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.

CJASN 15: 1595–1602, 2020. doi: https://doi.org/10.2215/CJN.04710420

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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Due to the number of

Correspondence: Dr. Brad H. Rovin, The Ohio State University Wexner Medical Center, Nephrology Division, 395 West 12th Avenue, Ground Floor, Columbus, OH 43210. Email: Rovin. 1@osu.edu 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										
		All Studies	Influential Studies Excluded							
Complication Domain	Proportion	95% Confidence Interval	<i>I</i> ² , %	Proportion	95% Confidence Interval	<i>I</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 <i>et al.</i> (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, <i>n</i>	Biopsies, n	Estimate	95% Confidence Interval	I ² , %	Modifier Test: <i>P</i> 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 18gauge 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.

Disclosures

S. Bansal reports other from Home Therapy Institutes, Osprey Medical, and UpToDate outside the submitted work. K. Kiryluk reports employment by Columbia University and grants from the National Institutes of Health (the National Institute of Diabetes and Digestive and Kidney Diseases, the National Center for Advancing Translational Sciences, the National Human Genome Research Institute) during the conduct of the study and reports other from Goldfinch Bio and nonfinancial support from AstraZeneca outside the submitted work. G.M. McMahon reports receiving nonfinancial support from GSK. P.M. Palevsky reports receiving personal fees from Baxter and grants from BioPorto and Dascena outside the submitted work. S. Parikh reports receiving grant U01: IN4687813OSU from the National Institute of Diabetes and Digestive and Kidney Diseases/the National Institutes of Health during the conduct of the study. E.D. Poggio reports receiving consulting fees from CareDx. S.E. Rosas reports attending one scientific advisory board each for Bayer HealthCare Pharmaceuticals Inc. and Reata in 2019, for which she was compensated. She has received grant support from Bayer HealthCare Pharmaceuticals Inc. and is about to start a study with MedImmune Limited, a whollyowned subsidiary of AstraZeneca AB; both are clinical trials related to diabetic nephropathy. B.H. Rovin reports receiving personal fees from AstraZeneca, Aurinia, Bristol Myers Squibb, Callidatis, Chemocentryx, EMD Serono, Janssen, Morphosys, Novartis, Omeros, and Retrophin; nonfinancial support from the Lupus Foundation of America; and grants from the National Institutes of Health outside the submitted work. K. Tuttle reports receiving personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, and Novo Nordisk and grants and personal fees from Goldfinch Bio outside the submitted work. A. Vijayan reports receiving personal fees from Boeringher Ingelheim, NxStage, and Sanofi Aventis outside the submitted work. All remaining authors have nothing to disclose.

Funding

The KPMP is funded by National Institute of Diabetes and Digestive and Kidney Diseases grants UH3DK114861, UH3DK114866, UH3DK114870, UH3DK114908, UH3DK114915, UH3DK114926, UH3DK114907, UH3DK114920, UH3DK114923, UH3DK114933, and UH3DK114937.

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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Received: April 9, 2020 Accepted: July 21, 2020

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Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "How Safe Is a Native Kidney Biopsy?" and article, "Major Bleeding and Risk of Death after Percutaneous Native Kidney Biopsies: A French Nationwide Cohort Study," on pages 1541–1542 and 1587–1594, respectively.

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Supplemental Material

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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

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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	СС	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

