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REVIEW ARTICLE

Oral regimen for high dose methotrexate urine alkalinization: a systematic review and meta-analysis

Romina Kaveh-Ahangaran[1] · Mohammad Abdollahi[2,3] · Mohammad Vaezi[1] · Amir Kasaeian[1,4,5] · Zhalleh Bahlouli[6] · Ghasem Janbabaei[7] · Amirmahdi Mojtahedzadeh[8] · Mojtaba Mojtahedzadeh[6] · Shirin Djalalinia[9,10] · Bita Shahrami[1,6]

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Abstract

Objective Urine alkalinization prevents nephrotoxicity in patients receiving high-dose methotrexate (HDMTX). While the standard approach involves IV sodium bicarbonate, alternative oral bicarbonate regimens are crucial in drug shortages and outpatient settings. This study aims to review the efficacy and safety of such regimens.

Methods PubMed, WOS, and Scopus were systematically searched using the PRISMA protocol for relevant studies involving human subjects, including randomized clinical trials, retrospective, prospective, cohort, case reports, and case series studies. There were no restrictions on language, time, or age group. Qualified and eligible papers were used to extract data on efficacy and safety indicators, and the final relevant records were assessed for quality using the Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I) assessment tool.

Results 12 studies with 1212 participants were included in the systematic review, with pooled data from 8 studies used for meta-analysis. No significant differences in mean differences (MDs) or odds ratio (OR) were found after the oral bicarbonate regimen, except for when urine pH fell to < 7 (MD: 0.91, 95% CI: 0.32, 1.5, $P < 0.05$) and the incidence of diarrhea (OR: 2.92, 95% CI: 1.69, 5.05, $P < 0.05$).

Conclusion An oral bicarbonate regimen is a safe and effective way to alkalize HDMTX urine, providing a viable and cost-effective alternative to IV protocols. Further prospective multicenter studies are necessary.
Systematic review registration identifier: CRD42023379666.

Keywords Sodium Bicarbonate · Methotrexate (MTX) · Chemotherapy · Urine Alkalinization · Drug Shortage

✉ Bita Shahrami
bita.shahrami@gmail.com

1 Hematology, Oncology, and Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology, and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran

2 Department of Toxicology & Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

3 Toxicology and Diseases Group (TDG), Pharmaceutical Sciences Research Center (PSRC), Tehran University of Medical Sciences, Tehran, Iran

4 Digestive Diseases Research Center, Digestive Diseases Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

5 Clinical Research Development Unit, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

6 Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

7 Hematologic Malignancies Research Center, Research Institute for Oncology, Hematology, and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran

8 Faculty of Medicine, Semmelweis University, Budapest, Hungary

9 Development of Research and Technology Center, Deputy of Research and Technology, Ministry of Health and Medical Education, Tehran, Iran

10 Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Introduction

MTX, a folate antimetabolite, is used in various oncology and non-oncology treatments. HDMTX, defined as doses greater than or equal to 500 mg/m2, is commonly used for central nervous system (CNS) prophylaxis and in chemotherapy protocols for malignancies like lymphoma, leukemia, and osteosarcoma. MTX intracellularly interferes with folate metabolism by inhibiting the key enzyme DHFR, suppressing the conversion of dihydrofolate to its active form, resulting in cell death. This mechanism inhibits DNA synthesis, repair, and cellular replication.

When administered intravenously (IV), MTX is widely distributed throughout the body, with a half-life of approximately 8 to 12 h. MTX serum levels decrease over time; the highest levels are achieved during the first 24 h of administration, then drop to less than 0.3 µmol/L after about 72 h. It is mainly excreted unchanged in urine, with only 10% metabolizing the drug. Clearance of MTX can be impeded by genetics, impaired kidney function, and drug interactions.

Although valuable as a treatment, HDMTX and its metabolites can lead to serious adverse health effects like nephrotoxicity. This side effect can cause a reduction in MTX clearance and additional adverse effects such as mucositis, hepatotoxicity, and myelosuppression. Renal toxicity can occur due to MTX's direct effect on kidney tubules or transient reduction in glomerular filtration. However, adequate hydration can prevent renal toxicity by maintaining urine output. Although providing valuable therapeutic effects, HDMTX and its metabolites may cause serious adverse health effects like nephrotoxicity, one of the most crucial side effects leading to a reduction in MTX clearance and the occurrence of additional adverse effects such as mucositis, hepatotoxicity, and myelosuppression. This renal toxicity can occur either as a result of MTX's direct effect on kidney tubules or transient reduction in glomerular filtration [1, 2]; but can be prevented through adequate hydration to maintain urine output, urine alkalinization before starting and during the infusion, and monitoring MTX serum level, serum creatinine, and electrolytes. Also, leucovorin rescue can be used in nephrotoxicity cases [3]. As the precipitation of MTX in urine—which happens in an acidic environment—increases the incidence of renal toxicity, urine alkalinization and maintaining the pH above 7 is necessary before the initiation of MTX and during its infusion to reduce precipitation. One mEq/kg of IV sodium bicarbonate (SB) every 4 to 6 h is traditionally used to reach the mentioned urine pH goal [3].

Reaching the urine pH goal as the cornerstone of nephrotoxicity prevention in patients receiving HDMTX became challenging during national IV SB shortages—like the situations North America and Iran confronted in 2015–2017 and 2022, respectively. Therefore, alternative alkalinization strategies with oral bicarbonate were administered [4]. The hypothesis was to conserve the supply of IV formulations for critically ill patients and life-saving conditions and provide an alternative regimen appropriate for the outpatient setting, possibly decreasing the overall hospitalization days. Although some studies and local guidelines have recommended oral SB as an effective alternative to mitigate the situation [4–15], mainly derived from single-centered retrospective cohort studies after national shortages, the administration of oral SB is not well practiced yet. This study aimed to review the current evidence on the safety and efficacy of administering oral regimens of bicarbonate for HDMTX urine alkalinization and settle a reasonable conclusion regarding the cost–benefit of using the oral protocols.

Materials and methods

The present systematic review was performed per the 2023 guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. The review protocol was registered in the PROSPERO international prospective register of systematic reviews (CRD42023379666).

Inclusion and exclusion criteria

Types of studies

All relevant types of original studies, such as randomized clinical trials (RCTs), retrospective, prospective, cohort, and chart reviews, and case series on humans, were included in this review. Case series with fewer than 4 participants and studies on the oral regimens without a control IV arm were excluded from the meta-analysis. Studies in all languages were considered for inclusion.

Types of participants

Both adult and pediatric patients with solid tumors or hematologic malignancies who had received an HDMTX regimen were considered for inclusion.

Types of interventions

The intervention was defined as administering an oral regimen (based on oral SB or sodium citrate) ± acetazolamide for urine alkalinization to achieve urine pH ≥ 7. Administration of standard IV SB regimen for urine alkalinization was the comparator.

Types of outcome measures

Primary outcomes All reported indicators of efficacy and safety were compared between the oral versus IV bicarbonate regimens for HDMTX urine alkalinization. The following parameters assessed the efficacy: time to MTX clearance, the incidence of delayed MTX clearance (defined as failure to meet any protocol-specific goals for MTX plasma concentrations), total SB required to reach goal urine pH, time to urine alkalinization, instances urine pH fells to < 7, low serum bicarbonate (i.e., measured serum bicarbonate < 20 mEq/L), hospital length of stay (LOS), creatinine clearance (CrCl) 24 or 48 h post-MTX, urine output (UO) within 24 or 48 h post-MTX, and time to reach UO goal (i.e., time to urine output > 125 mL/hr). The parameters used for evaluation of safety were as follows: the incidence of high serum bicarbonate (i.e., measured serum bicarbonate > 35 mEq/L), development of nephrotoxicity (defined according to the criteria introduced by the Kidney Disease Improving Global Outcomes (KIDGO) and graded considering the definition of increased serum creatinine by the Common Terminology Criteria for Adverse Effects (CTCAE) [17, 18]), hepatotoxicity (defined as elevation in aminotransferases and again graded per CTCAE.), myelosuppression, mucositis (assessed for occurrence regardless of grading), gastrointestinal (GI) complication, hypernatremia, and neurologic complications.

Secondary outcomes The secondary outcomes were the number of required leucovorin doses to achieve MTX clearance and the overall protocol cost in dollars.

Data sources and search strategies

The systematic search strategy used the most comprehensive related international databases, including PubMed, WOS, and Scopus (for published scientific papers and peer review studies).

On July 16, 2022, a search strategy was developed based on two main axes of "Oral Sodium Bicarbonate" and "Urine Alkalinization" for RCTs and Cross-over trials, human subject, and without restriction on language or limitation on age groups. Also, searches were re-run on August 13, 2022, before the final analysis (Supplementary Table S1). The selection process was recorded in a PRISMA flow diagram (Fig. 1) [16].

Study selection

The searched records were imported using Endnote software. After removing the duplicates, three steps of relevance assessment were done based on titles, abstracts, and full texts. In the case of including review articles, the complete list of their references was reviewed to retrieve the relevant studies. In the case of identifying studies in languages other than English, translation was required. The quality of relevant papers was evaluated before data extraction. Two authors independently followed all processes, and a third reviewer resolved any probable disagreements.

Data extraction and management

Data were extracted from the qualified, eligible papers, including citation, study year, publication year, the country that the study was carried out, the scope of the study, the aim of the study, the type of study, the study population, sample size (defined as the number of cycles HDMTX was administered), sex, mean age, regimen and doses administered, the interested outcomes of efficacy, indicators of safety, and other information.

After all, an attempt was made to contact the original corresponding authors of included studies to complete the missing data as much as possible. For studies in which mean and standard deviation (SD) was not reported, imputed mean and SD were calculated using sample size, median, mid-range, and/or mid-quartile range [19, 20].

Assessment of risk of bias in included studies

The Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) assessment tool (version for cohort-type studies, September 19, 2016) was used for quality assessments of final relevant records [21]. Two authors independently assessed the risk of bias, and a third opinion resolved probable disagreements. A summary of the risk of biased judgment for all studies is presented in Fig. 2.

Data synthesis and meta-analysis

The proportion of the interested outcomes between the two groups (i.e., those who received standard IV regimens and those who received oral alkalinization regimens) was compared using an odds ratio (OR) with a 95% confidence interval (CI). Pooled mean differences (MDs) or ORs and their corresponding 95% CIs of the interested outcomes were calculated using the random-effects model to pool the data in significant heterogeneity; otherwise, a fixed-effect model was adopted. The DerSimonian and Laird method was used for the random-effects models, and the inverse variance method was used for the fixed-effect models [22, 23].

Heterogeneity was assessed using the Q statistic and the I^2 test, in which I^2 more significant than 50% or $P < 0.10$ were considered significant [24].

