

# Mortality and morbidity of extremely low birth weight infants in Hong Kong, 2010-2017: a single-centre review

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## ABSTRACT

**Background:** Extremely low birth weight (ELBW) infants exhibit high rates of mortality and morbidity. We retrospectively assessed factors associated with mortality and morbidity among ELBW infants.

**Methods:** Perinatal demographic data were reviewed for all ELBW infants born between 2010 and 2017 at a tertiary neonatal unit.

**Results:** For non-survivors (21% of ELBW infants) and survivors, the median gestational ages were 24.1 and 26.2 weeks, respectively, and median birth weights were 650 g and 780 g, respectively (all  $P < 0.001$ ). Regression analyses showed that non-survival was positively associated with lower gestational age (adjusted odds ratio [aOR]=6.71 for every 1-week decrease; 95% confidence interval [CI]=1.73-26.00;  $P=0.006$ ) and grade 3 or 4 intraventricular haemorrhage (aOR=29.23; 95% CI=1.39-613.84;  $P=0.030$ ); non-survival was negatively associated with the presence of bronchopulmonary dysplasia (aOR=0.01; 95% CI= <0.001-0.23;  $P=0.005$ ); length of neonatal intensive care unit stay for survivors was positively associated with the presence of necrotising enterocolitis (B-coefficient=89.60; 95% CI=43.86-135.34;  $P < 0.001$ ); and length of hospital stay for survivors was positively associated with the presence of necrotising enterocolitis (B-coefficient=2.08; 95% CI=0.43-3.73;  $P=0.015$ ) and a low Apgar score at 1 minute (B-coefficient= -0.63; 95% CI= -1.04 to -0.22;  $P=0.003$ ).

**Conclusion:** Extremely low birth weight infants

exhibited significant mortality and morbidity; there was no survival prior to 23.6 weeks' gestation or below 550 g birth weight. The presence of grade 3 or 4 intraventricular haemorrhage was independently associated with non-survival. Survivors were significantly more likely to exhibit bronchopulmonary dysplasia; survivors with necrotising enterocolitis were more likely to require longer stays in the neonatal intensive care unit and in hospital.

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### New knowledge added by this study

- Extremely low birth weight infants in Hong Kong showed significant mortality and morbidity: there was no survival prior to 23.6 weeks' gestation or below 550 g birth weight in this series.
- The presence of grade 3 or 4 intraventricular haemorrhage was independently associated with non-survival.
- Survivors were significantly more likely to exhibit bronchopulmonary dysplasia.
- Survivors with necrotising enterocolitis were significantly more likely to require longer stays in both the neonatal intensive care unit and hospital.

### Implications for clinical practice or policy

- Parents in Hong Kong with extremely low birth weight infants should be counselled regarding expectations for infant survival and associated complications.
- Hong Kong hospitals can modify their practices to support an increased rate of survival and decreased rate of complications among extremely low birth weight infants.
- These findings may guide future neonatal health policy and funding in Hong Kong.

## Introduction

Extremely low birth weight (ELBW) infants (birth weight <1000 g) have high rates of mortality and morbidity.<sup>1,2</sup> The survival of ELBW infants has improved significantly with the widespread use of exogenous surfactant agents, maternal steroids, mechanical ventilation, and advancements in neonatal technologies.<sup>1,3-7</sup> The minimum age of viability is currently regarded as 21 to 22 weeks' gestation; accordingly, there have been scattered reports of survivors born at 21 to 22 weeks' estimated gestation.<sup>2,8-11</sup> Perivable birth is defined as delivery occurring from 20 weeks to 25 weeks 6 days of gestation.<sup>12</sup> Notably, the rate of survival at 3 years for infants born at 22 weeks' gestation has been reported as approximately 36% in some centres.<sup>13</sup> This study aimed to review mortality and morbidity of ELBW infants at a tertiary neonatal unit in Hong Kong.

