Original Research Paper

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DIAGNOSTIC VALUE OF PREOPERATIVE SERUM ALBUMIN AND LYMPHOCYTE-MONOCYTE RATIO FOR PREDICTING THE PRESENCE OF MALIGNANCY IN PATIENTS WITH INDETERMINATE THYROID NODULES (BETHESDA III AND IV)

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KEYWORDS :

INTRODUCTION

The American Thyroid Association (ATA) defines a thyroid nodule as a discrete lesion within the thyroid gland. Some nodules are incidentally detected on imaging and have the same malignancy risk as palpable nodules of similar size. Palpable thyroid nodules occur in approximately 5% of women and 1% of men in iodine-sufficient regions, whereas ultrasound can detect nodules in up to 68% of individuals, especially in women and the elderly.

Indeterminate thyroid nodules (Bethesda III & IV) pose a diagnostic challenge, occurring in 7.7–29.6% of fine-needle aspiration biopsies (FNAB), with malignancy risks of 6–18% for AUS/FLUS and 10–40% for FN/SFN. Approximately 20% of thyroid nodules have indeterminate (ID) cytology and classified as Bethesda categories III and IV. In patients with Thyroid nodules of these two categories, varying risks of malignancy are reported (6–18% and 10–40%, respectively) and discussions remain as to whether the best approach is the follow-up with FNACs, or surgery. Repeat FNAC improves diagnostic accuracy, reducing false negatives from 5.2% to <1.3%, particularly for initially non-diagnostic or indeterminate results. MicroRNAs (miRNAs) regulate gene expression and show promise in improving preoperative diagnosis. Molecular tests are classified as: "Rule-out" tests (high negative predictive value), e.g., Afirma, reducing unnecessary surgeries. "Rule-in" tests (high positive predictive value), e.g., ThyroSeq v2.1 and ThyGenX/ThyraMir, identifying high-risk nodules.

Subcategorisation and molecular testing can help stratify cancer risk, reducing unnecessary surgeries. While diagnostic lobectomy remains common (48.3–75.2% for indeterminate nodules), improved risk stratification may aid personalised management . Recent research has identified two molecular profiles in thyroid tumors: RAS-like and BRAFV600E-like, which can aid in the management of indeterminate nodules [21].Despite these advancements, challenges remain in optimizing test performance, cost-effectiveness, and integration into clinical workflows. Molecular tests are costly and not always accessible. Their role in routine practice remains debated. A cost-effective, easily applicable scoring system like mSIS may improve malignancy risk assessment and aid clinical decision-making.

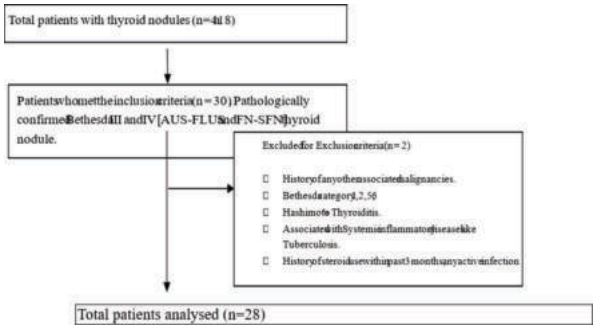
Emerging biomarkers, including the Modified Systemic Inflammatory Score (mSIS), which incorporates albumin levels and lymphocyte-to-monocyte ratio (LMR), show potential in malignancy prediction. Lymphocytes play a key role in tumor immunity, while monocytes contribute to tumor burden. Higher mSIS scores correlate with increased malignancy risk . mSIS, which combines these markers, has shown promise in predicting malignancy and outcomes in different malignancies, but its role in thyroid nodules, particularly indeterminate ones, remains underexplored. We aimed To evaluate the diagnostic value of preoperative modified systemic inflammatory score (mSIS) for predicting the presence of malignancy in patients with indeterminate thyroid nodules (Bethesda III AND IV)

METHODOLOGY

The prospective study included inpatients who got admitted for thyroid evaluation for Bethesda III and IV, in the department of General Surgery in a tertiary centre, after taking informed consent. It was conducted from June 2022 to February 2024. The hospital ethical committee clearance was obtained before undertaking the study.

All 28 patients required surgical management and was stratified into 3 groups preoperatively.

	Serum Albumin	LMR
mSIS 0	>/= 4.0g	>/=3.4
mSIS 1	<4.0g	<3.4
mSIS 2	<4.0g	<3.4



Statistical Analysis

Data were entered into Microsoft Excel and statistical analysis was carried out in SPSS software version 17.0. Comparison between mSIS and malignancy, age group and Bethesda classification, and duration and Bethesda classification were done with chi squared test. Independent t test was used to compare the age, BMI, ALB, LMR across the participants with and without malignancy. ALB and LMR values were compared across the mSIS scoring, which was done with one-way ANOVA. Receiver operating characteristics[ROC] curve was used to predict the malignancy using mSIS, ALB and LMR. Area under the curve was reported. A p value of less than 0.05 was considered as statistically significant.

