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REVIEW

Risk of urinary adverse effects of Bevacizumab therapy in patients with ovarian cancer: A systematic review and meta-analysis

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Summary *Background: Ovarian cancer is one of the most lethal malignancies affecting women, often diagnosed at advanced stages. Bevacizumab, a novel therapeutic agent, has recently demonstrated efficacy in the management of this disease. However, its use has been associated with various adverse effects reported in clinical trials. This systematic review and meta-analysis aimed to provide a comprehensive evaluation of urinary complications linked to Bevacizumab therapy in ovarian cancer patients.*

Methods: This systematic review and meta-analysis involved a comprehensive search of databases such as PubMed, Scopus, Embase, Cochrane Library, Web of Science, and Google Scholar, covering studies up to October 2024. Eligible studies were randomized controlled trials (RCTs) that compared ovarian cancer patients undergoing Bevacizumab treatment with those receiving other therapeutic options. The primary outcome was the relative risk (RR) of developing urinary complications, categorized based on disease grade and stage.

Results: A total of 11 interventional studies were ultimately included in the analysis. The relative risk (RR) of urinary complications in patients receiving Bevacizumab in combination with chemotherapy, compared to the control group treated with chemotherapy without Bevacizumab, was significantly elevated for key adverse events. The overall risk of complications, regardless of type, was 1.76 times higher (RR = 1.76, 95% CI: 1.18-2.61, p = 0.005). Specific adverse events included a 6.13-fold increase in the risk of proteinuria (RR = 6.13, 95% CI: 2.84-13.25, p < 0.001), a 5.03-fold increase for hyponatremia (RR = 5.03, 95% CI: 1.08-23.52, p = 0.039), and a 2.41-fold increase for hyperkalemia (RR = 2.41, 95% CI: 0.57-10.22, p = 0.232). Additionally, subgroup analysis based on grading revealed that the risk of proteinuria in the treatment group compared to controls was 6.35-fold higher for patients with grade ≤ 2 and 6.55-fold higher for those with grade ≥ 3.

Conclusions: This study demonstrated that the use of Bevacizumab in patients with ovarian cancer significantly increases the overall risk of urinary complications, particularly proteinuria. These findings could contribute to enhanced awareness, facilitating the early identification and management of these adverse effects.

KEY WORDS: *Bevacizumab; Ovarian cancer; Urinary complications; Proteinuria; Meta-analysis, Anti-angiogenic Therapy; Adverse drug events; Gynecological malignancies.*

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INTRODUCTION

Ovarian cancer is one of the deadliest cancers affecting women, with approximately 230,000 new cases diagnosed annually and 150,000 deaths attributed to the disease each year (1). Approximately 75% of ovarian cancer cases are identified at advanced stages, leading to a high mortality rate. The 5-year survival rate for these patients is reported to be as low as 29% (2). Early symptoms, such as fatigue, early satiety, and changes in bowel habits, are often nonspecific. Although these symptoms frequently manifest long before a formal diagnosis, patients typically do not seek medical evaluation for them (3). Given the high mortality associated with this malignancy, identifying novel and effective therapeutic approaches remains a critical priority.

The initial step in the treatment of ovarian cancer typically involves surgery aimed at tumor debulking or complete removal. If the tumors are confined to the ovaries, surgery alone can lead to a potential cure (4). Following surgery, chemotherapy is commonly administered using agents such as carboplatin and intravenous paclitaxel. These drugs are generally prescribed in cycles of three weeks, spanning 3 to 6 cycles or more, depending on the case (5). Despite the use of these chemotherapeutic regimens, the mortality rate for ovarian cancer remains high, prompting the exploration of novel therapeutic options. One such therapy is Bevacizumab, a humanized recombinant monoclonal antibody that exerts its effect by inhibiting *vascular endothelial growth factor* (VEGF) (6). Bevacizumab inhibits VEGF, thereby disrupting angiogenesis, the process of forming new blood vessels that are critical for cancer cell growth and survival. Several studies have demonstrated the efficacy of incorporating Bevacizumab into standard ovarian cancer treatment protocols.

Several significant adverse effects have been reported with the use of Bevacizumab, including gastrointestinal perforation and obstruction, thromboembolic events, and hypertension (7, 8). Although chemotherapy and targeted therapies have markedly enhanced cancer treatment outcomes, their administration is frequently associated with notable systemic toxicities, impacting various organ

systems and complicating clinical management efforts (9). Another critical adverse effect is proteinuria, which has been observed in up to 63% of patients receiving Bevacizumab (10). VEGF plays a crucial role in protecting the endothelial cells of glomeruli in the kidneys. By inhibiting VEGF, Bevacizumab disrupts the repair mechanisms of glomerular damage, potentially leading to proteinuria (11). Additionally, hypertension, another common adverse effect of Bevacizumab, may further impair renal function. Hypertension can damage renal vasculature, exacerbating protein loss through the kidneys (12). Various studies have reported a range of urinary complications associated with the use of Bevacizumab in patients with ovarian cancer. However, these complications have not been specifically investigated in prior research. This systematic review and meta-analysis aims to provide a detailed evaluation of urinary adverse effects linked to Bevacizumab use in this patient population.

Materials and methods

Study design

This systematic review with meta-analysis has been conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (13).

Search strategy and resources

The literature review encompassed various databases, including PubMed/Medline, Scopus, Embase, Cochrane Library, and Web of Science. Moreover, clinical trial registries like *ClinicalTrials.gov* and the *International Clinical Trials Registry Platform* (ICTRP) were also explored through October 2024. Gray literature was also reviewed to identify additional studies. The search was performed without any restrictions on time frame or language. The search strategy included both MeSH (*Medical Subject Headings*) and non-MeSH keywords such as: Bevacizumab, Ovarian Neoplasms, Ovarian Tumors, Ovarian Malignancies, Ovarian Carcinomas, Ovarian Masses, Adverse Effects, Side Effects, Proteinuria, Incontinence, Hematuria, Acidosis, Hyperkalemia, Hypokalemia, Infections, Dehydration, Hyponatremia, Hypernatremia, Urinary, Pain, RCT, Trial, Randomized, Randomized Controlled Trials. A multi-step process was employed to identify the relevant search terms and design the search syntax. This strategy utilized a combination of common free-text keywords and Medical Subject Headings (MeSH) terms (Appendix 1).

