Surgical Necrotizing Enterocolitis: Outcomes and Factors Affecting Mortality

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บทคัดย่อ : โรคลำไส้อักเสบรุนแรงที่ได้รับการผ่าตัด ผลลัพธ์และปัจจัยที่มีผลต่อการเสียชีวิต

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กลุ่มงานศัลยศาสตร์ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี กรุงเทพมหานคร 10400

ภูมิหลัง: โรคลำไส้อักเสบรุนแรง (Necrotizing enterocolitis/NEC) เป็นหนึ่งในโรคที่สำคัญของทารกแรกเกิดเนื่องจากอัตราตายสูง สามารถเกิดภาวะทุพลภาพตามหลังการเกิดโรคได้และยังมีค่าใช้จ่ายในการรักษาสูงอีกด้วย **วัตถุประสงค์:** เพื่อศึกษาอัตราตาย ปัจจัยที่มีผลต่ออัตราตาย ภาวะแทรกซ้อน และผลการรักษาในระยะยาวของโรคลำไส้อักเสบรุนแรงที่ได้รับการผ่าตัดในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี **วิธีการ:** ศึกษาย้อนหลังในผู้ป่วยทารกแรกเกิดที่ได้รับการวินิจฉัยโรคลำไส้อักเสบรุนแรงและได้รับการผ่าตัดในสถาบันสุขภาพเด็กแห่งชาติมหาราชินีระหว่าง พ.ศ.2554 ถึง พ.ศ. 2559 ผู้ป่วยที่ได้รับการผ่าตัดจากโรงพยาบาลอื่นมาก่อนถูกตัดออกจากการศึกษาโดยเก็บข้อมูลจากเวชระเบียนของผู้ป่วยใบรายงานผลทางรังสีวิทยา ผลตรวจทางห้องปฏิบัติการ ใบรายงานการผ่าตัด ใบรายงานผลพยาธิวิทยา และนำข้อมูลทั่วไป ลักษณะทางคลินิก ลักษณะของภาพรังสี การผ่าตัด ปัจจัยที่พบว่ามีนัยสำคัญทางสถิติจะนำมาคำนวณต่อเพื่อหาขนาดของความสัมพันธ์ โดยใช้ค่าสถิติ Relative risk และ Number needed to harm **ผล:** ผู้ป่วยโรคลำไส้อักเสบที่ได้รับการผ่าตัดเข้าร่วมในการศึกษาทั้งหมด 40 ราย มีอัตราเสียชีวิต 30% พบปัจจัยที่มีผลต่อการเสียชีวิตมีทั้งหมด 7 ปัจจัย ดังนี้ อายุครรภ์น้อยกว่า 28 สัปดาห์ ความดันโลหิตต่ำ ค่าการแข็งตัวของเลือดผิดปกติ (INR>1.5) น้ำหนักตัวแรกคลอดน้อยกว่า 1,000 กรัม ภาวะซีด (ความเข้มข้นเลือด<30%) การได้รับการใส่สายสวนหลอดเลือดทางสายสะดือ และภาวะเกล็ดเลือดต่ำ (<50,000/mm^3) เรียงตามลำดับผลการรักษาในระยะยาวของผู้ป่วยที่รอดชีวิตทั้งหมด 28 ราย มีภาวะแทรกซ้อนที่พบบ่อย คือ ภาวะติดเชื้อร้อยละ 53.6 ภาวะแทรกซ้อนทางลำไส้ร้อยละ 50 ภาวะน้ำดีคั่งในตับร้อยละ 28.57 และยังพบภาวะลำไส้อักเสบรุนแรงเกิดซ้ำร้อยละ 21 โดยมีอัตราตายร้อยละ 33 ซึ่งใกล้เคียงกับการเกิดโรคครั้งแรก นอกจากนี้ยังพบร้อยละ 7 ของผู้ป่วยที่รอดชีวิตมีภาวะลำไส้ตีบตันภายหลังการเป็นโรคลำไส้อักเสบรุนแรง โดยผู้ป่วยทั้งหมดได้รับการรักษาโดยการผ่าตัด **สรุป:** ผลการรักษาของโรคลำไส้อักเสบรุนแรงในทารกแรกเกิดในปัจจุบันของสถาบันสุขภาพเด็กแห่งชาติมหาราชินีดีขึ้นมากเมื่อเทียบกับการศึกษาที่ผ่านมา โดยมีอัตรารอดชีวิตร้อยละ 70 ปัจจัยที่มีผลต่ออัตราตายมากที่สุดคือ อายุครรภ์น้อยกว่า 28 สัปดาห์และความดันโลหิตต่ำ ซึ่งปัจจัยเหล่านี้จะช่วยการพยากรณ์โรคในผู้ป่วยก่อนผ่าตัดแพทย์ผู้รักษาจึงสามารถให้การรักษาอย่างรวดเร็วและครบถ้วนตั้งแต่แรกรับผู้ป่วยลำไส้อักเสบรุนแรง อาจช่วยลดอัตราตายของผู้ป่วยลงได้ในอนาคต