Study	Hematomas	Biopsies	Proportion	95% C.I.	
Arora 2012	1	50	0.0200	[0.0000; 0.0839]	_ ;
Bataille 2012	2	535	0.0037	[0.0001: 0.0112]	
Branger 1986	2	108	0.0185	[0.0003: 0.0550]	
Carrington 2011	2	192	0.0104	[0.0002: 0.0311]	
Castoldi 1993	96	230	0.4174	[0.3543: 0.4818]	
Chunduri 2015	44	137	0.3212	[0.2453: 0.4020]	
Cluzel 2000	1	400	0.0025	[0.0000: 0.0107]	
Cui 2016	25	86	0.2907	[0.1990; 0.3916]	——
DiPalma 2010	10	110	0.0909	[0.0433; 0.1527]	-
Doyle 1994	10	155	0.0645	[0.0305; 0.1093]	•
Eiro, M 2005	149	394	0.3782	[0.3309; 0.4267]	-
Elahi 2017	20	75	0.2667	[0.1720; 0.3731]	
Fisi_2012	160	353	0.4533	[0.4016; 0.5055]	-
Granata_2011	15	561	0.0267	[0.0148; 0.0419]	
Guerrero-Ramos_2014	9	180	0.0500	[0.0222; 0.0874]	₽-
Helenius_1983	7	57	0.1228	[0.0483; 0.2225]	- -
Hojs_2004	2	144	0.0139	[0.0002; 0.0414]	
llsam_2010	11	56	0.1964	[0.1015; 0.3119]	
Ishikawa_2009	273	317	0.8612	[0.8208; 0.8972]	-
Jordan_2014	29	215	0.1349	[0.0922; 0.1841]	-
Joseph_2010	44	170	0.2588	[0.1955; 0.3275]	
Kitterer_2015	37	205	0.1805	[0.1306; 0.2363]	
Kohli_2006	1	210	0.0048	[0.0000; 0.0203] 🖪	
Korbet_2014	92	1055	0.0872	[0.0709; 0.1050]	
Lin_2006	55	330	0.1667	[0.1283; 0.2089]	-
Lubomirova_2014	15	230	0.0652	[0.0365; 0.1012]	-
Mackinnon_2008	2	1120	0.0018	[0.0000; 0.0054]	
Mai_2013	19	934	0.0203	[0.0122; 0.0305]	
Maixnerova_2015	133	9051	0.0147	[0.0123; 0.0173] 🔳	
Manno_2011	36	162	0.2222	[0.1613; 0.2897]	
Manno_2004	157	471	0.3333	[0.2914; 0.3766]	-
Margaryan_2010	4	146	0.0274	[0.0059; 0.0615]	•
Marwah_1996	11	394	0.0279	[0.0136; 0.0468]	
Mauer_2002	4	285	0.0140	[0.0030; 0.0317] 🖿	
Maya_2009	13	100	0.1300	[0.0703; 0.2038]	
McMahon_2012	4	105	0.0381	[0.0083; 0.0850]	-
Mendelssohn_1995	13	305	0.0426	[0.0225; 0.0685]	
Mishra_2011	2	86	0.0233	[0.0004; 0.0688]	_
Miura_1984	14	52	0.2692	[0.1563; 0.3990]	
MUNID_2017	2	120	0.0167	[0.0003; 0.0496]	
Ori_2002	1	85	0.0824	[0.0318; 0.1517] -	
Paivansaio_1984	46	150	0.6571	[0.0414, 0.7644]	
Princon_2010	0	100	0.0333	[0.0094, 0.0692]	_
Preda_2003	30	207	0.1760	[0.1220, 0.2377]	
RdU_2010 Dichards 1994	10	276	0.0326	[0.0152, 0.0556]	
Poccatello 2017	15	462	0.0030	[0.0000, 0.0100]	
Dollino 1994	10	201	0.0020	[0.0100, 0.0000]	·
Pollino 2014	44	131	0.0611	[0.1045; 0.2705]	_
Shidam 2005	6	645	0.0093	[0.0233, 0.1035]	
Tan 2017	9	400	0.0225	[0.0099: 0.0397]	
Tanaka 2017	386	462	0.8355	[0.8002: 0.8680]	-
Tang 2002	2	141	0.0142	[0 0002 0 0423]	
Tikkakoski 1994	11	101	0.1089	[0.0546: 0.1780]	- i
Torres-Munoz 2011	96	623	0.1541	[0.1268: 0.1836]	-
Tung 1992	2	104	0.0192	[0.0003: 0.0571]	
Wang 2015	84	1985	0.0423	[0.0339; 0.0516]	1
Werner 2007	12	77	0.1558	[0.0824; 0.2464]	- -
Whittier 2004	51	750	0.0680	[0.0510; 0.0872]	•
Yang 2015	5	288	0.0174	[0.0049; 0.0363]	
Yesudas_2010	1	65	0.0154	[0.0000; 0.0649]	-
Zhang_2011	84	280	0.3000	[0.2476; 0.3551]	-
Random effects model Heterogeneity: $l^2 = 99\%$, $\tau^2 =$	0.0621, χ ₆₁ ² = 56	47.04 (p = 0)	0.1050	[0.0691; 0.1471]	<u>←</u>

