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Original Research Article

Microscopic Hematuria: A Classical Definition in a Modern Lab Era

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Abstract: **Purpose:** This study endeavors to elucidate the diagnostic intricacies surrounding microhematuria, a prevalent indication for urological consultation. Specifically, the research seeks to assess the diagnostic value of urinalysis and cystoscopy procedures in minimizing the need for invasive cystoscopies, given the evolving landscape of technology-driven urinalysis. The primary objective is to provide nuanced insights for clinicians to optimize diagnostic pathways in cases of microhematuria. **Method:** In this retrospective case-control study, conducted at our university-based hospital, patient records spanning January 2017 to January 2022 were scrutinized following approval from the local ethics committee. The study focused on individuals diagnosed with microhematuria and subsequently subjected to cystoscopy and urine cytology. Exclusion criteria encompassed urinary tract infection, positive or suspicious urine cultures, urolithiasis, bladder pain syndrome/interstitial cystitis, pregnancy, and pre-existing bladder cancer. Urine analyses were carried out using the FUS-200 automatic urinalysis system. **Results:** Cystoscopy identified lesions in 17% of cases, leading to biopsy/endoscopic resection. Dipstick analysis revealed mean RBC/hpf values of 8.93±3.78 (24.61) for RBC+, 22.08±12.30 (52.77) for RBC++, and 763.56±1993.63 (78.08) for RBC+++. Among cytologies, 1% exhibited atypia with normal follow-up. Patients with detected lesions displayed varying pathology, with 23% benign cases and 77% urothelial carcinoma. Levels of measured RBC/hpf across tumor stages and histological grades were statistically insignificant, yet the median levels significantly differed between cases with and without lesions. The study outcomes indicate a significant difference in median RBC/hpf levels between cases with lesions present (77.38) and absent (45.66) (p=0.001). ROC analysis yielded an AUC of 0.814 (p=0.001, 95% CI 0.677-0.952). However, diagnostic value was suboptimal at lower cut-offs and appeared to be optimum within the range of 35-40 RBC/hpf. **Conclusion:** This study provides nuanced insights into the specificity of urinalysis in cases of microhematuria by correlating modern urinalysis results with cystoscopic outcomes, the research contributes to a refined decision-making framework for clinicians. It emphasizes the need for evidence-based guidelines in assessing microhematuria comprehensively, considering the evolving landscape of diagnostic technologies.

Keywords: Microhematuria, urinalysis, cystoscopy, urothelial carcinoma.

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INTRODUCTION

One of the most common indications for a urological consultation is hematuria hence its presence might suggest urinary tract calculi, infections or even malignancies [1]. Microhematuria is defined as the urine microscopy showing ≥3 red blood cells per high-power field (RBC/HPF) on a properly collected urine specimen and is highly frequent that population based studies estimates that up to 41% of adults show this finding on urinalysis [2-4]. Among the possible etiologies for microhematuria, presence of three or more RBC/HPF on a properly collected single urine microscopy is associated with malignancy in 2.3% to 5.5% of patients [4,5]. The high prevalence of microhematuria and its potential role as a harbinger of malignancy bestows significant attention on the matter of diagnostic algorithms for its assessment. Given the perils of substantial pathology, macrohematuria is acknowledged as an indication for further investigation [6]. The necessity to deeper evaluate a patient with a microhematuria, per contra, is still a matter of debate [7]. Individuals with microhematuria have a wide risk spectrum for malignancies and constitute a heterogeneous population. Therefore, regarding the age thresholds and risk profiles of the patients, current policy makers differ whether one entails further investigation. For instance, National Institute for Health and Care Excellence (NICE) of the UK recommends

investigation of patients with microhematuria if only one is over 60 years of age with either leukocytosis or dysuria [6]. American Urological Association (AUA) guidelines suggest investigating patients over 35 years of age with ≥3 RBC/HPF [7]. European Association of Urology (EAU) guidelines recommend performing urine culture to exclude hemorrhagic cystitis and if hematuria persists, perform cystoscopy to evaluate presence of bladder cancer [8].

The preference of subsequent diagnostic protocols for individuals with microhematuria have vast clinical and economic considerations. Dipstick urinalysis is a rapid, cheap, and simple way to detect microhematuria and is also widely available [9]. At the same time, expenses on the subsequent evaluation procedures carries substantial financial burden on the public health expenses (10). Ipso facto, cystoscopy investigation and computed tomography urography methods are expensive, invasive, and distressing as well as carry the possibilities of getting infection, contrast induced nephropathy and exposure of ionizing radiation. All of which bring about health care costs as well as affect the quality of life (11). These trade-offs (malignancy risk versus damage from evaluation) need to be weighed, as it is reported that approximately 95% of microhematuria investigations were found negative for malignancy [12,13].