The Galbraith plot and sensitivity analysis was carried out to assess the potential sources of heterogeneity in the

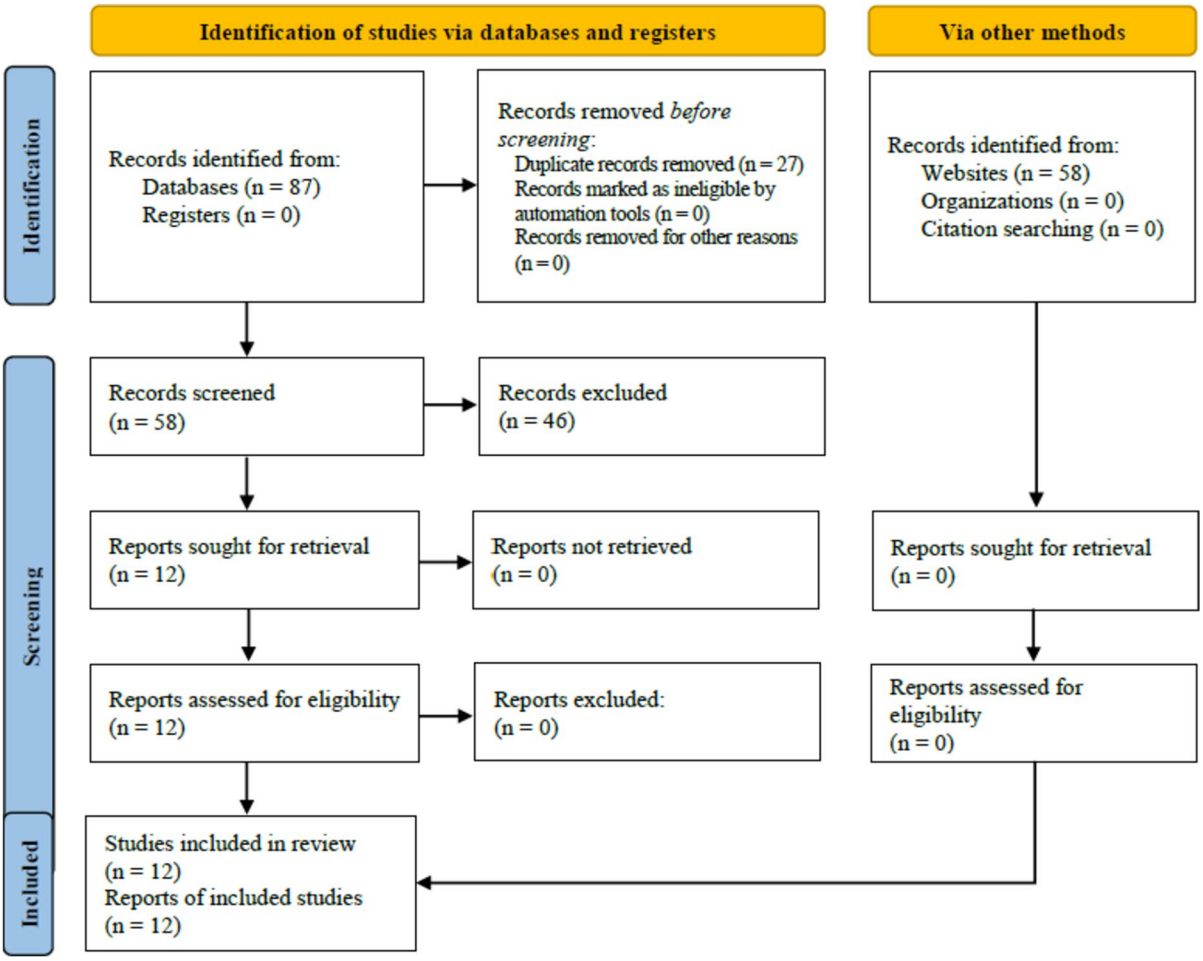

Fig. 1 Study selection flow diagram

results. Galbraith plot analysis was performed to detect the outliers as potential sources of heterogeneity [25].

In addition, sensitivity analysis, which eliminates any single study at a time, was used to assess each study's effect on the overall results of a meta-analysis to show the stability and robustness of the results [26]. Notably, a sensitivity analysis for those interested outcomes was not performed when there were only 2 eligible studies, as it does not make sense.

The Egger regression test assessed the publication bias, with a $P < 0.10$ considered significant [27]. Remarkably, the Egger test could not be calculated for those interested outcomes when there were only 2 studies.

The trim-and-fill method was used to identify and correct the funnel plot asymmetry arising from publication bias [28].

Ethical considerations

All included studies that have influenced the reported outcomes have been cited within this article and will be cited in all of the publications extracted from this study. Further information could be referred to the corresponding author.

Results

Results of the search

Running the search strategy at the first step led to 87 papers. After removing duplicates, there were 58 records for title and abstract screening; one was a review article. Bibliography, citation, and grey literature searching identified 58

Fig. 2 Risk of bias summary

records that none of them appeared to meet the inclusion criteria. Refining for the relevancy of titles, abstracts, and full-texts, 12 studies were included (Fig. 1). The exclusion at this stage was due to irrelevancy, such as performing animal studies or acetazolamide-only regimens for urine alkalinization. The re-running of searches resulted in the identification of 2 records, from which one was repeated, and the other was a 'letter to editorial' on one of the previously included studies without any effective comments, as far as the current study concerned.

Characteristics of the primary studies

Of the 12 primary included studies, eight were related to the USA [4, 8–12, 14, 15], and two studies related to Canada [6, 7]. Most studies were designed at the local one-center level, except for Heisler et al. and Diachinsky et al. [6, 7]. All of the studies were retrospective except for Cohen et al. and Reed et al., which were prospective analyses [5, 10] and one case report [15]. Three studies did not mention any control groups with standard IV regimens [5, 13, 14], and the details of IV protocol were unclear in two others [11, 15]. One of the studies had not described any of the treatment protocols [4]. In the case of the study population, seven studies were performed on adults [5, 7–12], two on pediatrics [6, 13], and 2 on both adult and pediatric participants [4, 14]. Whiteside et al. had not stated the study population [15]. Cohen et al. investigated the efficacy of an oral protocol among healthy volunteers, which was excluded from meta-analysis due to the study group characteristics and not including the control

arm [5]. Three other studies were also excluded from the meta-analysis: two for the absence of the control group and one for the minimal population size [15]. There were no studies in languages other than English. The studies' complete characteristics and outcomes are described in Table 1 and 2, respectively.

Risk of bias across studies

The detailed results from thee risk of bias assessment are documented in Fig. 2. None of the included studies were at critical risk of bias for the assessed domains.

Several studies were judged as having severe risk of bias due to confounding, as not controlling for the exact amount of fluid, MTX, and overall SB administration between two groups, acetazolamide doses, outpatient alkalinization, and probable IV SB, sodium acetate or leucovorin administration with the oral protocol. The other sources were very short follow-up periods, adverse events due to the participants for the report, potential variations due to the verbal recommendations, variable presence of medications suspected to delay methotrexate excretion, and inconsistent documentation of outpatient medication compliance. Wherever confounding was expected, but all known important confounding domains were appropriately measured and controlled, the risk of bias was considered moderate. No studies were at low risk in this domain without any expected confounding.

Individuals at the goal urine pH from the beginning were excluded, possibly due to the probable outpatient administration of oral SB, which could also be neglected for the follow-up. Furthermore, this practice was not standardized due to the variation in time of outpatient SB administration [4, 12]. In the case of cost evaluation, bolus doses were not encountered in one study [7]. Three studies were judged as having a severe risk of bias in the selection of participants into the study for the above reasons. Also, three others were considered as a moderate risk; one with an additional 76 encounters for safety outcomes [11], one other for excluding the patients who received doses greater than 5 g/m^2 of MTX [10], and the third one for considering the first set of lab data after administration of SB as the baseline condition which could interfere with the coincidence of intervention and follow-up. It was unclear that selection might have been relayed to the outcomes for all of the 3 studies.

Only one study was considered as high risk of bias in the classification of interventions due to unclear characteristics of the control group and not defining the intervention status [11]. No information was reported for 2 other studies [4, 15].

Two studies were judged as having a severe risk of bias due to deviations from intended interventions. One study reported that some providers instructed their patients to begin oral alkalinization before hospital admission, which was not standardized [4]. These participants were not excluded. The other study reported probable undocumented switches to IV sodium acetate with oral protocol due to inadequate alkalinization or intolerance and poor compliance with the oral regimen [14]. Three studies were considered to have a moderate risk of bias in this domain, all with limited adherence complications [6, 7, 13].

One study was considered a severe risk of bias due to missing data as data were eliminated because of unreliable urine samples or the patient being managed based on drug availability. Also, data was not wholly reported for the included cycles with IV protocol [15]. For 3 studies, cycles were excluded due to incomplete data, which slightly differed across intervention groups and were judged as moderate risk [6, 7, 14]. No information was available from one other study about the potential for data to be missing [11].

Four studies were judged as having a moderate risk of bias in the measurement of outcomes; for unscheduled urine pH measurement [5], uncertain documentation of baseline values [9], longer hospitalization on the first admission due to the diagnosis procedures [8], and not considering the concomitant chemotherapy which could affect the risk of emesis [14].

Two studies were considered to have a moderate risk of bias in selecting the reported result. In one study, subgroup analysis was done for only some efficacy parameters between adults and pediatric encounters [4]. The other study did not demonstrate the detailed results from subgroup analysis [7]. No information was reported about the outcome assessment methods for one of the studies [11].

Results of meta-analyses

Indicators of efficacy

Time to MTX clearance (h) Fixed effect meta-analysis of 5 studies, pooling results from including 630 participants (303 cases and 327 controls), did not show any significant differences in the average time to MTX clearance (h) after oral bicarbonate regimen ((MD: 0.06, 95% CI: -1.00, 1.12), $P = 0.91$) (Fig. 3). There was low heterogeneity among studies ($p = 0.236$; $I^2 = 27.81\%$). Egger test did not provide evidence of publication bias or small-study effect (Egger's regression intercept: -0.36 (95% CI: -1.96, 2.68), $P = 0.653$). Begg's funnel plot of standard error versus effect size (MD) was symmetric (Fig. S1a).

A Galbraith plot revealed no studies outside the 95% CI, meaning no outliers (Fig. S1b).

The trim-and-fill correction suggested no potentially missing studies on any sides of the funnel plot (Fig. S1c).

