Key Inflammatory Biomarkers Differentiate MIS-C from Convalescent COVID-19 and Kawasaki Disease.

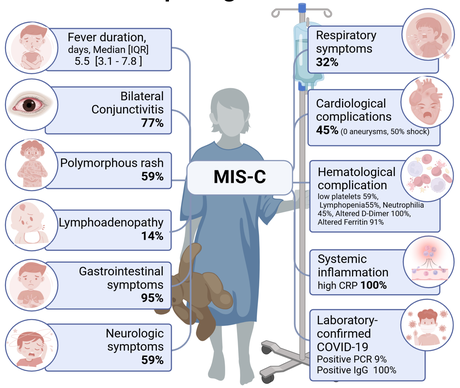
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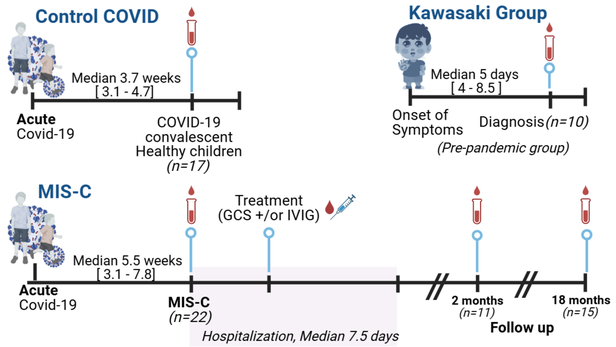
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BACKGROUND

SARS-CoV-2 is usually mild in children, but, in rare cases it can trigger **MIS-C,** a severe post-infectious condition emerging **2-6 weeks after infection**. MIS-C, driven by a **cytokine storm**, causes **systemic inflammation** and **multi-organ damage**, with **half** of the cases **requiring ICU care**.



The study analyzed **92 blood inflammatory proteins** to distinguish between convalescent children without MIS-C, acute MIS-C, and acute Kawasaki disease.



METHODS

Three groups were included: **Convalescent COVID-19**, **MIS-C** (including **follow-ups at 2 months and 18 months**), and **Kawasaki disease** (**pre-pandemic** patients).

Sera were collected at Hospital Sant Joan de Déu, Barcelona (March 2020 – February 2022) and analyzed with the **Olink Technology**.



The Olink Target 96 Inflammation panel

RESULTS

- We identified a set of biomarkers that help differentiate MIS-C from Convalescent COVID-19 and Kawasaki disease.
- Six key biomarkers could predict worse outcomes of MIS-C.
- Longitudinal analysis showed complete inflammation remission and symptom resolution by 2 months.

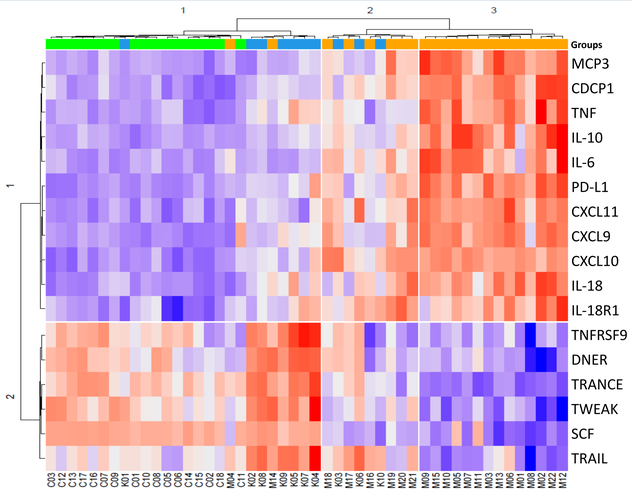


Figure 1. Distinct Inflammatory Signatures in Control Covid, Kawasaki Disease and MIS-C. First Random Fores identified the top 17 cytokines distinguishing MIS-C from control COVID-19 and KD. Heatmap clustering revealed distinct inflammatory profiles: a clear separation between Control COVID-19 and acute MIS-C, with KD samples forming two intermediate clusters. Notably, three KD cases resembled MIS-C, while one MIS-C sample clustered within the KD cohort, highlighting shared immune features.

