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A Systematic Review of Complications Associated With Percutaneous Native Kidney Biopsies in Adults in Low- and Middle-Income Countries

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Introduction: Kidney biopsy is an important tool for making diagnoses and for assessing the drug treatment requirements and disease prognosis in the management of kidney diseases. There are variations in the rate of complications associated with kidney biopsies across countries, and this depends on various clinical and technical factors. The aim of this study is to report on complications associated with kidney biopsy performed in low- and middle-income countries.

Methods: Two reviewers searched studies in MEDLINE, Embase, Cochrane Reviews, and African Journals Online. A random effects meta-analysis method was used to pool estimates of complications.

Results: We identified 39 studies reporting on 19,500 kidney biopsies with overall complications (major + minor) rate of 14.9% (95% confidence interval = 11.4%–18.7%). Fewer complications were reported in biopsies performed with real-time ultrasound scans compared to those pre-marked using ultrasound or blind procedures (12.4% vs. 14.9% vs. 24.5%; $P = 0.037$), respectively. Complications, albeit lower for procedures performed with automated needles (13.3%), were not significantly different from those performed with nonautomated needles (17.3%; $P = 0.588$). Major complications included macroscopic hematuria (1.48%), nephrectomy (0.04%), blood loss requiring red cell transfusion (0.24%), angiographic intervention (0.22%), and death (0.01%).

Conclusion: Complications associated with kidney biopsy in low- and middle-income countries are low, are comparable to those in other settings, and occur more sparingly when real-time ultrasound techniques or automated kidney biopsy needles are used. This suggests the need to expand the use of this procedure to improve diagnosis of kidney pathologies and choice of therapy when indicated.

Kidney Int Rep (2021) **6,** 78–90; https://doi.org/10.1016/j.ekir.2020.10.019
KEYWORDS: bleeding; complications; kidney biopsy; low-to-middle-income countries; needle biopsy; ultrasound-guided biopsy

Percutaneous native kidney biopsy (PNKB) is an important tool for guiding clinicians towards making diagnosis of kidney diseases, deciding on treatment options and prognosticating on disease outcomes.[1] Kidney biopsy was introduced to medicine in 1944 and later in 1951 by Iversen and Brun, and has since provided clinicians with valuable information about kidney disease and its management.[2,3] Improvements in the technique, including use of ultrasound and use of automated mechanisms, have been associated with reduced complications.[1,3] Although some studies show that PNKB is a safe procedure and frequently show that significant complication to occur in less than 1% of cases,[4,5] higher rates of kidney

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Received 22 May 2020; revised 22 May 2020; accepted 20 October 2020; published online 3 November 2020

biopsy−related complications have been reported in other studies.[6−8] In a single-center study of 1055 adults from the United States, major complications occurred in 6.6% of biopsies, transfusions were required in 5.3%, and 1 death (0.09%) resulted following PNKB bleeding.[7] However, a 5-year nationwide study in the United States involving 118,064 adults who had PNKB reported 1.8% mortality, some of which was thought to be related to pre-existing comorbidities in the patients.[6] Factors associated with biopsy complications have been found to include the biopsy technique, size of the biopsy needle, experience of the operator, and range of the biopsy protocol (including complete blood count, international normalized ratio/prothrombin time, activated partial thromboplastin time, serum creatinine, and medication review).[9]

In a previous systematic review on kidney biopsy complications, the focus was mainly on bleeding complications and procedures that were carried out using automated needles and real-time ultrasound guidance.[5] The authors reported macroscopic hematuria in 3.5% of cases (95% confidence interval [CI] = 2.2%−5.1%), blood transfusion in 0.9% (95% CI = 0.4%−1.5%) and a significantly higher rate of transfusion with 14-gauge compared with smaller needles (2.1% vs. 0.5%; P = 0.009). Their review did not include low- and middle-income countries (LMICs).[5] The aim of this systematic review and meta-analysis is to summarize available evidence on the rates of complications in patients undergoing PNKB in LMICs. It is anticipated that the results of our study will be useful in improving kidney care in this region, where conditions requiring PNKB for diagnosis and for guiding decisions on treatment (e.g., glomerulonephritis) are very common.[10,11]

METHODS

This systematic review and meta-analysis is reported in accordance of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[12]

Protocol Registration

The protocol for this review was registered in PROSPERO (CRD42017077656) and has been published.[13]

Eligibility Criteria

Studies were included if they were performed in LMICs reporting on complications post-PNKB from 1 January 1980 to 31 December 2019, if the study design was cohort, cross-sectional, or case-control studies from LMICs without language restriction, and if the study was performed in patients 18 years and older. Studies that were excluded were those that reported kidney histologies of tumors or kidney masses, those with fewer than 30 patients, editorials and review articles, studies on complications of PNKB from high-income countries, studies reporting complications of kidney biopsies in transplant patients, those with duplicate publications (in such cases, we considered only the most recent one) and comprehensive publication, and studies with inaccessible data even after a request from the authors.

Search Strategy for Identifying Relevant Studies

We searched several databases including, MEDLINE, Embase, Cochrane Reviews, and African Journals Online databases for relevant abstracts (Supplementary Table S1). The search was performed from 1 January 1980 to 31 December 2019 with no language restriction. All identified relevant entries were scrutinized and full papers downloaded from the databases or journal websites. Also, the reference lists of eligible articles and relevant reviews were examined to identify additional potentially eligible studies. We used a 2-stage collaborative review process to screen and select references. The first stage involved screening of the title/abstract; the second stage involved obtaining full texts that met the inclusion criteria for further screening.

Study Selection

Two reviewers (SK and MWM) independently screened the titles and abstracts of the records retrieved by database searches. Then, the full texts of all potentially eligible articles were obtained and further assessed for final inclusion. Disagreements were resolved by a third reviewer (IGO).

