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Clinical relevance of serum α-L-fucosidase activity in the SARS-CoV-2 infection

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ABSTRACT

Background and aims: The reduced fucosylation in the spike glycoprotein of SARS-CoV-2 and the IgG antibody has been observed in COVID-19. However, the clinical relevance of α-L-fucosidase, the enzyme for defucosylation has not been discovered.
Materials and methods: 585 COVID-19 patients were included to analyze the correlations of α-L-fucosidase activity with the nucleic acid test, IgM/IgG, comorbidities, and disease progression.
Results: Among the COVID-19 patients, 5.75% were double-negative for nucleic acid and antibodies. All of them had increased α-L-fucosidase, while only one had abnormal serum amyloid A (SAA) and C-reactive protein (CRP). The abnormal rate of α-L-fucosidase was 81.82% before the presence of IgM, 100% in the presence of IgM, and 66.2% in the presence of IgG. 73.42% of patients with glucometabolic disorders had increased α-L-fucosidase activity and had the highest mortality of 6.33%. The increased α-L-fucosidase was observed in 55.8% of non-severe cases and 72.9% of severe cases, with an odds ratio of 2.118. The α-L-fucosidase mRNA was irrelevant to its serum activity.
Conclusion: The change in α-L-fucosidase activity in COVID-19 preceded the IgM and SAA and showed a preferable relation with glucometabolic disorders, which may be conducive to virus invasion or invoke an immune response against SARS-CoV-2.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious viral pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The present researches focus on the infectivity of SARS-CoV-2 and vaccine development [2–5], which mainly target the heavily glycosylated spike (S) protein and IgG/IgM antibodies [6,7]. A recent study demonstrated an unusual fucosylated LacdiNAc in the receptor-binding domains of the spike protein [8]. Reduced fucosylation was also found in a specific Fc domain of IgG antibodies in COVID-19 patients that enhanced the interactions with the activating FcγR, FcγRIIIa [9]. These findings indicated the alteration of fucosylation is not only involved in the infectivity of viruses but also impacts the immune response to SARS-CoV-2 infection. α-L-fucosidase is the enzyme used to catalyze the hydrolytic removal of L-fucose from the fucosylated glycans in the glycoproteins and glycolipids [10]. Removal of fucose from the airway mucus not only impaired the wound closure of the airway [11] but also regulated the function of immune cells to defense against bacteria and viruses [12,13]. Therefore, the alteration of α-L-fucosidase activity may be a novel pathophysiological mechanism or potential therapeutic target for COVID-19. However, the correlation between SARS-CoV-2 infection and the change in serum α-L-fucosidase activity has not been reported. This study was designed to discover the clinical relevance of α-L-fucosidase activities in COVID-19 patients.

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2. Materials and methods

2.1. Data collection

We retrospectively reviewed the clinical records, laboratory data, and chest x-rays or CT scans for all patients in the Hubei Integrated Traditional Chinese and Western Medicine Hospital, from December 26, 2019, to March 9, 2020. A total of 585 cases were included in this study who were diagnosed according to the "Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment" published by the China National Health Committee. The diagnosis and classification of comorbidities in 585 COVID-19 patients are provided in the Supplementary Materials. Patients who met any of these three criteria were defined as severe case. (1) breathlessness, respiratory rate $\geq$ 30 times/minute; (2) In a resting state, blood oxygen saturation $\leq$ 93%; (3) arterial oxygen partial pressure (PaO2)/ fraction of inspired oxygen (FiO2) $\leq$ 300 mmHg. The project was approved by the hospital's ethics committee (ZE2020-027-01).

2.2. Laboratory tests

An automated hematology analyzer was used to perform blood count (Sysmex Corporation). Analysis of peripheral blood lymphocyte subsets was performed by BD FACSCanto II (Becton, Dickinson, and Company). The clinical biochemical analytes were measured on Roche Cobas 701 (Roche Diagnostics). In particular, the SAA and CRP measurements were performed based on latex immunoturbidimetry (Guangzhou Weimi Bio-Tech Co., Ltd., and SEKISUI MEDICAL CO., LTD).

