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Mismatch repair deficiency and microsatellite instability in urothelial carcinoma: a systematic review and meta-analysis

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Abstract

Background—Mismatch repair deficiency (dMMR) and microsatellite instability-high (MSI-H) occur in a subset of cancers and have been shown to confer sensitivity to immune checkpoint inhibition (ICI); however, there is a lack of prospective data in urothelial carcinoma (UC).

Methods and analysis—We performed a systematic review to estimate the prevalence of dMMR and MSI-H in UC, including survival and clinical outcomes. We searched for studies published up to 26 October 2022 in major scientific databases. We screened 1745 studies and included 110. Meta-analyses were performed if the extracted data were suitable.

Results—The pooled weighted prevalences of dMMR in bladder cancer (BC) and upper tract UC (UTUC) were 2.30% (95% CI 1.12% to 4.65%) and 8.95% (95% CI 6.81% to 11.67%),

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respectively. The pooled weighted prevalences of MSI-H in BC and UTUC were 2.11% (95% CI 0.82% to 5.31%) and 8.36% (95% CI 5.50% to 12.53%), respectively. Comparing localised versus metastatic disease, the pooled weighted prevalences for MSI-H in BC were 5.26% (95% CI 0.86% to 26.12%) and 0.86% (95% CI 0.59% to 1.25%), respectively; and in UTUC, they were 18.04% (95% CI 13.36% to 23.91%) and 4.96% (95% CI 2.72% to 8.86%), respectively. Cumulatively, the response rate in dMMR/MSI-H metastatic UC treated with an ICI was 22/34 (64.7%) compared with 1/9 (11.1%) with chemotherapy.

Conclusion—Both dMMR and MSI-H occur more frequently in UTUC than in BC. In UC, MSI-H occurs more frequently in localised disease than in metastatic disease. These biomarkers may predict sensitivity to ICI in metastatic UC and resistance to cisplatin-based chemotherapy.

INTRODUCTION

Approximately 83 000 cases of urothelial carcinoma (UC) are diagnosed annually in the USA, with upper tract (including renal pelvis and ureter) UC (UTUC) accounting for 5%–10% of diagnoses.[1–3] About one-third of UC patients present with muscle-invasive disease which carries a significant risk of progression to metastatic disease. For most of these patients, radical surgery offers the best likelihood of cure, especially when combined with perioperative systemic therapies.[4–7] In the metastatic setting, systemic options have expanded significantly in recent years, including immune checkpoint inhibitors (ICI), enfortumab vedotin, erdafitinib for patients with *FGFR3*-altered tumours, sacituzumab govitecan and new treatment combinations such as enfortumab vedotin with pembrolizumab[8–12]; however, UC remains an aggressive disease with generally poor outcomes.[3]

Mismatch repair deficiency (dMMR) occurs when there is a loss of one or more of the four MMR proteins: MLH1, MSH2, MSH6 and PMS2. This results in impaired correction of spontaneous mutations in repetitive DNA sequences, leading to a high frequency of nucleotide gain or loss from microsatellite tracts, known as microsatellite instability (MSI).[13 14] Lynch syndrome is an autosomal-dominant inherited deficiency in MMR associated with malignancies including colorectal, endometrial and UTUC.[15 16] A variant of Lynch syndrome, known as Muir-Torre syndrome, is characterised by sebaceous neoplasms or keratoacanthoma in addition to one or more Lynch syndrome-related malignancies.[17 18] Tumours with dMMR or microsatellite instability-high (MSI-H) are associated with a higher expression of tumour neoantigens, which facilitates immune recognition. This immunogenic phenotype increases the susceptibility of tumours to reactivation of an anticancer immune response by ICI.[19–21] Pembrolizumab has a tumour-agnostic FDA approval for use in dMMR/MSI-H metastatic cancers based on phase 2 data.[22 23] Furthermore, recent clinical trials have demonstrated exquisite sensitivity of locally advanced dMMR/MSI-H rectal and colon cancer to ICI, making this a promising treatment modality that could avoid life-altering radical treatment for some patients.[24–26] Based on mostly retrospective data, it is estimated that about 3%–10% of UC will have dMMR or MSI-H.[27 28]

This study aimed to conduct a systematic review and meta-analysis of UC with dMMR or MSI. Our objectives were (1) to estimate the prevalence of dMMR and MSI in localised and

metastatic bladder cancer (BC) and UTUC, (2) to evaluate the activity and/or efficacy of ICI, cisplatin-based chemotherapy and/or other treatment modalities and (3) to estimate survival in this subgroup of patients.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see online supplemental material).[29] The study protocol was approved by all authors and registered on the PROSPERO database (CRD42022365690). Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our study.

We included studies or publications which included patients with BC or UTUC and reported on dMMR and/or MSI-H. Types of studies or publications included clinical trials, prospective observational studies, retrospective studies, case series, case reports,and review articles.

