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ABSTRACT

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A RETROSPECTIVE STUDY OF JAUNDICE IN INFANTS IN KYIV FROM 2017 TO 2021

Study objectives. The aim of the study was to evaluate the effectiveness of inpatient medical care in Kyiv (diagnostic capabilities and prescription of phototherapy) for newborns with various clinical forms of jaundice during 2017–2021.

Methods. We performed a retrospective analysis of 616 infant jaundice cases of various clinical forms at the Department of Neonatal Pathology at Children's Clinical Hospital No. 6 in Kyiv (2017–2021), diagnosed as ICD P59 neonatal jaundice (NJ) and prolonged jaundice (PJN) and P55 hemolytic disease of the newborn (HDN) based on the relevant criteria. For statistical analysis, MedStat (v2.6.2) and EZR (v1.61) were used.

The analysis showed that hospitalization with various forms of jaundice decreased in 2021 by about 2.1 times vs. 2018 and by 1.5 times vs. 2017 ($p < 0.001$). PJN was more common (55.0%) than NJ (39.8%) and HDN (5.2%), $p < 0.001$. A logistic regression model (AUC = 0.785) showed that the manifestation of PJN might be influenced by a history of cesarean section. At the time of hospitalization, there was no significant difference between the bilirubin levels measured by two methods: total serum bilirubin (TSBa) and transcutaneous bilirubin (TcBa), $p = 0.380$. Children with HDN (84.4%) were more likely to require phototherapy for more than 5 days than children with NJ (63.7%) and PJN (62.2%), $p < 0.05$.

Conclusion. The study showed a decrease in the number of hospitalizations for jaundice in infants from 2017 to 2021. The prevalence of PJN was higher than NJ. A history of cesarean section was associated with PJN. Median bilirubin levels showed no significant difference between the two methods. Children with HDN more often required prolonged phototherapy, which was probably due to a less effective daily decline in bilirubin levels.

Keywords. Bilirubin, Cesarean Section, Hyperbilirubinemia, Infant, Jaundice Neonatal, Phototherapy.

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РЕТРОСПЕКТИВНЕ ДОСЛІДЖЕННЯ ЖОВТЯНИЦЬ У НЕМОВЛЯТ У М. КИЇВ З 2017 ПО 2021 РІК

Мета дослідження: оцінити ефективність надання медичної допомоги у стаціонарних умовах м.Києва (діагностичних можливостей та призначення фототерапії) новонародженим з різними клінічними формами жовтяниць протягом 2017–2021 років.

Матеріали і методи. Ретроспективний аналіз 616 випадків різних клінічних форм жовтяниць немовлят у відділенні патології новонароджених Дитячої клінічної лікарні № 6 м. Києва (2017–2021 рр.), діагностованих як за МКХ Р59 неонатальна (NJ) і затяжна жовтяниця (PJN), та Р55 гемолітична хвороба новонароджених (HDN) на основі відповідних критеріїв. Для статистичного аналізу використовували програми MedStat (версія 2.6.2) та EZR (версія 1.61).

Результати. Аналіз показав, що госпіталізація з різними формами жовтяниць зменшилась в 2021 році приблизно в 2,1 рази порівняно з 2018 роком та у 1,5 рази порівняно з 2017 роком ($p < 0.001$). PJN зустрічалась частіше (55,0%), ніж NJ (39,8%) та HDN (5,2%), $p < 0,001$. Логістична модель регресії (AUC = 0,785) показала, що на маніфестацію PJN може впливати наявність кесаревого розтину в анамнезі. На момент госпіталізації не було виявлено достовірної різниці між рівнями білірубіну виміряними двома методами: загальним білірубіном сироватки крові (TSBa) та транскутанним білірубіном (TcBa), $p = 0,380$. Діти з HDN (84,4%) частіше потребували фототерапії більше 5 днів, ніж діти з NJ (63,7%) та PJN (62,2%), $p < 0,05$.

Висновок. Дослідження показало зменшення кількості госпіталізацій з жовтяницями немовлят з 2017 по 2021 рр. Поширеність PJN перевищувала NJ та HDN. Кесарев розтин в анамнезі був асоційований з PJN. Медіани білірубіну не показали суттєвої різниці між двома методами. Діти з HDN частіше потребували тривалої фототерапії, що може пояснюватись менш ефективним добовим зниженням рівня білірубіну.

Ключові слова: білірубін, кесарів розтин, гіпербілірубінемія, немовля, жовтяниця новонароджених, фототерапія.

