Section: Pathology

Original Research Article

INTERNATIONAL SYSTEM FOR REPORTING SEROUS FLUID CYTOPATHOLOGY (TIS): CURRENT UPDATES AND DIAGNOSTIC IMPLICATIONS

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ABSTRACT

Background: Cytological assessment of serous effusions represents a cornerstone in diagnostic pathology, offering a rapid, minimally invasive, and cost-effective approach for identifying both benign and malignant diseases. However, inconsistencies in reporting terminology and interpretative variability have historically hindered reproducibility and clinical utility. To overcome these challenges, the International System for Reporting Serous Fluid Cytopathology (TIS) was introduced, providing standardized diagnostic categories, uniform terminology, and defined risks of malignancy (ROM)[1]. This review discusses contemporary concepts in fluid cytology, elaborates on the TIS framework, and highlights its clinical relevance, diagnostic advantages, limitations, and future perspectives[2].

Materials and methods: A prospective study of 150 cases was conducted over a period of 12months in tertiary care centre. Cases were categorized according to the International system for reporting serous fluid cytopathology (TIS) and Risk of malignancy for each TIS category was calculated based on the histopathological and clinical follow-up wherever available.

Results: Malignant cytology was observed in 27 of 150 cases (18%). Pleural fluid constituted the majority of samples (43.3%) followed by ascitic fluid (36.7%), cerebrospinal fluid (13.3%) and other fluid (6.7%). Risk of malignancy for each TIS category was calculated based on the histopathological and clinical follow-up wherever available.

Key words: International reporting system, Serous effusions, Cytopathology, Risk of malignancy (ROM).

INTRODUCTION

Serous effusions involving the pleural, peritoneal, and pericardial cavities frequently accompany inflammatory, infectious, systemic, and neoplastic disorders.[3] Cytological examination of serous fluids plays a pivotal role in diagnosing malignancy, staging disease, and guiding clinical management.[4] The technique is particularly valuable due to its high sensitivity, minimal invasiveness, and ability to provide rapid diagnostic information.[5]

Despite its importance, reporting of serous fluid cytology has traditionally lacked uniformity, leading to inconsistent interpretations and communication gaps between pathologists and clinicians.[5]

Recognizing this need, the International Academy of Cytology (IAC) and American Society of Cytopathology (ASC) jointly developed the International System for Reporting serous Fluid cytopathology (TIS) aiming to standardize diagnostic criteria, reduce observer variability and improve patient outcomes.[1,6]

Types of Serous Fluids:

Serous cavity fluids commonly evaluated include pleural, ascitic and pericardial effusions as well as peritoneal washings used primarily in staging gynaecological malignancies.[3,7]

Clinical Indications for Fluid Cytology:

- Detection of malignancy
- Tumour staging and prognostication
- Evaluation of undiagnosed effusions
- Monitoring therapeutic response
- Identification of infectious or inflammatory conditions.[4,7]

Specimen Collection and Processing:

Adequate specimen volume (≥50-100 mL) and prompt processing significantly improve diagnostic yields. Standard laboratory processing includes centrifugation, preparation of conventional smears, cytospin slides and cell blocks. Cell block techniques enhance architectural assessment and facilitate immunocytochemistry (ICC) and facilitate immunocytochemistry (ICC) and molecular testing.[10]

Cytomorphological Features:

Benign Components

Normal and reactive effusions contain mesothelial cells, macrophages, lymphocytes, and occasional neutrophils. Reactive mesothelial cells may exhibit nuclear enlargement, binucleation and prominent nucleoli, potentially mimicking malignancy.[11]

Malignant Cells

Malignant effusions typically show increased cellularity, three-dimensional clusters, nuclear pleomorphism, irregular nuclear membranes and coarse chromatin. Common malignancies include adenocarcinomas of lung, breast, ovary and gastrointestinal tract as well as mesothelioma and lymphoma.[12-14]