The novel coronavirus (2019-nCov) Ab test (Colloidal Gold) (Innovita Biological Technology Co. Ltd) was used to detect the IgM/IgG antibody in the serum. The SARS-CoV-2 was detected in the nasal swab or throat swab specimens based on a multiple fluorescence RT-PCR method (BioPerfectus technologies, Jiangsu). The positive criteria were Ct $\leq$ 37.

2.3. Performance evaluation of serum α-L-fucosidase activity

The serum α-L-fucosidase activity was quantified using MG-2-chloro-4-nitrobenzene-α-L-fucoside (CNPF) as the substrate (Maccura Biotechnology Co., Ltd) on Roche Cobas 701[14,15]. Before clinical use, the performance evaluation of this assay was executed in accordance with the relevant Clinical and Laboratory Standards Institute guidelines protocols. The details were provided in the Supplementary Materials. All testing parameters met the requirements of the manufacturer. Briefly, the within-run CVs were 0.43% and 0.35%, and the total CVs were 1.36% and 0.53% at two levels of quality controls, respectively. The linear analysis showed a good correlation over the entire range tested ($y = 1.0028x - 1.529$, $R^2 = 0.9996$, from 1 to 150 U/L). The clinical reportable range was 0.00–2234.13 U/L. All sera from twenty healthy individuals were within the reference interval (<40 U/L).

2.4. GEO database analysis

To determine the source of α-L-fucosidase in COVID-19 patients and to compare it with that in patients with HCC, we downloaded a dataset from the GEO database to analyze the expression levels of α-L-fucosidase mRNA. The differential expression for α-L-fucosidase mRNA (FUCA 1 and FUCA 2) was analyzed using the Deseq2 package and limma of R software. Finally, the logFc and *P* values of FUCA 1 and FUCA 2 were calculated.

2.5. Statistical analysis

The data are expressed as percentage (%) or median (IQR). For categorical data, we used the chi-square test or Fisher's exact test to compare the proportions of patients with abnormal variables or in different groups. For variable data, an independent *t*-test or Wilcoxon–Mann–Whitney test was used to compare the median levels of the laboratory parameters. The correlation between α-L-fucosidase activity and other variables was performed with Spearman correlation analysis. The odds ratios (OR) and the 95% confidence intervals were calculated by using logistic regression. We used GraphPad Prism 8.0.2 to draw a forest plot of the risk factors. The statistical analysis was performed using SPSS 19.0 with a two-sided statistically significant p-value < 0.05.

3. Results

3.1. Occurrence time of increased α-L-fucosidase activity in COVID-19 patients

Complete data of nucleic acid and antibodies were only available in 87 cases, of which 75.86% were negative for nucleic acid test because the serum antibodies were used as an effective adjunctive to the real-time reverse-transcription polymerase chain reaction (RT-PCR) test in these patients at that time. Based on the occurrence time of viral RNA and its serum antibodies [16], we divided these patients into nine situations. In this study, 5.75% of the patients were double-negative for nucleic acid and antibodies, and were defined as clinically confirmed cases. All these patients had increased serum α-L-fucosidase activity, while only one patient had abnormal CRP and SAA (Table 1). The abnormal rates of serum α-L-fucosidase activity were 81.82% before the presence of IgM, 100% in the presence of IgM, and 66.2% in the presence of IgG (Fig. 1). Nevertheless, the trends of SAA and CRP were reverse; they increased along with the appearance of IgM and IgG (Fig. 1). In addition, the first nucleic acid test had a good correlation with serum α-L-fucosidase activity and SAA (Table 1). Moreover, patients with detectable viral RNA were inclined to develop into severe cases that showed slight correlations with the timing of detection or antibodies (Table 1). Our findings indicated that the elevation of α-L-fucosidase activity may precede the IgM and SAA.

3.2. α-L-fucosidase activity in patients with different comorbidities

Previous studies indicated that the disease status may be responsible for the alterations of α-L-fucosidase activity [17]. In this study, the increased α-L-fucosidase activity was observed in COVID-19 patients with glucometabolic disorders, whether a single comorbidity or those co-existing with other illnesses (Table 2). They showed a significantly higher α-L-fucosidase activity than the patients without comorbidities (Figure S1). More than 50% of these patients developed into severe cases who also had higher mortality. However, the α-L-fucosidase activity was not different in the severe groups.