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ABBREVIATIONS

DOP	Duration of phototherapy
HDN	Haemolytic disease of the newborn
IQR	Interquartile range
NJ	Neonatal jaundice
Me	Median
PJN	Prolonged jaundice of the newborn
TcBa	Transcutaneous bilirubin at the time of admission
TcBa _d	Transcutaneous bilirubin at the time of discharge
TSBa	Total serum bilirubin at the time of admission
TSBa _d	Total serum bilirubin at the time of discharge

INTRODUCTION / ВСТУП

Neonatal jaundice, characterized by the visible yellow discoloration of a newborn's skin, sclera, and/or mucous membranes, stems from elevated levels of bilirubin in the bloodstream [1]. The relevance of this problem is determined by the high incidence of neonatal jaundice, which tends to increase. There are numerous population-based studies on the assessment, treatment and incidence of jaundice and the need for phototherapy [1]. Guidelines for the investigation of prolonged neonatal jaundice vary from country to country [2]. The American Academy of Pediatrics recommends universal risk assessment for neonatal hyperbilirubinaemia based on the results of universal transcutaneous bilirubin screening, followed by confirmation by serum total bilirubin testing [3]. Similar studies on the incidence of neonatal jaundice in Ukraine show that an increase in blood bilirubin levels results in jaundice in 60% of term and 80% of preterm infants. At the present stage of jaundice treatment in Ukraine, neonatologists act in accordance with the Order of the Ministry of Health of Ukraine No. 783 "On Approval of the Unified Clinical Protocol of Specialized Medical Care "Jaundice of Newborns" dated 27.04.2023" [4] and Queensland Clinical Guideline: Neonatal Jaundice [5].

Severe neonatal hyperbilirubinaemia is a serious condition, so early recognition with bilirubin determination is key to the management of jaundice [6]. The imperative to enhance the overall management of jaundice underscores the urgency and significance of ongoing research and clinical practices in this domain.

The aim of this study was to analyze the types of jaundice, the quality of medical care and the prescription of phototherapy in infants with jaundice according to current recommendations.

Materials and methods of the study. A retrospective analysis was conducted on 618 case histories of pediatric patients presenting with jaundice, who were admitted to the Department of Neonatal Pathology at Children's Clinical Hospital No. 6 in Kyiv during the period from 2017 to 2021. The medical records were collected until 2021, as the department was closed after that year due to the restructuring of the secondary healthcare sector. Criteria for inclusion in the study were: gestational age > 38 weeks, birth weight > 2500 g. The criteria for exclusion from the study were: congenital malformations, including those of the hepatobiliary system (atresia biliary tract), congenital and acquired infectious diseases, including hepatitis, congenital hypothyroidism, congenital metabolic disorders, delayed intrauterine development, and gestational age of less than 38 weeks. Two individuals diagnosed with biliary atresia were excluded from the study cohort as they were transferred to specialized

hospitals. Consequently, the final study group comprised a total of 616 children. Various clinical forms of infant jaundice cases were diagnosed as ICD P59 neonatal jaundice (NJ) and prolonged jaundice (PJN) and P55 hemolytic disease of the newborn (HDN) based on the relevant criteria. Neonatal jaundice (NJ) was diagnosed if jaundice developed in infants later than 24 hours after birth but within the first 14 days of life. A diagnosis of prolonged jaundice of the newborn (PJN) was considered when jaundice appeared or persisted after day 14 in term newborns. Hemolytic disease of the newborn (HDN) was diagnosed in the presence of jaundice and in case of mother-child incompatibility according to the Rh and ABO antigenic systems.

Statistical processing of the collected data was performed utilizing MedStat (version 2.6.2, released on 22.01.2019) and EZR (version 1.61, released on 11.11.2022). For the sample that differed from the normal distribution, the median (Me) and interquartile range (IQR) were calculated. Quantitative features were analyzed using Spearman correlation coefficient. Fisher's chi-square test with Yates' correction compared qualitative attribute proportions. Logistic regression modeled Y based on X₁, X₂, ... X_m, and model effectiveness was assessed using the ROC curve for sensitivity and specificity.

Results: According to the results of the analysis, the total number of infants hospitalised with a diagnosis of jaundice tended to decrease (Fig. 1). Thus, in 2017, 139 newborns (22.5%) were hospitalised, in 2018 – 156 children (25.3%), in 2019 – 134 (21.7%), in 2020 – 113 (19.9%) and in 2021 – 74 children (12%).

