Nutritional Support With Oral Polymeric Formulation Enriched With Transforming Growth Factor beta 2 (TGF-β2) in Allogenic Hematopoietic Stem Cells Transplantation (Allo-hsct): A Prospective Interventional Study

Francesco Arena (arena.nutrizione@gmail.com)
Dietitan

Morello Enrico
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Turra Alessandro
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Malagola Michele
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Farina Mirko
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Polverelli Nicola
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Cavagna Elsa
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Meris Manuel
University of Brescia Department of Medical and Surgical Sciences: Universita degli Studi di Brescia Dipartimento Specialita Medico-Chirurgiche Scienze Radiologiche e Sanita Pubblica

Gandolfi Lisa
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Zollner Tatiana
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Accorsi Buttini Eugenia
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Ricci Chiara
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Leoni Alessandro
University of Brescia Department of Medical and Surgical Sciences: Universita degli Studi di Brescia Dipartimento Specialita Medico-Chirurgiche Scienze Radiologiche e Sanita Pubblica

Samarani Emanuela
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia
Bertulli Alice
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia
Simona Bernardi
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia
Russo Domenico
ASST Spedali Civili di Brescia: Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

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Research Article

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Abstract

Purpose

In the allogeneic transplant setting (allo-HSCT), the prevalence of malnutrition at admission is usually low, but at discharge, may be 60% or more and it may affect the transplant outcome.

The aim of this study was to reduce the incidence of severe malnutrition (PG-SGA C) at day + 28 days from allo-HSCT in patients supported with an oral polymeric formulation enriched with Transforming Growth Factor beta 2 (TGF-β2).

Methods

Fifty-one patients were consecutively enrolled between March 2020 and June 2021 in this prospective interventional study. As a group of control, we have retrospectively analyzed an observational cohort composed by thirty patients submitted to allo-HSCT from august 2017 and august 2018 in our institution.

Results

The incidence of severe malnourished patients (PG-SGA C) at + 28 days was significantly lower in the group with an oral nutritional support (ONS) treatment ratio (TR) major than 50% (TR>50%) in comparison to the ones with less than 50% ONS assumption (TR<50%) (13% vs 88.9% P=0.000).

Interestingly, cumulative incidence of gastrointestinal (GI) aGVHD was significantly lower in patients assuming 50% or more of the prescribed ONS dose in comparison to those who assumed less than 50% of ONS (0%, vs 29.6%; p=0.005). Pneumonia was more frequent in patients with TR < 50% compared to patients with TR > 50% (48.1 % and 12.5 % respectively)(p=0.006).

Conclusion

MODULEN-IBD® seems to be a promising ONS to reduce malnutrition in allogeneic stem cell transplantation and should be tested in a randomized controlled prospective trial. MODULEN-IBD® may also have some positive immunological effects on gastrointestinal GVHD and infections that should be explored in larger studies.

Introduction

Allogenic hematopoietic stem cells transplantation (allo-HSCT) is a curative treatment for several hematologic malignancies(1). Conditioning regimens based on high-dose chemotherapy, with or without body irradiation, frequently induce dysgeusia, oral mucositis, nausea/vomiting, diarrhea, anorexia, and abdominal pain that can severely affect food intake and nutritional status (2–6). Moreover, severe

malnutrition can affect the transplant outcome by prolonging time to engraftment, increasing the infectious risk, the duration of hospital stay and mortality (7–9).

In this scenario, nutritional assessment and nutritional support appear to be crucial for managing allo-HSCT patients and improving the transplant outcome (8–11). This aspect is even more important if we consider that over the last ten years the age limit for transplantation has risen to 75 years and the patients over 60 years of age who have been transplanted exceed 30% (14).

The Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire has been recently validated in Italian language (12) and is actually recommended as the gold standard tool for nutritional screening, assessment, monitoring and triaging for nutritional interventions in patients with cancer (13–15).

Regarding nutritional support, enteral nutrition (EN) is generally considered the better approach in oncology but, if it cannot be pursued, parenteral nutrition (PN) is recommended (16). In HSCT, PN is generally reserved in case of severe mucositis (Grade 3-4), ileus, or intractable vomiting (16) and should be continued until resolution of the complications (17). Although ASPEN and ESPEN guidelines recommend EN as the first choice in nutritional support in HSCT (17, 18), parenteral nutrition is still most widely used in HSCT settings (19). Even more, it is well known that PN may be associated with gut mucosal atrophy, metabolic and hepatic complications, central venous catheter infections, fluid overload and hyperglycemia, that increase the risk of systemic infections and inflammation as well (11, 19–22).

GVHD is the main cause of transplant-related morbidity and mortality after disease relapse (26). From a clinical and pathogenetic point of view, gastrointestinal (GI) aGVHD shares many aspects with chronic inflammatory bowel diseases (IBD), such as, the loss of the intestinal epithelial barrier, alterations in the intestinal microbiota, and also the use of immunosuppressive therapies for clinical interventions (23–30). In IBD setting, TGF-b2 is the most studied bioactive peptide for nutritional support (31). TGF-b2 is an anti-inflammatory cytokine and it’s a key modulator of the microbiota. It has also a relevant role in host immune cell cross talk, in particular it controls the differentiation, proliferation and activation state of lymphocytes, macrophages and dendritic cells, and it plays a critical role in mechanisms of tolerance, prevention of autoimmunity and in anti-inflammatory processes in gut as well (31, 32).

Patients And Methods

Study Protocol

The study was approved by the local ethical committee in March 2020. After signing informed consent and nutritional evaluation by a dietitian with PG-SGA score. Nutritional support with MODULEN-IBD® was proposed to all enrolled patients.

Patients aged over 18 years old submitted to allogeneic bone marrow transplantation were included into the study, while exclusion criteria were unsigned informed consent, gastrointestinal perforations and fistulas, intractable vomiting.

Fifty-one patients were consecutively enrolled between March 2020 and June 2021 in this prospective interventional study exploring the use of an oral polymeric nutritional supplement (ONS) enriched with Transforming Growth Factor beta 2 (TGF-β2) (MODULEN IBD®) in the prevention of malnutrition at day + 28 in allo-HSCT. Modulen IBD® (Nestle, Switzerland) is an oral polymeric supplement rich in TGF-β2 widely used in IBD settings (31).

