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Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

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Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

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Running title: Outpatient renal biopsy

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Abstract

Objectives: We aim to evaluate the safety of performing percutaneous native kidney biopsy (PKB) as an outpatient procedure (implying an observation period of 6 hrs) compared to the traditional inpatient policy.

Design, setting, participants, and measurements: Group I, in whom PKB was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom PKB was performed and followed by at least 1-day hospital admission. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as in patient procedure. All biopsies were performed by a single nephrologist following a structured protocol.

Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7±17.9 years. One-hundred and twenty-nine (27.9%) of these biopsies were performed in outpatients. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arteriovenous fistula (6 cases, 1.2%), ischaemic stroke (2; 0.4%), thromboembolic pulmonary embolism (1; 0.2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases,2.6%), haematomas on sonography not requiring intervention (15 cases, 3.2%)]. When comparing the complication rate between group I and II, no statically difference were observed. When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95% CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy nor the degree of proteinuria.

Conclusions: Outpatient biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

Article summary

Strengths and limitations of this study

- This is the largest reported cohort of percutaneous kidney biopsies (PKB) performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol.
- Our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.
- One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied.

INTRODUCTION

Percutaneous biopsy of native kidneys is an important diagnostic tool for clinicians seeking a diagnosis for patients with kidney disease. The primary risks for percutaneous kidney biopsy (PKB) range from mild complications such as post-procedural pain and gross hematuria to major complications such as large hematomas requiring blood transfusion, uncontrolled bleeding requiring embolization or surgical nephrectomy, and rarely death[1]. The technique for obtaining tissue has evolved with the emergence of direct ultrasound guidance as the standard of care, dramatically improving procedural safety and diagnostic yield[2]. While a number of centres worldwide require overnight inpatient observation (IO) following PKB, several studies have suggested the safety of the outpatient 'day surgery' (ODS) approach[2,3]. However, to date, debate still exists on the appropriate observation time after PKB. In fact, despite some studies have shown that discharging patients within 4–6 h after biopsy seems to be safe[4–6] , Whittier and Korbet found that an observation period of less than 8 hours following biopsy missed 33% of complications[7].

We carried out a prospective observational study over a 5-year period of consecutive outpatient native renal biopsies to evaluate safety of ODS-PKB. Outcomes and the rate of complications after ODS-PKB were compared to IO-PKD performed in our Institution between January 2000 and November 2012. Besides, we aimed to identify pre-procedure risk factors for complications (either minor or major) after a PKB.

MATERIALS AND METHODS

Patients selection

For the purpose of this study, two groups of patients were considered: group I, in whom renal biopsy was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom kidney biopsy was performed and followed by at least 1-day hospital admission.

Patients in group I were prospectively enrolled since January 2012, when we began performing renal biopsies as outpatient procedures in all consecutive patients using a standardized outpatient protocol (as provided in the supplementary material). A prospective computerized database was used to enter the data. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as in patient procedure.

Pre-ODS-PKB Standardized procedures

Patients are scheduled within 3 to 7 days from the day of call. Pre-ODS-PKD standardised procedures includes cell blood count (CBC), renal function panel, coagulation profile (prothrombin time, partial thromboplastin, bleeding time, fibrinogen, PFA-100, platelets count), and ECG. Anti-platelets/anticoagulant therapies are screened and hematologic evaluation is routinely requested in patients requiring therapy adjustment prior to biopsy.

Real-time ultrasound-guided renal biopsy

All biopsies were performed by a single nephrologist (DR) with the guidance of an expert radiologist who also performed an ultrasound examination of the kidney prior to PKB. PKB, is performed following a structured protocol . In brief, the skin is prepped with antiseptic solution and draped in the customary fashion. A sterile cover is placed over the ultrasound probe and the kidney visualized. The skin and subcutaneous tissue are anesthetized with lidocaine. The automated biopsy gun (needle 18 gauge, 15 mm) was used. Under real-time ultrasound guidance the biopsy needle gun is advanced. Once it is close to the renal capsule, the gun is fired with the patient holding his or her breath. The biopsy needle is retrieved and the specimen placed in a media container and sent to surgical pathology. Three passes are performed per patient.

Post- ODS-PKB Standardized monitoring

Patients are placed in a prone position on the bed for at least 2 hours. Patients received e.v. hydration and are observed for symptoms of urine retention. Monitor urine-analysis for microscopic or macroscopic hematuria is routinely performed. Half-hourly measurements of pulse and blood pressure for two hours after PKD and then hourly till discharge are performed. Postbiopsy imaging wasdone following the protocol or when clinically indicated at the discretion of the attending physician.

Minor or major complications definition

Post-biopsy bleeding complications were categorized as either minor or major. Minor complications included gross hematuria and/or subcapsular perinephric hematoma(<5 cm diameter) that spontaneously resolved without need for further intervention. Major complications were defined as those that required an intervention for resolution, either the transfusion of blood products or an invasive procedure (angiography, surgery), and those that might potentially led to acute renal obstruction or failure, septicaemia, or death. The size of post-biopsy hematomas (surface area) was defined as the product of the longest and the shortest diameters on the two dimensional sonographic pictures.

Data Analysis

The prospective database included demographic and clinical features, laboratory values, biopsy complications, and diagnostic or therapeutic procedures to manage hemorrhagic complications. In addition, the surgical pathology reports were used to ascertain the adequacy of renal tissue and pathologic diagnosis. Univariate analysis was performed to assess the association between complications and risk factors using the Pearson, χ2 and Fisher exact tests. Multivariate survival analysis was performed using the proportional hazards model (Cox model) to identify significant independent factors adjusted for the potential confounding risk factors able to predict a complication. The forward conditional techniques were used to find the final model. The results are expressed as ORs with 95% CI.

RESULTS

A total of 462 biopsies (group I and group II) were included in this study, 210 (45.5%) of patients were female and the mean age was 54.7 ± 17.9 years. Table 1 summarised demographic, clinical, and laboratory findings in the whole cohort.

Twenty-three per cent of biopsies were performed for the diagnostic workup of nephrotic range proteinuria, 16% for rapidly progressive renal insufficiency, 8% for acute kidney injury, 14% for a chronic kidney disease, and the remaining 39% for non-nephrotic proteinuria and/or hematuria.

A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arterio-venous fistula(6 cases, 1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary embolism (1, 0,2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2,6%), haematomas on sonography not requiring intervention (15 cases, 3,2%)].

Inpatients and Outpatients

One-hundred and twenty-nine (27.9%) of these biopsies were performed as outpatients and prospectively included. Data from 333 PKD performed as inpatients were retrospectively collected and analysed. Table 2 summarised demographic, clinical, and laboratory findings, dividing patients in group I and II.

Outpatients differed from inpatients with regard total glomeruli obtained (median = 23 [1-71] vs. median = 20 [3-58], p = 0.01), prevalence of pre-biopsy haematuria (78.4% Vs 88.4%) and severe hypertension (13.2% Vs 27.9%). When comparing the complication rate between group I and II, no statically difference were observed [overall 24 (7,2%) complications in group 1 and 12 (9,3%) in group II; 5 (1,5%) and 4(3,1%) major, 19 (5,5%) and 8 (6.2%) minor complications, respectively in group I and II].

Assessment of potential predictors of post-biopsy complications

When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy

nor the degree of proteinuria. When focusing the analysis only on group I, a similar trend was observed, but it failed to reach a statistical significance.

DISCUSSION

The main finding in the present study is that a renal biopsy should be regarded as a safe procedure being overall rate of major complications less than 2%. Importantly, when comparing the complication rate between group I and II, no statically difference was observed, also when stratifying patients for major and minor complications (overall 7.2% complications in group 1 and 9.3% in group II; 1.5% and 3.1% major, 5.5% and 6.2% minor complications, respectively in group I and II). Although the study was not randomized, it was performed prospectively with a proper follow-up of the patients.

These results are in line with Lin et al.[8] who found that there is no difference in the rate of complications between patients who are admitted and those observed for a 6-hour period, the latest being acceptable. By contrast, Whittier and Korbet [7] found that 42% of complications following native kidney biopsy manifested at ≤ 4 h, 67% at ≤ 8 h, 85% at ≤ 12 h, and 89% at ≤ 24 h.

The main reason for overnight stay in the hospital is basically as a safety net in case there is a major complication[9]. The major complication, which one could encounter, is severe bleeding causing a large retroperitoneal hematoma. This complication can be catastrophic and should be addressed immediately by performing a selective renal arteriogram with embolization of the bleeding arteriole, which will infarct a small portion of the kidney. This complication is in the order of 0 to 6 % depending on the authors[2,7–17]; the reasons for these differences are not cleared but may be related to the technique used (blind vs. ultrasound guided biopsy), operator experience, gauge of the biopsy needle and the number of passes. We demonstrated lower frequency of hemorrhagic complications with real-time ultrasound-guided biopsies, as compared with blind biopsies[10].

Some authors believe that patients are still at risk for type complication beyond the 8 hours observation post-biopsy; we hypothesize that under a controlled environment (see standardized protocol) and a proper technique (real-time ultrasound) we can minimize this risk and be able to have the renal biopsy performed

as an outpatient procedure. In detail, Marwah and Korbet[9] in their study accounted together all complications (minor and major) and in their cohort only 42% of the patients had the biopsy performed with an automated gun, the rest were performed with a manual biopsy device and all biopsies were performed with 14-gauge needles and there was no report on how many passes were performed. They timed the major complications, which accounted for 24 out of a total of 394 biopsies (6.6%), and reported that 19 of them were observed before the 8-hour mark. Thus, only 5 major complications were captured after 8 hours of observation. Subsequently, when Whittier and Korbet [7] re-evaluated the data and reported a series of 750 patients, in which they added the patients from the prior study, they concluded that less than 8-hour period of observation was not optimal and they reported that it could miss up to 33% of complications. Again, all complications (minor and major) were placed in the same category. Out of 750 biopsies, 45 had a major complication (6.6%). Thirty of them were diagnosed before 8-hours of observation, the other 15 were diagnosed between 9 to 24 hours. On the contrary, there at least four studies showing different results. Farazier and Fairley reported only minor complications in a series of 118 patients (only 2 patients) [4]. Oviasu and Ugdodaga [5] from Nigeria reported in no complications in a series of 20 patients. Murphy et al[6], had similar data. Bairy M et al, reported on 178 outpatient renal biopsies and reported no major complications with only 13.2% of minor complications to include 4 patients with gross hematuria, 16 patients with small peri-nephric hematomas and 3 with both hematuria and hematoma[3]. No interventions were needed and only two patients stayed overnight.

