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**1 Pattern of SARS-CoV-2 infection among dependant elderly residents living in long-term
2 care facilities in Marseille, France, March-June 2020**

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38 **Running title:** dependant elderly residents and COVID-19

39

40 **Keywords:** COVID-19; SARS-CoV-2; elderly resident; long-term care facility; mass testing;
41 hydroxychloroquine.

42 **Abstract (250/250 words)**

43 **Objectives.** We aimed to report the results of SARS-CoV-2 PCR-based screening campaigns
44 conducted on dependent elderly residents (compared to staffs members) in long-term care
45 facilities (LTCFs) in Marseille, France, and the follow-up of positive cases.

46 **Methods.** Data from 1,691 elderly residents and 1,000 members of staff were retrospectively
47 collected through interviewing the medical teams in 24 LTCFs and using the hospitals'
48 electronic health recording systems.

49 **Results.** Elderly residents were predominantly female (64.8%) with a mean age of 83.0 years.
50 SARS-CoV-2 detection among residents (226, 13.4%) was significantly higher than among
51 staff members (87, 8.7%), with $p < 0.001$. Of the 226 infected residents, 37 (16.4%) were
52 detected on a case-by-case basis due to their COVID-19 symptoms and 189 (83.6%) were
53 detected through mass screening. Most (77.0%) had possible COVID-19 symptoms, including
54 respiratory symptoms and signs (44.5%) and fever (46.5%) and 23.0% were asymptomatic. 116
55 (51.4%) patients received a course of oral hydroxychloroquine and azithromycin (HCQ-
56 AZM) for ≥ 3 days, and 47 (20.8%) died. Through multivariate analysis, the death rate was
57 positively associated with being male (30.7%, vs. 14.0%, OR=3.95, $p=0.002$), being older than
58 85 years (26.1%, vs. 15.6%, OR=2.43, $p=0.041$), and receiving oxygen therapy (39.0%, vs.
59 12.9%, OR=5.16, $p < 0.001$) and negatively associated with being diagnosed through mass
60 screening (16.9%, vs. 40.5%, OR=0.20, $p=0.001$) and receiving HCQ-AZM treatment ≥ 3 days
61 (15.5%, vs. 26.4%, OR=0.37, $p=0.02$).

62 **Conclusion.** High proportion of asymptomatic COVID-19 patients and independent factors
63 for mortality suggests that early diagnosis and treatment of COVID-19 patients in LTCFs may
64 be effective in saving lives.

65 **Introduction**

66 In France, as of 2 June 2020, 10,350 elderly residents living in long-term care facilities or
67 medical-social establishments had died from COVID-19 (27.6% lethality rate) accounting for
68 55.6% of COVID-19 deaths in France [1]. Similar pictures have also been reported in many
69 European countries [2] and worldwide [3]. The prevalence of chronic conditions such as
70 cardiovascular diseases, hypertension and diabetes mellitus is high among elderly persons
71 living in long-term care facilities; coronavirus disease (COVID-19) in this population may
72 therefore have severe outcomes with a high mortality rate [2, 4, 5]. Other drivers of mortality
73 among elderly persons living in long-term care facilities already include type of facility, the
74 amount of persons visiting the facilities during the week previous to lockdown, staff ratios [3],
75 and lagged infection in staff members [6].

76 The treatment of COVID-19 has been the subject of widespread controversy, in particular
77 with regards to the use of hydroxychloroquine (HCQ) [7]. It appears to us that some of the
78 elements of the controversy are the heterogeneity of protocols using HCQ, with doses ranging
79 from 800 mg to 1200 mg per day, the duration of treatment, whether or not it is combined
80 with azithromycin (AZM), and the stage of the disease at which patients were being treated. It
81 can be considered that there is a purely viral phase of the disease with a more or less strong
82 immune response, which can become predominant in what has been referred to as the
83 cytokine storm, followed in a number of cases, by necrotic lesions, linked to pulmonary
84 infarctions [8]. Furthermore, mortality depends very significantly on age and thus, in Europe,
85 almost all deaths have been among persons over the age of 60, with more than 50% in persons
86 over the age of 85 years [9]. Under these conditions, it is very difficult to carry out
87 comparative studies addressing the effect of HCQ on COVID-19-associated deaths. Very few
88 randomised studies have been conducted and their interpretations have also led to heated

89 debate. To assist the debate, we believe that it may be important to assess whether there is a
90 clear reduction in mortality in the most at-risk groups.

91 In Marseille, over a period of approximately two months, we were able to test and treat
92 COVID-19 patients in long-term care facilities (Etablissement d'Hébergement pour Personnes
93 Agées Dépendantes –EHPAD) with a combination of HCQ-AZM, as we have described it on
94 several occasions [8, 10-12]. The objective of this study was to estimate the prevalence of
95 SARS-CoV-2 carriage among elderly residents and among staff members working in 24
96 EHPAD, Marseille, France. We also aimed to estimate the lethality among elderly residents
97 treated in these EHPADs and informally compare it to the lethality of patients in these EHPAD
98 who were not treated and the general lethality of patients in EHPADs in France.

