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Original article

Cholestasis in the newborn: experience of a level III Neonatal Intensive Care Unit during 19 years

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Abstract

Introduction: Neonatal cholestasis is a rare and always pathological condition that must be distinguished from physiologic jaundice of the newborn. It is characterized by a conjugated hyperbilirubinemia with accumulation of biliary products due to multiple causes, some of which need prompt treatment. The objectives of this study are to characterize a population of neonates with neonatal cholestasis in a level III Neonatal Intensive Care Unit (NICU) and to identify predictors of mortality.

Materials and methods: All patients presenting cholestasis and admitted to "Centro Hospitalar São João" NICU from January 1996 to December 2014 were included.

Results: A total of 83 newborns were included with a prevalence of prematurity of 78.3% and of major malformations of 30.1%. Sixty-seven newborns developed sepsis and 71 needed total parenteral nutrition for a median length of 32 days. A multifactorial etiology for cholestasis was found in 57.8%; extra- and intrahepatic diseases accounted for 19.3% and 22.9% of the cases, respectively. Maximum values for total bilirubin (TB) and direct bilirubin (DB) were significantly higher in newborns who died (TB: median 22.9 versus 13.5 mg/dl, p = 0.005; DB: median 15.0 versus 6.4 mg/dl, p = 0.009). The same was observed for minimum values of albumin and total proteins. Ursodeoxycholic acid (UDCA) was more often used in patients that survived than in those that died (50.9% versus 19.2%) and this difference was statistically significant (p = 0.007).

Conclusions: Cholestasis in our NICU has a multifactorial etiology and a prevalence of 1%. TB and total proteins can be used as predictors of mortality in newborns with cholestasis. Higher levels of DB and lower levels of albumin were also associated with worse prognosis with a statistically significant difference between the groups. UDCA is a possible agent in this context and clinicians should be reminded of its utility.

Keywords

Cholestasis, conjugated hyperbilirubinemia, newborns, neonatal intensive care unit, neonatal jaundice, prognosis.

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Introduction

Cholestasis is a condition caused by a deficient canalicular biliary flow that leads to accumulation of biliary products in blood and other tissues [1, 2]. In practice, it is characterized by conjugated hyperbilirubinemia and/or increased levels of gamma-glutamyl transpeptidase (GGT) and/or alkaline phosphatase (ALP) [1].

Cholestasis is defined as conjugated or direct bilirubin (DB) levels greater than 1 mg/dL when the total bilirubin (TB) is less than 5 mg/dL or more than 20% of the TB, if the TB is greater than 5 mg/dL [3].

Conjugated hyperbilirubinemia is always pathological and it is essential to differentiate it from unconjugated hyperbilirubinemia that is benign in most of the cases [3]. Therefore, any jaundice that persists beyond two weeks of age should be evaluated [4].

Clinically, cholestasis is usually manifested with prolonged jaundice, pale stools (acholia), which is a cardinal sign, and dark urine (choluria). Some infants may present with disturbed coagulation due to a deficiency of clotting factors or vitamin K deficiency [5].

Neonatal cholestasis is a complex diagnostic problem. This entity has a prevalence that varies between 1:2,500 to 1:5,000. However, it is well known that this prevalence is much higher in the context of a Neonatal Intensive Care Unit (NICU) [1]. Some studies described values 50-fold higher than in general population. Additionally, multifactorial cholestasis is much more common in preterm newborns admitted to NICU due to their vulnerability to common serious diseases and situations with higher oxidative stress, such as asphyxia, intrauterine growth restriction (IUGR), sepsis, necrotizing enterocolitis (NEC), surgeries and hemodynamic instability [6].

The initial approach should aim at distinguishing between intrahepatic and extrahepatic causes. In fact, some extrahepatic diseases, such as extrahepatic biliary atresia, warrant prompt treatment, since earlier surgical correction correlates with a better prognosis [7]. Furthermore, even when cholestasis is caused by an entity that does not have specific or curative treatment, early diagnosis with adequate medical and nutritional management is beneficial [3].

Neonatal cholestasis is considered an unspecific indicator of metabolic and biliary canalicular dysfunction and may be an expression of different pathologic entities such as infection (sepsis and TORCH infections – toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus [CMV], and herpes infections), total parenteral nutrition (TPN) or cholestatic drugs. This entity is more common in neonates with comorbidities such as IUGR, apnea, prematurity, eclampsia, neonatal asphyxia, NEC and congenital malformations (cardiac and digestive) [6, 8].