Nutritional status was assessed through the PG-SGA questionnaire (15) at admission and at day 0, +7, +14,+21 and + 28 from transplant (day 0 was the CSE re-infusion).

Incidence of malnutrition (PG-SGA C) at + 28 days from allo-HSCT was the primary outcome.

PG-SGA is composed of an objective section and a patient reported one.

The first reports the overall nutritional status in an alphabetical score (A= good nutritional status; B= moderate malnutrition; C= severe malnutrition).

The second one is a numeric score that is calculated from 4 items patients reported (weight loss, food intake, symptoms with a nutritional impact and physical activity).

As group of control, we have retrospectively analyzed 30 patients submitted consecutively to allo-HSCT from august 2017 and august 2018 at our Institution. Also, in this retrospective cohort, the nutritional evaluation was performed weekly by a dietitian with PG-SGA score. In the control group, nutritional support was the Parenteral Nutrition (PN) when oral food intake was less than 60% of hospital meals for at least three days and /or oral mucositis grade 3-4, intractable diarrhea and vomiting were present, according to the criteria reported in ESPEN Guidelines 2009 (16).

Nutritional support plan

The oral polymeric nutritional supplement (ONS) with TGF-β2 (MODULEN IBD®) was diluted in a bottle of mineral water and proposed one or more times a day if necessary. The nutritional support started at – 7 day to + 28 day from allo-HSCT. Refusal and reasons for refusal of the proposed treatment have been recorded.

The amount of calories derived by oral supplement was calculated at admission on BMI and Total daily energy expenditure (TDEE) multiplying BMR (Mifflin St Jeor BMR estimation formula was used) by 1.3 (Physical activity level). From admission to the day of transplant, the amount calories derived from oral formulation enriched with Transforming Growth Factor beta 2 was:

- if BMI less than 22: 20% of TDEE;

- if BMI between 22.1 and 24.9: 12 % of TDEE;

- if BMI between 25 and 29.9: 10% of TDEE;

- if BMI between 30 and 34.9: 8% of TDEE;

- if BMI was more than 35: 5% of TDEE.

From day 1 to day + 28 from transplantation, the quantity of supplement has been increased by 10% compared to the initial dose if the patient shows a weight loss of less than 5% during hospitalization; with a weight loss of more than 5%, the dose of oral formulation has been increased by 20% compared to the starting dose.

Once reconstituted by the staff, the supplement could be flavored according to the patient's taste with barley coffee or decaffeinated coffee.

Compliance in ONS intake was investigated with a specific questionnaire and percentage of administered dose compared to prescribed dose was registered daily (Treatment Ratio - TR).

Adverse events were reported according to good clinical practice (GCP).

Statistics

The goal of the study was to reduce the incidence of severe malnutrition (PG-SGA C) at day + 28 from allo-HSCT to less than 50% in comparison to an historical control (in which the incidence of severe malnutrition at +28 days after allo-HSCT was 75%). The study was closed when at least 24 subjects took at least 50% of the prescribed ONS (sample size calculation with power of 75% and alpha 0.05).

In the analysis all the 51 patients were reported.

Impact on malnutrition and clinical outcomes were explored according to ONS intake in percentage on prescribed dose (TR). No minimal dose was defined as clinically effective, but in the protocol design 50% of the prescribed ONS was considered adequate.

Mann-Whitney test was used for statistical analysis regarding association between TR and malnutrition, acute GVHD onset or clinical events (sepsis or pneumonia). Overall survival at 365 days after transplant was estimated with Kaplan Mayer curves and Log-Rank test was used for univariate analysis. Cumulative incidence of acute GVHD was calculated at 4 months after transplantation. For the log-rank and fisher tests patients were grouped according to the treatment ratio (TR) (TR > or < 50% based on study protocol). Treatment ratio (TR) is defined as the percentage of ONS intake on prescribed dose. No differences were found in patients' characteristics at admission between groups with TR<50 %, TR>50% and historical control group.

Results

1) Patients characteristics

The study cohort was composed of fifty-one patients: twenty-two women and twenty-nine men. Most of the patients (78.5%) were diagnosed with Acute myeloid leukemia, Myelodysplastic syndrome or Myeloproliferative disease. All characteristics are resumed in Table 1.

Between the historical control group and study cohort, at admission patient's characteristics were similar to the study cohort (TAB 1b).

2) MODULEN IBD ® Safety

Among 51 patients no adverse events attributable to ONS administration were reported.

Percentage of ONS intake on prescribed dose was reported (TR) and cause of refusal registered. Mean TR of the whole population was 60%, median 46%, minimum 3%-maximum 224%.

Main reasons for refusal of the oral formulation were due to a disgusting sensation in 19/27 cases (70%), mucositis in 10/27 (37%) or respiratory complications involving the use of non-invasive ventilation in 5/27 (18.5%). In the dedicated questionnaire, patients could report more than one reason for refusal.
3) MODULEN IBD ® Efficacy

PG-SGA assessment was performed twice weekly and registered at admission, day of transplant (day 0), +7, +14, +21 and +28 days from allo-HSCT.

At admission, thirty-eight (74,5%) patients were well nourished (PG-SGA score A), twelve (23,5%) patients were moderately malnourished (PG-SGA score B) and only one (2%) patient was admitted in severe malnutrition conditions (PG-SGA score C).

At day + 28 from allo-HSCT, seven (13.8%) patients were well nourished (PG-SGA score A), seventeen (33,3%) patients were moderately malnourished (PG-SGA score B) and twenty-seven (52.9%) patients had a severe malnutrition (PG-SGA score C).

The mean percentage of TR in the group with PG-SGA score A (well nourished) was 129%, in the group with PG-SGA score B (moderate malnutrition) was 85% and 27% in the group with PG-SGA C (severe malnutrition). The difference was proved to be statistically significant (between A and B p=0.045 and between both A+B and C p=0.000; Mann-Whitney Test) (FIGURE 1).

