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CT Evaluation of Hematuria in Adults Younger Than 50 Years in Military Service: Is Contrast-Enhanced Phase Needed?

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Abstract: Key Points :1. **Diagnostic Efficacy of Unenhanced CT**: The study reveals that unenhanced CT can detect 91% of clinically significant findings in young military personnel with hematuria, suggesting it may be sufficient as a first-line evaluation, reducing the need for contrast-enhanced phases.2. **Low Incidence of Malignancy**: AmoFng patients under 50, no cases of urinary malignancy were detected, reinforcing the idea that invasive contrast-enhanced imaging may be unnecessary in this low-risk population.3. **Selective Use of Contrast**: The study shows that contrast-enhanced imaging was required in only 5.4% of cases, primarily for benign conditions, supporting a more targeted use of contrast phases in specific clinical scenarios.

Keywords: hematuria; CT; urography; military; young adults

Introduction

Hematuria is a common urologic finding in adults, with an estimated prevalence of 2.5%-38.7% in population-based screening studies [1,2]. It may be visible to the naked eye (macroscopic hematuria) or microscopic, defined as the presence of more than 3 red blood cells per high power field in the urine.

Potential causes range widely, including renal calculi, infection, trauma, renal parenchymal disease, recent instrumentation, prolonged exercise, drug toxicity, coagulopathy, and neoplasm [3]. However, hematuria is often a benign incidental finding, and the etiology remains unknown in 70% of patients. Urinary malignancy is detected in only 0.4-3.4% of patients [4–6].

The American Urological Association and the American College of Radiology recommend computed tomography urography (CTU), in addition to cystoscopy of the urinary bladder and urine cytology, as the modality of choice for evaluating new-onset microhematuria in adults, with no age stratification [7,8]. Chlapoutakis et al. [9], in a meta-analysis of CTU for the detection of urothelial malignancy, confirmed its high sensitivity and specificity relative to intravenous pyelography, but several studies have reported limited diagnostic benefit over unenhanced CT in younger adults <50 years) with asymptomatic hematuria [10–12]. Furthermore, given the increased risk of CTU posed by radiation and need for iodine contrast injection, the Dutch Association of Urology recommended that ultrasound should serve as the study of choice in young adults in whom the incidence of urinary malignancy is quite low [12,13].

Nevertheless, there are adult patient groups at high risk of urinary malignancies compared to the general papulation, such as military veterans who may be exposed to such potential carcinogens as metallic materials, aircraft machines, and certain toxic materials associated with urinary malignancy [10,14]. Sohn et al. [15] found that the rates of kidney and bladder cancer increased by 35% and 33%, respectively, in US military veterans over a 3-year period. In addition, smoking is the most significant risk factor for urinary malignancies [14], and according to a study of 30,000 Israel

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Defense Forces (IDF) soldiers from 1987 to 2017 by Zarka et al. [16], active smoking increased by 39% during compulsory military service, from 26.2% at recruitment to 36.5% at discharge.

The purpose of the present study was to compare the diagnostic yield of CTU with unenhanced CT in soldiers less than 50 years old with hematuria.

Materials and Methods

Patients

The study was conducted in accordance with the Helsinki Declaration and approved by the local Institutional Review Board of the Chief Medical Corps of the IDF, which waived the need for informed consent.(IRB 322016)

The study group consisted of 277 consecutive patients younger than 50 years in active military service in the IDF who were diagnosed with new-onset hematuria by a military urologist between January 2011 and March 2020 and referred to our CT unit for evaluation of the upper urinary tract. Exclusion criteria were age more than 50 years, history of nephrolithiasis, history of urological malignancy, and recurrent urinary tract infections.

