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Prevalence of Urinary Tract Infection in Iranian Newborns with Jaundice: A Meta-Analysis

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ABSTRACT

Background: Jaundice is the most common clinical problem among newborns. It could be caused by different factors, including infections such as urinary tract infection (UTI). We investigated the prevalence of UTI in Iranian newborns with jaundice and prolonged jaundice in this study based on a larger sample of existing data.

Methods: We searched the databases of PubMed, Web of Sciences, Scopus, CNKI, SciELO, and Google Scholar for English articles, and a search was also done in Persian in Magiran and Scientific Information Database (SID) published until July 2021. Data analysis was performed by Comprehensive Meta-Analysis (CMA) version 2.0 software.

Results: This study included 19 eligible articles out of approximately 240 retrieved articles**.** The prevalence of UTIs in neonates with jaundice was estimated by pooling the data from 7416 neonates with jaundice. Of those, 369 cases had UTI. Combined data revealed that the prevalence of UTI in neonates with jaundice was 5.4% (95% CI 0.032-0.089, $P \leq 0.001$) and there was no publication bias.

Conclusion: The overall prevalence of UTI in Iranian newborns with jaundice was 5.4%. However, more studies with a large sample size are required for better results. Also our review showed a screening of UTI should be considered for infants with jaundice, especially prolonged jaundice.

Introduction

Neonatal jaundice occurs as a result of the accumulation of unconjugated bilirubin (UCB) in tissues and blood during 28 days after birth.[1] Neonatal jaundice can be commonly classified into two types: physiological and pathological. Physiological jaundice is induced by abnormal metabolism of bilirubin, which appears after 2-3 days of birth. Without using medications, it can disappear by itself in about 1-2 weeks after birth.[2] Pathological jaundice, notwithstanding, appears within 24h of birth, and the neonate's serum level of bilirubin continues to grow over time. Jaundice can remain longer than 2 weeks for full-term newborns and remain longer than 4 weeks for premature newborns, throughout which time jaundice may be recurring or exacerbating. Also, Jaundice is divided into non-prolonged and prolonged jaundice. Prolonged jaundice in the neonate is described as jaundice that continues longer than 14 days and has various probable causes. It is longer than two weeks in mature newborns (37 weeks and more) and three weeks in premature newborns (less than 37 weeks).[3,4]

Some studies have described that Jaundice may be correlated with bacterial infections in the newborn, such as UTI.[5] Clinical statistics confirmed that the frequency of neonatal jaundice is on the increase, and bacterial infection is the major factor inducing neonatal jaundice.[6] Consequently, in the determination of neonatal jaundice, in addition to clinical symptoms, screening of UTI is of high importance for the complete evaluation of neonatal jaundice.[7]

UTI in neonates is a usual complication, it is present in 0.7 to 1.4% of asymptomatic term neonates, about 5 to 11% of febrile newborns, 6.5% of neonates with jaundice and 55% of them have structural deformities in the urinary tract system.[8] The signs of UTI spectrum from asymptomatic to unspecific (nausea, vomiting, fever, jaundice, and poor feeding) and sometimes severe ones. Therefore, jaundice may be the initial sign of UTI.[9,10,11] It may be ordinarily continued asymptomatic, in most of the cases. The event of UTI can result in critical diseases events such as growth failure, critical gastrointestinal manifestations, fever ,lethargy, irritability, and jaundice.[12] UTI has often been mentioned as a potential cause of prolonged neonatal jaundice in newborns,[13,14] thus urine culture is routinely done in neonates with jaundice aged more than 3 weeks.[5] But, there is insufficient data to describe the physiological mechanism and cause-effect correlation between UTI and neonatal jaundice. Although there is a large variation in the rate of UTI in neonates with jaundice the disease load is yet high in certain areas of the world. However, there are various results on the load of UTI among newborns with jaundice published in Iran, there had been one systematic review and meta-analysis administered to harmonize such different data by Tola et al., in 2018. Also they estimate the overall prevalence of UTI in newborns with prolonged jaundice was 11% in Iran. Based on their study published from various parts of Iran, the load of UTI among newborns with prolonged jaundice changed between 0.6-53.9%. Also they conducted in Iran have strongly recommended screening for UTI.[13,15] In urine screening in Iranian newborns with jaundice, some approve it and others do not consider it necessary. As well, there is evidence that does not support the screening of UTI for newborns with jaundice and prolonged jaundice from other parts of the world.[16,17] In this study, we generally determine the prevalence of UTI in neonates with jaundice both prolonged and non-prolonged jaundice in Iranian population. We also assessed the need for urine culture in newborns with jaundice.