Table 1 Characteristics of included studies

Roy et al. (2019) [12]	
Country	USA
Scope	Adults who received at least one cycle of HDMTX during 50 days of shortage protocol usage and at least one cycle using standard alkalinization protocol during either the 50 days directly before or after
Aim	Compare the safety and efficacy of the two protocols
Oral regimen	IV fluid of choice (usually NS) infused at 125–200 mL/h plus SB 3250 q2h and Acetazolamide 250–500 orally or IV q6h as PRN to urine pH < 7.5. Outpatient alkalinization on the day of admission was considered with SB 3250 q4h
IV regimen	IV fluid of choice (usually D5W or sterile water for INJ) with 150 mEq/L SB infused at 125–200 mL/h plus SB 3250 mg orally q4h PRN urine pH < 7.5
Mean age, yrs (range)	61 (21–80)
The proportion of male subjects	0.46
Method of data collection	Retrospective, single-center cohort study
The sample size of the oral regimen arm	37
The sample size of the IV regimen arm	39
Cohen et al. (2013) [5]	
Country	Israel
Scope	Adult healthy male volunteers
Aim	Evaluated the efficacy of a fixed oral regimen of SB to achieve rapid-onset urine alkalinization
Oral regimen	4 g of SB tablets q8h, for a total daily dose of 12 g
IV regimen	N/A
Mean age, yrs (range)	31[a] (21–45)
The proportion of male subjects	1.00
Method of data collection	Prospective, open-label trial
The sample size of the oral regimen arm	9
The sample size of the IV regimen arm	N/A
Reed et al. (2018) [11]	
Country	USA
Scope	Adults who received HDMTX
Aim	Assess the safety and the impact on time to start MTX with oral versus IV regimen
Oral regimen	Oral SB 2600 q4h and acetazolamide 250 q6h were the initial doses and titrated to maintain a urine pH ≥ 7
IV regimen	Not stated
Mean age, yrs (range)	51[a] (21–69)
The proportion of male subjects	Not reported
Method of data collection	Retrospective chart review
The sample size of oral regimen arm	54
The sample size of IV regimen arm	32
Kramer et al. (2020) [9]	
Country	USA
Scope	Adults who received HDMTX
Aim	Compare outcomes and adverse effects between the previously used IV and newly implemented oral protocols
Oral regimen	Oral SB 2600 q6h one day prior to admission, and one dose plus acetazolamide 125 mg once on the morning of admission
IV regimen	The total fluid rate was maintained at 125 ml/h combined between SB and N/S. SB drips are made with 150 mEq in 1150 mL
Mean age, yrs (range)	46 (21–69)
The proportion of male subjects	0.80
Method of data collection	Single-center, retrospective, cohort study
The sample size of the oral regimen arm	93
The sample size of the IV regimen arm	102

Table 1 (continued)

Whiteside et al. (2017) [15]	
Country	USA
Scope	Not reported
Aim	Rapidly induce urinary alkalosis
Oral regimen	SB 1300 q6h the day prior to admission, SB 1300 q4h on admission plus Acetazolamide 500 mg IV × 1 dose followed by 250 mg IV q6h
IV regimen	Not stated
Mean age, yrs (range)	Not stated
The proportion of male subjects	Not reported
Method of data collection	Case report
The sample size of the oral regimen arm	3
The sample size of the IV regimen arm	3
Rouch et al. (2015) [4]	
Country	USA
Scope	Adults and pediatrics who received HDMTX with at least one dose of urine alkalinizing agent prior to achieving their goal urine pH
Aim	Establish the safety and efficacy of oral urine alkalinization
Oral regimen	Not stated
IV regimen	Not stated
Mean age, yrs (range)	49.5[a] (Not stated)
The proportion of male subjects	0.65
Method of data collection	Single-center, retrospective, cohort study
The sample size of the oral regimen arm	59
The sample size of the IV regimen arm	59
Diachinsky et al. (2020) [6]	
Country	Canada
Scope	Pediatrics who received HDMTX in at oncology setting
Aim	Adopt an alternative protocol, including oral SB and IV hydration with LR
Oral regimen	LR at 125 mL/m^2/h before, during (separate from MTX), and after MTX infusion until clearance parameters are met. SB 650 mg/m^2 or 7.8 mL/m^2 sodium citrate/citric acid solution q6h starting 1 day prior to admission
IV regimen	30 or 40 mmol/L SB at 125 mL/m^2/h prior to, during (mixed with MTX), and after MTX infusion until clearance parameters met
Mean age, yrs (range)	13.5[a] (> 18)
Proportion of male subjects	0.61
Method of data collection	Retrospective, multicenter chart review
Sample size of oral regimen arm	62
Sample size of IV regimen arm	50
Kintzel et al. (2011) [8]	
Country	USA
Scope	Adults who received HDMTX during 2008–2009
Aim	Achieving adequate urinary alkalinization and output for patients receiving single-agent HDMTX
Oral regimen	Oral SB q4h beginning in the morning of scheduled admission
IV regimen	IV hydration with DW5% containing 100 or 150 mEq/L SB after hospitalization in order to attain a urine pH exceeding 7 or 7.5 and UO exceeding 100 mL/h
Mean age, yrs (range)	67 (56–78)
The proportion of male subjects	0.05
Method of data collection	Retrospective chart review
The sample size of the oral regimen arm	36
The sample size of the IV regimen arm	43
Heisler et al. (2022) [7]	
Country	Canada

Table 1 (continued)

Scope	Adults who received HDMTX with oral SB for urine alkalinization
Aim	Compare efficacy and safety of oral and IV SB for HDMTX urine alkalinization
Oral regimen	SB 1300 to 1500 mg q6h plus LR 2 mL/kg/h until MTX clearance
IV regimen	SB 100 mmol/L in D5W plus 20 mmol/L KCl at 200 mL/h
Mean age, yrs (range)	51.3 (Not stated)
The proportion of male subjects	0.38
Method of data collection	Retrospective, multicenter chart review
The sample size of the oral regimen arm	78
The sample size of the IV regimen arm	84
Visage et al. (2018) [14]	
Country	USA
Scope	Adults and pediatrics who received cycles of HDMTX with at least one dose of oral SB tablets or sodium citrate-citric acid oral solution
Aim	Determine the safety and efficacy of oral alkalinization strategies for HDMTX administration
Oral regimen	SB tablets (1950 mg/m^2/dose, maximum initial dose 1950 mg) or sodium citrate-citric acid oral solution (22.5 mEq/m^2/dose, maximum dose 25 mEq) q6h with the initiation of IV hyperhydration
IV regimen	N/A
Mean age, yrs (range)	13.5[a] (1–21.8)
The proportion of male subjects	0.63
Method of data collection	Retrospective observational cohort study
The sample size of the oral regimen arm	94
The sample size of the IV regimen arm	N/A
Reed et al. (2019) [10]	
Country	USA
Scope	Adults who received HDMTX for hematologic malignancies
Aim	Describe the safety of alternative PO SB regimens
Oral regimen	Oral SB 2600 mg 6 times daily and Acetazolamide 250 mg q6h plus H/S IV continuous infusion at 175 mL/h
IV regimen	SB 75–150 mEq/L IV continuous infusion at 175 mL/h
Mean age, yrs (range)	53.8 (21–77)
The proportion of male subjects	0.18
Method of data collection	Single institution, prospective analysis
The sample size of the oral regimen arm	83
The sample size of the IV regimen arm	43
Villegas-Rubio et al. (2017) [13]	
Country	Argentina
Scope	Pediatrics who received ambulatory HDMTX for osteosarcoma
Aim	Demonstrate that HDMTX administration with oral hyperhydration, alkalinization, and leucovorin rescue is feasible and safe in a population with poor resources in a developing country
Oral regimen	HDMTX was given IV after urine alkalinization with IV bicarbonate. Patients were discharged home, and they were instructed to take 3L/m^2/d of oral fluid and oral SB, beginning with a 1 g per 15 kg of body weight and adjusting the dose to maintain a urine pH between 7 and 8
IV regimen	N/A
Mean age, yrs (range)	12.6 (7–17)
The proportion of male subjects	0.09
Method of data collection	Retrospective analysis
The sample size of the oral regimen arm	149
The sample size of the IV regimen arm	N/A

IV Intravenous, *HDMTX* High-dose methotrexate, *SB* Sodium bicarbonate, *LR* Ringer lactate, *N/S* Normal saline, *H/S* Half saline

[a] Median age

Table 2 Outcomes of included studies

Study	Outcomes															
	Average time to MTX clearance (SD)		Number of delayed MTX clearance (%)		Average time to urine alkalinization (SD)		Average instances urine pH fells to < 7 (SD)		Average time of hospital LOS (SD)		Number of serum bicarbonate > 35 (%)		Number of AKI grades 1 and 2 (%)		Number of AKI grades 3 and 4 (%)	
	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen
Roy et al. (2019) [12]	64.1 (45.8)	64.2 (45.3)	Not reported	Not reported	15.4 (8.48)	14.9 (10)	1.3 (1.7)	0.4 (0.8)	151 (193)	112 (76)	Not reported	Not reported	1 (2.7)	2 (5.1)	1 (2.7)	1 (2.5)
Cohen et al. (2013) [5]	Not reported	N/A	Not reported	N/A	8 (Not stated)	N/A	Not reported	N/A	Not reported	N/A	Not reported	Not reported	0 (0)	N/A	0 (0)	N/A
Reed et al. (2018) [11]	Not reported	Not reported	14 (26.5)	8 (25.3)	Not reported	Not reported	Not reported	Not reported	90.72 (Not stated)	75.6 (Not stated)	Not reported	Not reported	Not reported (14.5)	Not reported (8.9)	Not reported	Not reported
Kramer et al. (2020) [9]	98 (38)	88 (36)	Not reported	Not reported	7.6 (3.16)	9 (3.53)	Not reported	Not reported	153 (185)	162 (182)	2 (2)	13 (13)	10 (11)	22 (22)	1 (1)	1 (1)
Whiteside et al. (2017) [15]	Not reported	Not reported	Not reported	Not reported	3.22 (N/A)[a]	2.3 (0.78)	1.67 (1.53)	0.33 (0.58)	4.67 (1.15)	5 (1)	Not reported	Not reported	0 (0)	0 (0)	0 (0)	0 (0)
Rouch et al. (2015) [4]	57.66 (31.23)	63.5 (18.2)	Not reported	Not reported	9 (5.3)[b]	8 (3.61)[b]	Not reported	Not reported	Not reported	Not reported	15 (25)	15 (25)	3 (5)	3 (5)	1 (2)	0 (0)
Diachinsky et al. (2020) [6]	57 (Not stated)	61 (Not stated)	5 (8)	5 (10)	Not reported	Not reported	1 (Not stated)	1.6 (Not stated)	65 (Not stated)	72 (Not stated)	Not reported	Not reported	10 (16)	9 (18)	Not reported	Not reported
Kintzel et al. (2011) [8]	5.5 (1.7)	5.5 (2.9)	Not reported	Not reported	5.4 (3.9)	10.8 (8.2)	7 (19)	5 (12)	6.4 (2.4)	7.1 (3.9)	7 (19)	13 (30)	9 (25)	9 (21)	0 (0)	2 (33)
Heisler et al. (2022) [7]	95.8 (44)	91.6 (35.4)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	7 (9)	14 (17)	Not reported	Not reported	4 (5)	10 (12)	Not reported	Not reported
Visage et al. (2018) [14]	Not reported	Not reported	2 (2)	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A
Reed et al. (2019) [10]	Not reported	Not reported	22 (26.5)	16 (37.2)	4.8 (2.2)[c]	4.8 (1.8)[c]	Not reported	Not reported	3.8 (5.6)[c]	3.1 (0.9)[c]	Not reported	Not reported	12 (14.5)	4 (9.3)	Not reported	Not reported
Villegas-Rubio et al. (2017) [13]	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A	13.5 (Not stated)	N/A	Not reported	Not reported	0 (0)	N/A	Not reported	N/A

Table 2 (continued)

Study	Outcomes													
	Number of hepatotoxicity grades 1 and 2 (%)		Number of hepatotoxicity grades 3 and 4 (%)		Number of myelosuppression grades 1 and 2 (%)		Number of myelosuppression grades 3 and 4 (%)		Number of mucositides (%)		Number of diarrheas (%)		Number of emesis (%)	
	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen	with oral regimen	with IV regimen
Roy et al. (2019) [12]	17 (45.9)	17 (43.6)	3 (8.1)	5 (7.7)	12 (32.4)	21 (53.8)	4 (10.8)	2 (5.1)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Cohen et al. (2013) [5]	0 (0)	N/A	0 (0)	N/A	0 (0)	N/A	0 (0)	N/A	0 (0)	N/A	0 (0)	N/A	0 (0)	N/A
Reed et al. (2018) [11]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Kramer et al. (2020) [9]	58 (62)	75 (74)	11 (12)	5 (5)	33 (32)	26 (25)	30 (32)	43 (42)	22 (24)	24 (24)	26 (28)	10 (10)	25 (27)	24 (24)
Whiteside et al. (2017) [15]	0 (0)	0 (0)	0 (0)	0 (0)	Not reported	Not reported	Not reported	Not reported	0 (0)	0 (0)	Not reported	Not reported	Not reported	Not reported
Rouch et al. (2015) [4]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	15 (25)	3 (5)	Not reported	Not reported
Diachinsky et al. (2020) [6]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	7 (11)	7 (14)	9 (15)	8 (16)	10 (16)	6 (12)	5 (8.1)	10 (20)
Kintzel et al. (2011) [8]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Heisler et al. (2022) [7]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	14 (18)	14 (17)	0 (0)	1 (1)	14 (18)	3 (4)
Visage et al. (2018) [14]	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A	Not reported	N/A
Reed et al. (2019) [10]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table 2 (continued)

Villegas-Rubio et al. (2017) [13]	Not reported	N/A	Not reported	N/A	Not reported	N/A	38 (25.7)		N/A	6 (4)	N/A	1 (0.7)	N/A	6 (4)	N/A

IV Intravenous, *AKI* Acute kidney injury.