CTU Protocol

CT procedures were performed using a 64-slice multidetector scanner (Brilliance-64, Philips Medical Systems, Best, The Netherlands) with the following specifications: tube voltage 120 Kv, quality reference tube current–time-product 100 mAs, pitch, 0.9. Scans were obtained under inspiratory breath-hold in the cranio-caudal direction. Collimation was 64 x 1.5 mm, and reconstruction slice width was 3 mm. The CT protocol was done without oral contrast or bowel preparation. Injection of 100 ml of nonionic contrast agent (Ultravist 300; Schering, Berlin, Germany) into the antecubital vein was performed at a rate of 3-4 ml/sec using a dual-head automatic injector (Stellant; Medrad, Warrendale, PA) and 30 ml saline flush. Thereafter, 3-mm reconstructed axial images were acquired in three phases: non-contrast phase (plain series of the total abdomen and pelvis, nephrographic phase (after 110 seconds), and excretory phase (after 10 minutes). Coronal and sagittal reconstruction images were forwarded to a picture archiving and communication system (PACS).

Image Analysis

All examinations including axial and multiplane reconstructions were reviewed on the PACS workstation by one of two board-certified abdominal radiologists with 10 years' experience (C.E., T.I). The radiologists were blinded to the patients' clinical histories but were aware that the purpose of the imaging study was initial evaluation of hematuria. For each study, the reader first interpreted the unenhanced images and recorded all urological and other findings. The reader then reviewed the nephrographic and excretory phases with a different window level for evaluation of the renal parenchyma, calyces, and collecting system ureters and recorded all urological findings. Findings detected only on contrast-enhanced images were tabulated as such. If no urological finding was detected on both the unenhanced examination and the enhanced series, the study was evaluated by a third board-certified abdominal radiologist (B.N.G.) with 20 years' experience (the adjudicator) who was also blinded to the clinical interpretation and the clinical history of the patient. The adjudicator characterized any findings visible on non-contrast CT alone or requested the contrast-enhanced images.

Diagnosis

Demographic variables (age, sex), medical history, reason for referral, pathology tests, radiological evaluation including ultrasound and MRI, further urologic work-up (cystoscopy, ureteroscopy, and biopsy), and final diagnosis were recorded for each patient in an electronic

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database. In cases of a negative work-up, clinical follow-up consisting of review of the patient's medical records was performed to determine if urinary tract abnormalities were ultimately diagnosed.

Results

The study group consisted of 277 consecutive patients with new-onset hematuria, 229 men (82.7%) and 48 women of mean age 30.44±10.3 years, as shown in Table 1. Micro-hematuria was diagnosed in 270 and macro-hematuria in 7. The mean duration of follow-up was 40 months (range 6-86 months).

Positive CTU findings were recorded for 119 patients (43.0%) and negative findings for 158 (57.0%) (Table 2). None of the patients had a urological malignancy.

Among the CTU-positive patients, 46 (16.6%) had clinically significant findings that required treatment (Table 2). In 42 patients (91%), the findings were detectable on the unenhanced images. They included mainly urinary tract calculi: renal (n=32), ureteral (n=4), and bladder (n=1). In one of these patients, a pre-sacral multi-lobulated 5*4 cm mass consistent with tail-gut duplication cyst was detected, and in another, with microscopic hematuria, a 3 mm polyp resected by cystoscopy was found to be consistent with inverted papilloma of the urinary bladder. In the remaining 4 patients, the significant positive findings were detected on the contrast-enhanced images only. Three of these patients, all with recurrent microscopic hematuria and flank pain, had a striated nephrogram caused by pyelonephritis and were treated with antibiotics. On follow-up, cystoscopy and magnetic resonance scan were normal. The fourth patient, aged 35 years, had undergone nephrectomy due to a posterior urethral vale in childhood. CT demonstrated hydronephrosis and hydroureter, and contrast-enhanced CT showed reflux.

Another 21 patients had clinically significant findings that required observation only. Two had atrophic kidneys and 2 had hyperdense complicated cysts, enhanced on CT, that were consistent with hemorrhagic cyst (Bosniak 2F); these patients were followed with magnetic resonance imaging for 5 years. In 3 patients, a thickened and trabeculated bladder wall was detected on excretory phase images but was not apparent on unenhanced images, when the bladder was under-distended. Cystoscopy was normal in all cases. Two patients had a thickened and enhanced distal ureter with normal findings on ureteroscopy. Left uretrocele was detected in one patient with polycystic kidney disease, and one patient had a thickened appendix (up to 13 mm) with peri-appendicular straining. She was diagnosed with appendicitis and treated conservatively (Table 1).

