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ANALYSIS OF SEROUS EFFUSIONS USING INTERNATIONAL SYSTEM FOR REPORTING SEROUS FLUID CYTOLOGY – A STUDY IN A TERTIARY CARE CENTRE.

Pathology

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ABSTRACT

Cytology serves as a primary diagnostic method for evaluating serous effusions and play a vital role in identifying and classifying tumor cells in serous effusions distinguishing them between benign and malignant (MAL) conditions. Variations in reporting terms caused confusion and miscommunication, leading to the introduction of ISRSFC (TIS) in 2020 to ensure standardized and clear cytology reporting. TIS aims to unify reporting practices, improve diagnostic accuracy, and enhance collaboration between cytopathologists and clinicians. **Methods-** A total of 346 serous effusions samples in this study were evaluated using TIS criteria over a period of 15 months in a tertiary care hospital and histology, radiology or clinical follow-up were used wherever available. Performance analysis was done to calculate diagnostic accuracy for cytology samples. **Results-** Over 15 months, 346 serous effusion samples (201 peritoneal, 144 pleural, 1 pericardial) were evaluated using TIS. In our study, NFM was the most common category (80.1%), followed by ND (8.1%), MAL (5.8%), AUS (3.8%), and SFM (2.3%), indicating a predominance of benign effusions. The risk of malignancy (ROM) increases with higher TIS categories—3.24% in TIS 2, 14% in TIS 1, 84.6% in TIS 3, and 100% in both TIS 4 and TIS 5. **Conclusion-** Serous effusion cytology shows high specificity and moderate sensitivity. The tiered ISRSFC system enhances reporting accuracy and clinical communication. AUS should be monitored as a key quality metric, not a wastebasket category.

KEYWORDS

TIS, Serous effusions, ISRSFC

INTRODUCTION

As early as the 18th and 19th centuries, the art and science of cytology and cytopathology were applied and acknowledged. George Papanicolaou, the man who gave his name to the well-known Papanicolaou (Pap) smear and Pap stain, was among the first to draw attention to the science of diagnosing a patient by looking at slides containing a cell smear between 1917 and 1928. Exfoliative and aspiration biopsy are the two main branches of the currently well-standardized science of cytopathology [1]. Serous fluids are frequently used specimens in the cytopathology labs and are thought to be a highly useful source of diagnostic information [2]. Pathological serous fluid accumulation has a wide range of etiologies, encompassing benign conditions like infection and inflammation as well as malignant diseases like metastatic carcinomas and mesothelioma[3] .Clinical presentation, radiological results, laboratory testing, such as cytology and biochemical assays with / without ancillary procedures and the molecular testing, and laboratory testing are the foundation for a clinical diagnosis [4].A serous effusion must be examined cytologically because the presence of the cancer cells in this type of specimen indicates that the patient's cancer is advanced and nearly always incurable[5] . In order to provide standard definitions, criteria, and diagnostic terminology, a number of categorization systems had been developed for the reporting of cytology specimens. These systems aim to increase diagnostic categorization reproducibility by using standardized estimates of cancer risk [6] . Serous effusion cytology is a quick, affordable, easy, safe, and minimally invasive procedure that can assist in establishing the patient's initial diagnosis, the cause of the cancer, the stage, prognosis, and status regarding recurrence [7]. In 2020, the International System for Reporting Serous Fluid Cytopathology (ISRSFC) emerged as 6 the groundbreaking initiative to create a tier system for serous effusion reporting terminology standardization [8]. The most recent reported data, expert consensus, and best international practices were taken into consideration when developing the international system for reporting serous fluid cytology (TIS), with the goal of standardizing procedures [9]. With the release of Cytopathology (TIS), pathologists and clinicians could now report effusion cytology more quickly and consistently thanks to an internationally accepted system [10]. Five diagnostic classifications are proposed by this system: atypia of undetermined significance (AUS), malignant (MAL), non-diagnostic (ND), suggestive for malignancy (SFM), and negative for malignancy (NFM)[10]. TIS also provides appropriate clinical management and follow-up, with defined expected incidences and risk-of-malignancy (ROM) which help in expediting better patient care.

MATERIAL AND METHODS

346 samples over duration of 15 months, consisting peritoneal, pleural and pericardial fluids were evaluated and categorized according to TIS system. Risk of Malignancy and performance analysis (sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy) was calculated depending on the histology, radiology and clinical follow up wherever available. Performance analysis were conducted, considering M as positive; M and SFM as positive; M, SFM and AUS as positive. The presence or absence of malignancy was confirmed by histopathology and clinical-radiological impression wherever available.

