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Systemic Inflammatory Response and Time-Dependent Changes Following Exchange Transfusion in Newborns with Severe Indirect Hyperbilirubinemia

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Abstract

Background

Severe indirect hyperbilirubinemia may be associated with an increased systemic inflammatory response, particularly in newborns requiring exchange transfusion (ET).

Objective

To compare systemic inflammatory indices between infants undergoing ET for indirect hyperbilirubinemia and controls and to evaluate time-dependent changes in these indices after ET.

Methods

This retrospective case-control study was conducted in a tertiary-level neonatal intensive care unit between January 2020 and December 2024. Systemic inflammatory indices, including the systemic immune–inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune inflammation value (PIV), were calculated at baseline in infants who underwent ET and in matched controls. In the ET group, these indices were also assessed at 1–6, 6–24, and 24–48 hours following ET. Receiver operating characteristic (ROC) analysis was performed to determine optimal cut-off values, sensitivity, and specificity of the indices for predicting ET requirement.

Results

Eighty infants were included in the study: 40 in the ET group and 40 in the control group. GA, BW, mode of delivery, and gender of the study infants were comparable between the groups. Infants in ET group had significantly higher SII ($p = 0.017$), SIRI ($p = 0.013$), and PIV ($p = 0.009$) values compared to the control group. After ET, SII and PIV decreased sharply within 6 h and then increased gradually during follow-up, without returning to pre-ET levels at 24 to 48 hours. However, SIRI reached its nadir at 6–24 hours and returned to baseline by 24–48 hours. ROC analysis yielded cut-off value of 666 for SII (80% sensitivity, 67% specificity; AUC = 0.766), 2.98 for SIRI (75% sensitivity, 73% specificity; AUC = 0.803), and 786 for PIV (75% sensitivity, 67% specificity; AUC = 0.749) (all $p < 0.001$).

Conclusions

Severe indirect hyperbilirubinemia is associated with increased systemic inflammation, and ET modulates the inflammatory response in an index-specific and time-dependent manner. Further prospective studies are warranted to clarify the clinical implications of these findings.

Introduction

Neonatal jaundice is one of the most common clinical conditions in the neonatal period. Delayed diagnosis or inadequate treatment substantially increases the risk of progression to severe hyperbilirubinemia and, consequently, the likelihood of developing bilirubin-induced neurologic dysfunction (BIND) (1). Despite increased awareness, the use of screening nomograms, and widespread implementation of phototherapy, severe hyperbilirubinemia and bilirubin encephalopathy remain important causes of morbidity and mortality in newborns (2). Exchange transfusion (ET), which is performed when the response to phototherapy is insufficient, rapidly reduces bilirubin levels but carries a significant risk of serious complications (3, 4).

Emerging evidence suggests that severe hyperbilirubinemia may be associated with a systemic inflammatory response in newborns. Hemolytic processes, oxidative stress, and the cellular toxic effects of unconjugated bilirubin may trigger neutrophil activation, endothelial dysfunction, and the release of proinflammatory cytokines (5, 6). Animal studies have demonstrated a direct biological link between inflammatory responses and neurovascular dysfunction, supporting the concept that hyperbilirubinemia is not merely a metabolic condition but may also be associated with systemic inflammation and tissue responses (7). Clinical studies have further shown that inflammatory responses can be more pronounced in cases of severe hyperbilirubinemia, reporting a positive correlation between total serum bilirubin levels and the proinflammatory marker TNF-α (8). In addition, in hyperbilirubinemia associated with hemolysis (e.g., G6PD deficiency), significant associations have been reported between systemic inflammatory indices (such as NLR and SII) and enzyme levels, suggesting that inflammatory responses may be more prominent in the setting of concomitant hemolysis (9).

