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1 **Vitamin D supplementation prior to or during COVID-19 associated with better 3-**
2 **month survival in geriatric patients: Extension phase of the GERIA-COVID study**

3

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Cédric Annweiler, MD, PhD^{a,b,c,d,e}

5

Méline Beaudenon, MS^b

6

Romain Simon, MS^b

7

Mialy Guenet, MS^b

8

Marie Otekpo, MD^b

9

Thomas Célarier, MD, MS^{f,g,h}

10

Jennifer Gautier, MS^b

11

on behalf of the GERIA-COVID study group

12

13 a: School of Medicine, Health Faculty, University of Angers, Angers, France; b: Department
14 of Geriatric Medicine and Memory Clinic, Research Center on Autonomy and Longevity,
15 University Hospital, Angers, France; c: UPRES EA 4638, University of Angers, Angers,
16 France; d: Gérontopôle Autonomie Longévité des Pays de la Loire, France; e: Robarts
17 Research Institute, Department of Medical Biophysics, Schulich School of Medicine and
18 Dentistry, the University of Western Ontario, London, ON, Canada; f: Department of Clinical
19 Gerontology, University Hospital of Saint-Etienne, Saint-Etienne, France; g: Chaire Santé des
20 Aînés, University of Jean Monnet, Saint-Etienne, France; h: Gérontopôle Auvergne-Rhône-
21 Alpes, Saint-Etienne, France

22 **Corresponding author:** Cédric Annweiler, MD, PhD, Department of Geriatric Medicine,
23 Angers University Hospital, F-49933 Angers, France; E-mail: Cedric.Annweiler@chu-
24 angers.fr; Phone: ++33 2 41 35 47 25; Fax: ++33 2 41 35 48 94

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35

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37

38 **ABSTRACT**

39

40 **Background.** The objective of this extension phase of the quasi-experimental GERIA-
41 COVID study was to determine whether vitamin D3 supplementation taken prior to or during
42 COVID-19 was associated with better 3-month survival in geriatric patients hospitalized for
43 COVID-19.

44 **Methods.** Intervention group was defined as all participants supplemented with vitamin D3
45 prior to or during COVID-19 (n=67). Supplements were either bolus vitamin D3 (ie,
46 50,000IU per month, or 80,000IU or 100,000IU or 200,000IU every 2-3 months), or daily
47 supplementation with 800IU. Comparator group involved those without vitamin D
48 supplements (n=28). Outcome was 3-month mortality. Covariables were age, sex, functional
49 abilities, history of malignancies, cardiomyopathy, undernutrition, number of acute health
50 issues, antibiotics use, systemic corticosteroids use, and 25(OH)D concentration.

51 **Results.** 76.1% (n=51) of participants survived at 3 months in Intervention group, compared
52 to only 53.6% (n=15) in Comparator group (P=0.03). The fully-adjusted hazard ratio for 3-
53 month mortality was HR=0.23[95%CI:0.09;0.58](P=0.002) in Intervention group compared to
54 Comparator group. Intervention group had also longer survival time (log-rank P=0.008).

55 **Conclusions.** Vitamin D3 supplementation was associated with better 3-month survival in
56 older COVID-19 patients.

