Incidence of Urologic Disease Among 95 Consecutive Filipino Patients Presenting With Asymptomatic Microscopic Hematuria

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ABSTRACT

Objective: One of the common clinical problems warranting urologic evaluation is asymptomatic microscopic hematuria (AMH). According to some studies, it has prevalence as high as 38% with a possibility of urologic disease or malignancy around 23%. The presence of AMH would be quite a dilemma to a urologist in terms of how aggressive urologic evaluation and follow up is recommended. The present study was to determine the incidence of significant urologic diseases among Filipino patients with AMH on initial evaluation and on follow-up. This study would also determine if there would be a significant difference in terms of incidence of urologic disease among patients less than 35 years old and more than 35 years old with AMH.

Methods: A total number of 95 patients (38 male, 57 female) were included in this study. All patients presented with AMH. They were grouped in terms of age, gender, and duration of follow-up. All patients underwent cystoscopy and a diagnostic imaging (ultrasound, CT urogram, or CT stonogram) on initial evaluation. Patients then were followed up. They were divided into two groups, those less than 2 years of follow-up and those more than 2 years of follow-up. Excluded from the study are those patients with gross hematuria, on indwelling catheter, with urinary tract infection, with previous malignancy, history of pelvic irradiation, and those who did not undergo cystoscopy, or any urologic imaging.

Results: Out of 95 patients with AMH who underwent urologic evaluation, the incidence of urologic disease was noted to be 12% (11 out of 95). There was no malignancy related cause of AMH discovered. Age and gender failed to show any significant difference in terms of developing urologic disease. Among patients with negative findings on initial urologic evaluation, no urologic disease was noted even on follow-up. Among those with positive findings on initial evaluation, no new urologic disease was discovered on follow-up.

Conclusion: AMH has a low incidence of urologic disease or any GUT malignancy. Age and gender alone are not sufficient risk factors warranting an invasive endoscopic procedure. They are recommended only to those patients with high risk of urologic disease and can be avoided in majority of the population. We would recommend a kidney, urinary bladder, and prostate (KUBP) ultrasound as the initial imaging of choice since the only findings noted on evaluation through imaging were just two cases of nephrolithiasis, one via CT stonogram and the other through a CT urogram, which can also be diagnosed with a regular KUBP ultrasound. This would be more cost-effective as well as beneficial in terms of the patient's risk regarding radiation and contrast-related effects. Clinicians may decrease unnecessary repeated urologic evaluation and

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follow-ups on patients with AMH, as the results of the study failed to show any significant difference in developing urologic disease for patients with persistent AMH on initial assessment and even on follow-up.

Key Words: Urologic disease, microscopic hematuria, hematuria.

INTRODUCTION

Asymptomatic microscopic hematuria (AMH) is one of the most common clinical problems requiring urological evaluation in adults with a prevalence of 0.2–38%.[1-4] It can be a sign of potentially life-threatening diseases such as urological malignancies in around 23% of cases,[1] or other benign diseases of urologic concern like urolithiasis. Thus, clinicians must be able to screen or catch these diseases at their early onset, to be able to prevent complications like renal insufficiency/failure. It can be one of the earliest signs that physicians may look into in terms of detecting significant urologic lesions that can be prevented or managed at its earliest stage.

According to the American Association of Urology (AUA) guidelines of 2020, AMH will be defined as >3 RBC/HPF on microscopic evaluation of urinary sediment gathered from at least one urine specimen with no evidence of urinary tract infection. [5] Asymptomatic being defined as the absence of fever, dysuria, hematuria, and flank pains. Currently, the consensus of different guidelines recommend cystoscopic evaluation for all patients aged 35 years and over[5,6] and for those younger than 35, imaging is highly recommended and cystoscopy only depends on the surgeon's discretion. [5,6] However, for those patients with risk factors cystoscopy must be done regardless of age.[3,5] With regards to imaging, the AUA guidelines, and American College of Radiology Appropriateness Criteria, choose multiphase computed tomography (CT) urogram as the preferred study for the initial AMH evaluation due to its high sensitivity and specificity for identifying upper tract pathology. [3,5] However, if CT urogram is contraindicated, magnetic resonance urography, plain CT stonogram, or renal ultrasound can be alternative options. It is likewise recommended to have patients followed up despite initial negative AMH evaluation due to the risk potential of developing a not yet identifiable urologic pathology.[3,5] The AUA recommends annual subsequent urinalysis, stopping only if negative for two consecutive years but if AMH persists, the guidelines suggest yearly urinalysis and repeat evaluation should be considered within three to five years.[5]