Materials and Methods

Search Strategy: The current systematic review was planned to determine the prevalence of UTI in neonatal jaundice and update the previous reviews about the research topic. Electronic databases were searched, including Web of Sciences, Scopus,

PubMed/Medline, Iranian Scientific Information Database (SID), and Iranmedex, for both English and Persian language articles that were published between 2002 and 2021. After searching the relevant words in the Medical Subject Headings (MeSH) database, finally, the keywords included "infant" OR "infants" OR "newborn" OR "newborns" OR "neonate" OR "neonates" OR "neonatal" AND "icterus" OR "hyperbilirubinemia" OR "jaundice" OR "jaundices" AND "urinary tract infection" OR "UTI" AND "Iran" OR "Iranian". This systematic review and meta-analysis were conducted according to the guideline of PRISMA (preferred reporting items for systematic review and meta-analysis).

Inclusion Criteria: The search included cross-sectional studies that reported the prevalence of UTI in infants with jaundice and prolonged jaundice. Articles with the following criteria were included in the study: (1) studied population should be Iranian neonates. (2) Articles in Persian and English language, (3) Neonatal jaundice is identified. (4) Investigating the prevalence of Jaundice with UTI. (5) Availability of adequate knowledge about the results of studies.

Exclusion Criteria: The subsequent articles were excluded from the study so that only suitable and related articles were reviewed: (1) Papers that addressed adults. (2) Papers related to the diagnosis and treatment of neonatal jaundice. (3) Papers those were only available in the abstract.

Data Extraction: The search included cross-sectional studies that stated the prevalence of UTI in newborns with jaundice, managed in any parts of Iran on jaundice, term or preterm neonates, and admitted to clinics, hospitals, or neonatal intensive care units (NICU). A total of 240 articles were included in the study and imported to Mendeley software. Out of which, 64 duplicates were deleted. Then, the titles and abstracts of the remaining articles were reviewed and 126 articles were removed due to irrelevancy. In the next step, 50 papers were omitted due to inadequate data, clarity of the study process, and lack of full text. Eventually, 19 articles related to the research topic were studied.

Quality assessment: Two researchers separately evaluated the full text of eligible articles using a standardized checklist. In the event of disagreements, two reviewers discussed with a third reviewer to reach an agreement. The subsequent data were extracted from the full-text articles and entered in standardized extraction checklist: name of the first author, city or province, study duration, most etiology of jaundice, type of study, type of jaundice, recommendation for urine culture, gestational age, number of neonates with jaundice, number of the infected neonates with UTI, and type of pathogen. If a duplicate publication was found or the same population was used in multiple studies, the publication with the larger sample size was included in the meta-analysis.

Statistical analysis: All of the statistical calculations were done utilizing Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided $P < 0.05$ were analyzed statistically significantly. Random-effect model meta-analysis was used to estimate the prevalence of UTI in neonatal jaundice, and binomial distribution to calculate standard error in each study. Heterogeneity in the results of different studies was examined using a Chi-squared-based Q-test with a significant level of P75% as significant heterogeneity. Subgroup examination was used to discover the pooled estimated prevalence of UTI based on the study population. In addition, a moment-based meta-regression model was used to examine the effects of the potential heterogeneity factors on the prevalence of UTI. A visible examination of the funnel plot was done to evaluate potential publication bias. Furthermore, Egger's test was done to assess the publication bias statistically, in which $P < 0.05$ was considered statistically significant. If the publication bias tests showed bias existed, the Duval and Tweedie ''trim and fill'' method was used to set the bias.

