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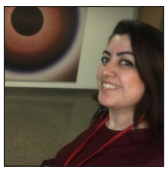
*Research Article*

# Cytohistological correlation of pleural fluids using the international system for reporting serous fluid cytopathology: A single-center experience

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## ABSTRACT

**Objectives:** The cytologic examination of serous effusions is a widely used, inexpensive, and minimally invasive diagnostic method with high sensitivity for detecting malignancy. However, there are limited studies evaluating the validity, cytohistological correlation, and diagnostic performance of the recently proposed International System for Reporting Serous Fluid Cytopathology (TIS) in pleural effusions. This study aimed to reclassify pleural effusion cytology specimens according to the TIS system, determine the risk of malignancy (ROM) for each category, and assess the diagnostic correlation with histopathological findings.

**Material and Methods:** A total of 167 pleural effusion cases with both cytologic and histopathologic diagnoses, evaluated between 2011 and 2023, were included. Cytologic specimens were reclassified according to TIS categories as: Non-diagnostic (ND), negative for malignancy (NFM), atypia of undetermined significance (AUS), suspicious for malignancy (SFM), and malignant (MAL). The results were compared with those obtained from our previous institutional reporting system (ND/Inadequate, NFM, SFM, MAL) and correlated with biopsy findings.

**Results:** Based on our institutional system, the diagnostic distribution was 61.1% NFM, 20.4% MAL, 16.2% SFM, and 2.4% ND/inadequate. According to the TIS classification, 59.9% were NFM, 21.6% MAL, 11.4% SFM, 4.8% AUS, and 2.4% ND. Histopathology confirmed 50.9% benign and 49.1% MAL cases. A statistically significant correlation was observed between the previous reporting system and TIS ($P$ <0.001), as well as between cytological and histological results ($P$ <0.001). The ROM was 25% for AUS and 89.5% for SFM.

**Conclusion:** Adequate cytologic sampling remains crucial for diagnostic accuracy in pleural effusions. The TIS provides a standardized, reproducible, and user-friendly classification scheme that facilitates communication and reduces false-positive and false-negative interpretations. Our findings support the diagnostic value of the TIS system and emphasize the importance of adopting internationally standardized reporting systems for consistent patient management.

**Keywords:** Cytohistological correlation, Cytology, Pleural effusion, Risk of malignancy, The International System for Reporting Serous Fluid Cytopathology

## INTRODUCTION

Serous effusion cytology is a rapid, simple, minimally invasive, and cost-effective technique for evaluating malignancy and guiding patient management.[1] However, the cytologic interpretation of effusion specimens remains challenging due to the morphological overlap

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between malignant (MAL) cells and reactive mesothelial proliferations.[1,2] Despite the increasing reliance on effusion cytology, variability in terminology and diagnostic thresholds has contributed to inconsistencies in reporting and patient follow-up.

To address these challenges, an international panel of cytopathology experts introduced the International System for Reporting Serous Fluid Cytopathology (TIS) in 2020, as a collaborative initiative of the International Academy of Cytology and the American Society of Cytopathology.[3,4] TIS provides a standardized framework for reporting cytologic findings from pleural, peritoneal, and pericardial effusions. It outlines adequacy criteria, diagnostic categories, and corresponding risks of malignancy (ROM), thereby improving interobserver consistency and communication between pathologists and clinicians.[2,5]

TIS classifies effusion cytology into five diagnostic categories: Category I, non-diagnostic (ND); Category II, negative for malignancy (NFM); Category III, atypia of undetermined significance (AUS); Category IV, suspicious for malignancy (SFM); and Category V, MAL.[3,6]

Each category is associated with a defined ROM and evidence-based management recommendations. Specimen adequacy depends on several factors, including sample volume, cellularity, and preservation. Cases with poor cellularity, extensive degeneration, or heavy blood contamination are typically classified as ND, whereas small but adequately cellular specimens may still yield diagnostic information. The presence of mesothelial cells is not required for adequacy, as some effusions, especially those rich in lymphocytes, may remain diagnostically sufficient.[3]