57

58 **1. INTRODUCTION**

59

60 The COVID-19 caused by SARS-CoV-2 spreads worldwide, affecting millions of people and
61 causing hundreds of thousands deaths, notably in older adults. With the lack of effective
62 therapy and the emergence of immune-escape variants (1), the search for a treatment in
63 parallel with the vaccine efforts remains crucial and focusing on the repurposing of existing
64 drugs gives hope of curbing the pandemic. Importantly, an *in-silico* study has identified
65 vitamin D among the three molecules most likely to attenuate the effects of COVID-19
66 through its effects on gene expression (2). Consistently, we previously reported in a quasi-
67 experimental study among frail elderly hospitalized for COVID-19 that the use of vitamin D3
68 supplements was associated with less severe COVID-19 and better survival at day 14 (3).
69 Such follow-up made it possible to include the mortality risk linked to the cytokine storm
70 generally occurring between 7 and 10 days of the SARS-CoV-2 infection (1). However,
71 recent data shows that COVID-19 may also have medium and long-term consequences on
72 morbidity and mortality that go beyond the acute stage of the infection (4). In this perspective,
73 finding a treatment capable of improving the vital prognosis in the short but also in the longer
74 term appears crucial. We had the opportunity to follow the GERIA-COVID participants
75 beyond their hospitalization for up to 3 months. Since bolus vitamin D3 supplementation
76 improves vitamin D status for weeks (5) and given the short-term improvement in survival
77 observed in COVID-19 patients under vitamin D3 supplementation (3,6), we hypothesized
78 that vitamin D3 supplementation could be effective in improving 3-month survival in geriatric
79 patients with COVID-19. The main objective of this extension phase of the quasi-
80 experimental GERIA-COVID study was to determine whether vitamin D3 supplementation
81 taken either prior to or during COVID-19 was associated with better 3-month survival among
82 geriatric COVID-19 patients.

83 **2. MATERIALS AND METHODS**

84 **2.1 Participants**

85 We studied all consecutive participants enrolled during the first wave of the pandemic
86 (between March and June 2020) in the quasi-experimental GERIA-COVID study within the
87 geriatric acute care unit of the University Hospital of Angers, France (3). A first analysis of
88 14-day mortality was previously published on a subsample of this cohort (the patients
89 included between March and May 2020, at the time of writing the first report)(3). Inclusion
90 criteria for the present analysis were as follows: 1) COVID-19 diagnosed with RT-PCR
91 and/or chest CT-scan; 2) data available on the serum measures and on the usual treatments; 3)
92 vital status available 3 months after the diagnosis of COVID-19.
93 Ninety-seven patients with COVID-19 were consecutively admitted into the unit during the
94 study period and recruited in the GERIA-COVID study. Among them, 2 participants had
95 missing values of serum albumin and 25-hydroxyvitamin D (25(OH)D) concentrations.
96 Finally, 95 participants were included in the present analysis.

97

98 **2.2 Intervention: vitamin D3 supplementation**

99 The Intervention group was defined as all COVID-19 participants who had orally received
100 vitamin D3 supplements either prior to hospitalization (systematically noted from the primary
101 care physicians' prescriptions and/or sought by questioning the patients and their relatives)
102 and/or during hospitalization and/or at hospital discharge. Bolus included either 50,000 IU
103 vitamin D3 per month, or 80,000 IU or 100,000 IU or 200,000 IU vitamin D3 every 2-3
104 months. One patient was supplemented with 800 IU vitamin D3 per day. None received D2 or
105 intramuscular supplements.

106 The Comparator group was defined as all COVID-19 participants who had not received any
107 vitamin D supplements prior to or following the diagnosis of COVID-19; the absence of
108 vitamin D treatment being mostly explained by the patients' refusal to be supplemented.

109

110 **2.3 Main outcome: 3-month all-cause mortality**

111 The primary outcome was the 3-month all-cause mortality. Follow-up started from the day of
112 COVID-19 diagnosis for each patient and continued for 3 months or until death when
113 applicable. Vital status was recovered by contacting the patients and their relatives by
114 telephone, and by monitoring the National Institute of Statistics and Economic Studies
115 (INSEE) register (<https://www.insee.fr/fr/information/4190491>).

116

117 **2.4 Covariables**

118 Potential confounders were age, sex, functioning, severe undernutrition, history of
119 malignancies, cardiomyopathy, number of acute health issues on hospital admission, hospital
120 use of antibiotics, of systemic corticosteroids, and serum 25(OH)D concentration at the time
121 of COVID-19 diagnosis. Functioning prior to COVID-19 was measured from 1 (worst) to 6
122 (best) with the Iso-Resources Groups (GIR) (7). Serum albumin and 25(OH)D concentrations
123 were measured concomitantly with the diagnosis of COVID-19. Severe undernutrition was
124 defined as albumin < 30g/L. Serum 25(OH)D concentration was measured by
125 immunoanalysis on the automated LIAISON platform (DiaSorin Inc., Saluggia, IT) in nmol/L
126 (to convert to ng/mL, divide by 2.496). Acute health issues were defined as diseases with
127 sudden onset and rapid progression, whatever their nature or site (3). History of hematological
128 and solid malignancies and of cardiomyopathy was noted from the medical register, and by
129 interviewing patients, family physicians and relatives. The use of systemic corticosteroids

