Serum Albumin, Ferritin, and Zinc as Biomarkers in Oral Chronic Graft-Versus-Host Disease

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SUMMARY

Oral chronic graft-versus-host disease (oral cGvHD) is a common, complex, and multifactorial complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Clinically applicable biomarkers that could support early recognition and risk stratification still remain insufficiently defined. Therefore, this study aimed to evaluate the association of selected inflammatory laboratory parameters with the occurrence and severity of oral cGvHD in comparison to non-oral cGvHD.

This prospective observational study included 84 allo-HSCT recipients (50% female), median age 48 years (range 14–68), followed by a multidisciplinary cGvHD team at University Hospital Centre Zagreb, Croatia. Chronic GvHD was diagnosed in 69 patients. According to the National Institutes of Health (NIH) criteria, oral cGvHD was present in 49 patients and 20 patients had systemic cGvHD without oral involvement. Laboratory markers were compared between oral cGvHD and the non-oral cGvHD cohort.

Serum albumin levels were significantly lower (38.78 g/L vs 40.10 g/L, $P = 0.008$), whereas ferritin levels were significantly higher (928.9 µg/L vs 556.5 µg/L, $P = 0.041$) in patients with oral cGvHD compared to those with non-oral cGvHD. Zinc concentrations were also significantly lower in the oral cGvHD group (10.8 µmol/L vs 12.1 µmol/L, $P = 0.012$). These findings indicate that hypoalbuminemia, hyperferritinemia, and reduced zinc levels are associated with oral cGvHD and may represent clinically relevant biomarkers of disease severity. Although larger prospective studies are needed to confirm the association of these biomarkers with cGvHD severity and clinical applicability, this study provides new insight into the correlation of zinc and oral cGvHD.

KEYWORDS

Albumin; Ferritin; Zinc; Chronic graft-versus-host disease; Oral chronic graft-versus-host disease

Introduction

Chronic graft-versus-host disease (cGvHD) is a multisystem disorder that may develop as a complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT)[1]. It represents the leading cause of long-term morbidity and non-relapse mortality among transplant survivors[2-5]. Chronic graft-versus-host disease (cGvHD) arises from an immune-mediated reaction in which immunocompetent donor cells recognize recipient tissues as foreign. The disease evolves through complex alloimmune and autoimmune mechanisms affecting multiple organs and tissues in an unpredictable manner, with heterogeneous clinical manifestations and a variable course.

After skin, the oral cavity is the second most commonly affected site of cGvHD, occurring in approximately 43–83% of transplant recipients. Oral cGvHD most frequently develops as part of a systemic disease, with concomitant involvement of other organs, such as the skin and gastrointestinal tract[6].

The clinical manifestations of oral cGvHD range from asymptomatic lichenoid lesions to severely painful ulcerations. Tissue damage may compromise nutritional intake, mastication, speech, swallowing, social interaction, and the ability to maintain adequate oral hygiene, particularly in the presence of salivary gland dysfunction[7,8].

Biomarkers are measurable biochemical or clinical indicators that reflect physiological or pathological processes and may also serve as markers of therapeutic response[9-11]. At the 2020 NIH Consensus Conference, the identification of clinically applicable biomarkers was highlighted as one of the key unresolved challenges in the field of cGvHD research[12,13]. Despite extensive investigation of numerous candidate markers — including cytokines, chemokines, genetic polymorphisms, circulating RNA and DNA, autoantibodies, immune cell subsets, and cellular signatures — no biomarker has yet been incorporated into routine clinical practice[14-19]. Accurate patient stratification based on reliable biomarkers could enable a timely initiation of targeted therapeutic interventions, thereby reducing the risk of progression to severe disease forms. At the same time, low-risk patients could be spared unnecessary immunosuppression, minimizing the risk of infections and relapse of the underlying disease. Ultimately, biomarker-driven risk assessment may facilitate a more personalized treatment approach based on the predicted therapeutic response[20].

The aim of this study was to evaluate the correlation of albumin, ferritin, and zinc between oral chronic GvHD and non-oral chronic GvHD as selected biochemical markers of inflammation and endothelial injury.

Patients and methods

This prospective observational study was conducted at University Hospital Centre (UHC) Zagreb and the School of Dental Medicine, University of Zagreb in collaboration with the School of Medicine, University of Zagreb, within the framework of the research project “New Biomarkers of Chronic Graft-versus-Host Disease” (IP-2016-06-8046), funded by the Croatian Science Foundation.