คำสำคัญ: โรคลำไส้อักเสบรุนแรง อัตราตาย ปัจจัยที่มีผลต่ออัตราตาย ผลการรักษาและภาวะน้ำดีคั่งตับ

Abstract:

Background: Necrotizing Enterocolitis (NEC) remains a major cause of neonatal deaths worldwide. The morbidity and medical cost of these patients are still high. **Objectives:** The purpose of this study is to determine the overall mortality of surgical NEC, prognostic factors affecting mortality and to review the outcome of surgical NEC. **Methods:** Retrospective descriptive study of patients with the diagnosis of NEC at Queen Sirikit National Institute of Child Health (QSNICH) between 2011 and 2016 was conducted. Only the patients who had undergone surgical interventions (surgical NEC) were included into the study. The patients who received previous surgery from other hospitals were excluded. Data collection including patient demographics, clinical, laboratory and radiographic findings, surgical interventions, operative findings, complicationsand outcome were obtained. Statistical significance for all was defined as p-value less than 0.05. The significant prognostic factors were calculated for risk difference and number needed to harm. **Results:** Total of 40 newborns with surgicalNEC were enrolled into the study. The mortality rate was 30%. There were 7 prognostic factors which effect mortality, extremely preterm (GA<28 weeks), shock, coagulopathy (INR>1.5),

extremely low birth weight (BW<1,000gm), anemia (Hct<30%), umbilical catheter insertion, and thrombocytopenia (platelet <50,000/mm^3), respectively. The factors affecting the mortality rate were extremely preterm (GA<28 weeks) and shock. For long term outcomes of the 28 survivors, infectious complications (53.6%) were the most common complication followed by gastrointestinal complications (50%) and intestinal failure associated liver disease or IFALD (28.57%). Twenty-one percent developed recurrent NEC. The mortality rate of 33.3% was similar to primary NEC. Seven percent of survivors developed post NEC stricture which all required surgery. **Conclusion:** The recent outcome of surgical NEC at QSNICH has improved significantly with 70% survival rate. The factors affecting the mortality rate are extremely preterm and shock. These factors will help to predict the prognosis of patients with surgical NEC prior to surgical intervention. Hopefully, with aggressive measures starting from admission will help to reduce the mortality in the future.

Keywords: Surgical necrotizing enterocolitis, Mortality, Prognostic factors, Long term outcomes and Intestinal failure associated liver disease

Introduction

Necrotizing enterocolitis (NEC) is the most common gastrointestinal(GI) emergency in neonates. It is primarily a disease of prematurity, with over 90% of affected infants being born before 36 weeks gestation.[1] NEC was first described over 30 years ago in anecdotal reports. NEC remains the major cause of death in neonates and also a complex disease with high morbidity and medical cost. Queen Sirikit National Institute of Child Health(QSNICH) is the main neonatal center in Thailand. It is a super-tertiary hospital with about 400 neonatal surgeries per year. From previous study conducted at QSNICH, the mortality rate of surgical NEC was 51.3%.[2] The objective of this study is (1) to determine the overall mortality of surgical NEC, (2) prognostic factors affecting mortality, (3) to review the outcome of surgical NEC; determine the complications and long-term outcome of survivors.

