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Isabella Quadras, Fernanda Aparecida Stresser, Stephanie Warnawin, Sandra Regina da Silva, Vaneuza Araujo Moreira Funke, Rafael Zancan Mobile, Juliana Lucena Schussel

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CAN NLR BE A BIOMARKER FOR MUCOSITIS AND GVHD IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION?

Isabella Christina Costa Quadras[1] - isabellaquadras@gmail.com

https://orcid.org/0000-0003-0541-7254

Fernanda Aparecida Stresser[1] - fstresser7@gmail.com

https://orcid.org/0000-0002-7995-3466

Stephanie Von Stein Cubas Warnavin[2] - stephanie.warnavin@gmail.com

https://orcid.org/0000-0001-9829-6230

Sandra Regina da Silva[3] - sandra.silva8@hc.ufpr.br

https://orcid.org/0000-0002-3298-2825

Vaneuza Araujo Moreira Funke[3] - vfunke@gmail.com

https://orcid.org/0000-0002-2122-7277

Rafael Zancan Mobile[2] - zancan.rafael@gmail.com

https://orcid.org/0000-0002-8603-2614

Juliana Lucena Schussel[2] - juliana.schussel24@gmail.com

https://orcid.org/0000-0001-5204-0782

[1] Undergraduate School of Dentistry, Department of Stomatology, Universidade Federal do Paraná, Curitiba, Paraná, Brazil

[2] Post Graduate Program in Dentistry, Department of Stomatology, Universidade Federal do Paraná, Curitiba, Paraná, Brazil

[3] Bone Marrow Transplantation Program, Complexo Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Paraná, Brazil

Corresponding author

Juliana Lucena Schussel DDS, PhD

Department of Stomatology, Federal University of Paraná,

Av. Lothário Meissner 632 Jardim Botânico

Curitiba - Paraná - Brazil

CEP:: 80210-170

Telephone: +55 41 3360-4024 Fax: +55 41 33604053

E-mail: juliana.schussel24@gmail.com

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment for many diseases, however can induce important complications such as Oral Mucositis (OM) and Graft-versus-Host Disease (GVHD). The neutrophil-lymphocyte ratio (NLR) is a peripheral biomarker of systemic inflammation and an independent prognostic factor in several inflammatory diseases. Objective: The aim of this study was to evaluate the association of NLR with OM and GVHD in patients undergoing allogeneic HSCT. Methods: Patients who underwent allogeneic HSCT at the Bone Marrow Transplant Service at the Hospital de Clínicas Complex of the Federal University of Paraná were included in the study. Sociodemographic data and blood count were collected from patients' medical records. NLR was calculated and associated with OM and GVHD. Results: 45 patients were included in the study. NLR was considerably higher in patients who had OM and oral GVHD when compared to patients who did not present these conditions, nonetheless no statistically significant difference was observed. Conclusion: Although both OM and GVHD are associated with inflammatory response as well as to the immune system, it was not associated with NLR. A further investigation considering other variables related to the HSCT might find possible association as it could favor patients management and prevention.

Keywords: Neutrophils, Lymphocytes, Hematopoietic Stem Cell Transplantation, Mucositis, Graft vs Host Disease.

Abbreviations

HSCT, Hematopoietic stem cell transplantation; OM, Oral Mucositis; GVHD, Graft-versus-Host Disease; NLR, Neutrophil-lymphocyte ratio; STMO-CHC, Serviço de Transplante de Medula Óssea of the Complexo Hospital de Clínicas; MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology; SPSS, Statistical Package for the Social Sciences.

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1. INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is considered a curative treatment for a variety of neoplastic and non-neoplastic hematological diseases [1, 2] that cause bone marrow defects, such as anemia, leukemia and lymphoma [1, 3] . It occurs by replacing the receptor cells, by infusing hematopoietic progenitor cells [4].

Oral mucositis (OM) and Graft-versus-Host Disease (GVHD) are possible consequences of HSCT. OM is an inflammation of the mucosa that occurs in approximately 75% of patients who receive ablative chemotherapy or total body irradiation as conditioning for HSCT, intensifying in the first two weeks after transplantation, which may reduce the ability to ingest food, due to pain and discomfort [5].