## Methods

Demographic and clinical data were analysed for consecutive neonates admitted to the neonatal unit of a university-affiliated teaching hospital (Prince of Wales Hospital) in Hong Kong between 1 January 2010 and 30 June 2017. During the study period, the Prince of Wales Hospital provided regional neonatal intensive care service for the Eastern New Territories of Hong Kong, with a catchment population of over 1.1 million (approximately 25% were children aged <12 years). A standard data form was used for data abstraction by the investigators. All Clinical Management System records, inpatient records, and computerised laboratory data were examined. Numerical data were expressed as median (interquartile range) and compared by using the Mann-Whitney *U* test; categorical data were compared by using the Chi squared test, or Fisher's exact test for data fields that contained >20% cells with an expected count <5. Backward binary logistic regression was conducted on mortality; backward linear regressions were conducted on lengths of neonatal intensive care unit (NICU) stay and hospital stay for survivors. Corresponding Kaplan-Meier survival curves were constructed with survival distribution comparisons by log-rank test using SPSS (Windows version 20.0; IBM Corp, Armonk [NY], US). Two-tailed *P* values <0.05 were considered statistically significant.

## Results

A total of 78 ELBW neonates were admitted to the NICU between 1 January 2010 and 30 June 2017; 16 of these neonates died (mortality 21%) [Table 1]. For non-survivors and survivors, the median gestational ages were 24.1 and 26.2 weeks, respectively, and birth weights were 650 and 780 g, respectively

## 2010年至2017年間香港極低出生體重嬰兒的死亡率和發病率：單中心回顧

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背景：極低出生體重嬰兒的死亡率和發病率高。本研究追溯並評估與極低出生體重嬰兒死亡率和發病率相關的因素。

方法：對2010年至2017年間在第三級新生兒醫護單位出生的所有極低出生體重嬰兒的圍產期人口統計學數據進行審查。

結果：非倖存的（佔總體21%）和倖存的極低出生體重嬰兒的孕齡中位數分別為24.1和26.2週，出生體重中位數分別為650 g和780 g（*P*值均<0.001）。迴歸分析顯示非倖存與孕齡較輕（每少1週的經調整比值比=6.71；95%置信區間=1.73-26.00；*P*=0.006）和第3或4級腦室內出血（經調整比值比=29.23；95%置信區間=1.39-613.84；*P*=0.030）呈正相關；非倖存與支氣管肺發育不良呈負相關（經調整比值比=0.01；95%置信區間=<0.001-0.23；*P*=0.005）；新生兒重症監護病房的生存時間與出現壞死性小腸結腸炎呈正相關（*B*係數=89.60；95%置信區間=43.86-135.34；*P*<0.001）。倖存者的住院時間與出現壞死性小腸結腸炎（*B*係數=2.08；95%置信區間=0.43-3.73；*P*=0.015）和1分鐘Apgar評分低（*B*係數=-0.63；95%置信區間=-1.04至-0.22；*P*=0.003）呈正相關。

結論：極低出生體重嬰兒有顯著的死亡率和發病率。本研究顯示在妊娠23.6週前或出生體重低於550 g的極低出生體重嬰兒沒法倖存。出現第3或4級腦室內出血單單與非倖存相關。倖存者較大機會出現支氣管肺發育不良，而患有壞死性小腸結腸炎的倖存者更可能須在新生兒重症監護病房和醫院留院較長時間。

(*P*<0.001). The median (interquartile range) of NICU stay before death was 2.5 (2.0-11.5) days. The median durations of NICU stay and total hospital stay among survivors before discharge were 93.5 days and 4.1 months, respectively. Backward binary logistic regression analysis showed that non-survival was associated with lower gestational age (adjusted odds ratio [aOR]=6.71 for every 1-week decrease; 95% confidence interval [95% CI]=1.73-26.00; *P*=0.006) and grade 3 or 4 intraventricular haemorrhage [IVH] (aOR=29.23; 95% CI=1.39-613.84; *P*=0.030); non-survival was negatively associated with the presence of bronchopulmonary dysplasia (BPD) [aOR=0.01; 95% CI=<0.001-0.23; *P*=0.005), after adjustment for multiple births, caesarean section, birth weight, Apgar score at 1 minute, antenatal steroid administration, infant apnoea, necrotising enterocolitis (NEC), retinopathy of prematurity (ROP), and anaemia of prematurity in the first step of the regression analysis (Table 2). Backward linear regression revealed that the length of NICU stay for survivors was positively associated with the presence of NEC (*B*-coefficient=89.60; 95% CI=43.86-135.34; *P*<0.001), after including gestational age, caesarean section, birth weight, Apgar score at 1 minute,