Contrast images were requested by the readers in 15 cases (5.4%) in order to confirm and characterize benign findings. They included pyelonephritis, trabeculated and thickened bladder wall, and renal scar (n=3 each); renal complicated cyst (Bosniak 2F) and thickened and enhanced distal ureter (n=2 each); and tail-gut duplication cyst and reflux in a single kidney (n=1 each).

Clinically insignificant findings were detected in 67 patients: benign renal cortical cyst, in 29 patients (21 Bosniak 1, 6 Bosniak 2, 1 Bosniak 2F), all seen on unenhanced images, in addition to a double collecting system in 12 (unilateral in 10, bilateral in 2), uretro-pelvic junction obstruction in 12, also detected on unenhanced images, and prostate enlargement (benign prostate hypertrophy) in 3. Urachal diverticulum, urachal cyst, urachal sinus, pelvic kidney, and horseshoe kidney with uretero-pelvic junction obstruction were each detected in one patient on unenhanced images.

An adverse reaction to intravenous iodinated contrast material occurred in 2 of the 277 patients (0.7%), manifested as rash and shortness of breath.

The CT scanner recorded the effective radiation dose to which patients were exposed. The mean dose per patient was 18-25 mSv.

Discussion

This study sought to determine if the concerns regarding the appropriateness of CTU for adults aged less than 50 years with hematuria raised by the Dutch Association of Urology [12,13] and others

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[11,17] also hold true for members of this age group with particular risk factors for urinary malignancy.

CTU has been found beneficial for evaluation of the urinary tract in adults with persistent hematuria and is recommended for this purpose by the American College of Radiology [8]. In 2010, Chlapoutakis et al. [9] reviewed and analyzed the published literature and found CTU to have a pooled sensitivity of 96% and specificity of 99% for the detection of urothelial malignancies. Chow et al. [18], in a study of 500 adult patients, reported corresponding rates of 100% and 99%, with positive and negative predictive values of 80% and 100%, respectively. However, when the population was restricted to adults younger than 50 years with asymptomatic hematuria and no risk factors, two studies found that although CTU had diagnostic benefit, unenhanced CT alone could serve as an efficient diagnostic modality [3,11]. Yet neither study assessed the added value of CTU in high-risk young adults.

In the present study, CTU was used to evaluate patients aged 18 to 50 with hematuria in active military service and hence at increased risk of urologic malignancies due to occupational exposure [10]. Moreover, running and strength training are common military practices, and many studies have shown a link between intense exercise and hematuria. Siegel et al. [19] found that 18% of 50 marathon runners with normal pre-race samples had microscopic hematuria, and Jones et al. [20] reported a 90% rate of post-workout hematuria in middle-distance track athletes. In a retrospective study of 1000 young (age <40 years) military servicemen in the Israel Air Force, Froom et al. [21] found a 38% prevalence of asymptomatic hematuria over a 15-year period.

In the present study, more than half the evaluated patients with hematuria had no upper urinary tract abnormalities on CT study. This high rate of negative findings is in accordance with other studies [2,10,11] and is probably a consequence of the young age of the patients and the likelihood of exercised-induced hematuria. It suggests that CTU may be inappropriate as the first-line investigation of asymptomatic hematuria in this population because it may expose healthy young adults to unnecessary radiation and contrast medium.

Furthermore, among the total 119 patients (43.0%) who had a positive urological study, the findings were clinically insignificant in 73 (61.3%), consisting of benign renal cortical cyst, double collecting system, and uretero-pelvic junction obstruction. All insignificant findings were detected on unenhanced CT scans. The remaining 46 patients (16.6%) had clinically significant findings, mainly renal or ureteral calculi, also detected on unenhanced CT scans. Contrast images were requested by the readers in only 15 cases (5.4%) in order to confirm and characterize benign findings, including pyelonephritis, renal complicated cysts, thickened and trabeculated bladder wall, renal scar, thickened and enhanced distal ureter, tail-gut duplication cyst (1 patient) and reflux in a single kidney (1 patient).

