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Review Article

Factors Affecting Prevalence of Urinary Tract Infection in Neonates with Unexplained Hyperbilirubinemia: A Systematic Review and Meta-Analysis Study in Iran

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Abstract

Background: The prevalence and risk factors of urinary tract infection (UTI) in neonates with unexplained hyperbilirubinemia are not studied thoroughly. Since the prevalence of UTI is highly variable in different areas and countries, this study aimed to review the existing data of Iranian neonates with UTI presented with unexplained hyperbilirubinemia.

Methods: This study is a meta-analysis of Iranian newborns with unexplained hyperbilirubinemia. We identified all studies indexed in international (Web of Science, PubMed, Scopus, Google Scholar) and national (Science Information Database, Magiran) databases from 2000-2018. Search terms included: Urinary Tract Infections OR UTI AND urine OR culture OR microbio, jaundice OR icter OR hyperbili, AND Iran.

Results: Overall, 4210 neonates from 17 studies were included. The pooled prevalence of UTI in neonates with unexplained hyperbilirubinemia was 6.81% (95% CI: 4.86-8.77). Considering the subgroups analyses; the prevalence of UTI was higher in the prolonged vs. not-prolonged state (8.34% vs. 4.00%), low birth weight vs. normal birth weight (7.81% vs. 4.51%), and exclusive vs. non-exclusive breastfeeding (8.84% vs. 4.72%). Male gender and low birth weight increased the risk of UTI about two times compared to the female gender and normal birth weight, respectively. The results of the analyses in neonates with unconjugated hyperbilirubinemia also showed the above-mentioned subgroup differences.

Conclusion: Due to considerable prevalence of UTI in neonates with unexplained hyperbilirubinemia and risk factors in this age group, investigation for UTI is essential for the workup in this situation.

Keywords: Urinary tract infection; Neonates; Hyperbilirubinemia; Systematic review; Meta-analysis; Iran

Introduction

In the first few months of life, infants are at higher risk of developing urinary tract infection (UTI) due to the undeveloped immune system (1, 2). Although fever is a noteworthy sign of UTI in neonates (1), a large proportion of neonatal UTI does not present with fever or specific urinary tract symptoms. Therefore, the knowledge of non-specific signs and symptoms of neonatal UTI is essential to identify appropriate situations, which require early diagnosis to prevent long-term complications.

Neonatal hyperbilirubinemia in the absence of any other symptoms or signs (unexplained hyperbilirubinemia) may be the only clinical manifestation of UTI in neonates (3, 4). In this regard, the American Academy of Pediatrics (AAP) guideline recommends performing urinalysis and urine culture in neonates with conjugated hyperbilirubinemia (5). Moreover, according to the national institute for health and care excellence (NICE) guideline, urinalysis and urine culture are recommended in neonates with prolonged hyperbilirubinemia(6). Nowadays, unconjugated hyperbilirubinemia can be an important or even the first presentation of UTI in newborns (4, 7, 8). In other words, one of the challenging issues of neonatal hyperbilirubinemia is asymptomatic afebrile (or unexplained) hyperbilirubinemia, in which UTI can be a missing ring. Unfortunately, according to the current guidelines, there is no clear recommendation for screening UTI in this group of neonates with unexplained hyperbilirubinemia.

Some recent local systematic reviews assessed the prevalence of UTI in infants with prolonged jaundic (9, 10). However, the burden of the UTI in neonates with unexplained hyperbilirubinemia is not assessed in these studies. Since the prevalence of UTI is highly variable in different areas and countries (9), local assessment of UTI prevalence and risk factors in other countries is of value. This study aimed to review the existing data of the unexplained hyperbilirubinemia in Iranian neonates and assess the prevalence and risk factors of UTI in this group of neonates.

Objective

1- Assess the pooled prevalence of UTI in Iranian neonates with unexplained hyperbilirubinemia
2- Assess the effect of risk factors including gender, state of conjugation, duration of the hyperbilirubinemia (prolonged or not), feeding method, gestational age, birth weight, and the city of study on the prevalence of UTI in neonates with unexplained hyperbilirubinemia.
3- All risk factors mentioned earlier on the prevalence of UTI in neonates with unconjugated hyperbilirubinemia.

Materials and Methods

This review was conducted according to the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the specific guidelines for reporting meta-analyses of cross-sectional and case-control studies and guidelines for undertaking systematic reviews of prevalence studies (11, 12). All study protocols were following the ethical standard of institutional review board of the Urology Nephrology Research Center.

Eligibility criteria

All studies written in English or Persian assessed neonates younger than 28 days and born in Iran with unexplained hyperbilirubinemia and no other accompanying signs and symptoms (such as fever, poor feeding, lethargy, or hemolysis), were eligible to be included in our study. In addition, abstract or full text of peer-reviewed studies published in English or Persian were required to report data on point or period prevalence of UTI in Iranian neonates.