130 and/or antibiotics (i.e., quinolones, beta-lactams, sulfonamides, macrolides, lincosamides,
131 aminoglycosides, among others) was noted from prescriptions during hospitalization.

132

133 **2.5 Statistical analysis**

134 Participants' characteristics were appropriately summarized using means and standard
135 deviations (SD) or numbers and percentages. Firstly, comparisons according to the study
136 groups (i.e., Intervention versus Comparator) were performed using Student *t* test or Chi-
137 square test, as appropriate. Secondly, a partially-adjusted (accounting for age, gender, GIR
138 score and 25(OH)D concentration) and a full adjusted Cox regression were used to examine
139 the associations of 3-month mortality (dependent variable) with vitamin D3 supplementation
140 and covariables (independent variables). Finally, the elapsed time to death was studied by
141 survival curves according to Kaplan-Meier method and compared by log-rank test. P-values
142 <0.05 were considered significant. All statistics were performed using SAS® version 9.4
143 software (Sas Institute Inc) and R (R core Team, 2018).

144

145 **2.6 Ethics**

146 The study was conducted in accordance with the ethical standards set forth in the Helsinki
147 Declaration (1983). No participant or relatives objected to the use of anonymized clinical and
148 biological data for research purposes. Ethics approval was obtained from the Ethics Board of
149 the University Hospital of Angers, France (2020/100). The study protocol was also registered
150 on ClinicalTrials.gov (NCT04560608) and declared to the French National Commission for
151 Information Technology and civil Liberties (CNIL; ar20-0087v0) and.

152

153

154

155 **3. RESULTS**

156 Ninety-five participants (mean±SD, 88.0±5.5 years; 48.4% women) were included in this
157 quasi-experimental study. The follow-up was complete for all participants. Sixty-six
158 participants survived COVID-19 at 3 months while 29 died.

159 Table 1 indicates the participants' characteristics in the Intervention (n=67) and Comparator
160 groups (n=28). The two groups were similar at baseline, except for the proportions of women
161 and of history of malignancies (Table 1). The 3-month mortality was lower in the Intervention
162 group compared to the Comparator group (respectively, 23.9% versus 46.4%, P=0.030).

163 Table 2 shows that, while considering the Comparator group as the reference (hazard ratio
164 (HR)=1), the HR for mortality in the Intervention group was 0.38 [95% confidence interval
165 (CI): 0.18;0.80] (P=0.010) in the unadjusted model, and HR=0.30 [95% CI: 0.13;0.70]
166 (P=0.005) after partial adjustment, and HR=0.23 [95% CI: 0.09;0.58] (P=0.002) after full
167 adjustment. Consistently, Kaplan-Meier distributions showed that COVID-19 participants in
168 the Intervention group had longer survival time than participants in the Comparator group
169 (log-rank P=0.008; Figure 1).

170

171 **4. DISCUSSION**

172 The present quasi-experimental study in geriatric patients with COVID-19 found that,
173 irrespective of all measured potential confounders, vitamin D3 supplementation was
174 associated with better survival after 3 months.