Furthermore, there are other diseases that are associated with neonatal cholestasis such as extrahepatic diseases – biliary atresia, choledochal cysts, gallstones or biliary sludge; intrahepatic diseases – idiopathic neonatal hepatitis, hemophagocytic lymphohistiocytosis; neonatal hemochromatosis; genetic disorders and inborn errors of metabolism – galactosemia, cystic fibrosis, tyrosinemia, α1-antitrypsin deficiency, among others [3, 8].

Ursodeoxycholic acid (UDCA) is commonly used to treat this condition. This is a hydrophilic bile acid that acts stimulating bile flow and replacing of the hydrophobic bile acids. UDCA has shown to be effective in improving cholestasis blood biomarkers and may improve the natural history in some cholestasis cases [5, 9].

The objectives of this study were to characterize a population of neonates with neonatal cholestasis in a level III NICU (regarding demographic, clinical and analytical data) and to identify, in such a population, predictors of mortality.

Methodology

In this retrospective study, all newborns with a diagnosis of neonatal cholestasis and hospitalised

at "Centro Hospitalar São João" (CHSJ) NICU between January 1996 and December 2014 were included. Medical records of these newborns were reviewed and data regarding demographic characteristics, clinical and analytical data were obtained.

Data concerning maternal age and history were collected. Information regarding the occurrence of hydrops fetalis, chromosomal abnormalities, type of delivery, place of birth, gender, gestational age at birth, Apgar scores at 1st and 5th minutes and birth weight was obtained. Furthermore, IUGR and major malformations were also registered. For this study, major malformation was defined as an anomaly or malformation that creates significant medical problems for the patient, or that requires specific surgical or medical management [10].

Neonatal morbidities such as bronchopulmonary dysplasia (BPD; diagnosed according to the National Institute of Child Health and Human development criteria) [11]; TORCH infection; NEC (grade ≥ 2A; diagnosed and classified according to the modified Bell criteria) [12]; intraventricular hemorrhage (IVH; grade > 3) [13]; retinopathy of prematurity (diagnosed and graded according to International Classification of Retinopathy of Prematurity) [14]; cystic periventricular leukomalacia (diagnosed when hypoechoic cysts were observed in the periventricular white matter) were also registered [15].

TPN use and its duration and development of sepsis (defined as any systemic bacterial or fungal infection documented by a positive blood culture) were documented. Development of symptoms suggestive of cholestasis such as choluria or acholia was also evaluated.

Analytical data (TB, DB, alanine aminotransferase [ALT], aspartate aminotransferase [AST], GGT, ALP, total proteins and albumin) were registered. This evaluation included minimum (albumin and total protein) and maximum (for the remaining parameters) values. Disorders of coagulation and thrombocytopenia were also registered.

Treatment with UDCA was also registered. The NICU protocol is to administer 15 mg/kg per dose orally every 12 hours until discharge.

Duration of hospital stay and age at discharge were evaluated.

In our NICU, the assessment and the treatment of newborns with cholestasis is based on the Neonatal Cholestais Consensus of the Neonatal Portuguese Society [6].

Outcomes of patients survivors at discharge were compared with those died during hospitalization.

This study was approved by the ethics commission ("Comissão de Ética para a Saúde") of CHSJ.

Data collection was performed using Microsoft Excel® v.14.0.0 and the statistical analysis was performed using SPSS® for Windows®, version 23. Continuous variables were characterized by mean (± standard deviation) or median (and interquartile range) if they had symmetric or asymmetric distribution, respectively, and categorical variables by absolute and relative frequencies. To compare continuous variables, parametric tests (independent t test) or non-parametric tests (Mann-Whitney U test) were used. Chi-Squared, Fisher's exact test or Monte Carlo's test were used to compare categorical variables. A multivariate analysis by logistic regression was performed to evaluate predictive factors of mortality. Receiver operating characteristic (ROC) curve was performed to study the effect of TB and DB in predicting prognosis. Both the best specificity and sensitivity were used to select the cut-off limits of TB and DB. A p-value less than 0.05 was considered statistically significant.

Results

A total of 83 patients admitted to the NICU during the study period presented cholestasis. 50 (60.2%) patients were males; 52 (62.7%) were inborn and 49 (59.0%) were delivered by C-section (**Tab. 1**).

