Systematic Review and Meta-Analysis of Native Kidney Biopsy Complications

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Abstract

Background and objectives Native kidney biopsies are commonly performed in the diagnosis of acute kidney diseases and CKD. Because of the invasive nature of the procedure, bleeding-related complications are not uncommon. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases–sponsored Kidney Precision Medicine Project requires that all participants undergo a kidney biopsy; therefore, the objective of this analysis was to study complication rates of native kidney biopsies performed using automated devices under kidney imaging.

Design, setting, participants, & measurements This is a systematic review and meta-analysis of the literature published from January 1983 to March 2018. The initial PubMed search yielded 1139 manuscripts. Using predetermined selection criteria, 87 manuscripts were included in the final analysis. A random effects meta-analysis for proportions was used to obtain combined estimates of complication rates. Freeman–Tukey double-arcsine transformations were used to stabilize variance as complications were rare.

Results A total of 118,064 biopsies were included in this study. Patient age ranged from 30 to 79 years, and 45% of patients were women. On the basis of our meta-analysis, pain at the site of biopsy is estimated to occur in 4.3% of biopsied patients, hematomas are estimated to occur in 11%, macroscopic hematuria is estimated to occur in 3.5%, bleeding requiring blood transfusions is estimated to occur in 1.6%, and interventions to stop bleeding are estimated to occur in only 0.3%. Death attributed to native kidney biopsy was a rare event, occurring only in an estimated 0.06% of all biopsies but only 0.03% of outpatient biopsies. Complication rates were higher in hospitalized patients and in those with acute kidney disease. The reported complications varied on the basis of study type and geographic location.

Conclusions Although the native kidney biopsy is an invasive diagnostic procedure, the rates of bleeding complications are low. Albeit rare, death can occur postbiopsy. Complications are more frequently seen after kidney biopsies of hospitalized patients with AKI.

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Introduction

The native kidney biopsy was introduced into clinical practice in the 1950s, but the technique has evolved over time. Since the late 1980s, kidney biopsies have been done with the assistance of automated biopsy devices and imaging of the kidneys, mostly ultrasonography. This evolution of the procedure has therefore changed the type and severity of postbiopsy complications. The primary complications of native kidney biopsies are related to hemorrhagic events that can manifest in the form of pain, hematuria, perinephric bleeding that is self-contained as a hematoma, or active bleeding requiring red blood cell transfusions or interventions to control the bleed. Albeit rare, the most serious adverse event is death.

The medical literature on complications related to native kidney biopsies is vast and dates back more than a half century, but it is of limited quality due to study heterogeneity, variability in the definition of complications, and reporting bias. Most studies described single-center experiences from different regions of the world. From the numerous available publications, there has been one meta-analysis and systematic review of 34 studies (9474 biopsies) that focused on bleeding complications after biopsies that were performed under kidney imaging with an automated biopsy device (1).

In the Kidney Precision Medicine Project (KPMP), protocol kidney biopsies will be performed for research purposes. The overarching goal of the KPMP is to conceptually change the paradigms of CKD and acute kidney disease by integrating deep molecular phenotyping of kidney tissue with patient characteristics and disease outcomes. Native kidney biopsies

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from such patients will undergo regional and single-cell interrogation with a variety of techniques, including RNA sequencing, proteomics, and metabolomics. The current meta-analysis was undertaken to obtain an estimate of percutaneous native kidney biopsy complications in order to provide patients in the KPMP with accurate risk information during the informed consent process. We did an intentional and detailed review of the literature describing the risks and complications associated with native kidney biopsies. The KPMP Kidney Biopsy Working Group expanded upon the prior meta-analysis by adding relevant publications from June 2011 to 2017 (1). The focus of this investigation was again on complication rates of native kidney biopsies performed using automated devices in conjunction with kidney imaging for acute kidney diseases and CKD.

Materials and Methods

Search Strategy and Review Process

Our initial literature search captured articles published from January 1983 to March 2018 and used MEDLINE, Embase, and the Cochrane Library; it was restricted to publications in English. The following medical subject headings terms were used to identify potential papers: kidney, biopsy/kidney, biopsy/fine needle, biopsy/adverse effects, and biopsy/complication. Each medical subject heading term was then combined with "biopsy" and "kidney."

This search strategy identified 1139 potential papers. The review of these papers was conducted in three phases. In the first phase, the papers were randomly divided among 16 reviewers. The title and abstract for each paper were evaluated by a single reviewer. Papers were eliminated on the basis of one or more of the following criteria: abstract only (no accompanying paper); <50 biopsies; non-native biopsies included and unable to be excluded; pediatric patients included and unable to be excluded; no image guidance; no complication data provided; biopsy for kidney mass; open kidney biopsy; nonkidney biopsy; review or editorial; patient report; and use of a transjugular approach. In the first round of review, 936 papers were eliminated, leaving 203 papers for full-text review. In the full-text review, the 203 papers were again randomly divided and evaluated by a single reviewer. The entire paper was assessed, and the reasons for exclusion (same as the first round) were recorded in detail for each paper. In this phase, 88 additional papers were excluded.

For full data abstraction, the remaining 115 papers were randomly assigned to two reviewers. The reviewers entered general descriptive data from the paper (*e.g.*, country of origin, number of patients, number of biopsies, number of sites, study design, average age, percent women), the procedures (*e.g.*, needle gauge, average number of passes, duration of monitoring), and the complications reported from our prespecified list of complications (pain, hematomas, macroscopic hematuria, need for transfusion, need for interventions to stop bleeding, and death). All extracted data elements ($n=46$) were then compared between the two reviewers by an independent third reviewer. Of 115 papers, 90 had at least one data element for which the two reviewers disagreed. There were a total of 185 disagreements overall, of a possible 5290 comparisons. The disagreements were sent back as queries to the original two reviewers who then discussed and resolved *via* consensus. This protocol was not registered online.

Statistical Methods

We conducted a meta-analysis of proportions on the basis of a random effects model (2). This model divides the heterogeneity into two components: the between-study variance due to the true variation among different studies, and the within-study variance due to sampling error. The between-study variance is denoted by τ^2. We tested the null hypothesis $H_0 : \tau^2=0$ using Cochran Q and a chi-squared test to determine P values. Heterogeneity was quantified by the I^2statistic, which is the percentage of total variation across studies that is due to heterogeneity rather than chance (3). We estimated the random effects model using the restricted maximum likelihood (4) for all complications except death. Because of the number of zero proportions, we used the Freeman–Tukey double-arcsine transformation (5) to avoid bias and stabilize the variance for the estimated effect sizes (6). We used back transformation (7) to find the estimated proportion for the total effect estimate. Because of the rarity of death, the random effects model was unable to provide a stable estimate for the true proportion of death. Thus, we used a β-binomial model to model the number of deaths using a binomial distribution and the underlying proportion of deaths with a β-distribution (8). We did not report any heterogeneity statistics for this approach as it was not comparable with the other analyses. This is because we do not calculate a value for τ^2 in this approach. Outlier studies were identified on the basis of visual inspection of forest plots and absolute residuals more than two. Influential studies were identified on the basis of leave-one-out analysis. We conducted subgroup analysis for all complications except death. We assumed common between-study variance for subgroups and used an omnibus test to examine if there was a significant difference between subgroup estimates. All analyses were conducted using R version 3.6.1 with the Meta, Metafor, and Forestplot packages.

Results

After extensive review of the English literature and application of the selection process described in Figure 1, 87 papers were used for this meta-analysis. These studies were published between 1983 and March 2018 and included 182,546 kidney biopsies. The largest study comprised 118,064 biopsies, and the smallest had 50 biopsies. Most of these investigations described clinical cohorts, but seven were randomized controlled trials. The average age of the patients included in each study ranged from 30 to 79 years, and 45% were women. The details of the reported studies are given in Supplemental Table 1.