Selection criteria

The results from the mentioned databases were independently imported into EndNote software by two researchers. Duplicate records were identified and removed using EndNote. The remaining articles were then screened by both researchers to determine their eligibility. Discrepancies between the two were addressed and resolved by consulting a third researcher.

This study included randomized controlled trials (RCTs) involving patients with ovarian cancer who received Bevacizumab as part of their treatment and reported urinary complications as an adverse event. Eligible studies were required to have a control group receiving alternative treatments, such as chemotherapy without Bevacizumab. Review articles, case studies, cohort studies, and trials that did not report outcomes related to urinary complications were excluded. Urinary complications were graded according to the *Common Terminology Criteria for Adverse Events* (CTCAE) version 5.0 (14).

Disagreements between evaluators were resolved through discussion with a third reviewer. The *relative risk* (RR) was calculated as the effect size for the analysis.

Data extraction

The outcomes included the frequency of various urinary complications, such as overall urinary adverse events (without specifying the exact type), proteinuria, urinary tract infections, hyponatremia, dehydration, hyperkalemia, and hypokalemia, in both the intervention and control groups. The following data were extracted from each study: the first author's name, publication date, years of data collection, intervention and control groups, disease grade, disease stage, participating countries, age range of patients in the intervention and control groups, intervention drug dosage, sample size, and the type of urinary complications observed in the intervention and control groups.

Quality appraisal

Bias in the included *randomized controlled trials* (RCTs) was systematically evaluated using the Cochrane RoB 2.0 tool, first introduced in 2016 and last updated on August 22, 2019. This revised tool assesses several domains, including the randomization process, deviations from planned interventions, missing outcome data, outcome measurement, and selection of reported results (15). The studies were classified into three categories: low risk of bias, high risk of bias, and some concerns. Screening, study selection, validation, data extraction, and quality assessment were carried out independently by two researchers, with any disagreements resolved by a third reviewer to achieve consensus.

Publication bias

Publication bias was assessed using funnel plots and Eggar's weighted regression (16). A p-value > 0.05 was considered indicative of no significant publication bias.

Subgroup analysis

Subgroup analyses were conducted based on grade (grade ≤ 2 and grade ≥ 3) and disease stage (I-IV).

Statistical analysis

The data were input into a statistical software program, and analyses were conducted using STATA version 14.0 (*Stata Corporation, College Station, TX*). A random effects model was applied to address heterogeneity across studies. Heterogeneity was assessed using Cochran's Q test and Higgins' I^2 test, alongside qualitative evaluation of differences between studies by the researchers. Forest plots were generated to illustrate the effect size of each study and pooled estimates. A p-value of less than 0.05 was considered statistically significant.

Results

Study selection

A total of 563 articles were identified through the search across all international databases. After removing duplicates, 457 articles proceeded to the title and abstract screening stage. Following this screening, 21 articles were selected for further review. During this phase, the full texts of the articles were reviewed, resulting in the inclusion of 11 studies in the final analysis. Furthermore, the references of these articles were examined to identify and incorporate any additional relevant studies. The study selection process is depicted in Figure 1.

Characteristics of studies

The included studies were up to October 2024. A total of 11 studies, encompassing 18 records within the specified timeframe, met the eligibility criteria and addressed one or more of the reported urinary complications associated with Bevacizumab use, classified by grade and stage of the complication. Most studies collected data as multicenter trials and included patients across stages I-IV. Three studies in the control group utilized monochemotherapy, while the remaining studies employed multidrug regimens. Descriptive details of these studies are presented in Table 1 (7, 8, 17-25).

Quality appraisal

The results of the quality assessment are illustrated in Figure 2. Based on the evaluation using the specified checklist, six studies were classified as having good quality (low risk), five studies were rated as having some concerns, and none were deemed to have poor quality (high risk). Notably, all included studies were randomized trials.

Heterogeneity

The results of the chi-squared test and I^2 index indicated significant heterogeneity among studies reporting on proteinuria, which included nine studies (I^2 = 69.45%, Q-value = 29.10, p = 0.0003). For other complications, the number of studies was smaller, and the heterogeneity was not statistically significant. However, due to the inherent qualitative differences between studies, a random effects model was applied to all analyses.

Results of the meta-analysis

Relative risk of Bevacizumab side effects

The random effects model revealed that the *relative risk* (RR) of urinary complications was generally higher in patients receiving Bevacizumab in combination with chemotherapy compared to those in the control group undergoing chemotherapy alone. Key findings showed

Figure 1.
PRISMA flow chart.