TABLE 1. Demographics and clinical factors of ELBW infants (n=78)\*

	Non-survival (n=16)	Survival (n=62)	P value
Male sex	10 (62.5)	32 (51.6)	0.436‡
Gestational age, weeks	24.1 (24.0-24.3)	26.2 (25.0-27.7)	<0.001†
Multiple births	7 (43.8)	13 (21.0)	0.105§
Caesarean section	3 (18.8)	25 (40.3)	0.109‡
Birth weight, kg	0.648 (0.6-0.7)	0.780 (0.7-0.9)	<0.001†
Apgar score			
1 Min	4.0 (3.0-6.0)	5.0 (4.0-7.0)	0.010†
5 Min	7.0 (6.5-8.0)	8.0 (7.0-8.0)	0.238†
Maternal problems <sup>  </sup>	3 (18.8)	6 (9.7)	0.380§
Antenatal steroid	11 (68.8)	54 (87.1)	0.126§
BPD	2 (12.5)	50 (80.6)	<0.001‡
Infant apnoea	2 (12.5)	45 (72.6)	<0.001‡
IVH	12 (75.0)	30 (48.4)	0.057‡
Grade 1 or 2	2 (16.7)	24 (80.0)	<0.001§
Grade 3 or 4	10 (83.3)	6 (20.0)	
NEC	0	16 (25.8)	0.032§
ROP	1 (6.3)	21 (33.9)	0.031§
Blood stream infection	2 (12.5)	14 (22.6)	0.501§
Anaemia of prematurity	7 (43.8)	55 (88.7)	<0.001§
NICU stay, days	2.5 (2.0-11.5)	93.5 (79.0-125.0)	<0.001†
Discharge age, months	N/A	4.1 (3.6-5.3)	N/A

Abbreviations: BPD = bronchopulmonary dysplasia; ELBW = extremely low birth weight; IVH = intraventricular haemorrhage; N/A = not applicable; NEC = necrotising enterocolitis; NICU = neonatal intensive care unit; ROP = retinopathy of prematurity

\* Data are shown as No. (%) of subjects, or median (interquartile range)

† Mann-Whitney U test

‡ Chi squared test

§ Fisher's exact test

|| Maternal problems included sepsis, diabetes, and cervical incontinence

and blood stream infection in the first step of the regression analysis (Table 3). The length of hospital stay was positively associated with presence of NEC (B-coefficient=2.08; 95% CI=0.43-3.73; P=0.015), but negatively associated with Apgar score at 1 minute (B-coefficient= -0.63; 95% CI= -1.04 to -0.22; P=0.003), after including gestational age, birth weight, Apgar score at 1 minute, and Apgar score at 5 minute in the first step of the regression analysis (Table 3).

Survival curves were constructed for gestational age (Fig 1) and birth weight (Fig 2). Median Kaplan-Meier survival estimates for gestational ages <24, 24, and 26 weeks were 43%, 52%, and 92%, respectively (no death records were available for other groups), during the period of postnatal NICU stay before discharge; importantly, their survival distributions were significantly different ( $\chi^2=31.1$ ; P<0.001). Median Kaplan-Meier survival estimates for birth weights <600 g, 600 to 699 g, and 700 to 799 g were

55%, 63%, and 81%, respectively (no death records were available for other groups); their survival distributions were significantly different ( $\chi^2=13.9$ ; P=0.008) [Fig 2].

## Discussion

Extremely low birth weight infants, especially those born at periviable gestations of 22 to 23 weeks, exhibit significantly higher mortality. In this cohort of ELBW infants, we confirmed two independent factors associated with ELBW non-survival: gestation age below 24 weeks and the presence of grade 3 or 4 IVH. Although not specifically analysed in this series, congenital anomalies did not appear to be a pertinent risk factor influencing survival among ELBW infants. Among infants in the non-survival group, the median time until death was 2.5 days after birth; in our series, no survival was observed for ELBW infants whose birth occurred prior to 23.6

weeks or who exhibited birth weight of <550 g. These local data are expected to be useful in counselling pregnant women who are at risk for the delivery of ELBW infants. Non-survival was associated with an increased aOR of 6.7 for every 1-week decrease in gestation.