3.3. Correlation of serum α-L-fucosidase activity with clinical severity of COVID-19

Increased serum α-L-fucosidase activity was observed in 55.80% of non-severe cases and 72.90% of severe cases with a median level of 44.50 U/L and 67.15 U/L, respectively (Table S1 and Table S2). All significant variables were further included in the relative risk analysis. α-L-fucosidase activity showed a relatively low correlation with the severity of COVID-19, with an odds ratio of only 2.118 (Fig. 2). The most relevant risk factors associated with the disease severity were SAA, CRP, and eosinophil, with odds ratios of 5.890, 5.293, and 5.114, respectively (Fig. 2). Moreover, α-L-fucosidase showed a significantly positive correlation with fibrinogen, SAA, and CRP (Table S3).

3.4. Expression levels of α-L-fucosidase mRNA in different tissues and cells infected with SARS-CoV-2 and in patients with HCC

To find out the cause of elevated α-L-fucosidase activity, we next investigated gene expression profiles in datasets from the GEO databases

Table 1
The correlation of α-L-fucosidase activity with serum IgM/IgG and nucleic acid of SARS-CoV-2, inflammatory markers, and the severity of the disease.

	Antibodies		Nucleic acid tests						
States	IgM	IgG	First[a]	Second[b]	No.	CRP	SAA	AFU	Severity
I	–	–	–	–	5	1/5	1/5	5/5	0/5
II	–	–	+		3	1/3	3/3	3/3	2/3
III	+	–	+		2	1/2	2/2	2/2	0/2
IV	+	–	–	–	3	1/3	1/3	3/3	0/3
V	–	–	–	+	3	1/3	2/3	1/3	1/3
VI	+	+	+		16	14/15	15/15	14/16	11/16
VII	+	+	–	+	10	6/10	7/10	6/10	7/10
VIII	+	+	–	–	44	17/42	33/43	27/44	14/44
IX	–	+	–	–	1	0/1	0/1	0/1	0/1

[a] The first nucleic acid test was performed the same day or 1–2 days before the serological assays for SARS-CoV-2 infection. [b] The second nucleic acid test was performed 3–10 days after the first test or the serological assays. AFU, α-L-fucosidase activity.

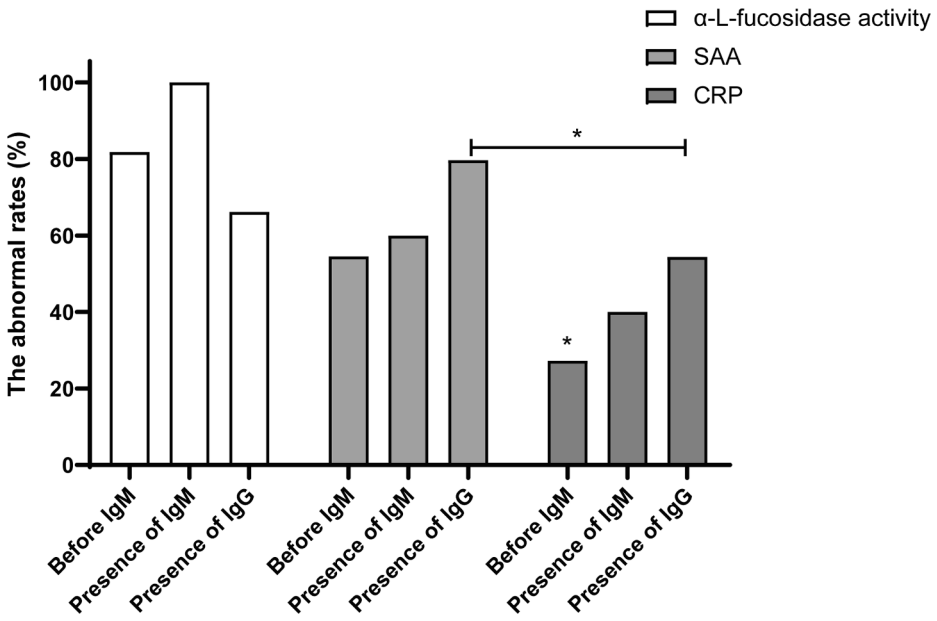

Fig. 1. The abnormal rates of α-L-fucosidase activity, SAA, and CRP at different stages of COVID-19. * $P < 0.05$ compared with α-L-fucosidase activity.

