Giannattasio *et al.*
Journal of Translational Medicine (2025) 23:99
https://doi.org/10.1186/s12967-025-06123-z

Journal of Translational Medicine

RESEARCH

Open Access

Serum HDL and their subfractions are impaired in multisystem inflammatory syndrome in children (MIS-C)

Antonietta Giannattasio[1], Alice Castaldo[2,3], Michela Grieco[1], Monica Gelzo[4,5*], Gustavo Cernera[4,5], Giuseppe Castaldo[4,5] and Vincenzo Tipo[1]

Abstract

Background Multisystem inflammatory syndrome in children (MIS-C) is a severe post-COVID condition due to a delayed hyperimmune response to SARS-CoV-2. High-density lipoproteins (HDL) are pivotal players in inflammatory and immune modulation through the remodeling of their subfractions.

Methods This study aimed to evaluate serum levels of cholesterol, HDL, and HDL subfractions (HDL-SUB) to define their role in the pathogenesis of MIS-C and their potential use as biomarkers of this condition. We analyzed serum cholesterol, HDL and HDL-SUB (by capillary electrophoresis) in relation to serum values of biomarkers of inflammation and endothelial damage (by microfluidic immunoassays) in 48 patients with MIS-C at hospital admission and in 48 age- and sex-matched healthy controls.

Results Serum cholesterol, as well as HDL, were significantly lower in MIS-C patients than controls. Serum cholesterol was inversely correlated with all biomarkers of inflammation, confirming the impact of cytokines on reverse cholesterol transport, whereas HDL values were inversely correlated with serum biomarkers of endothelial damage, suggesting a role of HDL in endothelial damage in MIS-C patients. Furthermore, we found a remodeling of HDL-SUB with a more pronounced decrease in small HDL that have anti-inflammatory activity.

Conclusions These data confirm the severe impairment of reverse cholesterol transport in MIS-C and indicate serum HDL and HDL-SUB as potential useful diagnostic biomarkers of MIS-C.

Keywords Cholesterol, Sepsis, Inflammation, Biomarkers

Background

The relationship between cholesterol and the immune system was firstly described by a study showing that patients undergoing radical prostatectomy had a fatal outcome for sepsis when postoperative cholesterol values were lower than 12.5th percentile. The authors suggested a correlation between hypocholesterolemia and reduced antibody production [1]. After a century, the relationships among cholesterol metabolism, inflammation and the immune system represent one of the most active fields of research in sepsis [2] aiming at the development of novel biomarkers and new therapies [3].

*Correspondence:
Monica Gelzo
monica.gelzo@unina.it
[1] Dipartimento di Pediatria Generale e d'Urgenza, AORN Santobono-Pausilipon, Naples, Italy
[2] SC di Pneumologia e UTSIR, AORN Santobono-Pausilipon, Naples, Italy
[3] Dipartimento di Scienze Mediche Traslazionali, Sezione di Pediatria, Università di Napoli Federico II, Naples, Italy
[4] Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università di Napoli Federico II, Via Pansini 5, 80131 Naples, Italy
[5] CEINGE-Biotecnologie Avanzate Franco Salvatore, Naples, Italy

High-density lipoproteins (HDL) are pivotal players in inflammation and immune modulation and have a role in supporting endothelial physiology [4]. During infection, acute phase proteins hinder the efflux of endogenous cholesterol, resulting in a reduction of serum HDL with a consequent decrease of anti-inflammatory activity. In addition, HDL remodeling occurs with a pro-inflammatory effect further reducing reverse cholesterol transport. The dual effect of HDL also depends on HDL subfractions (HDL-SUB) with different size, structure, molecular composition and anti- or proinflammatory activity [5, 6].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused about 7 million deaths so far. Systemic inflammation [7–9] induced by massive cytokine release and subsequent lymphocyte exhaustion [10] are the hallmark of severe acute COVID-19 [11], particularly during the first wave [12]. We have described severe dysregulation of lipid metabolism related to pathological inflammation in patients with acute COVID-19 [13], and other studies have reported the reduction of HDL and the remodeling of HDL-SUB in serum from patients with severe COVID-19 [14] and the correlation between altered cholesterol metabolism and the cytokine storm [15].

