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CLINICAL & BASIC RESEARCH

Incidence and Risk Factors of Parenteral Nutrition-Associated Cholestasis in Omani Neonates

Single centre experience

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عوامل و نسبة حدوث الإصابة بالركود الصفراوي المرتبط بالتغذية الوريدية في الأطفال العمانيين حديثي الولادة

خبرة مركز

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ABSTRACT: ***Objectives:*** Parenteral nutrition-associated cholestasis (PNAC) is one of the most challenging complications of prolonged parenteral nutrition (PN) in neonates. There is a lack of research investigating its incidence in newborn infants in Oman and the Arab region. Therefore, this study aimed to assess the incidence of PNAC and its risk factors in Omani neonates. ***Methods:*** This retrospective study took place between January and April 2014. All neonates who received PN for ≥14 days during a four-year period (June 2009 to May 2013) at the neonatal intensive care unit (NICU) in Sultan Qaboos University Hospital, Muscat, Oman, were enrolled. ***Results:*** A total of 1,857 neonates were admitted to the NICU over the study period and 135 neonates (7.3%) received PN for ≥14 days. Determining the incidence of PNAC was only possible in 97 neonates; of these, 38 (39%) had PNAC. The main risk factors associated with PNAC were duration of PN, duration of enteral starvation, gastrointestinal surgeries, blood transfusions and sepsis. Neonates with PNAC had a slightly higher incidence of necrotising enterocolitis in comparison to those without PNAC. ***Conclusion:*** This study found a PNAC incidence of 39% in Omani neonates. There were several significant risk factors for PNAC in Omani neonates; however, after logistic regression analysis, only total PN duration remained statistically significant. Preventive strategies should be implemented in NICUs so as to avoid future chronic liver disease in this population.

Keywords: Cholestasis; Parenteral Nutrition; Neonates; Incidence; Risk Factors; Oman.

الملخص: الهدف: يعتبر الركود الصفراوي من أكثر مضاعفات استخدام التغذية الوريدية لفترات طويلة في الأطفال حديثي الولادة تحديا. لا توجد دراسات تبحث نسبة ومعدلات حدوثه في الدول العربية وسلطنة عمان. هدفت هذة الدراسة الى تحديد معدلات الإصابة بالركود الصفراوي المرتبط بالإستخدام المطول للتغذية الوريدية ومسبباته في الأطفال العمانيين حديثي الولادة. **الطريقة:** أجريت هذه الدراسة الإسترجاعية خلال الفترة من شهر يناير الى أبريل 2014. وتم حصر كل الأطفال العمانيين حديثي الولادة والذين تلقوا التغذية الوريدية لفترة أطول من أو تساوي 14 يوم خلال فترة 4 سنوات بين يونيو 2009 وحتى مايو 2013 في وحدة العناية المركزة للأطفال حديثي الولادة بمستشفى جامعة السلطان قابوس بمسقط، سلطنة عمان. **النتائج:** تم حصر عدد 1,857 طفلا حديث الولادة أدخلوا الوحدة لتلقي العناية خلال فترة الحصر. تلقى135 منهم التغذية الوريدية لفترة أطول من أو تساوي 14 يوم بنسبة مئوية تعادل 7.3%. تحديد معدل الركود الصفراوي كان ممكنا في 97 طفلا فقط حيث حدث الركود الصفراوي في 38 طفل (39%). كانت أكثر عوامل الإصابة بالركود الصفراوي شيوعا هي مدة تلقي التغذية الوريدية، مدة المجاعة المعوية، تعرض الجهاز الهضمي للعمليات الجراحية ، نقل الدم وحدوث إلتهاب في الدم. وبالمقارنة للأطفال حديثي الولادة والذين لم يصابوا بالركود الصفراوي، حديثي الولادة المصابين بإلتهاب الامعاء والقولون الناخر كانوا أكثر عرضه لحدوث الركود الصفراوي المرتبط بالتغذية الوريدية. **الخلاصة:** حددت هذة الدراسة حدوث الركود الصفراوي المرتبط بالتغذية الوريدية بنسبة 39% في الأطفال العمانيين حديثي الولادة المتلقين للتغذية الوريدية وقد تم حصر العديد من عوامل الإصابة ولكن بعد إستخدام تحليل الإنحدار اللوجستي وجد أن مدة التغذية الوريدية هو العامل الذي ظل له دلالة إحصائية هامة. من المهم تنفيذ إستراتيجيات وقائية في وحدات العناية المركزة للأطفال حديثي الولادة لتجنب حدوث أمراض الكبد المزمنة مستقبلا في هذة الفئة.

