

# EVALUATING THE RISK OF MALIGNANCY IN SEROUS EFFUSIONS USING THE INTERNATIONAL SYSTEM FOR REPORTING SEROUS FLUID CYTOPATHOLOGY (TIS)

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## ABSTRACT

*Background:* Serous effusions are a common clinical presentation encountered in cytopathology. The International System (TIS) for Reporting Serous Fluid Cytopathology provides a standardized five-tier diagnostic framework to improve consistency and uniformity in diagnosis and clinical communication.

*Objective:* To categorize serous effusion samples according to TIS and assess the risk of malignancy (ROM) in each category.

*Methods:* This prospective observational study analyzed 438 serous fluid samples (pleural, peritoneal, and pericardial) at a tertiary care center. Cytological smears were categorized into Non-Diagnostic (ND), Negative for Malignancy (NFM), Atypia of Undetermined Significance (AUS), Suspicious for Malignancy (SFM), and Malignant (MAL). ROM was calculated based on follow-up histopathology, immunohistochemistry (IHC), or radiology.

*Results:* Distribution across categories was: ND (1.14%), NFM (90.86%), AUS (1.36%), SFM (2.28%), and MAL (4.33%). The corresponding ROMs were 20%, 11.55%, 66.67%, 80%, and 100%, respectively. ROM varied by fluid type, with the highest predictive value observed in SFM and MAL categories across all sample types.

*Conclusion:* The TIS framework effectively stratifies the risk of malignancy in serous effusions, aiding in diagnostic precision and clinical decision-making. High ROM in AUS and SFM highlights the need for vigilant follow-up and additional investigations in these groups.

*Key words* – effusion cytology, pleural fluid, peritoneal fluid, pericardial fluid, risk of malignancy.

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## INTRODUCTION

Serous effusion is defined as an excessive accumulation of fluid in a body cavity which includes pleural, pericardial and peritoneal cavities<sup>1</sup>. Cytopathological studies of various serous fluids are useful for detecting various etiologies including inflammatory, benign and malignant neoplasm<sup>2</sup>. To standardize the diagnostic criteria and nomenclature used in fluid cytopathology reporting, The International System (TIS) for reporting serous fluid cytopathology was proposed by the international academy of cytology and the American society of cytopathology<sup>3</sup>. Serous cavity fluids are one of the most common specimen types received in cytopathology laboratory for initial evaluation of the etiology of effusion<sup>4</sup>. Cytological evaluation of serous fluids is useful for detecting underlying etiologies, such as inflammatory, benign and malignant. It can be even useful for evaluating tumor stage as well as providing information for treatment customization<sup>5</sup>. Serous fluid cytology is very cost effective, simple, minimally invasive and safe procedure. The purposes of TIS to improve reproducibility of cytopathology reports, improve the communication between pathologists and clinicians and provide guidance for patient management<sup>6</sup>. TIS defines a five-tier category system consisting of nondiagnostic (ND), negative for malignancy (NFM), atypia of uncertain significance (AUS), suspicious for malignancy (SFM) and malignant categories. Majority of the malignant effusions are caused by metastasis from adenocarcinoma of lung, breast, gastrointestinal tract and ovaries. Many times, serous effusion is the first or only sign of malignancy in patients<sup>7</sup>.

## MATERIALS AND METHODS

The study was a prospective observational study conducted at the Department of Pathology, KVV, Karad. The data regarding demographic details, clinical features, radiological investigations, cytology, histopathology reports and immunohistochemistry were collected, wherever they were available. The

received samples were processed within 2 hours of receipt. The specimens were centrifuged at 1500 rpm for 10 mins. Supernatant was discarded and sediment was used for smear preparation. Smears were prepared and stained with routinely used stains as H & E, Giemsa and PAP stains. Microscopic examination was done and reporting was done according 'The International system for reporting serous fluid cytopathology for reporting serous fluid cytology'<sup>3,6</sup>.

All cases were classified according to proposed TIS system into five categories as follows

1. ND (Non-Diagnostic): These smears were either hemorrhagic or contained very few cells (fewer than 10), or no cells at all. The cells that were present included scattered mesothelial cells, macrophages, lymphocytes, or polymorphonuclear cells.
2. NFM (Negative for Malignancy): The cell morphology—including mesothelial cells, macrophages, lymphocytes, and polymorphs—appeared benign, regardless of the patient's clinical history or imaging findings. There was no evidence of either primary or secondary malignancy.
3. AUS (Atypia of Undetermined Significance): This category included smears with a small number of cells showing atypical features, but not clearly enough to be classified as neoplastic. It also included cases with a benign clinical suspicion, but occasional cells displayed atypia.
4. SFM (Suspicious for Malignancy): These smears showed cells with atypical features suggestive of malignancy, though not definitive enough for a malignant diagnosis. The atypia was observed in mesothelial cells, epithelial cells, lymphocytes, or other potentially malignant cells like those from melanoma.
5. MAL (Malignant): Smears in this category had high cellularity, with malignant cells seen in clusters as well as dispersed singly across the cytology slides<sup>7</sup>.