When analysing the percentage of hospitalized children based on the day of admission, no significant difference was found between 2017 and 2021. However, when comparing the data between 2018 and 2021, it was found that in 2021, a significantly higher number of children (50.7%, 95% CI 39.1–62.2) were admitted on days 5–14 than in 2018 (33.5%, 95% CI 26.3–41.2), $p = 0.022$. Conversely, there was a statistically significant decrease in hospitalizations on days 15–30 in 2021 – 41.1% (95% CI 30.0–52.7) compared to 2018 – 60.0% (95% CI 52.2–67.6), $p = 0.012$ (Fig.2).

According to medical record review, 4.1% (95% CI 2.6–5.8) of children were born by caesarean section for medical reasons and 95.9% (95% CI 94.2–97.4) children were born by physiological delivery, $p < 0.001$. Anesthesia was administered in 56.4% of all births.

As shown in Fig. 3, 416 mothers had their first birth, 162 had their second, 29 had their third, and 9 had their fourth. Among women who gave birth for the first time, 83.4% had their first pregnancy, 10.8% had their second pregnancy, 3.8% had their third pregnancy, and 1.9%

had their fourth, fifth, sixth, and seventh pregnancies in total. For women with a second childbirth, 75.9% had a second pregnancy, 16.0% had a third, and 8.0% had a fourth or fifth pregnancy. Among those with a third

childbirth, 68.9% had their third pregnancy, and 31.1% had their fourth and fifth pregnancies. For women with a fourth childbirth, one had her eighth pregnancy, while all others had their fourth pregnancy and fourth birth.

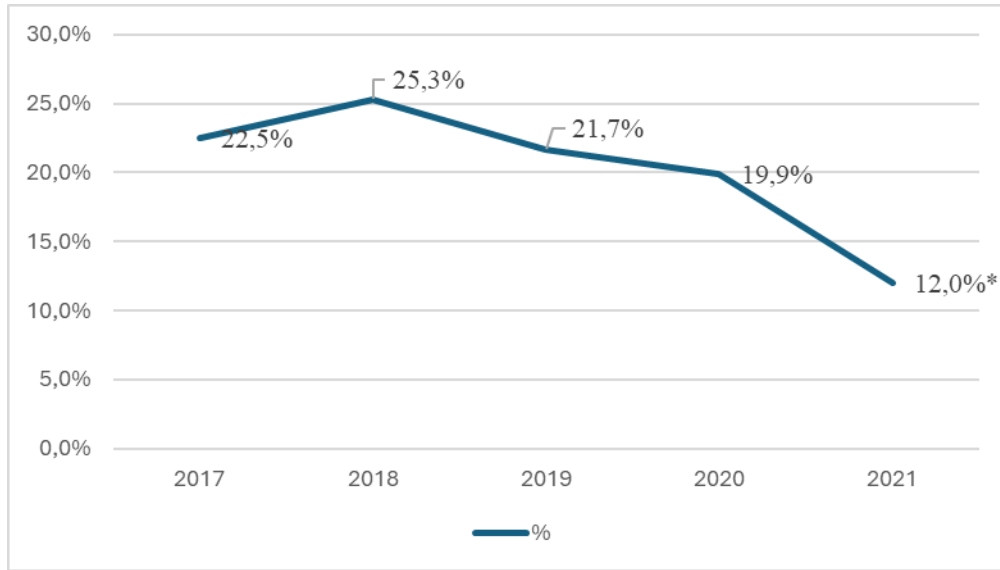


Figure 1 – The number of children hospitalised in the Department of Neonatal Pathology at Children's Clinical Hospital No. 6 in Kyiv for the period 2017–2021 (* p < 0.001 in comparison of data for 2021 and 2017, 2018)