مفتاح الكلمات: الركود الصفراوي؛ التغذية الوريدية؛ حديثي الولادة؛ معدل حدوث؛ عوامل الإصابة؛ عمان.

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Advances in Knowledge

- *To the best of the authors' knowledge, this study is the first to investigate the incidence and risk factors of parenteral nutrition-associated cholestasis (PNAC) in an Omani neonatal population.*
- *The risk factors for developing PNAC in this population were similar to those reported elsewhere. Significant risk factors for PNAC in this population were related to the duration of parenteral nutrition (PN) and enteral starvation, as well as the presence of late-onset sepsis and the number of blood transfusions and gastrointestinal surgeries a neonate had undergone.*

Application to Patient Care

- *Understanding the incidence of PNAC and its risk factors in Oman will aid in the implementation of preventive strategies. These could include reducing the duration of PN and promoting enteral feeds soon after birth by adopting appropriate early feeding protocols in neonatal intensive care units. These strategies may help minimise the incidence of PNAC and prevent chronic liver disease in this age group.*

In Oman, the use of parenteral nutrition (PN) in neonatal intensive care units (NICUs) is increasingly practiced as preterm infants as young as 24 gestational weeks are resuscitated. PN has fundamentally changed the care of neonates who cannot achieve adequate growth through enteral feeding.[1] Today, many patients in different age groups depend on PN for their survival.

Parenteral nutrition-associated cholestasis (PNAC) is one of the most challenging complications arising from the prolonged administration of PN and has long been recognised as a risk factor for neonatal cholestasis.[2] PNAC is defined as serum conjugated bilirubin levels of >2 mg/dL (34.2 µmol/L) associated with sustained exposure to PN for ≥14 days.[3–5] Other conditions which can potentially cause cholestasis in infants receiving PN and which must be ruled out include biliary atresia and infections as well as a variety of other metabolic, endocrine and genetic disorders.[6,7] PNAC is predominantly a paediatric disease, with premature neonates being the most predisposed age group with high morbidity and mortality rates.[4] The incidence, severity and duration of cholestasis varies substantially among reports depending on the study population and duration of PN exposure;[3] it can vary from 10–60% depending on the population studied and the criteria used.[4,8]

PNAC remains a frequent and poorly understood complication of PN therapy in infants, despite improvements in the components of PN and neonatal intensive care measures.[9] In addition, and despite an enhanced understanding of the molecular basis of neonatal cholestasis, the precise mechanism by which PN induces liver injury remains uncertain.[10,11] Several risk factors for PNAC have been identified, including caloric overload, nutritional deficiencies, toxicity of specific PN constituents, oxidative stress and altered bile composition.[12,13] In addition, intrauterine growth retardation, immaturity of the biliary excretory system, absence of enteral feeding, bacterial overgrowth, sepsis, hypotension or hypoxia, gastrointestinal (GI) surgeries, a cumulative high intake of amino acids and lipids and short bowel syndrome have been described as risk factors.[9,14–21] Nutritional deficiencies, including essential fatty acids, carnitine, choline, taurine, vitamin E and selenium, are also thought to contribute to PNAC.[22]

Histologically, PNAC is associated with cholestasis, steatosis, steatohepatitis and, in severe cases, fibrosis and cirrhosis.[3] The resolution of PNAC and normalisation of liver enzymes may occur gradually after the alteration or withdrawal of PN and the initiation of enteral feeding. However, some infants may develop persistent or progressive liver disease or hepatic failure.[12] PNAC can lead to high morbidity and mortality rates.[13,23] Numerous studies have documented an association between PNAC and risk of sepsis, liver failure and mortality.[5,9] However, there is a lack of research investigating the incidence of PNAC in newborn infants in the Arab region. To the best of the authors' knowledge, no studies of this kind have yet been undertaken in Oman. Hence, the aim of this study was to determine the incidence and risk factors of PNAC in Omani neonates for the first time.