RESULTS:

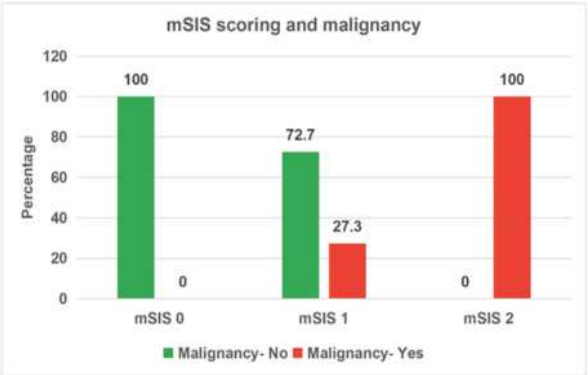
In the analysed (n=28) patients of indeterminate thyroid nodule, females are the predominant gender in the sample. Swelling is the most common complaint, reported by 100.0% (n = 28) of the sample .The duration of symptoms does not significantly differ between those with malignancy and those without malignancy. Palpation findings were The consistency of the swelling was predominantly firm in 92.9% of the participants (n = 26), while 7.1% (n = 2) had variable. The trachea was centrally located in all participants (100%, n = 28). Similarly, the carotid arteries were normal in all participants (100%, n = 28), and no lymph nodes were palpable in any of the cases (100%, n = 28). The most common management approach was Total Thyroidectomy (TT), utilized in 60.7% of cases (n = 17). Right Hemithyroidectomy (RHT) was performed in 28.6% of participants (n = 8), while Left Hemithyroidectomy (LHT) was the management strategy for 10.7% of cases (n = 3). The most common diagnosis was Papillary Carcinoma Thyroid (PCT), accounting for 25.0% of cases (n = 7). Both Multinodular Goiter (MNG) and Nodular Goiter (NG) were diagnosed in 21.4% of participants each (n = 6 for both). Follicular Adenoma (FA) and Follicular Carcinoma (FC) each accounted for 10.7% of cases (n = 3 for both). Insular Carcinoma (IC) was identified in 3.6% of participants (n = 1), and micro-Papillary Carcinoma (mPCA) was present in 7.1% of cases (n = 2). These findings indicate that PCT is the most prevalent HPE diagnosis, followed by MNG and NG, with a variety of other conditions present in smaller proportions.

Characteristic		Malignancy (n=13)	Non- Malignancy (n=15)	P-Value
Age (years)		Median = 45 (range 30-70)	Median = 35 (range 20-60)	0.15
Gender	male	2 (15.4%)	1 (6.7%)	-

	female	11 (84.6%)	14 (93.3%)	-
Duration ofSwelling (mean months)		22.8	7.2	0.15
BethesdaCategory		Grade III: 5 (38.5%)	Grade III: 12 (80.0%)	0.03
		Grade IV: 8 (61.5%)	Grade IV: 3 (20.0%)	
BMI(mean)		20.8 (SD: 2.0)	21.6 (SD: 1.6)	0.28
mSIS Score	0	0 (0%)	7 (100%)	<0.001
	1	3 (27.3%)	8 (72.7%)	
	2	10 (100%)	0 (0%)	
LMR(Mean)		2.8 (SD: 0.7)	3.5(SD: 0.4)	0.004
ALB		Mean: 3.3 (SD: 0.6)	Mean: 4.1 (SD: 0.5)	0.001

Among participants with an mSIS of 0, all (100.0%, n = 7) were in the non-malignant group.

For those with an mSIS of 1, 72.7% (n = 8) were in the non-malignant group, while 27.3% (n = 3) had malignancy. In contrast, all participants with an mSIS of 2 (100.0%, n = 10) were in the malignant group. The total distribution shows that 53.6% (n = 15) of participants did not have malignancy, while 46.4% (n = 13) were diagnosed with malignancy. The chi-square test revealed a significant association between mSIS and malignancy status ($p < 0.001$), indicating that higher mSIS scores are significantly associated with the presence of malignancy.



Diagnosis	Area under the curve	95 % CI for AUC	P value
mSIS	0.94	0.87-1	<0.001
ALB	0.92	0.82-1.0	<0.001
LMR	0.83	0.66-0.99	<0.001

Receiver operating characteristics [ROC]curve was done with mSIS, ALB and LMR to predict the malignancy and it yielded the area under the curve of 0.94, 0.92 and 0.83 respectively. And the were significant with the p value of <0.001.

Key Observations:

- **Age**: The median age is higher in the malignancy group, but the difference is not statistically significant.
- **Gender**: Females are predominant in both groups.
- **Duration of Swelling**: The mean duration is longer in the malignancy group, though not statistically significant.
- **BMI**: The mean BMI is slightly lower in the malignancy group, but the difference is not statistically significant.
- **mSIS Score**: A higher mSIS score is significantly associated with malignancy.
- **LMR**: Lower LMR is significantly associated with malignancy.
- **ALB**: Lower ALB levels are significantly associated with malignancy.