Data Extraction and Management

Data were extracted onto a pre-developed data capture sheet and reviewed by 2 investigators (SK and UEE) for accuracy and completeness. We collected information on country of participants, author, year of publication, study design, sample size, mean age, sex, method of biopsy (blind, ultrasound-guided, or ultrasound marking), needle size, type of needle used for the biopsy (automatic, manual), indication for biopsy, kidney biopsy complication rates, factors associated with major bleeding, for example, elevated blood pressure, platelet count, and coagulation parameters and operator (nephrologist, radiologist, or trainee). We then assigned each study to a country-income group based on the 2017 World Bank income country grouping (low, lower-middle, upper-middle, and high-income countries).[14] Two studies (Pokhrel *et al.*[15] and Pongsittisak *et al.*[16]) compared and reported the frequency of complications between biopsy methods, thus, each arm of each study was regarded as a single study for ease of data analysis.[15,16] Another study was also split into 2

parts, as it compared complications between blind technique and real-time ultrasound technique.[17]

We defined the methods used for performing the biopsies as: "blind" method if kidney biopsy was performed without use of radiological guidance, as a "premarking (USS-PM)" method as the procedure performed using ultrasound for kidney localization before obtaining biopsy, and "real time ultrasound (USS-RT)" technique if there was use of ultrasound guiding the needle in real time during the biopsy. We also grouped the countries according to the World Bank regions, namely, East Asia and Pacific; Europe and Central Asia; Latin America and the Caribbean; Middle East and North Africa; South Asia and sub-Saharan Africa.[14] We defined a major complication as those requiring an intervention post-biopsy (e.g., blood transfusion, invasive radiological or surgical procedure, acute kidney obstruction, extended hospitalization, septicemia, or death). Finally, minor complications were defined as those that did not require any further invasive or clinical intervention and included transient hematuria, hematoma, and significant pain at the biopsy site but did not require any radiological or surgical interventions.

Risk of Bias in Individual Studies

We adapted and used the 9-item tool developed by Hoy *et al*.[18] and used it to assess the methodological quality of included studies (Supplementary Table S2). Studies were classified according to their overall score as high (1–3), medium (4–6), or low (7–10) quality. Two reviewers (SK and UEE) independently assessed the quality of the studies, and we assessed interrater agreement for study inclusion using the kappa (κ) coefficient.[19]

Statistical Analysis and Synthesis of Results

We pooled the study-specific estimates using the DerSimonian–Laird random-effects meta-analysis model to obtain an overall summary estimate of the rates of complications across studies after stabilization of the variances using the square root transformation. The estimates were back transformed for reporting. Heterogeneity was assessed using the χ^2 test on Cochrane's Q statistic[20] and quantified by calculating the I^2 (with values of 25%, 50%, and 75% representing low, medium, and high heterogeneity, respectively).[21] Subgroup analysis was undertaken to compare the pooled rates by country socioeconomic level (low-income vs. middle-income), needle size, biopsy technique used, and time era of study, divided into the 3 categories (i) studies published before the year 2000, (ii) studies published between 2000 and 2009, and (iii) studies published between 2010 and 2019, using the Q-test based on the analysis of variance. We were unable to determine accurate estimates of extremely rare complications (e.g., infections, nephrectomy, death) by meta-analysis and instead determined the raw rates for these outcomes. A cumulative meta-analysis was done to assess the effect of time on the frequency of overall and major kidney biopsy complications. We assessed the presence of publication bias using funnel plots and the Egger test.[21] A P value <0.05 was considered indicative of a statistically significant difference between subgroups. All analyses were performed using STATA 15.1 (StataCorp, College Station, TX).

RESULTS

General Characteristics of Included Studies

The initial literature search yielded 1306 articles, of which 67 were selected for full-text review after title and abstract screening. A total of 39[4,8,15–17,21–54] were eligible for data extraction, reporting on 19,500 kidney biopsies performed in 19,338 patients in 18 countries located in 6 regions of the world (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow chart provided in Figure 1). These regions include the following: sub-Saharan Africa (5 studies)[24,27–29,52]; South Asia (15 studies)[15,22,23,30–39,54,55]; Middle East and North Africa (7 studies)[8,17,25,26,40–42]; Latin America and the Caribbean (2 studies)[50,51]; Europe and Central Asia (3 studies)[48,49,53]; and East Asia and the Pacific (7 studies).[4,16,44–47,56] There were 5 studies from low-income countries[15,22–24,55]; 18 from lower middle-income countries[8,17,25–39,54]; and 16 studies from upper middle-income countries.[4,16,40-42,44–53,56] Based on quality assessment (with an interrater agreement of 79.4%), most studies (22/39; 56.4%) were of moderate quality,[8,15,22,23,25,27,30,32–36,39–42,47–49,52,54,55] 12 studies (30.8%) were of high quality,[4,16,31,37,38,45,46,50,51,53,56] and 5 studies (12.8%) were low quality[17,24,26,28,29] (Table 1).

Biopsy techniques using USS-RT were reported in 20 studies (48.8%),[4,15,16,24,31,32,34,37–41,44,47,48,50–54] USS-PM in 15 studies (36.6%),[8,15,16,22,23,27,33,35,36,42,45,46,49,55,56] fluoroscopic technique in 1 study (2.4%),[26] and no imaging guidance (blind technique) in 5 studies (12.2%).[17,25,28–30] In 11 studies, the biopsies were performed by nephrology staff (6 by nephrologists and 5 by nephrology trainees),[15,16,22,34,51] in 5 studies by a nephrologist assisted by radiologists,[23,31,32,50,55] and in 3 studies by radiologists only.[38,41,52] However, 20 of the studies (51.4%) did not document the level of experience or specialty of the individuals performing the procedure[4,8,17,24–28,30,33,35,36,43,45–49,53,54] (Table 1).

