

Impact of Hyperuricemia on Long-Term Clinical Outcomes of Renal Transplant Recipients: A Systematic Review and Meta-Analysis

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ABSTRACT -- Purpose: To evaluate the effect of hyperuricemia on clinical outcomes of renal transplant recipients (RTRs). **Methods:** A literature search of PubMed, Cochrane, Embase was conducted up to March 20, 2020. The primary outcome was the estimated glomerular filtration rate (eGFR). The second outcomes were the risk of graft loss, death, cardiovascular event and the level of triglyceride. The following search terms were utilized: ((Hyperuricemic group) OR (Hyperuricaemia) OR (Hyperuric) OR (Urea acid) OR (Uric acid) OR (Acid urate) OR (Urate) OR (Gout)) and ((Transplantation) OR (Transplantations) OR (Transplant) OR (Transplants) OR (Graft)). **Results:** 28 studies with 18224 patients were eligible for inclusion. There was no significant difference in eGFR (<12 months, $p=0.07$), the risk of graft loss (<60 months, $p=0.07$) and death (<60months, $p=0.19$) between the hyperuricemic and normouricemic group in the early post-transplantation period. But increased uric acid levels contributed to the long-term decline of eGFR, the risk of graft loss and death increased after transplantation. Hyperuricemia increased the risk of cardiovascular event with no significant difference in the level of triglyceride between the two groups. **Conclusions:** Increased uric acid levels contributed to the long-term decline of eGFR, increased risk of graft loss and death after transplantation. Although there was no significant effect on triglyceride, hyperuricemia increased the risk of cardiovascular event.

INTRODUCTION

Kidney transplantation is considered the best treatment for patients with end-stage renal disease. However, there are many complications after transplantation, such as hypertension, dyslipidemia, obesity, diabetes, bone metabolism, blood system problems, malignant tumor, electrolyte and acid-base balance disorder and hyperuricemia. It is reported that the incidence of hyperuricemia in renal transplant recipients ranged from 25% to 84% (1). The risk factors of hyperuricemia after transplantation are: a decreased estimated glomerular filtration rate (eGFR), diuretic use, cyclosporine therapy, increasing age of the transplant, obesity, metabolic syndrome, as well as the presence of pre-transplant hyperuricemia (2).

In recent years, many studies have been published dealing with the impact of hyperuricemia on the clinical outcomes of renal transplant recipients (RTRs). However, whether hyperuricemia is an independent risk factor, or a marker of progressive graft dysfunction remains a controversial topic (3-4). Huang et al conducted a meta-analysis which included 12 cohort studies in 2012 and found that RTRs with hyperuricemia had a lower estimated glomerular filtration rate (eGFR)

and higher serum creatine (SCr) than those with a normal uric acid level. Meta-analysis showed that hyperuricemia might be a risk factor of chronic allograft nephropathy and graft loss (5). However, due to the small sample size of meta-analysis, no clear conclusion could be drawn. In addition, they did not take into account the relationship between the duration of hyperuricemia since transplantation and the clinical outcomes. Many new studies with large samples and comprehensive clinical outcomes have been published in recent years (6-25). Therefore, it is important and necessary to systematically investigate the clinical effect of hyperuricemia on the RTRs in order to produce an evidence-based recommendation for clinical practice.

METHODS

Search Strategy

Relevant studies included in this study were identified using PubMed, Cochrane and Embase (from inception up to March 20, 2020). References of relevant articles were also reviewed. The following search terms were utilized: ((Hyperuricemic group) OR (Hyperuricaemia) OR (Hyperuric) OR (Urea acid) OR (Uric acid) OR (Acid urate) OR (Urate) OR (Gout)) and

((Transplantation) OR (Transplantations) OR (Transplant) OR (Transplants) OR (Graft)). No language restriction was applied to the search. The details of the search strategy were summarized in the Supplementary Table 1s.

Study selection

Studies were included according to the following criteria: (1) population-based studies including cohort, case-control, and randomized controlled trial (RCT) studies, and (2) articles that reported the association between hyperuricemia and clinical outcomes in RTRs.

Studies were excluded if the following items were identified: without control group, without available clinical outcomes, and duplicates.

Data extraction

Two reviewers (QC and HY) independently extracted relevant information for the meta-analysis. The extracted data included the characteristics of each study (author, study design, publication year, country), patient population (numbers of patients, age), length of follow up, definition of hyperuricemic group, time of evaluating eGFR since transplant, adjusted factors and clinical outcomes (glomerular filtration rate, graft loss, overall graft failure, hazard of death, overall survival, cardiovascular event, triglyceride) in each study.

Outcomes

The primary outcome was eGFR, and the secondary outcomes were the risk of graft loss, death, cardiovascular event, and the level of triglyceride.

Quality assessment

The methodological quality of the RCTs was evaluated using the criteria developed by the Cochrane risk of bias tool (26): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The Newcastle-Ottawa Scales (NOS) was used to assess the quality of observational studies (27). Two authors (QC and HY) independently assessed the quality of the studies selected. Discrepancies were resolved by involvement of the third author (XJY).

Statistical analysis

All statistical analyses were performed using Review Manager for Windows (version 5.3). Mean and standard deviation (SD) were calculated for primary outcomes. Hazard ratio (HR) and 95% confidence interval (CI) were calculated for secondary outcomes.

Heterogeneity was assessed using the Q statistic and the I² method. Mantel-Haenszel fixed effects model was used when there was no significant heterogeneity between studies; otherwise, a random effects model was chosen. Publication bias was evaluated using the funnel plot method, of which funnel plot asymmetry was assessed by Egger's linear regression test (28). Sensitivity analysis was performed by exclusion of each study one by one.

RESULTS

Literature search

2269 titles and abstracts were yielded through search strategy. And 12 articles were retrieved from a systematic review and meta-analysis by Huang et al. A total of 2191 articles were excluded after the review of abstracts, and 43 articles were excluded after full-text review. Overall, 28 studies with 18224 patients were eligible for inclusion in the meta-analysis (6-25), (29-36). The whole literature search process was summarized in Figure 1.