99 **Methods**

100 **Setting, study design and population**

101 SARS-CoV-2 cross-sectional mass screening campaigns were conducted among residents and
102 staff members from 24 long-term care facilities (EHPADs) in Marseille, between 24 March
103 and 2 June 2020. In some centres, screening campaigns were conducted following the
104 diagnosis of confirmed COVID-19 cases in symptomatic patients who were sampled on a
105 case-by-case strategy. In other centres, screening campaigns were conducted systematically.
106 In all cases, screening campaigns were conducted following a request from the directors and
107 medical staff of the long-term care facilities. Nasopharyngeal samples were processed for
108 SARS-CoV-2 PCR testing at the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection
109 at Assistance Publique-Hôpitaux de Marseille (AP-HM), as previously described [13] or in
110 private laboratories in Marseille, in some cases. Residents who tested positive were either i)
111 treated at their long-term care facilities by local medical staff only, ii) treated at their long-
112 term care facilities in coordination with the AP-HM Home Hospitalisation Unit (HHU), iii)

113 admitted to the IHU (day-care hospital or conventional units), or iv) transferred to AP-MH
114 Intensive Care Units (ICU). For confirmed cases, information on demographics, chronic
115 medical conditions, COVID-19 treatment and clinical data including fever, asthenia, anorexia
116 and weight loss, respiratory symptoms and signs (cough, rhinorrhoea, dyspnoea, chest pain,
117 acute respiratory distress syndrome) and death was collected retrospectively from interviews
118 with the medical team of 24 long-term care facilities and the electronic health recording systems
119 of the AP-HM.

120 **Statistical methods**

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

129 **Results**

130 Over the study period, 1,691 elderly residents and 1,000 staff members were tested (Table 1).
131 For residents, the sex ratio (male to female) was 1:1.8 and the mean age (\pm standard derivation
132 [SD]) was 83.0 (\pm 10.6) years (ranging from 50 to 106 years). For staff members, the sex ratio
133 was 1:3.5 and the mean age (\pm SD) was 40.8 (\pm 12.8) years (ranging from 18 to 87 years). It
134 should be noted that two religious staff members at one long-term care facility were aged 75
135 and 87, respectively.

136 Overall, 313 participants (of 2,691, 11.6%) were confirmed positive for SARS-CoV-2. The
137 prevalence among residents (226 of 1,691, 13.4%) was significantly higher than among staff
138 members (87 of 1,000, 8.7%), $p < 0.001$). With regard to the housing facilities, at least one
139 individual was positive in 11/24 (45.8%) centres with prevalence of SARS-CoV-2 detection
140 ranging from 0% to 57.6% among residents and from 0% to 24.1% among staff members (Table
141 1). The lethality rate among residents was 20.8% while no deaths occurred among staff
142 members ($p < 10^{-4}$).

143 **Characteristics of 226 elderly residents testing positive for SARS-CoV-2 (Tables 2 and 3)**

144 Of the 226 SARS-CoV-2-positive elderly residents, 37 were diagnosed on a case-by-case basis
145 through selected sampling of patients with COVID-19 symptoms and 189 (83.4%) were
146 detected through mass screening. Regarding co-morbidities, the most frequent chronic condition
147 was hypertension (39.6%), followed by other cardiovascular diseases (37.1%), dementia
148 (28.9%) and other mental disorders (23.6%). In terms of clinical findings, 77.0% had possible
149 COVID-19 symptoms, including respiratory symptoms and signs (44.5%), and fever (46.5%);
150 and 23.0% had no COVID-19 symptoms representing 24.8% (40/161) of individuals tested
151 through mass screening (Table 2).

152 When it came to therapeutic management, 62 (27.4%) patients were managed within their
153 long-term care facilities by local medical staff only, 117 (51.8%) were managed within their
154 long-term care facility in collaboration with the HHU, 16 (7.1%) were admitted to IHU, and
155 31 (13.7%) were transferred to ICU. Overall, 116 (51.4%) patients received an oral HCQ (200
156 mg three times daily for ten days), and AZM (500 mg on day 1 followed by 250 mg daily for
157 the next four days) for at least three days and were monitored as described in previous studies
158 [10-12]. Of the 110 others (48.6%), one (0.4%) received a two-day course of HCQ-AZM, one
159 (0.4%) received HCQ alone, 37 (16.4%) received AZM alone, and 71 (31.4) did not receive
160 either drug. The prevalence of HCQ-AZM treatment for at least three days ranged from 0%-

161 87.5% according to the housing facilities. Other treatments are described in Table 2. A total of
162 179 patients survived (79.2%) and 47 (20.8%) died.

