Original Article

Risk factors for parenteral nutrition-dependence and mortality with the short bowel syndrome: a 10-year retrospective study in Thailand

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Background and Objectives: Short bowel syndrome (SBS) is a rare and life-threatening disease. Few studies have investigated risk factors for parenteral nutrition (PN)-dependence and death in SBS. Accordingly, the aim of this study was to investigate the risk factors for PN-dependence and long-term mortality in SBS. **Methods and Study Design:** This retrospective study reviewed and evaluated children and adults who were diagnosed with SBS at King Chulalongkorn Memorial Hospital from October 2005 to January 2015. Age, causes of SBS, length of remnant bowel, type of anastomosis, types of nutrition support, SBS-associated complications, PN-dependence rate, duration of PN-dependence, mortality rate, and causes of death were evaluated. **Results:** Twenty-two adults and 19 children were reviewed. The median follow-up time was 48 months. At the end of follow-up, PN-dependence rate was 51.2%. The residual colon ≥50% group had a significantly lower PN-dependence rate, with a hazard ratio of 0.36 (95% CI: 0.14-0.93; p=0.03). The most frequent cause of death was infection, with the highest percentage of mortality occurring within the first 2 years after surgery. The mortality rate was 53.8% and the residual colon ≥50% group had a significantly lower mortality rate, with a hazard ratio of 0.36 (95% CI: 0.14-0.88; p=0.03). **Conclusions:** PN-dependence and death occurred in about half of all patients. Residual colon ≥50% was significantly associated with lower death rate and PN-dependence. The crucial role of colon in continuity as a protective factor should be investigated further in prospective studies.

Key Words: short bowel syndrome, parenteral nutrition-dependence, catheter-related bloodstream infection (CRBSI), residual colon, survival

INTRODUCTION

Short bowel syndrome (SBS) is a rare and often life-threatening condition. SBS is characterized by the loss, either in length or in function, of a significant portion of the small intestine, which results in inadequate absorption of enteral nutrients. Short bowel is generally defined as small bowel remnant less than 150-200 cm in adults or loss of at least 50% of the small bowel in pediatric patients.[1-3] Patients with this condition usually suffer from dehydration, electrolyte imbalance, diarrhea, and malnutrition. A significant portion of patients with SBS depend on permanent parenteral nutrition (PN), as in cases of intestinal failure, or transient PN, as in cases of intestinal insufficiency. Intestinal adaptation is a process that facilitates weaning of the patient away from PN. SBS is associated with high rates of serious morbidity and mortality, which is due to both the condition itself and treatment-related complications, especially PN-related infections and PN-associated liver disease.

Many factors contribute to PN-dependence and high mortality in SBS, including age, type of intestinal resection (end-enterostomy, jejunocolic anastomosis, or jejunoileocolic anastomosis), length of small and large bowel remnant, and presence of ileocecal (IC) valve.[4-7] Studies in SBS are few and insufficient. Most studies that have focused on clinical course, complications, and risk factors for PN-dependence and mortality are outdated, given the advances in SBS treatment. Additionally, very few studies have been conducted in Asian populations, and none of those was reported from Thailand.

The aim of this study was to identify risk factors for PN-dependence and long-term mortality in patients with SBS. Differences in clinical characteristics of SBS between children and adults were also evaluated.

METHODS

Medical charts of all consecutive children and adults who were diagnosed with SBS (ICD-10 code 91.20) at King Chulalongkorn Memorial Hospital (KCMH) (Bangkok, Thailand) during the October 2005 to January 2015 study

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period were reviewed. KCMH is one of Thailand's largest university-based national tertiary referral centers. SBS is defined on the basis of a remnant of small bowel beyond the ligament of Treitz with a length ≤200 cm in adults or loss of ≥50% of small bowel length from surgical resection or congenital defect in children. Patients who died within 1 month after SBS diagnosis were excluded, given that the aim of the study was to evaluate long-term outcomes. Patients who died from malignancy were also excluded. Small bowel length data was collected from intraoperative record or small bowel follow-through. The protocol for this study was approved by the Institutional Review Board (IRB; number 485/58) of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Study design

