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SUMMARY

**CORRELATIONS BETWEEN MARKERS OF
INFLAMMATION AND TUMOR FORMATIONS IN
THE OMF AND GASTROINTESTINAL REGION**

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CONTENT

- 1. Introduction**
- 2. The stage of knowledge**
 - 2.1. Epidemiology**
 - 2.2. Risk factors**
 - 2.3. Oral lesions in gastrointestinal cancers**
 - 2.4 Inflammation**
 - 2.5 Inflammatory markers in the literature**
- 3. Personal contribution**
 - 3.1 Working hypothesis and general objectives**
 - 3.2 Material and methods**
 - 3.3. Results**
 - 3.3.1. Study 1
 - 3.3.2. Study 2
 - 3.3.3. Study 3
- 4. Discussions**
- 5. Conclusions**
- 6. Abbreviations used in the text**
- 7. Bibliography**
- 8. Annexes**

Cuvinte cheie: cancer, localizare oro-maxilo-facială și gastrointestinală, markeri inflamatori: NLR, PLR, LMR.

1. INTRODUCTION

In recent years, more and more studies have discussed the link between inflammation and the appearance and development of various types of tumors.

Various markers highlighting the presence of an inflammatory process in the body have been correlated with tumor aggression as well as an unfavorable prognosis for several types of cancer. They are sometimes used in some types of cancer to monitor the effectiveness of the treatment applied.

The study in this paper aimed to investigate in the peripheral blood of patients known to have various tumor diseases in the OMF and gastrointestinal tract the value of 3 markers of inflammation, namely: NLR (neutrophils to lymphocytes ratio), PLR (platelets to lymphocytes ratio) and LMR (lymphocytes to monocytes ratio).

At the same time, this paper aims to find a more efficient and cost-effective way to detect possible cancers.

Thus, the objective of this paper was to investigate the correlation between the type of tumor and three inflammatory markers, namely NLR, PLR and LMR.

The paper comprises two distinct parts: the stage of knowledge and that of personal contributions.

2. Current state of knowledge

It includes clear and concise notions in about 25 pages about cancer epidemiology, incidence and risk factors. Also, of particular importance is information on the role of inflammation in the onset and development of cancer.

A special chapter was dedicated to existing studies in the literature regarding the value of the inflammatory markers NLR, PLR and LMR, their predictive role for the detection of malignancies, as well as the evolution of cases.

3. Personal contributions

This chapter is dedicated to personal contribution and includes personal studies on the values of three markers of inflammation that we followed in the lesions of the oro-maxillo-facial region and gastrointestinal tract.

It is structured on several separate subchapters, as follows: working hypothesis and general objectives, material and methods, results, discussions and conclusions for the 3 personal studies.

The subchapter on "Working Hypothesis and General Objectives" contains the reasons for choosing the research topic, the motivation and the general objectives.

The choice of this theme was made taking into account the increasing morbidity and mortality of tumors, as well as the severe consequences the cancer has on patients.

That is why we wanted to check if inflammatory markers can be useful in the early detection of tumors, possible local or remote metastases, especially since simple blood tests are among the routine tests at any hospitalization.

The present paper aims to study the correlation between the type of tumor formation and three inflammatory markers. The choice of these markers was motivated especially knowing that they are part of the tests that are usually done, mandatory when hospitalized.

The subchapter "Research methodology" describes in detail how to approach the topic but also the material and method used during the research.

The study was performed by a clinical-statistical analysis of the lesions in the OMF region but also at the gastrointestinal level with the help of paraclinical examinations and supported by the result of histopathological examinations.

The selection of patients began by finding all cases that were diagnosed with tumor lesion in the two clinics (Oral and Maxillofacial Surgery Clinic and Surgery Clinic I) of the Emergency County Clinical Hospital from January 2017 to June 2019.

The criteria for including patients in this study were: complete blood count, the result of histopathological examination of the tumor.

From this study we excluded all patients who: were known to have infectious or inflammatory conditions, acute or chronic; those who did not had the number of neutrophils, lymphocytes, platelets or monocytes, as well as patients whose histopathological examination was inconclusive or not performed.

To statistically process the data, they were entered in Microsoft Excel 2016 v1809 and were used to calculate and analyze the three inflammatory markers, namely NLR, PLR and LMR in relation to the type of tumor formation identified following histopathological examination.

Statistics were performed using "independent samples t-test" and "Receiver Operating Characteristic" (ROC) using MedCalc 18.11.3.

The subchapter "Results" describes the cases according to gender, location, separate histopathological result on each study performed.