The biopsy complications of interest were pain, kidney hematoma, macroscopic hematuria, red blood cell transfusion, need for surgical/radiologic intervention to control bleeding from the kidney, and death. Not all of these domains were specifically examined in each investigation. There was significant heterogeneity between studies in the various domains (Table 1). Heterogeneity for all of the

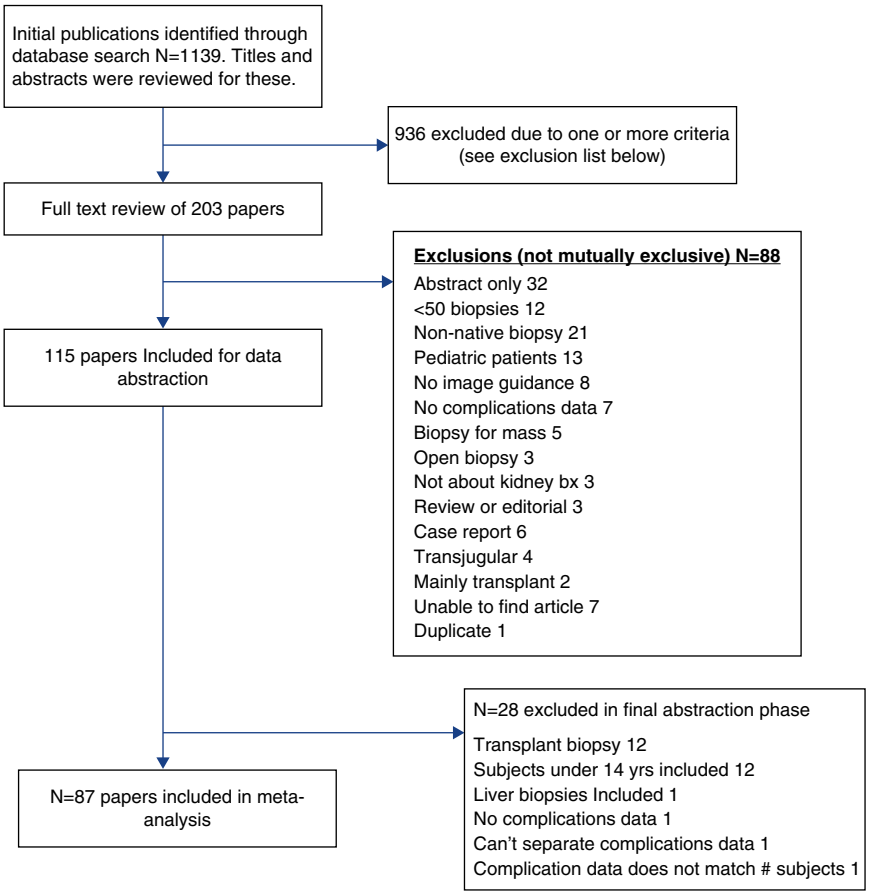

Figure 1. | **This flow chart describes the number of papers reviewed at each of the three rounds of review.** At each stage, papers were excluded from further review on the basis of one or more of the exclusion criteria. The final meta-analysis was conducted on the basis of data from 87 papers. bx, biopsy.

complication domains is visually depicted through forest plots of the proportion of events found in each study contributing to that domain (Supplemental Figures 1–6).

The proportion of patients who experienced one or more of these biopsy complications is summarized in Table 1. For each complication domain except death, a more detailed examination of occurrence stratified by geographical region, biopsy vintage, and biopsy needle gauge is given in Tables 2 and 3. The overall incidence of complications was low, especially for the serious adverse events of interventions to stop bleeding and death. These interventions and red blood cell transfusions occurred significantly less frequently in Asia than the United States or Europe, and Europe had a lower incidence of macroscopic hematuria than the United States and Asia. There were more pain events when a smaller needle (18 versus 16 gauge) was used, but this analysis included <1500 biopsies. There was also a numerical trend toward more hematomas and transfusions with the smaller needle, but statistical significance was not reached.

The most serious complication, death, was highly influenced by one study (8). This study investigated over 100,000 patients and recorded 2125 deaths. All of the other studies together reported only 15 deaths in 42,066 biopsies. Unlike any of the other studies, the investigation of Al Turk *et al.* (8) interrogated a nationwide inpatient database to

Table 1. Summary of kidney biopsy complications

Complication Domain	All Studies			Influential Studies Excluded		
	Proportion	95% Confidence Interval	I^2, %	Proportion	95% Confidence Interval	I^2, %
Pain	0.043	0.02 to 0.07	94			
Hematoma	0.11	0.07 to 0.15	99	0.088	0.06 to 0.12	98
Hematuria	0.035	0.03 to 0.04	99			
Transfusion	0.016	0.01 to 0.02	99	0.014	0.01 to 0.02	88
Intervention	0.003	0.00 to 0.01	73			
Death	0.0006	0.00 to 0.00		0.0003	0.00 to 0.00	

Table 2. Pain, hematoma, and macroscopic hematuria complications stratified by region, year, and needle gauge

Subgroup	Papers, *n*	Pain or Hematoma, *n*	Biopsies, *n*	Estimate	95% Confidence Interval	I^2, %	Modifier Test: *P* Value
Pain							
America	3	10	1440	0.0110	[0.00 to 0.06]	76.5	
Asia	7	118	1485	0.0596	[0.02 to 0.11]	94.6	
Europe	8	66	1488	0.0455	[0.02 to 0.09]	88.3	0.24
Pre-2000	6	57	763	0.0728	[0.03 to 0.13]	84.1	
2000–2009	6	115	1938	0.0427	[0.01 to 0.09]	96.2	
2010–2018	6	22	1712	0.0212	[0.00 to 0.06]	85.3	0.21
16 Gauge	3	13	612	0.0230	[0.00 to 0.08]	85.6	
18 Gauge	3	106	812	0.1274	[0.06 to 0.22]	93.7	0.02
Overall	18	194	4413	0.0429	[0.02 to 0.07]	93.8	
Hematoma							
America	15	428	5012	0.0947	[0.03 to 0.18]	95.7	
Asia	19	1136	6658	0.1319	[0.07 to 0.22]	99.3	
Europe	26	877	15,989	0.0924	[0.04 to 0.16]	98.6	0.67
Pre-2000	12	257	2053	0.1249	[0.04 to 0.24]	97.4	
2000–2009	16	765	5639	0.1060	[0.04 to 0.20]	99.3	
2010–2018	34	1419	19,967	0.0980	[0.05 to 0.16]	98.9	0.88
16 Gauge	23	420	8423	0.0574	[0.02 to 0.11]	95.9	
18 Gauge	9	534	1728	0.1614	[0.07 to 0.29]	99.1	0.06
Overall	62	2441	27,659	0.1050	[0.07 to 0.15]	98.9	
Macroscopic hematuria							
America	14	15,466	122,779	0.0481	[0.03 to 0.07]	97.3	
Asia	25	280	7321	0.0397	[0.03 to 0.05]	84.4	
Europe	25	722	27,511	0.0244	[0.02 to 0.04]	93.5	0.05
Pre-2000	14	138	2389	0.0518	[0.03 to 0.07]	43.5	
2000–2009	16	449	9543	0.0318	[0.02 to 0.05]	94.1	
2010–2018	34	15,881	145,679	0.0305	[0.02 to 0.04]	99.3	0.10
16 Gauge	22	232	8614	0.0249	[0.01 to 0.04]	88.9	
18 Gauge	9	78	1659	0.0351	[0.02 to 0.06]	68.5	0.37
Overall	64	16,468	157,611	0.0347	[0.03 to 0.04]	98.8	

identify patients who had a kidney biopsy at some point during their hospitalization. Deaths occurred during the hospitalizations and could not necessarily be attributed to the kidney biopsy. Excluding the study of Al Turk *et al.* (8) decreased the meta-analyzed estimated proportions of death from 0.0006 to 0.0003. Similarly, the need for blood transfusion postbiopsy was influenced by the study by Al Turk *et al.* (8), but removing that study did not change the

