Original article

Predictive Value of Ultrasound in the Detection of Complications After 1 Hour of Renal Biopsy.

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ABSTRACT

Introduction: Renal biopsy became a standard technique in diagnosing renal diseases. It had many complications in the past being performed blindly. But since the presentation of ultrasound-directed renal biopsy in the field, the procedure became much safer with less complication rate and better yield.

Aim of the study: In this work, we aim to assess the capability of ultrasound examination to detect early complications after one hour of renal biopsy and predict the course of cases.

Methods: This is a prospective study performed during the period from October 2017 to the end of March 2018, and included cases experiencing Percutaneous Renal Biopsy in the Pediatric Nephrology Unit at Cairo University Children's Hospital.

Results: The present work enrolled 60 patients; 29-male (48.3%) and 31-female (51.7%); their mean weight was 24.2 kg, with a mean age of 89.3 months. Out of 60 patients who performed the biopsy, only 21.6% had complications. We detected two cases with subcapsular hematomas (3.3%), another 2 cases with bladder hematoma (3.3%), 9 cases with back pain (15%) and gross hematuria (as a complication, not related to original disease) occurred in 6 cases (10%). We found that the sensitivity of ultrasound is 66.6% in the first hour after renal biopsy with 98.3 % specificity to possible bleeding complications with 66.6% positive predictive value (PPV) and 98.2% negative predictive value (NPV). However clinical presentation was the only predictor in one case for complication which was detected late by ultrasound.

Conclusion: Our study suggests that combined ultrasound and clinical examination in the first hour after renal biopsy is the best indicator of postrenal biopsy complications.

Keywords: renal biopsy- complications- ultrasound- nephrology- hematoma

Running title: Predictive value of ultrasound in the detection of complications after 1 hour of renal biopsy.

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geget : The Journal of the Egyptian Society of Pediatric Nephrology and Transplantation (ESPNT)

geget https://geget.journals.ekb.eg/

Published by ESPNT http://espnt.net/

Cohosted by Egyptian Knowledge Bank https://www.ekb.eg

INTRODUCTION

Since the introduction of renal biopsy in the 1950s, developments were performed in the biopsy method to upgrade diagnostical outcomes while lessening complications and it has been the golden standard method in diagnosing and managing many conditions [1].

A renal biopsy is a process utilized to get a segmental sample of renal tissues, frequently using a needle or another operative device. Pathological analysis of these tissues is then utilized in diagnosing renal conditions [2].

Nevertheless, renal biopsy may result in major complications like hematoma (either perinephric or bladder) and profuse hemorrhage with the resulting necessity for blood transfusion, further operations like nephrectomy, and infrequent, mortality [3].

US-guided renal biopsy is frequently utilized but not yet commonly used as a standard technique. Findings of a multicenter report done on behalf of the British Association of Pediatric Nephrology highlight the necessity of protocol recommendations for renal biopsies that permits comparison of success and complications [4].

Waldo and colleagues noted that the absence of perinephric bleeding by renal ultrasonography one hour post-biopsy is predictive of an uncomplicated course, while the presence of a perinephric haematoma is not reliably predictive of a clinically significant complication post-renal biopsy [5].

Our work aimed to assess the predictive value of ultrasound in the detection of complications one-hour post-biopsy to minimize hospital stay after renal biopsy.

METHODS

This prospective study was performed using the data obtained from 60 children between the age of 6 months till 13 years old who underwent percutaneous renal biopsy of the innate and transplanted kidneys in the pediatric nephrology unit (PNU) at Cairo University Children's Hospital in October 2017 till March 2018.

Ethics: A knowledgeable agreement was attained from the cases' guardians previous to the registration with clarification of the kind of research. Agreement of ethical committee of Faculty of Medicine, Cairo University has been gotten.

Patients' inclusion criteria: Children under 13 years old who underwent renal biopsy at the pediatric nephrology department who are diagnosed with unexplained renal failures, acute nephritic condition, nephrotic syndrome (either in 1st year of life or SRNS), isolated glomerular hematuria, isolated non-nephrotic albuminuria, renal masses (primary or secondary), renal transplant rejections, post transplantation protocol biopsy and connective tissues conditions (e.g., systemic lupus erythematosus (SLE).