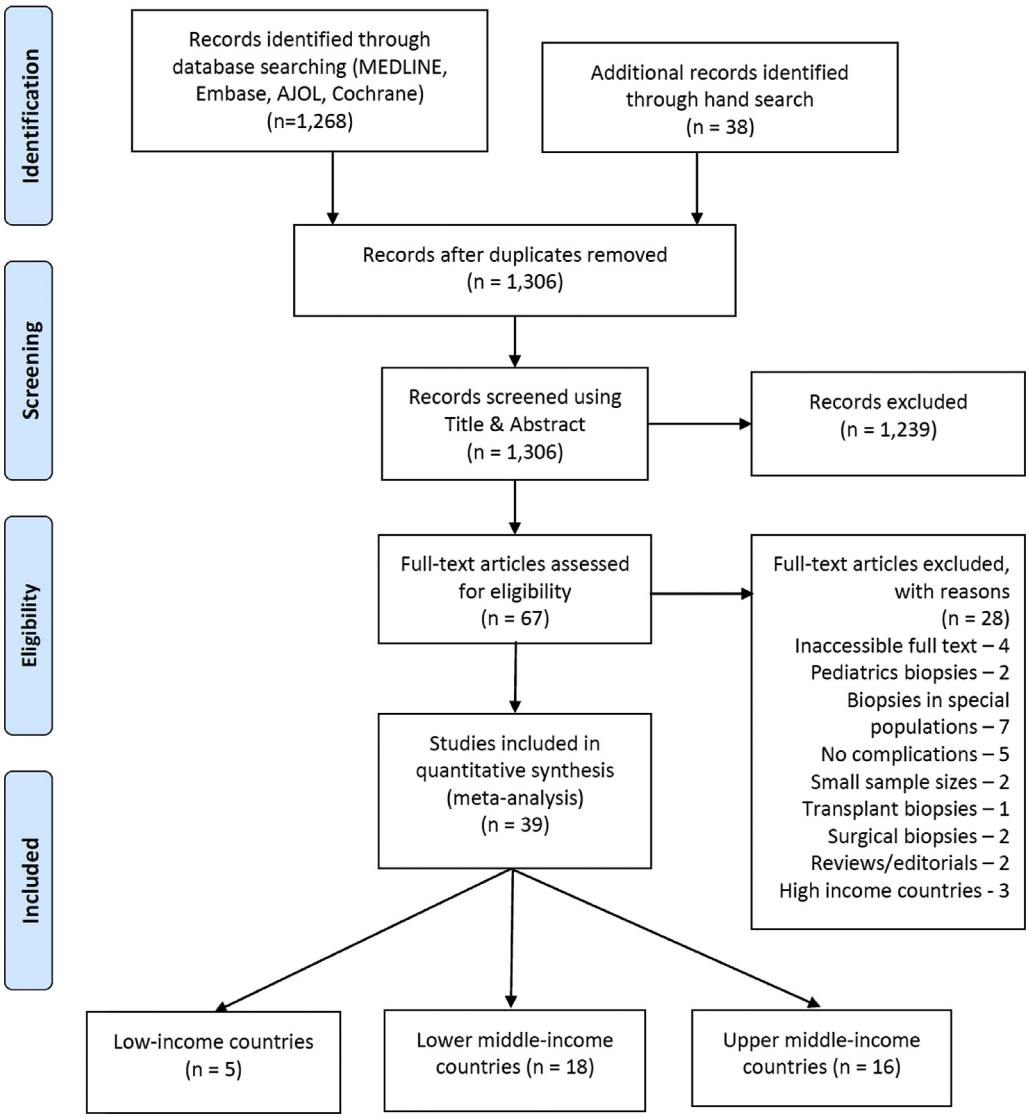

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. AJOL, African Journals Online.

The main indication for the biopsy was nephrotic syndrome in 17 studies (43.6%),[8,15,16,23–25,27,28,30–32,34,47,48,50,54,55] subnephrotic proteinuria in 3 studies,[22,35,53] and nephritic syndrome in 3 studies.[39,41,42] Other indications included CKD evaluation in 2 studies,[26,41] lupus nephritis in 1 study[51] and asymptomatic urine abnormalities in another study.[49] In 12 studies (34.3%) the main indication for kidney biopsy was not reported.[4,17,29,33,37,38,40,43–46,52]

Twenty studies (51.3%) reported use of 16G and 18G automated needles[4,8,15,16,23,31,32,34–36,39–42,46,50–53,55]; nonautomated biopsy needles such as the Vim-Silverman, Menghini, and Trucut were reported in 8 studies (20.5%) studies,[17,27–30,33,42,49] whereas in 10 studies (25.6)[24–26,38,43–45,47,48,54] did not record the type of needle used was not reported. Only 1 study used a 14G needle[37] (Table 1).

Only 1 study (2.8%), from South Africa, reported the presence of a pathologist during kidney biopsy[52]; 11 studies reported on the average number of glomeruli obtained after a kidney biopsy[23,25,31,32,34–36,40,41,48,55]; and 17 studies reported, from a range of 71%–100%, that glomeruli obtained were adequate to make diagnosis of the underlying condition[4,16,17,26,28–35,37,39,40,48,50,52–54] (Table 1 and Supplementary Table S3).

Complications of Kidney Biopsy

Overall Complications

The overall rate of kidney biopsy complications was 14.9% (95% CI = 11.4%–18.7%, I^2 = 97.8%, $P < 0.0001$) (Figure 2). All complications ranged from as low as 1.1% (95% CI = 0.8% –1.5%)[4] to as high as 52.6% (95% CI = 40.9%–64.0%).[26] Complication rates based on technique were 24.5%, 14.9%, and 12.4% for blind, USS-PM,

