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Subcategorization of the AUS/FLUS Thyroid Nodule Based on the 2017 Bethesda System at Dr. Cipto Mangunkusumo Hospital from 2018-2021

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ABSTRACT

Introduction
The AUS/FLUS (Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance) category is one of the most challenging diagnoses in thyroid fine-needle aspiration biopsy (FNAB) for pathologists. This is due to the heterogeneous cytomorphological features with low Risk of Malignancy (ROM) accuracy, which is crucial to determining further management. The 2017 Bethesda System introduced subcategorization of AUS/FLUS to improve ROM accuracy. However, the widespread adoption of this subcategorization remains limited.

Methods
A retrospective analytical cross-sectional study was carried out using secondary data of thyroid FNAB cases diagnosed with AUS/FLUS followed by surgical procedures at the Department of Anatomical Pathology, Faculty of Medicine, University Indonesia/Dr. Cipto Mangunkusumo Hospital from 2018 to 2021. Furthermore, a review and subcategorization into AUS-C1 (focal nuclear atypia), AUS-C2 (mild nuclear atypia), AUS-A (architectural atypia), AUS-C&A (nuclear and architectural atypia), AUS-H (Hűrthle cell aspiration), AUS-NOS (atypia not otherwise specified), and AUS-L (lymphoid cell atypia other than lymphoma) was performed.

Result
Among a total of 2,082 patients, 599 (28.7%) were diagnosed as AUS/FLUS. There were 75 patients with AUS/FLUS who proceeded with surgery, while 64 (85.3%) showed malignancy. The most common subcategory was AUS-C1 (60%), followed by AUS-NOS (21.3%), AUS-C&A (9.3%), AUS-C2 (8%), and AUS-H (1.4%). ROM subcategory AUS-C1 was significantly higher compared to AUS-C2 (p=0.009) and AUS-NOS (p=0.011).
Conclusion: The percentage of AUS/FLUS diagnoses at Dr. Cipto Mangunkusumo Hospital from 2018 to 2021 was 28.7% with ROM ranging from 10.6% to 85.3%. There was a significant difference in ROM between AUS-C1 and AUS-C2, as well as AUS-C1 and AUS-NOS. Therefore, it was concluded that AUS-C1 thyroid nodules with or without architectural atypia require more aggressive management compared to those with AUS-C2 and AUS-NOS features.

Keywords: AUS/FLUS, thyroid FNAB, thyroid nodules, ROM, 2017 Bethesda System

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INTRODUCTION

Thyroid nodules are a common endocrinological health issue encountered in everyday clinical practice.[1,2] According to the American Thyroid Association (ATA) guidelines, these nodules are discrete lesions within the thyroid gland, appearing distinct from the surrounding parenchyma on radiological scans.[1,2] A meta-analysis study by Mu et al[2] in 2022 reported that one in four individuals in the general population has thyroid nodules. The worldwide prevalence is approximately 24.83%, with a higher prevalence in developing countries compared to developed ones.[2] Data from Dr. Cipto Mangunkusumo Hospital between 2012 to 2016 recorded 68.7% of thyroid nodules were found out of 7,384 thyroid cases.[3]

Thyroid nodules are found 1.5 times more frequently in women than in men, and their frequency increases with age.[2] In adults, this disease is generally benign, with an estimated malignancy rate of only 7-15%.[1] One of the diagnostic tools used to detect malignancy is fine-needle aspiration biopsy (FNAB).[4] This is a safe, cost-effective, and minimally invasive diagnostic method with a sensitivity of 85.6% (95% CI, 79.9-89.5%), a specificity of 71.4% (95% CI, 61.1-79.8%), and an accuracy of 86.1%.[5] The reporting of thyroid FNAB refers to the 2017 Bethesda System for Reporting Thyroid Cytopathology, which is standardized and concise.[6,7] This system classifies the cytopathological diagnosis of thyroid into 6 categories, such as (1) Nondiagnostic, (2) Benign, (3) Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS), (4) Follicular Neoplasm or Suspicious for a Follicular Neoplasm (SFN), (5) Suspicious for Malignancy (SFM), and (6) Malignant.[6,7] Additionally, each category includes recommendations for further management by clinicians.[6]

