ORIGINAL RESEARCH

Need for Cautious Adoption of American Academy of Pediatrics Guidelines for Management of Neonatal Hyperbilirubinemia in Different Parts of the World

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Abstract

Background: Early hospital discharge (<72 hours following birth) of healthy-term and near-term infants is favored to promote family care but may have increased hyperbilirubinemia-related hospital readmissions. In this study, we compared the 2009 and 2022 American Academy of Pediatrics (AAP) discharge guidelines in the United Arab Emirates (UAE) for the impact on hyperbilirubinemia-related readmissions.

Materials and methods: This was a retrospective cohort single-center study conducted in the UAE. We reviewed records from the period January 2021 to November 2021; the infants included those with a gestational age (GA) ≥35 weeks and a birth weight (BW) ≥2,500 gms and GA ≥36 weeks/BW ≥ 2,000 gms. Infants were classified into risk zones based on pre-discharge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) levels (AAP 2009 hyperbilirubinemia nomograms). We compared the 2009 and 2022 AAP discharge thresholds for the needs for follow-up and readmissions for hyperbilirubinemia.

Results: We studied 895 newborns; 672 (75%) were born at term with a mean (± standard deviation) GA of 38 ± 1.3 weeks. Most (75.3%) were classified as appropriate for GA and 637 (71%) attended the 1st follow-up as recommended. Based on the 2009 AAP guidelines, 13 (2.9%) out of 447 (70%) were low risk; 12 (6.6%) out of 183 (29%) were low-intermediate risk; and 3 out of 7 (42.9%) were high-intermediate risk. A total of 49 (5.5%) infants were readmitted to the hospital for phototherapy. Unlike in the United States, the 2022 guidelines would have recommended follow-up visits within 2 days in a larger number [579 (64.7%)] than the 2009 recommendations [308 (34.4%)] in UAE; the overall need for phototherapy would also have been higher. However, the frequency of severe hyperbilirubinemia requiring phototherapy would have remained similar. Our population did not have more specific risk factors such as scalp bleeds, ABO isoimmunization, or glucose-6-phosphate dehydrogenase deficiency for developing severe neonatal hyperbilirubinemia. We did have a high number of missed follow-up appointments.

Conclusion: In our region, the adoption of the 2022 AAP early hospital discharge guidelines may have increased the number of follow-up visits within 2 days after discharge from the hospital and the overall need of phototherapy. These guidelines need to be specifically evaluated in different ethnic groups in various parts of the world.

Keywords: American academy of pediatrics, Bilirubin, Bilirubin encephalopathy, Direct antiglobulin test, Early discharge, Follow-up timing, Infant, Kernicterus, Low intermediate-risk, Middle East, Monitoring, Nomograms, Pre-discharge bilirubin, Readmission risks, Retrospective cohort study, Rhesus incompatibility, Serum bilirubin, Transcutaneous bilirubin.

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Keypoints

1. Hyperbilirubinemia is seen frequently in neonates; those with high bilirubin levels require close monitoring to prevent bilirubin-induced neurotoxicity.
2. We evaluated the 2009 and 2022 recommendations of the American Academy of Pediatrics (AAP) for early hospital discharge (≤72 hours after birth) on the rates of readmission for hyperbilirubinemia in the United Arab Emirates.
3. This retrospective single-center study included 895 infants with gestational age (GA) ≥35 weeks and birth weight (BW) ≥2,500 gms or GA ≥ 36 weeks/BW ≥2,000 gms.
4. In our population, the relatively liberal AAP 2022 guidelines for early hospital discharge have increased the number of follow-up visits for evaluation of hyperbilirubinemia and the overall need for phototherapy. We need to review and interpret these guidelines cautiously.

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Introduction

Hyperbilirubinemia is seen frequently in neonates and requires close follow-up, particularly within the first week of life.[1,2] Failure to promptly identify and manage it may lead to irreversible bilirubin-induced neurotoxicity (kernicterus), which can sometimes be fatal.[2,3]

Risk factors for significant neonatal hyperbilirubinemia include prematurity, low birth weight (BW), obscure sites of hemorrhage such as a large cephalohematoma, family history of neonatal hyperbilirubinemia, iso-immune hemolytic anemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[4] These infants are more likely to require readmission and treatment with phototherapy. Glucose-6-phosphate dehydrogenase deficiency, an inherited red blood cell enzymatic deficiency, has been seen in 7.4% of all infants in the United Arab Emirates (UAE). It can cause severe hyperbilirubinemia with a high risk of kernicterus.[4–6]