The primary outcome of interest was the prevalence of UTI, diagnosed by a positive urine culture. Therefore, we only considered the studies that obtained the urine specimen by either suprapubic aspiration or catheterization of the bladder. According to European Association of Urology (EAU)/European Society for Pediatric Urology (ESPU) guidelines, the suprapubic urine samples considered positive if any colony-forming unit (CFU) of a single pathogen was isolated, while samples collected with urine catheterization were accepted as positive in case the growth of single microorganism with an amount of at least 1000 CFU/ml was reported (13). In addition, unconjugated hyperbilirubinemia and prolonged jaundice defined according to guidelines. (5, 6, 9).

Search Strategy

International (Web of Science, PubMed, Scopus, and Google Scholar) and highly qualified national (Science Information Database, Magiran) databases were searched for the following keywords: 1. Urinary Tract Infections OR UTI AND urine* OR culture OR microbio*, 2. jaundice OR icter* OR hyperbili*, 3. infant OR newborn OR neonate, and 4. Iran. All searches were limited to publications from Jan 2000 to Dec 2018. To gather a complete list of relevant studies, we searched the reference list of included studies manually, as well. Besides, we contacted study authors to acquire information not included in their articles.

Study selection and data collection process

Search results were collected into Endnote version X8 (Clarivate Analytics/ USA), and duplicate records were removed. Two authors independently screened titles and abstracts for assessing eligibility criteria. After initial screening, the above-mentioned authors independently assessed the full text of the retrieved articles for compliance with eligibility criteria. In the next step, the full texts of the selected studies were evaluated by two authors independently, to qualify the articles according to six selected items from Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (14): (a) the eligibility criteria for including participants; (b) a clear definition of outcome, i.e. UTI; (c) description of locations, settings, and relevant dates of studies; (d) demographic characteristics of participants; (e) how the sample size has arrived; and (f) report of the interesting outcomes of each exposure variable. The corresponding author resolved any disagreement between the two authors who assessed the articles. Finally, the selected articles were reassessed and data was extracted for analyses.

Data items

The variables of interest include the year and city of study in Iran, sample size, total number of neonates with positive urine culture, detected pathogens, and urinary tract anomalies. The pooled prevalence of UTI in asymptomatic neonates with unexplained hyperbilirubinemia was also calculated about the gender, state of conjugation, duration of the hyperbilirubinemia (prolonged or not), feeding method (exclusive breastfeeding or non-exclusive breastfeeding), gestational age (preterm or term), birth weight (normal birth weight (NBW) or LBW), circumcision, urinary sampling method and city of the study. Some of the variables mentioned above were also considered as risk factors, which could affect the prevalence of UTI in neonates with unconjugated hyperbilirubinemia.

Synthesis of results

The prevalence of UTI in Iranian neonates with unexplained hyperbilirubinemia was pooled in the statistical meta-analysis using STATA version 14 (Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: Stata Corp LP). The pooled prevalence outcome was measured and reported with point and 95% confidence intervals. The heterogeneity, which refers to the variation in study outcomes between studies, was assessed statistically using the Q-test and I^2 statistic. The random-effects model was used when the heterogeneity test had a *P*-value less than 0.1 or I^2 statistic higher than 0.5. The pooled prevalence of mentioned subgroups was also calculated. Subgroup analysis was performed to determine the pooled estimate prevalence of UTI based on the variables discussed earlier. The Meta-regression method was used to assess the relationship between the main effect size and the study characteristics of interest, which might influence or led to the suspected source of heterogeneity. Publication bias was explored using the Egger and Begg tests, which showed there is no evidence of publication bias (P=0.097 and 0.389, respectively).

Results

Overall, 633 studies retrieved in the initial search, from which 92 publications were duplicate records. The title and abstract of the remaining 541 studies screened and 491 irrelevant studies excluded. The full texts of the remaining 50 studies

were qualified and assessed for the eligibility criteria. Finally, 17 studies included (Fig. 1) (15-31).

Four thousand two hundred ten neonates with unexplained hyperbilirubinemia from 17 studies included in the analyses (Table 1).