Material and Methods

The case notes of all infants whom were diagnosed with NEC at QSNICH during January 2011 - December 2016 were reviewed. Only patients that were operated at QSNICH were included in this study. Patients with NEC whom received previous surgical treatment from other hospitals were excluded.

All patients were resuscitated with intravenous fluids, nasogastric tube decompression and broad-spectrum antibiotics. Surgical intervention was performed when there was evidence of intestinal perforation, peritonitis, clinical deterioration despite aggressive medical treatment or intestinal obstruction. Surgical procedure comprised of bedside peritoneal drainage (PD) and/or intestinal resection with primary anastomosis, intestinal resection with proximal stomal formation and proximal stomal formation without intestinal resection.

Data collection included demographics, clinical, laboratory, radiologic, operative data, complications and outcomes. This retrospective cohort study mainly focused on outcome; therefore, the patients were divided and compared in two groups; non-survivors and survivors. For descriptive analysis, mean, range and percentage were used. Then data comparison was done by Student T-test, Chi-square with Yates' correction. Statistic significance for all was defined as p-value less than 0.05. The significant prognostic factors were calculated for risk difference and number needed to harm(NNH). This study was approved by the Institutional Review Board at QSNICH.

Results

The total of 40 neonates with surgical NEC enrolled this study. The majority (67.5%) were premature babies. The overall mortality was 30%.

From the demographic data, the non-survivors were characterized by lower birth weight, lower gestational age and most had an umbilical catheter (Table1). The mortality significantly increased in smaller neonates and the extremely premature (p-value 0.01, 0.03) (Fig.1a, 1b). The most common presenting signs and symptoms for all patients with surgical NEC were feeding intolerance, abdominal distension and erythema of abdominal wall (Table2). Half of all the patients had symptoms within the first week of life and the remainders presented up to 45 days after birth. There were almost no differences of the clinical findings between both groups except for shock (p-value 0.003). All of the non-survivors presented with shock on admission.

Table 1. Demographic Data

Demographic data	Non survivors (N=12)	Survivors (N=28)	p-value
Gender			
Male (N/%)	9 (75%)	14 (50%)	0.2641
Mode of Birth			
Normal Labor	7 (58.3%)	19 (67.9%)	0.8282
Birth weight (grams)	1405 (730-3038)	2098 (870-3760)	0.0096
Gestational age(weeks)	31.1(23-38)	34.4 (28-40)	0.0262
APGAR at 5minutes	8 (5-10)	8.7 (6-10)	0.1910
NSAIDs use	2 (16.7%)	4 (14.3%)	0.8468
Aminophylline use	3 (25%)	2 (7.1%)	0.2968
Umbilical catheter insertion	7 (58.3%)	6 (21.4%)	0.0323
Maternal factors			
Dexamethasone received	4 (33.3%)	5 (17.9%)	0.5086
Chorioamnionitis	1 (8.3%)	0	0.6585

