Cross-sectional Study

Assessment and comparison of mortality and short-term outcomes among premature infants before and after 32-week gestation: A cross-sectional analysis

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ABSTRACT

Background: Prematurity is a major cause of neonatal morbidity and mortality. The aim of this study is to assess the rate of prematurity and determine the mortality rate and short-term outcomes among premature infants admitted at King Abdullah University Hospital (KAUH) in Jordan.

Materials and methods: A retrospective cross-sectional review of all premature infants admitted at KAUH between August 2016 and August 2018 was conducted. Collected data include characteristics, medical interventions, morbidities, mortality, and discharge outcomes. Included infants were divided into two groups: less than 32-week gestation (group 1) and ≥32-week gestation (group 2). The outcomes were compared between both groups and reported accordingly.

Results: Out of 7020 newborns, 1102 were delivered before 37-week gestation, representing a prematurity rate of 15.7%. The mean gestational age and birth weight were 33.8 weeks and 2116 grams respectively. Group 1 comprised 13%. Late preterm infants (gestational age 34 to 36 6/7 weeks) accounted for 74%. The mortality rate was 4.6%. More infants died from group 1 (29% vs. 1.5%, p < 0.05). Group 1 infants had higher rates of respiratory distress syndrome (92% vs. 30%), bronchopulmonary dysplasia (28.4% vs. 1.1%), severe intraventricular hemorrhage (5.9% vs. 0.1%), high-stage retinopathy of prematurity (6.6% vs. 0.2%), necrotizing enterocolitis (9.2% vs. 0%), and sepsis (18.4% vs. 2.1%). At discharge, there was a significant difference in the length of stay, corrected gestational age, and weight in favor of group 2 (p < 0.05).

Conclusions: Although high rate of prematurity was observed, the majority were late preterm with reassuring outcomes. Compared with >32-week infants, the mortality and short-term complications were more frequent among those born before 32 weeks. Still, the overall mortality rate and risk of morbidities were reasonable. Population-based analysis of the risk factors among the more vulnerable very preterm and extremely premature infants is recommended to better understand the outcomes.

1. Introduction

Prematurity remains the leading cause of mortality in the first month of life and the second most common cause of infant mortality [1,2]. The advance in neonatal care over the past few decades has increased the survival rate of more premature infants. The introduction of invasive and non-invasive ventilatory support, antenatal steroids, and postnatal surfactant administration have significantly led to increasing survival and decreasing mortality. Consequently, more short-term and long-term complications have been seen among this group of infants [3].

According to the WHO, nearly 15 million premature babies are born each year all around the world of whom one million don’t survive beyond the neonatal period. Globally, the reported rate of prematurity is from 5 to 18%. In the US, 10–12% of the newborns are delivered prematurely [2]. According to the EMRO statistics, neonatal mortality continues to comprise nearly 50% of all under-5 deaths in Jordan with prematurity being responsible for nearly half of these mortalities. In the majority of cases, neonatal deaths are preventable if optimal neonatal care is provided [4].

The outcome of prematurity depends on the exact gestational age (GA) and birth weight. Prematurity, defined as birth before completed 37-week gestation, is categorized into late preterm (34–36.6 weeks),

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moderate (fractionated inspired oxygen of 21% to intraparenchymal extension or periventricular infarction. Germinal matrix bleeding, grade 2 to intraventricular bleeding without dilatation, grade 3 to intraventricular bleeding with dilatation, and grade 4 to intraparenchymal extension or periventricular infarction. Severe IVH refers to grade 3 or 4. Cystic PVL refers to periventricular cystic lesions seen by ultrasonographic brain assessment at one month of age or later [18].

The International classification of ROP was utilized in assessing the stage of ROP with stage 1 referring to demarcation line, stage 2 to visible ridge, stage 3 to ridge blood vessels, stage 4 to subretinal detachment, and stage 5 to total retinal detachment. High-stage ROP refers to stage 3 and above [19]. Our policy is to perform dilated eye exam for ROP screening for all premature infants with GA ≤32 weeks or birth weight of ≤1500 g at the age of 28 days or PCA of 32 weeks whichever comes later.

NEC was diagnosed according to Bell’s classification system and we only included definitive cases of stage 2 (pneumatositis intestinalis or portal venous gas) or stage 3 (pneumoperitoneum) [20].

Sepsis was defined as bacterial isolation from blood or cerebrospinal fluid (CSF) samples. Early-onset sepsis (EOS) refers to any case of sepsis in the first 72 hours of life while late-onset sepsis (LOS) used for cases diagnosed after 72 hours [21].