175 This result is consistent with observational data collected during the pandemic
176 showing that vitamin D status is associated with COVID-19 outcomes; cases with COVID-19
177 and hypovitaminosis D being more likely to experience severe forms of COVID-19 (8), to
178 require non-invasive ventilation (9), to have prolonged hospital stay (10), and to die from
179 COVID-19 (8). Overall, these results suggest that improving vitamin D status may prevent

180 and/or improve severe forms of COVID-19. Consistently, preliminary results of the
181 *Koronastudien.no* study in Norway showed that regular consumers of cod liver oil had a
182 lower risk of COVID-19 and, in case of infection, to develop severe COVID-19 (11).
183 Similarly, a randomized placebo-controlled clinical trial in 40 COVID-19 patients initially
184 deficient in vitamin D showed that a greater proportion of those who received a high dose of
185 vitamin D (i.e., 60,000 IU/day for 7 days) no longer had SARS-CoV-2 viral RNA detectable
186 at 21 days on oropharyngeal samples compared to the placebo group (63% versus 21%
187 respectively; P=0.018) (12). Two French quasi-experimental studies also reported that vitamin
188 D3 supplementation was associated with better 14-day survival in older COVID-19 cases
189 either hospitalized (3) or living in nursing-homes (6). In Spain, a pilot randomized trial found
190 in 76 adults (mean, 53 years; 40.8% women) hospitalized for COVID-19 that calcifediol
191 treatment (i.e., 25(OH)D) combined with standard care reduced the number of admissions to
192 intensive care units compared to standard care alone (respectively, 2% versus 50%; P<0.001)
193 (13), suggesting prevention of severe forms of COVID-19 by this metabolite of vitamin D.
194 Finally, a randomized controlled trial conducted in Brazil, which randomly assigned 240
195 patients hospitalized for moderate- to-severe Covid-19 to 200,000 IU vitamin D3
196 supplementation or placebo administered 10.3 days after symptoms onset on average, did not
197 find any effect of vitamin D supplementation on the length of hospital stay (14). The latter
198 study was however limited by the late administration of vitamin D (10.3 days after symptoms
199 onset on average), the relative young age of the participants (mean, 56 years), and the high
200 proportion of patients who already had a satisfactory vitamin D status at baseline and for
201 whom no extra benefits were expected from an extra dose of vitamin D supplements (15).

202 How vitamin D supplementation improves COVID-19 outcomes is not fully elucidated
203 (16,17). First, vitamin D modulates the renin-angiotensin system, notably the angiotensin-2
204 converting enzyme (ACE2) (18), the expression of which is downregulated by the SARS-

205 CoV-2 (19) with potential consequences on inflammatory chain reaction (i.e., cytokine storm)
206 complicated by acute respiratory distress syndrome (ARDS) (1). A study in rats with
207 chemically-induced ARDS showed that levels of ACE2 mRNA and proteins were increased
208 following vitamin D administration, and ARDS symptoms and lung damages were milder
209 under vitamin D compared to controls (20). Second, vitamin D exerts antiviral effects both by
210 induction of antimicrobial peptides with direct antiviral activity and by immunomodulatory
211 and anti-inflammatory effects (21). These are important to limit the cytokine storm by
212 reducing the production of pro-inflammatory cytokines by T helper 1 cells (Th1), such as
213 Tumor Necrosis Factor-alpha (TNF- α) and interferon- γ (21), and by increasing the expression
214 of anti-inflammatory cytokines by macrophages (21). This may explain why the prevention of
215 mortality in the vitamin D group was most apparent in the first 14 days of the disease (Figure
216 1), which corresponds to the cytokine storm when inflammatory lung damage is most severe.
217 Our study confirms the slowing of deaths beyond this period in the non-supplemented group
218 and reports a similar evolution of the death curve in the vitamin D group, which is crucial in
219 the perspective of increased use of vitamin D supplements during COVID-19. Third, vitamin
220 D may have beneficial effects over time on comorbidities that are risk factors for severe forms
221 of COVID-19, such as malignancies, diabetes mellitus, high blood pressure, chronic
222 cardiovascular and respiratory diseases for example (5).

