Journal of Translational Autoimmunity 7 (2023) 100222

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

Impact of the COVID-19 pandemic on temporal trends of biological indicators of autoimmunity

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ARTICLE INFO

Handling editor: Y Renaudineau

Keywords:
COVID-19
SARS-CoV-2
Autoimmunity
Autoantibody
Diabetes
Antiphospholipid

ABSTRACT

Background and objective: Coronavirus Disease 2019 (COVID-19) has been associated with the onset of autoimmune conditions, but whether this relationship is causal remains unknown, partly because robust evidence based on the detection of autoantibodies is lacking. This study explored the potential impact of COVID-19 pandemic on the temporal trends of autoimmunity.

Methods: Retrospective analysis of all consecutive autoimmune tests performed at one central laboratory at a University hospital, operating services for 18 other hospitals and clinical laboratories in Belgium, from January 01, 2015 to May 31, 2022. Longitudinal changes in the positivity rates of autoimmunity tests were analyzed, *i.e.* before and after the onset of the COVID-19 pandemic (March 11, 2020). The tests notably included the detection of autoantibodies associated with type 1 diabetes, thyroid diseases, connective tissue diseases, antiphospholipid syndrome, vasculitis and other organ-specific conditions. Kendall rank correlation test was applied to assess temporal trends.

Results: Over a period of 89 months, a total of 301,720 consecutive tests for 24 different autoantibodies among 87,674 unique patients were performed (87% adults, 68% women, mean age 44 ± 20 years). Overall, 52,862 (18%) tests returned positive, with positivity rates for each test ranging between 1% and 46%. No increase in the positivity rate of autoimmunity tests was observed after the start of the pandemic.

Conclusion: The onset of the COVID-19 pandemic was not associated with increased positivity rates of a large panel of autoimmune tests. Whether the higher incidence of autoimmune disorders associated with COVID-19 reflects detection bias or reverse causality, or is linked to seronegative autoimmune disorders requires further investigation.

1. Introduction and objective

In addition to potentially life-threatening pneumonia and various systemic manifestations, Coronavirus Disease 2019 (COVID-19) has also been associated with the onset of autoimmune conditions [1]. The association is supported by the results from three large cohort studies, which included almost 2 million individuals from Europe and the United States and reported a 20–40% increase in the risk of autoimmune disorders among COVID-19 patients compared to matched controls [2–4]. A broad spectrum of autoimmune manifestations has been reported after COVID-19, with a particularly high risk of new-onset diabetes and connective tissue diseases, and the presence of antiphospholipid antibodies has been suggested to contribute to thrombotic complications in patients with SARS-CoV-2 infection [5].

However, the retrospective design of these studies; potential detection and misclassification biases; possible reverse causality (*i.e.* susceptibility to more severe COVID-19 in patients with undiagnosed autoimmune diseases); and the lack of robust evidence including the detection of autoantibodies preclude any formal conclusion about the causal relationship between COVID-19 and the increased incidence of autoimmunity.

To shed light on the association between COVID-19 and occurrence of autoimmunity, we assessed temporal trends in the incidence of a wide range of biological indicators of autoimmunity between 2015 and 2022, and evaluated whether the onset of the pandemic was associated with increased positivity rates for autoimmunity tests.

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https://doi.org/10.1016/j.jtauto.2023.100222
Received 7 October 2023; Received in revised form 16 November 2023; Accepted 23 November 2023
Available online 29 November 2023

Table 1
Techniques and positivity cut-off values of autoimmune tests.