163 The baseline characteristics of 116 patients who received HCQ-AZM treatment for at least
164 three days compared with 110 patients who did not receive the treatment were largely similar
165 (Table 3). A higher proportion of patients with a history of stroke was observed in the treated
166 group (15.8%) compared with the untreated group (5.2%, $p=0.04$).

167 Table 4 shows the lethality rate among elderly residents with SARS-CoV-2 infection, according
168 to demographics, chronic conditions, circumstance of diagnosis, type of medical management
169 of patients, use of HCQ-AZM and housing facility effect according to prevalence of HCQ-
170 AZM treatment for at least three days in each housing facility. Under univariate analysis, death
171 from COVID-19 was significantly associated with male gender. In addition, patients who were
172 diagnosed on a case-by case basis due to their COVID-19 symptoms were more likely to die
173 (40.5%) than those diagnosed through systematic screening (16.9%). Finally, patients who
174 received oxygen treatment were more likely to die (39.0%) than those who did not receive such
175 a treatment (12.9%), by contrast, patients who received HCQ-AZM treatment for at least three
176 days were less likely to die (15.5%) than those who did not receive such a treatment (26.4%).
177 Through multivariate analysis, the death rate was positively associated with being male
178 (30.7% vs. 14.0%, $OR=3.95$ [1.65-9.44], $p=0.002$), being older than 85 years (26.1% vs. 15.6%,
179 $OR=2.43$ [1.04-5.69], $p=0.041$), and receiving oxygen therapy ($OR=5.16$ [2.26-11.76], $p<10^{-4}$)
180 and negatively associated with being diagnosed through mass screening (16.9%, vs. 40.5%,
181 $OR=0.20$ [0.08-0.53], $p=0.001$) and receiving HCQ-AZM treatment for at least three days
182 ($OR=0.37$ [0.17-0.86], $p=0.02$).

183

184 **Discussion**

185 In Marseille, the first case of COVID-19 in the general population was diagnosed on 3 March
186 2020 and the epidemic peaked during the first week of April and remained active until the end
187 of the month. Our survey of long-term care facilities began when the entire French population
188 was placed under a strict lockdown (17 March) and when the epidemic was active in Marseille.
189 All long-term care facilities became confined environments with very strict restrictions being
190 place upon visits. We found a 13.4% SARS-CoV-2 positivity rate among dependant elderly
191 residents in Marseille that was significantly higher than the 5.4% positivity rate among all
192 French dependant elderly residents according to a national survey (37,405 confirmed cases in an
193 estimated 695,060 French dependant elderly residents, $p < 0.001$, 2 June update) [1, 14]. We
194 observed an overall 20.8% COVID-19 lethality rate among infected residents in Marseille that
195 was significantly lower than that in all French long-term care facilities or medical-social
196 establishments (27.7% lethality rate, $p = 0.026$, 2 June update) [1]. The main drivers of
197 mortality in Marseille residents were older age and male sex, as already reported in many
198 studies [15]. In addition, systematic screening by PCR was identified as an independent
199 protective factor against death from COVID-19. A symptom-based diagnostic strategy is less
200 effective in long-term care facilities, most likely because elderly patients with comorbidities
201 such as chronic respiratory or cardiovascular diseases may be unable to accurately report new
202 symptoms suggestive of COVID-infection or may present with atypical symptoms that
203 challenge medical staff [13, 17]. Furthermore, in our experience, more than 23% of SARS-
204 CoV-2 infected residents had no symptoms at the time of sampling. A very high prevalence
205 (around 80%) was observed in a cross-sectional study conducted on elderly residents living in
206 2074 Belgian long-term care facilities [18]. In this study, we show that there was a significant
207 difference in lethality between patients treated with our standardised treatment and untreated
208 patients, as already reported in study conducted among elderly patients living in a Spanish

209 public nursing home in the same period [14]. Treatment with HCQ alone was demonstrated to
210 be associated with lower mortality in patients admitted with COVID-19 [20-23]. Another
211 cohort study conducted among American patients with rheumatic conditions showed an
212 association between long-term HCQ treatment and reduced COVID-19 lethality rate [24]. The
213 potential mechanisms of HCQ in the decrease of mortality in COVID-19 might be its
214 inhibitory effects upon the production of pro-inflammatory cytokines interleukin (IL)-1- β ,
215 TNF- α and IL-6, and chemokines (CCL2 and CCL3) involved in the recruitment of pro-
216 inflammatory cells in the lung [25].

217 There are some limitations to our study. Our study population was not randomly and
218 homogenously recruited. Data regarding demographics, chronic conditions and clinical status
219 was not systematically documented. Frailty that has been shown to be a major risk factor for
220 mortality in COVID-19 was not evaluated in this study due to its retrospective design [26]. The
221 use of individual preventive measures was not documented.