Table 1. General characteristics of included studies

Authors, reference	Country	Region	Income group	Year	Setting	Mean age (yr)	Female (%)	Patients (n)	Biopsies (n)	Technique	Operator	Needle type	Needle size	Quality score[a]
Tuladhar *et al.*[54]	Nepal	South Asia	LIC	2014	Inpatient	NR	56	75	75	USS-PM	Neph + Rad	Automated	16G, 18G	Moderate
Ghimire *et al.*[20]	Nepal	South Asia	LIC	2014	Inpatient	30.3 ± 12.5	56	75	75	USS-PM	Neph trainee	Automated	16G, 18G	Moderate
Manandhar *et al.*[21]	Nepal	South Asia	LIC	2016	Inpatient	31.3 ± 11.9	56	75	75	USS-PM	Neph + Rad	Automated	16G, 18G	Moderate
Pokhrel *et al.*[15]	Nepal	South Asia	LIC	2019	Inpatient	33.0	59	37	37	USS-PM	Neph trainee	Automated	18G	Moderate
Pokhrel 2 *et al.*[15]	Nepal	South Asia	LIC	2019	Inpatient	33.9	37	38	38	USS-RT	Neph trainee	Automated	18G	Moderate
Abdou *et al.*[22]	Senegal	SSA	LIC	2003	Inpatient	28	44.3	115	115	USS-RT	NR	NR	NR	Low
Aatif *et al.*[23]	Morocco	M/East + N/Afr	LMIC	2012	Inpatient	40.4 ± 15	37.3	161	171	Blind	NR	Automated	NR	Moderate
Zajjari *et al.*[8]	Morocco	M/East + N/Afr	LMIC	2015	Inpatient	44.8 ± 17.9	33.8	130	130	USS-PM	NR	Automated	16G	Moderate
Sobh *et al.*[24]	Egypt	M/East + N/Afr	LMIC	1988	Inpatient	NR	34.2	120	78	Fluoroscopic	NR	NR	NR	Low
Hachicha *et al.*[25]	Tunisia	M/East + N/Afr	LMIC	1987	Inpatient	36.7	53.3	30	30	Blind	NR	Non-automated	NR	Low
Hachicha 2 *et al.*[25]	Tunisia	M/East + N/Afr	LMIC	1987	npatient	33.4	66.7	30	30	USS-RT	NR	Non-automated	NR	Low
Nadium *et al.*[26]	Sudan	SSA	LMIC	2013	Inpatient	34.6 ± 18	40	83	83	USS-PM	NR	Non-automated	16G, 18G	Moderate
Musa *et al.*[27]	Sudan	SSA	LMIC	1980	Inpatient	24.4	31.1	61	61	Blind	NR	Non-automated	NR	Low
Obineche *et al.*[28]	Nigeria	SSA	LMIC	1982	Inpatient	21	24.4	90	105	Blind	Neph	Non-automated	NR	Low
Krishna A[53]	India	South Asia	LMIC	2018	inpatient	31.5	34.8	270	270	USS-RT	NR	Automated	NR	Moderate
Prakash *et al.*[29]	India	South Asia	LMIC	1994	Inpatient	32	10.5	305	320	Blind	NR	Non-Automated	NR	Moderate
Prasad *et al.*[30]	India	South Asia	LMIC	2015	Inpatient	35.7 ± 15.6	31	2138	2138	USS-RT	Neph + Rad	Automated	16G, 18G	High
Yesudas *et al.*[31]	India	South Asia	LMIC	2010	Inpatient	41.1	31.1	74	74	USS-RT	Neph + Rad	Automated	18G, 20G	Moderate
Sakhuja *et al.*[32]	India	South Asia	LMIC	1990	Inpatient	NR	NR	150	150	USS-PM	NR	Non-automated	NR	Moderate
Golay *et al.*[33]	India	South Asia	LMIC	2013	Inpatient	28.9	46.5	403	403	USS-RT	Neph trainee	Automated	16G, 18G	Moderate
Arora *et al.*[34]	India	South Asia	LMIC	2012	Inpatient	NR	NR	50	50	USS-PM	NR	Automated	16G, 18G	Moderate
Ahmed *et al.*[35]	Pakistan	South Asia	LMIC	2003	Inpatient	26.9	30	40	40	USS-PM	NR	Automated	18G	Moderate
Azmat *et al.*[36]	Pakistan	South Asia	LMIC	2017	Inpatient	41.7 ± 8.6	62.8	220	220	USS-RT	Neph	Automated	14G	High
Mansoor *et al.*[37]	Pakistan	South Asia	LMIC	2016	Outpatient	45.5 ± 11	17	100	100	USS-RT	Rad	NR	NR	High
Yaqub *et al.*[38]	Pakistan	South Asia	LMIC	2017	Inpatient	41 ± 16	42.3	433	433	USS-RT	Neph	Automated	16G, 18G	Moderate
Habas *et al.*[39]	Libya	M/East + N/Afr	UMIC	2016	Outpatient	34 ± 1.8	57.6	118	118	USS-RT	Neph	Automated	16G	Moderate
Mishra *et al.*[40]	Libya	M/East + N/Afr	UMIC	2011	Outpatient	NR	73.3	86	86	USS-RT	Rad	Automated	16G	Moderate
Ghnaimat *et al.*[41]	Jordan	M/East + N/Afr	UMIC	1999	Inpatient	29.1	37.7	191	191	USS-PM	Neph	Non-automated	NR	Moderate
Chen *et al.*[55]	China	E/Asia + Pacific	UMIC	1993	Inpatient	NR	NR	1000	1000	USS-PM	NR	NR	NR	High
Hu *et al.*[43]	China	E/Asia + Pacific	UMIC	2016	inpatient	33 ± 12	54	2639	2639	USS-RT	Neph	NR	NR	High
Tao *et al.*[44]	China	E/Asia + Pacific	UMIC	2008	Inpatient	NR	NR	1262	1262	USS-PM	NR	NR	NR	High
Wang *et al.*[45]	China	E/Asia + Pacific	UMIC	2015	Inpatient	40 ± 15.4	39.3	1342	1314	USS-PM	NR	Automated	16G	High
Xu *et al.*[4]	China	E/Asia + Pacific	UMIC	2017	Inpatient	40.5 ± 16.3	48.9	3577	3577	USS-RT	NR	Automated	16G,18G	High
Pongsittisak W[16]	Thailand	E/Asia + Pacific	UMIC	2019	Inpatient	44	52	100	100	USS-PM	Neph trainee	Automated	16G	High
Pongsittisak W 2[16]	Thailand	E/Asia + Pacific	UMIC	2019	Inpatient	39	60	104	104	USS-RT	Neph trainee	Automated	16G	High
Kanjanabuchi *et al.*[53]	Thailand	E/Asia + Pacific	UMIC	2005	Inpatient	37 ± 14.2	69.8	506	506	USS-RT	NR	NR	NR	Moderate
Covic *et al.*[47]	Romania	Europe	UMIC	2006	Inpatient	38.5 ± 15.2	48.5	635	635	USS-RT	NR	NR	NR	Moderate
Trajceska L[52]	Macedonia	Europe	UMIC	2019	Inpatient	47.8 ± 15.5	39	342	345	USS-RT	NR	Automated	16G	High
Kovacevic *et al.*[48]	Serbia	Europe	UMIC	1996	Inpatient	NR	23.7	558	582	USS-PM	NR	Non-automated	NR	Moderate
Munoz *et al.*[49]	Mexico	Lat Am/Car	UMIC	2010	Inpatient	34.4 ± 14.2	70.5	623	623	USS-RT	Neph + Rad	Automated	16G	High
Gonzalez-Michaca *et al.*[50]	Mexico	Lat Am/Car	UMIC	2000	NR	37.7 ± 13.1	66.9	840	1005	USS-RT	Neph trainee	Automated	16G	High
Kruger *et al.*[51]	South Africa	SSA	UMIC	2011	Inpatient	41.5	50.9	112	112	USS-RT	Rad	Automated	16G	Moderate

E/Asia + Pacific, East Asia and Pacific; LIC, low-income country; Lat Am/Car, Latin America and the Caribbean; LMIC, low- and middle-income country; M/East + N/Afr, Middle East and North Africa; Neph, nephrologist; NR, not reported; Rad, radiologist; SSA, sub-Saharan Africa; UMIC, upper- and middle-income country; USS-PM, pre-marking technique with ultrasound; USS-RT, real time ultrasound.
[a]Quality score: high, 1–3; moderate, 4–6; low, 7–10.