0 0.2 0.4 0.6 0.8 1 Proportion of Hematomas

Supplemental Figure 3.	Overall Macroscopic H	ematuria Forest Plot

Study	Hematurias	Biopsies	Proportion	95% C.I.	
AI Turk_2018	15230	118064	0.1290	[0.1271; 0.1309]	•
Arora_2012	1	50	0.0200	[0.0000; 0.0839]	
Branger_1986	2	108	0.0185	[0.0003; 0.0550]	
Carrington_2011	4	192	0.0208	[0.0045; 0.0469]	
Castoldi_1993	16	230	0.0696	[0.0399; 0.1064]	_
Chikamatsu_2017	36	252	0.1429	[0.1022; 0.1890]	
Chunduri_2015	1	137	0.0073	[0.0000; 0.0311]	
Cozens 1992	2	400	0.0050	[0.0001, 0.0150]	•
DiPalma 2010	1	110	0.0091	[0.0000: 0.0386]	
Doyle 1994	8	155	0.0516	[0.0215; 0.0929]	- <u>-</u>
Eiro, M_2005	29	394	0.0736	[0.0497; 0.1016]	_ _
Elahi_2017	5	75	0.0667	[0.0193; 0.1362]	
Granata_2011	21	561	0.0374	[0.0231; 0.0549]	
Guerrero-Ramos_2014	4	180	0.0222	[0.0048; 0.0500]	
Hojs_2004	4	144	0.0278	[0.0060; 0.0623]	
IISam_2010 Isbikawa 2009	0 10	217	0.0893	[0.0261, 0.1805]	
Jordan 2014	12	215	0.0379	[0.0135, 0.0020]	
Khaiehdehi 1999	3	59	0.0508	[0.0065: 0.1249]	-
Kohli 2006	11	210	0.0524	[0.0258: 0.0872]	÷
Korbet_2014	76	1055	0.0720	[0.0572; 0.0885]	
Lin_2006	21	330	0.0636	[0.0396; 0.0928]	_
Mackinnon_2008	4	1120	0.0036	[0.0008; 0.0081]	•
Mai_2013	13	934	0.0139	[0.0073; 0.0226]	-
Maixnerova_2015	138	9051	0.0152	[0.0128; 0.0179]	_ •
Manno_2011	0	162	0.0000	[0.0000; 0.0106]	-
Margaryan 2010	2	4/1	0.0042	[0.0001, 0.0126]	
Marwah 1996	23	394	0.0584	[0.0372: 0.0839]	-
Mauer 2002	8	285	0.0281	[0.0116: 0.0509]	_ _
McMahon 2012	5	105	0.0476	[0.0136; 0.0982]	
Mendelssohn_1995	27	305	0.0885	[0.0590; 0.1232]	_
Mishra_2011	2	86	0.0233	[0.0004; 0.0688]	
Miura_1984	3	52	0.0577	[0.0074; 0.1411]	
Munib_2017	9	120	0.0750	[0.0337; 0.1299]	
Nadium_2013	4	83	0.0482	[0.0105, 0.1069]	
Dendon-Duiz 2014	19	2/1	0.0116	[0.0000, 0.0496]	
Pincon 2010	1	150	0.0067	[0.0000 0.0284]	-
Preda 2003	3	170	0.0176	[0.0022; 0.0443]	
Rao_2018	19	307	0.0619	[0.0374; 0.0919]	_
Richards_1994	8	276	0.0290	[0.0119; 0.0526]	
Roccatello_2017	12	462	0.0260	[0.0132; 0.0427]	
Rollino_1994	21	201	0.1045	[0.0656; 0.1509]	
Rollino_2014	3	131	0.0229	[0.0028; 0.0572]	
Rychilk_2004 Sakaci 2015	2/3	4004	0.0662	[0.0606, 0.0762]	
Sakhuja 1990	9	150	0.0600	[0.0268: 0.1045]	
Shah 1993	4	100	0.0400	[0.0087: 0.0891]	
Shidam 2005	12	645	0.0186	[0.0094; 0.0307]	
Tan_2017	1	400	0.0025	[0.0000; 0.0107]	■-
Tanaka_2017	5	462	0.0108	[0.0030; 0.0227]	—
Tang_2002	5	141	0.0355	[0.0101; 0.0736]	
Tikkakoski_1994	3	101	0.0297	[0.0037; 0.0739]	
Torros Munoz 2011	167	85/3	0.0195	[0.0167; 0.0225]	
Tung 1992	10	104	0.0101	[0.0073, 0.0276]	
Wang 2015	57	1985	0.0287	[0.0218: 0.0365]	-
Werner 2007	6	77	0.0779	[0.0268: 0.1501]	
Whittier 2004	56	750	0.0747	[0.0569; 0.0946]	————
Yang_2015	4	288	0.0139	[0.0030; 0.0314]	
Yesudas_2010	2	65	0.0308	[0.0005; 0.0905]	
Zhang_2011	20	280	0.0714	[0.0439; 0.1048]	
Dandom offects med-			0.0047	10 0074: 0 04003	
Heterogeneity: $I^2 = 99\%$, $T^2 =$	0.0054, χ ₆₃ ² = 54	105.02 (p = 0	0.0347))	[0.0274; 0.0428]	

