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ORIGINAL

Hyperbilirubinemia is a predictor of appendiceal perforation in children: A meta-analysis

La hiperbilirrubinemia es un factor predictivo de perforación apendicular en niños: Un metaanálisis

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Abstract

Objective: In this meta-analysis, our goal was to examine the diagnostic utility of bilirubin in identifying complicated from uncomplicated pediatric appendicitis.

Materials and methods: Using the databases Embase, PubMed, Scopus, and Cochrane, we carried out a thorough literature search up to 2022. Studies comparing complicated appendicitis (CA) and simple appendicitis (SA) in terms of hyperbilirubinemia in the pediatric population were included.

Results: A total of 5 studies with 2740 acute appendicitis patients (1097 complicated appendicitis and 1643 simple appendicitis) were included in this meta-analysis. Five studies have discussed the diagnostic value of total bilirubin (TB). When compared to simple appendicitis, complicated appendicitis had a significantly higher TB count (I^2=94%), (WMD=0.18, 95% CI -0.00 to 0.37; P=0.05), DB count (I^2=0%), (WMD=0.11, 95% CI 0.04 to 0.18; P=0.002), and IB count (I^2= not applicable), (WMD=0.04, 95% CI 0.01 to 0.07; P=0.02).

Conclusions: In conclusion, in this meta-analysis, total bilirubin, direct bilirubin, and indirect bilirubin values were higher in complicated appendicitis compared to simple appendicitis. Both total bilirubin and direct bilirubin can be used as diagnostic parameters in childhood appendicitis to differentiate complicated appendicitis from simple appendicitis.

Key words: Appendicitis, children, direct hyperbilirubinemia, hyperbilirubinemia.

Resumen

Objetivo: En este metanálisis, nuestro objetivo fue examinar la utilidad diagnóstica de la bilirrubina para identificar la apendicitis pediátrica complicada frente a la no complicada.

Materiales y métodos: Utilizando las bases de datos Embase, PubMed, Scopus y Cochrane, realizamos una búsqueda bibliográfica exhaustiva hasta 2022. Se incluyeron estudios que compararan apendicitis complicada (AC) y apendicitis simple (AS) en términos de hiperbilirrubinemia en la población pediátrica.

Resultados: Se incluyeron en este metanálisis un total de 5 estudios con 2740 pacientes con apendicitis aguda (1097 complicada y 1643 simple). Cinco estudios han discutido el valor diagnóstico de la bilirrubina total (TB). En comparación con la apendicitis simple, la apendicitis complicada tuvo un recuento de TB significativamente mayor (I^2=94 %), (DMP=0,18, IC del 95 %: -0,00 a 0,37; P=0,05), recuento de DB (I^2=0 %), (DMP = 0,11, IC del 95 %: 0,04 a 0,18; P = 0,002) y recuento de BI (I^2 = no aplicable), (DMP = 0,04, IC del 95 %: 0,01 a 0,07; P = 0,02).

Conclusiones: Tanto la bilirrubina total como la directa pueden usarse como parámetros de diagnóstico en la apendicitis infantil para diferenciar la apendicitis complicada de la apendicitis simple.

Palabras clave: Apendicitis, niños, hiperbilirrubinemia directa, hiperbilirrubinemia.

Introduction

One of the most typical causes of acute abdomen is acute appendicitis[1]. This disease has a perforation risk of up to 20% and a lifetime incidence of about 7%[1,2]. Early diagnosis can occasionally be difficult, despite the well-known classical signs and clinical features of acute appendicitis. Acute appendicitis is primarily diagnosed based on clinical symptoms, with radiological examinations being reserved for specific patients. A perforation, which can be linked to considerable morbidity and even fatality, may occur if acute appendicitis is not diagnosed at an early stage[3,4].