The mean gestational age was 32 (± 5) weeks. The median and interquartile range birth weight was 1,364 (940-2,644) grams.

Among patients, 78.3% were preterm, nine neonates were born with IUGR, and although 25 patients presented major malformations, no chromosomal abnormalities were observed.

Clinical data are shown in **Tab. 2**. Among all 83 patients, during hospitalization 18 (21.7%) developed BPD, 13 (15.7%) had NEC, 41 (49.4%) presented with digestive disease, 38 (45.8%) had non-surgical cardiac disease and 7 (8.4%) were submitted to cardiac surgery. Sepsis occurred in 67 (80.7%) neonates and 12 (14.5%) had a TORCH group infection; none of the patients developed neonatal hepatitis. We did not find any clinical predictors of mortality after uni- and multivariate analysis.

TPN was administered in 71 (85.5%) neonates with a median and interquartile range duration of 32.0 (14-57) days. Concerning symptoms of cholestasis, 5 newborns developed acholia and 1 choluria.

Table 1. Demographic characteristics.

	Total (n = 83)	Survivors (n = 57)	Deceased (n = 26)	p-value
Maternal age, mean (± SD)	29.00 (± 6.068)	29.16 (± 6.027)	28.68 (± 6.270)	0.743[c]
Maternal medical history, n (%)	27 (32.5)	20 (35.1)	9 (34.6)	0.865[a]
Hydrops, n (%)	6 (7.2)	4 (7.0)	2 (7.7)	0.999[b]
C-section delivery, n (%)	49 (59.0)	31 (54.4)	18 (69.2)	0.202[a]
Birthplace, n (%)				
Inborn	52 (62.7)	36 (63.1)	16 (61.5)	0.888[a]
Outborn	31 (37.3)	21 (36.8)	10 (38.5)	
Gender, n (%)				
Male	50 (60.2)	34 (59.6)	16 (59.3)	0.870[a]
Female	33 (39.8)	23 (40.4)	10 (37.0)	
Gestational age (weeks), mean (± SD)	32 (± 5)	32(± 5)	32(± 5)	0.876[c]
Birth weight (g), median and interquartile range	1,364 (940-2,644)	1,385 (948-2,670)	1,300 (785-2,722)	0.753[d]
1st min < 7, n (%)	40 (48.2)	23 (40.4)	17 (65.4)	**0.021**[a]
5th min < 7, n (%)	18 (21.7)	14 (24.6)	4 (15.4)	0.559[b]
Prematurity, n (%)	65 (78.3)	46 (80.7)	19 (73.1)	0.434[a]
IUGR, n (%)	9 (10.8)	6 (10.5)	3 (11.5)	0.999[b]
Major malformations, n (%)	25 (30.1)	17 (29.8)	8 (30.8)	0.745[a]

[a]Chi-square test; [b]Fisher's exact test; [c]Independent t test; [d]Mann-Whitney U test.
IUGR: intrauterine growth restriction.
Maternal factors: infertility, pre-eclampsia, asthma, previous diabetes, tobacco, alcohol, chronic arterial hypertension, ulcerative colitis, HELLP syndrome and other risk factors such as cerebellar arteriovenous malformation, leiomyomas, atopy, cervicitis by ureaplasma, gestational diabetes, previous miscarriage, drug addiction, human immunodeficiency virus infection, depression, antiphospholipid syndrome, thyroid disease, breast cancer.

Table 2. Neonatal clinical data.