(Table 3). Unexpectedly, most tissues or cells from COVID-19 patients showed no expression or non-significant expression of α-L-fucosidase mRNA. The expression was even lower in the transformed lung alveolar (A549) cells, which were overexpressed ACE2 (Table 3). Although α-L-fucosidase was a specific biomarker of HCC, both types of α-L-fucosidase mRNA were undetected in one dataset of HCC. In another scRNA-seq, the expression of FUCA 1 was increased, but the change in FUCA 2 was the opposite (Table 3).

4. Discussion

The catastrophic outburst of COVID-19 has swept the world. Scientists are doing their part to contain this contagious virus by disclosing its pathogenesis and laboratory characteristics. Our study demonstrated that the elevation of α-L-fucosidase activity may precede the IgM and SAA and may have a close correlation with glucometabolic disorders.

The nucleic acid test and antibody detection are widely used in SARS-CoV-2 infection diagnosis, but high false-negative rates have been reported [18,19]. In our study, all the double-negative population had increased serum α-L-fucosidase activity. Up until now, the mechanism of its production and elevation has not been clarified [20]. It has been suggested that the expression and activity of α-L-fucosidase were fueled by the cytokines derived from the lymphocyte subset [14]. However, our results from GEO databases showed that serum α-L-fucosidase activity was not correlated with the expression levels of its mRNA in both COVID-19 and HCC, which was consistent with other studies [10,20,21]. In addition, the correlation coefficient of α-L-fucosidase activity and lymphocyte subsets was not inadequate. We speculate that the increased serum α-L-fucosidase activity may be related to the lysosome because the total α-L-fucosidase activity is mainly contributed by α-L-fucosidase 1 (an acid glycosidase located in lysosome) [10]. The acid glycosidase of lysosomal origin changes their activity when cells are fueled by external stimuli [22]. SARS-CoV can enter the cytoplasm through endocytosis/endosomes and use the enzyme in the lysosome to promote the fusion of the viral and host cell membrane [17]. From another perspective, the functional changes of the innate cells may be much earlier than the immune response after the virus invasion.

Previous studies showed that α-L-fucosidase could protect against bacterial infection by creating ligands for bacterial to bind in the airway, which increases susceptibility to pulmonary infection [23,24]. In COVID-19, both the spike protein of SARS-CoV-2 and its receptor, hACE2 showed unusual fucosylation in their binding sites that might assist in the virus-receptor interaction [8,25,26]. Moreover, a specific Fc domain of IgG antibodies in COVID-19 patients was characterized by reduced fucosylation, which enhances interactions with the activating FcγR, FcγRIIIa [9]. The enzyme responsible for the fucosylated glycan degradation is just α-L-fucosidase [10]. Therefore, the α-L-fucosidase in COVID-19 patients may be conducive to virus invasion or to invoke

Table 2
Increased α-L-fucosidase activity in 585 COVID-19 patients with different comorbidities.

Comorbidity	α-L-fucosidase increased	Median (IQR)	Severity	Severity with α-L-fucosidase increased	Death
None	95/171 (55.88%)	44.65 (43.15)	35/171 (20.59%)	25/35 (71.43%)	0/171 (0.00%)
CCD	74/132 (56.06%)	47.00 (47.30)	49/132 (37.12%) *	36/49 (73.47%)	5/132 (3.79%) *
GD	58/79 (73.42%) *	66.60 (39.60) *	43/79 (54.43%) *	32/43 (74.42%)	5/79 (6.33%) *
CCD + GD	61/87 (70.11%) *	61.80 (42.00) *	48/87 (55.17%) *	36/48 (75.00%)	2/87 (2.30%)
LD	14/22 (63.64%)	61.35 (37.08)	8/22 (36.36%)	7/8 (87.50%)	0/22 (0.00%)
CCD + GD + LD	24/27 (88.89%) *	72.50 (28.25) *	14/27 (51.85%) *	12/14 (85.71%)	1/27 (3.70%)
Others	38/67 (56.72%)	43.80 (38.60)	17/67 (25.37%)	9/17 (52.94%)	0/67 (0.00%)