The current study shows similar results.

It is worth noting that we observed three thrombotic events after PKD (2 ischaemic strokes and one venous thromboembolism). As our protocol included the pre-PKD use of desmopressin, once could speculate a role of this agent in increasing the thrombotic risk. However, Manno and co-workers[18] when demonstrating in double-blind randomized controlled clinical trial that pre-biopsy desmopressin administration decreases the risk of bleeding and hematoma size in patients undergoing percutaneous kidney, they did not observer any episodes of thrombotic events in both desmopressin and control groups.

Strengths and limitations

This is the largest reported cohort of biopsies performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol. Despite the single center cohort design may potentially limit the external validity of our findings, our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.

One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied. These criteria were set *a priori* with the knowledge that cohort studies are prone to unpredictable bias and confounding by unknown factors and retrospective data analysis would only add to this risk. However, we used multivariate analysis to ascertain the factors that contribute to postbiopsy complications, allowing for adjusting for potential known confounders, although unknown factors may not be accounted for.

Finally, this study has also identified serum creatinine >3 mg/dl and known severe hypertensionas significant independent predictors of complications; however, when comparing group I and II, a similar trend was observed, but it failed to reach a statistical significance. This may be due to the small number of major complications, especially major, observed in this study, and whether or not these same parameters are also important predictors of the major episodes occurring in ODS-PKD patients requiring intervention is uncertain.

In conclusion**,** our study provides further evidence that it is safe to perform PKB as outpatients procedure after careful screening for bleeding risk, using and automated needle-gun system under ultrasound guide, following a standardized protocol. Therefore, same-day discharge with a 6-hour observation period seems a medically adequate procedure in carefully and this represent significant finding, since outpatient biopsies are economically advantageous.

Contribution authorship statement: Dario Roccatello performed the kidney biopsies. Dario Roccatello and Savino Sciascia designed the study, collected the data and drafted the manuscript. Daniela Rossi, Carla Naretto, Mario Bazzan participated in the clinical evaluation, patients selection, data collection and critically reviewed the manuscript. Laura Solfietti, Elisa Menegatti, Simone Baldovino perfomered the laboratory investigations and critically reviewed the manuscript. Simone Baldovino partecipated in the data analysis.

Competing interests The authors declare no conflict of interest and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work

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Data sharing statement: the applied protocol for percutaneous kidney biopsies is attached and shared as supplementary material

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Table 1: Demographic, clinical, and laboratory findings in the whole cohort.

	2000-2015 N. (%)
Biopsies	462
Passages (mean±SD/median[range])	2.6±0.7/ 3[1-5]
Glomeruli (mean±SD/median[range])	19.9±11.3/18[6-71]
Age (mean±SD)	54.7 ± 17.9
Female	210 (45.5)
Admission duration (for inpatients only) (days, mean±SD/median[range])	1.1 ±0.6/1[1-7]
sCr (mg/dl, mean±SD/median[range])	1.67±1.2/1.3[0.5-7]
sCr >3 mg/dl	124 (26,8)
Proteinuria (g/24h, mean±SD/median[range])	2.6±2.3/2[0.0-13]
Haematuria	375 (81.2)
Uncontrolled Hypertension	110 (23.9)
Complications (any)	36 (7.8)
Major	27 (5.8)
Minor	9 (1.9)

Table 2: Demographic, clinical, and laboratory findings, dividing patients in group I and II.

	2000-2012 (Inpatients) N. (%)	2012-2015 (Outpatients) N. (%)	p=
Biopsies	333	129	
Passages (mean±SD/median[range])	2.9±0.6/ 3[1-5]	3.1±0.6/3[2-5]	NS
Glomeruli (mean±SD/median[range])	21.6±12.4/20[1-71]	23.9±12/23[3-58]	p=0.01
Age (mean±SD)	56 ± 19	52 ± 17.6	NS
Female	114 (34)	66 (51)	NS
Admission duration (days, mean±SD/median[range])	1.1 ±0.6/1[1-7]	-	
sCr (mg/dl, mean±SD/median[range])	1.56±0.9/1.3[0.5-6]	1.8±1.24/1.4[0.5-7]	NS
Proteinuria (g/24h, mean±SD/median[range])	2.7±2.2/2[0.0-10]	2.6±2.2/2[0.2-13]	NS
Pre-biopsy haematuria	261 (78.4)	114 (88.4)	p=0.01
Severe Hypertension	93 (27.9)	17 (13.2)	p=0.008
Complications (any)	24 (7.2)	12 (9.3)	NS
Minor	19 (5.7)	8 (6.2)	NS
Major	5 (1.5)	4 (3.1)	NS

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			**4-6**
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

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Abstract

Objectives: We aim to evaluate the safety of performing percutaneous native kidney biopsy (PKB) as an outpatient procedure (implying an observation period of 6 hrs) compared to the traditional inpatient policy.

Design, setting, participants, and measurements: Group I, in whom PKB was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom PKB was performed and followed by at least 1-day hospital admission. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as inpatient procedure. All biopsies were performed by a single nephrologist following a structured protocol.

Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7±17.9 years. One-hundred and twenty-nine (27.9%) of these biopsies were performed in outpatients. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arteriovenous fistula (6 cases, 1.2%), ischaemic stroke (2; 0.4%), thromboembolic pulmonary embolism (1; 0.2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases,2.6%), haematomas on sonography not requiring intervention (15 cases, 3.2%)]. When comparing the complication rate between group I and II, no statically difference were observed. When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95% CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy nor the degree of proteinuria.

Conclusions: Outpatient biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

Article summary

Strengths and limitations of this study

- This is the largest reported cohort of percutaneous kidney biopsies (PKB) performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol.
- Our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.
- One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied.

INTRODUCTION

Percutaneous biopsy of native kidneys is an important diagnostic tool for clinicians seeking a diagnosis for patients with kidney disease. The primary risks for percutaneous kidney biopsy (PKB) range from mild complications such as post-procedural pain and gross hematuria to major complications such as large hematomas requiring blood transfusion, uncontrolled bleeding requiring embolization or surgical nephrectomy, and rarely death[1]. The technique for obtaining tissue has evolved with the emergence of direct ultrasound guidance as the standard of care, dramatically improving procedural safety and diagnostic yield[2]. While a number of centres worldwide require overnight inpatient observation (IO) following PKB, several studies have suggested the safety of the outpatient 'day surgery' (ODS) approach[2,3]. However, to date, debate still exists on the appropriate observation time after PKB. In fact, despite some studies have shown that discharging patients within 4–6 h after biopsy seems to be safe[4–6] , Whittier and Korbet found that an observation period of less than 8 hours following biopsy missed 33% of complications[7].

We carried out a prospective observational study over a 5-year period of consecutive outpatient native renal biopsies to evaluate safety of ODS-PKB. Outcomes and the rate of complications after ODS-PKB were compared to IO-PKD performed in our Institution between January 2000 and November 2012. Besides, we aimed to identify pre-procedure risk factors for complications (either minor or major) after a PKB.

MATERIALS AND METHODS

Patients selection

For the purpose of this study, two groups of patients were considered: group I, in whom renal biopsy was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom kidney biopsy was performed and followed by at least 1-day hospital admission.

Patients in group I were prospectively enrolled since January 2012, when we began performing renal biopsies as outpatient procedures in all consecutive patients using a standardized outpatient protocol (as provided in the supplementary material). A prospective computerized database was used to enter the data. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as inpatient procedure. Patients whose data set was not fully available were excluded from our analysis (3 cases).

Percutaneous kidney biopsies were performed when needed as part of good clinical practise for patients refereed to our department. Data collection was performed according to the local legislation of the institutional review board.

Pre-ODS-PKB Standardized procedures

Patients are scheduled within 3 to 7 days from the day of call. Pre-ODS-PKD standardised procedures includes cell blood count (CBC), renal function panel, coagulation profile (prothrombin time, partial thromboplastin, bleeding time, fibrinogen, PFA-100, platelets count), and ECG. Anti-platelets/anticoagulant therapies are screened and hematologic evaluation is routinely requested in patients requiring therapy adjustment prior to biopsy.

Real-time ultrasound-guided renal biopsy

All biopsies were performed by a single nephrologist (DR) with the guidance of an expert radiologist who also performed an ultrasound examination of the kidney prior to PKB. PKB, is performed following a structured protocol . In brief, the skin is prepped with antiseptic solution and draped in the customary fashion. A sterile cover is placed over the ultrasound probe and the kidney visualized. The skin and subcutaneous tissue are anesthetized with lidocaine. The automated biopsy gun (needle 18 gauge, 15 cm) was used. Under real-time ultrasound guidance the biopsy needle gun is advanced. Once it is close to the renal capsule, the gun is fired with the patient holding his or her breath. The biopsy needle is retrieved and

the specimen placed in a media container and sent to surgical pathology. Three passes are performed per patient.