Exclusion criteria: Age over 13 years old or below 6 months, Uncontrolled severe hypertension, bleeding disorder, active renal or perirenal infections, skin infections at biopsy location, un-cooperative case, anatomic abnormalities of the kidney which may increase risk of complications (e.g., horseshoe kidneys, hydronephrosis), small atrophic kidneys and solitary kidney.

Prebiopsy preparation: Relevant history details of all included patients were taken in the form of age, sex, weight, clinical diagnosis, history of hypertension, history of medications including antihypertensives, history of hematuria, history of edema, the indication of renal biopsy was revised with the ordering physician, thorough physical examination of the included patient & blood pressure was measured. **Informed consent:** An appropriate informed consent is obtained from parents where all possible complications are explained.

Laboratory results were collected in the form of CBC (hemoglobin, platelet count), coagulation profile "PC", bleeding time, and chemistry (serum creatinine, BUN, Albumin).

Biopsy procedure: Personal and machine: The renal biopsy is performed by expert pediatric nephrologists guided by real-time ultrasound Siemens machine with a 3500 kHz convex transducer, equipped with a biopsy adapter with a needle director **[Figure 1a]**, a semi-automated, spring loaded, 18 gauge biopsy needle was used **[Figure 1b]**. Patient preparation: adequate intravenous access is established, being anxious and uncooperative, patients took either anxiolytics (midazolam or ketamine) or local anesthetic (subcutaneous zylocaine) or both. Position: patient was placed prone for native kidney biopsy while supine for the graft one. Procedure: overlying skin sterilization by povidone iodine solution, real time ultrasonography is used to guide the biopsy needle directly into the lower pole (at which the risk of puncturing a major vessel is minimized).

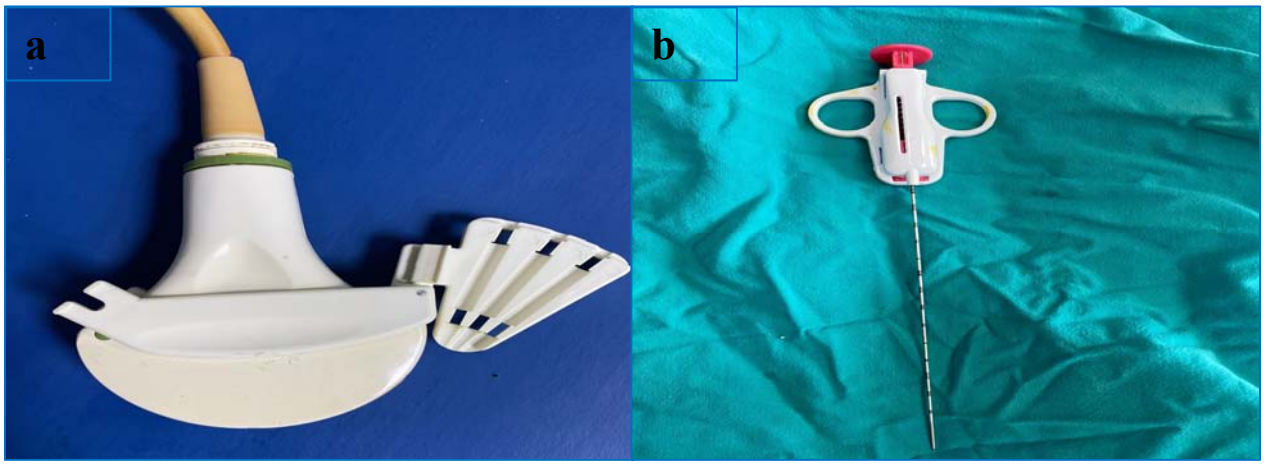

Figure 1: a: Convex transducer, equipped with a biopsy adapter with a needle director
b: 18 gauage biopsy needle.