The study was approved by the institutional ethics committees of UHC Zagreb (*Ethics statement approval: Class: 8.1.-17/41-2; number: 02/21/JG/2019, issued on March 7, 2017*), the School of Dental Medicine of the University of Zagreb (*Ethics statement approval number: 05-PA-30-III/2019, issued on January 18, 2019)* and the School of Medicine of the University of Zagreb (*Ethics statement approval: Case number:380-59-10106-17-100/96; Class: 641-01/17-02/01, issued on March 23, 2017*).

Prior to enrollment, all participants were informed about the study’s objectives and procedures, and provided a written informed consent. The study

was conducted in compliance with the ethical principles for medical research involving human subjects of the Helsinki Declaration.

The study was performed between February 1, 2019 and March 1, 2022, and included a total of 84 consenting patients who had undergone allo-HSCT.

All study participants were evaluated by the Multidisciplinary team for the management of cGvHD and long-term complications after allo-HSCT, established at UHC Zagreb in 2013. The team consists of specialists from various disciplines, including clinicians and laboratory experts, with extensive experience in the management of patients diagnosed with cGvHD.

Within the multidisciplinary framework, the patients were first examined by a hematologist. A comprehensive medical history was obtained and a physical examination was performed, including an assessment of the underlying disease, post-transplant course, current medications, infectious complications, the level of reintegration into daily activities, and quality of life. Data regarding prior acute GvHD, the onset and duration of current symptoms suggestive of cGvHD, and the involvement of individual organs (skin, eyes, oral cavity, gastrointestinal tract, liver, lungs, urogenital, and musculoskeletal systems) were systematically recorded.

Patients

Participants were eligible for inclusion in the cGvHD group if they met all of the following criteria: age >12 years; a confirmed diagnosis of cGvHD according to the 2014 NIH consensus criteria[21,22]; enrollment in the cGvHD study conducted within a multidisciplinary team framework; and provision of a written informed consent (or parental/legal guardian consent, where applicable).

Participants were eligible for inclusion in the control group if they were older than 12 years, enrolled in the study within the same multidisciplinary framework, had no diagnosis of cGvHD according to the NIH consensus criteria, and provided a written informed consent (or parental/legal guardian consent, where applicable).

Participants were excluded if any of the following criteria were met: age ≤ 12 years; the presence of active acute GvHD; inability to understand the nature of the study and provide an informed consent; or inability to comply with study procedures due to medical or other reasons.

Oral evaluation was performed using assessment scales and criteria proposed by NIH[7,8,21]. The NIH criteria for the assessment of oral cGvHD are part of the NIH Consensus Criteria for cGvHD, initially published in 2005[21], and revised in 2014[22]. These criteria are widely applied in both clinical practice and research settings[8].

Methods

The NIH assessment of oral cGvHD consists of two components: an objective (clinical) evaluation of oral signs and a subjective assessment of symptoms, including their impact on oral function. The severity of oral cGvHD was assessed using the NIH Oral cGvHD Severity Scoring System. In this scale, grade 1 reflects disease that does not significantly interfere with oral intake, whereas grade 3 indicates severe symptoms resulting in major limitations of food consumption. Asymptomatic oral lichenoid changes, although considered diagnostic features of cGvHD, do not influence the global severity score because they do not compromise nutritional intake[8,23]. The intensity of immunosuppression was determined by the state of chronic GvHD activity (active vs inactive) and the therapeutic intention (reduction or increase of immunosuppression). The intensity of current systemic immunosuppression was evaluated according to the scale introduced by Mitchell et al[24].

Statistical analysis

Data are presented in tables and figures. The normality of distribution was assessed using the Kolmogorov–Smirnov test. As the data were not normally distributed, nonparametric statistical tests were applied, and continuous variables were summarized using medians and interquartile ranges (IQR). Differences in categorical variables were analyzed using the chi-square (χ^2) test or Fisher's exact test, as appropriate. The Fisher–Freeman–Halton exact test was applied for contingency tables larger than 2 × 2 when expected cell counts were fewer than eight observations. For 2 × 2 contingency tables, *P* values were calculated using Yates' continuity correction. Differences between patients with and without oral cGvHD were assessed using the Mann–Whitney U test. Comparisons across multiple groups were performed using the Kruskal–Wallis test. When statistically significant differences were identified, post hoc pairwise comparisons were conducted using Dunn's test. Spearman's rank correlation coefficient (ρ) was used to evaluate the association between the severity of oral cGvHD and other clinical parameters. All *P* values <0.050 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0.1 (IBM Corp., Armonk, NY, USA).