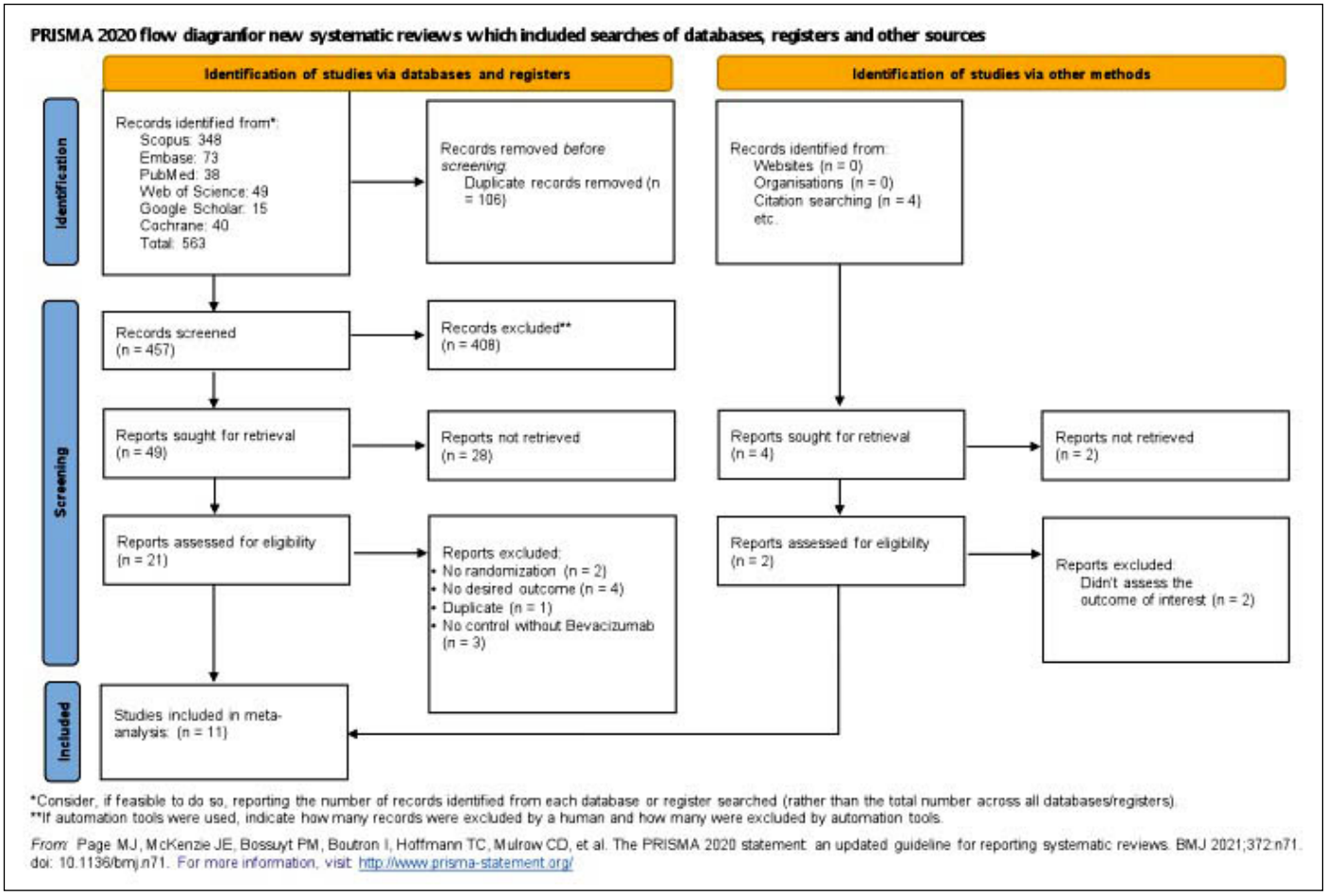

Table 1.
Demographic characteristics of the included studies in the systematic review and meta-analysis.

ID	Author	Data collection duration	Country	Ovarian cancer stage	Age range intervention/ control	Intervention	Control	Dose of intervention drug	Treatment plan	Grade of adverse effect	N total
1	*Burger et al. (2011)* (17)	2005-2009	Multicenter	III-IV	22-89/25-86	bevacizumab	Multi Chemotherapy	15 mg/kg	every 21 days	≥ 2	1816
2	*Pignata et al. (2021)* (8)	2013-2016	Multicenter	IIIB-IV	52-68/53-68	bevacizumab	Multi Chemotherapy	15 mg/kg OR 10 mg/kg	every 21 days	1 to 5	401
3	*Garcia Garcia et al. (2019)* (19)	2013-2015	Spain	III-IV	36-82/36-82	bevacizumab	Multi Chemotherapy	15 mg/kg	every 21 days	3 to 5	68
4	*Roque (2022)* (24)	2017-2020	USA	I-IV	40 - 78/50-88	bevacizumab	Mono Chemotherapy	10 mg/kg	every 14 days	1 to 3	1574
5	*Mirza et al. (2019)* (21)	2016-2018	Multicenter	I-IV	59-70/58-70	bevacizumab	Mono Chemotherapy	15 mg/kg	every 21 days	1 to 5	97
6	*Perren et al. (2011)* (7)	2006-2009	Multicenter	I-IV	24-80/18-81	bevacizumab	Multi Chemotherapy	7.5 mg/kg	every 21 days	1 to 5	1528
7	*Gore et al. (2019)* (20)	2010-2013	USA, UK	II-IV	28 - 60/20-82	bevacizumab	Multi Chemotherapy	15 mg/kg	every 21 days	1 to 4	50
8	*Shoji et al. (2022)* (25)	2015-2019	Japan	I-IV	mean ± SD: 60.3 ± 9.71/60.7 ± 12.15	bevacizumab	Multi Chemotherapy	15 mg/kg	every 21 days	3 to 5	103
9	*Pujade-Lauraine et al. (2014)* (22)	2009-2011	Multicenter	III-IV	25-80/25-84	bevacizumab	Multi Chemotherapy	15 mg/kg OR 10 mg/kg	every 21 days or every 14 days	2 to 5	360
10	*Coleman et al. (2017)* (18)	2007-2011	Multicenter	I-IV	26-84/23-85	bevacizumab	Multi Chemotherapy	15 mg/kg	every 21 days	1 to 5	654
11	*Ray-Coquard et al. (2020)* (23)	2013-2016	Multicenter	I-IV	37-61/53-64	bevacizumab	Mono Chemotherapy	10 mg/kg then 15 mg/kg	every 14 days then every 21 days	1 to 4	59

SD: standard deviation.