For calculating the rates of outcomes that pertain to specific PCA such as IVH, ROP, and BPD, we only included infants who survived till screening was done or until that particular age was achieved.

An Institutional Review Board (IRB) approval was obtained from Jordan University of Science and Technology (IRB number 611–2020). Parental consent was waived as this study involves chart review. Patient data privacy and confidentiality are maintained as this study was conducted in compliance with the ethical standards per Helsinki declaration. This report is based on STROCSS 2019 guideline [22], and has been registered at Research Registry database with unique identification number 6000.

Statistical analyses were performed using IBM SPSS Statistics Software version 25 (IBM Corp., Armonk, N.Y, USA). Continuous variables were reported as means ± standard deviation, whereas categorical variables as frequency distributions and proportions. A p value of 0.05 was considered statistically significant. To examine the significance of association between categorical variables, Pearson chi square test was used, while student’s t-test and ANOVA were applied to examine the significance level for continuous variables.

2. Methods

We conducted a retrospective descriptive analysis of all premature infants who were delivered at KAUI in North of Jordan in the period August 2016 to August 2018. KAUI is the major tertiary academic institution in North of Jordan. Through its 620 beds, it provides access to healthcare services for nearly two million of the Jordanian population with an annual birth of approximately 3500. A list for all newborns who were delivered before 37-week gestation was obtained from the hospital electronic database and included in our analysis. We excluded infants born before 24 weeks of gestation and preterm infants who were born alive and died before admission to the NICU. The GA was determined as documented in the medical records of the pregnant mothers and their newborns. Included infants were subdivided into very preterm to extremely preterm group for babies delivered at less than 32-week gestation (Group 1), and moderate to late preterm group for those delivered between 32 and 36 6/7-week gestation (Group 2).

In addition to survival rate, outcomes of interest reported in our analysis include respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and sepsis.

RDS diagnosis was used in any case exhibiting signs of respiratory distress and typical radiographic findings of hyaline membrane disease including reticulogranular shadows and/or air bronchogram. BPD was defined in any baby with oxygen dependence at 28 days of life and classified according to the oxygen requirement at 36-week post-conceptional age (PCA) or at discharge into: mild BPD (room air), moderate (fractionated inspired oxygen of 21–30%) and severe (fractionated inspired oxygen of more than 30%) [17].

For IVH diagnosis, our unit’s policy is to perform head ultrasonography screening for all premature infants with GA ≤32 weeks or birth weight ≤1500 grams between the 7th and 10th day of life. IVH was graded according to Papile’s classification with grade 1 referring to germinal matrix bleeding, grade 2 to intraventricular bleeding without dilatation, grade 3 to intraventricular bleeding with dilatation, and grade 4 to intraparenchymal extension or periventricular infarction.

During the study period, a total of 1102 premature babies were delivered at our institution. With a 7020 total number of deliveries during the study period, the prematurity rate was 15.7%. Of those, 815 (74%) were born at late preterm gestation. Very preterm and extremely preterm infants comprised 9% and 4% respectively. 54% were males. 815 (74%) were born by CS. VLBW accounted for 11.3% (124). The included infants had a mean GA of 33.8 (± 2.6) weeks and a mean birth weight of 2116 (± 616) grams. The rate of NICU admission among all premature births was 75%. Of the late preterm infants, 270 (33%) didn’t require intensive care services. Antenatal steroids were administered to the mothers of 302 infants (27%). Table 1.

Table 2 shows the interventions performed during the NICU stay. Group 1 required longer respiratory support with invasive ventilation, CPAP or HFNC for a mean duration of 5.8, 11.2 and 2.7 days respectively compared with 0.65, 3.3 and 0.36 days respectively in group 2 (p 0.0005). Similarly, more infants in group 1 received medical treatment for PDA with NSAID and were prescribed diuretics and both systemic and inhaled steroids for evolving BPD (<0.05).

Table 3 highlights the distribution of the studied prematurity-related complications comparing the outcomes between both groups. Overall, the more premature infants (group 1) had higher rates of all the studied comorbidities (p <0.05).

Out of the 141 infants in the first group, 130 (92.2%) were diagnosed with RDS of whom 101 received surfactant at least once compared with 143 (15%) in group 2 (p 0.0005). The overall incidence of BPD among premature infants who survived till 36 weeks PCA is 3.8% compared
with 28.4% (29/102) among the less than 32-week survivors. Further analysis showed that BPD affected 44% (7/16) of the extremely premature survivors (less than 28 weeks).

