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Unexpected diagnosis of COVID-19-associated disorders by SARS-CoV-2-specific serology

Running title: Unexpected SARS-CoV-2 diagnosis by serology

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1 **Abstract**

2

3 Facing the ongoing pandemic caused by SARS-CoV-2, there is an urgent need for serological
4 assays identifying individuals with on-going infection as well as past coronavirus infectious
5 disease 2019 (COVID-19). We herein evaluated the analytical performances of the CE IVD-
6 labeled Abbott SARS-CoV-2 IgG assay (Des Plaines, IL, USA) carried out with the
7 automated Abbott Architect™ i2000 platform at Hôpital Européen Georges Pompidou, Paris,
8 France, using serum sample panels obtained from health-workers with COVID-19 history
9 confirmed by positive nucleic acid amplification-based diagnosis and from patients randomly
10 selected for whom serum samples were collected before the COVID-19 epidemic. The Abbott
11 SARS-CoV-2 IgG assay showed sensitivity of 94% and specificity of 100%, demonstrating
12 high analytical performances allowing convenient management of suspected on-going and
13 past-infections. In addition, the SARS-CoV-2 IgG positivity rates were compared in COVID-
14 19 positive and COVID-19 free areas from our hospital. Thus, the frequency of SARS-CoV-
15 2-specific IgG was around 10-fold higher in COVID-19 areas than COVID-19 free areas
16 (75% versus 8%; $P < 0.001$). Interestingly, several inpatients hospitalized in COVID-19 free
17 areas suffering from a wide range of unexplained clinical features including cardiac, vascular,
18 renal, metabolic and infectious disorders, were unexpectedly found seropositive for SARS-
19 CoV-2 IgG by systematic routine serology, suggesting possible causal involvement of SARS-
20 CoV-2 infection. Taken together, these observations highlight the potential interest of SARS-
21 CoV-2-specific serology in the context of COVID-19 epidemic, especially to assess past
22 SARS-CoV-2 infection as well as possible unexpected COVID-19-associated disorders.

23

24 **Keywords.** SARS-CoV-2; COVID-19; Serology; Diagnosis; Abbott SARS-CoV-2 IgG assay;

25

26 **Introduction**

27 Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was declared by the
28 World Health Organization (WHO) as global pandemic on March 11, 2020[1–3].

29 Controlling the outbreak in the community and in hospitals mainly relied on the
30 availability and the sensitivity and specificity of RT-PCR testing[4, 5]. Rapidly, it was
31 demonstrated that serological testing looking for specific SARS-CoV-2 IgG and/or IgM could
32 increase the sensitivity of the diagnosis[6–10]. On March 2, 2020, the WHO recommended
33 serological testing in addition to molecular diagnosis for the diagnosis of strongly suspected
34 patients of SARS-CoV-2 infection with negative RT-PCR[11].

35 At April, the Abbott SARS-CoV-2 IgG assay (Abbott GmbH, Rungis, France)
36 received CE-IVD label and was installed on our automated i2000 platform (Abbott
37 Architect™ i2000) at *Hôpital Européen Georges Pompidou* (HEGP). Our hospital, belonging
38 to the *Assistance Publique-Hôpitaux de Paris*, which represents the largest group of university
39 hospitals in Europe, has been organized since mid-March to attend to patients with COVID-
40 19 related conditions (COVID-positive area) in distinct areas from the patients without
41 COVID-19 related conditions (COVID-free area). To analytically and clinically validate the
42 Abbott SARS-CoV-2 IgG assay, we tested pre-epidemic sera, sera from pauci-symptomatic
43 health-worker with SARS-CoV-2 positive RT-PCR and sera from hospitalized patients from
44 both the COVID-positive area and the COVID-free area. To date, few data are available on
45 serology testing, focusing mainly on the time of seroconversion after the onset of symptoms
46 and the neutralizing capability of the produced antibodies[9, 12, 13, 14].

47 We herein report on lessons learned from our analytical and clinical validation of the
48 Abbott SARS-CoV-2 IgG assay, including unexpected diagnosis of COVID-19 associated
49 disorders by SARS-CoV-2-specific serology assay.