	Technique	Cut-off
Hematology		
Anti-β2-Glycoprotein-I IgG	ELISA	>7 U/mL
Anti-Cardiolipin IgG	ELISA	>10 U-GPL/mL
Lupus Anticoagulant	Chronometric	–
Anti-Platelet-Factor-4 IgG	ChLIA	>2.5 U/mL
Endocrinology		
Anti-GAD65 Ab	ELISA	>10 U/mL
Anti-IA2 Ab, Jan 2015-Feb 2017	RIA	>1.5 U/mL
Anti-IA2 Ab, Mar 2017-May 2022	ELISA	>10 IU/mL
Anti-Thyroid Peroxidase Ab	ECLIA	>34 U/mL
Anti-Thyroglobulin Ab	ECLIA	>115 U/mL
Anti-TSH Receptor Ab	TRACE	≥1.8 IU/L
Nephrology/Rheumatology		
Antinuclear Ab	IIF	≥1/80
Anti-CCP Ab	ELISA	≥10 U/mL
Anti-GBM Ab	ELISA	≥7 AU
Anti-PR3 Ab	ELISA	≥2 AU
Anti-MPO Ab	ELISA	≥3.5 AU
Anti-PLA2R Ab	ELISA	≥20 RU/mL
Rheumatoid Factor Test	ELISA	≥14 IU/mL
Hepato-Gastroenterology		
Anti-Gliadin IgA	ELISA	≥7 U/mL
Anti-Gliadin IgG	ELISA	≥7 U/mL
Anti-Transglutaminase IgA	ELISA	≥7 U/mL
Anti-LKM Ab	IIF	≥1/40
Anti-Mitochondria M2 Ab	IIF	≥1/40
Neurology		
Anti-Aquaporin-4 Ab	IIF	–
Anti-MAG Ab	Western Blot	–
Anti-Striated Muscle Ab	IIF	≥1/40

IgG, immunoglobulin G; GAD65, glutamic acid decarboxylase 65 kDa isoform; Ab, antibody; IA2, islet antigen-2; TSH, thyroid stimulating hormone; CCP, cyclic citrullinated peptides; GBM, glomerular basement membrane; PR3, proteinase 3; MPO, myeloperoxidase; PLA2R, phospholipase A2 receptor; IgA, immunoglobulin A; LKM, liver and kidney microsome; MAG, myelin-associated glycoprotein; ELISA, enzyme-linked immunosorbent assay; ChLIA, chemiluminescence immunoassay; RIA, radioimmunoassay; ECLIA, electrochemiluminescence immuno assay; TRACE, time resolved amplified cryptate emission; IIF, indirect immunofluorescence.

2. Methods

We retrospectively collected the results of consecutive autoimmune tests analyzed at the reference laboratory of the Cliniques universitaires Saint-Luc, operating services for 18 other hospitals and clinical laboratories in Belgium, between January 01, 2015 and May 31, 2022, ordered by 7329 different physicians (Table 1). Positivity rates were compared before and after the start of the COVID-19 pandemic (March 11, 2020). Kendall rank correlation was applied to assess temporal trends. All autoimmunity assays remained similar during the period of observation, except for anti-IA2 antibodies, for which radioimmunoassay was replaced by enzyme-linked immunosorbent assay in March 2017.

Statistical analyses were performed with Stata v17 and temporal trends were graphed using GraphPad Prism v9. The study was conducted in accordance with the World Medical Association's Declaration of Helsinki; the Belgian law related to experiments in humans dated May 7, 2004; the General Data Protection Regulation 2016/679; and the Belgian law of July 30, 2018, regarding the protection of personal data. The Ethical Review Board of Cliniques universitaires Saint-Luc/UCLouvain approved the study and waived the need for an informed consent because of its retrospective design (ref. 2022/09MAR/112).

3. Results

Over a period of 89 months, the clinical laboratory of the Cliniques universitaires Saint-Luc, in Brussels, Belgium, performed 301,720 consecutive tests for 24 different autoantibodies among 87,674 unique patients (Table 2). The total number of tests remained stable during the study period (~40,000 tests per year, ~3300 tests per month). Eighty-seven percent of the patients were adults; mean age (SD) was 44 years (20) and 68% were women. The tests notably included the detection of autoantibodies associated with type 1 diabetes, thyroid diseases, connective tissue diseases, antiphospholipid syndrome, vasculitis and other organ-specific conditions. Overall, 52,862 (18%) tests returned positive, with positivity rates for each autoantibody ranging between 1% and 46% (Table 2).