The percentage of prescribed dose ranging from 3–224%, median 46%. Higher TR, less subjective PG-SGA values (patients reported numeric score) were registered at 28 days after transplantation (correlation R2 0.288, p=0.000) (FIGURE 2).

The percentage of severe malnourished patients (PG-SGA C) at + 28 days was significantly lower in the group with a treatment ratio (TR) major than 50% in comparison to the group with insufficient ONS assumption (TR<50%) (13% vs 88.9% P=0.000) (TAB 2).

In the historical control group, the incidence of severe malnutrition (PG-SGA C) at + 28 day from allo-HSCT was 75% (21 of 28 evaluable patients) (TAB 3)

Both in groups with TR < 50 % and historical control group, no patient was in PG-SGA score A (good nutritional status); while in group TR > 50% seven out twenty patients (30.4%) were well nourished (PG-SGA A).

No statistical differences were found in baseline patients' characteristics at admission in patients with a treatment ratio >50% in comparison to those who did not and the historical control group.

No statistically significant correlation was found between type of conditioning and nutritional status at day + 28 from allo-HSCT.

4) Infective complications

In study cohort, sepsis occurred in 22 patients (43.1%), and pneumonia in 15 (29.4%) ones.

Pneumonia was more frequent in patients with TR < 50% compared to patients with TR > 50% (48.1 % and 12.5 % respectively)(p=0.006).

Sepsis was more frequent in patients with TR < 50% compared to patients with TR > 50% (55.5 % and 29.1 % respectively) (n.s.) (TAB 2).

5) GVHD

Cumulative incidence at 100 days of aGVHD was 41%.

No hepatic aGVHD was registered. No statistical differences were proved between TR and aGVHD incidence. Cumulative incidence of aGVHD according to TR was: 29.1 % in patients with TR > 50% and 51.8% in patients with TR < 50%.

Acute gastrointestinal GVHD (GI GVHD) (any grade) was reported in 8 patients (15.7%), none died due to aGVHD.

The mean ONS dose in patients developing acute GI GVHD was 18%, whereas patients not developing acute GI GVHD assumed a mean percentage of 68% of ONS (p=0.002; Mann-Whitney Test) (SUPPLEMENTARY FIGURE 1).

Cumulative incidence of GI aGVHD was significantly lower in patients assuming at least 50% of the proposed treatment in comparison to those who assumed less than 50% of ONS (0% vs 29.6%; p=0.005) (SUPPLEMENTARY FIGURE 2).

In the historical control group, the cumulative incidence of GI GVHD was 20%.

6) Mortality

Transplant related mortality (TRM) at + 100 days from transplantation was 11,7 %.

Overall survival at + 365 days from transplantation was 61.5 %.

No statistical differences were found in overall survival between patients with TR> 50% and those with TR< 50% (50% vs 73.7% respectively).

In the historical control group, overall survival was 63.3%.

Transplant related mortality (TRM) at + 100 days from transplantation in historical control group was 20 %.

Discussion

The main objective of this prospective interventional study was to evaluate the incidence of severe malnutrition (PG-SGA C) at 28 days after bone marrow transplantation in a cohort of 51 patients supported, from admission to day + 28, with an oral polymeric nutritional supplement (ONS) enriched with Transforming Growth Factor beta 2.

From August 2017 to August 2018, an observational study was conducted in 30 patients submitted to allo-HSCT in order to evaluate the nutritional status during allo-transplantation. A standardized nutritional assessment protocol was created. This protocol provided a weekly nutritional assessment with PG-SGA score from admission to day + 28. PG-SGA is a score recognized as the gold standard for nutritional assessment in oncology/hematology settings (12, 15, 35–37).

In this observational study, 74% of the patients had a good nutritional status (PG-SGA A) at admission. Severe malnutrition (PG-SGA C) increased by a factor 10 from admission to day + 7 (from an incidence of 3.25 % to 32.5%) and at day + 28 no patients were in good nutritional status and 75% of them were severely malnourished (PG-SGA C). During hospitalization, nutritional status progressively worsened and a statistically significant delta in the incidence of severe malnutrition was found between admission to +7 days from allo-HSCT. In the first two weeks of transplantation, patients often showed chemotherapy side effects such as mucositis, nausea, vomiting, diarrhea and dysgeusia. All these signs and symptoms of the conditioning regimen may lead patients to eat less and results in a rapidly worsen nutritional status, that in an oncology/transplant setting is often irreversible in the short-term period and is associated with a higher risk of infection, pneumonia, GVHD, mortality and longer hospitalization (6, 38).

These data shown how the first two weeks after allo-HSCT are crucial for the nutritional status of transplanted patients and led us to define them as the “golden nutritional weeks". Preserving a good nutritional status in this period may result in benefit for patients’ outcome. So, assessing the nutritional status with a standardized, specific and dynamic score; managing all the nutritional symptoms; starting an early and personalized nutritional support (preferably enterally), monitoring its effect on the nutritional status, are fundamental steps that should be part of the clinical practice of all transplant centers during all transplantation period, in particular from admission to day + 28.

For these reasons, a prospective study was designed to investigate the safety and effects of earlier prophylactic oral nutritional support in 51 patients submitted to allo-HSCT. The nutritional support consisted of an oral polymeric nutritional supplement (ONS) enriched with Transforming Growth Factor beta 2 (TGF-β2) (MODULEN IBD®). This supplement administration has been started from admission to day + 28 from transplantation.

Actually, many oral nutritional supplements are available in order to fight and prevent malnutrition, but MODULEN-IBD® was chosen thanks to the data derived from several researches showing that this oral supplement is safe, useful and effective both in improving nutritional status and gastrointestinal inflammation in IBD patients (39). In particular, one randomized clinical study showed that exclusive enteral nutrition with MODULEN-IBD® is more efficient to achieve mucosal healing than corticosteroids; proving in addition that this ONS have a trophic, anti-inflammatory and microbiota modulating effects on gastrointestinal tract (40). The anti-inflammatory effect of MODULEN-IBD® is attributable to the high rich in TGF-β: an immunosuppressive cytokine involved in the development and functions of immune cells, including T and B cells and also dendritic cells (DCs) (32).

