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REVIEW ARTICLE

Incidence characteristics of testicular microlithiasis and its association with risk of primary testicular tumors in children: a systematic review and meta-analysis

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Abstract

Background To systematically evaluate the incidence characteristics of testicular microlithiasis (TM) in children and its association with primary testicular tumors (PTT).

Methods A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. A priori protocol was registered in the PROSPERO database (CRD42018111119), and a literature search of all relevant studies published until February 2019 was performed. Prospective, retrospective cohort, or cross-sectional studies containing ultrasonography (US) data on the incidence of TM or the association between TM and PTT were eligible for inclusion.

Results Of the 102 identified articles, 18 studies involving 58,195 children were included in the final analysis. The overall incidence of TM in children with additional risk factors for PTT was 2.7%. In children, the proportion of left TM in unilateral cases was 55.7%, the frequency of bilateral TM was 69.0%, and proportion of classic TM was 71.8% [95% confidence interval (CI) 62.4–81.1%, $P=0.0$, $I^2=0.0\%$]. About 93.5% of TM remained unchanged, and newly detected PTT rate was very low (4/296) during follow-up. The overall risk ratio of TM in children with a concurrent diagnosis of PTT was 15.46 (95% CI 6.93–34.47, $P<0.00001$).

Conclusions The incidence of TM in children is highly variable. Nonetheless, TM is usually bilateral, of the classic type, and remains stable or unchanged at follow-up. Pediatric patients with TM and contributing factors for PTT have an increased risk for PTT; however, there is no evidence to support mandatory US surveillance of children with TM.

Keywords Children · Incidence · Primary testicular tumors · Testicular microlithiasis

Introduction

Testicular microlithiasis (TM) is usually incidentally detected by scrotal ultrasonography (US) and is characterized by calcium deposits in the seminiferous tubules [1]. TM can be identified as punctuate, nonshadowing echogenic foci on US [2]. Clinically, the most accepted

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classification of TM is classic TM (CTM) and limited TM (LTM). LTM is defined as < 5 echogenic foci in both testes, while CTM is defined as ≥ 5 foci in either or both testes [3]. TM is thought to be due to abnormal calcification or the presence of debris in the spermatogenic tubules. However, the exact cause of these calcifications is unknown.

The incidence of TM varies considerably between children according to the study periods, age groups and geographic locations [2]. The incidence of TM ranges from 0.7% to 8.7% in children with potential risk factors for primary testicular tumors (PTT) (testicular pain, testicular masses, infertility/subfertility, personal or family history of TT, cryptorchidism, or other reasons for scrotal US) [2, 4–11], and 4.1% to 4.2% in asymptomatic children [1, 12] according to currently published papers.

The annual incidence of PTT is 3–5 cases per 100,000 men. PTT is the most common tumor in young adults, in which the prognosis is favorable if the condition is diagnosed and treated early. Although many studies determined the prevalence of TM and its association with PTT in the past 20 years, the association between TM and PTT is still under debate, especially in pediatric population [2, 4, 9, 10, 13–21]. Some studies found that TM was benign and did not require regular follow-up whereas more contemporary studies recommended a strict follow-up. Consequently, the condition is clinically significant because of its association with testicular malignancy and the potentially elevated risk of malignancy in patients with isolated TM (without a concurrent diagnosis of TT).

To the best of our knowledge, several systematic reviews and meta-analysis have been conducted to determine the association between TM and PTT in adult population [22–24], while no systematic reviews on pediatric patients with TM has ever been conducted. And this relevance remains eagerly to be clarified. In addition, there was no systematic review to date determined the incidence characteristics of TM in pediatric populations, including asymptomatic patients with otherwise good clinical outcomes and patients with concurrent urinogenital abnormalities, subtypes of CTM or LTM, unilateral and bilateral TM, according to study periods and age groups. Furthermore, the association between TM and PTT in children remains to be revealed.

There are currently no evidence-based guideline for pediatric urologists and clinicians to guide decision-making for patients with TM. The aim of this systematic review and meta-analysis is to critically explore these topics and their relevance between TM and PTT to aid decision-making and guide future research in children.

Methods

Registry

This study was registered in the PROSPERO database (CRD42018111119). The aims and methods of the investigation were described on February 22, 2019. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [25].