In infants with hyperbilirubinemia, the prediction of a sudden and significant rise in the TSB levels remains challenging.[7,8] In recent years, we have followed the recommendations of the AAP for early discharge of newborn infants from hospitals to promote family care. Bhutani et al.[1] developed nomograms (1999) to predict the risk of neonatal hyperbilirubinemia in 2,840 healthy-term and near-term neonates eligible for discharge between 24 and 72 hours of age. The authors recommended measuring pre-discharge serum bilirubin and evaluating the associated risk factors to provide hour-specific serum bilirubin thresholds and risk zones. These guidelines were modified in 2009, incorporating additional risk factors for neurotoxicity, such as sepsis, low serum albumin, clinical instability, and iso-immune hemolytic anemia.[9] The importance of pre-discharge bilirubin screening using TSB or transcutaneous bilirubin (TcB) measurements was stressed. Specific follow-up guidelines were also provided to assess the risk of subsequent severe hyperbilirubinemia.[9] All these additions resulted in a lower threshold for initiating phototherapy.[9–12] A new set of guidelines was introduced in 2022 for managing hyperbilirubinemia in infants born at ≥35 weeks' gestation.[4] The authors defined two new calculated metrics, "delta TSB" and "delta TcB," as the difference between the bilirubin concentrations measured by biochemical or estimated by a transcutaneous method. These are useful to predict the need for phototherapy. The pre-discharge evaluation of all neonates at risk of significant hyperbilirubinemia should include gestational age (GA), risk factors for neurotoxicity, and the delta TSB or TcB to determine the interval between discharge and follow-up, as well as the need for additional bilirubin measurements.

In our region in the Middle East, these newer guidelines seem to have increased, not lowered, the likelihood of readmissions particularly when the infants were discharged within 72 hours after birth.[8,9] To the best of our knowledge, no studies in our region have neither validated the 2022 AAP follow-up recommendations nor compared these with the hour-specific bilirubin nomogram suggested in the 2009 guidelines.[4,9] In this retrospective medical record-based cohort study, we compared the 2009 AAP hour-specific nomogram of pre-discharge bilirubin levels, which is currently employed in our hospital, with the 2022 AAP delta TSB recommendations to determine whether either of these guidelines was better for predicting significant neonatal hyperbilirubinemia. To ascertain that the two cohorts were comparable, we tabulated the risk factors associated with substantial neonatal hyperbilirubinemia in the two groups.

Materials and Methods

This retrospective, medical record-based cohort single-center study was conducted between January 2021 and November 2021 in the well-baby nursery at Tawam Hospital. The hospital is one of the largest tertiary teaching hospitals in the UAE, with ~ 2,300 deliveries annually. All necessary hospital/institutional review board permissions for the study were obtained before the initiation of the study (reference: KD/AJ/877).

We have been using the 2009 AAP guidelines in our nursery; the universal TcB screening is performed on all newborn infants at 18 hours of age. If the TcB levels were recognized as high based on the 2009 AAP hour-specific bilirubin nomogram or if specifically requested by the clinicians, TSB measurements were obtained. The last TSB levels prior to discharge were compared based on the 2009 AAP and the 2022 AAP thresholds. For this study, we defined "significant hyperbilirubinemia" when there was an indication for readmission to the hospital for phototherapy or exchange transfusion.

Inclusion Criteria

- Gestational age ≥35 weeks with BW ≥2,500 gms.
- Gestational age ≥36 weeks with BW ≥2,000 gms.

Exclusion Criteria

- Requirement of phototherapy during the initial newborn admission.
- Transfer to the neonatal intensive care unit (NICU) for any medical or surgical conditions.
- Neonates with major or multiple congenital anomalies.

Data Collection

The data were retrieved from the electronic medical records of all neonates born during the study period. These included demographic details, such as gestational age, BW, and the last TSB or TcB levels prior to discharge. Transcutaneous bilirubin measurements were performed using the JM instruments (Draeger, Inc.). The blood sample was obtained by a heel stick performed by an experienced laboratory technician or nurse, and serum bilirubin concentrations were measured using the standard direct spectrophotometry.

