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► To cite this version:

Hélène Péré, Benoit Védie, Raphaël Vernet, Nathalie Demory, Najiby Kassis, et al.. Unexpected diagnosis of COVID-19-associated disorders by SARS-CoV-2-specific serology. Journal of Clinical Virology, 2020, 132, pp.104568 - 10.1016/j.jcv.2020.104568 - hal-03491642

HAL Id: hal-03491642 https://hal.science/hal-03491642

Submitted on 5 Sep 2022

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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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Word count of the text: 2493 Word count of the abstract: 233

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1 Abstract

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

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

26 Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was declared by the
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].

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

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

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

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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.

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

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

Statistical analysis. The index value results and the time between the onset of symptoms and the serological test were compared between seropositive and seronegative subjects using the Wilcoxon-Mann-Whitney test. The seroprevalence was compared between subjects hospitalized for COVID-19 related and non-COVID-19 related conditions using the Chisquare test. **Ethical statement:** Our non-interventional study was carried out in accordance with the Declaration of Helsinki without extra sample collection compared to usual procedures. In particular, serum sample specimens and clinical data were obtained only for standard diagnostic following medical prescriptions and care. Under these conditions, the study was exempted from informed consent application, according to the French public health code (*CSP*, article L 1121-1.1; https://www.legifrance.gouv.fr/). Data analyses were carried out using anonymized database.

82

83 **Results**

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

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

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

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

Out of the 63 patients hospitalized for COVID-19 related conditions that were tested for SARS-CoV2 IgG, 47 (74.6%) tested positive (Table 1). The delay between the onset of symptoms and the time of sampling was statistically different between the serology positive patients and the serology negative patients (median delay=17.2 days, IQR=8.5 days, *versus* median delay=6.5 days, IQR=3.8 days, respectively; *P*=0.0005). All patients tested at least 20 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 hospitalized patients was statistically significant (P<0.0001). Six patients out of 8 were tested for SARS-CoV-2 by RT-PCR, all of them tested negative.

126

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

131 The original clinical presentations of these unexpected COVID-19 associated disorders are132 described below:

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

Patient #2. A 33-year-old Ivorian male, was referred by his general practitioner for
 incidental finding of severe renal insufficiency (serum creatinine 2,086 µmol/L)
 associated with nephrotic syndrome. His past medical history was notable only for
 tuberculosis. He only complained of abdominal pain. Physical examination was
 unremarkable except for high blood pressure. Kidney biopsy revealed extensive

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

153

154 Two other patients suffered from cardiac related disorders:

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

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

165

166 Two other patients presented with vascular related disorders:

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

suggestive of COVID-19. The patient had no symptoms suggestive of COVID-19.
Pre-operative and post-operative SARS-CoV-2 RT-PCR (n=2) were negative.
Vascular surgeons performed immediate limb salvage with catheter embolectomy. At
the follow-up consultation one month after surgery, the patient was asymptomatic.
Index value of SARS-CoV-2 IgG was 8. 9.

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

188

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

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

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

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

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211 Discussion

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

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

236 In our study, we took advantage of our hospital organization, which was structured in COVID-positive area and COVID-free area to test some patients from the COVID-free area. 237 238 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 collected by mid-April, at the time of the epidemic peak in France and that a greater 240 percentage of the population had been exposed to the virus at this time. Nevertheless, these 241 results confirmed that the organization in COVID-positive and COVID-free area was efficient 242 as the IgG positivity was highly different between both sectors. 243

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

Acknowledgments. We thank the patients, the nurses and clinical staff who are providing care for the patients. The authors gratefully thank the Clinical Biochemistry department of Hôpital Européen Georges Pompidou, especially the technicians from the serological platform.

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

267 Declarations of interest: none.
268
269 Funding. None.
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Table 1. Summary of demographic data and SARS-CoV-2 serology results according to patient status.

		Patients from	Patients from	Total	
	LOVID +	COVID +	COVID-free	Hospitalized	Р
	nearth-workers	area	area	patients	
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+ healt-workers

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

347 348

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	М	34	Ν	7.2	Acute renal failure with nephrotic syndrome
	2	М	33	ND	7.7	Severe renal insufficiency with nephrotic syndrome
Cardiac	3	Μ	65	ND	7.1	Cardiac arrest
	4	М	22	Ν	1.5	Aortic root replacement (Bentall procedure)
Vascular	5	Μ	68	Ν	8.9	Acute limb ischemia
	6	М	75	Ν	2.6	Recent claudication of the left calf
Endocrine	7	F	65	Ν	6.2	Diabetic disorder
Infectious	8	М	32	Ν	2.1	Streptococcus pneumoniae acute pneumonia

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







Positive rate according to time since onset of symptoms