0 0.05 0.1 0.15 0.2 Proportion of Hematurias

Supplemental Figure 4. Overall Erythrocyte Transfusion Forest Plot

Study	Tranfusions	Biopsies	Proportion	95% C.I.	
Al Turk 2018	30815	118064	0.2610	[0.2585: 0.2635]	•
Altindal 2015	6	290	0.0207	[0.0069; 0.0408]	
Arora 2012	0	50	0.0000	0.0000; 0.0341]	•
Bataille_2012	2	535	0.0037	[0.0001; 0.0112]	
Carrington_2011	2	192	0.0104	[0.0002; 0.0311]	-
Chen_2012	5	219	0.0228	[0.0064; 0.0476]	
Chikamatsu_2017	12	252	0.0476	[0.0243; 0.0778]	
Chunduri_2015	10	137	0.0730	[0.0346; 0.1233]	
Cluzel_2000	1	400	0.0025	[0.0000; 0.0107]	-
Cozens_1992	3	154	0.0195	[0.0024; 0.0488]	-
DIPalma_2010	0	110	0.0000	[0.0000; 0.0156]	
Elio, W_2005 Fisi 2012	2	353	0.0000	[0.0000, 0.0044]	
Granata 2011	2	561	0.0036	[0.0001; 0.0170]	
Hois 2004	0	144	0.0000	[0.0000 ⁻ 0.0119]	
llsam 2010	4	56	0.0714	[0.0158: 0.1565]	
Ishikawa 2009	1	317	0.0032	[0.0000; 0.0135]	
Jordan_2014	8	215	0.0372	[0.0154; 0.0673]	
Joseph_2010	13	170	0.0765	[0.0407; 0.1218]	_ _
Kitterer_2015	3	205	0.0146	[0.0018; 0.0368]	—
Kohli_2006	4	210	0.0190	[0.0041; 0.0429]	-
Korbet_2014	56	1055	0.0531	[0.0403; 0.0675]	
Lees_2017	46	2563	0.0179	[0.0131; 0.0235]	
LIN_2006 Maakinnan_2008	2	330	0.0061	[0.0001; 0.0182]	
Mai 2013	10	03/	0.0134	[0.0074, 0.0211]	2
Manno 2011	0	162	0.0000	[0.0000; 0.0107]	
Manno 2004	2	471	0.0042	[0.0001: 0.0128]	
Margaryan 2010	1	146	0.0068	[0.0000; 0.0292]	
Marwah_1996	22	394	0.0558	[0.0351; 0.0809]	
Maya_2009	0	100	0.0000	[0.0000; 0.0171]	-
Miura_1984	0	52	0.0000	[0.0000; 0.0328]	•
Munib_2017	2	120	0.0167	[0.0003; 0.0496]	-
Nadium_2013	2	83	0.0241	[0.0004; 0.0713]	
Dendon-Duiz 2014	4	60 241	0.0471	[0.0103, 0.1044]	
Pendon-Ruiz_2014 Pincon 2010	3	150	0.0373	[0.0165, 0.0655]	
Preda 2003	4	170	0.0200	[0.0050: 0.0529]	
Rao 2018	2	307	0.0065	[0.0001; 0.0195]	.
Richards_1994	2	276	0.0072	[0.0001; 0.0217]	-
Sakaci_2015	0	78	0.0000	[0.0000; 0.0219]	•
Sakhuja_1990	1	150	0.0067	[0.0000; 0.0284]	-
Sethi_2013	8	100	0.0800	[0.0336; 0.1424]	
Shidam_2005	16	645	0.0248	[0.0140; 0.0384]	-
Soares_2008	6	289	0.0208	[0.0069; 0.0410]	-
Tabatabal_2009	24	1116	0.0215	[0.0137; 0.0309]	_ _
Tang 2002	2	402	0.0043	[0.0001, 0.0130]	
Tikkakoski 1994	2	101	0.0142	[0.0002; 0.0423]	
Tondel 2012	78	8573	0.0091	[0.0072: 0.0112]	
Torres-Munoz_2011	11	623	0.0177	[0.0086; 0.0297]	÷-
Tung_1992	3	104	0.0288	[0.0036; 0.0718]	
Wang_2015	71	1985	0.0358	[0.0280; 0.0444]	=
Werner_2007	0	77	0.0000	[0.0000; 0.0222]	•
whittier_2004	38	750	0.0507	[0.0360; 0.0676]	
ramamoto_2015	76	15191	0.0050	[0.0039; 0.0062]	
Tally_2010 Vesudas 2010	0	288	0.0000	[0.0000; 0.0060]	
Zhang 2011	0	280	0.0000	[0.0000, 0.0203] [0.0000 ⁻ 0.0061]	
znang_zorn	0	200	0.0000	[0.0000, 0.0001]	_
Random effects model	l		0.0160	[0.0102; 0.0229]	<u> </u>
Heterogeneity: $I^2 = 100\%$, τ^2	= 0.0073, χ ₅₈ ² = 2	4434.73 (p =	: 0)	-	
					0 0.05 0.1 0.15 0.2 0.25 0.3