[a] with a total group size of 1 for the oral cohort. [b] with a total group size of 41 for both oral and IV cohorts. [c] with a total group size of 54 and 12 for oral and IV cohorts, respectively.

Sensitivity analysis was done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from -0.05 (-1.11, 1.02) to 1.72 (-4.05, 7.48), which indicates strong robustness of the pooled estimates of prevalence (Fig. S1d).

Time to urine alkalinization (h) A random effect meta-analysis of 5 studies, pooling results from including 498 participants (261 cases and 237 controls), did not show any significant differences in the average time to alkalinization (h) after oral bicarbonate regimen ((MD: -1.00, 95% CI: -3.04, 1.04), $P = 0.34$) (Fig. 4). There was high heterogeneity among studies ($p = 0.003$; $I^2 = 83.94\%$). Egger test did not provide evidence of publication bias or small-study effect (Egger's regression intercept: -0.15 (95% CI: -7.38, 7.08), $P = 0.951$). Begg's funnel plot of standard error versus effect size (MD) was asymmetric (Fig. S2a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S2b).

The trim-and-fill correction suggested no potentially missing studies on any sides of the funnel plot (Fig. S2c).

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from -1.55 (-3.89, 0.79) to -0.28 (-1.52, 0.96), which indicates the high robustness of the pooled estimates of prevalence (Fig. S2d).

Instances urine pH fell to < 7 Fixed effect meta-analysis of 2 studies, pooling results from including 155 participants (73 cases and 82 controls), showed a significant difference in the average of instances urine pH fell to < 7 after oral bicarbonate regimen ((MD: 0.91, 95% CI: 0.32, 1.5), $P = 0.003$) (Fig. 5). There was no heterogeneity among studies ($p = 0.76$; $I^2 = 0.00\%$). Begg's funnel plot of standard error versus effect size (MD) was asymmetric (Fig. S3a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S3b).

The trim-and-fill correction suggested one potentially missing study on the left side of the funnel plot (Fig. S3b). Imputation for this potentially missing study yielded an effect size of 0.90 (95% CI: 0.31, 1.49), which was also statistically significant.

Hospital LOS (h) A random effect meta-analysis of 5 studies, pooling results from including 578 participants (298 cases and 280 controls), did not show any significant differences in the average of hospital LOS (h) following the oral bicarbonate regimen ((MD: -1.93, 95% CI: -6.11, 2.26), $P = 0.37$) (Fig. 6). There was high heterogeneity among studies ($p = 0.03$; $I^2 = 73.20\%$). Egger test did not provide evidence of publication or small-study effect bias (Egger's

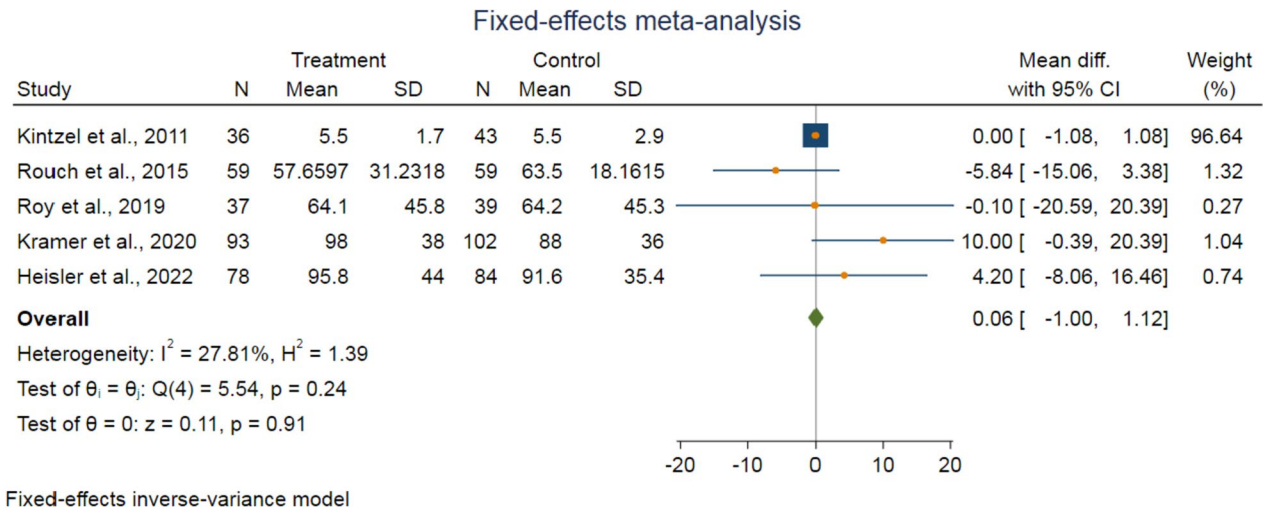

Fig. 3 Forest plot of the pooled MDs between the standard IV and the oral alkalinization regimens regarding time to MTX clearance (h)

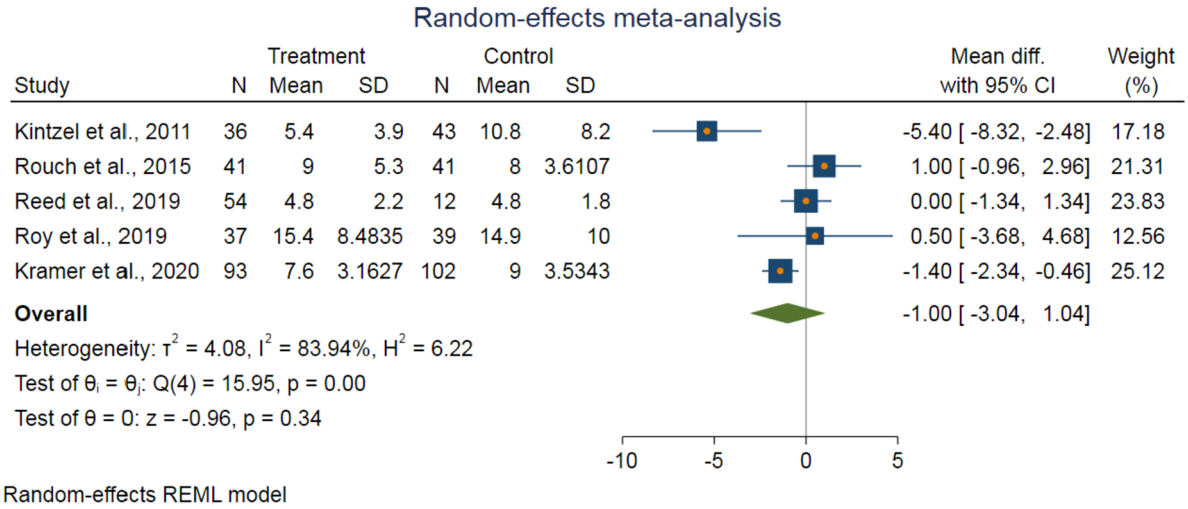

Fig. 4 Forest plot of the pooled MDs between the standard IV and the oral alkalinization regimens regarding time to alkalinization (h)

regression intercept: -0.14 (95% CI: -3.96, 3.67), $P = 0.951$). Begg's funnel plot of standard error versus effect size (MD) was asymmetric (Fig. S4a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S4b).

The trim-and-fill correction suggested no potentially missing studies on any side of the funnel plot (Fig. S4c).

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from -3.23 (-9.16, 2.70) to -0.45 (-1.78, 0.88), which indicates high robustness of the pooled estimates of prevalence (Fig. S4d).

Incidence of delayed MTX clearance Fixed effect meta-analysis of 3 studies, pooling results from including 324 participants (199 cases and 125 controls), did not show any significant differences in the frequency of delayed MTX clearance in individuals after oral bicarbonate regimen compared with those who underwent the standard IV protocol ((OR: 0.76, 95% CI: 0.43, 1.32), $P = 0.33$) (Fig. 7). There was no heterogeneity among studies ($p = 0.703$; $I^2 = 0.00\%$). Egger test did not provide evidence of publication bias or small-study effect (Egger's regression intercept: 1.40, (95% CI: -24.15, 26.93), $P = 0.615$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S5a).

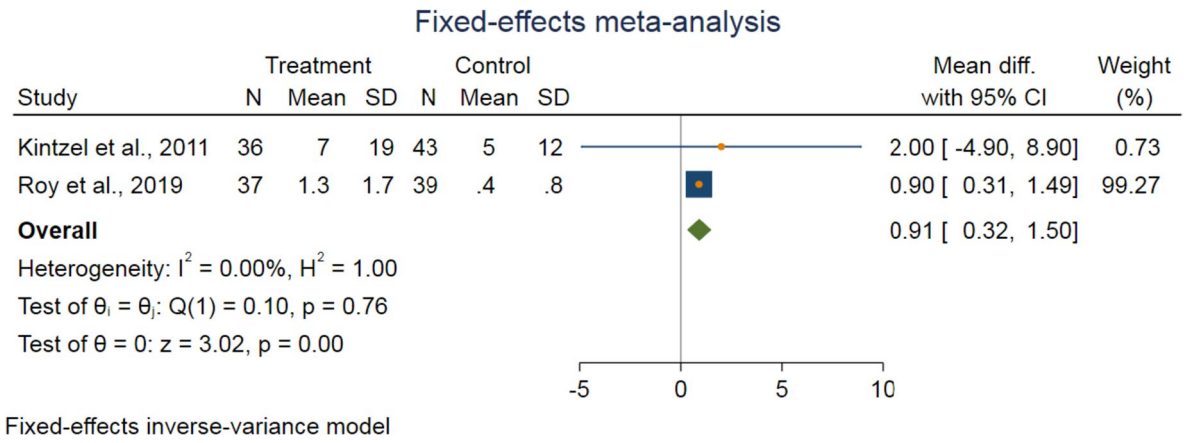

Fig. 5 Forest plot of the pooled MDs between the standard IV and the oral alkalinization regimens in terms of instances urine pH fell to < 7

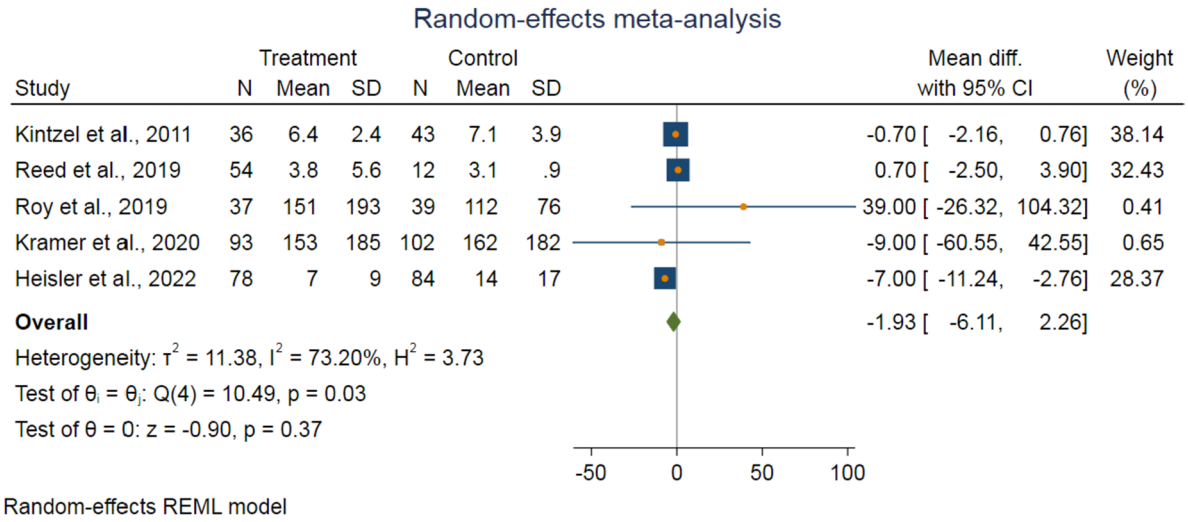

Fig. 6 Forest plot of the pooled MDs between the standard IV and the oral alkalinization regimens regarding hospital LOS (h)

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S5b).