In addition to perinatal mortality, long-term survival was also low. A previous report stated that first-year survival was 15.5% for infants whose birth weight was <500 g.<sup>14</sup> Infants with ELBW are more susceptible to all complications of prematurity, both during the immediate neonatal period and after discharge from the nursery. A study by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network,<sup>15</sup> undertaken to relate other known risk factors with the likelihood of survival and impairment, reported that 83% of infants born at 22 to 25 weeks' gestation received intensive care involving mechanical ventilation. Of the infants whose outcomes were known at 18 to 22 months, 49% died, 61% died or had profound impairment, and 73% died or had impairment.

Additional reports have suggested that other factors should be considered, in combination with gestational age, when determining the likelihood of favourable outcomes with intensive care.<sup>15-19</sup> According to the data from a 2011 cohort study, infants born at 23 to 25 weeks' gestation who received antenatal exposure to corticosteroids exhibited a lower rate of mortality and complications, compared with infants who did not have such exposure.<sup>16</sup> Recently, chorioamnionitis was linked to preterm birth and neonatal infection. In a longitudinal observational study that included 2390 extremely preterm infants (gestational age <27 weeks), Pappas et al<sup>20</sup> reported that antenatal exposure to chorioamnionitis appeared to increase the odds of cognitive impairment, as well as death/neurodevelopmental impairment.

Survival occurred in 79% of ELBW infants at our centre. Extremely low birth weight survivors exhibited significant morbidity. Our series showed that BPD, severe IVH, NEC, and ROP were present in 81%, 20%, 26%, and 34% of survivors, respectively. Notably, the survivors experienced long stays in the NICU and hospital prior to discharge. Necrotising enterocolitis is particularly associated with long stays in the NICU and hospital. The sequelae of low birth weight have been well-studied, but less information is available regarding sequelae of ELBW.<sup>21</sup> Low birth weight is generally closely associated with fetal and perinatal mortality and morbidity, inhibited growth and cognitive development, and a risk of chronic diseases later in life. At the population level, the proportion of infants with low birth weight is an indicator of a multifaceted public health problem that includes long-term maternal malnutrition,

TABLE 2. Logistic regression analysis of mortality (n=78)

	Adjusted odds ratio	95% Confidence interval	P value
Gestational age	0.15	0.04-0.58	0.006
BPD	0.01	<0.001-0.23	0.005
IVH grade 3 or 4	29.23	1.39-613.84	0.030

Abbreviations: BPD = bronchopulmonary dysplasia; IVH = intraventricular haemorrhage

TABLE 3. Linear regression analysis of length of NICU or hospital stay for survivors (n=62)

	B	95% Confidence interval	P value
<b>NICU stay</b>			
NEC	89.60	43.86-135.34	<0.001
<b>Hospital stay</b>			
Apgar score at 1 min	-0.63	-1.04 to -0.22	0.003
NEC	2.08	0.43 to 3.73	0.015

Abbreviations: NEC = necrotising enterocolitis; NICU = neonatal intensive care unit

