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Risk Factors for Major Hemorrhage Following Percutaneous Image-Guided Renal Biopsy: What is the "core" of the Problem? A Retrospective Case–control Study

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ABSTRACT

Objectives: Percutaneous renal biopsy (PRB) plays a critical role in the work-up of renal parenchymal disease. Although it is considered a low-risk procedure, additional interventions may be required in about 7% of the cases following biopsy. The purpose of this study was to identify risk factors for major hemorrhage by microscopic analysis of the cores obtained following PRB, with an intent to enhance the sensitivity and specificity of the risk stratification process, especially in patients undergoing this procedure in an outpatient setting.

Material and Methods: A retrospective review identified 17 of 179 patients (9.50%) with major hemorrhage following PRB between July 2014 and June 2019. Using propensity score matching, 26 controls (without major hemorrhage) were matched to 17 cases (with major hemorrhage). The biopsy cores obtained from the cases and controls were analyzed by a single pathologist for medullary, cortical, total (medullary + cortical) lengths, and the number of arcuate arteries (AAs). Medullary:cortical (M:C), cortical:total (C:T), and medullary:total (M:T) length ratios were then calculated.

Results: A stratified version of logistic regression was used to test for an association between each of the variables identified on the cores and the probability of a major hemorrhage. The analysis revealed that there was a statistically significant association between the number of AAs per specimen with the risk of major hemorrhage ($P = 0.0006$). When 0, 1, or >2 AAs were identified, the frequency of major hemorrhage was 13.04%, 66.67%, and 75.00%, respectively. The odds of major hemorrhage were 6 times higher with one AA and (95% CI, 1.28–32.30) and 15 times higher with >2 AAs (95% CI, 1.41–169.57). No significant association was found between medullary length ($P = 0.228$), medulla:cortex (M:C) ($P = 0.089$), medulla:total (M:T) ($P = 0.108$), or cortex:total (C:T) ($P = 0.112$) length ratios and major hemorrhage.

Conclusion: There was a strong and incremental correlation between major renal hemorrhage following PRB and the number of AAs per core specimen. Identification of AAs by the pathologist, while assessing for sample adequacy, in the US suite can help predict major hemorrhage in patients undergoing PRBs.

Keywords: Ultrasound, Percutaneous renal biopsy, Renal hemorrhage, Renal angiogram, Coil embolization, Blood transfusion

INTRODUCTION

Percutaneous renal biopsy (PRB) is an important step in the work-up of renal parenchymal disease. To improve biopsy yield and reduce complications, majority of PRBs are performed with

ultrasound (US) guidance.[1] However, despite the widespread use of US guidance, hemorrhage following PRB has been reported to occur in as many as 30% of cases, with up to 7% being life-threatening or needing additional procedures such as blood transfusion, endovascular interventions, major operations, and prolonged hospitalization.[1-5]

Several factors have been associated with an increased risk of post-biopsy hemorrhage, including patient gender, age, serum creatinine, bleeding diathesis, hypertension, operator experience, biopsy needle size, position within the kidney, angle, depth, and number of needle passes.[2,6-11]

To the best of our knowledge, no prior studies have analyzed the microscopic findings of the cores obtained following PRBs, with an intent to identify risk factors associated with major post-biopsy hemorrhage. Identification of pertinent findings in the biopsy cores that would predict the odds of a major hemorrhage following PRB would help to enhance the sensitivity and specificity of the risk stratification process, which would, in turn, help to decide if prolonged observation is necessary, especially in situations, where PRB is performed as an ambulatory/outpatient procedure.

Research ethics standards compliance

This original research was completed under an Institutional Review Board (IRB) approved protocol which waived the need for an informed consent. The IRB number was 2004777. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

MATERIAL AND METHODS

Patient selection

A retrospective review of 179 patients who underwent US-guided PRB in a single large tertiary care hospital between July 2014 and June 2019 was performed. The electronic medical records of these patients were evaluated for major hemorrhage within 30 days of the procedure. Major hemorrhage was defined as one that required blood transfusions, endovascular procedures, nephrectomy, or resulted in death within 30 days of the PRB. Subjects who received multiple biopsies on the same day, those who were under the age of 18, and biopsies performed for a focal renal lesion were excluded from the study. After appropriate matching was performed, the biopsy cores obtained from the cases (with major hemorrhage) and controls (without major hemorrhage) were analyzed by a single pathologist for medullary, cortical, total (Medullary + Cortical), lengths, and number of arcuate arteries (AAs) [Tables 1 and 2]. The medullary:cortical (M:C), medullary:total (M:T), and cortical:total (C:T) length ratios were also generated and recorded.