Results

Between February 2019 and March 2022, a total of 84 patients who had undergone allo-HSCT were enrolled in the study. Chronic GvHD was diagnosed in 69 patients (82.2%), whereas 15 patients (17.8%) showed no signs of cGvHD. Among the patients with cGvHD, 45 presented with both systemic and oral

Table 1. Demographic and clinical characteristics of patients treated with allo-HSCT (N = 84).

Patient characteristics		Total / N=84
Sex	M/F	42/42
Age (years)	Median (range)	48 (14-68)
Diagnosis	Myeloproliferative neoplasms Lymphoproliferative neoplasms Non-malignant	63 (75.0%) 17 (20.2%) 4 (4.8%)
Time from transplantation to enrollment (months)	Median (range)	19 (4-315)
Chronic GvHD	Yes *Systemic* *Systemic + oral* *Isolated oral* No	69 (82%) 20 (23.8%) 45 (53.6%) 4 (4.8%) 15 (18%)
Oral cGvHD	Yes No	49 (58.3%) 35 (41.7%)
Immunosuppression	No Mild Moderate Severe	43 (51.2%) 5 (6.0%) 32 (38.1%) 4 (4.8%)

involvement, 20 had exclusively extraoral manifestations, and 4 patients had isolated oral cGvHD. Patient demographic and clinical characteristics are presented in Table 1.

The total sample consisted of an equal number of men and women (42/42), and the median age was 48 years (range 14–68 years). Three quarters of the subjects (63/84) had a primary diagnosis of myeloproliferative disease, 20.2% (17/84) patients had a lymphoproliferative disease, and 4.8% (4/84) had a non-malignant hematological disease. The mean time from transplantation to follow-up was 19 months (range 4–215 months). Forty-three patients (51.2%) did not receive immunosuppressive therapy, in contrast to 41 (49.8%) patients who did; 5 (12.2%) subjects were on mild immunosuppression, 32 (78%) on moderate, and 4 (9.8%) on severe immunosuppression. Chronic GvHD was observed in over 82.1% of the patients (69/84), while oral cGvHD occurred in 49 (58.3%) patients.

The correlation of the overall severity and activity of the disease between oral and systemic cGvHD is shown in Figure 1. A slight upward trend was observed: as the intensity of systemic cGVHD increased, so did the intensity of oral cGVHD. In other words, patients with more pronounced oral