Post- ODS-PKB Standardized monitoring

Patients are placed in a prone position on the bed for at least 2 hours. Patients received i.v. hydration and are observed for symptoms of urine retention. . Monitor urine-analysis for microscopic or macroscopic hematuria is routinely performed. Half-hourly measurements of pulse and blood pressure for two hours after PKD and then hourly till discharge are performed. Post-biopsy imaging was done in all the patients following the protocol. Additional imaging investigations, including additional sonography were performed when clinically indicated at the discretion of the attending physician

Minor or major complications definition

Post-biopsy bleeding complications were categorized as either minor or major. Minor complications included gross hematuria and/or subcapsular perinephric hematoma(<5 cm diameter) that spontaneously resolved without need for further intervention. Major complications were defined as those that required an intervention for resolution, either the transfusion of blood products or an invasive procedure (angiography, surgery), and those that might potentially led to acute renal obstruction or failure, septicaemia, or death. Subcapsular haematoma 5>cm and/or those requiring intervention (despite the size) were considered as major complications

The size of post-biopsy hematomas (surface area) was defined as the product of the longest and the shortest diameters on the two dimensional sonographic pictures.

Data Analysis

The prospective database included demographic and clinical features, laboratory values, biopsy complications, and diagnostic or therapeutic procedures to manage hemorrhagic complications. In addition, the surgical pathology reports were used to ascertain the adequacy of renal tissue and pathologic

diagnosis. Univariate analysis was performed to assess the association between complications and risk factors using the Pearson, χ2 and Fisher exact tests. Multivariate survival analysis was performed using the proportional hazards model (Cox model) to identify significant independent factors adjusted for the potential confounding risk factors able to predict a complication. For univariate analysis, the following variables were included in the model: number of biopsy passes, gender, age, diagnosis, kidney size at sonographic investigations, presence of haematuria before the kidney biopsy, the degree of proteinuria, haemoglobin level before the kidney biopsy, thrombocytopenia, severe arterial hypertension, serum creatinine level before the kidney biopsy, the use of anti-platelets, LMWH, anti-hypertensive agents. For the multivariate analysis included variables were included: gender, age, diagnosis, the degree of proteinuria, haemoglobin level before the kidney biopsy, severe arterial hypertension, serum creatinine level before the kidney biopsy, the use of anti-platelets agents (as described in table 1S) The forward conditional techniques were used to find the final model. The results are expressed as ORs with 95% CI.

RESULTS

A total of 462 biopsies (group I and group II) were included in this study, 210 (45.5%) of patients were female and the mean age was 54.7 ± 17.9 years. Table 1 summarised demographic, clinical, and laboratory findings in the whole cohort.

Twenty-three per cent of biopsies were performed for the diagnostic workup of nephrotic range proteinuria, 16% for rapidly progressive renal insufficiency, 8% for acute kidney injury, 14% for a chronic kidney disease, and the remaining 39% for non-nephrotic proteinuria and/or hematuria.

A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arterio-venous fistula(6 cases, 1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary embolism (1, 0,2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2,6%), haematomas on sonography not requiring intervention (15 cases, 3,2%)].

Inpatients and Outpatients

One-hundred and twenty-nine (27.9%) of these biopsies were performed as outpatients and prospectively included. Data from 333 PKD performed as inpatients were retrospectively collected and analysed. Table 2 summarised demographic, clinical, and laboratory findings, dividing patients in group I and II.

Outpatients differed from inpatients with regard total glomeruli obtained (median = 23 [1-71] vs. median = 20 [3-58], p = 0.01), prevalence of pre-biopsy haematuria (78.4% Vs 88.4%) and severe hypertension (13.2% Vs 27.9%). When comparing the complication rate between group I and II, no statically difference were observed [overall 24 (7,2%) complications in group 1 and 12 (9,3%) in group II; 5 (1,5%) and 4(3,1%) major, 19 (5,5%) and 8 (6.2%) minor complications, respectively in group I and II].

Assessment of potential predictors of post-biopsy complications

When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, kidney size at sonographic investigations, presence of haematuria before the kidney biopsy nor the degree of proteinuria. When focusing the analysis only on group I, a similar trend was observed, but it failed to reach a statistical significance. Table 1S summaries the factors associated with the presence of complication I the univariate and multivariate model (supplementary materials).

DISCUSSION

The main finding in the present study is that a renal biopsy should be regarded as a safe procedure being overall rate of major complications less than 2%. Importantly, when comparing the complication rate between group I and II, no statically difference was observed, also when stratifying patients for major and minor complications (overall 7.2% complications in group 1 and 9.3% in group II; 1.5% and 3.1% major, 5.5% and 6.2% minor complications, respectively in group I and II). Although the study was not randomized, it was performed prospectively with a proper follow-up of the patients.

These results are in line with Lin et al.[8] who found that there is no difference in the rate of complications between patients who are admitted and those observed for a 6-hour period, the latest being acceptable. By contrast, Whittier and Korbet [7] found that 42% of complications following native kidney biopsy manifested at ≤ 4 h, 67% at ≤ 8 h, 85% at ≤ 12 h, and 89% at ≤ 24 h.

The main reason for overnight stay in the hospital is basically as a safety net in case there is a major complication[9]. The major complication, which one could encounter, is severe bleeding causing a large retroperitoneal hematoma. This complication can be catastrophic and should be addressed immediately by performing a selective renal arteriogram with embolization of the bleeding arteriole, which will infarct a small portion of the kidney. This complication is in the order of 0 to 6 % depending on the authors[2,7–17]; the reasons for these differences are not cleared but may be related to the technique used (blind vs. ultrasound guided biopsy), operator experience, gauge of the biopsy needle and the number of passes. We demonstrated lower frequency of hemorrhagic complications with real-time ultrasound-guided biopsies, as compared with blind biopsies[10].

Some authors believe that patients are still at risk for type complication beyond the 8 hours observation post-biopsy; we hypothesize that under a controlled environment (see standardized protocol) and a proper technique (real-time ultrasound) we can minimize this risk and be able to have the renal biopsy performed as an outpatient procedure. In detail, Marwah and Korbet[9] in their study accounted together all complications (minor and major) and in their cohort only 42% of the patients had the biopsy performed with an automated gun, the rest were performed with a manual biopsy device and all biopsies were performed with 14-gauge needles and there was no report on how many passes were performed. They timed the major complications, which accounted for 24 out of a total of 394 biopsies (6.6%), and reported that 19 of them were observed before the 8-hour mark. Thus, only 5 major complications were captured after 8 hours of observation. Subsequently, when Whittier and Korbet [7] re-evaluated the data and reported a series of 750 patients, in which they added the patients from the prior study, they concluded that less than 8-hour period of observation was not optimal and they reported that it could miss up to 33% of complications. Again, all complications (minor and major) were placed in the same category. Out of 750

biopsies, 45 had a major complication (6.6%). Thirty of them were diagnosed before 8-hours of observation, the other 15 were diagnosed between 9 to 24 hours. On the contrary, there at least four studies showing different results. Farazier and Fairley reported only minor complications in a series of 118 patients (only 2 patients) [4]. "Oviasu and Ugdodaga [5] from Nigeria reported no complications in a series of 20 patients.Murphy et al[6], had similar data. Bairy M et al, reported on 178 outpatient renal biopsies and reported no major complications with only 13.2% of minor complications to include 4 patients with gross hematuria, 16 patients with small peri-nephric hematomas and 3 with both hematuria and hematoma[3]. No interventions were needed and only two patients stayed overnight.

The current study shows similar results.

It is worth noting that we observed three thrombotic events after PKD (2 ischaemic strokes and one venous thromboembolism). As our protocol included the pre-PKD use of desmopressin, once could speculate a role of this agent in increasing the thrombotic risk. However, Manno and co-workers[18] when demonstrating in double-blind randomized controlled clinical trial that pre-biopsy desmopressin administration decreases the risk of bleeding and hematoma size in patients undergoing percutaneous kidney, they did not observer any episodes of thrombotic events in both desmopressin and control groups.

Strengths and limitations

This is the largest reported cohort of biopsies performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol. Despite the single center cohort design may potentially limit the external validity of our findings, our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.

One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied. These criteria were set *a priori* with the knowledge that cohort studies are prone to unpredictable bias and confounding by unknown factors and retrospective data analysis would only add to this risk. However, we used multivariate analysis to ascertain the factors that contribute to postbiopsy

complications, allowing for adjusting for potential known confounders, although unknown factors may not be accounted for.

Finally, this study has also identified serum creatinine >3 mg/dl and known severe hypertensionas significant independent predictors of complications; however, when comparing group I and II, a similar trend was observed, but it failed to reach a statistical significance. This may be due to the small number of major complications, especially major, observed in this study, and whether or not these same parameters are also important predictors of the major episodes occurring in ODS-PKD patients requiring intervention is uncertain.

In conclusion**,** our study provides further evidence that it is safe to perform PKB as outpatients procedure after careful screening for bleeding risk, using and automated needle-gun system under ultrasound guide, following a standardized protocol. Therefore, same-day discharge with a 6-hour observation period seems a medically adequate procedure in carefully and this represent significant finding, since outpatient biopsies are economically advantageous.

Contribution authorship statement: Dario Roccatello performed the kidney biopsies. Dario Roccatello and Savino Sciascia designed the study, collected the data and drafted the manuscript. Daniela Rossi, Carla Naretto, Mario Bazzan participated in the clinical evaluation, patients selection, data collection and critically reviewed the manuscript. Laura Solfietti, Elisa Menegatti, Simone Baldovino perfomered the laboratory investigations and critically reviewed the manuscript. Simone Baldovino partecipated in the data analysis.

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Table 1: Demographic, clinical, and laboratory findings in group I and II.