A comprehensive search strategy was developed by a National Institutes of Health librarian (GB) and two authors (EBAC and GMI). The search was performed on 28 October 2022, by GB in PubMed, then translated into multiple databases and peer reviewed. We searched the following electronic databases: PubMed (National Library of Medicine), EMBASE (Elsevier), Cochrane Library (Wiley & Sons), CINAHL (EBSCOhost) and Web of Science (Clarivate Analytics). Grey literature was searched including conference proceedings, and preprints (bioRxiv and medRxiv). In addition to database searches, reference lists of the included publications were evaluated for potentially eligible publications by two authors (EBAC and GMI). The search strategy is available in online supplemental material.

Study selection and data collection

After completing database searches, results were imported by GB into EndNote V.2.0 (Clarivate Analytics), a citation management software. Records were screened using Covidence screening software (Covidence, Melbourne, Victoria, Australia). Selection of eligible publications was conducted independently by two authors (EBAC and GMI), beginning with title and abstract screening followed by full-text screening. Only studies of patients with UC histology were included. Studies which included patients with pure variant histology or other solid tumours were only included if individual patient data on UC patients were available. Studies reporting prevalence of dMMR or germline MMR gene alterations were only included if they tested and/or reported on all four MMR proteins or genes (MLH1, MSH2, MSH6 and PMS2). Given the smaller number of studies reporting prevalence of somatic MMR gene alterations, studies were included even if they did not report data on all four MMR genes. Studies reporting prevalence of MSI-H were included if they used a standardised definition of MSI-H, which was the presence of at least two unstable microsatellite loci either by PCR or next-generation sequencing (NGS). A pathologist (DA) assessed older studies which reported MSI-H based on PCR to ensure that they were included only if the methodology was comparable to more contemporary studies and suitable for meta-analysis. Studies reporting clinical outcomes or survival of dMMR/MSI-H UC patients were included. Case reports were included if the histology was UC and

if they reported outcomes with either local or systemic treatment, or survival. Case reports of patients with multiple malignancies were included if they described the outcome of the UC with local or systemic treatment. Review articles were included if they were on MMR/MSI in UC. Studies reporting prevalence of dMMR/MSI-H/MMR gene alterations which only included patients with special characteristics for example, positive family history were also included in this study; however, their data were reported separately to avoid skewing the results. The exclusion of citations required the agreement of both authors, and in case of disagreements, a third author (ABA) was consulted.

Data extraction was performed independently by three authors (EBAC, GMI and SOA) using a Microsoft Excel template previously developed by all the authors. Meta-analyses were performed if the extracted data were suitable.

Definitions of outcomes

Prevalence was extracted as the number of patients with the characteristic of interest divided by the total number of patients tested. dMMR was defined as loss of expression in at least one MMR protein. The prevalence of dMMR or germline MMR gene alterations could be assessed if all four MMR proteins or genes were tested. Given the smaller number of studies reporting somatic MMR gene alterations in UC, the outcome of interest was modified to the frequency of patients with at least one somatic MMR gene alteration.

To assess the activity and/or efficacy of different modalities of therapy in dMMR/MSI-H UC, the following outcome measures were identified: objective response rate (ORR), disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS). In studies which statistically compared the outcomes of dMMR/MSI-H patients with MMR-proficient (pMMR)/MSI-low (MSI-L)/microsatellite stable (MSS) patients, the summaries of their statistical analyses were extracted, such as HRs, ORs and/or p values.

Risk of bias (quality) assessment

For non-randomised studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental Studies[30] was selected. For descriptive cross-sectional studies, the JBI Critical Appraisal Checklist for Prevalence Studies[31] was used. For case reports and case series, the JBI Critical Appraisal Checklist for Case Reports[32] was used. Assessment of the risk of bias was conducted by two authors (EBAC and SOA). Disagreements were resolved by a third author (ABA).

Statistical analyses

The extracted prevalences for dMMR, MSI-H and germline or somatic gene alterations were separately pooled. Pooled estimates were quantified if there were at least two studies reporting the results of the same outcome using a random intercept logistic regression model.[33] Pooled weighted estimates were reported as prevalences with 95% CIs. The inconsistency index (I^2) was calculated to measure heterogeneity. According to prespecified cutoffs, low heterogeneity was defined as an I^2 of <25%, moderate heterogeneity when I^2 fell between 25% and 75%, and high heterogeneity when I^2 was >75%. Due to the potential heterogeneity among some of the pooled studies, subgroup analyses were explored

but did not yield improved or clinicopathologically valid models. Summaries of these effect measures were calculated using a random effects model to remedy potential heterogeneity among the included studies. Publication bias was assessed using funnel plot asymmetry and Egger's test. All statistical analyses were performed with R V.4.2.2 (The R Foundation for Statistical Computing, 2022), with the use of the meta package.[34]

RESULTS

Study selection and clinicopathological characteristics

The results of the literature search and the study selection process are shown in the PRISMA flow diagram[29] (figure 1). A total of 1745 studies were screened, of which 110 were included: 2 clinical trials,[35 36] 86 retrospective studies,[27 28 37–120] 13 case reports[121–133] and 9 review articles[134–142] (online supplemental table S1). Among all included studies, sex was reported in 13 445 patients (73.4% male; 26.6% female). Age ranged from 17 to 97 years. Among 29 782 patients, primary sites were BC (69.8%), UTUC (19.7%) and not stated (10.5%). No studies included urethral tumours. Disease stage was reported in 7257 patients: localised (M0) in 66.3% and metastatic (M1) in 33.7%. Tumour stage was reported in 4009 patients with localised disease: Ta–T1 (36.7%); T2–T4 (63.3%).