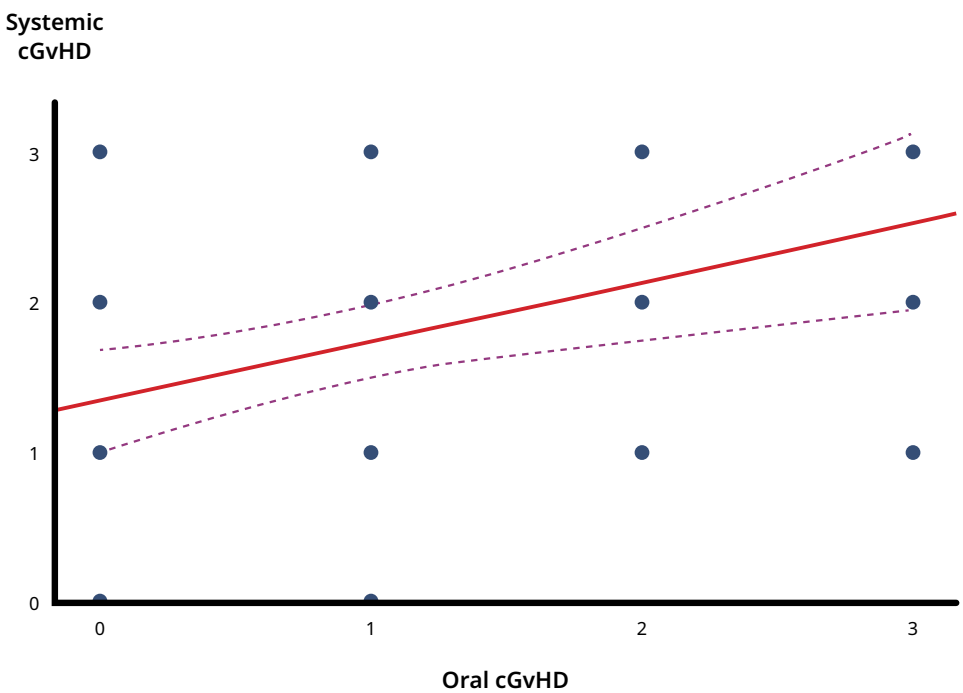


Figure 1. Correlation of overall severity and activity between oral cGvHD (N = 49) and of systemic cGvHD (N = 20) shows a statistically significant, but relatively weak positive association between oral and systemic cGvHD (Spearman's ρ = 0.306; *P* = 0.005). The severity of both variables (oral and systemic cGvHD) are scored from 0 to 3 (0 = no disease, 1 = mild, 2 = moderate, 3 = severe). Each point represents a particular severity category, while the red regression line shows the overall trend, and the dashed lines the 95% confidence interval. A slight upward trend is observed: as the intensity of systemic cGvHD increased, so did the intensity of oral cGvHD. However, the scatter of the points shows that this relationship is not strong — at almost every level of oral cGvHD, a wide range of values of systemic cGvHD was present, suggesting that more pronounced oral manifestations are associated with a higher likelihood of more pronounced systemic disease, but with significant variability among patients.

manifestations tended to have more pronounced systemic manifestations of the disease, albeit with considerable interindividual variability.

Spearman's correlation coefficient was ρ = 0.306, indicating a weak to moderate positive correlation between oral and systemic cGvHD. The *P* value was 0.005, indicating that the observed association was statistically significant ($P < 0.05$), meaning that it is unlikely that this result occurred by chance. Clinically, this finding suggests that oral cGvHD may reflect the overall intensity of systemic disease, but is not a strong enough indicator to independently predict the systemic form or severity of cGvHD. In other words, oral involvement may be a useful clinical indicator and part of the overall assessment of disease activity, but it cannot replace a comprehensive systemic evaluation of the patient.

The association between laboratory markers of inflammation, potential laboratory biomarkers of cGvHD and the severity of oral chronic cGvHD is presented in Table 2.

Patients with oral cGvHD had significantly lower serum albumin concentrations compared to non-oral GvHD patients (38.78 g/L vs 40.10 g/L; $P = 0.008$). Conversely, ferritin concentrations were significantly higher in the study group compared to controls (928.9 µg/L vs 556.5 µg/L; $P = 0.012$). Zinc concentrations were significantly lower in the oral cGvHD group (10.8 mmol/L vs 12.1 mmol/L; $P = 0.012$). Hypoalbuminemia, hyperferritinemia, and lower zinc levels showed potential prognostic value for oral cGvHD in our study.

No statistically significant differences were observed between the study groups for other biomarkers of inflammation and endothelial injury,

Table 2. Comparison of laboratory characteristics between oral and non-oral cGVHD patients

Characteristic	Non-oral cGVHD (n=20) Median (range)		Oral cGvHD (n=49) Median (range)		*P* value
ESR (mm/h)	29	(4 – 104)	24	(2 – 150)	0.513
Platelets (x10^9/L)	190	(37 – 383)	180	(31 – 423)	0.853
CRP (mg/L)	1.55	(0.30 – 24.10)	4.6	(0.3 – 132.9)	0.805
Fibrinogen (g/L)	3.6	(2.2– 6.5)	3.8	(2.2 – 8.1)	0.649
D-dimers (mg/l, FEU)	0.38	(0.13 – 6.24)	0.65	(0.14 – 6.17)	0.143
Albumin (g/L)	40.10	(24.78– 51.72)	38.78	(22.5 – 45.92)	**0.008**
Total complement	104.5	(63 – 130)	112	(85 – 130)	0.901
C3 (g/L)	1.27	(0.94 – 2,01)	1.19	(0.75 – 1.85)	0.825
C4 (g/L)	0.24	(0.15 – 0,5)	0.25	(0.14 – 0.44)	0.627
Ferritin (µg/L)	556.5	(26.9 –2429.5)	928.9	(53.1 – 8000)	**0.041**
Zn (µmol/L)	12.1	(6.2 – 16.1)	10.8	(5.7– 18)	**0.012**
Mg (mmol/L)	0.83	(0.44 – 0.96)	0.81	(0.59 – 0.99)	0.856

