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Effect of Seasonal Variation on the Bilirubin Content and Hematological Indices among Neonates in Southern Gaza, Palestine

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Abstract

Background and Objectives: Premature newborns' bilirubin conjugation and excretion mechanisms are undeveloped. Seasonal changes and other variables affect the severity of newborns' physiological jaundice. This study examined blood indices, bilirubin levels, and birth season in neonates in the southern Gaza Strip of Palestine.

Methods: A cross-sectional study of 366 neonates aged one to 14 days was conducted in Medical Nasser Complex-Southern Gaza, Palestine.The newborns were divided into four groups based on season of birth: spring (n = 72), winter (n = 96), autumn (n = 103) and summer (n = 95). Blood samples were collected in plain vacutainers for assaying bilirubin profile and complete blood count. Bilirubin and complete blood count were assayed by commercial kits. SPSS software was used for data analysis.

Results: Indirect and total bilirubin showed significant seasonal variations, whereas direct did not. Spring and winter have increased indirect and total bilirubin. Seasonal hemoglobin levels varied significantly. Red blood cells, hemoglobin, and hematocrit positively correlated with total and indirect bilirubins.

Conclusion: Spring and winter births exhibited higher indirect and total bilirubin in the first two weeks. The birth season appears to affect newborn jaundice. Short sunshine duration may increase neonatal hyperbilirubinemia risk.

Keywords: Bilirubin content, hematological indices, neonates, Palestine

1. Introduction

1.1 Introduce the Problem

Bilirubin is a non-polar, water-insoluble yellow pigment that is produced from hemoglobin during erythrocyte destruction (Amin & Lamola, 2011). Bilirubin can only be efficiently eliminated from the body following conjugation (Fevery, 2008). In fetal life, bilirubin production begins as early as 12 weeks' gestation, with the placenta acting as the primary route of elimination. Daily bilirubin production in newborns is approximately 6 to 8 mg per kg (Reiser, 2004), (Porter & Dennis, 2002). The mechanism responsible for the conjugation (catalyzed by bilirubin UDP glucuronyl transferase) and excretion of bilirubin is underdeveloped in newborns, especially those born prematurely. This causes a condition called "physiological jaundice of neonates," in which bilirubin levels are at their highest on days 3–4, when they are above 5 mg/dl (85 mmol/l) (Cohen, Wong, & Stevenson, 2010; Outlaw et al., 2020; Jenabi, Bashirian, & Khazaei, 2020; Pace, Brown, & DeGeorge, 2019).

1.2 Explore Importance of the Problem

Elevated bilirubin levels in the blood are the cause of the distinctive physiological jaundice seen in the vast majority of newborns (Mitra & Rennie, 2017; Ullah, Rahman, & Hedayati, 2016). These elevated levels are the result of high red cell turnover, immature hepatic conjugation, and enhanced resorption of bilirubin by the enterohepatic circulation (Iijima, Baba, Kondo, Fujita, & Ohishi, 2021; Salia et al., 2021). Moreover, the severity of physiological jaundice in most newborns is affected by the pattern of eating, seasonal changes, glucose-6-phosphate dehydrogenase deficiency, suboptimal breast milk intake or dehydration, isoimmune hemolysis, and neonatal jaundice incompatibilities (Hojat, Zarezadeh, & Mogharab, 2018; Bhutani et al., 2013). In the first week of life, jaundice affects approximately 60% of full-term newborns and 80% of preterm infants

(Anderson & Calkins, 2020). Yellowing of the skin, sclera, and mucosa is characteristic of newborns with neonatal jaundice (Asefa et al., 2020). Neonatal jaundice can result in severe neurological complications, such as kernicterus, which entails a high risk of neonatal mortality, as well as long-term neurologic damage such as cerebral palsy, sensory neural hearing loss, intellectual challenges, or severe developmental delays. Consequently, it should cause serious alarm (Wan Mohd Hanafi, Wan Ibrahim, & Hashim, 2021; Magai et al., 2020). According to the 2016 Global Burden of Disease report, preventing neonatal jaundice in the first week of life is important in the vast majority of nations that have the highest burden of neonatal mortality. Preventing neonatal jaundice from progressing into kernicterus lessens the likelihood of mortality and the degree of any neurologic deficits' survivors may experience (Olusanya, Teeple, & Kassebaum, 2018). Seasonal variation may influence the prevalence and severity of neonatal jaundice, according to empirical neonatological evidence.