In addressing the uncertainty surrounding the evaluation of microhematuria, our study investigates the diagnostic value of urinalysis and cystoscopy procedures, seeking to minimize unnecessary and burdensome cystoscopies. The evolution from manual to technology-driven urinalysis prompts a reconsideration of the need for invasive investigations. By assessing the correlation between modern urinalysis results and cystoscopy outcomes, our research aims to streamline diagnostic pathways. We aspire to contribute insights that guide clinicians in judiciously allocating resources, optimizing patient care for this prevalent and clinically significant condition.

MATERIALS AND METHODS

In this retrospective case-control study, conducted at our university-based hospital, patient records spanning January 2017 to January 2022 were scrutinized following approval from the local ethics committee. The study focused on individuals diagnosed with microhematuria and subsequently subjected to cystoscopy and urine cytology. Exclusion criteria encompassed urinary tract infection, positive or suspicious urine cultures, urolithiasis, bladder pain syndrome/interstitial cystitis, pregnancy, and pre-existing bladder cancer. Urine analyses were carried out using the FUS-200 automatic urinalysis system. In our investigation, we systematically compared levels of measured hematuria between individuals with detected malignant lesions and those without. By scrutinizing this key parameter, we aim to discern any discernible patterns or significant differences that may serve as diagnostic indicators. Statistical analysis employed the SPSS software, with a significance threshold set at $p < 0.05$. Approval for the study was obtained from the Health Sciences University Istanbul Training and Research Hospital's Clinical Research and Ethics Committee.

Results

Including a total of 101 patients with a mean age of 53.06±11.56 (37% female, mean age 48.00±10.89; 63% male, mean age 55.98±10.98), our study observed lesions in 17% of cases during cystoscopy, leading to biopsy/endoscopic resection. For cases without lesions, urine cytology were sampled, revealing an inhomogeneous distribution of RBC/hpf (3-10518 RBC/hpf).

Dipstick analysis demonstrated mean RBC/hpf values of 8.93±3.78 (24.61) for RBC+, 22.08±12.30 (52.77) for RBC++, and 763.56±1993.63 (78.08) for RBC+++. Among cytologies, 1% showed atypia with normal follow-up. In patients with detected lesions, 23% had benign pathology, while the remaining 77% (13% of the cohort) exhibited urothelial carcinoma, predominantly high grade (54%) and pTa (54%), pT1 (31%), and pT2 (15%).

Male patients comprised all but one case of pT2. Levels of measured RBC/hpf across T stages and histological grades were insignificant. Median RBC/hpf levels differed significantly between cases with lesions present (77.38) and absent (45.66) (p=0.001), with a ROC analysis yielding an AUC of 0.814 (p=0.001, 95% CI 0.677-0.952). However, diagnostic value was suboptimal at lower cut-offs and appeared to be optimum within the range of 35-40 RBC/hpf.

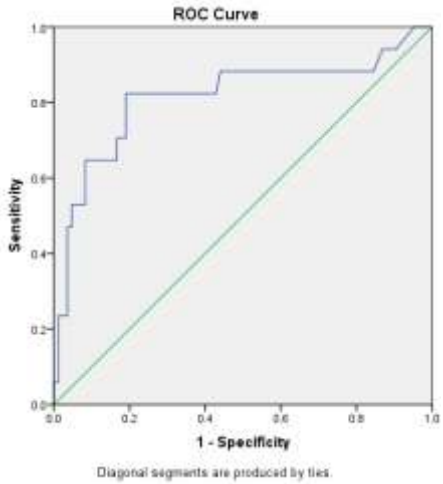

Figure 1. Receiver Operating Characteristic (ROC) curve derived from our study, depicting the diagnostic performance of measured red blood cell count per high-power field (RBC/hpf) in distinguishing between cases with and without detected lesions.

Table 1. Sensitivity and Specificity of Measured RBC/hpf in Detecting Lesions

Positive if greater than or equal to cut-off below listed	Sensitivity	Specificity
3.5	1	0.952
6.5	0.882	0.845
35.5	0.824	0.214
37.5	0.824	0.202
40.5	0.824	0.19
42.5	0.706	0.19

DISCUSSION

Among the possible etiologies for microhematuria, studies suggest that the presence of three or more RBC/HPF on a single urine microscopy is associated with malignancy in 2.3% to 5.5% of patients [2-5]. In examinations made for the detection of hematuria; peroxidase activity for erythrocytes is determined using benzidine and it might give false results in the presence of factors such as a urine sample not taken under appropriate conditions, dehydration, use of povidone iodine, high-dose vitamin C intake, and myoglobinuria [2]. Also, detection of microhematuria before it transforms into macrohematuria might help reveal patients at an earlier stage of malignancy and at that point, approximately 40% of individuals with bladder cancer are diagnosed with an advanced state of disease which is not suitable for the curative management [14,15]. Despite the higher the level of microhematuria is known to be related with an elevated malignant entity rate as a result of the assessment, it has been suggested that setting the cutoff threshold more than three RBC/HPF would result in occult numbers of unnoticed diagnostic opportunities.

