Functional & Integrative Genomics (2022) 22:429–433
https://doi.org/10.1007/s10142-022-00841-z

SHORT COMMUNICATION

Organ-specific or personalized treatment for COVID-19: rationale, evidence, and potential candidates

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Received: 6 November 2021 / Revised: 3 March 2022 / Accepted: 4 March 2022 / Published online: 15 March 2022

Abstract

Although extrapulmonary manifestations of coronavirus disease 2019 (COVID-19) are increasingly reported, no effective therapeutic strategy for these multisystemic complications is available due to a poor understanding of the pathophysiology of COVID-19 multiorgan involvement. In this study, differentially expressed genes (DEGs) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected extrapulmonary organs including human pluripotent stem cells (hPSCs)-derived liver organoids and choroid plexus organoids besides transformed lung alveolar (A549) cells were analyzed. First, pathway enrichment analysis was done to compare the underlying biological pathways enriched upon SARS-CoV-2 infection in different organs. Then, these lists of DEGs were used in a connectivity map (CMap)-based drug repurposing experiment. Also, protein–protein interaction (PPI) network analysis was done to compare the associated hub genes. The results revealed different biological pathways and genes responsible for SARS-CoV-2 multisystemic pathogenesis based on the organ involved that highlighted the need for considering organ-specific treatments or even personalized therapy. Besides, some FDA-approved drugs were proposed as the potential therapeutic candidates for each infected cell line.

Keyword COVID-19; SARS-CoV-2; Organ-specific treatment; Personalized medicine; Drug repurposing

Coronavirus disease 2019 (COVID-19) was first reported in China rapidly spreading across the world. Although initial studies showed COVID-19 as a respiratory tract infection, recent investigations have revealed the multisystemic nature of this virus. However, the mechanism of SARS-CoV-2 multiorgan involvement is still unknown. Since available experiments analyzing SARS-CoV-2-infected extrapulmonary tissues are scant, we aimed to analyze transcriptomic signatures of SARS-CoV-2-infected cell lines belonging to different organs to compare the genes and their associated functional pathways responsible for viral pathogenesis in each organ. Since infectious microorganisms such as the SARS-CoV-2 virus change the host transcriptome and gene expression of the infected cells in the way optimal for their replication, gene expression analysis can help to understand the underlying mechanisms involved in SARS-CoV-2 pathogenesis and host immune system dysregulation through COVID-19. Besides, we set out to perform a drug repurposing experiment. Transcriptomic signatures of SARS-CoV-2-infected cells were compared with genomic signatures of cell lines treated with various compounds known as connectivity map (CMap). Results of the CMap analysis would be shown with a connectivity score for each drug-disease pair ranging from −1 to +1. A negative connectivity score shows that the compound can reverse the genomic signature of the disease; so, it can be proposed as the therapeutic option for the mentioned disease (Qu and Rajpal 2012).

Differentially expressed genes

Gene Expression Omnibus (GEO) database of National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/geo/) was searched for "COVID-19" or "SARS-CoV-2" related datasets. A total of 3200 datasets were found and 2500 of them were conducted on "homo sapiens." The datasets were manually searched for datasets that contained transcriptomic data of SARS-CoV-2-infected extrapulmonary organs. Seven datasets were identified. All