1.3 Describe Relevant Scholarship

In the literature, there are a few contradictory studies that have looked into whether or not infants' serum bilirubin levels follow a seasonal trend.

1.4 State Hypotheses and Their Correspondence to Research Design

The present study aimed to examine the relationship between blood indices and bilirubin levels, as well as explore possible impact of the season of birth on serum bilirubin levels of neonates in the southern Gaza Strip of Palestine. In addition, the study aimed to find out if there was any link between the bilirubin profile and the hematological parameters.

2. Method

2.1 Study Design and Population

This is a descriptive, population-based cross-sectional study conducted in the Medical Nasser Complex-Southern Gaza, Palestine in which 366 newborns were involved. The newborns were divided into four groups based on season of birth: spring (n = 72), winter (n = 96), autumn (n = 103) and summer (n = 95). Newborns male and female who aged from one day to 14 days (8.63±3.55 days) were included in the study, while newborns aged more than 14 days were excluded.

2.2 Blood Samples Collection

Blood samples were collected from newborns by medical doctors in the Medical Nasser Complex-Southern Gaza in plain vacutainers for assaying the bilirubin profile (direct, indirect, and total bilirubin) and complete blood count (CBC).

2.3 Biochemical Markers Analyses

2.3.1 Determination of Bilirubin

The concentration of bilirubin was determined by the Jendrassik-Grof Method (Diazo Method) using commercial kits manufactured by the RANDOX company on the Mindray BS-480 instrument. Briefly, in an alkaline medium, direct (conjugated) bilirubin reacts with diazotized sulphanilic acid in the presence of caffeine to generate a blue-colored complex. The system monitors the change in absorbance at 520 nm at a fixed-time interval. This change in absorbance is directly proportional to the concentration of total bilirubin in the sample.

2.3.2 Complete Blood Count (CBC)

CBC was carried out using the Sysmex XN-450/XN-430 automatic hematology analyzer. The diagnostic parameters assayed include: white blood cells (WBCs), red blood cells (RBCs), hemoglobin (Hb), hematocrit (HCT), and platelets (PLT).

Sysmex is an instrument based on the flow cytometry technique (using a semiconductor laser) and the SLS-hemoglobin method. RBC and PLT were counted and measured using hydrodynamic impedance counting. At the same time, HCT was estimated by using the RBC pulse height detection technique. Cytometry was used to investigate the physiological and chemical characteristics of cells and other biological particles.

2.4 Ethical Consideration

Al-Aqsa University's Faculty of Medical Sciences provided the ethical approval. The parental consent was obtained after parents were given a thorough explanation of the study's objectives. Participation was voluntary, and all newborns and their parents who agreed to participate in the study remained anonymous, and their privacy was protected.

2.5 Statistical Analysis

For data entry and analysis, we utilized the Statistical Package for Social Science (SPSS) version 25 program. For continuous and categorical variables, descriptive data were expressed as mean ± SD, min-max, or frequency (%). A comparison of the mean bilirubin levels across the different seasons, examined parameters (direct bilirubin, indirect bilirubin. total bilirubin, WBCs, RBCs, Hb, HCT, and PLT), and blood groups was carried out with the analysis of variance (ANOVA) test. Then, a post hoc test was used to find out which group means differ from one another that have a P-value <0.05 by ANOVA, such as indirect bilirubin, total bilirubin and Hb. The Pearson correlation (r) is used to evaluate the statistical relationship between two continuous variables. A P-value less than 0.05 was considered statistically significant.