This 10-year retrospective medical chart review included 41 children and adults that were diagnosed with SBS during the study period. Gender, age at onset of SBS, causes of SBS, length of remnant small bowel, percentage of residual large bowel, type of intestinal resection, presence/absence of an IC valve, hospital length of stay, types of nutrition support (in the hospital and at the end of follow-up), SBS-associated complications, PN-dependence rate, duration of PN-dependence, mortality rate, and causes of death were evaluated. Age, type of intestinal resection, length of remnant small bowel, percentage of residual large bowel, and presence of IC valve were analyzed as potential risk factors for PN-dependence and death. Type of intestinal resection was classified into the following three subtypes: end-enterostomy, jejunocolic anastomosis, and jejunoileocolic anastomosis. PN-associated liver disease (PNALD) is defined as liver biochemical abnormalities (total bilirubin ≥2 mg/dL) in patients who receive PN without other causes of abnormal liver function such as drug-induced liver injury, viral hepatitis, sepsis, and bile duct obstruction. Patients who were unable to successfully wean off of PN or who relapsed within 1 year of PN cessation were defined as PN-dependent. All patients were followed-up until death or until January 2015.

Nutritional and SBS care

After massive bowel resection, all patients needed total PN to guarantee nutrition support. In adult patients; target calories, protein, lipids and volume from nutritional support were 25-35 kcal/kg/day, 1.2-2 g/kg/day, 1-2 g/kg/day, and 25-40 mL/kg/day, respectively, which depended upon age, sex, baseline nutritional status, comorbidities, and other factors. In children, these nutritional requirements were calculated according to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines.[8] After adequate fluid, electrolytes and recovering of bowel function (diarrhea less than 2,000 mL/day), enteral nutrition (EN) was started with standard polymeric isotonic formula (usually at the second to third week after surgery). Standard whole food diets without sugar-containing beverages and sweets were encouraged as soon as possible.

All patients received proton-pump inhibitors to reduce gastric hypersecretion for at least 6 months after bowel resection. Oral loperamide (2 mg with each meal) was started and then titrated to achieve optimal fecal content. Short term octreotide was prescribed in patients who still had fluid and electrolyte imbalance despite conventional therapy (4/41 patients). Antibiotics for treatment of small intestinal bacterial overgrowth (mostly ciprofloxacin or metronidazole) were ordered in 7 patients who were diagnosed with positive breath test. Neither growth hormone nor glucagon-like peptide-2 (GLP2) analog (teduglutide) was ever given. Moreover, intestinal transplantation was never performed since our center lacks surgeon expertise for this type of surgery.

Statistical analysis

Data were analyzed using SPSS Statistics Version 17 (SPSS, Inc., Chicago, IL, USA). Differences in clinical characteristics, PN-dependence, SBS-related complications, and death between pediatric and adult patients were analyzed by Pearson's chi-square for categorical parameters and independent samples t-test for continuous data. Median follow-up time was determined by Kaplan-Meier survival analysis. Risk factors for PN-dependence and long-term mortality were evaluated and identified using Cox regression analysis. Data are shown as number, number and percentage, mean ± standard deviation, median and range, or median and interquartile range. A p-value of less than 0.05 was regarded as statistically significant.

RESULTS

Clinical characteristics

A total of 62 patients were diagnosed with SBS during the study period. The 15 patients who died within 1 month after diagnosis and the 6 patients who died from malignancy were excluded. The remaining 41 patients were enrolled, including 22 adult patients (8 men, 14 women) and 19 pediatric patients (11 men, 8 women). The median follow-up time was 48 months (range: 2-111). Two patients (1 adult and 1 child) were lost to follow-up. Mean age at the onset of SBS in children and adults were 1.6±4.1 years and 54.9±19.6 years, respectively. The median length of residual small bowel was 50 cm (range: 0-90) in pediatric patients and 45 cm (range: 0-200) in adults. The most common type of intestinal resection was jejunocolic anastomosis (46.3%), followed by jejunoileocolic anastomosis (31.7%), and end-enterostomy (22%). The most common cause of SBS was necrotizing enterocolitis (NEC; 36.8%) in children and mesenteric ischemia (50%) in adults. There were 8 cancer patients who did not develop cancer recurrence by the end of the study follow-up period. The etiologies of SBS in cancer patients were gut obstruction (either from cancer or postsurgical adhesion) (75%), mesenteric ischemia from emboli (12.5%), and trauma (12.5%). The median length of hospital stay was 104 days (range: 12-768). Catheter-related bloodstream infection (CRBSI) occurred in 58.5% of patients (24/41). CRBSI occurred in 68.4% (13/19) of children and 50% (11/22) of adults (p=0.233). The rate of CRBSI was 3.3 per 1,000 catheter-days. Twenty-two percent of patients developed PNALD during the follow-up period. Mean±SD of total bilirubin in patients with PNALD was 9.2±6.3 mg/dL. There were

