

Outcome and Factors Associated with Mortality of Extremely Low Birth Weight Infants in Chiang Rai Prachanukroh Hospital: A 10-Year Review

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ABSTRACT

Background: Extremely low birth weight (ELBW, birth weight <1000 grams) infants have high rate of mortality and morbidities. Survival of ELBW infants has increased with advance neonatal intensive care managements especially widespread use of antenatal steroids, mechanical ventilation and surfactant replacement therapy.

Objectives: To determine outcome and mortality risk factors of ELBW infants admitted at Chiang Rai Prachanukroh Hospital.

Methods: A ten-year retrospective review of ELBW infants admitted to neonatal intensive care unit between July 1, 2011 and June 30, 2021 was performed. Antenatal and perinatal data were extracted and neonatal outcome to discharge was analyzed.

Results: During the study period, 203 live-ELBW infants were enrolled. One hundred and twenty-two infants (60.1%) survived to discharge. Major morbidities were found in 55.7% of survivors. Sepsis and respiratory distress syndrome were major causes of death. No infant of birth weight less than 600 grams survived. Median birth weight of non-survivors and survivors were 814 (interquartile range [IQR], 695-872.5) grams and 880 (IQR, 807-946) grams respectively ($p < 0.001$). Multivariate logistic regression analysis showed that lower birth weight (adjusted odds ratio [aOR]=1.61 for every 100-gram decrease, 95% CI 1.21-2.15; $p = 0.001$), Apgar score at 5 minutes <7 (aOR=1.96, 95% CI 1.03-3.73; $p = 0.042$) and intraventricular hemorrhage (aOR=3.14, 95% CI 1.32-7.44; $p = 0.009$) were significantly associated with in-hospital mortality.

Conclusions: Every 100-gram decrease of ELBW infants, especially birth weight below 600 grams, exhibited high risk of mortality. Birth asphyxia and intraventricular hemorrhage were also predictors for non-survival. This study can be useful for counseling and planning of care for ELBW infants in tertiary care hospitals.

Introduction

WHO newborn mortality report 2022 states that 47% of children under-5 deaths happen in the first 28 days of life or in neonatal period. One of the most important causes of death is preterm birth which mostly suffer from lack of quality care at or immediately after birth or in the first days of life¹. Majority of preterm births occur in Africa and southern Asia. From many previous studies, morbidities and mortality of preterm infants have significant relation to lower gestational age, lower birth weight and initial care especially in the respiratory system.

Extremely low birth weight (ELBW) infants are infants born with a birth weight less than 1000 grams. In which almost the entire population of ELBW infants are preterm birth, causing higher rates of morbidities and mortality for these children. Furthermore, disability and long term care are often following after discharge of ELBW infants and may lead to caregiver problems and caregiver burden after that.

Survival of ELBW infants is increasing, results from advance critical neonatal care and development of medical technologies used in neonatal intensive care units (NICU). However, in Thailand, there is still limited study about ELBW infants despite an increasing of this population. This research focused on morbidities and mortality of ELBW infants to obtain more information leading to an upgrade in the standard of care and improve survival of these vulnerable infants.

Methods

This study was a retrospective cohort study which clinical data were collected from ELBW infants admitted in NICU of Chiang Rai Prachanukroh Hospital from July 1, 2011 to June 30, 2021. Demographic data including maternal characteristics, antenatal and perinatal information were collected from summary of labor record for inside born infants and referral document for outside born patients.

Statistical analysis

Descriptive analyses were performed for demographic characteristics and expressed in percentage and median [interquartile range]. Comparison between survived and non-survived infants was determined by Chi-square or Fisher's exact test for categorical data and by Mann-Whitney U test for continuous data. Kaplan-Meier survival curves were constructed with survival distribution comparison by Log-Rank test. Mortality risk factors were determined using binary logistic regression analysis. Statistical significance was accepted at p-value < 0.05. All data were analyzed using the Statistical Package for Social Sciences (SPSS).