2.6 Limitations Involved in the Study

The present study exhibits a number of constraints that necessitate careful consideration when interpreting its findings. A potential constraint of the study is the limited sample size, which may not adequately reflect the broader neonatal population in Southern Gaza or Palestine. Furthermore, the absence of a control group poses a challenge in terms of comparing the results with those of neonates who are in good health. The study utilized a cross-sectional methodology, thereby constraining the capacity to establish a causal association between the season of birth and neonatal bilirubin levels.

3. Results

3.1 Sociodemographic Data and Blood Group among the Study Population

19.7% of the neonates were born in the spring, 26.2% were born during the winter, 28.1% were born in the autumn, and 26% were born during the summer. There were approximately 1.04 males for every female. The vast majority of neonates have a positive Rh factor (89.6%), and approximately one-third of newborns belong to blood group A, as can be seen in Table 1 and Figure 1.

Table 1. Sociodemographic data and blood groups among the study population

Variable		Frequency (n)	Percent (%)
Seasons (n =366)	Spring	72	19.7
	Winter	96	26.2
	Autumn	103	28.1
	Summer	95	26.0
Gender (n=366)	Male	179	48.9
	Female	187	51.1
Rh (n= 366)	Positive	328	89.6
	Negative	38	10.4
Blood group (n= 366)	A	129	35.2
	B	105	28.7
	AB	30	8.2
	O	102	27.9

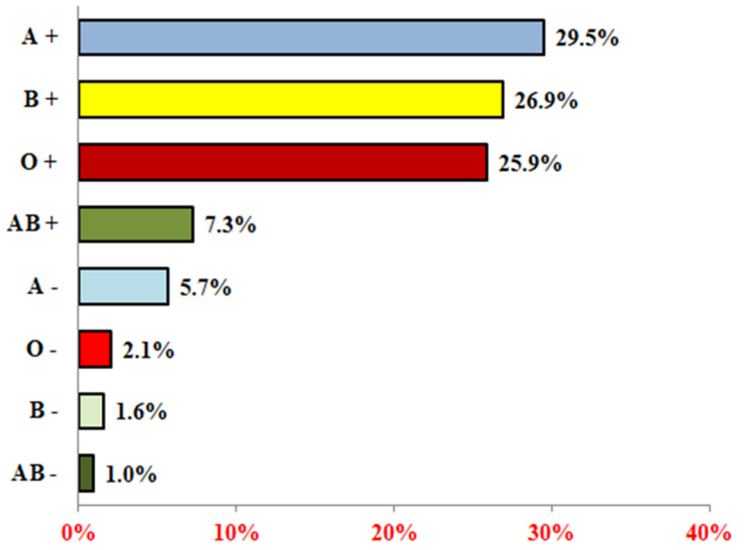

Figure 1. Distribution of the study population according to blood group (Rh)

3.2 Determination of Bilirubin Profile & CBC Parameters According to Season among the Study Population

Table 2-A. showed that the mean direct, indirect, and total serum bilirubin level of newborns born in spring were 0.77±0.45 mg/dl, 11.54±4.43 mg/dl and 12.31±4.42 mg/dl, respectively; while those born in winter were 0.70±0.24 mg/dl, 10.44±3.87 mg/dl and 11.13±3.88 mg/dl respectively. The mean direct, indirect, and total serum bilirubin levels of newborns born in autumn were 0.81±0.86 mg/dl, 9.04±3.59 mg/dl and 9.84±3.73 mg/dl, respectively; while those born in summer were 0.74±0.5 mg/dl, 8.63±3.55 mg/dl and 9.35±3.58 mg/dl respectively. There was no statistically significant variation observed in the level of direct bilirubin across the four seasons. Nevertheless, significant differences were observed among seasons with regards to indirect bilirubin and total bilirubin. The seasons of spring and winter exhibited the highest levels of indirect bilirubin and total bilirubin. Statistically significant variations were observed in the levels of indirect bilirubin across different seasons, including spring vs. autumn, spring vs. summer, winter vs. autumn, and winter vs. summer. Also, the amounts of total bilirubin were much higher in spring than in autumn, in spring than in summer, and in winter than in summer.