Study 1 Benign and malignant tumors of the oro-maxillo-facial region

Of the total clinical cases admitted to the OMF Surgery Department, tumor lesions accounted for about a quarter (24.28%), 246 patients with malignant tumors and 141 with benign tumors. Thus, we have 236 men, representing 61% of all cases, compared to only 151 women (39%), resulting in a ratio of 1.5. The malignant group was found to be significantly older (65.5 ± 1.48 years) compared to the benign group (56.47 ± 2.82 years).

We obtained an average NLR value of: 2.26 with variations between 2.03 - 2.48 for patients with benign oral lesions and 3.13 (2.85 - 3.41) in patients with malignant oral lesions. The result obtained shows us a difference of 0.87 of the mean NLR between benign and malignant lesions.

The mean PLR in patients with benign oral lesions was 107.9 while PLR in malignant oral lesions was 129.8. It is observed that the value is higher in the case of malignant lesions.

The mean LMR was 4.88 (with variation between 4.54-5.22) in patients with benign oral lesions and 3.9 (with variation between 3.62-4.24) in malignant oral lesions.

Patients with metastases had a mean NLR of 3.68, PLR of 141.64 and LMR of 3.65 compared with patients without metastases where the mean NLR was 2.96, PLR of 118.38, and LMR. of 4.39.

Analysis of the ROC curve for the three markers NLR, PLR and LMR in predicting malignancy suggests a value of 1.9609 for NLR, 113.9565 for PLR and 3.2 for LMR.

Study 2 Squamous cell carcinoma of the OMF

Taking into account the histopathological examination, the 205 patients are divided as follows: 51 (25%) have basal cell carcinoma (BCC), 7 (3%) well-differentiated squamous cell carcinoma, 36 (18%) well and moderately differentiated squamous cell carcinoma, 67 (33%) moderately differentiated squamous cell carcinoma, 21 (10%) moderate and poorly differentiated squamous cell carcinoma, 23 (11%) poorly differentiated squamous cell carcinoma. In our study, 142 were men (representing 69% of cases) and 63 women (31%), with a ratio of 2.25 for men. The mean age of the patients in this study was 66.62 ± 1.65 with significant differences between men and women (65.77 ± 2 years and 68 ± 2.86 years, respectively) of approximately 3 years in favor of women.

In the case of BCC, we had 51 cases, of which 28 were women and 23 men. We also recorded 154 cases of SCC, of which 119 men and 35 women.

Thus, for BCC we found an NLR of 2.47, PLR of 105.67 and LMR of 4.5 and for SCC the average values for NLR were 3.39, PLR of 138.4 and LMR of 3.63.

Analyzing the degree of cell differentiation, it can be seen that the values of NLR, PLR and LMR are closely related to it. In our study, six times more men had moderately differentiated squamous cell carcinoma compared to women. The group of patients with moderately differentiated squamous cell carcinoma accounted for one-third of the total cases in this study.

Of the total cases with poorly differentiated squamous cell carcinoma, 47.8% had latero-cervical metastases compared to only 1.9% of patients with BCC; 0% of those with well-differentiated squamous cell carcinoma; 33.3% of those with well and moderately differentiated squamous cell carcinoma; 25.3% of those with moderately differentiated squamous cell carcinoma and 23.8% of those with moderate and poorly differentiated squamous cell carcinoma. Thus, out of 205 patients, of which 142 men (69%) and 63 women (31%), 28.8% of all men (41 cases) and only 7.9% of all women (5 cases) had lymph node metastases. Patients with latero-cervical metastases have higher mean NLR and PLR, while the mean value for LMR is lower suggesting an increased inflammatory response in the metastatic population.

Study 3 The value of inflammation markers in gastrointestinal tumors

Of the 1942 patients hospitalized for various digestive pathologies that required diagnosis, investigation and specialized treatment, only 145 patients met the inclusion criteria and were selected for this study, representing 7.46% of all cases admitted to the clinic in the period studied.

Of these, 53 were women (36.55%) and 92 men (63.45%) with a ratio of 1.73 for men. The mean age for women was 68.09 ± 2.86 , about 3 years higher than for men 65.77 ± 2.04 .

Analyzing the 3 markers, average NLR was 4.61, PLR was 185.96 and average LMR was 3.08. Values for all three markers are suggestive of malignant tumor lesions.

For the women in this study, the mean values for the three markers were as follows: 5.02 for NLR, 214.46 for PLR and 3.25 for LMR.

While in the case of men, the average values for the three markers were: 4.37 for NLR, 169.54 for PLR and 2.97 for LMR.