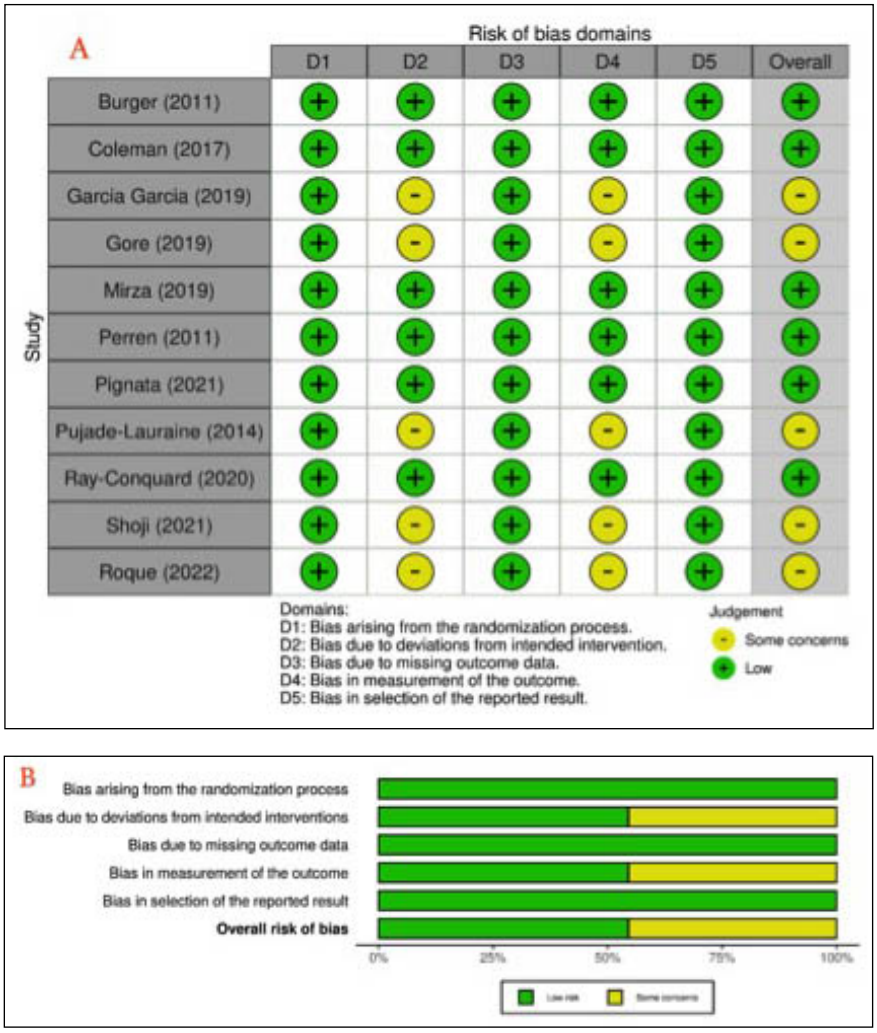

Figure 2.
Risk of bias Assessment;
Risk of bias assessment of included randomized control trials (RCTs).

(A) Risk of bias summary of all included RCTs.

(B) Risk of bias.

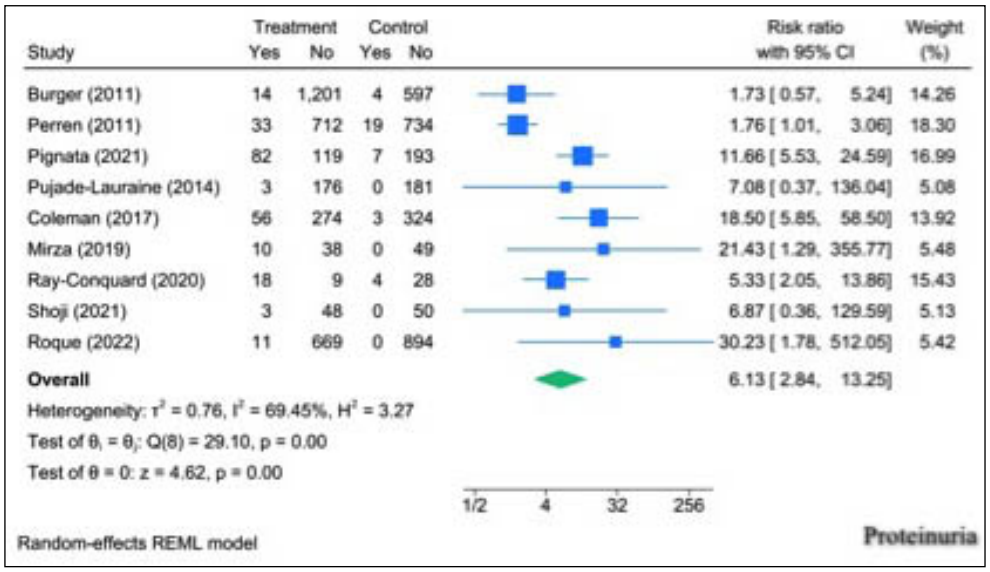

Figure 3.
Meta-analysis of the relative risk of proteinuria complications in patients taking Bevacizumab.

that Proteinuria, reported in nine studies, had the highest relative risk at 6.13 (95% CI: 2.84-13.25, p < 0.001) (Figure 3). The overall risk of unspecified urinary complications, based on three studies, was 1.76 times higher (95% CI: 1.18-2.61, p = 0.005). Hyponatremia, as reported in three studies, had a relative risk of 5.03 (95% CI: 1.08-23.52, p = 0.039), while Hyperkalemia, observed in two studies, had a relative risk of 2.41 (95% CI: 0.57-10.22, p = 0.232). The forest plot illustrating the relative risks for other urinary complications is presented in Figure 4,

Figure 4.
Meta-analysis of the relative risk of urinary complications in patients taking Bevacizumab.