According to the findings presented in Table 2-B, there was no statistically significant variation observed in the levels of white blood cells, red blood cells, hematocrit, or platelets based on seasonal differences. However, there were significant differences observed in hemoglobin levels across various seasons. The levels of hemoglobin exhibited significant variation between the seasons of spring and summer, as well as between the seasons of spring and autumn. The concentration of hemoglobin exhibited its peak levels during the spring season, which was subsequently followed by the winter season.

Table 2-A. Determination of bilirubin profile according to season among the study population. Results expressed as mean ± SD and Min- Max range

Parameters	Total (n=366)	Seasons				Statistical test		
		Spring (n=72)	Winter (n=96)	Autumn (n=103)	Summer (n=95)	F	P-value	Post Hoc
D. Bil (mg/dl) (Min-Max)	0.75±0.57 (0.2-4)	0.77±0.45 (0.3-4)	0.70±0.24 (0.2-1.7)	0.81±0.86 (0.3-9)	0.74±0.5 (0.2-1.1)	0.591	0.621	-
ID. Bil (mg/dl) (Min-Max)	9.79±3.97 (0.4-21.7)	11.54±4.43 (0.4-21.7)	10.44±3.87 (0.4-19.2)	9.04±3.59 (2.6-17.7)	8.63±3.55 (0.6-16.3)	9.914	0.000	0.069 [a]
								0.000 [b*]
								0.000 [c*]
								0.012 [d*]

								0.001 [e*]
								0.454 [f]
T. Bil (mg/dl)		12.31±4.42	11.13±3.88	9.84±3.73	9.35±3.58	9.582	0.000	0.054 [a]
(Min-Max)	10.54±4.01 (1-22)	(1.9-22)	(1.3-20.5)	(3-18.3)	(1-17.1)			0.000 [b*]
								0.000 [c*]
								0.021 [d*]
								0.002 [e*]
								0.384 [f]

[*] P≤0.05: Significant, P>0.05: Not significant;

Post Hoc test ([a] Spring compare to Winter; [b] Spring compare to Autumn; [c] Spring compare to Summer; [d] Winter compare to Autumn; [e] Winter compare to Summer; [f] Autumn compare to Summer);

Abbreviations: T. Bil: Total bilirubin; D. Bil: direct bilirubin; ID. Bil: indirect bilirubin; N: number of the subjects; SD: standard deviation; Min: Minimum; Max: Maximum & F: one-way ANOVA.

Table 2-B. Determination of CBC parameters according to season among the study population. Results expressed as mean ± SD and Min- Max range

Parameters	Total	Seasons				Statistical test		
	(n=366)	Spring (n=72)	Winter (n=96)	Autumn (n=103)	Summer (n=95)	F	P-value	Post Hoc
WBCs (K/µL)	12.02±5.13	12.36±6.1	11.88±4.63	12.51±5.79	11.41±3.99	0.743	0.527	-
(Min-Max)	(1-39.5)	(3.3-39.5)	(1-23.4)	(1.4-29.4)	(4.7-26.8)			
RBCs (M/µL)	4.34±0.87	4.39±1.06	4.39±0.76	4.25±0.88	4.34±0.82	0.438	0.726	-
(Min-Max)	(1.3-6.45)	(1.5-6.4)	(2.7-6.01)	(1.3-6.45)	(2.34-5.7)			
Hb (g/dL)	15.3±2.87	15.97±2.78	15.67±2.88	14.82±2.92	14.97±2.79	2.671	0.048	0.539 [a]
(Min-Max)	(8.1-23.6)	(10.9-23.1)	(8.8-23.1)	(8.1-23.6)	(8.1-19.6)			
								0.018 [b*]
								0.042 [c*]
								0.060 [d]
								0.125 [e]
								0.737 [f]
HCT (%)	44.77±8.22	46.7±8.33	44.96±7.65	43.89±8.2	44.13±8.6	1.576	0.195	-
(Min-Max)	(24.1-70.8)	(29.7-64.9)	(27.2-65.7)	(24.1-70.8)	(24.7-60.6)			
PLT (K/µL)	297±110	272±79	303±116	300±118	307±116	1.228	0.300	-
(Min-Max)	(75-675)	(142-617)	(86-631)	(79-675)	(75-632)			