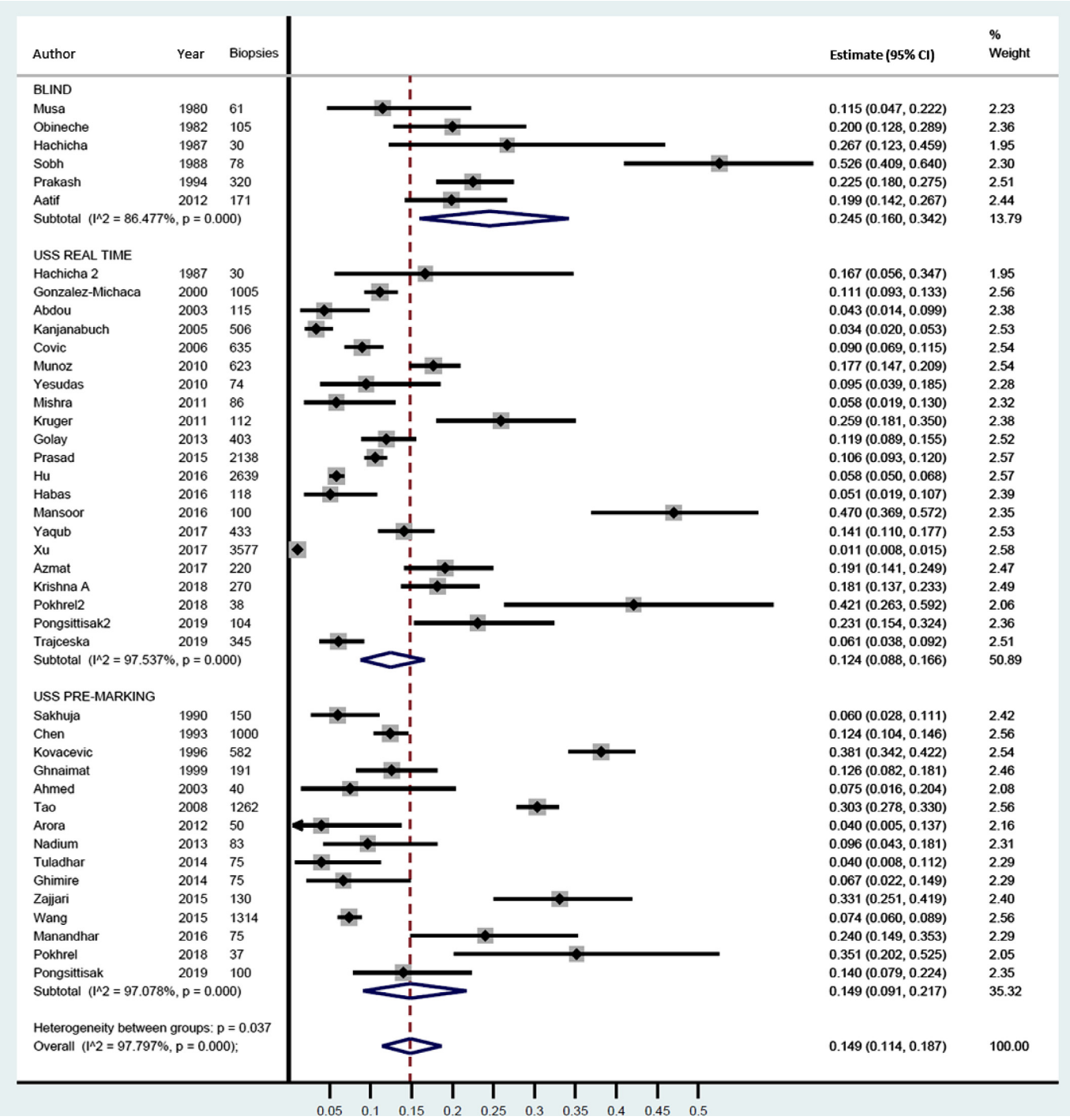

Figure 2. Overall complications grouped by biopsy technique.

and USS-RT, respectively ($P = 0.037$; (Figure 2). Cumulative meta-analysis did not show a significant trend for overall complications by study era ($P = 0.205$), and for studies that reported use of a single biopsy needle size for procedures, there was no significant difference in the overall complication rate between 16G and 18G needles ($P = 0.334$) (Supplementary Figures S1 and S2). There was no difference in overall complication rates by income groups ($P = 0.256$), region ($P = 0.425$), or needle type ($P = 0.588$). (Supplementary Figures S3–S5). The funnel plot for our study (Figure 3) showed asymmetry; a further formal test for bias (Egger test) revealed no evidence of publication bias ($P = 0.25$).

Major Complications

The pooled rate of major complications from all the studies was 1.6% (95% CI = 0.9%–2.5%) (Figure 4). However, we excluded the study by Sobh *et al*. from this analysis, as their study had combined open surgical techniques (lumbotomy) in 35% of their biopsies,

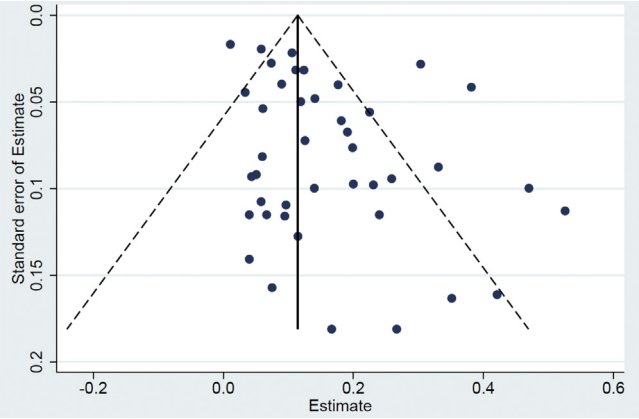

Figure 3. Funnel plot assessing publications bias (with pseudo 95% confidence interval [CI]).