Proportion of Transfusions

Supplemental Figure 5. Overall Surgical/IR Intervention Forest Plot

Study	Interventions	Biopsies	Proportion	95% C.I.	
AI Turk 2018	165	118064	0.0014	[0.0012: 0.0016]	0
Altindal 2015	2	290	0.0069	[0.0001; 0.0207]	
Arora_2012	0	50	0.0000	[0.0000; 0.0341]	•
Bataille_2012	3	535	0.0056	[0.0007; 0.0142]	
Carrington_2011	2	192	0.0104	[0.0002; 0.0311]	
Castoldi_1993	2	230	0.0087	[0.0001; 0.0260]	
Chen_2012	3	219	0.0137	[0.0017; 0.0344]	
Chikamatsu_2017	2	252	0.0079	[0.0001; 0.0238]	
Chunduri_2015	4	137	0.0292	[0.0063; 0.0654]	
Cluzel_2000	3	400	0.0075	[0.0009, 0.0189]	
Cui 2016	2	104	0.0130	[0.0002, 0.0387]	
DiPalma 2010	2	110	0.0233	[0.0004, 0.0666]	
Dovle 1994	1	155	0.0065	[0.0000; 0.0100]	
Eiro M 2005		394	0.0000	[0 0000: 0 0044]	
Fisi 2012	8	353	0.0227	[0.0093: 0.0412]	_
Gesualdo 2008	1	110	0.0091	[0.0000; 0.0386]	
Granata 2011	1	561	0.0018	[0.0000; 0.0076]	-
Guerrero-Ramos_2014	3	180	0.0167	[0.0021; 0.0418]	
Hojs_2004	0	144	0.0000	[0.0000; 0.0119]	
llsam_2010	0	56	0.0000	[0.0000; 0.0305]	•
Ishikawa_2009	0	317	0.0000	[0.0000; 0.0054]	
Jordan_2014	6	215	0.0279	[0.0093; 0.0549]	
Kitterer_2015	1	205	0.0049	[0.0000; 0.0208]	
Kohli_2006	0	210	0.0000	[0.0000; 0.0082]	
Korbet_2014	11	1055	0.0104	[0.0051; 0.0176]	
Lees_2017	9	2563	0.0035	[0.0015; 0.0062]	-
Mackinnon_2008	2	1120	0.0018	[0.0000; 0.0054]	
Mai_2013	0	934	0.0000		
Manno_2011	0	162	0.0000	[0.0000; 0.0106]	
Margaryan 2010	4	4/1	0.0000	[0.0016, 0.0192]	
Manyah 1996	0	140	0.0000	[0.0000, 0.0117]	
Mauer 2002	0	285	0.0070	[0.0009, 0.0192]	
Mava 2009	0	100	0.0000	[0.0000; 0.0000]	
McMahon 2012	1	105	0.0095	[0.0000; 0.0404]	
Mendelssohn 1995	0	305	0.0000	[0.0000; 0.0056]	
Mishra 2011	1	86	0.0116	[0.0000; 0.0493]	
Miura 1984	0	52	0.0000	[0.0000; 0.0328]	•
Munib 2017	0	120	0.0000	[0.0000; 0.0143]	•
Nadium_2013	0	83	0.0000	[0.0000; 0.0206]	•
Ori_2002	0	85	0.0000	[0.0000; 0.0201]	
Pendon-Ruiz_2014	2	241	0.0083	[0.0001; 0.0248]	
Pincon_2010	0	150	0.0000	[0.0000; 0.0114]	•
Rao_2018	4	307	0.0130	[0.0028; 0.0295]	
Roccatello_2017	6	462	0.0130	[0.0043; 0.0257]	
Rollino_2014	1	131	0.0076	[0.0000; 0.0325]	
Sakaci_2015	0	/8	0.0000	[0.0000; 0.0219]	
Sakhuja_1990	0	100	0.0000	[0.0000, 0.0114]	
Setti_2013 Shidom 2005	1	100	0.0100	[0.0000; 0.0424]	
Sniuani_2005	4 5	280	0.0002	[0.0013, 0.0141]	
Tabatabai 2009	8	1116	0.0072	[0.0029: 0.0131]	-
Tanaka 2017	0	462	0.0000	[0 0000: 0 0037]	
Tang 2002	2	141	0.0142	[0.0002; 0.0423]	
Tikkakoski 1994	0	101	0.0000	[0.0000; 0.0170]	•
Tondel 2012	17	8573	0.0020	[0.0011; 0.0030]	•
Torres-Munoz_2011	3	623	0.0048	[0.0006; 0.0122]	
Tung_1992	1	104	0.0096	[0.0000; 0.0408]	•
Wang_2015	16	1985	0.0081	[0.0045; 0.0125]	-=-
Werner_2007	0	77	0.0000	[0.0000; 0.0222]	
Whittier_2004	5	750	0.0067	[0.0019; 0.0140]	
Yamamoto_2015	15	15191	0.0010	[0.0005; 0.0016]	
Yang_2015	0	288	0.0000	[0.0000; 0.0060]	
resudas_2010	1	65	0.0154	[0.0000; 0.0649]	
Znang_2011	0	280	0.0000	[0.0000; 0.0061]	
Dandom offects medal			0 0022	10 0020: 0 00403	1
Heterogeneity: $l^2 = 73\%$ $\tau^2 =$	0 0008 v ² = 230	27 (p < 0.01)	[0.0020, 0.0049]	-
	5.5555, A65 - 235.	2. 0.01	,	(0.02 0.04 0.06 0.08
				,	Proportion of Interventions