Multisystem inflammatory syndrome in children (MIS-C) is a severe post-COVID condition. It occurs about 2–6 weeks after acute SARS-CoV-2 infection possibly due to a delayed hyperimmune response to SARS-CoV-2 [16, 17]. The syndrome shares clinical features with Kawasaki Disease [17, 18], even if the lymphocyte exhaustion [19] and a clear pathogenetic relationship with SARS-CoV-2 [20] are peculiar to MIS-C. We demonstrated that in MIS-C patients, genetic variants predispose to pro-inflammatory events that promote cytokine release and tissue damage triggered by self-antigens exposure [21]. Similarly, endothelial hyperinflammation and vasculitis, which are known features of acute COVID-19 [22, 23], typically appear also in MIS-C [19, 21].

Therefore, the present study aimed to explore serum cholesterol, HDL, and HDL-SUB in MIS-C patients and age- and sex-matched healthy controls, relating these indices to cytokine levels to evaluate their pathogenic role in acute MIS-C and the potential use as diagnostic biomarkers.

Materials and methods

Study design and participants

The study was approved by the Ethics Committee of the University Federico II of Naples. Written informed consent to participate in this study was provided by the legal guardian/next relative of the participants. The only exclusion criterion was refusal or inability to obtain informed consent. We enrolled 48 children at admission to the Santobono-Pausilipon Pediatric Hospital (Naples), diagnosed with MIS-C according to the Center for Disease Control and Prevention definition [24]. MIS-C patients had a median age of 7 years (interquartile (IQ) range: 5–10 years) and 20/48 (41.7%) patients were females. At admission, all patients presented with fever and gastrointestinal symptoms (abdominal pain and/or diarrhea and/or vomiting). Although no data are available on the SARS-CoV-2 variant since RT-PCR analyses of the nasal swab were negative at admission, during the enrollment period, the Delta variant, i.e. B.1.617.2, was the most frequent for COVID-19 cases in Italy. The healthy control (HC) group included 48 children matched for age and sex (median age: 7 years; IQ range: 5–10; 20/48 were females (41.7%)).

Biochemical parameters

Whole blood samples were collected at admission in EDTA-containing tubes and immediately analyzed for total lymphocyte count. Serum samples were separated from blood cells in tubes without anticoagulant and analyzed within 1 h for biochemical parameters. Cholesterol, HDL, and C-reactive protein (CRP) were assessed in serum by an automated biochemical analyzer (Architect ci 16,200 Integrated System, Abbott Diagnostics) using specific commercial kits (Abbott Diagnostics). Serum interleukin (IL)−6, 10, and 17A, interferon (IFN)γ, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)−1, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), and vascular endothelial growth factor A (VEGF-A) levels were analyzed by automated microfluidic immunoassay cartridges on ProteinSimple Ella (Bio-Techne), according to the manufacturer' instructions [25, 26]. The analysis of HDL-SUB was performed by polyacrylamide gel electrophoresis using the Quantimetrix kit (Quantimetrix Corp.). Briefly, serum (25 µL) was added to precast high-resolution polyacrylamide gel tubes together with Lipoprint HDL Loading Gel solution (300 µL). After mixing, the tubes were photopolymerized at room temperature for 30 min. Electrophoresis with tubes containing serum samples was performed at a constant of 3 mA/tube for 50 min. Then, the tubes were scanned and analyzed using the Lipoprint LDL/HDL subfraction system. Subfraction lanes were identified by their mobility using low-density lipoprotein (LDL) + very low-density lipoprotein (VLDL) as the starting setpoint (LDL/VLDL = 0) and albumin as the final setpoint (Albumin = 1). HDL-SUB were differentiated between LDL/VLDL peaks and albumin, and the ten HDL-SUB were grouped into Large (HDL-1 to HDL-3), Intermediate (HDL-4 to HDL-7), and Small (HDL-8 to HDL-10) classes. The results were expressed as serum

concentrations (mg/dL) and percentage in relation to total HDL value (%).

Statistical analyses

Continuous parametric and nonparametric data were reported as mean (standard deviation) and median (interquartile range, IQR), respectively. Categorical data were reported as frequency (percentage). The Shapiro–Wilk test was applied to assess the normality of distributions. Comparisons between two groups of independent samples were assessed by Student t-test and Mann–Whitney U-test for parametric and nonparametric data, respectively. Correlations between variables were assessed by Spearman correlation analysis. Statistical analyses were performed by SPSS (version 28, IBM SPSS Statistics). Graphs were made using Graph Pad Prism 8 software (GraphPad Software). P values < 0.05 were considered significant.

