass screening (16.9%, vs. 40.6%, OR=0.20, p=0.001) and receiving HCQ-AZ treatment for at least 3 days (15.5% vs. 26.4%, OR=0.39, p=0.026).

Discussion

In Marseille, the first case of COVID-19 in the general population was diagnosed on March 3rd, 2020 and the epidemic peaked during the first week of April and remained active until the end of the month. Our survey at retirement homes started at the time the whole French population have been placed under strict lockdown (17 March) and the epidemic was active in Marseille. All retirement homes became confined environments with very strict restrictions of visits. We found a 13.4% SARS-CoV-2 positivity rate among dependant elderly residents in Marseille that was significantly higher than the 5.4% positivity rate among overall French dependant elderly residents according to a national survey (37405 confirmed cases of an estimated 695 060 French dependant elderly residents, p<0.0001, June 2nd update) [4, 10]. We observed an overall 20.8% COVID-19 lethality rate among infected residents in Marseille that was significantly lower than that in overall French retirement homes or medico-social establishments (27.7% lethality rate, p=0.026, June 2nd update) [4]. Mains drivers of mortality in Marseille residents were older age and male sex as already reported in many studies [11]. In addition, systematic screening by PCR was identified as an independent protective factor against COVID-19 death. Symptom-based diagnosis strategy is less effective in retirement homes, likely because elderly patients with comorbidity such as respiratory or cardiovascular chronic diseases may be unable to accurately report new symptoms suggestive of COVID-infection or may present with atypical symptoms that challenge medical staffs [12]. Also, in our experience, 16% of SARS-CoV-2 infected residents had no symptoms at the time of sampling. In this work, we show that there was a significant difference in lethality between patients treated with our standardized treatment and untreated patients. This work has some limitations. Our study population was not randomly and homogenously recruited. Data regarding demographics, chronic conditions and clinical status was not systematically documented. The use of individual preventive measures was not documented.

Nevertheless, we believe that even if there are biases, as in any comparative study including randomization, these biases are relatively neutralized by the multifactorial study and above all we show that the mortality in patients treated in EHPADs in Marseille is half of the mortality of patients in nursing homes in France who in most cases have not received specific treatment. We believe that focusing on the population with the highest mortality, to show a significant effect, is important and we agree in this sense with several studies that have shown a reduction in mortality of 30 to 50% by HCQ-AZ in populations most at risk [13, 2].

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Table 1. SARS-CoV-2 testing among residents and staff members at 24 retirement homes in Marseille, France, March 27th –June 2nd , 2020

Characteristics	Residents				Staff members					Total	
	Date of mass testing	No. tested	No. (%) positive	No. (%) death among positive cases (lethality rate)	No. tested	No. (%) positive	No. (%) death among positive cases (lethality rate)	p-value[1]	p-value[2]	No. tested	No. (%) positive
Total		**1691**	**226 (13.4)**	**47 (20.8)**	**1000**	**87 (8.7)**	**0 (0)**	**4.10^{-4}**	**$<10^{-4}$**	**2691**	**313 (11.6)**
Centre (2691)											
Center-01	01 April, 08 April, 19 April	99	57 (57.6)	17 (29.9)	83	20 (24.1)	0 (0)	2.10^{-3}	0.04	182	77 (42.3)
Center-02	08 April, 19 April, 20 May	112	50 (44.6)	9 (18.0)	71	17 (24.0)	0 (0)	7.10^{-3}	0.053	183	67 (36.6)
Center-03	20 April, 26 April, 04 May, 11 May, 18 May, 25 May, 02 June	52	23 (44.2)	2 (8.7)	35	7 (20.0)	0 (0)	2.10^{-3}	N/A	87	30 (34.5)
Center-04	06 April, 21 April	89	24 (27.0)	8 (33.3)	108	12 (11.1)	0 (0)	7.10^{-3}	0.03	197	36 (18.3)
Center-05	08 April, 29 April	37	10 (27.1)	3 (30.0)	32	1 (3.1)	0 (0)	0.035	N/A	69	11 (16.0)
Center-06	08 April, 17 April, 22 April	230	45 (18.0)	7 (15.6)	180	15 (8.3)	0 (0)	2.10^{-3}	0.18	410	60 (14.9)
Center-07	02 Avril, 27 April, 25 May	81	8 (9.9)	0 (0)	57	11 (19.3)	0 (0)	0.18	N/A	138	19 (13.8)
Center-08	13 April, 06 May	77	7 (9.1)	1 (14.3)	24	1 (4.2)	0 (0)	0.67	N/A	101	8 (7.9)
Center-09	21 April	54	0 (0)	N/A	44	3 (6.8)	0 (0)	0.08	N/A	98	3 (3.1)
Center-10	23 April	46	1 (2.2)	0 (0)	12	0 (0)	N/A	N/A	N/A	58	1 (1.7)
Center-11	15 April	118	1 (0.9)	0 (0)	60	0 (0)	N/A	N/A	N/A	178	1 (0.6)
Center-12	15 April	66	0 (0)	N/A	18	0 (0)	N/A	N/A	N/A	84	0 (0)

