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Risk Factors of Pathological Unconjugated Hyperbilirubinemia among Yemeni Newborn

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Abstract

Background: Jaundice is a clinical condition that is often present in pediatric practice and constitutes one of the major issues within the neonatal period and it is either physiological or pathological. Although most newborn who have jaundice are otherwise healthy, they need close monitoring for serum bilirubin level as bilirubin is potentially toxic to the central nervous system. Risk factors may be maternal or neonatal in origin. This preliminary study focuses on the detection of the risk factors of pathological unconjugated hyperbilirubinemia due to lack of information on this topic in Yemen.

Aim of Study: To determine the most common aetiology and risk factors of pathological unconjugated hyperbilirubinemia and their relation to serum bilirubin.

Patients and Methods: The study was prospective cross-sectional descriptive study of newborns with pathological unconjugated hyperbilirubinemia admitted to neonatal intensive care unit (NICU) at Al-Thawra General Modern Teaching Hospital and Al-Sabeen Maternity and Childhood Teaching Hospital during a period of 12 months starting on June 2012 to end of May 2013.Of the total admitted cases, two hundred cases were selected according to the inclusion and exclusion criteria. Data was collected, tabulated and analyzed by using Statistical Package for the Social Sciences (SPSS) version 20.

Results: The risk factors of pathological hyperbilirubinemia were Neonatal sepsis which was the most common aetiology and associated risk factor and was present in 70% of the cases, ABO incompatibility was present in 14% of the cases, Rh incompatibility was present in 8% of the cases, Cephalohaematoma (excessive bruising) was present in 6% of the cases, and G6PD deficiency was present in 2% of the cases.

Conclusion: Pathological unconjugated hyperbilirubinemia is one of the major problems in neonatal morbidity and mortality in Yemen. Neonatal sepsis was the commonest aetiology and associated risk factor of pathological hyperbilirubinemia and the major cause of death in this study. We need to do early screening for detecting hyperbilirubinemia and we need to adopt early essential newborn care and resuscitation guideline on a national level to conduct appropriate management.

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Key Words: *Unconjugated hyperbilirubinemia – Newborn – Neonatal intensive care unit – Phototherapy – Neonatal sepsis – Risk factors.*

Introduction

JAUNDICE is a clinical condition that is often present in pediatric practice and constitutes one of the major issues within the neonatal period [1]. Neonatal hyperbilirubinemia is extremely common. Jaundice in neonates is common affecting nearly 60% of fullterm and 80% of preterm neonates during the first week of life [2]. Neonatal Hyperbilirubinemia is extremely common as almost every newborn develops unconjugated serum bilirubin level of more than 30 umol/L (1.8mg/dl) during the first week of life [1]. Neonatal Hyperbilirubinemia can be both physiological and pathological processes in newborns. Although most newborn with jaundice are otherwise healthy, they need to be monitored because bilirubin is potentially toxic to the central nervous system [1]. However, few term newborns with hyperbilirubinemia have serious underlying pathology. Jaundice is considered pathologic if it presents within the first 24 hours after birth, the total serum bilirubin level rises by more than 5mg per dL (86mol per L) per day or is higher than 17mg per dL (290mol per L) [3]. The common risk factors for unconjugated hyperbilirubinemia include fetal-maternal incompatibility, prematurity, low birth weight, previous sibling with history of jaundice, breastfeeding, cephalohaematoma, trauma from instrumental delivery, or delayed meconium [4,5]. Hyperbilirubinemia may require therapy, which is mainly in the form of phototherapy or exchange transfusion [6]. No information was found about pathological unconjugated hyperbilirubinemia in Yemen. The aim of this study was to determine the most common aetiology and risk factors of pathological unconju-

gated hyperbilirubinemia, and their relation to serum bilirubin.