222 Nevertheless, we believe that even if there are biases, as in any comparative study including
223 randomisation, these biases are relatively neutralised by the multifactorial study. Above all,
224 we demonstrate that the mortality in patients treated in EHPADs in Marseille was half that of
225 patients in nursing homes across France who, in most cases very likely did not receive
226 specific treatment since its use is restricted to the hospital setting [27, 28]. We believe that
227 focusing on the population with the highest mortality, to show a significant effect, is
228 important and agree in this sense with several studies that have shown a reduction in mortality
229 of 30 to 50% by HCQ-AZM in populations most at risk [29, 8].

230

231 **Declarations**

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239

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243

244 **Authors’ contributions statement:**

245 Writing – original draft: TD, PG

246 Writing – review & editing: TD, DZ, VL, SA, SG, HM, MF, DM, OQ, PM, AM, PL, GD, BL,
247 AM, AC, PA, PP, EC & DR

248 Conceptualization: PG

249 **References**

- 250 [1] Santé Publique France. COVID-19 [COVID-19: epidemiological update of 2 June 2020].
251 St Maurice : Santé Publique France ; 2 June 2020 ; c2020 [cited 2020 October 25].
252 Available from: <https://www.gouvernement.fr/info-coronavirus/carte-et-donnees>
- 253 [2] Danis K, Fonteneau L, Georges S, Daniau C, Bernard-Stoecklin S, Domegan L, et al. High
254 impact of COVID-19 in long-term care facilities, suggestion for monitoring in the
255 EU/EEA, May 2020. *Euro Surveill.* 2020;25(22):2000956.
- 256 [3] Comas-Herrera A, Zalakain J, Lemmon E, Henderson D, Litwin C, Hsu AT, et al. Updated
257 report: Updated international report on COVID-19 related mortality in care homes.
258 International long-term care policy network; c2020 [cited 2020 October 25]. Available
259 from: [https://ltccovid.org/wp-content/uploads/2020/10/Mortality-associated-with-](https://ltccovid.org/wp-content/uploads/2020/10/Mortality-associated-with-COVID-among-people-living-in-care-homes-14-October-2020-3.pdf)
260 [COVID-among-people-living-in-care-homes-14-October-2020-3.pdf](https://ltccovid.org/wp-content/uploads/2020/10/Mortality-associated-with-COVID-among-people-living-in-care-homes-14-October-2020-3.pdf).
- 261 [4] Etard JF, Vanhems P, Atlani-Duault L, Ecochard R. Potential lethal outbreak of
262 coronavirus disease (COVID-19) among the elderly in retirement homes and long-term
263 facilities, France, March 2020. *Euro Surveill.* 2020;25(15) :2000448.
- 264 [5] Moraes EN, Viana LG, Resende LMH, Vasconcellos LS, Moura AS, Menezes A, et al.
265 COVID-19 in long-term care facilities for the elderly: laboratory screening and disease
266 dissemination prevention strategies. *Cien Saude Colet.* 2020;25(9):3445-3458. English,
267 Portuguese. <http://doi.org/10.1590/1413-81232020259.20382020>.
- 268 [6] Fisman DN, Bogoch I, Lapointe-Shaw L, McCready J, Tuite AR. Risk Factors Associated
269 With Mortality Among Residents With Coronavirus Disease 2019 (COVID-19) in
270 Long-term Care Facilities in Ontario, Canada. *JAMA Netw Open.* 2020;3(7):e2015957.
271 <http://doi.org/10.1001/jamanetworkopen.2020.15957>.

- 272 [7] Zou L, Dai L, Zhang X, Zhang Z, Zhang Z. Hydroxychloroquine and chloroquine: a
273 potential and controversial treatment for COVID-19. *Arch Pharm Res.* 2020;1:1-8.
- 274 [8] Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al.
275 Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin
276 and other regimens in Marseille, France: A retrospective analysis. *Travel Med Infect*
277 *Dis.* 2020;36:101791.
- 278 [9] European Centre for Disease Prevention and Control (ECDC). Coronavirus disease 2019
279 (COVID-19) in the EU/EEA and the UK – eleventh update, 10 August 2020; c2020
280 [cited 2020 August 20]. Available from:
281 [https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-](https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-20200810.pdf)
282 [assessment-20200810.pdf](https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-20200810.pdf)
- 283 [10] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al.
284 Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an
285 openlabel non-randomized clinical trial. *Int J Antimicrob Agents.* 2020;105949.
- 286 [11] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and
287 microbiological effect of a combination of hydroxychloroquine and azithromycin in 80
288 COVID-19 patients with at least a six-day follow up: an observational study. *Travel*
289 *Med Infect Dis.* 2020:101663.
- 290 [12] Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment
291 of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective
292 analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis.* 2020:101738.
- 293 [13] Amrane S, Tissot-Dupont H, Doudier B, Eldin C, Hocquart M, Mailhe M, et al. Rapid
294 viral diagnosis and ambulatory management of suspected COVID-19 cases presenting at