In this prospective study, an early oral nutritional support was feasible and safe. Patients who took at least the half of the protocol-prescribed dose seems to have a reduced incidence of severe malnutrition at 28 days after transplant; indeed, similar to historical control group, the prevalence of malnutrition at admission in this fifty-one patients was low (3.25%), but at day + 28 there is a statistically significant difference in severe malnutrition incidence (PG-SGA score C) between patients that took at least 50% of prescribed ONS and patients that for many reasons took less than 50% of prescribed ONS (13 % vs 88.9 %; p=0.000) (TAB 2).

These data are confirmed by the fact that the mean percentage of Treatment Ratio (TR) in the group with PG-SGA score A at + 28 days from allo-HSCT (well nourished) was 129%, in the group with PG-SGA score B (moderate malnutrition) was 85% and 27% in the group with PG-SGA C (severe malnutrition). The difference was proved to be statistically significant (between A and B p=0.045 and between both A+B and C p=0.000; Mann-Whitney Test) and the effect on nutritional status may be dose dependent (FIGURE 1). The dose dependency of MODULEN-IBD® was also reported in the PG-SGA score assessment: more was the intake of ONS, less was the PG-SGA numeric score (Figure 2). Higher the score, the worse is nutritional status patients reported.

As explained in the introduction, both in IBD and bone marrow transplantation settings, malnutrition and immunity response on gastrointestinal tract are relevant. Both from a clinical and pathogenetic point of view, GI aGVHD shares many aspects with chronic inflammatory bowel diseases (IBD), such as, the loss of the intestinal epithelial barrier; alterations in the intestinal microbiota; cascade of T cell activation, proliferation, and cytotoxic activity; and also, the use of immunosuppressive therapies (25, 27). In bone marrow transplantation, acute GVHD may appear in 20% – 40% of patients with match related donor, and in over 50% of haploidentical stem cells transplantation (41). Regarding gastrointestinal acute GVHD, up to 50% of patients with acute GVHD experience gastrointestinal symptoms (41).

All these observations allow us to hypothesize that MODULEN-IBD® may also reduce the risk of GI GVHD thanks to its trophic, anti-inflammatory and microbiota modulating effects on gastrointestinal tract.

Reducing GI GVHD cumulative incidence was not the primary goal of the study, but patients assuming more than 50% of the protocol-prescribed ONS did not experience GI aGVHD (SUPPLEMENTARY FIGURE 2) and the effect seems to be dose dependent (SUPPLEMENTARY FIGURE 1).

Explaining the reasons under these data is not trivial. Probably may be essential to evaluate the role of a prophylactic and earlier oral intake of MODULEN-IBD® from admission to + 28 days from admission. This choice probably allowed to avoid or reduce microbiota dysbiosis: an important risk factor for GI GVHD (42, 44).

Furthermore, loss of microbiota diversity and the reduction of short chain fatty acids production has been observed in patients with GVHD (42, 44). Acetate, propionate, and butyrate are metabolites produced by microbiota and play an important role in the interaction between the microbiota and host immune cells, influencing systemic autoimmune responses and participating in different steps of inflammation process (42, 45). So, MODULEN-IBD® administration in patients submitted to allo-HSCT may to reduce the risk of GI GVHD thanks to its microbiota modulating, anti-inflammatory and trophic effects. Regarding intestinal tropism, often patients with mucositis refuse food and this further worsens intestinal dysbiosis. However, thanks to the consistency of MODULEN-IBD®, patients often continued to take the supplement by mouth despite oral pain, avoiding fasting. This may allow patients to maintain microbiota feed and diversify.

Regarding infectious diseases, several studies demonstrated that malnutrition is a primary risk factor for several complications after allo-HSCT, in particular infection and GVHD (43).

In particular, in this prospective study pneumonia was more frequent in patients with TR < 50% compared to patients with TR > 50% (48.1 % and 12.5 % respectively)(p=0.006) (TAB 2). Due to the low number of patients experiencing pneumonia, the role of MODULEN-IBD® could be only speculated: pneumonia and in particular noninvasive ventilation (used in 5 patients) impaired oral assumption of ONS and food, this could explain the difference between these two groups. On the other side, in these 5 patients was observed a reduced intake of ONS before pneumoniae onset and maybe malnutrition could favor pneumonia onset. Furthermore, a non-significant trend regarding sepsis incidence was more frequent in patients with TR < 50% compared to patients with TR > 50% (55.5 % and 29.1 % respectively)(ns) (TAB 2).

Conclusions

In this study, an early and prophylactic oral nutritional support, started at admission to day + 28 from transplantation, has reduced with no side effects the incidence of severe malnutrition at day + 28 (PG-SGA C) in patients submitted to allo-HSCT.

ONS seems to have a protective role also in prevention of gastrointestinal GVHD and infections, maybe due to anti-inflammatory, immunomodulating and trophic effects on gastrointestinal tract and

microbiota, but larger randomized studies are warranted. In the design of such studies the role of nasogastric tube could overcome problems such as the taste of MODULEN-IBD® and the chemotherapy side effects that impede patients from eating orally.

Declarations

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Nestlé Health Science did NOT provide MODULEN-IBD®.

Conflicts of interest/Competing interests: (include appropriate disclosures)

Availability of data and material: This research is not registered on publicly available databases. All the data are saved in anonymous database and a subsequent analysis should be performed.

