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Short communication

Unsaturated fatty acids, omega-3 index and hospitalization in MISC

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ABSTRACT

The growing interest in Omega-3 fatty acids as diagnostic markers or new therapeutic approaches also for COVID-19 disease, led us to investigate the presence of potential correlations between Omega-3 fatty acids' levels in whole blood and days of hospitalization or admission to the paediatric intensive care unit (PICU) in 51 children with MIS-C diagnosis following SARS-CoV-2 infection. A statistically significant negative correlation was observed between days of hospitalization and docosapentaenoic acid (22:5n-3,DPA), docosahexaenoic acid (DHA) and total Omega-3 FA levels. Dividing the study group into quartiles according to Omega-3-Index (O3I), no statistically significant difference was observed with respect to the PICU admission rate. In contrast, the number of days of hospitalization in Q4 (O3I $\geq$ 2.51 %) was different from the number observed in groups Q1-3 (O3I $<$ 2.51 %), with subjects showing higher O3I needing shorter hospitalizations than the subjects with lower O3I. According to previous study investigating O3I in adults affected by Sars-cov-2 we explored the levels of this nutrients in children with MIS-C. Our exploratory study shows that high DPA, DHA and O3I levels could be effective in reducing the length of hospitalization.

1. Introduction

SARS-CoV-2 infection in children and adolescents is known to have markedly different outcomes from those observed in adults. In most cases young people develop mild symptoms and recover rapidly, but in less than 1 % of kids who contract SARS-CoV-2 approximately 4 to 6 weeks after the infection severe symptoms may develop, more frequently in presence of comorbidities as diabetes, obesity or cardiovascular diseases. The World Health Organization (WHO) defined this hyper-inflammation state as the Multisystem Inflammatory Syndrome in Children (MIS-C) in 2020.

MIS-C may result in multiple organ failure, with the involvement of gastrointestinal, cardiovascular, hematological, cutaneous and respiratory systems and, as noted above, the syndrome is post-infectious rather than related to the acute phase of the infection. Thus, it has been hypothesized that it is a delayed immunological phenomenon associated with the hyperinflammatory phase following symptomatic or asymptomatic SARS-CoV-2 infection [1]. The infection appears to trigger the activation of macrophages followed by stimulation of T-helper cells. This leads to the release of cytokines, additional activation of macrophages, neutrophils and monocytes, as well as the activation of B-cells and plasma cells with the production of antibodies leading to a hyperimmune response.

We previously reported an altered blood fatty acid profile in children affected by MIS-C, with levels of arachidonic acid (AA, 20:4 n-6), linoleic acid (LA, 18:2 n-6), and docosahexaenoic acid (DHA, 22:6 n-3) markedly lower than that of healthy children. In contrast, the levels of α-linolenic acid (ALA, 18:3 n-3) and eicosapentaenoic acid (EPA, 20:5 n-3) were in line with those found in the literature [2].

The observed alteration may be the result of an increased metabolism of fatty acids (FA) into lipid mediators that participate in the hyperinflammatory state observed. The lower levels of AA in children with MIS-C would therefore be the result of its marked release from phospholipids followed by its conversion into pro-inflammatory lipid mediators. Indeed, oxygenated metabolites derived from Omega-6 may participate in both the propagation and resolution of the inflammatory

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response, but they mainly exert potent pro-inflammatory and pro-thrombotic activities. At the same time, an increased usage of Omega-3 fatty acids may also be expected following the production of specialized pro-resolving mediators (SMPs), resulting from reactions mediated by lipoxygenases as part of the natural history of the inflammatory response that should lead to its spontaneous resolution. In fact, SMPs are reported to possess powerful anti-inflammatory and pro-resolution activities, so they can promote the physiological resolution of the inflammatory process [3,4].

In light of the potential role of SPMs in the resolution phase of the inflammatory response, it has long been hypothesized that the availability of their precursors (namely DHA and EPA), and therefore their plasmatic levels, may affect their production during the inflammatory process, ultimately affecting its course of action leading to resolution rather than chronic inflammation as final outcome.