50

51 **Material and methods**

52

53 **SARS-CoV-2 serology.** Abbott SARS-CoV-2 IgG assay detecting IgG against SARS-CoV-2
54 nucleoprotein was used on Architect analyzer (Abbott Architect™ i2000), according to
55 manufacturer's instructions. Index value threshold for positivity was 1.4. Qualitative results as
56 well as index values were used for analysis.

57

58 **Serum samples.** Left over sera from pre-epidemic period (collected from October 2019 to
59 January 2020), available at the virology laboratory of HEGP, were used for specificity
60 evaluation. Some of these sera came from patients with recent clinical history of viral
61 respiratory infection including common coronaviruses (229E; NL63; OC43) as well as
62 clinical history of malaria.

63 Sensitivity was assessed using sera from hospital staff who had a history of positive
64 SARS-CoV-2 RT-PCR at least one month before serology testing. Specimens were collected
65 by occupational medicine.

66 Finally, sera were also obtained from patients attending the hospital during the
67 pandemic period, in April 2020, either for COVID-19 related conditions in COVID-positive
68 area of the hospital or for non-COVID-19 related conditions in COVID-free area, for further
69 SARS-CoV-2 IgG serological testing.

70 **Statistical analysis.** The index value results and the time between the onset of symptoms and
71 the serological test were compared between seropositive and seronegative subjects using the
72 Wilcoxon-Mann-Whitney test. The seroprevalence was compared between subjects
73 hospitalized for COVID-19 related and non-COVID-19 related conditions using the Chi-
74 square test.

75 **Ethical statement:** Our non-interventional study was carried out in accordance with the
76 Declaration of Helsinki without extra sample collection compared to usual procedures. In
77 particular, serum sample specimens and clinical data were obtained only for standard
78 diagnostic following medical prescriptions and care. Under these conditions, the study was
79 exempted from informed consent application, according to the French public health code
80 (*CSP*, article L 1121-1.1; <https://www.legifrance.gouv.fr/>). Data analyses were carried out
81 using anonymized database.

82

83 **Results**

84

85 **Abbott SARS-CoV-2 IgG assay specificity.** Out of 117 pre-epidemic sera collected from
86 October 2019 to January 2020, none tested positive for SARS-CoV-2 IgG. The specificity of
87 the Abbott SARS-CoV-2 IgG assay was 100% (95% CI: 97%-100%). Median index value
88 was 0.03 (IQR=0.04). Among the 117 sera, 6 and 7 patients had a recent history of malaria
89 and common coronavirus upper respiratory tract infection (4 coronavirus NL63, 2 coronavirus
90 229E and one coronavirus OC43), respectively. Only 4 results showed index value results
91 above 0.7 (0.7, 0.77, 0.77 and 0.78 respectively), 2 of which had a recent history of malaria
92 (0.78 and 0.77), the first one having also a recent history of coronavirus 229E upper
93 respiratory tract infection.

94

95 **Abbott SARS-CoV-2 IgG assay sensitivity.** Hundred sera collected from hospital health-
96 workers previously positive for SARS-CoV-2 RT-PCR were tested for SARS-CoV-2 IgG. In
97 this group of health-workers, 69% were female and the median age was 34 (IQR=19.5 years)
98 (Table 1). Median delay between RT-PCR and serology was 39.5 days (IQR=9.25 days).
99 Ninety-four serum tested positive for SARS-CoV-2 IgG. The sensitivity of the Abbott SARS-

100 CoV-2 IgG assay was 94% (95% IC: 87%-98%) (Table 1). Median index value of SARS-
101 CoV-2 IgG positive samples was 5.35 (IQR=3.51) while the median index value of SARS-
102 CoV-2 IgG negative samples was 0.535 (IQR=0.31, $P=0.00004$). Difference between median
103 index value of pre-epidemic sera and median index value of these negative sera was
104 statistically significant (0.03 *versus* 0.53; $P=0.0069$) (Figure 1). All of the negative serum
105 from hospital staff with positive RT-PCR were collected at least 30 days after the initial
106 diagnosis (mean = 44 days; range, 37 to 52).