Statistical analysis was conducted using Microsoft Office Excel 2016. The cases in each category were reviewed for the presence of malignancy. To calculate ROM, malignancy was confirmed by cytology, tissue histopathology, immunohistochemistry, or radiology. ROM was calculated for each category and is presented as the proportion of cases with confirmatory tests.

## RESULTS

Table. 1 : Distribution of total cases into different categories and ROM for each category.

| Category                                                    | ND<br>(No. and<br>percentage) | NFM<br>(No. and<br>percentage) | AUS<br>(No. and<br>percentage) | SFM<br>(No. and<br>percentage) | MAL<br>(No. and<br>percentage) | Total<br>(No. and<br>percentage) |
|-------------------------------------------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|----------------------------------|
| No. of cases                                                | 5<br>(1.14%)                  | 398<br>(90.86%)                | 6<br>(1.36%)                   | 10<br>(2.28%)                  | 19<br>(4.33%)                  | 438<br>(100%)                    |
| Nonmalignant<br>cases                                       | 4<br>(80%)                    | 352<br>(88.45%)                | 2<br>(33.33%)                  | 2<br>(20%)                     | 0<br>(0%)                      | 360<br>(82.19%)                  |
| Total no. of<br>malignant<br>cases after final<br>Diagnosis | 1<br>(20%)                    | 46<br>(11.55%)                 | 4<br>(66.67%)                  | 8<br>(80%)                     | 19<br>(100%)                   | 78<br>(17.81%)                   |
| ROM                                                         | 20%                           | 11.55%                         | 66.67%                         | 80%                            | 100%                           | 17.81%                           |

AUS - atypia of undetermined significance, MAL - malignant, ND - nondiagnostic, NFM - negative for malignancy, SFM- suspicious for malignancy, ROM - risk of malignancy.

In the present study, a total of 438 serous fluid cytology samples were analyzed and categorized according to the International System for Reporting Serous Fluid Cytopathology (TIS). These samples included pleural, peritoneal, and pericardial effusions. The categorization was done into five well-defined diagnostic tiers: Non-Diagnostic (ND), Negative for Malignancy (NFM), Atypia of Undetermined Significance (AUS), Suspicious for Malignancy (SFM), and Malignant (MAL). The purpose of this

classification was to evaluate the distribution of cases, and more importantly, to assess the risk of malignancy (ROM) associated with each category.

The ND (Non-Diagnostic) category accounted for only 5 cases (1.14%). Among these, 1 case (20%) turned out to be malignant upon follow-up, resulting in a ROM of 20%. This highlights the clinical significance of even inadequate samples and underscores the need for careful review and possibly repeat sampling in ND cases.

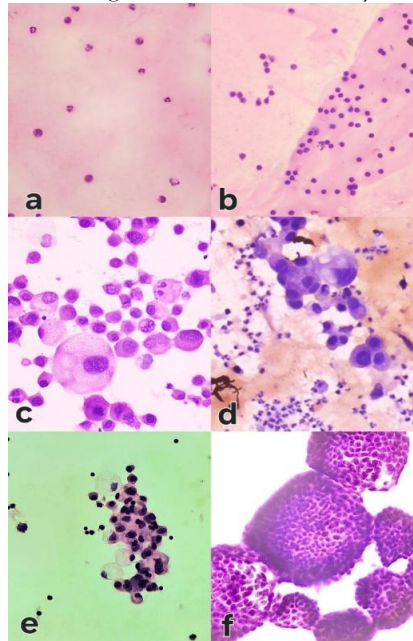
The largest proportion of cases fell into the NFM (Negative for Malignancy) category, with 398 cases (90.86%). On follow-up, 46 of these cases (11.55%) were found to be malignant, giving this group a ROM of 11.55%. While this category is generally considered benign, the significant number of false negatives indicates that clinical correlation and close monitoring remain essential, especially in patients with strong clinical suspicion of malignancy.