The pathophysiology of GVHD is not yet fully understood [6], however it is known to date that it results from an immunological attack by donor immunocompetent T cells in the recipient patient's tissues [7], either directly or through exaggerated inflammatory responses after allogeneic HSCT, manifesting in 30 to 50% of cases [7, 8, 9]. GVHD can affect one or more sites in the body, being considered one of the main causes of morbidity and mortality after HSCT. The oral cavity is frequently affected, especially chronic variants which correspond to the manifestations present after the +100 day of HSCT and affects between 25% and 83% of patients [1, 3, 8, 10].

The neutrophil-lymphocyte ratio (NLR), initially described by Zahorec et al. [11], is a peripheral biomarker of systemic inflammation and an independent prognostic factor in several inflammatory, cardiovascular diseases and solid and hematological neoplasms [11, 12, 13, 14]. It is an indirect measure of the imbalance between the innate immune (neutrophils) and adaptive or humorous (lymphocytes) system, obtained by the absolute count of neutrophils divided by the absolute count of lymphocytes, being a biomarker of low cost, reliability and simple collection through a common peripheral blood count [11, 13, 15, 16, 17, 18]. It can be used in a series of inflammatory diseases [11, 16, 17, 18, 19, 20, 21, 22] and is an important marker of poor prognosis and overall survival and disease-free survival [19].

As far as is known, there is little evidence of the use of NLR as a biomarker after HSCT [30], and perhaps no evidence of its application in the assessment of OM and GVHD in HSCT. OM and GVHD are exacerbated inflammatory processes that impact the prognosis of the patient undergoing allogeneic HSCT. Therefore, it is essential to take into account the search for markers that can assist in the prediction, management and treatment of these conditions. Considering the applicability of NLR to a series of inflammatory diseases, the aim of this study was to evaluate the association of NLR with OM and GVHD in patients undergoing allogeneic HSCT.

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2. MATERIALS AND METHODS

This longitudinal observational study had a convenience sample of 45 patients, older than 18 years old, admitted to the Serviço de Transplante de Medula Óssea of the Complexo Hospital de Clínicas of the Universidade Federal do Paraná and submitted to the allogeneic HSCT.

The study was approved by the Research Ethics Committee of the Complexo Hospital de Clínicas of the Universidade Federal do Paraná under number 4.414.355. Those who agreed to participate in the study signed the Informed Consent Form. Inclusion criteria consisted of patients undergoing HSCT, older than 18 years. Exclusion criteria consisted of patients undergoing autologous HSCT, and those with Fanconi Anemia as an underlying disease. Sociodemographic data and blood count results were collected from patients' medical records. The NLR was calculated on a spreadsheet in the Excel for Windows software. Oral mucositis (OM) and Graft versus Host Disease (GVHD) were assessed by physical examination and classified according to MASCC/ISOO guidelines 2020 [24] and NIH 2014 classifications, respectively [25]. NLR data for association with OM were collected from the blood count at 15 days post-HSCT, since it is the time when there is the most severe manifestation. For GVHD, patients were followed up for 180 days after HSCT, monthly. NLR data for association with GVHD were collected from blood counts corresponding to the day of GVHD diagnosis, whereas NLR data from patients who did not manifest GVHD were collected from the last follow-up visit, 180 days after HSCT. Statistical analysis was performed using SPSS version 20.0 (IBM - Armonk, New York).

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3. RESULTS

The sample of 45 patients was mostly male (61.7%), with an average age of 37 years old. The most frequent underlying disease was Severe Aplastic Anemia (31.9%) followed by Acute Myeloid Leukemia (29.8%), and 66% of donors were related and 55.3% were matched.

Mostly, men had a higher frequency of OM when compared to women. The most common underlying disease was Severe Aplastic Anemia. Most allogeneic HSCT were related and those who found an unrelated donor with good match, almost entirely showed OM. Most patients manifested OM regardless of graft compatibility.