Therefore, growing evidence suggests that hyperbilirubinemia may be linked to systemic inflammatory responses; however, this relationship has not been clearly elucidated. Systemic inflammatory indices, which are readily available, cost-effective, and reproducible markers derived from routine laboratory parameters, have emerged as valuable tools for assessing inflammatory status in various neonatal conditions, including neonatal sepsis, necrotising enterocolitis and hypoxic ischemic encephalopathy (10, 11, 12). Despite their increasing use, data regarding whether these indices differ in newborns with severe indirect hyperbilirubinemia are scarce. Moreover, although ET is known to rapidly reduce serum bilirubin levels, its impact on systemic inflammation remains largely unexplored. Clarifying these associations might be useful for improving the understanding of the underlying pathophysiology, refining risk stratification, and potentially guiding clinical decision-making in the management of newborns with severe indirect hyperbilirubinemia.

The primary aim of this study was to evaluate whether systemic inflammatory indices differ in newborns with severe indirect hyperbilirubinemia and to examine the effects of exchange transfusion on these indices.

Materials and methods

This retrospective cohort study was conducted in a tertiary-level neonatal intensive care unit between January 2020 and December 2024. This retrospective study was approved by the Ethics Committee of (Ankara Bilkent City Hospital, Turkey) (Approval No: TABED1-24-815, Date: 18/12/2024).

Infants who underwent ET for indirect hyperbilirubinemia were included. Indications for ET were determined according to national neonatal jaundice management guidelines (13,14), based on postnatal age, total serum bilirubin levels, gestational age, and associated risk factors. Infants with congenital malformations or genetic syndromes, metabolic disorders, clinical or laboratory evidence of sepsis, necrotizing enterocolitis, or other inflammatory or hematologic conditions were excluded, as were infants with incomplete laboratory data.

The control group consisted of gestational age- and birth weight–matched newborns born during the study period who did not require phototherapy and had no evidence of infection or inflammatory disease.

Demographic and clinical data, including gestational age, birth weight, sex, mode of delivery, indication for ET, and ET-related complications, were retrieved retrospectively from medical records.

Systemic Inflammatory Indices

Systemic inflammatory indices were calculated from peripheral complete blood count parameters. The systemic immune–inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune–inflammation value (PIV) were calculated using established formulas: SII = platelet × neutrophil / lymphocyte; SIRI = neutrophil × monocyte / lymphocyte; and PIV = platelet × neutrophil × monocyte / lymphocyte. All indices were expressed as dimensionless values (15).

Study Protocol

Baseline systemic inflammatory indices were compared between the ET and control groups. In the ET group, the indices were assessed serially at 1–6, 6–24, and 24–48 hours following ET.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using Kolmogorov–Smirnov or Shapiro–Wilk test. Continuous variables were presented as median (interquartile range, IQR) since they were not normally distributed. Categorical variables were summarized as counts and percentages. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Time-dependent changes in systemic inflammatory indices in ET group was analyzed using the Friedman test due to repeated measurements. Receiver operating characteristic (ROC) analysis was used to calculate the optimal cut-off values, sensitivity, and specificity of systemic inflammatory indices to predict ET. A p value of < 0.05 was considered statistically significant.

Results

A total of 80 newborns were included in the study, comprising 40 infants in the ET group and 40 in the control group. Baseline demographic characteristics including gestational age, birth weight, mode of delivery, and gender were summarized in Table 1 and did not differ significantly between the groups ($p>0.05$).

The most common indication for ET was ABO incompatibility (n=14, 35%), followed by Rh incompatibility (n=10, 25%) and subgroup incompatibility (n=6, 15%). Prematurity and glucose-6-phosphate dehydrogenase deficiency were less frequent indications (n=3 each, 7.5%). Other causes accounted for 10% of cases, and no metabolic disease, pyruvate kinase deficiency, or hemoglobinopathy was identified. ET-related complications included thrombocytopenia (n=21), sepsis (n=7), hypocalcemia (n=2), and thrombosis (n=2). S**ome infants experienced more than one complication.**

Infants in the ET group had significantly higher SII, SIRI and PIV values compared with the control group ($p=0.017$, $p=0.013$ and $p=0.009$; respectively) (►Figure 1).