Considering all tests either together or separately, the temporal trends showed no increase in the positivity rate of autoantibodies after the start of the pandemic (Fig. 1, Table 3). Positivity rates before *vs.* after the start of the COVID-19 pandemic were 18% *vs.* 16% for all autoimmune tests considered together; 7–13% *vs.* 6–11% for the different antiphospholipid antibodies; 19–21% *vs.* 13–14% for autoantibodies associated with type 1 diabetes; 45% *vs.* 46% for antinuclear antibodies; and 4–5% *vs.* 4% for anti-neutrophil cytoplasm antibodies, respectively (Fig. 2). Sex ratio (69% *vs.* 66% women) and mean (±SD) age at the time of testing (43 [±20] *vs.* 44 [±20]) were similar before *vs.* after the start of the COVID-19 pandemic. Of note, the positivity rate of some autoantibodies, notably those associated with type 1 diabetes, even declined over the study period.

4. Discussion

Using a large database of more than 300,000 consecutive tests among ~90,000 unique patients over a period of almost eight years, a comprehensive analysis of the temporal trends did not reveal any increase in the positivity rates of a panel of 24 different autoantibodies associated with common and rare autoimmune conditions after the start of the COVID-19 pandemic.

Our results are in line with previous observations which showed no increase in the overall positivity rate of autoimmunity tests in 2020 compared to 2019 [6]. This study, performed in 15 countries, covered a shorter period of time and analyzed a smaller panel of autoantibodies. The lack of increased positivity rates of autoimmune tests after the onset of the pandemic questions the potential causative role of SARS-CoV-2 in the development of new-onset autoimmunity and indirectly suggests that additional factors, including earlier detection or reverse causality, may contribute to the increased incidence of autoimmune disease after COVID-19. Indeed, many studies linking SARS-CoV-2 infection to autoimmune manifestations did not include non-COVID-19 patients with similar degree of disease severity as controls [7]. The lack of appropriate control groups prevents drawing any conclusion on the potential causality between SARS-CoV-2 infection and the appearance of autoimmune phenomena.

Although the incidence of diabetes has consistently been found to be

Table 2
Yearly numbers and positivity rates of autoimmunity among different organ systems.