Among these six categories, AUS/FLUS remains a subject of debate among pathologists.[8,9] This is because not all aspirates show cells with clearly definable biological characteristics.[10] Microscopically, the criteria for diagnosis consist of atypical cells, either in the nuclei and/or architecture, which are qualitatively and quantitatively insufficient to be classified as follicular neoplasms/SFN and SFM but show higher atypical features compared to benign categories.[8,10] The use of AUS/FLUS diagnosis is often considered excessive due to this heterogeneous cytomorphological appearance.[11] On the other hand, the 2017 Bethesda System recommends the use of this diagnosis should not exceed 10% of all thyroid FNAB cases.[8]

Based on this system, the Risk of Malignancy (ROM) for AUS/FLUS ranges from 10-30% with varying recommendations for further management such as repeat FNAB, molecular testing, and surgery.[6] This wide range results in low accuracy as only low percentage of cases undergo surgical intervention.[12] Calculations based on surgical cases only can lead to an overestimation of the actual risk.[8] To improve accuracy, previous studies have classified AUS/FLUS into various subcategories. This aims to evaluate the ROM within each subcategory to facilitate similar management recommendations.[9,12] A meta-analysis study by Ahn et al[13] emphasized the need for standardized subcategorization of AUS/FLUS.

In 2017, the Bethesda system introduced six subcategorizations, namely AUS-C (nuclear atypia), AUS-A (architectural atypia), AUS-C&A (nuclear and architectural atypia), AUS-H (Hürthle cell aspiration), AUS-NOS (atypia not otherwise specified), and AUS-L (lymphoid cell atypia other than lymphoma). However, their widespread adoption remains limited,[8,9] posing a challenge for pathologists in assessing the ROM for each subcategory.

ATA also emphasizes the importance of assessing ROM, particularly in the indeterminate categories including AUS/FLUS, SFN, and SFM, at each institution. This assessment provides valuable information for clinicians in making further management.[1] Therefore, this study aims to determine the percentage and ROM of AUS/FLUS at Dr. Cipto Mangunkusumo Hospital, as well as to assess ROM for each subcategory based on the 2017 Bethesda System.

METHODS

This retrospective study is an analytical cross-sectional study design. The sample used consisted of secondary data obtained from the archives of the Department of Anatomical Pathology, Faculty of Medicine, University Indonesia/Dr. Cipto Mangunkusumo Hospital. The data included all thyroid FNAB examinations conducted from January 2018 to December 2021 by clinicians and pathologists using a 25G needle with or without ultrasound guidance.

Inclusion criteria encompassed all patients subjected to thyroid FNAB with an

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AUS/FLUS diagnosis, and subsequently underwent surgery (partial or total thyroidectomy). For patients with repeated FNAB, the last result before surgery was selected. Exclusion criteria included cases with reviewed results other than AUS/FLUS, histopathological results of a microcarcinoma (tumor <1 cm), core biopsy specimens, and cases where no slides were found. Cytological specimens were stained using Papanicolaou (Pap) and Giemsa.

Clinical data were obtained from the hospital's online medical records and cytology forms. The collected clinical variables were age, gender, as well as radiological features of thyroid nodules based on USG results, including location, size, characteristics, and Thyroid Imaging Reporting and Data System (TIRADS) score. The selected USG data were obtained from examinations conducted before thyroid FNAB.

A review of cytopathological diagnosis and determination of AUS/FLUS subcategories based on the 2017 Bethesda System was then performed. This was accomplished by a senior pathologist who review all slides in a randomized and blinded manner with respect to the histopathological results. The results were classified into 7 subcategories namely AUS-C1 (focal nuclear atypia), AUS-C2 (mild nuclear atypia), AUS-A, AUS-C&A, AUS-H, AUS-NOS, and AUS-L. Additionally, a cellularity assessment of the specimens was performed.

Statistical Analysis

After all the cases fulfilling the inclusion and exclusion criteria were collected, the percentage and ROM of the AUS/FLUS category were calculated. The ROM for each subcategory based on the 2017 Bethesda System was also calculated. Histopathological results were used as the gold standard for diagnosis, while statistical analysis was performed using SPSS software version 25. The comparison of ROM among AUS/FLUS subcategories was conducted using the Chi-square test. However, when the Chi-square test requirements were not fulfilled, Fisher's exact test was used. The results were considered statistically significant when the p-value was < 0.05 with a confidence interval of 95%.

Results

Based on the archives of the Department of Anatomical Pathology in the Faculty of Medicine, University Indonesia/Dr. Cipto Mangunkusumo Hospital from January 2018 to December 2021, a total of 2,082 patients underwent thyroid FNAB. Within this time frame, 2,396 thyroid FNAB procedures were performed. A total of 599 patients (28.7%) were diagnosed to have AUS/FLUS, with 142 patients in 2018, 162 patients in 2019, 131 patients in 2020, and 164 patients in 2021. Among these patients, 120 (20%) underwent repeated FNAB. The results showed that 55 patients (45.8%) were reclassified as benign, and 4 (3.4%) as malignant.