One hour after renal biopsy

After one hour of PRB, the nephrologist performed an ultrasound using a Sony ultrasound machine in the PNU with a 3.5 MHz convex transducer. The kidney on the biopsy site and the urinary bladder were examined for any perinephric collection, subcapsular or bladder hematoma as follows: In case we found a subcapsular hematoma, we measure its size and monitor closely the vital signs and progression of the other complications as flank pain or signs of bleeding as hematuria and a CBC post-biopsy is done.

And a follow-up ultrasound is performed daily to make sure its size is stationary or reducing: In case a urinary bladder hematoma is found; we measure its size and the patient is admitted for labs (CBC withdrawal) and urinary bladder irrigation every 6 hours with sodium bicarbonate (NaHCO3) and saline (2 ampoules of NaHCO3 for every 500 ml saline) through a urinary foley's catheter. In case of hematuria only without any other association; we advise the patient to drink plenty of water to get more urine, if it is getting clear, then we may discharge, if hematuria is getting darker then a CBC is done for possible hemoglobin drop. In case of flank pain without another association, we may prescribe an analgesic in the form of paracetamol oral.

We defined complications as a major complications when needed intervention (e.g. blood transfusion or urinary bladder irrigation) and minor complications for others who needed no intervention. Uncomplicated cases were discharged after 4 hours of observation without any further labs or any additional home treatment and were advised to contact us if any warnings occur after discharge and no complications reported in them the next few days post biopsy.

Statistical analysis

Quantitative data have been introduced as mean ± SD and range values. Qualitative data have been introduced as frequency (n) and percent **(%)**. Association analysis was done using Pearson-Spearman correlation tests. Accuracy, sensitivity, and specificity of ultrasound were done as well. All these tests were used as tests of significance at $P \leq 0.05$. Statistical analysis has been done via windows-based IBM SPSS v-23.

RESULTS

This was prospective observational research performed during the period from October 2017 to the end of March 2018 and included sixty cases who experienced a Percutaneous Renal Biopsy in the Pediatric Nephrology Unit at Cairo University Children's Hospital.

As shown in **(Table 1)**, indications of the renal biopsy were variable but the most common among our patients was nephrotic patients (38.3 %, n=23), including 21.7% (n=5) who were indicated for biopsy due to nephrotic range proteinuria in the first year of life (i.e., congenital and infantile nephrosis), and 78.2% (n=18) who were indicated for biopsy due to steroid-resistant nephrotic syndrome (SRNS). Post-transplant cases involved in our study constituted 21.6% (n=13) of all cases, where 84.6% (n=11) were indicated for biopsy due to graft dysfunction and 15.3% (n=2) were among biopsy protocol (to detect subclinical rejection). Renal involvement in systemic disease was present in (11.6%, n=7) including (28.5%, n=2) as Juvenile Rheumatoid Arthritis (JRA) and (71.4%, n=5) as SLE referred from rheumatology clinic.

Prothrombin concentration and bleeding time were performed for all the patients. Both were found within the normal range in all studied patients with a mean prothrombin concentration of 94.8 % and a mean bleeding time of 1.4 minutes. Mean BUN was 41.2±29.2 (11-108) mg/dl while mean creatinine was 1.1±0.7 (0.4-2.8) mg/dl. 31 cases (51.7%) were known to be hypertensive controlled on antihypertensive medications. In 58.3% of cases (n=35)

kidneys were enlarged according to age, no small-sized kidneys were involved in the study. 73.4% (n=44) had increased echogenicity and only 1.7% (n=1) had poor differentiation by US examination; however, both findings were not found to be correlated with any complication.

One puncture was sufficient to get a core in 53.3% (n=32), whereas 31.7% (n=19) required 2 punctures, 10% (n=6) had 3 punctures, while 5% (n=3) required more than 3 punctures.

Out of 60 patients who performed the biopsy, only 21.6% (n=13) had complications. We detected two subcapsular hematomas (3.3%), another 2 cases with bladder hematoma (3.3%), 9 cases with back pain (15%) and gross hematuria (as a complication, not related to original disease) occurred in 6 cases (10%), **(Table 2)**.