Results

During the study period, there were 208 live-ELBW infants admitted to the NICU of Chiang Rai Prachanukroh Hospital. Five infants received no ventilation or interventions as parents' wishes and were excluded from the study. The remaining 203 ELBW infants were enrolled. Two of these had congenital heart diseases (Tetralogy of Fallot and Double outlet of right ventricle) from prenatal diagnosis. One hundred and forty-nine infants (73%) were inside born. Median [IQR] of maternal age was 29 [23-34] years. Pregnancy induced hypertension was the most common obstetric complication (22%). Complete course of antenatal steroid was given in about 40% of cases. Seventy-nine (39%) infants were born by cesarean section. (Table 1)

The median [IQR] of birth weight and gestational age of enrolled infants were 849 [770-931] grams and 27 [26-29] weeks respectively. About half of them (52%) were extremely preterm (<28 weeks) and 34% were small for gestational age infants. Median Apgar scores at 1 and 5 minute were 4 and 7 respectively. During resuscitation, 175 (86%) infants received intubation and 27 (13%) infants needed CPR.

Table 1 Demographic characteristics of 203 ELBW infants

Maternal		Neonatal	
Age, years (median [IQR])	29 [23-34]	Birth weight, grams (median [IQR])	849 [770-931]
Significant medical problems, n (%)		Gestational age, weeks (median [IQR])	27 [26-29]
Chronic hypertension	11 (5.4)	Extreme preterm (<28 weeks), n (%)	106 (52.2)
Diabetes	2 (1.0)	Male, n (%)	96 (47.3)
Cardiac	2 (1.0)	Multiple birth, n (%)	49 (24.1)
Renal	3 (1.5)	Inside born, n (%)	149 (73.4)
Hematology	4 (2.0)	Small for gestational age, n (%)	69 (34.0)
HELLP syndrome	2 (1.0)	Apgar score (median [IQR])	
Significant obstetric issues, n (%)		1-minute	4 [2,6]
PIH	45 (22.2)	5-minute	7 [5,8]
PPROM	31 (15.3)	Resuscitation details, n (%)	
Antepartum hemorrhage	8 (4.0)	Intubation	175 (86.2)
Gestational diabetes	5 (2.5)	CPR	27 (13.3)
Prolapse cord	4 (2.0)		
Oligo/polyhydramnios	7 (3.5)		
Multifetal gestation	49 (24.1)		
TTTS	4 (2.0)		
In vitro fertilization, n (%)	3 (1.5)		
Complete ANS, n (%)	81 (39.9)		
Cesarean section, n (%)	79 (38.9)		

PIH Pregnancy induced hypertension

PPROM Preterm premature rupture of membranes

TTTS Twin-to-twin transfusion syndrome

ANS Antenatal steroid

Survival and morbidities

Of 203 ELBW infants, 122 (60.1%) survived to discharge. No infant of birth weight less than 600 grams survived, but survival rate improved with increasing birth weight (*Figure 1*). In survival group, 68 infants (55.7%) had major morbidities. Bronchopulmonary dysplasia (BPD) (moderate/severe) was the most common morbidity, diagnosed in 50.8%. The incidence of all stages retinopathy of prematurity (ROP) was 20.5% and 19 of them (15.6%) required treatments (\geq Stage III). Median [IQR] hospital stay of the death and survival group were 7 [4-12.5] and 78.5 [65-99] days respectively (*Table 2*). Kaplan-Meier survival curves of all ELBW infants stratified by birth weight were constructed (*Figure 2*). Survival curves were significantly better according to increasing birth weight ($p=0.001$ by Log-Rank

test). Eighty-one (39.9%) infants died. The major causes of death were sepsis (43%), respiratory distress syndrome (RDS) (17%) and pneumonia (14%) as summarized in *Table 3*.

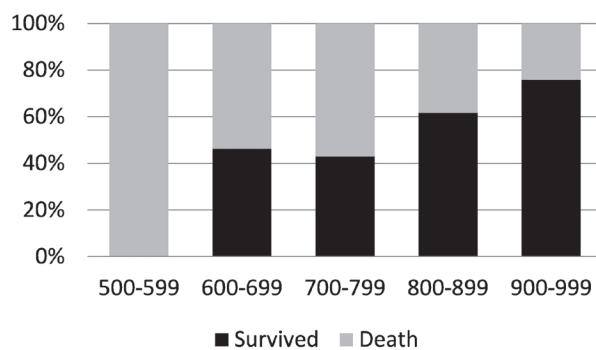
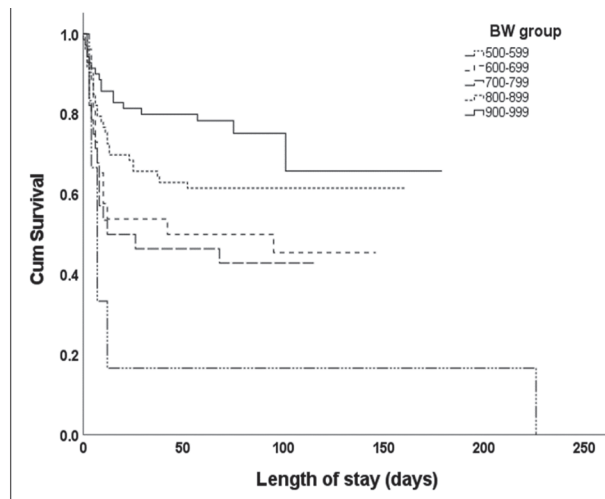