Currently, there are only a few studies presenting the low prevalence of malignancies and other urologic diseases in patients with AMH, but none encompasses on the Filipino population in the Philippine setting. A study by Madeb, et al. stated that patients with AMH and a negative workup have only <1% chance of developing bladder cancer.[7] Another study stated that incidence of urinary tract malignancy does not exceed 5% for patients with non-visible asymptomatic hematuria. [3] A journal noted that patients being referred to for AMH have a relatively lower (0.5% to 5.0%) but nontrivial probability of underlying occult cancer[4] that is estimated to range only from 7% to greater than 20% in those with higher-risk subgroups. [4] Knowing the incidence of significant urologic disease would help urologists, in terms of following up patients with AMH. There is likewise a tendency to either over-evaluate or under-evaluate Filipino patients with AMH due to its unknown incidence; thus, it would be helpful for physicians, especially Filipino urologists in terms of evaluating whether what guideline would be suitable to follow, and whether or not these guidelines would be applicable in our setting.

MATERIALS AND METHODS

This is a retrospective review of a collected database. From 1997 to 2017, all patients with AMH as the initial presentation seen by a single urologist were included in the study. These patients were followed up from the time of diagnosis. All patients underwent urologic evaluation via cystoscopy, and a GUT imaging (either a CT urogram, MR urogram, a CT stonogram, or KUB ultrasound) depending upon the physician's discretion. Those with identifiable urologic disease after initial evaluation were included as positive results. Those patients who underwent urologic evaluation which revealed negative findings were separated into two groups: those who were able to follow up in less than 2 years and those more than 2 years.