223 The low number of patients consuming daily vitamin D supplements in the present
224 study did not allow a comparison of the effect of daily versus bolus doses on the prognosis of
225 COVID-19. It has been previously shown in a meta-analysis, which included individual
226 intention-to-treat data from almost 11,000 patients from 25 randomized controlled trials (22),
227 a reduction in the risk of acute respiratory infections that was the greatest (ie, -70% [95CI%: -
228 47;-83]) when daily or weekly doses were administered to individuals deficient in vitamin D.
229 However, if the superiority of long-term vitamin D daily consumption is confirmed for the

230 prevention of infections, the reasoning cannot be the same within those already infected for
231 the prevention of serious forms and mortality. Supplementation at small daily doses started
232 during COVID-19 is very unlikely to correct hypovitaminosis D fast enough and exert
233 immunomodulatory effects to improve the prognosis of the infection. In contrast, vitamin D
234 boluses administered before or early in the disease are most likely to quickly increase the
235 25(OH)D concentration and to improve the prognosis of COVID-19 (if confirmed).
236 Compared to daily doses, bolus doses have the additional merit of being preferred by patients
237 (23) and of improving treatment adherence in older adults (24).

238 We also found that increased 25(OH)D concentrations at the time of COVID-19
239 diagnosis were associated with lower 3-month mortality (Table 2). This result is consistent
240 with previous literature that reported higher mortality risk in COVID-19 patients exhibiting
241 hypovitaminosis D (8), which validates the consistency of our cohort and thereby of our main
242 finding on the benefits of vitamin D3 supplementation on the survival of older adults with
243 COVID-19.

244 The strengths of the present study include i) the originality of the research question on
245 a pandemic for which there is no scientifically validated treatment and for which the initial
246 optimism regarding the development of COVID-19 vaccines has been tempered by the
247 emergence of new variants of SARS-CoV-2 (1), ii) the long follow-up and the measure of
248 longitudinal associations according to initial vitamin D intervention, and iii) the standardized
249 collection of data from a single research center.

250 Several limitations also existed. First, participants were restricted to a limited number of
251 geriatric patients who might be unrepresentative of all older adults. Second, although we were
252 able to control for important characteristics that could modify the association, residual
253 potential confounders might still be present, such as the 25(OH)D concentration ultimately
254 reached following supplementation or the date of the most recent vitamin D intake. A

255 supplement taken in the month preceding the infection seems however to be more protective
256 than an earlier supplementation (6). Third, the quasi-experimental design of our study is less
257 robust than a randomized controlled trial. Participants in the Comparator group did not
258 receive vitamin D placebo and there was no randomization. It is plausible that patients refused
259 taking vitamin D supplementation in the Comparator group due to comorbidities such as
260 malignancies that were too severe to take the supplements. It should yet be noted that most
261 characteristics did not differ between the two groups, except for the history of malignancies
262 and the proportion of women (who are likely to suffer from osteoporosis and may have
263 received corresponding treatment that includes vitamin D).

264 In conclusion, we found that vitamin D3 supplementation prior to or during COVID-
265 19 was associated with better survival after 3 months in older adults with COVID-19. Vitamin
266 D supplementation may represent an effective, accessible, and well-tolerated adjuvant
267 treatment for COVID-19.

268

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274 Affiliations: 1: Department of Geriatric Medicine, University Hospital, Angers, France.

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278

279 **CONFLICT OF INTEREST STATEMENT**

280 CA occasionally serves as a consultant for Mylan Laboratories Inc (2020). All authors declare
281 they do not have any other financial and personal conflicts of interest with this manuscript.

282 **SPONSOR'S ROLE**

283 None.

284

285 **AUTHORS CONTRIBUTION**

286 – CA has full access to all of the data in the study, takes responsibility for the data, the
287 analyses and interpretation and has the right to publish any and all data, separate and apart
288 from the attitudes of the sponsors. All authors have read and approved the manuscript.

289 – Study concept and design: CA.

290 – Acquisition of data: CA, MB, RS, MG, MO and JG.

291 – Analysis and interpretation of data: CA, TC and JG.

- 292 – Drafting of the manuscript: CA.
- 293 – Critical revision of the manuscript for important intellectual content: MB, RS, MG, MO,
294 TC and JG.
- 295 – Obtained funding: Not applicable.
- 296 – Statistical expertise: JG.
- 297 – Administrative, technical, or material support: CA.
- 298 – Study supervision: CA.