Figure 1 Survival rate of ELBW infants by birth weight

Table 2 Outcome of 203 ELBW infants according to birth weight

	Birth weight (grams)					Total (N=203)
	500-599 (N=6)	600-699 (N=26)	700-799 (N=28)	800-899 (N=73)	900-999 (N=70)	
Death, n (%)	6 (100)	14 (53.8)	16 (57.1)	28 (38.4)	17 (24.3)	81 (39.9)
Hospital stay, days (median [IQR])	7 [4-65.5]	6.5 [5-10.5]	6.5 [3-9.5]	7 [3.5-13]	9 [2.5-24.5]	7 [4-12.5]
Survival, n (%)	0	12 (46.2)	12 (42.9)	45 (61.6)	53 (75.7)	122 (60.1)
Survival with major morbidities	0	9 (75.0)	8 (66.7)	28 (62.2)	23 (43.4)	68 (55.7)
NEC (\geq stage II)	0	1	2	5	1	9 (7.4)
IVH (\geq grade III)	0	0	0	0	2	2 (1.6)
BPD (moderate/severe)	0	8	6	25	23	62 (50.8)
ROP (\geq stage III)	0	4	2	6	7	19 (15.6)
Hospital stay, days (median [IQR])	0	105.5 [99-115]	85 [75-102]	79 [65-97.5]	71 [61-92.5]	78.5 [65-99]

Figure 2 Kaplan-Meier survival curves of ELBW infants stratified by birth weight

One case of 568 grams (29 weeks, triplet-B) female infant died from sepsis at 226 days of hospital stay.

Table 3 Causes of death among 81 infants

Causes of death	n (%)
Sepsis	35 (43.2)
Culture confirmed	5 (6.2)
Respiratory distress syndrome	14 (17.3)
Pneumonia (HAP/VAP)	11 (13.6)
Intraventricular hemorrhage	7 (8.6)
CHD (TOF, DORV, Arrhythmia)	3 (3.7)
Severe birth asphyxia	2 (2.5)
Tension pneumothorax	2 (2.5)
Pulmonary hemorrhage	2 (2.5)
Others (PPHN, PIE, Cirrhosis)	5 (6.2)

HAP Hospital acquired pneumonia

VAP Ventilator-associated pneumonia

CHD Congenital heart disease

TOF Tetralogy of Fallot

DORV Double outlet of right ventricle

PPHN Persistent pulmonary hypertension of newborn

PIE Pulmonary interstitial emphysema

Clinical characteristics of non-survival and survival groups

Clinical characteristics compared among non-survivors and survivors revealed that infants who died had significantly lower birth weight ($p < 0.001$) and lower gestational age ($p = 0.015$) (Table 4). The rate of birth asphyxia (Apgar score

at 5-minute <7) and hypothermia (admission temperature <36.5°C) were significantly higher in the mortality group (p=0.003 and p=0.006 respectively).

One hundred and eighty-five (91%) infants required mechanical ventilation. Median [IQR] duration of mechanical ventilation was 10 [4-29] days. Ninety-three (46%) infants received surfactant replacement therapy. Both mechanical ventilated and surfactant replacement infants were not different between non-survival and survival groups.

Respiratory distress syndrome was the most common morbidity, diagnosed in 86% of all ELBW infants and higher in non-survivors, but did not reach statistical difference (p=0.061). However, other neonatal morbidities such as

patent ductus arteriosus (PDA) which requiring treatments, culture-confirmed sepsis, pneumonia (HAP/VAP) and bronchopulmonary dysplasia were significantly lower in non-survivors, except intraventricular hemorrhage (IVH) was the only morbidity that significantly higher in mortality group (p<0.001).