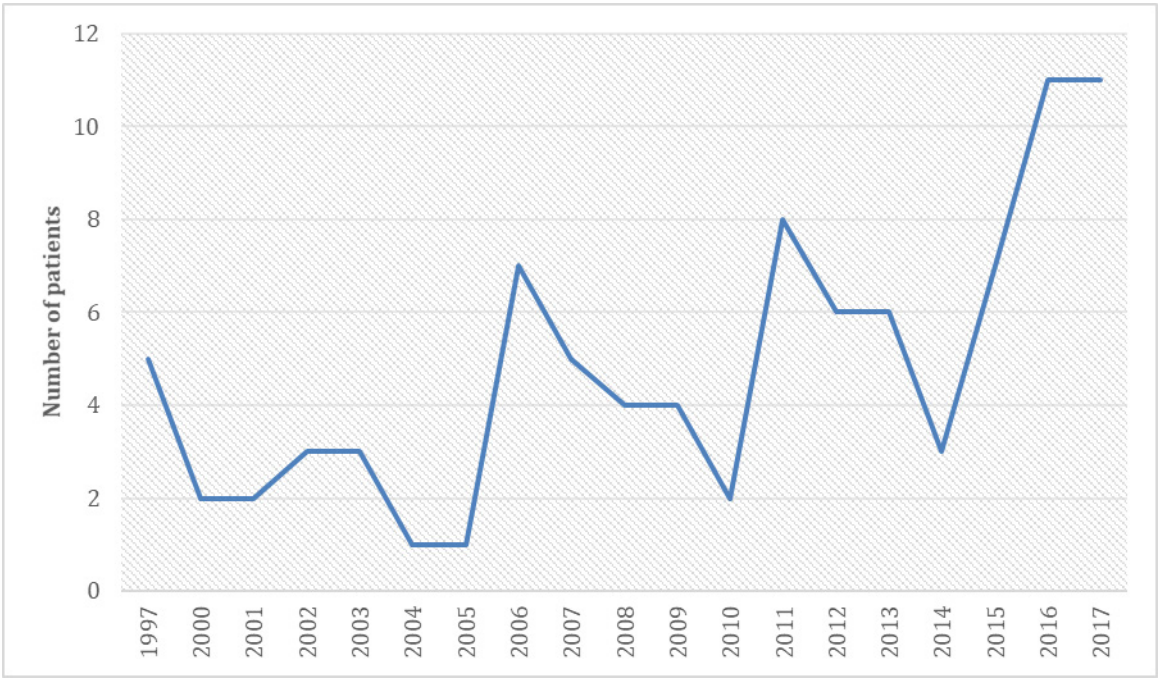

Figure 1. Number of patients diagnosed with asymptomatic microscopic hematuria by year (1997-2017) by a single investigator

All identified urologic diseases were included as positive results. We separated the follow-up period in order for us to determine if there would indeed be any significant difference in detecting significant urologic disease among patients over time. Medical history, laboratory results, and diagnostic findings were identified from an electronic medical record. Patients were classified into two groups, those less than 35 years of age and those more than 35 years old. This was to see whether patients more than 35 years old would really have a higher risk of detecting malignancies or any urologic disease upon initial evaluation compared to those less than 35 years of age. Patients' records were then reviewed and followed up for diagnosis or development of any urologic diseases like any urologic malignancies (renal cancer, upper tract urothelial cancer, bladder cancer) or urolithiasis. All Filipino adult patients aged 18 years and above who presented with AMH as confirmed via routine urinalysis in at least one specimen as defined by the AUA guidelines were included. Those patients with gross hematuria, on indwelling catheter, with the presence of urinary tract infection and previous malignancies at the onset were excluded from the study. Likewise, patients who did not undergo any urologic evaluation were excluded as well.

Table 1. Demographic characteristics of AMH patients (n=95)

CHARACTERISTICS	
Sex	
Male	38 (40)
Female	57 (60)
Age (in years), mean	55.92 ± 14.37
<35 years old	9 (9)
≥35 years old	86 (91)

RESULTS

Data were encoded by the researcher in MS Excel. Stata MP version 14 was used for further processing and analysis. Continuous variables were presented as mean/SD and analyzed using independent t-test. Categorical variables were presented as frequency/percentage and analyzed using chi square test or Fisher's exact test. P values ≤0.05 were considered statistically significant. Charts and graphs were created using MS Excel.

From 1997 to 2017, a total of 95 patients were diagnosed with AMH. Figure 1 shows the increasing trend in number of patients being seen with AMH from 1997 to 2017.

Table 1 showed the specific characteristics of patients included in the study. Majority of the patients

Table 2. Diagnostic procedure results among AMH patients

PROCEDURES	n(%)
Cystoscopy (n=95)	
Positive	9 (9)
Negative	86 (91)
Ultrasound (n=77)	
Positive	0
Negative	77 (100)
CT stonogram (n=7)	
Positive	1 (14)
Negative	6 (86)
CT urogram (n=13)	
Positive	1 (7)
Negative	13 (93)

were females. The mean age was 56 years (range: 20-85). Ninety-one percent of the patients with AMH were more than 35 years old on their first visit.

Aside from routine urinalysis, other diagnostic procedures such as CT stonogram, CT urogram, and ultrasound were requested depending on the primary physician's discretion for patients at the time of first visit which heeled in the diagnosis of urologic disease. Table 2 showed the results of different diagnostic procedures done. All patients underwent cystoscopy, of which 9 (9%) were positive for urologic disease at the time of initial evaluation. None of the patients who underwent ultrasound had a significant finding. Seven patients underwent CT stonogram, of which one patient had a positive finding despite a negative cystoscopy result. Thirteen patients underwent CT urogram, of which one patient had a positive finding despite a negative cystoscopy result. The positive findings noted in both the CT stonogram and CT urogram group were non-obstructing nephrolithiasis.