Study description

There was no RCT studies reporting the effects of hyperuricemia on clinical outcomes of renal transplant recipients, therefore this meta-analysis was based on the comparison of observational studies. Characteristics of the eligible studies were presented in Table 1. The clinical outcomes of included studies were presented in Table 2.

Quality of included studies

Risk of bias was assessed using the NOS for all studies. Nine factors were used to assess study quality according to NOS. 5 studies (6-8), (12), (19) missed two indicators, 13 studies (9), (10), (17), (18), (22), (23), (29), (32-35) missed one indicator, and the other 12 studies (11), (13-16), (20), (21), (24), (25), (30), (31), (36) got the full score. All in all, all included observational studies were of high quality (Supplementary Table 2s.).

eGFR

Twenty studies contained eGFR data for renal transplant recipients (6), (7), (9-11), (13), (15-18), (20), (23), (29-36). Meta-analysis showed that eGFR was significantly lower in the hyperuricemic group than normouricemic group (11104 patients, MD=-9.21, 95% CI -12.42, -6.00, $p<0.00001$, Figure 2). There was no significant difference between the two groups in the first year after transplantation ($p=0.07$). But, hyperuricemia was associated with significantly lower eGFR after a year post-transplantation (12-36 months, $p<0.00001$; 36-60 months, $p<0.0001$;

Table 1. The characteristics of included studies

Author, year, [reference]	Study design, years, country	Patients enrolled (HG/NG)	Median age (years)	Follow up (months)	Definition of hyperuricemia	Data analysis	Adjusted factors
Akalin, 2008, [36]	Retrospective cohort study, 2001.1 – 2004.12, USA	307 (144/163)	H: 50.0 ± 1.0 N: 47.7 ± 1.0	51.6	≥7.0 in men, ≥6.5 mg/dL in women	multivariate analysis	age, race, sex, eGFR, having received a cadaveric transplant and cyclosporin use
Karbowska, 2009, [35]	NA, 2003 - 2006, Poland	78 (48/30)	H:47.8 N:45.3	H: 30.5 N: 32.0	NS	NS	unadjusted
Min, 2009, [33]	Cohort study, 1999.8 - 2006.7, Korea	281 (121/160)	H:41.2 ± 12.3 N:39.8 ± 12.2	60	≥8.0 mg/dl	multivariate analysis	unadjusted
Bandukwala, 2009, [34]	NA, 2005.1 - 2008.4, Canada	405 (180/225)	H:50.2 ± 11 N:50.3 ± 12	H: 87.6 ± 72 N: 72 ± 72	>7.1 mg/dl in men, >6.1 mg/dl in women.	multivariate analysis	unadjusted
Kim, 2010, [32]	Retrospective cohort study, 1990 - 2008, Korea	356 (55/301)	H: 36.80 ± 10.08 N: 39.71 ± 10.28	102.63 ± 27.25	≥7.0 mg/dL in men, ≥6.0 mg/dL in women	multivariate analysis	unadjusted
Haririan, 2010, [31]	Retrospective cohort study, 2000.1 - 2001.12, USA	212 (45/167)	47.9 ± 13.7	68.3 ± 27.2	>6.5 mg/dl for women, >7.0 mg/dl for men	NS	age, retransplantation, diabetes and induction
Zou, 2010, [29]	Retrospective cohort study, 2003.1 - 2005.12, China	142 (58/84)	males: 40.98 ± 11.09; females: 40.01 ± 11.62	12 - 36	>420 µmol/L in males, >380 µmol/L in females	Univariate analysis	unadjusted
Chung, 2010, [30]	Retrospective study, 1996.9 - 2004.8, Korea	350 (148/202)	38.8 ± 10.4	103.4 ± 32.8	>7.0 mg/dl in males, >6.0 mg/dl in females	NS	age, sex, postoperative recovery pattern, the presence of diabetes or hypertension, BMI, donor type, retransplantation, HLA mismatch number, immunosuppressant type, and acute rejection episodes
Kim, 2011, [23]	Retrospective cohort study, 1990.1 - 2009.2, Korea	556 (118/438)	38.74 ± 10.08	48	> 6.0 mg/dl for women; > 7.0 mg/dl for men	Multivariate analysis	unadjusted
Caliskan, 2011, [24]	Single-center study, NA, Turkey	141 (28/113)	37 ± 11	> 6	> 6.5 mg/dl for women, > 7.0 mg/dl for men	NS	potential confounding factor affecting left ventricular mass index

Table 1 continues...

Haririan, 2011, [25]	Retrospective cohort study, 2004.1 - 2006.6, USA	488 (NA)	52.6 ± 13.1	41.1 ± 17.7	NS	Univariate analysis	eGFR, race, donor, peak-PRA, HLA-mismatch, delayed graft function, acute cellular rejection, MMF dose, ACEI/ARB
Choi, 2013, [22]	Retrospectively cohort study, 1991.4 - 2011.5, Korea	378 (152/226)	39.37 ± 10.50	132.36 ± 69.49	>7 mg/dL	Multivariable analysis	unadjusted
Weng, 2014, [19]	Prospective cohort study, 1999.12 - 2013.3, China	880 (389/491)	H:50.03 ± 12.07, N:47.59±12.57	43.3 ± 26.3	NA	Time-Varying Analysis	unadjusted
Weng, 2014, [20]	Prospective, case-control study, 2010.9 - 2012.12, China	124 (57/67)	H: 50.92 ±11.30, N: 48.05 ± 11.52	14.27	NA	Multivariate analysis	age, gender and body mass index.
Dahle, 2014, [21]	Cohort study, 2000 - 2011, Norway	881 (440/441)	53.0	88.8	NS	Multivariable analysis	recipient age, gender, eGFR, diuretics, BMI, diabetes, impaired glucose tolerance, cardiovascular disease, number of antihypertensives, preemptive transplant, first transplant, donor age, living donor, HLA-DR mismatches, simultaneous pancreas transplant, delayed graft function, previous rejection or cytomegalovirus infection, prednisolone dose, and immunosuppressive medication.
Kim, 2015, [14]	Retrospective cohort study, 2000.1 - 2010.12, Canada	1170 (247/923)	49.3 ± 13.1	120	>7.0 mg/dL for man, >6.0 mg/dL for woman	Multivariable Cox proportional hazards models	recipient age, sex, race, body mass index, eGFR, systolic and diastolic blood pressure at baseline, peak PRA, time on dialysis, donor age, sex, history of hypertension, body mass index, donor type, delayed graft function, acute rejection at baseline, type of CNI at baseline and transplant era.
Zhang, 2015, [15]	Retrospective cohort study, 2008.1 - 2011.12, China	573 (155/418)	41.37 ± 9.45	41.86 ± 15.49	>7.0 mg/dl for man, >6.0 mg/dl for woman	Cox proportional hazard model, and multiple regression equation	age, body mass index and male gender
Muela, 2015, [16]	Observational study, 1999.7 - 2011.6, Brazil	199 (66/133)	52.1 ± 10.7	19	NS	Multivariable analysis	confounding factors, including GFR;
Erkmen Uyar, 2015, [17]	Retrospectively cohort study, 2008.1 - 2010.3, Turkey	100 (27/73)	38.7 ± 11	45.9 ± 9.6	≥6.5 mg/dL that persisted for at least 2 consecutive tests.	Multivariate analysis	unadjusted
Fidan, 2015, [18]	Retrospectively cohort study, 2000.12 - 2012.12, Turkey	81 (14/67)	16.9 ± 5.6	42 ± 5.64	≥6 mg/dL.	NS	unadjusted