- 295 the infectious diseases referral hospital in Marseille, France, - January 31st to March 1st,
296 2020: A respiratory virus snapshot. *Travel Med Infect Dis* 2020:101632.
- 297 [14] Belmin J, Um-Din N, Donadio C, Magri M, Nghiem QD, Oquendo B, et al. Coronavirus
298 Disease 2019 Outcomes in French Nursing Homes That Implemented Staff
299 Confinement With Residents. *JAMA Netw Open*. 2020;3(8):e2017533.
- 300 [15] The OpenSAFELY Collaborative, Elizabeth Williamson, Alex J Walker, Krishnan J
301 Bhaskaran, Seb Bacon, Chris Bates, et al. OpenSAFELY: factors associated with
302 COVID-19-related hospital death in the linked electronic health records of 17 million
303 adult NHS patients. [Preprint]. 2020 [cited 2020 August 20] Available from:
304 <https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1>
- 305 [16] Louie JK, Scott HM, DuBois A, Sturtz N, Lu W, Stoltey J, et al. Lessons from Mass-
306 Testing for COVID-19 in Long Term Care Facilities for the Elderly in San Francisco.
307 *Clin Infect Dis*, 2020:ciaa1020.
- 308 [17] Blain H, Rolland Y, Benetos A, Giacosa N, Albrand M, Miot S, Bousquet J. Atypical
309 clinical presentation of COVID-19 infection in residents of a long-term care facility. *Eur*
310 *Geriatr Med*. 2020:1–4. <http://doi.org/10.1007/s41999-020-00352-9>.
- 311 [18] Hoxha A, Wyndham-Thomas C, Klamer S, Dubourg D, Vermeulen M, Hammami N, et
312 al. Asymptomatic SARS-CoV-2 infection in Belgian long-term care facilities. *Lancet*
313 *Infect Dis*. 2020:S1473-3099(20)30560-0. [http://doi.org/10.1016/S1473-](http://doi.org/10.1016/S1473-3099(20)30560-0)
314 [3099\(20\)30560-0](http://doi.org/10.1016/S1473-3099(20)30560-0).
- 315 [19] Heras E, Garibaldi P, Boix M, Valero O, Castillo J, Curbelo Y, et al. COVID-19
316 mortality risk factors in older people in a long-term care center. *Research square*.
317 [Preprint]. 2020 [cited 2020 September 29]. Available from:
318 <https://www.researchsquare.com/article/rs-70219/v1>.

- 319 [20] Ayerbe L, Risco-Risco C, Ayis S. The association of treatment with hydroxychloroquine
320 and hospital mortality in COVID-19 patients. *Intern Emerg Med.* 2020:1–6.
321 <http://doi.org/10.1007/s11739-020-02505-x>.
- 322 [21] Arshad S, Kilgore P, Chaudhry ZS, Jacobsen G, Wang DD, Huitsing K, et al. Treatment
323 with hydroxychloroquine, azithromycin, and combination in patients hospitalized with
324 COVID-19. *Int J Infect Dis.* 2020;97:396-403. <http://doi.org/10.1016/j.ijid.2020.06.099>.
- 325 [22] Catteau L, Dauby N, Montourcy M, Bottieau E, Hautekiet J, Goetghebeur E, et al. Low-
326 dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-
327 19: a nationwide observational study of 8075 participants. *Int J Antimicrob Agents.*
328 2020;56(4):106144. <http://doi.org/10.1016/j.ijantimicag.2020.106144>.
- 329 [23] COVID-19 RISK and Treatments (CORIST) Collaboration. Use of hydroxychloroquine
330 in hospitalised COVID-19 patients is associated with reduced mortality: Findings from
331 the observational multicentre Italian CORIST study. *Eur J Intern Med.* 2020:S0953-
332 6205(20)30335-6. <http://doi.org/10.1016/j.ejim.2020.08.019>.
- 333 [24] Gentry CA, Humphrey MB, Thind SK, Hendrickson SC, Kurdgelashvili G, Williams RJ
334 2nd. Long-term hydroxychloroquine use in patients with rheumatic conditions and
335 development of SARS-CoV-2 infection: a retrospective cohort study. *Lancet*
336 *Rheumatol.* 2020;2(11):e689-e697. [http://doi.org/10.1016/S2665-9913\(20\)30305-2](http://doi.org/10.1016/S2665-9913(20)30305-2).
- 337 [25] Dauby N, Bottieau E. The unfinished story of hydroxychloroquine in COVID-19: the
338 right anti-inflammatory dose at the right moment? *Int J Infect Dis.* 2020:S1201-
339 9712(20)32236-0. <http://doi.org/10.1016/j.ijid.2020.10.032>.
- 340 [26] Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect
341 of frailty on survival in patients with COVID-19 (COPE): a multicentre, European,

342 observational cohort study. *Lancet Public Health*. 2020;5(8):e444-e451.
343 [http://doi.org/10.1016/S2468-2667\(20\)30146-8](http://doi.org/10.1016/S2468-2667(20)30146-8).