	Total (n = 83)	Survivors (n = 57)	Deceased (n = 26)	p-value
Bronchopulmonary dysplasia, n (%)	18 (21.7)	12 (21.1)	6 (23.1)	0.836[a]
Necrotizing enterocolitis (≥ 2A), n (%)	13 (15.7)	6 (10.5)	7 (26.9)	0.100[b]
Sepsis, n (%)	67 (80.7)	45 (78.9)	22 (84.6)	0.544[a]
Non-cardiac surgery, n (%)	38 (45.8)	26 (45.6)	12 (46.2)	0.963[a]
Cardiac surgery, n (%)	7 (8.4)	5 (8.8)	2 (7.7)	0.999[b]
Digestive disease, n (%)	41 (49.4)	27 (47.4)	14 (53.8)	0.584[a]
TORCH, n (%)	12 (14.5)	10 (17.5)	2 (7.7)	0.324[a]
Intraventricular hemorrhage (≥ grade 3), n (%)	12 (14.5)	7 (12.3)	5 (19.2)	0.404[a]
Retinopathy of prematurity ≥ 2, n (%)	7 (8.4)	6 (10.5)	1 (3.8)	0.425[a]
Cystic periventricular leukomalacia, n (%)	7 (8.4)	3 (5.3)	4 (15.4)	0.198[b]
Infants on total parenteral nutrition, n (%)	71 (85.5)	46 (80.7)	24 (92.3)	0.322[b]
Duration of TPN (days), median and interquartile range	32.0 (14-57)	37.5 (15-59)	30.0 (14-52)	0.424[c]
Treatment with UDCA, n (%)	34 (41.0)	29 (50.9)	5 (19.2)	**0.007**[a]
Days of hospitalization, median and interquartile range	41.0 (18-76)	42.0 (17-77)	33.5 (24-75)	0.802[c]
Age at discharge (days), median and interquartile range	56.0 (27-89)	61.0 (30-90)	40.5 (25-81)	0.348[c]

[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test.
TORCH: toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus (CMV), and herpes infections; TPN: total parenteral nutrition; UDCA: ursodeoxycholic acid;

Regarding the etiology of cholestasis (established on clinical, analytical and necropsy data), a multifactorial etiology was considered in most neonates (57.8%). In 16 (19.3%) patients, an extrahepatic disease was found: 5 patients with extrahepatic biliary atresia, 1 with Caroli disease, 1 with choledochal cyst, 2 with gallstones, 5 with biliary sludge, 1 with anomaly of the biliary tract and 1 with complex malformation of the biliary tract (**Tab. 3**).

Intrahepatic diseases were considered probable causes of the cholestasis in 19 (22.9%) patients. These included 2 cases of hemochromatosis, 1 intrahepatic venous malformation, 4 metabolic diseases (1 mevalonic aciduria and 3 unspecified metabolic disease); 1 with hemophagocytic lymphohistiocytosis; 12 with TORCH infections (6 due to CMV, 2 due to *T. pallidum*, 2 due to *T. gondii* and 2 due to human immunodeficiency virus).

Compared with surviving patients, deceased patients presented higher maximum TB (median 22.9 versus 13.5 mg/dl, p = 0.005) and DB (median 15.0 versus 6.4 mg/dl, p = 0.009) values. Maximum median values of GGT were 250.0 U/L in surviving patients and 146.0 U/L in deceased ones (p = 0.050). Furthermore, deceased patients presented significantly lower levels of albumin (median 18.5 versus 25.7 g/L, p < 0,001) and total proteins (median 31.0 versus 41.1 g/L, p = 0.001). Analytical data is shown in **Tab. 4**.

During the study period, 34 newborns received treatment with UDCA: 29 (50.9%) in the "survivors" group versus 5 (19.2%) in the "deceased" group (p = 0.007), with no differences across the years.

The ROC curve identified a TB value of about 22.8 mg/dl (p = 0.005; Sens = 52%; Spec = 85%, Area under the curve [AUC] = 0.70), and a DB value of about 14.1 mg/dl (p = 0.011; Sens = 52%; Spec = 81%, AUC = 0.68) as predictors of worse prognosis (**Fig. 1**).

After logistic regression, TB (OR = 1.07; 95%CI 1.01-1.13, p = 0.024) and total proteins (OR = 0.89 for 95%CI 0.82-0.97, p = 0.009) were identified as predictors of mortality. The other parameters were not statistically significant.

Discussion

Neonatal cholestasis is caused by impairment in bile excretion and is a condition that we should be aware of, particularly in the presence of persistent jaundice in neonates.

During the 19 years of duration of this study, the prevalence of cholestasis in our NICU was 1.0%, much higher than the prevalence in the general population (1:2,500 to 1:5,000). This difference is in accordance with results obtained by other

Table 3. Probable etiology of cholestasis.

