



Timing of enterostomy closure for neonatal isolated intestinal perforation

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ABSTRACT

Purpose: No consensus guidelines exist for timing of enterostomy closure in neonatal isolated intestinal perforation (IIP). This study evaluated neonates with IIP closed during the initial admission (A1) versus a separate admission (A2) comparing total length of stay and total hospital cost.

Methods: Using 2012 to 2017 Pediatric Health Information System (PHIS) data, 359 neonates with IIP were identified who underwent enterostomy creation and enterostomy closure. Two hundred sixty-five neonates (A1) underwent enterostomy creation and enterostomy closure during the same admission. Ninety-four neonates (A2) underwent enterostomy creation at initial admission and enterostomy closure during subsequent admission. For the A2 neonates, total hospital length of stay was calculated as the sum of hospital days for both admissions. A1 neonates were matched to A2 neonates in a 1:1 ratio using propensity score matching. Multivariate models were used to compare the two matched pair groups for length of stay and cost comparisons.

Results: Prior to matching, the basic demographics of our study population included a median birthweight of 960 g, mean gestational age of 29.5 weeks, and average age at admission of 4 days. Eighty-seven pairs of neonates with IIP were identified during the matching process. Neonates in A2 had 91% shorter total hospital length of stay compared to A1 neonates (HR: 1.91; 95% CI for HR: 1.44–2.53; $p < .0001$). The median length of stay for A1 was 95 days (95% CI: 78–102 days) versus A2 length of stay of 67 days (95% CI: 56–76 days). Adjusting for the same covariates, A2 neonates had a 22% reduction in the average total cost compared A1 neonates (RR: 0.78; 95% CI for RR: 0.64–0.95; p -value = 0.014). The average total costs were \$245,742.28 for A2 neonates vs. \$315,052.21 for A1 neonates ($p < 0.001$).

Conclusion: Neonates with IIP have a 28 day shorter hospital length of stay, \$75,000 or 24% lower total hospital costs, and a 22 day shorter post-operative course following enterostomy closure when enterostomy creation and closure is performed on separate admissions.

Type of Study: Prognosis Study.

Level of Evidence: Level II.

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Exploratory laparotomy and enterostomy creation are often unavoidable in cases of neonatal isolated intestinal perforation (IIP) when immediate restoration of bowel continuity is not possible [1, 2]. Traditionally, the timing of enterostomy closure is variable and is often influenced by surgeon experience, neonatal weight, and gestational age [1, 3, 4]. Several studies have demonstrated that neonates with lower weight, younger gestational age, and suboptimal nutritional

status have increased morbidities including ventilator-dependence, nutritional-dependence, length of hospitalization, and lower weight and height 7–10 months following enterostomy closure [3, 5, 6]. Despite this evidence, some surgeons advocate for early enterostomy closure to avoid inherent enterostomy related complications, maintain fluid and electrolyte balances, and decrease parental psychologic stress of a neonatal enterostomy [3]. Thus, there is no clear consensus to help pediatric surgeons guide clinical management. Furthermore, few studies have evaluated the impact of enterostomy closure timing on hospital resource utilization [6].

The aim of this study was to evaluate the difference in neonates with IIP closed during a separate admission (A2) versus the initial admission (A1) comparing total length of stay and total hospital cost.

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1. Methods

1.1. Study design

After obtaining IRB approval, the Pediatric Health Information System (PHIS) data was queried. The PHIS database is maintained by the Child Health Corporation of America (Shawnee Mission, KS, USA) and includes demographic, diagnostic, and charge data for freestanding, noncompeting, children's hospitals. The PHIS includes both diagnoses and procedures coded using the *International Classification of Diseases, Ninth Revision (ICD-9)* and the *International Classification of Diseases, Tenth Revision (ICD-10)* as well as Current Procedural Terminology (CPT) codes. We identified cases of neonatal IIP over a 5 ½ year interval (January 1, 2012 to June 30, 2017). Neonates were identified using ICD 9 and 10 codes for IIP (ICD 9: 777.6, 569.83 or ICD 10: P78.0, K63.1). All neonates underwent enterostomy creation [CPT: 44125, 44,130, 44,310 or PX ICD 9: 46.01 or ICD 10: Z43.2, Z43.4, Z43.8, Z93.2] and enterostomy closure (CPT: 44620, 44,625, 44,626 or PX ICD 9: 46.50; 46.51 or ICD 10: Z43.2, Z43.4, Z43.8, Z93.2) on the same or a separate subsequent admission.

