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REVIEW

Prognostic significance of pretreatment hydronephrosis in radiotherapy-based bladder-preserving strategies for muscle-invasive bladder cancer: A systematic review and meta-analysis

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Summary *Introduction & objectives: Radiotherapy-based bladder-preserving strategies are established alternatives to radical cystectomy for selected patients with muscle-invasive bladder cancer (MIBC), yet survival outcomes remain heterogeneous and prognostic stratification is imprecise. Pretreatment hydronephrosis has shown adverse prognostic associations in cystectomy and trimodality therapy cohorts, but its impact across the broader spectrum of radiotherapy-based bladder preservation is unclear. This systematic review and meta-analysis aimed to quantify the prognostic significance of pretreatment hydronephrosis on survival outcomes in MIBC patients treated with radiotherapy-based bladder-preserving strategies.*

Materials & methods: The study was designed as a systematic review with quantitative synthesis, structured around a predefined PICO framework. The protocol was prospectively registered in PROSPERO (CRD420261305703). Eligible studies included observational cohorts and clinical trials enrolling adults with MIBC treated with definitive radiotherapy-based bladder preservation, including radiotherapy alone, concurrent chemoradiotherapy, or trimodality therapy. Searches of PubMed, ScienceDirect, the Cochrane Library, Google Scholar, and Wiley Online Library were performed from January 2000 to December 2025. Risk of bias was assessed with ROBINS-I and study quality with Newcastle-Ottawa Scale. Time-to-event outcomes were extracted as hazard ratios (HRs) with 95% confidence intervals (CIs), prioritizing multivariable-adjusted estimates. Evidence synthesis was performed using random-effects models with inverse-variance weighting of log-transformed HRs according to the DerSimonian-Laird method.

Results: Forty-two studies comprising 8,586 participants met the inclusion criteria. Pretreatment hydronephrosis was significantly associated with inferior overall survival (HR 1.65, 95% CI 1.43-1.91; I^2 29.8%). This adverse effect was consistent across treatment modalities, including definitive chemoradiotherapy (HR 1.74, 95% CI 1.30-2.32; I^2 34%), radiotherapy alone (HR 1.65, 95% CI 0.38-7.19; I^2 0%), and trimodality therapy (HR 1.64, 95% CI 1.25-2.14; I^2 39.6%), with no evidence of subgroup interaction ($p = 0.93$). Hydronephrosis was also associated with worse cancer-specific survival (HR 2.00, 95% CI 1.68-2.37; I^2 8.9%). Disease control endpoints were consistently inferior in patients with hydronephrosis, including disease-free survival (HR 1.83, 95% CI 1.12-3.01; I^2 48.7%), progression-free survival (HR 1.59, 95% CI 1.02-2.49; I^2 0%), and metastasis-free survival (HR 1.56, 95% CI 1.32-1.84; I^2 0%). The overall risk of bias across included studies was predominantly moderate.

Conclusion: Pretreatment hydronephrosis is a robust, treatment-independent adverse prognostic factor in radiotherapy-based bladder-preserving management of muscle-invasive bladder cancer, conferring consistently increased hazards for mortality and disease progression across all major oncologic endpoints. Its presence should be systematically integrated into baseline prognostic stratification, patient counseling, and risk-adapted surveillance strategies in bladder-preserving treatment paradigms.

KEY WORDS: *Muscle-invasive bladder cancer; Hydronephrosis; Bladder-preserving therapy; Radiotherapy; Meta-analysis.*

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INTRODUCTION

Definitive radiotherapy-based bladder preservation strategies, encompassing radiotherapy alone, concurrent chemoradiotherapy, and trimodality therapy, represent a recognized bladder-sparing treatment option for carefully selected patients with muscle-invasive bladder cancer in lieu of radical cystectomy (1, 2). In the phase III BC2001 trial with 10-year follow-up, adding concomitant 5-fluorouracil/mitomycin C to radiotherapy significantly improved locoregional control and invasive locoregional control, and reduced the 5-year cystectomy rate, supporting durable bladder-preservation benefits of radiotherapy-based treatment (3).

Nevertheless, outcomes after definitive bladder-preserving radiotherapy remain heterogeneous, and baseline prognostic stratification to optimise counselling, selection, and surveillance intensity is still imprecise (4).

Hydronephrosis – a radiologic marker of ureteric obstruction – shows a robust adverse prognostic association in a meta-analysis of cystectomy cohorts: prevalence 27.4%, with worse overall survival and cancer-specific survival, but its independent prognostic value in radiotherapy-based bladder preservation remains uncertain (5, 6).

Although recent TMT-focused meta-analysis reported hydronephrosis was associated with worse overall survival, whether this association holds consistently across the broader spectrum of radiotherapy-based bladder-preserving strategies remains unclear (1). We therefore conducted a systematic review and meta-analysis to quantify its prognostic impact on survival outcomes across the full spectrum of radiotherapy-based bladder-preserving strategies.

Methods

Study design and protocol registration

The study was conducted using a systematic review methodology combined with quantitative meta-analytic synthesis. Reporting adhered to PRISMA 2020 guidance, and the study question was prespecified using a PICO framework. The protocol was prospectively registered with PROSPERO (CRD420261305703).

Eligibility criteria

Eligible studies comprised observational cohorts and clinical trials of adults with MIBC treated with radiotherapy-based bladder preservation. A PICO framework was applied, in which the intervention component represented the exposure of interest, to guide study identification and eligibility assessment and to quantify its prognostic impact on survival outcomes among patients undergoing radiotherapy-based bladder-preserving therapy for *muscle-invasive bladder cancer* (MIBC) by pooling *hazard ratios* (HRs).

Review questions

- *Participants*
  The study population comprised adult patients aged 18 years or older with muscle-invasive bladder cancer who underwent radiotherapy-based bladder-preserving treatment approaches, including radiotherapy alone, concurrent chemoradiotherapy, and trimodality therapy frameworks, in which patients first underwent maximal TURBT, followed by radiotherapy administered either alone or in combination with concurrent chemotherapy. Studies including mixed stage populations were eligible if outcomes for the MIBC subgroup treated with radiotherapy-based bladder preservation could be extracted. Studies reporting only palliative radiotherapy without a separable definitive-intent cohort were excluded, along with intravesical-only bladder preservation studies, non-human studies, and non-original publications.
  The setting is in the hospital/tertiary urology centers; any country/era (January 2000 to December 2025).
- *Exposure*
  The exposure of interest was pretreatment hydronephrosis, assessed prior to radiotherapy initiation (e.g., imaging-based), categorized as present versus absent.
- *Comparator*
  The comparator group was patients with no pretreatment hydronephrosis.
- *Outcomes*
  Overall survival (OS) was the primary endpoint. Secondary outcomes included *cancer- or disease-specific survival* (CSS/DSS), *disease- or progression-free survival* (DFS/PFS), *local recurrence-free survival* (LRFS), *metastasis-free survival* (MFS), and bladder-preserved survival. Hazard ratios with 95% confidence intervals were extracted, prioritizing multivariable-adjusted estimates where available.

Systematic literature searching and screening

Three investigators (R.F.G.N., S.M.W., and F.F.P.) independently performed the literature search. The literature search was structured to capture studies addressing bladder cancer, hydronephrosis or urinary tract obstruction, radiotherapy-based bladder preservation strategies, and survival outcomes by integrating controlled vocabulary and keyword terms with Boolean operators. Searches were executed in PubMed, ScienceDirect, the Cochrane Library, Google Scholar, and Wiley Online Library, covering publications from January 2000 through December 2025. The authors jointly reviewed eligibility decisions and finalized the study framework and objectives prior to analysis.
The PICO framework guided study identification and eligibility assessment throughout the screening process. In addition, the reference lists of relevant articles were manually reviewed to identify any further eligible studies.

Study selection

Study selection procedures were aligned with PRISMA guidance for systematic reviews and meta-analyses.
Eligibility was determined using prespecified inclusion criteria, detailed below:

1. Full-text article.
2. Accessible.
3. English-written.
4. Reporting radiotherapy-based bladder preservation cohorts and providing extractable survival effect estimates for hydronephrosis vs no hydronephrosis (preferably HR with 95% CI).

Studies were excluded if they were review articles (including systematic reviews or meta-analyses), editorials, commentaries, guidelines, book chapters, conference abstracts without full text, methodological papers, pilot studies, or experimental research conducted in animals or laboratory settings. Retracted publications were also removed to preserve the integrity of the analysis.
All records identified through the search were compiled and duplicates were eliminated prior to screening. Titles and abstracts were assessed independently by the investigators against the predefined eligibility criteria. Articles considered potentially relevant underwent full-text evaluation, with each reviewer examining the complete manuscript to determine final inclusion. The level of agreements between authors was satisfying, with Cohen kappa value κ: 0.93, suggesting almost perfect agreements between all the raters involved (7). Any further discrepancies and disagreements arose between authors were resolved in group discussion.

Data extraction

The components of the studies extracted was as following:

- *Participants*: total number analysed, baseline characteristics (age, stage distribution if reported), prevalence of hydronephrosis, inclusion and exclusion criteria.
- *Methods*: Design of the study, the duration of the study

follow-up, study settings, and the date of study.
- *Interventions*: radiotherapy-based bladder preservation details.
- *Outcomes*: HRs with 95% CIs for OS (primary) and secondary survival outcomes, prioritizing multivariable-adjusted estimates.
- *Additional highlights*: covariates included in adjustment models, study limitations, and conflicts of interest.

Data were organized in Microsoft Excel and subsequently analysed in R.

Risk of Bias and study quality assessments

The evidence base consisted exclusively of observational cohorts. Risk of bias was assessed using the ROBINS-I tool. Given the prognostic focus of the review, pretreatment hydronephrosis was treated as the exposure of interest when applying the ROBINS-I domains, rather than as a therapeutic intervention.