Results

We analyzed serum total cholesterol (Fig. 1A) and HDL (Fig. 1B) in MIS-C and HC patients. For both parameters, the values were significantly lower in MIS-C patients compared to HC ($p < 0.0001$). Therefore, we evaluated the correlations between serum cholesterol and HDL values versus serum biomarkers of inflammation and endothelial damage. The values of all these biomarkers are reported in Supplementary Table 1. Serum cholesterol was inversely correlated with all serum biomarkers of inflammation, i.e., IL-6, IL-10, IL-17A, IFN-γ, TNF-α, MCP-1, except CRP. While, serum HDL was inversely correlated with serum IL-17A and serum biomarkers of endothelial damage, namely p-ANCA and VEGF-A (Table 1).

Next, we analyzed HDL-SUB in the serum of MIS-C and HC patients. Figure 2A shows the levels of the three main classes of HDL-SUB (i.e., large, intermediate, and small). All three classes were significantly lower in MIS-C patients compared to HC. When considering the percentages of the three HDL classes in relation to total HDL (Fig. 2B), the value of large HDL

Table 1 Spearman correlation analysis between serum cholesterol and HDL versus serum biomarkers of inflammation and endothelial damage in 48 patients with multisystem inflammatory syndrome in children (MIS-C)

	Cholesterol (mg/dL)		HDL (mg/dL)	
	p value	rs	p value	rs
IL-6 (pg/mL)	**0.001**	−0.538	0.479	−0.130
IL-10 (pg/mL)	**< 0.001**	−0.735	0.089	−0.089
IL-17A (pg/mL)	**0.025**	−0.396	**0.038**	−0.369
IFN-γ (pg/mL)	**0.026**	−0.396	0.989	0.003
TNF-α (pg/mL)	**0.041**	−0.363	0.134	−0.271
CRP (mg/dL)	0.988	0.002	0.162	−0.223
MCP-1 (pg/mL)	**0.01**	−0.394	0.895	−0.021
p-ANCA (AU)	0.120	0.243	**0.009**	−0.396
VEGF-A (pg/mL)	0.852	−0.030	**0.023**	−0.351

IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; CRP: C-reactive Protein; MCP: monocyte chemoattractant protein; pANCA: perinuclear anti-neutrophil cytoplasmic antibodies; VEGF-A: vascular endothelial growth factor A; rs: Spearman's correlation coefficient

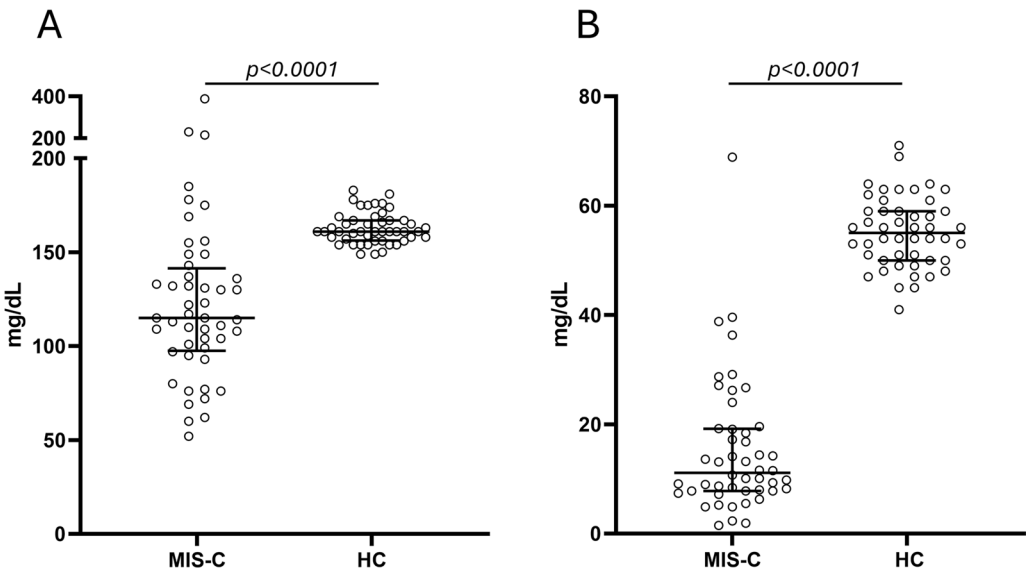

Fig. 1 Scattergram of serum cholesterol (panel A) and HDL (panel B) in 48 patients with multisystem inflammatory syndrome in children (MIS-C) and in 48 healthy controls (HC). The comparisons for both cholesterol and HDL were assessed by Mann–Whitney U-test