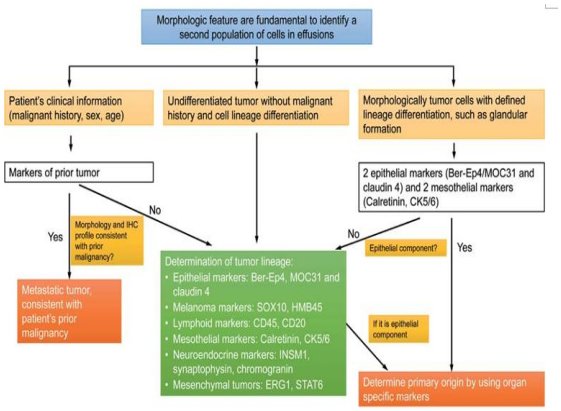
International System for Reporting Serous Fluid Cytopathology (TIS):

TIS categorizes serous fluid cytology into five diagnostic groups, each associated with a defined risk of malignancy (ROM) enabling consistent reporting and clinical risk stratification.[1,6]

TIS Diagnostic Categories and Risk of Malignancy:

CATEGORY	DESCRIPTION	ROM
Non-diagnostic (ND)	Inadequate cellularity	17-25%
Negative for malignancy (NFM)	Benign/reactive findings	0-5%
Atypia of undetermined significance (AUS)	Limited atypia	20-30%
Suspicious of malignancy (SFM)	Strong suspicion, insufficient material	60-75%
Malignancy (MAL)	Definitive malignant features	90-100%

DIAGNOSTIC ALGORITHM[21]:



ANCILLARY DIAGNOSTIC TECHNIQUES:

Immunocytochemistry (ICC):

ICC plays a vital role in distinguishing mesothelial from epithelial tumours and in identifying tumour origin[15].

Diagnostic aim	Common markers
Mesothelial cells	Calretinin, WT1, D2-40
Epithelial tumours	Ber-EP4, MOC31
Lung adenocarcinoma	TTF-1, Napsin A
Ovarian carcinoma	PAX8, CA125
Lymphoma	CD45, CD20, CD3

Molecular Testing:

Molecular profiling for EGFR, ALK, KRAS, and BRAF mutations is increasingly incorporated into effusion cytology, allowing targeted therapy and personalized oncology management[16-18].

Advantages of TIS:

- Standardized terminology
- Reduced diagnostic ambiguity
- Improved clinician-pathologist communication
- Risk-based clinical management
- Enhanced prognostic assessment.[1,6]

Limitations

- Overlap between reactive and malignant mesothelial changes
- Hypocellular samples
- Dependence on ancillary studies
- Potential false-negative diagnosis[11,13]

MATERIALS AND METHODS

A prospective study of 150 cases was conducted over a period of 12months in tertiary care centre. Cases were categorized according to the International system for reporting serous fluid cytopathology (TIS) and Risk of malignancy for each TIS category was calculated based on the histopathological and clinical follow-up wherever available.

RESULTS

Table 1: TIS Diagnostic distribution:

TIS Category	Cases	Percentage
Non-diagnostic	9	6%
Negative for malignancy	78	52%
AUS	21	14%
Suspicious for malignancy	15	10%
Malignant	27	18%
Total	150	100%

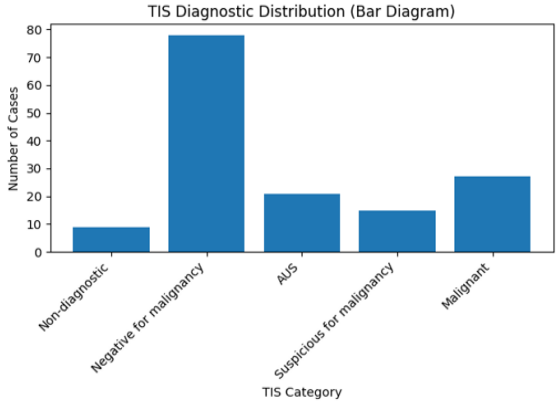


Figure 1:

Statistical result

FLUID TYPE	CASES	PERCENTAGE
Pleural fluid	65	43.3%
Ascitic fluid	55	36.7%
Cerebrospinal fluid	20	13.3%
Others	10	6.7%
Total	150	100%

OTHERS

Includes Synovial fluid, urine, peritoneal washings, bronchoalveolar lavage (BAL), sputum and cysts fluid (Ovarian, pancreatic cyst) in this study.