In 2021 a pilot study with 100 adult patients positive for SARS-CoV-2 was conducted to test the hypothesis that EPA and DHA levels, expressed as Omega-3-Index (O3I), were inversely associated with the risk of death. The results showed that patients with an O3I of 5.7 % or higher had an approximately 75 % lower risk of death than those with a lower O3I value [5]. This difference in the risk of death resulted not being statistically significant, but it is nevertheless a strong trend suggesting the existence of a potential relationship supporting the idea that EPA and DHA and or their metabolites may play a role in indeed reducing severity and mortality in SARS-CoV-2 infection.

Based on our previous results and under the working hypothesis of a possible correlation between Omega-3 fatty acid levels and the outcome of COVID-19 disease caused by SARS-CoV-2, with the present study we investigated this potential correlation in children affected by MIS-C. We therefore assessed the fatty acid profile in whole blood in 51 MIS-C diagnosed children admitted to Vittore Buzzi Hospital in Milan, to determine the O3I and its possible correlations with the number of days of hospitalization or whether or not the children went along to be admitted to the paediatric intensive care unit (PICU) as a result of the progression of the multisystem inflammatory response.

2. Subjects and methods

2.1. Subjects

A group of 51 children and adolescents (2–18 years old) with MIS-C, as defined according to the CDC classification [CDC. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). Available online: https://www.cdc.gov/mis-c/hcp/.html (accessed on 1 June 2023)], were enrolled at the Paediatric Department of Children's Hospital Vittore Buzzi in Milan, Italy, from December 1st 2020 to the end of March 2022. Standard drug therapy was administered to all patients (intravenous immunoglobulin, corticosteroids, antiplatelet therapy and antiplatelet therapy). Inflammatory blood values and anthropometric measurements were recorded.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the hospital (protocol number 2021/ST/004). Children's caregivers gave their written consent for inclusion after being informed about the nature of the study.

3. Fatty acid analysis

Within 72 h from hospital admission, a drop of blood was collected on a special card embedded with butylated hydroxy toluene (BHT) as antioxidant, and stored in a refrigerator until the analysis.

The FA profile was evaluated after direct transmethylation and FA methyl esters were analyzed by gas chromatography using a GC-2010 (Shimadzu Italia S.r.l., Milano, Italy) equipped with a 15 m capillary column (DBB Agilent), PTV injector and FID detection, as reported previously [6,7]. 22 FA are considered and reported as relative percentages; classes of FA, i.e. total saturated FA (SAT), monounsaturated FA (MUFA) and PUFA and FA series, i.e. n-6 and n-3 were also reported. In addition, the O3I was calculated in accordance with Stark et al. applying the suggested equation, Omega-3-Index = 1.1 * (EPA + DHA in whole blood) + 0.65, to convert the sum of EPA and DHA from whole blood (WB) to O3I in red blood cells [8].

4. Statistical analysis

The statistical analyses were performed using IBM SPSS statistics 28.01v. Non-parametric tests were used to analyze the data: Spearman correlation coefficient was used to test FA versus days of hospitalization, Kruskal Wallis test was used to compare the same variable in different groups and Chi-squared test was used to assess possible associations between O3I and admission to PICU. Differences were considered statistically significant for $p < 0.05$.

5. Results

Table 1 summarizes the characteristics of the sample population; the mean age of the subjects was 8.6 ± 3.7 years old ($n = 51$), and about 74 % of them were males, BMI z-score were 0.43 ± 1,04 according to CDC, C-reactive protein (CRP),erythrocyte sedimentation rate (ESR),Interlukin-6 (IL-6) shown inflammatory status. The days of hospitalization ranged from 6 to 26 with an average of 14.1 days. The subjects were divided in two groups, the first including the children subsequently admitted to PICU upon worsening of the general condition, and the second the children that did not required admission to PICU (No PICU). No significant differences were found between these two groups with respect to the age of children and the overall number of days of hospitalization.