Ultrasonography one hour post biopsy detected one case with subcapsular hematoma and 2 cases with bladder hematoma **(Figure 2 a & b)**, while one case of subcapsular hematoma detected when ultrasonography repeated after 3 hours when the patient clinically suspected to have hemoglobin drop and CBC show hemoglobin drop 2.1 gm **(Table 3)**. No statistically significant difference was found between the patients with subcapsular hematoma detected by U/S early (in the 1st hour) and those who was detected later on by the US. The Sensitivity of the U/S examination in detecting major complications was found to be 66.7% with the NPV at 98.2%, specificity of the U/S examination was 98.2%, and PPV at 66.7%.

Correlation analysis to determine the factors significantly correlated with post-procedure complications in studied patients showed no statistically significant correlation between complication incidence and hypertension. A statistically significant correlation was found between the presence of vasculitis (SLE cases) and the incidence of subcapsular hematoma (r = + 0.442). A statistically significant correlation was found between age and weight and the incidence of hematuria (r = - 0.363).

Correlation analysis to determine the factors significantly correlated with post-procedure complications in studied patients showed no statistically significant correlation between complication incidence and BUN. A statistically significant correlation was found between creatinine level and incidence of subcapsular hematoma as well as back pain with a higher correlation index (r = + 0.283).

Correlation analysis to determine the factors significantly correlated with post-procedure complications in studied patients showed a statistically significant correlation between platelet count and hematuria (r = - 0.361). A statistically significant correlation was found between prothrombin concentration and back pain (r = - 0.300).

Correlation analysis to determine the factors significantly correlated with post-procedure complications in studied patients showed a statistically significant correlation between the number of core punctures and back pain (r = - 0.283).

Table 1: Indications of renal biopsy in studied patients

Indications	Studied patients N=60 (100%)
Nephrotic syndrome **(n, %)**[a]	23 **(38.3)**
Nephritis **(n, %)**	6 **(10)**
Chronic kidney disease **(n, %)**	3 **(5)**
Post-transplant **(n, %)b**	13 **(21.6)**
Recurrent gross Hematuria **(n, %)**	4 **(6.6)**
Persistent asymptomatic Proteinuria **(n, %)**	2 **(3.3)**
Unexplained AKI	2 **(3.3)**
Renal involvement in a systemic disease [c]	7 **(11.6)**

[a]: Including 5 cases with nephrotic syndrome in the 1st year of life &18 cases with steroid resistant nephrotic syndrome.

[b]**:** Including 11 cases with graft dysfunction and 2 cases among post transplantation protocol biopsy.

[c]**:** Including 2 cases with juvenile rheumatoid arthritis and 5 cases with systemic lupus erythromatosis

Table 2: Descriptive data of each one of the complicated cases (n=13):

Patient's no.	Back pain	Gross hematuria	Subcapsular hematoma	Urinary bladder hematoma	Hemoglobin drop	Intervention needed
No. 3	Yes					
No. 5	Yes	Yes		Yes 23x25mm	1.5 gm	Bladder irrigation
No. 8		Yes				
No. 11	Yes					
No. 18	Yes	Yes		Yes 31x15mm	2 gm	Bladder irrigation
No. 22*	Yes		Yes 56x28mm		2.1 gm	Blood transfusion
No. 24	Yes					
No. 32		Yes				
No. 35	Yes					
No. 38	Yes		Yes 47x23mm		1.2 gm	
No. 39		Yes				
No. 52		Yes				
No. 55	Yes					

*: a case whose subcapsular hematoma detected by late ultrasound (after 3 hours)

Table 3: Results of complications detected by U/S examination of all cases

Patient data	Early US detection (n= 60) (100%)	Late US detection (n = 60) (100%)	P – VALUE*
Hematoma by U/S			
Detected (n, %)	3 **(5)**[a]	1 **(1.7)**[b]	0.625
No hematoma (n, %)	57 **(95)**	59 **(98.3)**	

*: Significance at $P \leq 0.05$, [a]**:** 2 cases with urinary bladder hematoma (23x25mm, 31x15mm) and one case with subcapsular hematoma (47x23), [b]: case with subcapsular hematoma (56x28mm).