	2015	2016	2017	2018	2019	2020	2021	01-05/2022	Total
Total	6115/37863 (16)	7601/39978 (19)	7321/41110 (18)	7499/41939 (18)	8332/43832 (19)	6496/36890 (18)	6681/42029 (16)	2817/18079 (16)	52862/301720 (18)
Hematology									
Anti-β2-Glycoprotein-I IgG	23/265 (9)	49/412 (12)	78/728 (11)	73/1082 (7)	75/1295 (6)	91/1428 (6)	116/2089 (6)	47/938 (5)	552/8237 (7)
Anti-Cardiolipin IgG	84/1298 (6)	112/1298 (9)	122/1391 (9)	92/1401 (7)	85/1488 (6)	110/1462 (8)	133/1872 (7)	54/818 (7)	792/11028 (7)
Lupus Anticoagulant	95/936 (10)	150/972 (15)	136/977 (14)	124/949 (13)	109/908 (12)	84/927 (9)	104/1022 (10)	67/478 (14)	869/7169 (12)
Anti-Platelet-Factor-4 IgG	12/211 (6)	18/174 (10)	11/138 (8)	13/160 (8)	16/169 (9)	18/217 (8)	20/266 (8)	6/113 (5)	114/1448 (8)
Endocrinology									
Anti-GAD65 Ab	146/647 (23)	132/650 (20)	100/591 (17)	107/584 (18)	111/690 (16)	95/642 (15)	169/1295 (13)	83/602 (14)	943/5701 (17)
Anti-Islet Antigen-2 Ab	46/166 (28)	41/179 (23)	29/157 (18)	29/159 (18)	33/173 (19)	27/173 (16)	41/318 (13)	15/131 (11)	261/1456 (18)
Anti-Thyroid Peroxidase Ab	2110/9563 (22)	2172/9574 (23)	2146/9582 (22)	2127/9425 (23)	2047/9324 (22)	1649/7661 (22)	1596/7962 (20)	617/3243 (19)	14464/66334 (22)
Anti-Thyroglobulin Ab	1107/5665 (20)	1193/5672 (21)	1154/5839 (20)	1130/5945 (19)	1046/5802 (18)	794/4449 (18)	730/4145 (18)	272/1655 (16)	7426/39172 (19)
Anti-TSH Receptor Ab	/	405/1675 (24)	632/2148 (29)	601/2383 (25)	604/2474 (24)	374/1628 (23)	416/1785 (23)	177/734 (24)	3209/12827 (25)
Nephrology/Rheumatology									
Antinuclear Ab	1483/4257 (35)	2346/4564 (51)	1908/4829 (40)	2178/5024 (43)	3002/5463 (55)	2295/4849 (47)	2326/5239 (44)	1018/2219 (46)	16556/36444 (45)
Anti-CCP Ab	159/1285 (12)	149/1250 (12)	145/1229 (12)	130/1396 (9)	161/1759 (9)	114/1381 (8)	157/1778 (9)	64/735 (9)	1079/10813 (10)
Anti-GBM Ab	4/210 (2)	29/220 (13)	15/240 (6)	11/255 (4)	8/237 (3)	15/274 (5)	16/443 (4)	0/167 (0)	98/2046 (5)
Anti-PR3 Ab	125/2346 (5)	120/2497 (5)	118/2687 (4)	130/2721 (5)	138/2729 (5)	119/2343 (5)	104/2536 (4)	44/1187 (4)	898/19046 (5)
Anti-MPO Ab	91/2346 (4)	79/2491 (3)	142/2686 (5)	124/2720 (5)	114/2731 (4)	92/2344 (4)	112/2538 (4)	44/1187 (4)	798/19043 (4)
Anti-PLA2R Ab	48/269 (18)	37/266 (14)	72/368 (20)	69/437 (16)	45/464 (10)	51/454 (11)	84/679 (12)	33/298 (11)	439/3235 (14)
Rheumatoid Factor Test	324/1774 (18)	297/1773 (17)	288/1886 (15)	340/2002 (17)	413/2383 (17)	280/1804 (16)	356/2329 (15)	178/1012 (18)	2476/14963 (17)
Hepato-Gastroenterology									
Anti-Gliadin IgA	60/974 (6)	44/879 (5)	34/724 (5)	24/416 (6)	35/402 (9)	16/285 (6)	32/550 (6)	13/267 (5)	258/4497 (6)
Anti-Gliadin IgG	51/973 (5)	27/694 (4)	19/453 (4)	27/747 (4)	64/1101 (6)	51/929 (5)	34/797 (4)	25/406 (6)	298/6100 (5)
Anti-Transglutaminase IgA	88/2634 (3)	85/2760 (3)	55/2400 (2)	55/2248 (2)	72/2340 (3)	60/1981 (3)	46/2118 (2)	32/950 (3)	493/17431 (3)
Anti-LKM Ab	2/780 (0.3)	5/719 (0.7)	3/724 (0.4)	1/704 (0.1)	3/678 (0.4)	6/477 (1.3)	1/411 (0.2)	7/178 (3.9)	28/4671 (0.6)
Anti-Mitochondria M2 Ab	34/665 (5)	40/652 (6)	33/696 (5)	44/678 (6)	31/701 (4)	25/610 (4)	18/710 (3)	6/304 (2)	231/5016 (5)
Neurology									
Anti-Aquaporin-4 Ab	–	0/2 (0)	1/104 (1)	4/126 (3)	3/140 (2)	4/130 (3)	2/232 (1)	1/110 (1)	15/844 (2)
Anti-MAG Ab	–	0/3 (0)	3/70 (4)	3/86 (3)	5/98 (5)	6/92 (7)	11/285 (4)	2/126 (2)	30/760 (4)
Anti-Striated Muscle Ab	23/599 (4)	71/602 (12)	77/463 (17)	63/291 (22)	112/283 (40)	120/350 (34)	57/630 (9)	12/221 (5)	535/3439 (16)

Results are expressed as the number of positive tests/total tests (positivity rate, %). IgG, immunoglobulin G; GAD65, glutamic acid decarboxylase 65 kDa isoform; Ab, antibody; TSH, thyroid stimulating hormone; CCP, cyclic citrullinated peptides; GBM, glomerular basement membrane; PR3, proteinase 3; MPO, myeloperoxidase; PLA2R, phospholipase A2 receptor; IgA, immunoglobulin A; LKM, liver and kidney microsome; MAG, myelin-associated glycoprotein.

