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| RESEARCH ARTICLE

The Diagnostic Value of the Modified mSIS Score in Predicting Sentinel Axillary Lymph Node Positivity in Patients with Early-Stage Breast Cancer

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| ABSTRACT

Axillary lymph node metastasis is the most important prognostic factor in breast cancer. No method exists to diagnose the metastasis of the axillary lymph nodes before surgery. Sentinel lymph node biopsy is a procedure for axillary staging. Hematological parameters and systemic inflammation play a role in cancer metastasis. This study aims to evaluate the modified Systemic Inflammation Score (mSIS) score predicting sentinel axillary lymph node positivity in early breast cancer patients and to determine if there is a need to modify it. This is a retrospective study conducted in Ankara City Hospital General Surgery Department from March 2019 to July 2021. One hundred fifty-nine patients were analyzed according to age, albumin parameters, Thrombocyte, Lymphocyte and Monocyte count, histopathological type of cancer, and lymph node metastasis status. The collected information was entered into SPSS 24.0 program. Lymph node metastasis was detected in 51 of these 159 patients. Results showed no significant difference between the lymph node metastasis group and no lymph node metastasis group after applying the mSIS score to each group. This result is due to normal albumin levels in early breast cancer patients. Platalet lymphocyte ratio (PLR) is associated with lymph node metastasis in breast cancer. PLR is applied to mSIS score instead of albumin.The new modified early-stage breast cancer SIS(mebcSIS) was established as follows: Score 0: LMR ≥ 5.7 and PLR < 141, Score 1: LMR < 5.7 or PLR ≥ 141, Score 2: LMR < 5.7 or PLR ≥ 141. The relationship between mebcSIS and LNM was statistically significant (p = 0.003). There is a positive correlation between mebcSIS score and lymph node metastasis in early breast cancer patients.

| KEYWORDS

Early-stage breast cancer; Sentinel lymph node metastasis, Modified systemic inflammation score, Platelet/lymphocyte ratio(PLR), Lymphocyte/Monocyte ratio (LMR)

| ARTICLE INFORMATION

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1. Introduction

Breast cancer is the most diagnosed cancer in women worldwide (11.7%), excluding skin malignancies (Sung et al., 2021). The most important prognostic factor in breast cancer is the presence of axillary lymph node metastasis. Sentinel lymph node biopsy (SLNB) is the standard procedure for axillary staging in clinically lymph node-negative (N0) breast cancer patients (Qui et al.,2018). No method can diagnose axillary lymph node metastasis with high precision before surgery. However, in addition to imaging methods, thrombocyte/lymphocyte ratio (PLR), a hematological parameter, can be used in diagnosing metastatic lymph nodes for early breast cancer. (Morkavuk et al.,2021). Neutrophils, lymphocytes, and platelets have been shown to play an important role in tumor cell metastasis. (Wang et al.,2014). Platelets protect circulating tumor cells from immune destruction through numerous mechanisms and facilitate tumor metastasis by inducing epithelial-mesenchymal transition (Labelle et al.,2011- Gil-Bernabé et

al.,2012). Neutrophils support the development and spread of cancer via the microenvironment they create through the secretion of cytokines and chemokines (Gregory & Houghton., 2011). Lymphocytes play a crucial role in cancer immune surveillance and defense by inducing cytotoxic cell death, inhibiting tumor cell proliferation and migration (Montavani et al.,2008). Inflammatory biomarkers obtained from routine blood tests before surgery have been reported to be used to predict the prognosis of cancers. (Kim et al.,2015- Lin et al.,2017). Systemic inflammation score (SIS), using preoperative serum albumin (Alb) and Lymphocyte/Monocyte ratio (LMR), has also been reported as a new scoring system to predict the prognosis of malignant tumors in colorectal and gastric cancers (Suzuki et al.,2018-Inagaki et al., 2021). It has also been demonstrated that the mSIS marker can be more sensitive through disease-specific adjustments. (Lin et al.,2019). This study aims to evaluate whether the mSIS score can be useful for predicting sentinel lymph node metastasis and to determine if there is a need to modify the mSIS score.