Table 4: Results of major complications detected by U/S examination

Patient data	Patient with no major complication (n = 57) (100%)[a]	Patient with major complications (n = 3) (100%)[b]
Normal US (n, %)	56 **(98.2)**	1 **(33.3)**
Detected hematoma by US (n, %)	1 **(1.8)**	2 **(66.7)**

[a]**:** cases who need no intervention, [b]**:** cases who need intervention (blood transfusion or bladder irrigation)

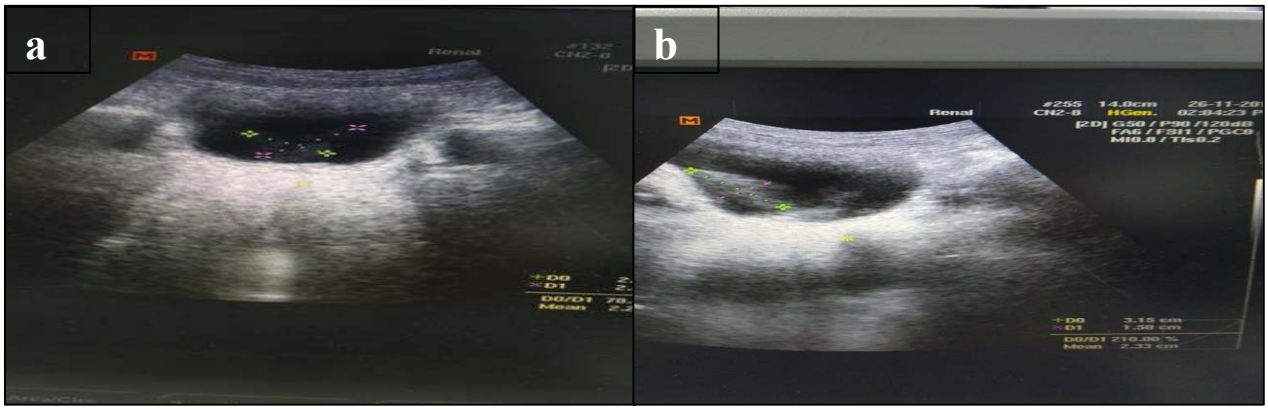

Figure 2 a : urinary bladder hematoma in patient no. 5 measuring 23x25mm
b : urinary bladder hematoma in patient no. 18 measuring 31x15mm

Table 5: Person-Spearman correlation between the demographic and clinical data and incidence of complications detected in patients

	Hematuria	Subcapsular hematoma	Bladder hematoma	Back pain
Age				
p-value	0.004	0.500	0.599	0.112
R	-0.363	-0.089	+0.069	+0.207
Weight				
p-value	0.014	0.391	0.815	0.815
R	-0.317	-0.113	-0.031	+0.032
Hypertension				
p-value	0.105	0.142	0.523	0.240
R	+0.211	-0.192	-0.084	-0.154
Vasculitis[a]				
p-value	0.286	0.000	0.370	0.098
R	-0.140	+0.442	+0.118	+0.216

*: Significant at $P \leq 0.05$, **[a]:** SLE cases.

Table 6: Person-Spearman correlation between the kidney functions and incidence of complications detected in patients

	Hematuria	Subcapsular hematoma	Bladder hematoma	Back pain
BUN				
p-value	0.094	0.355	0.252	0.588
R	+0.218	+0.122	+0.150	+0.071
Creatinine				
p-value	0.160	0.041	0.355	0.029
R	+0.184	+0.265	+0.127	+0.283

*: Significant at $P \leq 0.05$

Table 7: Person-Spearman correlation between the platelet count and prothrombin concentration and incidence of complications detected in patients

	Hematuria	Subcapsular hematoma	Bladder hematoma	Back pain
Platelet count				
p-value	0.005	0.417	0.773	0.797
R	-0.361	-0.107	+0.038	-0.034
Prothrombin concentration				
p-value	0.761	0.383	0.606	0.020
R	-0.040	-0.115	-0.068	-0.300