Table 3. Transfusion and surgical/radiologic intervention complications stratified by region, year, and needle gauge

Subgroup	Papers, *n*	Transfusion or Intervention, *n*	Biopsies, *n*	Estimate	95% Confidence Interval	I^2, %	Modifier Test: *P* Value
Transfusion							
America	15	31,029	123,864	0.0460	[0.03 to 0.07]	99.5	
Asia	23	195	22,141	0.0075	[0.00 to 0.02]	85.9	
Europe	21	187	16,800	0.0103	[0.00 to 0.02]	65.0	<0.001
Pre-2000	7	33	1231	0.0172	[0.00 to 0.04]	69.0	
2000–2009	17	119	6759	0.0108	[0.00 to 0.02]	81.3	
2010–2018	35	31,259	154,815	0.0187	[0.01 to 0.03]	99.8	0.49
16 Gauge	21	219	10,711	0.0574	[0.02 to 0.11]	95.9	
18 Gauge	9	31	2777	0.1614	[0.07 to 0.29]	99.1	0.06
Overall	59	31,411	162,805	0.0160	[0.01 to 0.02]	99.8	
Surgical/radiologic intervention							
America	19	216	124,630	0.0047	[0.00 to 0.01]	80.3	
Asia	23	43	21,897	0.0006	[0.00 to 0.00]	59.5	
Europe	24	74	17,467	0.0052	[0.00 to 0.01]	62.8	0.04
Pre-2000	9	9	1645	0.0033	[0.00 to 0.01]	0.0	
2000–2009	17	34	6654	0.0029	[0.00 to 0.01]	35.2	
2010–2018	40	290	155,695	0.0036	[0.00 to 0.01]	77.6	0.80
16 Gauge	24	55	10,799	0.0024	[0.00 to 0.01]	39.8	
18 Gauge	11	12	2994	0.0005	[0.00 to 0.00]	23.7	0.28
Overall	66	333	163,994	0.0033	[0.00 to 0.01]	72.8	

proportion of transfusions needed or study heterogeneity much (Table 1).

Another common complication of kidney biopsy was perinephric hematoma. Two studies were identified as influential for hematoma occurrence, each finding hematomas in over 80% of the cohort (9,10). Excluding these studies only decreased the proportion of hematomas from 11% to 8.8% (from one in nine to one in 11) and had little effect on study heterogeneity (Table 1). In both of these studies, kidney imaging was done postbiopsy to prospectively assess for hematomas as opposed to waiting for a clinical indication to do postbiopsy imaging. Most hematomas were small (<2 cm). Several other studies reported relatively high hematoma rates (>30%), and postbiopsy imaging was also done routinely in these studies.

Discussion

This analysis was done to obtain an estimate of percutaneous native kidney biopsy complications in order to provide patients undergoing research biopsies for the KPMP with accurate risk information during the informed consent process. We determined the occurrence of adverse events using six biopsy complication domains of importance to patients and clinicians. The most severe adverse event was death, with an incidence of 0.008% (one in 12,500), followed by an intervention to stop bleeding with an incidence of 0.3% (one in 333). The need for a red blood cell transfusion was 1.6% (one in 62.5). Gross hematuria developed in 3.5% of patients (one in 29), and pain developed in 4.3% of patients (one in 23). The incidence of perinephric hematoma was 11% (one in nine).

These risk estimates were on the basis of available data largely from retrospective reports of patient series for biopsies performed for clinical indications. As such, the overall data quality was modest, and the studies were not large. Although the ranges of patients and kidney biopsies assessed were wide, the median number of patients per study was 210. There were no studies that were both prospective and designed specifically to identify complication rates. Additionally, many of the studies did not assess the full range of biopsy complication domains considered important for the KPMP. Although several biopsy complications were readily quantified, such as death, interventions to stop bleeding, red blood cell transfusions, and presence of macroscopic hematuria, the postbiopsy observation period was highly variable; therefore, events could have been missed, and rules for attribution to the biopsy procedure were not in place. Pain and hematoma were more difficult to assess. Pain is subjective, and no uniform pain assessment standard was applied in the few studies that reported pain. Similarly, there was no uniform approach to the identification or measurement of perinephric hematomas. These issues produced significant heterogeneity between studies, at least in part due to reporting bias. Because of this heterogeneity, we suggest that it is reasonable to use the upper limit of the confidence intervals provided for each complication domain (Table 1) to provide patients with the most conservative estimate of risk.

The most frequent complication of the percutaneous native kidney biopsy seems to be a postbiopsy perinephric hematoma. Although the overall incidence of hematoma was 11%, this was derived from a mixture of studies that routinely imaged the kidney after biopsy to look for bleeding and studies that only imaged the kidney if there was a clinical indication, such as pain or a fall in hemoglobin. We speculate that if hematomas are specifically sought by imaging the kidney postbiopsy, they will be found often. However, many hematomas will be small and of arguable clinical significance. In many of the reviewed papers, the size of the hematoma was not reported, so size of a clinically relevant hematoma is unclear.

A particularly difficult complication to assess was pain related to the kidney biopsy. Only 18 papers attempted to quantify pain, and only 194 pain events were reported in nearly 4400 biopsies. No standard method of assessing pain was used across studies, and an accepted amount of pain after an uncomplicated kidney biopsy has not been determined. Therefore, the pain domain is the least accurately evaluated complication. The development of a standardized pain assessment is needed.

Death and need for red blood cell transfusion were highly influenced by one study that interrogated the US Nationwide Inpatient Sample database between 2008 and 2012 (9). All included patients (n=118,064) were identified by the International Classification of Disease code for percutaneous native kidney biopsy. In general, these patients may have been sicker than typical patients having elective outpatient diagnostic kidney biopsies. For example, only 27% of these patients had a diagnosis of GN on the basis of administrative codes. Notably, two thirds of the patients had AKI, and 15% had a pathologic diagnosis of acute tubular necrosis. Administrative codes were also used to identify complications. Mortality in this cohort was 1.8%, but it was twice as high (2%) in patients admitted to the hospital nonelectively compared with electively (0.99%). Red blood cell transfusions were administered to a quarter of the patients. These complication rates are greater than those reported in other studies of native kidney biopsy. The findings may be explained by the acuity of illness for many of the hospitalized patients, including the presence of comorbidities such as coagulopathies or BP instability, and inability to accurately attribute complications to the biopsy itself as opposed to other conditions occurring during hospitalization. These results are similar to those from a recent investigation that examined native kidney biopsy complications in patients with acute kidney disease that was mainly AKI (11). Mortality was 3% in this cohort, but none of the deaths were directly attributed to the kidney biopsy. Red blood cell transfusions were required in 8% of patients, and 2% needed an intervention to stop bleeding; these adverse events were biopsy complications. These higher complication rates may more accurately reflect risk of performing native kidney biopsies in patients with AKI in the KPMP who are often hospitalized with significant comorbidities, as opposed to those undergoing elective, outpatient kidney biopsies.

Difficulty arises when analyzing the mortality end point due to the rarity of the event. The paper by Al Turk *et al.* (8), which has a much higher death rate then all of the other studies where death was reported, caused issues in the initial analysis (9). Furthermore, with many studies reporting zero deaths, the preferred analysis that uses random

effects could not be used. Instead, we fit a β-binomial model, a method that has been shown to be useful in the setting of meta-analysis of proportions for very rare outcomes (8).