The AUS and SFM categories represent diagnostically challenging gray zones between benign and MAL interpretations. AUS encompasses atypical features that are insufficient for a definitive diagnosis yet too worrisome to classify as benign, while SFM includes cases highly suggestive of malignancy but lacking definitive cytologic criteria.[2,6] Previous studies have demonstrated that the ROM for SFM is significantly higher than that for AUS ($P$ <0.01), supporting their separation into distinct diagnostic categories.[7]

Cytologic evaluation of pleural effusions is further complicated by the wide range of metastatic malignancies that may involve serous cavities, with adenocarcinomas being the most frequent. Morphologic overlap among tumors of various origins and the absence of tissue architecture may obscure diagnosis, underscoring the importance of ancillary techniques such as special stains, immunocytochemistry, and molecular testing. Primary malignancies, including MAL mesothelioma, although less common, may also be encountered and can often be diagnosed accurately using a combination of cytomorphologic features and ancillary studies.[2]

Given these diagnostic complexities, the adoption of standardized systems such as TIS is critical for improving diagnostic reproducibility, accuracy, and communication. The present study aims to evaluate the diagnostic utility of TIS in pleural effusion cytology by correlating cytologic findings with corresponding histopathological diagnoses and calculating the ROM for each TIS category in a single-center cohort.

## MATERIAL AND METHODS

This retrospective study included patients who underwent both pleural effusion cytology and corresponding pleural biopsy at the Department of Pathology, Sivas Cumhuriyet University, between 2011 and 2023. No sampling or selection criteria were applied; all patients with available histopathological diagnoses were included.

Cytologic smears of pleural effusion samples were prepared using May-Grünwald-Giemsa and Papanicolaou stains. A cell block was also prepared for each case. In specimens interpreted as suspicious or MAL, an immunohistochemical panel was applied to the corresponding cell block based on cytomorphologic, clinical, and radiologic findings. Calretinin and D2-40 were used as mesothelial markers to support the diagnosis of mesothelioma, whereas claudin-4, Ber-EP4, and thyroid transcription factor-1 were employed as epithelial markers in favor of adenocarcinoma. All cytological materials were retrospectively reviewed independently by two pathologists experienced in cytopathology.

Cytologic smears were re-evaluated and reclassified according to the TIS into the following five diagnostic categories[3,6]:

1. ND: Samples classified as ND demonstrated insufficient cellularity, excessive degeneration, inadequate preservation, or heavy blood contamination.
2. NFM: Specimens showing benign mesothelial cells, macrophages, lymphocytes, and polymorphonuclear leukocytes were categorized as NFM.
3. AUS: Specimens lacking adequate cytologic features for definitive benign or MAL interpretation, but not meeting ND criteria, were classified as AUS. Atypical features were more suggestive of benign, reactive, or degenerative processes than malignancy.
4. SFM: Specimens exhibiting cytologic features generally associated with malignancy but lacking sufficient quality or quantity for a definitive MAL diagnosis were classified as SFM.
5. MAL: Specimens showing unequivocally MAL cells with moderate to high cellularity, either singly or in clusters, were placed in this category. Diagnoses included mesothelioma or metastatic malignancy, alone or in conjunction with ancillary studies.

Results obtained from our institution's previous cytological reporting system (ND/Inadequate, NFM, SFM, MAL) were compared with those derived from TIS-based reclassification. Cytological findings from both systems were also correlated with histopathological diagnoses from paired pleural biopsies.

The dependent variable for this study was the histopathological diagnosis of the pleural biopsy (benign vs. MAL). Independent variables included the cytological evaluation method (initial classification vs. TIS classification), cytologic diagnostic category (ND, NFM, AUS, SFM, MAL), and demographic characteristics such as age and sex.