Supplemental Figure 6. Overall Death Forest Plot

Albu_2010 2123 110540 0.0124 0.0124 0.0124 0.0124 0.0124 Albu_2010 0 200 00000 0.0000	Study	Deaths	Biopsies	Proportion	Lower Bound	Upper Bound	
Aread_John I Bit Dotto Dotto Dotto Basil_JON 0 100 00000 000000 000000 000000 Basil_JON 0 100 00000 000000 000000 000000 Basil_JON 0 100 00000 000000 <td< td=""><td>Al Turk_2018</td><td>2125</td><td>118064</td><td>0.01800</td><td>0.01724</td><td>0.01876</td><td>+</td></td<>	Al Turk_2018	2125	118064	0.01800	0.01724	0.01876	+
Areg_2012 0 90 0.00000 0.0000 0.00000	Altindal_2015	1	290	0.00345	0.00000	0.01020	
Altar_203 0 0000 000000 00000 00000 <th< td=""><td>Arora_2012</td><td>0</td><td>50</td><td>0.00000</td><td>0.00000</td><td>0.00874</td><td>•</td></th<>	Arora_2012	0	50	0.00000	0.00000	0.00874	•
Banis_2012 0 555 00000 00002 000002 00002 00002 <th< td=""><td>Azhar_2005</td><td>0</td><td>200</td><td>0.00000</td><td>0.00000</td><td>0.00219</td><td>•</td></th<>	Azhar_2005	0	200	0.00000	0.00000	0.00219	•
Carrows Description 0 192 0.0000 0.0000 0.0112	Bataille 2012	0	535	0.00000	0.00000	0.00082	•
Carabi Open Displat Open Displat Open Displat Carabi 0 219 0.0000 0.0000 0.0010	Carrington_2011	0	192	0.00000	0.00000	0.00228	•
Cim_1212 0 1910 0.0000 0.0000 0.0000	Castoldi 1993	0	230	0.00000	0.00000	0.00190	-
Channel0171 0 222 00000 00000 00174	Chen 2012	0	219	0.00000	0.00000	0.00200	
Charder of the set	Chikamatsu 2017	ő	252	0.00000	0.00000	0.00174	
Carbon C </td <td>Chunduri 2015</td> <td>ő</td> <td>137</td> <td>0.00000</td> <td>0.00000</td> <td>0.00320</td> <td></td>	Chunduri 2015	ő	137	0.00000	0.00000	0.00320	
Lambe 1 2000 0 0000 0 0000 0 0000 0 0000 0 0000 0	Chandan_2010	š	400	0.00000	0.00000	0.00320	I
Cal Dan Control Control Con	Ciuzei_2000	0	400	0.00000	0.00000	0.00110	T
City_Dia O BO CONCOLD CONCOLD<	Cozens_1992	0	154	0.00000	0.00000	0.00284	
Distant_2010 0 110 00000 00000 00011	Cui_2018	0	86	0.00000	0.00000	0.00509	
Dome_1044 0 198 0.00000 0.0000 0.00000 <td>DiPalma_2010</td> <td>0</td> <td>110</td> <td>0.00000</td> <td>0.00000</td> <td>0.00398</td> <td>•</td>	DiPalma_2010	0	110	0.00000	0.00000	0.00398	•
En M ₂ 007 En M ₂	Doyle_1994	0	155	0.00000	0.00000	0.00283	-
Elang. 2017 0 0 75 0.00000 0.0	Eiro, M_2005	0	394	0.00000	0.00000	0.00111	••
Execute_2019 0 337 0.0000 0.00100 0.00100 0.00110 General_ADD1 0 151 0.0000 0.0000 0.00178	Elahi_2017	0	75	0.00000	0.00000	0.00583	•
Fig. 2012 0 353 0.0000 0.0000 0.00124	Esposito_2018	0	337	0.00000	0.00000	0.00130	
General, 2019 0 110 0.0000 0.0000 0.0038 General, 2014 0 180 0.0000 0.0000 0.0074 Heretan, 100 0 17 0.0000 0.0000 0.0074 Heretan, 2010 0 17 0.0000 0.0000 0.0074 Heretan, 2010 0 17 0.0000 0.0000 0.0171 Josep, 2016 0 17 0.0000 0.0000 0.0171 Josep, 2016 0 120 0.0000 0.0113 + Josep, 2016 0 120 0.0000 0.0113 + Les, 2017 1 2253 0.0000 0.0013 + Les, 2017 1 2253 0.0000 0.0013 + Les, 2017 1 2253 0.0000 0.0013 + Les, 2017 1 120 0.0000 0.00114 + Les, 2017 1 120 0.0000 0.00014 +	Fisi_2012	0	353	0.00000	0.00000	0.00124	₽-