Since performing this systematic analysis, four additional investigations of complications in adults undergoing a native kidney biopsy have been published (12–15). Death was examined in three studies and occurred in one of 17,125 biopsies, less than the one in 1667 we found in our meta-analysis (12,14,15). The need for blood transfusion postbiopsy was variable. The rate was below 0.5% in an all-outpatient cohort (12), but it was 4.3% in a mixed outpatient-inpatient cohort and 5.7% in an all-inpatient cohort (13,15). Importantly, the mixed cohort observed a 57% transfusion rate among inpatients who needed an urgent kidney biopsy (15). The all-inpatient cohort data were obtained from the Nationwide Inpatient Sample database using diagnostic codes and included 35,183 biopsies (13). Most biopsies (70%) were done for AKI, and 28% of the patients had diabetes. The meta-analysis found an overall need for blood transfusion in 1.6% of patients, but when stratified by region, transfusions were needed in 4.6% of patients from America, perhaps reflecting a large number of inpatient biopsies. This estimate may be more relevant when discussing biopsy complications with potential research subjects who are inpatients. Finally, the need for angiography or surgical intervention to control bleeding was 0.6% or less in all four studies, a bit higher than the meta-analysis rate of 0.3%. A meta-analysis of 23 investigations of kidney biopsy complications in pediatric patients also demonstrated a low incidence of major bleeding events (16). Blood transfusions were required in 0.6% of patients, and an intervention to control bleeding was needed in 1.2% of patients.

Relevant to the underlying question of whether an extra research core of kidney tissue can be safely obtained during native kidney biopsy, the Transformative Research in Diabetic Neproplathy (TRIDENT) study recently reported its initial biopsy experience (17). The TRIDENT is examining the molecular pathology of diabetic kidney disease. In the first 160 biopsies, 11 patients (7%) had complications, including three patients who needed a blood transfusion, three patients who had gross hematuria, and seven patients who had large (>5-cm) hematomas. Importantly, no patient required an invasive procedure to control bleeding, and there were no deaths.

This analysis did not find an advantage of using an 18-gauge biopsy needle over a 16-gauge needle for any of the complication domains; however, we cannot exclude the possibility that the 18-gauge needles were used for a specific indication in these observational studies. Nonetheless, this suggests that a 16-gauge biopsy needle may be safely used to comfortably obtain enough tissue for histologic diagnosis and research purposes.

This large meta-analysis of all published literature related to native kidney biopsies is limited to some extent by the heterogeneity of the available literature, but its strength relies in the comprehensive approach taken by the KPMP to evaluate all complication domains that are clinically relevant. By systematically reviewing and evaluating all reported complications, especially from recent single-center experiences in the United States and abroad, the presented estimates most likely reflect current practice by minimizing single-center biases.

In conclusion, this meta-analysis has considered the best available data to guide clinicians and patients to make an informed decision regarding the safety of a kidney biopsy. Overall, the data suggest the percutaneous native kidney biopsy, when done for diagnostic and prognostic purposes, is usually very safe and, by extension, is expected to be correspondingly safe in the setting of biopsies being done electively for research purposes, such as the KPMP. However, patients who are hospitalized may be at higher risk for complications than patients undergoing an elective outpatient biopsy.

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.04710420/-/DCSupplemental.

Supplemental Figure 1. Overall pain forest plot.

Supplemental Figure 2. Overall hematoma forest plot.
Supplemental Figure 3. Overall macroscopic hematuria forest plot.
Supplemental Figure 4. Overall erythrocyte transfusion forest plot.
Supplemental Figure 5. Overall surgical/IR intervention forest plot.
Supplemental Figure 6. Overall death forest plot.
Supplemental Material. References.
Supplemental Table 1. Study characteristics.

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Supplemental Material

Supplemental Table 1. Study Characteristics

Supplemental Figure 1. Overall Pain Forest Plot

Supplemental Figure 2. Overall Hematoma Forest Plot

Supplemental Figure 3. Overall Macroscopic Hematuria Forest Plot

Supplemental Figure 4. Overall Erythrocyte Transfusion Forest Plot

Supplemental Figure 5. Overall Surgical/IR Intervention Forest Plot

Supplemental Figure 6. Overall Death Forest Plot

Supplemental References

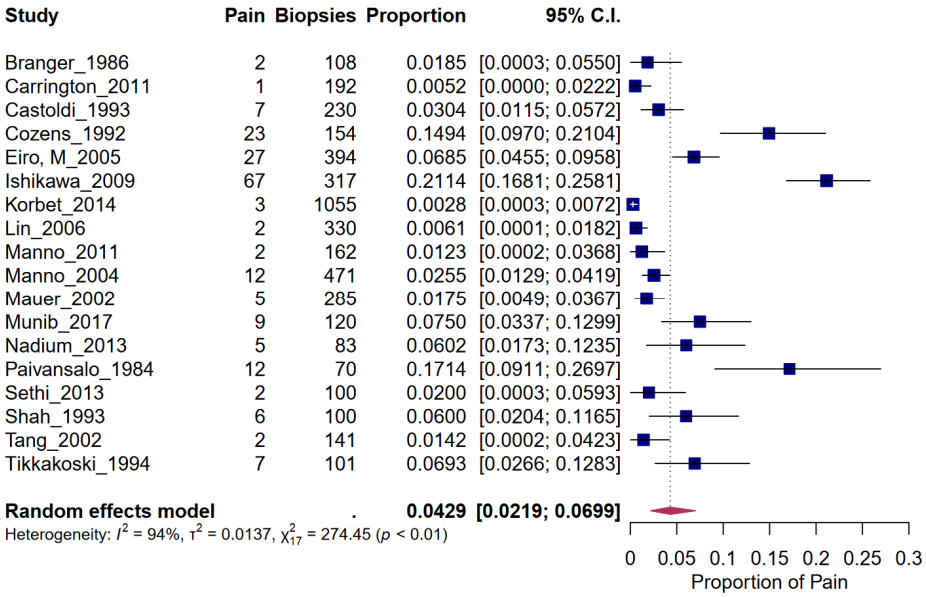
Supplemental Table 1. Study Characteristics * Outlier Study ^ Influential Study