RESULTS

In the present study the distribution of TIS categories among the participants is presented in the table no.1.There was a female predominance with majority of cases of age group 40-60 yrs. A large proportion of samples were pale yellow and hazy (84%). The majority of participants (80.1%) fell into the NFM category, making it the most common. ND was observed in 8.1% of participants, while MAL accounted for 5.8%. The AUS category comprised 3.8% of the cases, and SFM was the least common, representing only 2.3% of the total. This distribution highlights that the NFM category is predominant among the study population.

(ND Non diagnostic, NFM Negative for malignancy, AUS Atypia of undetermined significance, SFM Suspicious for malignancy, MAL Malignancy)

Table No. 1: Distribution According to TIS Category.

TIS	FREQUENCY	PERCENT
ND	28	8.1%
NFM	277	80.1%
AUS	13	3.8%
SFM	8	2.3%
MAL	20	5.8%
TOTAL	346	100%

Among patients with ascitic fluid (AF), 76.1% had a TIS of 2, while 10.0% had a TIS of 1. In patients with pleural fluid (PF), 85.4% had a TIS of 2, with 5.6% having a TIS of 1. The single case of pericardial fluid had a TIS of 2. Overall, the majority of patients across all fluid types had a TIS of 2, with similar distributions across the fluid types.

Table no.2 : Distribution According to TIS

	TIS					
	ND	NFM	AUS	SFM	MAL	TOTAL
AF	10%	76%	5.5%	3.5%	5.0%	100
PF	5.6%	85%	1.4%	0.7%	6.9%	100%
Pe F	0%	100%	0%	0%	0%	100%
TOTAL	8.1%	80.1%	3.8%	2.3%	5.8%	100%

(AF Ascitic fluid, PF Pleural fluid, Pe F Pericardial fluid)

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Performance Analysis

The diagnostic performance of serous effusion cytology was assessed using TIS categories, histopathology and clinical radiological correlation wherever available as reference. Considering AUS, SFM and MAL positive, then SFM and MAL, and MAL positive.

Sensitivity = True positive/ (True positive + False negative) x 100. Specificity = True negative/ (True negative + False positive) x 100 PPV = True positive/ (True positive + False positive) x100. NPV = True negative/ (True negative + False negative) x100

For ascitic fluid (AF), sensitivity was highest when AUS, SFM, and MAL were considered positive (68.42%), and decreased when only SFM+MAL (44.74%) or MAL alone (26.32%) were included. Specificity remained high across all groups, up to 100%. PPV ranged from 92.86% to 100%, and NPV from 85.34% to 93.06%.

For pleural fluid (PF), sensitivity was higher—92.86% for MAL+SFM+AUS, 78.57% for MAL+SFM, and 71.43% for MAL. Specificity and PPV were 100% across all categories, while NPV ranged from 97.01% to 99.24%, indicating strong diagnostic accuracy. Pericardial fluid had insufficient cases for analysis.

Risk of Malignancy

Based on the follow-up information available as per histopathology and clinical record, the estimated risk of malignancy (ROM) in serous effusion samples was calculated. The ROM was calculated as follows: the number of patients with a diagnosis of malignancy x 100/total number of cases in a given category with available follow-up diagnosis.

Table No. 3: Risk of Malignancy

	TIS				
ROM	(ND)	(NFM)	(AUS)	(SFM)	(MAL)
	14%	3.24%	84.6%	100%	100%
	4/28	9/277	11/13	8/8	20/20

The risk of malignancy varies significantly according to the TIS. The risk is lowest in participants with TIS 2, with malignancy rates of 3.24%, respectively. While ROM is slightly higher in TIS 1 which is 14%. However, the risk increases sharply for higher TIS scores. Participants with TIS 3 have a 84.6% risk of malignancy, which rises further to 100% for both TIS 4 and TIS 5.

Ovarian cancer and gastrointestinal malignancy in peritoneal and lung cancer in pleural fluid were predominant cases.

DISCUSSION

The current study has a relatively younger population (mean age 47.7 years), whereas Pergaris et al's [4] study involves older individuals (mean age 67.6 years). Mandava et al's. [8]. Our study leans slightly toward females which is similar to study conducted by Pergaris et al[4]. Mandava et al's [8] study shows an almost equal distribution of gender. In comparing the TIS classifications between the current study and Mandava et al. [8]. both studies show similar rates for the Negative for Malignancy (NFM) category, with 80.1% and 82.2% respectively. However, the current study has a higher proportion of Non-Diagnostic (ND) cases (8.1% vs. 2.2%) and Atypia of Undetermined Significance (AUS) (3.8% vs. 2.2%). While Mandava et al[8] reported more cases of Suspicious for Malignancy (SFM) (4.8% vs. 2.3%) and Malignant (MAL) cases (8.6% vs. 5.8%).