Patients and Methods

The study was prospective cross-sectional descriptive of newborn with pathological unconjugated hyperbilirubinemia admitted to neonatal intensive care unit (NICU) at Al-Thawra General Modern Teaching Hospital and Al-Sabeen Maternity and Childhood Teaching Hospital from June 01, 2012 to May 31, 2013. A total number of 1183 of newborns were admitted to the NICU during the period of 12 months. Of them 200 cases were selected according to the inclusion and exclusion criteria. The inclusion criteria included the following, (1) Clinical jaundice appearing in the first 24 hours of life. (2) Increases in the level of total bilirubin of more than 8.5umol/1 (0.5mg/dl) per hour or 85umol/1 (5mg/dl) per 24 hours. (3) Total bilirubin of more than 331.5umol/1 (19.5mg/dl). The Exclusion criteria were all newborn with physiological or conjugated hyperbilirubinemia. The study collected detailed case history for all the newborn which included comprehensive clinical examination and specific investigations, specifically serum bilirubin level (total, direct and indirect levels), blood group and Rh typing of baby and mother, hemoglobin levels, complete blood picture, septic screening which included CRP, band cells, reticulocyte count, Coombs test (direct), G6PD enzyme assay, chest X-ray. Data was collected, tabulated and analyzed by using Statistical Package for the Social Sciences (SPSS) version 20 and significance was assessed by Chi square test where p-value <0.05 was considered significant.

Results

During the period of one year starting from June 01, 2012 to May 31, 2013, there was a total of 19050 live birth born in two hospitals. Of those newborns, 1183 neonates were admitted to nursery and to the NICU. Two hundred cases were enrolled in this study which fulfilled the inclusion criteria. Five readings of the mean were taken and were 9.9mg/dl (±2.9SD), 13.1mg/dl (±3.5SD), 14mg/dl (±3.8SD), 11.4mg/dl (±3.7SD), and 7.3mg/dl (±2.4SD) respectively. The mean peak of total serum bilirubin of the five readings was 16.3mg/dl (±2.9SD). Neonatal sepsis was the most common aetiology and associated risk factor and was present in 70% of cases. ABO incompatibility was present in 14% of cases. Rh incompatibility was present in 8% of the cases. Cephalohaematoma (excessive bruising) was present in 6% of the cases. G6PD deficiency was present in 2% of the cases. The incidence in Preterm babies was higher than fullterm babies and were 73%, 27%, respectively. There was a male predominance as males represented 64% of the cases. Pathological hyperbilirubinemia was more common in low birth weight ≤2.5kg and represented 80% of the cases. History of pathological jaundice in siblings was present in 7% of the cases. Infant of diabetic mother represented 5% of the cases, see (Fig. 1). The neonatal sepsis was higher in preterm babies 82% than fullterm babies 18%, and this difference was statistically significant (p=0.000). ABO incompatibility was higher in fullterm babies 52% in comparison to preterm babies 48%, and this difference was statistically significant (p=0.002). G6PD deficiency was found in fullterm babies 100%, and was statistically significant (p=0.02). Rh incompatibility was high in preterm babies 56% than fullterm babies 44%, and this difference was not statistically significant (p=0.1), see (Fig. 2). The risk factors in relation to the mean total serum bilirubin (TSB) of five readings was high in Rh incompatibility followed by ABO incompatibility, neonatal sepsis, cephalohaematoma and G6PD deficiency and were 17mg/dl (±2.8SD), 16.7mg/dl (±3.2SD), 16.3mg/dl (±2.8SD), 14.9mg/dl (±2.6SD) and 13.5mg/dl (±2.3SD) respectively, and the differences were statistically not significant. The mean total serum bilirubin in preterm babies was 16.5mg/dl (±2.7SD) and in fullterm babies was 15.6mg/dl (±3.3SD), and this difference was statistically not significant (p=0.05). The mean TSB of five reading in male babies were higher than female babies and were 16.3mg/dl (±2.6SD) and higher 16.4mg/dl (±2.8SD) respectively, and this difference was not statistically significant (p=0.9). In low birth weight babies ≤2.5kg, the mean TSB was higher than babies with birth weight >2.5kg and were 16.4mg/dl (±2.8SD), 15.8mg/dl (±3.3SD) respectively, and this difference was statistically not significant (p=0.3). The mean TSB was high in babies with siblings who have history of pathological jaundice and was 17.7mg/dl (±2.4SD), and this difference was statistically not significant (p=0.05). Also, the mean TSB in infant of diabetic mother was high and was statistically not significant (p=0.05). In our study, we found that all cases were treated by phototherapy. Only two cases were found to be treated by exchange transfusion (1%). In the current study the outcome of the cases was as follows, 83% of the cases were discharged in good condition, 4% were discharged against medical advice (DAMA), and 13% of the cases passed away. In the present study, we found that 13% of the cases who passed away had neonatal sepsis. Out of them, 12% were preterm babies and 1% were fullterm babies.