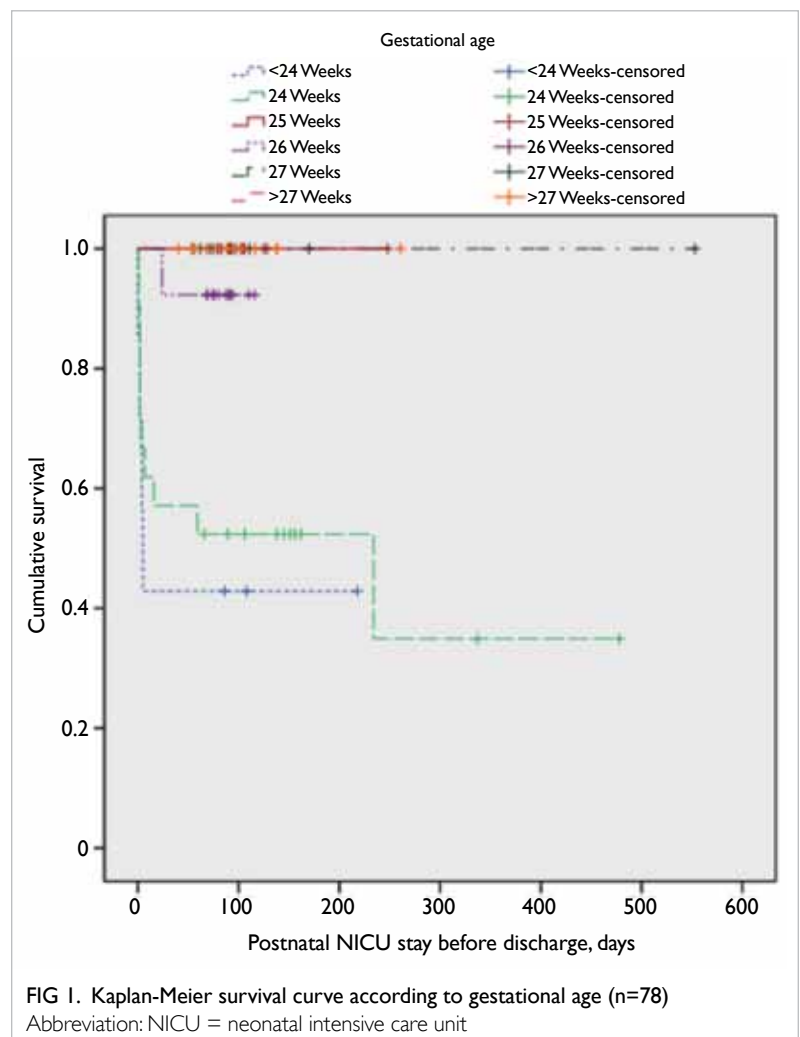
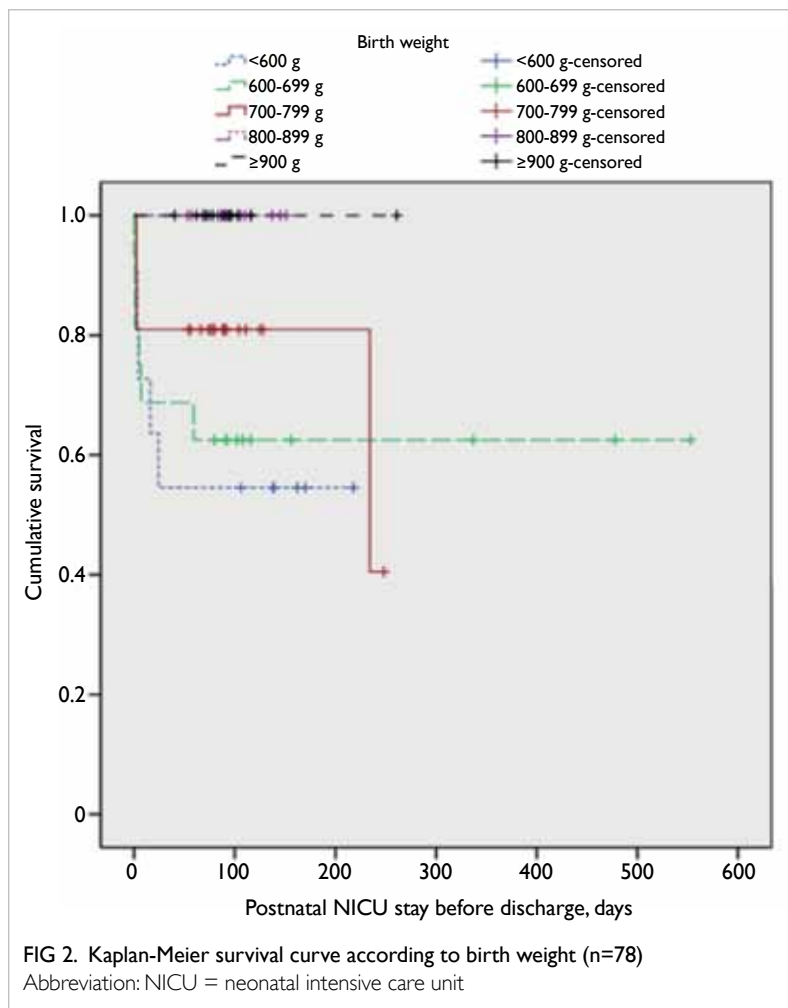