The methodological quality of the included nonrandomized studies was evaluated using the *Newcastle-Ottawa Scale* (NOS). The assessment was divided into three components, the selection, comparability, and outcome of the study. The final judgement of the studies quality was converted to *Agency for Healthcare Research and Quality* (AHRQ) standards (good, fair, and poor). The scoring system spans from 0 to 9 stars, and studies achieving a rating of 5 or more were deemed methodologically sufficient for inclusion in the analysis (8).

Statistical design and evidence syntheses

The analysis focused on synthesizing time-to-event effect estimates comparing patients with pretreatment hydronephrosis versus those without. Each study contributed a study-level *hazard ratio* (HR) for the outcome of interest, preferentially derived from multivariable Cox regression models when available. Hazard ratios were logarithmically transformed, and corresponding standard errors were calculated from reported 95% confidence intervals. A DerSimonian-Laird random-effects model with inverse-variance weighting was applied to derive pooled estimates, accounting for expected variability across observational cohorts.

We assessed variability between studies using the I^2 statistic, considering values below roughly 30% as low, 30-60% as moderate, and above 60% as indicating more pronounced heterogeneity. For outcomes supported by at least ten studies, the possibility of small-study effects was explored by visually examining funnel plots and subsequently evaluated using Egger's regression test. Because all included data derived from radiotherapy-based bladder-preserving cohorts examined in a prognostic framework, analyses focused on within-study time-to-event comparisons between patients with and without pretreatment hydronephrosis, expressed as hazard ratios. Subgroup analyses were carried out where the available data allowed. Statistical analyses were performed using R.

Results

A comprehensive search across five electronic databases yielded 6,386 records, comprising PubMed (n = 150), ScienceDirect (n = 959), the Cochrane Library (n = 27), Google Scholar (n = 5,130), and Wiley Library (n = 120). After eliminating 180 duplicate records, the remaining articles were evaluated based on their titles and abstracts. A total of 6,146 citations were excluded during this initial screening because they were not relevant to the predefined research question. These primarily consisted of review articles, conference materials, guidelines, editorials, case reports, and studies outside the scope of the research question.

Sixty full-text records were obtained for in-depth evaluation. After full-text screening, 18 articles were excluded: three for designs not appropriate for prognostic assessment, three for non-eligible populations or clinical settings, and twelve because exposure information was either not reported or not comparable for synthesis.

In total, 42 studies fulfilled the prespecified inclusion criteria and were incorporated into the qualitative synthesis, as presented in Figure 1.

Every study incorporated into the present analysis employed an observational design framework, with no randomized trials identified, comprising a total of approximately 8,586 patients across 42 cohorts. Most studies were retrospective, with a smaller number of prospective cohorts and pooled multicenter analyses. Bladder-preserving treatment strategies varied, but trimodality therapy predominated, being evaluated in about 50% of cohorts, while definitive chemoradiotherapy accounted for roughly 43%. In contrast, radiotherapy alone and intra-arterial chemoradiotherapy were uncommon, together representing fewer than 10% of the included studies.

Study size varied widely, ranging from small single-institution series with fewer than 50 patients to large multicenter cohorts enrolling over 800 patients. Across studies, patients were predominantly older adults, with median or mean ages most commonly in the seventh to eighth decade, and men consistently represented the majority of participants, accounting for approximately 70-90% of each cohort. Geographically, the evidence base was internationally diverse, with roughly two-thirds of studies originating from non-Asian regions – mainly Europe and North America – and just over one-third conducted in East and South Asia, reflecting real-world bladder-preservation practice across varied healthcare settings.

Methodological quality was generally high, with Newcastle-Ottawa Scale (NOS) scores ranging from 6 to 9, with the majority of studies scoring ≥ 8.

Baseline disease characteristics varied substantially across cohorts. The proportion of patients with locally advanced tumors (T3-4) ranged from below 10% in more selected series to nearly 70% in radiotherapy-based cohorts. Nodal involvement was absent in many studies but reached approximately 10-18% in others, reflecting meaningful differences in case mix. Pretreatment hydronephrosis was consistently reported, with prevalence varying from less than 10% to approximately 30-35% of patients across cohorts. Collectively, these findings underscore pronounced heterogeneity in baseline tumor burden and risk profiles among populations treated with radiotherapy-based bladder preservation.

Follow-up duration varied widely across cohorts and was most commonly reported as median values, ranging

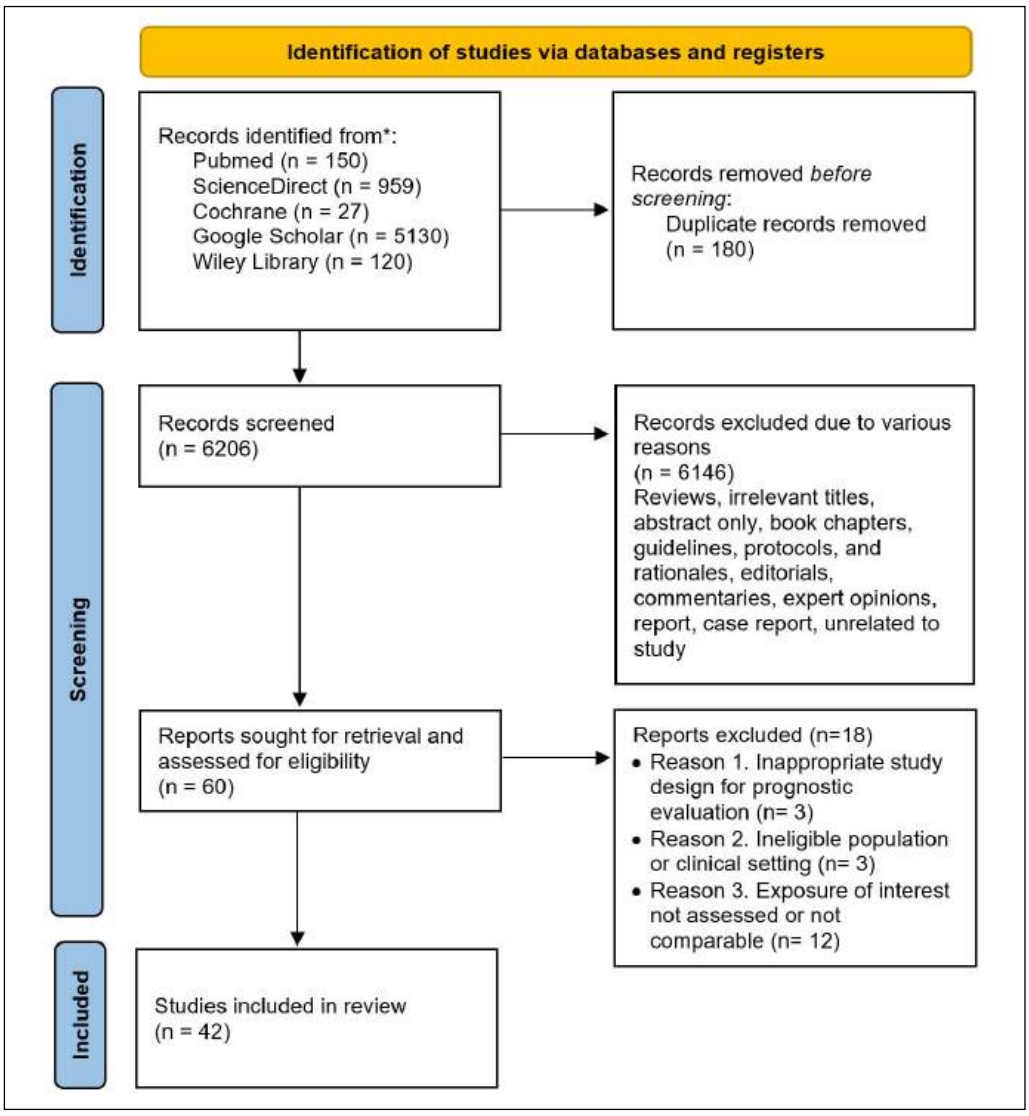


Figure 1.
PRISMA flow diagram of study selection.

from under one year to more than seven years, with several studies providing extended observation beyond five years. Overall survival was the most frequently reported outcome, with hazard ratios for pretreatment hydronephrosis generally indicating an adverse association and spanning a broad range across studies. Cancer-specific or disease-specific survival was reported less consistently but similarly showed elevated risk estimates in several cohorts. Secondary endpoints, including disease-free survival, progression-free survival, local control, metastasis-free survival, and bladder-preserved survival, were reported only in selected subsets of the included studies, with the magnitude of association varying across outcomes.

Overall, outcome reporting was heterogeneous, both in terms of follow-up duration and endpoints assessed, reflecting differences in study design, treatment strategy, and analytical focus across the included cohorts. Table 1 outlines the overall design and treatment characteristics of the included studies. The baseline demographic and tumor profiles of the cohorts are detailed in Table 2. Study-level overall survival estimates, presented alongside the corresponding follow-up durations, are shown in Table 3. Additional survival outcomes not detailed above are presented independently in Table 4.

The potential for bias across included studies was appraised using the ROBINS-I tool, as displayed in Figure 2. Most cohorts were classified as having low or moderate risk across the evaluated domains, reflecting the typical limitations of observational prognostic studies.

Bias due to confounding was generally low, as most studies adjusted for key clinical variables such as tumor stage, nodal status, and patient characteristics. Participant selection was appropriate in the majority of cohorts, with consecutive or well-defined bladder-preservation populations. Assessment of exposure definition and protocol adherence indicated low risk in most studies, given that hydronephrosis was documented before treatment and therapeutic strategies were well described.

Moderate risk most commonly arose from missing data or incomplete reporting of covariates and secondary outcomes. Outcome measurement for overall and cancer-specific survival was largely robust, resulting in low risk in this domain. Selective reporting was uncommon, although some studies did not provide fully extractable estimates for all outcomes of interest.

Table 1.
Characteristics of included studies.