Table 1: Characteristics of the studies included in the systematic review, 2000- 2018

First author	*Sample size*	*Study Date*	*Prevalence (95%CI)*	*Place of the study*	*State of conjugation*	*Prolonged hyper-bilirubinemia*	*Gender*		*Referance*
							Female	Male	
Eghbalian F.	316	2009	6.65 (4.16-9.98)	Hamedan	Unconjugated	Yes	132	184	(15)
Eslami Z.	100	2009	11.00 (5.62-18.83)	Yazd	N.A.	N.A.	42	58	(16)
Fallahi M.	160	2009	0.0	Tehran	Unconjugated	N.A.	N.A.	N.A.	(17)
Ghaemi S.	400	2007	5.75 (3.68-8.50)	Isfahan	N.A.	N.A.	147	253	(18)
Hajebrahim Tehrani F.	750	2004	0.53 (0.15-1.36)	Tehran	Unconjugated	N.A.	293	457	(19)
Hemmatyar M.	400	2009	1.75 (0.71-3.57)	Tehran	Unconjugated	N.A.	180	220	(20)
Jafarzadeh M.	85	2009	8.24 (3.38-16.23)	Mashhad	N.A.	N.A.	36	49	(21)
Khalesi N.	230	2007	7.39 (4.36-11.57)	Zahedan	N.A.	Yes	92	138	(22)
Maamouri G.	434	2013	23.50 (19.60-27.78)	Mashhad	N.A.	N.A.	N.A.	N.A.	(23)
Mosayebi Z.	377	2007	3.45 (1.85-5.82)	Kashan	Unconjugated	N.A.	N.A.	N.A.	(24)
Najati N.	100	2010	7.00 (2.86-13.89)	Tabriz	N.A.	Yes	33	67	(25)
Pashapour N.	100	2007	6.00 (2.23-12.60)	Urumiea	Unconjugated	Yes	43	57	(26)
Sabzehei MK.	100	2015	14.00 (7.87-22.37)	Hamedan	Unconjugated	Yes	51	49	(27)
Shaian M.	120	2012	12.5 (7.17-19.78)	Shiraz	Unconjugated	N.A.	47	73	(28)
Sharif MR.	384	2014	4.17 (2.40-6.68)	Kashan	N.A.	No	185	199	(30)
Sharif MR.	237	2014	12.24 (8.35-17.10)	Kashan	Unconjugated	Yes	108	129	(29)
Zarkesh M.	314	2015	3.82 (1.99-6.58)	Rasht	Unconjugated	No	133	181	(31)