The relative amounts of Omega-3 fatty acids, expressed as percentages, are reported in Table 2; the comparison of PICU group ($n = 30$) with No PICU group ($n = 21$) did not show statistically significant differences in FA levels and in O3I, the latter averaging 2.27 % in the PICU group versus 2.34 % in No PICU group. The whole fatty acids are showed in Supplemental table 1.

The mean value of O3I in all MIS-C subjects was compared to values obtained from articles in which the FA profile of healthy children and adolescents was reported (Table 3) ([9–19] resulting significantly lower in children with MIS-C than in healthy children, either taking into account all the studies referenced, or only those reporting values from Italian children (mostly obtained in our laboratory)(3.31 ± 0.86 %, 3.33 ± 0.61 % and 2.30 ± 0.51 %; healthy children from all the studies, healthy children from Italian studies only, and MIS-C children,

Table 1
Characteristics of the sample at the study.

	All subjects $n = 51$	PICU $n = 30$	No PICU $n = 21$
Sex-male n, %	38 (74.5%)	24 (80 %)	14 (67 %)
Age *y* mean ± SD (min-max)	8.6 ± 3.7 (3–17)	9.2 ± 4.1 (3–17)	7.8 ± 2.9 (3–14)
BMI z-score (CDC) mean ± SD	0.43 ± 1,04 (−1.77;+2.24)	0.26 ± 1.04 (-−1.77;+2.24)	0.71 ± 0.99 (-−1.39;+1.64)
ESR (mm/h)	49.9 ± 30.3 (12–111)	44 ± 32.4 (22–120)	54 ± 31.2 (12–120)
CRP (mg/L)	177.7 ± 102.73 (20–456,2)	190.4 ± 109.6 (20–456.2)	159.24 ± 91.4 (54.8–295.3)
IL-6	23.75 ± 45.75 (0.37–256.68)	16.50 ± 54.77 (0.37–256.68)	7.69 ± 133.52 (0.37–59.85)
Days of H mean ± SD (min-max)	14.1 ± 4.2 (6–27)	14.7 ± 4 (6–27)	13 ± 3.5 (10–26)

PICU, paediatric intensive care unit,ESR = erythrocyte sedimentation rate,CRP = C-reactive protein,IL-6 = interlukin-6.

Table 2
Whole blood omega 3 fatty acid levels, expressed as relative percentages, in patients admitted or not to the pediatric intensive care unit.

Fatty acids	All subjects $n = 51$	PICU $n = 30$	No PICU $n = 21$
ALA	0.20 ± 0.09	0.21 ± 0.09	0.19 ± 0.09
EPA	0.38 ± 0.09	0.39 ± 0.10	0.36 ± 0.08
DPA	0.44 ± 0.16	0.42 ± 0.12	0.47 ± 0.21
DHA	1.12 ± 0.46	1.08 ± 0.47	1.17 ± 0.45
Total omega3	2.14 ± 0.63	2.11 ± 0.58	2.19 ± 0.72
O3I	2.30 ± 0.51	2.27 ± 0.49	2.34 ± 0.55

The values reported represent the mean ± standard deviation (SD). ALA, alpha linolenic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid; O3I, omega-3 Index (calculated as reported in methods); PICU, paediatric intensive care unit.

Table 3
O3I in healthy children and adolescents, based on literature data vs our sample.

Author, Year of publication	Country	Population, yo	specimen	O3I
Ryan AS, 2008 [7]	USA	Children 4 y	WB	2.08
Burrows T, 2011 [15]	Australia	Children 5–12 y	RBC	5.00
Risé P, 2013 [17]	Italy	Children 2–9 y	WB	2.44
Van der Wurff, 2016 [9]	the Netherlands	Adolescents 13–15 y	WB	3.92
Crippa A, 2018 [10]	Italy	Children 7–14 y	WB	4.02
Al-Ghannami SS, 2018 [12]	Oman	Children 9–10 y	RBC	4.10
Crippa A, 2019 [11]	Italy	Children 7–14 y	WB	3.39
Van der Wurff, 2019 [8]	The Netherlands	Adolescents 13–15y	WB	3.93
Bonafini,2020 [13]	Italy	Children 9–10 y	WB	4.19
Murphy A, 2021 [14]	USA	Children 3–5 y	plasma	2.36
		Children 6–11 y		2.47
		Adolescents 12–19y		2.46
Syrèn ML, 2022 [16]	Italy	Children <2 y	WB	3.26
		Children 2-<10 y		3.03
		Adolescents 10–19y		2.99
Our sample $n = 51$		Children 3–17y	Whole blood	2.30