[*] P≤0.05: Significant, P>0.05: Not significant;

Post Hoc test ([a] Spring compare to Winter; [b] Spring compare to Autumn; [c] Spring compare to Summer; [d] Winter compare to Autumn; [e] Winter compare to Summer; [f] Autumn compare to Summer);

Abbreviations: WBCs: White blood cells; RBCs: Red blood cells; Hb: hemoglobin; HCT: hematocrit; PLT: platelets; N: number of the subjects; SD: standard deviation; Min: Minimum; Max: Maximum & F: one-way ANOVA.

3.3 Relationships between Bilirubin Profile and Hematological Profile

The results presented in Table 3 and Figures 2 and 3 demonstrate a positive correlation between total bilirubin and RBCs (r = 0.150, P = 0.010), Hb (r = 0.178, P = 0.002), and HCT (r = 0.155, P = 0.007). Furthermore, the study

revealed a significant association between indirect bilirubin and red blood cells (r = 0.154, P = 0.008), hemoglobin (r = 0.170, P = 0.003), and hematocrit (r = 0.148, P = 0.011).

Table 3. The correlation between bilirubin profile and hematological profile among the study population

Parameters	D. Bil (mg/dl)		ID. Bil (mg/dl)		T. Bili (mg/dl)	
	r	P-value	r	P-value	r	P-value
WBCs (K/µL)	0.074	0.209	-0.054	0.355	.049	0.404
RBCs (M/µL)	-0.045	0.450	0.154	0.008 *	0.150	0.010 *
Hb (g/dL)	0.030	0.613	0.170	0.003 *	0.178	0.002 *
HCT (%)	0.026	0.654	0.148	0.011 *	0.155	0.007 *
PLT (K/µL)	-0.096	0.103	0.052	0.372	0.047	0.420

* P≤0.05: Significant, P>0.05: Not significant; WBCs: White blood cells; RBCs: White blood cells; Hb: Hemoglobin; HCT: hematocrit; PLT: platelets; T. Bil: Total bilirubin; D. Bil: direct bilirubin; ID. Bil: indirect bilirubin &r: Pearson correlation.

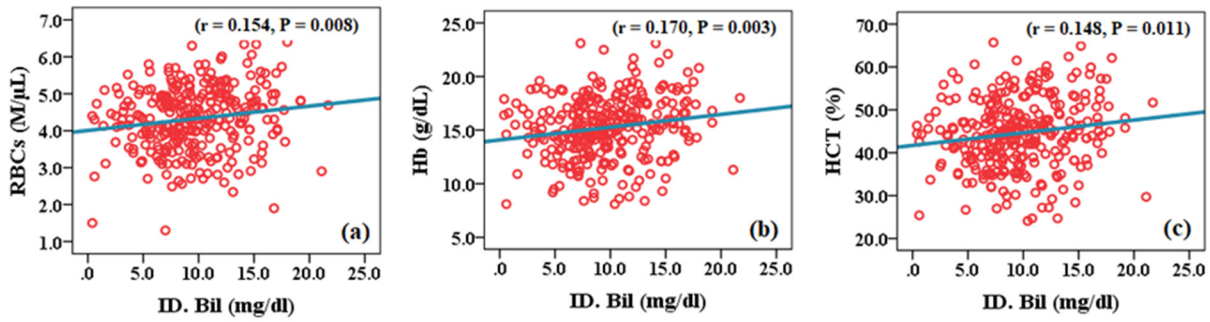

Figure 2. The relationship between indirect bilirubin and a) red blood cells, b) hemoglobin, and c) hematocrit