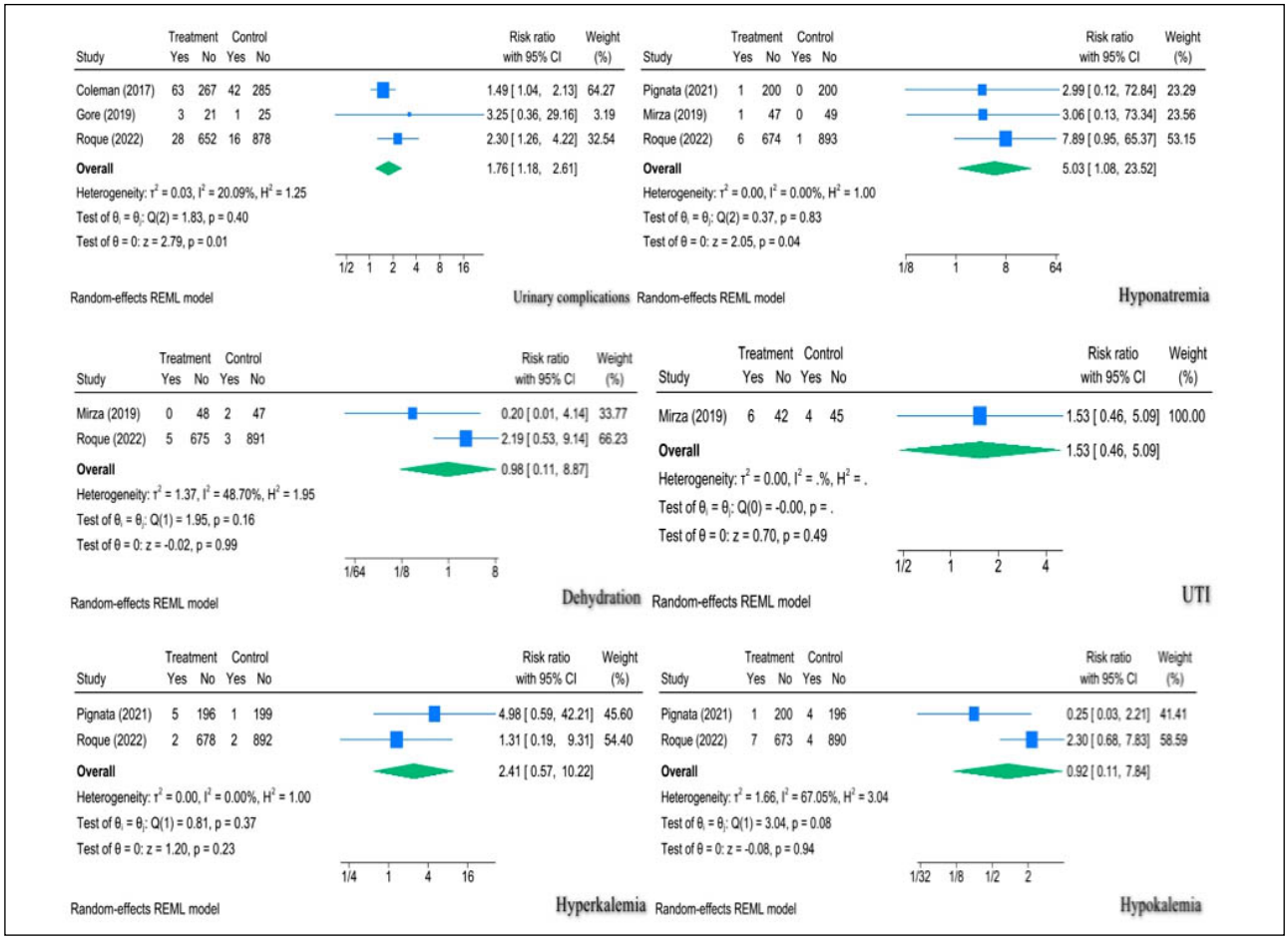

Table 2.
Demographic characteristics of the included studies in the systematic review and meta-analysis.

Type of	Number of studies	Effect estimate (Relative risk)	95 % CI	p.value	Heterogeneity			Subgroup analysis		
					Q-Value	I^2	p.value	Grade	Number of records	Effect estimate (95 % CI)
Urinary complications*	3	1.76	1.18 to 2.61	0.005	1.83	20.09	0.401	2 ≥	3	1.89 (1.13 to 3.18)
								≥ 3	3	1.49 (0.53 to 4.14)
Proteinuria	9	6.13	2.84 to 13.25	< 0.001	29.10	69.45	0.0003	2 ≥	6	6.35 (2.72 to 14.85)
								≥ 3	7	6.55 (2.15 to 19.95)
UTI	1	1.53	0.46 to 5.09	0.486	-	-	-	2 ≥	1	1.70 (0.43 to 6.73)
								≥ 3	1	1.02 (0.07 to 15.86)
Hyponatremia	3	5.03	1.08 to 23.52	0.039	0.37	0.00	0.831	2 ≥	3	2.82 (0.37 to 21.27)
								≥ 3	3	3.45 (0.70 to 17.02)
Dehydration	2	0.98	0.11 to 8.87	0.987	1.95	48.70	0.162	2 ≥	2	1.51 (0.14 to 15.74)
								≥ 3	2	0.91 (0.17 to 4.80)
Hyperkalemia	2	2.41	0.57 to 10.22	0.232	0.81	0.00	0.368	2 ≥	2	2.60 (0.47 to 14.46)
								≥ 3	2	1.87 (0.23 to 15.16)
Hypokalemia	2	0.92	0.11 to 7.84	0.936	3.04	67.05	0.081	2 ≥	2	1.04 (0.20 to 5.57)
								≥ 3	2	1.14 (0.10 to 12.92)

SD: standard deviation.

and a detailed summary of these findings is provided in Table 2.

Subgroup analysis and sensitivity analysis

Subgroup analysis based on grade (categorized as ≤ 2 and ≥3) indicated that in the treatment group, the *relative risk* (RR) of Proteinuria was 6.35 times higher for patients with grade ≤ 2 (6 studies; RR = 6.35, 95% CI: 2.72-14.85) and 6.55 times higher for those with grade ≥ 3 (7 studies; RR = 6.55, 95% CI: 2.15-19.95) compared to the control group (Appendix 2). All subgroup analyses based on grade are detailed in Table 2. Similarly, subgroup analysis based on disease stage (categorized as I-IV and III-IV) showed that the risk of Proteinuria was 7.03 times higher for patients in stage I-IV (RR = 7.03, 95% CI: 2.50-19.76) and 5.11 times higher for those in stage III-IV (RR = 5.11, 95% CI: 1.25-20.92) compared to the control group (Appendix 3). Additionally, sensitivity analysis for Proteinuria revealed that excluding any single study did not alter the effect size or the statistical significance of the P-value, which remained robust and meaningful (Appendix 4).

Publication bias

Finally, funnel plots were generated to assess publication bias for the urinary complications associated with Bevacizumab therapy. Results of the Egger test did not indicate significant publication bias for studies reporting on Proteinuria (bias = 0.08, SE = 0.89, p = 0.228) (Appendix 5).