For this study, the number of patients eligible for assessment with an AUS/FLUS diagnosis was 75. This comprised 68 patients who underwent surgery directly after the initial diagnosis, as well as 7 who underwent surgery after repeated FNAB and remained diagnosed as AUS/FLUS diagnosis, as shown in Figure 1.

The mean age of the patients was 46.5 years, the majority were female at 85.3%, the male-to-female ratio was 1:5.8, and 4 (5.3%) were children. Based on the USG data, the mean size of thyroid nodules was 3.2 cm, with 40% located in the right and characterized by mixed solid and cystic features (45.3%). TIRADS scores were generally difficult to evaluate due to missing data (48%) in most cases. The two highest scores that could be collected were 4 (26.7%) and 5 (10.7%). The majority of FNAB procedures were performed by clinicians (60%) with aspirate cellularity ranging from low (41.3%) to moderate (49.3%). The detailed characteristics of the samples are shown in Table 1.

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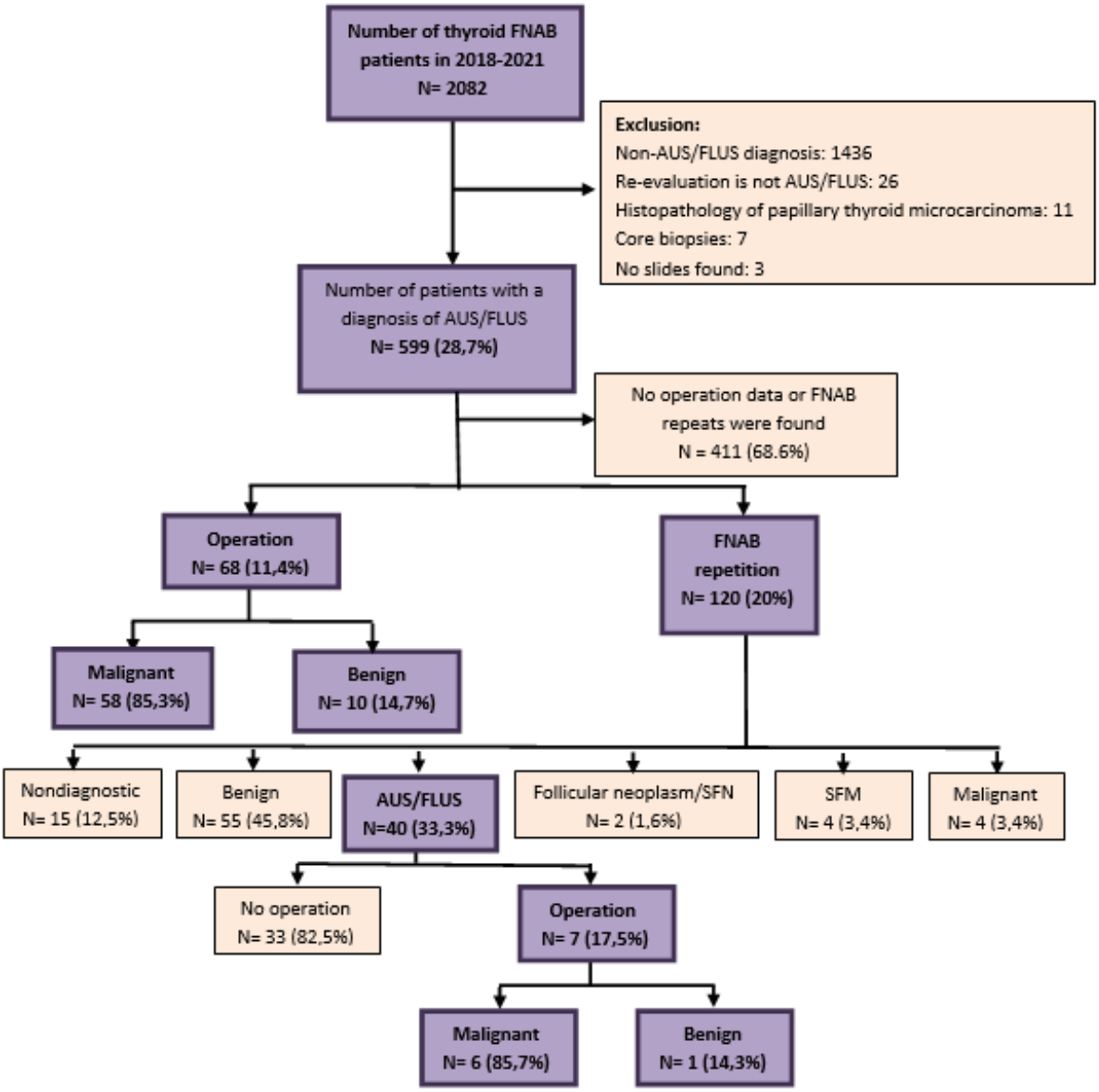

Figure 1. Sample recruitment flowchart.