*: Significant at $P \leq 0.05$

Table 8: Person-Spearman correlation between the number of punctures and the incidence of complications detected in patients

	Hematuria	Subcapsular hematoma	Bladder hematoma	Back pain
Number of punctures				
p-value	0.212	0.298	0.424	0.138
R	-0.163	+0.137	+0.105	+0.194
Core punctures				
p-value	0.192	0.116	0.425	0.029
R	-0.171	+0.205	+0.105	+0.283

*: Significant at P ≤ 0.05

DISCUSSION

Renal biopsy became a standard technique in diagnosing renal diseases that cannot be outlined by laboratory and imaging investigations. It held many complications in the past being performed blindly. But since the introduction of real-time US-directed renal biopsy in the field, the procedure became much safer with less complication rate and better yields [6].

In the current study, we aimed at the introduction of ultrasound in post-biopsy follow-up also, to minimize the hospital stay as the procedure is done in an outpatient basis setting. Also, to detect early any possible complications mainly those related to bleeding to prompt the proper intervention as early as possible for a better prognosis.

This is a prospective study held on 60 children who underwent PRB in PNU at Cairo university Children hospitals during the time between October 2017 and March 2018 where we performed an ultrasound after one hour of the renal biopsy and monitored the course of each case to detect whether US examination was useful to detect early complication and predict its course or not.

The indications of our candidates who performed the biopsy were variable including nephrotic syndrome (n= 23, 38.3%) as the commonest cause behind renal biopsy in our studied patients the same was evident in a study performed by Ali A et al., [7] where they had the same finding besides they found that minimal change disease (MCD) was the commonest pathological lesion after that focal segmental glomerulosclerosis (FSGS), that was in agreement with the majority of the regional reports. Another study included indicated renal biopsy in 54 pediatric patients showed that pure nephrotic syndrome was the main indication of renal biopsy in 25.9%; 57.14% due to steroid dependence & 28.57% due to steroid resistant [8], unlike our study in which the majority of indications of renal biopsy in nephrotic syndrome patients were due steroid resistant. While in another study done by Ding and colleagues including 183 children showed that the commonest indication for renal biopsy were suspected glomerulonephritis in 71.6% followed by nephrotic syndrome 16.9%, in this study complications reported in 15.9% but only 3% with major complications defined due to the need of intervention in the form of perirenal hematoma (2%), perirenal abscess (1%) and arteriovenous fistula (1%) [9].

In the current study, we revealed a rate of complication of 21.6% (13 out of 60 biopsies), only 5% with major complications in the form of subcapsular hematoma (1.7%) & urinary bladder

hematoma (3.3%). In our study, we revealed a statistically significant association between creatinine levels and incidence of subcapsular hematoma as well as back pain with a higher correlation index (r = + 0.283). However, a study by Zhu et al., [10] concluded that none of the several clinical risk factors stated by literature (renal failures, uncontrolled blood pressure, extended hemorrhage time, elevated PTT at base-line, post-biopsy decrease of hemoglobin, etc.) permits us to precisely expect which biopsies will have an unfavorable course.

Also, a statistically significant correlation was found between prothrombin concentration and back pain (r = - 0.300). However, Prothrombin concentration was not found to be significant concerning the incidence of complications as reported by Waldo et al., [5]. The same was found in the correlation between platelets and hematuria (r = - 0.361) which may refer indirectly to a small undetected subcapsular collection that stretches the capsule causing pain however this was not. This was also observed by Chen et al., [11] in a cohort study of 219 consecutive cases with age ≥18 years with SLE, they reported bleeding complications in 10.5%, where they found that every 10k platelet count/mm3 reduces the overall odds of any complication rise by 8 percent and that pre-biopsy platelet count was predominantly predictive of main bleeding complications with the rise of 27% in odds for every 10k platelet count/mm3 reduction.