Information sources and search strategy

The systematic literature search of databases was conducted by two independent reviewers on February 22, 2019. The articles that contained relevant information on TM and PTT of pediatrics were initially searched from PubMed, Cochrane Library, Web of Science Database, Science Direct, China National Knowledge Infrastructure and Wanfang Data. The string terms TM and PTT or synonyms were searched using Boolean operators. Only pediatric population were considered to be included. A MeSH terms search and keywords search were combined. The references of the included studies and reviews were also manually searched.

Definitions and study design

The study population was divided into three groups according to the reasons for US for subgroup analysis: (1) asymptomatic, military volunteers or healthy controls with otherwise good clinical outcomes; (2) symptomatic, including patients with scrotal pain, scrotal masses, swelling, testicular torsion, varicocele, hydrocele or other urogenital symptoms; (3) referral for US examination without providing specific reasons for this examination. The latter two groups were combined as the TM patients with potential risk factors for PTT. The rates of these complications were analyzed separately and then combined to assess the overall effect.

Given the recent advances in US technology, the study period was stratified into three categories—until 2009, 2009–2013, and after 2013—to determine whether the incidence of TM and its association with PTT varied with time. The subtypes of CTM or LTM, unilateral and bilateral TM, and the association of TM and PTT were also analyzed. No other analyses consider age group differences because of the complexity of the analysis of this variable and data limitations.

Apart from comparing the rate of concurrent diagnosis of PTT in patients with and without TM, we also made effort to investigate the interval development of TT. The follow-up information of patients with isolated TM was assessed. And a new incidence rate (number of cases per 10,000 person-months of follow-up) was measured to determine the incidence of PTT in these patients with time concerned.

Eligibility criteria

(1) Pediatric studies (pediatrics defined as age under 19) with statistical data on the incidence/follow-up information of TM or comparative data on the association between TM and PTT; (2) detection of TM by US; (3) when overlapping or duplicate data were found, the most recent or complete data were considered.

Exclusion criteria

(1) Case reports, clinical series, reviews, comments, editorial letters and animal studies; (2) repeated studies or studies with incomplete data; (3) studies that performed the pathological diagnosis of TM without radiological diagnosis; (4) cellular, molecular, or histological studies on TM; (5) studies focused on radiological features/improvements in the detection of TM or microlithiasis in other locations; (6) studies containing only adult patients.

Study selection and data extraction

Two collaborators independently reviewed the electronically and manually retrieved articles. After screening the titles and abstracts, potentially relevant studies were selected. A full-text review was performed subsequently. All disagreements were solved by discussion or by a third reviewer.

Each included article was thoroughly reviewed. The following data were extracted (Table 1): first author, year, location, study period, sample size, population and transducer frequency of US. In addition, the following seven items were marked with "$\surd$" for convenience of recognizing the paper contents: incidence of TM, subtypes of PTT, type of TM, follow-up period, laterality of TM, additional risk factors for PTT and stratification according to age groups.

The incidence of TM was determined using data from specific groups (asymptomatic patients, patients with additional risk factors for PTT and patients with CTM/LTM) and data on the laterality of TM and stratification according to age groups (Supplementary Table 1).

The association between TM, overall incidence of testicular germ-cell tumor (TGCT) and the incidence of TGCT in children in different periods according to sample size and follow-up time and strategy is depicted in Table 2. An e-mail was sent to the authors when the included articles published in the past 10 years contained incomplete data.

Quality assessment

The quality of the studies was assessed using the Agency for Healthcare Research and Quality (AHRQ), with modifications to match the needs of the current meta-analysis. The questionnaire contained 11 items, in which each item had three possible answers: "Yes," "No," or "Unclear" (Supplementary Table 2).

Statistical analysis

STATA software version 15.0

The mean incidence of TM was determined by meta-analysis of single rate. The meta-analysis of risk ratios (RRs) was performed using STATA 15.0 software (Stata Corporation, College Station, Texas, USA) and the random effects model, which assigned a weight to each study based on both within-study variance and between-study heterogeneity. The commands used in the meta-analysis after installing the meta package were ssc install metan (data editing); gen rate = case/total; gen ser = sqrt(rate*(1–rate)/total); metan rate ser, label (namevar = author year) by (subgroup) random. The mean incidence of TM in asymptomatic patients and patients with additional risk factors for PTT according to the study periods, CTM/LTM and age groups was measured separately using these commands. The laterality of TM was also determined. Begg's adjusted rank correlation test and Egger's regression asymmetry test were used for assessing publication bias. Publication biases with a P value larger than 0.05 in both tests were considered not significant.