Table (1): The risk factors of pathological unconjugated hyperbilirubinemia in relation to mean total serum bilirubin.

Factors	The mean peak of total Serum bilirubin levels (-}SD)	*p*-value
Aetiolgy:		
Rh incompatibility:		
Yes	17.0 (-}2.8)	0.3
No	16.2 (-}2.9)	
ABO incompatibility:		
Yes	16.7 (-}3.2)	0.5
No	16.2 (-}2.9)	
G6PD deficiency:		
Yes	13.5 (-}2.3)	0.1
No	16.3 (-}2.9)	
Neonatal sepsis:		
Yes	16.3 (-}2.8)	0.9
No	16.2 (-}3.0)	
Cephalohaematoma:		
Yes	14.9 (-}2.6)	0.1
No	16.4 (-}2.9)	
Gestational age:		
Preterm	16.5 (-}2.7)	0.05
Fullterm	15.6 (-}3.6)	
Gender:		
Male	16.3 (-}2.9)	0.9
Female	16.2 (-}3.0)	
Birth weight:		
2.5 kg	16.4 (-}2.8)	0.3
>2.5 kg	15.8 (-}3.3)	
History of pathological jaundice in siblings:		
Yes	17.7 (-}2.4)	0.05
No	16.2 (-}2.9)	
Infant of diabetic mother:		
Yes	18 (-}3.3)	0.05
No	16.2 (2.9)	

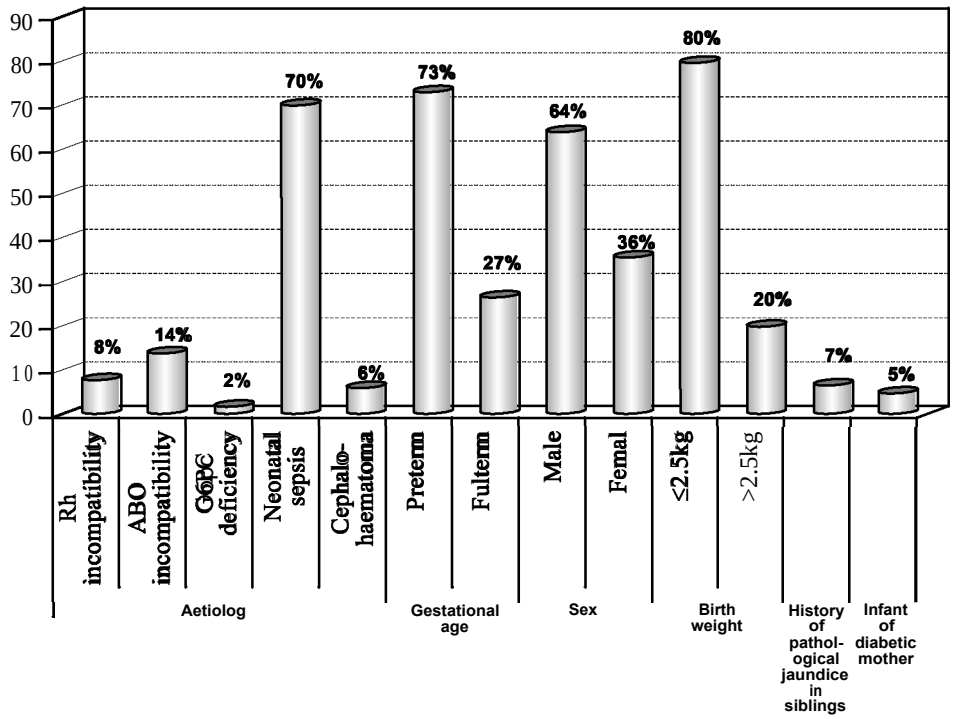

Fig. (1): The risk factors of pathological unconjugated hyperbilirubinemia.