Time-dependent changes were observed in systemic inflammatory indices following ET. SII and PIV values decreased sharply after ET within 6 hours, reaching their lowest values at this time point, and then gradually increased during the 6–24 and 24–48 hour intervals. However, neither index returned to pre-exchange levels during follow-up. In contrast, SIRI values began to decline after ET, reached their nadir at 6–24 hours, and subsequently increased, returning to pre-ET values within 24–48 hours (►Figure 2).

ROC analysis demonstrated that systemic inflammatory indices had predictive ability for identifying infants who underwent ET. The optimal cut-off value for SII was 666, yielding 80% sensitivity and 67% specificity (AUC = 0.766, $p<0.001$). SIRI showed the highest accuracy, with a cut-off of 2.98 providing 75% sensitivity and 73% specificity (AUC = 0.803, $p<0.001$). For PIV, the optimal cut-off value was 786, resulting in 75% sensitivity and 67% specificity (AUC = 0.748, $p<0.001$) (►Figure 3).

Discussion

In this study, infants who underwent ET exhibited elevated systemic inflammatory indices, including SII, SIRI, and PIV. Exchange transfusion was associated with distinct time-dependent changes in inflammatory indices. SII and PIV showed an immediate post-ET decrease followed by a gradual increase over 48 hours without reaching pre-exchange levels, whereas SIRI demonstrated a delayed decline and subsequently increased to return to pre-ET values by 24–48 hours. Overall, these findings indicate that infants requiring ET exhibit an enhanced inflammatory profile and that the inflammatory response following ET varies according to the specific index evaluated. To our knowledge, this is the first report describing time-dependent systemic inflammatory responses in neonates with indirect hyperbilirubinemia undergoing ET.

Neonatal hyperbilirubinemia is a complex clinical condition that could not be explained solely by bilirubin accumulation, as it also involves neurovascular and inflammatory processes. Preclinical studies have

demonstrated that elevated bilirubin levels can affect vascular network development, disrupt blood–brain barrier integrity, and alter cytokine profiles in the cerebrospinal fluid (7). In a neonatal rat model study conducted by Blondel et al., the jaundiced rats exhibited impaired vascular architecture, increased blood–brain barrier permeability, and elevated levels of proinflammatory cytokines such as IL-1β and TNF-α (7). These findings indicate a direct biological link between hyperbilirubinemia and inflammatory responses and neurovascular dysfunction, supporting the concept that neonatal hyperbilirubinemia might represent more than a purely metabolic condition and may also be associated with systemic inflammation and tissue responses.

In the study by Abolurin et al., a rapid and marked decline in serum bilirubin following ET was reported, and this effect was attributed primarily to the mechanical removal of circulating bilirubin rather than metabolic degradation (16). Beyond bilirubin clearance, the same mechanical exchange process may also partially eliminate cellular and humoral components such as erythrocytes, platelets, leukocyte subpopulations, and inflammatory mediators. In this context, the early post-ET decline observed in systemic inflammatory indices in our study may reflect a reduction in circulating inflammatory cellular load and may indicate a transient immunomodulatory or anti-inflammatory effect in infants with severe hyperbilirubinemia In our study, particularly, the marked decrease in SII and PIV to their lowest levels immediately after ET suggests that ET may exert a suppressive effect on the systemic inflammatory response in the acute period. This observation is biologically consistent with prior reports indicating that ET can reduce circulating proinflammatory mediators, endotoxins, and activated immune cells in severe inflammatory clinical conditions such as sepsis (17). The early reduction in SII and PIV could, at least in part, be related to dilutional effects and short-term alterations in circulating neutrophil and platelet counts, along with temporary suppression of platelet- and neutrophil-driven inflammatory pathways. Their subsequent partial rebound, without full normalization to baseline, may reflect gradual re-equilibration of inflammatory components, ongoing subclinical inflammatory activity, or delayed immune reconstitution. In contrast, the delayed nadir and subsequent normalization of SIRI may indicate differing kinetics in monocyte-related inflammatory processes, potentially reflecting slower redistribution dynamics of innate immune cells following ET. Overall, these findings support an enhanced inflammatory profile in infants requiring ET and highlight that post-ET inflammatory responses vary depending on the specific index evaluated. However, the tendency of some inflammatory indices to rise again during subsequent time intervals suggests that the inflammatory response is a dynamic process and that the underlying pathophysiological mechanisms may persist even after ET. This rebound may be explained by ongoing hemolysis, a rebound increase in bilirubin burden, post-ET stress response or concurrent clinical factors such as post-ET related complications.