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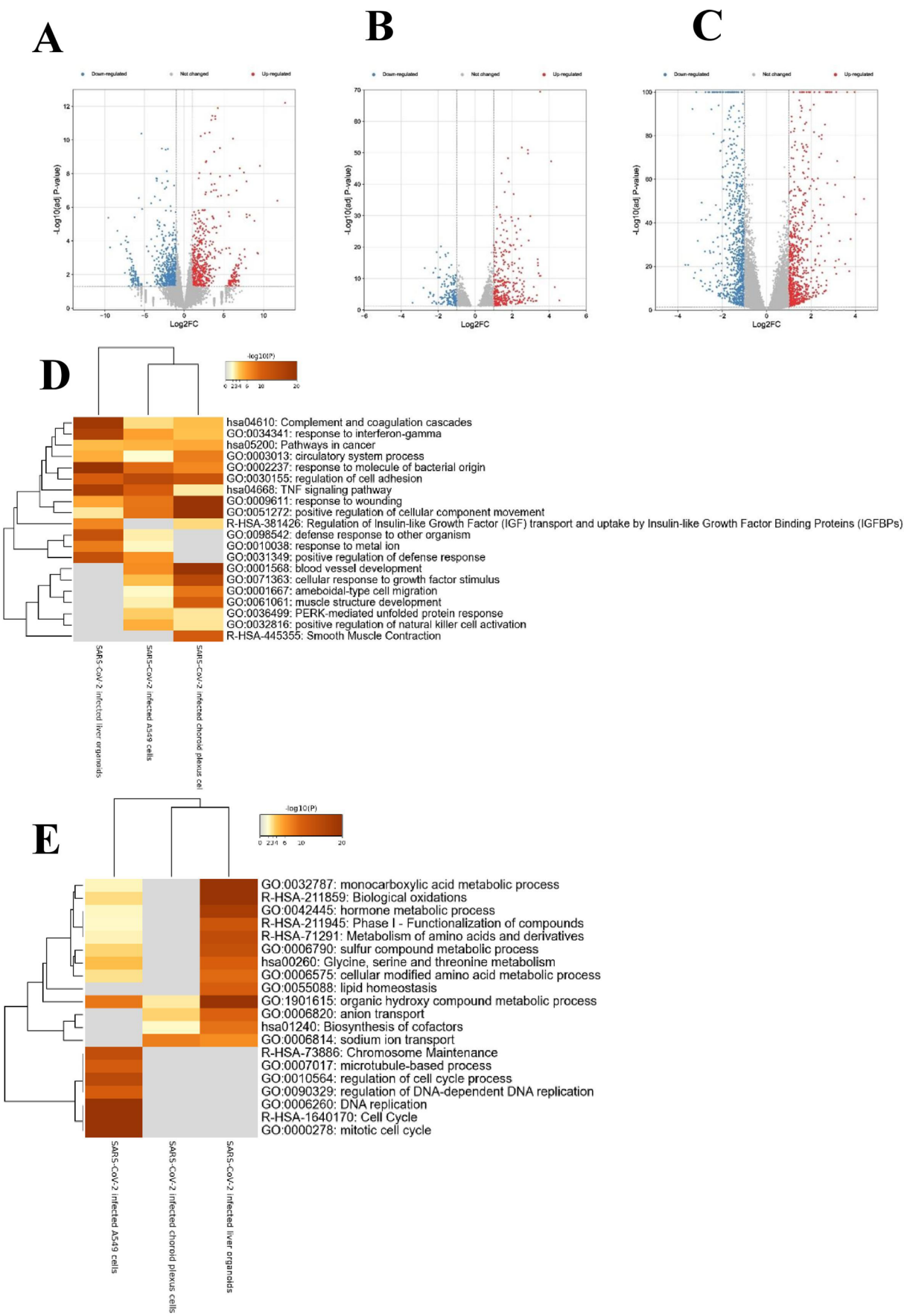
A
B
C
Down-regulated
Not changed
Up-regulated
-Log10(adj P-value)
Log2FC
D
-log10(P)
hsa04610: Complement and coagulation cascades
GO:0034341: response to interferon-gamma
hsa05200: Pathways in cancer
GO:0003013: circulatory system process
GO:0002237: response to molecule of bacterial origin
GO:0030155: regulation of cell adhesion
hsa04668: TNF signaling pathway
GO:0009611: response to wounding
GO:0051272: positive regulation of cellular component movement
R-HSA-381426: Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)
GO:0098542: defense response to other organism
GO:0010038: response to metal ion
GO:0031349: positive regulation of defense response
GO:0001568: blood vessel development
GO:0071363: cellular response to growth factor stimulus
GO:0001667: ameboidal-type cell migration
GO:0061061: muscle structure development
GO:0036499: PERK-mediated unfolded protein response
GO:0032816: positive regulation of natural killer cell activation
R-HSA-445355: Smooth Muscle Contraction
SARS-CoV-2 infected liver organoids
SARS-CoV-2 infected A549 cells
SARS-CoV-2 infected choroid plexus cel
E
-log10(P)
GO:0032787: monocarboxylic acid metabolic process
R-HSA-211859: Biological oxidations
GO:0042445: hormone metabolic process
R-HSA-211945: Phase I - Functionalization of compounds
R-HSA-71291: Metabolism of amino acids and derivatives
GO:0006790: sulfur compound metabolic process
hsa00260: Glycine, serine and threonine metabolism
GO:0006575: cellular modified amino acid metabolic process
GO:0055088: lipid homeostasis
GO:1901615: organic hydroxy compound metabolic process
GO:0006820: anion transport
hsa01240: Biosynthesis of cofactors
GO:0006814: sodium ion transport
R-HSA-73886: Chromosome Maintenance
GO:0007017: microtubule-based process
GO:0010564: regulation of cell cycle process
GO:0090329: regulation of DNA-dependent DNA replication
GO:0006260: DNA replication
R-HSA-1640170: Cell Cycle
GO:0000278: mitotic cell cycle
SARS-CoV-2 infected A549 cells
SARS-CoV-2 infected choroid plexus cells
SARS-CoV-2 infected liver organoids