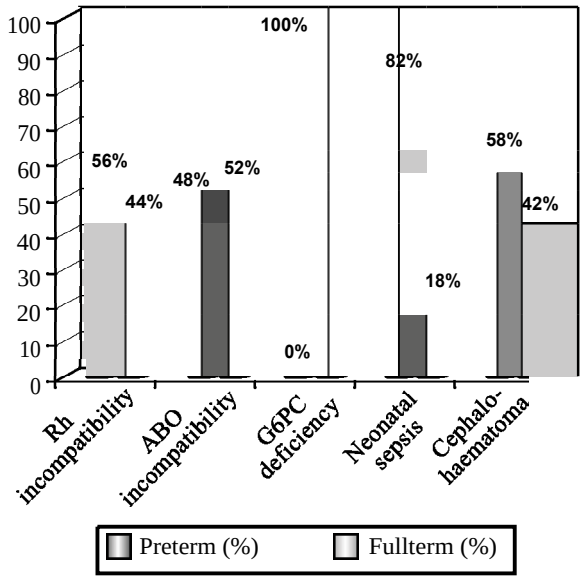

Fig. (2): Aetiology of pathological unconjugated hyperbilirubinemia by gestational age.

Discussion

Jaundice is a clinical condition that is often present in pediatric practice and constitutes one of the major issues within the neonatal period. It can be both physiological and pathological processes in newborns [1]. In our study, the incidence of pathological unconjugated hyperbilirubinemia was (16.9%) of newborn admitted to the NICU in the two hospitals and this is in agreement with the results reported by Sarici et al., [5]. Olusanya et al., reported that the incidence of infants that were admitted to the NICU and had pathologic jaundice were 6.7% [7]. Our study revealed that 73% of the cases were preterm and 27% of the cases were fullterm, and this is in agreement with a study conducted by Kavitha et al., [8]. In contrast to our study, Iacob D et al., reported that 71.42% of cases were fullterm and 28.57% of cases were preterm [9]. In our study, there was a male predominance as males represented 64% of the cases, with male to female ratio being 1.8:1. This is in agreement with studies conducted by Zabeen et al. and Henny-Harry and Trotman [10,11]. In contrast to our study, Kavitha et al., 2016 found that a female predominance was present in 56.6% of the cases [8]. In the present study the pathological hyperbilirubinemia was more common in low birth weight <2.5kg than in those with birth weight >2.5kg and represented 80%, 20% of the cases respectively. This is similar to what has been reported by Kavitha et al. [8] in his study which showed that the incidence of pathological jaundice was found to be more in low birth weight babies with a weight less than 2.5kg 80% compared to 20% in those who had weight above 2.5kg. Abdolahad et al. and Medhi et al., reported that the history of pathological jaundice in the siblings has observed to be 13.5% and 12.2% of cases respectively [1,12]. In our study, we found that 7% of the cases had history of pathological jaundice in the siblings. Plotz postulated that this may be due to the repetition of blood group incompatibility within the family, or other familial conditions including glucose-6-phosphate dehydrogenase (G6PD) deficiency and hereditary spherocytosis [13]. Pathological jaundice in our study was found in 5% of the cases in infant of diabetic mother (IDM), and this is in accordance to what has been reported by Arrif and Bhutta which found that only 3.3% of cases were IDM [14]. In contrast to our study, Zabeen et al., found that 35% of cases were IDM [10]. The higher incidence might be that their study had a higher number of diabetic mothers who delivered their babies at the hospital. In the present study, neonatal sepsis was the commonest aetiology and associated risk factor of pathological hyperbilirubinemia. This is in agreement with Kavitha et al., study which found that neonatal sepsis was found as a major associated risk factor in neonates with jaundice [8]. This is explainable because the majority of neonates who had sepsis were preterm and had low birth weight [15]. ABO incompatibility was observed in 14% of the cases. This is similar to what has been reported by Singhal et al., who found that 14.3% of cases were associated with ABO incompatibility [16]. In contrast to our study, Henny-Harry and Trotman found that ABO incompatibility was present in 35% of cases [11]. Rh incompatibility was found in 8% of the pathological jaundice cases; these results were similar to what has been reported by Medhi et al., and Singhal et al. [1,16]. In contrast to our study, Haque et al., 2004 found that 34% of cases had Rh incompatibility [17]. In this study, G6PD deficiency was observed in 2% of the cases, and this is nearly similar to what has been reported by Kavitha et al. [8]. In contrast to our study, Verle et al. found that the prevalence of G6PD deficiency was high as 31% of the cases [18].

Cephalohematoma was present in 6% of cases with pathological jaundice and this is in agreement with Najib et al. and Medhi [19,1]. In our study, we found that the neonatal sepsis was more common in preterm babies than in fullterm babies and this was highly statistically significant (p=0.000). This in contrast to what has been reported by a study done by Rasul et al., which found that there is no correlation between prematurity and sepsis [20]. In our study, ABO incompatibility was significantly higher in fullterm babies (p=0.002). This is similar to what have been reported by Zabeen et al. [10].