299

300 **DATA AVAILABILITY**

301 Patient level data are freely available from the corresponding author at
302 Cedric.Annweiler@chu-angers.fr. There is no personal identification risk within this
303 anonymized raw data, which is available after notification and authorization of the competent
304 authorities.

305

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375

376 **Table 1. Characteristics and comparisons of participants with COVID-19 according to**
 377 **the study group (n=95)**

378

	All COVID-19 participants (n=95)	Study group		P-value*
		Comparator group (n=28)	Vitamin D group (n=67)	
Demographical data				
Age (years), mean±SD	88.0±5.5	88.6±5.7	87.7±5.4	0.694
Female gender	46 (48.4)	8 (28.6)	38 (56.7)	0.012
GIR score (/6), mean±SD	3.5±1.5	3.6±1.7	3.5±1.4	0.679
Comorbidities				
Severe undernutrition [†]	27 (28.4)	10 (35.7)	17 (25.4)	0.308
History of malignancies	32 (33.7)	14 (50.0)	18 (26.9)	0.030
History of cardiomyopathy	50 (52.6)	16 (57.1)	34 (50.8)	0.569
Hospitalization				
Number of acute health issues, mean±SD	3.0±1.6	2.6±1.9	3.0±1.5	0.224
Use of antibiotics [‡]	64 (67.4)	19 (67.9)	45 (67.2)	0.948
Use of systemic corticosteroids	17 (17.9)	4 (14.3)	13 (19.4)	0.553
Serum 25(OH)D concentration (nmol/L), mean±SD	65.2±34.8	73.9±32.1	61.6±35.4	0.086
Follow-up				
3-month mortality	29 (30.53)	13 (46.4)	16 (23.9)	0.030

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380

381 Data presented as n (%) where applicable; 25(OH)D: 25-hydroxyvitamin D; COVID-19:

382 Coronavirus Disease 2019; GIR: Iso Resource Groups; *: between-group comparisons based

383 on Chi-square test and Student *t* test, as appropriate; †: serum albumin concentration < 30 g/L;

384 ‡: quinolones, beta-lactams, sulfonamides, macrolides, lincosamides, aminoglycosides,

385 among others.