107

108 **SARS-CoV-2 IgG positivity from hospitalized patients during epidemic period**
109 **according to COVID-19 hospitalization status.** During the epidemic, specific geographical
110 sectors of the hospital were used to attend COVID-19 positive patients while patients without
111 COVID-19 related conditions were hospitalized in other parts of the hospital.

112 The median age of the hospitalized patients was 60 years (IQR=25) and 31% of them
113 were female. The difference between the demographic data (age and sex) within the health
114 workers and the hospitalized patients were statistically significant ($P=2.85 \times 10^{-17}$ and
115 $P=1.94 \times 10^{-8}$, respectively) (Table 1).

116 Out of the 63 patients hospitalized for COVID-19 related conditions that were tested
117 for SARS-CoV2 IgG, 47 (74.6%) tested positive (Table 1). The delay between the onset of
118 symptoms and the time of sampling was statistically different between the serology positive
119 patients and the serology negative patients (median delay=17.2 days, IQR=8.5 days, *versus*
120 median delay=6.5 days, IQR=3.8 days, respectively; $P=0.0005$). All patients tested at least 20
121 days after the onset of symptoms were positive for SARS-CoV-2 IgG (Figure 2).

122 Out of the 96 patients hospitalized for non-COVID-19 related conditions that were
123 tested for SARS-CoV2 IgG, 8 (8.3%) tested positive. The difference with COVID-19 positive

124 hospitalized patients was statistically significant ($P < 0.0001$). Six patients out of 8 were tested
125 for SARS-CoV-2 by RT-PCR, all of them tested negative.

126

127 **Unexpected potential COVID-19 related disorders.** Out of the 8 patients hospitalized in
128 non-COVID-19 area that showed positive SARS-CoV-2 IgG serology, 2 presented renal
129 failure, 2 presented cardiac related disorders, 2 presented vascular related disorders, the last 2
130 patients were hospitalized for hyperglycemia and pneumonia, respectively (Table 2).

131 The original clinical presentations of these unexpected COVID-19 associated disorders are
132 described below:

133 ✓ *Patient #1.* A 34-year-old Senegalese male, presented with acute renal failure and
134 nephrotic syndrome. He had a history of stage 4 chronic renal failure (baseline serum
135 creatinine 310 $\mu\text{mol/L}$) secondary to hypertensive nephrosclerosis with congenital
136 unique kidney. Two weeks before hospital admission, the patient presented flu-like
137 syndrome that was treated with paracetamol. Ten days later he developed edema of the
138 lower limbs and aqueous diarrhea. Laboratory test showed acute renal failure with
139 serum creatinine of 989 $\mu\text{mol/L}$ with nephrotic range proteinuria. Kidney biopsy
140 revealed focal segmental glomerulosclerosis with podocytes hypertrophy and
141 hyperplasia associated with interstitial fibrosis. He partially recovered with a serum
142 creatinine at discharge at 742 $\mu\text{mol/L}$. SARS-CoC-2 RT-PCR was negative at the time
143 of hospital admission and index value of SARS-CoV-2 IgG was 7.2.

144 ✓ *Patient #2.* A 33-year-old Ivorian male, was referred by his general practitioner for
145 incidental finding of severe renal insufficiency (serum creatinine 2,086 $\mu\text{mol/L}$)
146 associated with nephrotic syndrome. His past medical history was notable only for
147 tuberculosis. He only complained of abdominal pain. Physical examination was
148 unremarkable except for high blood pressure. Kidney biopsy revealed extensive

149 fibrosis with collapsing focal segmental glomerulosclerosis. The presentation was
150 consistent with end-stage renal disease and the patient required chronic hemodialysis.
151 RT-PCR was not performed at the time of hospital admission and index value of
152 SARS-CoV-2 IgG was 7.7.

153

154 Two other patients suffered from cardiac related disorders:

155 ✓ *Patient #3.* A 65-year-old male, was directly admitted to the intensive care unit after
156 cardiopulmonary resuscitation at home for a cardiac arrest. Patient had no past medical
157 history. Medical evaluation found a massive intracranial hemorrhage likely due to the
158 rupture of a left middle cerebral artery aneurysm. The patient died within 48 hours
159 after admission. Index value of SARS-CoV-2 IgG was 7.1.