* $P < 0.05$, compared with the patients without comorbidities. CCD, cardio-/cerebrovascular diseases; GD, glucometabolic disorder; LD, liver disease. Others contained diseases including allergic diseases, chronic gastritis, thyroid disease, and anemia.

immune response by reducing the fucosylation of N-glycans in either the spike protein and its receptor-ACE2 or the immune antibodies.

Decreased serum α-L-fucosidase activity has been reported in the type 2 diabetes mellitus [10]. However, our results demonstrated that COVID-19 patients with glucometabolic disorder had a higher abnormal rate of α-L-fucosidase and a higher risk of developing into severe cases. Previous studies showed that patients with diabetic complications had higher α-L-fucosidase [27,28], which was involved in the endothelial cell dysfunctions in diabetic microangiopathy [29]. In COVID-19, the loss of ACE2 vascular protective function by SARS-CoV-2 binding and the elevation of α-L-fucosidase activity might be a double whammy to the vasculature of the lung leading to increased mortality. This might explain why patients with diabetes are susceptible to SARS-CoV-2 infection and have higher mortality.

There were several limitations to this study. This study was just a clinical retrospective analysis. It lacked experimental data for the elevation of α-L-fucosidase activity. More patients with complete data on nucleic acid and antibodies are required to verify the exact chronological order of α-L-fucosidase and the detectable viral RNA/antibodies. Moreover, the change in serum α-L-fucosidase activity in other viral infections could be evaluated in further research.

5. Conclusion

The present study indicated that the elevation of serum α-L-fucosidase activity in COVID-19 may precede the IgM and SAA and are particularly associated with glucometabolic disorders. It may be a molecular mechanism conducive to virus invasion or a defense mechanism to invoke an immune response and inflammation against SARS-CoV-2.

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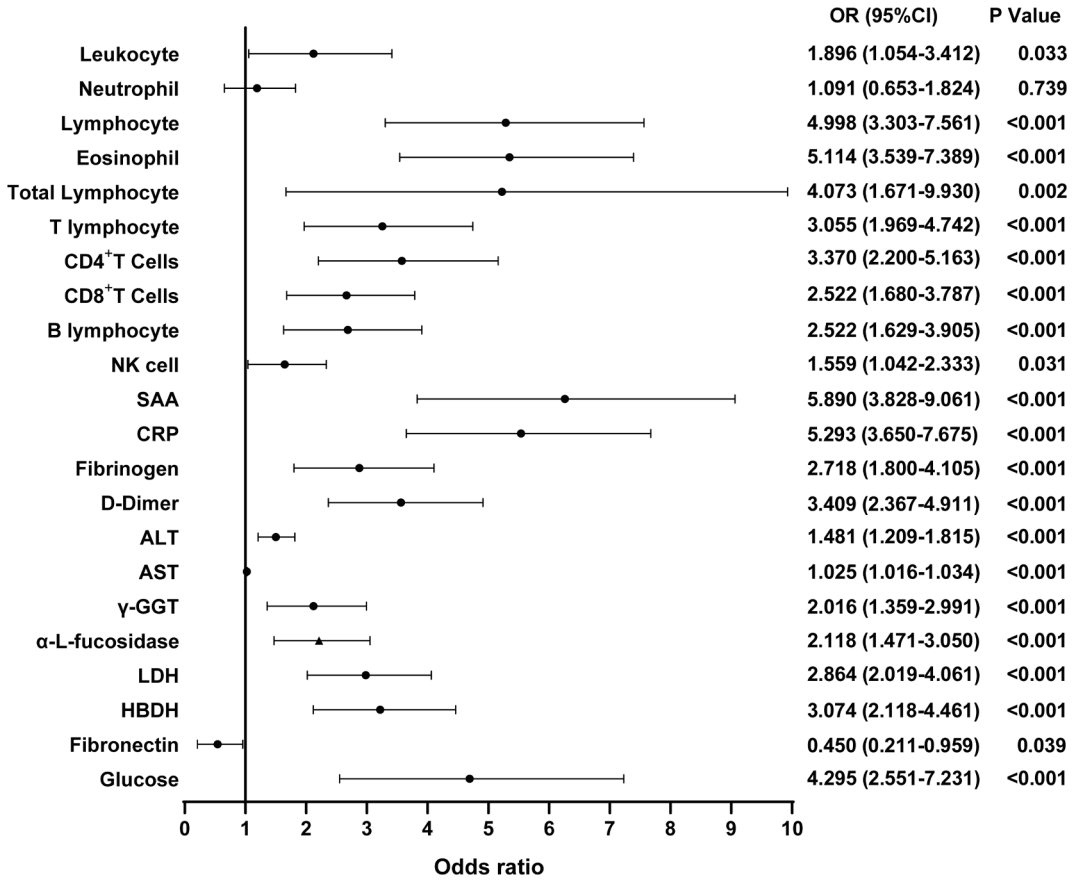