Table 1 continues...

Han, 2016, [12]	Retrospective, multi-center cohort study, NA, Korean	2440 (661/1779)	NS	71.0	≥ 7.0 mg/dL for man, ≥ 6.0 mg/dL for woman	Multiple Cox regression analysis	NS
Oh, 2016, [13]	Retrospective cohort study, 1991.1 - 2020.12, Korea	132 (70/62)	38 ± 11	199 ± 5	NS	Multiple linear regression analysis	eGFR
Eyupoglu, 2017, [9]	Retrospective cohort study, 2005.12 - 2016.2, Turkish	141(39/102)	37.1 ± 12.1	83.09 ± 20.30	>7.0 mg/dL for man, >6.0 mg/dL for woman	Multivariate analyses	NS
Kalil, 2017, [10]	Post hoc cohort study, 2002 - 2007, US, Canada, Brazil	3512 (2398/1114)	51.7 ± 69.4	46.8	>7 mg/dL for man, >6 mg/dL for woman.	Multivariable analyses	NS
Han, 2017, [11]	Multi-center cohort study, 1999.1 - 2012.8, Korean	1296 (648/648)	42.1 ± 11.4	85.9 ± 53.3	≥ 7.0 mg/dL in males, ≥ 6.0 mg/dL in females	Multivariate analyses	Recipient age, gender, eGFR, and donor type.
Ou, 2017, [8]	Hospital-based cohort study, 2010 - 2015, China	742 (NS)	NS	NS	NS	NS	NS
Biyik, 2018, [6]	Retrospective cohort study, 2015-2017, Turkey	61 (23/38)	H: 47.8 ± 13.4 N: 40.5 ± 12.9	≥ 12	≥ 7 mg/dL for man, ≥ 6 mg/dL for woman	Multivariate analyses	NS
Kim, 2018, [7]	Retrospective cohort study, 1992.1 - 2014.12, Korea	2198 (676/1522)	H: 39.5 ± 10.9 N: 41.3 ± 11.1	160 ± 64.6	> 7.0 mg/dL for man, > 6.0 mg/dL for woman	Multivariate analyses	NS

NS, not stated; NG, normouricemic group; HG, hyperuricemic group; eGFR, estimated glomerular filtration rate; US, United States.

Table 2. The clinical outcomes of included studies

Author, year, [Reference]	Glomerular filtration rate			Graft loss	Death	Cardiovascular event	Triglyceride (mg/dL)		
	HG	NG	p	HR (95%CI)	HR (95%CI)	HR (95%CI)	HG	NG	P
Akalin, 2008, [36]	50.4±1.3	68.7±1.6	<0.001	NR	NR	1.70(0.94-3.07)	NR	NR	NR
Karbowska, 2009, [35]	68.8 ±17.2	76.9±17.58	NR	NR	NR	NR	NR	NR	NR
Bandukwala, 2009, [34]	45.1±16	58.5±17	<0.0001	NR	NR	5.62(1.94-16.28)	NR	NR	NR
Min, 2009, [33]	73.3±13.1	71.6±9.5	NR	2.01(1.09-3.72)	NR	NR	NR	NR	NR
Kim, 2010, [32]	73.56 ±8.84	78.33±13.83	0.014	NR	NR	NR	NR	NR	NR

Table 2 continues...