Table 3. Incidence of urologic disease among AMH patients (n=95)

UROLOGIC DISEASE	N	PREVALENCE (%)
Urethral caruncle	4	0.04%
Non-obstructing nephrolithiasis	2	0.02%
Cystolithiasis	1	0.01%
Urethral stricture	1	0.01%
Chronic inflammation	1	0.01%
Cystitis glanduralis	1	0.01%
Squamous metaplasia	1	0.01%

The incidence of urologic disease among AMH patients was recorded to be 12% (11 out of 95). Table 3 presents the incidence of each specific urologic disease among AMH patients. All patients were diagnosed using cystoscopy except for two cases of non-obstructing nephrolithiasis. One was diagnosed via CT stonogram and the other one via CT urogram.

Table 4 compared the characteristics of patients with urologic findings noted on initial evaluation. A higher proportion of patients with urologic disease at baseline were females compared to males, however, no significant difference was observed. In terms of age, those with urologic disease were noted to be more than 35 years old, but statistical analysis likewise failed to show any significant difference.

Patients were then followed up to determine if significant urologic disease will develop from microscopic hematuria. All patients who had a negative urologic finding at baseline did not develop any urologic disease on follow-up. Among the 11 patients who had a positive finding at initial

Table 4. Demographic characteristics of AMH patients by presence of urologic disease at baseline (n=95)

	UROLOGIC DISEASE		
CHARACTERISTICS	POSITIVE n (%)	NEGATIVE n (%)	P-VALUE
Sex			
Male	3 (8)	35 (92)	0.359
Female	8 (14)	49 (86)	
Age (in years), mean	60.91 ± 8.60	55.26 ± 14.88	0.2223
<35 years old	0	9 (100)	0.592
≥35 years old	11 (13)	75 (87)	

Table 5. Number/percentage of urologic disease on follow-up among AMH patients

	UROLOGIC DISEASE AT FOLLOW-UP		
	POSITIVE n (%)	**NEGATIVE n (%)**	**P-VALUE**
Negative urologic disease at baseline (n=74)			
Age (in years), mean			
<35 years old	0	9 (100)	-
≥35 years old	0	65 (100)	
Follow-up year			
<2 years	0	35 (100)	-
≥2 years	0	39 (100)	
Positive urologic disease at baseline (n=11)			
Age (in years), mean			
<35 years old	0	0	-
≥35 years old	4 (36)	7 (64)	
Follow-up year			
<2 years	2 (100)	0	0.109
≥2 years	2 (22)	7 (78)	

evaluation for AMH, 7 (64%) of them were already negative on follow-up after more than 2 years. In contrast to the four patients who had urologic disease both at baseline and on follow-up, two patients remained to have the same urologic finding, which were non-obstructing nephrolithiasis even after 2 years of follow-up. Persistent AMH was recorded in 85 patients, but none of them had any urologic disease on baseline and on follow-up. Ten patients were lost to follow-up, of which two of them expired, both from non-urologic causes.

DISCUSSION

The study showed that there was an increase in trend of patients being diagnosed with AMH as illustrated in Figure 1. This may be due to Filipinos currently having a higher health seeking behavior and being more cautious in terms of their medical concerns and doing executive check-ups. Although majority of the Filipinos still shoulder medical expenses in an out-of-pocket basis, availing of medical health insurance by the Filipino population, is somewhat increasing, hence probably the reason for increase in the trend of patients with AMH.

Majority of patients with AMH in this study were females. The mean age was around 56 years (range: 20-85). Ninety-one percent of patients with AMH were more than 35 years old on their first visit. One limitation of this study was the obvious discrepancy between number of patients less than 35 years, and those more than 35 years of age seen with AMH. Only nine patients less than 35 years old had to seek medical assistance because of AMH, and this is probably due to the majority of Filipino patients in this age group not really cautious in seeking medical attention. Despite that discrepancy, statistical analysis failed to show any significant difference among patients with urologic disease at baseline or upon initial evaluation in terms of age and gender as shown in Table 4. This finding is important since according to the AUA guidelines on asymptomatic hematuria, male gender and age of more than 35 years old are considered risk factors warranting invasive urologic evaluation. [8] The reason behind this recommendation is due to the gender differences in etiologies of AMH, with results showing an increase in male predominance of genitourinary cancers and higher rates of urinary tract infections and contaminations with menstrual

blood among women.[9] The study would show that doing urologic evaluation like cystoscopy to patients because of age and gender alone may be unnecessary. Only sparse evidence was found for doing cystoscopy in patients younger than 40 years as stated in Niemi, et al.[9] Among the population screening studies cited in the AUA guideline, only one patient with AMH younger than 40 years was noted to have GU cancer.[9,10] Hence, before recommending cystoscopy as part of initial evaluation, we must first evaluate patients thoroughly, if there would be other risk factors present aside from age and gender alone, that would warrant invasive diagnostic procedures because most often than not, such procedures would be quite excessive.