First Author	Country	Year	Study Design	Average Age	% Female	Biopsies (n)	Pain (n)	Hematomas (n)	Macroscopic Hematuria (n)	Erythrocyte Transfusion (n)	Surgical Intervention (n)	Death (n)
Al Turk*^[1]	USA	2018	Cohort	55	48	118064	NR	NR	15230*	30815*^	165	2125*^
Altindal[2]	Turkey	2015	CC	40	40	290	NR	NR	NR	6	2	1
Arora[3]	India	2012	RCT	NR	NR	50	NR	1	1	0	0	0
Azhar[4]	Pakistan	2005	Cohort	NR	NR	200	NR	NR	NR	NR	NR	0
Bataille[5]	France	2012	Cohort	55	41	535	NR	2	NR	2	3	0
Branger[6]	France	1985	RCT	NR	NR	108	2	2	2	NR	NR	NR
Carrington[7]	Wales	2011	Cohort	52	2	192	1	2	4	2	2	0
Castoldi[8]	Italy	1993	Cohort	NR	NR	230	7	96	16	NR	2	0
Chen[9]	USA	2012	Cohort	37	86	219	NR	NR	NR	5	3	0
Chikamatsu*[10]	Japan	2017	Cohort	62	39	252	NR	NR	36*	12	2	0
Chunduri*[11]	USA	2015	Cohort	47	68	137	NR	44	1	10	4*	0
Cluzel[12]	France	2000	CC	49	26	400	NR	1	2	1	3	0
Cozens[13]	UK	1992	Cohort	47	41	154	23	NR	7	3	2	0
Cui[14]	USA	2016	Cohort	56	49	86	NR	25	NR	NR	2	0
DiPalma[15]	Italy	2010	Cohort	68	36	110	NR	10	1	0	0	0
Doyle[16]	USA	1994	Cohort	32	50	155	NR	10	8	NR	1	0
Eiro, M[17]	Japan	2005	Cohort	44	NR	394	27	149	29	0	0	0
Elahi[18]	Pakistan	2017	Cohort	36	36	75	NR	20	5	NR	NR	0
Esposito[19]	Italy	2018	Cohort	58	30	337	NR	NR	NR	NR	NR	0
Fisi*[20]	Hungary	2012	Cohort	49	42	353	NR	160	NR	2	8*	0
Gesualdo[21]	Italy	2008	Cohort	45	NR	110	NR	NR	NR	NR	1	0
Granata[22]	Italy	2011	CC	NR	43	561	NR	15	21	2	1	0
Guerrero[23]	Spain	2014	Cohort	56	NR	180	NR	9	4	NR	3	0
Helenius[24]	Finland	1983	RCT	39	50	57	NR	7	NR	NR	NR	0
Hojs[25]	Slovenia	2004	Cohort	45	45	144	NR	2	4	0	0	0
Ilsam[26]	USA	2010	Cohort	44	38	56	NR	11	5	4	0	0
Ishikawa*^[27]	Japan	2009	Cohort	45	46	317	67*	273*^	12	1	0	0
Jordan*[28]	UK	2014	Cohort	35	86	215	NR	29	3	8	6*	1
Joseph[29]	USA	2010	Cohort	41	73	170	NR	44	NR	13	NR	0
Khajehdehi[30]	USA	1999	Cohort	NR	45	59	NR	NR	3	NR	NR	NR
Kitterer[31]	Germany	2015	Cohort	58	39	205	NR	37	NR	3	1	0
Kohli[32]	India	2006	Cohort	39	32	210	NR	1	11	4	0	NR
Korbet[33]	USA	2014	Cohort	46	62	1055	3	92	76	56	11	1
Kriegshauser[34]	USA	2015	Cohort	59	43	293	NR	NR	NR	NR	NR	0
Lees[35]	Scotland	2017	Cohort	57	43	2563	NR	NR	NR	46	9	1
Lin[36]	Taiwan	2006	Cohort	46	NR	330	2	55	21	2	NR	0
Lubomirova[37]	Bulgaria	2014	Cohort	46	48	230	NR	15	NR	NR	NR	NR
Mackinnon[38]	UK	2008	Cohort	56	40	1120	NR	2	4	15	2	0
Mai[39]	Australia	2013	Cohort	NR	47	934	NR	19	13	8	0	0

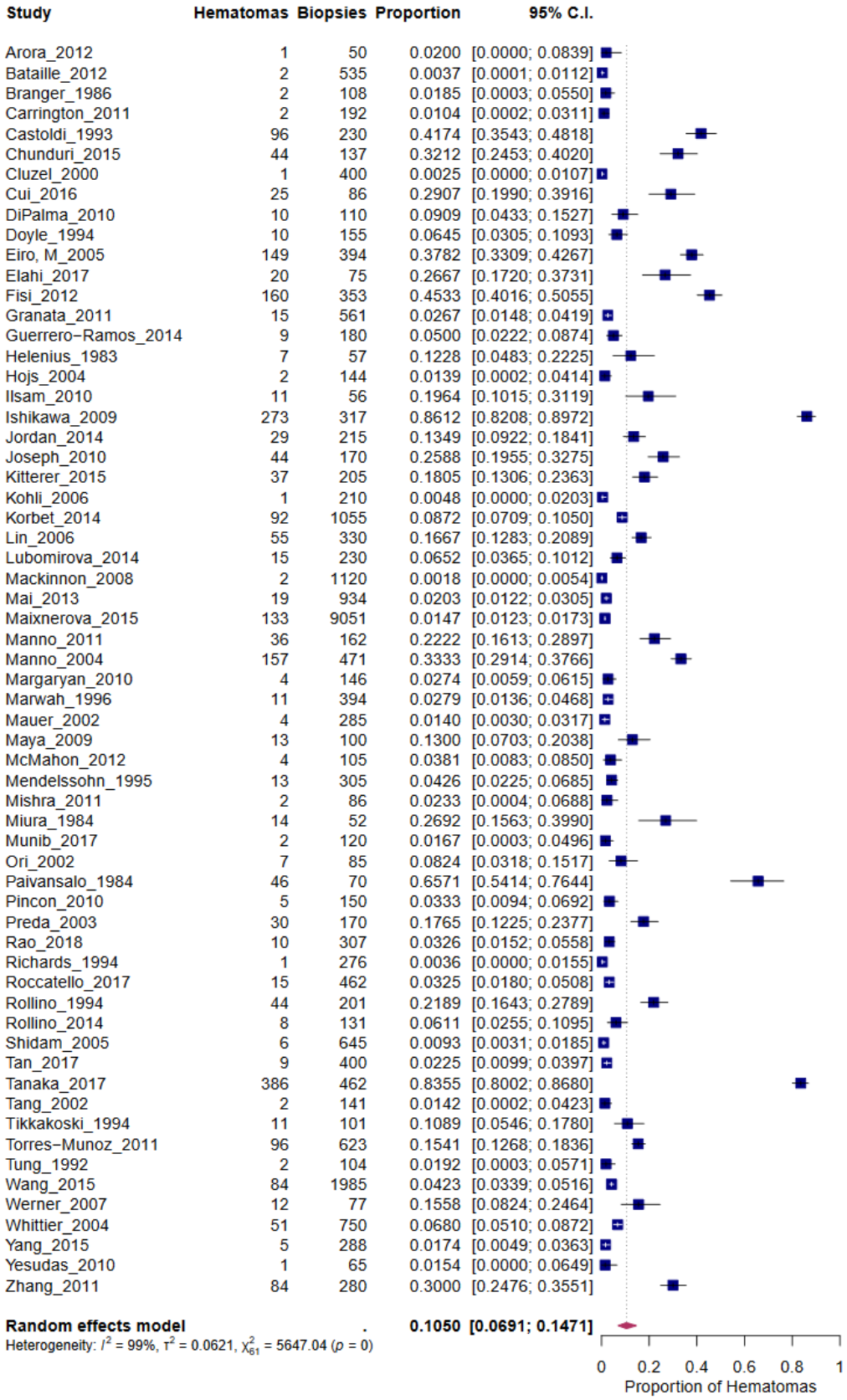
Maixnerova[40]	Czech Rep	2015	Cohort	45	42	9051	NR	133	138	NR	NR	NR
Manno[41]	Italy	2011	RCT	41	NR	162	2	36	0	0	0	0
Manno[42]	Italy	2004	RCT	39	41	471	12	157	2	2	4	0
Margaryan[43]	USA	2010	Cohort	44	56	146	NR	4	2	1	0	0
Marwah[44]	USA	1996	Cohort	44	2	394	NR	11	23	22	3	0
Mauer[45]	USA	2002	RCT	30	53	285	5	4	8	NR	0	0
Maya[46]	USA	2009	Cohort	42	60	100	NR	13	NR	0	0	0
McMahon[47]	USA	2012	Cohort	49	NR	105	NR	4	5	NR	1	0
Mendelssohn[48]	Canada	1995	Cohort	NR	NR	305	NR	13	27	NR	0	0
Mishra[49]	Libya	2011	Cohort	NR	73	86	NR	2	2	NR	1	0
Miura[50]	Japan	1984	Cohort	38	46	52	NR	14	3	0	0	0
Munib[51]	Pakistan	2017	Cohort	28	32	120	9	2	9	2	0	0
Nadium[52]	Sudan	2013	Cohort	34	44	83	5	NR	4	2	0	0
Nyman[53]	Saudi Arabia	1997	Cohort	NR	57	168	NR	NR	NR	NR	NR	0
Ori[54]	Israel	2002	Cohort	53	47	85	NR	7	1	4	0	0
Paivansalo*[55]	Finland	1984	Cohort	41	44	70	12	46*	NR	NR	NR	0
Pendon-Ruiz[56]	Spain	2014	Cohort	49	3	241	NR	NR	19	9	2	NR
Pincon[57]	France	2010	Cohort	77	48	150	NR	5	1	3	0	0
Prasad[58]	India	2015	Cohort	34	31	2138	NR	NR	NR	NR	NR	0
Preda[59]	Netherlands	2003	Cohort	NR	NR	170	NR	30	3	4	NR	0
Rao[60]	India	2018	CC	37	40	307	NR	10	19	2	4	0
Richards[61]	UK	1994	Cohort	41	NR	276	NR	1	8	2	NR	0
Roccatello[62]	Italy	2017	Cohort	55	39	462	NR	15	12	NR	6	0
Rollino[63]	Italy	1994	RCT	NR	NR	201	NR	44	21	NR	NR	0
Rollino[64]	Italy	2014	Cohort	79	45	131	NR	8	3	NR	1	0
Rychlik[65]	Czech Rep	2004	Cohort	42	41	4004	NR	NR	273	NR	NR	NR
Sakaci[66]	Turkey	2015	Cohort	71	38	78	NR	NR	1	0	0	0
Sakhuja[67]	India	1990	Cohort	NR	NR	150	NR	NR	9	1	0	0
Sethi[68]	USA	2013	Cohort	47	59	100	2	NR	NR	8	1	0
Shah[69]	Singapore	1993	Cohort	32	NR	100	6	NR	4	NR	NR	0
Shidam[70]	USA	2005	Cohort	42	50	645	NR	6	12	16	4	0
Soares[71]	USA	2008	Cohort	NR	44	289	NR	NR	NR	6	5	0
Sosa-Barrios[72]	Spain	2017	Cohort	44	58	175	NR	NR	NR	NR	NR	0
Tabatabai[73]	USA	2009	CC	NR	61	1116	NR	NR	NR	24	8	0
Tan[74]	China	2017	Cohort	40	50	400	NR	9	1	NR	NR	0
Tanaka*^[75]	Japan	2017	Cohort	50	47	462	NR	386*^	5	2	0	0
Tang[76]	Hong Kong	2002	Cohort	NR	NR	141	2	2	5	2	2	0
Tikkakoski[77]	Finland	1994	Cohort	43	47	101	7	11	3	2	0	0
Tondel[78]	Norway	2012	Cohort	51	NR	8573	NR	NR	167	78	17	NR
Torres-Munoz[79]	Mexico	2011	Cohort	34	71	623	NR	96	10	11	3	0
Tung[80]	UK	1992	Cohort	45	38	104	NR	2	4	3	1	0
Wang[81]	China	2015	Cohort	40	41	1985	NR	84	57	71	16	0