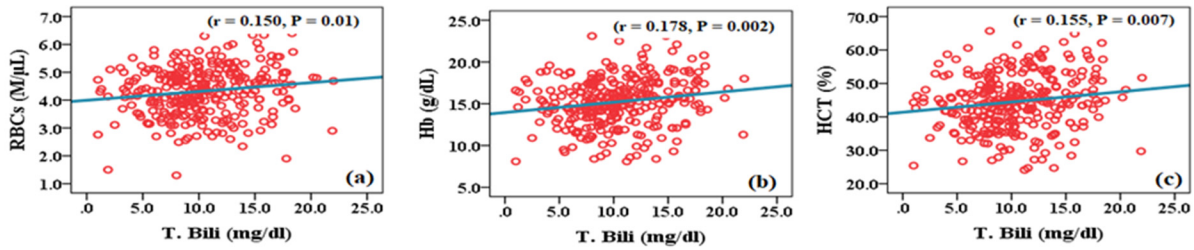

Figure 3. The relationship between Total Bilirubin and a) red blood cells, b) hemoglobin, and c) hematocrit

4. Discussion

Increased amounts of serum bilirubin in the first week of life cause the yellowing of the skin and conjunctiva, a physiological condition known as neonatal jaundice (Greco et al., 2016). The central nervous system is extremely vulnerable to the effects of unconjugated bilirubin. Infants' jaundice symptoms can range from mild to severe depending on variables like their race, diet, environment, and even the season of birth (Hojat, Zarezadeh, & Mogharab, 2018). Hyperbilirubinemia is the most common morbidity observed during the neonatal period, and a significant proportion of newborns (5-10%) require medical intervention to address pathological jaundice (Mishra, Agarwal, Deorari, & Paul, 2008). Findings of the present study found that 19.7% of the 366 infants studied were born in the spring, 26.2% were born in the winter, 28.1% were born in the autumn, and 26.0% were born in the summer. The majority of study subjects were Rh-positive (89.6%), with approximately 29.5% being A+ and 26.9% being B+ (Table 1, Figure 1). The results of this study revealed that direct bilirubin levels did not vary significantly across the year. Indirect and total bilirubin levels, however, varied considerably with the seasons. As per the

findings of the current study, newborns delivered during the spring and winter seasons exhibited elevated levels of indirect and total bilirubin as compared to those born in the autumn and summer seasons. The levels of indirect and total bilirubin exhibited a steady decline from the season of spring to winter, followed by autumn, and finally summer. Indirect and total bilirubin levels are lowest in the summer. The observed results may be attributed to the comparatively reduced duration of daylight during winter as compared to summer, which may potentially elevate the likelihood of hyperbilirubinemia (Anttolainen, Similä, & Wallgren, 1975). The emission of blue-green light by sunshine has the potential to prevent hyperbilirubinemia by promoting the conversion of bilirubin to its water-soluble isomers, thereby facilitating its excretion. The inverse correlation observed between the duration of sunshine and the incidence of neonatal hyperbilirubinemia at the prefectural level could potentially be attributed to the impact of sunlight exposure penetrating the living environments of infants (Kuniyoshi et al., 2022).

There haven't been many studies done on the association between bilirubin levels and the birth season. Consistent with the results of the present study, (Bottini, Dituri, & Gloria-Bottini, 2000) conducted a prospective study of 343 newborns in the Rome population to examine the relationship between serum bilirubin levels in the first week of life and the season of birth. The authors reported an increase in blood bilirubin during the first 24 hours of life that was related to the season of birth: winter (3.6±1.3 mg/dl), spring (3.3±1.3 mg/dl), summer (3.5±1.9 mg/dl), and autumn (2.9±1.3 mg/dl). However, the increase in serum bilirubin during the winter and autumn seasons was not substantially different between males and females. Also, in a retrospective analysis of 3,344 healthy term newborns, (Iijima, Baba, Kondo, Fujita, & Ohishi, 2021) observed that the total serum bilirubin level was significantly higher ($p = 0.01$) in the cold season (October to March) than in the warm season (April to September). In December, the median total blood bilirubin amount was 202 μmol/L, and in July, it was 190 μmol/L. Male infants had substantially higher total serum bilirubin levels during the cold season ($p = 0.001$), whereas female infants did not show this trend.