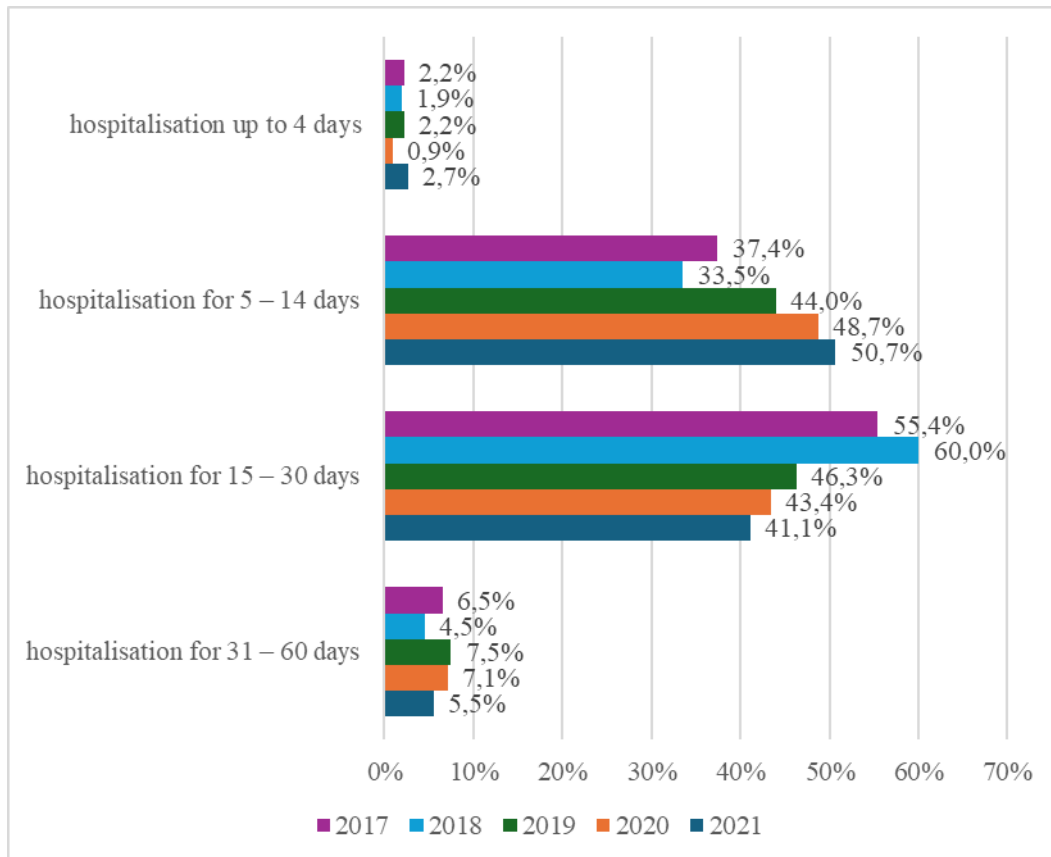


Figure 2 – "Proportion of hospitalised infants in 2017 – 2021 by term of hospitalisation" shows the percentage of children divided into categories of hospitalisation terms: up to 4 days, 5 –14 days, 15 – 30 days, and 31 – 60 days

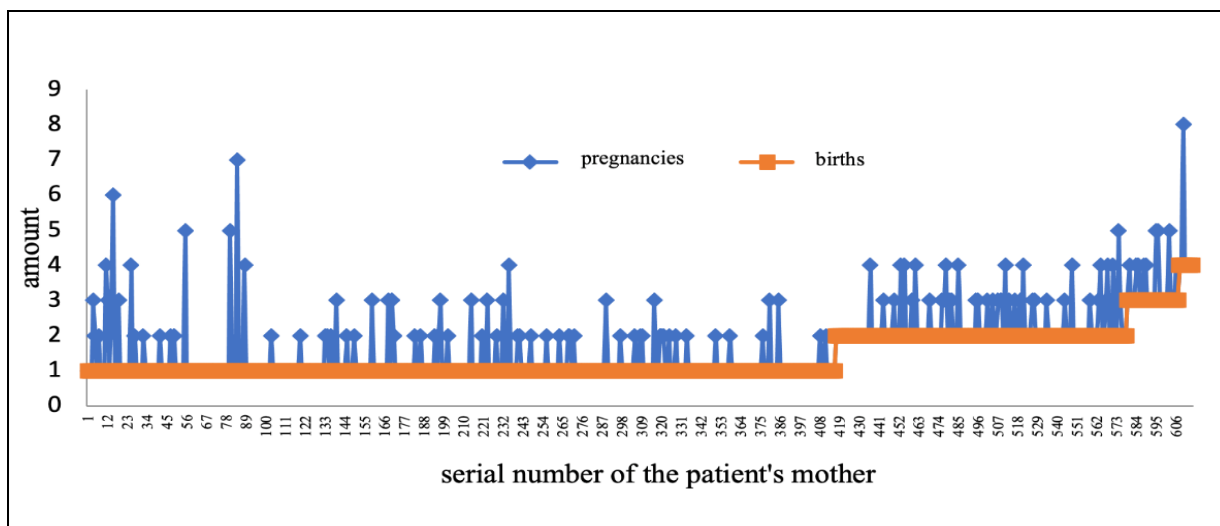


Figure 3 – The ratio of the amount of pregnancies and births among mothers in hospital

The number of pregnancies and births showed a positive correlation with maternal age, with $r_1 = 0.394$ and $r_2 = 0.391$, respectively, $p < 0.05$.