Results

A total of 19 eligible articles with a whole sample size of 7416 newborns, were retrieved from 2002 to 2021. These articles were heterogeneous in terms of inclusion criteria for newborns, sample size, study place, and results (Table 1). They were disseminated in different cities of Iran (15 cities). In total, 7416 newborns that had jaundice were pooled for estimating the prevalence of UTI in newborns with jaundice. Of those, 369 cases were diagnosed with UTI. The majority of the study members included in this review was obtained from hospital wards or mixed hospital and NICU. Table 1 displays the 19 articles involved in this review, and their characteristics. Figure 1 represents the article collection method based on a PRISMA flow diagram. The overall prevalence of UTI in infants with jaundice was 5%. The most current etiologic agents of infantile hyperbilirubinemia consisted of ABO incompatibility, infections, and sepsis. But the most common etiologic cause of prolonged jaundice was Breastfeeding (Table 2). The overall most risk factors of infantile hyperbilirubinemia consisted of unknown. Our results showed that 16 articles evaluated the need for urine culture. In 13 articles they recommend urine culture and in three articles, they stated that urine culture was not necessary.

Sensitivity Analysis and Heterogeneity Test: We used a leave-one-out sensitivity analysis to identify the effects of individual publications on the overall pooled ORs. The significance of the pooled ORs was not influenced by excluding those studies, indicating that this study pooled ORs were statistically robust and our findings were not dependent on a single study. In the current study there was statistically a significant between-study heterogeneity (I^2 = 95.13; $P_H \leq 0.001$) overall in neonates with jaundice.

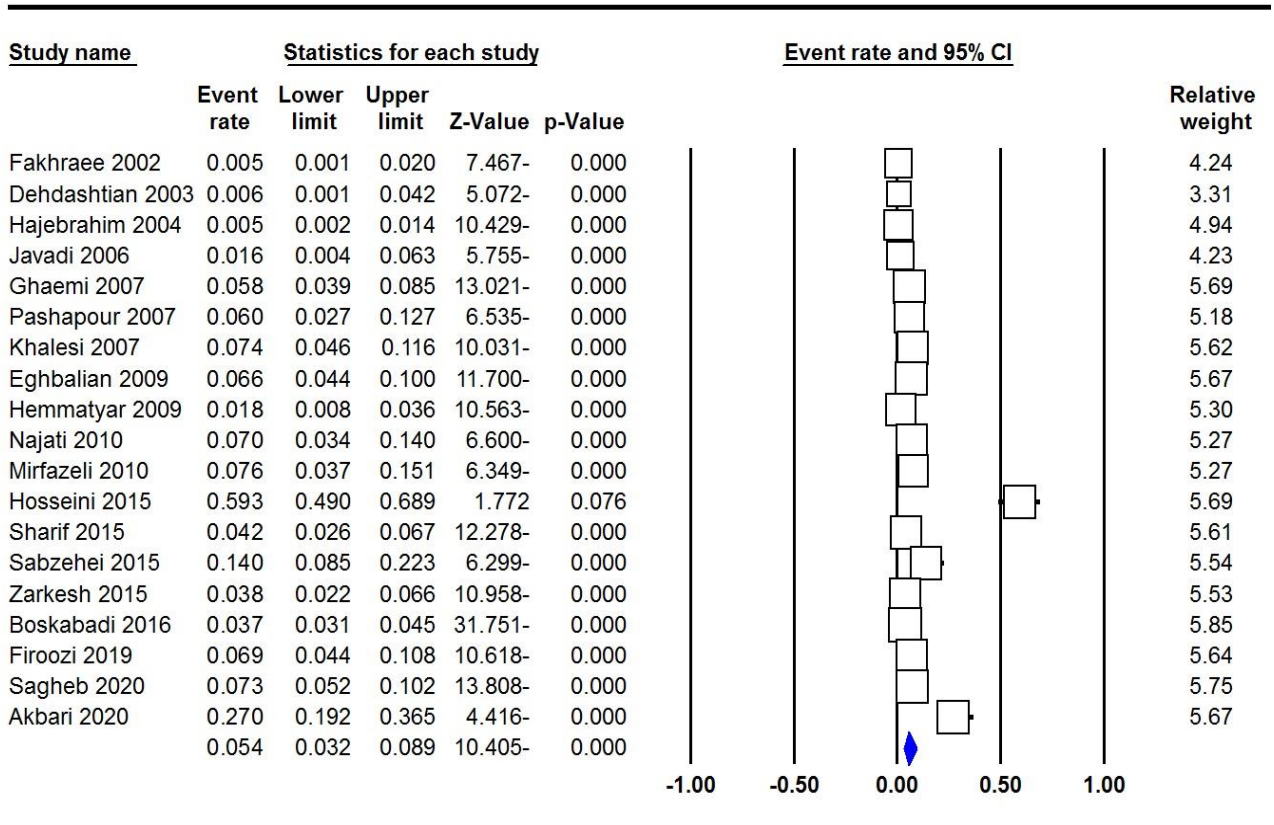

Figure 1. Forest plot for prevalence of UTI in Iranian Neonates with Jaundice in Overall