Study (year)	Country	Study design	Treatment strategy	N	NOS score
Fokdal 2004 (27)	Denmark	Retrospective Cohort	RT	292	8
Hashine 2009 (28)	Japan	Retrospective cohort	IACRT	94	8
Zapatero 2010 (29)	Spain	Prospective Cohort	TMT	74	8
Tunio 2011 (30)	Pakistan	Prospective Cohort	TMT	116	8
Efstathiou 2012 (18)	USA	Pooled prospective Cohort	TMT	348	8
Wu 2013 (20)	Taiwan	Retrospective Cohort	TMT	61	7
Inoue 2014 (31)	Japan	Retrospective cohort	Definitive CRT	119	6
Raymond 2014 (19)	Multicenter	Pooled prospective RTOG	Definitive CRT	468	8
Shilkrut 2014 (32)	USA	Retrospective Cohort	Definitive CRT	39	8
Teo 2014 (33)	UK	Prospective Cohort	Definitive CRT	186	8
Hafeez 2015 (13)	United Kingdom	Retrospective cohort	TMT	94	7
Caffo 2016 (34)	Multicenter	Prospective Interventional Trials	Definitive CRT	190	8
Giacalone 2017 (35)	USA	Retrospective cohort	TMT	475	8
Krasnow 2017 (36)	USA	Retrospective Cohort	TMT	303	6
McPherson 2017 (12)	Canada	Retrospective Cohort	Definitive CRT	40	8
Christodoulou 2018 (37)	United Kingdom	Retrospective Cohort	Definitive CRT	167	8
Jiang 2018 (38)	Canada	Retrospective cohort	TMT	57	8
Matsushita 2018 (39)	Japan	Retrospective Cohort	TMT	90	6
Buchser 2019 (40)	Spain	Retrospective Cohort	TMT	90	8
Meng 2019 (41)	USA	Retrospective Cohort	TMT	40	8
Nguyen 2019 (26)	Canada	Retrospective Cohort	Definitive CRT	115	8
Gergelis 2020 (42)	USA	Retrospective Cohort	Definitive CRT	84	7
Gofrit 2020 (16)	Israel	Retrospective Cohort	TMT	105	8
Miyata 2020 (24)	Japan	Retrospective Cohort	TMT	38	8
Wu 2020 (43)	Taiwan	Retrospective Cohort	TMT	193	8
Aynaci 2021 (44)	Turkey	Retrospective Cohort	Definitive CRT	93	6
Fabiano 2021 (45)	France	Retrospective Cohort	TMT	313	8
Kool 2022 (46)	Canada	Retrospective Cohort	TMT	176	8
Alati 2022 (47)	France	Retrospective Cohort	TMT	85	9
Kotha 2022 (25)	USA	Retrospective Cohort	Definitive CRT	369	8
de Ruiter 2022 (21)	Netherlands	Retrospective Cohort	Definitive CRT	240	8
Kool 2023 (48)	Canada	Retrospective Cohort	TMT	864	8
Meunier 2023 (49)	France	Retrospective Cohort	Definitive CRT	194	9
Mignot 2023 (50)	France	Retrospective Cohort	TMT	122	8
Moore 2023 (51)	USA	Retrospective Cohort	Definitive CRT	40	8
Avolio 2024 (52)	Canada	Retrospective Cohort	TMT	757	9
Chang 2024 (14)	Taiwan	Retrospective Cohort	Definitive CRT	149	8
Cho 2024 (53)	South Korea	Post-hoc pooled (2 phase II)	Definitive CRT	76	8
Miyake 2024 (54)	Japan	Retrospective Cohort	Definitive CRT	37	8
Kotha 2025 (55)	USA	Retrospective Cohort	TMT	347	7
Kikuchi 2025 (11)	Japan	Retrospective Cohort	RT	304	8
MacIntyre 2025 (23)	Canada	Retrospective Cohort	Definitive CRT	542	8

CRT = chemoradiotherapy; TMT = trimodality therapy; OS = overall survival; CSS/DSS = cancer-specific survival / disease-specific survival; DFS = disease-free survival; PFS = progression-free survival; LRFS = local recurrence-free survival; MFS = metastasis-free survival.

Table 2.
Baseline demographic and tumor characteristics.

Study (year)	Age (median/mean)	Male (%)	Stage T3-4 (%)	Node+ (%)	Hydronephrosis (%)
Fokdal 2004 (27)	Median 72.3 (45- 83)	80.8	74	96	40
Hashine 2009 (28)	Median 67	83	36.2	0	19.1
Zapatero 2010 (29)	Median 63 (41-77)	91.8	46	4	8
Tunio 2011 (30)	Mean 61.95 ± 10.53 (40-85)	86.2	59.5	0	30.2
Efstathiou 2012 (18)	Median 66.3 (27.3-88.6)	73.9	46	0	16.7
Wu 2013 (20)	Median 72 (49-84)	78.7	68.9	18	19.7
Inoue 2014 (31)	NR	78.2	46	0	75.6
Raymond 2014 (19)	Median 66 (34-93)	82.5	39.4	0	8.5
Shilkrut 2014 (32)	Median 72 (IQR 67-80)	NR	NR	NR	26
Teo 2014 (33)	Median 79 (55-93)	74.7	32.4	3.3	27.5
Hafeez 2015 (13)	Median 65 (34-83)	87.2	25.5	0	9.6
Caffo 2016 (34)	Median 70 (42-87)	86.8	28.9	NR	10
Giacalone 2017 (35)	Median 67.3 (IQR 60.2-74.6)	75	34	NR	12
Krasnow 2017 (36)	NR	77.2	17.8	0	5.9
McPherson 2017 (12)	Mean 84.5 (IQR 83-86)	70	12.5	7.5	32.4
Christodoulou 2018 (37)	NR	77.2	27.5	NR	19.1
Jiang 2018 (38)	Median 72 (45-87)	77	24.6	18	25
Matsushita 2018 (39)	Median 66.5 (32-83)	85	35	NR	23.3
Buchser 2019 (40)	Median 63 (41-77)	87.8	44.4	8.9	8.9
Meng 2019 (41)	Median 66.4 (IQR 52.5-74.7)	NR	52.5	0	15
Nguyen 2019 (26)	Median 79 (47-95)	75.7	17.4	7	32.2
Gergelis 2020 (42)	Median 81 (70-94)	78.6	36.9	7.1	32.1
Gofrit 2020 (16)	Mean 75.4 ± 10.6; Median 78 (IQR 69-82)	71.7	NR	0	22.8
Miyata 2020 (24)	Median 80 (IQR 73-83)	76.3	44.7	0	23.7
Wu 2020 (43)	NR	NR	31.1	7.3	15.5
Aynaci 2021 (44)	Mean 73.86 ±9.1 (44-91)	90.3	20.4	10.1	17.4
Fabiano 2021 (45)	Mean 67.3 ± 9.3; Median 68.3 (IQR 62.1-73.8)	81.1	16.6	0	19.5
Kool 2022 (46)	Median 75 (IQR 66-82)	76.1	11.4	9.7	18.7
Alati 2022 (47)	Median 80.4 (IQR 77.7-83.4)	75.3	8.2	NR	19
Kotha 2022 (25)	Median 78	99.2	16	4.6	33.9
de Ruiter 2022 (21)	Median 74 (IQR 67-81)	78	34	2	17
Kool 2023 (48)	Median 77 (IQR 68-82)	74	21	9	25
Meunier 2023 (49)	Mean 77.3 ± 7.1; Median 70 (55-94)	74	15	11	32
Mignot 2023 (50)	Median 81 (75-93)	NR	13.9	6.6	22.1
Moore 2023 (51)	Median 82 (60-96)	62.5	30	0	10
Avolio 2024 (52)	Median 77 (IQR 68-82)	73	22	9	24
Chang 2024 (14)	NR	67.8	38.9	12	34.9
Cho 2024 (53)	Median 67 (40-85)	82.9	13.2	0	9.2
Miyake 2024 (54)	Mean 77 ± 8.6; Median 79 (58-94)	74	24.4	NR	27
Kotha 2025 (55)	Median 76 (53-93)	99.1	15.6	4.3	32.6
Kikuchi 2025 (11)	Median 78 (42-95)	73	69	0	24
MacIntyre 2025 (23)	NR	73.2	17.5	8.3	18.5

Stage (T3–4) and nodal status (Node+) are baseline percentages as reported in the original studies; nodal assessment may be clinical and/or pathological depending on study design.
NR = not reported; indicates that the data were not clearly defined in the original study, not separable or extractable using available information, or not available for the outcome of interest.

Table 3.
Overall survival outcomes and follow-up duration according to pretreatment hydronephrosis.