RevMan software version 5.3

Dichotomous variables were analyzed using Review Manager version 5.3 (Cochrane Collaboration, Oxford, United Kingdom) and the Mantel–Haenszel method. The crude RRs and their 95% confidence intervals (CIs) were calculated using random effects models to determine the association between TM and PTT. The heterogeneity of the studies was tested using both the χ^2 test ($P \geq 0.1$ indicated low heterogeneity) and inconsistency index (I^2) statistics. Publication bias was assessed by funnel plots. Begg's test and Egger's test were adopted (by STATA) if the funnel plot symmetry was not easy to recognize. The χ^2 test was used to determine inter-subgroup differences. P values smaller than 0.05 were considered significant.

Table 1 Extracted fundamental materials and data of included studies

Authors	Year	Country/zone	Study type	Study period	Sample size	Populations	Transducer frequency of US (MHz)	Definition of microlithiasis	Prevalence of TM	Subtypes of PTT	Specific type of TM	Follow-up info	Laterality of TM	Additional risk factors for PTT	Stratification of age category
Chiang et al. [4]	2012	Singapore	Retrospective cross-sectional study	January 2002–September 2007	563	Pediatric population with clinical indications	12.5	NR	√			√		√	
Cooper et al. [2]	2014	USA	Retrospective cohort study	January 2003–December 2012	3370	Patients younger than 18 y	12–17	CTM, LTM	√	√	√	√	√	√	√
Dagash et al. [26]	2007	UK	Retrospective cross-sectional study	January 1990–April 2004	623	All children referred for scrotal US	NR	NR	√			√		√	
Deganello et al. [5]	2012	London, UK	Retrospective cohort study	September 2006–April 2011	516	Patients less than 19 y	NR	LTM, CTM	√		√				
Dutra et al. [6]	2011	Brazil	Prospective cohort study	January 2005–January 2010	1504	Children ranging from 1 to 15 y	10	Hyperechogenic microliths measuring less than 3 mm in diameter; diffuse or focal	√		√	√	√	√	
Furness et al. [27]	1998	Illinois, USA	Multi-institutional prospective study	NA	26	Pediatric population with incidentally diagnosed TM	NR	NR				√			
Goede et al. [3][a]	2010	The Netherlands	Prospective cohort study	Since mid-1990s	501	Boys and young men	12	CTM, LTM	√		√	√		√	√

Table 1 (continued)

Authors	Year	Country/zone	Study type	Study period	Sample size	Populations	Transducer frequency of US (MHz)	Definition of microlithiasis	Prevalence of TM	Subtypes of PTT	Specific type of TM	Follow-up info	Laterality of TM	Additional risk factors for PTT	Stratification of age category
Leenen et al. [7]	2002	Germany	Retrospective cross-sectional study	January 1996–July 1999	850	Pediatrics patients referred for US in one institution	7.5	Diffuse TM, focal TM	√		√	√	√		
Marte et al. [28]	2017	Italy	Multicenter prospective cohort study	January 2008–December 2014	81	Patients with TM from 11 units		CTM, LTM		√	√	√			
Miller et al. [29]	2007	UK	Retrospective cohort study	May 1995–May 2000	3477	All patients referred for US in a single institution	8–4	TM or non-TM testicular calcification	√					√	
Nishimura et al. [30]	2017	Japan	Retrospective cross-sectional study	January 2009–May 2016	65	Children who underwent orchiopexy	6–18	CTM, LTM	√		√		√	√	
Otite et al. [20]	2001	UK	Retrospective cohort study	1994–1999	3026	All patients underwent US examination of the scrotum for various testicular symptoms	7	CTM	√	√	√[b]	√	√	√	√

Table 1 (continued)

Authors	Year	Country/zone	Study type	Study period	Sample size	Populations	Transducer frequency of US (MHz)	Definition of microlithiasis	Prevalence of TM	Subtypes of PTT	Specific type of TM	Follow-up info	Laterality of TM	Additional risk factors for PTT	Stratification of age category
Poyrazoglu et al. [1]	2010	Turkey	Retrospective cross-sectional study	2007–2008	90	Pediatric patients with congenital adrenal hyperplasia and a healthy control group	12	CTM, LTM, and CTM divided into grade 1–3	√		√		√	√	
Rhee et al. [8]	2012	USA	Retrospective cross-sectional study	January 2003–August 2011	2484	All patient referred for US younger than 19 y	NR	NR	√	√		√			
Trout et al. [9]	2017	USA	Multisite retrospective study	January 2000–May 2014	37,863	Boys younger than 18 y	9–15	CTM, LTM	√	√	√[b]		√		
Volokhina et al. [10]	2014	USA	Retrospective cohort study	2000–2011	2266	Pediatric patients referred for US with various reasons	NR	CTM	√	√	√[b]	√		√	
Xia et al. [31]	2002	China	Retrospective cross-sectional study	March 1999–April 2001	453	Pediatric patients referred for US	4–10	NR	√			√	√		
Yesil et al. [11]	2016	Turkey	Retrospective cross-sectional study	2008–2015	2477	Children	NR	Diffuse TM, focal TM, CTM, LTM	√		√	√	√	√	√[c]