whereas the remainder (65%) were done percutaneously under fluoroscopy.[26] The biopsy technique had no significant effect on major complications as these were reported in 1.7% (95% CI = 0.7%–3.1%), 0.9% (95% CI = 0.2%–1.9%) and 3.9% (95% CI = 0.2%–10.7%), respectively for USS-RT, USS-PM, and blind techniques ($P = 0.271$) (Figure 4). There was also no significant difference in the occurrence of major complications by the type of needle used ($P = 0.974$), by needle gauge ($P = 0.103$), by era ($P = 0.753$), or by region ($P = 0.055$) (Supplementary Figures S6–S10). However, there was significant difference observed for major complications by income group ($P = 0.003$) (Supplementary Figure S10). Major complications did not occur in 9 studies,[22–24,29,35,36,38,52,55] and only 2 studies reported post-kidney biopsy-related deaths with the death rate assessed as 0.01%[40,51] (Table 2). Other major complications are summarized in Table 2, and include nephrectomy (complication rate of 0.04%),[8,25,40,41,50,51] blood loss requiring blood transfusion (0.24%), need for angiographic interventions (0.22%), and biopsy-related infections (0.12%).

Minor Complications

The pooled estimate of all minor complications was 12.8% (95% CI = 8.9%–17.2%). Only 1 study, from Nigeria, reported 100% occurrence of minor complications post-biopsy (all patients had pain at the biopsy site).[29] The lowest occurrence of minor complications was from a study in China that showed minor complications in 0.7% (95% CI = 0.45%–1.03%) of all patients[4] (Figure 5)

DISCUSSION

Despite the complications associated with the procedure, kidney biopsy remains a useful tool for diagnosis and guiding clinicians with treatment decisions in patients with kidney disease. To our knowledge, this is the first study to have systematically and comprehensively assessed the rates of complications that occur following PNKB in LMICs. Although kidney biopsies are not readily available in many LMICs,[57] it is nevertheless important to document the occurrence of complications following this procedure in LMICs, to guide further clinical practice. Unlike other large observational studies or systematic reviews that have often focused on bleeding complications associated with kidney biopsy,[5,6,58] this study has documented all complications (grouped as major and minor) that occur following kidney biopsies in studies from LMICs meeting inclusion criteria. With an overall complication rate of 14.9% (95% CI = 11.4%–18.7%) and major complication rate of 1.6% (95% CI = 0.9%–2.5%), our study affirms that use of PNKB is safe in LMICs. This is considering that less than half (48.8%) of all the studies used real-time ultrasound guidance and only 51.3% of studies used automated needles for the procedure. The complication rates in our study are similar to that reported from a study in Spain that documented complications from PNKB using only ultrasound guidance and automated needles, and that showed overall complication to be 16.6% with major and minor complications in 1.5% and 15.1%, respectively.[59] In 1 of the studies that we included, even though the rate of complications was not significantly different between ultrasound-guided and blind procedures, ultrasound-guided procedures had better tissue yield than blind procedures.[16] Other studies from developed countries that have used automated needles only and imaging guidance have also reported similar or even higher rates of complications.[6,7] Although our study shows low rates of complication even as some studies used blind techniques for performing kidney biopsy, we strongly discourage the performance of kidney biopsy carried out without imaging guidance as some studies reported.[17,25,28–30] The Kidney Health Australia - Caring for Australians and New Zealanders with Kidney Impairment (KHA-CARI) guidelines[60] for kidney biopsy recommend that real-time ultrasound guidance be used as the first-line imaging modality for PNKB. The guideline also recommends the use of a spring-loaded automatic needle device for native kidney biopsy, as these are associated with fewer complications and better tissue samples. Also, it is not clear whether level of expertise of the operator played a role in the observed complications. In many centers, kidney biopsy is performed by the nephrologist or nephrology trainee, often with some guidance from radiologists, although there may be no difference in complications or yield of tissue for biopsies performed by nephrologists or radiologists.[61] In a survey-based evaluation of self-perceived competency after nephrology fellowship training in the United States, although <30% of