Table 1: Summary statistics for the non-bleed group.

Variable	Mean	Std. dev.	Median	Min.	Max.
Medullary length (mm)	3.85	5.60	1.50	0.00	18.00
Cortical length (mm)	21.77	9.10	19.00	10.00	47.00
Total length	25.85	11.64	24.00	10.00	51.00
M:C ratio	0.18	0.61	0.06	0.00	0.38
C:T ratio	0.84	0.78	0.79	1.0	0.92
M:T ratio	0.14	0.48	0.06	0.00	0.35
Number of cores	4.73	1.59	4.00	3.00	10.00
Arcuate arteries	0.31	0.62	0.00	0.00	2.00
Interlobar arteries	0.96	0.92	1.00	0.00	3.00

Table 2: Summary statistics for major bleed cases.

Variable	Mean	Std. dev.	Median	Min.	Max.
Medullary length (mm)	5.88	8.64	3.00	0.00	33.00
Cortical length (mm)	17.32	8.57	17.00	3.00	38.50
Total length (mm)	23.21	11.12	20.00	11.00	44.00
M:C ratio	0.34	1.07	0.17	0.00	0.85
C:T ratio	0.74	0.76	0.89	0.21	0.87
M:T ratio	0.25	0.77	0.15	0.00	0.75
No. of cores	4.35	1.37	4.00	3.00	8.00
Arcuate arteries	1.29	0.99	1.00	0.00	4.00
Interlobar arteries	1.35	1.37	1.00	0.00	5.00

Biopsy procedural details

For each procedure, written informed consent was obtained. About 1% lidocaine was used for local anesthesia. Conscious sedation with fentanyl and midazolam (Hospira Inc., Lake Forest, IL, USA) was used in all cases. US-guided PRBs were performed most often using an 18-gauge Bard Mission (Bard Biopsy Systems, Tempe, AZ) or Biopince (Argon Medical Devices, Frisco TX) devices. The biopsies were performed either by board certified and fellowship trained interventional radiologists or radiology residents under their supervision. The lower pole of the kidney was targeted in all the cases. In most of the cases, the biopsy tract was packed with gel foam slurry, injected through the coaxial needle before its withdrawal. Each kidney sample was evaluated immediately following biopsy for adequate glomeruli by a board-certified pathologist. Per protocol, at least three adequate core samples were obtained during the biopsy procedure.

Pathologist procedure details

The slide with the most tissue present was selected, and a micrometer was used to measure the total, medullary, and cortical lengths of the biopsy cores. The AAs [Figure 1] were defined as any medium-sized arteries that are surrounded by soft tissue and not by renal parenchyma. Almost all of these were partially cut through their longitudinal walls.

Statistical analysis

The statistical analysis was done with a commercially available statistical package, SPSS for Windows, Version 15.0 (IBM SPSS for Windows, Version 15.0). Intergroup comparisons between cases and controls before propensity score matching (PSM) analysis were performed using an unpaired *t*-test assuming unequal variances (Welch's *t*-test). A PSM analysis was used to avoid selection bias, to improve comparability, and to ensure an even distribution of confounders such as sex, age, body mass index, blood pressure, international normalized ratio, platelet (PLT) count, blood urea nitrogen (BUN), creatinine (Cr), estimated glomerular filtration rate (eGFR), needle size, and core number, between the groups. Seventeen cases were matched to 26 controls. Intergroup comparisons between cases and controls after PSM analysis were again performed using an unpaired *t*-test assuming unequal variances (Welch's *t*-test). A paired *t*-test was used to explore statistical significance between several characteristic of the cores obtained from PRBs and the possibility of a major hemorrhage. A stratified version of logistic regression was used to test for an association between each of the variables identified on the cores and the probability of a major hemorrhage. A significance level ($P < 0.05$) was applied for all analysis. As the sample size was small, exact tests of significance were used. The odds ratio was used to quantify the change in odds of a major hemorrhage, for a one-unit change in the predictor.