Discussion

The findings of this study revealed that Bevacizumab use in ovarian cancer patients significantly increases the overall risk of urinary complications. The most notable complication was proteinuria, which was more than six times higher in patients receiving this drug. Hyponatremia and hyperkalemia followed, with increases of over fivefold and twofold, respectively. Other noteworthy complications included unspecified urinary adverse events and urinary tract infections, which showed increases of 76% and 53%, respectively.

Bevacizumab has been shown in numerous studies, including the current one, to increase the risk of proteinuria to varying extents. *Lafayette et al.* reviewed 17 randomized clinical trials involving a total of 14,584 cancer patients. Their analysis revealed that the incidence of proteinuria was 8.2% in patients treated with Bevacizumab, compared to 4.6% in the control group (26). Similarly, *Ghoerche et al.* reported a 33% incidence of proteinuria among 60 patients with metastatic colorectal cancer receiving Bevacizumab (27). In another meta-analysis by *Wu et al.*, which included 16 randomized clinical trials and over 12,000 patients with various tumor types, the relative risk (RR) of grade 3 and 4 proteinuria in the Bevacizumab group was more than four times higher than in the control group. Furthermore, they calculated the relative risk of nephrotic syndrome, a condition characterized by significant proteinuria, as over sevenfold higher in the Bevacizumab group (28). Another meta-analysis by *Zhao et al.*, involving 17 randomized clinical trials with a total of 16,592 cancer patients, reported that the *risk ratio* (RR) of proteinuria in Bevacizumab users was over three times higher than in the control group, with the RR for severe proteinuria exceeding fivefold (29). In contrast to Zhao's findings, our study demonstrated a nearly identical increase in risk for proteinuria in subgroup analyses based on grade, with both grade < 3 and grade ≥ 3 showing an over sixfold increase in risk. The likely mechanism underlying proteinuria in patients receiving Bevacizumab is the inhibition of *vascular endothelial growth factor A* (VEGF-A) (30). Podocytes in the glomeruli produce VEGF to activate endothelial cells, which play a critical

role in repairing glomerular vasculature and maintaining renal filtration capacity. VEGF inhibition disrupts this repair process, leading to increased glomerular permeability and subsequent protein leakage into the urine (31). Another potential mechanism for proteinuria in these patients is the development of glomerular thrombotic microangiopathy due to VEGF inhibition (32). A study conducted in Japan involving 19 breast cancer patients treated with Bevacizumab found that the early onset of proteinuria (within 56 days) was indicative of stronger antitumor activity and served as a predictor of better therapeutic outcomes (33). However, this complication can lead to treatment discontinuation in many patients. Therefore, early intervention should be considered upon its onset. Periodic monitoring of patients for proteinuria is recommended, and management can be initiated using *angiotensin-converting enzyme inhibitors* (ACEIs) or *angiotensin receptor blockers* (ARBs) (31).

Other significant complications identified in this study were electrolyte disturbances, including hyponatremia and hyperkalemia. Hyponatremia associated with Bevacizumab has been previously reported as a dose-limiting factor in breast cancer treatment (34). A probable mechanism for this complication is Bevacizumab-induced proteinuria, which can lead to hypervolemia and subsequently hypervolemic hyponatremia (35). In contrast to the hyperkalemia observed in this study, a previous study reported hypokalemia in patients receiving Bevacizumab, attributing the cause to proximal tubular damage (36).

This study represents the first systematic review and meta-analysis specifically focusing on urinary complications in ovarian cancer patients treated with Bevacizumab. Additionally, subgroup analyses were performed to assess these complications based on their severity. However, the study has certain limitations. Many studies were excluded due to the lack of randomization or control groups, limiting the scope of the analysis. Variability in control groups across the included studies may have influenced the comparability of outcomes. Furthermore, differences in the dosage of Bevacizumab, concurrent use of the drug with other chemotherapeutic agents, and varying treatment durations in the primary studies may contribute to inconsistencies in the results.

Conclusions

The findings of this study demonstrated that Bevacizumab use in ovarian cancer patients significantly increases the overall risk of urinary complications. Proteinuria was identified as the most prominent complication, with an approximately sixfold increase in risk. Following proteinuria, hyponatremia and hyperkalemia were observed, with relative risk increases of over fivefold and twofold, respectively. These findings can contribute to enhanced awareness, enabling earlier detection and timely management of these complications.

Declarations

Ethical approval and consent for participate: *This article is a systematic review and meta-analysis and does not contain any new studies with human participants or animals performed by any of the authors. Therefore, ethical approval was not required.*

Consent for publication: *For this type of study, formal informed consent is not required.*

Availability of data and material: *The data that support the findings of this systematic review and meta-analysis are available from the corresponding author upon reasonable request. All included studies are cited in the reference list*

Competing interests: *The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*

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Authors' contributions: *Mazen Karama: Conceptualization, Methodology, Writing - Original Draft; Mohammed Qaid: Data Curation, Formal Analysis, Validation; Adham Alkhammar: Investigation, Resources, Writing - Review & Editing; Farida Noman: Methodology, Project Administration, Software; Ahmed Karama: Visualization, Writing - Review & Editing; Faisal Ahmed: Supervision, Validation, Writing – Review & Editing. All authors have read and approved the final version of the manuscript.*