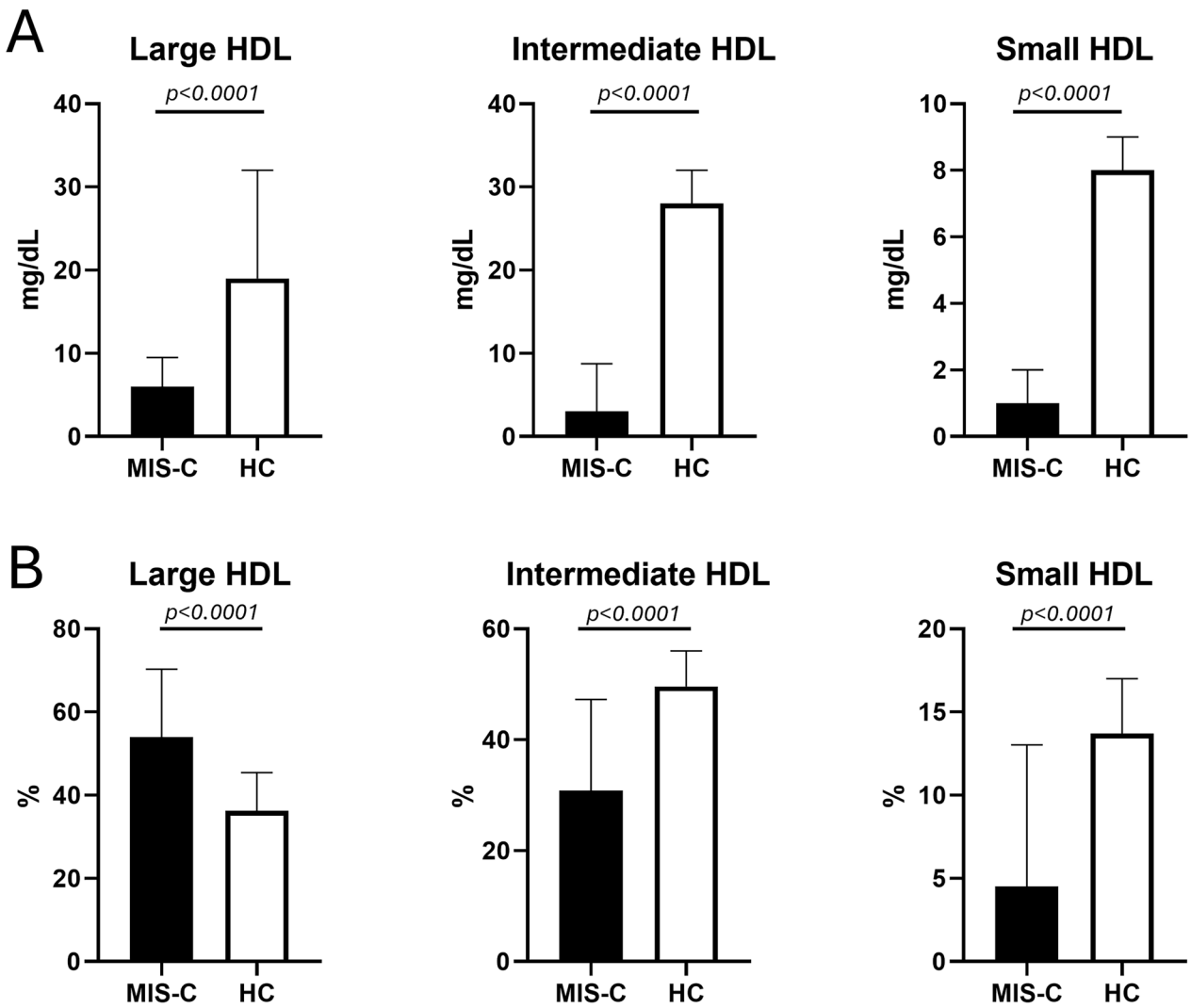

Fig. 2 HDL subfractions in serum from patients with multisystem inflammatory syndrome in children (MIS-C) and in healthy controls (HC) expressed as absolute value (panel A) and as percentage of total HDL (panel B). The comparisons for large, intermediate and small HDL as absolute value and small HDL as percentage were assessed by Mann–Whitney U-test. The comparisons for large and intermediate HDL as percentage were evaluated by Student t-test