	2000-2015 N. (%)	2000-2012 (Inpatients) N. (%)	2012-2015 (Outpatients) N. (%)	p=
Biopsies	462	333	129	
Passages (mean±SD/median[range])	2.6±0.7/ 3[1-5]	2.9±0.6/ 3[1-5]	3.1±0.6/3[2-5]	NS
Glomeruli (mean±SD/median[range])	19.9±11.3/18[6-71]	21.6±12.4/20[1-71]	23.9±12/23[3-58]	0.01
Age (mean±SD)	54.7 ± 17.9	56 ± 19	52 ± 17.6	NS
Female (%)	180 (39)	114 (34)	66 (51)	NS
Admission duration (days, mean±SD/median[range])	-	1.1 ±0.6/1[1-7]	-	
sCr (mg/dl, mean±SD/median[range])	1.67±1.2/1.3[0.5-7]	1.56±0.9/1.3[0.5-6]	1.8±1.24/1.4[0.5-7]	NS
sCr > 3 mg/dl	124 (26.8)	89 (29.6)	35 (27.1)	NS
Proteinuria (g/24h, mean±SD/median[range])	2.6±2.3/2[0.0-13]	2.7±2.2/2[0.0-10]	2.6±2.2/2[0.2-13]	NS
Pre-biopsy haematuria	375 (81.2)	261 (78.4)	114 (88.4)	0.01
Resistant hypertension*	110 (23.9)	93 (27.9)	17 (13.2)	0.008
Complications (any)	36 (7.8)	24 (7.2)	12 (9.3)	NS
Minor	27 (5.8)	19 (5.7)	8 (6.2)	NS
Major	9 (1.9)	5 (1.5)	4 (3.1)	NS

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	Univariate model				Multivariate Model			
	Major Complications		Minor complication		Major Complications		Minor complication	
	OR (95%CI)	p=	OR (95%CI)	p=	OR (95%CI)	p=	OR (95%CI)	p=
Number of biopsy passes	1.15 (0.41-3.22)	0.78	1.882 (0.23-3.68)	0.83	-	-	-	-
Diagnosis*	1.00 (0.31-3.20)	0.99	1.70 (0.54-5.50)	0.41	-	-	-	-
Male	0.40 (0.10-0.95)	0.039	0.46 (0.06-3.40)	0.71	0.56 (0.11-1.11)	0.071	0.51 (0.36-4.10)	0.89
Age (≥60)	2.30 (1.50-3.50)	0.032	1.20 (0.80-2.00)	0.12	2.07 (0.89-2.70)	0.056	1.12 (0.87-2.99)	0.34
Kidney size at sonographic investigations#	0.63 (0.25-1.60)	0.54	0.79 (0.31–2.00)	0.32	-	-	-	-
Haematuria**	1.21 (0.38-3.90)	0.75	0.92 (0.28–3.00)	0.88	-	-	-	-
Nephrosic proteinuria**	1.60 (1.07–3.00)	0.048	1.60 (0.84–3.00)	0.14	1.54 (0.91–3.24)	0.37	1.70 (0.82–3.12)	0.17
Haemoglobin level**(<10 g/dl)	1.98 (1.40-3.00)	0.041	1.27 (1.01–2.43)	0.047	1.32 (0.98-2.11)	0.067	1.17 (0.89–2.21)	0.071
Thrombocytopenia	3.40 (0.33–34.00)	0.87	2.80 (0.29-8.00)	0.91	-	-	-	-
Severe arterial hypertension**	2.90 (1.30–4.10)	0.003	1.60 (1.02–2.50)	0.04	2.01 (1.2-4.7)	0.037	1.05 (0.97-2.6)	0.065
Serum creatine >3 mg/dl*	2.50 (1.86-3.60)	0.001	2.98 (1.61-6.90)	0.029	2.02 (0.95-3.06)	0.053	OR 2.03 (1.18-6.81)	0.025
Anti-platelets*	2.29 (1.50-3.60)	0.001	2.07 (1.12-4.02)	0.031	2.10 (0.69-2.80)	0.48	1.57 (0.91-3.02)	0.059
LMWH*	1.21 (0.38-3.90)	0.49	0.92 (0.28-3.00)	0.88	-	-	-	-
Anti-hypertensive agents*	3.40 (0.54-31.00)	0.75	2.77 (0.67-17.00)	0.53	-	-	-	-

* categorised in primary glomerulopathy or systemic autoimmune condition; **before the kidney biopsy; # < 8 cm (as defined as J Ultrasound. 2007 Dec;10(4):161-7.)

Outpatient PKB Protocol

Pre-PKB

Cell blood count, renal function panel, coagulation profile (prothrombin time, partial thromboplastin, bleeding time, fibrinogen, PFA-100, platelets count), and ECG. Anti-platelets/anticoagulant therapies are screened. In general, antiplatelet agents stopped 1 week prior to the biopsy. Hematologic evaluation is routinely requested in patients requiring therapy adjustment prior to biopsy.

On the day of PKB

Admission at 8:00 AM on the day of the biopsy.

Biopsy to proceed if blood pressure is 170/95 mm Hg or less. Otherwise, discuss with attending physician*.

Written consent and explanation of procedure and potential complications of PKB (according to risk in this center).

Ensure biopsy equipment available according to checklist and inform pathology department of expectation of sample for processing.

Desmopressin acetate is routinely administered prior to PKB (0.4 microgr/Kg).

PKB Procedure

Biopsy is performed by a consultant nephrologist with the guidance of the sonographer who also performs an ultrasound examination of the kidney prior to discharge patient. A 18G x 15 cm needle is used.

Post-PKB Management

Pulse and blood pressure post-biopsy are constantly monitored: half-hourly measurements of pulse and blood pressure for 2 hours, then hourly for remainder of stay (up to 4 hours or until discharge). Patient to remain in prone position for at least 2 hours.

Saline administration (1,000-1,500 ml) unless fluid retention to reduce risk of clot formation.

Monitor urinalysis for microscopic or macroscopic hematuria. Observe patient for symptoms of urinary retention.

Review by physician prior to discharge.

Resting for two days.

Advice to Patient

Avoid heavy lifting or exercise for 1 week.

Observe urine for clots and blood. If present, call the renal unit for advice.

If severe back pain experienced, contact the renal unit.

Avoid non-steroidal anti-inflammatory drugs for pain relief.

If any concerns, contact the renal unit.

Note

* If the patient presents with values above 170/95 mm Hg, we administer nifedipine oral drops (up to 10 mg) and/or captopril 25 mg and monitor blood pressure every 10 minutes. PKB is performed if blood pressure is stably controlled at 170/95 mm Hg or less, otherwise PKD is postponed till blood pressure stabilization.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			**4-6**
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

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Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

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Abstract

Objectives: We aim to evaluate the safety of performing percutaneous native kidney biopsy (PKB) as an outpatient procedure (implying an observation period of 6 hrs) compared to the traditional inpatient policy.

Design, setting, participants, and measurements: Group I, in whom PKB was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom PKB was performed and followed by at least 1-day hospital admission. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as inpatient procedure. All biopsies were performed by a single nephrologist following a structured protocol.

Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7±17.9 years. One-hundred and twenty-nine (27.9%) of these biopsies were performed in outpatients. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arteriovenous fistula (6 cases, 1.2%), ischaemic stroke (2; 0.4%), thromboembolic pulmonary embolism (1; 0.2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases,2.6%), haematomas on sonography not requiring intervention (15 cases, 3.2%)]. When comparing the complication rate between group I and II, no statically difference were observed. When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95% CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy nor the degree of proteinuria.

Conclusions: Outpatient biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

Article summary

Strengths and limitations of this study

- This is the largest reported cohort of percutaneous kidney biopsies (PKB) performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol.
- Our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.
- One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied.

INTRODUCTION

Percutaneous biopsy of native kidneys is an important diagnostic tool for clinicians seeking a diagnosis for patients with kidney disease. The primary risks for percutaneous kidney biopsy (PKB) range from mild complications such as post-procedural pain and gross hematuria to major complications such as large hematomas requiring blood transfusion, uncontrolled bleeding requiring embolization or surgical nephrectomy, and rarely death[1]. The technique for obtaining tissue has evolved with the emergence of direct ultrasound guidance as the standard of care, dramatically improving procedural safety and diagnostic yield[2]. While a number of centres worldwide require overnight inpatient observation (IO) following PKB, several studies have suggested the safety of the outpatient 'day surgery' (ODS) approach[2,3]. However, to date, debate still exists on the appropriate observation time after PKB. In fact, despite some studies have shown that discharging patients within 4–6 h after biopsy seems to be safe[4–6] , Whittier and Korbet found that an observation period of less than 8 hours following biopsy missed 33% of complications[7].

We carried out a prospective observational study over a 5-year period of consecutive outpatient native renal biopsies to evaluate safety of ODS-PKB. Outcomes and the rate of complications after ODS-PKB were compared to IO-PKD performed in our Institution between January 2000 and November 2012. Besides, we aimed to identify pre-procedure risk factors for complications (either minor or major) after a PKB.

MATERIALS AND METHODS

Patients selection

For the purpose of this study, two groups of patients were considered: group I, in whom renal biopsy was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom kidney biopsy was performed and followed by at least 1-day hospital admission.

Patients in group I were prospectively enrolled since January 2012, when we began performing renal biopsies as outpatient procedures in all consecutive patients using a standardized outpatient protocol (as provided in the supplementary material). A prospective computerized database was used to enter the data. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as inpatient procedure. Patients whose data set was not fully available were excluded from our analysis (3 cases).

Percutaneous kidney biopsies were performed when needed as part of good clinical practise for patients refereed to our department. Data collection was performed according to the local legislation of the institutional review board.

Pre-ODS-PKB Standardized procedures

Patients are scheduled within 3 to 7 days from the day of call. Pre-ODS-PKD standardised procedures includes cell blood count (CBC), renal function panel, coagulation profile (prothrombin time, partial thromboplastin, bleeding time, fibrinogen, PFA-100, platelets count), and ECG. Anti-platelets/anticoagulant therapies are screened and hematologic evaluation is routinely requested in patients requiring therapy adjustment prior to biopsy.