◂**Fig. 1** Volcano plots of the differentially expressed genes (DEGs) in SARS-CoV-2-infected liver organoids (**A**), SARS-CoV-2-infected choroid plexus organoids (**B**), and SARS-CoV-2-infected A549 cells (**C**). Red and blue dots respectively indicated the upregulated and downregulated genes. Also, heatmaps of the top-level enriched biological terms across upregulated (**D**) and downregulated (**E**) genes of SARS-CoV-2-infected liver organoids, SARS-CoV-2-infected choroid plexus organoids, and SARS-CoV-2-infected A549 cells 24 hpi are shown colored by *p*-values. "Log10(*P*)" is the *p*-value in log base 10

these seven datasets were reviewed to select the datasets with the most similar protocols. Finally, GSE151803 and GSE157852 were selected.

The GSE157852 (Jacob et al. 2020) includes transcriptomic analysis of human-induced pluripotent stem cells (hiPSCs)-derived choroid plexus organoids that were mock-treated or infected with SARS-CoV-2 at 24 h post-infection (hpi) and the GSE151803 (Yang et al. 2020) contains the transcriptomic analysis of SARS-CoV-2-infected versus mock-treated human pluripotent stem cells (hPSCs)-derived cells including liver organoids 24 hpi. Besides, the GSE147507 dataset (Blanco-Melo et al. 2020) containing the transcriptomic profile of SARS-CoV-2-infected versus mock-treated transformed lung alveolar (A549) cells 24 hpi was also selected for comparison with the previously mentioned datasets.

For the differential expression analysis of these datasets, genes with p-value < 0.05 and $|\text{fold-change}| > 2$ were identified as differentially expressed genes (DEGs). A total of 1039 genes were identified to be modulated by SARS-CoV-2 infection in hPSCs-derived liver organoids (499 upregulated and 540 downregulated genes). For hiPSCs-derived choroid plexus organoids, a total of 460 genes were modulated by SARS-CoV-2 infection (317 upregulated and 143 downregulated genes) and for A549 cells, a total of 1458 genes were differentially expressed upon SARS-CoV-2 infection (690 upregulated and 768 downregulated genes). Volcano plots of the differentially expressed genes were plotted by http://www.bioinformatics.com.cn, a free online platform for data analysis and visualization (Fig. 1).

Gene analysis and functional pathway enrichment

The identified DEGs were analyzed with the Metascape web tool (http://metascape.org/) (Zhou et al. 2019). First, the upregulated genes of these three cell lines were uploaded separately. Pathway enrichment analysis was performed for each given gene list with the following ontology sources: Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway, Gene Ontology (GO) Biological Processes, Reactome Gene Sets, Canonical Pathways, and Comprehensive Resource of Mammalian Protein Complexes (CORUM). The pathways enriched in each gene list were furtherly compared. All the mentioned steps were repeated with the downregulated genes.

Upregulated genes of SARS-CoV-2-infected hPSCs-derived liver organoids were mainly enriched in "complement and coagulation cascades," "response to molecule of bacterial origin," and "response to interferon-gamma." However, the most significantly enriched pathways in upregulated genes of SARS-CoV-2-infected hiPSCs-derived choroid plexus organoids were "response to wounding," "positive regulation of cellular component movement," "blood vessel development," and "regulation of cell adhesion."

Then, downregulated genes were uploaded. For infected hPSCs-derived liver organoids, "biological oxidations," "monocarboxylic acid metabolic process," and "hormone metabolic process" were the most enriched biologic terms. Downregulated genes of infected hiPSCs-derived choroid plexus organoids were mainly enriched in "sodium ion transport" and "anion transport." However, downregulated genes of infected A549 cells were enriched in "DNA replication" and "cell cycle." Figure 1 demonstrates the mentioned results.