160 ✓ *Patient #4.* A 21-year-old male was admitted for a scheduled aortic root replacement
161 (Bentall procedure). In the course of his mucopolysaccharidosis type II or Hunter
162 syndrome, he developed a symptomatic severe aortic regurgitation with left ventricle
163 dilatation associated with aortic root aneurysm. Pre-operative SARS-CoV-2 RT-PCR
164 was negative and index value of SARS-CoV-2 IgG was 1.5.

165

166 Two other patients presented with vascular related disorders:

167 ✓ *Patient #5.* A 68-year-old male was admitted for acute limb ischemia, with no past
168 medical history. At the emergency room, the patient had acute pain in his left foot with
169 paresthesia and palsy 3 hours ago. The left popliteal, posterior tibial and pedal pulses
170 were abolished with pallor and coldness of the foot from the toes to the ankle. The
171 electrocardiogram was in sinus rhythm and the angio-computed tomography revealed
172 a thrombus of the infra-renal aorta, with complete occlusion of the left popliteal artery
173 without any atherosclerotic lesions on the arterial tree. Chest scan findings were

174 suggestive of COVID-19. The patient had no symptoms suggestive of COVID-19.
175 Pre-operative and post-operative SARS-CoV-2 RT-PCR (n=2) were negative.
176 Vascular surgeons performed immediate limb salvage with catheter embolectomy. At
177 the follow-up consultation one month after surgery, the patient was asymptomatic.
178 Index value of SARS-CoV-2 IgG was 8.9.

179 ✓ *Patient #6.* A 75-year-old male was admitted for recent claudication of the left calf.
180 The patient had already been treated for peripheral arterial disease with a left femoro-
181 popliteal bypass in 2008. The patient had consulted his cardiologist for new onset of
182 his calf claudication one week ago. The duplex ultrasound found an occlusion of the
183 femoro-popliteal bypass. A recanalization of the native left superficial femoral artery
184 was rapidly scheduled. After 48 hours, recanalization was still patent and the patient
185 was discharged with a dual antiplatelet therapy. He had no symptom suggestive of
186 COVID-19. Pre-operative and post-operative SARS-CoV-2 RT-PCR (n=2) were
187 negative. Index value of SARS-CoV-2 IgG was 2.6.

188

189 Finally, the last 2 patients showed hyperglycemia and pneumonia, respectively:

190 ✓ *Patient #7.* A 64-year-old female was admitted for hyperglycemia, weakness and
191 diarrhea. Her past medical history included hypertension and type 2 diabetes. Two
192 weeks before hospital admission, she presented with cough and rhinorrhea. She
193 progressively recovered, but complained of moderate abdominal pain, diarrhea
194 without blood nor mucus, nausea and hyperglycemia within the next days. Physical
195 examination showed mild tenderness around the upper abdomen and minor basal
196 crackles in the left lung. Laboratory tests showed moderate acute kidney injury with
197 serum creatinine of 111 $\mu\text{mol/l}$. Her usual medication was suspended and
198 physiological saline solution was administrated intravenously. The patient's condition

199 rapidly improved and she was discharged from the hospital 2 days after her admission.
200 Nasopharyngeal SARS-CoV-2 RT-PCR was negative at the time of hospital admission
201 and index value of SARS-CoV-2 IgG was 6.2.

202 ✓ *Patient #8.* A 31 years old man was admitted for fever and shortness of breath. He had
203 been coughing for several months. Previous medical history included dilated and
204 hypertrophic cardiomyopathy, and renal transplant for IgA nephropathy. Physical
205 examination revealed bronchi and crackles in lung basis. SARS-CoV-2 RT-PCR was
206 negative. He was discharged. He came back four weeks later for similar symptoms.
207 Chest CT-scan findings were only suggestive of acute bronchitis. SARS-CoV-2 RT-
208 PCR was negative again, while index value of SARS-CoV-2 IgG was 2.1.