344 [27] Ministère Des Solidarités Et De La Santé. Arrêté du 26 mai 2020 complétant l'arrêté du
345 23 mars 2020 prescrivant les mesures d'organisation et de fonctionnement du système
346 de santé nécessaires pour faire face à l'épidémie de covid-19 dans le cadre de l'état
347 d'urgence sanitaire ; c2020 [cited 2020 October 25]. Available from:
348 https://www.legifrance.gouv.fr/download/file/7G_W7qKa5tskdozh9I5NxL2kvypbGYC
349 [AoGuH3TEM5IM=/JOE_TEXTE](https://www.legifrance.gouv.fr/download/file/7G_W7qKa5tskdozh9I5NxL2kvypbGYC)

350 [28] Ministère Des Solidarités Et De La Santé. Décret n° 2020-314 du 25 mars 2020
351 complétant le décret n° 2020-293 du 23 mars 2020 prescrivant les mesures générales
352 nécessaires pour faire face à l'épidémie de covid-19 dans le cadre de l'état d'urgence
353 sanitaire ; c2020 [cited 2020 October 25]. Available from:
354 https://www.legifrance.gouv.fr/download/file/_bhGSZpQEI4f_HjbyCJsdOJEkRkiRL9V
355 [jTUPGPz6rP8=/JOE_TEXTE](https://www.legifrance.gouv.fr/download/file/_bhGSZpQEI4f_HjbyCJsdOJEkRkiRL9V)

356 [29] Davido B, Lansaman T, Bessis S, Alvarez JC, Bouchand F, Moine P, et al. Impact of
357 medical care, including use of anti-infective agents, on prognosis of COVID-19
358 hospitalized patients over time. *Int J Antimicrob Agents*. 2020 Oct;56(4):106129.
359 <http://doi.org/10.1016/j.ijantimicag.2020.106129>.

360 **Table 1.** SARS-CoV-2 testing among residents and staff members at 24 long-term care
361 facilities in Marseille, France, 27 March– 2 June 2020

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

364 **Table 3.** Characteristics of group receiving HCQ-AZ for at least 3 days and untreated group.

365 **Table 4.** Associations between multiple factors and SARS-CoV-2 deaths among 226 infected
366 elderly residents (univariate and multivariate analysis)

367

Table 1. SARS-CoV-2 testing among residents and staff members at 24 long-term care facilities in Marseille, France, 27 March– 2 June 2020

Characteristics	Date of mass testing	Residents			Staff members			p-value ¹	p-value ²	Total	
		No. tested	No. (%) positive	No. (%) deaths among positive cases (lethality rate)	No. tested	No. (%) positive	No. (%) deaths among positive cases (lethality rate)			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⁾											
Centre-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)
Centre-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)
Centre-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)
Centre -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)
Centre -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)
Centre -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)
Centre -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)
Centre -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)
Centre -09	21 April	54	0 (0)	N/A	44	3 (6.8)	0 (0)	0.08	N/A	98	3 (3.1)
Centre -10	23 April	46	1 (2.2)	0 (0)	12	0 (0)	N/A	N/A	N/A	58	1 (1.7)
Centre -11	15 April	118	1 (0.9)	0 (0)	60	0 (0)	N/A	N/A	N/A	178	1 (0.6)

Centre -12	15 April	66	0 (0)	N/A	18	0 (0)	N/A	N/A	N/A	84	0 (0)
Centre -13	28 April	96	0 (0)	N/A	39	0 (0)	N/A	N/A	N/A	135	0 (0)
Centre -14	30 April	45	0 (0)	N/A	12	0 (0)	N/A	N/A	N/A	57	0 (0)
Centre -15	17 April	64	0 (0)	N/A	27	0 (0)	N/A	N/A	N/A	91	0 (0)
Centre -16	22 April	48	0 (0)	N/A	19	0 (0)	N/A	N/A	N/A	67	0 (0)
Centre -17	25 April	61	0 (0)	N/A	29	0 (0)	N/A	N/A	N/A	90	0 (0)
Centre -18	15 April	52	0 (0)	N/A	18	0 (0)	N/A	N/A	N/A	70	0 (0)
Centre -19	27 April	32	0 (0)	N/A	24	0 (0)	N/A	N/A	N/A	56	0 (0)
Centre -20	27 April	29	0 (0)	N/A	15	0 (0)	N/A	N/A	N/A	44	0 (0)
Centre -21	24 April	25	0 (0)	N/A	11	0 (0)	N/A	N/A	N/A	36	0 (0)
Centre -22	20 April	53	0 (0)	N/A	22	0 (0)	N/A	N/A	N/A	75	0 (0)
Centre -23	14 April	100	0 (0)	N/A	52	0 (0)	N/A	N/A	N/A	152	0 (0)
Centre -24	24 April	25	0 (0)	N/A	8	0 (0)	N/A	N/A	N/A	33	0 (0)
Sex ⁽²⁴⁷¹⁾											
Female, n (%)		1,069 (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;

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

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

³Number 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.