Code availability: Not Applicable

Authors' contributions:

- Arena Francesco: Conceptualization; Methodology; Formal analysis; Investigation; Data Curation; Writing - Original Draft; Visualization.
- Morello Enrico: Conceptualization; Methodology; Principal Investigator; Investigation; Data Curation; Formal analysis; Writing - Original Draft; Visualization; Project administration.
- Turra Alessandro: Investigation; Writing - Review & Editing.
- Malagola Michele: Investigation; Writing - Review & Editing.
- Farina Mirko: Investigation; Writing - Review & Editing.
- Polverelli Nicola: Investigation; Writing - Review & Editing.
- Cavagna Elsa: Writing - Review & Editing.
- Meris Manuel: Data Curation; Formal analysis.
- Gandolfi Lisa: Investigation; Writing - Review & Editing.
- Zollner Tatiana: Investigation; Writing - Review & Editing.
- Accorsi Buttini Eugenia: Investigation; Writing - Review & Editing.
- Andreoli Marco: Writing - Review & Editing.
- Ricci Chiara: Validation; Writing - Review & Editing.
- Leoni Alessandro: Data Curation.
- Samarani Emanuela: Investigation.
- Bertulli Alice: Investigation.
- Simona Bernardi: Investigation; Writing - Review & Editing.

- Russo Domenico: Conceptualization; Methodology; Writing - Review & Editing; Visualization; Supervision; Project administration.

Ethics approval: This study was approved by Ethical Committee in February 2020 (number of procedure NP 3832).

Consent to participate: a specific informed consent has been created and approved by the ethics committee.

Consent for publication: in the informed consent given to patients in the enrolling phase, it was specified that the data collected would be used anonymously for research purposes.

References

1. Baumgartner A, Bargetzi A, Zueger N, Bargetzi M, Medinger M, Bounoure L, et al. Revisiting nutritional support for allogeneic hematologic stem cell transplantation—a systematic review. Bone Marrow Transplant. 9 gennaio 2017;52:506–13.

2. Espinoza M, Perelli J, Olmos R, Bertin P, Jara V, Ramírez P. Nutritional assessment as predictor of complications after hematopoietic stem cell transplantation. Rev Bras Hematol E Hemoter. gennaio 2016;38(1):7–14.

3. Sommacal HM, Gazal CHA, Jochims AMK, Beghetto M, Paz A, Silla LM da R, et al. Clinical impact of systematic nutritional care in adults submitted to allogeneic hematopoietic stem cell transplantation. Rev Bras Hematol E Hemoter. 2012;34(5):334–8.

4. Imataki O, Nakatani S, Hasegawa T, Kondo M, Ichihashi K, Araki M, et al. Nutritional support for patients suffering from intestinal graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Am J Hematol. ottobre 2006;81:747–52.

5. Gyurkocza B, Rezvani A, Storb RF. Allogeneic hematopoietic cell transplantation: the state of the art. Expert Rev Hematol. giugno 2010;3(3):285–99.

6. Brotelle T, Lemal R, Cabrespine A, Combal C, Hermet E, Ravinet A, et al. Prevalence of malnutrition in adult patients previously treated with allogeneic hematopoietic stem-cell transplantation. Clin Nutr. aprile 2018;37(2):739–45.

7. Rzepecki P, Barzal J, Sarosiek T, Szczylik C. Biochemical indices for the assessment of nutritional status during hematopoietic stem cell transplantation: are they worth using? A single center experience. Bone Marrow Transplant. 16 luglio 2007;40:567–72.

8. Wang B, Yan X, Cai J, Wang Y, Liu P. Nutritional assessment with different tools in leukemia patients after hematopoietic stem cell transplantation. Chin J Cancer Res. 2013;25(6):8.

9. Liu P, Wang B, Yan X, Cai J, Wang Y, Department of Clinical Nutrition, et al. Comprehensive evaluation of nutritional status before and after hematopoietic stem cell transplantation in 170 patients with hematological diseases. Chin J Cancer Res. 2016;28(6):626–33.

10. Hadjibabaie M, Iravani M, Taghizadeh M, Ataie-Jafari A, Shamshiri AR, Mousavi SA, et al. Evaluation of nutritional status in patients undergoing hematopoietic SCT. Bone Marrow Transplant. ottobre 2008;42(7):469–73.

11. Morello E, Guarinoni MG, Arena F, Andreoli M, Bernardi S, Malagola M, et al. A Systematic Review of the Literature and Perspectives on the Role of Biomarkers in the Management of Malnutrition After Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 6 gennaio 2021;11:535890.

12. Ripamonti C.I., Arena F, Ferrara ML, Jager-Wittenaar H. Linguistic and content validation of the Patient-Generated Subjective Global Assessment (PG-SGA) translated and culturally adapted to the Italian setting. 2018;1.

13. Gangadharan A, Choi SE, Hassan A, Ayoub NM, Durante G, Balwani S, et al. Protein calorie malnutrition, nutritional intervention and personalized cancer care. Oncotarget [Internet]. 4 aprile 2017 [citato 18 ottobre 2018];8(14). Disponibile su: http://www.oncotarget.com/fulltext/15103

14. Falda M, Busca A, Baldi I, Mordini N, Bruno B, Allione B, et al. Nonmyeloablative allogeneic stem cell transplantation in elderly patients with hematological malignancies: Results from the GITMO (Gruppo Italiano Trapianto Midollo Osseo) multicenter prospective clinical trial. Am J Hematol. ottobre 2007;82(10):863–6.

15. de Defranchi RLB, Bordalejo A, Cañueto I, Villar A, Navarro E. Evolution of nutritional status in patients with autologous and allogeneic hematopoietic stem cell transplant. Support Care Cancer. 28 ottobre 2014;23:1341–7.

16. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M. ESPEN Guidelines on Parenteral Nutrition: Non-surgical oncology. Clin Nutr. agosto 2009;28(4):445–54.

17. August DA, Huhmann MB. A.S.P.E.N. Clinical Guidelines: Nutrition Support Therapy During Adult Anticancer Treatment and in Hematopoietic Cell Transplantation. J Parenter Enter Nutr. 27 agosto 2009;33:472–500.

18. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr. ottobre 2017;36:1187–96.

19. Arfons LM, Lazarus HM. Total parenteral nutrition and hematopoietic stem cell transplantation: an expensive placebo? Bone Marrow Transplant. agosto 2005;36(4):281–8.

20. Verdi Schumacher M, Moreira Faulhaber GA. Nutritional status and hyperglycemia in the peritransplant period: a review of associations with parenteral nutrition and clinical outcomes. Rev Bras

Hematol E Hemoter. aprile 2017;39(2):155–62.