General-Sarol Heteria, 1613 0 61 0.0000 0.0000 0.0078 Heteria, 1613 0 57 0.0000 0.0000 0.00778 Heteria, 2041 0 17 0.0000 0.00000 0.00778 Lisan, 204 0 12 0.0000 0.00000 0.00078 Lisan, 204 0 12 0.0000 0.00000 0.0000 0.0000 Addat, 204 0 12 0.0000 0.0000 0.0000 0.0000 Addat, 2014 1 1255 0.0000 0.0000 0.0000 0.0000 0.0000 Lise0017 1 2550 0.0000 0.0000 0.0000 0.0000 0.0000 Man_2013 0 44 0.0000 0.0000 0.0000 0.0000 Man_2014 0 160 0.0000 0.0000 0.0000 0.0000 Man_2013 0 44 0.0000 0.0000 0.0000 0.0000 Man_2014 0	Gesualdo 2008	0	110	0.00000	0.00000	0.00398	•
Guerrand Control District Control District Hear 100 00000 00000 00000 00000 Hear 100 100 00000 00000 00000 Hars 100 100 00000 00000 00000 Hars 100 100 00000 00000 00000 Hars 100 00000 00000 00000 00000 Hars 100	Granata 2011	0	561	0.00000	0.00000	0.00078	
Hear 1943 0 17 0.00000 0.0000 0.00000	Guerrero-Ramos 2014	0	180	0.00000	0.00000	0.00243	-
integ_200 0 14 0.00000 0.0000 0.00000 <td>Helenius 1983</td> <td>0</td> <td>57</td> <td>0.00000</td> <td>0.00000</td> <td>0.00767</td> <td></td>	Helenius 1983	0	57	0.00000	0.00000	0.00767	
Internation 0 150 0.0000 0.0000 0.0000 Jordar 2014 1 215 0.0048 0.0000 0.00214	Hois 2004	0	144	0.00000	0.00000	0.00304	
Description C C C CONCORD Description Statel 2014 1 0 25 0.00000 0.00000 0.00001 Kiberg 2015 0 226 0.00000 0.00000 0.00001 0.00001 Kiberg 2015 0 283 0.00000 0.00000 0.00001 0.00001 Ling 2017 1 283 0.00000 0.00000 0.00001 0.00001 Makinerg 2013 0 644 0.00000 0.00001 0.00001 0.00001 Makinerg 2011 0 471 0.00000 0.00001 0.00001 0.00001 Marg 2013 0 471 0.00000 0.00000 0.00014 - Marg 2013 0 471 0.00000 0.00000 0.00014 - Marg 2010 0 471 0.00000 0.00000 0.00014 - Marg 2011 0 84 0.00000 0.00000 0.00014 - Marg 2012	llsam 2010	ő	88	0.00000	0.00000	0.00304	I
cathod 0 317 0.0000 0.0000 0.0000 0.0000 0.0000 0.0013	Ishikawa 2000		00	0.00000	0.00000	0.00781	
	Isnikawa_2009	U	317	0.00000	0.00000	0.00138	
	Jordan_2014	1	215	0.00465	0.00000	0.01375	•
indereg_2015 0 205 0.0000 0.0	Joseph_2010	0	170	0.00000	0.00000	0.00258	-
idental_2014 1 1055 0.0000 0.0000 0.0000 0.0015	Kitterer_2015	0	205	0.00000	0.00000	0.00214	•
Michagenater_2015 0 283 0.0000 0.0000 0.0015	Korbet_2014	1	1055	0.00095	0.00000	0.00280	-
Lee 2017 1 2263 0.0003 0.0000 0.015 F Hacking 2008 0 1120 0.0000 0.0000 0.0003 F Macking 2014 0 122 0.0000 0.0000 0.0003 F Mang 2011 0 471 0.0000 0.0000 0.0000 F Margang 2010 0 148 0.0000 0.0000 0.0014 F Margang 2010 0 128 0.0000 0.0000 0.0014 F Margang 2017 0 158 0.0000 0.0000 0.0014 F Margang 2017 0 158 0.0000 0.0000 0.0055 F Margang 2017 0 150 0.0000 0.0000 0.0055 F Margang 2018 0 150 0.0000 0.0000 0.0005 F Margang 2018 0 150 0.0000 0.0000 0.0005 F Margang 2017 0 150 0.0000 0.0000 0.0005 F Margang 2018 0 150 0.0000 0.0000 0.0002 F Margang 2018 0 150 0.0000 0.0000 0.0000 0.0000 F Margang 2018 0 150 0.0000 0.0000 0.0000 F Margang 2018 0 150 0.0000 0.0000 0.0000 F Marg	Kriegshauser_2015	0	293	0.00000	0.00000	0.00150	+-