Table 1. Demographic and clinical characteristics of 41 patients with short bowel syndrome

Factors	Children (n=19)	Adults (n=22)	Total (n=41)
Gender, n (%)			
Man	11/19	8/22	19 (46.3%)
Woman	8/19	14/22	22 (53.7%)
Follow-up time, median (range)	72 (2.3-111) (months)	18 (2-108) (months)	48 (2-111) (months)
Length of hospital stay (days), median (range)	201 (30-602)	69 (12-768)	104 (12-768)
Type of intestinal resection, n (%)			
End-enterostomy (Type 1)	3/19	6/22	9 (22%)
Jejunocolic anastomosis (Type 2)	10/19	9/22	19 (46.3%)
Jejunoileocolic anastomosis (Type 3)	6/19	7/22	13 (31.7%)
Indications for bowel resection, n (%)			
NEC	7/19	0/22	7 (17.1%)
Gut volvulus	4/19	1/22	5 (12.2%)
Jejunal atresia	5/19	0/22	5 (12.2%)
Hirschsprung disease	2/19	0/22	2 (4.9%)
Gut obstruction	1/19	6/22	7 (17.1%)
Mesenteric ischemia (thrombosis)	0/19	7/22	7 (17.1%)
Mesenteric ischemia (embolism)	0/19	4/22	4 (9.7%)
Trauma	0/19	4/22	4 (9.7%)
Length of remnant small bowel			
Median (range) (cm)	50 (0-90)	45 (0-200)	50 (0-200)
Mean±SD (cm)	45±29.4	66±66	56±52.8
<75 cm, n (%)	14/19	14/22	28 (68.3%)
≥75 cm, n (%)	5/19	8/22	13 (31.7%)
PN during hospitalization, n (%)	19 (100%)	22 (100%)	41 (100%)
PN at the end of follow-up*, n (%)	10 (52.6%)	11 (50%)	21 (51.2%)
PNALD**, n (%)	7 (36.8%)	2 (9.1%)	9 (22%)
CRBSI*, n (%)	13 (68.4%)	11 (50%)	24 (58.5%)
Death***, n (%)	7/18 (38.9%)	14/21 (66.7%)	21/39 (53.8%)
Cause of death, n (%)			
CRBSI	3/7	2/14	5 (23.8%)
Sepsis	2/7	2/14	4 (19%)
Hospital-acquired pneumonia	0/7	3/14	3 (14.3%)
Acute pyelonephritis	1/7	0/14	1 (4.8%)
Intra-abdominal infection	1/7	0/14	1 (4.8%)
Infective endocarditis	0/7	1/14	1 (4.8%)
Ischemic heart disease	0/7	4/14	4 (19%)
Liver failure	0/7	1/14	1 (4.8%)
Unknown	0/7	1/14	1 (4.8%)

CRBSI: catheter-related bloodstream infection; IQR: interquartile range; NEC: necrotizing enterocolitis; PN: parenteral nutrition; PNALD: parenteral nutrition-associated liver disease; SBS: short bowel syndrome; SD: standard deviation.
p-value <0.05 indicates statistical significance; (*$p>0.05$, **$p=0.032$, ***$p=0.083$).

significantly more patients with PNALD in children than in adults (7 vs 2; $p=0.032$). Length of hospital stay, CRBSI, and death were not significantly different between children and adults. Demographic and clinical characteristics of the study population are shown in Table 1.

PN-dependence

Immediately after surgery, all patients received total PN and then gradually resumed enteral nutrition. At discharge, 23 of 41 patients (56.1%) were classified as PN-dependent, with 18 patients successfully able to discontinue PN. By the end of the follow-up period, 2 additional patients were able to discontinue PN, which left 21 of 41 patients (51.2%) as PN-dependent. There was no significant difference between the number of children and adults that were PN-dependent at the end of follow-up (55.6% vs 52.4%; $p=0.843$). The 9 children who were able to discontinue PN had a median residual small bowel length of 55 cm (range: 10-90), whereas the 11 adults had a median residual small bowel length of 85 cm (range: 15-200). The minimum small bowel length required for complete PN-weaning in children was 10 cm with colon and 50 cm without colon, while adults required 15 cm with colon and 200 cm without colon. The median time to PN discontinuation in both groups was 18 months; however, adults had a shorter median time to PN discontinuation than children (18 vs 60 months, respectively). Percentage of residual colon ≥50% was associated with significantly lower PN-dependence, with a hazard ratio of 0.36 (95% CI: 0.14-0.93; $p=0.03$). There was no statistically significant difference in hazard ratio for PN-dependence by Cox regression analysis for age group, type of intestinal resection, length of residual small bowel, or presence or absence of IC valve (Table 2 and Table 3).