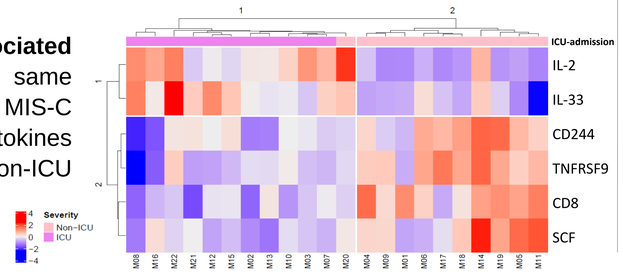


Figure 2. Inflammation biomarkers associated with ICU admission in MIS-C. Using the same random forest and clustering approach, only MIS-C cases were analyzed to identify key cytokines differentiating ICU admission from non-ICU patients.

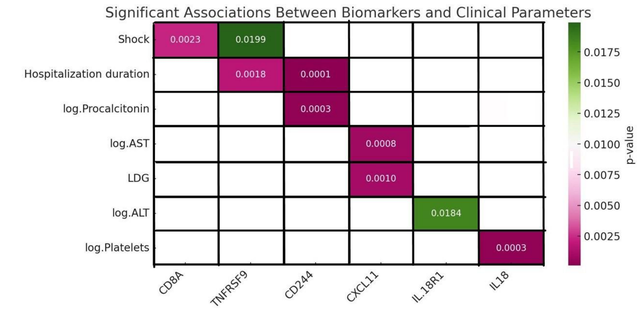


Figure 3. Co-associations between inflammatory biomarkers and clinical parameters. The association between key cytokines and clinical parameters was evaluated and adjusted for age and gender with regression models for accurate p-values.

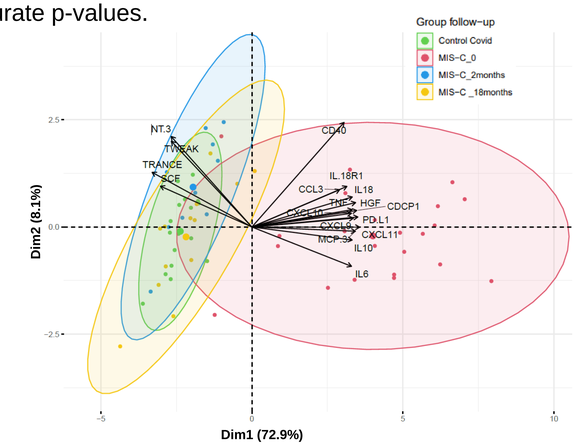


Figure 4. Cytokine Stabilization and Recovery Post-MIS-C Treatment. PCA visualization of cytokine profiles across acute, 2-month, 18-month MIS-C follow-ups, and the control group, highlighting the convergence of post-treatment cytokine behavior with control group patterns.

CONCLUSIONS

1. **TNFRSF9**, **DNER**, **TRANCE**, **TWEAK**, **SCF**, and **TRAIL** showed **opposite expression patterns** between MIS-C and Kawasaki
2. **IL-2, IL-33, SCF and soluble CD244, TNFRSF9, and CD8 could identify** the most **severe MIS-C presentations** (ICU admission).
3. Soluble **TNFRSF9** could predict MIS-C outcomes, **linking to shock and hospital stay**. Soluble **CD8** downmodulation was associated with **shock**. Low soluble TNFRSF9 and CD8 suggest CD8+ T cell dysregulation in the most severe MIS-C.
4. **CD244 downregulation** was associated with **longer hospital stay** and **severe progression**.
5. **CXCL10 and CXCL11** were identified as potential biomarkers for acute **liver injury**.
6. **Thrombocytopenia** was associated with **increased IL-18 levels**.
7. **Longitudinal** analysis post-treatment demonstrated **cytokine profile normalization** by 2 months.

ADDITIONAL INFORMATION

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