When analyzing mothers' previous pregnancies, it was found that in 14% of cases, children from their earlier pregnancies had jaundice that required phototherapy.

The analysis of medical records revealed that the majority of children – 525 (85.2%, 95% CI 82.3–87.9), were breastfed, while 91 (14.8%, 95% CI 12.1–17.7) were either fed a combination of breast milk and formula or exclusively formula-fed, $p < 0.001$ (Fig.4). Of the total number of children, 187 (30.3%) were reported to be receiving insufficient milk.

In the study, 55.0% of children ($n = 339$) had prolonged jaundice of the newborn (PJN) without haemolytic disease, which was significantly higher than the proportion of children with neonatal jaundice (NJ) – 39.8% ($n = 245$), $p < 0.001$. Haemolytic disease of the newborn (HDN) was observed in 5.2% of children ($n = 32$), Rh factor conflict in 3.25% of children ($n = 20$) and ABO system conflict in 1.95% of children ($n = 12$), $p = 0.208$ (Fig.5).

The median bilirubin levels upon admission showed no significant difference between serum measurements (TSB) – 271.1 [IQR 220.4–330] and transcutaneous bilirubinometer readings (TcB) – 270 [IQR 213–320] with $p = 0.380$ (Fig.6).

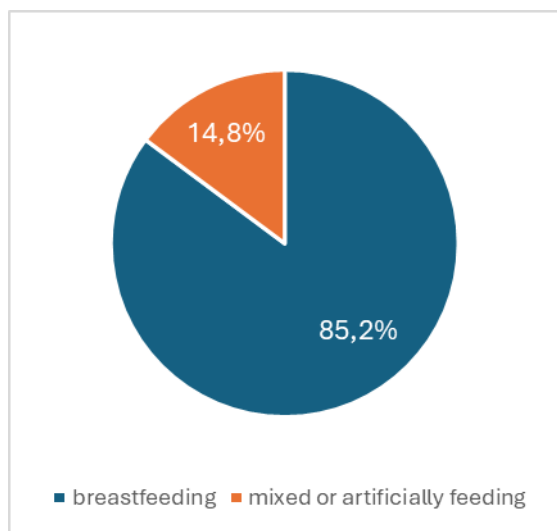


Figure 4 – Distribution of feeding methods among children: breastfeeding and mixed/artificial feeding