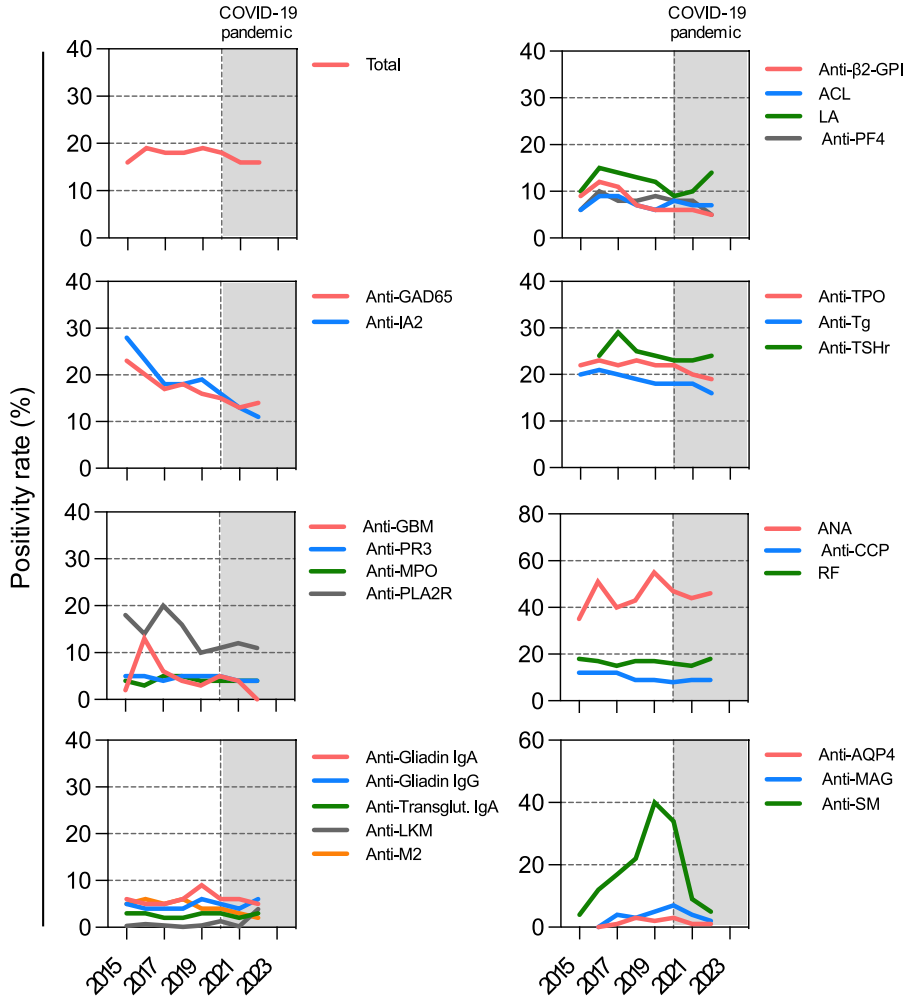

Fig. 1. Temporal trends in the positivity rates of autoantibodies. Anti-β2-GPI: Anti-β2-Glycoprotein-I IgG; ACL: Anti-Cardiolipin IgG; LA: Lupus Anticoagulant; Anti-PF4: Anti-Platelet-Factor-4 IgG; Anti-GAD65: Anti-Glutamic Acid Decarboxylase 65-kDa Isoform Antibody; Anti-IA2: Anti-Islet Antigen-2 Antibody; Anti-TPO: Anti-Thyroid Peroxidase Antibody; Anti-Tg: Anti-Thyroglobulin Antibody; Anti-TSHr: Anti-Thyroid Stimulating Hormone Receptor Antibody; Anti-GBM: Anti-Glomerular Basement Membrane; Anti-PR3: Anti-Proteinase 3 Antibody; Anti-MPO: Anti-Myeloperoxidase Antibody; Anti-PLA2R: Anti-Phospholipase A2 Receptor Antibody; ANA: Antinuclear Antibody; Anti-CCP: Anti-Cyclic Citrullinated Peptides Antibody; RF: Rheumatoid Factor Test; Transglut: Transglutaminase; Anti-LKM: Anti-Liver and Kidney Microsome Antibody; Anti-M2: Anti-Mitochondria M2 Antibody; Anti-AQP4: Anti-Aquaporin-4 Antibody; Anti-MAG: Anti-Myelin-Associated Glycoprotein Antibody; Anti-SM: Anti-Striated Muscle Antibody.

Table 3
Kendall correlation coefficients for changes in yearly positivity rates of autoantibodies.

	Kendall's tau-a	*P*-value
Total	−0.25	0.43
Hematology		
Anti-β2-Glycoprotein-I IgG	−0.75	0.01
Anti-Cardiolipin IgG	−0.11	0.80
Lupus Anticoagulant	−0.21	0.53
Anti-Platelet-Factor-4 IgG	−0.21	0.51
Endocrinology		
Anti-GAD65 Ab	−0.86	0.004
Anti-IA2 Ab	−0.82	0.006
Anti-Thyroid Peroxidase Ab	−0.54	0.06
Anti-Thyroglobulin Ab	−0.79	0.007
Anti-TSH Receptor Ab	−0.43	0.20
Nephrology/Rheumatology		
Antinuclear Ab	0.29	0.39
Anti-CCP Ab	−0.54	0.05
Anti-GBM Ab	−0.32	0.32
Anti-PR3 Ab	−0.32	0.23
Anti-MPO Ab	−0.04	1.00
Anti-PLA2R Ab	−0.46	0.13
Rheumatoid Factor Test	−0.18	0.60
Hepato-Gastroenterology		
Anti-Gliadin IgA	0.04	1.00
Anti-Gliadin IgG	0.21	0.50
Anti-Transglutaminase IgA	−0.04	1.00
Anti-LKM Ab	0.25	0.45
Anti-Mitochondria M2 Ab	−0.68	0.02