Increasing evidence suggests that systemic inflammatory indices derived from complete blood counts are associated with the diagnosis and severity of inflammatory diseases in neonates. It has been reported that SII is associated with the severity of necrotizing enterocolitis and the need for surgical intervention, and similarly, that multiple systemic inflammatory indices have been evaluated in the diagnosis of late-onset neonatal sepsis (11,18). In another recent study, systemic inflammatory indices were found to be significantly elevated in severe clinical conditions observed in the neonatal intensive

care unit, such as sepsis, respiratory failure, and perinatal asphyxia, and these indices were shown to be associated with disease severity (19). In this context, our findings indicate that neonates with indirect hyperbilirubinemia who require ET display distinct systemic inflammatory index profiles and significant post-procedural temporal changes, suggesting that these indices may serve as supportive tools for identifying high-risk infants without replacing established clinical and laboratory criteria.

The strengths of our study include the comparison of neonates who underwent exchange transfusion (ET) with a control group, as well as the longitudinal evaluation of the same infants at serial time points during the post-ET period. However, the retrospective single-center design, the relatively limited sample size, and potential confounding factors such as the severity of hemolysis and the duration or intensity of phototherapy may restrict the generalizability of our findings. ROC analysis suggests that systemic inflammatory indices derived from complete blood count parameters may serve as supportive tools in identifying neonates who require ET. In particular, SII, SIRI, and PIV appear to provide complementary information regarding inflammatory burden beyond bilirubin levels alone. Nevertheless, these indices should not be considered stand-alone predictors. Accordingly, the proposed cutoff values should be regarded as exploratory and require validation in larger, prospective multicenter cohorts. Further studies are also needed to determine the clinical utility of integrating these indices into existing treatment algorithms. **Overall, these findings suggest that inflammatory indices may offer additional clinical insight in evaluating ET requirements and could support decision-making, particularly in borderline cases approaching ET thresholds.**

In conclusion, infants undergoing ET exhibit an enhanced systemic inflammatory profile, with distinct and index-specific temporal changes following ET. These findings indicate a complex and heterogeneous inflammatory response rather than a uniform effect of ET, with incomplete normalization of some indices suggesting persistent low-grade inflammation beyond the immediate post-ET period. Monitoring systemic inflammatory indices may provide additional insight into post-exchange inflammatory status. Further prospective studies are warranted to clarify their clinical relevance and potential role in risk stratification and follow-up.

Declarations

Ethics Statement

This retrospective study was approved by the Ethics Committee of Ankara Bilkent City Hospital, Turkey (Approval No: TABED1-24-815; Date: December 18, 2024). Due to the retrospective design of the study, the requirement for written informed consent was waived by the Ethics Committee. All data were anonymized prior to analysis, and patient confidentiality was strictly maintained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Şeyma Bütün Türk: Conceptualization, Methodology, Data curation, Writing – original draft.
Mustafa Şenol Akın: Supervision, Formal analysis.
Nazmiye Bengü Karaçağlar: Data curation, Investigation.
Laser Şanal: Methodology, Validation.
Hüsniye Neşe Yaralı: Investigation, Resources.
Evrim Alyamaç Dizdar: Supervision, Writing – review & editing.
Fatma Nur Sarı: Conceptualization, Supervision, Project administration.

