The Potential Role of Circulating Cytokines and Chemokines in Predicting Intestinal Failure in Patients with Short Bowel Syndrome

Miriam Di Mattia[1,2*], Cesare Pane[1,2], Valentina Petito[3], Lamolinara A.[1], Iezzi M.[1], Elisa Foscarini[3], Francesca Profeta[3], Guia Becherucci[3], Letizia Masi[3], Sara Troisi[1,2,3], Valeria Emoli[3], Laura Turchini[3], Antonio Gasbarrini[3,4,5], Alfredo Papa[4,5], Franco Scaldaferri[3,4,5], Loris Riccardo Lopetuso[1,2,4]

1. Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy.
2. Department of Medicine and Ageing Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy.
3. CeMAD Translational Research Laboratories, Digestive Disease Center (CeMAD), Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy.
4. IBD Unit, Digestive Disease Center (CeMAD), Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy.
5. Department of Translational Medicine and Surgery, Catholic University of the Sacred Heart, Rome, Italy.

Background and aim: Short bowel syndrome (SBS) is a life-altering and life-threatening disease resulting from massive small bowel resections, often occurring in patients with Crohn's disease (CD), a severe chronic gastrointestinal disorder characterized by the infiltration of inflammatory cells into the intestinal mucosa and submucosa[1,2]. Currently, no biomarkers indicate a higher risk of developing SBS or intestinal failure (IF); thus, the present study aims to evaluate the circulating cytokine/chemokine profile in patients affected by IF/SBS and CD patients at high risk of developing IF, to identify disease severity-related biomarkers.

Methods: A total of 150 CD patients were enrolled in this study, and they were stratified into four subgroups based on the disease severity: SBS patients with IF and parenteral nutrition (A1 group) or without IF and inactive disease (A3 group); CD patients with high (B group) or low risk of IF (C2 group). Circulating cytokine and chemokine levels were determined using the human 27-PLEX assay on sera collected from patients at the time of enrollment (T0, n = 70) and after 6 months (T6, n = 10).

Results: Comparisons between groups highlighted divergent cytokine signatures correlating with disease severity and nutritional support requirements. Serum cytokines and chemokines profiling at baseline (T0) and after six months (T6) revealed distinct inflammatory patterns across the study groups. Patients with SBS and IF (group A1) showed persistently elevated levels of IP-10, IL-12, MIP-1α, and G-CSF, reflecting sustained immune activation. Whereas patients at high risk of IF (group B) displayed increased levels of Eotaxin, bFGF, IL-15, and IL-6, indicative of subclinical inflammation and possible tissue remodeling. A general reduction in cytokine levels was observed at T6 compared to T0, although anti-inflammatory mediators remained minimally modulated, suggesting ongoing low-grade inflammation.

Conclusions: The differences in the levels of cytokines/chemokines among the various patient groups suggest that specific circulating cytokines may serve as potential biomarkers for the early identification of patients at risk of IF. Literature data also confirmed a role for these cytokines/chemokines in CD severity and progression[3,4]. However, further large-scale studies are needed to validate these preliminary results and to fully establish their prognostic significance.

References

1. Friedrich M, Pohin M, Powrie F. Cytokine Networks in the Pathophysiology of Inflammatory Bowel Disease. *Immunity*. 2019;50(4):992-1006. doi:10.1016/j.immuni.2019.03.017
2. Singh UP, Singh NP, Murphy EA, et al. Chemokine and cytokine levels in inflammatory bowel disease patients. *Cytokine*. 2016;77:44-49. doi:10.1016/j.cyto.2015.10.008
3. Mello JDC, Gomes LEM, Silva JF, et al. The role of chemokines and adipokines as biomarkers of Crohn's disease activity: a systematic review of the literature. *Am J Transl Res*. 2021;13(8):8561-8574.

