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Original Article

Can NLR be a biomarker for mucositis and gvhd in patients undergoing allogeneic HSCT?

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a treatment for many diseases; however, it can induce 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 for several inflammatory diseases. **Aim:** This study aimed 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 of the Hospital de Clínicas Complex of the Federal University of Paraná were included in the study. Socio-demographic data and blood counts were collected from patients' medical records. The NLR was calculated and associated with OM and GVHD. **Results:** 45 patients were included in the study. Although NLR was higher in patients with OM and oral GVHD, no statistical difference was observed, and no relationship between OM and GVHD with NLR could be stated. **Conclusion:** Although both OM and GVHD are associated with an inflammatory response as well as the immune system, it was not associated with NLR. Further investigation considering other variables related to HSCT might find possible associations, as it could favor patient 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.

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]. HSCT occurs by replacing receptor cells with hematopoietic progenitor cells[4].

Oral mucositis (OM) and Graft-versus-Host Disease (GVHD) are potential 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 their 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 result 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 30–50% of cases[7-9]. GVHD can affect one or more sites in the body and is considered one of the main causes of morbidity and mortality after HSCT. The oral cavity is frequently affected, especially chronic variant that correspond to the manifestations present after the +100 day after HSCT and affect 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 hematological neoplasms[12-15]. NLR is an indirect measure of the imbalance between the innate immune (neutrophils) and adaptive or humorous (lymphocytes) systems, obtained by the absolute count of neutrophils divided by the absolute count of lymphocytes, which is a biomarker of low cost, reliability, and simple collection through a common peripheral blood count[12,14,16,17]. It can be used in a series of inflammatory diseases[12,17-22] and is an important marker of poor prognosis, overall survival, and disease-free survival[19].

To the best of our knowledge, there is little evidence of the use of NLR as a biomarker after HSCT[23], and perhaps no evidence of its application in the assessment of OM and GVHD after HSCT. OM and GVHD are exacerbated inflammatory processes that affect the prognosis of allogeneic HSCT patients. Therefore, it is essential to consider markers that can assist in the prediction, management, and treatment of these conditions.

Aim

Considering the applicability of NLR to a series of inflammatory diseases, this study aimed to evaluate the association of NLR with OM and GVHD in patients undergoing allogeneic HSCT.

Materials and Methods

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

This study was approved by the Research Ethics Committee of the Complexo Hospital de Clínicas of the Universidade Federal do Paraná (number 4.414.355). Those who agreed to participate signed an informed consent form. The inclusion criteria consisted of patients older than 18 years who underwent HSCT. Exclusion criteria consisted of patients undergoing autologous HSCT, and those with Fanconi Anemia as an underlying disease were excluded. Sociodemographic data and blood count results were collected from patients' medical records. NLR was calculated using a spreadsheet in Excel for Windows software. Oral mucositis (OM) and graft versus Host Disease (GVHD) were assessed by physical examination and classified according to the MASCC/ISOO guidelines 2020[24] and NIH 2014 classifications, respectively[25]. Patients were evaluated pre-HSCT and 15, 30, 60, 90, 120, 150, and 180 days after HSCT. NLR data for association with OM were collected from the blood counts at 15 days post-HSCT, since this is the time when there is the most severe manifestation. For GVHD, patients were followed up monthly for 180 days after HSCT. 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. All patients underwent dental consultation and had oral cavity adequacy before the chemotherapy regimen. All patients received photobiomodulation to prevent OM from the first day of the conditioning regimen, following the MASSC/ISSO clinical practice guidelines. Statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, New, USA).

Results

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

Men had a higher frequency of OM than women. The most common underlying disease is Severe Aplastic Anemia. Most allogeneic HSCT cases were related, and those who found an unrelated donor with a good match almost entirely showed OM. Most patients manifested OM regardless of graft compatibility. Regarding the OM grade, six cases were classified as grade 0; three as grade 1; eight as grade 2, and 14 as grades 3 and 4.

There was no statistically significant difference in OM associated with sex, underlying disease, donor relation, match, age, or 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 below.

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)	
Unrelated	14(93,3)	1(6,7)	15(100)	0,647*
Total	39(86,7)	6(13,3)	45(100)	
Match- n(%)				
Matched	22(88)	3(12)	25(100)	
Unmatched	17(85)	3(15)	20(100)	1,000*
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.