Results of quantitative analyses

Mismatch repair deficiency—29 studies (4759 patients) reported frequencies of dMMR. The pooled weighted prevalence of dMMR in UC patients was 6.03% (95% CI 4.17% to 8.64%) (figure 2). The three most frequent MMR protein loss patterns in UC, BC and UTUC are shown in table 1.

12 studies with 2542 patients reported prevalence of dMMR in BC. The pooled weighted prevalence of dMMR in BC was 2.30% (95% CI 1.12% to 4.65%) (online supplemental figure S1). Four studies reported prevalence of dMMR in localised BC, among which the pooled weighted prevalence of dMMR was 3.09% (95% CI 0.99% to 9.20) (online supplemental figure S2). One study of patients with localised BC had a significantly higher dMMR prevalence[113]; when the meta-analyses were rerun without it, the pooled weighted prevalences of dMMR were 1.78% (95% CI 1.04% to 3.02%) in BC and 1.52% (95% CI 0.98% to 2.34% in localised BC (online supplemental figures S1a and S2a, respectively). No studies specifically reported dMMR prevalence in metastatic BC.

18 studies (2074 patients) reported the prevalence of dMMR in UTUC. The pooled weighted prevalence of dMMR in UTUC was 8.95% (95% CI 6.81% to 11.67%) (online supplemental figure S3). Five studies reported prevalence of dMMR in localised UTUC, among which the pooled weighted prevalence of dMMR was 8.47% (95% CI 5.80% to 12.21%) (online supplemental figure S4). One study of four patients reported dMMR in metastatic UTUC with a prevalence of 25%.[44]

Microsatellite instability-high—38 studies (17 070 patients) reported the prevalence of MSI-H in UC; 21 used PCR and 17 used NGS. The pooled weighted prevalence of MSI-H in UC was 4.54% (95% CI 2.83% to 7.19%) (figure 3). In BC, the pooled weighted prevalence of MSI-H among 16 studies (12 292 patients) was 2.11% (95% CI 0.82% to 5.31%) (online

supplemental figure S5). For localised BC, the pooled weighted prevalence was 5.26% (95% CI 0.86% to 26.12%) (online supplemental figure S6). For metastatic BC, it was 0.86% (95% CI 0.59% to 1.25%) (online supplemental figure S7).

In UTUC, the pooled weighted prevalence of MSI-H among 17 studies (2427 patients) was 8.36% (95% CI 5.50% to 12.53%) (online supplemental figure S8), with pooled weighted prevalence for localised and metastatic UTUC of 18.04% (95% CI 13.36% to 23.91%) and 4.96% (95% CI 2.72% to 8.86%), respectively (online supplemental figures S9 and S10).

Studies of MSI among special populations, that is, patients with PD-L1 positivity, age ≤45 and with *FGFR3* alterations are presented in online supplemental material.

Germline mismatch repair gene alterations—Nine studies (3077 patients) reported germline MMR gene alterations in UC, among which the pooled weighted prevalence was 4.81% (95% CI 2.52% to 8.98%) (online supplemental figure S11). In UTUC, it was 6.53% (95% CI 2.98% to 13.74%) among 6 studies (783 patients) (online supplemental figure S12). As there was a study with significantly outlying results,[40] these meta-analyses were rerun without it, yielding pooled weighted prevalence of germline MMR gene alterations in UC of 3.82% (95% CI 2.36% to 6.12%) and in UTUC of 4.97% (95% CI 2.55% to 9.46%) (online supplemental figures S11a and S12a, respectively). Only one study reported the prevalence of germline MMR gene alterations in BC: 0.43%; 2/463 patients, both of which were *MSH2* gene alterations.[45] The most common germline MMR gene alterations are shown in table 1. Studies of germline MMR gene alterations among special populations, for example, patients with positive family history, are presented in online supplemental material.

Somatic mismatch repair gene alterations—13 studies (5237 patients) reported somatic MMR gene alterations in UC. The pooled weighted frequency of patients with at least one somatic MMR gene alteration was 4.39% (95% CI 1.82% to 10.23%) (online supplemental figure S13). The most common somatic MMR gene alterations are shown in table 1.

In BC, the pooled weighted frequency of patients with at least one somatic MMR gene alteration was 3.02% (95% CI 0.46% to 17.46%) among 5 studies (3286 patients) (online supplemental figure S14). For localised BC, it was 23.81% (95% CI 17.61% to 31.35%); for metastatic BC, it was 1.60% (95% CI 1.13% to 2.25%); however, there were only two studies in each of these meta-analyses (online supplemental figures S15 and S16).