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Table 1. Basic sample characteristics.

Characteristic (n=75)	Frequency
Age (years old)	
Mean	46.5
Median	48
Range	8-75
Pediatric patients (18 years old), n (%)	4 (5.3)
Gender, n (%)	
Male	11 (14.7)
Female	64 (85.3)
FNAB operator, n (%)	
Pathologist	30 (40)
Clinician	45 (60)
Nodule location, n (%)	
Right and left thyroid	17 (22.7)
Right thyroid	30 (40)
Left thyroid	28 (37.3)
Nodule size (cm)	
Mean	3.2
Median	3
Range	0.4-8
Missing data, n (%)	22 (29.3)
Thyroid nodule size <1 cm, n (%)	4 (5.3)
Thyroid nodule characteristics, n (%)	
Solid	24 (32)
Custic	1 (1.4)
Mixed solid and cystic	34 (45.3)
Missing data	16 (21.3)
TIRADS score, n (%)	
2	7 (9.3)
3	4 (5.3)
4	20 (26.7)
5	8 (10.7)
Missing data	36 (48)
Cellularity, n (%)	
Low	31 (41.3)
Moderate	37 (49.3)
High	7(9.4)

Among the 75 patients who underwent surgery, 64 (85.3%) showed histopathological results indicating malignancy, with the most common type being papillary thyroid carcinoma (PTC) (82.6%). A total of 11 patients (14.7%) exhibited benign histopathological results, with the most common type being adenomatous goiter (10.6%). There were no borderline lesion diagnoses. The ROM of the AUS/FLUS category was 85.3%. When all non-operated AUS/FLUS nodules were considered benign, the ROM was 10.6%. Therefore, the ROM of the AUS/FLUS category in this study ranged from 10.6% to 85.3%. The results of subcategorization and ROM of AUS/FLUS subcategories based on the 2017 Bethesda System are shown in Table 2.

The most commonly found AUS/FLUS subcategories were AUS-C1 (60%), AUS-NOS (21.3%), AUS-C&A (9.3%), AUS-C2 (8%), and AUS-H (1.4%) as shown in Figure 2 and 3.

The highest ROM was found in the AUS-C&A subcategory (100%), followed by AUS-C1 (95.5%), AUS-NOS (68.75%), and AUS-C2 (50%). The analysis for AUS-A, AUS-H, and AUS-L subcategories could not be evaluated in this study.

There were significant differences between the ROM of AUS-C1 and AUS-C2 (p=0.009) as well as AUS-C1 and AUS-NOS (p=0.011). In contrast, there were no significant differences in ROM between AUS-C1 and AUS-C&A (p=1), AUS-C2 and AUS-C&A (p=0.07), AUS-C2 and AUS-NOS (p=0.6), as well as AUS-C&A and AUS-NOS (p=0.27).

Table 2. Results of subcategorization and ROM of AUS/FLUS subcategories based on the 2017 Bethesda System compared to histopathological diagnoses.

Histopathological diagnosis	AUS-C1 (N=45)	AUS-C2 (N=6)	AUS-A (N=0)	AUS-C&A (N=7)	AUS-H (N=1)	AUS-NOS (N=16)	AUS-L (N=0)
Benign							
Adenomatous goiter	1	3	0	0	0	4	0
Hashimoto's thyroiditis with Hürthle cell metaplasia	0	0	0	0	1	1	0
Graves' disease	1	0	0	0	0	0	0
Malignant							
PTC	42	3	0	7	0	10	0
Non-PTC	1	0	0	0	0	1	0
Subcategory ROM	95.5%	50%	n/a	100%	n/a	68.75%	n/a