To make clinical decisions, we compared the bilirubin levels with the established risk zones in the 2009 AAP guidelines. In addition, we also computed the delta TSB as recommended by the 2022 AAP guidelines to assess the variance between the bilirubin level at discharge and the phototherapy thresholds. The follow-up strategies were defined and compared per the 2009 and 2022 AAP guidelines.[4,9] Infants who attended the follow-up clinic visits within the recommended time frame or earlier were monitored for the development of severe hyperbilirubinemia. We also evaluated the risk factors associated with the development of severe hyperbilirubinemia.

Continuous data were reported as mean ± standard deviation (SD). Nominal variables were reported as numbers and percentages and were compared using the Pearson Chi-square test or the Fisher's exact test for small values. All statistical analyses were performed using the Stata 17 software (StataCorp, Texas, USA), and a two-sided *p*-value was used to define statistical significance.

Results

In the study period from January 1, 2021 to November 21, 2021, a total of 2,110 neonates with a GA ≥35 weeks and a BW >2,000 gms were born at Tawam Hospital**.** Of these, 1,063 were excluded based on pre-defined criteria. Although the remaining 1,047 neonates met the inclusion criteria, 152 (14.5%) babies missed their first follow-up visit and hence, had to be excluded. All the remaining 895 infants had measurements of TcB and TSB in the hospital before discharge (Fig. 1).

Among the 895 infants enrolled (Table 1), 672 (75%) were born full-term with a GA ± SD 38 ± 1.3 weeks and a BW of