FIG 1. Kaplan-Meier survival curve according to gestational age (n=78)  
Abbreviation: NICU = neonatal intensive care unit



poor health, hard work, and poor health care during pregnancy. On an individual basis, low birth weight is an important predictor of newborn health and survival, and is associated with a higher risk of infant and childhood mortality.<sup>21</sup> In this regard, ELBW represents the most severe subset of low birth weight outcomes.

Bronchopulmonary dysplasia, grade 3 or 4 IVH, and ROP occurred in a significant proportion of the survivors. Our morbidity data are comparable to those reported in multiple large studies.<sup>8,22,23</sup> In recent years, ELBW infants have constituted more than 97% of cases of BPD.<sup>24</sup> Importantly, NEC is the most common intestinal emergency in preterm infants.<sup>25,26</sup> The routine use of antenatal steroids and surfactant therapy has resulted in increased survival of infants with ELBW, thereby increasing the survival rate in the group at the greatest risk.<sup>27</sup>

The incidence and severity of IVH are inversely related to gestational age. Infants with ELBW are at particular risk for IVH; however, the use of antenatal steroids decreases the incidence of IVH. Prognosis is correlated with the grade of IVH<sup>28</sup>; up to 40% of

infants with grade 3 IVH exhibit significant cognitive impairment, and up to 90% of infants with grade 4 IVH exhibit major neurologic sequelae, requiring lifetime care. Notably, a study of 1064 infants born at  $\leq 28$  weeks' gestation found that, unless it was accompanied or followed by a white matter lesion, low-grade IVH was associated with a modest to non-existent risk of adverse developmental outcomes during infancy.<sup>29</sup>

The outcomes of ELBW infants are evolving as therapy and supportive care continue to change.<sup>1</sup> Clinical focus should be placed on the prevention of premature births, as well as equipping NICU staff and facilities with the necessary skills and resources, respectively, to implement evidence-based interventions that improve the survival of ELBW infants. Efforts to minimise injury, preserve growth, and identify interventions focused on antioxidant and anti-inflammatory pathways are currently being evaluated. Thus, treatment and prevention of long-term deficits must be developed in the context of an evolving target. Ensuring health in cases of extreme prematurity ( $\leq 23$  weeks' gestation) is extremely difficult.<sup>2</sup> Most centres do not have minimum birth weight criteria for resuscitation; often, a "trial of life" may be discussed with the parents before the birth of the infant so that the infant can be resuscitated and evaluated for viability after birth. Viability is the term frequently used to indicate the potential for a fetus to be liveborn and capable of surviving to a specified endpoint (eg, a designated time, attainment of a certain age or landmark event, admission to the NICU, or discharge from the hospital). Many institutions have generated centre-specific data regarding the probability of survival to aid in discussions with families prior to delivery. Discussions regarding the withdrawal of treatment or support are often necessary when the family and medical team agree that the continuation of medical treatment is not in the infant's best interests. Naturally, these circumstances involve numerous ethical, moral, and legal issues; they may generate more questions than answers. Therefore, each centre caring for ELBW infants must carefully follow and analyse their particular survival statistics, in order to better inform and guide parents concerning the outcomes and prognoses of these periviable infants.

**Author contributions**

Concept or design: KL Hon, S Liu, JCY Chow.  
Acquisition of data: KL Hon, S Liu, JCY Chow.  
Analysis and interpretation of data: KL Hon, KYC Tsang.  
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Critical revision for important intellectual content: All authors.

**Declaration**

As an editor of the journal, KL Hon was not involved in the peer

review of the article. All authors have disclosed no conflicts of interest. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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### Ethical approval

Ethics approval for this study was obtained from the Clinical Research Ethics Committee of The Chinese University of Hong Kong.

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