CI: Confidence Interval. N.A.: Not assessed or reported in the study

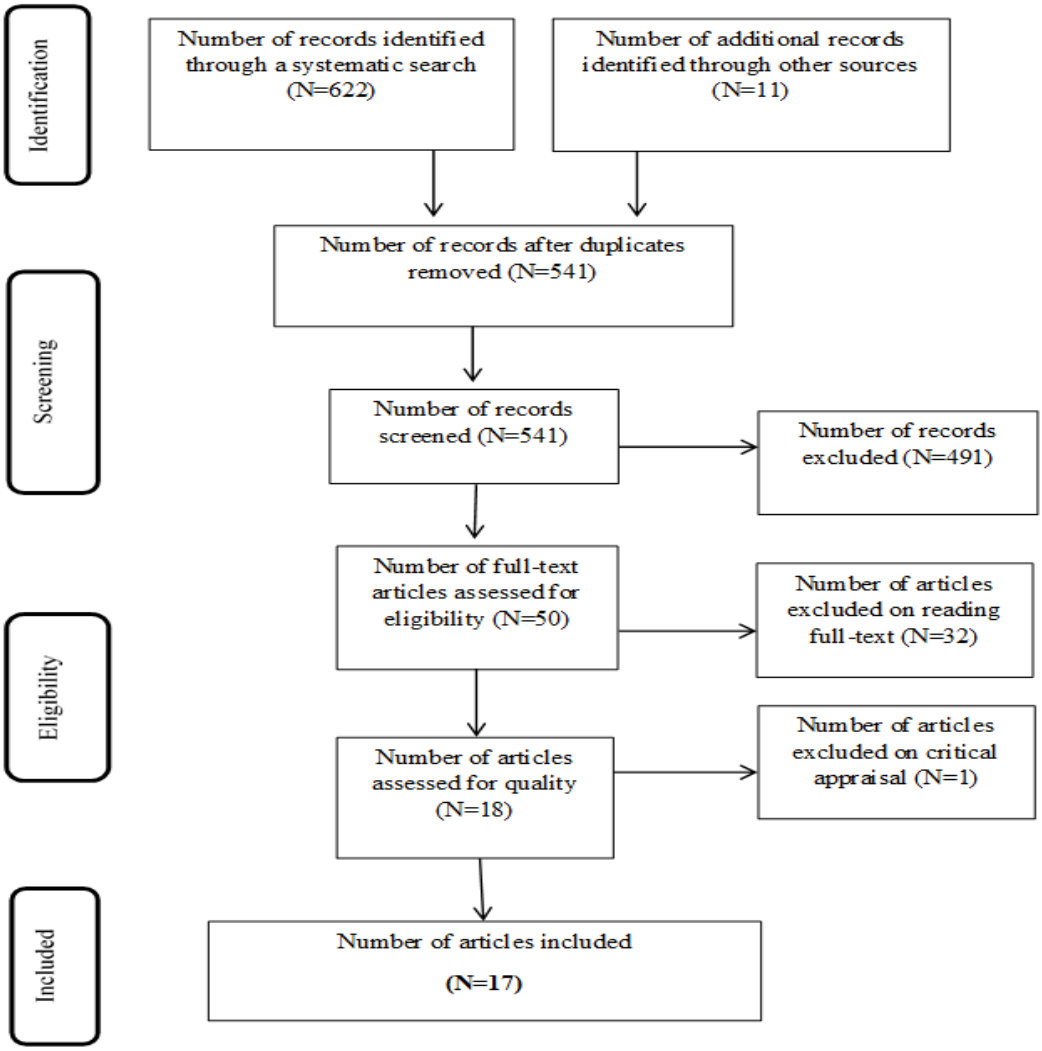

Fig. 1: The flow diagram of search and study selection process according to PRISMA guideline (11)

The random-effects method was used for the analyses because of the high heterogeneity of the studies (Q= 268.65, I^2 =94.04, *P*<0.001). Using the random-effects model, the overall pooled prevalence of UTI in neonates with unexplained hyperbilirubinemia was 6.81% (95% CI: 4.86-8.77 I^2=94.5%) (Fig. 2). Due to the high heterogeneity, we performed subgroup analyses. The prevalence of UTI in male neonates (8.74%; 95% CI: 5.95-11.54) was higher than in females (3.83%; 95% CI: 2.06-5.60). The prevalence of UTI in neonates with unconjugated unexplained hyperbilirubinemia was 4.01% (95% CI: 2.61-5.41). According to the duration of hyperbilirubinemia, the prevalence of UTI in neonates with prolonged unexplained hyperbilirubinemia (8.34%, 95% CI: 6.07-10.60) was higher than neonates with not prolonged disease (4.00%, 95% CI: 2.55-5.46) (Table 2). The prevalence of UTI in neonates with exclusive breastfeeding was more than in neonates with nonexclusive breastfeeding (8.84% vs. 4.72%). The UTI was more prevalent in preterm neonates compared to the term neonates (15.55% vs. 4.85%). Neonates with LBW had a higher prevalence of UTI compared to the NBW neonates (7.81% vs. 4.51%) (Table 2).