	Total (n = 83)	Survivors (n = 57)	Deceased (n = 26)	p-value
Probable etiology of cholestasis				
Multifactorial, n (%)	48 (57.8)	33 (57.9)	15 (57.7)	0.981[a]
Extrahepatic disease, n (%)	16 (19.3)	11 (19.3)	5 (19.2)	
Intrahepatic diseases, n (%)	19 (22.9)	13 (22.8)	6 (23.1)	

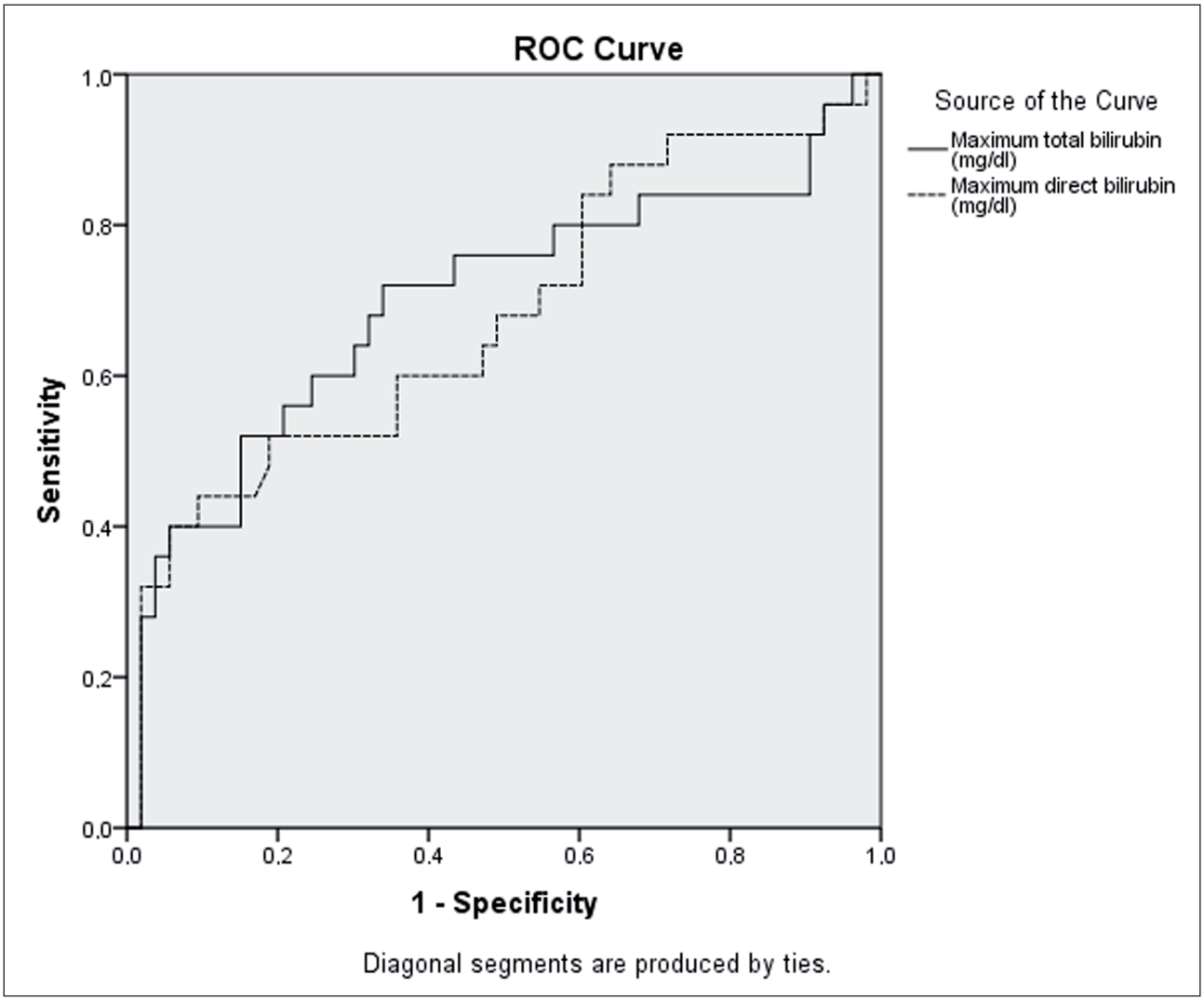
[a] Chi-square test.

Table 4. Neonatal analytical data.