4. Discussions

If we consider that the mean values of NLR in healthy adults turned out to be 1.65 [± 1.96 SD: 0.78-3.53], it means that the values we found in our analysis of those 387 patients in study 1, 151 women and 236 men, 141 with benign lesions and 146 with malignant lesions in the OMF area support the hypothesis that NLR may be a marker of tumor inflammation. Thus, we observed in this study that the average values of NLR in patients with malignant tumors in the OMF sphere the values were almost twice as high as normal (3.13 compared to 1.65).

Thus, while the mean NLR in subjects without metastases was only 2.96 (with limits between 2.66 and 3.26), in 58 patients (representing 15% of cases) who had metastases in the latero-cervical region we found a much higher average NLR value of 3.68 (2.96 - 4.4), respectively. The fact that the value of the marker increases with the appearance of metastases supports exactly what we set out to analyze in this research.

The patients from the first study in our evaluations of the mean value of PLR we found an average of 107.97 (with variations between 100.44 and 115.50 with SD: 45.22) in those who had benign oral lesions and 129, 83 (with values between 122.09 and 137.5865 with SD: 61.69) in those with malignant oral lesions. It turns out that there is a significant difference in response between benign and malignant groups, with higher values for the malignant group.

LMR in healthy individuals was reported to be 5.31 while in our study on patients with oral lesions, the mean LMR was 4.88 (with variations between 4.54 and 5.22; SD 4.19) in patients with benign oral lesions, respectively 0.89 higher than LMR found in patients with malignant oral lesions of 3.9 (3.62 to 4.24 with SD: 2.46), the result obtained suggesting a high association between LMR values and the presence of a tumor formations.

Following the ROC and correlating the values obtained with the results of histopathological examinations, we observed that of the 387 patients in the first study, only 83 (21.44%) had all three inflammatory markers, namely NLR, PLR and LMR, in the malignant area. The histopathological results of these 83 cases showed that 71 (85.54%) had malignant lesions and only 12 cases (14.45%) had benign tumors.

Next, we observed that 67 patients (representing 17.31% of cases) who had two inflammatory markers NLR and PLR located in the area suggesting a malignant tumor and an LMR marker indicating a benign lesion. In these cases, the histopathological result was 47 patients with malignant lesions (70.15% of cases) and 20 patients with benign lesions (29.85%).

This suggests that the prediction regarding the nature of the lesions may be more accurate and in accordance with the histopathological examination when all 3 markers of inflammation are taken into account.

Thus, combining the values suggested by ROC for malignancy for the three markers of inflammation, respectively NLR, PLR and LMR, there is a higher chance to differentiate a malignant tumor from a benign one.

In study 2 we continued the research from the first focusing only on the values of inflammation markers in patients with malignancies in the OMF sphere in which histopathological examination indicated basal cell carcinoma or squamous cell carcinoma seeking to make a comparison between the two types. We observed a higher incidence in men, respectively 142 cases representing 69% compared to 63 women representing only 31% cases, thus resulting in a ratio of 2.25. The study found that the mean value for NLR in patients diagnosed with BCC was 2.47 (with ranges between 2.15 - 2.78; SD: 1.12) while patients with SCC had a mean NLR of 3.39 (with limits between 2.98 - 3.8 and 2.56 SD), meaning 0.92 higher. The values recorded for both cancers are well above the value set for healthy adults of 1,65 [\pm 1,96 SD: 0,78-3,53].

In addition, we also observed that the mean value of NLR is higher in patients with a squamous

cell carcinoma with a lower degree of differentiation (3.72), compared with patients with a higher degree of differentiation (3.08). This confirms the idea that this marker may suggest the severity of the malignant lesion. The increase in the mean value of the NLR marker with advancing the degree of tumor differentiation in the study is similar to data from the literature.

The mean value of PLR increases depending on the degree of cell differentiation of histopathological results. Thus, while in the case of well-differentiated squamous cell carcinoma we have an average value of 123.63 in the case of poorly differentiated, the value reaches 139.91 (112.41-167.40), while the average PLR in healthy adults is 132, 4.

In the case of the average values of the LMR, we noticed a minimal difference in terms of the inflammatory response between the two groups. Thus, the mean value was 4.5 (3.81 - 5.19; SD: 2.44) in patients with BCC and 3.63 (3.29 - 3.98; SD: 2, 16) in those with SCC, with a difference of 0.87.

The values we obtained for all three markers signify a greater inflammatory response to SCC just as we expected.

We then tracked the mean values of the three markers in patients with metastases and easily noticed that compared to patients without lymph node metastases, where the values are $NLR = 2.99 \pm 0.32$, $PLR = 126.08 \pm 9.15$, patients with latero-cervical metastases have higher mean values for $NLR = 3.63 \pm 0.72$ and $PLR = 143.2 \pm 18.39$ while the mean value for LMR is lower for both tumors.