Study (year)	Treatment Strategy	OS HR (95% CI)	Follow-up (months)
Fokdal 2004 (27)	RT	1.51 (1.13-2.01)	Median 66 (18-121)
Hashine 2009 (28)	IACRT	NR	Median 72.9
Zapatero 2010 (29)	TMT	13.68 (3.14-59.51)	Mean 54 (9-156)
Tunio 2011 (30)	TMT	NR	Median 36 (14-43)
Efstathiou 2012 (18)	TMT	1.30 (0.89-1.90)	Median 92.4 (1.44–255.6)
Wu 2013 (20)	TMT	NR	Median 34.6
Inoue 2014 (31)	Definitive CRT	NR	Median 52 (5-180)
Raymond 2014 (19)	Definitive CRT	1.41 (0.92-2.16)	Median 51.6
Shilkrut 2014 (32)	Definitive CRT	NR	Median 19 (IQR 11-50)
Teo 2014 (33)	Definitive CRT	NR	Median 76 (20.3-104.6)
Hafeez 2015 (13)	TMT	4.90 (1.95-12.32)†	Median 39 (4-127)
Caffo 2016 (34)	Definitive CRT	NR	Median 44.5
Giacalone 2017 (35)	TMT	1.51 (1.06-2.15)	Median 54.6 (IQR 22.8-112.8)
Krasnow 2017 (36)	TMT	2.33 (1.34-4.04)	NR
McPherson 2017 (12)	Definitive CRT	2.82 (0.98-8.15)	NR
Christodoulou 2018 (37)	Definitive CRT	2.43 (1.32-4.47)†	Median 38
Jiang 2018 (38)	TMT	3.4 (1.2-9.7)†	Median 19.3 (4.8-96.1)
Matsushita 2018 (39)	TMT	4.54 (1.31-15.69)	Median 55
Buchser 2019 (40)	TMT	NR	Median 93 (9-285)
Meng 2019 (41)	TMT	1.68 (0.56-5.05)	NR
Nguyen 2019 (26)	Definitive CRT	3.09 (1.59-6.03)	Median 21
Gergelis 2020 (42)	Definitive CRT	1.3 (0.8-2.2)†	Median 68.4 (3.6-135.6)
Gofrit 2020 (16)	TMT	1.63 (0.89-2.98)	Median 29 (IQR 15-65)
Miyata 2020 (24)	TMT	1.86 (0.62-5.15)†	Median 28 (3-161)
Wu 2020 (43)	TMT	NR	Median 37 (1.4-162.3)
Aynaci 2021 (44)	Definitive CRT	3.6 (1.4-9.3)	Median 34.1(4-99.1)
Fabiano 2021 (45)	TMT	NR	Median 59 (IQR 26-103)
Kool 2022 (46)	TMT	NR	Median 46
Alati 2022 (47)	TMT	0.84 (0.25-2.83)	Median 63 (2.1-213.3)
Kotha 2022 (25)	Definitive CRT	1.45 (1.14-1.85)	Median 77
de Ruiter 2022 (21)	Definitive CRT	1.80 (1.00-3.25)	Median 27 (IQR 11-44)
Kool 2023 (48)	TMT	1.50 (1.17-1.91)	Median 34
Meunier 2023 (49)	Definitive CRT	1.15 (0.64-2.06)	Median 37.5 (1-213.5)
Mignot 2023 (50)	TMT	2.04 (1.04-4.03)	Median 51.1 (0.5-210.8)
Moore 2023 (51)	Definitive CRT	NR	Median 32
Avolio 2024 (52)	TMT	1.39 (1.06-1.83)	Median 27
Chang 2024 (14)	Definitive CRT	1.94 (1.20-3.12)	Median 27.5
Cho 2024 (53)	Definitive CRT	NR	Median 64
Miyake 2024 (54)	Definitive CRT	1.31 (0.15-11.2)†	Median 26 (3-86)
Kotha 2025 (55)	TMT	NR	Median 77
Kikuchi 2025 (11)	RT	1.92 (1.31-2.81)	Median 21
MacIntyre 2025 (23)	Definitive CRT	NR	Median 30

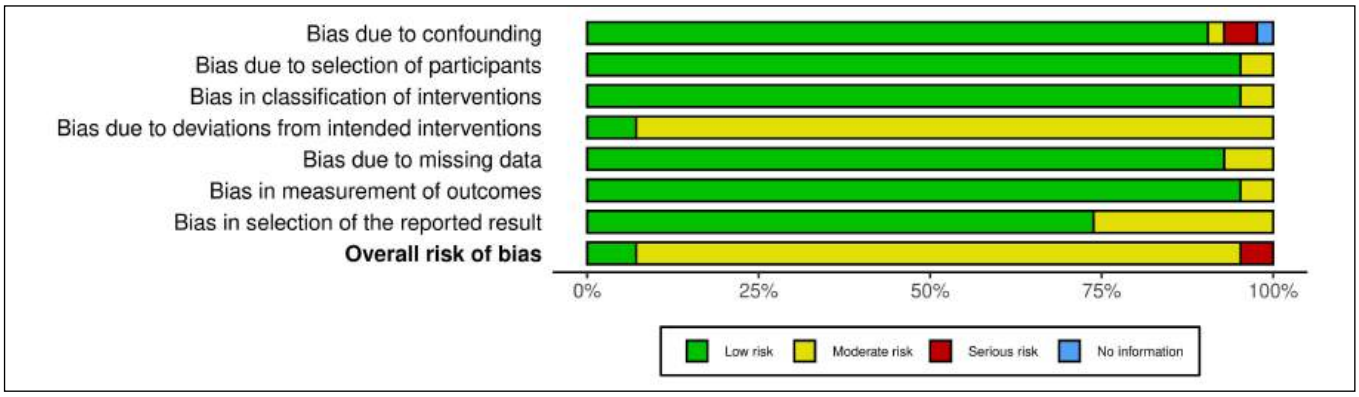
FU reported as median or mean (range or IQR), as provided in the original studies.
† Univariable hazard ratio.
CRT = chemoradiotherapy; TMT = trimodality therapy; OS = overall survival; CSS/DSS = cancer-specific survival / disease-specific survival; DFS = disease-free survival; PFS = progression-free survival; LRFS = local recurrence-free survival; MFS = metastasis-free survival.
NR = not reported; indicates that the data were not clearly defined in the original study, not separable or extractable using available information, or not available for the outcome of interest.

Table 4.
Survival outcomes according to pretreatment hydronephrosis.

Study (year)	CSS/DSS HR (95% CI)	DFS HR (95% CI)	PFS HR (95% CI)	Local control/ LRFS HR (95% CI)	MFS HR (95% CI) (95% CI)	Bladder-preserved survival HR (95% CI)
Fokdal 2004 (27)	NR	NR	NR	1.61 (1.15-2.25)†	NR	NR
Hashine 2009 (28)	NR	NR	NR	NR	NR	NR
Zapatero 2010 (29)	NR	NR	NR	NR	NR	NR
Tunio 2011 (30)	NR	NR	NR	NR	NR	NR
Efstathiou 2012 (18)	1.31 (0.81-2.14)	NR	NR	NR	NR	NR
Wu 2013 (20)	NR	NR	NR	NR	NR	NR
Inoue 2014 (31)	3.0 (1.24-7.27)	NR	NR	NR	NR	NR
Raymond 2014 (19)	1.70 (0.99-2.91)	NR	NR	NR	NR	NR
Shilkrut 2014 (32)	1.9 (0.43-8.4)	NR	NR	3.5 (0.52-23.54)†	3.7 (0.72-18.7)	NR
Teo 2014 (33)	1.21 (0.66-2.22)	NR	NR	NR	NR	NR
Hafeez 2015 (13)	5.11 (1.65-15.81)†	NR	2.54 (1.13-5.70)†	NR	NR	NR
Caffo 2016 (34)	NR	NR	NR	NR	NR	NR
Giacalone 2017 (35)	NR	NR	NR	NR	NR	1.89 (1.33-2.63)
Krasnow 2017 (36)	2.51 (1.20-5.27)	NR	NR	NR	NR	NR
McPherson 2017 (12)	NR	NR	NR	3.95 (1.29-12.1)	NR	NR
Christodoulou 2018 (37)	2.01 (0.85-4.74)†	2.37 (1.27-4.42)†	1.86 (0.80-4.32)†	NR	NR	NR
Jiang 2018 (38)	NR	NR	NR	NR	NR	2.3 (0.8-6.5)
Matsushita 2018 (39)	NR	NR	NR	NR	NR	NR
Buchser 2019 (40)	NR	NR	NR	NR	NR	NR
Meng 2019 (41)	NR	NR	NR	NR	NR	NR
Nguyen 2019 (26)	NR	2.03 (1.13-3.63)	NR	NR	NR	NR
Gergelis 2020 (42)	1.1 (0.6-2.1)†	NR	NR	0.6 (0.2-1.5)†	1.4 (0.6-3.0)†	NR
Gofrit 2020 (16)	1.86 (0.95-3.63)	1.39 (0.72-2.71)	NR	NR	NR	NR
Miyata 2020 (24)	1.05 (0.23-3.65)†	NR	NR	NR	NR	NR
Wu 2020 (43)	NR	NR	1.68 (0.92-3.08)	NR	NR	3.17 (1.56-6.44)
Aynaci 2021 (44)	5.6 (1.8-17.3)	2.7 (1.1-6.5)	NR	NR	NR	NR
Fabiano 2021 (45)	NR	NR	NR	NR	NR	1.9 (1.1-3.2)
Kool 2022 (46)	2.66 (1.43-4.95)	NR	NR	NR	NR	NR
Alati 2022 (47)	0.96 (0.29-3.18)	NR	NR	0.96 (0.21-4.42)	1.30 (0.36-4.70)	0.84 (0.31-2.26)
Kotha 2022 (25)	NR	NR	NR	NR	NR	NR
de Ruiter 2022 (21)	1.70 (0.80-3.60)	NR	NR	NR	NR	NR
Kool 2023 (48)	2.36 (1.79-3.10)	NR	NR	NR	NR	NR
Meunier 2023 (49)	NR	NR	1.27 (0.76-2.15)	NR	NR	NR
Mignot 2023 (50)	NR	3.61 (1.62-8.05)	NR	3.61 (1.62-8.05)	NR	NR
Moore 2023 (51)	NR	3.27 (0.91-11.7)†	NR	NR	NR	NR
Avolio 2024 (52)	1.95 (1.40-2.73)	1.36 (1.08-1.72)	NR	NR	1.52 (1.18-1.95)	NR
Chang 2024 (14)	NR	NR	1.79 (1.18-2.71)	1.99 (1.22-3.23)	NR	NR
Cho 2024 (53)	NR	NR	NR	NR	NR	NR
Miyake 2024 (54)	3.45 (0.31-38.2)†	NR	NR	NR	1.09 (0.13-9.33)	NR
Kotha 2025 (55)	NR	NR	NR	1.01 (0.66-1.54)	1.62 (1.11-2.36)	NR
Kikuchi 2025 (11)	NR	NR	NR	NR	NR	NR
MacIntyre 2025 (23)	2.23 (1.43-3.48)	NR	NR	NR	NR	NR

† Univariable hazard ratio.
CRT = chemoradiotherapy; TMT = trimodality therapy; OS = overall survival; CSS/DSS = cancer-specific survival / disease-specific survival; DFS = disease-free survival; PFS = progression-free survival; LRFS = local recurrence-free survival; MFS = metastasis-free survival.
NR = not reported; indicates that the data were not clearly defined in the original study, not separable or extractable using available information, or not available for the outcome of interest.