TM testicular microlithiasis, *CTM* classic TM, *LTM* limited TM, *PTT* primary testicular tumors, *TGCT* testicular germ-cell tumors, *US* ultrasonography, *NR* not reported. [a]Pediatrics + young people, divided into the children group; [b]Only the classic testicular microlithiasis; [c]Available data on the stratification of age category on diffuse and focal testicular microlithiasis

Results

Identification and eligibility of the studies

The initial database search yielded 102 articles (Fig. 1). Another two articles were found by manual searching. After eliminating eight duplicate articles, 96 titles and abstracts were screened. After comprehensively screening 25 full texts, 18 manuscripts complied with the eligibility criteria of this meta-analysis [1–11, 20, 26–31], 16 studies evaluated the incidence of TM and 5 manuscripts compared the association between TM and PTT.

Quality assessment

There is no quantitative evaluation of the AHRQ questionnaire. The 11 items used to score the included studies are shown in Supplementary Table 2. Almost all the studies that determined the association between TM and PTT had an acceptable quality.

Incidence of TM

The individual incidence of TM in children is shown in Supplementary Table 1. The pooled mean incidence of TM with 95% CI using I^2 in children is shown in Table 3.

Overall incidence of TM

Eighteen studies involving 58,195 children were evaluated to determine the incidence of TM. Two studies assessed the incidence of TM in asymptomatic patients. The mean incidence of TM in the asymptomatic pediatric population was 4.2% (95% CI 2.7–5.6%, $P=0.0$, $I^2=0\%$).

The population with potential risk factors for PTT was stratified into two main subgroups—symptomatic, referred for US—according to the reasons for scrotal US. The overall incidence of TM in children with additional risk factors for PTT was 2.7% (95% CI 2.0–3.3%, $P=0.0$, $I^2=92.0\%$). The mean incidence of TM in children who were symptomatic and referred for US was 3.7% and 2.5%, respectively.

Incidence of TM in different periods

To analyze the variance in the incidence of TM in different periods, the appropriate data were stratified according to the following time intervals: before 2009, 2000–2013 and after 2013 (using data from 5, 6, 5 studies).

In children, the mean incidence was 1.6%, 3.8% and 3.0%, respectively. Considering only two study periods—after 2009 and before 2009, the mean incidence of TM after 2009 was 3.3% in children. The incidence of TM tended to increase with time.

Incidence of CTM/LTM

Seven and five studies determined the pooled incidence of CTM and LTM in children, respectively. The pooled mean incidence of CTM and LTM was 2.5% and 0.9%, respectively.

Four pediatric studies investigated the incidence of both CTM and LTM at the same time. The rate of CTM and LTM in TM was determined by analyzing data on the individual incidence of these complications. The proportion of CTM in children was 71.8% (95% CI 62.4–81.1%, $P=0.0$, $I^2=0.0\%$).

Incidence of TM according to laterality

In children, the pooled mean incidence of left, right, unilateral and bilateral TM was 0.9%, 0.8%, 0.7% and 1.6%, respectively (Table 3). We also determined the proportion of left or right TM in unilateral cases and the incidence of unilateral and bilateral TM without considering the incidence of CTM/LTM.

In children, the prevalence of left TM in unilateral cases was 55.7%, while the frequency of bilateral TM was 69.0%. These results indicated that bilateral TM was much more common than unilateral TM in pediatric population.

Incidence of TM according to age groups

Two pediatric studies determined the incidence of TM in 2–3-year prepubertal age groups [2, 12]. Data are shown in Table 3. The inter-study heterogeneity was very high. And the results were not significant.