Table 1. Characteristics of studies included in meta-analysis

First Author	City	Study duration	Type of study	Type of Jaundice	Gestational Age	Number of Jaundice	Number of UTI (%)	Type of pathogen
Fakhraee 2002[18]	Tehran	1997-1999	Cross-sectional	Jaundice		400	2 (0.5)	E. coli
Dehdashtian 2003[19]	Ahvaz	2002-2003	Descriptive	Prolonged	Term	163	1 (0.6)	E. coli (0.6%)
Hajebrahim 2004[20]	Tehran	1997-2000	Descriptive	Jaundice	Term	750	4 (0.53)	-
Javadi 2006[21]	Khorram-Abad	2003	Cross-sectional	Jaundice	Preterm (35.8%)	123	2 (1.6)	-
Ghaemi 2007[22]	Isfahan	2001-2002	Cross-sectional	Prolonged	Term	400	23 (5.8)	E-coli (74%)
Pashapour 2007[23]	Uremia	2005-2006	Cross-sectional	Prolonged	Term	100	6 (6.0)	E. Coli (3%), KP (2%), Proteus (1%)
Khalesi 2007[24]	Zahedan	2005	Cross-sectional	Prolonged	Term/preterm	230	17 (7.4)	E. coli (5.6%), KP (1.3%), S. aureus (0.4%)
Eghbalian 2009[25]	Hamadan	2002-2006	Descriptive	Prolonged	Term/preterm	316	21 (6.6)	E. coli (5.4%), S. saprophyticus (0.9%), S. aureus (0.3%)
Hematyar 2009[26]	Tehran	2005-2007	Cross-sectional	Jaundice	Term (97%)	400	7 (1.8)	E. coli (85.7%), KP (14.3%)
Najati 2010[27]	Tabriz	2009	Cross-sectional	Prolonged	Preterm (3%)	100	7 (7.0)	E. coli (6%), KP (1%)
Mirfazeli 2010[28]	Gorgan	2004-2005	Cross-sectional	Severe	Term	92	7 (7.6)	-
Hosseini 2015[15]	Kermanshah	2010-2013	Descriptive	Prolonged	Term/preterm	91	54 (59.3)	-
Sharif 2015[29]	Kashan	2012-2013	Cross-sectional	Jaundice	Term	384	16 (4.2)	
Sabzehei 2015[30]	Hamadan	2007-2012	Cross-sectional	Prolonged	Term/preterm	100	14 (14.0)	E. coli (7%), KP 5%, Proteus (2%), Enterobacter cloacae (1%)
Zarkesh 2015[31]	Rasht	2010-2011	Cross-sectional	Unexplained	Term	314	12 (3.8)	E. coli (83.3%), Enterobacter (16.7%)
Boskabadi 2016[32]	Mashhad	2005-2014	Cross-sectional	Unexplained	-	2658	99 (3.7)	-
Firoozi 2019[33]	Tonekabon	2015	Cross-sectional	Jaundice	-	259	18 (6.9)	E. coli (4.6%), Proteus (2.3%)
Akbari 2020[4]	Bam	2015	Cross-sectional	Prolonged	Term/preterm	100	27 (27.0)	E. coli (19%), KP (4%)
Sagheb 2020[14]	Tehran	2013-2014	Cross-sectional	Unexpected	Term	436	32 (7.3)	KP (37.5%), E. coli (21.9%), Staphylococcus (9.4%), Pseudomonas (3.1%), Enterococcus (15.6%), Enterobacter (9.4%), Group B Streptococcus (3.1%)

CS: Clinical sign; BC: Blood culture; E. coli: Escherichia coli; KP: Klebsiella pneumonia; S. Aureus: Staphylococcus aureus; S. saprophyticus: Staphylococcus saprophyticus