Figure 2.
Risk of bias assessment of included studies using the ROBINS-I tool.



Overall, most studies were classified as having moderate risk of bias, reflecting limitations inherent to retrospective prognostic analyses rather than major methodological flaws. A smaller proportion achieved an overall low risk of bias, while only a few studies were judged to be at serious risk. Collectively, the evidence base provides a reasonable methodological foundation for assessing the prognostic impact of hydronephrosis in bladder-preserving treatment settings.Overall survival was available in 21 cohorts. Patients presenting with hydronephrosis before treatment tended to experience inferior survival. The random-effects pooled analysis demonstrated a significantly increased risk of mortality in this group (hazard ratio 1.65, 95% CI 1.43-1.91; Figure 3).

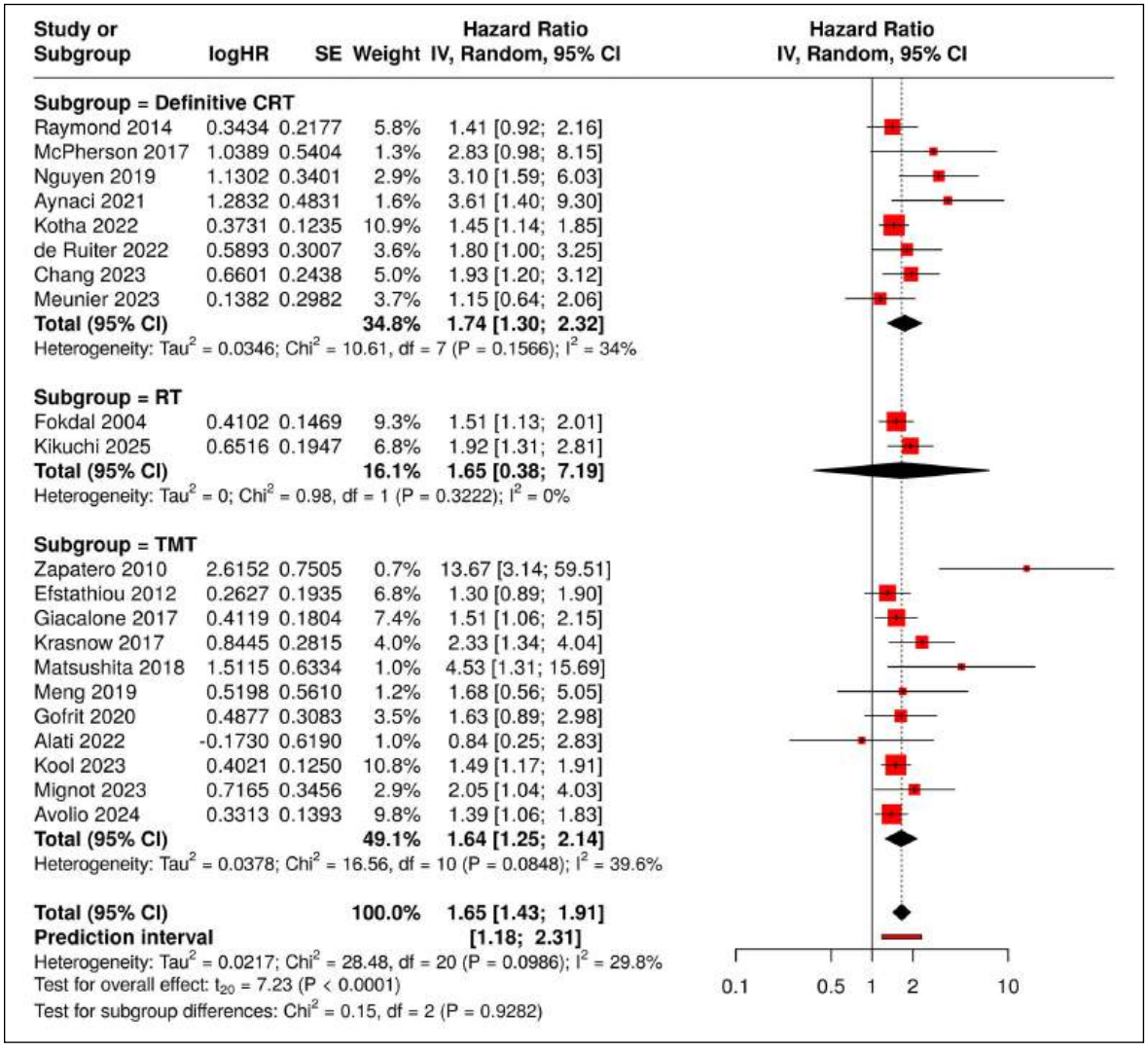
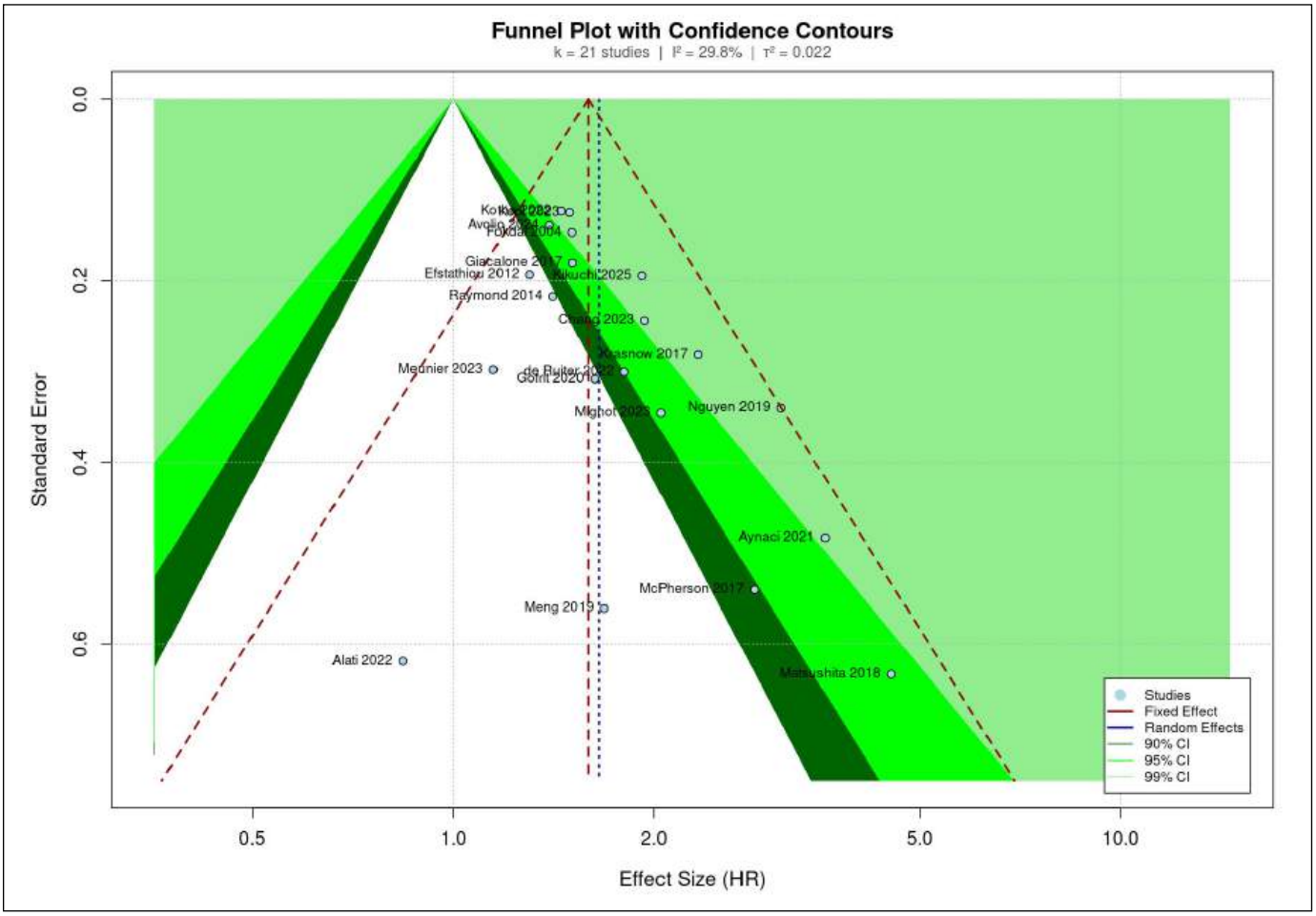