Haririan, 2010, [31]	43.2±15.9	56.1±19.4	NR	1.92(1.1-3.4)	1.39(0.8-3.0)	NR	NR	NR	NR
Chung, 2010, [30]	68.3±20.4	77.9±19.2	0.00001	2.3(0.9-5.8)	2.37(1.34-4.22)	2.8(1.1-7.1)	NR	NR	NR
Zou, 2010, [29]	29.99±13.05	46.59±23.21	<0.05	NR	NR	NR	NR	NR	NR
Haririan, 2011, [25]	NR	NR	NR	1.15(1.05-1.27)	NR	NR	NR	NR	NR
Caliskan, 2011, [24]	NR	NR	NR	NR	NR	NR	150 ± 57	166 ± 88	0.368
Kim, 2011, [23]	56.48±14.38	65.06±17.14	<0.001	NR	NR	NR	NR	NR	NR
Choi, 2013, [22]	NR	NR	NR	NR	1.86(1.16-2.99)	2.79(0.73-10.71)	NR	NR	NR
Dahle, 2014, [21]	NR	NR	NR	1.67(1.18-2.37)	1.57(1.09-2.25)	NR	NR	NR	NR
Weng, 2014, [20]	25.48±14.07	27.60±14.24	0.408	NR	1.68(0.94-3.01)	NR	NR	NR	NR
Weng, 2014, [19]	NR	NR	NR	NR	1.37(1.06-1.77)	NR	NR	NR	NR
Fidan, 2015, [18]	68.03±21.84	81.70±42.23	≤0.05	NR	NR	NR	126.27±46.01	136.38±92.74	>0.05
Erkmen Uyar, 2015, [17]	55.4±21.7	68.6±23.8	0.014	NR	NR	NR	205.3±98.8	167.6±72.7	0.042
Muela, 2015, [16]	40.72±57	54.85±117	0.0003	NR	0.90(0.59-1.34)	1.6(1.03–2.54)	NR	NR	NR
Zhang, 2015, [15]	96.0 ± 26.6	95.51±19.13	0.0001	1.587(0.733–3.435)	NR	NR	1.96±0.72	1.88±0.69	0.032
Kim, 2015, [14]	NR	NR	NR	0.92(0.54-1.59)	1.05(0.52-2.10)	NR	NR	NR	NR
Oh, 2016, [13]	60±19	71±24	<0.0001	2.668(1.124-6.332)	NR	NR	147±77	144±65	0.0181
Han, 2016, [12]	NR	NR	NR	1.383(1.01-1.894)	0.891(0.504-1.574)	0.965(0.412-2.262)	NR	NR	NR
Han, 2017, [11]	61.2±18.5	62.8±16.9	0.103	1.65(1.13-2.42)	1.44(0.92-2.26)	NR	NR	NR	NR
Kalil, 2017, [10]	45.5±16.0	55.8±18.5	<0.001	1.04(0.99-1.10)	1.04(0.99-1.10)	1.02(0.97-1.06)	NR	NR	NR
Eyupoglu, 2017, [9]	57.62±14.16	74.14±15.7	<0.001	0.52(0.06-4.34)	2.66(0.56-12.67)	NR	NR	NR	NR
Ou, 2017, [8]	NR	NR	NR	NR	2.63(1.20-5.93)	NR	NR	NR	NR
Kim, 2018, [7]	58.6±17.4	67.8±16.9	<0.001	2.27(1.33–3.78)	NR	NR	NR	NR	NR
Biyik, 2018, [6]	53.8±19.7	70.5±18.9	0.002	NR	NR	NR	NR	NR	NR

HG, hyperuricemic group; NG, normouricemic group; NR, not report.

≥ 60 months, $p=0.0006$, Figure 2). No obvious asymmetry was found in the funnel plot, which indicated that there is no publication bias in the analysis. The results of sensitivity analysis showed that the result was reliable after the exclusion of individual study one by one.

The risk of graft loss

A total of 13 studies evaluated the risk of graft loss in RTRs (7), (9-15), (21), (25), (30), (31), (33). The results showed that RTRs in hyperuricemic group had significantly higher risk of graft loss than normouricemia group (13674 patients, $HR=1.43$, 95%CI 1.23-1.67, $p<0.00001$; Figure 3). Stratification by months after transplantation showed that no significant difference was found between two groups during the first 60 months posttransplant (<60 months, $HR=1.13$, 95CI 0.99-1.29, $p=0.07$, Figure 3). But since then, the hyperuricemic group had a significantly increased risk of graft loss than normouricemia group with time (60-84 months, $HR=1.55$, 95%CI 1.21-1.98, $p=0.0006$; >84 months, $HR=1.69$, 95%CI 1.29-2.22, $p=0.0001$; Figure 3). Therefore, the results suggested that hyperuricemia increased the risk of graft loss with time. No obvious asymmetry was found in the funnel plot. Sensitivity analysis showed that the result was reliable after the exclusion of individual study one by one.

The risk of death

A total of 13 studies evaluated the risk of death in RTRs (8-10), (11-12), (14), (16), (19), (20-22), (30), (31). The results showed that uric acid concentration was associated with the risk of death (12325 patients, $HR=1.42$, 95% CI 1.17-1.72, $p=0.0004$; Figure 4), but the association was only observed after 60 months post-transplantation in subgroup analysis, and the risk increased with time (<60 months, $HR=1.15$, 95%CI 0.93-1.42, $p=0.19$; 60-84 months, $HR=1.49$, 95%CI 1.05-2.11, $p=0.03$; >84 months, $HR=1.74$, 95%CI 1.32-2.30, $p=0.0001$; Figure 4). No obvious asymmetry was found in the funnel plot. The results of the sensitivity analysis showed that the result was reliable after the exclusion of individual study one by one.

The risk of cardiovascular event

A total of 7 studies evaluated cardiovascular event data for RTRs (10), (12), (16), (22), (30), (34), (36). Statistical difference was found in the risk of cardiovascular event between the hyperuricemic group and normouricemic group in RTRs (7591 patients, $HR=1.70$, 95% CI 1.11-2.60, $p=0.01$; Figure 5). No obvious asymmetry was found in the funnel plot, and sensitivity analysis showed that the

result was reliable after the exclusion of individual study one by one.

The level of triglyceride

Five studies evaluated triglyceride level for RTRs (13), (15), (17), (18), (24). The meta-analysis showed that there was no significant difference in the level of triglyceride between the hyperuricemic group and normouricemic group. (1027 patients, $MD=0.08$, 95% CI -0.05-0.21, $p=0.23$; Figure 6). No obvious asymmetry was found in the funnel plot, which indicated that there is no publication bias in the analysis. The results of sensitivity analysis showed that the result was reliable.

DISCUSSION

Hyperuricemia is a common comorbid condition experienced in RTRs (37). It is unclear, however, whether hyperuricemia plays a casual role in the development of graft dysfunction. To the best of our knowledge, this was the most comprehensive systematic review and meta-analysis to evaluate the association between hyperuricemic status and RTRs' long-term outcomes. Besides, we took into account the relationship between the duration of hyperuricemia since transplantation and the clinical outcomes. Our study found that there was no significant difference in eGFR, the risk of graft loss and death at the early time post-transplantation between the hyperuricemic and normouricemic group. However, increased uric acid levels contributed to the long-term decline of eGFR, the risk of graft loss and death increase after transplantation. Hyperuricemia increased the risk of cardiovascular event with no significant difference in the level of triglyceride between the two groups.