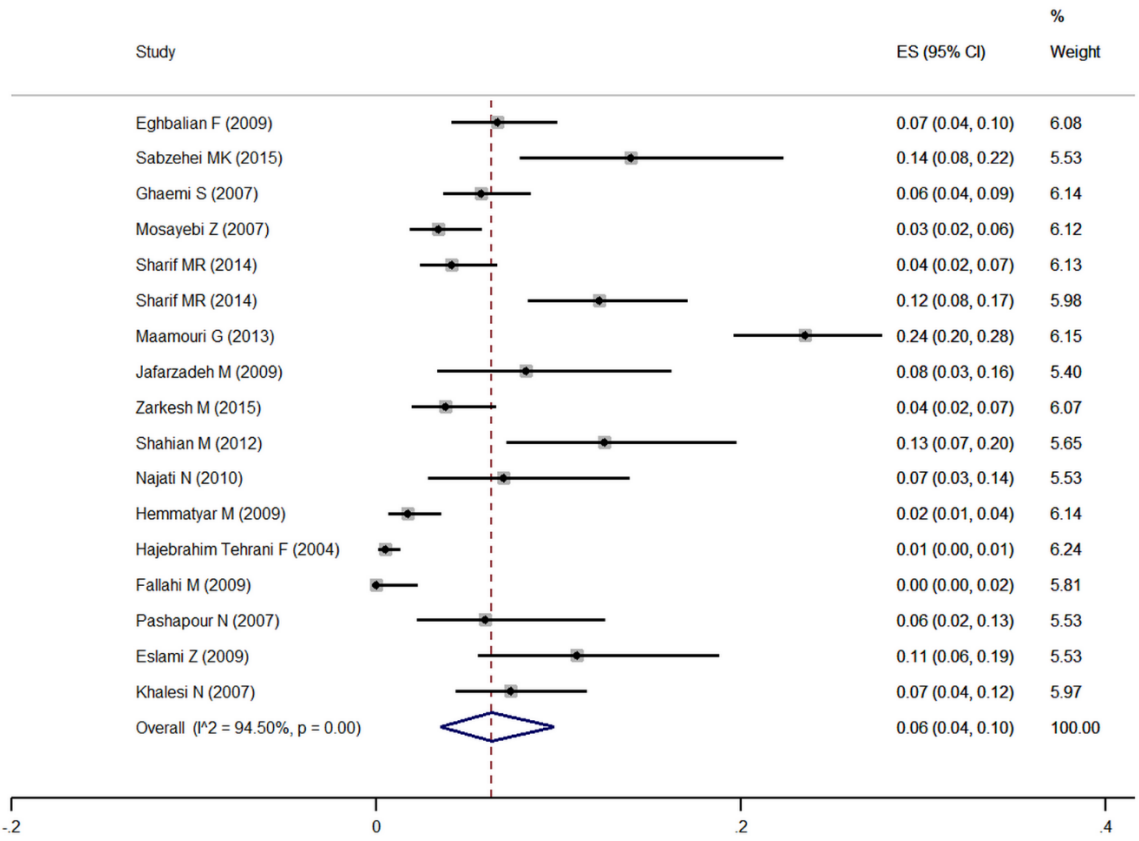

Fig. 2: Forest plot of estimated results from the studies included in the meta-analysis addressing the prevalence of UTI in Iranian neonates, along with the overall results

The prevalence of UTI in uncircumcised male neonates had been evaluated in four studies and was 13.34% (95% CI: 8.66-18.03) (18, 26-28). It was not possible to assess the pooled prevalence of UTI in circumcised male neonates since it was reported only in one study (18). According to the subgroup analysis based on the city of study, the highest and lowest prevalence of UTI was seen in Mashhad and Tehran, respectively (18.65% vs. 0.51%).

Regarding the high heterogeneity of the studies, univariate meta-regression showed that only 'the location of the study' (Tehran vs. other cities) was significantly predicted the heterogeneity among the studies (P<0.001). Other variables, including the sample size, time of the study, prolonged hyperbilirubinemia, and state of conjugation, did not predict the heterogeneity.

Regarding the effect of risk factors, the relative risk (RR) of UTI was assessed according to potential risk factors, i.e., variables investigated as subgroups. Only the risk factors with enough sample size were included in the analyses. The forest plots addressing the RR of UTI along with the overall effect size are presented in Fig. 3. Based on the fixed-effects model, the male gender increased the risk of UTI compared to the female gender (RR=2.03, 95% CI: 1.45-2.85; P<0.001; I^2=0%), and the risk of UTI in the LBW neonates was 2.47 times higher than the risk for NBW neonates (RR=2.47, 95% CI: 1.37-4.47, P=0.003; I^2=32%). The effect of the feeding method and gestational age on UTI risk was evaluated using a random-effects model. The risk of UTI in preterm neonates was about two times higher than the risk in term neonates; however, the effect was not statistically

significant (RR=2.06, 95% CI: 0.86-4.92, *P*=0.103; I^2=63.5 %). Moreover, the type of feeding did not have a significant effect on the risk of UTI in neonates using the random-effects model (RR=0.35, 95% CI: 0.04-3.01, *P*=0.34; I^2=88%). Unfortunately, the small number of studies limited us to perform further analyses related to the heterogeneity in this step.

Table 2: The prevalence of urinary tract infection (UTI) in subgroups of neonates with unexplained hyperbilirubinemia, systematic review and meta-analysis of prevalence of UTI in Iranian neonates, 2000-2018

Variables	*Subgroups*	*Number of studies*	*Pooled prevalence (95% CI)*	*I²%*	*P-value*	*References*
Gender	Male	11	8.74(5.95-11.54)	72.51	<0.001	(15, 16, 20-22, 26-31)
	Female	11	3.83 (2.06-5.60)	60.27	0.005	(15, 16, 20-22, 26-31)
State of hyperbilirubinemia	Unconjugated	10	4.01 (2.61-5.41)	93.20	<0.001	(15, 17, 19, 20, 24, 26-29, 31)
	Undefined	7	9.48 (4.81-14.14)	92.11	<0.001	(16, 18, 21-23, 25, 30)
Prolonged hyperbilirubinemia	Yes	6	8.34 (6.07-10.60)	43.65	0.11	(15, 22, 25-27, 29)
	No	2	4.00 (2.55-5.46)	99.43	<0.001	(30, 31)
	Undefined	9	7.75 (4.29-11.21)	96.01	<0.001	(16-21, 23, 24, 28)
Feeding method	Exclusive breast-feeding	4	8.84 (2.78-14.89)	83.39	<0.001	(18, 21, 27, 28)
	Nonexclusive breastfeeding	4	4.72 (0.00-9.77)	81.21	<0.001	(18, 21, 27, 28)
Gestational age	Preterm	4	15.55 (9.50-21.59)	49.87	0.05	(15, 21, 27, 28)
	Term	8	4.85 (3.82-5.88)	0.00	0.74	(15, 18, 21, 26-28, 30, 31)
Birth Weight	Low birth weight	3	7.81 (6.67-11.94)	77.08	0.013	(15, 28, 31)
	Normal birth weight	4	4.51 (3.31-5.71)	30.85	0.22	(15, 28, 30, 31)
Urinary sampling method	supra pubic	14	6.13 (4.49-7.76)	95.81	<0.001	(15, 17-20, 27, 31) (21-26, 29)
	bladder catheterization	3	8.60 (2.33-14.87)	81.59	0.005	(16, 28, 30)
City of study	Hamedan	2	7.68 (5.13-10.22)	99.71	<0.001	(15, 27)
	Isfahan	1	5.75 (3.68-8.50)	-		(18)
	Kashan	3	6.09 (2.29-9.89)	86.26	<0.001	(18, 21, 27, 28)
	Mashhad	2	18.65(15.36-21.95)	93.13	<0.001	(21, 23)
	Rasht	1	3.82 (1.99-6.58)	-		(31)
	Shiraz	1	12.50 (7.17-19.78)	-		(28)
	Tabriz	1	7.00 (2.86-13.89)	-		(25)
	Tehran	3	0.51 (0.00-1.21)	82.05	<0.003	(17, 19, 20)
	Urmia	1	6.00 (2.2312.60)	-		(26)
	Yazd	1	11.00 (5.62-18.83)	-		(16)
	Zahedan	1	7.39 (4.36-11.57)	-		(22)