The risk of malignancy (ROM) for each TIS category was calculated as the proportion of cases confirmed as MAL by histopathology using the following formula:

$$\text{ROM} = (\text{Number of MAL cases/Total number of cases in the category}) \times 100$$

The calculated ROM values were compared with reference ranges reported by Chandra *et al*. (2019) and Wang *et al*. (2023) to assess the predictive performance of the TIS classification system.[3,4]

### Statistical analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (min-max), according to data distribution. Diagnostic concordance between cytologic and histopathologic classifications was assessed using Cohen's kappa test. Diagnostic performance parameters – including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy – were calculated for each reporting system.

### Ethics statement

This study was approved by the Ethics Committee of the University (Approval No: 2023-07/34) and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

## RESULTS

Among the 167 patients included in the study, 62.3% (n = 104) were male, and 37.7% (n = 63) were female. The mean age was 61.7 ± 15.3 years (range, 21–88). According to the initial cytologic evaluation, the diagnostic distribution was as follows: 61.1% (n = 102) NFM, 20.4% (n = 34) MAL, 16.2% (n = 27) SFM, and 2.4% (n = 4) ND. Based on the TIS classification, 59.9% (n = 100) of the cases were categorized as NFM, 21.6% (n = 36) as MAL, 11.4% (n = 19) as SFM, 4.8% (n = 8) as AUS, and 2.4% (n = 4) as ND [Table 1].

**Table 1:** Diagnostic distributions according to initial cytological evaluation and TIS classification.

| Diagnosis | Initial cytology n (%) | TIS n (%) |
|---|---|---|
| Negative for malignancy | 102 (61.1) | 100 (59.9) |
| Malignant | 34 (20.4) | 36 (21.6) |
| Suspicious for malignancy | 27 (16.2) | 19 (11.4) |
| Atypia of undetermined significance | - | 8 (4.8) |
| Non-diagnostic | 4 (2.4) | 4 (2.4) |

TIS: International system for reporting serous fluid cytopathology

According to the biopsy results, 50.9% (n = 85) of the cases were benign, whereas 49.1% (n = 82) were MAL.

### Diagnostic reclassification and cytohistological correlation

Of the 102 initially reported NFM cases, 100 remained NFM, and 2 were reclassified as AUS upon reevaluation. On retrospective review, the two cases initially categorized as NFM but found to be MAL on biopsy showed subtle atypical cytomorphologic features, including mild nuclear enlargement, irregular nuclear contours, rare atypical cells, and focal 3D clustering. Because these findings were limited and not unequivocally diagnostic of malignancy, they were initially considered regenerative findings, but have been reclassified as AUS, an intermediate category in the new classification.

Among the 100 cases classified as NFM in both assessments, biopsy findings revealed malignancy in 23 cases. Both cases reclassified from NFM to AUS were also MAL on biopsy [Figure 1]. Because the background was inflammatory, there were cells intermixed with mesothelial cells whose nature could not be clearly identified. Initially, assuming reactive changes, the cytology was classified as benign. However, on re-evaluation, it was interpreted as AUS due to the presence of cells that could not be definitively distinguished. Biopsy diagnoses revealed metastatic adenocarcinoma**,** originating from the lung and stomach. Of the 27 cases initially categorized as SFM, 19 remained SFM upon reevaluation, 17 of which were confirmed as MAL on biopsy. Among the remaining eight cases, six were reclassified as AUS (four benign and two MAL on biopsy), while two were reclassified as MAL and were confirmed MAL [Figure 2]. In cases assigned to the AUS category, the cytomorphologic features suggestive of malignancy were not fully developed; marked degeneration and an inflammatory background were present. On biopsy, one case was diagnosed as fibrinous pleuritis, whereas the remaining two were diagnosed as mesothelioma [Figure 3].

Cases classified as MAL exhibited overt MAL features, and the corresponding biopsy diagnoses were mesothelioma.

All 34 cases initially diagnosed as MAL were confirmed MAL in both the TIS re-evaluation and biopsy results. Similarly, all 36 cases categorized as MAL according to TIS were histologically MAL [Figure 2c]. Of the four cases reported as ND in both evaluations, two were MAL and two were benign on biopsy.