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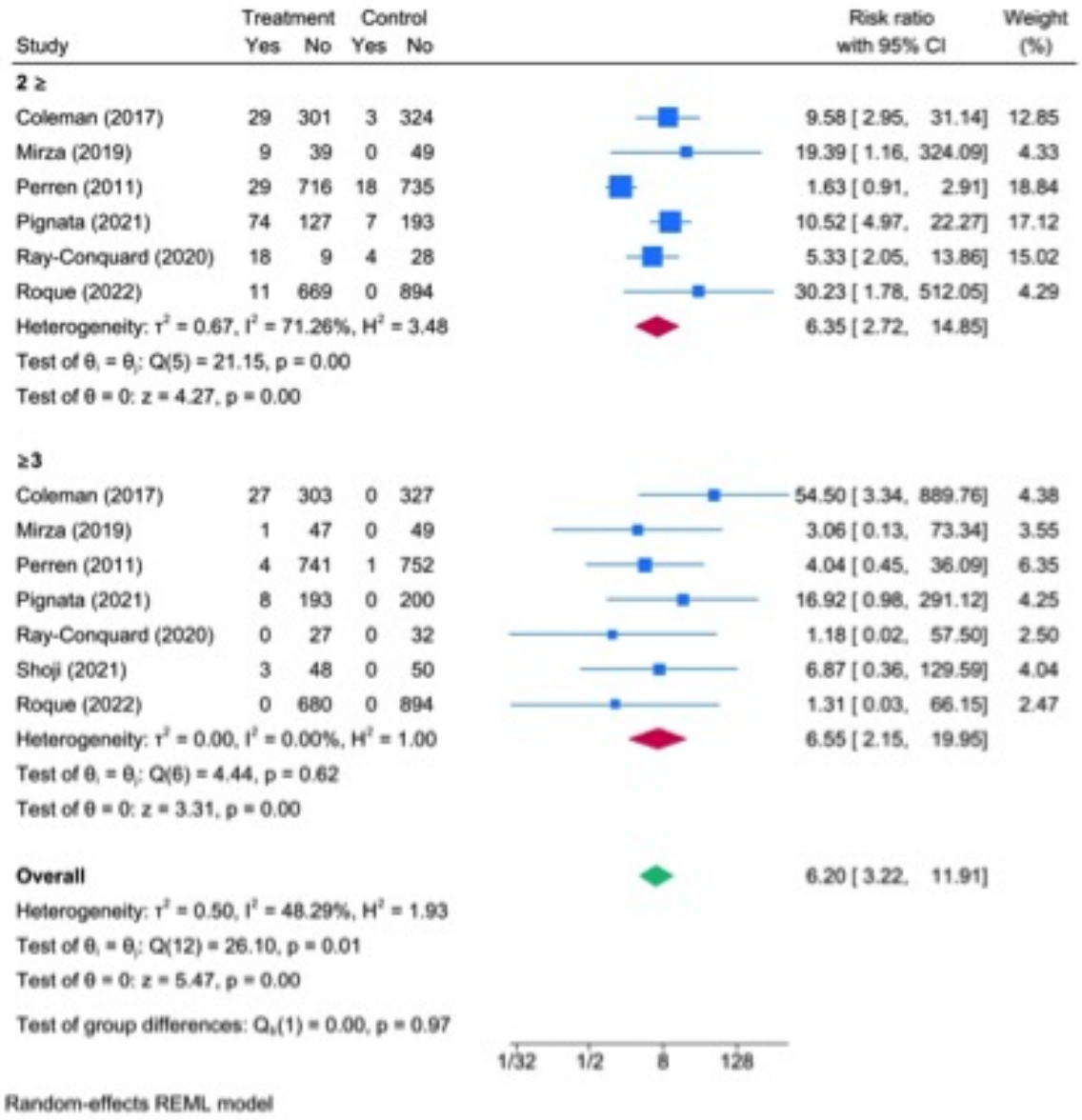
Appendix 1:

Search strategy

PubMed:
ALL: ((((((((((((((((((("Ovarian Neoplasms"[Mesh]) OR (Ovary tumor)) OR (Ovary tumors)) OR (Ovarian tumor)) OR (Ovarian tumors)) OR (Ovary malignancy)) OR (Ovary malignancies)) OR (Ovarian malignancy)) OR (Ovarian malignancies)) OR (Ovary carcinoma)) OR (Ovary carcinomas)) OR (Ovarian carcinoma)) OR (Ovarian carcinomas)) OR (Ovary mass)) OR (Ovary masses)) OR (Ovarian mass)) OR (Ovarian masses)) AND ((((((("adverse effects" [Subheading] OR "Long Term Adverse Effects"[Mesh]) OR (side effect)) OR (complications)) OR (disadvantageous)) OR (unfavorable)) OR (complication))) AND (("Bevacizumab"[Mesh]) OR (anti-VEGF monoclonal antibody))) AND ((((((((((((((((((((((((((((((((("Proteinuria"[Mesh]) OR "Urinary Incontinence"[Mesh]) OR "Hematuria"[Mesh]) OR "Urinary Bladder, Overactive"[Mesh]) OR "Acute Kidney Injury"[Mesh]) OR "Lower Urinary Tract Symptoms"[Mesh]) OR "Urinary Tract Infections"[Mesh]) OR "Hyponatremia"[Mesh]) OR "Dehydration"[Mesh]) OR "Hyperkalemia"[Mesh]) OR "Hypokalemia"[Mesh]) OR "Hypernatremia"[Mesh]) OR "Acidosis, Renal Tubular"[Mesh]) OR "Nephritis"[Mesh]) OR "Crystalluria"[Mesh]) OR "Polyuria"[Mesh]) OR "Cystitis, Interstitial"[Mesh]) OR "Glomerulonephritis"[Mesh]) OR (Urinary frequency)) OR (Incontinence)) OR (Overactive)) OR (Urgency)) OR (Pain)) OR (Pains)) OR (Frequent urination)) OR (Hesitancy)) OR (Straining)) OR (weak urinary stream)) OR (dribbling)) OR (incomplete bladder emptying)) OR (Infection)) OR (Infections)) OR (UTI)) OR (Urinary)) OR (Hyponatremias)) OR (Stress)) OR (Nephrotoxicity))) AND ((((((((((((("Non-Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR "Pragmatic Clinical Trials as Topic"[Mesh] OR "Clinical Trials, Phase III as Topic"[Mesh] OR "Clinical Trials, Phase IV as Topic"[Mesh] OR "Clinical Trials, Phase II as Topic"[Mesh] OR "Clinical Trials, Phase I as Topic"[Mesh] OR "Adaptive Clinical Trials as Topic"[Mesh]) OR "Random Allocation"[Mesh]) OR ("Clinical Trial" [Publication Type] OR "Adaptive Clinical Trial" [Publication Type] OR "Clinical Trial Protocol" [Publication Type] OR "Clinical Trial, Phase I" [Publication Type] OR "Clinical Trial, Phase II" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Pragmatic Clinical Trial" [Publication Type])) OR (Intervention)) OR (Experimental)) OR (RCT)) OR (Non RCT)) OR (trial)) OR (Trials)) OR (double-blind method)) OR (single-blind method)) OR (RCTs)) OR (Non RCTs)) OR (Randomized))