Abbreviations: ESR = erytrocyte sedimentation rate; CRP = C-reactive protein; Zn = zinc; Mg = magnesium

including erythrocyte sedimentation rate, platelet count, C-reactive protein, fibrinogen, D-dimers, total complement activity and complement components C3 and C4, and magnesium level, as shown in Table 3.

Table 3. Correlation of potential laboratory biomarkers and the severity of oral cGvHD (n = 49).

Laboratory variables	ρ	*P* value
ESR	–0.01	0.931
CRP	0.22	0.055
Fibrinogen	0.655	0.259
D-dimers	0.259	**0.029**
Albumin	–0.382	**0.001**
Ferritin	0.288	**0.017**
Platelets	–0.029	0.803
Zinc	–0.355	**0.002**
Total complement	–0.081	0.741
C3	–0.231	**0.076**
C4	–0.072	0.582
Magnesium	–0.267	**0.019**

Abbreviations: ρ = Spearman's rank correlation coefficient

More severe forms of oral cGvHD showed significant positive correlations with D-dimer (Spearman's ρ = 0.259, $P = 0.029$) and ferritin (ρ = 0.288, $P = 0.017$). In contrast, significant negative correlations were observed with serum albumin (ρ = –0.382, $P = 0.001$), zinc (ρ = –0.355, $P = 0.002$), and magnesium levels (ρ = –0.267, $P = 0.019$). These findings indicate that higher disease severity was associated with increased levels of D-dimer and ferritin, whereas lower concentrations of albumin, zinc, and magnesium were linked to more severe oral involvement (Table 3).

Discussion

The aim of our study was to investigate the association of selected laboratory parameters with the occurrence and severity of oral cGvHD in comparison to systemic cGvHD. Our results demonstrated that hypoalbuminemia and hyperferritinemia, as well reduced serum zinc levels, are significantly associated with the occurrence of oral cGvHD. In our study, 58% of the patients developed oral cGvHD, aligning with previously published data[6]. According to the NIH criteria, the majority of patients presented with mild disease (59%). Although the distribution of severity differed between systemic and oral cGvHD, a significant positive correlation was observed between their respective severity grades. These findings indicate that more severe systemic cGvHD was associated with more pronounced oral involvement. Due to its high prevalence, accessibility to direct clinical examination, and substantial impact on patient well-being, the oral cavity may serve as a clinically informative "window" into overall disease activity[25].

In this study, serum ferritin levels were significantly higher in patients who developed cGvHD compared to those without the disease ($P = 0.041$). Comparable findings were reported by Lelas, who observed significantly elevated ferritin levels in patients with cGvHD compared to those without the disease ($P = 0.036$)[26]. However, in contrast to our findings, other published studies do not support a direct association between elevated ferritin levels and increased incidence of cGvHD[27,28]. Elevated ferritin levels in patients with cGvHD warrant further investigation. Prospective, multidisciplinary studies incorporating serial ferritin measurements, local biological markers (e.g., salivary parameters), and a detailed assessment of oral manifestations are needed to clarify its potential role in disease stratification.

In this study, patients with oral cGvHD had significantly lower mean serum albumin levels

compared to patients without oral involvement (38.78 g/L vs 40.1 g/L, $P < 0.005$). In our cohort, albumin was negatively associated with oral cGvHD. In patients with oral cGvHD, the association with hypoalbuminemia is likely multifactorial, with reduced oral intake representing a contributing factor. Painful ulcerations, lichenoid lesions, xerostomia, and fibrosis impair mastication and swallowing, ultimately leading to decreased nutritional intake and a decline in serum albumin levels.

Grković et al. demonstrated that hypoalbuminemia is a significant and independent biomarker of cGvHD severity[29]. Similar findings were reported by Fassil et al. in an NIH-based study evaluating oral cGvHD. Patients with clinically significant oral involvement had significantly lower serum albumin levels ($P = 0.0008$) compared to those without oral manifestations[29]. Similarly, Lelas et al. reported a statistically significant difference in albumin levels between patients with and without cGvHD (42.0 g/L vs 44.3 g/L; $P = 0.005$), further supporting the clinical relevance of albumin as a marker of disease activity[30].