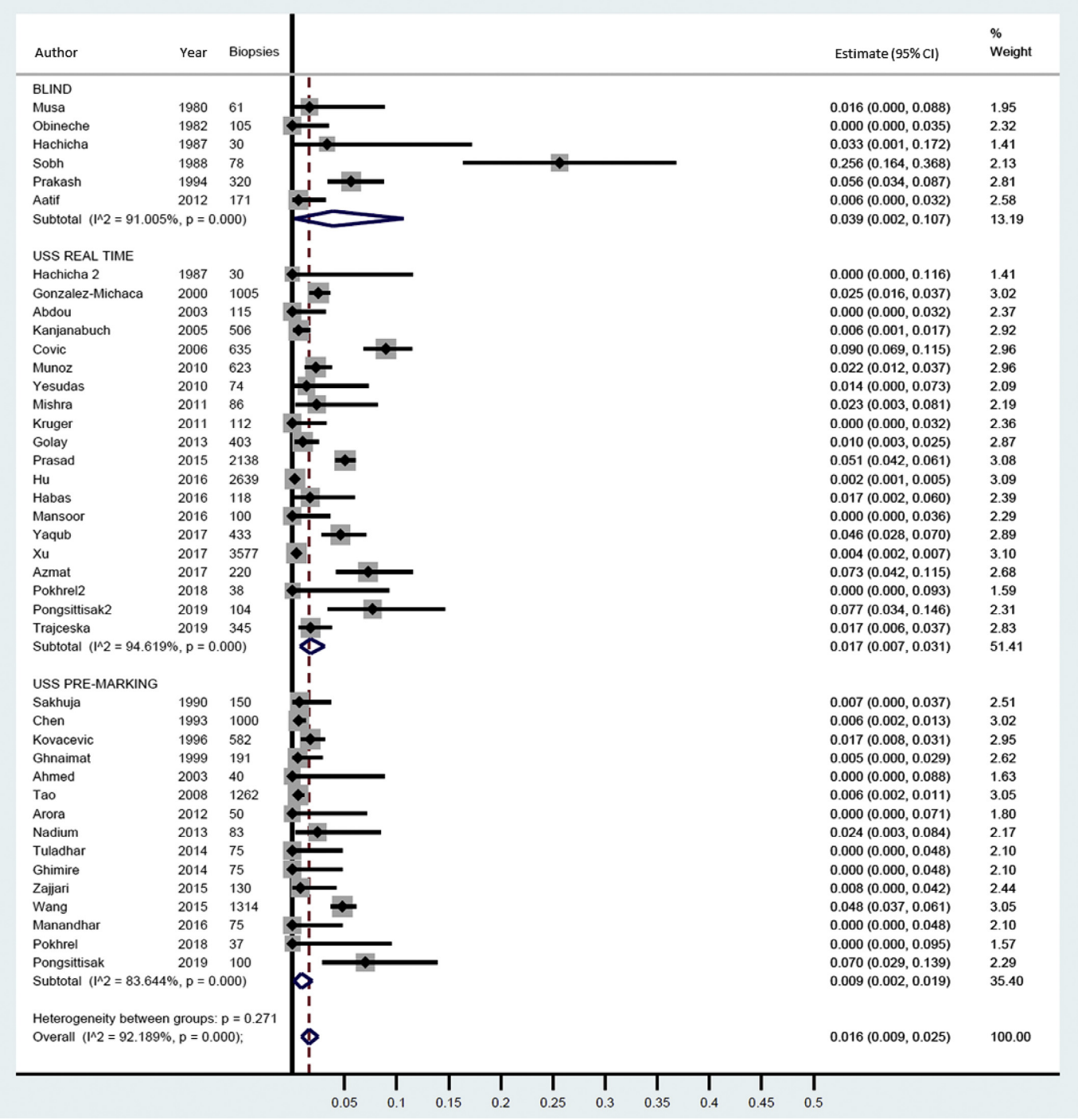

Figure 4. Major complications grouped by biopsy technique. CI, confidence interval.

participants reported competence with performance of USS for kidney biopsy, and >80% said that they were competent performing a kidney biopsy.[62] Training in the use of ultrasound of the kidneys and competence in all aspects of kidney biopsy (both native and transplant) should be a part of all nephrology training curricula in LMICs.

Bleeding complications, including microscopic hematuria, peri-nephric hematoma collections, and macroscopic hematuria needing blood transfusion and/or surgical or radiological interventions, are often the most common complications and have been the focus of some studies.[5,58] Several factors contribute to the risk of bleeding following the biopsy of the kidney, including the needle size, use of medications that can affect the coagulation, pre-existing co-morbidities, number of needle passes made to obtain adequate kidney tissue, abnormal laboratory indices (e.g., azotemia, thrombocytopenia, abnormal international normalized ratio and prothrombin time, etc.), and

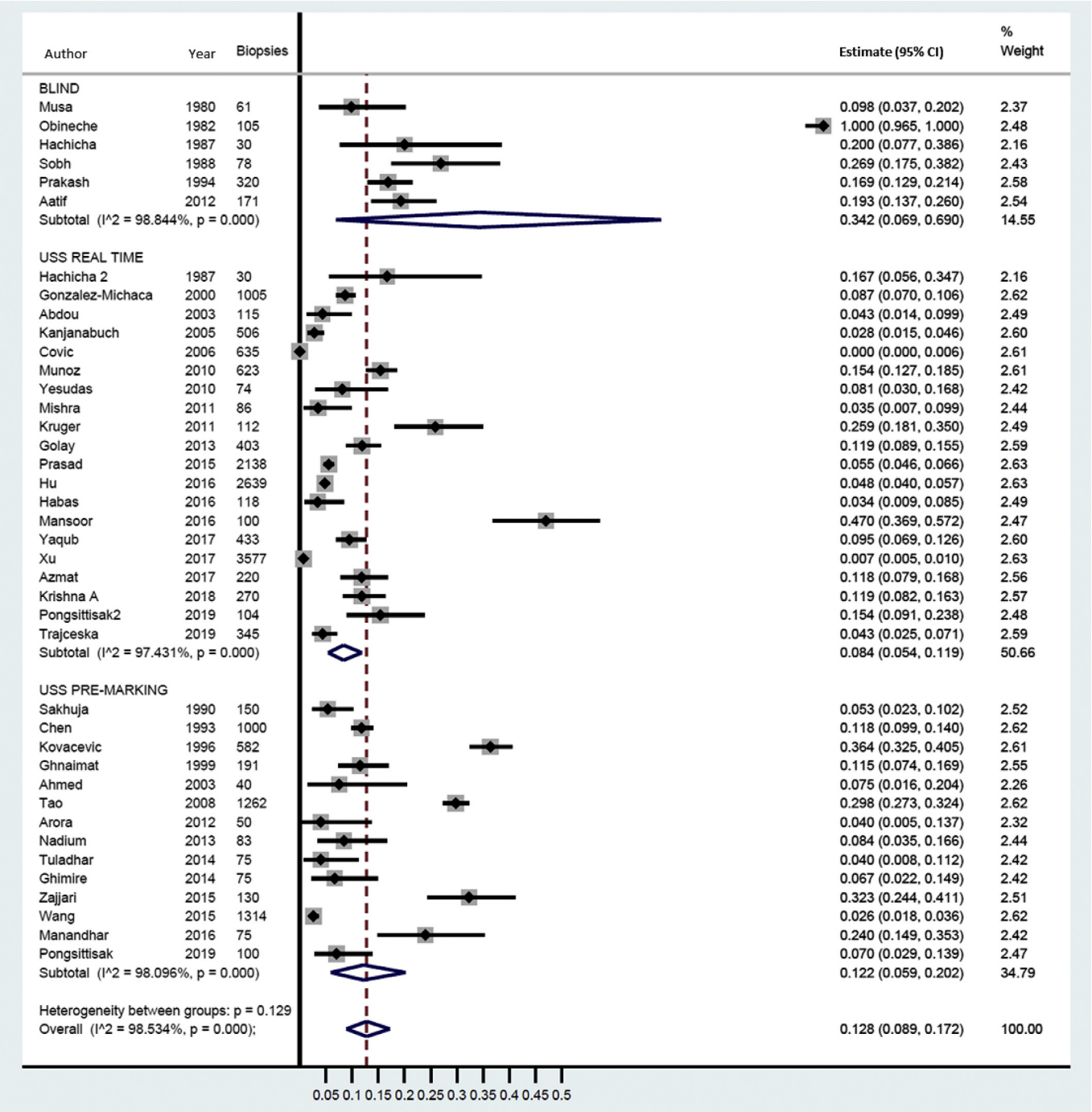

Figure 5. Minor complications. CI, confidence interval.