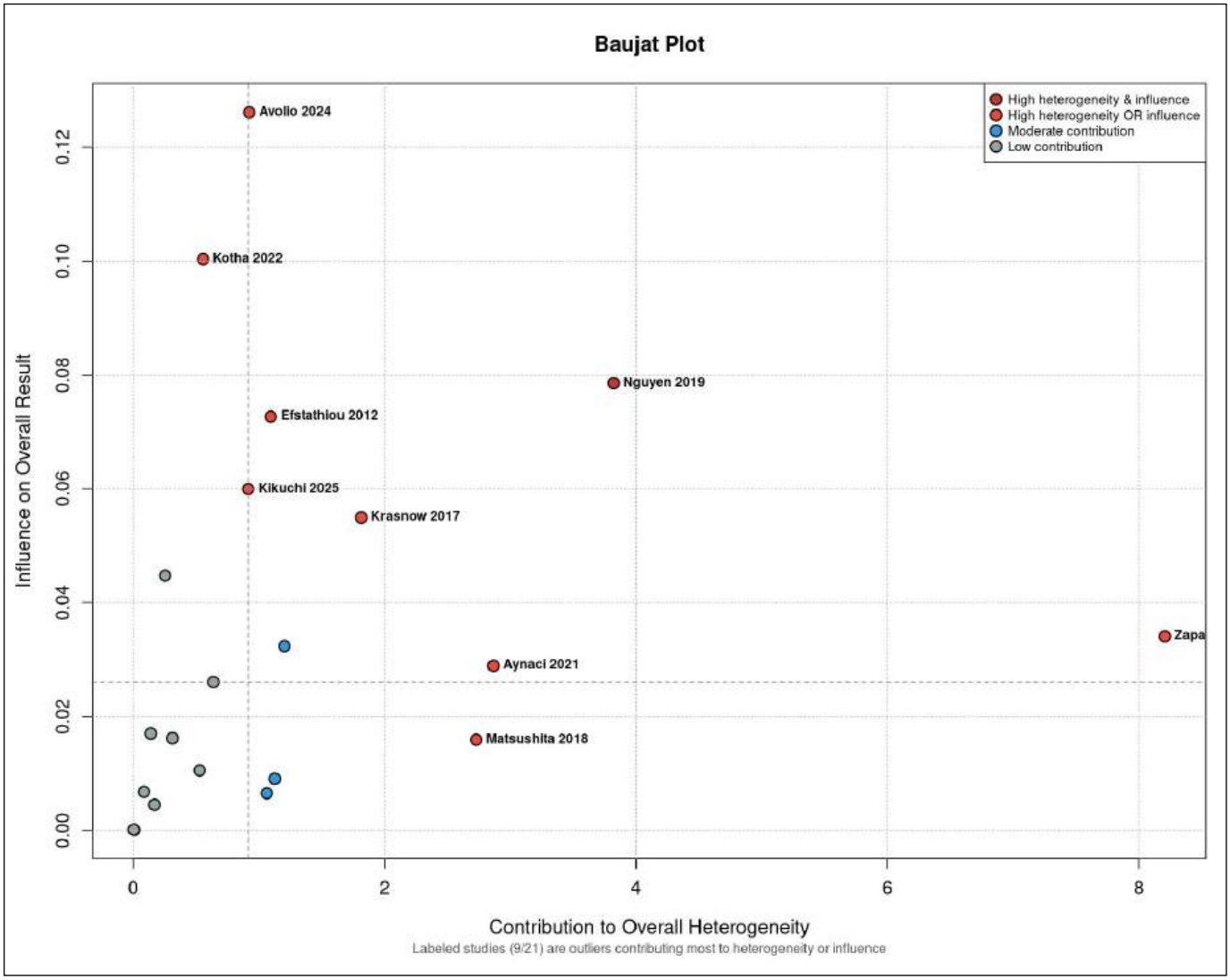
Figure 3.
Forest plot of the association between pretreatment hydronephrosis and overall survival (OS).

Figure 4.
Funnel plot assessing publication bias for OS.



Although some variability was observed between studies, heterogeneity remained moderate ($I^2 \approx 30\%$, $p = 0.09$).
When studies were examined according to treatment strategy – including definitive chemoradiotherapy, radiotherapy alone, and trimodality therapy – the direction and magnitude of the association were broadly similar. No statistically significant differences were detected between treatment subgroups ($p > 0.90$), indicating that the adverse prognostic impact of hydronephrosis was consistent across bladder-preserving approaches.
Sequential leave-one-out sensitivity analyses showed that removing any single study did not meaningfully affect the pooled hazard ratio. Across all iterations, the association remained statistically significant, with only trivial changes in effect size and persistently negligible between-study heterogeneity ($I^2 \approx 0\%$, $\tau^2 = 0$), supporting the overall stability of the results.
In line with this, the Baujat plot indicated that most studies made only minor contributions to both overall heterogeneity and influence on the pooled estimate. Although a small number of studies contributed relatively more on one or both dimensions, excluding these studies did not materially alter the magnitude, direction, or statistical significance of the pooled effect in leave-one-out analyses. This suggests that the overall findings were not driven by any single influential study.
Visual inspection of the contour-enhanced funnel plot revealed some asymmetry among smaller and less precise studies. This pattern was corroborated by several formal tests for small-study effects, including Egger's regression test ($t = 3.44$, $df = 19$, $p = 0.003$), the Thompson-Sharp test ($t = 3.31$, $df = 19$, $p = 0.004$), and Begg's rank correlation test ($z = 2.54$, $p = 0.011$), indicating possible publication bias. Trim-and-fill analysis suggested that up to five studies might be missing; after adjustment, the pooled random-effects estimate was attenuated from 1.65 to 1.55, consistent with a moderate degree of bias. Importantly, the association remained stable, and fail-safe N analyses further supported the robustness of the findings, with Rosenthal's fail-safe N indicating that 208 unpublished null studies would be required to render the results non-significant. Taken together, while small-study effects and publication bias cannot be entirely ruled out, the main conclusions of the meta-analysis appear robust.
Cancer-specific survival outcomes were synthesized under a random-effects model. The presence of hydronephrosis before treatment was linked to a substantially elevated risk of cancer-related death, with a summary hazard ratio of

Figure 5.
Baujat plot assessing study influence on heterogeneity and pooled effect.



2.00 (95% CI 1.68-2.37), as illustrated in Figure 6. Between-study heterogeneity was low ($I^2 \approx 8.9\%$, $p = 0.36$), indicating a high level of consistency across studies.

In subgroup analyses, hydronephrosis remained an adverse prognostic factor among patients treated with definitive chemoradiotherapy (HR 1.97, 95% CI 1.36-2.86) and trimodality therapy (HR 2.02, 95% CI 1.58-2.57). No statistically significant differences were observed between treatment subgroups ($p = 0.897$). Overall, these findings indicate a robust and consistent association between pretreatment hydronephrosis and poorer cancer-specific outcomes across bladder-preserving treatment strategies.

Five studies reported disease-free survival. Using a random-effects meta-analysis, pretreatment hydronephrosis was associated with significantly worse DFS, with a pooled hazard ratio of 1.83 (95% CI 1.12-3.01), as depicted in Figure 7.

Between-study variability was in the moderate range ($I^2 \approx 49\%$, $p = 0.099$), indicating some variability in effect size, although the overall association consistently favored worse outcomes in patients with hydronephrosis.

Three studies provided progression-free survival data. In the random-effects pooled analysis, baseline hydronephrosis was significantly associated with poorer PFS, with a combined hazard ratio of 1.59 (95% CI 1.02-2.49), as presented in Figure 8.

There was no detectable heterogeneity ($I^2 = 0\%$, $p = 0.60$), with similar effect sizes reported across studies.

Local control-related endpoints, including local recurrence-free survival, were evaluable in four studies. Using a random-effects model, the pooled analysis suggested a tendency toward higher local failure in patients with pretreatment hydronephrosis, with an overall hazard ratio of 1.90 (95% CI 0.87-4.18), as displayed in Figure 9.

Substantial heterogeneity was observed across studies ($I^2 \approx 67\%$, $p = 0.016$), suggesting considerable variability in effect estimates, and the overall association did not reach statistical significance.

Metastasis-free survival outcomes were available from five

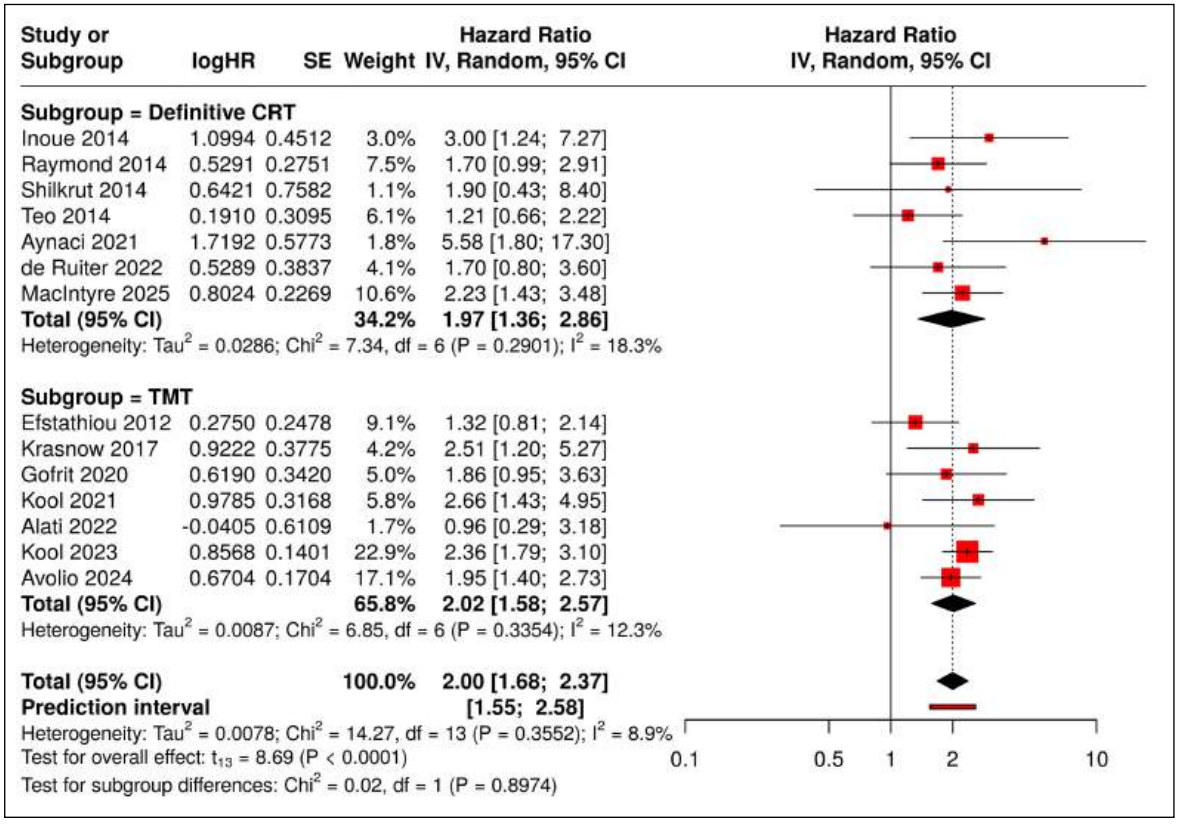


Figure 6.
Forest plot of the association between pretreatment hydronephrosis and cancer-specific or disease-specific survival (CSS/DSS).