Center-13	28 April	96	0 (0)	N/A	39	0 (0)	N/A	N/A	N/A	135	0 (0)
Center-14	30 April	45	0 (0)	N/A	12	0 (0)	N/A	N/A	N/A	57	0 (0)
Center-15	17 April	64	0 (0)	N/A	27	0 (0)	N/A	N/A	N/A	91	0 (0)
Center-16	22 April	48	0 (0)	N/A	19	0 (0)	N/A	N/A	N/A	67	0 (0)
Center-17	25 April	61	0 (0)	N/A	29	0 (0)	N/A	N/A	N/A	90	0 (0)
Center-18	15 April	52	0 (0)	N/A	18	0 (0)	N/A	N/A	N/A	70	0 (0)
Center-19	27 April	32	0 (0)	N/A	24	0 (0)	N/A	N/A	N/A	56	0 (0)
Center-20	27 April	29	0 (0)	N/A	15	0 (0)	N/A	N/A	N/A	44	0 (0)
Center-21	24 April	25	0 (0)	N/A	11	0 (0)	N/A	N/A	N/A	36	0 (0)
Center-22	20 April	53	0 (0)	N/A	22	0 (0)	N/A	N/A	N/A	75	0 (0)
Center-23	14 April	100	0 (0)	N/A	52	0 (0)	N/A	N/A	N/A	152	0 (0)
Center-24	24 April	25	0 (0)	N/A	8	0 (0)	N/A	N/A	N/A	33	0 (0)
Sex (2471)											
Female, n (%)		1069 (64.8)	135 (12.6)	19 (14.1)	646 (77.7)					1705 (69.0)	
Male, n (%)		581 (35.2)	91 (15.7)	28 (30.8)	185 (22.3)					766(31.0)	
Age (years) (2556)											
Mean±SD		83.0±10.6	83.4±10.6	86.8±10.2	40.8±12.7					68.3±23.1	
Range (min-max)		50-106	56-103	59-103	18-87					18-106	
18-34,n (%)		0 (0)	N/A	N/A	326 (36.4)					326 (12.8)	
35-49, n (%)		0 (0)	N/A	N/A	292 (32.6)					292 (11.4)	
50-59, n (%)		34 (2.1)	3 (8.8)	1 (33.3)	236 (25.4)					270 (10.6)	
60-69, n (%)		189 (11.4)	25 (13.2)	3 (12.0)	38 (4.2)					227 (8.9)	
70-79, n (%)		348 (21.0)	46 (13.2)	5 (10.9)	1 (0.1)					349 (13.7)	
80-89, n (%)		552 (33.2)	78 (14.1)	16 (20.5)	1 (0.1)					553 (21.6)	
90-99, n (%)		505 (30.3)	67 (13.3)	19 (28.4)	0 (0)					505 (19.8)	
>99, n (%)		34 (2.1)	7 (20.6)	3(42.9)	0 (0)					34 (1.3)	

Abbreviation: N/A, not applicable;

[1]Comparison of positive testing prevalence between resident group and staff member group.

[2]Comparison of lethality rates between infected resident group and infected staff member group.

[3] Number of individuals for whom data was available.

Table 2. Comorbidities, symptoms and signs, diagnostic and therapeutic management among 226 elderly residents testing positive for SARS-CoV-2.

Parametters	n (%)
Comorbidities (143) [1]	
Hypertension	57 (39.9)
Cardiovascular diseases (other than hypertension)	52 (36.4)
Dementia	40 (28.0)
Mental disorder	35 (24.5)
Diabetes millitus	21 (14.7)
Chronic lung diseases	17 (11.9)
Stroke	16 (11.2)
Cancer	13 (9.1)
Chronic neurological disorder	11 (7.7)
Obesity	7 (4.9)
Chronic kidney diseases	6 (4.2)
Asthma	3 (2.1)
Symptoms and signs (200)	
Respiratory symptoms and signs	89 (44.5)
Fever	93 (46.5)
asthenia, anorexia, weight loss	21 (10.5)
Circumstances of diagnosis (226)	
Case-by-case testing in patients with COVID-19 symptoms	37 (16.4)
Mass testing	189 (83.6)
Medical management of patients (226)	
Managed at retirement homes by local medical staffs only	62 (27.4)
Managed at retirement homes in coordination with the HHU	117 (51.8)

	Admitted to IHU	16 (7.1)
	Transferred ICU	31 (13.7)
HCQ-AZ therapy (226)		
	At least a 3-day course	116 (51.4)
	2-day course	1 (0.4)
	HCQ alone	1 (0.4)
	AZ alone	37 (16.4)
	No HCQ, no AZ	71 (31.4)
Oxygen therapy (183)		60 (32.8)
Ceftriaxone or ertapenem therapy (183)		41 (22.6)
Low-molecular-weight heparin therapy (183)		22 (12.0)

Abbreviation: HCQ, hydroxychloroquine; AZ, azithromycin; HHU, Home Hospitalization Unit, Institut Hospitalo-Universitaire; ICU, Intensive Care Units.