Long-term mortality

By the end of follow-up, 21 of 39 patients (53.8%) had died. The mortality rate in children and adults with SBS in this study was 38.9% (7/18) and 66.7% (14/21), respectively ($p=0.083$). The most common cause of death

Table 2. Hazard ratio of factors for parenteral nutrition dependence and death in short bowel syndrome by univariate Cox regression analysis

Factors	PN dependence			Death		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Patient type						
Children	1	-	-	1	-	-
Adult	2.61	0.94-7.24	0.065	2.74	1.05-7.2	0.04
Type of intestinal surgery						
End-enterostomy	1	-	-	1	-	-
Jejunocolic anastomosis	0.98	0.32-3.07	0.98	1.98	0.54-7.23	0.30
Jejunoileocolic anastomosis	0.4	0.13-1.21	0.11	1.10	0.34-3.54	0.88
Presence of IC valve						
No	1	-	-	1	-	-
Yes	1.25	0.45-3.52	0.67	0.58	0.19-1.74	0.33
Length of remnant SB						
<75 cm	1	-	-	1	-	-
≥75 cm	0.77	0.22-2.69	0.69	0.9	0.35-2.37	0.84
Percentage of residual colon						
<50%	1	-	-	1	-	-
≥50%	0.36	0.14-0.93	0.03	0.36	0.14-0.88	0.03
PN dependence						
No				1	-	-
Yes				2.16	0.85-5.49	0.1

CI: confidence interval; IC: ileocecal; PN: parenteral nutrition; SB: small bowel.
p-value<0.05 indicates statistical significance.

Table 3. Hazard ratio of factors for parenteral nutrition dependence and death in short bowel syndrome by multivariate Cox regression analysis

Factors	PN dependence			Death		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Patient type						
Children	1	-		1	-	
Adult	1.83	0.86-9.23	0.18	3.52	0.98-11.42	0.06
Percentage of residual colon						
<50%	1	-	-	1	-	-
≥50%	0.36	0.14-0.93	0.03	0.36	0.14-0.88	0.03

CI: confidence interval; IC: ileocecal; PN: parenteral nutrition; SB: small bowel.
p-value <0.05 indicates statistical significance.
Adjusted variables: type of intestinal surgery, presence of IC valve, length of remnant SB, PN-dependence.

was infection (100% in children, 57% in adults). The remaining adults died from ischemic heart disease (4/14), liver failure from PNALD (1/14), and unknown (1/14). The death rate was highest in the first 2 years after diagnosis of SBS. Adults had a significantly higher mortality rate than children, with a hazard ratio of 2.74 (95% CI: 1.05-7.2; p=0.04) on univariate Cox regression analysis. However, the significant finding of age group was not found on multivariate Cox regression analysis (p=0.06). Additionally, percentage of residual colon ≥50% was significantly associated with lower mortality rate, with a hazard ratio of 0.36 (95% CI: 0.14-0.88; p=0.03) (Table 2 and Table 3). Kaplan-Meier survival analysis also showed a significantly higher survival rate in children than in adults (median survival 168 months vs 18 months; p=0.032), and a significantly higher survival rate in patients with ≥50% residual colon vs. patients with less than 50% residual colon (median survival 85.8 months vs 13 months; p=0.02) (Figure 1). No statistically significant association was found between survival and type of intestinal resection, presence or absence of IC valve, length of remnant small bowel, and PN-dependence.