Regarding oral GVHD, the majority of the patients were men. The most frequent underlying hematological disease was Severe Aplastic Anemia, followed by Acute Myeloid Leukemia. As for the donor relationship for allogeneic HSCT, most were related and matched. Over 30% (10/31) of patients 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 was men, mostly diagnosed with Severe Aplastic Anemia, with a related and matched donor in most cases. NLR was considerably higher in individuals who developed non-oral GVHD than in those who did not.

However, no statistically significant difference was observed for oral and non-oral GVHD in terms of sex, underlying disease, donor relation, match, age, and NLR, except for the donor relation in non-oral GVHD, as shown in Tables 2 and 3.

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)	
Unrelated	1(14,3)	6(85,7)	7(100)	0,379*
Total	10(32,3)	21(67,7)	31(100)	
Match- n(%)				
Matched	7(36,8)	12(63,2)	19(100)	
Unmatched	3(25)	9(75)	12(100)	0,697*
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.

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)	
Unrelated	0(0)	7(100)	7(100)	0,029*
Total	12(37,5)	20(62,5)	32(100)	
Match- n(%)				
Matched	8(42,1)	11(57,9)	19(100)	
Unmatched	4(30,8)	9(69,2)	13(100)	0,713*
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.

Discussion

NLR is a simple parameter that assesses a subject's inflammatory state. It has been proven to be a strong prognostic factor in several types of cancer, major cardiac events, and markers of inflammation, infectious diseases, and postoperative complications[26,27]. Therefore, this study aimed to evaluate the association of NLR with OM and GVHD in patients undergoing allogeneic HSCT. No association was observed between OM, GVHD, and NLR.

Considering the association of NLR with inflammatory diseases and that OM and GVHD are also associated with the activity of inflammatory cells, we hypothesized that NLR could serve as a biomarker for these manifestations. Nonetheless, to the best of our knowledge, this is the first study to associate NLR with complications related to allogeneic HSCT.

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[28]. 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 with malignant blood diseases manifested OM (86.7%), a prognostic biomarker can help in the management of the condition.

There is evidence that patients undergoing allogeneic HSCT develop OM more often and more severely than autologous transplant recipients[12]. But to the best of our knowledge, no studies have compared related and unrelated grafts in allogeneic HSCT. In the present study, related HSCT constituted the majority of allogeneic transplants (66.66%), which explains the large number of patients with OM who received HSCT from a related donor compared to unrelated HSCT.

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. However, when HSCT occurs from a female donor to a male host, the risk of GVHD development increases[29].

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% of oral GVHD and 50% of non-oral GVHD. This result corroborates with others[29]. Carlens et al.[29] (1998) suggests that AML is a risk factor for acute GVHD.

Although we did not observe a statistically significant difference in terms of age, donor relationship, and match in oral and non-oral GVHD, a lower frequency was observed in individuals who were younger, had a related donor, and received a matched transplant. These data reaffirm the results of other studies by indicating that the age of the recipient and donor, the mismatch 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[3,29]. According to Bassim et al.[8] (2015), patients undergoing transplantation with unrelated donors are at a risk of up to 80% to develop GVHD[8].

An exception was the donor relationship 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, these data contradict the results of other studies[3,29] that show that GVHD occurs more frequently as a result of unrelated donors. We believe that our results do 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 majority of the individuals received related and matched transplants.

In our sample, we did not find a statistically significant difference in NLR associated with OM, oral GVHD, and non-oral GVHD. To the best of our knowledge, this is the first study to analyze this association. The search for biomarkers with easy access, low cost, and that can provide 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 OM, oral GVHD, and non-oral GVHD, is a great challenge; for this reason, we believe that future multicenter studies can help infer the results of the NLR associations with OM, oral GVHD, and non-oral GVHD for the general population of patients undergoing allogeneic HSCT.

In conclusion, although both OM and GVHD are associated with the inflammatory response as well as the immune system, they are not associated with NLR.

Declarations of interest

None. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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.

Author Contribution

- 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.

All authors actively participated in the manuscript's findings, revised, and approved the final version of the manuscript.

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