was significantly higher in MIS-C patients compared to HC, whereas the percentages of small and intermediate HDL were significantly lower. Table 2 reports the results of Spearman correlation analysis between percentages of the three main classes of serum HDL-SUB and serum biomarkers of inflammation and endothelial damage in MIS-C patients. The values of large HDL were positively correlated with serum IL-6 levels; the values of intermediate HDL were inversely correlated with serum IL-10, IL-17A, and p-ANCA levels; the values of small HDL were inversely correlated with serum IL-6, MCP-1, and VEGF-A levels.

Discussion

We analyzed serum cholesterol, HDL and HDL-SUB in 48 patients with MIS-C at hospital admission and in 48 HC. MIS-C patients had a significant reduction of serum cholesterol and HDL, that were inversely correlated with serum biomarkers of inflammation and endothelial damage, respectively. We also observed a significant reduction of HDL-SUB, mainly in small and intermediate HDL, as compared to the values obtained in our HC and in healthy children from other studies [27]. The reduction of serum cholesterol and HDL was previously reported in adults and in children with severe infectious diseases and sepsis [28],

Table 2 Spearman correlation analysis between the three classes of serum HDL subfractions and serum biomarkers of inflammation and endothelial damage in 48 patients with multisystem inflammatory syndrome in children (MIS-C)

	Large HDL%		Intermediate HDL%		Small HDL%	
	p-value	rs	p-value	rs	p-value	rs
IL-6 (pg/mL)	**0.042**	0.362	0.159	−0.255	**0.016**	−0.423
IL-10 (pg/mL)	0.091	0.304	**0.035**	−0.373	0.078	−0.316
IL-17A (pg/mL)	0.291	0.193	**0.042**	−0.361	0.716	−0.067
IFN-γ (pg/mL)	0.800	0.047	0.875	−0.029	0.273	−0.200
TNF-α (pg/mL)	0.408	0.151	0.428	−0.145	0.262	−0.204
CRP (mg/dL)	0.660	0.071	0.894	−0.021	0.591	−0.087
MCP-1 (pg/mL)	0.252	0.181	0.435	−0.124	**0.039**	−0.320
p-ANCA (AU)	0.092	0.264	**0.006**	−0.420	0.847	−0.031
VEGF-A (pg/mL)	0.051	−0.187	0.316	−0.159	**0.009**	−0.396

IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; CRP: C-reactive Protein; MCP: monocyte chemoattractant protein; pANCA: perinuclear anti-neutrophil cytoplasmic antibodies; VEGF-A: vascular endothelial growth factor A; rs: Spearman's correlation coefficient

and in patients with common variable immunodeficiency (CVID) during infectious or autoimmune complications, suggesting that the reduction of HDL would amplify inflammation in CVID patients [29]. Similarly, the remodeling of HDL with depletion of small HDL was observed both in healthy subjects after the infusion of the lipo-polysaccharide and in patients with infectious diseases [30], and more recently in severe COVID-19 [31] representing a negative prognostic biomarker. The present study firstly describes HDL and their subfractions in MIS-C and demonstrates that also in this condition there is a reduction of HDL and a remodeling of HDL-SUB with a more relevant reduction of intermediate and small HDL.

The impairment of cholesterol metabolism that we observed in MIS-C shares the pathogenic mechanism previously demonstrated in bacterial sepsis [32, 33] and in CVID patients with infectious and autoimmune complications [29]. In fact, the cytokine storm causes the alteration of cholesterol release and the impairment of cholesterol reverse transport. This is confirmed by the significant inverse correlation that we found between serum cholesterol and all analyzed serum cytokines. On the other hand, we previously observed that in MIS-C patients different cytokine pathways are activated [21]. Interestingly, also serum IL-10 levels were inversely related to serum cholesterol suggesting that the known protective role toward inflammation and the immunomodulatory effect of this cytokine [34] should be reconsidered. As consequence of the impaired cholesterol release and reverse transport, there is a reduction of circulating HDL, that causes the hyperactivation of TLR2 and TLR4 receptors with the subsequent inhibition of ATF3 expression and further release of cytokines by macrophages [29, 35] creating a vicious circle.