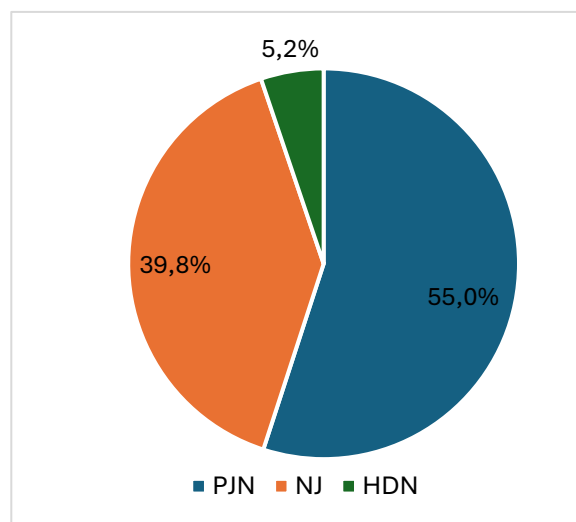


Figure 5 – Distribution of jaundice among studied infants

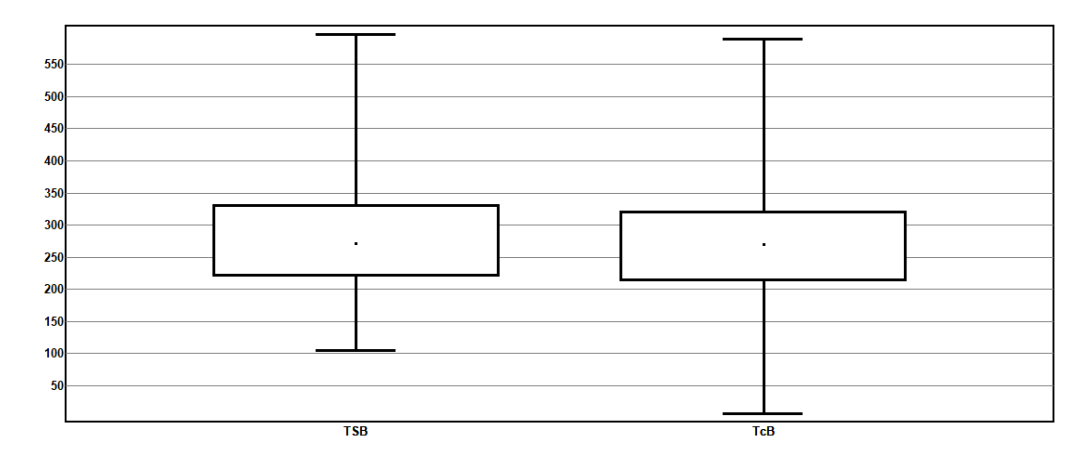


Figure 6 – Interval evaluation of TSB and TcB

Table 1 – Analysis of clinical and laboratory features in different types of jaundice

Features	Neonatal jaundice (n = 245)	Hemolytic disease of the newborn (n = 32)	Prolonged jaundice without hemolytic disease (n = 339)	p
	Me [QI; QIII]			
Mother's age, years	29 [25; 33]	27 [24; 32]	29 [25; 33]	$p_{1,2,3} = 0.739$
DOP, days	7 [5; 8]	7 [6; 8.5]	6 [5; 8]	$p_{1,2,3} = 0.095$
TSB _a , mg/dL	296.3 [247.1; 370]	271.1 [245.25; 335.3]	252.5 [203.4; 312]	$p_{1,2,3} < 0.001$ $p_{1,2} > 0.05$ $p_{1,3} < 0.01$ $p_{2,3} > 0.05$
TSB _d , mg/dL	144 [117.5; 165.65]	156.55 [137.75; 179.8]	132.4 [108.4; 155]	$p_{1,2,3} < 0.001$ $p_{1,2} > 0.05$ $p_{1,3} < 0.01$ $p_{2,3} < 0.01$
TSB _a -TSB _d , mg/dL	158 [104.2; 215.1]	112.9 [91.45; 154.85]	118.2 [73.1; 173.5]	$p_{1,2,3} < 0.001$ $p_{1,2} > 0.05$ $p_{1,3} < 0.01$ $p_{2,3} > 0.05$
TSB _{ddb} , mg/dL	22.8 [13.2; 37.2]	16.15 [11.8; 24.6]	20.75 [12; 29.15]	$p_{1,2,3} = 0.026$ $p_{1,2} > 0.05$ $p_{1,3} > 0.05$ $p_{2,3} > 0.05$
TcB _a , mg/dL	294.5 [240; 358]	282.5 [240; 311]	241.5 [188; 291]	$p_{1,2,3} < 0.001$ $p_{1,2} > 0.05$ $p_{1,3} < 0.01$ $p_{2,3} > 0.05$
TcB _d , mg/dL	142.5 [121; 153]	143 [136; 146]	126 [106; 150]	$p_{1,2,3} = 0.109$

Note: DOP – duration of phototherapy, TSB_a – total serum bilirubin at the time of admission, TSB_d – total serum bilirubin at the time of discharge, TSB_a-TSB_d – difference between total serum bilirubin from admission to discharge, TSB_{ddb} – daily decrease in serum bilirubin, TcB_a – transcutaneous bilirubin at the time of admission, TcB_d – transcutaneous bilirubin at the time of discharge

The serum bilirubin exhibited a median difference of 132 [IQR 86.8–194.7] from admission to discharge, with a corresponding median daily decrease of 20.85 [IQR 12.65–30.75].

It was found that the duration of phototherapy did

not vary depending on the type of jaundice, $p_{1,2,3} = 0.095$. The TSB level at the time of admission was statistically higher in the group of children with neonatal jaundice than in those with prolonged jaundice, $p_{1,3} < 0.01$. The difference in the drop in TSB level from

admission to discharge was statistically higher in the group of children with neonatal jaundice than in those with prolonged jaundice and haemolytic jaundice, $p_{1,2,3} < 0.001$. Similarly, TcB, like TSB, was statistically higher at admission in the group of children with neonatal jaundice than in the group of children with prolonged jaundice ($p_{1,3} < 0.01$), but at discharge, there was no statistical difference between the groups ($p_{1,2,3} = 0.109$), Table 1.