Real-time ultrasound-guided renal biopsy

All biopsies were performed by a single nephrologist (DR) with the guidance of an expert radiologist who also performed an ultrasound examination of the kidney prior to PKB. PKB, is performed following a structured protocol . In brief, the skin is prepped with antiseptic solution and draped in the customary fashion. A sterile cover is placed over the ultrasound probe and the kidney visualized. The skin and subcutaneous tissue are anesthetized with lidocaine. The automated biopsy gun (needle 18 gauge, 15 cm) was used. Under real-time ultrasound guidance the biopsy needle gun is advanced. Once it is close to the renal capsule, the gun is fired with the patient holding his or her breath. The biopsy needle is retrieved and

the specimen placed in a media container and sent to surgical pathology. Three passes are performed per patient.

Post- ODS-PKB Standardized monitoring

Patients are placed in a prone position on the bed for at least 2 hours. Patients received i.v. hydration and are observed for symptoms of urine retention. . Monitor urine-analysis for microscopic or macroscopic hematuria is routinely performed. Half-hourly measurements of pulse and blood pressure for two hours after PKD and then hourly till discharge are performed. Post-biopsy imaging was done in all the patients following the protocol. Additional imaging investigations, including additional sonography were performed when clinically indicated at the discretion of the attending physician

Minor or major complications definition

Post-biopsy bleeding complications were categorized as either minor or major. Minor complications included gross hematuria and/or subcapsular perinephric hematoma(<5 cm diameter) that spontaneously resolved without need for further intervention. Major complications were defined as those that required an intervention for resolution, either the transfusion of blood products or an invasive procedure (angiography, surgery), and those that might potentially led to acute renal obstruction or failure, septicaemia, or death. Subcapsular haematoma 5>cm and/or those requiring intervention (despite the size) were considered as major complications

The size of post-biopsy hematomas (surface area) was defined as the product of the longest and the shortest diameters on the two dimensional sonographic pictures.

Data Analysis

The prospective database included demographic and clinical features, laboratory values, biopsy complications, and diagnostic or therapeutic procedures to manage hemorrhagic complications. In addition, the surgical pathology reports were used to ascertain the adequacy of renal tissue and pathologic

diagnosis. Univariate analysis was performed to assess the association between complications and risk factors using the Pearson, χ2 and Fisher exact tests. Multivariate logistic regression analysis was performed to identify significant independent factors adjusted for the potential confounding risk factors able to predict a complication, the results are expressed as Odds Ratios (OR) with 95% Confidence Interval (CI).

. Multivariate survival analysis using the proportional hazards model (Cox model) was performed in the prospective arm of the study. For univariate analysis, the following variables were considered in the model: number of biopsy passes, gender, age, diagnosis, kidney size at sonographic investigations, presence of haematuria before the kidney biopsy, the degree of proteinuria, haemoglobin level before the kidney biopsy, thrombocytopenia, severe arterial hypertension, serum creatinine level before the kidney biopsy, the use of anti-platelets, LMWH, anti-hypertensive agents. For the multivariate analysis included variables were included: gender, age, diagnosis, the degree of proteinuria, haemoglobin level before the kidney biopsy, severe arterial hypertension, serum creatinine level before the kidney biopsy, the use of anti-platelets agents (as described in table 1S). The forward conditional techniques were used to find the final model.

RESULTS

A total of 462 biopsies (group I and group II) were included in this study, 210 (45.5%) of patients were female and the mean age was 54.7 ± 17.9 years. Table 1 summarised demographic, clinical, and laboratory findings in the whole cohort.

Twenty-three per cent of biopsies were performed for the diagnostic workup of nephrotic range proteinuria, 16% for rapidly progressive renal insufficiency, 8% for acute kidney injury, 14% for a chronic kidney disease, and the remaining 39% for non-nephrotic proteinuria and/or hematuria.

A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arterio-venous fistula(6 cases, 1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary

embolism (1, 0,2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2,6%), haematomas on sonography not requiring intervention (15 cases, 3,2%)].

Inpatients and Outpatients

One-hundred and twenty-nine (27.9%) of these biopsies were performed as outpatients and prospectively included. Data from 333 PKD performed as inpatients were retrospectively collected and analysed. Table 1 summarised demographic, clinical, and laboratory findings, dividing patients in group I and II.

Outpatients differed from inpatients with regard total glomeruli obtained (median = 23 [1-71] vs. median = 20 [3-58], p = 0.01), prevalence of pre-biopsy haematuria (78.4% Vs 88.4%) and severe hypertension (13.2% Vs 27.9%). When comparing the complication rate between group I and II, no statically difference were observed [overall 24 (7,2%) complications in group 1 and 12 (9,3%) in group II; 5 (1,5%) and 4(3,1%) major, 19 (5,5%) and 8 (6.2%) minor complications, respectively in group I and II].

Assessment of potential predictors of post-biopsy complications

When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, kidney size at sonographic investigations, presence of haematuria before the kidney biopsy nor the degree of proteinuria. When focusing the survival prospective analysis only on group I, a similar trend was observed, but it failed to reach a statistical significance. Table 1S summaries the factors associated with the presence of complication I the univariate and multivariate model (supplementary materials).

DISCUSSION

The main finding in the present study is that a renal biopsy should be regarded as a safe procedure being overall rate of major complications less than 2%. Importantly, when comparing the complication rate between group I and II, no statically difference was observed, also when stratifying patients for major and

minor complications (overall 7.2% complications in group 1 and 9.3% in group II; 1.5% and 3.1% major, 5.5% and 6.2% minor complications, respectively in group I and II). Although the study was not randomized, it was performed prospectively with a proper follow-up of the patients.

These results are in line with Lin et al.[8] who found that there is no difference in the rate of complications between patients who are admitted and those observed for a 6-hour period, the latest being acceptable. By contrast, Whittier and Korbet [7] found that 42% of complications following native kidney biopsy manifested at ≤ 4 h, 67% at ≤ 8 h, 85% at ≤ 12 h, and 89% at ≤ 24 h.

The main reason for overnight stay in the hospital is basically as a safety net in case there is a major complication[9]. The major complication, which one could encounter, is severe bleeding causing a large retroperitoneal hematoma. This complication can be catastrophic and should be addressed immediately by performing a selective renal arteriogram with embolization of the bleeding arteriole, which will infarct a small portion of the kidney. This complication is in the order of 0 to 6 % depending on the authors[2,7–17]; the reasons for these differences are not cleared but may be related to the technique used (blind vs. ultrasound guided biopsy), operator experience, gauge of the biopsy needle and the number of passes. We demonstrated lower frequency of hemorrhagic complications with real-time ultrasound-guided biopsies, as compared with blind biopsies[10].

Some authors believe that patients are still at risk for type complication beyond the 8 hours observation post-biopsy; we hypothesize that under a controlled environment (see standardized protocol) and a proper technique (real-time ultrasound) we can minimize this risk and be able to have the renal biopsy performed as an outpatient procedure. In detail, Marwah and Korbet[9] in their study accounted together all complications (minor and major) and in their cohort only 42% of the patients had the biopsy performed with an automated gun, the rest were performed with a manual biopsy device and all biopsies were performed with 14-gauge needles and there was no report on how many passes were performed. They timed the major complications, which accounted for 24 out of a total of 394 biopsies (6.6%), and reported that 19 of them were observed before the 8-hour mark. Thus, only 5 major complications were captured after 8 hours of observation. Subsequently, when Whittier and Korbet [7] re-evaluated the data and

reported a series of 750 patients, in which they added the patients from the prior study, they concluded that less than 8-hour period of observation was not optimal and they reported that it could miss up to 33% of complications. Again, all complications (minor and major) were placed in the same category. Out of 750 biopsies, 45 had a major complication (6.6%). Thirty of them were diagnosed before 8-hours of observation, the other 15 were diagnosed between 9 to 24 hours. On the contrary, there at least four studies showing different results. Farazier and Fairley reported only minor complications in a series of 118 patients (only 2 patients) [4]. "Oviasu and Ugdodaga [5] from Nigeria reported no complications in a series of 20 patients.Murphy et al[6], had similar data. Bairy M et al, reported on 178 outpatient renal biopsies and reported no major complications with only 13.2% of minor complications to include 4 patients with gross hematuria, 16 patients with small peri-nephric hematomas and 3 with both hematuria and hematoma[3]. No interventions were needed and only two patients stayed overnight.

The current study shows similar results.

It is worth noting that we observed three thrombotic events after PKD (2 ischaemic strokes and one venous thromboembolism). As our protocol included the pre-PKD use of desmopressin, once could speculate a role of this agent in increasing the thrombotic risk. However, Manno and co-workers[18] when demonstrating in double-blind randomized controlled clinical trial that pre-biopsy desmopressin administration decreases the risk of bleeding and hematoma size in patients undergoing percutaneous kidney, they did not observer any episodes of thrombotic events in both desmopressin and control groups.

Strengths and limitations

This is the largest reported cohort of biopsies performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol. Despite the single center cohort design may potentially limit the external validity of our findings, our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.

One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied. These criteria were set *a priori* with the knowledge that cohort studies are prone to

unpredictable bias and confounding by unknown factors and retrospective data analysis would only add to this risk. However, we used multivariate analysis to ascertain the factors that contribute to postbiopsy complications, allowing for adjusting for potential known confounders, although unknown factors may not be accounted for.

Finally, this study has also identified serum creatinine >3 mg/dl and known severe hypertensionas significant independent predictors of complications; however, when comparing group I and II, a similar trend was observed, but it failed to reach a statistical significance. This may be due to the small number of major complications, especially major, observed in this study, and whether or not these same parameters are also important predictors of the major episodes occurring in ODS-PKD patients requiring intervention is uncertain.