Our study showed that hyperuricemia was associated with lower eGFR compared with normal serum UA levels. Previous studies reported that uric acid induced graft dysfunction and chronic allograft nephropathy and accelerated the progress of chronic kidney disease (38-39). The proposed mechanisms included that uric acid was a mediator of endothelial dysfunction, inflammation, and vascular disease (35), (40-41). Our results were similar with previous study, and our study found that this impact was only observed at 12-months following transplantation. Gerhardt et al found that patients with hyperuricemia demonstrated a 5-year graft survival rate of 68.8%, compared with 83.3% in patients with normouricemia (42). Our studies also found that hyperuricemia post-kidney transplantation reduced graft survival. Several mechanisms for the effect of

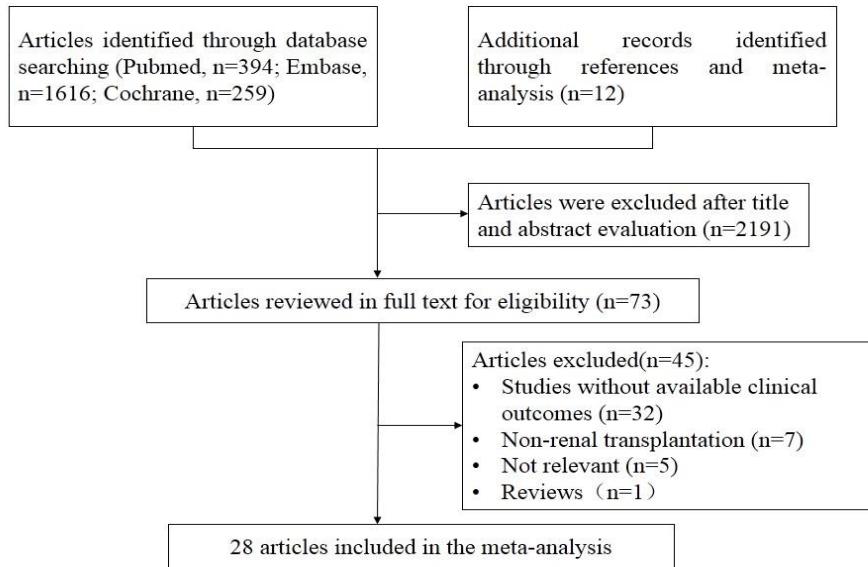


Figure 1. Flow chart depicting the selection process of studies included in the meta-analysis.