Factors associated with mortality

According to multivariate logistic regression analysis, lower birth weight (adjusted odds ratio [aOR]=1.61 for every 100-gram decrease, 95% CI 1.21-2.15; p=0.001), Apgar score at 5-minute <7 (aOR=1.96, 95% CI 1.03-3.73; p=0.042) and IVH (aOR=3.14, 95% CI 1.32-7.44; p=0.009) were significantly associated with neonatal mortality (Table 5).

Table 4 Clinical characteristics and morbidities of non-survivors compared with survivors

	Non-survivors (N=81)	Survivors (N=122)	p value
Maternal			
Preterm premature rupture of membranes	11 (13.6)	20 (16.4)	0.585
Pregnancy induced hypertension	19 (23.5)	26 (21.3)	0.719
Complete antenatal steroid	31 (38.3)	50 (41.0)	0.699
Cesarean section	26 (32.1)	53 (43.4)	0.105
Neonatal			
Birth weight (grams)	814 [695-872.5]	880 [807-946]	<0.001**
Gestational age (weeks)	27 [25-29]	28 [26-29]	0.015**
Extreme preterm (<28 weeks)	47 (58.0)	59 (48.4)	0.177
Inside born	56 (69.1)	93 (76.2)	0.263
SGA	25 (30.9)	44 (36.1)	0.444
Apgar score at 5-minute <7	47 (62.7)	47 (40.5)	0.003*
Admission temperature <36.5°C	45 (55.6)	44 (36.1)	0.006*
Surfactant replacement therapy	33 (40.7)	60 (49.2)	0.237
Mechanical ventilated	77 (95.1)	108 (88.5)	0.109
Morbidities			
Respiratory distress syndrome	74 (91.4)	100 (82.0)	0.061
Intraventricular hemorrhage	22 (27.2)	10 (8.2)	<0.001*
Necrotizing enterocolitis	7 (8.6)	22 (18.0)	0.067
Patent ductus arteriosus with treatments	21 (25.9)	65 (53.3)	<0.001‡
Culture-confirmed sepsis	6 (7.4)	26 (21.3)	0.008‡
Pneumonia (HAP/VAP)	25 (30.9)	89 (73.0)	<0.001‡
Bronchopulmonary dysplasia	10 (12.3)	104 (85.2)	<0.001‡

Data are presented as number (%) or median [IQR].

* Significant increase in non-survivors according to Chi-square test.

** Significant lower in non-survivors according to Mann-Whitney U test.

‡ Significant decrease in non-survivors according to Chi-square test.

Table 5 Logistic regression analysis of risk factors associated with mortality

Major predictors	Univariate	Multivariate	
	Odds ratio [95% CI]	Adjusted odds ratio [95% CI]	p value
Birth weight (every 100-g decrease)	1.79 [1.36-2.35]	1.61 [1.21-2.15]	0.001*
Apgar score at 5-minute <7	2.46 [1.36-4.48]	1.96 [1.03-3.73]	0.042*
Admission temperature <36.5°C	2.22 [1.25-3.93]	1.54 [0.82-2.88]	0.181
Intraventricular hemorrhage	4.18 [1.85-9.40]	3.14 [1.32-7.44]	0.009*

* Significant risk factors in predicting in-hospital mortality.

Discussion

In this study, the total survival rate of ELBW infants admitted in Chiang Rai Prachanukroh Hospital was 60.1%, which were concordant with the survival rate of ELBW infants from reported in Thailand's nationwide data analysis (63%)² and comparable with studies in other tertiary care centers in Thailand which range from 32-55%³⁻⁷. However, the survival rate was still lower than some excellent centers such as Chiang Mai University (78-81%) and Khon Kaen Hospital (64%)⁸⁻⁹. In comparison with different studies in other countries, the survival rate was comparable to the study by T. Sahoo et al. done in the tertiary care hospital in North India which reported the survival rate as 62%¹⁰. Other researchers from India also reported 52 - 61.3% of survived ELBW infants¹¹⁻¹³. However, the number of ELBW survivors was slightly higher in Hong Kong's Prince of Wales Hospital (79%) and 72.4% from a large study done in California¹⁴⁻¹⁵.