The O3I are those reported in the mentioned papers or calculated starting from the EPA+DHA levels in other specimens than RBC, as reported by Stark et al. [8].

respectively)(Fig. 1).

Omega-3 FA levels of all MIS-C children were also investigated with respect to days of hospitalization (H) and statistically significant negative correlations were found for DPA, DHA, and total Omega-3 FA (Table 4).

Subjects were finally divided into quartiles according to their O3I values [Q1 (O3I < 188 %), Q2 (1.88 ≤ O3I < 2.29 %), Q3 (2.29 % ≤ O3I < 2.51 %) and Q4 (O3I ≥ 2.51 %)](Table 5), showing that the number of days of H for the children belonging to upper quartile of O3I was statistically significant lower when compared to children in Q1–Q3. No differences relative to the admission to PICU were observed amongst the different O3I quartiles.

5.1. Discussion

During the SARS-CoV2 pandemic several reviews hypothesized a possible positive effect of an Omega-3 fatty acid supplementation modulating the inflammatory status of severe patients [20,21], based on the suggested correlation between plasma concentrations of Omega-3 FA and the final production of their anti-inflammatory, pro resolution metabolites, namely resolvins, maresins, and protectins (specialized proresolution mediators, SPM [22,23]. While the meaningfulness of assessing the production of SPM in plasma as a measure of their in vivo production remains much debated [24,25], the relevance of the fatty acid precursor availability, as measured in plasma, for the production of biologically active metabolites remains a potentially valid hypothesis.

We previously investigated and reported an altered FA profile in

Table 4
Correlations between omega 3 fatty acid levels and days of hospitalization.

Fatty acids	All subjects $n = 51$		PICU $n = 30$		No PICU $n = 21$	
	R	P-value	R	P-value	R	P-value
ALA	−0.025	0.431	0,002	0,497	−0.146	0,263
EPA	0.209	0.070	***0,408***	***0,013****	−0,305	0,090
DPA	***−0.347***	***0.006****	***−0,334***	***0,036****	−0,318	0,080
DHA	***−0.241***	***0.044****	−0,256	0.086	−0,173	0,227
Total omega 3	***−0.234***	***0.050****	−0,187	0,162	−0.230	0,158
O3I	−0.178	0.106	−0,157	0,203	−0,188	0,208

Fatty acid levels are expressed as relative percentages; the statistical significance was assessed administering the Spearman's non-parametric test. ALA, alpha linolenic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid; O3I, omega-3 Index; PICU, paediatric intensive care unit.