The cohort was stratified based on timing of enterostomy closure: A2 and A1. A2 neonates underwent enterostomy creation at initial admission and closure during a subsequent admission. A1 neonates underwent enterostomy creation and closure during the same admission. For the A2 neonates, total hospital length of stay was calculated as the sum of hospital days for both admissions.

1.2. Inclusion and exclusion criteria

Neonates aged less than 28 days with a diagnosis of IIP were considered for inclusion in the study. Neonates were excluded if they had any of the following: concurrent diagnosis of NEC, data error of enterostomy closure prior to creation, and incomplete PHIS data.

1.3. Variables, outcomes, definitions

The database records were reviewed for data regarding demographics (birthweight, gestational age, gender, race, ethnicity), use

and total days of mechanical ventilation, use and total days of TPN, infection (urinary tract infection, sepsis, shock, SIRS, CVL, bacteremia, septicemia, peritonitis, and peritoneal abscess), surgical complication flag, enterostomy problems (K453, K9412, K9413, K9419, 56,961, 56,962), concomitant cardiovascular abnormalities (PDA, ASD, VSD, and cardiac anomalies), operative PDA closure (PX codes: 02LR0CT, 02LR0ZT, 02LR0DT, 02LR3ZT, 02LR4DT, 02VR0ZT, 5491), Indomethacin use, primary peritoneal drain (PPD) placement (PX ICD: 0W9G30Z, 0W9G00Z, 0W9G0ZX, 0W9G0ZZ, 0W9G3ZX, 0W2GX0Z and CPT: 49020, 49,021, 49,082), other congenital or genetic defects, and hospital discharge disposition [7,8].

Hospital days for A1 and A2 included days from admission to enterostomy creation, days from enterostomy creation to enterostomy closure, days from enterostomy closure to discharge and total length of stay. Additionally, A2 neonates also had days from initial discharge to admission for enterostomy closure or number of days after discharge until subsequent admission.

Total cost is defined as the total patient costs based upon the Ratio of Cost to Charges (RCCs) submitted by the hospitals on their respective Medicare cost reports [8]. Adjusted total cost is defined as the total patient costs based on the RCCs submitted by the hospitals on their respective Medicare cost reports and adjusted by the CMS wage/price index for the hospital's location [8].

1.4. Statistical analysis

Discrete variables were summarized using frequency (percentages). Continuous variables were summarized with mean plus standard deviation and median plus interquartile range (IQR, range from 25th to 75th percentile).

To minimize biases associated with observational studies, we calculated propensity scores using binary logistic-regression. In order to delineate the surgical decision for enterostomy closure among equal groups, covariates were chosen that could potentially increase the length of hospitalization. They included gender, race, birthweight, gestational age, age at admission, days on ventilator, infection, surgical complications, PDA, treatment of PDA with