DISCUSSION

In this study, we investigated the clinical characteristics and outcomes of children and adults with SBS that were associated with different primary causes, type of surgical resection, PN-dependence rate, death rate, and factors that affected PN-dependence and death. In our study, the three most common etiologies of SBS in children were NEC (36.8%), jejunal atresia (26.3%), and gut volvulus (21.1%). This result was quite similar to the results of a previous study (NEC 45%, jejunal atresia 17.5%, and gut volvulus 17.5%).[9] In adults, the three most common causes of SBS were mesenteric ischemia (50%), gut obstruction (31.8%), and trauma (18.2%). From previous reports in adults, the most common cause of SBS was almost always mesenteric ischemia (13-43%) – similar to our study.[4,10-12] Crohn's disease, which is the leading cause of SBS in Western countries (6%-36%), was not found in this study due to a very low prevalence of inflammatory bowel disease in Thai population.

Jejunocolic anastomosis was the most common type of

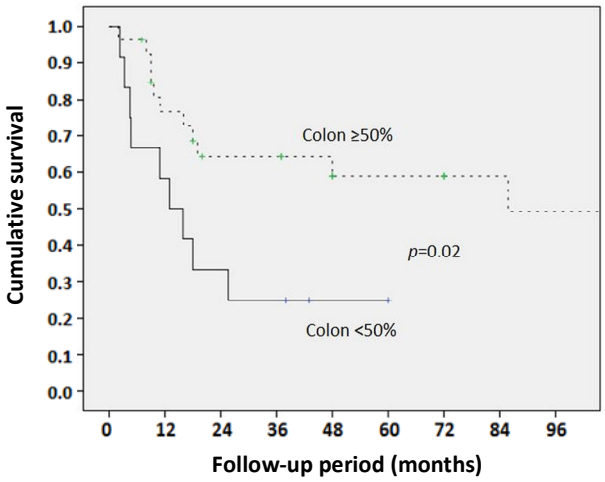

Figure 1. Probability of survival (Kaplan-Meier curve) between patients with ≥50% residual colon and <50% residual colon

intestinal resection in both children and adults with SBS, followed by jejunoileocolic anastomosis and end-enterostomy. This was similar to the findings of 2 previous studies.[10,13] The jejunum and ileum were the two most common parts of the small bowel to be affected in both children and adults.

The rate of CRBSI was very high in our study and it was the leading overall cause of death. Our rate of CRBSI per 1,000 catheter-days was 3.3. This result was higher than that reported in a previous study that found rates of CRBSI of 0.73 and 0.48 per 1,000 catheter-days in children and adults, respectively.[14] The high rate of CRBSI found in our study may have been due to the fact that our center did not have a well-established, effective CRBSI prevention program (especially specialized catheter insertion teams and nursing care teams) during the study period.[15] Accordingly, prevention and prompt treatment of infectious complications, especially CRBSI, is the key to reducing the mortality rate in patients with SBS.

PNALD was more common in pediatric patients than in adult patients (36.8% vs 9.1%; p=0.032); however, there was one case of overt liver failure among the adults, while there were none among pediatric patients. This result was similar to data from previous studies, which reported that PNALD occurred in 15%-85% of children and in 7%-14% of adults.[16-18] The incidence of PNALD was much greater in children, especially those born prematurely. The underlying causes of this finding were believed to be reduced bile acid pool size, immature enterohepatic recirculation, and specific underlying diseases, such as NEC, frequent infection, and the frequent use of antibiotics.[16]

The PN-dependence rate in our study was 51.2% at the median follow-up time of 48 months. A significant proportion of patients (43.9%) were able to wean themselves away from PN during hospitalization, which may have been due to a lengthy hospital stay (median 104 days). According to recent ESPEN guidelines, SBS is the leading cause of chronic intestinal failure (IF) in adults and children (75% and 50%, respectively).[19] The frequency of IF or PN-dependence in SBS patients from previous studies varied between 36-74% depending on follow-up period.[9,20] PN-dependence could be reversible because of intestinal adaptation process but unlikely to happen after 2-3 years.[19] PN-dependence rate in our study was comparable with other studies that reported 48% of PN-dependence rate in similar median follow-up time.[4,13] A previous study reported a minimum residual small bowel length required to facilitate complete discontinuation of PN of 25 cm in children and 40 cm in adults.[14] In our study, the minimum small bowel length required for complete PN-weaning in children was 10 cm with colon and 50 cm without colon, while adults required 15 cm with colon and 200 cm without colon. As such, patients with only 10-15 cm of residual small bowel and an intact colon still had the potential to achieve complete discontinuation of PN.