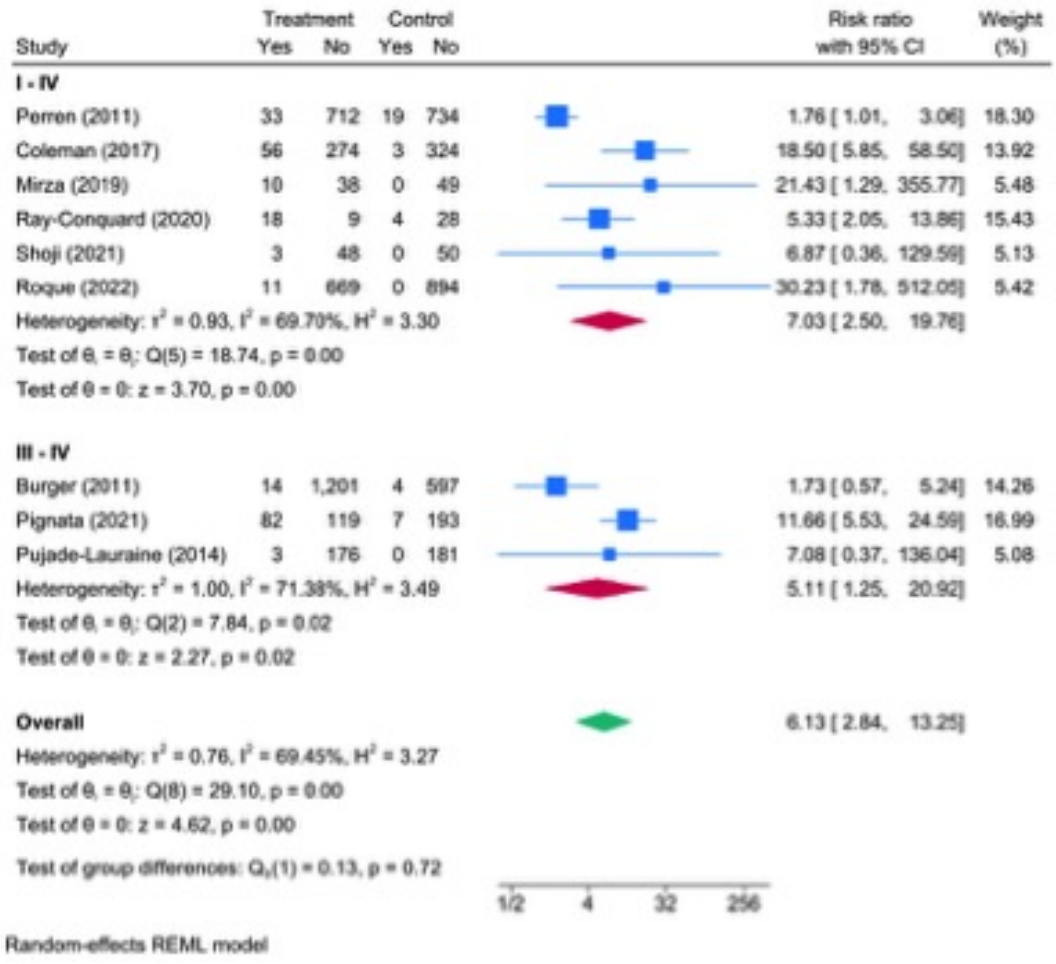
Appendix 2:

Subgroup meta-analysis of the proteinuria complications by disease grade



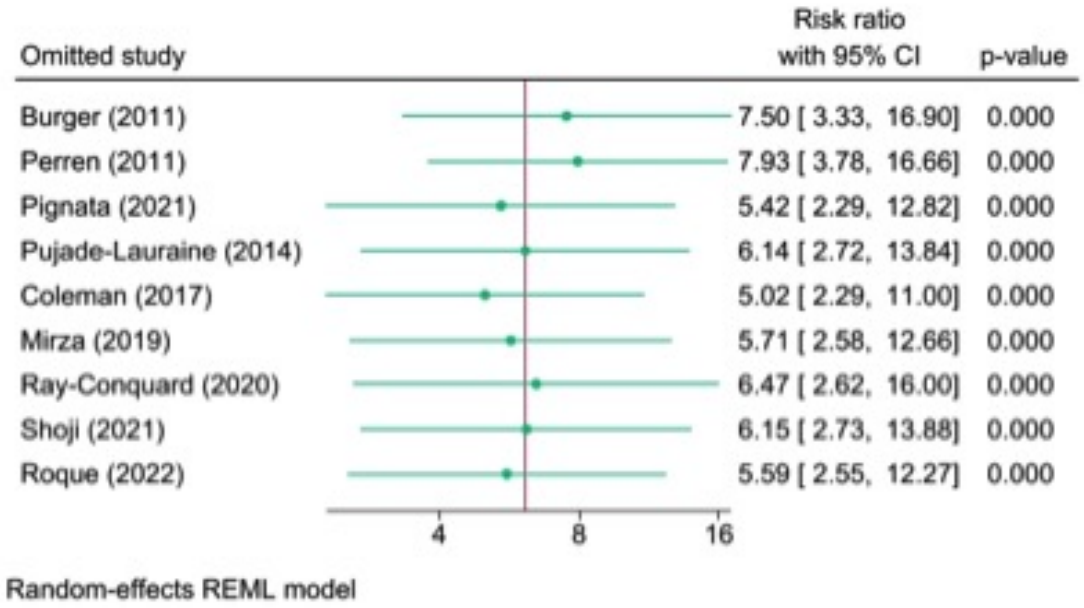
Appendix 3:

Subgroup meta-analysis of the proteinuria complications by disease stage



Appendix 4:

Sensitivity analysis results of the studies included in the meta-analysis with the exclusion of one study.



Appendix 5:

Funnel plot of studies evaluating urinary complications in patients receiving.