The NLR was considerably higher in patients who had OM when compared to patients who did not. There was no statistically significant difference for OM associated with sex, underlying disease, donor relation, match, age and NLR. The distribution of the sample according to sex, underlying disease, donor relation and match, associated with the presence or absence of OM is described in Table 1.

Regarding oral GVHD, the majority of the sample was men. The most frequent underlying hematological disease was Severe Aplastic Anemia, followed by Acute Myeloid Leukemia. As for the donor relation for allogeneic HSCT, most were related and matched. Over 30% (10/31) of the sample developed oral manifestations of GVHD. Regarding the NLR, it was analyzed that the result obtained was greater in patients who had oral GVHD compared to those who did not.

For non-oral GVHD, similar results were found: a large part of the sample were men, most diagnosed with Severe Aplastic Anemia, with a related and matched donor in most cases. The NLR was considerably higher in these individuals who developed non-oral GVHD compared to patients who did not.

However, no statistically significant difference was observed for oral and non-oral GVHD in the variables: sex, underlying disease, donor relation, match, age and NLR, except for the donor relation in non-oral GVHD, as can be seen in Tables 2 and 3.

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4. DISCUSSION

NLR is a simple parameter that assesses a subject's inflammatory state. It is proven to be a strong prognostic factor in several types of cancer, major cardiac events, in addition to a marker of inflammation or infectious diseases and postoperative complications [26, 27].

Ohtaka et al. (2018) [28] observed that NLR values continued to increase during follow-up in cases where malignant diseases developed after kidney transplantation. The association between NLR and bullous pemphigoid prognosis can also be explained by the inflammatory process associated with blistering [4]. In a review by Doo et al. (2020) [29], low NLR was considered associated with a good prognosis in sensorineural hearing loss. Other studies indicate that high levels of NLR were present in a number of inflammatory diseases, such as systemic lupus erythematosus [16, 17, 30], Kawasaki disease [30], allergic rhinitis [17], psoriasis [19], acute appendicitis and chronic hepatitis C [17], chronic obstructive pulmonary disease and asthma [17], Behçet's disease [21], multiple sclerosis and autoimmune encephalitis [30], rheumatoid arthritis [20], autoimmune inflammatory diseases [16, 19] metabolic syndrome [19], and more recently in patients with severe COVID-19 [22], thus being a useful biomarker associated with the assessment of these inflammatory diseases, as well as the activity, severity and prognosis of changes.

Considering the association of NLR with inflammatory diseases, and that OM and GVHD are also associated with the activities of inflammatory cells, we hypothesized that NLR could serve as a biomarker for these manifestations. In this study, a higher frequency of NLR was observed in patients who manifested OM, oral and non-oral GVHD, probably associated with the inflammatory process installed under these conditions. However, our results showed no statistically significant association. Nonetheless, as far as we know, this is the first study associating NLR with complications related to allogeneic HSCT.

In general, malignant blood diseases, such as leukemia and lymphoma, which in themselves cause bone marrow suppression, tend to be associated with oral complications with a high frequency. Lesions in oral tissues can serve as an entry vehicle for the spread of bacterial, fungal and viral infections, especially in patients undergoing myelosuppressive or immunosuppressive chemotherapy regimens for cancer treatment [31]. These patients develop oral problems 2 to 3 times more often than patients undergoing treatment for solid tumors. The results of the present study corroborate this statement, since the vast majority of patients who had malignant blood diseases manifested OM (86.7%), so that a prognosis biomarker can help in the management of the condition. On the other hand, oral GVHD had a low prevalence in the study sample.

There is evidence that patients undergoing allogeneic HSCT develop OM more often and more severely than autologous transplant recipients [11]. But as far as is known, there are no studies comparing related and unrelated grafts in allogeneic HSCT. In the present study, related HSCT constitutes the majority of allogeneic transplants (66.66%), which elucidates the large number of patients with OM who received HSCT from a related donor, compared to unrelated HSCT.

In this study, we did not find any statistically significant difference associated with gender when evaluating patients who developed oral and non-oral GVHD, as well as with sex. Although, when HSCT

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occurs from a female donor to a male host, the risk of developing GVHD increases [33, 34, 35]. We did not assess donor sex and recipient sex associated with GVHD.