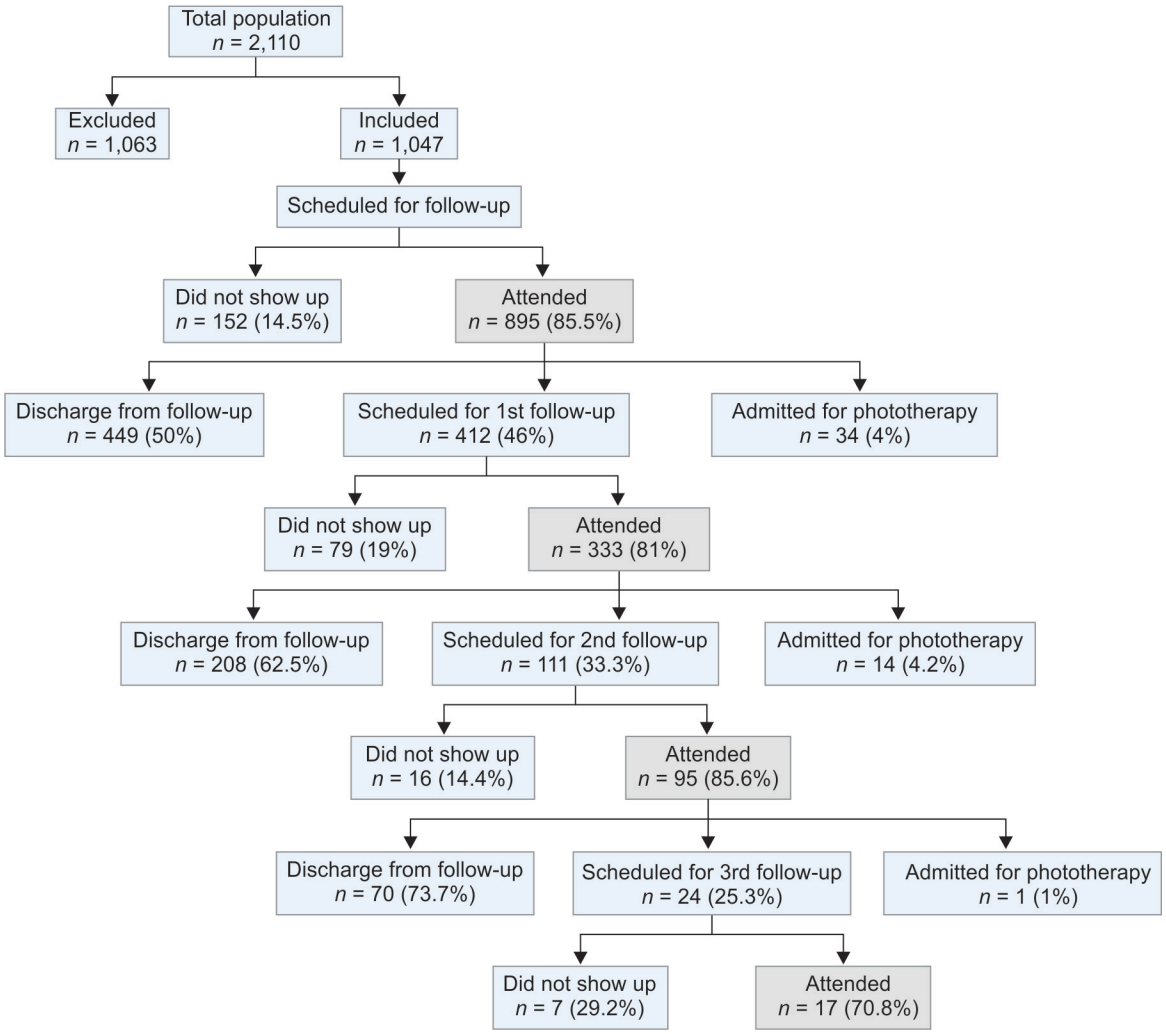

Fig. 1: Flow diagram of neonates with hyperbilirubinemia using the 2009 AAP guidelines

Table 1: Characteristics of 895 neonates with hyperbilirubinemia results expressed as number (percent) or mean ± standard deviation

Characteristics	*Results*
Gender	
Male	477 (53%)
Female	418 (47%)
Gestational age	38 ± 1.3 weeks
35–37 weeks	180 (20%)
38–40 weeks	672 (75%)
>41 weeks	43 (4.1%)
Birth weight	3,132 ± 449 gms
AGA	674 (75.3%)
SGA	204 (22.8%)
LGA	17 (1.9%)
Feeding	
Breastfeeding	805 (90%)
Formula feeding	8 (0.9%)
Mixed	82 (9.1%)
Mode of delivery	
Vaginal delivery	621 (69.4%)
Cesarean section	274 (30.6%)
Median age for the first bilirubin measurement	110 ± 60 hours

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small-for-gestational age

3,132 ± 449 gms. Four hundred and seventy-seven (53%) were males. Two hundred and four (22.8%) were small-for-gestational age (SGA). Vaginal deliveries accounted for 621 (69.4%), whereas C-sections were needed for 274 (30.6%). A large majority (805; 90%) received exclusive breastfeeding before hospital discharge. The median age for the bilirubin measurement was 110 ± 60 hours.

Out of the 895 newborns, 49 well newborns (5.5%) required readmission for phototherapy. The associated risk factors are displayed in Table 2. Small-for-gestational age status, gender, or the type of feeding did not predict readmission. Maternal diabetes

Table 2: Risk factors for readmission for phototherapy

Risk factors	*Required phototherapy (n = 49)*	*No phototherapy required (n = 846)*	*p-value*
Birth weight			0.46
AGA	31 (63%)	643 (76%)	0.22
SGA	18 (37%)	186 (22%)	0.22
LGA	0 (0%)	17 (2%)	1.0
Gestational age			
35–37 weeks	23 (47%)	157 (19%)	<0.001
38–40 weeks	26(53%)	646 (76%)	
>41 weeks	0	43 (5%)	
Gender			
Male	26 (53%)	451 (53%)	0.81
Female	23 (47%)	395 (47%)	
Mode of delivery			
Vaginal delivery	33 (67%)	588 (69%)	
Cesarean section	16 (33%)	258 (31%)	0.66
Feeding			
Breastfeeding	43 (88%)	762 (90%)	
Formula milk	0	8 (1% anker)	0.51
Mixed	6 (12%)	76 (9%)	
IDM	21 (42%)	240 (28.4%)	0.052
Cephalohematoma	2 (4%)	8 (0.9%)	0.10
ABO incompatibility	2 (4%)	61 (7.2%)	0.28
Rh incompatibility	0	18 (2.13%)	0.62
DAT positive	0	11 (1.3%)	1.00

AGA, appropriate for gestational age; DAT, direct antiglobulin test; IDM, Infant of diabetic mother; LGA, Large for gestational age; SGA, small-for-gestational age

Table 3: Outcomes of the 249 newborn infants tested for G6PD deficiency

G6PD	*Number (%)*	*Required phototherapy n = 43*	*No phototherapy required n = 206*	*p-value*
Deficiency	28 (11.2%)	2 (4.7%)	26 (12.6%)	0.18
Normal	221 (88.8%)	41 (95.3%)	180 (87.4%)	

Fisher's exact test

was present in 21 (42%) of the 49 neonates who were treated with phototherapy. None of the infants who required phototherapy had Rhesus incompatibility or a positive direct antiglobulin test (DAT).