A logistic analysis was performed to examine the influence of the following factors: mother's age, number

of pregnancies, number of births, caesarean section, type of feeding (artificial or breastfeeding), blood type, Rh factor, TSB_a and TcB_a (X1 , X2 ... X9) on the resulting indicator – the risk of prolonged jaundice (Y), as illustrated in Fig.7

Thus, it was found that the presence of prolonged jaundice in newborns may be influenced by the history of caesarean section, and demonstrated an inverse relationship with the level of bilirubin measured by the transcutaneous method (TcB_a). (Table 2).

Table 2 – The final model for assessing the impact of factor attributes on the presence of prolonged jaundice

Factor	Estimate	Standard Error	z-value	p-value
(Intercept)	3.131433	1.076904	2.908	0.00364 **
Cesarean Section	2.308836	1.159023	1.992	0.04637 *
TcB _a	-0.011844	0.003911	-3.028	0.00246 **

Note: The symbols ** and * indicate statistical significance at the 0.01 and 0.05 levels, respectively

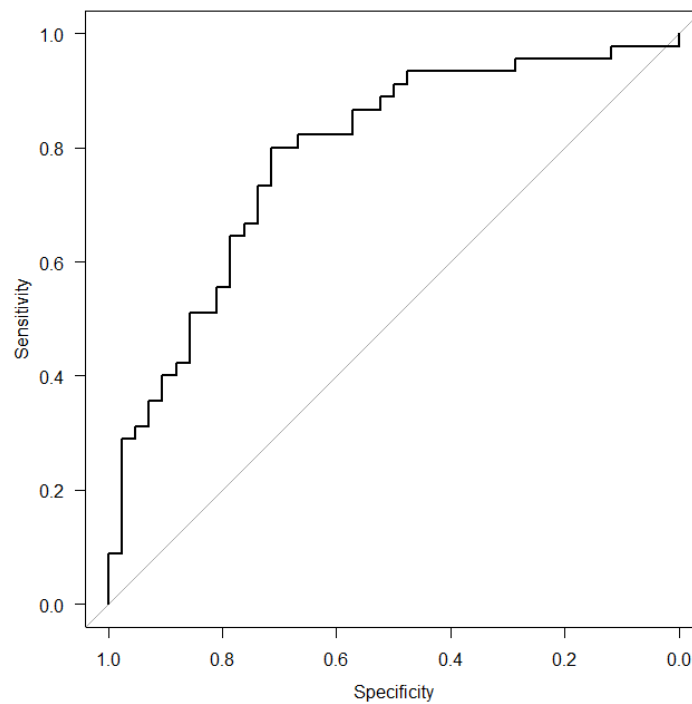


Figure 7 – ROC curve of the multivariate logistic regression model of the presence of prolonged jaundice in newborns (Area under the curve 0.785, 95% CI 0.687–0.883)

The median duration of phototherapy was 6 days with an interquartile range (IQR) of 5 to 8 days. Overall, more than five days of phototherapy were required for 63.9% of children (n = 394). Children with hemolytic disease of the newborn – 84.4% (95% CI 69.4–95.0) were significantly more likely to need phototherapy for a duration exceeding five days than children with

neonatal jaundice – 63.7% (95% CI 57.6–69.6) with p-value = 0.022, and prolonged jaundice – 62.2% (95% CI 57.0–67.3) with p-value = 0.012.

Considering the validity of the previous Order No. 255 dated 27.04.2006, which approved the Clinical Protocol for Neonatal Care titled "Newborn Jaundice," defining that jaundice is physiological if it does not

exceed 205, it was determined that 4.1% ($n = 10$) of all children with neonatal jaundice did not require hospitalization and phototherapy, as their serum bilirubin levels were within the physiological norm [7].