The most common underlying disease in patients with manifestations of oral and non-oral GVHD after allogeneic HSCT was Acute Myeloid Leukemia (AML), corresponding to 40% in oral GVHD and 50% in non-oral GVHD. This result corroborates with others [33, 36], with Carlens et al. (1998) suggests AML as a risk factor for acute GVHD.

Although we did not observe a statistically significant difference in terms of age, donor relation and match in oral and non-oral GVHD, a lower frequency was observed in individuals who were younger, had a related donor, and who received a matched transplant. These data reaffirm the results of other studies by indicating that the age of the recipient and donor, the unmatched of human leukocyte antigens (HLA) or HLA disparity between donor and recipient, and unrelated donors, are clinical risk factors that increase the chance for the development of GVHD [3, 33, 34, 35]. According to Castro Jr. et al. (2001) patients undergoing transplantation with unrelated donors are at risk of up to 80% to develop GVHD.

An exception was the donor relation in non-oral GVHD, in which a statistically significant difference was observed ($p = 0.029$), since none of the patients who received the unrelated transplant developed GVHD. However, this data goes against the results of other studies [3, 33, 34, 35] that show that GVHD occurs more frequently as a result of unrelated donors. We believe that our result does not indicate causality in this sample, since the small number of patients with manifestations of oral and non-oral GVHD can be explained by the fact that a large part of the sample was composed of young adults and the fact that a large part of individuals received the related and matched transplant.

To conclude, in our sample, we did not reach a statistically significant difference for the NLR associated with OM, oral GVHD and non-oral GVHD. However, as far as is known, this is the first study to analyse this association. The search for biomarkers of easy access, low cost, and that can bring important answers in the diagnosis, treatment and prognosis of consequent manifestations of allogeneic HSCT is of paramount relevance. Finding a larger sample, in which NLR could be paired by age, underlying disease, conditioning regime, donor relation and match, between patients who develop or not OM, oral GVHD and non-oral GVHD, is a great challenge, and for this reason, we believe that future multicenter studies can help the results of the NLR associations with OM, oral GVHD and non-oral GVHD to be inferred for the general population of patients undergoing allogeneic HSCT.

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DECLARATIONS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests: none.

Ethics approval: All procedures carried out in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the Helsinki Declaration of 1964 and its subsequent amendments or comparable ethical standards. The study was approved by the Research Ethics Committee of the Complexo Hospital de Clínicas of the Universidade Federal do Paraná (No. 4.414.355).

Consent to participate: Free and informed consent was obtained from all individual participants included in the study.

Consent for publication: Free and informed consent was obtained from all individual participants included in the study.

Authors' contributions:

Isabella Christina Costa Quadras: Conceptualization, Methodology, Data curation, Writing - Original draft preparation.

Fernanda Aparecida Stresser: Conceptualization, Methodology, Data curation, Writing - Original draft preparation.

Stephanie Von Stein Cubas Warnavin: Conceptualization, Methodology, Data curation, Writing - Original draft preparation, Review & Editing.

Sandra Regina da Silva: Conceptualization, Writing - Review & Editing.

Vaneuza Araújo Moreira Funke: Conceptualization, Writing - Review & Editing.

Rafael Zancan Mobile: Conceptualization, Methodology, Data curation, Writing - Original draft preparation, Review & Editing.

Juliana Lucena Schussel: Supervision, Conceptualization, Methodology, Data curation, Writing - Review & Editing.

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Table 1. Distribution of clinical data and NLR associated with Oral Mucositis.