This study showed that lower birth weight and lower gestational age had significant impact on the mortality rate of ELBW infants similar to many studies from developing and developed countries^{10, 14-15}. There was no infant born with birth weight less than 600 grams survived, as also reported by Neha T. et al who study in Kalawati Saran Children Hospital in New Delhi¹³. The improvement of survival rate was almost correlated to the increasing birth weight except for the birth weight range in 700-799 grams which had lower survival rate than the 600-699-gram group. However, the 700-799-gram group had less percentage of major morbidities presented in

the survivors. Apgar score at 5 minutes also had significant relation to the survival rate. Thorngren-Jerneck and Herbst's study indicated that Apgar score at 5 minutes <7 was associated with increased mortality and risk of severe neurologic morbidity in infants¹⁷. This study also presented the same result that ELBW infants whose Apgar score at 5 minutes <7 had significantly increased in mortality. Moreover, admission hypothermia also resulted in a significant effect on the mortality of ELBW infants. These factors indicated the importance of perinatal care and neonatal resuscitation to the morbidities and mortality of these infants. IVH was another factor that significantly associated with mortality. Due to further long term care and caregiver burden, most of severe IVH cases in our practice were advised for palliative care and resulted in fatality¹⁸.

In this study, while 22.2% of ELBW infants born from mothers diagnosed with pregnancy induced hypertension and 15.3% had preterm premature rupture of membranes, none of these maternal characteristic factors significantly affected ELBW mortality. This may result from under diagnosed prenatal conditions in patients living in rural areas which have difficulty in receiving medical service and lead to improper antenatal care.

The major causes of death in this study were sepsis (43.2%) followed by respiratory distress syndrome (17.3%) and pneumonia (13.6%) which were different from most of the previous studies. Many reports suggested that RDS was the leading mortality of ELBW infants^{10, 13}. The decreased mortality from RDS in this study encouraged the

advantage of exogenous surfactant administration which were used more commonly in later practical care. However, sepsis was always one of the poor prognosis conditions of ELBW infants.

As known that ELBW infants are vulnerable patients and always be challenged in neonatology practice, most of the ELBW infants hospitalized in NICU are discharged with some morbidities. Sixty-eight (55.7%) ELBW infants in this study were discharged with significant complications, which was comparable to study reported by James G. et al. that 67.6% of ELBW survivors had major morbidities¹⁵. Significant BPD and ROP were two of the most common morbidities. Moderate to severe BPD was the highest incidence (50.8%) of the major morbidities occurring in survived ELBW infants. This result correlated with a large number of ELBW infants were diagnosed with RDS (86%) and were supported by mechanical ventilation. Although survival of patients with RDS is rising from advance medical care technologies, the incidence of BPD is also increased. Nowadays, there are many studies focus on searching for a method to prevent BPD. Reducing duration in invasive ventilation, synchronizing non-invasive ventilation and postnatal corticosteroids are proved to decrease rate of BPD¹⁹⁻²¹. Further improvement in practice of ELBW infants care, especially early and proper use of non-invasive ventilation is recommended to facilitate better outcomes of these infants. ROP, which was the second most common morbidity in this study (15.6%) can also be prevented by lower oxygen concentration and reducing mechanical ventilator time²².

Conclusions

Lower birth weight was significantly related to mortality of ELBW infants as every 100-gram decrease, especially below 600 grams, exhibited the reduction of survivors. Birth asphyxia and intraventricular hemorrhage were also predictors for non-survival. This study can be useful for counseling and planning of care for ELBW infants in tertiary care hospitals and also can be a guideline to introduce new technology for the standard of care.