21. Azarnoush S, Bruno B, Beghin L, Guimber D, Nelken B, Yakoub-Agha I, et al. Enteral nutrition: a first option for nutritional support of children following allo-SCT? Bone Marrow Transplant. settembre 2012;47(9):1191–5.

22. Mattsson J, Westin S, Edlund S, Remberger M. Poor oral nutrition after allogeneic stem cell transplantation correlates significantly with severe graft-versus-host disease. Bone Marrow Transplant. novembre 2006;38(9):629–33.

23. Sheean P, Braunschweig C. The Incidence and Impact of Dextrose Dose on Hyperglycemia From Parenteral Nutrition (PN) Exposure in Hematopoietic Stem Cell Transplant (HSCT) Recipients. J Parenter Enter Nutr. luglio 2006;30(4):345–50.

24. Fuji S, Kim S-W, Mori S, Fukuda T, Kamiya S, Yamasaki S, et al. Hyperglycemia During the Neutropenic Period Is Associated With a Poor Outcome in Patients Undergoing Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation: Transplantation. ottobre 2007;84(7):814–20.

25. Fredricks DN. The gut microbiota and graft-versus-host disease. J Clin Invest. 1 maggio 2019;129(5):1808–17.

26. Couriel D, Caldera H, Champlin R, Komanduri K. Acute graft-versus-host disease: Pathophysiology, clinical manifestations, and management. Cancer. 2004;101(9):1936–46.

27. Nalle SC, Turner JR. Intestinal barrier loss as a critical pathogenic link between inflammatory bowel disease and graft-versus-host disease. Mucosal Immunol. 6 maggio 2015;8:720–30.

28. Bassim CW, Fassil H, Dobbin M, Steinberg SM, Baird K, Cole K, et al. Malnutrition in patients with chronic GVHD. Bone Marrow Transplant. 14 luglio 2014;49:1300–6.

29. Limketkai BN, Wolf AS, Parian AM. in the Patient with Inflammatory Bowel Disease. In 2018.

30. Naymagon S, Naymagon L, Wong S-Y, Ko HM, Renteria A, Levine J, et al. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. Nat Rev Gastroenterol Hepatol. dicembre 2017;14(12):711–26.

31. Hartman C, Berkowitz D, Weiss B, Shaoul R, Levine A, Adiv OE, et al. Nutritional Supplementation with Polymeric Diet Enriched with Transforming Growth Factor-Beta 2 for Children with Crohn's Disease. 2008;10:5.

32. Bauché D, Marie JC. Transforming growth factor β: a master regulator of the gut microbiota and immune cell interactions. Clin Transl Immunol. 7 aprile 2017;6(4):e136.

33. Grover Z, Lewindon P. Two-Year Outcomes After Exclusive Enteral Nutrition Induction Are Superior to Corticosteroids in Pediatric Crohn's Disease Treated Early with Thiopurines. Dig Dis Sci. ottobre 2015;60(10):3069–74.

34. Levine A, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. Gastroenterology. agosto 2019;157(2):440-450.e8.

35. Abbott J, Teleni L, McKavanagh D, Watson J, McCarthy AL, Isenring E. Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) is a valid screening tool in chemotherapy outpatients. Support Care Cancer. 19 aprile 2016;24:3883–7.

36. Nitichai N, Angkatavanich J, Somlaw N, Voravud N, Lertbutsayanukul C. Validation of the Scored Patient-Generated Subjective Global Assessment (PG-SGA) in Thai Setting and Association with Nutritional Parameters in Cancer Patients. Asian Pac J Cancer Prev. 1 aprile 2019;20(4):1249–55.

37. Shaw C, Fleuret C, Pickard JM, Mohammed K, Black G, Wedlake L. Comparison of a novel, simple nutrition screening tool for adult oncology inpatients and the Malnutrition Screening Tool (MST) against the Patient-Generated Subjective Global Assessment (PG-SGA). Support Care Cancer. gennaio 2015;23(1):47–54.

38. Fuji S, Einsele H, Savani BN, Kapp M. Systematic Nutritional Support in Allogeneic Hematopoietic Stem Cell Transplant Recipients. Biol Blood Marrow Transplant. ottobre 2015;21(10):1707–13.

39. Boumessid K, Barreau F, Mas E. How Can a Polymeric Formula Induce Remission in Crohn's Disease Patients? Int J Mol Sci. 14 aprile 2021;22(8):4025.

40. Pigneur B, Ruemmele FM. Nutritional interventions for the treatment of IBD: current evidence and controversies. Ther Adv Gastroenterol. gennaio 2019;12:175628481989053.

41. Moreno DF, Cid J. Graft-versus-host disease. Med Clínica Engl Ed. gennaio 2019;152(1):22–8.

42. Shono Y, Docampo MD, Peled JU, Perobelli SM, Jenq RR. Intestinal microbiota-related effects on graft-versus-host disease. Int J Hematol. 27 marzo 2015;101:428–37.

43. Garzón Herazo JR, Muñoz Velandia OM, Solano JC, Molina Pimienta L, Figueroa Lemus WJ. The nutrition risk index is associated with bacteremia within 30 days after autologous stem cell transplantation in patients with multiple myeloma. Transpl Infect Dis [Internet]. agosto 2020 [citato 1 ottobre 2021];22(4). Disponibile su: https://onlinelibrary.wiley.com/doi/10.1111/tid.13302

44. Whangbo J, Ritz J, Bhatt A. Antibiotic-mediated modification of the intestinal microbiome in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. febbraio 2017;52(2):183–90.

45. Yoshioka K, Kakihana K, Doki N, Ohashi K. Gut microbiota and acute graft-versus-host disease. Pharmacol Res. agosto 2017;122:90–5.