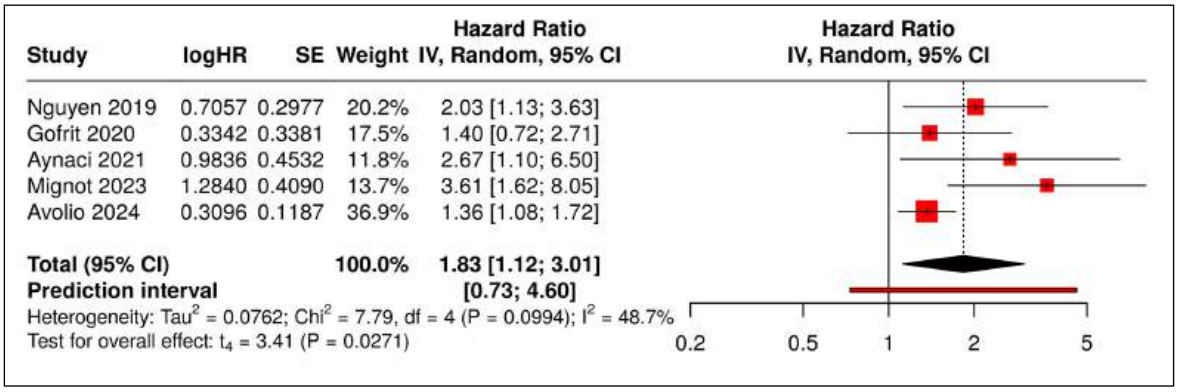


Figure 7.
Forest plot of the association between pretreatment hydronephrosis and disease-free survival (DFS).

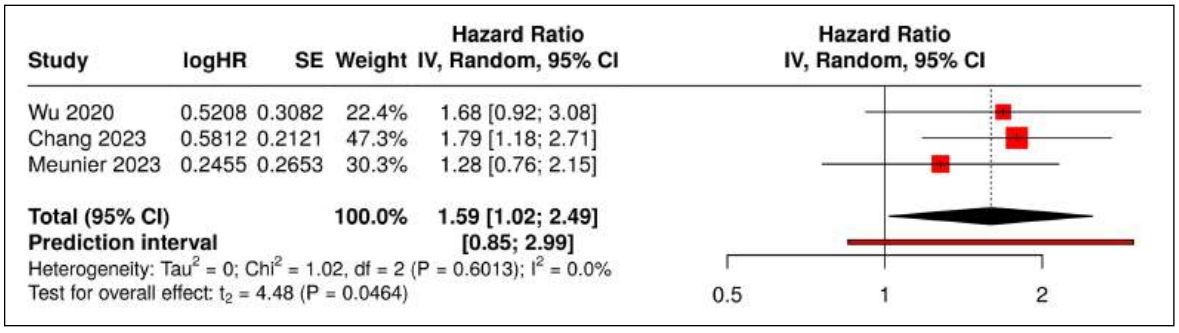


Figure 8.
Forest plot of the association between pretreatment hydronephrosis and progression-free survival (PFS).

studies. When synthesized using a random-effects model, pretreatment hydronephrosis was significantly associated with an elevated risk of metastatic events, with a pooled hazard ratio of 1.56 (95% CI 1.32-1.84), as depicted in Figure 10.

Heterogeneity was not detected ($I^2 = 0\%$, $p = 0.86$), and effect estimates were comparable across studies.

Five cohorts reported bladder-preserved survival. In the random-effects meta-analysis, baseline hydronephrosis was significantly associated with poorer bladder preserva-

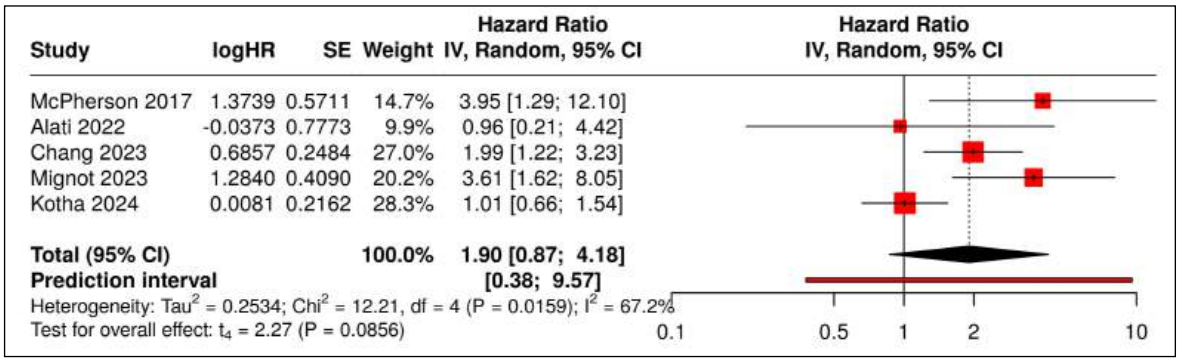


Figure 9.
Forest plot of the association between pretreatment hydronephrosis and local control or local recurrence-free survival (LRFS).

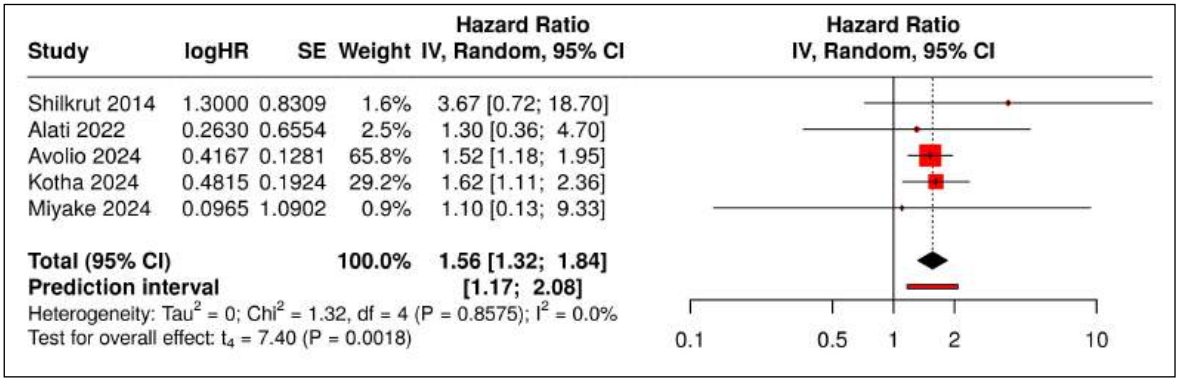


Figure 10.
Forest plot of the association between pretreatment hydronephrosis and metastasis-free survival (MFS).

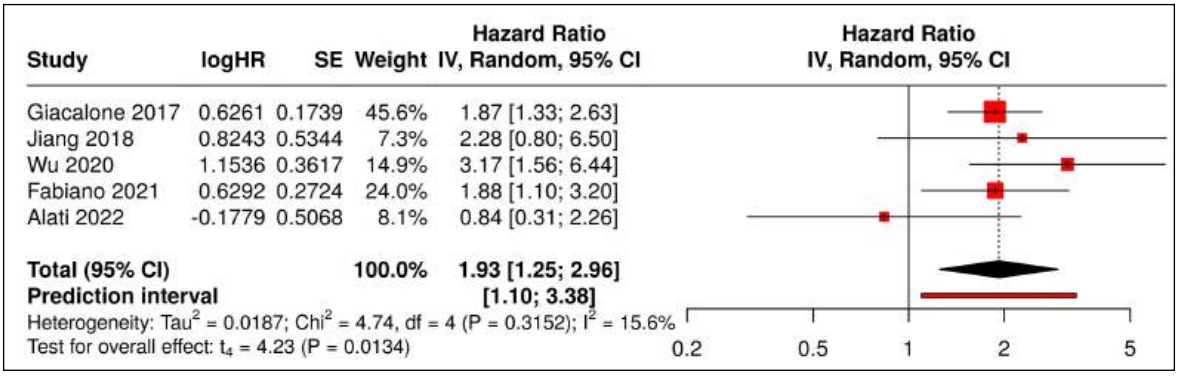


Figure 11.
Forest plot of the association between pretreatment hydronephrosis and bladder-preserved survival.

tion, with a pooled hazard ratio of 1.93 (95% CI 1.25-2.96), as illustrated in Figure 11.

Low to moderate heterogeneity was observed across studies ($I^2 \approx 16\%$, $p = 0.32$), indicating a largely consistent association among the included cohorts.

The pooled analysis demonstrated a consistent association with overall survival, with comparable estimates obtained under both random- and fixed-effects assumptions and no indication of substantial inconsistency across studies. Heterogeneity remained modest and did not substantially alter the pooled effect. Additional analyses, including subgroup comparisons, meta-regression, and evaluation of small-study effects, are summarized in Table 5.

Across predefined subgroup analyses, the direction and magnitude of the association remained largely consistent irrespective of age category, treatment modality, geographic region, disease extent, nodal status, or duration of follow-up. Formal tests for subgroup differences did not reach statistical significance, indicating no evidence that the effect differed meaningfully between subgroups.

Findings from univariable meta-regression were concordant with the subgroup analyses, as none of the examined study-level characteristics showed a significant association with variation in effect estimates. Similarly, multivariable meta-regression did not identify any independent modifiers of the treatment effect, suggesting that these covariates did not contribute to the observed variation between studies.

Evaluation of publication bias suggested the presence of small-study effects based on asymmetry detected by regression- and rank-based methods. While this raises the possibility of publication bias, the consistency of results across multiple analytical approaches supports the overall robustness of the findings.

The consistent association observed across treatment modalities, disease extent, geographic regions, and follow-up durations, together with the absence of meaningful effect modification, suggests that pretreatment

Table 5.
Overall meta-analysis, subgroup analyses, and meta-regression exploring sources of heterogeneity in overall survival.