Data Availability Statement

The data used in this study were obtained from the hospital database with appropriate measures taken to ensure the protection of personal data. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Table

Table 1. Demographic characteristics of the study groups

	ET (n=40)	Control (n=40)	p
Gestational age, week	37 (36-38)	37 (37-38)	0.14
Birth weight, g	2820 (2655-3325)	3040 (2835-3357)	0.081
Cesarean delivery, n (%)	20 (50)	19 (47.5)	0.82
Male gender, n (%)	20 (50)	19 (47.5)	0.82

Values are presented as median (interquartile range,**IQR) or n (%).**

Figures

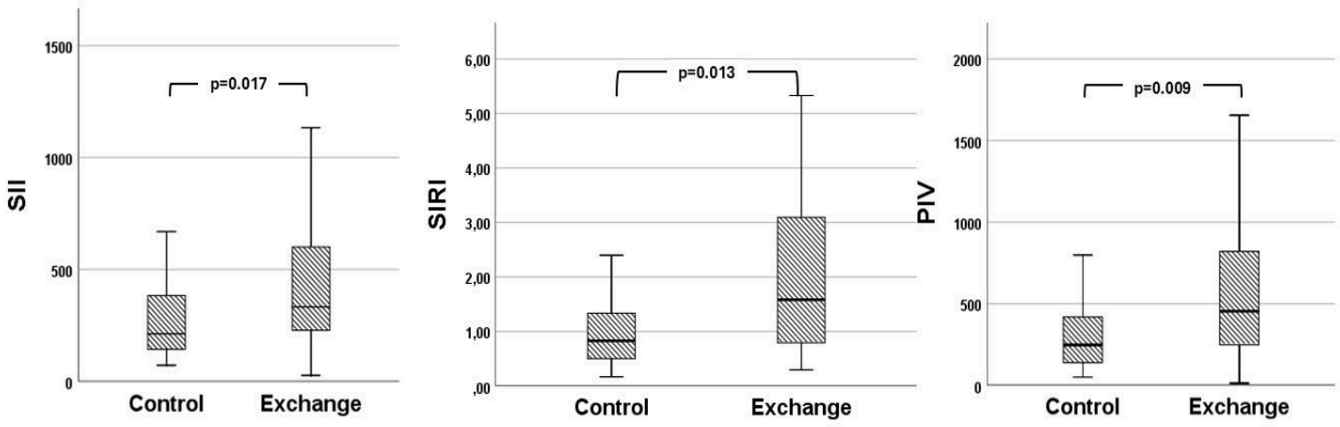


Figure 1

Systemic inflammatory indices of study groups

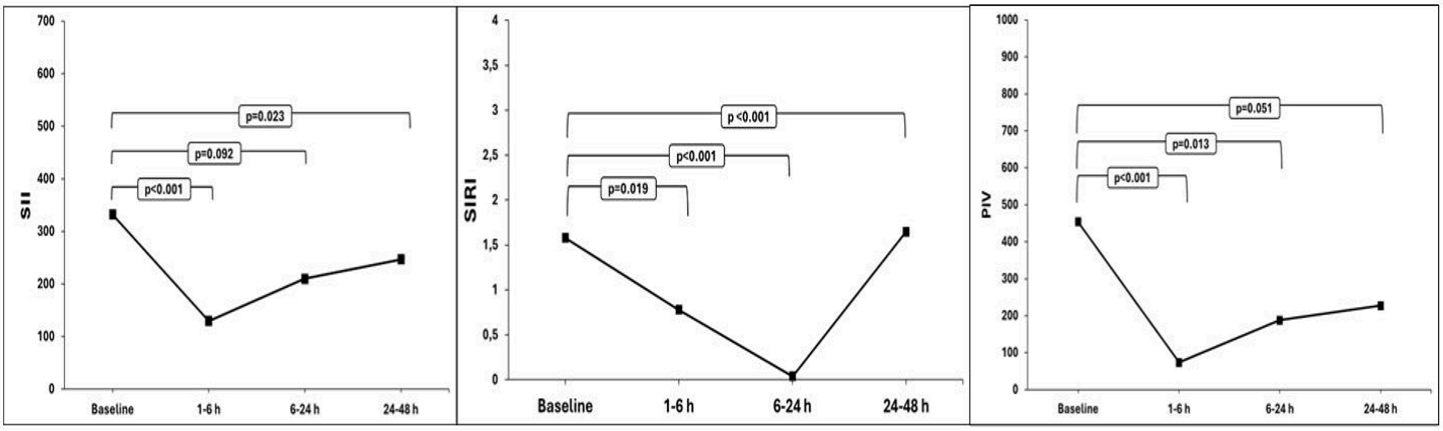


Figure 2

Time-dependent changes in systemic inflammatory indices following exchange transfusion

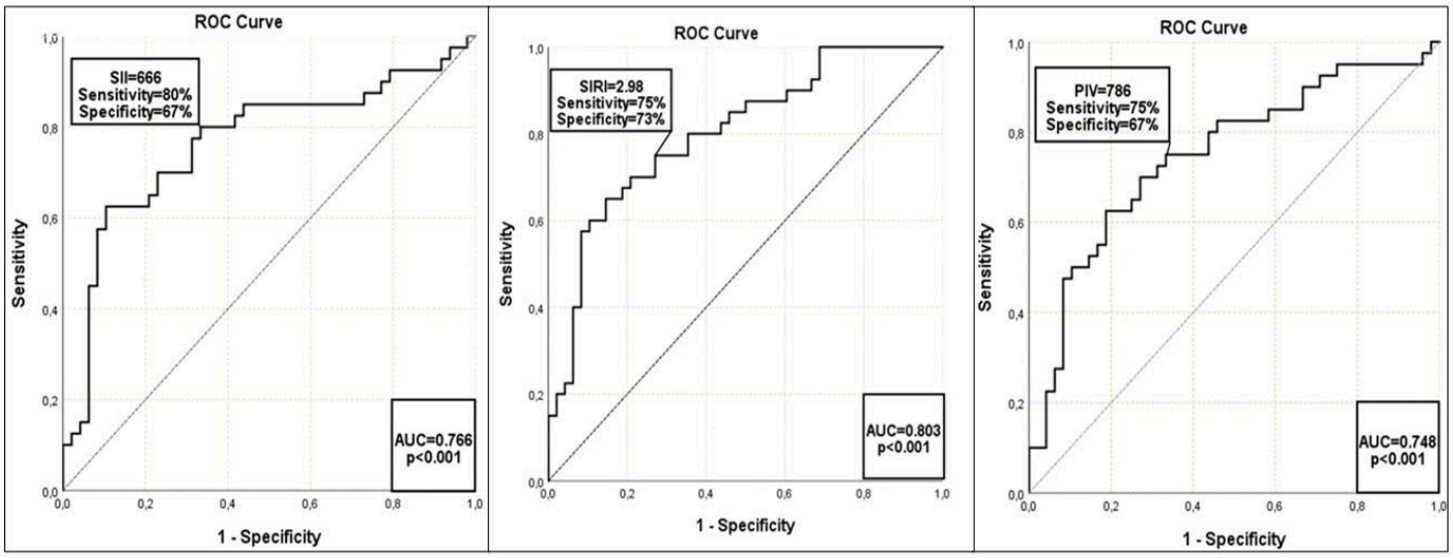


Figure 3

ROC curves of SII, SIRI and PIV to predict exchange transfusion