CI: Confidence Interval.

Regarding the urine culture results, *Escherichia coli* was the most common uropathogen of all neonates with unexplained hyperbilirubinemia, followed by *Klebsiella pneumonia* and *Enterobacter aero-*

genes. Imaging results of neonates with UTI, performed as a workup to detect urinary tract anomalies, were reported in six studies (16, 18, 20, 26, 28, 31), and the prevalence was 16.71% (95% CI: 8.35-25.06). The most prevalent types of anomalies were hydronephrosis of the pyelocaliceal system, vesicoureteral reflux, and pyelonephritis.

Table 3 presents data regarding unconjugated hyperbilirubinemia. Consistent with the results presented above, the prevalence of UTI was higher in the male gender, prolonged hyperbilirubinemia, exclusive breastfeeding, preterm birth, and LBW subgroups.

Discussion

UTI is one of the most common bacterial infections in childhood (8). However, the assessment of the true incidence of UTI in the first days of life is complex, thus, most studies have evaluated the UTI in broader age categories, and the reported prevalence was 7%–9% (32). In some studies, the incidence of UTI in the febrile infant has been reported between 10.7% and 15.4% (1). According to the literature, some points should be considered regarding neonatal UTI. First, the prevalence of UTI in infants is higher than in older children (13, 32). The natural defenses of the urinary tract, including antibacterial properties of urine and urinary tract mucosa, anti-adherence mechanisms, and presence of phagocytic cells, are weak in neonates, and this weakness facilitates UTI in this period. Therefore, in some studies, the neonatal period is an independent risk factor for UTI (2). Second, UTI symptoms in newborns are not the same as specific symptoms of UTI in adults. In infants, the disease may be presented with sepsis or nonspecific signs and symptoms, such as poor sucking, vomiting, irritability, lethargy, convulsions, hypothermia, respiratory signs and symptoms, and insufficient weight gain (8). Third, as with most infections in this age group, there is a high probability of bacteremia as well as a high rate of mortality (around 10%), due to the spread of infection to other sites of the body (33). Besides, since UTI can cause kidney damage, it may lead to recurrent infections, renal scarring, and end-stage renal failure in the later stage of life. Therefore, prompt diagnosis and treatment are essential to prevent the above-mentioned long-term complications (2).

Hyperbilirubinemia is one of the suggested nonspecific symptoms of neonatal UTI (3, 4). In previous studies on neonates with no other complaints other than hyperbilirubinemia, the incidence of UTI was 7.5%-8% (34, 35). In our study, the overall pooled prevalence of UTI in asymptomatic neonates with unexplained hyperbilirubinemia was 6.81%. Exposure to some risk factors of the neonatal period, such as preterm birth, increased the prevalence up to 15.55%.

Guidelines recommend UTI screening tests in neonates with prolonged jaundice. In our study, the overall prevalence of UTI in neonates with prolonged hyperbilirubinemia was 8.34% compared to 4% in the not-prolonged state. In a meta-analysis in Iran (10), the prevalence of UTI in prolonged hyperbilirubinemia was reported 11%. The difference between the prevalence of our findings and Tola's study is due to the variation between the inclusion criteria. Both studies emphasize the importance of UTI screening in prolonged jaundice.