Neurology		
Anti-Aquaporin-4 Ab	0.14	0.75
Anti-MAG Ab	0.19	0.65
Anti-Striated Muscle Ab	0.14	0.71

IgG, immunoglobulin G; GAD65: Glutamic Acid Decarboxylase 65 kDa isoform; Ab, antibody; IA2, islet antigen-2; TSH, thyroid stimulating hormone; CCP, cyclic citrullinated peptides; GBM, glomerular basement membrane; PR3, proteinase 3; MPO, myeloperoxidase; PLA2R, phospholipase A2 receptor; IgA, immunoglobulin A; LKM, liver and kidney microsome; MAG, myelin-associated glycoprotein.

increased in patients with COVID-19 [8–10], autoimmunity might not be the main driver of diabetes in this setting. Recent observations from a multinational prospective cohort study, involving 4586 teens (9–15 years of age) with systematic longitudinal testing for both SARS-CoV-2 and type 1 diabetes, failed to detect any increased islet autoimmunity or type 1 diabetes after COVID-19 [11]. Multilevel data also evidenced that SARS-CoV-2 causes a direct toxicity to pancreatic β-islet cells and adipocytes, thereby reducing adiponectin secretion and possibly leading to insulin resistance [12,13].

We did not find an increase in positivity rates of the main antiphospholipid antibodies after the start of the COVID-19 pandemic. Previous studies, which reported a prevalence of antiphospholipid antibodies of 5–71% in SARS-CoV-2 infected patients, lacked appropriate control groups, included a very small number of participants and, more importantly, failed to show any robust association between antiphospholipid positivity and severe COVID-19 or thrombosis [14]. Again, alternative mechanisms including increased expression of endothelial adhesion molecules, platelet activation, generation of neutrophil extracellular traps, and activation of the complement system have been shown to contribute to the development of thrombotic complications in COVID-19, irrespective of antiphospholipid antibodies [15].