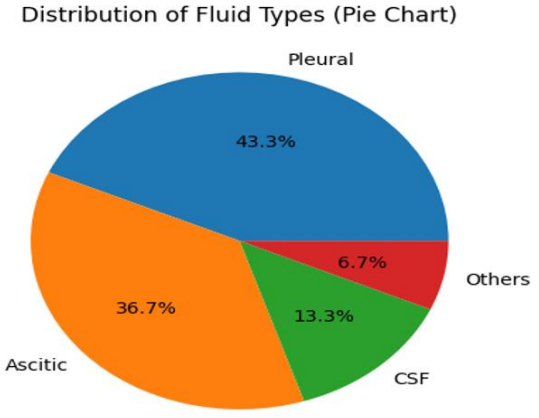


Figure 2

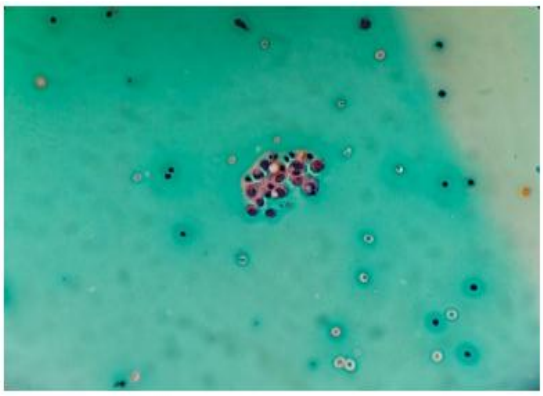


Figure 3: Pap-stained smear of pleural fluid with reactive mesothelial cells – Negative for malignancy.

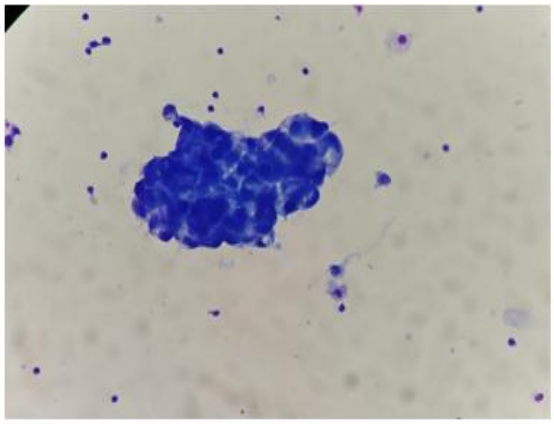


Figure 4: Giemsa stained smear of ascitic fluid with atypical cells – Suspicious of malignancy.

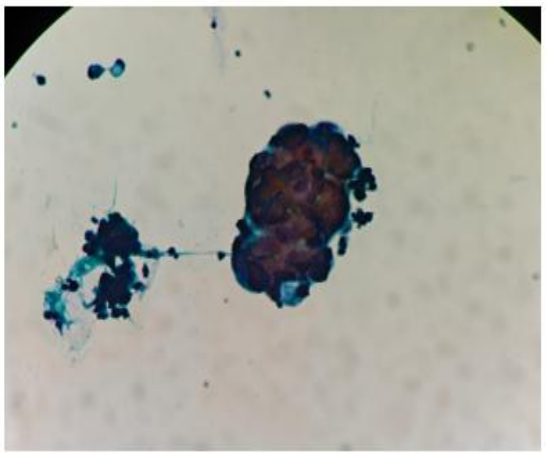


Figure 5: Pap-stained smear of ascitic fluid with frank atypical cells – Positive for Malignancy