The rates of severe IVH, PVL, and high-stage ROP in group 1 were 5.9%, 11.8%, and 6.6% compared with near zero in group 2 (p < 0.05). As shown in Table 4, there was a significant difference in the length of stay, discharge weight, and corrected GA at discharge in favor of the more mature infants (Group 2).

4. Discussion

In this single-center cross-sectional retrospective analysis, we reported a prematurity rate of 15.7% with the vast majority (75%) being late preterm infants born between 34 and 36 6/7 weeks of gestation. Collectively, prematurity related short-term morbidities and mortality rates were satisfactory. The majority of deaths and complications were encountered among extremely premature infants delivered at less than 28-week gestation who comprised 4% of all included infants. Although the rates of the studied complications were lower among moderate and late preterm infants, delivery between 32 and 36 6/7 weeks poses major short-term and long-term risks on this group of infants and this should not be underestimated.

A prematurity rate of 15.7% reported in the current study is higher than the previously reported rates from Jordan [5]. In a multi-center prospective study conducted by Abdel Razeq et al. involving 18 hospitals in Jordan and published in 2017, the rate of prematurity among singleton pregnancies was 5.8% with 85% being delivered after 32-week gestation [5]. Data from single-center studies showed a prematurity rate of 6.5% in Saudi Arabia, 6% in United Arab Emirates, and 9.7% in Oman [6,23]. The higher rate in our study could be attributed to the fact that our center is the main referral institution in North of Jordan where most high-risk pregnancies, including multiple gestations, are transferred for obstetric care and delivery. The high rate of CS delivery is another major contributor to the increase in the rate of prematurity. According to the WHO statistics, the global prematurity rate is 9–10%. Higher rates, up to 18%, are reported from low-income countries [2,24]. In USA, the rate of prematurity is variably reported with time but currently it is around 12% [12,24].

Our study demonstrated high proportion (75%) of late preterm infants among the included participants. This is consistent with other reports from Jordan and other countries [5]. In Saudi Arabia, 71% of the premature infants were late preterm [6]. In the US, the rate of late preterm birth is 70% among preterm deliveries and nearly 10% among all deliveries [25]. The high rate of late preterm birth can be explained by the increasing use of assisted reproduction, higher rates of labor induction, and the continuous uptrend in the rate of cesarean section delivery.

A total of 51 infants included in our study didn’t survive till discharge. This represents a 4.6% mortality rate among premature infants at our institution. Extreme prematurity and ELBW were the main factors accounting for 60% of the deaths. Of the mortalities, 28 (55%) were early neonatal deaths that occurred before seven days of life. To compare neonatal mortality rates (NMR) with others, the mortality rate reported per 1000 live births is 7.2 (51 deaths out of 7020 live births during the study period). This rate is very reassuring when compared to
other reports from Jordan or other Middle Eastern countries where NMR has been 10–15 per 1000 live births [4,15].

RDS, one of the most commonly encountered complications of prematurity, was observed in 38% of the included infants in our report. Of

Table 2
Interventions among NICU admissions*.

| Intervention                      | Group 1 (<32 weeks) | Group 2 (≥32 weeks) | P Value |
|-----------------------------------|---------------------|---------------------|---------|
|                                   | n (%) or mean (SD)  | n (%) or mean (SD)  |         |
| Surfactant doses                  | 1                   | 51 (36.2)           | 101 (14.6) | <0.05 |
| ≥2                                | 50 (35.4)           | 42 (6)              |         |
| Respiratory support               | IMV                 | 5.8 (12.4)          | 0.65 (2.4) | <0.05 |
| Mean days (SD)                    | CPAP                | 11.2 (13)           | 3.3 (5.1) |         |
|                                   | HFNC                | 2.7 (8.1)           | 0.36 (2.1) |         |
| Indometacin for PDA               | 38 (27)             | 7 (1)               | <0.05 |
| Diuretics                         | 23 (16.3)           | 19 (2.7)            | <0.05 |
| Inhaled steroids                  | 58 (41.1)           | 70 (10.1)           | <0.05 |
| Dexamethasone (DART)              | 15 (10.6)           | 6 (0.9)             | <0.05 |
| Central lines                     | UAC/UVC             | 49 (34.7)           | 35 (5)   | <0.05 |
|                                   | PICC                | 13 (9.2)            | 3 (0.4)  |         |
| Phototherapy                      | 99 (70.2)           | 278 (40.2)          | 0.08    |
| Feeding                           | Breastmilk          | 4 (2.8)             | 14 (2)   | 0.06   |
|                                   | Formula             | 102 (72.3)          | 578 (83.6) |         |
|                                   | mixed               | 33 (23.4)           | 99 (14.3)|         |
| PRBC Transfusion                  | 1                   | 30 (27)             | 40 (5.8) | <0.05 |
|                                   | >2                  | 32 (22.7)           | 12 (1.7) |         |
| Platelet transfusion              | 57 (40.7)           | 76 (11)             | <0.05 |