The Alvarado score and the RIPASA score are only two of the several screening and scoring instruments that have been developed to help in the diagnosis of acute appendicitis[1]. However, scoring methods like these have come under fire for lacking sensitivity and specificity as well as failing to foretell the severity of acute appendicitis. In addition, a number of blood tests are utilized to gauge the severity of appendicitis. However, a raised WBC count has no prognostic utility in identifying uncomplicated appendicitis from complicated appendicitis[1-4]. Blood cells (WBC) counts are typically elevated in patients with appendicitis. Many researchers are still interested in finding a method or marker that can predict the diagnosis of acute appendicitis and distinguish between uncomplicated and severe appendicitis with good sensitivity and specificity[5-7]. A straightforward, affordable, and easily calculable measure of subclinical inflammation is bilirubin. Although elevated blood bilirubin has been found to be a possible indicator of appendix perforation, its sensitivity and specificity are insufficient[8-10].

In this meta-analysis, our goal was to examine the diagnostic utility of bilirubin in identifying complicated from uncomplicated pediatric appendicitis.

Materials and Methods

Search Strategy

Using the databases Embase, PubMed, Scopus, and Cochrane, we carried out a thorough literature search up to 2022. Appendicitis, pediatric appendicitis, perforated appendicitis, gangrenous appendicitis, hyperbilirubinemia, direct bilirubin, elevated bilirubin, and children were the search phrases used. Furthermore, we searched also "simple appendicitis, complicated appendicitis, un-complicated appendicitis, non-complicated appendicitis, pediatric appendicitis, appendicitis in children, hyperbilirubinemia in appendicitis, serum bilirubin, laboratory marker for appendicitis". References and reviews were searched manually for further relevance.

Study Selection

Studies comparing complicated appendicitis (CA) and simple appendicitis (SA) in the pediatric population were included.

Inclusion criteria:[1] clinical studies comparing CA and SA, and[2] raw data including some of the following: total bilirubin, direct bilirubin, and indirect bilirubin.
Exclusion criteria:[1] no comparative case series as a control;[2] studies could not provide usable raw data or duplicate publications.

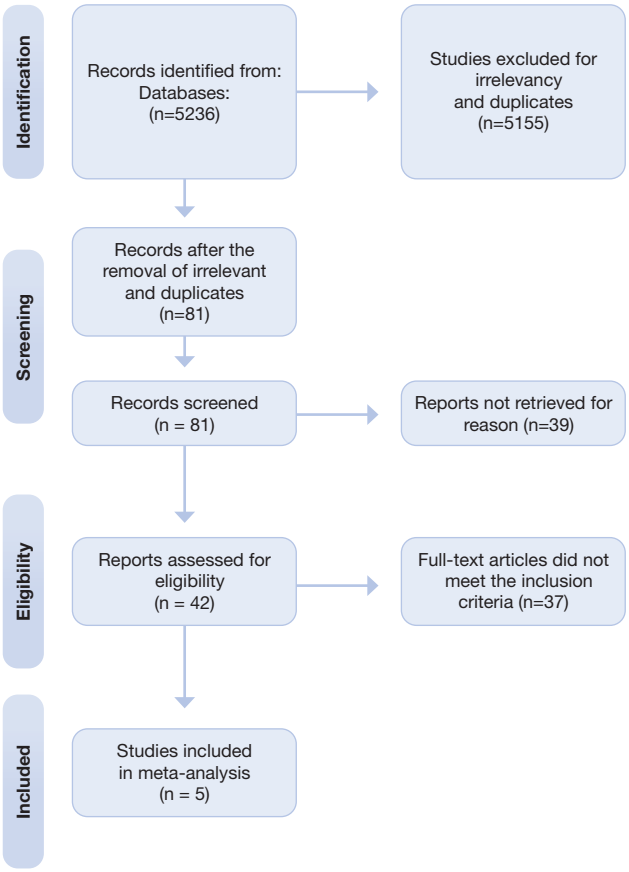
Data Extraction

Two authors independently reviewed the included studies (SA and MA). We extracted information on sample size, study design, and year of publication. Population data were obtained, including the type of appendicitis, and bilirubin values.

Risk of Bias Assessment

The risk of bias in the included studies was evaluated using the ROBINS-I (Risk Of Bias in Non-randomized Studies—of Interventions) method. The reviewers also evaluated the overall risk of bias across all studies for each relevant outcome and considered that information when making decisions about the "quality of evidence."