Werner[82]	Israel	2007	Cohort	46	38	77	NR	12	6	0	0	0
Whittier[83]	USA	2004	Cohort	NR	NR	750	NR	51	56	38	5	2
Yamamoto[84]	Japan	2015	Cohort	45	48	15191	NR	NR	NR	76	15	9
Yang[85]	China	2015	Cohort	67	39	288	NR	5	4	0	0	0
Yesudas[86]	India	2010	Cohort	43	44	65	NR	1	2	0	1	0
Zhang[87]	China	2011	Cohort	40	44	280	NR	84	20	0	0	0

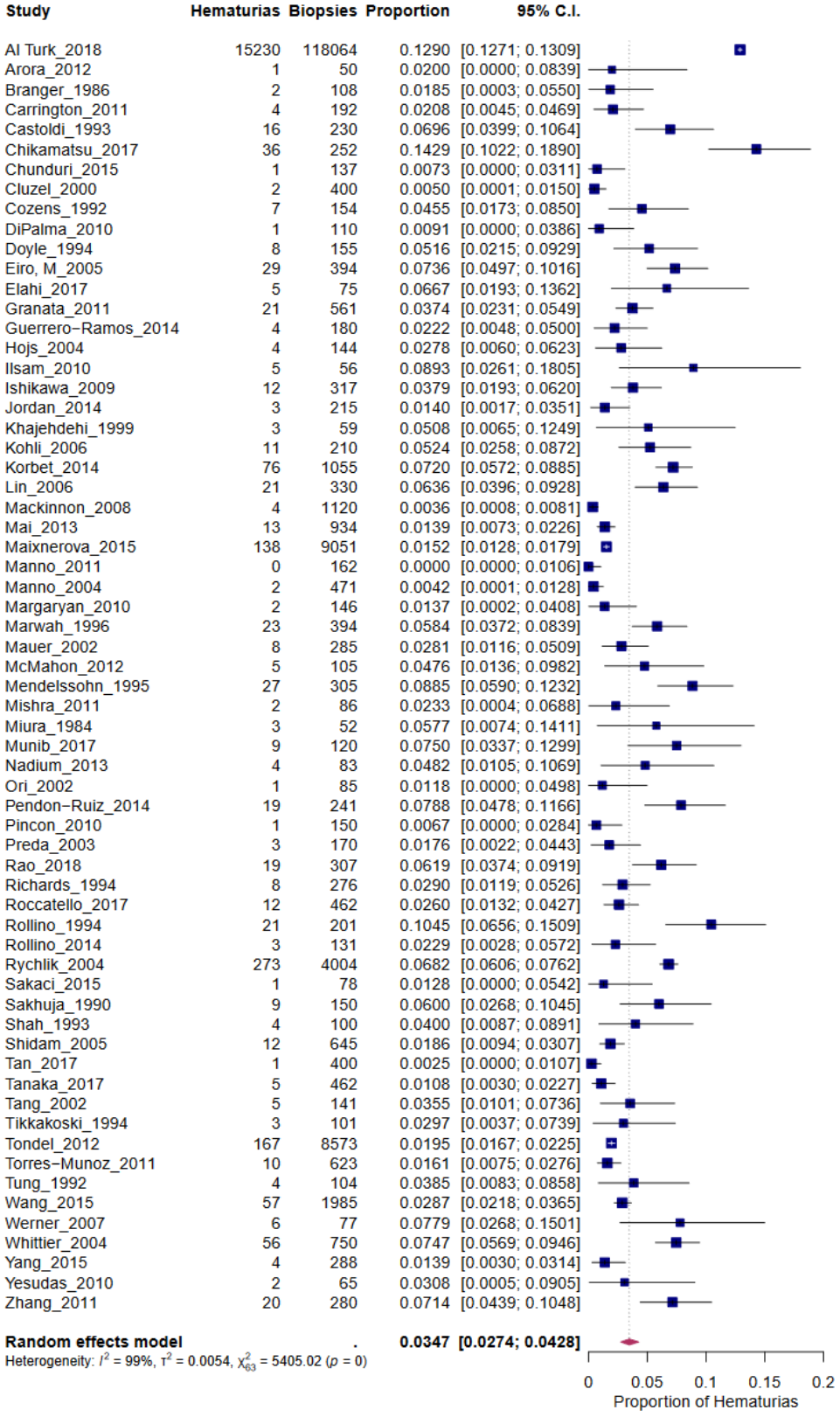
Supplemental Figure 1. Overall Pain Forest Plot