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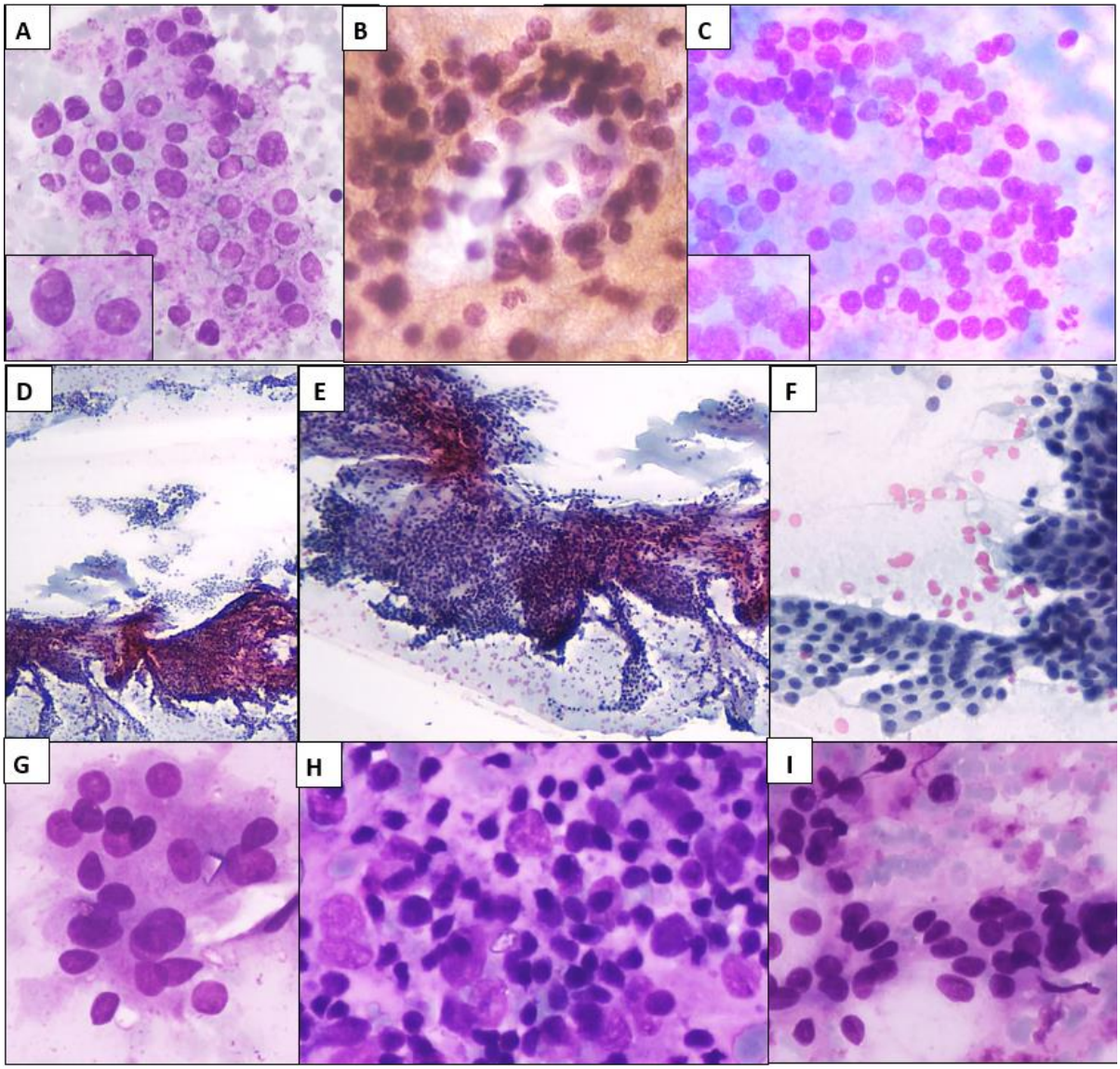

Figure 2. Cytology cases with benign histopathological results. A. Adenomatous goiter, AUS-C1 subcategory. Few follicular cells with enlarged nuclei, irregular nuclear membrane, and pseudo-inclusions (inset) (Giemsa, x400). B. Graves' disease, AUS-C1 subcategory. Few follicular cells with enlarged nuclei and pale chromatin (Pap, x400). C. Adenomatous goiter, AUS-C2 subcategory. Many slightly enlarged follicular cells with slightly pale chromatin, nuclear groove (inset) (Giemsa, x400). D-F. Adenomatous goiter with papillary hyperplasia, AUS-C2 subcategory. Monolayer arrangement of follicular cells, no true papillae (D. Pap, x40, E. x100, F. x400). G. Hashimoto's thyroiditis with Hürthle cell metaplasia, AUS-H subcategory. Low cellularity specimens, consisting of Hürthle cells (Giemsa, x400). H&I. Adenomatous goiter with papillary growth, AUS-NOS subcategory. Enlarged atypical cells with a background of numerous inflammatory cells. No PTC nuclei were found (Giemsa, x400).