In selected cases with available cell block material, particularly in ambiguous cases such as AUS and SFM, immunohistochemical studies were used as adjunctive tests to support cytomorphological interpretation. Final TIS categorization was based on an integrated assessment of morphology, cell block findings, and, where available, immunohistochemical results. Adjunctive immunohistochemical studies supported interpretation in selected cases but were not used alone to determine TIS categories. In MAL cases, however, they were used in tumor subtyping to aid clinical understanding, especially in tumors of unknown primary origin.

The interval between pleural fluid cytology and corresponding pleural biopsy ranged from 0 to 60 days, with a median of 10 days and a mean of 17.6 days.

### Distribution of malignancies

Among the 82 MAL cases confirmed by biopsy:

- 32 (39.0%) were mesotheliomas
- 40 (48.8%) were metastatic adenocarcinomas (most commonly lung, followed by breast and other sites)
- 2 (2.4%) were metastatic small cell carcinomas
- 1 (1.2%) was primary effusion lymphoma
- 1 (1.2%) was synovial sarcoma
- 1 (1.2%) was metastatic squamous cell carcinoma
- 1 (1.2%) was metastatic thymic carcinoma, and
- 4 (4.9%) represented lymphoma infiltration (diffuse large B-cell lymphoma, Hodgkin lymphoma, and chronic lymphocytic leukemia).

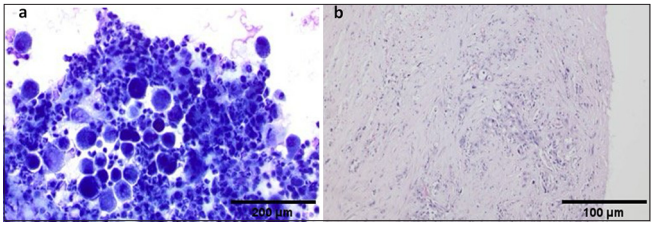



**Figure 1:** (a) Atypia of undetermined significance (May-Grünwald-Giemsa ×200). (b) Lung adenocarcinoma metastasis (Biopsy) (Hematoxylin and eosin ×100).

### Diagnostic performance

When compared with biopsy results, the diagnostic performance of the TIS classification was higher than that of the initial cytologic evaluation. The TIS system demonstrated improved sensitivity (69.5%) and specificity (92.8%), resulting in a higher accuracy of MAL case identification and a reduced rate of false-positive reporting [Table 2].

The PPV increased from 84.1% to 90.5%, and the NPV rose from 70.0% to 75.5%, demonstrating enhanced diagnostic reliability. Overall accuracy improved from 77.1% to 81.2%. Cohen's kappa coefficient increased from 0.52 to 0.60 ($P < 0.001$), indicating improved agreement between cytologic and histopathologic diagnoses. These findings support the superior diagnostic consistency of the TIS system [Table 2].

### ROM

ROM was calculated as the proportion of biopsy-confirmed MAL cases within each TIS diagnostic category. In this study, ROM values ranged from 23% for NFM to 100% for MAL [Table 3].

## DISCUSSION

Serous fluids serve as a valuable source of cytopathologic and molecular information in both benign and advanced MAL conditions. To promote standardized terminology and uniformity in reporting such specimens, international cytology organizations have developed algorithmic

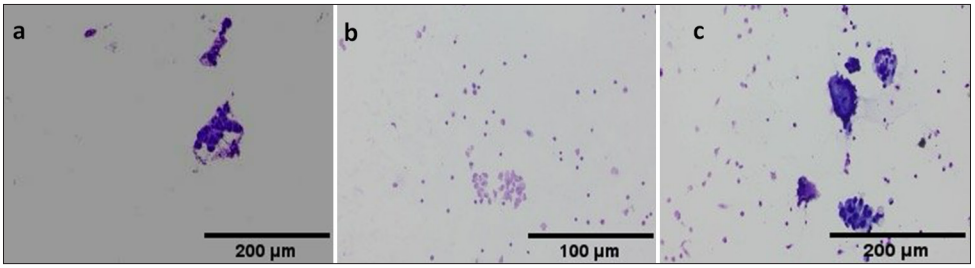



**Figure 2:** (a) Suspicious for malignancy (MGG ×200) (Biopsy result: Myoepithelial carcinoma metastasis). (b) Atypia of undetermined significance (MGG ×100) (Biopsy result: Mesothelioma). (c) Malignant (MGG ×200) (Biopsy result: Breast carcinoma metastasis). MGG: May–Grünwald–Giemsa stain.