Association between TM and PTT

Five studies involving 1299 children with TM and 43,117 children without TM were included in the meta-analysis to assess the association between TM and PTT. Among them, four original studies determined the association between TM and PTT in pediatric population with potential risk factors for PTT [2, 9, 10, 20]. Only one study investigated the relevance of TM and PTT in asymptomatic children [12]. Nonetheless, PTT was not detected in 28 asymptomatic children with TM and 642 asymptomatic children without TM.

The populations that were symptomatic and referred for US constituted the group with additional risk factors for PTT. The pooled RR of TT in the population with TM compared with that without TM is shown in Fig. 2. The RR of TM with a concurrent diagnosis of PTT in children was 15.46 (95% CI 6.93–34.47, $P<0.00001$, $I^2=58\%$),

Table 2 The follow-up information of pediatric patients with testicular microlithiasis and cumulative incidence of testicular germ-cell tumor during follow-up

Study category and reference	Characteristics of population	Population	Sample size	Median follow-up (range) (mon)	Follow-up strategy	Stable	Increased	Decreased	No. of tumors occurred/total; time	Type of tumor; characteristics	Incidence[a]
Furness et al., 1998 [27]	Asymptomatic and without any other abnormalities	Children	23	27.6[b] (1–84)	Yearly ultrasound and physical examination				1/23; a benign Sertoli cell tumor, the time not provided		15.75
Chiang et al., 2012 [4]	Asymptomatic	Children	26	39.6[b] (0–128.6)	Annual ultrasound scan or repeated ultrasound scan				0		0
Marte et al., 2017 [28]	Diagnosed with TM associated with other genital abnormalities	Children	81	56.4 (12–84)	Strictly yearly ultrasonographic follow-up	77/81	0/81	4/81	3/81; one seminoma appeared at 60 mon, and the other two remained unknown	Two seminoma (both of them had bilateral CTM) and one mature teratoma. One seminoma had a history of ipsilateral scrotal mass, and the patient with mature teratoma previously had a history of contralateral orchiectomy for benign testicular mass	6.57
Volokhina et al., 2014 [10]	Patients diagnosed with TM with otherwise well	Children	8	8.8[b] (0.3–48)	NR				0		0
Yesil et al., 2016 [11]	Patients diagnosed with TM with otherwise well	Children	78	32.9[b] (6–84)	Clinical and ultrasonographic evaluation as well as serum tumor markers at an interval of 6 mon				0		0
Cooper et al., 2014 [2]	Asymptomatic	Children	18	50.4[b] (12–174)	NA	13/18	4/18	1/18	0		0
Dagash et al., 2007 [26]	With other risk factors	Children	5	35[b] (8–67)	Yearly US follow-up	4/5	0/5	1/5	0		0
Leenen et al., 2002 [7]	NR	Children	5	19 (?-72)	NR	4/5		1/5	0		0

Table 2 (continued)

Study category and reference	Characteristics of population	Population	Sample size	Median follow-up (range) (mon)	Follow-up strategy	Stable	Increased	Decreased	No. of tumors occurred/total; time	Type of tumor; characteristics	Incidence[a]
Xia et al., 2002 [31]	Diagnosed with TM without testicular tumors	Children	7	19 (1–24)	Ultrasonographic examination as well as tumor markers				0		0
Nishimura et al., 2017 [30]	Underwent standard orchiopexy	Children	55	24.9 (0.33–85.1)	NR				0		0

TM testicular microlithiasis, *CTM* classic TM, *LTM* limited TM, *NR* not reported, *PTT* primary testicular tumors, *US* ultrasonography. [a]Cases per 10,000 person-mon of follow-up; [b]Mean value and corresponding range, rather than median

with high heterogeneity (P for heterogeneity < 0.00001, $I^2 > 50\%$). The funnel plot showed a roughly asymmetrical distribution, indicating suspicious publication bias. In the groups that were symptomatic and referred for US, TM was associated with an increased risk of PTT, with a RR of 5.97 and 21.57, respectively (Fig. 2). The test for subgroup difference ($\chi^2 = 2.16$, $P = 0.14$) showed that there were no significant differences in the relative RR between these two groups.

Follow-up outcomes of pediatric population with TM

Ten studies conducted the follow-up of pediatric population with previously diagnosed TM, the follow-up time, strategy and newly detected tumor characteristics are depicted in Table 2. A total number of 296 TM patients were included, in which the follow-up time ranged from 1–85 months. Among them, only four children with TM were diagnosed with newly detected PTT during a relatively long follow-up time. In addition, two of which had a history of ipsilateral or contralateral tumor or cryptorchidism. According to our analysis, about 93.5% of TM remained stable or unchanged during follow-up.