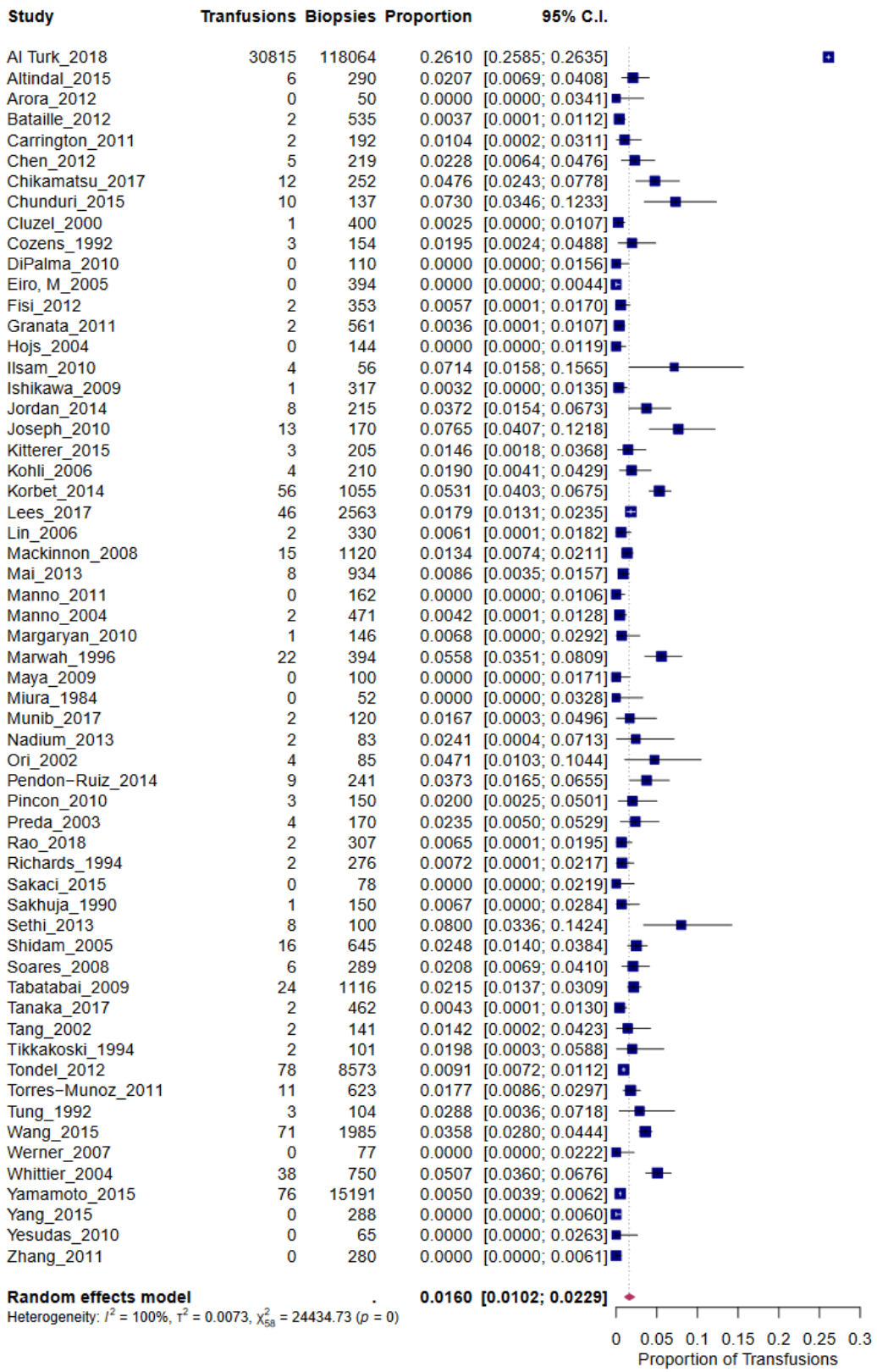
Supplemental Figure 2. Overall Hematoma Forest Plot



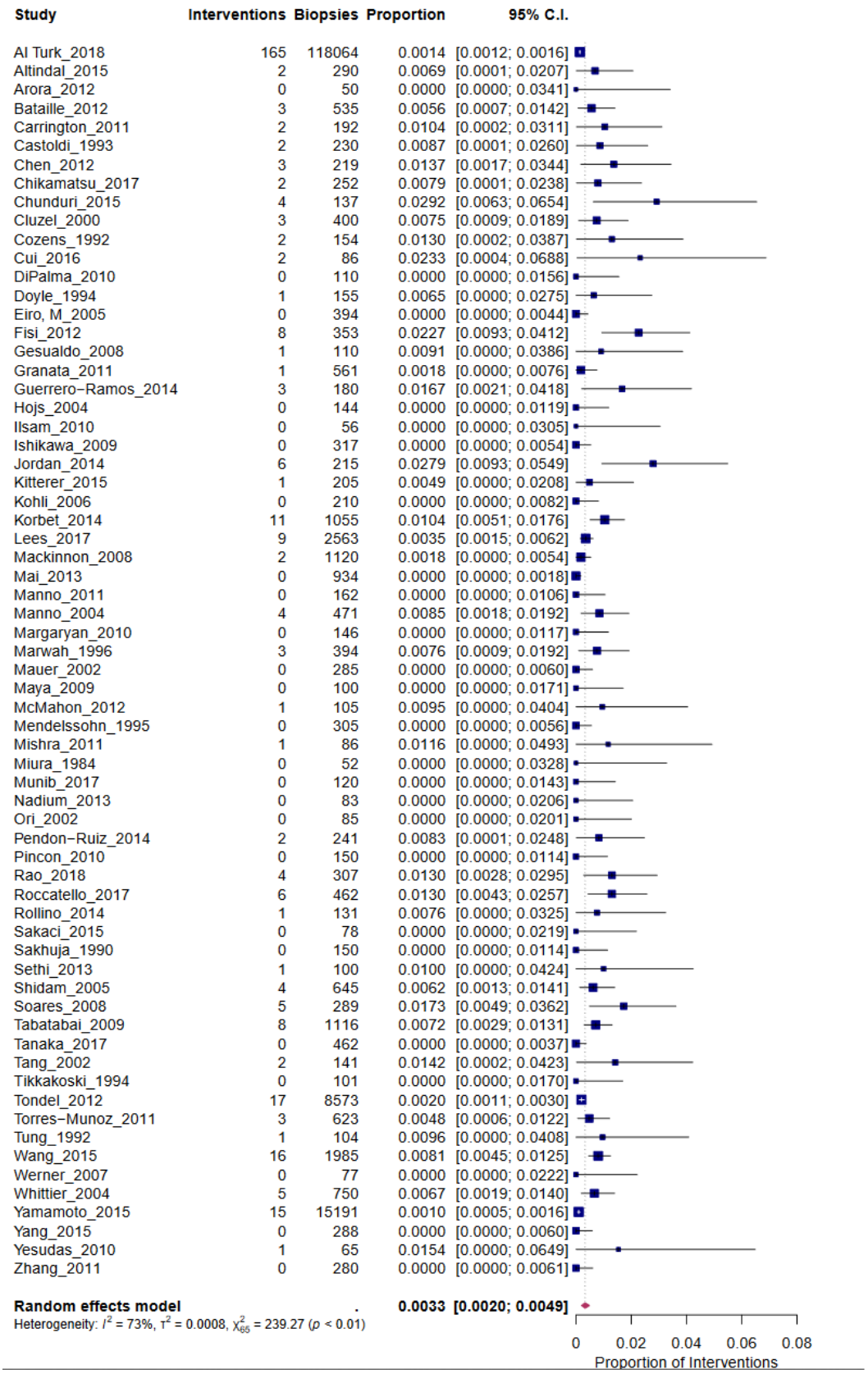
Supplemental Figure 3. Overall Macroscopic Hematuria Forest Plot