4. Ansari N, Abdulla J, Zayyani N, Brahmi U, Taha S, Satir AA. Comparison of RANTES expression in Crohn's disease and ulcerative colitis: an aid in the differential diagnosis? *J Clin Pathol*. 2006;59(10):1066-1072. doi:10.1136/jcp.2005.034983

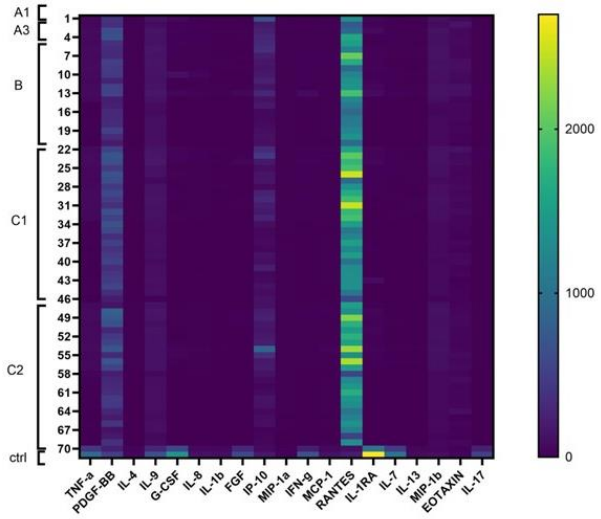

Figure 1. A heatmap of serum chemokines data analyzed using a multiplex protein assay.

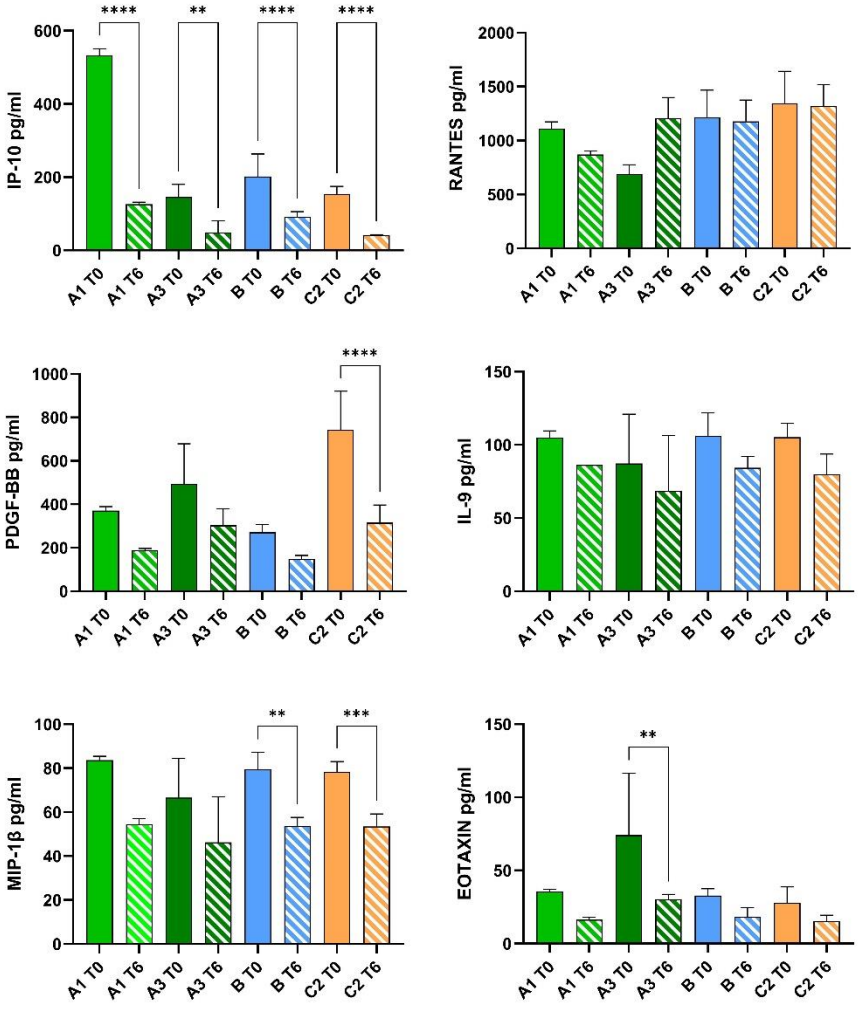

Figure2. Human circulating cytokines/chemokines profile detected using the bead-based Multiplex for the Luminex platform, at time points T0 and TM6. *P < .05, **P < .01, ***P < .001, ****P < .0001.