The strengths of our study include its original design based on the assessment of positivity rates of autoimmune tests, and the unbiased approach and the large number of consecutive tests performed at a central laboratory over a period of eight years. We also acknowledge some limitations including the retrospective design, absence of information about pre-existing autoimmune disease, or absence of correlation with COVID-19 test results. Our approach, solely based on biological indicators of autoimmunity, does not allow addressing the issue of seronegative forms of autoimmune diseases.

In summary, the onset of the COVID-19 pandemic did not influence the temporal trends of a large panel of biological indicators of autoimmunity. Whether the higher incidence of autoimmune disorders associated with COVID-19 reflects detection bias or reverse causality, or is linked to seronegative autoimmune disorders requires further investigation.

Author contributions

All authors contributed to the conception and design of the study. GZ collected data. JM performed statistical analysis. EV and JM wrote the manuscript, then all authors contributed, finalized and approved the article for publication.

List of participating centers: Cliniques universitaires Saint-Luc (Brussels, Belgium); Centre Hospitalier Valida (Berchem-Sainte-Agathe, Belgium); Clinique Saint-Pierre Ottignies (Ottignies, Belgium); Centre Médical Medibois (Woluwe-Saint-Pierre); Centre Hospitalier de Mouscron (Mouscron); Grand Hôpital de Charleroi (Charleroi); Laboratoire Luc Olivier (multiple locations in Belgium); Centre Hospitalier Nord-Ardennes (Libramont-Chevigny, Belgium); CHU UCL Namur (Namur); Hôpital de Braine l'Alleud-Waterloo (Braine-l'Alleud); Algemeen Klinisch Labo (Multiple locations in Belgium); Hôpital Delta (Auderghem); Laboratoire Bauduin (Enghien); Universitair Ziekenhuis Brussel (Jette); Algemeen Ziekenhuis Delta (Roeselare); Hôpital Civil Marie Curie (Charleroi); Centre médical Laennec (Woluwe-Saint-Lambert); Clinique Notre-Dame de Grâce (Gosselies).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E. Van Regemorter reports speaker honoraria for Baxter and AstraZeneca and travel grants from Vifor Pharma, Astellas and Pharmacosmos; all outside the submitted work. J. Morelle reports consultancy for Alexion Pharmaceuticals, AstraZeneca, Bayer, GlaxoSmithKline, and Sanofi-Genzyme; research funding from Alexion Pharmaceuticals, AstraZeneca, and Baxter Healthcare; advisory or leadership roles for Alexion Pharmaceuticals, AstraZeneca, Bayer, Sanofi-Genzyme, and Versantis; speaker honoraria for AstraZeneca, Baxter Healthcare, and Fresenius