In contrast to the findings of the present study, a total of 1000 infants with jaundice were analyzed; 500 of each sex were included, and they were evenly divided between the summer and winter months. In the winter, neonatal females had greater direct bilirubin levels than males ($P = 0.019$). On the other hand, males born in the summer were more likely to have serum indirect bilirubin than males born in the winter ($P = 041$). Summer-born female neonates had substantially higher total and indirect bilirubin levels ($P = 0.001$). The authors explained that hyperbilirubinemia is more severe when summer temperatures are high and when there is a larger impact from higher levels of breastfeeding (Bala et al., 2015). In another study, over 500 neonates with clinically confirmed jaundice were analyzed to determine whether or not there was a seasonal or gender-based difference in their bilirubin levels. Direct bilirubin was found to be significantly more common in females born in the winter than in winter-born males ($P = 0.020$) and summer-born females ($P = 0.003$). Children born in the winter are more vulnerable to other contributing factors, such as infections that cause inflammation of the liver-biliary system and obstructive jaundice, which increases direct bilirubin during the winter months due to less sunlight exposure (Ahmady, El-Sayed, Ali, & Baraka, 2015).

Interestingly, the authors (Hojat, Zarezadeh, & Mogharab, 2018) of a cross-sectional study conducted an analysis on one hundred infants who were randomly selected from each season. The study found that there was no statistically significant correlation between bilirubin levels in the first week of life and the season of birth (Sig. = 0.951; $r = -0.003$).

No significant seasonal variation was found in the hematological indices, notably white blood cell, red blood cell, hematocrit, and platelet levels, according to findings from the present study. Nonetheless, there were significant differences in hemoglobin levels between seasons. The levels of hemoglobin in the blood varied significantly from spring to summer and from spring to autumn. The amount of hemoglobin was highest in the spring, then in the winter. A study of 1141 children aged 12–59 months found that the mean values for the WBC and lymphocytes, monocytes, and neutrophils were higher in the wet season, contradicting the results of the current study. The authors reported that the wet season had a significantly lower mean haemoglobin level while the mean platelet values were higher (p 0.0001). Age and seasonality impact interval mean values for hematological parameters in the first five years of life. They concluded that age and seasonality have an impact on mean values for hematological parameter intervals in the first five years of life (Okebe et al., 2016). Also, in a cross-sectional study of 120 school-aged children and teens, the hematocrit was found to reduce significantly during the rainy season while red cell series and blood iron homeostasis had seasonal variation (Rodrigues, Ignotti, & Hacon, 2017). Moreover, in a study of 27,478 children aged 7–17, white blood cell counts were statistically significantly higher in

the winter and spring than in the summer and autumn ($p \leq 0.05$). When comparing winter/spring to summer/fall, HCT and RBC decreased while platelets were higher (Liu & Taioli, 2015).

According to the results of the current study, total bilirubin was positively correlated with RBCs ($r = 0.150$, $P = 0.010$), Hb ($r = 0.178$, $P = 0.002$), and HCT ($r = 0.155$, $P = 0.007$) in the hematological matrices (Table 3 and Figures 2 and 3). Additionally, it was found that indirect bilirubin had a positive correlation with RBCs ($r = 0.154$, $P = 0.008$), Hb ($r = 0.170$, $P = 0.003$), and HCT ($r = 0.148$, $P = 0.011$).

The current study's findings recommend that a longitudinal study design be used to better understand the effect of seasonal variation on bilirubin levels and hematological markers in newborns in Southern Gaza, Palestine. A longitudinal design lets researchers track these characteristics throughout time to learn about newborns' bilirubin metabolism. Furthermore, the use of a consistent sample of newborns throughout time would reduce the potential influence of individual differences on the results. Increase the sample size and conduct the study in multiple hospitals across Palestine can improve replicability.

5. Conclusion

This study investigated the association between birth season and neonatal jaundice in the southern Gaza Strip of Palestine. There was a significant relationship between birth season and serum bilirubin levels, with indirect and total bilirubin being higher in the first two weeks of life in the spring and winter. Based on our data, we hypothesize that seasonality of birth is an environmental influence on neonatal jaundice. The risk of neonatal hyperbilirubinemia may increase in areas with short durations of sunlight.

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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