Covariates	Subgroups	Number of studies	HR (95% CI)		Heterogeneity		Subgroup analysis		Univariable meta-regression			Multivariable meta-regression			Overall publication bias analysis	
			Random-effects sized	Fixed- effects sized	I^2	p-value	Qw	p-value	Coefficient estimate	SE	p-value	Coefficient estimate	SE	p-value	Egger's regression test	Begg and Mazumdar's rank correlation test
Overall		21	1.65 (1.43-1.91)	1.59 (1.45-1.75)	29.8	0.09									0.003	0.011
Age (years)	≥ 74	11	1.61 (1.43-1.81)	1.61 (1.43-1.81)	0	0.45	0.08	0.78	0.014	0.148	0.926	-0.101	0.282	0.730		
	< 74	10	1.68 (1.32-2.15)	1.57 (1.34-1.83)	48.7	0.03										
Treatment	TMT	11	1.64 (1.25-2.14)	1.55 (1.35-1.77)	39.6	0.08			-0.063	0.169	0.715	0.166	0.282	0.572		
	Definitive CRT	8	1.74 (1.30-2.32)	1.63 (1.39-1.92)	34	0.16	0.15	0.92								
	RT	2	1.65 (0.38-7.19)	1.65 (1.31-2.07)	0	0.32			-0.035	0.233	0.882	-0.160	0.341	0.651		
Region	Asia	5	2.03 (1.44-2.85)	2.03 (1.57-2.61)	0	0.45	3.16	0.07	-0.272	0.171	0.127	-0.576	0.412	0.199		
	Non-Asia	16	1.57 (1.34-1.84)	1.53 (1.38-1.70)	29.8	0.09										
Major advanced disease	High T3-T4	3	1.65 (1.17-2.33)	1.65 (1.31-2.06)	0	0.61	0.03	0.86	-0.003	0.204	0.990	-	-	-		
	Low T3-T4	17	1.68 (1.38-2.05)	1.58 (1.42-1.76)	41.6	0.04										
Any node positive present	N+ present	12	1.63 (1.29-2.05)	1.63 (1.34-1.98)	0	0.53	0.13	0.72	0.024	0.165	0.889	0.189	0.299	0.545		
	N0 only	6	1.71 (1.34-2.18)	1.58 (1.41-1.78)	46.2	0.04										
Follow-up (month)	≥ 38	9	1.70 (1.21-2.39)	1.58 (1.37-1.82)	48.2	0.05	0.07	0.79	0.011	0.157	0.944	0.231	0.280	0.435		
	< 38	10	1.62 (1.34-1.96)	1.59 (1.39-1.80)	24.4	0.22										

hydronephrosis reflects adverse baseline disease biology – most plausibly related to extensive local tumor involvement and ureteric obstruction – rather than a treatment-specific factor tied to any individual bladder-preserving radiotherapy strategy.

Discussion

This meta-analysis, incorporating data from 42 eligible studies, provides compelling and consistent evidence that the presence of hydronephrosis before treatment is strongly associated with inferior oncologic outcomes in patients with muscle-invasive bladder cancer managed with radiotherapy-based bladder preservation approaches. In our analysis, pretreatment hydronephrosis was significantly associated with worse overall survival, cancer-specific survival, disease-free survival, progression-free survival, metastasis-free survival, and bladder-preserved survival. This adverse effect remains consistent across definitive concurrent chemoradiotherapy, radiotherapy alone, and trimodality therapy.

These findings should be interpreted in light of emerging evidence suggesting that survival outcomes following bladder-preserving therapy may approach those of radical cystectomy in carefully selected patients, underscoring the importance of refined baseline prognostic stratification (9). This consistent observation across numerous cohorts underscores hydronephrosis's clinical value as a marker of aggressive disease biology in urothelial carcinoma (5, 6, 10). It often correlates with advanced tumor stage and lymphatic metastasis likely reflects extensive local tumor burden and ureteric obstruction preceding intervention (5, 6). For example, *Kikuchi et al.* identified hydronephrosis as the sole independent prognostic factor for worse OS in their cohort, with patients having hydronephrosis showing significantly shorter median survival (11) *McPherson et al.* similarly linked hydronephrosis to poorer OS and local recurrence-free survival in octogenarians (12). *Hafeez et al.* also associated it with worse PFS, OS, and disease-specific survival, suggesting it as a proxy for advanced local disease (13). Additionally, *Chang et al.* identified hydronephrosis as a significant parameter for both PFS and OS in multivariate analyses (14).

Compromised renal function from obstruction can also limit optimal systemic chemotherapy, thereby reducing treatment efficacy and survival (5). The mechanical effects of hydronephrosis, such as increased renal pelvic pressure and ureteral wall thinning, may facilitate local tumor invasion and metastatic spread (10, 15). *Gofrit et al.* reinforce this by suggesting that hydronephrosis acts as a surrogate for tumor volume, which directly influences the response to radiotherapy (16). Therefore, early identification and potentially aggressive management are crucial (15).

Despite the strong aggregate evidence, the precise prognostic significance of preoperative hydronephrosis can be debated due to methodological heterogeneity among studies. Some investigations have not found a statistically significant association with survival in multivariate analyses (5, 17). *Mak et al.* and *Efstathiou et al.*, for instance, found that while hydronephrosis showed an association in univariable analysis, it lost significance in multivariable models for OS or DFS (18, 19). *Wu et al.* similarly reported no significant prognostic role for tumor progression or survival in their specific cohort, potentially due to small sample size. *De Ruiter et al.* likewise observed that hydronephrosis lost its statistical significance in multivariable analyses for OS and DFS, despite an apparent trend for worse outcomes (20, 21).

This variability often stems from differences in sample size, population characteristics, treatment protocols, and inconsistent hydronephrosis grading and reporting among the 42 included studies (5, 6). For instance, *Hafeez et al.* highlighted the inherent difficulties in retrospectively verifying the completeness of transurethral resection of bladder tumor and the presence of confounding factors, such as the use of carboplatin instead of

cisplatin due to compromised renal function, when assessing treatment outcomes (13). *Zhao et al.* suggested symptomatic hydronephrosis might be a more reliable predictor of invasiveness than asymptomatic cases, implying a need for more timely intervention (22).
Kikuchi et al. also noted potential selection bias, as radiotherapy was often reserved for patients unsuitable for surgery or chemotherapy, and reported variations in radiotherapy protocols and prescribed doses (11).These inconsistencies highlight the need for standardized imaging protocols and classifications for more comparable prognostic evaluations (6, 10).
Given these findings, pretreatment hydronephrosis should be routinely integrated into initial patient evaluation and risk stratification. Clinicians must clearly communicate its prognostic impact to patients, aiding informed decision-making. Patients with hydronephrosis may require more intensive and personalized surveillance post-bladder-preserving therapy. Furthermore, multidisciplinary teams should discuss more aggressive multimodal therapy strategies, though prospective studies are needed to validate these approaches.
The primary strength of this meta-analysis is its comprehensive synthesis of 42 studies, providing robust evidence on hydronephrosis's prognostic impact in MIBC treated with bladder preservation. Our systematic search across five databases and use of random-effects models enhance the validity and generalizability of our aggregated findings, with sensitivity and fail-safe N analyses supporting robustness against publication bias.
However, limitations reflect those inherent in the included studies. Their observational and retrospective nature means we demonstrate association, not causality. Most cohorts were at moderate risk of bias, typical for retrospective prognostic analyses. For example, *MacIntyre et al.* noted variable treatment regimens and short follow-up periods in their multicenter study (23) *Miyata et al.* also highlighted their study's retrospective design, missing information, potential selection bias, and short follow-up period as limitations (24) *Kotha et al.* acknowledged the inherent limitations of their retrospective design, including variable documentation across different hospitals, and the inability to report treatment interruptions or detailed toxicity data, which ideally should be investigated prospectively (25). *Nguyen et al.* pointed out their study's retrospective design, heterogeneous population, short median follow-up time restricting long-term survival analysis, and being a single-center report as limitations (26).
Moderate to substantial heterogeneity in survival outcomes and local control was observed, suggesting underlying differences in patient populations or treatment delivery. Despite detection of potential publication bias, trim-and-fill analysis suggested our main findings remained stable. Variable reporting of hydronephrosis (present/absent) without standardized grading or laterality further contributed to heterogeneity.
Future research should prioritize standardizing hydronephrosis definitions and grading. Well-designed prospective studies, including randomized controlled trials where feasible, are crucial to confirm associations, establish causality, and mitigate biases. Investigating underlying molecular mechanisms linking hydronephrosis to aggressive tumor biology could identify novel therapeutic targets. Studies exploring interventions to alleviate urinary obstruction before or during therapy could determine if negative prognostic impacts can be mitigated. Finally, integrating hydronephrosis with established clinical and molecular biomarkers, as well as conducting comparative studies to inform treatment selection in patients with hydronephrosis, may refine risk-adapted decision-making without undermining bladder-preservation strategies.

Conclusions

The presence of hydronephrosis prior to treatment serves as a strong negative prognostic indicator among patients with muscle-invasive bladder cancer undergoing radiotherapy-based bladder preservation approaches. Its association with inferior survival and disease control is consistent across treatment modalities, supporting the interpretation that hydronephrosis reflects unfavorable baseline disease biology rather than modality-specific effects. Incorporation of hydronephrosis into baseline risk stratification may enhance prognostic accuracy and inform individualized surveillance and management within bladder-preservation pathways.

Declarations

Ethical approval and consent for participate: *Not applicable. This study is a systematic review and meta-analysis based exclusively on previously published studies and does not involve direct interaction with human participants, human data, or human tissue.*

Consent for publication: *Not applicable. The manuscript does not contain any individual person's data in any form.*

Availability of data and material: *The data supporting the findings of this study are contained within the article and its supplementary materials. Further information on the extracted datasets is available from the corresponding author upon request.*

Competing interests: *The authors declare that they have no competing interests.*

Funding: *This research received no external funding.*

Authors' contributions: *RFN conceived and designed the study. RFN and SMW performed the literature search and study selection. RFN and FFP extracted the data, assessed risk of bias, and interpreted the findings. RFN conducted the statistical analyses. RFN drafted the manuscript. SMW and FFP critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.*

Acknowledgments: *Not applicable.*

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