Also, in this study we found that Rh incompatibility were more common in preterm babies than in fullterm babies and this was statistically not significant (p=0.1). This is in agreement with the results that were reported by Zabeen et al. **[10]**. In the present study, we found that patients with ABO incompatibility were more than those with Rh incompatibility. The incidence of Rh incompatibility has decreased as a result of the introduction of Rh (D) immunoglobulin to Rh-negative mothers. In the current study, the mean total serum bilirubin level was 1 6.3mg/dl (±2.9SD). This is nearly similar to what has been reported by Zabeen et al., who found that the mean TSB was 15.4mg/dl (±2.3SD) **[10]**. The mean total serum bilirubin was higher in cases with Rh incompatibility than in ABO incompatibility cases and this difference was statistically not significant (p>0.05). This is in agreement with results reported by Cherepnalkovski et al. **[21]**. In our study, there was no significant correlation between mean total serum bilirubin and neonatal gender. The lack of significant correlation is similar to what has been reported by Agarwal et al but in contrast to our results, Garosi et al., 2016 found that there was a positive relationship between jaundice and neonate's gender **[22,23]**.

Also, there was no significant correlation between mean total serum bilirubin and birth weight. This is in agreement with Agarwal et al., who proved that there was no statistical significance in serum bilirubin of neonates with birth weights below 2.5kg and those with birth weight above 2.5kg **[22]**. The mean total serum bilirubin was high in those babies who had history of pathological jaundice in their siblings, and this is in agreement with Singh et al. **[24]**.

Conclusions:

Pathological unconjugated hyperbilirubinemia is one of the major problems in neonatal morbidity and mortality in Yemen. Neonatal sepsis was the commonest aetiology and associated risk factor of pathological hyperbilirubinemia and the major cause of death in our study. Most cases were treated by intensive phototherapy which was effective in reducing the need for using exchange transfusion in our study.

Recommendations:

- Early screening, detection of hyperbilirubinemia and appropriate management should be endorsed in the health system policy as it will help in decreasing the incidence of hyperbilirubinemia.
- Pregnant women should be encouraged to visit the antenatal care clinic as early as possible and attend consistently to prevent and reduce complications of maternal illnesses during pregnancy.
- Pregnant women should be encouraged to deliver in a professional environment, either under the supervision of skilled birth attendant or in health centers or in hospitals as it will allow early medical intervention which will consequently reduce the risk factors of hyperbilirubinemia.
- Strict hand washing should be practiced; strict asepsis should be followed during delivery. By following these simple measures sepsis can be prevented.
- Intensive phototherapy should be provided in health centers and hospitals and utilized as soon as needed as it was effective in reducing the need for exchange transfusion.
- Modern health facilities should be provided by the Ministry of Health to public hospitals.
- A national protocol for early essential neonatal care and resuscitation should be adopted and followed as a guide in neonatal health units.
- Regular refreshment training courses should be provided nationally to health workers in neonatal health units.
- Health workers should be incentivized to pursue neonatal specialties to increase the number of specialized doctors and nurses in newborn care.
- Monitoring and evaluation of the quality of the health services should be maintained in the Ministry of Health.

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عوامل الخطر لفرط خضاب الدم البيليروبين المرضى اللامقترن بين المواليد اليمنيين

الصفار هو حالة مرضية وتشكل إحدى المشاكل الرئيسية التى يعانى منها حديثى الولادة وذلك بسبب فرط البيليروبين. ويعانى ما يقارب من ٦٠٪ من المواليد مكتملين العمر الرحمى و ٨٠٪ من المواليد الخدج خلال الأسبوع الأول من العمر. وقد يكون الصفار أما عملية فسيولوجية أو مرضية لدى حديثى الولادة، على الرغم من أن معظم حديثى الولادة مع اليرقان يتمتعون بصحة جيدة ولكنهم يحتاجون للمتابعة لأن الارتفاع الشديد للبيليروبين اللامقترن سام جداً بالنسبة للجهاز العصبى المركزى.

\الأهداف: لمعرفة معدل انتشار حدوث الإصابة بفرط البيليروبين اللامقترن المرضية، وتحديد الاسباب الأكثر شيوعاً وعوامل الخطورة المصاحبة لفرط ارتفاع البيليروبين اللامقترن المرضى وأيضاً علاقتها بالمجموع الكلى للبيليروبين.