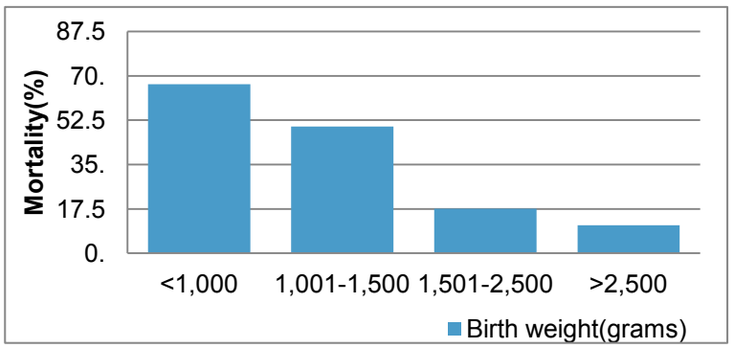

Figure1a. Mortality and birth weight

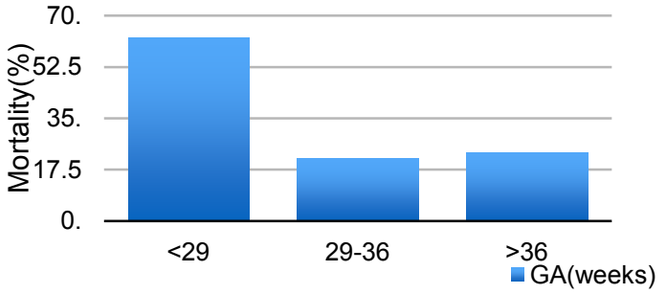

Figure 1 b. Mortality and gestational age

Table 2. Clinical findings

Clinical findings	Non-survivors (N=12) (Min, Max)	Survivors (N=28) (Min, Max)	p-value
Onset of symptoms (day of life)	14.1 (2-44)	8.1 (1-45)	0.0884
Feeding intolerance	10 (83.3%)	26 (92.9%)	0.7301
Vomiting	7 (58.3%)	22 (78.6%)	0.6019
Blood per rectum	6 (50%)	19 (37.9%)	0.476
Abdominal distension	12 (100%)	28 (100%)	1.00
Shock	12 (100%)	9 (32.1%)	0.003
Erythema of abdominal wall	10 (83.3%)	22 (78.6%)	0.7301
Palpable bowel loops	4 (33.3%)	2 (7.1%)	0.1004

Table3. Laboratory findings

Laboratory findings	Non-survivors (N=12) (Min, Max)	Survivors (N=28) (Min, Max)	p-value
WBC count (cells/cu.mm)	9,436 (720-19,780)	8,715 (2100-38,930)	0.775
Hemoglobin (g/dL)	10.5 (7.2-12.4)	12.4 (8-18)	0.007
Hematocrit (%)	31.2 (20.9-39.6)	36.4 (23.3-51.4)	0.012
Platelet count (cell/cu.mm)	72,250 (4,000-261,000)	162,160 (2,500-509,000)	0.039
INR	2.19 (1.63-4.0)	1.28 (0.92-2.09)	0.019
Metabolic acidosis	11 (91.7%)	16 (57.1%)	0.0771
Hemoculture positive within 94 hours	3 (25%)	7 (25%)	1.00
Ascitic fluid culture	5 (41.7%)	18 (64.3%)	0.3285

From the laboratory findings (Table3), the non-survivors group had significantly lower hematocrits, hemoglobins, platelet counts and prolonged coagulogram. As for the radiologic findings (Table4), the most common findings were bowel dilatation and pneumatosis intestinalis. However, there was no statistical difference between both groups. Although pneumoperitoneum is a clear indication for surgical intervention, only half of all surgical NEC patients had pneumoperitoneum (Fig.2). Peritonitis was the second common indication for first surgical intervention.

Table 4. Radiologic findings

Radiologic findings	Non-survivors (N=12)	Survivors (N=28)	p-value
Bowel dilatation	12 (100%)	27 (96.4%)	0.5073
Pneumatosis intestinalis	9 (75%)	17 (60.7%)	0.6126
Fixed bowel loops	5 (41.7%)	5 (17.9%)	0.2320
Pneumoperitoneum	4 (33.3%)	16 (57.1%)	0.3006
Portal vein gas	2 (16.7%)	3 (10.7%)	0.6019

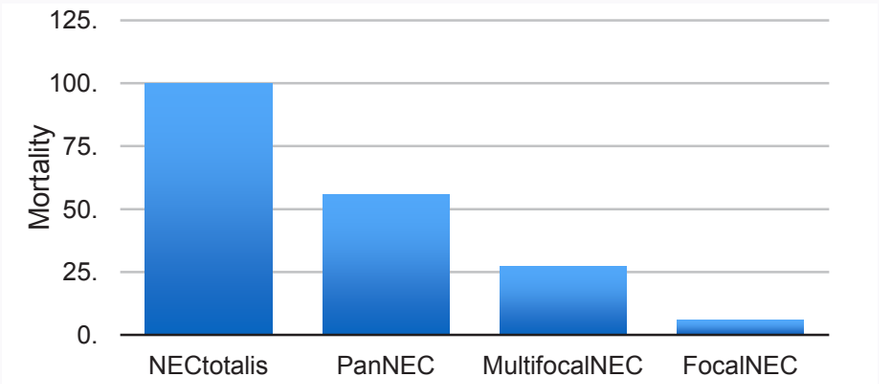

Figure 2. Indication for first surgical intervention

According to the extension of disease that was found intraoperatively, it significantly had impact on mortality. There were no survivors with NEC totalis, compared to pan NEC, multifocal NEC, and focal NEC (Fig.3). On the contrary to the preoperative staging of NEC and the option of first surgical intervention (Table5), which did not significantly affect mortality. Most patients underwent laparotomy as the first surgical intervention and all patients whom underwent bedside PD required a second operation.