Discussion

This systematic review and meta-analysis first determined the epidemiological incidence of TM according to CTM/LTM subtypes, age groups, study periods and TM laterality among pediatric population. The study also determined the association between TM and synchronous/heterochronous diagnosis of PTT and addressed the follow-up information and findings of pediatric patients with TM according to currently published papers.

This study is the most comprehensive review on the incidence of TM and its association with PTT among pediatric population, but still has some limitations. This systematic review included all relevant studies published worldwide from 1998 to 2017, regardless of frequency of US transducers. And there was no adjustment on these differences. The large time span of these studies and recent advances in US technology increased the variability in the detection level of TM. For these reasons, differences in multicenter approaches, US parameters and equipment between studies are unavoidable. Therefore, considering the within-study variance and between-study heterogeneity, the random-effect model was used in our study, no matter single-rate meta-analysis or dichotomous variables.

Cooper et al. pointed out that the incidence of TM varied from 4.60% to 9.02% considering two study periods: before 2001 and after 2001 [2]. Enlighted by his view, the prevalence data were divided into three time intervals—past 5 years (after 2013), past 5–10 years (2009–2013)

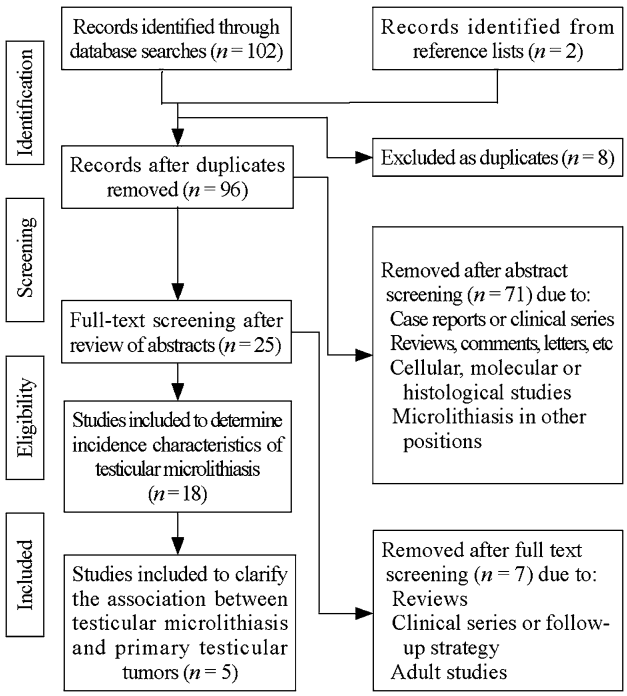

Fig. 1 Flow diagram of identification and eligibility of publications

and > 10 years (before 2009). And the results indicated that the prevalence tended to increase with time. Considering two study periods—before 2013 and after 2013, the prevalence of TM increased from 1.6% to 3.3% in the pediatric population. In our opinion, advances in US technology and health awareness led to the increased detection of TM.

The overall incidence of TM was 4.2% in asymptomatic children, whereas the overall incidence of TM in children with additional risk factors for PTT was 2.7%, according to currently available data. Publication bias seems to be the main reason why the incidence of TM in asymptomatic children is higher than that in children with pre-existing conditions.

Among TM patients, CTM accounted for approximately 71.8% in children. LTM may not be easily detected compared with CTM on US. Children do not usually cooperate with static US. For this reason, the detection of LTM in this population is more challenging, leading to a higher rate of CTM cases in children. Furthermore, advances in US technology in recent years have increased the detection rate of TM in children relative to adults.

The overall incidence of TM differed significantly according to the age groups (Table 3) and increased with age. Similarly, the overall incidence of TT increased with age regardless of the presence of TM. However, the incidence of TM did not increase linearly with advancing age. One peak occurred at age 6–14 years. Further cellular and molecular studies are necessary to address the pathogenesis of TM.

In asymptomatic pediatric populations with otherwise good clinical outcomes, there is no convincing evidence supporting that TM alone is premalignant. In populations with additional risk factors for PTT, the presence of TM increased the risk of TT with a relative RR of 15.46 for a concurrent diagnosis of PTT in children, but with strong evidence of heterogeneity and suspicious publication bias. After comprehensive summary of pediatric patients with TM, we found that more than 90% of TM remained unchanged. And the newly detection rate of PTT was very low (less than 1%, 2/296), if there was no ipsilateral or contralateral tumor or operation history. Our findings suggest that frequent US surveillance is not required in pediatric patients with TM, unless they had severe genitourinary abnormalities.