Previous studies described several key factors that affect intestinal adaptation and a resulting discontinuation of PN. Intestinal adaptation in children is usually better than in adults, as a result of better growth of remnant small bowel in children. Anatomic features that are associated with intestinal adaptation include the site of resection (ileum better than jejunum), remnant small bowel length, and percentage of remaining colon.[4-7] In our study, almost all determining factors, except for percentage of residual colon, had no significant influence on intestinal adaptation. The importance of colon in continuity in patients who lose a critical mass of small bowel is that it can help compensate for the small bowel by reabsorbing water and electrolytes. The colon also facilitates reabsorption of nutrients, especially short-chain fatty acids (SCFAs) and medium-chain triglycerides, which can provide 500-1,000 kcal/day. Moreover, the colon can slow the transit time and stimulate intestinal adaptation via several gut hormones, such as peptide YY, glucagon-like peptide-1, and glucagon-like peptide-2.[10,21,22]

In a retrospective study of 268 adults with SBS, residual colon more than 57% was significantly associated with a higher probability of successful discontinuation of PN.[4] More than two-thirds of the patients in our study had small bowel length less than 75 cm, which was found to be significantly associated with greater probability of permanent dependence on PN in a previous study.[4] Once again, our finding emphasizes the importance of residual colon, especially in patients with extremely short bowel. The role of IC valve for slowing gastric and small bowel transit time, which are factors that improve the probability of achieving successful independence from PN is still being debated. A study in 8 patients without IC valve showed similar gastric emptying/small bowel transit time, with no major colonoileal reflux compared to IC valve-intact patients.[23] In contrast, other studies found that the absence of IC valve was associated with severe and persistent malabsorption that finally led to failure of intestinal adaptation.[24,25]

One previous study reported an SBS-related mortality rate of 32% at a median follow-up time of 64 months.[13] Our study had a higher death rate (53.8%) at a shorter median follow-up time, which may be due to the high rate of infection. Most of the patients in a previous study died from the primary disease that caused the development of SBS.[13] In the present study, the highest rate of death occurred within the first 2 years after the diagnosis of SBS,

because most of the PN-related complications and infections occurred during this period. Therefore, the first 2 years after surgery is the critical period for prevention and early treatment of SBS-related complications. Adults had significantly higher mortality than children, with a hazard ratio of 2.74 in univariate Cox regression analysis. Adults usually have more underlying diseases, which leads to a higher death rate in adults than in children.[14] In our study, 28.6% of adults died from ischemic heart disease. Nevertheless, adults only tended to have a higher rate of death than children, with a hazard ratio of 3.52 (p=0.06) in multivariate analysis. These non-statistically significant results may be attributable to the small sample size, which could have the effect of underpowering the study.

Another risk factor that significantly influenced the mortality rate was percentage of residual colon. The importance of colon in continuity is again noted, but the underlying mechanism of this finding is not well-understood. Given that the major cause of death in our study was infection, it is plausible that the role of colon in continuity may be associated with improved immune function. SCFAs, which are bacterial fermentation products from undigested carbohydrates in the colon, can affect immune system regulation. After uptake by colonocytes, SCFAs increase the expression of antimicrobial peptides and modulate immune mediator production – particularly IL-18, which is a key cytokine for the repair and maintenance of epithelial integrity. SCFAs can also regulate the differentiation, recruitment, and activation of many immune cells, including neutrophils, macrophages, and T-lymphocytes.[26] This may result in less infection and less death. The length of small bowel and the presence or absence of IC valve were not shown to have significant influence on mortality in this study.

To the best of our knowledge and based on our review of the literature, this is the first study in SBS patients to be conducted in Asia. As such, this study provides additional information about clinical characteristics and outcomes relating to this rare and often deadly condition. This study also has some mentionable limitations. First, the retrospective design of this study suggests the possibility of missing or incomplete data. Second, the small sample size of our study can be attributed to the rarity of this disorder. Third and last, the absence of Crohn's disease as a cause of SBS in our study can be explained by a very low incidence of Crohn's disease among Thai people. All of these factors could play a role in reducing the power needed to reveal statistically significant risk factors for PN-dependence and long-term mortality.

Conclusion

In conclusion, PN-dependence and death occurred in about half of all patients. The most frequent cause of death was infection, with the highest percentage of mortality occurring within the first 2 years after surgery. Residual colon ≥50% was significantly associated with lower death rate and lower PN-dependence. The crucial role of colon in continuity as a protective factor for both PN-dependence and death should be investigated in a future prospective study.

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AUTHOR DISCLOSURES

The author declare no conflict of interest.

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