The AUS (Atypia of Undetermined Significance) category included 6 cases (1.36%). Though numerically small, this group had a relatively high ROM of 66.67%, as 4 of the 6 cases turned out to be malignant. This indicates that AUS cases carry considerable diagnostic uncertainty and should ideally prompt further diagnostic efforts, such as repeat cytology, radiological imaging, or biopsy to confirm or rule out malignancy.

The SFM (Suspicious for Malignancy) category included 10 cases (2.28%), with 8 confirmed malignancies, yielding a ROM of 80%. This high ROM supports the interpretation that SFM smears often represent a near-malignant cytological appearance, and such cases should be managed with high suspicion and investigated thoroughly to arrive at a definitive diagnosis.

Finally, the MAL (Malignant) category, comprising 19 cases (4.33%), showed a ROM of 100%, as all 19 cases were confirmed as malignant on follow-up. This demonstrates a strong correlation between cytological findings and final malignant diagnosis, validating the reliability of cytopathology when clear malignant features are present (Table 1).

figure 1. classification of all cases according to TIS system



- (a) Category 2 (NFM) shows inflammatory cells predominantly neutrophils.
- (b) Category 2 (NFM) shows inflammatory cells predominantly lymphocytes.
- (c) Category 2 (NFM) shows predominantly reactive mesothelial cells.
- (d) Category 3 (AUS) shows single cluster having overlapping.
- (e) Category 4 (SFM) shows atypical vacuolated cells, giving signet ring appearance.
- (f) Category 5 (MAL) shows 3D ball showing pleomorphism, high nuclear cytoplasmic ratio and hyperchromatism.

Table. 2: Distribution of cases in pleural, pericardial and peritoneal fluid and ROM in each category

| Type of Fluid | Follow up Diagnosis | ND  | NFM    | AUS | SFM | MAL  | Total  |
|---------------|---------------------|-----|--------|-----|-----|------|--------|
| Pleural       | Total               | 2   | 198    | 4   | 5   | 7    | 216    |
|               | Benign              | 1   | 172    | 1   | 1   | 0    | 175    |
|               | Malignant           | 1   | 26     | 3   | 4   | 7    | 41     |
|               | ROM                 | 50% | 13.13% | 75% | 80% | 100% | 18.98% |

|             |           |    |        |     |        |      |        |
|-------------|-----------|----|--------|-----|--------|------|--------|
| Peritoneal  | Total     | 2  | 187    | 2   | 3      | 12   | 206    |
|             | Benign    | 2  | 168    | 1   | 1      | 0    | 172    |
|             | Malignant | 0  | 19     | 1   | 2      | 12   | 34     |
|             | ROM       | 0% | 10.16% | 50% | 66.67% | 100% | 16.50% |
| Pericardial | Total     | 1  | 13     | -   | 2      | -    | 16     |
|             | Benign    | 1  | 12     | -   | 0      | -    | 13     |
|             | Malignant | 0  | 1      | -   | 2      | -    | 3      |
|             | ROM       | 0% | 7.69%  | -   | 100%   | -    | 18.75% |
| Total       |           | 5  | 398    | 6   | 10     | 19   | 438    |