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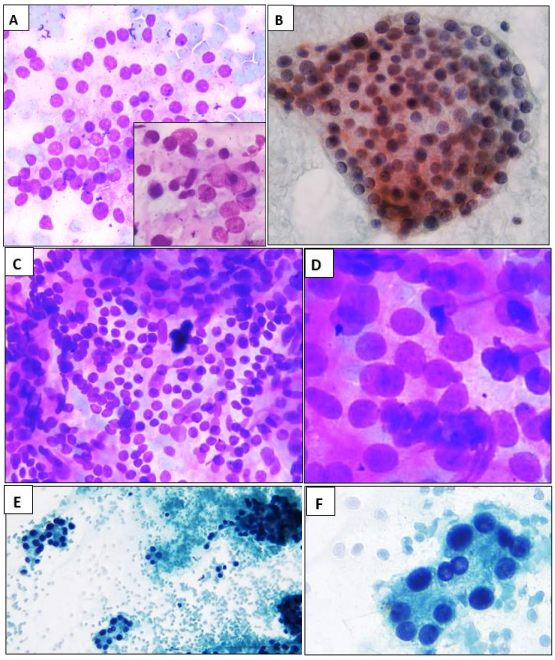

Figure 3. Cytology cases with malignant histopathological results. A. PTC, AUS-C1 subcategory. Generally benign follicular cells, some enlarged nuclei, pale chromatin, and nuclear groove (inset) (Giemsa, x400). B. Non-PTC, AUS-C1 subcategory. Few follicular cells with enlarged nuclei and pale chromatin (Pap, x400). C&D. PTC, AUS-C2 subcategory. Follicular cells generally slightly enlarged, slightly irregular nuclear membranes (C. Giemsa, x100. D. x400). E&F. PTC, AUS-C&A subcategory. Moderate cellularity with architectural atypia (microfollicles) and enlarged nuclei with pale chromatin (E. Pap, x100. F. x400).

DISCUSSION

The implementation of the Bethesda System in reporting thyroid FNAB plays an essential role in improving communication between pathologists and clinicians.[6] Among the six diagnostic categories, AUS/FLUS was found as one of the indeterminate categories that posed a significant challenge,[8,9] due to its heterogeneity and varying ROM (14.0-87.1%).[9,12]

This study was the first in Dr. Cipto Mangunkusumo Hospital to evaluate the ROM of AUS/FLUS subcategories based on the 2017 Bethesda System. The mean age of the patients was 46.5 years, with the majority being female (85.3%). The most frequently found histopathological diagnoses among malignant and benign groups were PTC (82.6%), and adenomatous goiter (10.6%), respectively. These findings are in line with previous studies which examined thyroid FNAB.[7,9,12,19–22]

Percentage of AUS/FLUS category

The percentage of AUS/FLUS category in Dr. Cipto Mangunkusumo Hospital in 2018-2021 was 28.7%. This percentage was nearly three times higher than the 2017 Bethesda System's recommendation, and almost four times higher than the overall pooled estimate of the frequency from a meta-analysis study by Guleria et al[23] in 2020, which was 7.3%.

One of the factors that contributed to the high percentage of AUS/FLUS cases was the study location, which was conducted in Dr. Cipto Mangunkusumo Hospital, as a referral center in Indonesia, with a high number of malignancy cases. Additionally, a significant number of FNAB results showed low cellularity and only less than 10% cases showed high cellularity. This low cellularity can be attributed to the use of FNAB procedures without USG guidance due to cost considerations. USG-guided FNAB was reserved for small-sized nodules, as well as those located deep within the thyroid, predominantly cystic nodules, and on repeat FNAB cases that previously showed non-diagnostic or indeterminate results. Similar findings were reported in India by Guleria et al.[12,23]

Our study showed that the majority of thyroid nodules have mixed solid and cystic features. FNAB of cystic nodules often results in low cellularity,[24] hence, USG-guided FNAB is recommended. A meta-analysis study carried out by Tarigan et al[3] in 2022 stated that USG-guided FNAB demonstrated better diagnostic accuracy for thyroid malignancy. Therefore, this technique is recommended to improve aspirate results with good cellularity.