RESULTS

The retrospective review identified 17 of 179 patients (9.50%) with major hemorrhage within 30 days following US-guided PRB. Of the 17 patients who had major hemorrhage, 4 had angiograms looking for a vascular abnormality, but these patients did not receive any other intervention. Two patients had an angiogram with coiling of the pseudoaneurysm/fistula [Table 3]. Sixteen patients received blood transfusions. Intergroup comparisons between cases and controls before PSM analysis [Table 4] showed that Hgb, BUN levels, and eGFR values were statistically significant for a major hemorrhage (P = 0.0348, 0.0055, and 0.0021, respectively). To avoid confounding bias and improve intergroup compatibility in terms of the histological parameters, PSM was [Table 5] done in 26 controls. Tables 1 and 2 demonstrate the summary data for histological parameters measured in renal core biopsy samples of the cases and controls. To evaluate the relationship between each histological parameter and the risk of major hemorrhage following PRB, a logistic regression was performed with risk of hemorrhage as the dependent variable. The analysis revealed that the number of AAs per specimen was a significant risk factor for a major hemorrhage (P = 0.0006). No significant association was found between medullary length (ML) (P = 0.228), M:C (P = 0.089), M:T (P = 0.108), or C:T (P = 0.112) length ratios

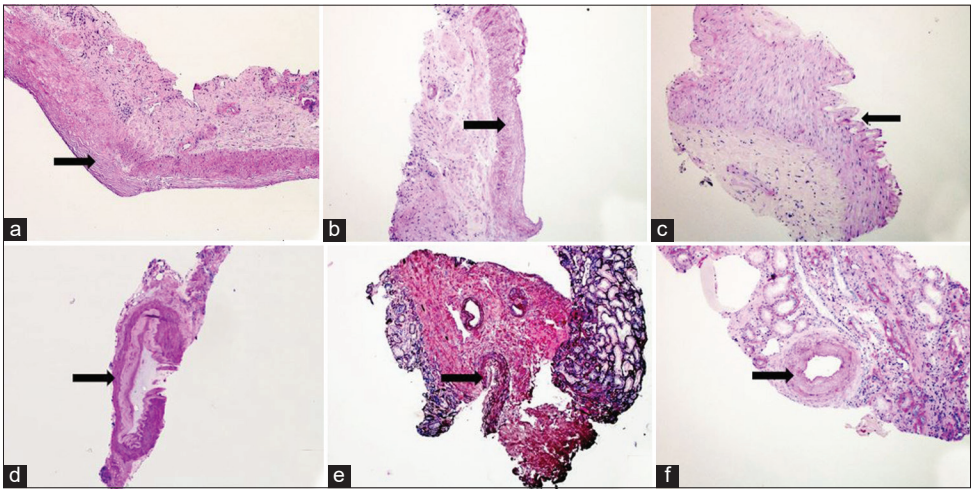

Figure 1: Photomicrographs of the percutaneous renal biopsy cores (PAS-D and PAM silver stains) of six different patients (both cases and controls) demonstrating the vessels that were included or excluded as arcuate arteries in the analysis. Photomicrographs of arteries (a-c) included as arcuate arteries as they are surrounded by abundant soft tissue having thick arterial wall (indicated by black arrows). Photomicrographs of arteries (d-f) that were excluded as arcuate arteries as they have thin arterial walls without substantial surrounding soft tissue (indicated by black arrows).

Table 3: Interventions for major hemorrhage following PRB.

Interventions	Incidence in major bleeders (%)	Overall incidence (%)
Angiogram without intervention	4/17 (24)	4/179 (2)
Angiogram with coiling	2/17 (11)	2/179 (1)
Blood transfusion	16/17 (94)	15/179 (8)

Table 4: Comparison of characteristics before PSM.