Methods

This four-year retrospective cohort study took place from January to April 2014. All neonates admitted to the NICU at Sultan Qaboos University Hospital (SQUH) in Muscat, Oman, and who received PN for ≥14 days during the period from June 2009 to May 2013 were enrolled in the study. Exclusion criteria included patients who died during their time in the NICU or those without conjugated bilirubin measurements (as the cause of cholestasis could not be determined retrospectively) as well as neonates with other causes of cholestasis. A diagnosis of PNAC relied on a history of PN for ≥14 days, direct bilirubin of >2 mg/dL (34 µmol/L) and the exclusion of other causes of neonatal cholestasis.

Demographic and clinical data were obtained from hospital electronic records, including gestational age (GA); birth weight (BW); gender; evidence of

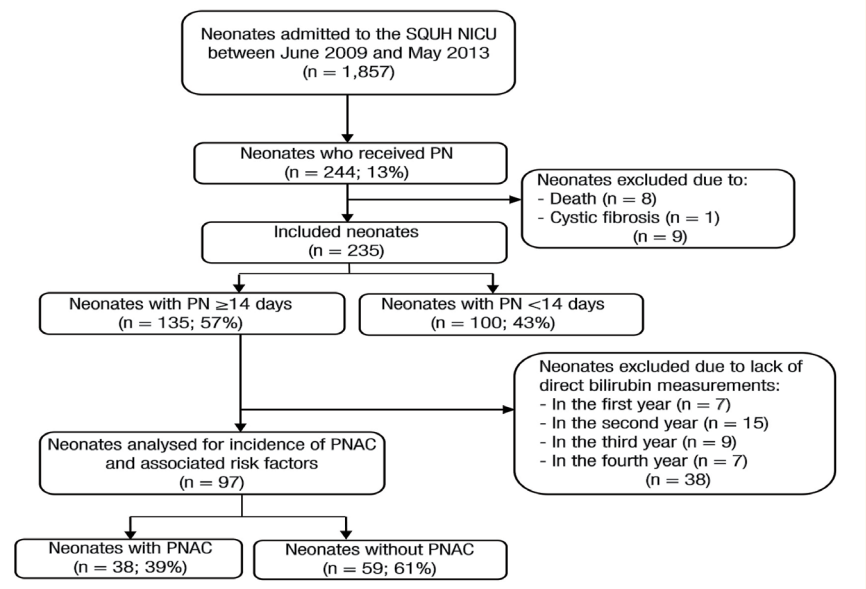

Figure 1: Flowchart of Omani neonates admitted to the Sultan Qaboos University Hospital neonatal intensive care unit over a four-year period with regards to parenteral nutrition and parenteral nutrition-associated cholestasis.

SQUH = Sultan Qaboos University Hospital; NICU = neonatal intensive care unit; PN = parenteral nutrition; PNAC= parenteral nutrition-associated cholestasis.

PNAC; total duration and number of PN courses; ventilation; significant desaturation (oxygen saturation below 89%); morbidities such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia ([BPD] a form of chronic lung disease that develops in preterm neonates treated with oxygen and positive-pressure ventilation), hypotension, patent *ductus arteriosus* (PDA) or necrotising enterocolitis (NEC) of any stage, enteral starvation, GI surgeries and a history of blood transfusions. The presence of late-onset sepsis was determined by positive blood culture results which are routinely done if there is any fever or suspicion of clinical sepsis. The use of antibiotics and potential hepatotoxic medications (including acetaminophen, diuretics, ibuprofen, morphine, sildenafil, midazolam and caffeine) was also documented.

Descriptive statistics were calculated and compared between the PNAC and non-PNAC groups (the latter group included neonates in the study who did not develop PNAC). For categorical variables, frequencies and percentages were reported. Group comparisons were performed using the Chi-squared test or Fisher's exact test where appropriate. Means ± standard deviation or medians with interquartile range (IQR) were used to present the data where appropriate. Comparisons of continuous data were performed using the Student's t-test for data with a normal distribution and the Mann-Whitney U test for continuous data without a normal distribution. Furthermore, a multivariate logistic regression model was utilised to determine risk factors for PNAC. The *a priori* two-tailed level of significance (*P* value) was set at 0.05. Data were analysed using the Statistical Package for the Social Sciences (SPSS), Version 20 (IBM Corp., Chicago, Illinois, USA).

Ethical approval for this study was obtained from the Medical Research & Ethics Committee at the College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman (MREC#622).