Lin_2006 0 130 0 00000 0.00000 0.0000 0.0000 Mai_0013 0 044 0.00000 0.0000 0.0003 0 0.0000 Mann_2014 0 147 0.00000 0.0000 0.0003 0 0.0000 Mann_2010 0 146 0.00000 0.00000 0.0003 0 0.0000 Marey 106 0 0 344 0.00000 0.00000 0.0011 0 - Marey 106 0 0 344 0.00000 0.00000 0.0011 0 - Marey 200 0 0 00 0.0000 0.0000 0.0011 0 - Marey 200 0 0 00 0.0000 0.0011 0 - Marey 200 0 0 0 0 0 0 0.0000 0.0011 0 - Marey 200 0 0 0 0 0 0 0.0000 0.0011 0 - Marey 200 0 0 0 0 0 0 0.0000 0.0011 0 - Marey 200 0 0 0 0 0 0 0 0 0.0000 0.0011 0 - Marey 200 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Lees_2017	1	2563	0.00039	0.00000	0.00115	•
Maximon_2008 0 1120 0.00000 0.00000 0.00000 0.00001 Mann_2014 0 452 0.00000 0.00000 0.00001 Mann_2010 0 446 0.00000 0.00000 0.00001 Margarya_2010 0 446 0.00000 0.00000 0.00114 - Maxesh_1906 0 285 0.00000 0.00000 0.00144 - May_2009 0 105 0.00000 0.00000 0.00144 - Margarya_2013 0 85 0.00000 0.00000 0.000477 - Margarya_2013 0 85 0.00000 0.00000 0.00001 0.00001 Margarya_2013 0 83 0.00000 0.00001 0.00001 0.00001 Margarya_1997 188 0.00000 0.00000 0.00001 0.00001 Margarya_1997 0 180 0.00000 0.00001 0.00001 Margarya_1997 0 0.00000	Lin_2006	0	330	0.00000	0.00000	0.00133	■-
Main 2013 0 024 0.0000 0.00001 0.00001 Manne 2004 0 412 0.00000 0.00000 0.00003 Manne 2004 0 444 0.00000 0.00000 0.00003 Marews 2010 0 444 0.00000 0.00000 0.00111 Marews 2002 0 285 0.00000 0.0044 - Mays 2009 0 105 0.00000 0.0044 - Mandaton 1960 0 305 0.00000 0.0044 - Mandaton 1960 0 305 0.00000 0.0044 - Mandaton 1960 0 305 0.00000 0.00001 0.00001 Mandaton 1960 0 82 0.00000 0.00001 0.00001 Mandaton 1960 0 83 0.00000 0.00002 0.00001 Mandaton 1970 0 0.00000 0.00002 0.00001 0.00002 Pressize 104 0 170 0.00000	Mackinnon 2008	0	1120	0.00000	0.00000	0.00039	
Name_201 0 112 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.0011 Marey_2002 0 255 0.00000 0.00000 0.00417	Mai 2013	0	934	0.00000	0 00000	0.00047	The second se
Hamm_2011 0 471 0.0000	Manno 2004	0	162	0.00000	0.00000	0.00270	T
mark_point 0 144 0.0000 0.0000 0.0000 Memer_2002 0 284 0.00000 0.00000 0.00001 Mayer_2002 0 284 0.00000 0.00000 0.00001 Mayer_2002 0 285 0.00000 0.00000 0.00001 Mayer_2012 0 105 0.00000 0.00000 0.00001 Mandent_0112 0 295 0.00000 0.00000 0.00001 Mandent_011 0 82 0.00000 0.00000 0.00001 Mandent_011 0 82 0.00000 0.00000 0.00001 Mandent_011 0 82 0.00000 0.00000 0.00001 Mandent_011 0 132 0.00000 0.00000 0.00001 Nader_0116 0 152 0.00000 0.00000 0.00001 Pricer_0116 0 152 0.00000 0.00000 0.00001 Prese_0116 0 276 0.00000 <td>Manno 2011</td> <td>ő</td> <td>471</td> <td>0.00000</td> <td>0.00000</td> <td>0.00003</td> <td></td>	Manno 2011	ő	471	0.00000	0.00000	0.00003	
Margang 2010 0 140 0.0000 0.0000 0.0000 Maxer 2002 0 285 0.0000 0.0014 - Marga 2010 0 100 0.0000 0.0014 - Mediatach 2012 0 105 0.0000 0.0014 - Marga 2010 0 205 0.0000 0.0014 - Marga 2011 0 85 0.0000 0.0004 0.0006 Marga 2017 0 120 0.0000 0.00021 - Marga 2013 0 88 0.0000 0.00021 - Paivansia, 164 0 70 0.0000 0.00021 - Privansia, 164 0 70 0.0000 0.00021 - Privansia, 164 0 70 0.0000 0.00021 - Privansia, 164 0 276 0.0000 0.00021 - Privansia, 164 0 307 0.00000 0.00051 -	Manno_2011		4/1	0.00000	0.00000	0.00093	T
Markar Markar Markar Status Markar	Margaryan_2010	0	140	0.00000	0.00000	0.00300	
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