#### Cytological diagnosis of pleural fluid and ROM according to TIS categories

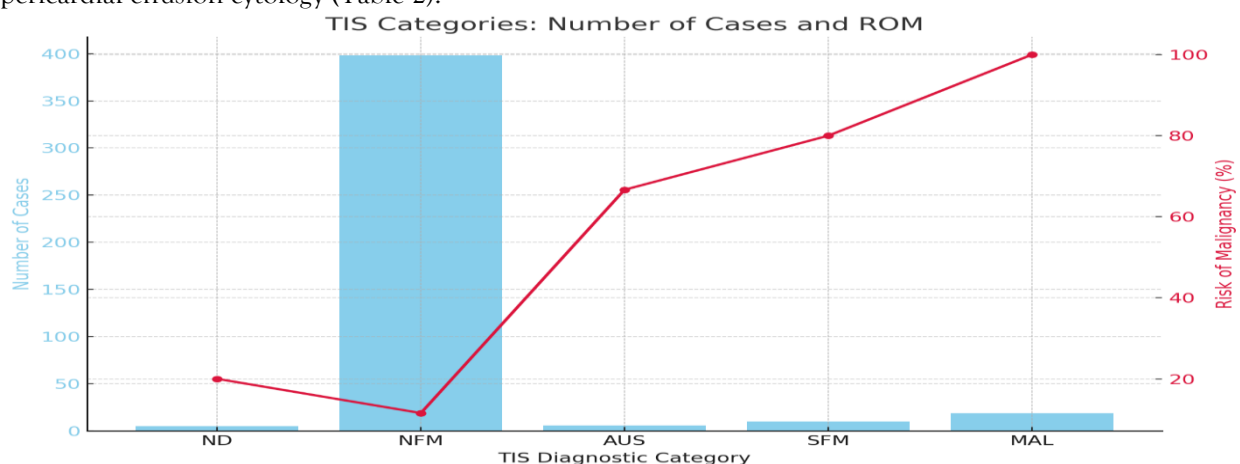
Of the 216 pleural effusion cases, the largest proportion (198 cases, 91.67%) fell under the NFM (Negative for Malignancy) category. On follow-up, 26 of these NFM cases were found to be malignant, resulting in a ROM of 13.13%. There were 2 cases categorized as ND (Non-Diagnostic), one of which was confirmed malignant, giving a ROM of 50% for this group. The AUS (Atypia of Undetermined Significance) category comprised 4 cases, with 3 confirmed as malignant on follow-up, leading to a high ROM of 75%. Among the 5 SFM (Suspicious for Malignancy) cases, 4 were malignant, yielding a ROM of 80%. The MAL (Malignant) category included 7 cases, all of which were corroborated as malignant, thus achieving a ROM of 100%. Overall, the ROM across all pleural fluid samples was 18.98%, with the majority of malignancies found in the MAL and SFM categories, reflecting a strong correlation between cytologic atypia and underlying malignancy.

#### Cytological diagnosis of peritoneal fluid and ROM according to TIS categories

In the 206 cases of peritoneal effusion, 187 cases (90.78%) were categorized as NFM, of which 19 cases were subsequently confirmed as malignant, corresponding to a ROM of 10.16%. There were 2 cases each in the ND and AUS categories. While both ND cases were benign, one AUS case showed malignancy, resulting in a ROM of 50% for AUS and 0% for ND. The SFM category included 3 cases, 2 of which turned out malignant, yielding a ROM of 66.67%. The MAL category included 12 cases, all of which were confirmed malignant on follow-up, giving a ROM of 100%. The overall ROM in peritoneal effusions was calculated to be 16.50%. These findings indicate a clear diagnostic gradient, where the likelihood of malignancy increases from NFM to MAL, with the SFM category again standing out as a high-risk group warranting further diagnostic workup.

#### Cytological diagnosis of pericardial fluid and ROM according to TIS categories

Out of the 16 pericardial effusion cases, 13 (81.25%) were categorized as NFM, with one case later found to be malignant, yielding a ROM of 7.69%. There was one case in the ND category, which was benign, resulting in 0% ROM. Interestingly, 2 cases were classified as SFM, and both were confirmed malignant, producing a ROM of 100%. No cases in the pericardial group fell into the AUS or MAL categories in this dataset. The overall ROM for pericardial effusion was 18.75%, comparable to that of pleural and peritoneal fluids. Despite the smaller sample size, the SFM group showed a strong association with malignancy, reinforcing the diagnostic value of identifying atypical but not definitively malignant cells in pericardial effusion cytology (Table 2).



Graph 1. Here's a visual summary showing both the number of cases and the Risk of Malignancy (ROM) across the TIS categories. The blue bars represent the case counts, while the red line illustrates how ROM increases sharply from ND to MAL, reinforcing the predictive value of this classification system.

## DISCUSSION

The implementation of the International System for Reporting Serous Fluid Cytopathology (TIS) has provided a standardized framework for classifying serous effusion cytology samples into five diagnostic categories: Non-Diagnostic (ND), Negative for Malignancy (NFM), Atypia of Undetermined Significance (AUS), Suspicious for Malignancy (SFM), and Malignant (MAL). In our study, which involved 438 effusion cytology samples across pleural, peritoneal, and pericardial fluids, the TIS system effectively stratified the cases based on the risk of malignancy (ROM), thus enhancing diagnostic precision and patient management strategies.

The ND category comprised a small fraction of cases (1.14%), consistent with the findings of Kala et al. (2023), who reported ND in only 0.17% of their 2318-case study<sup>8</sup>. In our study, the ROM for ND was 20%, while Kala et al. reported a slightly higher ROM of 25%<sup>8</sup>. These findings reflect the diagnostic challenge posed by pauci-cellular or hemorrhagic smears, where inadequate cellularity can obscure early malignant changes. The variability in ROM for ND cases across studies (ranging from 0% to 100% in literature) suggests that institutional protocols for adequacy assessment and sample processing can significantly influence diagnostic outcomes.