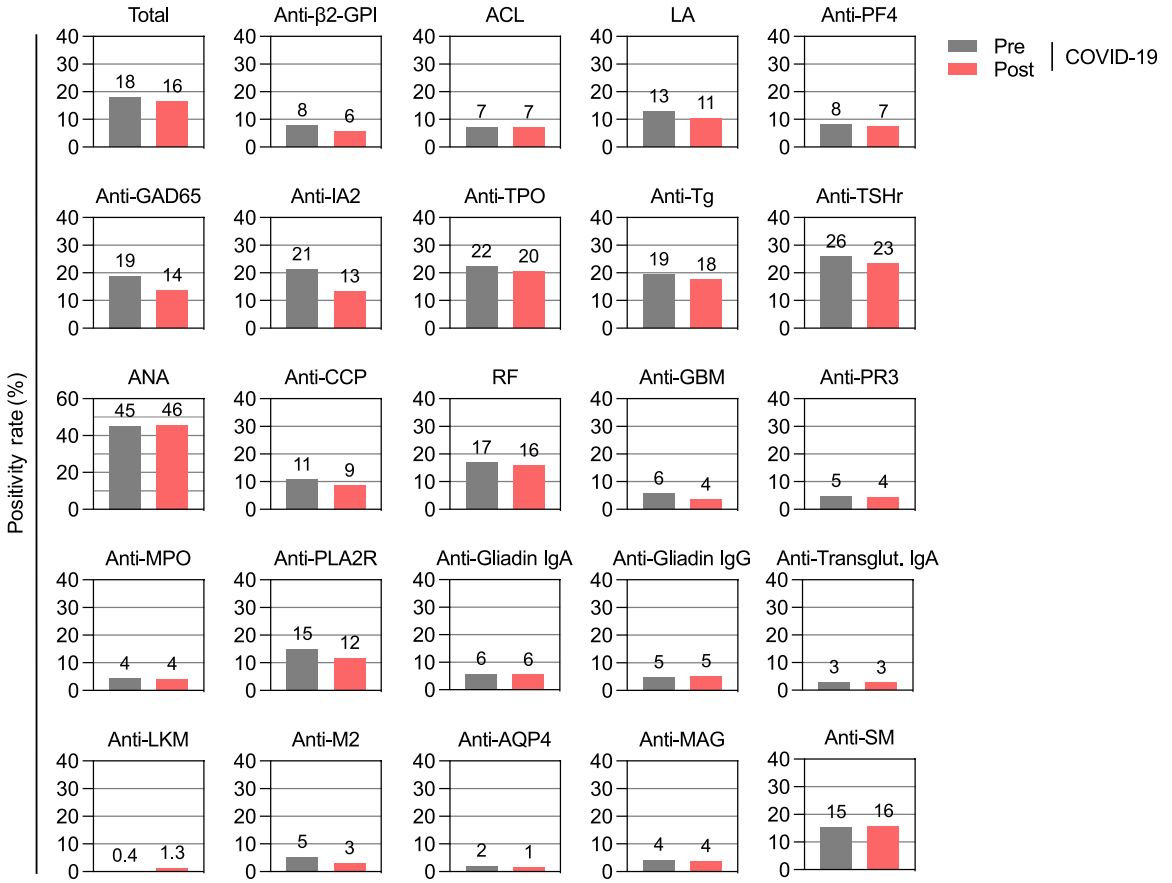

Fig. 2. Positivity rates of autoantibodies before and after the start of the COVID-19 pandemic. Anti-β2-GPI: Anti-β2-Glycoprotein-I IgG; ACL: Anti-Cardiolipin IgG; LA: Lupus Anticoagulant; Anti-PF4: Anti-Platelet-Factor-4 IgG; Anti-GAD65: Anti-Glutamic Acid Decarboxylase 65-kDa Isoform Antibody; Anti-IA2: Anti-Islet Antigen-2 Antibody; Anti-TPO: Anti-Thyroid Peroxidase Antibody; Anti-Tg: Anti-Thyroglobulin Antibody; Anti-TSHr: Anti-Thyroid Stimulating Hormone Receptor Antibody; Anti-GBM: Anti-Glomerular Basement Membrane; Anti-PR3: Anti-Proteinase 3 Antibody; Anti-MPO: Anti-Myeloperoxidase Antibody; Anti-PLA2R: Anti-Phospholipase A2 Receptor Antibody; ANA: Antinuclear Antibody; Anti-CCP: Anti-Cyclic Citrullinated Peptides Antibody; RF: Rheumatoid Factor Test; Transglut: Transglutaminase; Anti-LKM: Anti-Liver and Kidney Microsome Antibody; Anti-M2: Anti-Mitochondria M2 Antibody; Anti-AQP4: Anti-Aquaporin-4 Antibody; Anti-MAG: Anti-Myelin-Associated Glycoprotein Antibody; Anti-SM: Anti-Striated Muscle Antibody.

Medical Care; funding from the National Fund for Scientific Research (FRS-FNRS, Brussels, Belgium), the Association pour l'Information et la Recherche sur les Maladies Rénales Génétiques (AIRG, Brussels, Belgium), and the Saint-Luc Foundation (Brussels, Belgium); and travel grants from Sanofi-Genzyme and Vifor Pharma; all outside the submitted work. All other authors do not report any conflict of interest.

Data availability

Data will be made available on request.

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