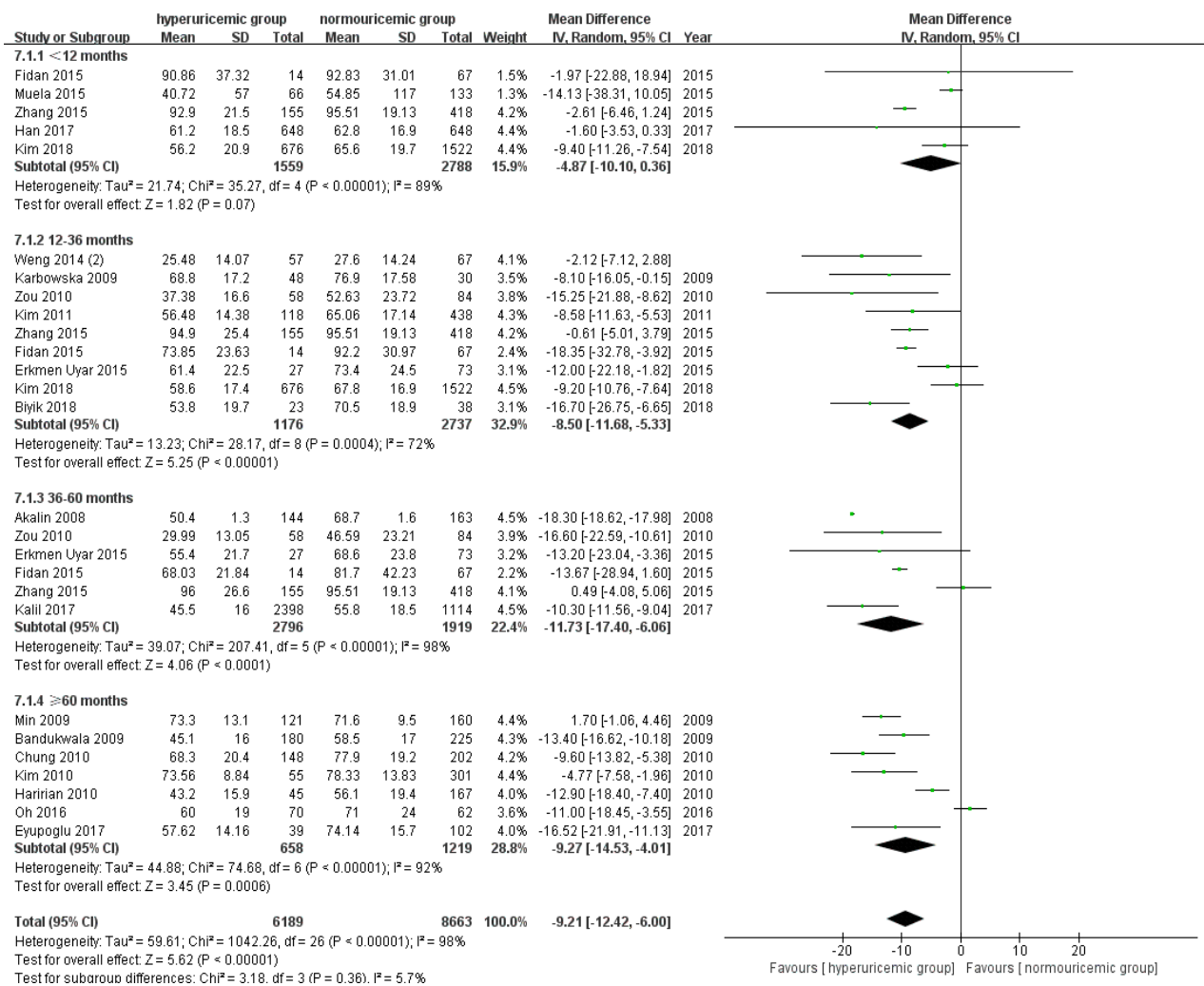


Figure 2. Forest plot for hyperuricemia and eGFR

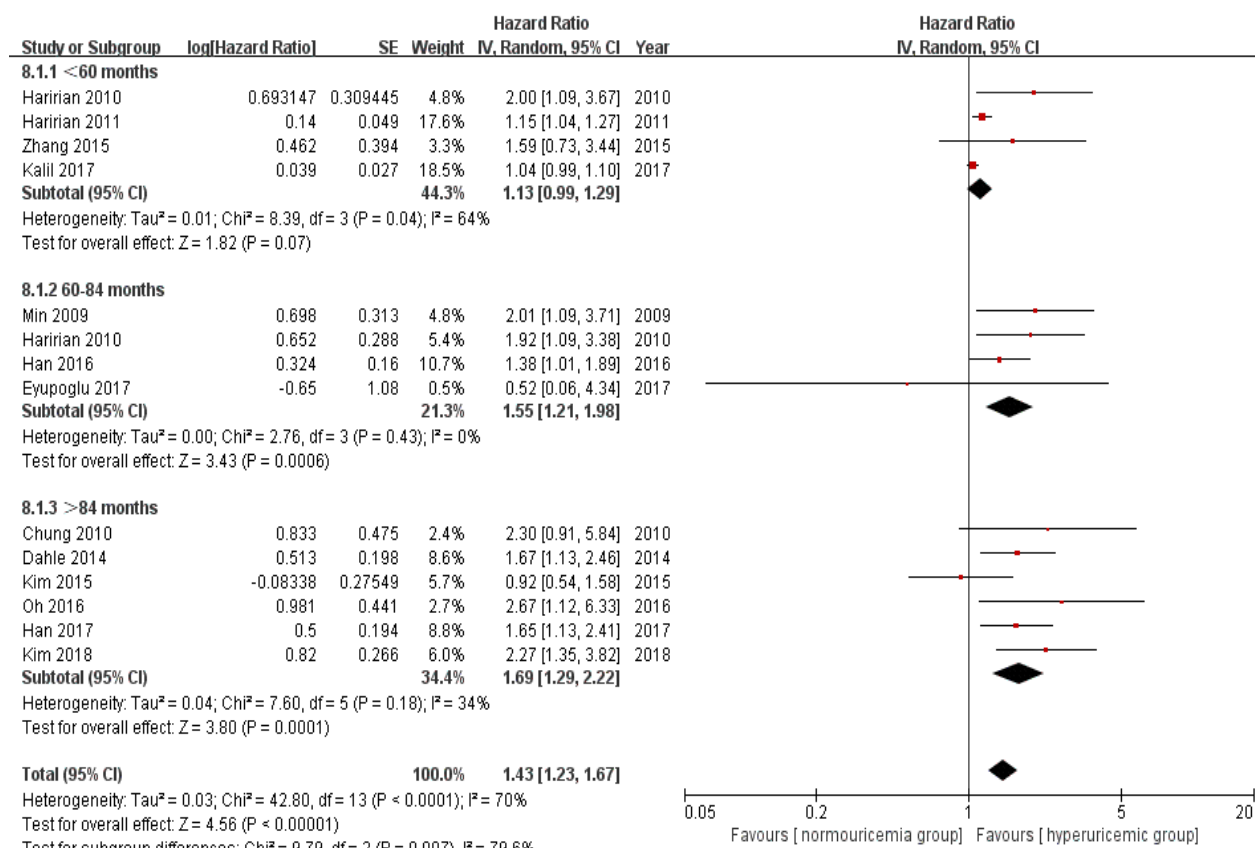


Figure 3. Forest plot for hyperuricemia and the risk of graft loss

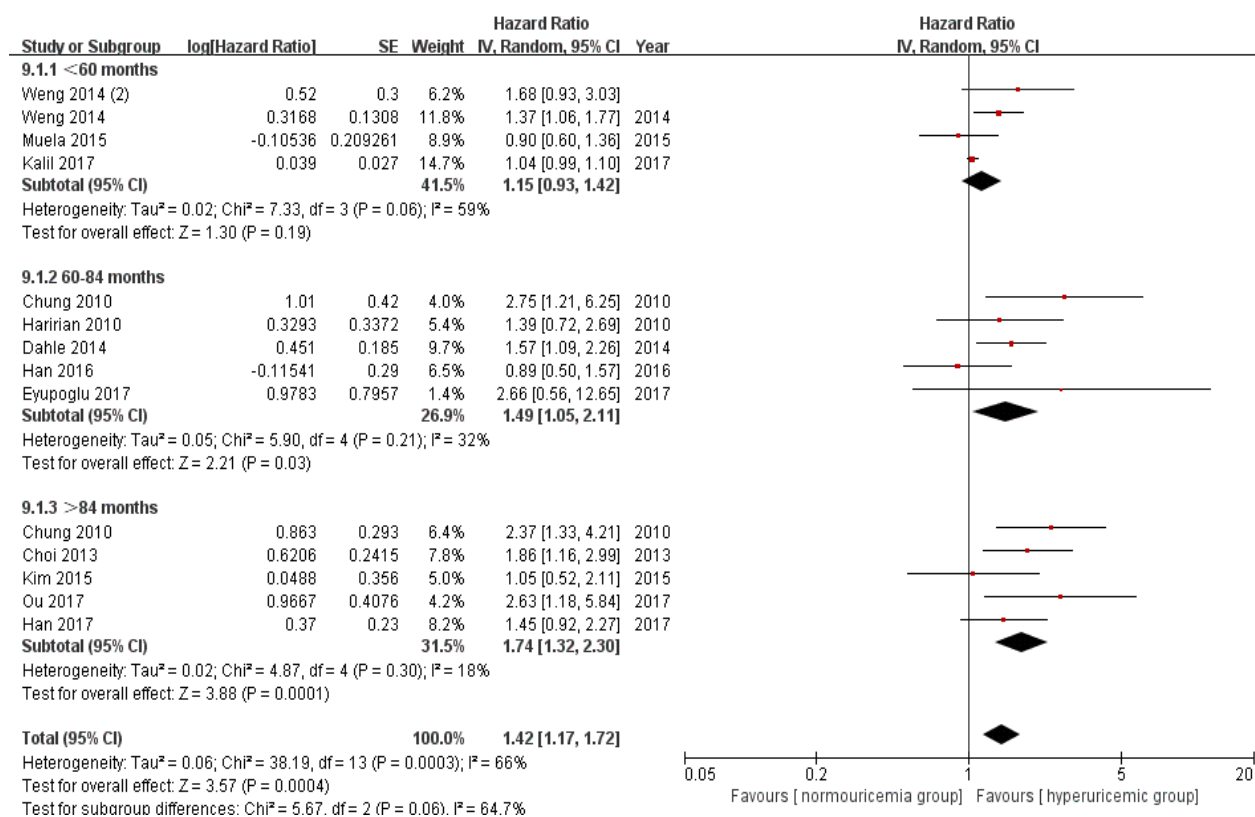


Figure 4. Forest plot for hyperuricemia and the risk of death

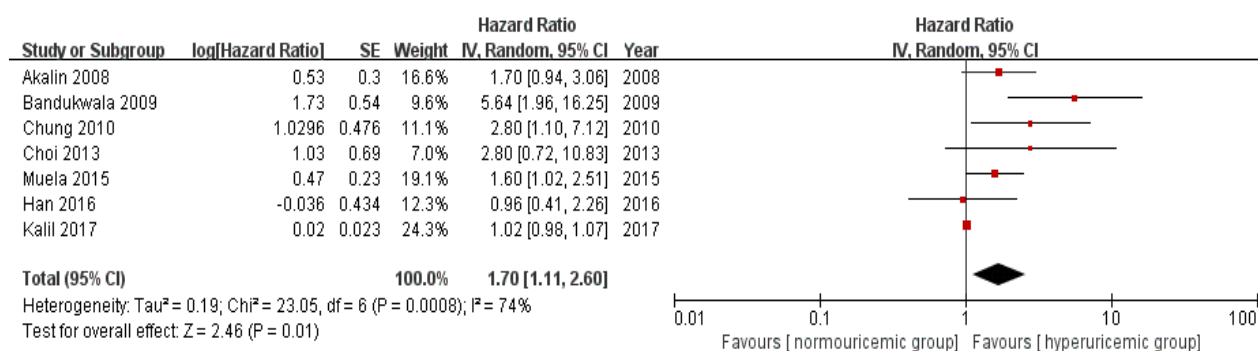


Figure 5. Forest plot for hyperuricemia and the risk of cardiovascular event

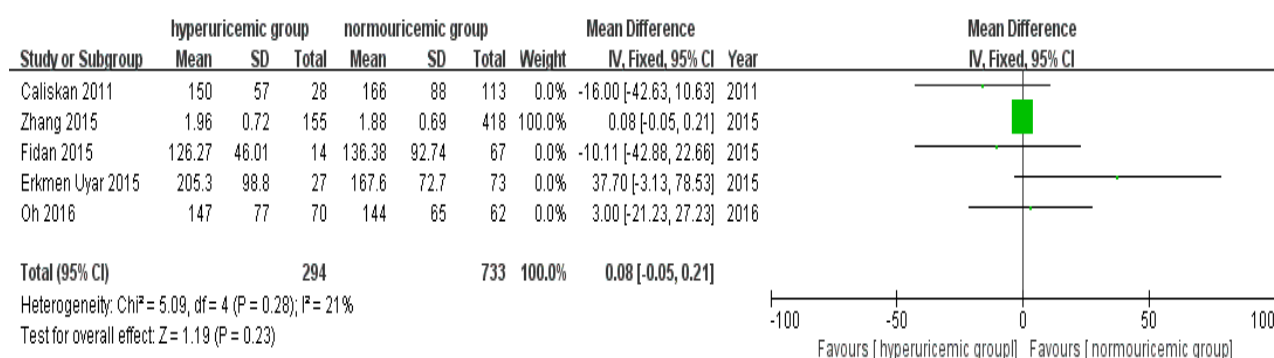


Figure 6. Forest plot for hyperuricemia and the level of triglyceride

UA on graft loss have been proposed. Hyperuricemia induced glomerular hypertrophy (43), renal arteriopathy (44), endothelial dysfunction (45) and arterial stiffness (46-47). These factors resulted in chronic allograft nephropathy, which were the major causes of late graft loss (48-49). And our study found that the association was only observed at 60 months after operation.

National Health and Nutrition Examination Survey (NHANES) has demonstrated an association between hyperuricemia/gout and cardiovascular disease (50). The uric acid (UA) levels are associated with coronary artery calcium (51). Viazzi et al demonstrated that each standard deviation increase in serum uric acid entailed a 75% higher risk of having cardiac hypertrophy and a 2-times greater risk of having carotid abnormalities (52). There are many proposed mechanisms for the influence of hyperuricemia on the cardiovascular risks. Uric acid causes cardiovascular disorders by stimulating the vascular renin-angiotensin systems, serving as a bridging mechanism mediating (enabling) or potentiating the deleterious effects of cardiovascular risk factors on vascular tissue and myocardium (53-54). The impact of uric acid concentrations on cardiovascular event is limited. This was the first meta-analysis to demonstrate this association.