[1] Number of individuals for whom data was available.

Table 3. Associations between multiple factors and SARS-CoV-2 death among 226 infected elderly residents (univariate and multivariate analysis)

Characteristics		Deaths N=47	Survivors N=179	Univariate		Multivariate	
				OR [95%CI]	p-value	aOR [95%CI]	p-value
Demographic factors (226) [1]							
Gender	Female, n (%)	19 (14.0)	116 (86.0)	Ref		Ref	
	Male, n (%)	28 (30.7)	63 (69.2)	**2.71 [1.40-5.24]**	**0.003**	**3.64 [1.48-8.90]**	**0.005**
Age (years)[2]	50-85, n (%)	18 (15.6)	97 (84.4)	Ref		Ref	
	>85, n (%)	29 (26.1)	82 (73.9)	**1.90 [0.99-3.67]**	**0.055**	**2.46 [1.03-5.87]**	**0.042**
Chronic conditions (143)							
Cardiovascular diseases	No, n (%)	20 (22.0)	71 (78.0)	Ref			
	Yes, n (%)	11 (21.2)	41 (78.8)	0.95 [0.42-2.18]	0.91		
Hypertention	No, n (%)	21 (24.4)	65 (75.6)	Ref			
	Yes, n (%)	10 (17.5)	47 (82.5)	0.65 [0.29-1.52]	0.33		
Dementia	No, n (%)	26 (25.2)	77 (74.8)	Ref			
	Yes, n (%)	5 (12.5)	35 (87.5)	**0.42 [0.15-1.19]**	**0.104**	-	-
Mental disorder	No, n (%)	23 (21.3)	85 (78.7)	Ref			
	Yes, n (%)	8 (28.9)	27 (77.1)	1.10 [0.44-2.73]	0.84		
Diabete millitus	No, n (%)	26 (21.3)	96 (78.7)	Ref			
	Yes, n (%)	5 (23.8)	16 (76.2)	1.15 [0.39-3.44]	0.80		
Chronic lung diseases	No, n (%)	24 (19.0)	102 (81.0)	Ref			
	Yes, n (%)	7 (41.2)	10 (59.9)	**2.97 [1.02-8.61]**	**0.044**	-	-

Stroke	No, n (%)	29 (22.8)	98 (77.2)	Ref			
	Yes, n (%)	2 (12.5)	14 (87.5)	0.48 [0.10-2.44]	0.35		
Cancer	No, n (%)	26 (20.0)	104 (80.0)	Ref			
	Yes, n (%)	5 (38.5)	8 (61.6)	**2.5 [0.75-8.27]**	**0.134**	-	-
Chronic neurological disorder	No, n (%)	28 (21.2)	104 (78.8)	Ref			
	Yes, n (%)	3 (27.3)	8 (72.7)	1.39 [0.34-5.59]	0.64		
Diagnostic and therapeutic management factors							
Circumstances of diagnosis (226)	Case-by-case testing in patients with COVID-19 symptoms, n (%)	15 (40.6)	22 (59.5)	Ref		Ref	
	Mass testing, n (%)	32 (16.9)	157 (83.1)	**0.29 [0.14-0.64]**	**0.002**	**0.20 [0.08-0.52]**	**0.001**
Facility management of patients (226)	In only retirement homes	12 (19.3)	50 (80.7)	Ref			
	Others	35 (21.3)	129 (78.7)	1.13 [0.54-2.35]	0.75		
HCQ/AZ treatment for at least 3 days (226)	No, n (%)	29 (26.4)	81 (73.6)	Ref		Ref	
	Yes, n (%)	18 (15.5)	98 (84.5)	**0.51 [0.26-0.99]**	**0.047**	**0.39 [0.17-0.89]**	**0.026**
Oxygen therapy (183)	No, n (%)	16 (13.0)	107 (87.0)	Ref		Ref	
	Yes, n (%)	23 (38.3)	37 (61.7)	**4.15 [1.98-8.71]**	**$<10^{-4}$**	**4.59 [1.99-10.55]**	**$<10^{-4}$**
Ceftriaxone or ertapenem therapy (183)	No, n (%)	26 (18.4)	115 (81.6)	Ref			
	Yes, n (%)	13 (31.7)	28 (68.3)	**2.05 [0.93-4.49]**	**0.073**	-	-
Low-molecular-weight heparin therapy (183)	No, n (%)	34 (21.1)	127 (78.9)	Ref			
	Yes, n (%)	5 (22.7)	17 (77.3)	1.09 [0.37-3.19]	0.86		

Abbreviation: Ref, Reference; NA, Not applicable; OR, Odd-ratio; aOR, adjusted Odd-ratio; HCQ, hydroxychloroquine

[1] Number of individuals for whom data was available.

[2] Median of the variable is used for analysis.

Bold lines indicate the variables recruited in initial multivariate mode.