Parameter	Cases	Controls	*P*-value
No. of patients	17	162	
Age (y)	48.8±19.2	46.1±17.1	0.5047
Male sex	44%	45%	
Body mass index (kg/m^2)	34.4±6.4	32.1±11.3	0.8438
Systolic blood pressure	147±17	141±20	0.5119
Diastolic blood pressure	88±12	81±13	0.5472
Hgb (g/dL)	9.1±2.7	10.5±2.3	0.0348
International normalized ratio	1.07±0.18	0.99±0.13	0.1066
Platelets (x109/L)	197.3±88.0	213.5±103.6	0.0617
BUN (mg/dL)	61.0±27.5	31.3±29.2	0.0055
Estimated glomerular filtration rate (mL/min/1.73 m^2)	21.5±17.7	26.6±32.2	0.0021
No. of cores	4.4±1.3	4.1±1.3	0.4660
Left laterality*	78%	73%	
Gel foam	67%	83%	0.0911

*Left laterality was the side of the biopsy. Values are mean±STD

and major hemorrhage [Table 6]. When 0, 1, or ≥2 AAs were identified, the frequency of major hemorrhage was 13%, 66%, and 75.00%, respectively. To determine the incremental risk of hemorrhage based on number of AAs, data were stratified into samples containing either one or two AAs. The odds of major hemorrhage were 6 times higher with one AA and (95% CI, 1.28–32.30) and 15 times higher with ≥2 AAs (95% CI, 1.41–169.57) [Table 7].

DISCUSSION

Kidney biopsy is an essential procedure for nephrologists to make a diagnosis, assess prognosis, and formulate a treatment plan and for the research of various kidney diseases.[12-14] It is the gold standard for diagnosis of native and transplant kidney diseases. Majority of the PRBs in the United States and around the world are being performed by fellowship trained interventional radiologists (IRs) comfortable with US-guided procedures.[15,16] Despite this, additional intervention in the form of blood transfusions or endovascular procedures is required after 0.3–9.0% of PRBs.[6,17-22] IRs perform coil embolization/stent placement for bleeding complications in several vascular territories, which makes them ideal to

Table 5: Comparison of matched characteristics after PSM.

Matched parameter	Cases	Controls	*P*-value
No. of patients	17	26	
Age (y)	48.8±19.2	45.3±17.5	0.5218
Male sex	44%	41%	
Body mass index (kg/m^2)	34.4±6.4	36.2±13.3	0.5317
Systolic blood pressure	147±17	148±18	0.8128
Diastolic blood pressure	88±12	87±13	0.4329
Hgb (g/dL)	9.1±2.7	9.2±1.8	0.9395
International normalized ratio	1.07±0.18	1.05±0.15	0.5682
Platelets (×10^9/L)	197.3±88.0	220.0±95.5	0.3131
BUN (mg/dL)	61.0±27.5	59.3±37.5	0.8081
Estimated glomerular filtration rate (mL/min/1.73 m^2)	21.5±17.7	22.8±20.3	0.8789
No. of cores	4.4±1.3	4.4±1.6	0.8112
Left laterality*	78%	89%	
Gel foam	67%	83%	0.4111

*Left laterality was the side of the biopsy. Values are mean±STD

Table 6: Relationship of histologic parameters to risk of major hemorrhage tested using a logistic regression model.

Variable	Odds ratio	95% confidence interval	*P*-value
M:C ratio	3.8	(0.89, 63.63)	0.089
C:T ratio	0.05	(<0.001, 1.78)	0.112
M:T ratio	19.55	(0.58, 985.00)	0.108
Medullary length	1.07	(0.96, 1.22)	0.228
Average medullary length	1.33	(0.91, 2.22)	0.162
Arcuate artery	4.8	(1.77, 18.72)	0.006
Interlobular artery	1.33	(0.69, 2.64)	0.393

Table 7: Incremental hemorrhage risk associated with arcuate arteries in the core sample.