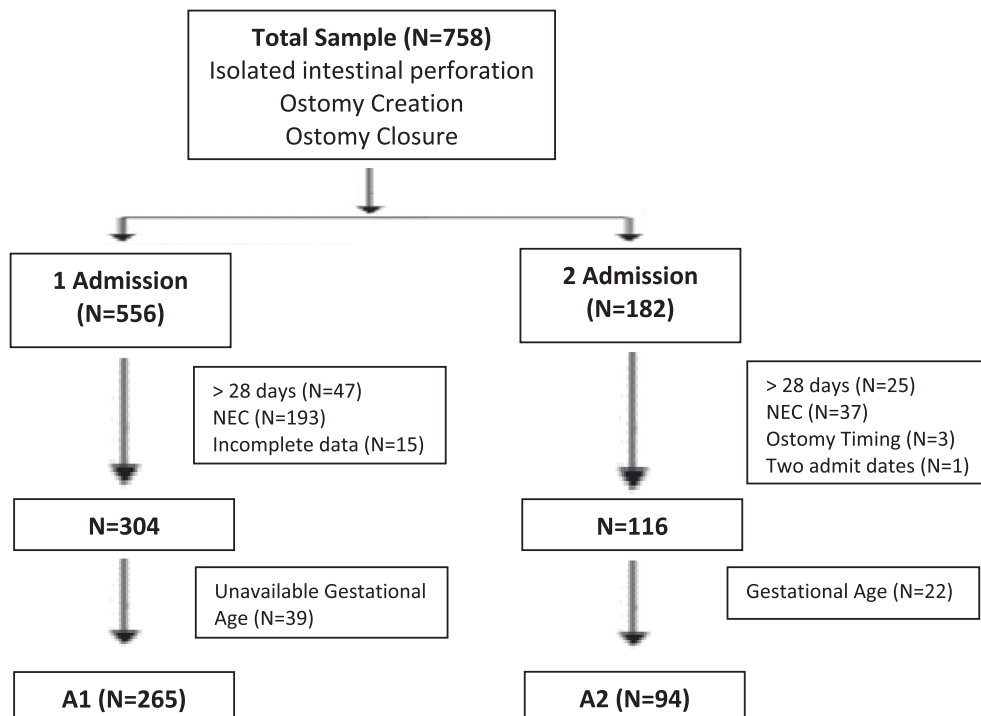


Fig. 1. Flow diagram of neonates included in the study analysis.

indomethacin, cardiac anomalies, and peritoneal drain placement prior to ostomy creation. There were 43 individual surgical complications. The surgical complication variable indicates if a neonate had either none or at least one of the 43 surgical complications. Neonates in each group were matched 1:1 using a Greedy matching of the propensity scores [9]. Greedy matching is a linear matching algorithm where a treatment subject is matched with user-specified control subject creating insignificant imbalance between two groups on the included covariates in the propensity score model. To ensure that the neonates were closely matched, we required that the propensity scores for matched pairs be within 0.2 pooled standard deviation units of the propensity score. Recent research has shown this method results in estimates of the treatment effect with lower mean squared errors as compared to other methods that are commonly used in medical literature [10]. Standardized differences instead of p-values were used to assess the balance between two groups of neonates in the propensity score matched samples and differences of less than 0.10 was used as a threshold to indicate an insignificant imbalance between two groups [11–14].

1.5. Multivariate analysis modeling for length of stay and cost (total and adjusted total)

Cox Proportional Hazard regression with robust standard errors to account for clustering in the matched pairs was used to model length of stay (or time to discharge) between A1 and A2 neonates. Generalized linear models with gamma distribution with adjustment for matched pairs were used to model total and adjusted total costs between two groups of neonates.

Using nonlinear regression models with generalized linear models allow response variables such as cost to have different distribution other than normal distribution. These types of modeling through log-link function avoids the disadvantages of ordinary least square models when the outcome is skewed. Gamma regression model is one of an expected conditional mean type model where quasi-maximum likelihood estimation is used to estimate β values. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

2. Results

2.1. Consort diagram and inclusion criteria

Data were reviewed for 758 neonates undergoing both enterostomy creation and enterostomy closure for IIP at PHIS participating institutions during our study period: 556 A1 and 182 A2. There were 252 neonates excluded from A1 and 66 excluded from A2. Four hundred twenty neonates were compared prior to excluding for missing gestational age and prior to matching. There were 39 neonates in A1 and 22 in A2 with missing gestational age who were excluded from propensity score matching. Three hundred fifty-nine neonates were 1:1 matched: 265 A1 and 94 A2. (See Fig. 1.)

2.2. Pre-matching covariates: All neonates

All 420 neonates combining A1 and A2 are described. Our study population was 66% male and 58% Caucasian. The median birthweight was 960 g. The mean gestational age was 29.5 weeks and average age at admission was 4 days. 96% required mechanical ventilation during the hospitalization with a mean time of 27 days on ventilator. TPN was used in 97% of neonates and 57% of neonates had at least one of the 43 surgical complications. Three-fourths of the neonates had an infection during the hospitalization. 13% were treated with peritoneal drain placement prior to

Table 1

Characteristics and demographics of neonates with isolated intestinal perforation.