Nowadays, the current guidelines have no clear recommendation for screening UTI in unconjugated neonatal hyperbilirubinemia. However, according to the literature, several studies showed a significant prevalence of UTI in unconjugated neonatal hyperbilirubinemia. Besides, studies showed that unconjugated hyperbilirubinemia might reportedly be a significant or even the first presentation of UTI in neonates (4, 7, 34-39). In our systematic review, the prevalence of UTI in neonates with unexplained unconjugated hyperbilirubinemia was 4.01%, which seems to be lower than the pooled prevalence of UTI in all studies (i.e., 6.81%). However, some subgroups of neonates with unconjugated hyperbilirubinemia had a relatively high prevalence of UTI (e.g., preterm and LBW neonates) (Table 3). Moreover, the severe complications of untreated UTI in neonates should be considered when establishing the screening recommendations for clinical guidelines.

Unfortunately, we did not have any report regarding the conjugated hyperbilirubinemia in our studies to compare with unconjugated hyperbilirubinemia.

In most studies investigating the relationship between UTI and neonatal hyperbilirubinemia, the male gender was a significant risk factor. However, some studies found no significant difference between the two genders (7, 37). Our results showed a higher prevalence in the male gender and confirmed the role of the male gender as a risk factor for UTI presented with unexplained hyperbilirubinemia.

Table 3: The prevalence of UTI in subgroups of neonates with unconjugated hyperbilirubinemia. Systematic review and meta-analysis of UTI prevalence in Iranian neonates, 2000-2018

Variables	*Subgroups*	*Number of neonates included in the analysis*	*Pooled prevalence (95% CI)*	*Reference*
Gender	Male	1350	7.54 (2.40-14.98)	(15, 19, 20, 26-29, 31)
	Female	987	2.91 (0.63-6.42)	(15, 19, 20, 26-29, 31)
Uncircumcised neonates	-	192	16.02 (10.27-22.69)	(26-28)
Prolonged hyperbilirubinemia	Prolonged	753	9.33 (5.86-13.47)	(15, 26, 27, 29)
	Non-prolonged	314	3.82[a] (1.99-6.58)	(31)
Feeding method	Exclusive breastfeeding	180	14.29 (9.47-19.86)	(27, 28)
	Nonexclusive breastfeeding	40	5.95 (0.10-16.69)	(27, 28)
Gestational age	Preterm	146	14.75 (8.85-21.71)	(15, 27, 28)
	Term	852	7.34 (3.60-12.18)	(15, 26-28, 31)
Birth weight	LBW	172	11.05 (3.26-22.06)	(15, 28, 31)
	NBW	626	5.17 (2.34-8.96)	(15, 28, 31)

CI: Confidence Interval. LBW: Low birth weight. NBW: Normal birth weight.

[a] The reported prevalence stands for one reference and is not a pooled value.

Regarding the feeding method, breastfed neonates had a lower prevalence of UTI compared with formula-fed neonates. However, the findings of studies investigating the association between breastfeeding and UTI presented with unexplained hyperbilirubinemia are controversial (4, 7, 38). Surprisingly, as mentioned in Table 2, the pooled prevalence of UTI in the exclusive breastfeeding pattern was higher than the nonexclusive feeding pattern (8.84% vs. 4.72%). However, an exclusive breastfeeding pattern did not increase the risk for UTI (Fig. 3). This finding warrants more studies on this issue. Regarding birth weight and gestational age, studies showed that LBW and preterm conditions are two important risk factors for both hyperbilirubinemia (40) and UTI (41) in the neonatal period. These findings are consistent with our results (Table 2). Like other age groups, the most common bacterial etiology of neonatal UTIs is *E. coli* (2). However, the overall burden of UTIs caused by *E. coli* was lower in this age group (about 50% of all positive cultures) compared to older age groups, in which *E. coli* was responsible for up to 80% of UTIs. In particular, UTI in male neonates with vesicoureteral reflux (VUR) was more likely to present with pathogens other than *E. coli* (42). In the present study, the first and second most common uropathogen were E. coli and Klebsiella,

respectively. According to Bilgen and Xinias (35, 38) the most common causative agent of UTI was *E. coli*, while Ozcan and Omar reported *Klebsiella* as the most common uropathogen (4,37).