In UTUC, the pooled weighted frequency of patients with at least one somatic MMR gene alteration was 6.79% (95% CI 2.62% to 16.47%) among 6 studies (867 patients) (online supplemental figure S17). One study reported the frequency of at least one somatic gene alteration in localised UTUC (6%).[53] For metastatic UTUC, the pooled weighted frequency between the two studies was 16.39% (95% CI 13.35% to 19.97%) (online supplemental figure S18).

Clinical outcomes of patients with dMMR or microsatellite instability

Eight retrospective studies reported outcomes of patients with localised disease undergoing local therapy (online supplemental table S2). 17 studies reported clinical outcomes of ICI in patients with dMMR/MSI-H UC: 2 clinical trials, 2 retrospective studies and 13 case reports (online supplemental tables S3 and S4). Between these studies, 36 patients had received ICI—35 as treatment for metastatic disease and one as adjuvant treatment post surgery. Disease response was reported in 34 of the 35 patients with metastatic disease. The pooled response rate was 22/34 (64.7%). Best overall response was reported in eight patients: complete response (CR) in 4/8, partial response (PR) in 3/8 and stable disease (SD) in 1/8. Nine patients received chemotherapy for metastatic disease, among whom the best overall responses were: PR in 1/9 (response rate 11.1%), SD in 1/9 and progressive disease in 7/9 (online supplemental tables S3 and S4).

Bias assessment

Assessments of risk of bias and publication bias are available in online supplemental material. Funnel plots were generated for dMMR and MSI-H in UC, BC and UTUC (online supplemental figures S19–S24). There is symmetry in the majority of assessments limiting publication bias, except for dMMR UC and UTUC (online supplemental figures S19 and S21, respectively) where publication bias may exist.

DISCUSSION

Detection of nuclear expression of MLH1, MSH2, PMS2 and MSH6 proteins by immunohistochemistry (IHC) is the gold standard for identifying MMR status, with nuclear loss of at least one of these markers within tumour cells considered dMMR.[143–145] Notably, dMMR is increasingly being detected indirectly by somatic MMR gene alterations on NGS, and small studies have demonstrated concordance with IHC MMR protein loss.[146 147] To determine MSI status, earlier studies employed PCR while more contemporary studies used NGS. The established Bethesda PCR panel consists of five mononucleotides (BAT25, BAT26, D2S123, D5S346 and D17S250), of which at least two must be altered to diagnose MSI-H.[148 149] Although developed for use in colorectal carcinoma, the panel has been used in other solid tumours including UC to detect MSI status.[47 87 95] When only one locus was altered, which defined microsatellite instability-low (MSI-L), the clinical and biological implications were equivocal. Additional mononucleotide repeats in the panel were suggested to increase sensitivity.[149] NGS studies including whole exome sequencing and targeted sequencing assays can determine MSI status by sequencing around microsatellite regions with comparison between tumour and normal tissue.[13 150–153] In large cohorts, validation with PCR and IHC showed 99.1%–99.4% concordance.[154 155] NGS-based methods are more sensitive as they are capable of assessing hundreds to thousands of loci, compared with a limited panel with PCR, which reduces the likelihood of detection of MSI-L tumours.[153] This overcomes the possible subjectivity that arises from using PCR by providing quantitative results. However, since the majority of MSI is caused by epigenetic changes, detecting these by NGS requires more complex analysis and interpretation.

Notably, the pooled weighted prevalences of MSI-H and somatic dMMR gene alterations were higher in localised BC (stage M0) compared with metastatic BC, and in UTUC, the pooled weighted prevalence of MSI-H was also higher in localised disease. The higher prevalence of these characteristics in localised disease has also been observed in colorectal cancer[156 157] and may be due to higher neoantigen load of MSI-H/dMMR tumours stimulating an antitumour immune response; hence reducing the likelihood of metastases.[157] Interestingly, there was also a difference in the pattern of MMR protein loss in UTUC compared with BC. In UTUC, MSH2 and MSH6 were the most frequent MMR proteins and/or genes lost or altered (both somatic and germline), whereas the trend was not as clear in BC. This contrasts with dMMR colorectal cancer, in which 90% of cases are due to loss of *MLH1* and *MSH2* genes.[158 159]

We found a higher prevalence of germline MMR gene alterations in patients with UTUC or a positive family history; hence, germline testing should be discussed in these situations. In colorectal cancer, in which the prevalence of Lynch syndrome is also relatively low, around 5%,[160] universal germline testing is recommended.[161] The increasingly routine performance of NGS, especially in metastatic UC, will identify more patients with either MSI-H or somatic MMR gene alterations, which will likely result in more germline testing being performed. Identification of a germline MMR gene alteration will have significant implications for patients and their families. A prior study showed that the standardised incidence ratio of developing BC was 8.2-fold and 16.2-fold higher in males and females, respectively, harbouring MMR germline variants compared with the general population.[162] The risk was highest for *MSH2* germline carriers. Moreover, the risk of developing subsequent urothelial cancers was >100 fold higher in MMR germline carriers. Another study showed that in patients harbouring pathogenic Lynch syndrome-associated variants, the risk of developing urinary tract tumours by age 75 was 24.9% for *MSH2* carriers, 11% for *MSH6* carriers and 8% for *MLH1* carriers. In comparison, risks of developing colorectal cancer were 43%, 15% and 45.8%, for *MSH2*, *MSH6* and *MLH1* carriers, respectively.[163] For individuals with germline MMR gene alterations, the National Comprehensive Cancer Network guidelines do not recommend routine surveillance for UC due to lack of clear supporting evidence, although it is recommended for individuals with a family history of UC. The considerably higher risk of developing BC, especially among *MSH2* carriers, could inform surveillance guidelines. For colorectal cancer, the detection of germline MMR gene alterations has clear surveillance implications, including earlier and more frequent colonoscopies.[161]