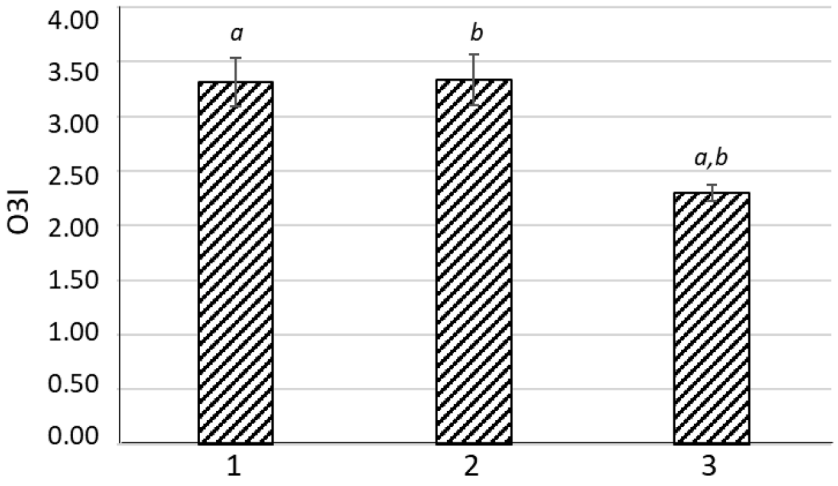

Fig. 1. Omega-3-Index in different groups of children and adolescents
Column 1, healthy children from all the studies; column 2, healthy children from Italian studies; column 3, MIS-C children; as reported in Table 3. OI3: Omega-3-Index. Columns showing the same letter (*a* or *b*) are significantly different for $p < 0.01$ (Student's T-test).

Table 5
Unadjusted associations of O3I quartiles and different variables.

Categorical by O3I quartile	Age mean ± SD	Sex–Male % (X/N)	Days of H (mean ± SD)	PICU % (X/N)
Q1: O3I < 1.88 %	8.00 ± 3.10	72.73 % (8/11)	12.58 ± 4.29	45.45 % (5/11)
Q2: 1.88 % ≤ O3I < 2.29 %	8.31 ± 3.40	75.00 % (12/16)	14.88 ± 4.29	65.20 % (10/16)
Q3: 2.29 % ≤ O3I < 2.51 %	8.64 ± 4.30	63.64 % (7/11)	15.91 ± 5.84	54.54 % (6/11)
Q4: O3I ≥ 2.51 %	8.79 ± 4.33	84.62 % (11/13)	11.21 ± 3.95	53.85 % (7/13)
p-value*	0.79	0.704	0.07	0.855
Q1–Q3 vs Q4				
Q1–Q3: O3I < 2.51 %	8.32 ± 3.51	71.05 % (27/38)	14.84 ± 4.15	60.53 % (23/38)
Q4: O3I ≥ 2.51 %	8.79 ± 4.33	84.62 % /11/13)	11.21 ± 3.95	53.85 % (7/13)
p-value*	0.367	0.333	***0.031***	0.67

O3I, omega 3 index; H, hospitalization; PICU, paediatric intensive care unit.
* The p-value was calculated administering the non parametric Kruskal-Wallis test for age and days of H, and the Chi-squared test for sex and PICU.

children diagnosed for MIS-C, with LA, AA and DHA levels lower than those of control children, indeed supporting the hypothesis of a significant conversion of these FA to molecules with pro and anti-inflammatory activities as a result of the hyper inflammatory status of these subjects [2].

Following this evidence, we aimed at validating the hypothesis that a more favorable profile of PUFA, as represented by higher O3I, may reflect a tilt in the balance of the production of FA-derived biologically active mediators and effectively affect the clinical outcome as represented by days of hospitalization (H) or the admission to the paediatric intensive care unit (PICU). Analysis of the FA profile in this set of MIS-C children confirmed the alterations observed in our previous work [2] and the assessment of the O3I also revealed values that were substantially lower than those of healthy children.

Several studies investigated the relationship between the severity of COVID-19 in adults and their O3I. Asher et al. investigated the potential association between O3I and the mortality by Covid-19 disease in adults and, even if not significant, a strong, negative trend was found [5]. In separate studies, patients with severe COVID-19 showed an inverse correlation between O3I values and major clinical indicators of the severity of the disease (mechanical ventilation, death) [26] and lower O3I was associated with an increased likelihood of developing severe COVID-19 after adjusting for potential confounders [27]. Finally, a retrospective study also confirmed that low Omega-3 levels (and O3I) are associated with an increased risk of testing positive for SARS-COV2 and being hospitalized.