Interestingly, HDL have also a role in maintaining the endothelial homeostasis [36] through different mechanisms [37] also mediated by the production of nitric oxide that is impaired in COVID-19 patients [38]. Likely, the reduction of circulating HDL and the remodeling of their structure, that we observed in MIS-C, alter their protective role. In fact, we found an inverse correlation between serum HDL and biomarkers of endothelial damage, i.e., VEGF-A and p-ANCA. This contributes to the endothelial damage that we previously observed in MIS-C [25], in acute COVID-19 [22, 23] and in frail patients after the COVID-19 vaccination [39, 40]. In agreement, we also found a decrease of intermediate and small HDL classes in MIS-C together with an inverse correlation between these HDL classes and inflammation and endothelial damage markers. The altered reverse cholesterol transport causes also a reduced production of small HDL, that have a relevant anti-inflammatory, antithrombotic and antioxidant role [31]. Small HDL, that are the native HDL-SUB, are converted in intermediate and large HDL [41]; these latter are depleted of cholesteryl esters and enriched of unesterified cholesterol, triglycerides and free fatty acid [42]. This conversion, with a reduction of small HDL that we observed in our MIS-C patients, was previously described in infectious diseases, increasing their morbidity and mortality [30], and in acute COVID [31], thus representing an acute-phase response. However, different procedures are available to assess HDL-SUB [6] and the results obtained with these different methodologies may not be comparable.

A study limitation is represented by the low number of patients, even if it should be considered that MIS-C is a rare syndrome, i.e., about 2% of children with acute COVID-19. Furthermore, it was not possible to subgroup the patients based on a severity

score. Unfortunately, clear data on the previous acute COVID-19 infection are lacking and this represents a further study limitation.

Conclusions

In conclusion, this study highlights the pivotal role of cholesterol, HDL, and HDL-SUB in immune modulation and endothelial homeostasis. Moreover, these data have some translational impacts. Firstly, our study revealed serum HDL as a new potential diagnostic biomarker of MIS-C. Its diagnostic sensitivity and specificity seem to be excellent and this analysis, that can be easily performed in a routine context, may help to diagnose MIS-C and, possibly, other severe multi-inflammatory diseases. Another relevant aspect concerns the therapy, i.e., the significant impairment of HDL levels and their composition and the impact on the pathogenesis of systemic inflammation, render conceivable the use of HDL-raising therapies [43] and therapies that modulate the amount of HDL-SUB [44].

Abbreviations

HDL	High density lipoproteins
MIS-C	Multisystem inflammatory syndrome in children
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
HC	Healthy control
CRP	C-reactive protein
IL	Interleukin
IFN	Interferon
TNF	Tumor necrosis factor
MCP	Monocyte chemoattractant protein
p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
VEGF-A	Vascular endothelial growth factor A
LDL	Low density lipoproteins
VLDL	Very-low density lipoproteins
IQR	Interquartile range
CVID	Common variable immunodeficiency
TLR	Toll Like Receptor
ATF	Activating transcription factor
rs	Spearman's correlation coefficient

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06123-z.

Supplementary material 1.

Author contributions

Design of the work: M.Ge., G.Ca. and V.T.; Methodology, investigation and data analysis: A.G., A.C., M.Ge., M.Gr. and G.Ce.; Manuscript writing and validation: A.G., M.Ge., G.Ca. and V.T. All authors read and approved the final manuscript.

Funding

This work was supported by the Italian Ministry of University and Research (PRIN 2020, code 20209TB4AX).

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Federico II of Naples. Written informed consent to participate in this study was provided by the legal guardian/next relative of the participants.

Competing interests

The authors declare that they have no competing interests.