In conclusion**,** our study provides further evidence that it is safe to perform PKB as outpatients procedure after careful screening for bleeding risk, using and automated needle-gun system under ultrasound guide, following a standardized protocol. Therefore, same-day discharge with a 6-hour observation period seems a medically adequate procedure in carefully and this represent significant finding, since outpatient biopsies are economically advantageous.

Contribution authorship statement: Dario Roccatello performed the kidney biopsies. Dario Roccatello and Savino Sciascia designed the study, collected the data and drafted the manuscript. Daniela Rossi, Carla Naretto, Mario Bazzan participated in the clinical evaluation, patients selection, data collection and critically reviewed the manuscript. Laura Solfietti, Elisa Menegatti, Simone Baldovino perfomered the laboratory investigations and critically reviewed the manuscript. Simone Baldovino partecipated in the data analysis.

Competing interests The authors declare no conflict of interest and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work

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Table 1: Demographic, clinical, and laboratory findings in group I and II.

	2000-2015 N. (%)	2000-2012 (Inpatients) N. (%)	2012-2015 (Outpatients) N. (%)	p=
Biopsies	462	333	129	
Passages (mean±SD/median[range])	2.6±0.7/ 3[1-5]	2.9±0.6/ 3[1-5]	3.1±0.6/3[2-5]	NS
Glomeruli (mean±SD/median[range])	19.9±11.3/18[6-71]	21.6±12.4/20[1-71]	23.9±12/23[3-58]	0.01
Age (mean±SD)	54.7 ± 17.9	56 ± 19	52 ± 17.6	NS
Female (%)	180 (39)	114 (34)	66 (51)	NS
Admission duration (days, mean±SD/median[range])	-	1.1 ±0.6/1[1-7]	-	
sCr (mg/dl, mean±SD/median[range])	1.67±1.2/1.3[0.5-7]	1.56±0.9/1.3[0.5-6]	1.8±1.24/1.4[0.5-7]	NS
sCr > 3 mg/dl	124 (26.8)	89 (29.6)	35 (27.1)	NS
Proteinuria (g/24h, mean±SD/median[range])	2.6±2.3/2[0.0-13]	2.7±2.2/2[0.0-10]	2.6±2.2/2[0.2-13]	NS
Pre-biopsy haematuria	375 (81.2)	261 (78.4)	114 (88.4)	0.01
Resistant hypertension*	110 (23.9)	93 (27.9)	17 (13.2)	0.008
Complications (any)	36 (7.8)	24 (7.2)	12 (9.3)	NS
Minor	27 (5.8)	19 (5.7)	8 (6.2)	NS
Major	9 (1.9)	5 (1.5)	4 (3.1)	NS

* Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013 Jul;31(7):1281-357.

	Univariate model				Multivariate Model			
	Major Complications		Minor complication		Major Complications		Minor complication	
	OR (95%CI)	p=	OR (95%CI)	p=	OR (95%CI)	p=	OR (95%CI)	p=
Number of biopsy passes	1.15 (0.41-3.22)	0.78	1.882 (0.23-3.68)	0.83	-	-	-	-
Diagnosis*	1.00 (0.31-3.20)	0.99	1.70 (0.54-5.50)	0.41	-	-	-	-
Male	0.40 (0.10-0.95)	0.039	0.46 (0.06-3.40)	0.71	0.56 (0.11-1.11)	0.071	0.51 (0.36-4.10)	0.89
Age (≥60)	2.30 (1.50-3.50)	0.032	1.20 (0.80-2.00)	0.12	2.07 (0.89-2.70)	0.056	1.12 (0.87-2.99)	0.34
Kidney size at sonographic investigations#	0.63 (0.25-1.60)	0.54	0.79 (0.31–2.00)	0.32	-	-	-	-
Haematuria**	1.21 (0.38-3.90)	0.75	0.92 (0.28–3.00)	0.88	-	-	-	-
Nephrosic proteinuria**	1.60 (1.07–3.00)	0.048	1.60 (0.84–3.00)	0.14	1.54 (0.91–3.24)	0.37	1.70 (0.82–3.12)	0.17
Haemoglobin level**(<10 g/dl)	1.98 (1.40-3.00)	0.041	1.27 (1.01–2.43)	0.047	1.32 (0.98-2.11)	0.067	1.17 (0.89–2.21)	0.071
Thrombocytopenia	3.40 (0.33–34.00)	0.87	2.80 (0.29-8.00)	0.91	-	-	-	-
Severe arterial hypertension**	2.90 (1.30–4.10)	0.003	1.60 (1.02–2.50)	0.04	2.01 (1.2-4.7)	0.037	1.05 (0.97-2.6)	0.065
Serum creatine >3 mg/dl*	2.50 (1.86-3.60)	0.001	2.98 (1.61-6.90)	0.029	2.02 (0.95-3.06)	0.053	OR 2.03 (1.18-6.81)	0.025
Anti-platelets*	2.29 (1.50-3.60)	0.001	2.07 (1.12-4.02)	0.031	2.10 (0.69-2.80)	0.48	1.57 (0.91-3.02)	0.059
LMWH*	1.21 (0.38-3.90)	0.49	0.92 (0.28-3.00)	0.88	-	-	-	-
Anti-hypertensive agents*	3.40 (0.54-31.00)	0.75	2.77 (0.67-17.00)	0.53	-	-	-	-

* categorised in primary glomerulopathy or systemic autoimmune condition; **before the kidney biopsy; # < 8 cm (as defined as J Ultrasound. 2007 Dec;10(4):161-7.)

Outpatient PKB Protocol

Pre-PKB

Cell blood count, renal function panel, coagulation profile (prothrombin time, partial thromboplastin, bleeding time, fibrinogen, PFA-100, platelets count), and ECG. Anti-platelets/anticoagulant therapies are screened. In general, antiplatelet agents stopped 1 week prior to the biopsy. Hematologic evaluation is routinely requested in patients requiring therapy adjustment prior to biopsy.

On the day of PKB

Admission at 8:00 AM on the day of the biopsy.

Biopsy to proceed if blood pressure is 170/95 mm Hg or less. Otherwise, discuss with attending physician*.

Written consent and explanation of procedure and potential complications of PKB (according to risk in this center).

Ensure biopsy equipment available according to checklist and inform pathology department of expectation of sample for processing.

Desmopressin acetate is routinely administered prior to PKB (0.4 microgr/Kg).

PKB Procedure

Biopsy is performed by a consultant nephrologist with the guidance of the sonographer who also performs an ultrasound examination of the kidney prior to discharge patient. A 18G x 15 cm needle is used.

Post-PKB Management

Pulse and blood pressure post-biopsy are constantly monitored: half-hourly measurements of pulse and blood pressure for 2 hours, then hourly for remainder of stay (up to 4 hours or until discharge). Patient to remain in prone position for at least 2 hours.

Saline administration (1,000-1,500 ml) unless fluid retention to reduce risk of clot formation.

Monitor urinalysis for microscopic or macroscopic hematuria. Observe patient for symptoms of urinary retention.

Review by physician prior to discharge.

Resting for two days.

Advice to Patient

Avoid heavy lifting or exercise for 1 week.

Observe urine for clots and blood. If present, call the renal unit for advice.

If severe back pain experienced, contact the renal unit.

Avoid non-steroidal anti-inflammatory drugs for pain relief.

If any concerns, contact the renal unit.

Note

* If the patient presents with values above 170/95 mm Hg, we administer nifedipine oral drops (up to 10 mg) and/or captopril 25 mg and monitor blood pressure every 10 minutes. PKB is performed if blood pressure is stably controlled at 170/95 mm Hg or less, otherwise PKD is postponed till blood pressure stabilization.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			**4-6**
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

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Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

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Abstract

Objectives: We aim to evaluate the safety of performing percutaneous native kidney biopsy (PKB) as an outpatient procedure (implying an observation period of 6 hrs) compared to the traditional inpatient policy.

Design, setting, participants, and measurements: Group I, in whom PKB was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom PKB was performed and followed by at least 1-day hospital admission. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as inpatient procedure. All biopsies were performed by a single nephrologist following a structured protocol.

Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7±17.9 years. One-hundred and twenty-nine (27.9%) of these biopsies were performed in outpatients. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arteriovenous fistula (6 cases, 1.2%), ischaemic stroke (2; 0.4%), thromboembolic pulmonary embolism (1; 0.2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases,2.6%), haematomas on sonography not requiring intervention (15 cases, 3.2%)]. When comparing the complication rate between group I and II, no statically difference were observed. When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95% CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy nor the degree of proteinuria.

Conclusions: Outpatient biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

Article summary

Strengths and limitations of this study

- This is the largest reported cohort of percutaneous kidney biopsies (PKB) performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol.
- Our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.
- One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied.

INTRODUCTION

Percutaneous biopsy of native kidneys is an important diagnostic tool for clinicians seeking a diagnosis for patients with kidney disease. The primary risks for percutaneous kidney biopsy (PKB) range from mild complications such as post-procedural pain and gross hematuria to major complications such as large hematomas requiring blood transfusion, uncontrolled bleeding requiring embolization or surgical nephrectomy, and rarely death[1]. The technique for obtaining tissue has evolved with the emergence of direct ultrasound guidance as the standard of care, dramatically improving procedural safety and diagnostic yield[2]. While a number of centres worldwide require overnight inpatient observation (IO) following PKB, several studies have suggested the safety of the outpatient 'day surgery' (ODS) approach[2,3]. However, to date, debate still exists on the appropriate observation time after PKB. In fact, despite some studies have shown that discharging patients within 4–6 h after biopsy seems to be safe[4–6] , Whittier and Korbet found that an observation period of less than 8 hours following biopsy missed 33% of complications[7].