The trim-and-fill correction suggested two potentially missing studies on the left side of the funnel plot (Fig. S5c). Imputation for this potentially missing study yielded an effect size of 0.61 (95% CI: 0.38, 0.96), which was statistically significant.

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 0.65 (0.33, 1.28) to 0.94 (0.43, 2.09), which indicates the high robustness of the pooled estimates of prevalence (Fig. S5d).

Indicators of safety

Serum bicarbonate greater than 35 mEq/L A random effect meta-analysis of 3 studies, pooling results from including 392 participants (188 cases and 204 controls), did not show any significant differences in the frequency of serum bicarbonate more outstanding than 35 mEq/L in the individuals who went through oral bicarbonate regimen compared with those with the IV regimen ((OR: 0.52, 95% CI: 0.19, 1.38), $P = 0.19$) (Fig. 8). There was moderate heterogeneity among studies ($p = 0.097$; $I^2 = 58.33\%$). Egger test provides evidence of publication bias or small-study effect (Egger's

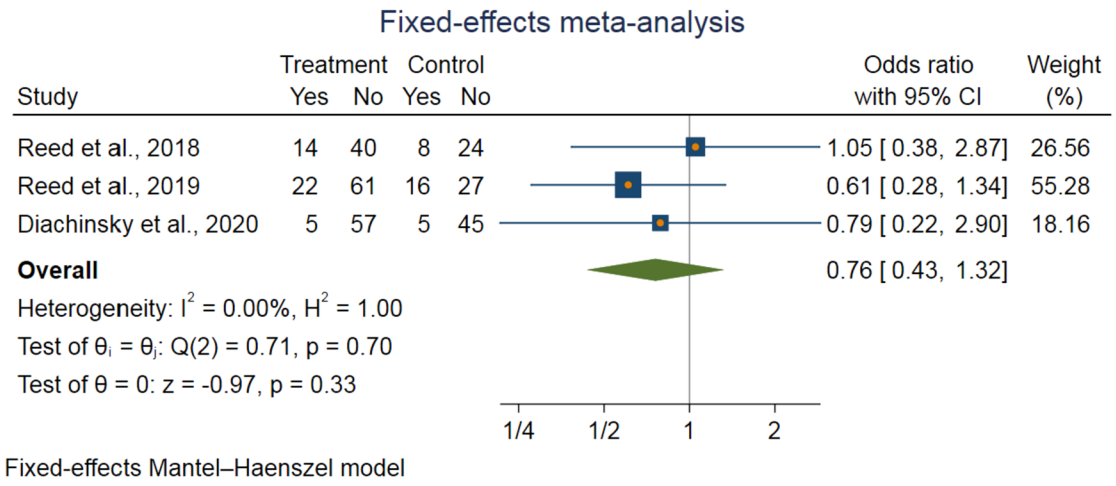

Fig. 7 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in terms of incidence of delayed MTX clearance

regression intercept: 5.38 (95% CI: -6.66, -4.10), $P=0.012$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S6a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S6b).

The trim-and-fill correction suggested no potentially missing studies on any sides of the funnel plot (Fig. S6c).

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 0.33 (0.09, 1.15) to 0.80 (0.42, 1.53), which indicates the high robustness of the pooled estimates of prevalence (Fig. S6d).

AKI grades 1 and 2 Fixed effect meta-analysis of 7 studies, pooling results from including 868 participants (448 cases and 420 controls), did not show any significant differences in the frequency of AKI grades 1 and 2 in individuals after oral bicarbonate regimen compared with the IV protocol ((OR: 0.74, 95% CI: 0.49, 1.12), $P=0.16$) (Fig. 9). There was no heterogeneity among studies ($p=0.464$; $I^2=0.00\%$). Egger test did not provide evidence of publication bias or small-study effect (Egger's regression intercept: 0.62 (95% CI: -2.92, 4.17), $P=0.670$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S7a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S7b).

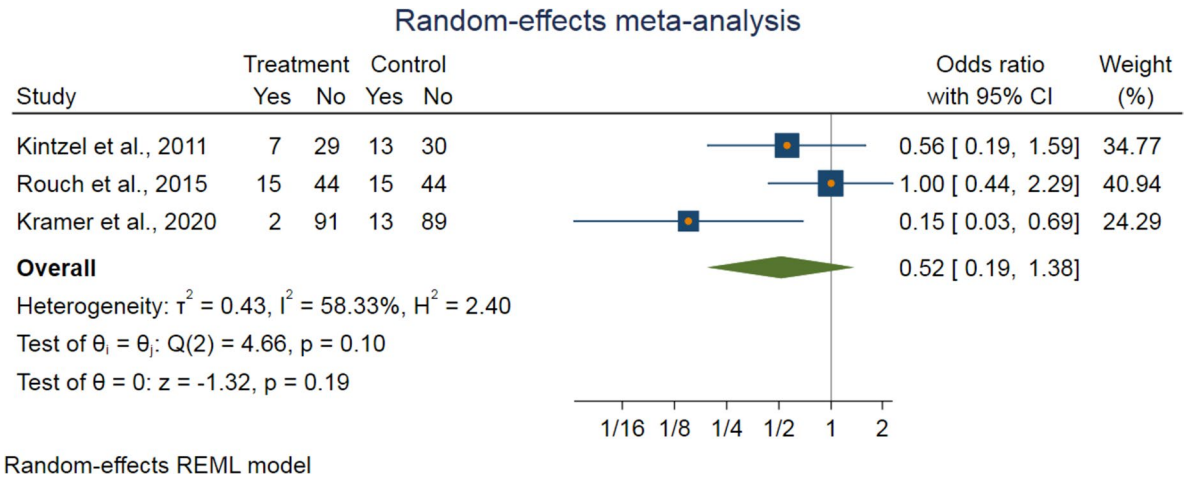

Fig. 8 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in terms of serum bicarbonate more significant than 35 mEq/L

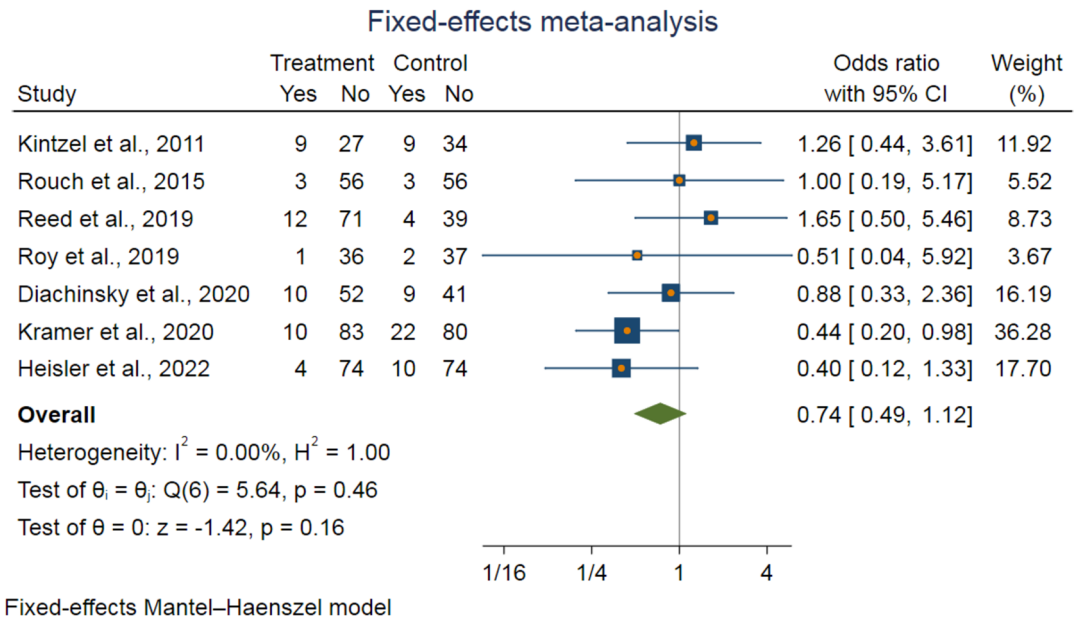

Fig. 9 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in AKI grades 1 and 2

The trim-and-fill correction suggested no potentially missing studies on any sides of the funnel plot (Fig. S7c).

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 0.65 (0.41, 1.03) to 0.91 (0.56, 1.49), which indicates the high robustness of the pooled estimates of prevalence (Fig. S7d).

AKI grades 3 and 4 Fixed effect meta-analysis of 4 studies, pooling results from including 468 participants (225 cases and 243 controls), did not show any significant differences in the frequency of AKI grades 3 and 4 in individuals after alternative oral bicarbonate regimen compared with those with standard IV regimen ((OR: 0.87, 95% CI: 0.23, 3.3), $P = 0.84$) (Fig. 10). There was no heterogeneity among studies ($p = 0.716$; I2 = 0.00%). Egger test did not provide evidence of publication bias or small-study effect (Egger's regression intercept: 1.01 (95% CI: -28.17, 30.19), $P = 0.670$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S8a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S8b).