	Total (n = 83)	Survivors (n = 57)	Deceased (n = 26)	p-value
Maximum TB (mg/dl), median and interquartile range	15.3 (10.3-23.2)	13.5 (9.6-19)	22.9 (13.7-33.1)	**0.005**[a]
Maximum DB (mg/dl), median and interquartile range	7.0 (4.5-16.3)	6.4 (3.8-10.5)	15.0 (5.5-24.2)	**0.009**[a]
Minimum albumin (g/L), median and interquartile range	23.1 (17.2-28)	25.7 (20.4-29.5)	18.5 (14-21)	**< 0.001**[a]
Minimum total proteins (g/L), median and interquartile range	37.1 (30-44.5)	41.1 (34.6-46.3)	31.0 (28-37.1)	**0.001**[a]

[a] Mann-Whitney U test.
TB: total bilirubin; DB: direct bilirubin.

Figure 1. Prognosis of cholestasis – ROC curve for total bilirubin and direct bilirubin.



authors, where a prevalence 25-50-fold higher than in the general population was described, with values ranging between 1-2% depending on the study [1, 5, 16].

Concerning the etiology of cholestasis, we consider that the majority of neonates (57.8%) probably had a multifactorial etiology as a cause of cholestasis, including factors such as TPN, prematurity, sepsis, major malformations, NEC and hemodynamic instability among others. This occurrence is easily understood if we note that these risk factors were strongly present in our study population: 78.3% of prematurity, 85.5% of newborns on TPN with a median duration of 32.0 days, 80.7% with at least one septic episode, 30.1% of neonates with some major malformations and a high prevalence of other comorbidities such as BPD, NEC, IVH, retinopathy of prematurity or cystic periventricular leukomalacia. In fact, it is described that the incidence of cholestasis in patients born before 28 weeks gestation is 100-200 times higher compared to term newborns [1], and that very low birth weight infants are particularly susceptible to the development of cholestasis due do the immaturity of their biliary tract. Furthermore, these infants are frequently exposed to other situations that promote cholestasis, such as long periods in TNP (longer than 2 weeks), drug toxicity, sepsis, hypoxia and surgeries among other insults [9, 17].

Intrahepatic diseases were the second most common etiology found and were probably responsible for 22.9% of the cases. In the past, the most common cause of neonatal cholestasis was a condition designed as idiopathic neonatal hepatitis (INH). Nowadays, however, thanks to the discovery of specific etiologies and with more accurate diagnostic methods, this etiology is significantly less prevalent [3]. In fact, we didn't find any patient

with this etiology in our study. In turn, for neonates with intrahepatic diseases we were able to attribute a specific diagnosis such as hemochromatosis, intrahepatic venous malformation, metabolic diseases, hemophagocytic lymphohistiocytosis, TORCH infections. Furthermore, it is also known that factors such as sepsis and TPN also contribute to cholestasis through an intrahepatic insult; these entities were very prevalent in our population (80.7% and 85.5%, respectively).

Lastly, we detected 16 cases of extrahepatic diseases, including 5 cases of extrahepatic biliary atresia. This condition affects 1 in 6,000 to 18,000 live births, it is responsible for 25-30% of neonatal cholestasis [3] and it is considered the leading cause of neonatal cholestasis in general population. Furthermore, it is the most common reason for pediatric liver transplantation, so its prompt diagnosis with Kasai hepatic portoenterostomy before 45-90 days of life is associated with a better prognosis [3, 17-20]. In fact, independent of the temporal cut-off used, all studies refer that, the sooner the surgery is made, the better the prognosis.

Concerning morbidity data, we did not find any statistic difference between survivors and deceased newborns in our study. Therefore, although the role of some clinical parameters such as prematurity, sepsis and TPN [21] is well known in the prognosis of cholestasis, we could not show the influence of comorbidities in the outcome of newborns with cholestasis (**Tab. 2**). .

We found that the maximum level of TB was significantly higher in patients with the outcome deceased (median 22.9 versus 13.5 mg/dl in the "survivors" group, $p = 0.005$). The same was true for DB levels (median deceased patients 15.0 versus 6.4 mg/dl in the "survivors" group, $p = 0.009$). Our results thus suggest that the maximum level of TB can be defined as a predictor of mortality in patients with cholestasis (OR 1.07, CI 1.01-1.13, $p = 0.024$).

Using TB and DB as predictors of prognosis with cut-offs of 22.8 mg/dl for TB and 14.1 for DB, we found values of 52% for sensitivity and values of 85% and 81% for specificity, respectively (TB: $p = 0.005$, DB: $p = 0.011$), revealing a high specificity in the evaluation of the prognosis of these patients (**Fig. 1**).