All patients with AMH in this study underwent cystoscopy plus a diagnostic imaging, either a KUB UTZ, CT urogram, or CT stonogram. According to the AUA guideline, CT urography is the study of choice for radiological evaluation of AMH, and due to the recent guideline stating that only one urinalysis specimen with microscopic hematuria would be necessary for urologic evaluation, the use of CT urography would definitely rise.[8,11] As illustrated in Table 2, this study demonstrated 11 positive findings for urologic disease on initial evaluation, nine were discovered on cystoscopy, one on CT urogram, one on CT stonogram, and none on ultrasound. A study by Lisanti, et al., concluded that CT urography had no additional diagnostic benefit versus unenhanced CT in evaluating urinary tracts of patients younger than 50 years with microscopic hematuria.[11] In this study of 442 patients who underwent CT urography (CTU) for microscopic hematuria, CTU reports showed zero malignancy-related hematuria findings, 64 non-malignancy-related hematuria findings (62 renal calculi and two others), and 138 incidental non-hematuria-related findings.[11] The unenhanced CT interpretation of these images by a blinded radiologist had a sensitivity of 100% and specificity of 89.2%; therefore, in conclusion, using CTU would have no additional diagnostic benefit compared to unenhanced CT imaging.[11] Based on the study, results showed that nine non-malignancy related findings were diagnosed via cystoscopy, CT stonogram was able to note a 0.5 cm nephrolithiasis, and CT urogram likewise was able to detect a 0.3 cm nephrolithiasis. None were detected on ultrasound, however, we believed that such findings may also be detected on ultrasound which is why we would recommend that for patients with AMH, a urologic evaluation of KUBP UTZ would suffice to reduce radiation and contrast associated effects.

The incidence of urologic disease in this study among AMH patients was recorded to be 12% (11 out of 95) as shown in Table 3. All positive urologic findings noted in this study were non-malignancy related (urethral/meatal caruncles, nephrolithiasis, cystolithiasis, urethral stricture, cystitis glandularis, and chronic infection). The incidence of developing urologic disease or any GUT malignancy was noted to be zero, as no patient developed any GUT malignancy during initial evaluation and follow-up. Those patients who had a negative urologic finding on initial evaluation remained disease-free despite having persistent AMH. Among those with positive findings on initial evaluation, 7 (64%) of them were already negative on follow-up after more than 2 years. In contrast to the four patients who had a urologic disease both at baseline and on follow-up, two patients remained to have the same urologic finding even after two years of follow-up. The study would somehow support studies stating the prevalence of urinary tract cancer in patients with AMH as quite low, as low as 0.01-3%.[12] The data on this study supports the fact that AMH is an unreliable indicator of urinary tract malignant tumors.[12] The study also failed to show any significant difference in terms of developing urologic disease among those patients with less than 2 years follow-up and those more than 2 years follow-up.

One limitation of the study was that there were 10 patients who were lost to follow-up and of which, two of them expired but both from non-urologic causes. Another limitation is the use of different diagnostic procedures upon initial evaluation and on follow-up.

CONCLUSION

These data suggest that AMH has a low prevalence of urologic disease or malignancy. Cystoscopy is recommended only to those patients with high risk of urologic disease and can be avoided in a majority of the population. A simple plain kidney, urinary bladder, and prostate ultrasound would suffice in

terms of initial diagnostic procedure of choice to avoid contrast risk effects in patients with AMH. These data may be used to guide clinicians on their evaluation and decrease unnecessary repeated evaluation and follow-up on patients with AMH.

DISCLOSURE

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