IMV: Invasive mechanical ventilation, CPAP: Continuous positive airway pressure. HFNC: High flow nasal cannula. PDA: Patent ductus arteriosus. UAC: Umbilical arterial catheter, UVC: Umbilical venous catheter. PICC: Peripherally inserted central catheter.

* N = 832.

Table 3
Complications among premature infants.

| Outcome                           | Group 1 (<32 weeks) | Group 2 (≥32 weeks) | P Value |
|-----------------------------------|---------------------|---------------------|---------|
|                                   | n (%) or mean (SD)  | n (%) or mean (SD)  |         |
| Intraventricular hemorrhage*       | 25 (21.2)           | 20 (2.1)            | <0.05   |
|                                   | 7 (5.9)             | 1 (0.1)             |         |
| Renalopathy of prematurity         | 7 (6.6)             | 1 (0.1)             | <0.05   |
|                                   | 7 (6.6)             | 2 (0.2)             |         |
| Respiratory distress syndrome      | 130 (92.2)          | 288 (30)            | <0.05   |
|                                   | 14 (9.9)            | 6 (0.6)             | <0.05   |
| Pulmonary hemorrhage               | 7 (5)               | 2 (0.2)             | <0.05   |
| Pulmonary hypertension             | 10 (7.1)            | 20 (2.1)            | <0.05   |
| BPD                               | Mild                | 12 (11.7)           | 8 (0.8) | <0.05 |
|                                   | Moderate            | 11 (10.8)           | 2 (0.2) |         |
|                                   | Severe              | 6 (5.9)             | 1 (0.1) |         |
| Sepsis                            | Total               | 26 (18.4)           | 20 (2.1) | <0.05 |
|                                   | EOS                 | 4 (2.8)             | 7 (0.7) |         |
|                                   | LOS                 | 22 (15.6)           | 13 (1.4)|         |
| Necrotizing enterocolitis          | 13 (9.2)            | 0 (0)               | <0.05   |

PVL: Periventricular leukomalacia, BPD: Bronchopulmonary dysplasia. EOS: Early-onset sepsis, LOS: Late-onset sepsis.

* For group 1, percentage was calculated out of 118 survivors till ultrasound screening.

* For group 1, percentage was calculated out of 106 survivors till eye exam screening.

* For group 1, percentage was calculated out of 102 survivors till 36-week post-conceptual age.

the less mature group (born before 32-week gestation) the risk of RDS was 90% which is slightly higher than the reported rates of 55%–85% [12,26]. Surfactant administration was given in 58%. Despite high rate of RDS, the lower severity can be explained by the increasing antenatal steroid use and postnatal CPAP application [27]. Despite all the advance in neonatal care, RDS remains the most common cause of death among premature infants and a major risk for cerebral palsy in the survivors [12].

Another serious complication of prematurity included in the short-term and long-term morbidities is BPD. Worldwide, the rate of BPD is variably reported between 5 and 75% depending on the GA and weight category of the included premature infants in the reported studies [28].

In our study’s participants who survived till 36-week PCA, BPD was reported in 28.4% of the very preterm infants and in 44% of the extremely premature infants. Luckily, the majority of infants diagnosed with BPD had mild disease and didn’t require oxygen supplement at discharge. The rate of BPD among VLBW infants is 30% in Saudi Arabia.