Received: 25 November 2024 Accepted: 8 January 2025
Published online: 21 January 2025

References

1. Macadam W, Shiskin C. The cholesterol content of the blood in relation to genito-urinary sepsis. Proc R Soc Med. 1924;17:53–5.
2. Hofmaenner DA, Kleyman A, Press A, Bauer M, Singer M. The many roles of cholesterol in sepsis: a review. Am J Respir Crit Care Med. 2022;205:388–96.
3. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol. 2015;15:104–16.
4. Pirillo A, Catapano AL, Norata GD. Biological consequences of dysfunctional HDL. Curr Med Chem. 2019;26:1644–64.
5. Asztalos BF, Tani M, Schaefer EJ. Metabolic and functional relevance of HDL subspecies. Curr Opin Lipidol. 2011;22:176–85.
6. Pirillo A, Norata GD, Catapano AL. High-density lipoprotein subfractions - what the clinicians need to know. Cardiology. 2013;124:116–25.
7. Gelzo M, Cacciapuoti S, Pinchera B, De Rosa A, Cernera G, Scialo F, et al. Matrix metalloproteinases (MMP) 3 and 9 as biomarkers of severity in COVID-19 patients. Sci Rep. 2022;12:1212.
8. Muscogiuri G, Bettini S, Boschetti M, Barrea L, Savastano S, Colao A. Low-grade inflammation, CoVID-19, and obesity: clinical aspect and molecular insights in childhood and adulthood. Int J Obes. 2022;46:1254–61.
9. Barrea L, Grant WB, Frias-Toral E, Vetrani C, Verde L, de Alteriis G, et al. Dietary recommendations for post-COVID-19 syndrome. Nutrients. 2022;14:1305.
10. Cacciapuoti S, De Rosa A, Gelzo M, Megna M, Raia M, Pinchera B, et al. Immunocytometric analysis of COVID patients: A contribution to personalized therapy? Life Sci. 2020;261: 118355.
11. Scalia G, Raia M, Gelzo M, Cacciapuoti S, Rosa A, Pinchera B, et al. Lymphocyte population changes at two time points during the acute period of COVID-19 Infection. J Clin Med. 2022;11:4306.
12. Scalia G, Raia M, Gelzo M, Cacciapuoti S, De Rosa A, Pinchera B, et al. Cytometric analysis of patients with COVID-19: what is changed in the second wave? J Transl Med. 2021;19:403.
13. Caterino M, Gelzo M, Sol S, Fedele R, Annunziata A, Calabrese C, et al. Dysregulation of lipid metabolism and pathological inflammation in patients with COVID-19. Sci Rep. 2021;11:2941.
14. Masana L, Correig E, Ibarretxe D, Anoro E, Arroyo JA, Jerico C, et al. Low HDL and high triglycerides predict COVID-19 severity. Sci Rep. 2021;11:7217.
15. Lee W, Ahn JH, Park HH, Kim HN, Kim H, Yoo Y, et al. COVID-19-activated SREBP2 disturbs cholesterol biosynthesis and leads to cytokine storm. Signal Transduct Target Ther. 2020;5:186.
16. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 Infection. J Pediatr. 2020;224:141–5.
17. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369: m2094.
18. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020;79:999–1006.