The presence of vasculitis (SLE cases) was very crucial in our study where it was strongly correlated to the incidence of subcapsular hematoma (r = + 0.442). The hematologic abnormalities often associated with SLE may partially explain the slight increase in risk of total complications that were observed in our patient population [11]. A study conducted by Lees et al., [12] revealed that those with worse renal functions and those with vasculitis experiencing the PRB process are at the highest risk.

In the current study renal biopsy was taken from 13 graft kidneys **(21.6%)** and 47 native kidneys (78.3%). On close inspection, we find that from the cases with major complications only one case with graft biopsy (1.6%) in the form of urinary bladder hematoma requiring irrigation but no blood transfusion, Varnell and colleagues showed that comparing native biopsies with transplant biopsies did not reveal that biopsy type whether native or graft was associated with the need for a blood transfusion or requirement of an additional intervention after biopsy [13].

Per literature and built on various definitions, the complications rate varies between 0 and 45% **[14].** In the current study, we revealed a rate of complication of 21.6% (13 out of 60 biopsies). However, the standards of the British Association of Pediatric Nephrology (BAPN) showed that the rate of complication shouldn't exceed 5% [4]. But, findings of a new multi-center report by Hussain et al. in 2010 revealed that the mean rate of complications is about 10.4% and consequently very high. This highlights the necessity of a standard procedure, both for indications of biopsy and staff training in kidneys biopsies operations **[4].**

The US-directed kidney biopsies have been utilized in the majority of reports for biopsies monitoring but the sonographic post-biopsy evaluation

(involving Doppler examination) is not routinely part of a standard procedure [15]. Here it is to risk, that under-diagnosis especially of the smaller fistulas was built on the absent US and duplex examination [16].

This may be a limitation to our study too, as Doppler US was not done for follow-up of patients after biopsy so cases of A-V fistulas were not detected as a complication.

Many studies as Prasad et al. and Hogan et al. labeled complications as major if they needed blood transfusions, invasive procedures (radiographic or operative treatment), those causing acute renal obstructions, prolonged hospital stay, septicemia, or mortality; and minor complications were included principally of small hematomas or transient hematuria that resolved impulsively [1]. In the current study in terms of major complications, we had only one case that needed blood transfusion (1.6%) and 2 cases (3.3%) with urinary bladder hematoma needing irrigation. While numerous larger reports have stated rates of minor complications ranged between 7.5 and 58.6% while major complications between 0.3 and 4.3% [17].

The main finding of this study was that sensitivity of the U/S examination in detecting major complications was found to be 66.6 % in the first hour, while Waldo et al. documented that sensitivity of a US examination 1h post-biopsy to detect related complications was specified with 77% [5]. The hemoglobin level was done in complicated cases only; post-procedure hemoglobin drop was used as an indicator of true complications in patients detected to have hematomas by ultrasound. A hemoglobin drop of >1gm/dL was considerable. This was noted in 4 patients (6.7%) who had subcapsular and bladder hematomas.

CONCLUSION

Despite the sensitivity of ultrasound in detecting major complications in the first hour in our study being less than that documented by other studies, ultrasound examination was found to be very useful when correlated with the clinical presentation of the patient. A combined clinical and ultrasound examination revealing a complication-free patient would highly suggest a favorable course. While if one of both factors suggests a complication so close monitoring and follow-up are highly recommended for the possibility of a complicated course.

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-authors.
All authors have contributed to authorship, have read and approved the manuscript.

Conception and design of study: Hafez Bazaraa
Acquisition of data: Amina Kholeif
Analysis and/or interpretation of data: Rasha Helmy
Drafting the manuscript: Amr Salem
Revising the manuscript critically for important intellectual content: Mervate Haroun
Approval of the version of the manuscript to be published: Hafez Bazaraa

STATEMENTS

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of research and informed written consent was obtained in every case from their legal guardians.

Consent for publication
Done

Availability of data and material
Done

Conflict of interest:
The authors declare no conflict of interest.

Funding
The authors declare that this research work did not receive any fund.

Acknowledgements
Authors would like to thank all patients and their family members for their valuable contributions to the study.

Submitted: 15/04/2022
Accepted: 28/05/2022
Published: 30/06/2022