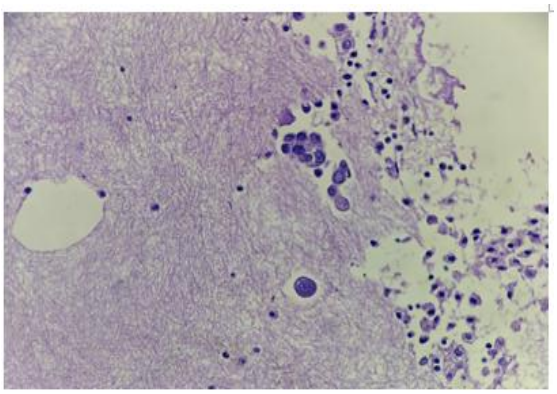


Figure 6: Cell block of the same ascitic fluid – Positive for malignancy

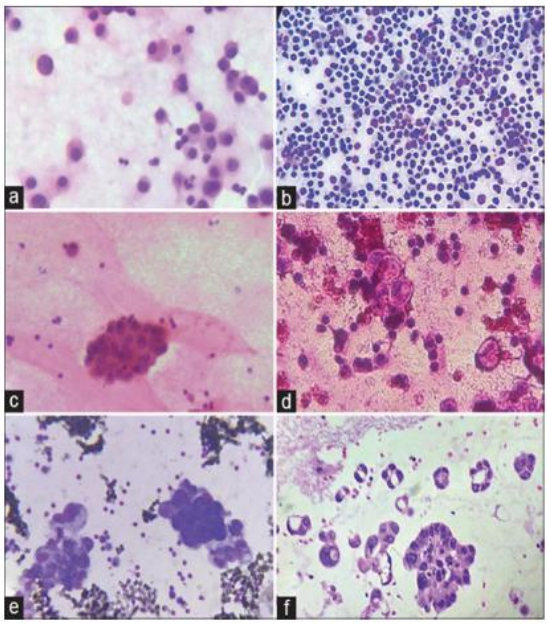


Figure – 7[21]:

a). Category 2 – NFM : Reactive mesothelial cells.
b). Category 2 – NFM : Reactive lymphoid cells with few reactive mesothelial cells.
c). Category 3 – AUS : Cells with mild pleomorphism & overlapping.
d). Category 4 – SFM : Atypical vacuolated cells with signet ring appearance.
e). Category 5 – MAL : Highly pleomorphic cell balls and nests.
f). Category 5 – Cell block preparation.

OVERALL MALIGNANCY RATE IN THE STUDY:

Malignant cytology cases = 27
Total number of cases = 150
Overall malignancy rate = 27/150 x 100 = 18%
Therefore, out of 150 serous fluid samples analysed, 27 cases were diagnosed as malignant giving overall malignancy rate of 18%.

RISK OF MALIGNANCY IN THE STUDY:

TIS CATEGORY	TOTAL CASES	MALIGNANT ON FOLLOW UP	ROM (%)
Non-diagnostic	9	0	0
Negative for malignancy	78	0	0
AUS	21	5	23.8
Suspicious for malignancy	15	8	53.3
Malignant	27	16	59.2

In the present study,

Malignant cytology was observed in 27 of 150 cases (18%). Pleural fluid constituted the majority of samples (43.3%) followed by ascitic fluid (36.7%), cerebrospinal fluid (13.3%) and other fluid (6.7%). Risk of malignancy for each TIS category was calculated based on the histopathological and clinical follow-up wherever available.

Future Directions:

Advances in digital pathology, artificial intelligence-based screening, molecular diagnostics, and liquid biopsy technologies are anticipated to further improve diagnostic accuracy and expand the role of serous fluid cytology in personalized medicine.[19,20]

DISCUSSION

The introduction of the International System for Reporting Serous Fluid Cytopathology (TIS) represents a significant advancement in the standardization of effusion cytology reporting. Prior to its implementation, variability in terminology and diagnostic thresholds led to inconsistencies in interpretation and communication between cytopathologists and clinicians.[22,23] The five-tiered classification—nondiagnostic (ND), negative for malignancy (NFM), atypia of undetermined significance (AUS), suspicious for malignancy (SFM), and malignant (MAL)—has addressed this gap by providing a uniform framework with defined diagnostic criteria and implied risk of malignancy (ROM) for each category.[22,28]