Table 4
Discharge outcomes of all premature infants.

| Outcome                                | Group 1 (<32 weeks) | Group 2 (≥32 weeks) | P Value |
|----------------------------------------|---------------------|---------------------|---------|
|                                       | n (%) or mean (±SD) | n (%) or mean (±SD) |         |
|                                       | NICU                | No NICU             |         |
| Survival                               | 100 (71)            | 681 (98.5)          | 270 (100)| <0.05 |
| Discharge weight (Grams)               | 1824 (±217)         | 2320 (±838)         | 2707 (±42) | <0.05 |
| Length of stay (Days)                  | 37 (±24.4)          | 9 (±10)             | 1.4 (±0.2) | <0.05 |
| Corrected GA (Weeks)                   | 35.5 (±2.3)         | 36.1 (±1.4)         | 36.1 (±0.46) | <0.05 |

GA: Gestational age. NICU: Neonatal Intensive Care Unit.
and 33% in United Arab Emirates [29,30]. Despite the reduction in the incidence of most prematurity complications, the epidemiologic pattern of BPD in major US centers remains constant, if not increasing, due to the increase in survival of more extremely premature infants. Therefore, the high number of early deaths among extremely preterm infants in low-income countries may falsely lower the BPD rate [28].

IVH and PVL are among the major devastating complications of prematurity. There continues to be no definitive therapy for these serious morbidities that carry a substantial long-lasting burden compromising neurodevelopment. Of the severe IVH (5.9%) and cystic PVL (11.8%) cases seen in the less than 32-week gestation infants included in our analysis, the majority affected babies born at 25–26 weeks with ELBW. This rate is consistent with the rate reported from Saudi Arabia where severe IVH was diagnosed in 13% and cystic PVL in 4% [9]. In UAE, the rate of combined severe IVH and PVL among VLBW infants was found to be 8% [8]. Globally, the rates of severe IVH and PVL are decreasing since introduction of antenatal steroids, better resuscitation at birth, and more judicious use of ventilatory support [31].

Among the survivors who underwent dilated eye exam for ROP screening, seven infants (6.6%) in the less than 32-week gestation group were diagnosed with high-stage ROP. They received intravitreal injection with Bevacizumab with good response in all cases [32]. With the strict guidelines in maintaining oxygen saturation within target and performing timely eye exam screening per policy, the risk of ROP is decreasing. Still, ROP remains the major cause of blindness in children. In Jordan, ROP was previously reported in 17% of VLBW infants from a single-center military hospital [33]. Similarly, high-stage ROP was diagnosed in 15.2% of the less than 32-week included from two tertiary hospitals in Saudi Arabia [34].

The present study demonstrated that about one out of five <32-week infants developed culture proven sepsis during the hospital stay. The majority being LOS. This group of premature infants was ten times more likely to develop sepsis compared with the more mature group. This is likely explained by more central line days, longer ventilatory support, higher chance of feeding related complications, and longer duration of hospitalization. The rate and epidemiological pattern of sepsis in our population is comparable to other reports from the region [35]. For example, the incidence of LOS in Saudi Arabia is 21.9% [9]. According to the NICHD data analysis, the rate of LOS is around 34% among extremely preterm infants in USA [36].

The significant difference in discharge weight and total length of hospital stay between both groups reported in our analysis is not unexpected. With the difference in birth weight and innate immaturity of all body systems, the less mature infants required longer intensive care services to maintain thermal regulation, wean off respiratory support, tolerate enteral feeding, and adjust to the extra-uterine environment.

The main limitation of our study is the retrospective design of this review in which all the extrapolated data reflects what is documented in the medical charts. Consequently, certain outcomes might be falsely overestimated or underestimated. Although the sample size is larger than most studies that examined the short-term outcomes of premature infants from the region, conclusions about the generalizability of our findings cannot be accurately made to represent the whole Jordanian population. Furthermore, this study reports a descriptive analysis of the short-term outcomes of two premature groups with different level of maturity and different underlying pathophysiology which makes the reported significant differences in certain outcomes not unexpected.

In conclusion, this study represents the first comprehensive analysis of the short-term outcomes among premature infants from a major tertiary center in Jordan and demonstrates a high prematurity rate of 15.7%. However, the vast majority of premature infants in our population are moderate and late preterm babies with low mortality rate and reassuring outcomes. Although extremely preterm infants, the more vulnerable group, comprised 4% of all premature infants, they accounted for the majority of deaths and serious prematurity-related comorbidities. Population-based analysis of the risk factors and outcomes among the more vulnerable very preterm and extremely premature infants is recommended to help establish national guidelines and bundles of care to improve the overall neonatal outcomes.

Declaration competing of interest

Both authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amsu.2020.10.017.

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Consent

Parental consent was waived as this study involves chart review.

Author contribution

Both authors made substantial contribution to study design and literature review. Participated in data collection, analysis and interpretation. Involved in drafting the manuscript and revising it critically for important intellectual content.

Trial registry number

1. Name of the registry: Research registry.
2. Unique Identifying number or registration 6000.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5f58a33ef38fe001746b365/

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