ROM of the AUS/FLUS category

The ROM of AUS/FLUS in this study was 85.3%, which was significantly higher than the 2017 Bethesda System's recommendation.[6] Several other studies, such as Zhao et al[9], Hong et al[25], and Guleria et al[12] also reported relatively high ROM in their results, with percentages of 83.3%, 72.9%, and 52%, respectively. One of the reasons for these higher values was the presence of selection bias due to the low proportion of AUS/FLUS cases that underwent surgical procedures. Surgery is typically performed on those with clinical and radiological suspicious features for malignancy, patient preference, a family history of thyroid malignancy, or a history of radiation exposure.[9,12,19,22] Suspicious USG features for malignancy were found in 42.7% of patients with TIRADS scores ranging from 3-5 in our

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study. However, seven patients (9.3%) had TIRADS 2 thyroid nodules, and five showed histopathological results of malignancy. This might be attributed to USG examinations conducted at an early stage of patient complaints or due to the rapid growth of malignant tumors.[26]

In this study, only about 11.4% of patients after the first AUS/FLUS diagnosis and 17.5% after repeat diagnosis underwent surgical procedures. This was supported by Guleria et al[23] highlighting that the Asian region has the lowest thyroid nodule surgery rate at 26.5%. This indicates that clinicians in the Asian region are more selective in performing surgical procedures and tend to choose conservative management including clinical and/or radiological monitoring for indeterminate thyroid FNAB categories.[23] The majority of patients (68.6%) in this study had no further data on surgical procedures or repeat FNAB. This group was mostly composed of patients who did not return for follow-up (loss to follow-up), received conservative management, underwent surgical procedures, or repeat FNAB at their original or other hospitals, considering that Dr. Cipto Mangunkusumo Hospital was a tertiary referral center. The ROM value in this study was 10.6% assuming that all non-operated AUS/FLUS thyroid nodules were benign. Therefore, the actual value ranged between 10.6% and 85.3%. This wide range was also found in Zhao et al[9] (17,6-83,3%), Hong et al[25](10,2-72,9%), and Guleria et al[12](14,9-52%).

Another factor contributing to the high ROM was the use of more stringent diagnostic criteria for SFM/malignancy and high diagnostic thresholds for nuclear PTC by pathologists in Asia compared to Western countries.[9,23,27,28] This approach is driven by the reluctance to accept false-positive diagnoses by patients and clinicians, which is particularly common in the Asian region.[9] Consequently, pathologists tend to underdiagnose thyroid FNAB specimens with low cellularity, leading to a higher average ROM AUS/FLUS in Asian, of approximately 44%.[9,27,28]

Aside from surgical procedures, other recommended alternatives for managing the AUS/FLUS category include repeat FNAB and molecular testing.[8] In this study, 49.2% of patients obtained definitive diagnoses (benign/malignant category) after repeat FNAB. This finding was consistent with the results of Elomami et al[19], which reported a 50% rate, suggesting repeat FNAB as a management option before surgery. Repeating FNAB aims to obtain clearer cytomorphological features and should be performed 3-6 months after the previous FNAB to decrease the reactive cell numbers.[22]

The molecular testing in AUS/FLUS cases is one of the methods used to determine further options including conservative management or surgery.[29] Additionally, this examination can significantly improve the accuracy of the AUS/FLUS diagnosis.[22,29] BRAF mutation, particularly V600E, is the most commonly found genetic mutation (50-80%) in PTC.[22] Patients diagnosed with AUS/FLUS and who have the BRAF mutation are strong candidates for total thyroidectomy.[22] Other molecular mutations implicated in thyroid malignancy include RAS, RET/PTC, and PAX8/PPARγ.[22,30] However, molecular testing is not yet available at Dr. Cipto Mangunkusumo Hospital.

AUS/FLUS subcategories

The establishment of AUS/FLUS subcategories based on the 2017 Bethesda system aims to enhance the accuracy of ROM and facilitate further modifications in the diagnostic criteria in the future.[8,22] In this study, the subcategories AUS-C were divided based on the degree of nuclear atypia into AUS-C1 and AUS-C2, following the classification proposed by Zhao et al.[9]

AUS-C1 with a percentage of 60% was the most commonly found subcategory in this study. Microscopically, the cytomorphological features showed significant nuclear atypia but were not sufficient to fit into the SFM category.[9] This finding was consistent with a study conducted by Zhao et al[9] where one of the factors contributing to the high prevalence of the AUS-C1 subcategory was inadequate sampling.[9] This inadequacy was associated with non-USG-guided thyroid FNAB procedures, although only 2 patients (2.6%) had thyroid nodules <1 cm and were classified as AUS-C1. Another reason was the tendency of pathologists in Asia, including Indonesia, to use AUS/FLUS diagnosis for aspirates with low cellularity but suspicious for malignancy based on nuclear features of PTC, as previously reported by Zhao et al[9] and Kim et al.[27]

The ROM for AUS-C1 was 95.5%, ranking as the second-highest after the AUS-C&A subcategory, which had a value of 100%. However, no significant difference was found between these two subcategories, as also reported by Zhao et al[9] and Babajani et al[21] Huhtamella et al[28] found that AUS-C&A had the

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highest ROM but no statistical analysis was conducted to compare the values between subcategories.