Table I: PRISMA flow diagram of study selection.



Statistical Analysis

For the statistical data analysis, Review Manager (RevMan) software version 5.4 was used. Both continuous and dichotomous variables were evaluated using measured mean differences and risk ratios. The I^2 statistic was employed to quantify the amount of statistical heterogeneity, and the Chi-square test was utilized to determine it. Significance was set at $P \leq 0.05$. We applied a random effect model.

Reporting

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analysis) was used to report the findings of this systematic review.

Results

Using a PRISMA flow diagram, **table I** presents an overview of the selection procedure of 42 studies identified during the initial search strategy were retrieved for full-text review, and 5 studies[8,9,10,11,12] with 2740 acute appendicitis patients (1097 complicated appendicitis and 1643 simple appendicitis) who met the inclusion criteria were selected.

Risk of Bias

Table II provides a summary of the ROBINS-I tool's risk of bias evaluation. A "moderate" risk of bias existed in three articles with regard to "Bias due to confounding." Given their retrospective character, all studies had a "moderate" risk of bias in the other categories.

Table II: Risk of Bias (ROBINS-I Tool).

Author	Year	Bias due to confounding	Bias for other domains
Chen et al.	2021	**Moderate:** Age under 3 years	Moderate
Güngör et al.	2021	**Moderate:** Age difference between groups	Moderate
Koirala et al.	2022	**Moderate:** Difference of number by gender	Moderate
Noh et al.	2012	**Moderate:** Age difference between groups	Moderate
Yang et al.	2019	**Moderate:** Age difference between groups	Moderate

Figure 1: The value of total bilirubin.

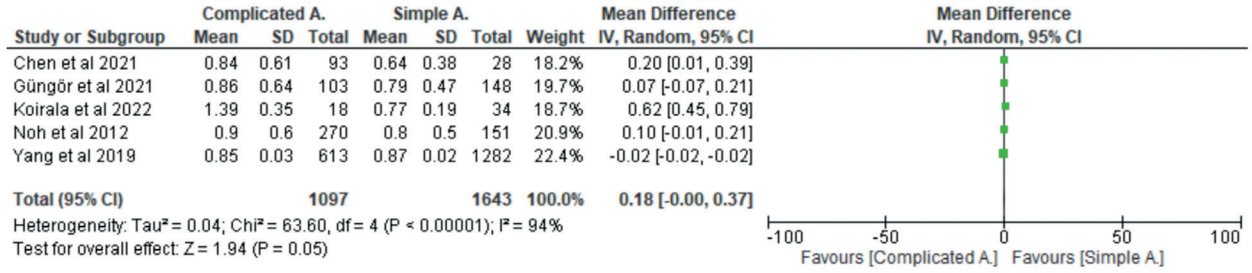


Figure 2: The value of direct bilirubin.

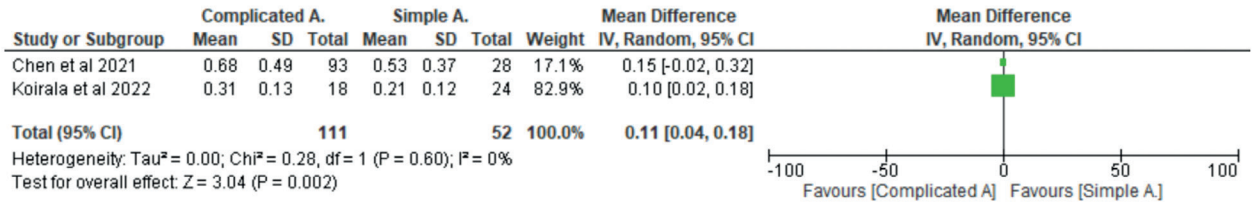
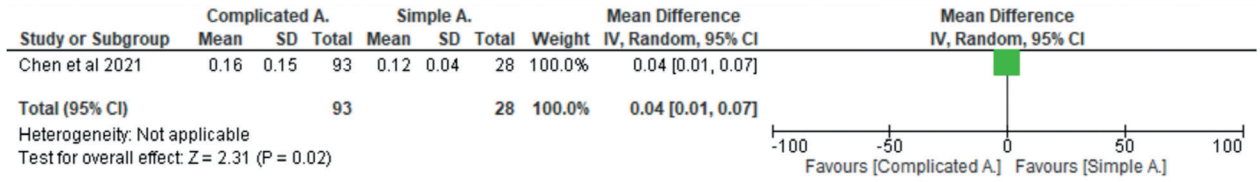


Figure 3: The value of indirect bilirubin.