A particularly noteworthy finding of our study was the association between reduced serum zinc levels and both the occurrence and severity of oral cGvHD. Zinc appears to play a multifaceted role in immune reconstitution, epithelial integrity, and possibly oral disease expression[31,32]. In our cohort, serum zinc levels were significantly lower in patients with oral cGvHD compared to those without the disease (10.8 vs 12.1 µmol/L, $P = 0.012$). This finding adds to the limited evidence suggesting an association between zinc deficiency and oral cGvHD severity, highlighting a potential novel biomarker and a possible target for supportive therapeutic intervention.

This study had several methodological limitations. Its cross-sectional design precluded a longitudinal assessment of biomarker dynamics. Moreover, most patients were more than one year post-transplantation, limiting insight into early disease phases.

Conclusion

The high prevalence of oral cGvHD in a Croatian post-transplant cohort is consistent with international data. We identified several laboratory parameters associated with oral cGvHD, including albumin, ferritin, and zinc. While hypoalbuminemia confirmed its established role as a marker of systemic disease severity, hyperferritinemia may reflect inflammatory burden rather than disease specificity. Notably, the association between zinc deficiency and oral cGvHD severity represents a novel observation. These results warrant validation in prospective, multicenter studies to determine whether the integration of these biomarkers into routine clinical practice could improve early detection, risk stratification, and individualized management of oral cGvHD.

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DISCLOSURE OF CONFLICT OF INTEREST The authors confirm that they have no conflict of interest.

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SAŽETAK

Serumski albumin, feritin i cink kao biomarkeri u oralnoj kroničnoj bolesti presatka protiv primatelja

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Kronična oralna bolest presatka protiv primatelja (cGvHD) česta je i složena komplikacija nakon alogenične transplantacije krvotvornih matičnih stanica (alo-HSCT). Klinički primjenjivi biomarkeri koji bi mogli pomoći u ranom prepoznavanju i stratifikaciji rizika još su nedovoljno definirani. Cilj ove prospektivne opservacijske studije bio je ispitati povezanost odabranih upalnih laboratorijskih parametara s pojavom i težinom oralnog cGvHD-a u odnosu na ne-oralni.

Studija je obuhvatila 84 bolesnika primatelja alo-HSCT-a (50 % žena), medijan dobi 48 godina (raspon 14–68), procijenjenih u okviru multidisciplinarnog tima za cGvHD Kliničkog bolničkog centra Zagreb, Hrvatska. Kronični GvHD dijagnosticiran je u 69 pacijenata. Prema kriterijima američkog Nacionalnog instituta za zdravlje oralni cGvHD bio je prisutan u 49 pacijenata, a 20 pacijenata imalo je sistemski cGvHD bez zahvaćene usne šupljine. Laboratorijski markeri uspoređeni su u kohorti bolesnika s oralnim cGvHD-om i bolesnika sa sustavnim cGvHD-om bez zahvaćene usne šupljine.

Rezultati su pokazali značajno nižu razinu serumskog albumina (38,78 g/L naspram 40,10 g/L, $P = 0,008$), dok su razine feritina bile značajno više (928,9 µg/L naspram 556,5 µg/L, $P = 0,041$) u bolesnika s oralnim cGvHD-om u usporedbi s bolesnicima s ne-oralnim cGvHD-om. Koncentracije cinka također su bile značajno niže u skupini s oralnim cGvHD-om (10,8 µmol/L naspram 12,1 µmol/L, $P = 0,012$). Ovi rezultati ukazuju na to da su hipoalbuminemija, hiperferitinemija i smanjene razine cinka povezane s oralnim cGvHD-om i mogu predstavljati klinički relevantne biomarkere intenziteta bolesti. Iako su potrebne veće prospektivne studije kako bi se potvrdila njihova povezanost sa cGvHD-om i klinička primjenjivost, ova studija pruža novi uvid u korelaciju cinka i oralnog cGvHD-a.

KLJUČNE RIJEČI

Albumin; Feritin; Cink; Kronična bolest presatka protiv primatelja; Oralna kronična bolest presatka protiv primatelja