Arcuate artery	Odds ratio	Lower confidence limits	Upper confidence limits
1 versus none	6.5	1.28	32.3
2 versus none	15.5	1.41	169.57

treat bleeding complications from PRBs that may need additional endovascular interventions.[23-26] Post-renal biopsy hemorrhage is likely the result of multiple factors including the intrinsic renal vascularity, the non-compressible location of the kidneys, the need for multiple needle passes to ensure an adequate tissue sample, and medical comorbidities such as obesity, liver dysfunction, and diabetes.[27-29] Post-biopsy bleeding can be further categorized into major and minor hemorrhage, with major hemorrhage requiring additional interventions, such as blood transfusion, endovascular intervention, or nephrectomy.[30,31]

Imaging-related risk factors such as cortical tangential angle, biopsy location, needle path distance from the capsule, and needle passes through the collecting system have been previously described to be associated with major hemorrhage following PRB.[10,11,17,32-34] Based on our search of the literature, we could not find a study which looked into the microscopic evaluation of the cores following PRB with the intent to identify risk factors that would be associated with major post-biopsy hemorrhage. To minimize the confounding influence of the other risk factors, the cases and controls were matched using the PSM method.[35,36]

The overall frequency of major hemorrhage in our study was 9.5%. After most previously described risk factors for biopsy-related hemorrhage were matched through PSM, microscopic analysis of the cores obtained in patients with and without major hemorrhage identified the number of AAs as a statistically significant risk factor associated with major post-biopsy hemorrhage. There was no significant association found between ML, M:C, M:T, or C:T length ratios and major bleeding.

Mejia-Vilet *et al*. formulated a risk score for major bleeding after PRB, which had a good discrimination capacity.[37] Each of the parameters used by Mejia-Vilet *et al*. has been previously described to be associated with renal hemorrhage.[2,3,7,37,38] The addition of the histologic features associated with a significant risk for major post-biopsy hemorrhage in our study (not previously described), could greatly enhance the sensitivity and specificity of such a risk score. In many centers, PRB is mainly performed as an outpatient procedure with shortening of in-hospital post-procedure surveillance.[39-41] Even though up to 85% of major hemorrhages present in the first 8 h post-procedure, there is still a risk of major hemorrhage after 24 h of the procedure.[4,18,19] In our study, about 6/17(35%) of the major bleeds were identified after 24 h of the biopsy. This makes it even more important to devise a risk score for accurate risk assessment, risk counseling, and risk reduction. An accurate risk score could also facilitate the use of preventive interventions such as desmopressin (DDAVP) in the high-risk population. Given the focus on cost-containing strategies, and classification of PRB as an "ambulatory" procedure, there is a need for a reliable and easy tool for risk stratification that can determine individual risk for major hemorrhage after PRB and thus plan accordingly.[4,13,18,39-41]

Based on previous studies that have alluded to the fact that deeper needle penetration into the renal sinus increases the chances of major hemorrhage, we thought that the ML and the M:C ratio would be major determinants of hemorrhage risk.[10] Of the two, M:C ratio was "nearly" significant ($P = 0.089$) but was not strongly significant as we expected.

There was an incrementally higher risk of major hemorrhage associated with the presence of AAs in the core sample. The presence of one AA versus none resulted in a 6.5 increase in the odds of a bleed while two AAs versus none, a 15.5-fold increase [Table 7]. About 75% of cases with major hemorrhage had 1 or 2 AAs in the core specimen. Similarly, 75% of the cases without major hemorrhage had no AAs in the sample. These results suggest that incorporation of the AA score into the risk stratification tool, devised by Mejia-Vilet *et al*., could make the score more specific and accurate.

Limitations of the present study include its retrospective nature, small sample size, and single-center experience with fixed practices. The availability of a board-certified pathologist to assess the adequacy of a sample and provide information regarding the number of AAs may limit its application for smaller hospitals that may not have the luxury of onsite pathology services. Another potential factor that could have contributed to major hemorrhage was biopsies performed by the radiology residents (under the supervision of the IRs) versus the IRs themselves, which we did not account for due to non-availably of relevant documentation.

CONCLUSION

After matching previously described risk factors for renal hemorrhage, we found a strong and incremental association between major renal hemorrhage following PRB and the number of AAs per core specimen. Identification of AAs by the pathologist, while assessing sample adequacy, in the US suite can help predict major hemorrhage in patients undergoing PRBs. The number of AAs could be used along with other risk factors to devise a simple score which can be used to assess the risk stratification following PRB.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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