Parameters	n (%)
Comorbidities (159) ¹	
Hypertension	63 (39.6)
Cardiovascular diseases (other than hypertension)	59 (37.1)
Dementia	46 (28.9)
Mental disorder	39 (23.6)
Diabetes mellitus	25 (15.7)
Chronic lung diseases	19 (12.0)
Stroke	17 (10.7)
Cancer	15 (9.4)
Chronic neurological disorder	12 (7.6)
Obesity	7 (4.4)
Chronic kidney diseases	7 (4.4)
Asthma	3 (1.9)
Symptoms and signs (200)	
Respiratory symptoms and signs	89 (44.5)
Fever	93 (46.5)
Asthenia, anorexia, weight loss	21 (10.5)
No COVID-19 symptoms	46 (23.0)
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 long-term care facilities by local medical staff only	62 (27.4)
Managed at long-term care facilities in coordination with the HHU	117 (51.8)

	Admitted to IHU	16 (7.1)
	Transferred ICU	31 (13.7)
<hr/>		
HCQ-AZM therapy ⁽²²⁶⁾		
	At least a three-day course	116 (51.4)
	two-day course	1 (0.4)
	HCQ alone	1 (0.4)
	AZM alone	37 (16.4)
	No HCQ, no AZM	71 (31.4)
<hr/>		
HCQ-AZM therapy at least a three-day course according to the housing facilities ⁽²²⁶⁾		
	Centre-07, n/N (%)	7/8 (87.5)
	Centre-01, n/N (%)	39/50 (78.0)
	Centre-02, n/N (%)	43/57 (75.4)
	Centre -05, n/N (%)	4/10 (40.0)
	Centre -06, n/N (%)	14/45 (31.1)
	Centre -04, n/N (%)	4/23 (17.3)
	Centre -03, n/N (%)	4/24 (16.7)
	Centre -08, n/N (%)	1/7 (14.3)
	Centre -10, n/N (%)	0/1 (0)
	Centre -11, n/N (%)	0/1 (0)
<hr/>		
Oxygen therapy ⁽¹⁹⁹⁾		59 (29.7)
<hr/>		
Ceftriaxone or ertapenem therapy ⁽¹⁹⁹⁾		63 (31.6)
<hr/>		
Low-molecular-weight heparin therapy ⁽¹⁹⁹⁾		24 (12.1)
<hr/>		

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

¹ Number of individuals for whom data was available.

Table 3. Characteristics of group receiving HCQ-AZ for at least 3 days and untreated group.

Characteristics		Patient receiving HCQ-AZ ≥ 3 days N=116	Patient not receiving HCQ-AZ ≥ 3 days N=110	p-value
Demographic factors ⁽²²⁶⁾ ¹				
Gender	Female, n (%)	70 (60.3)	65 (59.1)	0.85
	Male, n (%)	46 (39.7)	45 (40.9)	
Age (years) ²	50-85, n (%)	66 (56.9)	49 (44.5)	0.07
	>85, n (%)	50 (43.1)	61 (55.5)	
Chronic conditions ⁽¹⁵⁹⁾				
Cardiovascular diseases	No, n (%)	51 (62.2)	49 (63.6)	0.85
	Yes, n (%)	31 (37.8)	28 (36.4)	
Hypertension	No, n (%)	46 (56.1)	50 (64.9)	0.26
	Yes, n (%)	36 (43.9)	27 (35.1)	
Dementia	No, n (%)	61 (74.4)	52 (67.5)	0.34
	Yes, n (%)	21 (25.6)	25 (32.5)	
Mental disorder	No, n (%)	61 (74.4)	59 (76.6)	0.74
	Yes, n (%)	21 (25.6)	18 (23.4)	
Diabetes mellitus	No, n (%)	69 (84.1)	65 (84.4)	0.96
	Yes, n (%)	13 (15.9)	12 (15.6)	
Chronic lung diseases	No, n (%)	72 (87.8)	68 (88.3)	0.92
	Yes, n (%)	10 (12.2)	9 (11.7)	

Stroke	No, n (%)	69 (84.2)	73 (94.8)	0.04
	Yes, n (%)	13 (15.8)	4 (5.2)	
Cancer	No, n (%)	74 (90.2)	70 (90.9)	0.86
	Yes, n (%)	8 (9.8)	7 (9.1)	
Chronic neurological disorder	No, n (%)	76 (92.7)	71 (92.2)	0.9
	Yes, n (%)	6 (7.3)	6 (7.8)	
Circumstances of diagnosis (226)	Case-by-case testing in patients with COVID-19 symptoms, n (%)	23 (19.8)	14 (12.7)	0.1
	Mass testing, n (%)	93 (80.2)	96 (87.3)	
Facility management of patients (226) ³	In long-term care facilities only	0 (0)	62 (56.4)	N/A
	Other	116 (100)	48 (43.7)	
Oxygen therapy (199)	No, n (%)	79 (68.1)	61 (73.5)	0.4
	Yes, n (%)	37 (31.9)	22 (26.5)	
Ceftriaxone or ertapenem therapy (199)	No, n (%)	81 (69.8)	55 (66.3)	0.59
	Yes, n (%)	35 (30.2)	28 (33.7)	
Low-molecular-weight heparin therapy (199)	No, n (%)	98 (84.5)	77 (92.8)	0.08
	Yes, n (%)	18 (15.5)	6 (7.2)	

Abbreviation: HCQ, hydroxychloroquine; AZM, azithromycin; NA, Not applicable.