Fig. 2. The relative risk analysis of α-L-fucosidase activity and other laboratory parameters in predicting the disease severity. SAA, Serum amyloid A; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyltransferase; LDH, lactate dehydrogenase; HBDH, hydroxybutyrate dehydrogenase.

Table 3
The expression levels of α-L-fucosidase mRNA in different tissues and cells infected with SARS-CoV-2 and in patients with HCC.

No.	Types of cells or tissues	Comparison group	FUCA1		FUCA2	
			log_2 FC	*P*	log_2 FC	*P*
1	human PBMC derived dendritic cells	Mock vs SARS-CoV-2 infected	−0.122	1.000	0.050	1.000
	human PBMC derived macrophages		0.261	1.000	0.066	1.000
2	$CD8^+$ T cells	Healthy controls vs COVID-19 patients	–	–	–	–
3	BALF	Healthy controls vs COVID-19 patients	–	–	–	–
4	peripheral blood mononuclear cells (PBMCs)	Healthy controls vs COVID-19 patients	–	–	–	–
5	hPSC-derived liver Organoid	Mock vs SARS-CoV-2 infected	0.019	1.000	−0.062	1.000
6	transformed lung alveolar (A549) cells	Mock vs SARS-CoV-2 infected (MOI:2, 24hpi)	0.162	0.093	0.032	0.731
	A549 overexpressed human ACE2	Mock vs SARS-CoV-2 infected (MOI:2, 24hpi)	−0.597	<0.001	−1.276	<0.001
	transformed lung-derived Calu-3 cells	Mock vs SARS-CoV-2 infected (MOI:2, 24hpi)	−0.523	<0.001	−0.610	<0.001
	Human embryonic lung fibroblast (MRC5 cells)	Mock vs SARS-CoV-2 infected (MOI:3, 24hpi)	0.120	0.627	0.072	0.534
	post-mortem lung samples	Uninfected vs SARS-CoV-2 infected	1.111	0.177	−0.374	0.765
7	Liver samples of HCC	Benign adjacent liver vs primary tumor	–	–	–	–
8	Liver samples of HCC	Non-tumor liver vs primary tumor	1.075	<0.001	−0.265	<0.001
9	CD45 + immune cells for HCC patients	Adjacent liver vs primary tumor	0.002	0.998	0.344	0.432

The series number of the datasets (from 1 to 9) were GSE155106, GSE153931, GSE147143, GSE149689, GSE151803, GSE147507, GSE101432, GSE149614, and GSE140228. log_2 FC, log_2 Fold change; -, undetected; MOI, multiplicity of infection; hpi, hours post-incubation/inoculation (hpi); BALF, bronchoalveolar lavage fluid.

agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

En-yu Liang: Data curation, Methodology, Writing - original draft. **Guo-hua Li:** Data curation, Investigation, Resources. **Wen-gong Wang:** Data curation, Investigation, Resources, Validation. **Xin-min Qiu:** Software, Visualization. **Pei-feng Ke:** Formal analysis, Validation. **Min He:** Methodology, Supervision, Writing - review & editing. **Xian-zhang Huang:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2021.03.031.

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