Results

Between June 2009 and May 2013, a total of 1,857 neonates were admitted to the SQUH NICU; of these, 244 (13%) received PN during their stay. Nine neonates were excluded from the study either due to death (n = 8) or a diagnosis of cystic fibrosis (n = 1), which is known to cause cholestasis. Among the remaining 235

Table 1: Demographic characteristics of Omani neonates in a neonatal intensive care unit receiving parenteral nutrition for ≥14 days and evaluated for the presence of parenteral nutrition-associated cholestasis (N = 97)

Characteristic	Value
Gender	
Male, n (%)	56 (58)
Female, n (%)	41 (42)
GA in weeks, mean ± SD	**29 ± 3**
BW in g, mean ± SD	**1,165 ± 495**
Small for GA, n (%)	**36 (37)**

GA = gestational age; SD = standard deviation; BW = birth weight.

Table 2: Yearly and total incidence of parenteral nutrition-associated cholestasis among a population of Omani neonates in a neonatal intensive care unit receiving parenteral nutrition for ≥14 days (N = 97)

	Year				Total
	June 2009–May 2010	June 2010–May 2011	June 2011–May 2012	June 2012–May 2013	
Patients on PN for ≥14 days, n	16	19	25	37	97
PN duration in days, mean ± SD	36 ± 26	29 ± 14	28 ± 12	28 ± 15	30 ± 17
Patients with PNAC, n	8	5	10	15	38
Incidence of PNAC, %	50	26	40	41	39

PN = parenteral nutrition; SD = standard deviation; PNAC = parenteral nutrition-associated cholestasis.

neonates, the median duration of PN was 14 days (IQR: 8–21 days). A total of 135 neonates (57%) received PN for ≥14 days and were evaluated for PNAC. A total of 38 neonates were subsequently excluded from the study due to a lack of direct bilirubin measurements, resulting in a total number of 97 neonates [Figure 1]. The demographic characteristics of these neonates are shown in Table 1.

Out of the 97 neonates, 38 developed PNAC, giving an incidence of 39% over four years. The details of yearly PNAC incidence rates are shown in Table 2. The duration of PN ranged from 14–120 days (mean: 30 ± 13 days). The majority of the neonates (34%) received PN for 2–3 weeks (14–21 days); these neonates demonstrated the lowest incidence of PNAC (12%) [Figure 2]. The incidence of PNAC was higher in those who had received PN for a longer duration [Table 2].

Table 3 shows the comparison between the PNAC and non-PNAC groups. Using a univariate analysis, the following significant risk factors for PNAC were found: PN duration; enteral starvation; presence of late-onset sepsis; number of blood transfusions, and GI surgeries. The analysis showed that the PNAC group had a longer median initial PN duration (30 versus 20 days; P <0.001), received PN more than once (24% versus 12%; P = 0.038) and had a longer median total PN duration (30 versus 21 days; P <0.001) in comparison to neonates in the non-PNAC group. Although the median duration of initial enteral starvation was not significantly different between the PNAC and non-PNAC groups (four and three days, respectively; P = 0.250), the number of neonates who underwent enteral starvation later on during the course of their NICU stay was higher (63% versus 32%; P = 0.003) and the median duration of total enteral starvation was longer in the PNAC group (11 versus five days; P = 0.040) compared to the non-PNAC group.

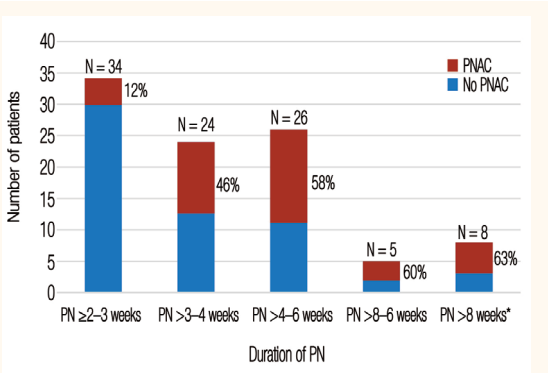

Figure 2: The incidence of PNAC in relation to the administration of PN for >14 days in a population of Omani neonates in a neonatal intensive care unit (N = 97).

PNAC = parenteral nutrition-associated cholestasis; PN = parenteral nutrition.

**Range of PN duration in this group was 57–73 days for seven patients and 120 days for one patient.*

Neonates with PNAC underwent more GI surgeries than those without PNAC (21% versus 5%; P = 0.015). Neonates in the PNAC group underwent the following GI surgeries: laparotomies for stage 3 NEC with intestinal resection (n = 3); exploratory laparotomies for stage 1 NEC (n = 2); laparotomy for duodenal atresia (n = 1), and laparotomies for malrotation and gastroschisis (n = 2). The non-PNAC group underwent the following GI surgeries: laparotomy for stage 1 NEC (n = 1); laparotomy and intestinal resection for stage 3 NEC (n = 1), and duodenal atresia repair (n = 1).