Glucose-6-phosphate dehydrogenase testing was performed in 249 newborns (Table 3). A total of 28 babies (11.2%), all of whom were males, were identified as G6PD-deficient. Only 2 (4.7%) G6PD-deficient newborns required admission for phototherapy.

The number of infants identified to be at risk of developing severe hyperbilirubinemia before discharge using the risk zones outlined in the AAP 2009 guidelines are presented in Table 4 and Figure 2. The proportion of those in the high-intermediate risk zone who needed phototherapy looks large but the absolute numbers are small (3; 42.9%).

Compared with 2009, the 2022 AAP guidelines have significantly increased early (<2 days) follow-up visits (Table 5). Among the 895 neonates in our study, 637 (71%) had their 1st follow-up visits per the 2009 AAP recommendations. The median follow-up time

Table 4: Risk zones of developing hyperbilirubinemia before discharge as per 2009 AAP guidelines in our hospital results expressed as number of neonates (percentage)

Risk zones	*Total*	*Required phototherapy*
High risk	0	0
High-intermediate	7 (1%)	3 (42.9%)
Low-intermediate	183 (29%)	12 (6.6%)
Low risk	447 (70%)	13 (2.9%)
Total	637 (100%)	28 (4.4%)

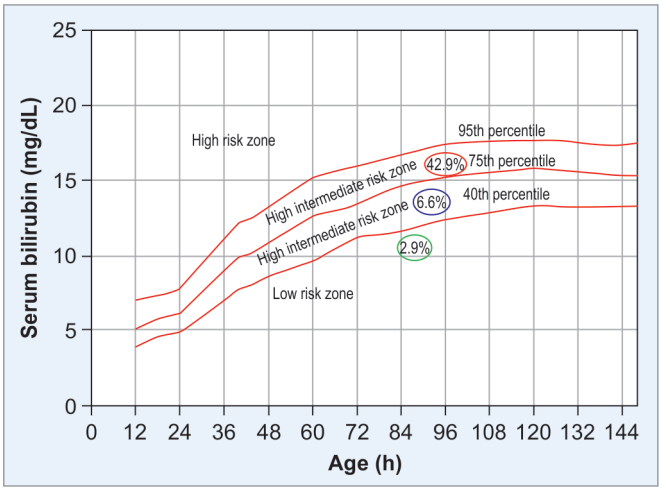

Fig. 2: Percentage of neonates in the different risk zones at risk of developing significant hyperbilirubinemia based on the risk factors (2009 AAP)

Table 5: Follow-up recommended by AAP 2009 vs 2022 guidelines

	2009 AAP		*2022 AAP*	
Timing of follow-up	*Number of infants*	*Percentage*	*Number of infants*	*Percentage*
<1 day	4	0.45%	22	2.46%
<2 days	308	34.41%	579	64.69%*
2–3 days	572	63.91%	286	31.96%*
>3 days	11	1.23%	8	0.89%
Total	895	100	895	100

*$p < 0.05$

following discharge was 104 hours (range 11–178); 28 infants (4.4%) developed severe hyperbilirubinemia. Application of the 2022 AAP recommendations has increased the number of follow-up visits and the overall need for phototherapy. The number of infants who would have been treated with phototherapy severe hyperbilirubemia was similar (Table 6).

Three hundred and thirty-three neonates were seen in the 2nd follow-up appointment. Fourteen (4.2%) were readmitted due to severe hyperbilirubinemia.

Discussion

In our region in the Middle East, neonatal hyperbilirubinemia seems to occur more frequently and reaches higher levels than in the West. Adopting the Bhutani guidelines seems to have actually increased the likelihood of readmissions, particularly when the

Table 6: Development of severe hyperbilirubinemia in neonates who presented earlier or at the recommended time after hospital discharge. The numbers below compare the 2009 and 2022 guidelines

Guideline	*Number of neonates presented at 2–3 days after birth*	*Number (%) admitted for phototherapy*
2009 AAP	637	28 (4.4%)
2022 AAP	557	24 (4.3%)

infants were discharged within 72 hours after birth.[8,9] To the best of our knowledge, no studies in our region have validated the 2022 AAP follow-up recommendations or compared these with the hour-specific bilirubin nomogram suggested in the 2009 guidelines.[4,9]

In our region, the proportion of infants in the high- and low-intermediate hyperbilirubinemia zones have been higher than those reported by Bhutani et al.[4,10] In this cohort, our absolute numbers are small, but there were more neonates with pre-discharge bilirubin levels in the high-intermediate risk (42.9 vs 12.9%; phototherapy was needed in 29 vs 19.5%, respectively) and the low-intermediate zone than in the Bhutani cohort (70 vs 61.8%, respectively; need for phototherapy in 6.6% vs none). Significant hyperbilirubinemia was seen in 2.9 vs 2.2%, respectively.