The NFM category accounted for the majority of cases in our cohort (90.86%), which is higher than that observed by Kala et al. (75.8%)<sup>8</sup>. Our ROM for this group was 11.55%, while Kala et al. observed a ROM of 17.9%<sup>8</sup>, and similar figures have been reported in other studies (e.g., Lobo et al., 2021<sup>9</sup> and Rodriguez et al., 2020<sup>10</sup>). This difference may reflect variability in sample populations or follow-up intensity, but in all cases, it reinforces that a negative cytology report should not preclude clinical suspicion—especially in patients with radiological or clinical features suggestive of malignancy. Diagnostic pitfalls, such as interpreting reactive mesothelial hyperplasia or degenerated cells, may contribute to false-negative findings in this category.

The AUS category, though small in number (1.36% in our study), demonstrated a significant ROM of 66.67%, aligning closely with the ROM of 66.7% reported by Kala et al.<sup>8</sup> and within the high range seen in other international studies. The high ROM for AUS confirms its critical role as an intermediate-risk category that mandates repeat sampling or further investigation. It also underscores the subjectivity involved in cytologic interpretation, where features may be suggestive but insufficient for a definitive diagnosis. This reinforces the importance of incorporating ancillary techniques such as cell block immunohistochemistry (IHC) or radiologic-pathologic correlation in AUS cases.

The SFM category exhibited a ROM of 80% in our study, consistent with the 75.4% ROM reported by Kala et al.<sup>8</sup> and findings from other literature such as Pinto et al. (2020)<sup>6</sup> and Xu et al. (2021)<sup>11</sup>. This category represents smears with pronounced atypia, often indicative of malignancy, but lacking the definitive features or quantity needed for a conclusive diagnosis. Our findings validate that SFM should be interpreted with a high index of suspicion and treated as a potentially malignant condition, warranting aggressive follow-up. Interestingly, in both our study and previous works, the SFM category showed close predictive value to that of the MAL group, highlighting its near-definitive diagnostic nature.

The MAL category demonstrated a 100% ROM in our study, compared to 96.5% in Kala et al.'s study<sup>8</sup>. This reinforces the high diagnostic accuracy and specificity of this category when classical malignant cytomorphological features are present. The strength of the MAL classification lies not only in confirming malignancy but also in guiding oncological management by enabling the identification of primary sites through IHC when cell blocks are available.

When analyzing fluid types individually, the pleural effusions showed an overall ROM of 18.98%, which is close to the 35.37% reported by Kala et al.<sup>8</sup>, though slightly lower—possibly due to differences in patient demographics or disease prevalence. Peritoneal effusions had a ROM of 16.50% in our dataset, similar to 38.72% in Kala et al.'s findings<sup>8</sup>, again possibly reflecting institutional or regional variations. Pericardial effusions, although limited in number (16 cases), had a ROM of 18.75%, consistent with other

studies reporting lower but clinically meaningful rates of malignancy in pericardial cytology (Gecmen et al., 2018)<sup>12</sup>.

## CONCLUSION

The application of the International System for Reporting Serous Fluid Cytopathology (TIS) in our study has proven to be a valuable and effective framework for the standardized evaluation of effusion cytology. Through categorizing 438 effusion samples into five well-defined diagnostic tiers, we were able to accurately stratify the risk of malignancy (ROM) and identify diagnostic trends across pleural, peritoneal, and pericardial fluids.

Our findings highlight that while the NFM category encompasses the majority of cases, a notable proportion of these may still harbor malignancy, underlining the importance of clinical correlation and follow-up. The AUS and SFM categories, though fewer in number, demonstrated a significantly higher ROM, reaffirming their critical role as intermediate-risk groups that demand further diagnostic evaluation. The MAL category, as expected, showed a strong predictive value with a ROM of 100%, reinforcing its reliability for definitive diagnosis.

Comparative analysis with previous studies, including the large dataset from Kala et al.<sup>8</sup>, shows consistency in the diagnostic performance and predictive accuracy of the TIS system. Despite some variation in ROM percentages, the overarching pattern of risk stratification holds true, validating the robustness of this classification system across different settings and sample types.

In conclusion, the TIS not only enhances diagnostic clarity and interobserver consistency but also plays a pivotal role in guiding clinical decision-making. By providing a structured approach to reporting, it ensures better communication between pathologists and clinicians, improves patient management, and facilitates future research in the field of effusion cytopathology.

Conflict of interest – None.

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