In addition, neonates with PNAC had a higher mean number of blood transfusions (six versus four; P = 0.037) and a greater frequency of late-onset sepsis (66% versus 41%; P = 0.016). Although neonates with PNAC had a higher incidence of NEC in comparison to those without PNAC (34% and 17% respectively), this difference was not significant (P = 0.051). Additionally, there were no significant differences between the PNAC and non-PNAC groups with regards to GA, BW, weight for GA, RDS, need for ventilation, presence

Table 3: Demographic and clinical characteristics of Omani neonates receiving PN for ≥14 days in a neonatal intensive care unit according to parenteral nutrition-associated cholestasis group (N = 97)*

Characteristic	Group		*P* value
	PNAC (n = 38; 39%)	Non-PNAC (n = 59; 61%)	
Demographic			
Male gender, n (%)	26 (68)	30 (51)	0.087
GA in weeks, mean ± SD	29 ± 3.2	28.6 ± 3.4	0.410
BW in g, mean ± SD	1,180 ± 530	1150 ± 480	0.747
SGA, n (%)	16 (42)	20 (34)	0.414
NICU finding/treatment			
RDS, n (%)	33 (87)	56 (95)	0.158
Ventilation, n (%)	34 (90)	54 (92)	0.734
Significant desaturation, n (%)	25 (66)	36 (61)	0.635
Significant hypotension, n (%)	7 (19)	12 (20)	0. 816
BPD, n (%)	15 (40)	24 (41)	0.853
PDA, n (%)	2 (5)	6 (10)	0.475
NEC, n (%)	13 (34)	10 (17)	0.051
Initial PN received in days, median (IQR)	30 (23–39)	20 (15–26)	<0.001*
PN received more than once, n (%)	9 (24)	7 (12)	0.038*
Total PN received in days, median (IQR)	30 (24–42)	21 (16–31)	<0.001*
Initial enteral starvation in days, median (IQR)	4 (2–9)	3 (2–6)	0.250
Subsequent enteral starvation, n (%)	24 (63)	19 (32)	0.003*
Total enteral starvation duration in days, median (IQR)	11 (4–17)	5 (2–13)	0.040*
GI surgery, n (%)	8 21)	3 (5)	0.015*
Blood transfusions, mean ± SD	6 ± 5	4 ± 3	0.037*
Infection			
Late-onset sepsis, n (%)	25 (66)	24 (41)	0.016*
Late-onset G+ sepsis, n (%)	16 (42)	16 (27)	0.125
Late-onset G- sepsis, n (%)	13 (34)	11 (19)	0.083
UTI, n (%)	1 (3)	5 (9)	0.399
AB use >7 days, n (%)	37 (97)	53 (90)	0.240
Total AB in days, mean ± SD	21 ± 15	20 ± 14	0.623
Hepatotoxic medication			
Paracetamol, n (%)	4 (11)	2 (3)	0.206
Diuretics, n (%)	12 (32)	19 (32)	0.712
Ibuprofen, n (%)	6 (16)	5 (9)	0.276
Morphine, n (%)	15 (40)	16 (27)	0.203
Sildenafil, n (%)	2 (5)	4 (7)	1.000
Midazolam, n (%)	5 (13)	6 (10)	0.650
Caffeine, n (%)	32 (84)	52 (88)	0.580

PNAC = parenteral nutrition associated cholestasis; GA = gestational age; SD = standard deviation; BW = birth weight; SGA = small for gestational age; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; PDA= patent ductus arteriosus; NEC = necrotising enterocolitis; PN = parenteral nutrition; IQR = interquartile range; GI = gastrointestinal; G+ = Gram-positive; G- = Gram-negative; UTI = urinary tract infection; AB = antibiotics.

**Statistically significant.*

of significant desaturation/hypotension, BPD or PDA (P >0.05) [Table 3].

Multivariate logistic regression revealed that only total PN duration was a statistically significant risk factor for developing PNAC (P = 0.027; odds ratio = 1.41; 95% CI = 1.04–1.90; for each additional week of PN) [Table 4].