2. Methodology

Three hundred twenty-one breast cancer patients operated on in Ankara City Hospital General Surgery Clinic between 01.03.2019 and 30.06.2021 were analyzed retrospectively. Of these breast cancer patients, 174 were early stage. The age and gender of the patients, Albumin parameters, Thrombocyte, Lymphocyte and Monocyte counts, histopathological type of cancer, and lymph node metastasis status were recorded. The inclusion criteria were that the patients older than 18 had undergone breast surgery in the Ankara City Hospital General Surgery clinic, had a pathology result of breast cancer, and had preoperative and postoperative laboratory tests performed in our hospital. Patients younger than 18 with systemic disease and whose preoperative and postoperative tests were conducted outside our hospital were excluded from the study. One hundred fifty-nine patients with early stage breast cancer who met the criteria in the research protocol were included in the study. SIS score was defined as follows: SIS Score 0: Alb≥4.0g/dL, Score 1: Alb<4.0 g/dL and LMR≥3.4, Score 2: Alb<4.0 g/dL and LMR <3.4. Modified SIS score was defined as follows: Modified SIS Score 0: Alb≥4.0g/dL and LMR≥3.4, Score 1: Alb<4.0 g/dL or LMR<3.4, Score 2: Alb<4.0 g/dL and LMR<3.4. Modified SIS was used to detect the presence of lymph node metastases. A decrease in albumin values is not expectable in patients with early-stage breast cancer. Therefore, a modification was made in mSIS by removing Albumin in patients with early stage breast cancer.

2.1 Statistical Analysis

SPSS 24.0 (IBM Corp., Armonk, NY) program was used for data analysis. Patients were divided into two groups positive sentinel axillary lymph node metastasis and negative sentinel axillary lymph node metastasis. The significance of the difference between groups for categorical variables was analyzed with the Pearson Chi-Square test. Whether the data showed normal distribution between groups was analyzed using the Kolmogorov-Smirnov test. Patient ages were normally distributed between the groups (P = 0.200). Since Albumin and hematological rate data did not show normal distribution between groups, these parameters were analyzed using the Mann-Whitney U test ($p < 0.05$). The ROC curve was used to determine the cut-off value for the hematological parameters whose Mann-Whitney analysis was significant.

3. Results

In one hundred fifty-nine patients with stage 1 and stage 2a breast cancer, lymph node metastasis was not detected in 108. It was detected in 51 of these patients. The patients were divided into two groups, and the mSIS score was applied to each group.

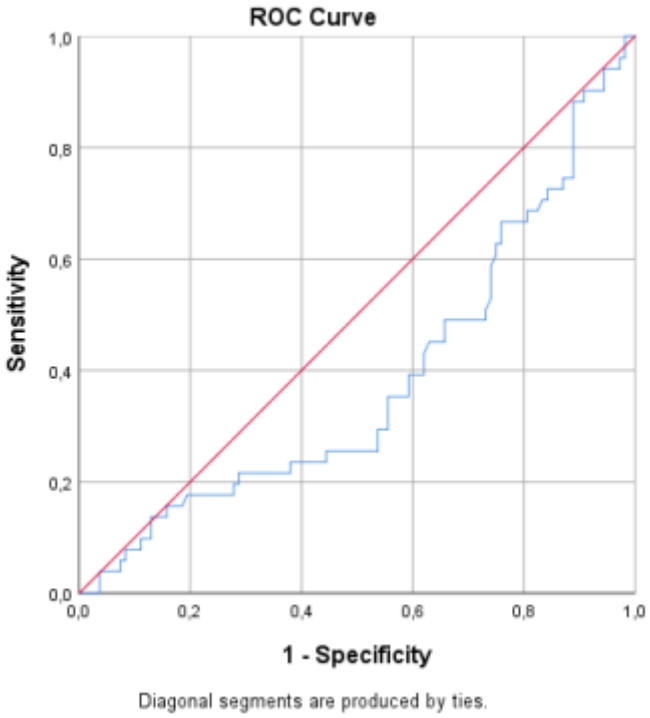
There is no significant difference between the groups with mSIS scoring in detecting the presence of lymph node metastasis.

Table 1. Comparison of groups with and without LNM with mSIS

			LNM		Total	*P* value
			No	Yes		
mSIS Score	0	N	94	46	140	0.567
		%	67,1	32,9	100	
	1 or 2	N	14	5	19	
		%	73,7	26,3	100	
Total		N	108	51	159	
		%	67,9	32,1	100	

No significant difference was found between groups with Albumin value (p = 0.953) and NLR (p = 0.396). The difference between groups with LMR (p = 0.018) and PLR (p = 0.001) was statistically significant. The cut-off value was 5.72 in the ROC analysis for LMR.