The trim-and-fill correction suggested one potentially missing study on the left side of the funnel plot (Fig. S8c). Imputation for this potentially missing study yielded an

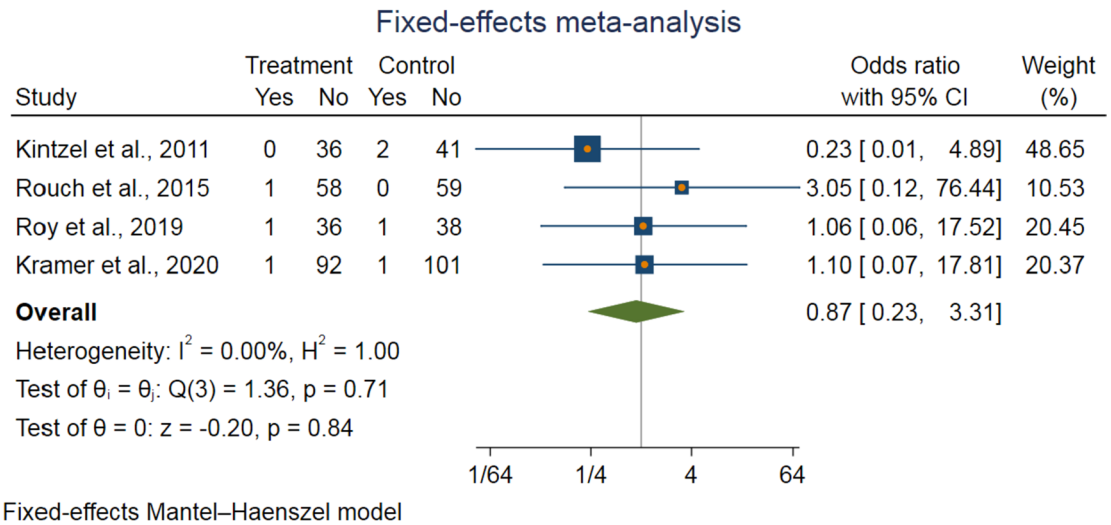

Fig. 10 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in AKI grades 3 and 4

effect size of 0.68 (95% CI: 0.18, 2.61), which was also not statistically significant.

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 0.61 (0.13, 2.95) to 1.48 (0.29, 7.64), which indicates the high robustness of the pooled estimates of prevalence (Fig. S8d).

Hepatotoxicity grades 1 and 2 Fixed effect meta-analysis of 2 studies, pooling results from including 271 participants (130 cases and 141 controls), did not show any significant differences in the frequency of hepatotoxicity grades 1 and 2 in individuals following the oral bicarbonate regimen compared with the standard IV one. ((OR: 0.72, 95% CI: 0.44, 1.19), $P=0.20$) (Fig. 11). There was no heterogeneity among studies ($p=0.271$; $I^2=17.39\%$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S9a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S9b).

The trim-and-fill correction suggested one potentially missing study on the left side of the funnel plot (Fig. S9c). Imputation for this potentially missing study yielded an effect size of 0.60 (95% CI: 0.38, 0.93), which was statistically significant.

Hepatotoxicity grades 3 and 4 A random effect meta-analysis of 2 studies, pooling results from including 271 participants (130 cases and 141 controls), did not show a significant difference in the frequency of hepatotoxicity grades 3 and 4 in individuals after oral bicarbonate regimen ((OR: 1.37, 95% CI: 0.33, 5.72), $P=0.66$) (Fig. 12). There was moderate heterogeneity among studies ($p=0.123$; $I^2=57.94\%$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S10a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S10b).

The trim-and-fill correction suggested one potentially missing study on the left side of the funnel plot (Fig. S10c). Imputation for this potentially missing study yielded an effect size of 2.60 (95% CI: 0.54, 12.63), which was also not statistically significant.

Myelosuppression grades 1 and 2 A random effect meta-analysis of 2 studies, pooling results from including 271 participants (130 cases and 141 controls), did not show any significant differences in the frequency of myelosuppression grades 1 and 2 in individuals after oral bicarbonate regimen compared with those with IV SB regimen ((OR: 0.85, 95% CI: 0.22, 3.23), $P=0.81$) (Fig. 13). There was high heterogeneity among studies ($p=0.017$; $I^2=82.50\%$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S11a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S11b).

The trim-and-fill correction suggested one potentially missing study on the left side of the funnel plot (Fig. S11c). Imputation for this potentially missing study yielded an effect size of 1.61 (95% CI: (0.36, 7.24), which was also not statistically significant.

Myelosuppression grades 3 and 4 Fixed effect meta-analysis of 3 studies, pooling results from including 383 participants (192 cases and 191 controls), did not show any significant differences in the frequency of myelosuppression grades 3

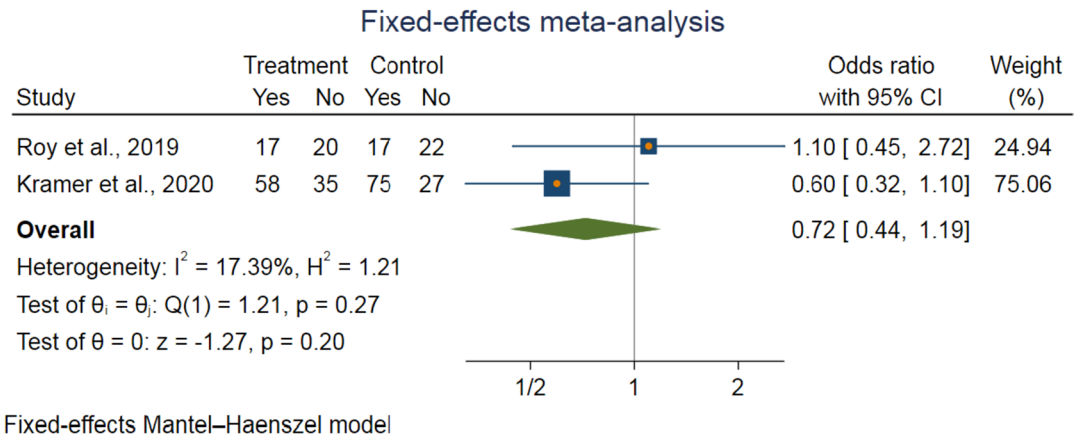

Fig. 11 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in terms of hepatotoxicity grades 1 and 2

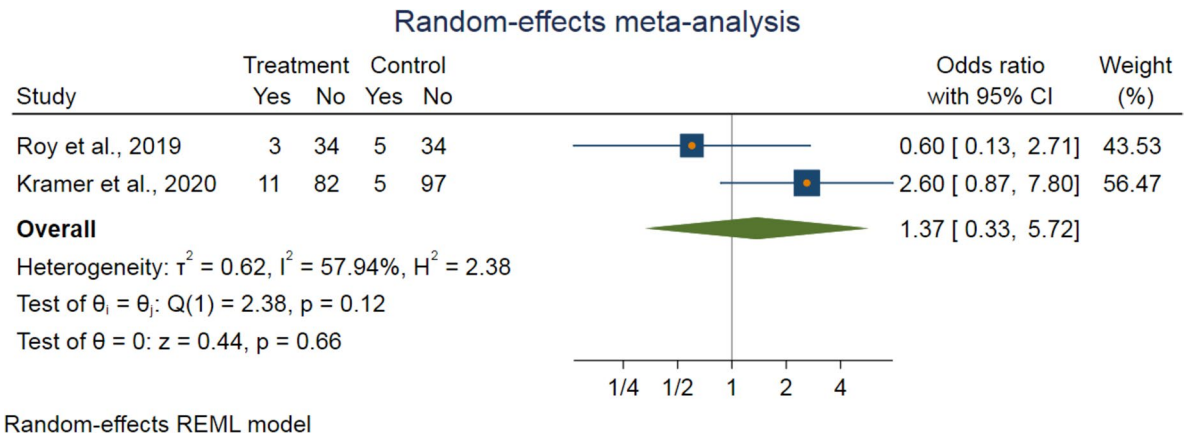

Fig. 12 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in terms of hepatotoxicity grades 3 and 4

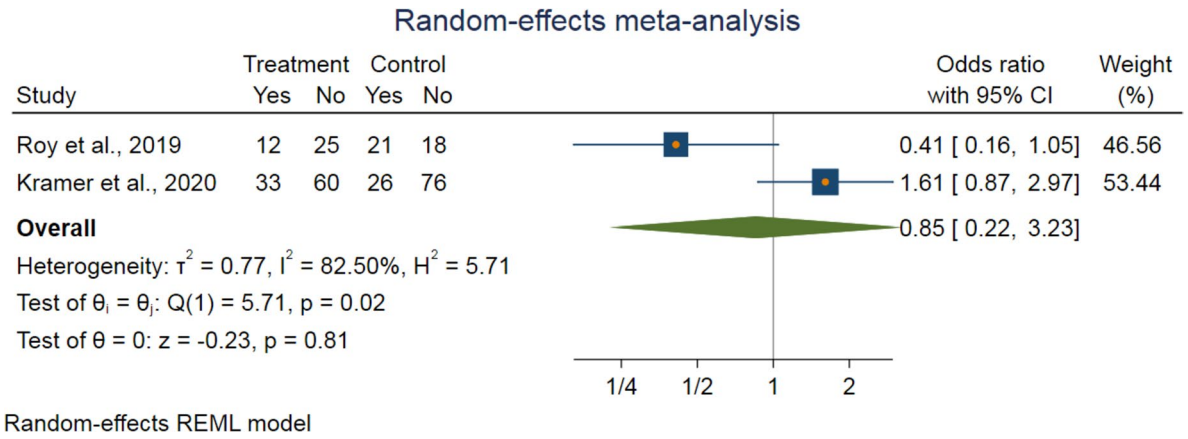

Fig. 13 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in terms of myelosuppression grades 1 and 2

and 4 in individuals who received oral bicarbonate regimen compared with those with IV regimen ((OR: 0.75, 95% CI: 0.46, 1.23), $P=0.26$) (Fig. 14). There was no heterogeneity among studies ($p=0.426$; I2 = 0.00%). Egger test provided no evidence of publication bias or small-study effect (Egger's regression intercept: 1.67 (95% CI: -7.73, 11.06), $P=0.266$). Begg's funnel plot of standard error versus effect size (OR) was asymmetric (Fig. S12a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S12b).

The trim-and-fill correction suggested one potentially missing study on the left side of the funnel plot (Fig. S12c). Imputation for this potentially missing study yielded an effect size of 0.65 (95% CI: (0.42, 1.01), which was also not statistically significant.

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 0.68 (0.40, 1.14) to 1.08 (0.43, 2.72), which indicates the high robustness of the pooled estimates of prevalence (Fig. S12d).

Mucositis Fixed effect meta-analysis of 3 studies, pooling results from including 469 participants (233 cases and 236 controls), did not show any significant differences in the frequency of mucositis in individuals after oral bicarbonate regimen compared with those with standard IV regimen ((OR: 1.01, 95% CI: 0.64, 1.60), $P=0.97$) (Fig. 15). There was no heterogeneity among studies ($p=0.955$; $I^2=0.00\%$). Egger test provides no evidence of publication bias or small-study effect (Egger's regression intercept: -0.51 (95% CI: -11.28, 10.26), $P=0.653$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S13a).