It is well known that GGT reflects inflammation and biliary obstruction and is a more sensitive marker of obstructive jaundice than other biomarkers such as ALT and AST [9, 22]. Although the normal GGT range values in neonates diverge from those in adults, with six to seven times higher values in term neonates, the levels found in our study are consistent with a median GGT activity higher than expected for healthy neonates, taking into account their age [23]. Preterm infants have GGT values that only diverge from those observed in term infants in the first day of life, when they are one and half times higher [22]. Another important fact is the different magnitude of elevation of GGT according to the type of underlying disease. In fact, diseases with extensive involvement of the biliary canaliculi are associated with higher values, such as biliary atresia in which values 10-fold higher can be found [22]. In our study, three of the five neonates with biliary atresia had values of this order (values of 1,626, 1,154 and 987 U/L). Although it was not evaluated in our study, it is described in literature that GGT values can be used to access the efficacy of treatment with UDCA [22].

Levels of albumin and total proteins were also significantly different in the two groups of patients, those deceased having lower levels of these two biomarkers (median 18.5 versus 25.7 g/L, $p < 0.001$ and median 31.0 versus 41.1 g/L, $p = 0.001$, respectively). These differences were expected since these biomarkers reflect underlying hepatic disease (neonatal cholestasis) and probably the worst state of nutrition of these newborns in the context of other comorbidities such as major malformations, cardiac and surgical digestive pathologies.

It is known that cholestasis is usually a reversible condition if treated actively, though it can cause serious complications such as malnutrition, developmental disorders and end-stage liver disease [24]. Furthermore, early diagnosis with adequate medical management and nutritional support is beneficial. Thus, it is recommended in the literature to exclude neonatal cholestasis in any infant who is still jaundiced at two to three weeks of life [25].

Bacterial infection, CMV infection, parenteral nutrition (more than seven days), asphyxia and preterm birth are independent adverse prognosis factors for cholestasis [2, 21]. Moreover, Liu et al. [21] were able to demonstrate a positive correlation between higher level of TB, DB, ALT and AST with longer duration of cholestasis, but not death, since their cohort did not include deceased patients, thus precluding any consideration as to mortality predictors. In turn, our study lists outcome of deceased and survivors and aims to find predictors of mortality instead of prognostic factors only [21].

UDCA, a hydrophilic dihydroxy bile acid that has a choleretic effect and promotes hepatocellular

bile acid excretion (among other properties such as immunomodulation, antiapoptotic and cytoprotective) is used for the treatment of cholestasis [26].

In neonatal cholestasis, divergent results regarding its efficacy were found depending on the study, with some authors reporting benefits with this treatment in some specific etiologies of neonatal cholestasis such as multifactorial cholestasis, parenteral-induced cholestasis, cystic fibrosis, biliary atresia. On the other hand, others refer that UDCA doesn't affect the clinical course in neonates with cholestasis [1, 9, 26, 27]. We found statistically significant differences between the two outcome groups, with a higher percentage of survivor patients receiving treatment with UDCA (50.9% vs 19.2%, p = 0.007), probably suggesting the need to increase clinicians awareness for the possible role of this drug in neonatal cholestasis. Further studies are necessary in order to find the role of this agent in this context.

This study struggles with some limitations. In fact, this is a retrospective study with all of its drawbacks. Furthermore, our study sample was small, which makes it difficult to generalize results.

Nevertheless, this study, according to our knowledge, was the first to review possible predictor factors for mortality in neonatal cholestasis. In fact, we found that TB and total proteins can be used as a predictor of mortality in neonates with cholestasis. Furthermore, higher levels of DB and lower levels of albumin were also associated with worse prognosis, with a statistically significant difference between the two groups.

Conclusions

Neonatal cholestasis presents a much higher prevalence in NICU patients than in general population, particularly when associated with a multifactorial etiology. This can be explained by the fact that these neonates have a special vulnerability due to a higher prevalence of various comorbidities.

Furthermore, since the occurrence of cholestasis can affect patients' prognosis, clinicians should pay particular attention to these newborns in order to prevent complications.

In this context, UDCA can be an agent to consider associated with other management measures such as adequate nutrition with TPN suspension, as soon as possible.

Additionally, according to our results, TB and total proteins can be used as predictors of mortality in neonatal cholestasis. These results need further confirmation in larger, ideally multicentric studies.

Declaration of interest

The Authors declare that no conflicts of interest exist and there was no financial support.

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