We carried out a prospective observational study over a 5-year period of consecutive outpatient native renal biopsies to evaluate safety of ODS-PKB. Outcomes and the rate of complications after ODS-PKB were compared to IO-PKD performed in our Institution between January 2000 and November 2012. Besides, we aimed to identify pre-procedure risk factors for complications (either minor or major) after a PKB.

MATERIALS AND METHODS

Patients selection

For the purpose of this study, two groups of patients were considered: group I, in whom renal biopsy was performed in the outpatient department (2012-2016) and followed by 6 hours' observation period and then by regular outpatient visits and group II, in whom kidney biopsy was performed and followed by at least 1-day hospital admission.

Patients in group I were prospectively enrolled since January 2012, when we began performing renal biopsies as outpatient procedures in all consecutive patients using a standardized outpatient protocol (as provided in the supplementary material). A prospective computerized database was used to enter the data. Group II included retrospectively retrieved patients who underwent PKB in our Institution between January 2000 and November 2012 as inpatient procedure. Patients whose data set was not fully available were excluded from our analysis (3 cases).

Percutaneous kidney biopsies were performed when needed as part of good clinical practise for patients refereed to our department. Data collection was performed according to the local legislation of the institutional review board.

Pre-ODS-PKB Standardized procedures

Patients are scheduled within 3 to 7 days from the day of call. Pre-ODS-PKD standardised procedures includes cell blood count (CBC), renal function panel, coagulation profile (prothrombin time, partial thromboplastin, bleeding time, fibrinogen, PFA-100, platelets count), and ECG. Anti-platelets/anticoagulant therapies are screened and hematologic evaluation is routinely requested in patients requiring therapy adjustment prior to biopsy.

Real-time ultrasound-guided renal biopsy

All biopsies were performed by a single nephrologist (DR) with the guidance of an expert radiologist who also performed an ultrasound examination of the kidney prior to PKB. PKB, is performed following a structured protocol . In brief, the skin is prepped with antiseptic solution and draped in the customary fashion. A sterile cover is placed over the ultrasound probe and the kidney visualized. The skin and subcutaneous tissue are anesthetized with lidocaine. The automated biopsy gun (needle 18 gauge, 15 cm) was used. Under real-time ultrasound guidance the biopsy needle gun is advanced. Once it is close to the renal capsule, the gun is fired with the patient holding his or her breath. The biopsy needle is retrieved and

the specimen placed in a media container and sent to surgical pathology. Three passes are performed per patient.

Post- ODS-PKB Standardized monitoring

Patients are placed in a prone position on the bed for at least 2 hours. Patients received i.v. hydration and are observed for symptoms of urine retention. Monitor urine-analysis for microscopic or macroscopic hematuria is routinely performed. Half-hourly measurements of pulse and blood pressure for two hours after PKD and then hourly till discharge are performed. Post-biopsy imaging was done in all the patients following the protocol. Additional imaging investigations, including additional sonography were performed when clinically indicated at the discretion of the attending physician

Minor or major complications definition

Post-biopsy bleeding complications were categorized as either minor or major. Minor complications included gross hematuria and/or subcapsular perinephric hematoma(<5 cm diameter) that spontaneously resolved without need for further intervention. Major complications were defined as those that required an intervention for resolution, either the transfusion of blood products or an invasive procedure (angiography, surgery), and those that might potentially led to acute renal obstruction or failure, septicaemia, or death. Subcapsular haematoma 5>cm and/or those requiring intervention (despite the size) were considered as major complications

The size of post-biopsy hematomas (surface area) was defined as the product of the longest and the shortest diameters on the two dimensional sonographic pictures.

Data Analysis

The prospective database included demographic and clinical features, laboratory values, biopsy complications, and diagnostic or therapeutic procedures to manage hemorrhagic complications. In addition, the surgical pathology reports were used to ascertain the adequacy of renal tissue and pathologic

diagnosis. Univariate analysis was performed to assess the association between complications and risk factors using the Pearson, χ2 and Fisher exact tests. For univariate analysis, the following variables were considered in the model: number of biopsy passes, gender, age, diagnosis, kidney size at sonographic investigations, presence of haematuria before the kidney biopsy, the degree of proteinuria, haemoglobin level before the kidney biopsy, thrombocytopenia, severe arterial hypertension, serum creatinine level before the kidney biopsy, the use of anti-platelets, LMWH, anti-hypertensive agents.

. Multivariate logistic regression analysis was performed to identify significant independent factors adjusted for the potential confounding risk factors able to predict a complication, the results are expressed as Odds Ratios (OR) with 95% Confidence Interval (CI).The final multivariate logistic regression model includes variables: gender, age, diagnosis, the degree of proteinuria, haemoglobin level before the kidney biopsy, severe arterial hypertension, serum creatinine level before the kidney biopsy, the use of antiplatelets agents (as described in table 1S). The forward conditional techniques were used to find the final model.

In order to analyse risk factors associated with time to complication, multivariate survival analysis was performed using the proportional hazards model (Cox model) in the prospective arm of the study Risk factors included sex, diagnosis (categorised in primary glomerulopathy or systemic autoimmune condition), age ≥60, Kidney size < 8 cm at sonographic investigations, haematuria, nephrosic proteinuria, haemoglobin level (<10 g/dl), thrombocytopenia, severe arterial hypertension, serum creatinine >3 mg/dl, use of anti-platelets, LMWH, anti-hypertensive agents.

RESULTS

A total of 462 biopsies (group I and group II) were included in this study, 210 (45.5%) of patients were female and the mean age was 54.7 ± 17.9 years. Table 1 summarised demographic, clinical, and laboratory findings in the whole cohort.

Twenty-three per cent of biopsies were performed for the diagnostic workup of nephrotic range proteinuria, 16% for rapidly progressive renal insufficiency, 8% for acute kidney injury, 14% for a chronic kidney disease, and the remaining 39% for non-nephrotic proteinuria and/or hematuria.

A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arterio-venous fistula(6 cases, 1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary embolism (1, 0,2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2,6%), haematomas on sonography not requiring intervention (15 cases, 3,2%)].

Inpatients and Outpatients

One-hundred and twenty-nine (27.9%) of these biopsies were performed as outpatients and prospectively included. Data from 333 PKD performed as inpatients were retrospectively collected and analysed. Table 1 summarised demographic, clinical, and laboratory findings, dividing patients in group I and II.

Outpatients differed from inpatients with regard total glomeruli obtained (median = 23 [1-71] vs. median = 20 [3-58], p = 0.01), prevalence of pre-biopsy haematuria (78.4% Vs 88.4%) and severe hypertension (13.2% Vs 27.9%). When comparing the complication rate between group I and II, no statically difference were observed [overall 24 (7,2%) complications in group 1 and 12 (9,3%) in group II; 5 (1,5%) and 4(3,1%) major, 19 (5,5%) and 8 (6.2%) minor complications, respectively in group I and II].

Assessment of potential predictors of post-biopsy complications

When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, kidney size at sonographic investigations, presence of haematuria before the kidney biopsy nor the degree of proteinuria. When focusing the survival prospective analysis only on group I, a similar trend was observed, but it failed to reach a statistical significance. Table 1S summaries the factors associated with the presence of complication I the univariate and multivariate model (supplementary materials).

DISCUSSION

The main finding in the present study is that a renal biopsy should be regarded as a safe procedure being overall rate of major complications less than 2%. Importantly, when comparing the complication rate between group I and II, no statically difference was observed, also when stratifying patients for major and minor complications (overall 7.2% complications in group 1 and 9.3% in group II; 1.5% and 3.1% major, 5.5% and 6.2% minor complications, respectively in group I and II). Although the study was not randomized, it was performed prospectively with a proper follow-up of the patients.

These results are in line with Lin et al.[8] who found that there is no difference in the rate of complications between patients who are admitted and those observed for a 6-hour period, the latest being acceptable. By contrast, Whittier and Korbet [7] found that 42% of complications following native kidney biopsy manifested at ≤ 4 h, 67% at ≤ 8 h, 85% at ≤ 12 h, and 89% at ≤ 24 h.

The main reason for overnight stay in the hospital is basically as a safety net in case there is a major complication[9]. The major complication, which one could encounter, is severe bleeding causing a large retroperitoneal hematoma. This complication can be catastrophic and should be addressed immediately by performing a selective renal arteriogram with embolization of the bleeding arteriole, which will infarct a small portion of the kidney. This complication is in the order of 0 to 6 % depending on the authors[2,7–17]; the reasons for these differences are not cleared but may be related to the technique used (blind vs. ultrasound guided biopsy), operator experience, gauge of the biopsy needle and the number of passes. We demonstrated lower frequency of hemorrhagic complications with real-time ultrasound-guided biopsies, as compared with blind biopsies[10].

Some authors believe that patients are still at risk for type complication beyond the 8 hours observation post-biopsy; we hypothesize that under a controlled environment (see standardized protocol) and a proper technique (real-time ultrasound) we can minimize this risk and be able to have the renal biopsy performed as an outpatient procedure. In detail, Marwah and Korbet[9] in their study accounted together all complications (minor and major) and in their cohort only 42% of the patients had the biopsy performed with an automated gun, the rest were performed with a manual biopsy device and all biopsies were

performed with 14-gauge needles and there was no report on how many passes were performed. They timed the major complications, which accounted for 24 out of a total of 394 biopsies (6.6%), and reported that 19 of them were observed before the 8-hour mark. Thus, only 5 major complications were captured after 8 hours of observation. Subsequently, when Whittier and Korbet [7] re-evaluated the data and reported a series of 750 patients, in which they added the patients from the prior study, they concluded that less than 8-hour period of observation was not optimal and they reported that it could miss up to 33% of complications. Again, all complications (minor and major) were placed in the same category. Out of 750 biopsies, 45 had a major complication (6.6%). Thirty of them were diagnosed before 8-hours of observation, the other 15 were diagnosed between 9 to 24 hours. On the contrary, there at least four studies showing different results. Farazier and Fairley reported only minor complications in a series of 118 patients (only 2 patients) [4]. "Oviasu and Ugdodaga [5] from Nigeria reported no complications in a series of 20 patients.Murphy et al[6], had similar data. Bairy M et al, reported on 178 outpatient renal biopsies and reported no major complications with only 13.2% of minor complications to include 4 patients with gross hematuria, 16 patients with small peri-nephric hematomas and 3 with both hematuria and hematoma[3]. No interventions were needed and only two patients stayed overnight.