Several case reports demonstrated a causal relationship between the pre-existence of TM and the subsequent development of TT [32–34]. Nonetheless, these studies had an unacceptable bias toward favorable outcomes: (1) the analysis of follow-up information from a clinical series of patients with isolated TM indicated that approximately 90% of the cases of TM remained stable during follow-up; (2) the cumulative incidence of newly detected PTT in a relatively short time was very low, ranging from 0 to 46.30 cases per 10,000 person-months; (3) most patients with newly detected tumors during follow-up had a history of ipsilateral or contralateral testicular abnormality or tumor; (4) the sample size was small, and the follow-up time was short.

In pediatric populations that were symptomatic and referred for US, TM was associated with an increased risk of PTT with a respective RR of 5.97 and 21.57, respectively (Fig. 2). Although the incidence of TM and TT in populations from clinical studies was higher than that in the general population, this finding indicates that the presence of TM should be considered, especially in subjects with scrotal or testicular abnormalities or symptoms. During follow-up, some studies recommend a testicular examination, surveillance imaging or both, whereas others indicate that these procedures are not necessary [35]. Although US contributes to the early detection of TTs, DeCastro et al. have pointed out that frequent US surveillance is not cost-effective and does not significantly improve the outcomes associated with TT [36]. So we do not recommend regular US surveillance for children with TM, but testicular examination by themselves or parents.

In conclusion, the incidence of TM varies significantly between pediatric populations according to age groups, study periods and laterality. TM is most commonly bilateral, of the classic type, and remains stable or unchanged at follow-up. The overall incidence of TM in children with additional risk factors for PTT is 2.7%, which is much higher than expected.

Table 3 The pooled mean incidence of testicular microlithiasis in pediatric populations

Variables	All included studies ($n=18$)	The average prevalence of TM	95% CI	P	I^2 (%)
Year interval[a]					
Before 2009	5	0.016	0.011–0.021	0.759	0.0
2009 through 2013	6	0.038	0.021–0.054	0.000	94.0
After 2013	5	0.030	0.026–0.034	0.058	56.3
Referral indications					
Asymptomatic	2	0.042	0.027–0.056	0.000	0.0
Symptomatic	6	0.037	0.020–0.055	0.000	95.4
Testicular pain	1				
Testicular masses	1				
Varicocele	1				
Testicular swelling	1				
Inguinal hernia	1				
Retractile testes	2	-	-	-	
Cryptorchidism	4[b]	0.039	0.016–0.062	0.001	45.4
Family or personal history of PTT	0				
Referred for US	7	0.022	0.017–0.027	0.000	77.9
Specific type of TM					
Classic TM	7	0.025	0.019–0.032	0.000	81.8
Limited TM	5	0.009	0.004–0.014	0.001	39.5
Diffuse TM	2	0.022	0.015–0.029	0.000	
Focal TM	1				
Laterality of TM					
Unilateral	8	0.007	0.004–0.010	0.000	83.9
Left	2	0.009	0.006–0.012	0.000	
Right	3	0.008	0.000–0.016	0.051	57.7
Bilateral	8	0.016	0.010–0.022	0.000	89.6
Stratification of age category	3				
0–2	2	0.002	–0.001–0.004	0.259	
3–5	2	0.012	0.005–0.019	0.001	
6–8	2	0.040	0.021–0.059	0.000	
9–11	2	0.051	0.033–0.069	0.000	
12–14	2	0.046	0.028–0.064	0.000	
15–17	2	0.028	0.016–0.040	0.000	
18–19	2	0.021	0.003–0.039	0.024	
Countries/zones	17[c]				
USA	4	0.028	0.024–0.033	0.000	
UK	4	0.032	0.006–0.058	0.017	
China	1				
Turkey	1				
Netherland	2	0.023	–0.012–0.058	0.204	
Japan	1				
Brazil	1				
Singapore	1				
Italy	1				
Germany	1				

TM testicular microlithiasis, *PTT* primary testicular tumors, *US* ultrasonography, *CI* confidence interval. [a]Two studies do not have data on prevalence of TM, but have information about follow-up of patients with TM; [b]Some included studies contain more than one piece of prevalence information on specific scrotal symptoms, while majority of them don't contain any; [c]Only participants with "additional risk factors for primary testicular neoplasm" (explained in main text) included in the analysis of prevalence of testicular microlithiasis by geographic difference. There is one asymptomatic population excluded in this part [1]