Discussion

To the best of the authors' knowledge, the present study is the first to investigate the incidence of and risk factors for PNAC in an Omani neonatal population at an NICU in a single tertiary centre. Over the study period, the yearly incidence of PNAC ranged from 26–50%, with an overall incidence of 39%. In general, the incidence of PNAC reportedly ranges between 10–60% depending on the population, criteria, duration

Table 4: Multivariate analysis for risk factors of parenteral nutrition-associated cholestasis among a population of Omani neonates in a neonatal intensive care unit (N = 97)

Significant risk factors	*P* value	OR	95% CI
Duration of PN	0.027	1.41	1.04–1.90
Late-onset sepsis	0.132	2.01	0.81–4.98
Duration of enteral starvation	0.458	1.02	0.97–1.07

PN = parenteral nutrition; OR = odds ratio; CI = confidence interval.

of PN exposure and the components of PN.[3,4,8,9] Unfortunately, little is known regarding the incidence of PNAC in Arab populations. In Saudi Arabia, Anabrees *et al*. reported an incidence of 10.7% among neonates with a very low BW.[1]

PNAC has been associated with various risk factors, including PN duration, prematurity, low BW, enteral starvation, sepsis and GI surgeries. In the present study, the most significant risk factor for the development of PNAC was PN duration, which remained significant after regression analysis. This is comparable with other studies.[9,24–26] In this cohort, the lowest PNAC incidence was observed in neonates who received PN for less than three weeks and the incidence of PNAC increased dramatically beyond the third week of PN. A similar study reported an incidence of 14% among infants receiving PN for 2–4 weeks; this increased with total PN duration to 85% when PN was used for >14 weeks.[9]

In the current study, late-onset sepsis was an important risk factor for PNAC. This finding has also been previously reported.[16,18,24,25,27] Another risk factor for PNAC in the studied Omani population was the total duration of enteral starvation; however, more importantly, undergoing enteral starvation later on during the course of the NICU stay was a significant risk factor. This was similarly reported in other studies.[17,28] GI surgeries are a frequently reported risk factor for PNAC. Many earlier studies, as well as the present one, have clearly confirmed this relationship.[9,24,25,28,29]

A significant correlation between the number of blood transfusions and PNAC was demonstrated in the current study. Although there are currently no other published studies supporting this finding, it is assumed that blood transfusions in the current study were required for patients who were sick, septic and/or possibly undergoing GI surgeries. Future studies are needed to investigate the relationship between blood transfusions and PNAC in order to determine its impact as an independent risk factor in the development of PNAC.

Despite its strong indication as a major risk factor in many other studies,[9,16,26,30] the association of NEC with PNAC in the present study was not significant. Suita *et al*. also found no correlation between NEC and PNAC.[28] While some studies have indicated that the incidence of PNAC is higher in neonates with lower GA and BW,[9,16,24,26] other studies, including the present study, found no causal relationship between these factors.[25,28] In the present study, RDS, ventilation, BPD and PDA were not significant risk factors for PNAC; this is contrary to other studies which have reported these factors to be associated with a higher risk of PNAC.[16,26] Furthermore, the current study did not identify an association between the use of potentially hepatotoxic medications and increased PNAC risk.

Understanding the incidence of PNAC and its risk factors is important as it may aid in the implementation of preventive strategies so as to avoid future chronic liver disease and related complications in this age group. These strategies could include reducing the duration of PN and promoting enteral feeds soon after birth by adopting early feeding according to appropriate NICU protocols. These strategies may help minimise the incidence of PNAC and prevent chronic liver disease among neonates.

The present study had some limitations, including its retrospective nature as well as the exclusion of many neonates without direct bilirubin measurements due to the lack of laboratory monitoring or undetermined aetiology of the cholestasis. Furthermore, the constitution of PN was not examined in this study. Further studies are recommended to examine PN constituents among neonates in Oman, as well as identifying the effect of PN components in the incidence and risk factors of PNAC.

Conclusion

In the studied Omani neonatal population, the overall incidence of PNAC was 39% over a four-year period. The duration of PN, sepsis, duration of enteral starvation, number of GI surgeries and number of blood transfusions were significant risk factors for developing PNAC. However, only total PN duration remained a statistically significant risk factor after a logistic regression analysis. With these risk factors in mind, preventive strategies should be implemented in NICUs so as to avoid future chronic liver disease and its complications in this age group. To the best of the authors' knowledge, this study is the first to report the incidence of PNAC and its risk factors among Omani neonates.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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