A key strength of TIS lies in its ability to stratify cases based on ROM, thereby aiding clinical decision-making. Multiple institutional studies and meta-analyses have demonstrated a progressive increase in ROM from ND to MAL categories, validating the biological relevance of this tiered approach.[24,25] The malignant and suspicious categories show high predictive value for malignancy, while the negative category reliably excludes it, reinforcing the system's diagnostic utility.[24,25] Such risk-based stratification allows clinicians to tailor further investigations, ranging from repeat sampling in indeterminate cases to definitive oncologic management in malignant diagnoses.[22,24]

Despite these advantages, challenges remain, particularly in the interpretation of indeterminate categories such as AUS and SFM. These categories often represent a diagnostic gray zone due to limited cellularity, overlapping cytomorphologic features, or reactive mesothelial changes.[22,27] Studies have highlighted that a significant proportion of AUS and SFM cases are later reclassified as malignant upon follow-up or ancillary testing, emphasizing the need for cautious interpretation and appropriate clinical correlation.[27] Consequently, maintaining a low threshold for ancillary techniques—such as cell block preparation, immunocytochemistry, and molecular testing—has become an essential component of modern effusion cytology.[22,24]

Recent updates and studies have further emphasized the role of ancillary techniques in improving diagnostic accuracy and reducing indeterminate rates. The integration of immunocytochemical markers and cell block evaluation enhances the differentiation between reactive mesothelial cells and malignant cells, particularly in challenging cases like mesothelioma versus metastatic adenocarcinoma [22,28]. Additionally, the AUS rate itself has been proposed as a quality indicator, with higher rates suggesting potential diagnostic uncertainty or technical limitations within a laboratory.[24]

Another important implication of TIS is its contribution to audit and quality assurance in cytopathology practice. By providing standardized categories and corresponding ROM, institutions can compare their diagnostic performance and outcomes with published benchmarks [22,23]. This facilitates continuous quality improvement and inter-laboratory consistency. Furthermore, the system enhances reproducibility among pathologists, although some degree of interobserver variability persists, particularly in borderline categories.[23,24]

The diagnostic accuracy of TIS has been supported by recent systematic reviews and meta-analyses, which report high sensitivity and specificity for detecting malignancy in serous effusions. The pooled diagnostic performance, with area under the curve values approaching 0.85–0.90, underscores the robustness of the system in routine clinical practice.[25,26] These findings reinforce the reliability of TIS as a diagnostic and prognostic tool.[25,26]

However, certain limitations should be acknowledged. The applicability of ROM values may vary across institutions due to differences in patient populations, prevalence of malignancy, and technical expertise.[24,25] Moreover, the ND category remains a concern, as inadequate sampling can delay diagnosis and necessitate repeat

procedures.[22,24] Therefore, emphasis on proper specimen collection, processing, and adequacy assessment is crucial.[22]

In summary, the International System for Reporting Serous Fluid Cytopathology has significantly improved the standardization, diagnostic accuracy, and clinical relevance of effusion cytology reporting.[22,25] Ongoing refinements, increased use of ancillary techniques, and accumulation of outcome-based data are expected to further enhance its diagnostic precision and clinical applicability.[25,26] Future studies focusing on molecular diagnostics and artificial intelligence may provide additional support in resolving indeterminate cases and further strengthening this reporting system.[22,28]

CONCLUSION

Fluid cytology remains an indispensable diagnostic tool in pathology. Adoption of the International System for Reporting Serous Fluid Cytopathology (TIS) significantly enhances diagnostic precision, reporting consistency and clinical relevance.

This system proposed a tiered scheme which places the effusion cytology into well-defined categories and therefore has lesser chances of false positive and false negative cases. Despite there being heterogenicity and morphological overlap between different categories, TIS caters to the need of cytopathologists because beside a simple, easy and user-friendly system, it has the benefit of risk stratification and ROM for each category [21].

Integration of cytomorphology with ancillary techniques and molecular testing ensures optimal patient care and diagnostic excellence.

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