The finding that neither the levels of these Omega-3 FA or the O3I were different in patients that required admission to the paediatric intensive care unit (PICU group) with respect to the other patients (NO PICU group) suggests that PUFAs alone may not be the critical factor dictating the severity of the pathological state. On the other hand, the observed negative, statistically significant correlation between the days of hospitalization and DPA, DHA, and total Omega-3 in the whole group of MIS-C children provide captivating evidence regarding the potential role of Omega-3 fatty acids (and possibly of their biologically active metabolites) in the resolution phase of the pathology, contributing to a faster recovery. However, it should be kept in mind that this is an exploratory study and further evidences in pediatric patients with similar conditions are advisable before a causal link can be established.

It must be noted that a negative correlation was observed between DPA in plasma and days of H also in the relatively small PICU subgroup, but on the contrary in the same subjects EPA presented a positive correlation. Within the Omega-3 FA metabolic pathway DPA (22:5 n-3), represents the elongation product of EPA (20:5 n-3) and in healthy adults, high levels of DPA correlate with a lower inflammation score (CRP and TNFa) [28], and with a better FEV1 in patients with compromised pulmonary function [29]. It may be possible that higher levels of EPA may reflect a decreased activity in the elongation process, therefore limiting, in the overall balance, the formation of DPA and DHA, and therefore the availability of precursors of the metabolites reported as most active in the resolution of the inflammatory reaction.

The lack of an evident correlation between O3I and days of hospitalization may reflect O3I being the sum of EPA and DHA, and not considering for example DPA. Nevertheless, a direct comparison of the upper quartile of O3I (Q4:O3I ≥ 2.51 %) versus the others (Q1–Q3:O3I < 2.51 %) still showed a significant difference in the number of days of H, suggesting that even with the intrinsic limitations of O3I, a role for Omega-3 FA may indeed be relevant in defining the ability of MIS-C subjects to recover from the widespread inflammation that is the hallmark of the pathology.

While no data are currently available for children, additional support for a potential role of Omega-3 FA in the inflammation resolution process comes from supplementation studies which showed amelioration in clinical symptoms in COVID-19 adult patients [30]. In elderly COVID-19 patients, the parenteral infusion of Omega 3 FA improved cellular immune response and decreased oxidative stress [31,32] and a meta-analysis supported significant benefits from Omega-3 supplementation in alleviating inflammatory response, as shown by reduced levels of CRP [33]. Supplementation of critically ill, ICU-hospitalized COVID-19 patients with 200 mg EPA and 400 mg DHA for 14 days, showed improved renal function and increased 1-month survival rate [34]. Similarly, hospitalized COVID-19 adult patients treated with a dietetic supplement containing 1 g of Omega-3 FA and other nutrients, showed decreased mortality, reduced need for mechanical ventilation and shorter period of intubation with respect to control patients following the hospital regimen of diet [35].

Finally, Omega-3 supplementation in critically ill subjects was recently reviewed, suggesting that the treatment with EPA and/or DHA in ICU patients, suffering by ARDS or COVID-19, sepsis, or organ injury, may ultimately improve clinical outcome [36].

While it must be stressed that all these results were obtained in adults or elderly, they nevertheless support the notion that increasing the plasmatic concentrations of Omega-3 FA may be beneficial to the massive inflammation typically observed in severe COVID-19 subjects, therefore providing support to the results of our study that a plasma FA profile skewed toward the Omega-3 FA may improve the ability to cope with the massive inflammatory response typical of MIS-C.

In conclusion, the results of this exploratory study may provide a first evidence that, in MIS-C subjects, higher plasmatic Omega-3 FA levels, also expressed as O3I, could support a faster resolution of the multisystem inflammatory condition, reducing the number of days of hospitalization needed for recovery.

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CRediT authorship contribution statement

Elisabetta Di Profio: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Patrizia Risé:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Lara Orlandi:** Writing – original draft, Formal analysis. **Elena Zoia:** Visualization, Validation, Investigation. **Christian Pinna:** Supervision, Formal analysis, Data curation. **Angelo Sala:** Visualization, Validation, Supervision. **Gianvincenzo Zuccotti:** Supervision. **Elvira Verduci:** Validation, Supervision, Methodology, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.plefa.2024.102627.

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