¹ Number of individuals for whom data was available.

² Median of the variable is used for analysis.

³ Indication of HCQ-AZ treatment was compulsorily administrated in coordination with hospital.

Table 4. Associations between multiple factors and SARS-CoV-2 deaths 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 <small>(226)</small> 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	3.95 [1.65-9.44]	0.002
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	2.43 [1.04-5.69]	0.041
Chronic conditions <small>(159)</small>							
Cardiovascular diseases	No, n (%)	21 (21.0)	79 (79.0)	Ref			
	Yes, n (%)	12 (20.3)	47 (79.7)	0.98 [0.43-2.12]	0.92		
Hypertension	No, n (%)	23 (24.0)	73 (76.0)	Ref			
	Yes, n (%)	10 (15.9)	53 (84.1)	0.59 [0.26-1.36]	0.22		
Dementia	No, n (%)	28 (24.8)	85 (75.2)	Ref			
	Yes, n (%)	5 (10.9)	41 (89.1)	0.37[0.13-1.02]	0.057		
Mental disorder	No, n (%)	25 (20.9)	95 (79.1)	Ref			
	Yes, n (%)	8 (20.5)	31 (79.5)	0.98 [0.40-2.39]	0.96		
Diabetes mellitus	No, n (%)	27 (20.2)	107 (79.8)	Ref			
	Yes, n (%)	6 (24.0)	19 (76.0)	1.25 [0.45-3.43]	0.66		
Chronic lung	No, n (%)	26 (18.6)	114 (81.4)	Ref			

diseases	Yes, n (%)	7 (36.9)	12 (63.1)	2.55 [0.91-7.12]	0.073		
Stroke	No, n (%)	31 (21.8)	11 (78.2)	Ref			
	Yes, n (%)	2 (11.7)	15 (88.3)	0.47 [0.1-2.20]	0.34		
Cancer	No, n (%)	28 (19.4)	116 (80.6)	Ref			
	Yes, n (%)	5 (33.3)	10 (66.7)	2.07 [0.65-6.54]	0.215		
Chronic neurological disorder	No, n (%)	30 (20.4)	117 (79.6)	Ref			
	Yes, n (%)	3 (25.0)	9 (75.0)	1.30 [0.33-5.10]	0.71		
Diagnostic and therapeutic management factors							
Circumstances of diagnosis ⁽²²⁶⁾	Case-by-case testing in patients with COVID-19 symptoms, n (%)	15 (40.5)	22 (59.5)	Ref		Ref	
	Mass testing, n (%)	32 (16.9)	157 (83.1)	0.30 [0.14-0.64]	0.002	0.20 [0.08-0.53]	0.001
Facility management of patients ⁽²²⁶⁾	In long-term care facilities only	12 (19.4)	50 (80.3)	Ref			
	Other	35 (21.3)	129 (78.7)	1.13 [0.54-2.35]	0.74		
HCQ-AZM treatment for at least three 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	0.37 [0.17-0.86]	0.02
Housing facility effect ³ ⁽²²⁶⁾	>75%	26 (22.6)	89 (77.4)	Ref			
	25%-75%	11 (20.0)	44 (80.0)	0.85 [0.38-1.89]	0.7		
	<25%	10 (17.9)	46 (82.1)	0.74 [0.33-1.67]	0.48		
Oxygen therapy ⁽¹⁹⁹⁾	No, n (%)	18 (12.9)	122 (87.1)	Ref		Ref	
	Yes, n (%)	23 (39.0)	36 (61.0)	4.33 [2.1-8.89]	<10⁻⁴	5.16 [2.26-11.76]	<10⁻⁴
Ceftriaxone or	No, n (%)	26 (19.1)	110 (80.9)	Ref			

ertapenem therapy (199)	Yes, n (%)	15 (23.8)	48 (76.2)	1.32 [0.64-2.71]	0.45
Low-molecular-weight heparin therapy (199)	No, n (%)	36 (20.6)	139 (79.4)	Ref	
	Yes, n (%)	5 (20.8)	19 (79.2)	1.01 [0.35-2.90]	0.97

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

¹ Number of individuals for whom data was available.

² Median of the variable is used for analysis.

³ According to prevalence of HCQ-AZM treatment for at least three days among infected residents in each housing facility as seen in Table 2.

Bold lines indicate the variables recruited in initial multivariate mode.