Tables

Table 1 Patients characteristics

Sex *(n; Female/Male)*	**22/29** *(43.1% / 56.9%)*
Age *(Median)*	**55** (range 20-72)
Median follow up *(days)*	**279 (29-564)**
Diagnosis *(Acute myeloid leukemia, Myelodysplastic syndrome or Myeloproliferative disease) vs (Linfoma or Myeloma)*	**40/11** *(78.5% / 21.5%)*
Disease status at admission *(Complete remission / Minimal Residual Disease / Adevance Disease)*	**22/21/8** *(43.2 % / 41.1% / 15.7%)*
Donor type *(Match Related Donor /MUD/Haploidentical)*	**21/20/10** *(41.2% / 39.2% / 15.7%)*
Stem cells Source *(Peripheral blood /Bone Marrow)*	**48/3** *(94.1% / 5.9%)*
Nutritional status at admission following PG-SGA *(Score A / B / C)*	**38 A / 12 B / 1 C** *(74,5% / 23,5% / 2%)*

Table 1b Comparison of characteristics between prospective interventional group and historical control group

	Interventional group	Historical control group	*P value*
Total number of patients	**51**	**30**	**n.s.**
Sex *(n; Female/Male)*	**22/29** *(43.1% / 56.9%)*	**16/14** *(53.5 % / 46.5 %)*	**n.s.**
Age *(Median)*	**55**	**58.9**	**n.s.**
Diagnosis *(Acute myeloid leukemia, Myelodysplastic syndrome or Myeloproliferative disease) vs (Linfoma or Myeloma)*	**40/11** *(78.5% / 21.5%)*	**24/6** *(80% /20%)*	**n.s.**
Disease status at admission *(Complete remission / Minimal Residual Disease / Adevance Disease)*	**22/21/8** *(43.2 % / 41.1% / 15.7%)*	**17/11/2** *(56.5%; 36.5 %/ 7%)*	**n.s.**
Donor type *(Match Related Donor /MUD/Haploidentical)*	**21/20/10** *(41.2% / 39.2% / 15.7%)*	**8/17/5** *(27% / 57% / 16%)*	**n.s.**
Nutritional status at admission following PG-SGA *(Score A / B / C)*	**38 A / 12 B / 1 C** *(74,5% / 23,5% / 2%)*	**22 A/ 7 B/ 1 C** *(74% A/ 23% B /3% C)*	**n.s.**

Table 2 Outcomes following Treatment Ratio (TR)

	Patients with **TR > 50%**	**Patients with TR < 50%**	**P Value**
Total (n)	24/51 (47%)	27/51 (53%)	
PG-SGA **Score A** at + 28 days (n) (%)	7/23 (30.4%)	0 (0%)	0.000
PG-SGA **Score B** at + 28 days (n) (%)	13/23 (56.5%)	3/27 (11.1%)	ns
PG-SGA **Score C** at + 28 days (n) (%)	3/23° (13%)	24/27 (88.9%)	0.000
Cumulative Incidence of **aGVHD** (%)	7/24 (29.1%)	14/27 (51.8%)	ns
Cumulative Incidence of **Gastrointestinal aGVHD** (n) (%)	0/24	8/27 (29.6%)	0.005
Incidence of **Sepsis** (%)	7/24 (29.1%)	15/27 (55.5%)	ns
Incidence of **Pneumonia** (%)	3/24 (12.5%)	13/27 (48.1%)	0.006

Table 3 Comparison between Historical and Interventional Groups

	Patients with **TR > 50%**	**Patients with TR < 50%**	**Historical Control Group**
Total (n)	24/51 (47%)	27/51 (53%)	30
PG-SGA **Score A** at + 28 days (n) (%)	7/23 (30.4%)	0 (0%)	0 (0%)
PG-SGA **Score B** at + 28 days (n) (%)	13/23 (56.5%)	3/27 (11.1%)	7/28 (25%)
PG-SGA **Score C** at + 28 days (n) (%)	3/23^ (13%)	24/27 (88.9%)	21/28 * (75%)
Cumulative Incidence of **aGVHD** (%)	7/24 (29.1%)	14/27 (51.8%)	11/30 (36.7%)
Cumulative Incidence of **Gastrointestinal aGVHD** (n) (%)	0/24	8/27 (29.6%)	6/30 (20%)

** At + 28 days from allo-HSCT it was possible to evaluate only 28 patients, two patients died before day + 28.*

^At + 28 days from allo-HSCT it was possible to evaluate only 23 patients, one patient died before day + 28.