We noted that late-preterm newborns were 2.5 times more likely to require phototherapy, which is consistent with previous reports and a meta-analysis that highlighted prematurity as a risk factor for neonatal hyperbilirubinemia.[13–15] This increased risk is attributed to hepatic immaturity affecting bilirubin conjugation.[13,15] However, in contrast to findings from a systematic review demonstrating that 70% of babies requiring phototherapy were male, we did not find any significant gender-based discrepancy.[14] Unlike other similar studies, ABO incompatibility, Rhesus incompatibility, or a positive DAT were not significant contributors to hyperbilirubinemia.[16]

Unlike previous reports,[14] we did not identify G6PD deficiency as a significant contributor to the development of significant hyperbilirubinemia in this cohort. Glucose-6-phosphate dehydrogenase deficiency was identified in 11.2% of our cohort, which is similar to earlier reports from our region.[17,18] In our cohort, G6PD deficiency was seen only in males, even though some female patients have been identified in previous studies; Amro et al.[18] reported a prevalence of 11.6% in males and 3.6% in females.

Nearly 90% of our newborns were exclusively breastfed on discharge, which may represent the effective education, counseling, and support to the mothers on the benefits of breastfeeding. In our study, exclusive breastfeeding was not associated with an increased risk of hyperbilirubinemia. These results contrasted with earlier studies,[18–20] which showed a higher incidence of hyperbilirubinemia in breastfed than in formula-fed infants. The use of delta TSB or TcB for monitoring as suggested in the 2022 AAP guidelines doubled the number of follow-up visits from 34 to nearly 65% of infants within the initial 48 hours.[4,9,10] However, the rates of readmission for phototherapy remained comparable.[4,9,10]

Our research does have some limitations. Although this study has been conducted in a large hospital in the UAE, it was a single-center report from a single country. Within our population, variations in health insurance schemes create difficulties in reimbursements for planned follow-up visits. Consequently, 24% of infants could not attend their initial follow-up appointments and 3% missed subsequent follow-up visits. Moreover, G6PD tests are not systematically indicated in our institution and were conducted on only 27.8% of infants; it is difficult to be certain about its prevalence and association with neonatal hyperbilirubinemia.

Conclusion

In our region in the Middle East, neonatal hyperbilirubinemia seems to occur more frequently than in the West and there is a need for further studies to identify its causes. There is a need for cautious adoption of the Bhutani guidelines in different parts of the world as it could increase the likelihood of readmissions following early discharge. Considering the higher bilirubin levels and the difficulties in follow-up, we need to be cautious in adopting the 2022 AAP guidelines in our region; further prospective studies are needed to create a tailored nomogram specific to our population. Additionally, the significant number of missed follow-up visits emphasizes the need for effective home monitoring of these infants.

Declarations

Ethics Approval

It was granted by the Institutional Review Board (reference: KD/AJ/877). Informed consent was waived as it was a retrospective anonymized medical record review.

Authors' Contribution

Dr Ola Shahrour: Contributed to the design of the work, data collection, data analysis, and interpretation, drafting of the article, critical revision of the article, and approved the final version to be published.

Dr Hassib Narchi: Contributed to the design of the work, data analysis and interpretation, drafting of the article, critical revision of the article, and approved the final version to be published.

Dr Zohra Siwij: Contributed to the design of the work, data analysis and interpretation, drafting of the article, critical revision of the article, and approved the final version to be published.

Dr Mustafa Abdullatif: Contributed to the design of the work, data analysis and interpretation, drafting of the article, critical revision of the article, and approved the final version to be published.

Dr Aiman Ben Ayad: Contributed to the drafting and critical revision of the article and approved the final version to be published.

Dr Aiman Rahmani: Contributed to the drafting of the article, critical revision of the article, and approved the final version to be published.

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Dr Alaa Sattar and Dr Amna Al Ani helped in data collection and interpretation.

Data Availability

Data availability can be made available by the corresponding author upon a reasonable request.

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