209

210

211 **Discussion**

212

213 To our knowledge, this is the second study assessing the analytical performances of the
214 Abbott SARS-CoV-2 IgG assay, the first one with samples collected in Europe. In the first
215 study, both specificity (99.9%) and sensitivity (100% after 17 days since the onset of
216 symptoms) were excellent[14]. Our results confirmed the excellent specificity of the assay
217 (100%) but our sensitivity results were not as good as expected, especially in the health-
218 worker group (sensitivity=94%). Our results from the patients hospitalized for COVID-19
219 were more comparable to the ones observed in the study of Bryan *et al.*[14]. Indeed, the
220 median delay before the detectability of SARS-CoV-2 IgG since the onset of symptoms was
221 17 days, as it has previously been described, and every tested patient after 20 days were
222 positive. Various hypotheses could be given to explain this discrepancy between hospitalized
223 patients and health-workers. Firstly, among health workers, only 2 were hospitalized and 98

224 were not hospitalized and had only little symptoms. Furthermore, the median ages as well as
225 the sex ratio between these 2 groups were statistically different. Whether any of these factors
226 (age, sex and symptoms) could be responsible for the relatively low sensitivity (94%) in our
227 health workers group would need further investigations. One could also hypothesize that the
228 sensitivity of the test might depend on the SARS-CoV-2 strain and that some specific
229 antibodies might be not detected by the assay. Furthermore, out of the 6 health workers that
230 tested negative with positive RT-PCR, only one had a very low index value at 0.1, all the
231 others had at least an index value of 0.4, which could indicate that some antibodies are
232 produced but are weakly detected. Among these 6 health-workers, one was tested for sero-
233 neutralizing antibodies in a research protocol context. He was positive with a low titer
234 according to the technique (data not shown), which is in agreement with the fact that some
235 antibodies are produced.

236 In our study, we took advantage of our hospital organization, which was structured in
237 COVID-positive area and COVID-free area to test some patients from the COVID-free area.
238 IgG positivity in this area was 8.3% which is much higher when compared to the 1.79%
239 described by Bryan *et al*[14]. This could be explained by the fact that our samples were
240 collected by mid-April, at the time of the epidemic peak in France and that a greater
241 percentage of the population had been exposed to the virus at this time. Nevertheless, these
242 results confirmed that the organization in COVID-positive and COVID-free area was efficient
243 as the IgG positivity was highly different between both sectors.

244 Finally, our work demonstrated that SARS-CoV-2 serology could be a useful tool to
245 retrospectively diagnose COVID-19 infections with 8 cases of unexpected COVID-19
246 diagnosis in the COVID-19 free area. Clinical features of these 8 patients were in agreement
247 with the wide variety of organs that could be affected by SARS-CoV-2[15–19]. Indeed, 2
248 patients presented with nephropathy, 2 patients with cardiac symptoms, 2 patients with

249 vascular symptoms, one patient with hyperglycemia and the last one with bacterial
250 pneumonia. To our knowledge, this is the first study that underlines the retrospective clinical
251 value of SARS-CoV-2 specific serology, especially when recent history of SARS-CoV-2
252 infection was not obvious. There is no doubt that generalizing the serology diagnosis would
253 reveal unexpected SARS-CoV-2 infections associated with various organ disorders.

254

255

256

257
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262
263 **Authors contribution.** HP, BV, LB, DV designed the research; HP, BV, RV, LB, DV
264 performed statistical analysis; ND, NK, TM, HL, GV, ED, DL provided clinical care and
265 specimens. HP, RV, TM, HL, GV, ED, LB, DV drafted the manuscript. All authors read and
266 approved the final manuscript.

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268

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270

271

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273

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346 **Table 1.** Summary of demographic data and SARS-CoV-2 serology results according to patient status.

| | COVID + health-workers | Patients from COVID + area | Patients from COVID-free area | Total Hospitalized patients | P |
|-------------------------|---------------------------|----------------------------------|-------------------------------------|-----------------------------------|---------------------------|
| Number | 100 | 63 | 96 | 159 | |
| Median age (IQR) | 34 (19.5) | 64 (21.5) | 58 (33.5) | 60 (25) | 2.85x10 ^{-17(a)} |
| Female / Male % | 69 / 31 | 30 / 70 | 31 / 69 | 31/69 | 1.94x10 ^{-8(a)} |
| Positive serology n (%) | 94 (94%) | 47 (75%) | 8 (8%) | 55 (35%) | 2.22x10 ^{-18(b)} |