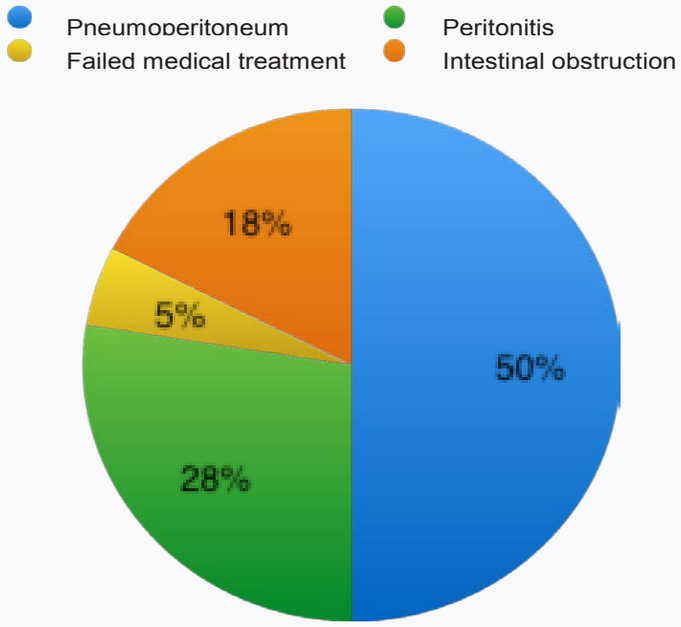

Figure3. Extend of the disease and Mortality

Table 5. Correlation of Mortality and Bell staging , First Surgical intervention

	Non survivors (N=12)	Mortality (%)	p-value
Bell staging [20]			0.6975
IIIA	2	40%	
IIIB	10	31.2%	
First Surgical intervention			0.8687
Bedside PD (N=9)	2	22.2%	
Laparotomy (N=31)	10	33.2%	

Table 6. Long-term outcomes of Survivors

Long-term outcomes	Survivors (N=28)
Infectious complications	15 (53.6%)
• Ventilator Associated Pneumonia (VAP) (N=24)	14 (58.3%)
• Hospital Acquired Pneumonia (HAP)	9 (32.1)
• Septicemia	8 (28.6%)
• Infective diarrhea	6 (21.4%)
GI complications	14 (50%)
• Intestinal failure	14 (50%)
• High output stoma (N=22)	8 (36.4%)
• Recurrence NEC	6 (21.4%)
• Post NEC stricture	2 (7.1%)
Intestinal failure associated liver disease (IFALD)	8 (28.6%)
Wound complication	5 (17.9%)
Total parenteral nutrition duration (days)	39.6 (14-101)
Intensive care unit duration (days)	32.5 (6-154)
Ventilator duration (days)	20.5 (3-133)
Hospital length of stay(days)	91.9 (24-255)
Follow-up time (months)	19.4 (0-67)

As for long-term outcomes of the 28 survivors (Table6), infectious complications (53.6%) were the most common complicationsfollowed by GI complications (50%) and intestinal failure associated liver disease (IFALD) (28.6%). Ventilator associated pneumonia (VAP) was the highest infectious complication in 24 of the 28 survivors required ventilator support and the mean ventilator days were 20 days. Intestinal failure defined as prolonged total parenteral nutrition duration(TPN) duration more than 28 days, was the most common GI complication followed by high output stoma. Stoma management is important to surgical NEC patients in 22 of the 28 survivors had stomas. More than one-third of the survivors with stomas had encountered with high output stomas. It was more commonly found in lower birth weight and younger gestational age babies (Table7). These patients have longer TPNduration, central line duration and length of hospital stay compared to low output stoma patients. Also there were a higher incidence of IFALD and stoma complications in high output stoma patients. Therefore, these patients had an earlier stoma closure at 117 days compared to 195 days in low output patients. IFALD is also a serious