diagnostic and management guidelines.[3] A primary goal of modern cytology reporting systems is to reduce the use of indeterminate diagnoses, particularly atypical and suspicious categories.[2]

A fundamental principle of TIS is that indeterminate categories should be used only as a last resort, after all reasonable efforts to reach a definitive diagnosis have been exhausted.[2] In recent years, several publications have evaluated the performance of TIS. Zhu *et al.* analyzed 3,633 effusion samples, including pleural, peritoneal, and pericardial fluids, and concluded that TIS is a user-friendly system with high specificity and PPV. They also reported that liquid-based preparations improve diagnostic sensitivity and that the combined use of multiple preparation methods provides optimal cytomorphologic assessment.[6]

Published sensitivity and specificity values for MAL pleural effusions range from 40% to 90% and 90% to 100%, respectively, whereas for MAL peritoneal effusions, they range from 22% to 81% and 97% to 100%.[8] In a retrospective study of 223 pleural effusion specimens, Maleki *et al.* evaluated the ROM for each TIS category using paired pleural biopsies. Their ROM values were 75% for ND, 23% for NFM, 45% for AUS, 80% for SFM, and 100% for MAL. Diagnostic accuracy was 79.4%, with sensitivity of 45%, specificity of 97.7%, PPV of 91.2%, and NPV of 77%. Most discordant cases were lymphomas, mesotheliomas, and sarcomas. The authors concluded that TIS is a standardized, reproducible, and clinically meaningful system for pleural effusion cytology, and that cytologic evidence of malignancy may carry similar clinical significance to tissue biopsy.[9]

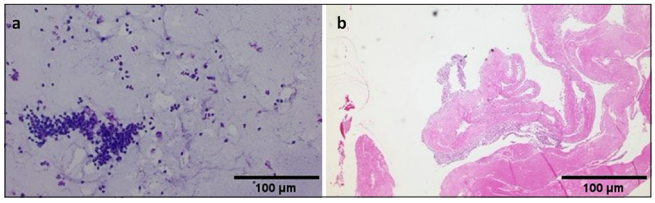



**Figure 3:** (a) Atypia of undetermined significance (MGG ×100). (b) Fibrinous pleuritis (Biopsy) (Hematoxylin and Eosin ×100). MGG: May–Grünwald–Giemsa stain.

**Table 2:** Diagnostic validity and concordance rates of the initial cytological evaluation and TIS classification with biopsy results.

| | Initial evaluation (%) | TIS (%) |
|---|---|---|
| Sensitivity | 61.2 | 69.5 |
| Specificity | 88.5 | 92.8 |
| Positive predictive value | 84.1 | 90.5 |
| Negative predictive value | 70.0 | 75.5 |
| Accuracy | 77.1 | 81.2 |
| Cohen's Kappa | 0.52 ($P$ <0.001) | 0.60 ($P$ <0.001) |

TIS: International system for reporting serous fluid cytopathology

Santos *et al.* reported ROM values of 66.67% for ND, 23.39% for NFM, 28.57% for AUS, 48.28% for SFM, and 84.17% for MAL, findings that deviated from recommended TIS reference ranges.[10]

In our study, the TIS classification demonstrated improved diagnostic performance compared with the initial cytologic evaluation. Sensitivity increased from 61.2 to 69.5%, and specificity increased from 88.5 to 92.8%, reflecting better identification of both MAL and benign cases. PPV (84.1–90.5%) and NPV (70.0–75.5%) also improved, indicating enhanced reliability in predicting malignancy status. Overall diagnostic accuracy increased from 77.1 to 81.2%. Cohen's kappa increased from 0.52 to 0.60 ($P$ <0.001), suggesting improved agreement between cytologic and histopathologic diagnoses after TIS reclassification. ROM values in our study were 50% for ND, 23% for NFM, 25% for AUS, 89.5% for SFM, and 100% for MAL.