Outcomes
A total of 5 studies were included in this meta-analysis. All of these studies were retrospective comparative studies To be used to distinguish complicated appendicitis from simple appendicitis; 5 studies evaluating total bilirubin, 2 direct bilirubin, and 1 study of indirect bilirubin were included in this meta-analysis.

Total bilirubin
Five studies have discussed the diagnostic value of total bilirubin (TB). When compared to simple appendicitis, complicated appendicitis had a significantly higher TB count (I^2=94%), (WMD=0.18, 95% CI -0.00 to 0.37; P=0.05; **Figure 1**).

Direct Bilirubin
Although three studies documented the diagnostic value of direct bilirubin (DB), only two studies (111 patients in CA group and 52 patients in SA group) were suitable for meta-analysis. However, the CA group had a significantly higher DB when compared to SA group (I^2=0%), (WMD=0.11, 95% CI 0.04 to 0.18; P=0.002; **Figure 2**).

Indirect Bilirubin
Only 1 study (93 patients in CA group and 28 patients in SA group) was suitable for meta-analysis investigating the effects of indirect bilirubin (IB). It is found that CA group had a significantly higher IB when compared to the SA group (I^2= not applicable), (WMD=0.04, 95% CI 0.01 to 0.07; P=0.02; **Figure 3**).

Discussion

Since all studies included in this meta-analysis had a moderate risk of bias, no studies were excluded due to bias.

In many previous studies, the effects and results of laboratory blood parameters on the differential diagnosis, diagnostic features, treatment, and complications of simple appendicitis and complicated appendicitis were examined[11,12]. Especially in recent years, relative parameters such as neutrophil-lymphocyte ratio and platelet-lymphocyte ratio have come to the fore[13-16].

The main goal of this study is to establish whether or not hyperbilirubinemia is a valid indicator of appendiceal perforation. The meta-analysis of previous studies emphasized that hyperbilirubinemia can be used to predict perforated appendicitis in adult patients[17]. There are studies suggesting that hyperbilirubinemia in children can be used in the differential diagnosis of complicated appendicitis and acute appendicitis, as in adults[10-12]. But there is no meta-analysis on this subject. However, this meta-analysis is the first meta-analysis suggesting that hyperbilirubinemia (both total, indirect and direct) can be used in the differential diagnosis of complicated and simple appendicitis in the pediatric population.

According to the study by Koirala et al., it shows that both direct and total bilirubin can be used in the differential diagnosis of complicated and simple appendicitis[8]. Similar results were found in the study by Chen et al. In the study by Chen et al., the mean of direct bilirubin in the complicated appendicitis group was almost twice that of appendicitis in the simple appendicitis group[9]. On the other hand, according to a study conducted by Güngör et al. in 2021, the mean total bilirubin in the complicated appendicitis group was almost twice as high as the total bilirubin in the simple appendicitis group[12]. It is noteworthy that the number of patients in this study is considerably higher than in equivalent studies. However, as a result, when complicated appendicitis and simple appendicitis were compared in our study, total bilirubin (p=0.05), direct bilirubin (p=0.002), and indirect bilirubin (p=0.02) values were higher in the complicated appendicitis group.

Conclusions

In conclusion, in this meta-analysis, total bilirubin, direct bilirubin, and indirect bilirubin values were higher in complicated appendicitis compared to simple appendicitis. Both total bilirubin and direct bilirubin can be used as diagnostic parameters in childhood appendicitis to differentiate complicated appendicitis from simple appendicitis.

Conflict of interest
The authors declare no conflict of interest

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No

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