Table 7. Clinical findings of Survivors with stoma

Clinical findings	High output (N=8) (Min, Max)	Low output (N=14) (Min, Max)
Gender		
Male (N/%)	2 (25%)	8 (57%)
Birth weight (grams)	1,524.7 (870-2,270)	2,168.7 (1,320-3,490)
Gastrational age (weeks)	31.1 (28-37)	35.5 (32-40)
Total parenteral nutrition duration (days)	117.4 (104-153)	29.4 (14-97)
Intestinal failure	8 (100%)	5 (35.71%)
Intestinal failure associated liver disease	5 (62.5%)	3 (21.42%)
Central line insertion	8 (100%)	4 (28.57%)
Central line duration (days)	78.88 (22-167)	18 (9-25)
Central line infection	4 (50%)	3 (75%)
Stoma complication	8 (100%)	10 (71.42%)
Stoma duration (days)	117.4 (104-153)	195.2 (50-587)
Hospital length of stay (days)	170.8 (82-254)	72.7 (25-255)

long-term complication of the survivors of surgical NEC. Half of the survivors had prolonged TPN use more 28 days, the mean TPN duration was 39 days. Mean maximum total bilirubin level was 13.3mg/dL (range 3.2-27.9), direct bilirubin 11mg/dL (range 3.7-24.3), AST 195.3U/L (range 27-438), ALT 137U/L (range 11-320) and GGT 342.6 U/L (153.8-531.5). However, it was reversible. No patient had liver failure and the serum liver function test returned to normal after a period of full enteral feeding.

Recurrent NEC was found at 21.4% which only one-third required surgery. Their mean gestational age was 31.2 weeks (range 27-40) and mean birth weight was 1,426g (range870-2,900). Two infants required surgery due to peritonitis and pneumoperitoneum. The mortality rate was 33.3% which was similar to primary NEC. Post NEC stricture was found at 7.1% which all required surgery. Their post operative course was uneventful.

Wound complications were found at 17.9%, the most common complication was wound infection. One patient had wound infection then developed wound dehiscence which required reoperation for wound re-suturing and eventually was discharged home uneventfully.

Mean length of hospital stay was 91 days, 78% achieved full oral feeding and remaining went home on tube feeding. The mean follow-up period was 19.4 months, unfortunately 2 patients lost to follow-up.

From all factors that were analysed, 7 prognostic factors were found to statistically affect the mortality of surgical NEC patients (Table8). Extremely preterm and shock had lowest Number needed to harm of 2 for mortality which meant for every 2 extremely preterm patients or patients with shock, one will die. Thombocytopenia had NNH of 6 for mortality which meant for every 6 patients with thrombocytopenia, one will die.

Table 8. Prognostic factors that affect mortality

Prognostic factors	Risk difference	Number needed to harm
Extremely preterm (Gestational age under 28weeks)	77.78	2
Shock	57.14	2
Coagulopathy (INR>1.5)	45.56	3
Extremely low birth weight (Birth weight under 1,000grams)	43.14	3
Anemia (Hct<30%)	40.48	3
Umbilical catheter insertion	35.33	3
Thrombocytopenia (Platelet<50,000 cells/cu.mm)	19.44	6

Discusstion

The incidence of NEC varies from 1-3 per 1000 live births in many neonatal intensive care units.[3-7] In the NICHD Neonatal Network cohort, rates of NEC were related to birth weight.[8] Lin and Stoll[5] reported that the rates of NEC were higher in very low birth weight (VLBW) infants. Other studies have confirmed that the incidence of NEC and the mortality from NEC are inversely proportional to birth weight and gestational age.[9,10] Mortality rates from NEC are high, ranging from 15-30%.[4,5,8,11,12] The highest mortality rates occurred in VLBW infants who were male.[4] About 27-50% of NEC cases required surgical intervention.[3,11-15] The medical case fatality rates were 5% to 10% and surgical fatality rates were 23% to 36%.[3] In NEC patients, most widely accepted indication for surgery is pneumoperitoneum. Ververidis, Kiely and Spitz[16] reported the indications for operation of neonates with NEC included pneumoperitoneum in 45%, clinical deterioration in 37% and intestinal obstruction in 18%. In our study, pneumoperitoneum was found only in 50% of surgical NEC patients, second indication for surgery was peritonitis in 28% and third, intestinal obstruction in 18%. It is confirmed that the presence of pneumoperitoneum is not demonstratable in neonates with intestinal perforations.[17-19] It is also reported that the patient who had thrombocytopenia, persistent metabolic acidosis reliably indicated the presence of gangrenous bowel.[1]