Supplemental Figure 4. Overall Erythrocyte Transfusion Forest Plot

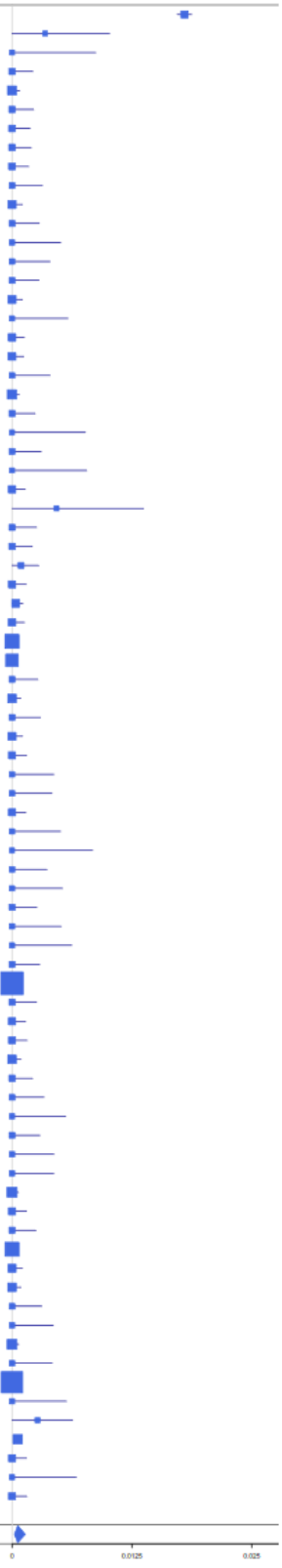


Supplemental Figure 5. Overall Surgical/IR Intervention Forest Plot



Supplemental Figure 6. Overall Death Forest Plot

Study	Deaths	Biopsies	Proportion	Lower Bound	Upper Bound
Al Turk_2018	2125	118064	0.01800	0.01724	0.01876
Altindal_2015	1	290	0.00345	0.00000	0.01020
Arora_2012	0	50	0.00000	0.00000	0.00874
Azhar_2005	0	200	0.00000	0.00000	0.00219
Bataille_2012	0	535	0.00000	0.00000	0.00082
Carrington_2011	0	192	0.00000	0.00000	0.00228
Castoldi_1993	0	230	0.00000	0.00000	0.00190
Chen_2012	0	219	0.00000	0.00000	0.00200
Chikamatsu_2017	0	252	0.00000	0.00000	0.00174
Chunduri_2015	0	137	0.00000	0.00000	0.00320
Cluzel_2000	0	400	0.00000	0.00000	0.00110
Cozens_1992	0	154	0.00000	0.00000	0.00284
Cui_2016	0	86	0.00000	0.00000	0.00509
DiPalma_2010	0	110	0.00000	0.00000	0.00398
Doyle_1994	0	155	0.00000	0.00000	0.00283
Eiro, M_2005	0	394	0.00000	0.00000	0.00111
Elahi_2017	0	75	0.00000	0.00000	0.00583
Esposito_2018	0	337	0.00000	0.00000	0.00130
Fisi_2012	0	353	0.00000	0.00000	0.00124
Gesualdo_2008	0	110	0.00000	0.00000	0.00398
Granata_2011	0	561	0.00000	0.00000	0.00078
Guerrero−Ramos_2014	0	180	0.00000	0.00000	0.00243
Helenius_1983	0	57	0.00000	0.00000	0.00767
Hojs_2004	0	144	0.00000	0.00000	0.00304
Ilsam_2010	0	56	0.00000	0.00000	0.00781
Ishikawa_2009	0	317	0.00000	0.00000	0.00138
Jordan_2014	1	215	0.00465	0.00000	0.01375
Joseph_2010	0	170	0.00000	0.00000	0.00258
Kitterer_2015	0	205	0.00000	0.00000	0.00214
Korbet_2014	1	1055	0.00095	0.00000	0.00280
Kriegshauser_2015	0	293	0.00000	0.00000	0.00150
Lees_2017	1	2563	0.00039	0.00000	0.00115
Lin_2006	0	330	0.00000	0.00000	0.00133
Mackinnon_2008	0	1120	0.00000	0.00000	0.00039
Mai_2013	0	934	0.00000	0.00000	0.00047
Manno_2004	0	162	0.00000	0.00000	0.00270
Manno_2011	0	471	0.00000	0.00000	0.00093
Margaryan_2010	0	146	0.00000	0.00000	0.00300
Marwah_1996	0	394	0.00000	0.00000	0.00111
Mauer_2002	0	285	0.00000	0.00000	0.00154
Maya_2009	0	100	0.00000	0.00000	0.00438
McMahon_2012	0	105	0.00000	0.00000	0.00417
Mendelssohn_1995	0	305	0.00000	0.00000	0.00144
Mishra_2011	0	86	0.00000	0.00000	0.00509
Miura_1984	0	52	0.00000	0.00000	0.00841
Munib_2017	0	120	0.00000	0.00000	0.00365
Nadium_2013	0	83	0.00000	0.00000	0.00527
Nyman_1997	0	168	0.00000	0.00000	0.00261
Ori_2002	0	85	0.00000	0.00000	0.00515
Paivansalo_1984	0	70	0.00000	0.00000	0.00625
Pincon_2010	0	150	0.00000	0.00000	0.00292
Prasad_2015	0	2138	0.00000	0.00000	0.00020
Preda_2003	0	170	0.00000	0.00000	0.00258
Rao_2018	0	307	0.00000	0.00000	0.00143
Richards_1994	0	276	0.00000	0.00000	0.00159
Roccatello_2017	0	462	0.00000	0.00000	0.00095
Rollino_1994	0	201	0.00000	0.00000	0.00218
Rollino_2014	0	131	0.00000	0.00000	0.00334
Sakaci_2015	0	78	0.00000	0.00000	0.00561
Sakhuja_1990	0	150	0.00000	0.00000	0.00292
Sethi_2013	0	100	0.00000	0.00000	0.00438
Shah_1993	0	100	0.00000	0.00000	0.00438
Shidam_2005	0	645	0.00000	0.00000	0.00068
Soares_2008	0	289	0.00000	0.00000	0.00152
Sosa−Barrios_2017	0	175	0.00000	0.00000	0.00250
Tabatabai_2009	0	1116	0.00000	0.00000	0.00039
Tan_2017	0	400	0.00000	0.00000	0.00110
Tanaka_2017	0	462	0.00000	0.00000	0.00095
Tang_2002	0	141	0.00000	0.00000	0.00311
Tikkakoski_1994	0	101	0.00000	0.00000	0.00433
Torres−Munoz_2011	0	623	0.00000	0.00000	0.00070
Tung_1992	0	104	0.00000	0.00000	0.00421
Wang_2015	0	1985	0.00000	0.00000	0.00022
Werner_2007	0	77	0.00000	0.00000	0.00568
Whittier_2004	2	750	0.00267	0.00000	0.00636
Yamamoto_2015	9	15191	0.00059	0.00021	0.00098
Yang_2015	0	288	0.00000	0.00000	0.00152
Yesudas_2010	0	65	0.00000	0.00000	0.00673
Zhang_2011	0	280	0.00000	0.00000	0.00156
Summary			**0.00060**	**0.00026**	**0.00138**



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