The most critical distinction within the TIS categories lies between AUS and SFM. The AUS category encompasses cases with a small number of cells showing features that make it difficult to confidently exclude malignancy, yet do not clearly exceed those that can also be seen in reactive changes. When the cytomorphologic features closely resemble malignancy, SFM is preferred. AUS is appropriate when atypical cytologic features cannot be confirmed because of artifacts (pre-analytical or analytical) or degeneration. These issues may distort morphology and hinder discrimination between MAL and non-MAL processes. Less degeneration and better

**Table 3:** ROM ranges.

| TIS category | Cases *n* (%) | Malignant (*n*) | ROM (%) | References ROM* (%) |
|---|---|---|---|---|
| Non-diagnostic | 4 (2.4) | 2 | 50.0 | 17–50 |
| Negative for malignancy | 100 (59.9) | 23 | 23.0 | 21–66 |
| Atypia of undetermined significance | 8 (4.8) | 2 | 25.0 | 66% (±10.6) |
| Suspicious for malignancy | 19 (11.4) | 17 | 89.5 | 82% (±4.8) |
| Malignant | 36 (21.6) | 36 | 100.0 | 99% (±0.1) |

*Reference ranges: Chandra *et al.* (2019)[3], Wang *et al.* (2023)[4]

specimen preparation increase the likelihood of reaching a more definitive interpretation. Experience and robust quality-control measures may also be helpful. Laboratory practices that correlate cytology with histology can refine diagnostic criteria, enabling more confident diagnoses and reducing reliance on indeterminate categories.[3,4]

These findings reinforce the clinical value of adopting TIS. By enhancing diagnostic precision and standardizing terminology, TIS supports more consistent communication between cytopathologists and clinicians and contributes to improved clinical decision-making in the evaluation of pleural effusions. Similar conclusions have been reported across multiple studies assessing TIS in serous effusion cytology, confirming its reliability and reproducibility as a diagnostic framework.[2,3,11-17]

Doğan *et al*. reclassified effusions initially reported as "atypical" using TIS, identifying ROM values of 27% for AUS and 49% for SFM. They emphasized that distinguishing AUS from SFM improves the accuracy of malignancy risk assessment.[18] In our study, ROM values for atypical effusions were 25% for AUS and 89.5% for SFM. ROM values were 50% in ND, 23% in NFM, and 100% in MAL categories.

A recent systematic review evaluating 257 articles published between 2020 and 2023 reported overall ROM values of 23.55% for ND, 16.46% for NFM, 50.78% for AUS, 91.34% for SFM, and 98.21% for MAL. When compared with TIS recommendations, ND fell within the expected range, SFM was higher than expected, and NFM, AUS, and MAL were lower.[19] In our study, most NFM cases in which malignancy was subsequently confirmed on biopsy were notable for low cellularity. Cellular degeneration was also present, and some cases showed prominent inflammation**.** Because the obtained cell blocks contained insufficient cellular material, further ancillary investigations could not be performed.

Although many studies have focused on serous effusions generally, fewer have evaluated pleural effusions specifically. Most MAL pleural effusions represent metastatic disease, particularly from lung carcinoma. In our cohort, metastatic adenocarcinoma accounted for 48.8% of MAL cases, with lung adenocarcinoma being the most common source. Accurate classification of these fluids using an internationally standardized system such as TIS contributes significantly to diagnostic accuracy and patient management. Cell block preparations derived from effusions provide a valuable substrate for immunohistochemistry and may also be used for molecular testing that can guide therapy.[20]

Although similar studies have evaluated the application of TIS in pleural effusions, our findings add a cytohistological correlation-based institutional experience and further support the practical utility of standardized TIS-based reporting in routine practice.