Table 2. Most common etiology of jaundice and recommendation for urine culture

Author	Type of	Most common etiology	Recommendation for urine culture
Fakhraee	Jaundice		No
Dehdashtian	Jaundice		No
Hajebrahim Tehrani	Prolonged		No
Javadi	Jaundice	breastfeeding	
Ghaemi	Jaundice	-	Yes
Pashapour	Prolonged	breastfeeding	Yes
Khalesi	Prolonged		Yes
Eghbalian	Prolonged	-	Yes
Hemmatyar	Prolonged		Yes in prolonged
Najati	Jaundice	Breastfeeding 75%	Yes
Mirfazeli	Prolonged	Unknown 44% Sepsis 27%	-
Hosseini	Severe	UTI 59.3%	Yse
Sharif	Prolonged	-	Yes
Sabzehei	Jaundice	Breastfeeding 70% UTI 14%	Yes
Zarkesh	Prolonged	-	Yes
Boskabadi	Unexplained	Day 1-3:blood in Day4-12:sepsis	-
Firoozi	Unexplained	-	Yes
Sagheb	Jaundice	-	Yes
Akbari	Prolonged	Prematurity Blood type incompatibilities	Yes

Publication Bias: The Begg's and Egger's linear regression tests were applied to test the potential publication bias in the literatures. As shown in figure 2, the shapes of the Begg's funnel plot did not show any evidence of publication bias in the current meta-analysis. Moreover, the Egger's tests did not show an evidence of publication bias statistically ($P_{Begg's}$ = 0.058; $P_{Egger's}$ = 0.698), indicating that our pooled data were statistically robust and reliable.

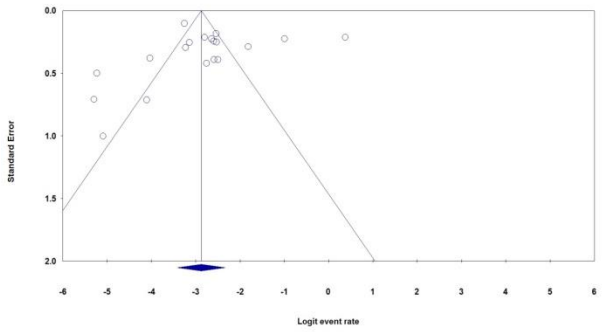

Figure 2. The funnel plots of publication bias for prevalence of UTI in neonates with jaundice in overall

Evaluation of prolonged jaundice: Prolonged jaundice is described as a kind of jaundice remaining over 14 days in term neonates or over 21 days in preterm neonates. Different pathologic problems such as UTIs may cause prolonged jaundice. Nine articles evaluated prolonged jaundice included 1,600 newborns, 170 of whom had jaundice with a UTI and an overall prevalence of 10.6%. Laboratory tests for UTI include Urinalysis, Urine culture (UTI was diagnosed by urine specimens collected by the bag or suprapubic aspiration).

Discussion

Jaundice is one of the most current clinical findings among newborns through the first days after birth. Furthermore, discovering the predisposing factors and aggravating or stabilizing factors of jaundice could be effective in decreasing the severity, controlling jaundice and the primary problem. Bacterial infection is one of these factors that include Urinary Tract Infection (UTI).[4,34] Bacterial infection and jaundice may be