We found that dMMR and MSI-H metastatic UC is responsive to ICI, with included studies reporting ORRs of 50%–90%,[35 36 39 101] deep responses[35 36 39 101 121 126 164] and long durations of response[121 123 126 132] (online supplemental tables S3 and S4). These data show that dMMR and MSI-H may be predictive biomarkers for response to ICI in UC, which has already been prospectively demonstrated in solid tumours.[20] Indeed, pembrolizumab received accelerated FDA approval for use in any metastatic solid tumours with dMMR or MSI-H based on clinical activity demonstrated in the phase 2 Keynote-158 trial.[20 23] The response of dMMR/MSI-H metastatic UC to chemotherapy is less encouraging, with high rates of primary progression[101 122 132 133] and short PFS.[101] The high rates and long durations of response to ICI and the lower likelihood of disease control with chemotherapy

shown in this systematic review raise the question of whether these patients should receive ICI monotherapy upfront for metastatic disease. This question remains even with the standard of care for untreated metastatic UC recently changing to enfortumab vedotin (EV) plus pembrolizumab as it is unknown whether this subset of patients will do just as well receiving the agents sequentially instead of concurrently, which will limit or delay treatment related toxicity.[165 166] For localised disease, there is conflicting evidence. Some studies suggest superior DFS compared with pMMR/MSI-L/MSS patients and high rates of local control[67 77]; other studies suggest no difference in outcomes.[96 98] Some studies suggest a propensity for dMMR/MSI-H patients to have multifocal, bilateral and/or both bladder and upper tract disease, either synchronously or metachronously.[67 77] A novel approach for the treatment of localised dMMR/MSI-H tumours which has seen impressive results in rectal[24] and colon cancer[25 26] is definitive treatment with ICI, known as immunoablation. In the phase 2 dMMR rectal cancer trial, there was a 100% clinical CR rate among the first 14 participants with stage II and stage III disease who were treated with the anti-PD-1 antibody dostarlimab, and no recurrences at a median follow-up of 6.8 months. None of the patients had required chemotherapy, radiotherapy or surgery up to the latest data cut-off; however, longer follow-up is needed to confirm the success of this approach.[24 167] In the phase 2 NICHE-2 trial which enrolled 112 patients with locally advanced dMMR colon cancer, patients were given two cycles of ICI (first ipilimumab/nivolumab, then nivolumab) before proceeding to surgery. Remarkably, 95% of patients attained a major pathological response, defined as <10% residual viable tumour, and 67% of patients attained a pathologic CR.[26] A systematic review assessing neoadjuvant ICI in 423 patients with dMMR/MSI-H localised colorectal cancer reported CR (pathological CR plus clinical CR) of 72% and a complete resection (R0) rate of 99.3%.[168] These results suggest a need to develop similar trials in dMMR/MSI-H muscle-invasive or locally advanced UC, as these could revolutionise the treatment landscape for these patients. This approach may allow patients to avoid the quality-of-life impacts of radical surgery or trimodality therapy and potentially be effective for multifocal localised disease without the need for multiple procedures.

Survival in patients with dMMR/MSI-H may be favourable. In one study, all 10 patients with advanced or metastatic disease survived beyond 15.5 months after ICI[39]; in another study, 77% of 26 patients lived beyond 2 years.[101] Univariate analyses have demonstrated superior OS in patients with dMMR/MSI-H compared with patients without these characteristics[84 95 113]; however, other studies show no difference in survival.[96 109] Of note, most of these studies are small and retrospective, which increases the risk of bias. Comparatively, in localised and advanced colorectal cancer, MSI-H has been shown to be favourably prognostic for survival.[169–171] In UC, it is likely that OS will depend on treatment for advanced disease. Newer studies with more patients receiving ICI may demonstrate a greater degree of improvement in survival compared with pMMR/MSI-L/MSS patients.

Study limitations

There was heterogeneity in MSI detection techniques among included studies due to their significant evolution over the last two decades. Consequently, the MSI-H prevalence data that were meta-analysed were likely not completely standardised. The focus of this

systematic review was on dMMR and MSI-H in UC; however, our search results also yielded studies focusing on germline and somatic gene alterations, which we included due to their relevance to the topic. As this study was not primarily designed to search for genetic and genomic studies, our search may not have comprehensively included these studies. The response rates of dMMR/MSI-H patients to ICI and chemotherapy were pooled from separate studies; hence, they are only crude estimates. Lastly, the survival of patients with dMMR or MSI-H UC and the prognostic value of these biomarkers could not be estimated or meta-analysed due to a lack of uniformity in the data.