Our study suggested that hyperuricemia

increased the risk of poor outcomes of RTRs. Therefore, the treatment of hyperuricemia is essential. But consensus on whether to treat asymptomatic hyperuricemia in CKD has not been established, treatment of asymptomatic hyperuricemia has not been generally recommended in the general population or KTRs, and it is only advocated in those with recurrent symptomatic episodes of gout, tophi, or radiographic changes of gout (55). But our analysis demonstrated that hyperuricemia was associated with lower eGFR, higher risk of graft loss, death and cardiovascular events. In addition, studies stated that using medication, like xanthine oxidase inhibition, was shown to reverse endothelial dysfunction (56), improve coronary and peripheral endothelial function (57), slow the GFR decline (58), defer the deterioration of renal dysfunction in CKD (59). Therefore, strengthening the management of asymptomatic hyperuricemia is needed. It is worth noting that low levels of serum UA appear also to contribute to poor clinical outcomes (21). The treatment of hyperuricemia should perhaps give priority to maintaining an appropriate serum UA level, rather than to simply lowering serum UA. We believe that it will be the next developments in the management for KTRs. Our review has the following limitations: first, all included studies were retrospective cohort studies, which might bring

estimation bias. Second, some studies have shown that dietary factors are associated with the hyperuricemic group, however these dietary factors have not been evaluated in most of the included studies. Third, since the study population was from different transplant centers and uric acid measurements were from different laboratories, there may be variability in uric acid values. Fourth, although the included studies have been adjusted for confounding factors, the specific adjustment factors are different which may lead to a biased estimation of the results.

CONCLUSION

Our analysis found that increased uric acid levels contributed to the long-term decline of eGFR, the risk of graft loss and death increase after transplantation. Hyperuricemia increased the risk of cardiovascular event with no significant difference in the level of triglyceride between the two groups. Future research is needed to verify whether lowering uric acid level could improve the kidney function and prognosis of RTRs with hyperuricemia.

ETHICAL APPROVAL. This study was a systematic review and meta-analysis and based on the published articles, so ethical approval was not required.

CONFLICT OF INTEREST. No conflict of interest to report.

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SUPPLEMENTARY DOCUMENTS

Table 1s

Pubmed: Search (((((((((((urate[Title/Abstract]) OR uric acid[Title/Abstract]) OR urea acid[Title/Abstract]) OR acid urate[Title/Abstract]) OR gout[Title/Abstract])) OR "Uric Acid"[Mesh]) OR "Hyperuricemia"[Mesh]) OR hyperuric[Title/Abstract]) OR hyperuricemia[Title/Abstract]) OR hyperuricaemia[Title/Abstract])) AND (((((((("Transplantation"[Mesh]) OR "Transplants"[Mesh]) OR transplants[Title/Abstract]) OR transplant[Title/Abstract]) OR transplantation[Title/Abstract]) OR transplantations[Title/Abstract]) OR graft[Title/Abstract])) AND ("2011/6"[Date - Publication] : "3000"[Date - Publication])

Cochrane library:

- #1 MeSH descriptor: [Hyperuricemia] explode all trees
- #2 (hyperuricemia):ti,ab,kw (Word variations have been searched)
- #3 (hyperuricaemia):ti,ab,kw (Word variations have been searched)
- #4 (urea acid):ti,ab,kw (Word variations have been searched)
- #5 (Uric acid):ti,ab,kw (Word variations have been searched)
- #6 (acid urate):ti,ab,kw (Word variations have been searched)
- #7 (urate):ti,ab,kw (Word variations have been searched)
- #8 (gout):ti,ab,kw (Word variations have been searched)
- #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 6582
- #10 MeSH descriptor: [Uric Acid] explode all trees
- #11 (hyperuric):ti,ab,kw (Word variations have been searched)
- #12 #9 or #10 or #11 6582
- #13 MeSH descriptor: [Transplantation] explode all trees
- #14 MeSH descriptor: [Transplants] explode all trees
- #15 (transplant):ti,ab,kw (Word variations have been searched)
- #16 (transplants):ti,ab,kw (Word variations have been searched)
- #17 (transplantation):ti,ab,kw (Word variations have been searched)
- #18 (transplantations):ti,ab,kw (Word variations have been searched)
- #19 (graft):ti,ab,kw (Word variations have been searched)
- #20 #13 or #14 or #15 or #16 or #17 or #18 or #19
- #21 #12 and #20
- #22 #12 and #20 with Cochrane Library publication date to Mar 2020

EMBASE:

- #21. #11AND#19AND[2011-2020]/py
- #20. #11AND#19
- #19. #12OR#13OR#14OR#15OR#16OR#17
- #18. 'transplants'/exp OR transplants
- #17. graft:ab,ti 20 Mar 2020
- #16. transplants:ab,ti 20 Mar 2020
- #15. transplant:ab,ti 20 Mar 2020
- #14. transplantations:ab,ti 20 Mar 2020
- #13.'transplantation':ab,ti 20 Mar 2020

- #12.'transplantation'/exp 20 Mar 2020
- #11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 20 Mar 2020
- #10.'gout':ab,ti 20 Mar 2020
- #9. hyperuric:ab,ti 20 Mar 2020
- #8. hyperuricaemia:ab,ti
- #7.'hyperuricemia':ab,ti 20 Mar 2020
- #6.'hyperuricemia'/exp 20 Mar 2020
- #5.'acid urate':ab,ti 20 Mar 2020
- #4.'urea acid':ab,ti 20 Mar 2020
- #3.'uric acid':ab,ti 20 Mar 2020
- #2. urate:ab,ti 20 Mar 2020
- #1.'uric acid'/exp 20 Mar 2020

Table 2s. Quality of observational studies (indicators from New-Castle-Ottawa scale)

Reference	1a	2b	3c	4d	5Ae	5Bf	6g	7h	8i	Total quality scores
6	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
7	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
8	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
9	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
10	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
11	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
12	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
14	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
15	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
17	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
18	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
19	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
20	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
21	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
22	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
23	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
24	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
25	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
29	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
30	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
31	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
32	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
33	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
34	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
35	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
36	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

a: Indicates exposed cohort truly representative; b: Non-exposed cohort drawn from the same community; c: Ascertainment of exposure from the same community; d: Outcome of interest not present at start of study; e: Cohorts comparable on basis of site and etiology of infection; f: Cohorts comparable on others factors; g: Assessment of outcome of record linkage or independent blind assessment; h: Follow-up long enough for outcomes to occur; I: Complete accounting for cohort.