Considering all the mentioned results, SARS-CoV-2 infection would modify gene expression of the choroid plexus cells in a way leading to direct brain tissue damage and subsequent wound healing processes, stimulation of pathways related to blood vessel development (angiogenesis) that can predispose the infected tissue to brain hemorrhages due to anatomical instabilities of new vessels, and initiation of inflammatory responses through the enrichment of pathways responsible for locomotion, cell adhesion, and chemotaxis. Interestingly, pathways associated with ion channels, intracellular respiration, and small molecule catabolic processes were significantly downregulated in infected choroid plexus cells supporting the hypothesis of a decrease in CSF production in infected cases.

Besides, enrichment analysis of infected liver organoids showed upregulation of pathways related to inflammatory and immune responses and downregulation of genes involved in organic compounds metabolic processes mediated through cytochromes and other associated cofactors as the critical function of hepatocytes.

Protein–protein interaction

The "Search Tool for the Retrieval of Interacting Genes/Proteins (STRING)" database version 11.5 (https://string-db.org/) was used for the construction of the protein–protein interaction (PPI) network for each gene list. Cytoscape software version 3.9.1 and the cytoHubba tool were also used to visualize the PPI networks and calculate the top 20 hub genes for each network.

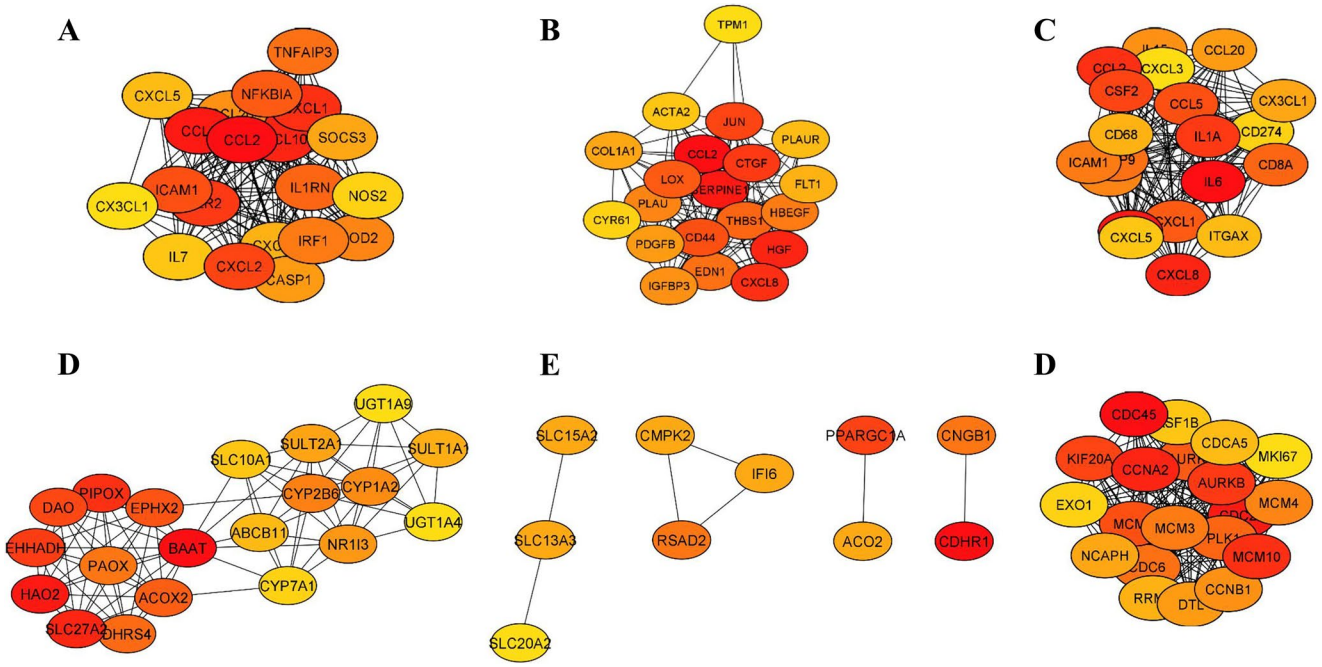

Fig. 2 The top 20 hub genes derived from protein–protein interaction networks based on upregulated genes of SARS-CoV-2-infected liver organoids (**A**), SARS-CoV-2-infected choroid plexus organoids (**B**), and SARS-CoV-2-infected A549 cells (**C**) besides downregulated genes of SARS-CoV-2-infected liver organoids (**D**), SARS-CoV-2-infected choroid plexus organoids (**E**), and SARS-CoV-2-infected A549 cells (**F**)