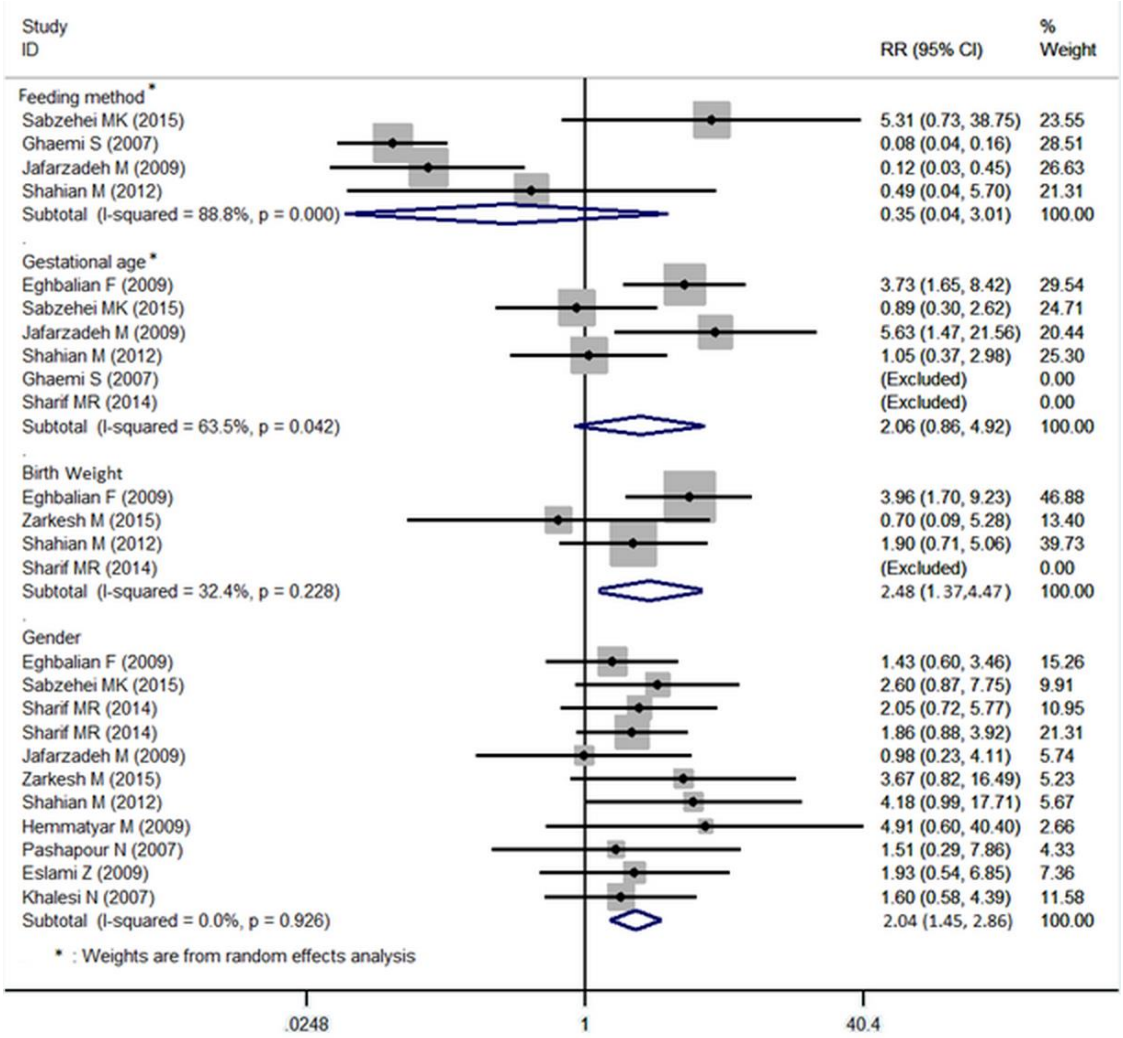

Fig. 3: Forest plot of univariate analysis for risk factor associated with UTI. The reference group for risk factors are as following: exclusive breast feeding for feeding method, term for gestational age, normal birth weight for birth weight and female for gender.
RR: Relative risk

This difference may suggest that geographical or environmental factors contribute to the etiology and epidemiology of UTI. UTI in neonates may indicate an underlying renal disorder or might be a sentinel event of underlying renal abnormality (8). In the present study, the prevalence of urinary tract anomalies in neonates with UTI was 16.71%. Some cases, such as vesicoureteral reflux or pyelonephritis, need long-term follow-up to prevent future complications.

Limitation

Due to the lack of some data in the reviewed studies, we could not evaluate the exact prevalence of UTI in neonates with conjugated or prolonged hy-

perbilirubinemia and circumcised neonates. Besides, the type of cultured uropathogen was not available in all studies. Furthermore, due to the lack of data regarding the prevalence of UTI in Iranian neonates without hyperbilirubinemia, we could not compare our results with the total prevalence of UTI in Iranian neonates. This comparison could be beneficial for whether neonatal hyperbilirubinemia was the initial presentation of the UTI, or they happened coincidentally.

Conclusion

Since the signs and symptoms of UTI in neonates are typically nonspecific, an accurate approach in suspicious conditions in this age group is challenging. The relationship between UTI and both prolonged and direct hyperbilirubinemia has been studied in current guidelines. UTI screening could be recommended in the workup of unexplained hyperbilirubinemia in neonates, especially if other risk factors, including male gender and LBW, are present.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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