The observed improvement in diagnostic performance after TIS-based reclassification was modest. Therefore, the practical value of TIS in this setting may lie more in standardized terminology, structured risk stratification, and improved communication between pathologists and clinicians than in substantial numerical gains in diagnostic metrics. Beyond standardizing terminology, TIS may facilitate risk-stratified clinical management. In our practice, ND and NFM interpretations require clinicoradiologic correlation and may prompt repeat sampling when clinical suspicion persists. AUS may justify closer follow-up, repeat thoracentesis, repeat cytology, optimization of cell block preparation, or ancillary studies. SFM may support further tissue confirmation, whereas MAL strongly supports malignancy-directed clinical management in the appropriate clinical context.

This study has several limitations. First, its retrospective design and single-center setting may limit generalizability. Second, inclusion of only biopsy-correlated pleural effusion cases may have introduced selection bias toward clinically suspicious cases, thereby limiting the generalizability of the ROM values to routine cytology practice. Third, the relatively small number of cases in certain categories, particularly AUS and ND, limits the precision of ROM estimates in these groups and warrants cautious interpretation. Although no significant discrepancies were observed between the two pathologists during independent case evaluation and differences were resolved by consensus, formal statistical assessment of interobserver agreement was not performed. This should be considered a limitation of the study, as reproducibility could not be quantitatively evaluated.

## SUMMARY

TIS provides a standardized, practical, and reproducible framework for reporting pleural effusion cytology. By categorizing cases into clearly defined diagnostic groups with established ROM values, it may help reduce false-positive and false-negative interpretations. Despite the inherent morphologic overlap among some categories, TIS offers a simple and user-friendly reporting approach for daily cytopathology practice. Its incorporation of risk stratification enhances communication between pathologists and clinicians and supports more accurate diagnostic and clinical decision-making. Our findings support the utility of TIS as a reliable and effective reporting system for pleural effusion cytology. We recommend its routine implementation, with particular attention to clinicoradiologic correlation and the selective use of repeat sampling or ancillary studies in indeterminate categories. In conclusion, despite the limitations of its retrospective single-center design, biopsy-selected cohort, and the small number of cases in some categories, our study supports the practical utility of TIS

in pleural fluid cytology. TIS standardizes terminology, facilitates ROM-based risk stratification, and may improve communication between cytopathologists and clinicians. Its greatest value in routine practice may lie in the structured interpretation of indeterminate categories and in guiding follow-up, repeat sampling, and ancillary evaluation when clinically indicated.

## AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality and institutional data protection requirements but are available from the corresponding author on reasonable request and subject to institutional approval.

## ABBREVIATIONS

AUS: Atypia of undetermined significance
MAL: Malignant
MGG: May-Grünwald-Giemsa
ND: Non-diagnostic
NFM: Negative for malignancy
NPV: Negative predictive value
PPV: Positive predictive value
ROM: Risk of malignancy
SFM: Suspicious for malignancy
SPSS: Statistical Package for the Social Sciences
TIS: The international system for reporting serous fluid cytopathology.

## AUTHOR CONTRIBUTION

TK: Conception and design, case review, interpretation of the findings, drafting of the manuscript; NÖ: Data collection, literature review, manuscript preparation; SK: Data interpretation and critical revision of the manuscript; ET: Pathological evaluation, supervision of the study, and critical revision of the manuscript; SÇ: Statistical analysis, interpretation of the data, and critical revision of the manuscript. All authors read and approved of the final manuscript. All authors are accountable for all aspects of the research, ensuring that issues related to the accuracy or completeness of any part of the research are properly investigated and resolved. All authors meet ICMJE authorship requirements.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the University (Approval No: 2023-07/34). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived in accordance with institutional policy and ethics committee approval.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## EDITORIAL/PEER REVIEW

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a **double-blind model** (authors are blinded for reviewers and vice versa) through an automatic online system.

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