In our research we also followed the value of the three markers of inflammation in the case of gastrointestinal localization of tumors.

The distribution of the 145 patients in our study with histopathological confirmation of gastrointestinal tumor shows that the disease is more common in men, respectively 63.45% of cases (92) compared to women and 36.55% of cases (53), which results in a ratio of 1.73. The mean age of patients diagnosed with malignant lesions was 68.09 ± 2.86 years, respectively, approximately 3 years above the mean age of men (65.77 ± 2.04 years).

The study of malignant lesions in the digestive tract performed by us shows that all the markers investigated have average values that are suggestive to suspect a malignant tumor. Thus, the average value of NLR was 4.61 (with variations between 3.93 - 5.28; SD: 4.11), a significantly higher value (approximately 2.8 times) compared to the normal value suggesting the presence of systemic inflammation. in patients with gastrointestinal cancer. If we research the values recorded by sex, we found that the average NLR in women had higher values 5.02 (with variations 3.97 - 6.06 and SD: 3.79) than in male patients 4.37 (with variations 3, 48 - 5.26 and SD: 4.29).

For the second marker researched by us PLR in patients with gastrointestinal tumor we found an average value of 185.96 (with variations between 168.54 - 203.38; SD: 106.13), much higher than the average value in the case of healthy people also suggesting the existence of inflammation in patients with gastrointestinal cancer. PLR is higher in women 214.46 (with variations between 180.02

and 248, 91; SD: 124.96) compared to that found in men 169, 54 (with limits between 150.84 and 188.25; SD: 90.3).

The mean value of the third inflammation marker, LMR was 3.08 (2.81 - 3.36; SD: 1.64) in gastrointestinal cancer patients while LMR in healthy individuals was reported as 5.31, thus suggesting an increased inflammatory response in patients with gastrointestinal malignancies. These values are consistent with other studies that suggest that a low LMR is a sign of a poor prognosis.

In our study, patients with metastases had mean values of NLR = 4.61; PLR = 164.53 and LMR = 2.58, while in patients without metastases the values were NLR = 4.58; PLR = 180.75 and LMR = 3.16. All these values support the marker value of the severity of the lesions and the prediction of the local invasion.

5. Conclusions

Rapid differentiation of a benign oral lesion from a malignant one can be a real challenge in some cases. Proper clinical examination of the patient by inspection and palpation of the lesion is essential for a diagnosis.

The research we did aimed to evaluate the role that NLR, PLR and LMR can play in detecting the type of tumor lesions in the OMF and gastrointestinal region.

1. I believe that the results obtained by current research have shown that these 3 markers of inflammation can be useful in predicting the type of tumor lesion, respectively benign or malignant. Thus, the inflammation markers showed a higher inflammation in cases with malignant tumor diseases.
2. The more the inflammation indicated by these markers is accentuated, the more the probability that the tumor lesion will be more aggressive and implicitly the subsequent evolution will be more reserved.
3. The results of the three studies for markers of inflammation are similar to those in the literature. In some cases, the values in the present research proved to be more relevant than those known from existing studies in the literature.
4. In our research, in the case of patients who had metastases, the inflammatory reactions were more pronounced compared to the group of patients with malignant tumors that did not have metastases. The mean values of the markers increase even more in patients with malignant lesions that metastasize. The fact that the value of the marker increases with the appearance of metastases supports exactly what we set out to analyze in this research.
5. The three markers studied, namely NLR, PLR and LMR, showed a higher degree of inflammation in SCC compared to BCC.
6. If we discuss / if we refer to the average age of patients with tumor pathology included in our research, we emphasize the following aspects:

- the average age is over 60,
 - it is higher in those with malignant tumors compared to those with benign tumors
7. The second important parameter in the study of tumor pathology refers to the gender of patients. In our research, we noticed that the male population predominates with an average between 61% and 69% representing a ratio of 1.5 to 2.25 to women.
 8. The combination of the three markers, after establishing a reference value by ROC, increased the predictability value of the type of tumor lesion, respectively benign or malignant.
 9. There are also some limitations of the research, which we must recognize, namely the small number of patients in whom the values of inflammation markers were analyzed, as well as the fact that this study is retroactive. This can be corrected by continuing / expanding the research and adding new cases.
 10. Early detection of malignancies is of vital importance as the establishment of early, well-managed specific treatment can reduce the cost to society, but above all it would increase the chances of survival, if not cure.