Figure 2 illustrates networks of the top 20 hub genes for each gene list. As the figure presented, SERPINE 1 (a gene involved in inhibition of fibrinolysis and stimulation of thrombophilia), HGF (a protein regulating cell growth, motility, and angiogenesis), and CCL2 (one of the cytokine-related genes) were the top 3 hub genes of infected choroid plexus' upregulated genes. On the other hand, top hub genes of downregulated genes of infected choroid plexus organoids were CDHR1 (a gene belonging to the cadherin family and mutation of this gene was associated with retinal dystrophies), PPARGC1A (a gene needed for energy metabolism), and RSAD2 (an antiviral gene).

For liver organoids, CCL2, CCL5, and CXCL10 involved in the cytokine response were the top upregulated hub genes. Also, HAO2, BAAT, and SLC27A2 were the top 3 downregulated hub genes mainly involved in hepatic metabolic processes.

CMap analysis

The "CMap build 02" (https://portals.broadinstitute.org/cmap/), available in the PharmacoGx package, was used for connectivity map analysis (Smirnov et al. 2016). Lists of the identified DEGs were uploaded as the input data separately followed by querying the CMap library of gene expression profiles of various compounds. The results were presented with a connectivity score for each drug/compound-disease pair.

Ten compounds significantly reversed genomic signatures of infected hPSCs-derived liver organoids; "fasudil," "dicoumarol," and "cycloserine" had the most negative connectivity scores. Interestingly, previous experiments have also shown substantial effectiveness of fasudil for a wide range of liver injuries (Thorlacius et al. 2006). Fasudil has been also proposed as the potential prophylactic and therapeutic agent for COVID-19-infected critically ill patients (Abedi et al. 2020).

For SARS-CoV-2-infected hiPSCs-derived choroid plexus organoids, "cimetidine," "6-azathymine," and "amylocaine" had the highest scores. Available studies have discussed potential therapeutic and prophylactic effects of histamine H2 receptor antagonists such as the cimetidine on COVID-19 mainly through H2 receptor-mediated immunomodulatory actions on mast cells (Ennis and Tiligada 2021). Furthermore, the possible effects of histamine H2 receptor antagonists on the brain are still under investigation. As Jiang et al. revealed, histamine H2 receptor antagonists can promote the oligodendrocyte differentiation, remyelination, and recovery of cognition and motor functions following hypoxic-ischemic encephalopathy (Jiang et al. 2021).

Besides, "tocainide," "amantadine," and "khellin" were identified to significantly reverse transcriptomic signatures of SARS-CoV-2-infected A549 cells (supplement 1).

In conclusion, comparing transcriptomic profiling of SARS-CoV-2-infected extrapulmonary organs in this

study has revealed that functional biological pathways enriched during the infection vary substantially among different organs. SARS-CoV-2 infection can trigger brain tissue damage and angiogenesis besides suppressing CSF production. However, infected hepatic cell lines showed a more significant inflammatory response with downregulation of essential metabolic and detoxification processes. This evidence strongly supports the theory that the virus involves various organs with different underlying mechanisms confirming that applying the same treatments for patients with the involvement of different organs is not reasonable. Moreover, proposing novel methods to apply personalized therapy based on the "omics" data should also be considered as a further step.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10142-022-00841-z.

Acknowledgements This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Besides, an earlier version of this study has been presented as a preprint in ChemRxiv with the following link: https://chemrxiv.org/articles/preprint/Organ-Specific_Treatment_for_COVID-19_Rationale_Evidence_and_Potential_Candidates/13274936.

Author contribution Seyedeh Zahra Mousavi has made substantial contributions to conceptualization and study design, formal analysis and interpretation of data, and writing the original draft. Mojdeh Rahmanian has made substantial contributions to conceptualization and study design, data acquisition and software, and writing the original draft. Ashkan Sami has made substantial contributions to conceptualization and study design, supervision, and revising and editing the manuscript. All authors have approved the final version to be published.

Data availability All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Non-applicable.

Consent for publication Non-applicable.

Competing interests The authors declare no competing interests.

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