Figure 1. LMR ROC curve according to whether there is LNM or not



When this value was used, the difference between the groups was significant (p = 0.018). However, its sensitivity in detecting lymph node metastasis was 39.2%, and its specificity was 39.8%.

Table 2. The significance of the difference between the groups according to the LMR cut-off value

			LNM		*P* value
			No	Yes	
LMR	LMR ≥ 5.7	N	65	20	0.013
		%	76.5	23.5	
	LMR < 5.7	N	43	31	
		%	58.1	41.9	
Total		N	108	51	
		%	67.9	32.1	

The ROC curve was also taken for the PLR, examined in previous studies, and the cut-off value was found to be 140.09. When the analysis was done using that ratio, it was found that there was a significant difference between the groups.(p = 0.001).

Figure 2. PLR ROC curve according to the presence of LNM or not

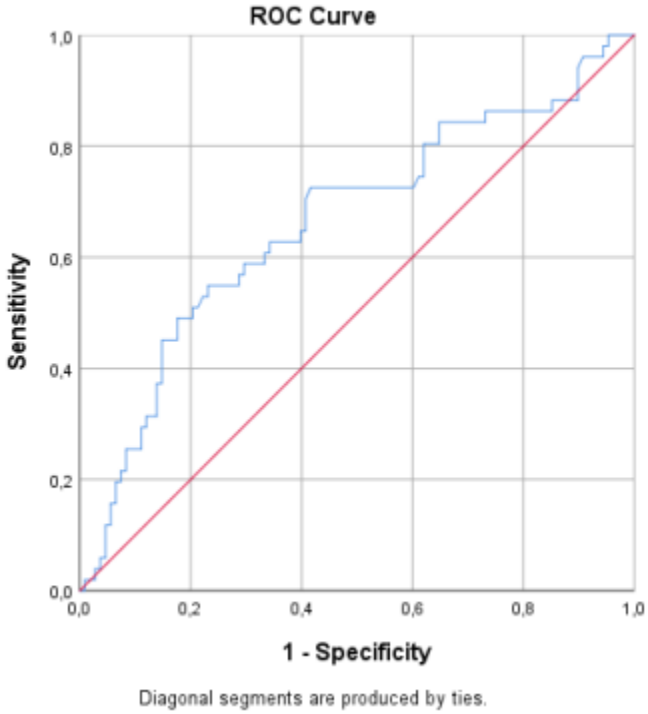


Table 3. The significance of the difference between the groups according to the PLR cut-off value

			LNM		*P* value
			No	Yes	
PLR	PLR < 141	N	68	19	0.002
		%	78.2	21.8	
	PLR ≥ 141	N	40	32	
		%	55.6	44.4	
Total		N	108	51	
		%	67.9	32.1	

The sensitivity of PLR in detecting LNM was 62.7%, and the specificity was 63%. Therefore, it has been decided to use it in modifying mSIS. The modified early-stage breast cancer SIS(mebcSIS) was established as follows: Score 0: LMR ≥ 5.7 and PLR < 141, Score 1: LMR < 5.7 or PLR ≥ 141, Score 2: LMR < 5.7 or PLR ≥ 141. When analyzing the significance of the difference between the groups with mebcSIS, the sensitivity was 76.5%, specificity 41.66%, PPV 38.2%, and NPV 78.9% in score 1 (p = 0.026). Similarly, sensitivity was 47.1%, specificity 79.6%, PPV 47.8%, and NPV 76.1% in mebcSIS score 2 (p = 0.001).

Table 4. Table showing the relationship between mebcSIS Score 1 and LNM

			LNM		*P* value
			No	Yes	
MebcSIS Score 1	Negative	N	45	12	0.026
		%	78.9	21.1	
	Positive	N	63	39	
		%	61.8	38.2	
Total		N	108	51	
		%	67.9	32.1	

Table 5. Table showing the relationship between MebcSIS Score 2 and LNM

			LNM		*P* value
			No	Yes	
MebcSIS Score 2	Negative	N	86	27	0.001
		%	76.1	23.9	
	Positive	N	22	24	
		%	47.8	52.2	
Total		N	108	51	
		%	67.9	32.1	

The relationship between mebcSIS and LNM was statistically significant (p = 0.003). As the mebcSIS score value increases, the probability of LNM increases. There is a positive correlation between mebcSIS and LNM (Pearson correlation test: 0.264, p = 0.001).