Two prospective studies suggest that screening of hematuria in asymptomatic patients is associated with lower stage malignancy at the time of diagnosis hence it might improve survival [16,17]. Moreover, a multicentric study of individuals who were diagnosed with bladder cancer suggests that those who initially presented with microhematuria had a lower muscle invasive bladder cancer rate than those who initially presented with macrohematuria [14]. Since approximately 95% of microhematuria examinations are reported to be negative for malignancy, it is essential to consider its cost-effectiveness, considering the financial burden on the health care system [13]. AUA guidelines strongly suggest that clinicians shouldn't diagnose microhematuria solely with the dipstick urinalysis. A microscopic evaluation of the urine should always be performed after a positive dipstick urinalysis [7].

In this modern quantitative appraisal, we seek to elucidate the certainty of urinalysis in distinguishing the origin of microhematuria, particularly in cases of unknown etiology. Our focus aims to provide a comprehensive understanding of the specificity of urinalysis as a diagnostic tool. Crucially, our investigation addresses the ongoing debate surrounding the necessity of subsequent cystoscopy examinations in cases of microhematuria by delving into the specificity of urinalysis, our study endeavors to offer clinicians a refined decision-making framework. The goal is to identify those cases where further invasive procedures, such as cystoscopy, may be avoided without compromising diagnostic accuracy. The multifaceted nature of microhematuria, encompassing its potential as an early indicator of malignancy and the challenges posed by false results in various conditions, necessitates

a nuanced approach to diagnostic decision-making. Our study, grounded in contemporary evidence and methodologies, seeks to bridge gaps in current knowledge and inform a more tailored and cost-effective strategy for managing patients with microhematuria.

In concert with our research, the evolving landscape of diagnostic technologies is evident in recent publications that explore novel approaches to improve the accuracy of microhematuria assessment. Notable studies have investigated the role of advanced imaging modalities, such as contrast-enhanced ultrasound and multiparametric magnetic resonance imaging, in enhancing the sensitivity and specificity of diagnostic evaluations [18].

Moreover, ongoing research has delved into the molecular and genetic markers associated with urological malignancies, seeking to refine risk stratification and personalize diagnostic algorithms [19]. These emerging frontiers in urological research hold promise for the future of microhematuria evaluation.

More studies on a large, diverse population might yield even greater benefits. In addition, we show that the overall accuracy of dipstick urinalysis for the diagnosis of microhematuria is similar comparing to microscopic evaluation of the urine specimen and also it is strongly related with the degree of microhematuria. Nonetheless, the choice of dipstick urinalysis as a screening method to assess microhematuria is still insufficient due to its minor sensitivity compared to the microscopic evaluation.

This retrospective single-center study, encompassing 101 patients, exhibits certain limitations inherent to its design and data sources. The reliance on historical records introduces the potential for biases in accuracy and completeness, given the retrospective nature of the investigation. Furthermore, the relatively modest sample size may constrain the generalizability of findings to broader populations. The application of specific exclusion criteria, notably for conditions like urinary tract infections, raises concerns about the possibility of selection bias influencing the external validity of the study. The use of the newer automated urinalysis system, while technologically advanced, brings into consideration the variability introduced compared to traditional manual methods. The absence of long-term follow-up data restricts insights into the dynamic nature of microhematuria and the trajectory of underlying pathologies over time. Non-uniformity in cystoscopy procedures and incomplete clinical history within hospital records contribute to potential biases, emphasizing the importance of interpreting findings with caution. Recognizing and transparently discussing these limitations is fundamental for appropriately contextualizing the study's outcomes and informing future research endeavors to address these constraints comprehensively. Also lack of information about smoking status of patients which is a major risk factor for BC. In addition, we only considered bladder cancer; therefore, hematuria might be associated with many other benign or malignant diseases. In an epoch where cancer-related deaths from bladder cancer have not changed and health care costs are increasing, it should be reassessed who will undergo cystoscopy in cases with microhematuria of unidentified etiology in urinalysis.

CONCLUSION

In conclusion, our study contributes valuable insights into the specificity of urinalysis in cases of microhematuria, navigating the complex interplay between diagnostic thoroughness and cost-effectiveness. The integration of our findings with the broader scientific landscape underscores the dynamic nature of urological research and the ongoing quest for refined diagnostic strategies to enhance patient outcomes. Also, there is still a need for up-to-date, evidence based recommendations of guidelines in the assessment of the patients with microhematuria that restrict unnecessary risk and expense of over-evaluating individuals at a lower risk for malignant processes while on the other hand, distinctly defines clinical framework in which entails further investigation so that there is no delay in the diagnosis of occult disorder.

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