The current study shows similar results.

It is worth noting that we observed three thrombotic events after PKD (2 ischaemic strokes and one venous thromboembolism). As our protocol included the pre-PKD use of desmopressin, once could speculate a role of this agent in increasing the thrombotic risk. However, Manno and co-workers[18] when demonstrating in double-blind randomized controlled clinical trial that pre-biopsy desmopressin administration decreases the risk of bleeding and hematoma size in patients undergoing percutaneous kidney, they did not observer any episodes of thrombotic events in both desmopressin and control groups.

Strengths and limitations

This is the largest reported cohort of biopsies performed in a single center by a single experience nephrologist using automated devices and ultrasound guidance following a structured protocol. Despite the

single center cohort design may potentially limit the external validity of our findings, our experience is not biased by heterogeneity in PKB approaches and level of expertise of the operator performing PKB.

One limitation of our study is ambispective fashion of study design. Both prospective and retrospective data were studied. These criteria were set *a priori* with the knowledge that cohort studies are prone to unpredictable bias and confounding by unknown factors and retrospective data analysis would only add to this risk. However, we used multivariate analysis to ascertain the factors that contribute to postbiopsy complications, allowing for adjusting for potential known confounders, although unknown factors may not be accounted for.

Finally, this study has also identified serum creatinine >3 mg/dl and known severe hypertensionas significant independent predictors of complications; however, when comparing group I and II, a similar trend was observed, but it failed to reach a statistical significance. This may be due to the small number of major complications, especially major, observed in this study, and whether or not these same parameters are also important predictors of the major episodes occurring in ODS-PKD patients requiring intervention is uncertain.

In conclusion**,** our study provides further evidence that it is safe to perform PKB as outpatients procedure after careful screening for bleeding risk, using and automated needle-gun system under ultrasound guide, following a standardized protocol. Therefore, same-day discharge with a 6-hour observation period seems a medically adequate procedure in carefully and this represent significant finding, since outpatient biopsies are economically advantageous.

Contribution authorship statement: Dario Roccatello performed the kidney biopsies. Dario Roccatello and Savino Sciascia designed the study, collected the data and drafted the manuscript. Daniela Rossi, Carla Naretto, Mario Bazzan participated in the clinical evaluation, patients selection, data collection and critically reviewed the manuscript. Laura Solfietti, Elisa Menegatti, Simone Baldovino perfomered the laboratory investigations and critically reviewed the manuscript. Simone Baldovino partecipated in the data analysis.

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Table 1: Demographic, clinical, and laboratory findings in group I and II.

	2000-2015 N. (%)	2000-2012 (Inpatients) N. (%)	2012-2015 (Outpatients) N. (%)	p=
Biopsies	462	333	129	
Passages (mean±SD/median[range])	2.6±0.7/ 3[1-5]	2.9±0.6/ 3[1-5]	3.1±0.6/3[2-5]	NS
Glomeruli (mean±SD/median[range])	19.9±11.3/18[6-71]	21.6±12.4/20[1-71]	23.9±12/23[3-58]	0.01
Age (mean±SD)	54.7 ± 17.9	56 ± 19	52 ± 17.6	NS
Female (%)	180 (39)	114 (34)	66 (51)	NS
Admission duration (days, mean±SD/median[range])	-	1.1 ±0.6/1[1-7]	-	
sCr (mg/dl, mean±SD/median[range])	1.67±1.2/1.3[0.5-7]	1.56±0.9/1.3[0.5-6]	1.8±1.24/1.4[0.5-7]	NS
sCr > 3 mg/dl	124 (26.8)	89 (29.6)	35 (27.1)	NS
Proteinuria (g/24h, mean±SD/median[range])	2.6±2.3/2[0.0-13]	2.7±2.2/2[0.0-10]	2.6±2.2/2[0.2-13]	NS
Pre-biopsy haematuria	375 (81.2)	261 (78.4)	114 (88.4)	0.01
Resistant hypertension*	110 (23.9)	93 (27.9)	17 (13.2)	0.008
Complications (any)	36 (7.8)	24 (7.2)	12 (9.3)	NS
Minor	27 (5.8)	19 (5.7)	8 (6.2)	NS
Major	9 (1.9)	5 (1.5)	4 (3.1)	NS

* Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013 Jul;31(7):1281-357.

	Univariate model				Multivariate Model			
	Major Complications		Minor complication		Major Complications		Minor complication	
	OR (95%CI)	p=	OR (95%CI)	p=	OR (95%CI)	p=	OR (95%CI)	p=
Number of biopsy passes	1.15 (0.41-3.22)	0.78	1.882 (0.23-3.68)	0.83	-	-	-	-
Diagnosis*	1.00 (0.31-3.20)	0.99	1.70 (0.54-5.50)	0.41	-	-	-	-
Male	0.40 (0.10-0.95)	0.039	0.46 (0.06-3.40)	0.71	0.56 (0.11-1.11)	0.071	0.51 (0.36-4.10)	0.89
Age (≥60)	2.30 (1.50-3.50)	0.032	1.20 (0.80-2.00)	0.12	2.07 (0.89-2.70)	0.056	1.12 (0.87-2.99)	0.34
Kidney size at sonographic investigations#	0.63 (0.25-1.60)	0.54	0.79 (0.31–2.00)	0.32	-	-	-	-
Haematuria**	1.21 (0.38-3.90)	0.75	0.92 (0.28–3.00)	0.88	-	-	-	-
Nephrosic proteinuria**	1.60 (1.07–3.00)	0.048	1.60 (0.84–3.00)	0.14	1.54 (0.91–3.24)	0.37	1.70 (0.82–3.12)	0.17
Haemoglobin level**(<10 g/dl)	1.98 (1.40-3.00)	0.041	1.27 (1.01–2.43)	0.047	1.32 (0.98-2.11)	0.067	1.17 (0.89–2.21)	0.071
Thrombocytopenia	3.40 (0.33–34.00)	0.87	2.80 (0.29-8.00)	0.91	-	-	-	-
Severe arterial hypertension**	2.90 (1.30–4.10)	0.003	1.60 (1.02–2.50)	0.04	2.01 (1.2-4.7)	0.037	1.05 (0.97-2.6)	0.065
Serum creatine >3 mg/dl*	2.50 (1.86-3.60)	0.001	2.98 (1.61-6.90)	0.029	2.02 (0.95-3.06)	0.053	OR 2.03 (1.18-6.81)	0.025
Anti-platelets*	2.29 (1.50-3.60)	0.001	2.07 (1.12-4.02)	0.031	2.10 (0.69-2.80)	0.48	1.57 (0.91-3.02)	0.059
LMWH*	1.21 (0.38-3.90)	0.49	0.92 (0.28-3.00)	0.88	-	-	-	-
Anti-hypertensive agents*	3.40 (0.54-31.00)	0.75	2.77 (0.67-17.00)	0.53	-	-	-	-

* categorised in primary glomerulopathy or systemic autoimmune condition; **before the kidney biopsy; # < 8 cm (as defined as J Ultrasound. 2007 Dec;10(4):161-7.)

Outpatient PKB Protocol

Pre-PKB

Cell blood count, renal function panel, coagulation profile (prothrombin time, partial thromboplastin, bleeding time, fibrinogen, PFA-100, platelets count), and ECG. Anti-platelets/anticoagulant therapies are screened. In general, antiplatelet agents stopped 1 week prior to the biopsy. Hematologic evaluation is routinely requested in patients requiring therapy adjustment prior to biopsy.

On the day of PKB

Admission at 8:00 AM on the day of the biopsy.

Biopsy to proceed if blood pressure is 170/95 mm Hg or less. Otherwise, discuss with attending physician*.

Written consent and explanation of procedure and potential complications of PKB (according to risk in this center).

Ensure biopsy equipment available according to checklist and inform pathology department of expectation of sample for processing.

Desmopressin acetate is routinely administered prior to PKB (0.4 microgr/Kg).

PKB Procedure

Biopsy is performed by a consultant nephrologist with the guidance of the sonographer who also performs an ultrasound examination of the kidney prior to discharge patient. A 18G x 15 cm needle is used.

Post-PKB Management

Pulse and blood pressure post-biopsy are constantly monitored: half-hourly measurements of pulse and blood pressure for 2 hours, then hourly for remainder of stay (up to 4 hours or until discharge). Patient to remain in prone position for at least 2 hours.

Saline administration (1,000-1,500 ml) unless fluid retention to reduce risk of clot formation.

Monitor urinalysis for microscopic or macroscopic hematuria. Observe patient for symptoms of urinary retention.

Review by physician prior to discharge.

Resting for two days.

Advice to Patient

Avoid heavy lifting or exercise for 1 week.

Observe urine for clots and blood. If present, call the renal unit for advice.

If severe back pain experienced, contact the renal unit.

Avoid non-steroidal anti-inflammatory drugs for pain relief.

If any concerns, contact the renal unit.

Note

* If the patient presents with values above 170/95 mm Hg, we administer nifedipine oral drops (up to 10 mg) and/or captopril 25 mg and monitor blood pressure every 10 minutes. PKB is performed if blood pressure is stably controlled at 170/95 mm Hg or less, otherwise PKD is postponed till blood pressure stabilization.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			**4-6**
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations			9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.