Given that the majority of clinically significant and insignificant findings in our study were evident on unenhanced images, we suggest that most young adults with hematuria may be optimally evaluated with unenhanced CT, reserving CTU for patients with persistent hematuria or other predisposing conditions.

Importantly, we found that in none of the subjects with hematuria did CTU detect renal cell or urothelial carcinoma. This low rate is in line with the results of Mace et al. [10] in 137 patients younger than 50 years with new-onset hematuria who had a history of military service. Similarly, Mishriki et al. [22], in a prospective study, found no malignancies in 292 patients in the same age group referred for evaluation of asymptomatic microscopic hematuria and followed for 13 years. According to epidemiologic studies, the average age at diagnosis of urological malignancy is 65 years [10], suggesting that older age (more than 50 years) is a risk factor [2,10] for cancer-associated hematuria.

Young age may also explain the lack of urological malignancy in the 7 patients (2.7%) with gross hematuria, a significant risk factor for urological malignancies and life-threatening disease. In a retrospective study of 1209 patients with hematuria, Song et al. [23] found an eightfold increase in malignant diagnoses in those with gross hematuria (18.4%) compared to those with microhematuria (2.3%). Similar findings were also reported by others [24,25].

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Radiation-induced cancer rates in the medical literature vary widely. According to some studies, approximately 1.5-2% of all cancer cases in the US are attributable to radiation [26]. In addition, CTU studies include multiple phases requiring an increased radiation dose, which has been reported as 25-35 mSv compared to 3-10 mSv for a single unenhanced CT study [23,27]. A low-dose unenhanced technique can further reduce radiation to 1.4-2.1 mSv [2,28]. In the present study, had CTU not been used, 95% of patients (262/277) would have been spared a mean effective radiation dose of 25-35 mSv, or a total of 6550 mSv for the whole study population.

An adverse reaction to intravenous iodinated contrast material was documented in 2 of our 277 patients (0.7%), manifested as rash and shortness of breath. The estimated risk ranges from 0.3% to 1.6%, with reported manifestations including hives, bronchospasms, laryngeal edema, contrast-induced nephropathy, and even death [2,29].

Overall, only 16.6% of our patients had clinically significant findings warranting follow-up or treatment. Thus, in 83%, the performance of CTU not only had no clinical impact on patient well-being but may also have had adverse medical and financial repercussions. In a retrospective study of 778 CTUs performed over a 3- year period, Bromage et al. [30] found that 56% yielded extraurinary findings and only 15% were clinically relevant. As a consequence, patients attended outpatient appointments and underwent radiological examinations and other high-cost procedures, most of which were unnecessary or not clinically beneficial [31].

Overall, our findings raise the question of whether CTU is the optimal modality for the evaluation of young adults with hematuria. This patient population has a low likelihood of malignancy and a high prevalence of urinary tract calculi. This is especially true for individuals in active military duty among whom exercise-induced hematuria is not uncommon. In terms of the imaging modality, CTU poses increased risks of radiation-related complications, allergic reaction to contrast medium, and contrast extravasation and nephropathy. These can be avoided by using non-contrast low-dose CT or ultrasound. Accordingly, ultrasound is recommended as the primary imaging modality for evaluation of hematuria by the European Society of Urogenital Radiology in patients younger than 40 years [32] and by the Dutch Association of Urology in patients younger than 50 years [13].

This study has several limitations. The study was performed in a single center using a retrospective design and was based on data only from patients who underwent CTU because of asymptomatic hematuria. Furthermore, although the follow-up period was sufficiently long (40 months), we have limited long-term follow-up in-patient whose CTU examination was normal.

In conclusion, we found that non-contrast CT may be more appropriate than CTU as the first line investigation examinations for the evaluation of asymptomatic hematuria in patients younger than 50 years, including those in military service.

Compliance with ethical standards.

Funding: No funding was procured for this work.

Ethical approval: Institutional Review Board approval was obtained.

Conflicts of Interest: The authors of this manuscript have no conflicts of interest to declare.

Abbreviations

CT	Computed tomography
CTU	CT urography
IDF	Israel Defense Forces
PACS	Picture archiving and communication system

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