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ผลการรักษาและปัจจัยที่สัมพันธ์กับการเสียชีวิต ของทารกแรกเกิดที่มีน้ำหนักน้อยกว่า 1000 กรัม ในโรงพยาบาลเชิงรายประชาชนเคราะห์: การศึกษาย้อนหลัง 10 ปี

กชมน ไตรรัตน์ภา, กาญจนา ปรีดิศรีพิพัฒน์, สุชฎาวีร์ ไทยใหม่

บทคัดย่อ

ความสำคัญและที่มา: ทารกที่มีน้ำหนักแรกเกิดน้อยกว่า 1000 กรัม เป็นกลุ่มทารกที่มีอัตราการเสียชีวิตและการเกิดภาวะแทรกซ้อนหลังคลอดสูง ด้วยความก้าวหน้าทางการแพทย์ในปัจจุบันตลอดจนเทคโนโลยีการรักษาที่มีความก้าวหน้า และมีคุณภาพดีขึ้น ส่งผลให้ทารกกลุ่มนี้มีอัตราการรอดชีวิตที่สูงขึ้น

วัตถุประสงค์: เพื่อศึกษาผลการรักษาและปัจจัยที่เกี่ยวข้องกับการเสียชีวิตในทารกที่มีน้ำหนักแรกเกิดน้อยกว่า 1000 กรัม ในโรงพยาบาลเชิงรายประชาชนเคราะห์

วิธีการศึกษา: โดยการเก็บข้อมูลจากเวชระเบียนย้อนหลังเป็นระยะเวลา 10 ปี ระหว่าง 1 กรกฎาคม พ.ศ.2554 ถึง 30 มิถุนายน พ.ศ.2564 ในทารกที่มีน้ำหนักแรกเกิดน้อยกว่า 1000 กรัม ซึ่งรับไว้ที่หน่วยดูแลทารกแรกเกิดระยะวิกฤต ข้อมูลที่นำมาวิเคราะห์ประกอบด้วย ข้อมูลเกี่ยวกับการตั้งครรภ์ของมารดา และการคลอด ข้อมูลการรักษาและภาวะแทรกซ้อนของทารก ตลอดระยะเวลาที่รักษาจนกระทั่งทารกได้รับการจำหน่ายออกจากโรงพยาบาล หรือเสียชีวิต

ผลการศึกษา: มีทารกเกิดมีชีพ 203 รายที่มีน้ำหนักแรกเกิดน้อยกว่า 1000 กรัม เข้าเกณฑ์การศึกษา พบว่าทารก 122 ราย (60.1%) มีชีวิตรอดเมื่อจำหน่ายออกจากโรงพยาบาล โดยพบภาวะแทรกซ้อนที่รุนแรง 55.7% ของทารกที่รอดชีวิต ส่วนในกลุ่มที่เสียชีวิตมีสาเหตุการตายที่พบบ่อยคือ การติดเชื้อในกระแสเลือด และภาวะปอดขาดสารลดแรงตึงผิว ไม่พบทารกรอดชีวิตในกลุ่มที่มีน้ำหนักแรกเกิดน้อยกว่า 600 กรัม โดยน้ำหนักแรกเกิดเฉลี่ยของทารกในกลุ่มที่เสียชีวิตเมื่อเปรียบเทียบกับกลุ่มที่รอดเท่ากับ 814 (IQR, 695-872.5) กรัม และ 880 (IQR, 807-946) กรัม ตามลำดับ ($p < 0.001$) โดยวิธีวิเคราะห์การถดถอยโลจิสติก พบว่าปัจจัยที่มีส่วนเกี่ยวข้องกับการเสียชีวิตในทารกคือ น้ำหนักแรกเกิดที่ลดลงทุก 100 กรัม (adjusted odds ratio [aOR]=1.61 95% CI 1.21-2.15; $p=0.001$) คะแนน Apgar ที่ 5 นาที < 7 (aOR=1.96, 95% CI 1.03-3.73; $p=0.042$) และภาวะเลือดออกในโพรงสมอง (aOR=3.14, 95% CI 1.32-7.44; $p=0.009$)

สรุป: น้ำหนักแรกเกิดของทารกที่ลดลงทุก 100 กรัม โดยเฉพาะกลุ่มที่ต่ำกว่า 600 กรัม มีความเสี่ยงสูงของการเสียชีวิต ภาวะขาดออกซิเจนขณะคลอดรวมทั้งภาวะเลือดออกในโพรงสมอง พบเป็นปัจจัยเสี่ยงในทารกกลุ่มที่เสียชีวิต ผลการศึกษานี้จะนำไปใช้เพื่อการตัดสินใจและเป็นแนวทางในการดูแลรักษาผู้ป่วย ตลอดจนการจัดสรรทรัพยากรอย่างเหมาะสมและมีคุณภาพ

* กลุ่มงานกุมารเวชกรรม โรงพยาบาลเชิงรายประชาชนเคราะห์