(a) Total hospitalized patient versus COVID+ health-workers

(b) Patients from COVID + versus patients from COVID-free area

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350 **Table 2.** Synthesis of patients with unexpected COVID-19 associated disorder.

| COVID-19 associated disorder | Patients ID | Sex | Age | RT-PCR results | SARS-CoV-2 IgG Index value | Reason for admission |
|------------------------------|-------------|-----|-----|----------------|----------------------------|--|
| Renal | 1 | M | 34 | N | 7.2 | Acute renal failure with nephrotic syndrome |
| | 2 | M | 33 | ND | 7.7 | Severe renal insufficiency with nephrotic syndrome |
| Cardiac | 3 | M | 65 | ND | 7.1 | Cardiac arrest |
| | 4 | M | 22 | N | 1.5 | Aortic root replacement (Bentall procedure) |
| Vascular | 5 | M | 68 | N | 8.9 | Acute limb ischemia |
| | 6 | M | 75 | N | 2.6 | Recent claudication of the left calf |
| Endocrine | 7 | F | 65 | N | 6.2 | Diabetic disorder |
| Infectious | 8 | M | 32 | N | 2.1 | Streptococcus pneumoniae acute pneumonia |

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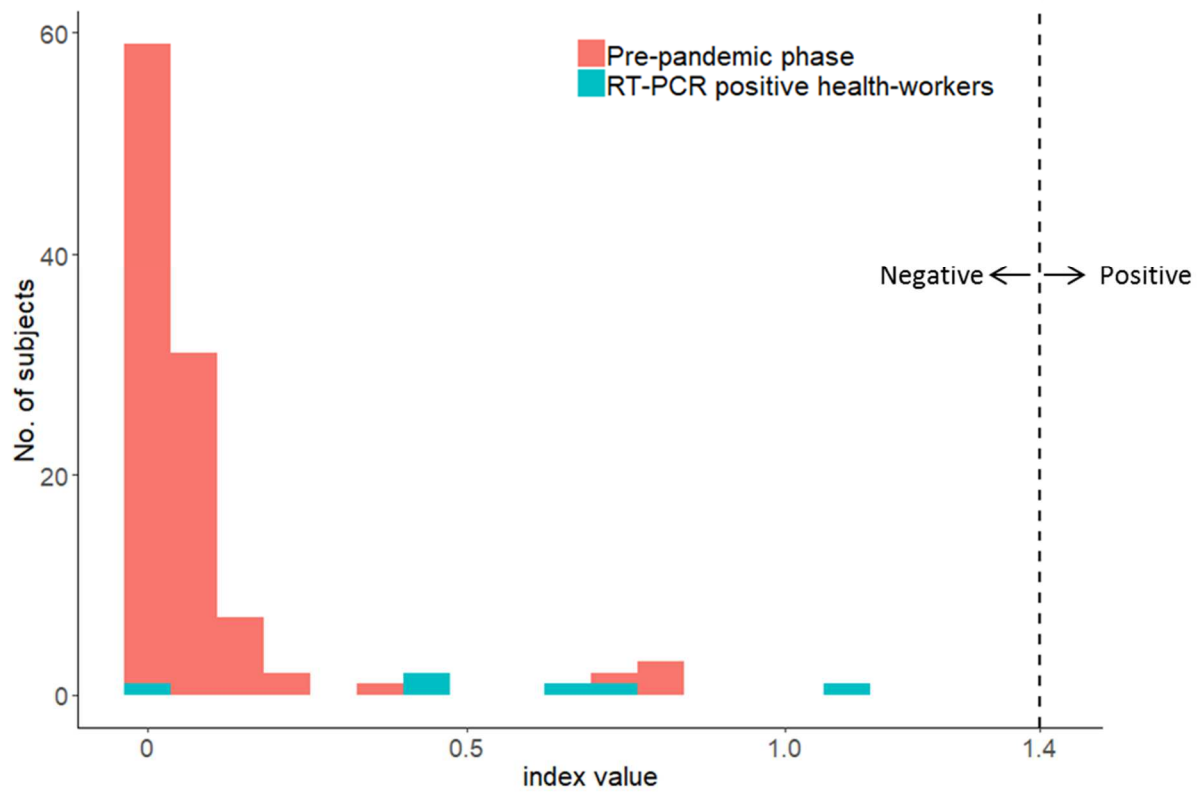
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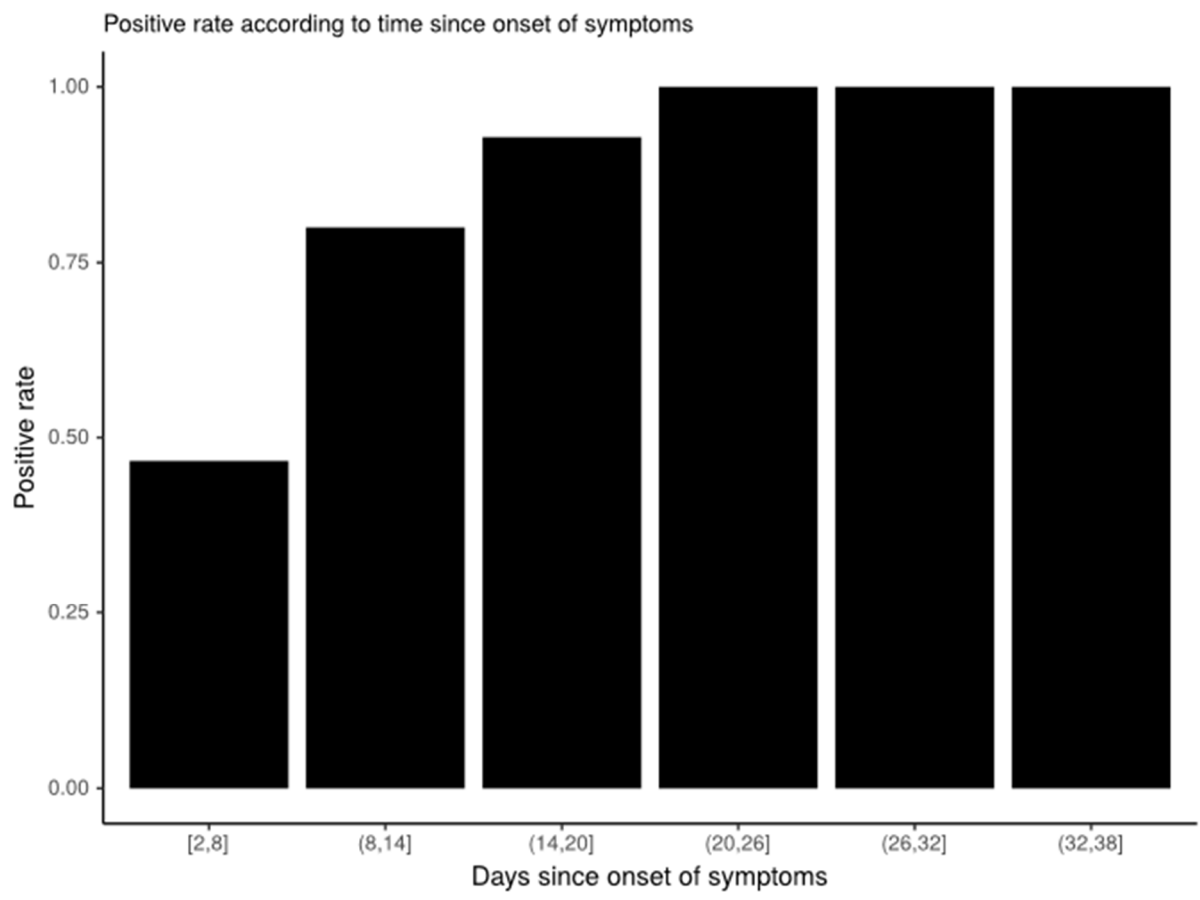
357 **Figure 1.** Distribution of Abbott SARS-CoV-2 IgG assay index values from pre-epidemic
358 patients and seronegative health-workers.



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361 **Figure 2.** SARS-CoV-2 IgG positive rate since onset of symptoms.



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