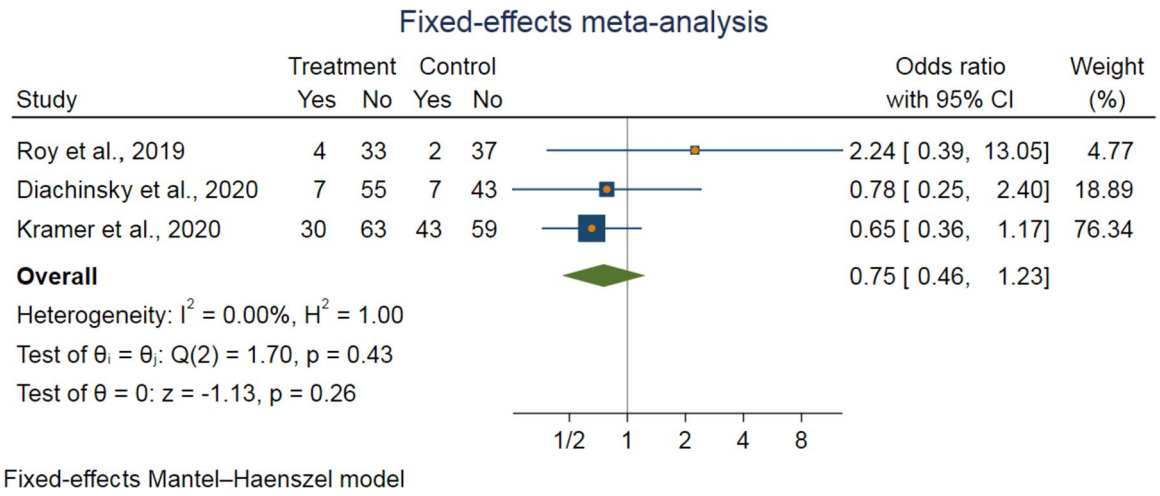

Fig. 14 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens in terms of myelosuppression grades 3 and 4

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S13b).

The trim-and-fill correction suggested one potentially missing study on the left side of the funnel plot (Fig. S13c). Imputation for this potentially missing study yielded an effect size of 1.04 (95% CI: 0.68, 1.58), which was also not statistically significant.

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 0.97 (0.56, 1.70) to 1.04 (0.62, 1.74), which indicates the high robustness of the pooled estimates of prevalence (Fig. S13d).

Diarrhea Fixed effect meta-analysis of 4 studies, pooling results from including 587 participants (292 cases and 295 controls), showed a significant difference in the frequency of diarrhea in individuals after oral bicarbonate regimen compared with those with IV protocol ((OR: 2.92, 95% CI: 1.69, 5.05), $P=0.0001$) (Fig. 16). There was no heterogeneity among studies ($p=0.173$; $I^2=39.90\%$). Egger test provides no evidence of publication bias or small-study effect (Egger's regression intercept: -1.42 (95% CI: -9.09, 6.25), $P=0.509$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S14a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S14b).

The trim-and-fill correction suggested one potentially missing study on the right side of the funnel plot (Fig. S14c). Imputation for this potentially missing study yielded an effect size of 3.08 (95% CI: 1.76, 5.39), which was also statistically significant.

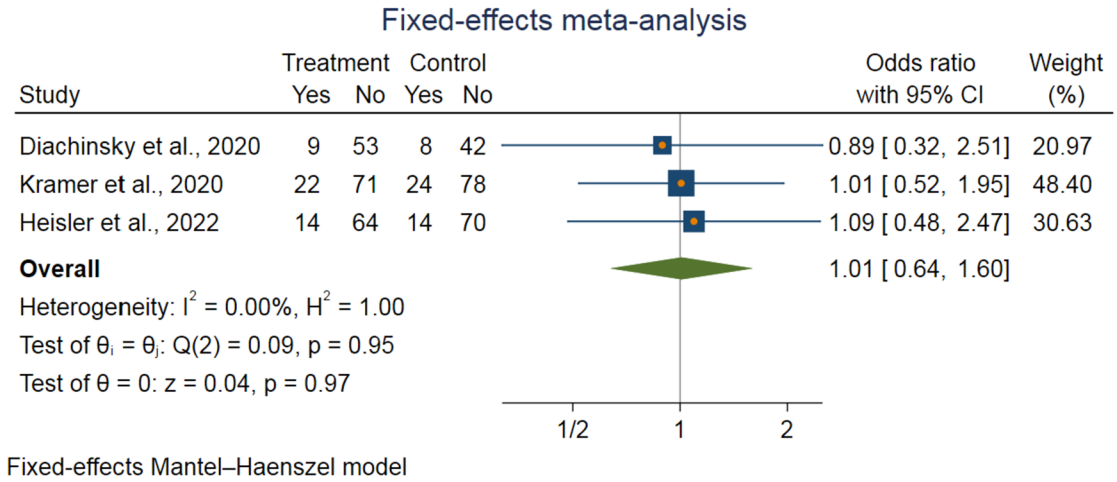

Fig. 15 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens regarding mucositis

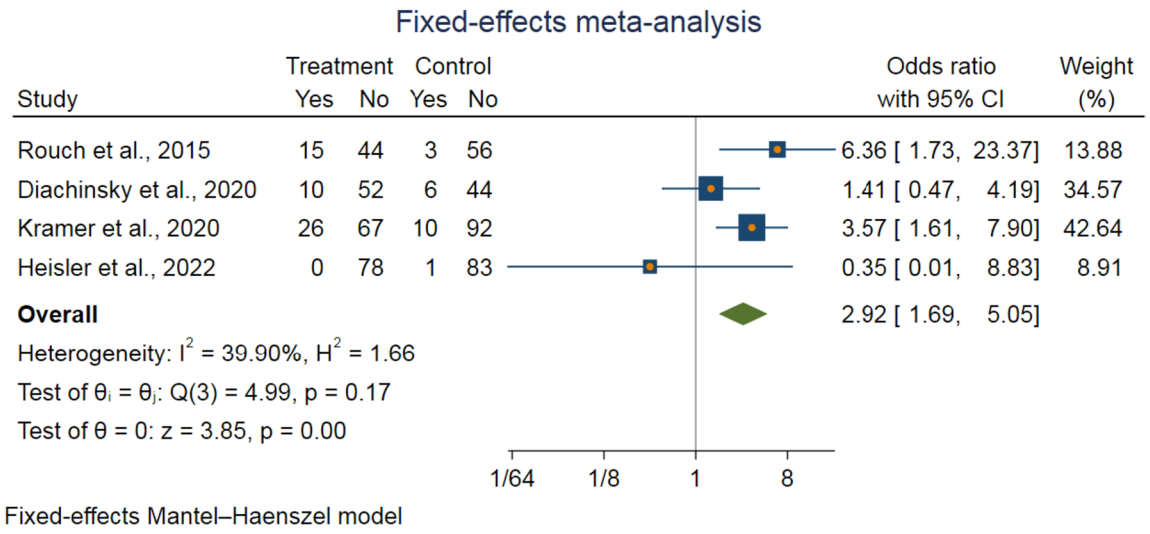

Fig. 16 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens regarding diarrhea

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 2.37 (1.29, 4.37) to 3.72 (1.96, 7.07), which indicates the high robustness of the pooled estimates of prevalence (Fig. S14d).

Emesis A random effect meta-analysis of 3 studies, pooling results from including 469 participants (233 cases and 236 controls), did not show any significant differences in the frequency of emesis in individuals after oral bicarbonate regimen compared with those with standard IV regimen ((OR: 1.32, 95% CI: 0.29, 5.98), $P=0.72$ (Fig. 17). There was no heterogeneity among studies ($p=0.006$; $I^2=85.13\%$). Egger test provides no evidence of publication bias or small-study effect (Egger's regression intercept: 1.02 (95% CI: -74.79, 76.82), $P=0.893$). Begg's funnel plot of standard error versus effect size (OR) was symmetric (Fig. S15a).

A Galbraith plot revealed no studies outside the 95% CI, meaning there were no outliers (Fig. S15b).

The trim-and-fill correction suggested no potentially missing studies on any side of the funnel plot (Fig. S15c).

Sensitivity analyses were done to test the robustness of the observed association. Elimination of any single study at a time from the meta-analysis did range from 0.71 (0.22, 2.33) to 2.40 (0.51, 11.35), which indicates the high robustness of the pooled estimates of prevalence (Fig. S15d).

The overall results of meta-analyzes for the indicators of efficacy and safety have been demonstrated in Table 3 and 4, respectively.

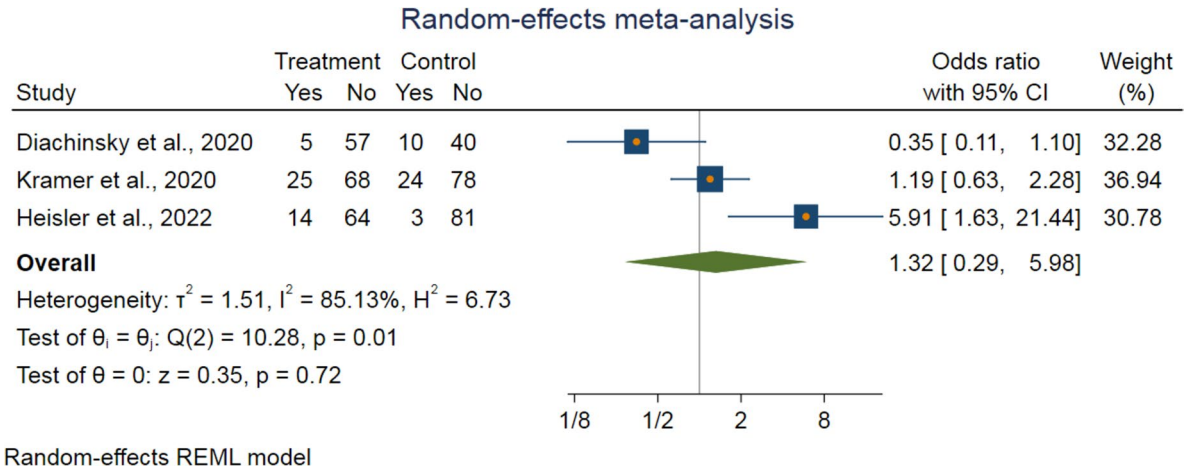

Fig. 17 Forest plot of the pooled OR of the association between the common IV and the oral alkalinization regimens regarding emesis

Table 3 Pooled MDs and ORs in Individuals with oral bicarbonate versus IV protocols

Efficacy Parameters								
Meta-Analysis	n	Total Sample Size	Pooled Mean Difference (95% CI%)	I^2 statistic%	Q Cochran *P*-value	Sensitivity analysis Minimum Estimate% (95% CI%)	Maximum Estimate% (95% CI%)	Egger's *P*-value
Time to MTX Clearance (h)[¥]	5	630	0.06 (−1.00, 1.12)	27.81	0.236	−0.05 (−1.11, 1.02)	1.72 (−4.05, 7.48)	0.653
Time to alkalinization (h)	5	498	−1.00 (−3.04, 1.04)	83.94	0.003	−1.55 (−3.89, 0.79)	−0.28 (−1.52, 0.96)	0.951
Instances urine pH fell to < 7[¥]	2	155	**0.91 (0.32, 1.50)** **0.90 (0.31, 1.49)**[Ψ]	0.00	0.76	–	–	–
Hospital LOS (h)	5	578	−1.93 (−6.11, 2.26)	73.20	0.03	−3.23 (−9.16, 2.70)	−0.45 (−1.78, 0.88)	0.912
Meta-Analysis	n	Total Sample Size	Pooled OR (95% CI%)	I^2 statistic%	Q Cochran *P*-value	Sensitivity analysis Minimum Estimate	Maximum Estimate	Egger's *P*-value
Delayed MTX clearance[¥]	3	324	0.76 (0.43, 1.32) 0.61 **(0.38, 0.96)**[Ψ]	0.00	0.703	0.65 (0.33, 1.28)	0.94 (0.43, 2.09)	0.615

Bolded parameters indicate significant differences between the two groups. *n* Number of studies, *OR* Odds Ratio, ¥ Fixed Effects Model, *Ψ* Imputed estimates based on trim & fill correction

Discussion

As MTX and its metabolites are poorly soluble at acidic pH, increasing urine pH to ≥ 7 enhances the solubility by five- to eightfold, thus decreasing the incidence of crystal formation and nephrotoxicity [2, 29]. By decreasing the drug's renal clearance, MTX nephrotoxicity can lead to other toxicities like myelosuppression, mucositis, GI complications, and hepatotoxicity. Therefore, an appropriate approach to this life-threatening adverse effect may reduce the incidence from 10% to less than 1% [30]. The administration of IV SB as an essential part of the standard pre-treatment with HDMTX has been supported by many studies regarding safety and efficacy [2, 31]. However, oral-based bicarbonate protocol is not well studied yet, even though several reports—mostly following shortages of the IV form—have represented promising results with an alternative of oral protocols (SB tablets or sodium citrate solutions with or without acetazolamide). This article is the first systematic review and meta-analysis comparing oral and IV regimens of bicarbonate for urine alkalinization, including 12 studies with 1296 participants in data analysis.