4. Discussion

Many ratios and scoring systems, such as LMR, NLR, PLR, and the modified Glasgow prognostic score, are used to predict cancer-specific and overall survival of surgical patients (Chan et al.,2017- Goto et al.,2018). The clinical use of scoring systems is simple and more consistent than hematological rates (Dolan et al.,2018). SIS, a new inflammation-based prognostic score based on preoperative serum Albumin level and LMR, demonstrates the comprehensive effects of nutrition and systemic inflammation on tumor progression. It has been reported that this system has a prognostic value in gastric and colorectal cancers (Lin et al.,2019). Lymphopenia caused by tumors inhibits lymphocyte-derived anti-tumor activity and angiogenesis, which leads to poor prognosis in patients (Azimi et al.,2012). Interaction between tumor and monocytes and endothelium contributes to tumor growth and metastasizing. (Evani et al.,2013). Chan et al. reported that, due to its simple and consistent clinical use, LMR is superior to other biomarkers in predicting Overall Survival (OS) in patients with colorectal cancer who underwent curative resection(Chan et al.,2017). Takeuchi et al. (2017), in a study conducted on breast cancers, reported that LMR and NLR, which are the contents of CBC, do not show a poor prognosis. In the same study, they reported that serum CRP level and PLR are markers based on inflammation that indicate a poor prognosis in breast cancer. Gu et al. (2016) reported that the threshold value of LMR varies in many different cancer types due to as yet unknown clinicopathological parameters. Therefore, our study determined a new LMR threshold value after using the ROC curve to predict lymph node metastasis in patients with early stage breast cancer.

In the Glasgow Prognostic Score (GPS) used by Murri et al. to detect the presence of metastasis in patients with metastatic breast cancer, patients with both high C-reactive protein (CRP) (> 10 mg) and hypoalbuminemia (< 35 g/dL) were considered positive. They reported that, in the presence of a systemic inflammatory response, GPS could be a valuable indicator of poor prognostic

outcomes in patients with metastatic breast cancer (Al Murri et al., 2006). However, in the absence of infection, CRP is not routinely used in breast cancer patients. Therefore CRP was excluded from the study.

In our study, there was no patient with hypoalbuminemia (< 35 g/dL). These results can be because the patients had early-stage breast cancer, and their nutrition was good. It has been shown that high PLR is associated with poor prognosis and clinicopathological features in breast cancer. In addition, it has been reported that there is a significant relationship between high PLR and the presence of lymph node metastases (Zhang et al.,2017). A recent study reported that sentinel lymph node metastasis (SLNM) positivity was significantly higher in patients with T1 breast cancer with high PLR than in patients with low PLR (Takada et al.,2020). Romero-Cordoba et al.(2019) reported that tumor aggressiveness score and PLR values showed a positive correlation in patients with triple-negative breast cancer (TNBC). Ma et al. showed a correlation between high PLR and low LMR and lymph node metastasis (Ma et al.,2021). Therefore, LMR and PLR, proven by previous studies to indicate the presence of lymph node metastases in early breast cancer, were used instead of Albumin when modifying the SIS score in our study. Our research found a positive correlation between mebcSIS and LNM.

5. Conclusion

Axillary lymph node metastasis is the most important prognostic factor in breast cancer. Although Sentinel lymph node biopsy has replaced standard axillary dissection, no method is currently sufficient to detect lymph node metastasis preoperatively. The mSIS score has been successful in predicting prognosis in malignant tumors. The mSIS score is based on Albumin and LMR. In our study, we aim to evaluate whether the mSIS score can be useful for predicting sentinel axillary lymph node positivity. Most early breast cancer patients have normal albumin values. Thus we need to modify the mSIS score. After PLR has replaced albumin in the mSIS score, the new score values increase LNM probability. Therefore our study shows that the mebcSIS score predicts LNM probability higher than PLR and LMR alone. This study presents limitations similar to previous retrospective studies. One limitation is the lack of reaching higher numbers in the patient cohort; the other is a single-centered study. Nevertheless, the positive data we obtained at the end may direct us to future multicenter studies.

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