\الأساليب: كانت الدراسة أنية وصفية مقطعية للمواليد الذين لديهم فرط للبيليروبين اللامقترن المرضى وتم ادخالهم بوحدة العناية المركزة لحديثى الولادة (NICU) فى مستشفى الثورة العام ومستشفى السبعين للأمومة والطفولة. وخلال ١٢ شهر تم ادخال حوالى ١١٨٣ من حديثى الولادة ومنهم تم اختيار ٢٠٠ حالة. وقد اختيرت الحالات للدراسة وفقاً لمعايير الاختيار. فى هذه الدراسة تم أخذ التاريخ المرضى بالتفصيل من الأم ومن ثم تم اخضاع المواليد للفحص السريرى الكامل وعمل تحاليل مختارة حسب الحالة مثل مستوى البيليروبين فى الدم (الكلى والمقترن واللامقترن) وفصيلة الدم للأم والطفل، ومستويات الهيموغلوبين، صورة دم كاملة، وعدد الخلايا الشبكية، واختبار كومبس (المباشر) وفحص إنزيم G6PD، وتحاليل أخرى لما تقتضيه حالة المولود كل البيانات تم تجميعها وتحليلها باستخدام نظام (SPSS) النسخة٢٠.

\النتائج: فى هذه الدراسة وجدنا أن نسبة حدوث فرط ارتفاع البيليروبين اللامقترن المرضى كانت ١.١٪ من العدد الكلى للمواليد فى تلك الفترة. ٧٠.٥٪ من الحالات يمثل نسبة المجموع الكلى للبيليروبين ≤٢٠ ملجم/ديسى لتر. فى الدراسة الحالية كان انتان الدم عند المواليد أكثر سبب وعامل خطورة فى فرط ارتفاع البيليروبين اللامقترن المرضى وقد لوحظ عند ١٤٢ (٧٠٪) من الحالات. المواليد الخدج كانوا أكثر من المواليد المكتملين بنسبة ١٤٥ (٧٣٪)، ٥٥ (٢٧٪) على التوالى. كما وجد أن انتان الدم عند المواليد الخدج أكثر منه عند المواليد المكتملين وكان المؤشر ذو أهمية إحصائية (p=0.000). كما لوحظ أن المواليد الذكور وكانوا يمثلون العدد الأكبر بنسبة ١٢٨ (٦٤٪) من الحالات. فرط ارتفاع البيليروبين اللامقترن المرضى كان أكثر شيوعاً عند المواليد ناقصى الوزن الولادى ≥٢.٥ كيلو جرام من المواليد ذوى الوزن الولادى <٢.٥ كيلو جرام بنسبة ٨٠٪، ٢٠٪ من الحالات على التوالى. عدم توافق الفصيلة ABO incompatibility كان أكثر عند المواليد المكتملين من المواليد الخدج وكان المؤشر ذو أهمية إحصائية (p=0.000). المتوسط الكلى لمستوى البيليروبين فى الدم كان أكثر عند المواليد الخدج من المواليد المكتملين وكان المؤشر ذو أهمية إحصائية (p=0.05). كل المواليد فى هذه الدراسة تمت معالجتهم بواسطة العلاج الضوئى ما عدا حالتين (١٪) منهم تمت معالجتهم بتغيير الدم الكامل. ستة وعشرون (١٣٪) من الحالات توفيت بسبب انتان الدم وأغلبهم كانوا من المواليد الخدج.

\الاستنتاجات: يعتبر فرط ارتفاع البيليروبين اللامقترن المرضى احدى المشاكل الكبيرة فى اليمن. انتان الدم كان أكثر سبب وعامل خطورة فى فرط ارتفاع البيليروبين اللامقترن المرضى وقد لوحظ عدد ٧٠٪ من الحالات وهذا بسبب أن أكثر المواليد الذين عندهم انتان بالدم كانوا من الخدج وناقصى الوزن الولادى. أيضاً انتان الدم وجد أنه أكثر سبب للوفيات فى هذه الدراسة. بينما الوفيات نتيجة اليرقان كسبب للوفاة لم توجد العلاج الضوئى كان ذو فعالية عالية فى علاج أغلب حالات فرط ارتفاع البيليروبين اللامقترن.