The TIS system delves into the gray zone of atypical cells by further categorizing them into Category 3 (AUS) and Category 4 (SFM). This classification fosters a stronger connection between cytopathologists and clinicians, facilitating more effective clinical management ([11]. According to TIS, 21 cases initially labelled as atypical were later reclassified into two categories: AUS (13 cases) and SFM (8 cases). This reclassification led to improved patient workup and enhanced clinical management. AUS, being a placeholder diagnosis, prompts to perform ancillary techniques if there is enough material, to finalize the report. Additionally, clinical and radiological correlation is necessary to support the diagnosis.[9].

While AUS generally leans towards the benign end of the spectrum [4]. our study found it leaned more towards malignancy. Therefore, AUS should not be seen as a trashcan category but rather as a quality indicator for institutions to assess and improve [2]. Like AUS, SFM acts as an indeterminate category where ancillary 86 techniques, if sufficient material available, can confirm suspected malignancy. Clinical and radiological data also help cytopathologists make a definitive diagnosis. [9]

Our study has moderate ROM in ND category which was in slight concordance to study by Farahani et al[11]. while discordant to Mandava et al[8] and Zhu et al[10]. which may also be attributed to nature of patient population in our center. Our study (3.24%) shows the lowest ROM in NFM, indicating high confidence in NFM diagnoses., compared to studies, like Zhu et al[10] and Farahani et al[11]. The current study (84.6%) shows the highest ROM for AUS compared to other studies, indicating a strong link between atypia and malignancy in our centre. The higher ROM in our AUS category is likely due to our referral base, which includes many patients with confirmed advanced malignancies. Even when cytology was negative but clinical suspicion remained high, we performed imaging and often biopsied, which contributed to the increased ROM. While ROM for SFM and MAL is highest in our study, suggesting a highly suspicious and aggressive diagnostic approach for potential malignancy. For SFM, the current study (100%) and Zhu et al[10] (99.4%) report the highest ROM, while Farahani et al[11] (81.8%) and Mandava et al[8] (77%) show lower ROM, reflecting a more cautious approach. For MAL (Malignant), all studies, except Farahani et al[11] (98.9%), report a 100% ROM, indicating universal agreement on the accuracy of malignancy diagnosis in this category.

A comparison of these studies shows that although the sensitivity for detecting malignancy is consistently high, there is considerable variation in the AUS category. This variability is likely influenced by differences in patient populations, sample processing methods, and the expertise of the cytopathologists.

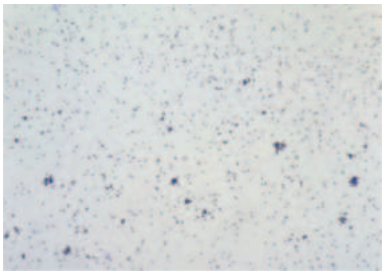

Figure No. 1: Negative For Malignancy, Cellular smear showing predominantly lymphocytes in pleural fluid.

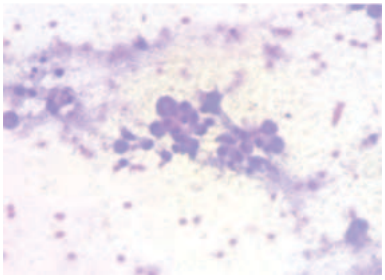

Figure No. 2: Atypia of Undetermined Significance (AUS) Moderately cellular smear showing cluster of cells showing mild nuclear enlargement, hyperchromatic nuclei and moderate cytoplasm. Ascitic fluid. (Pap stain)(400X)

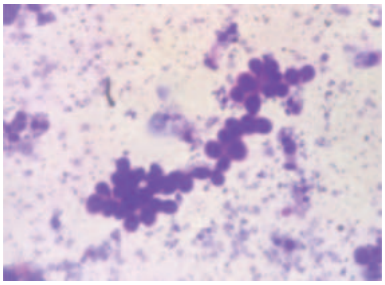

Figure No. 3: Suspicious For Malignancy (SFM) Moderately cellular

smear showing atypical cells arranged in papillary pattern. Atypical cells showing high N:C ratio, hyperchromatic nucleus. Ascitic fluid (Pap stain) (400X).