DISCUSSION

The results of the analysis showed that hospitalization with various forms of jaundice decreased by about 2.1 times in 2021 compared to 2018 and by 1.5 times compared to 2017. This may indicate a wider use of lamps for home phototherapy, including during COVID-19 [8]. Comparing data between 2018 and 2021, it was found that in 2021 significantly more children were hospitalized on days 5–14 than in 2018. On the other hand, there was a statistically significant decrease in hospitalizations on days 15–30 in 2021 compared to 2018. The study showed that 55.0% of children had prolonged neonatal jaundice without haemolytic disease, which was significantly ($p < 0.001$) higher than the percentage of children with neonatal jaundice – 39.8%. This prevalence may be associated with breastfeeding, inherited disorders that can only be confirmed genetically, such as Gilbert's disease, G6PD deficiency, or impaired bilirubin conjugation [9]. Haemolytic disease of newborns due to Rh conflict and ABO conflict occurred in 5.2%. The logistic regression model showed that a history of cesarean section also influenced the duration of jaundice in newborns, with children born via cesarean section having a higher risk of prolonged jaundice. Comparable findings were obtained in a study Adugna et al. showing a significant impact of the method of delivery on the occurrence of neonatal jaundice. The likelihood of neonatal jaundice in newborns born by caesarean section was 4 times higher than in those born naturally. This is explained by the fact that during a natural vaginal birth, the level of glucuronyl transferase increases, which leads to a decrease in bilirubin levels within three days after birth [10]. Interestingly, the study revealed an inversely proportional relationship between the level of

transcutaneous bilirubin at admission and the presence of prolonged jaundice. The obtained data suggests that the use of transcutaneous bilirubinometry is not an effective method in cases of prolonged jaundice. This is further supported by information from the updated protocol [4], which recommends refraining from using transcutaneous bilirubinometry in cases of prolonged jaundice in children. Maternal age, number of pregnancies and births, type of feeding, blood type and Rh factor were not associated with risk of prolonged jaundice. Most children required phototherapy for more than 5 days. Infants with HDN more often required prolonged phototherapy than those with other forms of jaundice, which may be explained by a less effective daily reduction in bilirubin (TSB_{dtdb} , mg/dL). In the context of the necessity of hospitalization and phototherapy, the research confirmed that 4.1% of children with neonatal jaundice did not require hospitalization and phototherapy once their bilirubin levels corresponded to the physiological norm, as defined by the Order No. 255 of April 27, 2006, which has currently expired. This may be due to the fact that the children may have been hospitalized at the insistence of their parents, given their family history. This suggests the potential for reconsidering reforms in management protocols, particularly in the context of home and outpatient care strategies for this group of children. Based on the obtained results, it is recommended for healthcare professionals to adhere to the new Order No. 783 of April 27, 2023, "On the Approval of the Unified Clinical Protocol for Specialized Medical Care 'Jaundice in Newborns,'" with bilirubin nomograms depending on the child's age to make decisions regarding the initiation of phototherapy. This approach reflects current requirements and standards in the management of neonatal jaundice and contributes to a more accurate determination of the need for phototherapy based on the individual characteristics of the child.

CONCLUSIONS / ВИСНОВКИ

1. The analysis showed that hospitalization with various forms of jaundice decreased in 2021 by about 2.1 times compared to 2018 and by 1.5 times compared to 2017 ($p < 0.001$).

2. PJN was more common (55.0%) than NJ (39.8%) which could be due to perinatal factors that interfere with bilirubin conjugation ($p < 0.001$). HDN was observed in 5.2 % of children with no statistically significant difference between the Rh factor conflict and the ABO system ($p = 0.208$).

3. A logistic regression model ($AUC = 0.785$)

showed that the manifestation of PJN may be influenced by a history of cesarean section.

4. At the time of hospitalization, there was no significant difference between the bilirubin levels measured by two methods: total serum bilirubin (TSB_a) and transcutaneous bilirubin (TcB_a), $p = 0.380$.

5. More than half (63.9%) of infants needed phototherapy for more than five days. Children with HDN (84.4%) more often ($p < 0.05$) required prolonged phototherapy than children with NJ (63.7%) and PJN (62.2%), which may be explained by a less effective daily decline in bilirubin levels.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

It is reasonable to assess the impact of the recently implemented Order No. 783 of April 27, 2023, "On the Approval of the Unified Clinical Protocol for Specialised Medical Care 'Jaundice in Newborns,'" with bilirubin nomograms adapted to the age of the child. This analysis aims to assess how these changes affect the rate of hospitalisation for jaundice, which is an important indicator for monitoring the quality and effectiveness of medical care.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

Kachalova Olga ^{E,F}	A – Concept and Design
Ipatii Nataliia ^{B,C}	B – Data Collection and Analysis
Gnyloskurenko Ganna ^{A,D}	C – Analysis and Interpretation of Data
Aliusef Maiia ^{C,D}	D – Writing the Article
Mityuryayeva Inga ^{E,F}	E – Critical Review
Molochek Nataliia ^{E,F}	F – Final Approval of the Article

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None.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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