AUS-C2 (8%) was the fourth most common subcategory in this study with a ROM percentage of 50%. Zhao et al[9] reported that the AUS-C2 subcategory ranked third (10.8%) with ROM 66.7%. Our study showed in line result with Zhao et al[9] that showed significant differences in ROM of AUS-C1 and AUS-C2 as well as between AUS-C1 and AUS-NOS.

This study did not identify any malignancy cases classified under the AUS-A subcategory, as also reported by Zhao et al[9] and Babajani et al.[21] This may be related to the lower prevalence of follicular neoplasms in Asia compared to the United States.[9]

The challenge faced by pathologists in interpreting thyroid FNAB specimens is the subjective assessment of PTC nuclear cyto-morphological features, both quantitatively and qualitatively. Therefore, the diagnosis of cases with atypical/non-classic depends heavily on the experience of each pathologist.[14,31]

Currently, the minimum number of neoplastic cells required for diagnosing thyroid malignancy remains unclear. The diagnosis is easier when numerous neoplastic cells are present, showing oval or convoluted shapes, irregular nuclear membranes, pseudo-inclusions, and/or nuclear grooves, with pale, and evenly dispersed (powdery) chromatin as well as dense cytoplasm. Other findings that need to be considered to distinguish malignant cells from benign ones include crowding, overlapping, and molding nuclei.[14,31]

Minimal changes in neoplastic cell nuclei or incomplete characteristics of PTC nuclei tend to make pathologists more cautious in making a malignancy diagnosis. This is due to the overlapping features between malignant and benign cells (reactive or metaplastic), such as pseudo-inclusions and nuclear grooves. Although rare, pseudo-inclusions may be found in adenomatous goiter, lymphocytic thyroiditis, and follicular adenoma, while nuclear grooves can be observed in lymphocytic thyroiditis and oncocytic neoplasms.[14,31]

Apart from nuclear characteristics, common cell arrangements or patterns found in malignancy tend to also occur in benign cases. Malignant cells arranged in a monolayer may resemble the macrofollicular appearance found in nodular thyroid hyperplasia. In such cases, nuclear characteristics can aid in making a diagnosis. Benign lesions show evenly spaced follicular cells, while malignancy often shows cell crowding. Furthermore, the swirling pattern is specific to malignancy.[14,31]

An interesting aspect of this study is the subcategorization of AUS-C based on the degree of nuclear atypia. The results showed that AUS-C1 had a higher ROM and was significantly different from AUS-C2. Meanwhile, the ROM value of AUS-C2 was found to be similar to AUS-NOS. This suggested that thyroid nodules exhibiting AUS-C1 features with or without architectural atypia have a higher ROM and deserve more aggressive management compared to AUS-C2 and AUS-NOS nodules.

Although this retrospective study was conducted over a significant observation period, only 75 patients with a diagnosis of AUS/FLUS fulfilled the inclusion and exclusion criteria. This constituted a major limitation of our study. The lack of available follow-up data for many cases culminated in a wide range and low accuracy of the calculated ROM. Another limitation was the inability to perform ROM analysis for the AUS-A, AUS-H, and AUS-L subcategories.

Conclusion

In conclusion, the percentage of AUS/FLUS cases at Dr. Cipto Mangunkusumo Hospital from 2018 to 2021 was 28.7%, with a ROM ranging from 10.6% to 85.3%. Significant differences were found between the ROM of AUS-C1 with AUS-C2, as well as AUS-C1 with AUS-NOS. Therefore, AUS-C1 thyroid nodules with or without architectural atypia require distinct and more aggressive management compared to those showing AUS-C2 and AUS-NOS features. Good collaboration between clinicians, radiologists, and pathologists is needed in managing patients with thyroid nodules.

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Conflict of Interest

The authors do not have any conflict of interest to disclose

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Authors Contribution

The authors contributed equally to the research

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