Summary of main results

Efficacy parameters

SB is orally well absorbed in approximately 15 min and distributed in all body fluids. The oral formulations are expected to be comparable efficacy with IV ones [32]. In the present study, the average time to MTX clearance (h) was not significantly different between the two arms, and this result was aligned with all of the included studies individually. This endpoint is mainly influenced by multiple factors, including the development of AKI contributing to impaired MTX renal clearance, renal hypoperfusion, co-administration of interacting drugs by competing for renal tubular secretion, the total MTX dose, rate of SB IV infusion, genetics, and some other factors which are not well studied [1, 33]; from which, the frequency of different grades of AKI—as the main effecting factor—was also similar between the two arms. The amount of administered SB, as well as the rate of IV hydration, can also impact the time to urinary alkalinization that may lead to the slightly—but not significantly—more rapid alkalinization with the enteral protocol, as discussed by Kintzel et al. [8]. The main idea

Table 4 Pooled ORs for safety parameters in individuals with oral bicarbonate versus IV protocols

Safety Parameters								
Meta-Analysis	n	Total Sample Size	Pooled OR (95% CI%)	I^2 statistic %	Q Cochran *P*-value	Sensitivity analysis		Egger's *P*-value
						Minimum Estimate	Maximum Estimate	
Serum bicarbonate greater than 35 mEq/L	3	392	0.52 (0.19, 1.38)	58.33	0.097	0.33 (0.09, 1.15)	0.80 (0.42, 1.53)	**0.012**
AKI grades 1 and 2¥	7	868	0.74 (0.49, 1.12)	0.00	0.464	0.65 (0.41, 1.03)	0.91 (0.56, 1.49)	0.670
AKI grades 3 and 4¥	4	468	0.87 (0.23, 3.31) 0.68 (0.18, 2.61)Ψ	0.00	0.716	0.61 (0.13, 2.95)	1.48 (0.29, 7.64)	0.895
Hepatotoxicity grades 1 and 2¥	2	271	0.72 (0.44, 1.19) 0.60 **(0.38, 0.93)**Ψ	17.39	0.271	–	–	–
Hepatotoxicity grades 3 and 4	2	271	1.37 (0.33, 5.72) 2.60 (0.54, 12.63)Ψ	57.94	0.123	–	–	–
Myelosuppression grades 1 and 2	2	271	0.85 (0.22, 3.23) 1.61 (0.36, 7.24)Ψ	82.50	0.017	–	–	–
Myelosuppression grades 3 and 4¥	3	383	0.75 (0.46, 1.23) 0.65 (0.42, 1.01)Ψ	0.00	0.426	0.68 (0.40, 1.14)	1.08 (0.43, 2.72)	0.266
Mucositis¥	3	469	1.01 (0.64, 1.60) 1.04 (0.68, 1.58)Ψ	0.00	0.955	0.97 (0.56, 1.70)	1.04 (0.62, 1.74)	0.653
Diarrhea¥	4	587	**2.92 (1.69, 5.05) 3.08 (1.76, 5.39)**Ψ	39.90	0.173	2.37 (1.29, 4.37)	3.72 (1.96, 7.07)	0.509
Emesis	3	469	1.32 (0.29, 5.98)	85.13	0.006	0.71 (0.22, 2.33)	2.40 (0.51, 11.35)	0.893

Bolded parameters indicate significant differences between the two groups. *n* Number of studies, *OR* Odds Ratio, ¥ Fixed Effects Model, *Ψ* Imputed estimates based on trim & fill correction

is that reduced water intake with oral SB may result in less diluted bicarbonate and more rapid equilibration of serum bicarbonate.

Regarding the discrepancies, the instance of urine pH falling to < 7 was significantly greater with oral SB protocol, which could result from poor patients' compliance for taking the medication on oral protocol or less total bicarbonate intake, as Roy et al. l had discussed [12]. Also, the chance of delayed MTX clearance was 24% lower with oral SB regimens after the imputation for 2 potentially missing studies. Since the difference was insignificant in none of the included studies, further investigation is needed to confirm the results. Due to the lack of equivalent information, the total amount of bicarbonate intake could be analyzed for none of the mentioned parameters.

Safety parameters

The primary safety concerns with oral SB regimens were nephrotoxicity and probable GI side effects, which can directly influence patients' tolerability. As prolonged MTX exposure can lead to very severe, life-threatening adverse events, the probable AKI following administration of HDMTX is a medical emergency and one of the key safety indicators. Many factors can lead to nephrotoxicity and AKI, including an acidic environment within the renal tubules

due to insufficient alkalinization and hydration and co-administration of interacting drugs with MTX clearance or plasma protein-binding [10]. The results from the present study demonstrated that oral SB is comparable to IV formulations in the case of preventing AKI, which was in line with the results from all of the included studies individually. As is known, other serious adverse events with MTX, like hepatotoxicity and myelosuppression, mainly result from a previously occurred nephrotoxicity [10]. Again, the imputation for a potentially missing study represented a 40% lower chance of hepatotoxicity grades 1 and 2 with the oral SB regimens, which may result from the small sample size.

Further studies are needed to confirm it. In the case of GI problems, the oral SB had enhanced the risk of diarrhea by approximately three-fold, which was expected because oral intake of hypertonic solutions like sodium citrate or bicarbonate solutions administered in enteral protocols for alkalinization, may lead to water shift to the intestinal lumen due to an intraluminal osmotic load as a possible mechanism for diarrhea [34]. As reported by Kahle et al., even a single ergogenic dose of SB can cause substantial GI distress, including 91% and 45% frequency of diarrhea and nausea, respectively [35]. Three of the 4 included studies for the analysis had reported the same results about diarrhea, except for Heisler et al., who stated that the discrepancy might be due to the administration of acetazolamide and higher doses of SB in the oral protocol in other studies [7]. Heisler et al. also reported a five-fold greater incidence of emesis with the oral SB protocol, which was far from the results of Kramer et al.—with a significantly larger sample size. Since a higher chance of nausea and emesis with oral SB is probable due to many studies [35, 36], further investigations with larger sample sizes and controlled condition of feeding are recommended, due to the important point that co-ingestion of SB with the meal can obviously reduce GI symptoms [36].

Secondary outcomes

Regarding the need for leucovorin rescue following HDMTX, Rouch et al. reported no significant differences in the number of cycles required for increased leucovorin administration [4]. The same results were reported by Heisler et al. [7], which is not far-fetched due to the other findings from efficacy and safety analyses. The other investigations had not reviewed the use of leucovorin rescue in this setting.

In the case of cost-effectiveness, three of included cohorts had reported that the oral protocol offers obvious cost benefits [6, 7, 10], which were not included in our meta-analysis due to different cost-reporting models. Whiteside et al. reported that the costs were fairly similar between the two protocols [15]. The other studies had not evaluated or reported the costs.

Table 5 Recommended commercially available oral alkalinizing preparations for HDMTX urine alkalinization

Name	Ingredient(s)	Dosage form, strength(s)	Alkalinization dosing
Sodium bicarbonate	• Sodium bicarbonate	Tablet, oral: 650 mg (7.7 mEq bicarbonate per tablet)	4 g stat, then 1–2 g q4h unless urine pH ≥ 7
		Powder, oral: 325 mg (3.85 mEq bicarbonate)	4 g stat, then 1–2 g q4h unless urine pH ≥ 7
		Solution, oral: 75 mg sodium bicarbonate per mL (0.89 mEq/mL)	50 mL at first, then 15–30 mL q2-4 h unless urine pH ≥ 7
Bicitra[@]	• Sodium citrate • Citric acid	Solution, oral: 100 mg sodium citrate and 60 mg citric acid per mL (1 mEq/mL)	22.5 mL/m^2/dose q6h unless urine pH ≥ 7
Shohl's[@]	• Sodium citrate • Citric acid	Solution, oral: 500 mg sodium citrate and 300 mg citric acid per 5 mL (1 mEq/mL)	22.5 mL/m^2/dose q6h unless urine pH ≥ 7
Polycitra[@]	• Sodium citrate • Potassium citrate • Citric acid	Solution, oral: 100 mg sodium citrate, 110 mg Potassium citrate and 66.8 mg citric acid per mL (3 mEq/mL)	2 mL/kg q6h unless urine pH ≥ 7
Polycitra K[@]	• Potassium citrate • Citric acid	Solution, oral: 220 mg Potassium citrate and 66.8 mg citric acid per mL (2 mEq/mL)	10–30 mL q6h unless urine pH ≥ 7
Baking soda powder	• Sodium bicarbonate	Powder, oral (59 mEq/ teaspoon)	One teaspoonful stat, then one-half teaspoonful q4h unless urine pH ≥ 7

Stat Immediately, *q4h* Every 4 h, *q6h* Every 6 h

Study implications

Considering previous investigations on oral SB regimens for HDMTX urine alkalinization, the present study has compared every possible reported indicator for assessing efficacy and safety for the first time. All available sources and the most comprehensive databases were employed to maximize the effectiveness of the systematic search. Despite all of the limitations of retrospective cohort studies, appropriate updated analyzing methods were used to demonstrate the outcomes practically. Recommended oral SB regimens based on the results of reviewed studies and concerning the availability of preparations have been represented in Table 5.

Study limitations

Several limitations were faced throughout the present study. First, the sample size was relatively small, which may increase the margin of error. Second, the available studies were mainly retrospective, single-centered cohorts with specific limitations and completely different study designs. Some data was reported in a different non-convertible way from other studies thus, could not be included. Also, results from 3 studies (two retrospective and one prospective) could not be included in the meta-analysis because there was no control IV group [5, 13, 14]. Third, it was not clarified in all the reported methods under exactly which conditions the oral medication was administered since it could have affected the safety outcomes relating to GI complications. Fourth, the effect of oral acetazolamide administration or pre-hospital alkalinization has not been analyzed in this paper, although it was included in the oral alkalinization protocol of several centers. Fifth, the pediatric population was not sub-grouped as there was no evidence implicating any different aspect of safety or efficacy, whereas, in nearly all of the studies, pediatrics were treated with oral citrate-based solutions since they could not digest SB in the form of tablets. Finally, several studies did not report the exact protocol of hydration and the total amount of administered bicarbonate.

Conclusion

Using an oral SB regimen proves to be a safe and effective method for urine alkalinization in patients receiving HDMTX. This approach offers a viable and cost-effective alternative to IV protocols. Further prospective multicenter studies with sub-grouping adult and pediatric populations are required.

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Declarations

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Consent for publication Not applicable.

Competing interests We have no conflict of interests related to this work.

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