CONCLUSION

To the best of our knowledge, this is the first systematic review and meta-analysis to examine dMMR and MSI-H in UC. We found that these characteristics occur more commonly in UTUC than in BC and may occur more frequently in localised disease than in metastatic disease. In UC, dMMR or MSI-H may be predictive of response to ICI and negatively predictive of response to cisplatin-based chemotherapy. Our findings support the development of studies employing novel immunotherapeutic approaches for this small but important subset of patients. Finally, the role of universal germline testing in UC is still unclear; however, it should be offered in patients with a positive personal or family history of Lynch-related malignancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

Data are available on reasonable request.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

In solid tumours, mismatch repair deficiency (dMMR) and microsatellite instability-high (MSI-H) confer a sensitivity to immune checkpoint inhibition (ICI); however, there is a paucity of prospective data on the prevalence of these characteristics in urothelial carcinoma, whether they are predictive for response to ICI or other treatment modalities, and whether they are prognostic. Their prevalence by primary tumour site (bladder vs upper tract) or stage (localised vs metastatic) is not well described.

WHAT THIS STUDY ADDS

Our study found that dMMR and MSI-Hare approximately three times more prevalent in upper tract urothelial carcinoma (dMMR 8.95%; MSI-H 8.36%) than in bladder cancer (dMMR 3.09%; MSI-H 2.11%), and that MSI-H occurs more frequently in localised disease compared with metastatic disease. We also found that dMMR or MSI-H may confer high sensitivity to ICI and resistance to chemotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Our findings provide a rationale for clinical trials of ICI in dMMR/MSI-H UC which in the localised setting, may spare patients the morbidities of radical surgery, and in the metastatic setting, allow them to avoid or delay the toxicities of chemotherapy or antibody-drug conjugates.

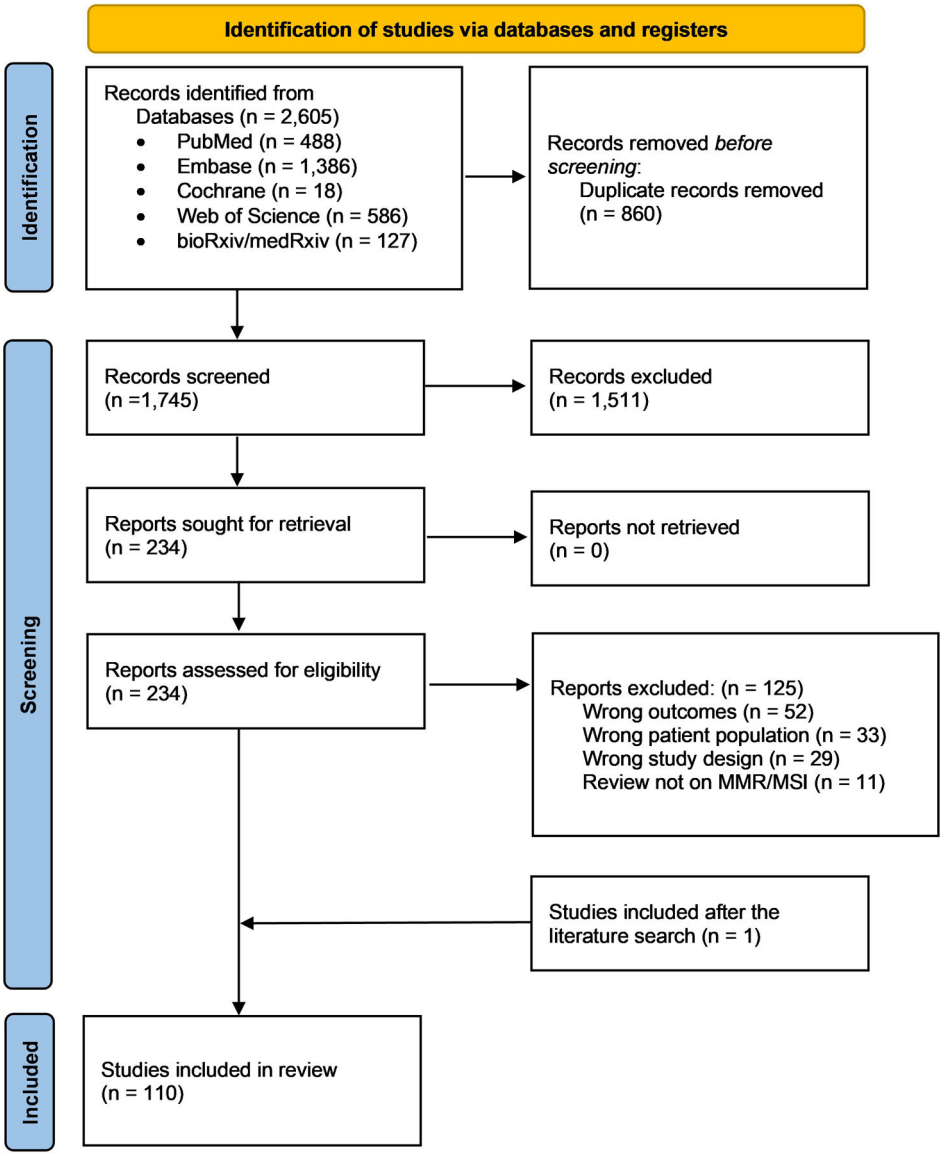

Figure 1.

PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

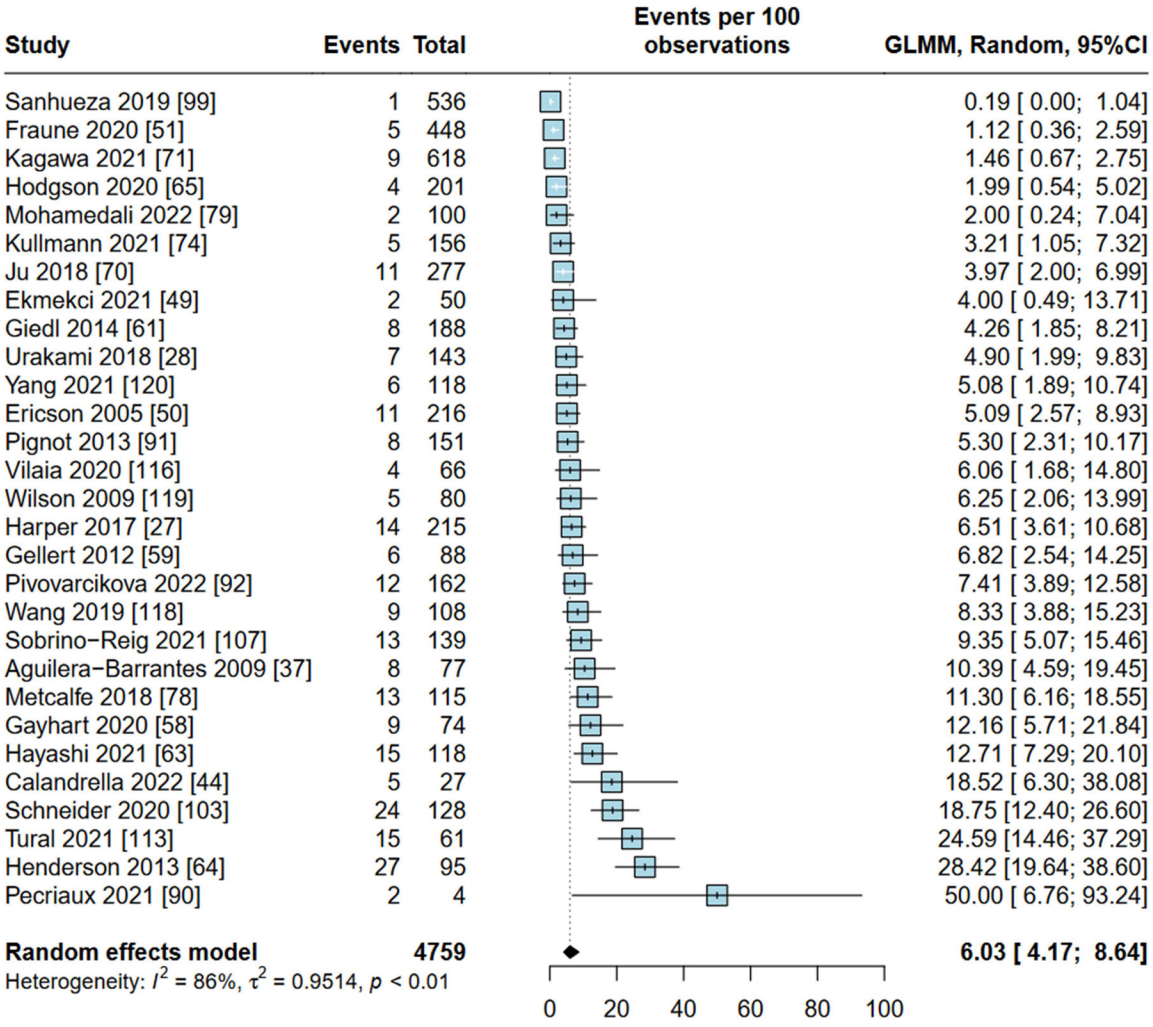

Figure 2.

Forest plot of included studies reporting on prevalence of mismatch repair deficiency in urothelial carcinoma. GLMM, generalised linear mixed models.