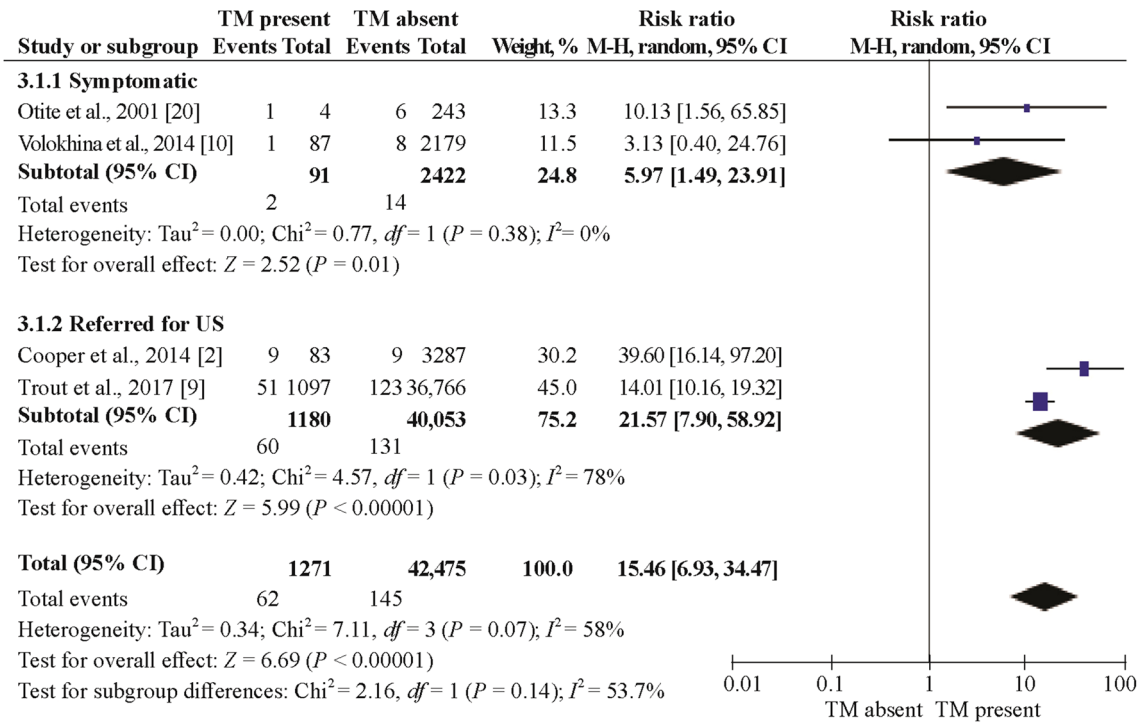

Fig. 2 The forest plot indicates the risk ratio of a concurrent diagnosis of primary testicular tumor (PTT) in the presence of testicular microlithiasis (TM) in a selected population with potential additional risk factors for PTT among pediatric population. *M-H*, Mantel–Haenszel odds ratio, *CI* confidence interval, *TM* testicular microlithiasis, *US* ultrasonography, *df* degrees of freedom, I^2 inconsistency index

There is no convincing evidence supporting that TM alone is premalignant. TM was strongly associated with increased diagnosis of PTT in children with potential risk factors for PTT. The incidence of TT in patients with isolated TM was very low during follow-up unless they had a history of ipsilateral or contralateral abnormality or tumor.

We currently do not recommend regular US surveillance for children with TM, but testicular examination by themselves or parents, unless they have severe genitourinary abnormalities or history of tumors or operations.

Author contributions CJY conceived and designed the meta-analysis, independently searched the electric databases, and independently extracted the data, led analysis and interpretation of data, drafted the manuscript and revised content based on feedback. JDL independently searched the electric databases, and independently extracted the data, led analysis and interpretation of data, drafted the manuscript and revised content based on feedback, and acted as second reviewer. JZ led analysis and interpretation of data, drafted the manuscript and revised content based on feedback. TXZ and YW assisted with the retrieval of the database and acquisition of data, assisted with the interpretation of data and provided critical revision of drafts. TL, DWH, and GHW assisted with the conception and design, interpretation of data, and critical revision of drafts. SDW conceived and designed the meta-analysis, and acted as the corresponding author, provided funding support, assisted with interpretation of data, provided critical revision of drafts and acted as the third (mediating) reviewer. All the authors approved the final version of the manuscript.

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Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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