Figures

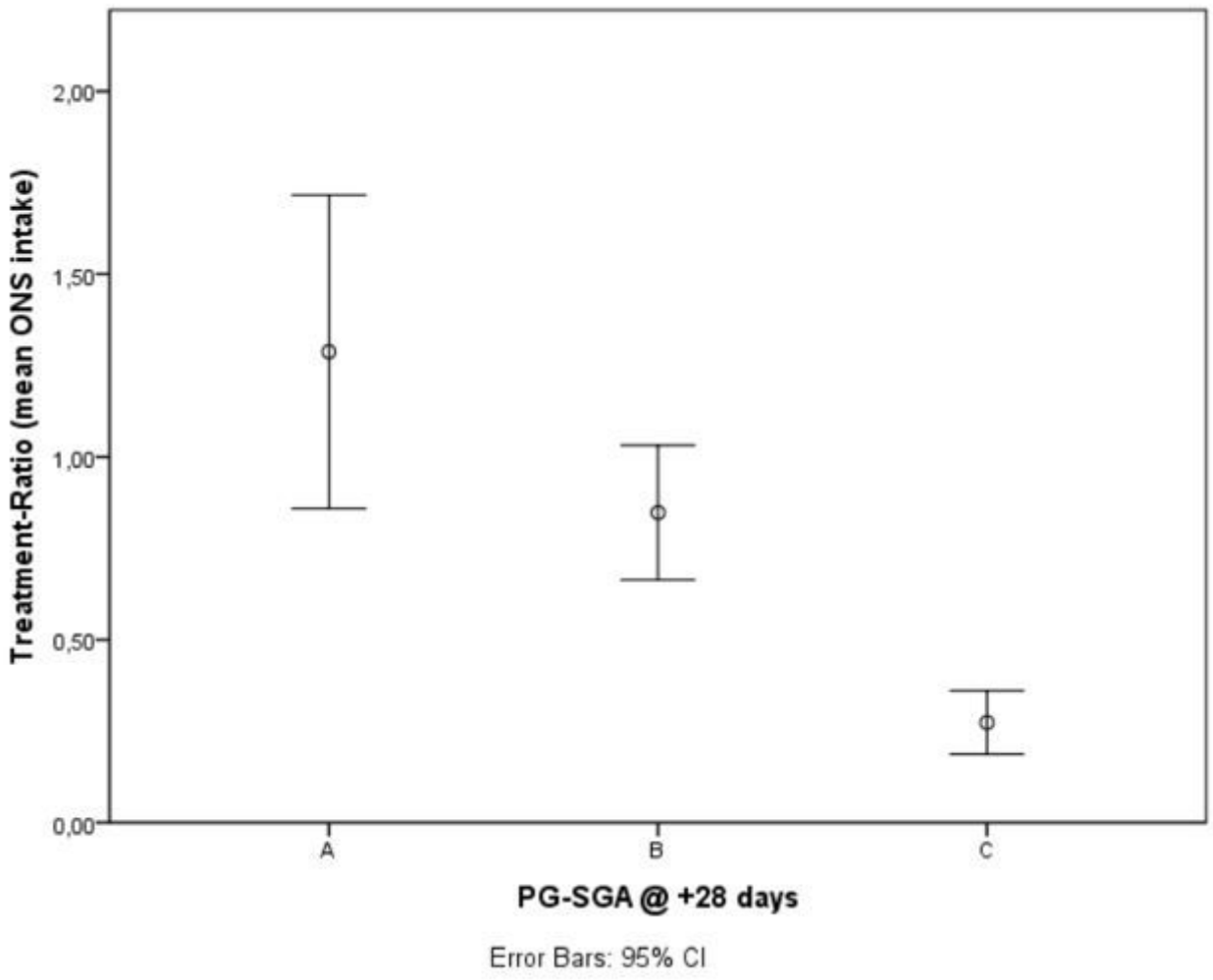

Figure 1

Correlation between PG-SGA score at + 28 from allo-HSCT and Treatment Ratio (TR)

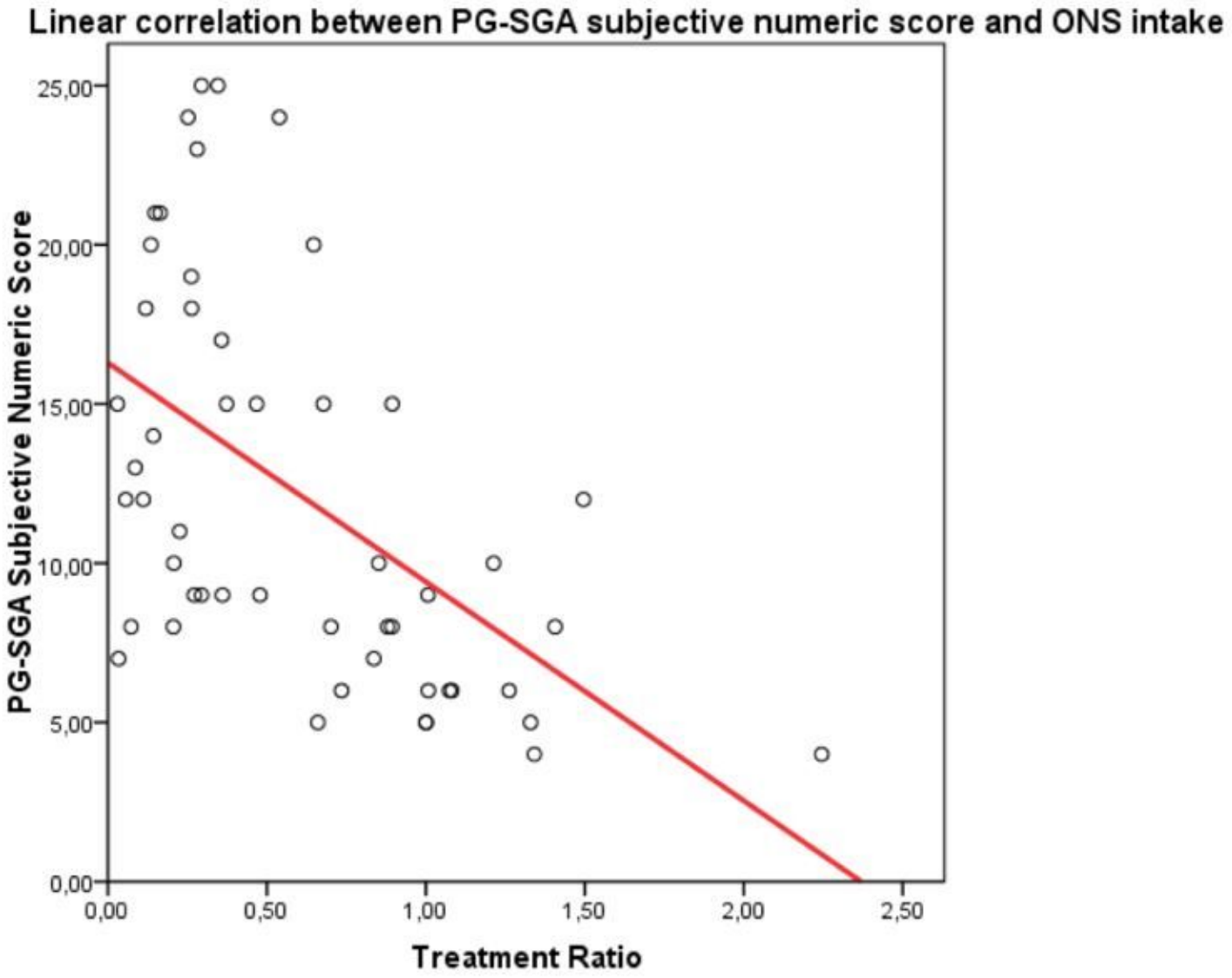

Figure 2

Linear correlation between PG-SGA subjective numeric score and ONS intake

Supplementary Files

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- SupplementaryMaterial.docx