correlated with higher morbidity. Numerous systematic reviews and meta-analyses assessed UTI and jaundice in Iranian newborns. The idiopathic hyperbilirubinemia may be related to sepsis or UTI especially in neonates with prolonged jaundice.[21] UTIs are well-known to produce prolonged jaundice and are investigated as a standard of care. Onward with prolonged jaundice, UTIs may hold the unexplained pathologic jaundice displaying in the first 2 weeks of life. It is yet uncertain to examine for UTI in patients with unexplained jaundice displaying in the first 2 weeks of life.[35] In this study, we evaluated the total prevalence of UTI in Iranian infants. We evaluated all jaundice cases included prolonged and non-prolonged jaundice in newborns to assess prevalence and need for urine culture. We selected 19 articles on the prevalence of UTI in jaundice that included 7416 Iranian infants with jaundice. We estimated the overall prevalence of UTI in Iranian newborns with jaundice was 5%. Our estimate was lower than the previous meta-analysis that was performed by tola, this difference may be that they just selected prolonged jaundice but we selected all cases. So this augments the hypothesis that UTI is more common in prolonged jaundice. Our results show the total prevalence of UTI in jaundice is 5.4% and the prevalence of UTI in prolonged jaundice is 10.6%. Tola et al., performed the most comprehensive meta-analysis of the prevalence of UTI in prolonged jaundice in Iran in 2018. They reviewed nine articles, including 1,750 infants with prolonged jaundice. They showed the prevalence of UTI in infants with prolonged jaundice had ranged from 0.6-53.9%. The estimated pooled prevalence of UTI among infants with prolonged jaundice in Iran was 11.0%. They reported prevalence of UTI decreased as the mean age of members increased, but this correlation was not statistically significant.[13] In 2013, Maamouri Gh A, et al. showed Neonatal infection was found in almost 10% of jaundiced newborns. The most current infection correlated with neonatal jaundice was UTI (77.9%), Sepsis (16.8%), and pneumonia (5.3%).[36] In 2007, Pashapour and et al., evaluated UTI in term neonates with prolonged jaundice. They showed UTI was identified in 6% of the jaundiced infants. Isolated microorganisms in this study were included *Escherichia coli*, *Klebsiella pneumonia*, and *Proteus mirabilis* that are among the common causes of UTI in the neonatal period. They observed the incidence of neonatal UTI varies from 0.1% to 1% in the overall population of healthy newborns while it was 6 times higher in their study. Doing urine cultures should be reconsidered as a routine examination in the evaluation of every newborn with prolonged jaundice. [31] In 2012, Shahian et al., assessed unexplained neonatal jaundice as a primary characteristic symptom of UTI. They showed UTI can happen in asymptomatic, afebrile newborns presenting with unconjugated hyperbilirubinemia in the first weeks of life. Their study showed the prevalence of UTI in asymptomatic jaundiced newborns was 12.5%, and jaundice may be the earliest sign of UTI before other signs become apparent. they suggested that urine culture should be considered as a part of the diagnostic evaluation of newborns older than 3 days with hyperbilirubinemia of unexplained etiology.[5] In 2013 Najib et al., evaluated the causes of prolonged jaundice among the newborns referred to Kashan Shahid-Beheshti hospital during 2011-2012. In their study, the prevalence of severe hyperbilirubinemia was 15 percent in all neonates with Icter. They showed it is more prevalent in males but they didn't evaluate UTI and didn't do urine culture.[37] In comparison, some studies from the United Kingdom (UK) have suggested that routine screening of UTI in neonates with prolonged jaundice is unnecessary.[13] Screening of UTI and urine culture should be considered for newborns with prolonged jaundice. In addition, the prevention of UTI between newborns should be taken into attention. Such as tola et al., in our systematic review and meta-analysis, the main limitation

was the skill difference between different on diagnosing of sepsis and UTI, and micro-organism culture and the kind of related patients might have influenced the pooled prevalence of prolonged jaundice and other types of jaundice. In addition, it could not find a source of heterogeneity among studies. Because the symptoms and signs of UTI in newborns are usually nonspecific, and an exact method in doubtful conditions in this age group is challenging. The relationship between UTI and both prolonged and direct hyperbilirubinemia has been studied in numerous articles. UTI screening could be suggested in the workup of unexplained jaundice in newborns, particularly if other risk factors, including male gender and LBW, are present.[38]

Despite extensive studies, there is still no clear guideline for screening for UTI in infants with jaundice, and there is no definitive recommendation for urine culture. Our results showed that 16 articles evaluated the need for urine culture. In 13 articles they recommend urine culture and in three articles, they stated that urine culture was not necessary. So we concluded urine culture is necessary for routine screening for UTI among neonates with jaundice especially urine culture should be considered a necessary evaluation in asymptomatic jaundiced neonates younger than 4 weeks. So requesting urine culture in all infants with prolonged jaundice should be considered. In this regard, National Institute for Health and Care Excellence (NICE) guidelines recommend this practice.

Conclusion

It's well known that the prevalence of UTI is high among newborns with jaundice. Therefore, it is better to order a urine culture test for all newborns with jaundice. The prevalence of UTI in newborns with prolonged jaundice is higher than those of healthy. So Screening of UTI should be held for infants with prolonged jaundice. Also, the prevention of UTI in newborns with jaundice should be taken into attention.

Conflict of Interests

Authors have no conflict of interests.

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