19. Castaldo A, D'Anna C, Gelzo M, Giannattasio A, Maglione M, Muzzica S, et al. Immunophenotyping of peripheral blood cells allows to discriminate MIS-C and Kawasaki disease. Transl Med Commun. 2022;7:22.
20. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest. 2020;130:5967–75.
21. Gelzo M, Castaldo A, Giannattasio A, Scalia G, Raia M, Esposito MV, et al. MIS-C: A COVID-19-associated condition between hypoimmunity and hyperimmunity. Front Immunol. 2022;13: 985433.
22. Gelzo M, Cacciapuoti S, Pinchera B, De Rosa A, Cernera G, Scialo F, et al. Further findings concerning endothelial damage in COVID-19 patients. Biomolecules. 2021;11:1368.
23. Gelzo M, Cacciapuoti S, Pinchera B, De Rosa A, Cernera G, Scialo F, et al. A transient increase in the serum ANCAs in patients with SARS-CoV-2 infection: a signal of subclinical vasculitis or an epiphenomenon with no clinical manifestations? A Pilot Study Viruses. 2021;13:1718.
24. CDC. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). 2020. https://stacks.cdc.gov/view/cdc/88595. Accessed 15 Dec 2023.
25. Gelzo M, Giannattasio A, Maglione M, Muzzica S, D'Anna C, Scialo F, et al. Biomarkers of endothelial damage in distinct phases of multisystem inflammatory syndrome in children. Metabolites. 2022;12:680.
26. Cortese P, Amato F, Davino A, De Franchis R, Esposito S, Zollo I, et al. The immune response to SARS-CoV-2 vaccine in a cohort of family pediatricians from southern Italy. Cells. 2023;12:1447.
27. Muchova J, Andrezalova L, Oravec S, Nagyova Z, Garaiova I, Durackova Z. High density lipoprotein subfractions and paraoxonase 1 in children. Acta Biochim Pol. 2016;63:555–63.
28. De Geest B, Mishra M. Impact of high-density lipoproteins on sepsis. Int J Mol Sci. 2022;23:12965.
29. Macpherson ME, Halvorsen B, Yndestad A, Ueland T, Mollnes TE, Berge RK, et al. Impaired HDL function amplifies systemic inflammation in common variable immunodeficiency. Sci Rep. 2019;9:9427.
30. Harslof M, Pedersen KM, Afzal S, Davey Smith G, Nordestgaard BG. Lower levels of small HDL particles associated with increased infectious disease morbidity and mortality: a population-based cohort study of 30 195 individuals. Cardiovasc Res. 2023;119:957–68.
31. Ballout RA, Kong H, Sampson M, Otvos JD, Cox AL, Agbor-Enoh S, et al. The NIH Lipo-COVID study: a pilot NMR investigation of lipoprotein subfractions and other metabolites in patients with severe COVID-19. Biomedicines. 2021;9:1090.
32. Ansell BJ, Fonarow GC, Fogelman AM. The paradox of dysfunctional high-density lipoprotein. Curr Opin Lipidol. 2007;18:427–34.
33. Cardoso D, Perucha E. Cholesterol metabolism: a new molecular switch to control inflammation. Clin Sci. 2021;135:1389–408.
34. Song GY, Chung CS, Chaudry IH, Ayala A. What is the role of interleukin 10 in polymicrobial sepsis: anti-inflammatory agent or immunosuppressant? Surgery. 1999;126:378–83.
35. Jorgensen SF, Macpherson ME, Skarpengland T, Berge RK, Fevang B, Halvorsen B, et al. Disturbed lipid profile in common variable immunodeficiency—a pathogenic loop of inflammation and metabolic disturbances. Front Immunol. 2023;14:1199727.
36. Robert J, Osto E, von Eckardstein A. The endothelium is both a target and a barrier of HDL's protective functions. Cells. 2021;10:1041.
37. Tran-Dinh A, Diallo D, Delbosc S, Varela-Perez LM, Dang QB, Lapergue B, et al. HDL and endothelial protection. Br J Pharmacol. 2013;169:493–511.
38. Gelzo M, Scialo F, Cacciapuoti S, Pinchera B, De Rosa A, Cernera G, et al. Inducible nitric oxide synthase (iNOS): why a different production in COVID-19 patients of the two waves? Viruses. 2022;14:534.
39. Cernera G, Gelzo M, De Placido P, Ottaviano M, Pietroluongo E, Raia M, et al. Immunocytometric analysis of patients with thymic epithelial tumors revealed that COVID-19 vaccine booster strongly enhanced the immune response. Front Immunol. 2023;14:1233056.
40. Cernera G, Gelzo M, De Placido P, Pietroluongo E, Raia M, Scalia G, et al. Serum biomarkers of inflammation and vascular damage upon SARS-Cov-2 mRNA vaccine in patients with thymic epithelial tumors. Clin Chem Lab Med. 2024;62:1198–205.
41. Colvin PL, Parks JS. Metabolism of high density lipoprotein subfractions. Curr Opin Lipidol. 1999;10:309–14.
42. Van der Westhuyzen DR, de Beer FC, Webb NR. HDL cholesterol transport during inflammation. Curr Opin Lipidol. 2007;18:147–51.
43. Marsche G, Saemann MD, Heinemann A, Holzer M. Inflammation alters HDL composition and function: implications for HDL-raising therapies. Pharmacol Ther. 2013;137:341–51.
44. Rizzo M, Otvos J, Nikolic D, Montalto G, Toth PP, Banach M. Subfractions and subpopulations of HDL: an update. Curr Med Chem. 2014;21:2881–91.

Publisher's Note