DISCUSSION:

Surgeons have to make a challenging decision between follow-up and surgical treatment in case of an Indeterminate cytological diagnosis of Thyroid nodule. The recommendation of international guidelines for patients with nodules classified AUS/FLUS is first repeating the FNAC, then if possible molecular testing and as a last option diagnostic surgery. In the case of FN/SFN, while the first recommendation is lobectomy, it is said that Total thyroidectomy preferred instead of lobectomy in the presence of malignancy- related risk factors, such as a family history of Thyroid cancer, nodules larger than 4 cm, presence of other nodules in the contralateral lobe or the presence of associated hyperthyroidism.[30]Although molecular tests are practical and cost-effective, they may not be easily accessible. On the other hand, recurrent FNACs can be uncomfortable and weary for patients. Moreover, in case of possible malignancy, the need for completion thyroidectomy following lobectomy will put patients at the risks of anesthesia and surgery for the second time. Therefore, besides cytological examination, an easy-to-apply, cost-effective scoring system with a high diagnostic value may be used to supplement malignancy risk and clinical decision making.

Inflammation plays a crucial role in thyroid cancer.[31,32] Most of the researchers investigating serumbiomarkers and thyroid carcinogenesis focus on the progressionand treatment response, and a few of them focus on the diagnosisand the risk of developing Thyroid cancers.[33]In the present study, which is designed to predict malignancy in patients with Indeterminate Thyroid nodule, Total Thyroidectomy wasperformed in 60.7% of the cases. Patients' preferences and clinicalfeatures were mostly effective in preferring Total Thyroidectomy. A 39.3% of the cases underwent hemithyroidectomy out of which 10.71 % of cases required completion thyroidectomy within 6 months. Based on surgically treated patients with histological followup, 46.4% of the cases turned out to be malignant. However, thisrate seems to be higher according to the literature[1]. After classifying the patients according to mSIS with preoperative ALB levels and LMR, it was found that all patients with mSIS 2 were malignant. All patients with mSIS 0 are Benign. In patientswith mSIS 1, the rate of malignancy was27.3%. This significant association between preoperative mSIS andmalignancy can be explained by several mechanisms. In the presence of chronic inflammation, ALB synthesis in theliver decreasesand hypoalbuminemia may develop[34,35]Therefore, Albumin is considered as animportant indicator of malnutrition and cachexia incancer patients. On the other hand, lymphocytes have a crucial rolein anticancer immunity, and a decreased count of lymphocytes isthought to be associated with poor prognosis. Contrary to lymphocytes, circulating monocytes differentiate into macrophagesand contribute to the progression of cancer by promoting tumor growth, vascularisation and metastasis. mSIS based on LMR and ALB is extremely possible to reflect this tumorassociated immune response as a diagnostic scoring system.

Recently, in the AMORIS study, Ghoshal et al. revealed an association between low serum ALB levels (ALB <40 g/L) and increased risk of developing a thyroid cancer.But somehow, this association was not observed for CRP, haptoglobin, or leukocytes[36] In another study, the combined use of plateletdistribution width (PDW) and ALB to distinguish thyroid cancer from benign thyroid masses showed similar results, and the lower serum ALB levels with increased PDW were also found to be associated with malignancy[37]On the other hand, preoperative low LMR levels have been associated with an increased risk of recurrence in papillary thyroid cancer by Yokota et al[38]Although many studies confirm the association of low ALB levels with Thyroid cancer, the existence of contradictory results related to other biomarkers of inflammation emphasizes that the role of inflammation in cancer development is more complicated than we anticipate.The present study has several limitations. We restricted our study population to patients with Bethesda category III or IV Thyroid nodules.The small sample size may have limited the statistical power of some subgroup analyzes in particular. Another limitation is the lack of data on anti-inflammatory drug use or nutritional support that might affect mSIS in the pre- operative period.

CONCLUSION:

In our study, mSIS is significantly associated with malignancy in patients with Indeterminate cytology. For an **LMR of less than 3.4,** The sensitivity, indicated that it correctly identified 69.2% of true positives. Thespecificity,accurately recognised 86.7% of true negatives. The positive predictive value suggested that 81.8% of those who tested positive actually had the condition. The negativepredictive valueindicated that 76.5% of those who tested negative were correctly classified asnot having the condition. For an **ALB of less than 3.9**, The sensitivity, indicated that the test correctly identified 84.6% of true positives. The specificity, reflected that the test accurately recognised 80.0% of true negatives. The positive predictive value, suggested that 78.6% of those who tested positive actually had the condition. The negative predictive value, indicated that 85.7% of those who tested negative were correctly classified as not having the condition. Thus , in Indeterminate Thyroid nodule with low LMR and ALB levels malignancy cannot be be ruled out, and appropriate surgical treatment should be performed without delay, due to the increased risk of

malignancy. On the other hand, besides being easy and cost-effective, mSIS is always evaluated from routine blood tests, and it can be used as an auxiliary method to assess the risk of malignancy in patients with Indeterminate cytology. Our results strongly support that.

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