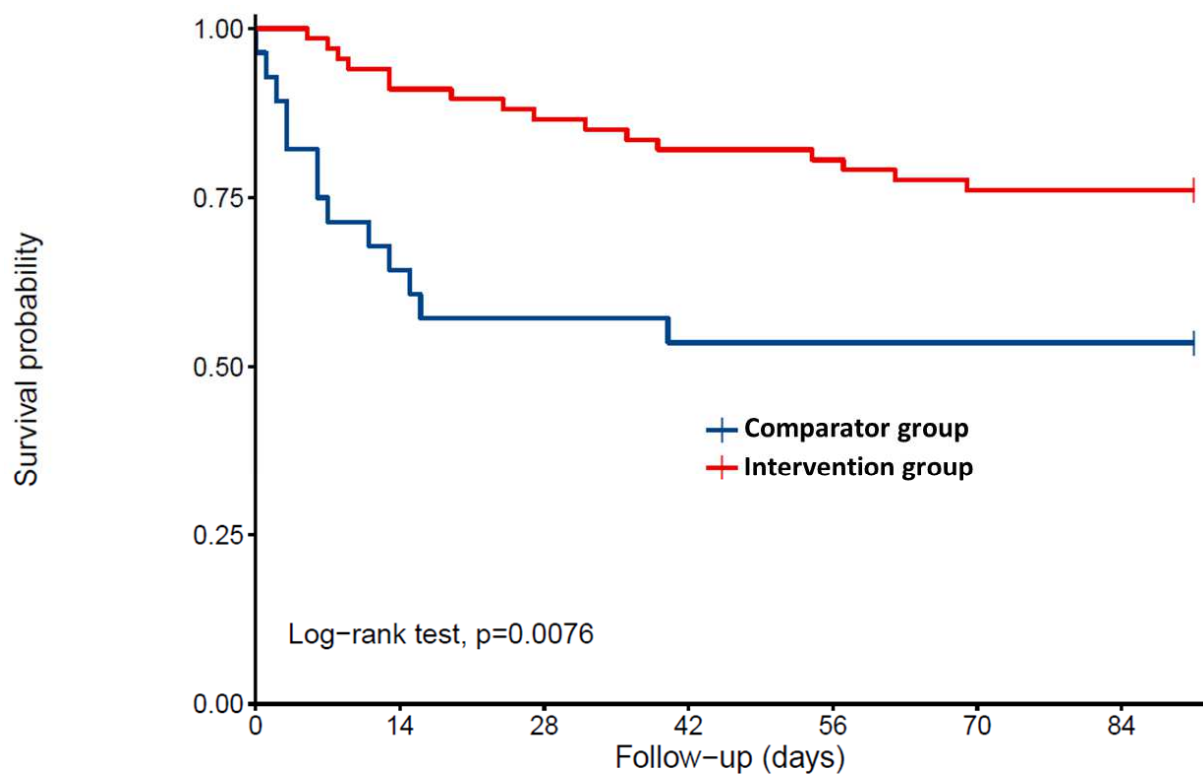
386

387 **Table 2. Multiple Cox proportional-hazards model showing the hazard ratio for 3-**
388 **month mortality among COVID-19 participants (dependent variable) according to**
389 **vitamin D intervention (independent variable) adjusted for potential confounders**
390 **(n=95).**
391

	3-month mortality					
	Unadjusted model		Partially-adjusted model*		Fully-adjusted model	
	HR [95% CI]	P- value	HR [95% CI]	P- value	HR [95% CI]	P- value
Vitamin D supplementation	0.38 [0.18;0.80]	0.010	0.30 [0.13;0.70]	0.005	0.23 [0.09;0.58]	0.002
Age	1.02 [0.95;1.09]	0.651	1.01 [0.94;1.08]	0.848	1.04 [0.95;1.13]	0.436
Female gender	0.53 [0.25;1.15]	0.109	0.82 [0.35;1.96]	0.656	0.65 [0.23;1.84]	0.417
GIR score	0.70 [0.53;0.92]	0.010	0.66 [0.50;0.86]	0.003	0.71 [0.52;0.97]	0.029
Serum 25(OH)D concentration	1.00 [0.99;1.01]	0.394	0.99 [0.98;1.00]	0.049	0.99 [0.97;1.00]	0.035
Severe undernutrition [†]	1.78 [0.84;3.78]	0.131	-	-	1.36 [0.57;3.26]	0.489
History of malignancies	3.11 [1.49;6.47]	0.003	-	-	2.99 [1.35;6.60]	0.007
History of cardiomyopathy	1.14 [0.55;2.37]	0.724	-	-	0.85 [0.37;1.97]	0.699
Number of acute health issues	1.30 [1.04;1.63]	0.024	-	-	1.34 [1.05;1.72]	0.018
Use of antibiotics [‡]	2.58 [0.98;6.76]	0.054	-	-	2.32 [0.78;6.94]	0.132
Use of systemic corticosteroids	0.78 [0.76;4.17]	0.184	-	-	2.39 [0.82;7.00]	0.111

392

393 25(OH)D: 25-hydroxyvitamin D; CI: confidence interval; COVID-19: coronavirus disease
394 2019; GIR: Iso Resource Groups; HR: hazard ratio; *: adjusted for age, sex, GIR score and
395 25(OH)D concentration; †: serum albumin concentration < 30 g/L; ‡: quinolones, beta-
396 lactams, sulfonamides, macrolides, lincosamides, aminoglycosides, among others.



Number at risk

Comparator	28	18	16	15	15	15	15
Intervention	67	61	58	55	54	51	51

Figure 1. Kaplan-Meier estimates of the cumulative probability of COVID-19 participants' survival according to vitamin D intervention (n=95).