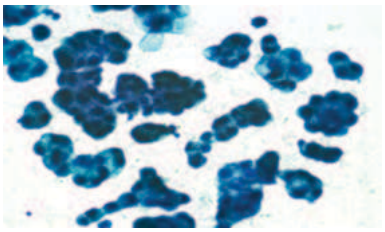

Figure No. 4: Low power (200X) showing highly cellular smear, with tumor cells arranged in 3D ball clusters and acinar pattern.

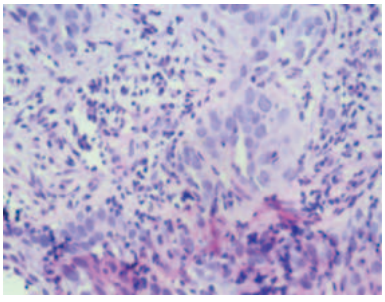

Figure No. 5: Pleural biopsy (H n E stained) diagnosed as non-small cell lung carcinoma. (Cytopathology diagnosis Suspicious for malignancy (SFM) in pleural fluid, turned out non-small cell lung carcinoma on histopathology.)

CONCLUSIONS

In conclusion, our study supports the effectiveness of the TIS system in improving diagnostic accuracy for serous fluid cytology, highlighting its high specificity and predictive value in identifying malignancy. Despite cytology's recognized sensitivity, a diagnostic gray zone persists globally, particularly in atypical and suspicious cases. The TIS framework, endorsed by ISRSFC, promotes standardized and consistent reporting, aiding clinical decisions. Our findings show that TIS is practical and user-friendly, with the AUS category serving as a valuable quality indicator rather than a diagnostic catch-all. To further enhance its utility, clearer category definitions and more research to determine the risk of malignancy (ROM) are needed. While easy to implement, TIS still offers meaningful insights into case distribution and cancer risk, and we advocate its adoption, anticipating improved diagnostic outcomes similar to those achieved in other cytology domains using standardized terminology.

REFERENCES

1. Al-Abbadi MA. Basics of cytology. Avicenna journal of medicine. 2011 Jul;1(01):18-28.
2. Shen Y, Gosnell JM, Nawgiri R, Muthukumarana V. Application of the newly published International System for Reporting Serous Fluid Cytopathology in atypical and suspicious diagnosis: a four-year retrospective analysis. Journal of the American Society of Cytopathology. 2024 Mar 19.
3. Li QK. Serous Effusion Cytology. In: Atlas of Non-Gynecologic Cytology. Cham: Springer International Publishing; 2018. p. 235–57.
4. Pergaris A, Stefanou D, Keramari P, Sousouris S, Kavantzas N, Gogas H, Mikou P. Application of the International System for Reporting Serous Fluid Cytopathology with cytohistological correlation and risk of malignancy assessment. Diagnostics. 2021 Nov 28;11(12):2223.
5. Naylor B. Pleural, peritoneal, and pericardial effusions. In: Comprehensive Cytopathology. 2008. p. 515–577.
6. Layfield LJ, Yang Z, Vazmitsel M, Zhang T, Esebua M, Schmidt R. The international system for serous fluid cytopathology: interobserver agreement. Diagnostic Cytopathology. 2022 Jan;50(1):3-7.
7. Sachan R, Gupta A, Awasthi PN, Singh P, Anand N, Chandra S, et al. Application of international system for reporting serous fluid cytology (ISRSFC) in effusion samples-a prospective study in an oncology setting. J Am Soc Cytopathol. 2023 Sep 1;12(5):351–61.
8. Mandava H, Renuka IV, Potti R, Mounica B, Kalla I. Deciphering Serous Effusions Using the New International System for Reporting Serous Fluid Cytopathology. Cureus. 2024 May;16(5).
9. Pinto D, Chandra A, Crothers BA, Kurtycz DFI, Schmitt F. The international system for reporting serous fluid cytopathology—diagnostic categories and clinical management. J Am Soc Cytopathol. 2020 Nov 1;9(6):469–77.
10. Zhu YL, Ren WH, Wang Q, Jin HZ, Guo YY, Lin DM. A retrospective analysis of serous effusions based on the newly proposed international system for reporting serous fluid cytopathology: a report of 3633 cases in an oncological centre. Diagnostic Pathology. 2022 Jul 2;17(1):56.
11. Farahani SJ, Baloch Z. Are we ready to develop a tiered scheme for the effusion cytology? A comprehensive review and analysis of the literature. Diagn Cytopathol. 2019 Nov 13;47(11):1145–59.