From our study, the mortality rate for surgical NEC was 30% which meant 70% of all patients survived and returned home to their parents. The survival rate of surgical NEC in our institute has greatly improved from 48.3% up to 70%.[2] We found 7 prognostic factors that affect mortality; extremely preterm (GA<28 weeks), shock, coagulopathy (INR>1.5), extremely low birth weight (BW<1,000gm), anemia (Hct<30%), umbilical catheter insertion, and thrombocytopenia (platelet <50,000/mm^3), respectively. Extremely preterm and shock were the factors that had the highest impact affecting mortality. The factors that do not affect mortality are APGAR score, WBC count, metabolic acidosis, positive hemoculture and ascitic fluid culture, radiologic findings, Bell staging of NEC and first surgical intervention.

Despite the mortality, surgical NEC survivors are more likely to have morbidities. This study showed complications which are comparable to other international studies[3,5,16,22] that reflect the standardization of care of surgical NEC patients in our institute. Survivors have long hospitalization due these variety of complications, the average was 3 months in total and at least 1 month in the ICU. These numbers are even higher in survivors with intestinal failure especially in patients with high output stoma. High output stoma patients are more challenging for post-operative care. High output stoma is more common in lower birth weight and younger gestational age patients. They require longer TPN duration and central line duration which resulted in higher incidence of IFALD and stomal complications compared to low output stoma patients. Surprisingly, there was higher incidence of central line infection in the low stoma output patients despite the lower central line duration. This might be the results of small sample size or the defect

of central line management which should be reviewed. Half of our survivors had intestinal failure which is a serious long-term complication. Intestinal failure develops when there is inadequate functional intestine to absorb the nutrients required for growth that results from intestinal resection or from poor functional of residual intestine.[20] Short bowel syndrome is one of the most serious long-term GI complications of NEC with an incidence of up to 23% in survivors.[21] Short bowel syndrome is considered the major cause of intestinal failure, however in our study there was no patient that had extensive short bowel syndrome. After optimal bowel rehabilitation and stomal closure to gain intestinal continuity, all patients were discharge with full enteral feeding. For IFALD, the well-known risk factor was prolonged TPN use and aggravated by episodes of sepsis. However, it was reversible and no patient succumbed into liver failure. Twenty-one percent of survivors developed recurrent NEC, our number is quite high compared to other studies that showed the incidence of recurrent NEC was under 10%.[22-24] The higher numbers presumably because of small sample size and all patients were NEC (Bell staging) stage 3. The mortality of patients with recurrent NEC were similar to primary NEC of 33.3%. However, for post NEC stricture, our study showed a lower incidence of only 7% compared to 10-35% from other studies.[25-27] All post NEC stricture patients required re-operation and all were discharged home, uneventfully. The mean follow-up time was more than 1.5 years and most were doing well except for 2 which lost to follow-up.

The limitation of our study is the retrospective nature which may lead to historical data loss. Secondly, a small sample size which a multi-center study should be conducted.

Conclusion

The outcome of surgical NEC has improved drastically. The survival rate is comparable to other large centers. The prognostic factors that have high impact for mortality are extremely preterm and shock. These factors will help predict the prognosis of patients with surgical NEC prior to the surgical intervention. Hopefully, with aggressive measures starting from admission will help reduce the mortality for these unfortunate babies

Further multiple centers studies are essential for NEC patients to find a cure or prevention to reduce the morbidity and mortality, and also systematic follow-up at a later stage is necessary to improve the quality of life of the survivors post-NEC.

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