VARIABLES	ORAL MUCOSITIS		TOTAL	P VALUE
	YES	NO		
Sex - n(%)				
Female	14(82,4)	3(17,6)	17(100)	0,658*
Male	25(89,3)	3(10,7)	28(100)	
Total	39(86,7)	6(13,3)	45(100)	
Underlying disease - n(%)				
Acute lymphoid leukemia	8(100)	0(0)	8(100)	-
Acute myeloid leukemia	13(92,9)	1(7,1)	14(100)	
Non-Hodgkin's lymphoma	2(50)	2(50)	4(100)	
Myelodysplastic syndrome	3(100)	0(0)	3(100)	
Severe aplastic anemia	11(78,6)	3(21,4)	14(100)	
Others	2(100)	0(0)	2(100)	
Total	39(86,7)	6(13,3)	45(100)	
Donor relation - n(%)				
Related	25(83,3)	5(16,7)	30(100)	0,647*
Unrelated	14(93,3)	1(6,7)	15(100)	
Total	39(86,7)	6(13,3)	45(100)	
Match- n(%)				
Matched	22(88)	3(12)	25(100)	1,000*
Unmatched	17(85)	3(15)	20(100)	
Total	39(86,7)	6(13,3)	45(100)	
Age – Median (min-max)	41(20-62)	24,50(19-60)	-	0,300**
NLR – Median (min-max)	1,13(0,00-22,45)	0,44(0,0027,70)	-	0,917**

* Fisher's exact test.

** Mann Whitney U test.

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Table 2. Distribution of clinical data and NLR associated with Oral GVHD.

VARIABLES	ORAL GVHD		TOTAL	P VALUE
	YES	NO		
Sex - n(%)				
Female	2(18,2)	9(81,8)	11(100)	0,262*
Male	8(40)	12(60)	20(100)	
Total	10(32,3)	21(67,7)	31(100)	
Underlying disease - n(%)				
Acute lymphoid leukemia	1(33,3)	2(66,7)	3(100)	-
Acute myeloid leukemia	4(40)	6(60)	10(100)	
Non-Hodgkin's lymphoma	2(66,7)	1(33,3)	3(100)	
Myelodysplastic syndrome	1(50)	1(50)	2(100)	
Severe aplastic anemia	2(16,7)	10(83,3)	12(100)	
Others	0(0)	1(100)	1(100)	
Total	10(32,3)	21(67,7)	31(100)	
Donor relation - n(%)				
Related	9(37,5)	15(62,5)	24(100)	0,379*
Unrelated	1(14,3)	6(85,7)	7(100)	
Total	10(32,3)	21(67,7)	31(100)	
Match- n(%)				
Matched	7(36,8)	12(63,2)	19(100)	0,697*
Unmatched	3(25)	9(75)	12(100)	
Total	10(32,3)	21(67,7)	31(100)	
Age – Median (min-max)	44,5(21-62)	32(19-60)	-	0,526**
NLR – Median (min-max)	2,63(0,43-14,50)	1,42(0,00-10,99)	-	0,310**

* Fisher's exact test.

** Mann Whitney U test.

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Table 3. Distribution of clinical data and NLR associated with Non-Oral GVHD.

VARIABLES	NON-ORAL GVHD		TOTAL	P VALUE
	YES	NÃO		
Sex - n(%)				
Female	2(18,2)	9(81,8)	11(100)	0,139*
Male	10(47,6)	11(52,4)	21(100)	
Total	12(37,5)	20(62,5)	32(100)	
Underlying disease - n(%)				
Acute lymphoid leukemia	2(66,7)	1(33,3)	3(100)	-
Acute myeloid leukemia	5(50)	5(50)	10(100)	
Non-Hodgkin's lymphoma	3(75)	1(25)	4(100)	
Myelodysplastic syndrome	0(0)	2(100)	2(100)	
Severe aplastic anemia	2(16,7)	10(83,3)	12(100)	
Others	0(0)	1(100)	1(100)	
Total	12(37,5)	20(62,5)	32(100)	
Donor relation - n(%)				
Related	12(48)	13(52)	25(100)	0,029*
Unrelated	0(0)	7(100)	7(100)	
Total	12(37,5)	20(62,5)	32(100)	
Match- n(%)				
Matched	8(42,1)	11(57,9)	19(100)	0,713*
Unmatched	4(30,8)	9(69,2)	13(100)	
Total	12(37,5)	20(62,5)	32(100)	
Age – Median (min-max)	45(21-62)	32(19-60)	-	0,520**
NLR – Median (min-max)	3,19(0,43-5,69)	1,43(0,00-14,50)	-	0,302**

* Fisher's exact test.

** Mann Whitney U test.

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