elevated blood pressure.[4,5,60] Our study showed that the rate of red cell transfusions was 0.24%, much lower than that in the studies of Corapi *et al*. (0.9%)[5] and Varnell *et al*. (0.9%).[58] Although the reasons for this are unclear, it might be related to differences in thresholds of instituting blood transfusion at different centers. It is not clear why there were significant differences between regions in the occurrence of major complications. This may be related to the number of studies included from each region and the estimate of complications from individual studies. Despite this, we believe that efforts should be made to mitigate factors that lead to bleeding following a kidney biopsy in LMICs. This should include adequate and appropriate workup of patients before biopsy, use of agents that reduce the risk of bleeding (e.g., desmopressin or cryoprecipitate) in those who are at increased risk, and adequate post-biopsy care and monitoring of patients.

Rates of other major complications such as nephrectomy, need for radiological or surgical interventions, and infections related to the PNKB were also low in our study. Death following PNKB is usually

Table 2. Rates of major complications of percutaneous native kidney biopsy

Complication	No. of studies	No. of procedures	No. of complications	Complication rate (%)
Macroscopic hematuria	34	15,630	231	1.48
Major hematoma	36	17,992	464	2.40
Nephrectomy	33	16,427	7	0.04
Blood transfusion	32	15,561	38	0.24
Angiographic/surgical interventions	36	16,234	35	0.22
Infections	35	15,635	18	0.12
Death	39	19,500	2	0.01

rare, with the risk believed to be <0.1% in most clinical practices and usually associated with severe/uncontrollable bleeding.[1] Only 2 deaths were reported from among all the included studies, giving a complication rate of 0.01%. A study that included 118,064 PNKB cases reported a high mortality rate of 1.8%.[6] Predictors of mortality were found to be advanced age, presence of metastatic cancer, acute kidney injury, coagulopathy or liver disease at baseline, need for blood transfusion, and hypotension. Fewer deaths were reported in patients admitted to hospital electively (0.99%) compared to nonelective admissions (2.01%); however, the authors still acknowledged that mortality was excessively high in their study, although it could be related to the nature of acute disease leading to hospitalization.[6] The low rates of major complications and death that we have shown is encouraging regarding the use of PNKB as a tool for diagnosis and treatment guidance in LMICs. Increased use of imaging techniques, as well as increased and continual training of those who carry out this procedure, may further reduce complications that occur following PNKB.

Minor complications are probably not well documented in several studies if patients remain in stable clinical condition. Also, most patients are not required to have imaging studies post-biopsy except those who have significant clinical problems, such as severe persistent pain at the site of kidney biopsy, hypotension, or those with dropping hematocrit. The KHA-CARI guidelines do not recommend post-biopsy imaging as a part of all patients' assessments.[60] The inclusion of pain as a minor complication in this study may have contributed to the higher rate of minor complications. One study from Nigeria reported 100% minor complication as a result of pain[29]; otherwise, the rate of minor complications in this study is similar to those in other studies.[59]

Our study has some limitations. Some studies did not report some important data on complications. Although we reported these as "not reported," it might be difficult to know whether these complications did not occur or if they were just left out by the authors. Although it was not possible to contact all authors about all data in their study, we think that the data that we have presented clearly and thoroughly reflect complications associated with PNKB from LMICs. Also, the sample sizes of some of the studies were quite low, despite meeting criteria for inclusion. However, we do not think that this had any effects on the pooled estimates. Also, although our study identified that there was heterogeneity among studies, subgroup analysis performed identified kidney biopsy technique ($P = 0.037$) and country income group ($P = 0.003$) as main reasons for heterogeneity among studies. Other subgroup analyses did not identify other sources of heterogeneity. However, we think that other factors that were not reported in several studies may have contributed to the observed heterogeneity, including, but not limited to, clotting profile and platelet counts. Despite this, our study was able to show that PNKB performed in LMICs is associated with low complication rates and should therefore be encouraged as an important diagnostic tool in these settings. The procedure should thus be encouraged following guidelines and using modern techniques to further reduce associated complications.

In conclusion, our study shows that the rates of complications following PNKB in LMICs are low, with rates similar to those of higher-income countries, despite limited resources. Increased use of modern techniques including real-time ultrasound and automated needles can further reduce the rates of complications associated with PNKB in LMICs and can increase their uptake for diagnosis and decision making for treatment of various kidney diseases.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Protocol registration: PROSPERO registration number CRD42017077656.

AUTHOR CONTRIBUTIONS

SK, JJN, and IGO conceived and designed the protocol for this study. SK drafted the manuscript. SK and MWM did the search, and IGO arbitrated any differences. SK and UE reviewed completeness and validity of extracted data. JJN, UE, MAO, USO, AKB, and APK assisted with revision of the manuscript and methodological design of the study. UE did the statistical analysis and meta-analysis. APK assisted UE with the data analysis. SK and IGO wrote the draft paper. All authors approved the final version of this manuscript.

ETHICS AND DISSEMINATION

This study used published data; therefore, there was no requirement for ethical approval, and patient consent was not required. This systematic review and meta-analysis is expected to inform health care providers about the occurrence of major complications following kidney biopsies and highlight possible actions needed to improve the safety of the procedure in LMIC.

DATA SHARING STATEMENT

Data extracted from the included studies in this review are available on request from the corresponding author

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. MEDLINE search strategy.

Table S2. Adapted tool for risk of bias assessment.

Table S3. Complication rates following percutaneous native kidney biopsies.

Figure S4. Cumulative analysis for overall complications by study era.

Figure S5. Overall complication rates grouped according to needle gauge.

Figure S6. Overall complication rates grouped according to income group.

Figure S7. Overall complication rates according to region.

Figure S8. Overall complication rates grouped according to needle type used.

Figure S9. Major complications by needle type.

Figure S10. Major complications by needle gauge.

Figure S11. Cumulative analysis for major complications by study era.

Figure S12. Major complications by region.

Figure S13. Major complications by income group.

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