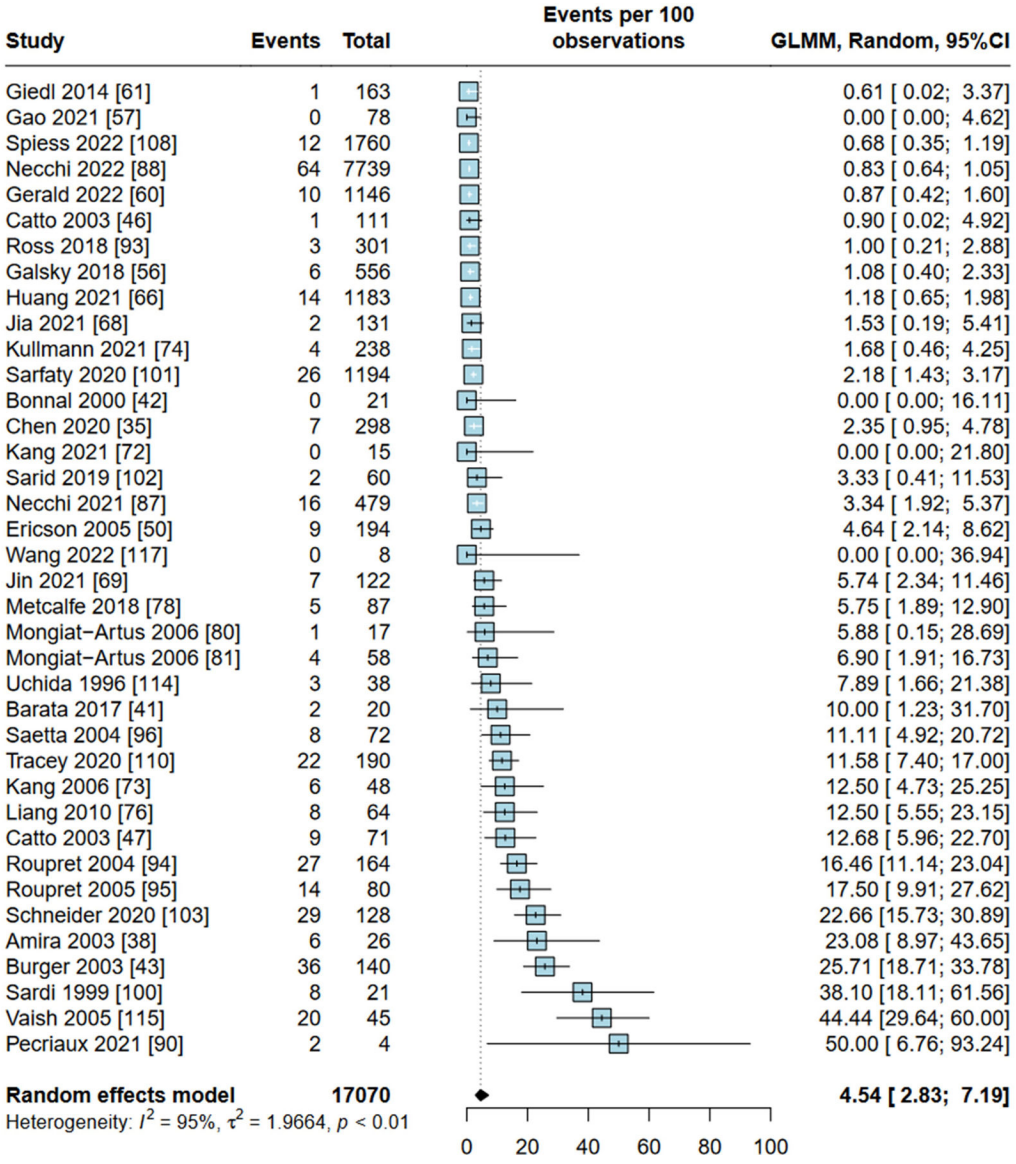

Figure 3.

Forest plot of included studies reporting on prevalence of microsatellite instability-high in urothelial carcinoma. GLMM, generalised linear mixed models.

Table 1

The three most common mismatch repair (MMR) protein losses and germline and somatic mismatch repair gene alterations in urothelial carcinoma (UC), bladder cancer (BC) and upper tract urothelial carcinoma (UTUC)

Tumour	UC	BC	UTUC
MMR protein loss pattern (frequency)	**MSH2 and MSH6** 63/3903 (1.6%)	**PMS2** 9/1671 (0.5%)	**MSH2 and MSH6** 56/1465 (3.8%)
	MSH6 57/3903 (1.5%)	**MLH1 and PMS2** 8/1671 (0.5%)	**MSH6** 49/1465 (3.3%)
	MLH1 and PMS2 13/3903 (0.3%)	**MSH6** 7/1671 (0.4%)	**MLH1 and PMS2** 4/1465 (0.3%)
Germline MMR gene alteration (frequency)	**MSH2** 33/1084 (3.0%)	**MSH2** 2/463 (0.4%)	**MSH2** 31/621 (5.0%)
	MSH6 10/1084 (0.9%)	Not available	**MSH6** 10/621 (1.6%)
	MLH1 8/1084 (0.7%)	Not available	**MLH1** 8/621 (1.3%)
Somatic MMR gene alteration (frequency)	**MSH6** 70/3895 (1.8%)	**MSH6** 24/3181 (0.8%)	**MSH6** 36/765 (4.7%)
	MLH1 41/3895 (1.1%)	**MSH2** 9/3181 (0.3%)	**MSH2** 25/765 (3.3%)
	MSH2 31/3895 (0.8%)	**MLH1** 8/3181 (0.3%)	**MLH1** 18/765 (2.4%)

MLH1, MutL protein homolog 1; MSH2, MutS protein homolog 2; MSH6, MutS protein homolog 6; PMS2, postmeiotic segregation increased 2.