Variable	N = 420
Birthweight (g)	
Median	960 g (710–2390 g)
Gestational Age (weeks)	
Mean (SD)	29.45 (5.57)
Gender	
Male	276 (65.7%)
Female	144 (34.3%)
Race	
White	244 (58.1%)
Black	79 (18.8%)
Other	97 (23.1%)
Ethnicity	
Hispanic or Latino	66 (17.8%)
Not Hispanic or Latino	305 (82.2%)
Admit Age (days)	
Mean (SD)	3.84 (5.19)
Median (IQR)	2.00 (0.00–6.00)
Mechanical Ventilation [Time on Ventilator (days)]	
Mean (SD)	27.22 (34.38)
Median (IQR)	14.00 (4.00–38.50)
TPN	408 (97.1%)
Infection	329 (78.3%)
Urinary tract infection (UTI)	57 (13.6%)
Sepsis	41 (9.8%)
Shock	29 (6.9%)
SIRS	3 (0.7%)
Central venous line (CVL)	19 (4.5%)
Bacteremia	41 (9.8%)
Septicemia	198 (47.1%)
Peritonitis	32 (7.6%)
Peritoneal abscess	12 (2.9%)
Disseminated intravascular coagulation (DIC)	23 (5.5%)
Surgical complication	239 (56.9%)
Concomitant cardiovascular abnormalities	
PDA	191 (45.5%)
ASD	131 (31.2%)
VSD	17 (4.1%)
Cardiac anomalies	40 (9.5%)
Other congenital or genetic defect	39 (9.3%)
Peritoneal drain placement prior to ostomy creation	56 (13.3%)
Indomethacin	45 (10.7%)

Gestational age has non-missing information on 359 neonates.

Ethnicity has non-missing information on 371 neonates.

enterostomy creation. 46% of the neonates had a PDA and a fourth of those neonates were treated with indomethacin (Table 1).

Before matching, standardized differences ranged from 0.051 (Other Race) to 0.608 (time on ventilator). These results indicated that our A1 and A2 groups differed on almost all of the baseline covariates that were chosen to be matched on in our propensity score model.

2.3. Post-matching covariates

Eighty-seven neonates in each group were matched. After matching the two groups, the differences reduced significantly with only two of our covariates being slightly larger than 0.10 (0.106 for black race and 0.126 for age at admission). The standardized differences in Table 2 indicate that the propensity score model was a good fit and showed insignificant imbalances between A1 and A2 neonate groups.

2.4. Multivariate analysis modeling for length of stay and post-operative length of stay

Neonates in A2 had 91% shorter total hospital length of stay compared to A1 neonates (HR: 1.91; 95% CI for HR: 1.44–2.53; $p < .0001$). The median total length of stay was 95 days for A1 (95% CI: 78–102 days) versus 67 days for A2 (95% CI: 56–76 days). Neonates in A2 had a shorter post-operative length of stay following enterostomy

Table 2
Standardized differences of baseline covariates in original and matched sample.

Variable	Standardized difference (original unmatched sample)	Standardized difference (matched sample)	Initial admission (n = 87)	Separate admission (n = 87)
Birthweight				
Mean	0.398	0.085	1908.26	1808.46
SD			1102.21	1249.63
Median			1580	1480
IQR			930–2720	758–2985
Gestational age (weeks)				
Mean (SD)	0.510	0.085	31.60 (5.43)	31.11 (5.93)
Gender				
Male	0.121	0.025	60 (69.0%)	61 (70.1%)
Race				
White	0.211	0.049	59 (67.8%)	57 (65.5%)
Black	0.218	0.106	9 (10.3%)	12 (13.8%)
Other	0.051	0.028	19 (21.9%)	18 (20.7%)
Admit age (days)				
Mean (SD)	0.083	0.126	2.72 (4.34)	3.24 (3.82)
Median (IQR)			1.00 (0.00–4.00)	2.00 (0.00–5.00)
Time on ventilator (days)				
Mean (SD)	0.608	0.038	15.02 (18.87)	15.79 (21.70)
Median (IQR)		0.074	9.00 (3.00–18.00)	7.00 (2.00–25.00)
Infection	0.277	0.078	65 (74.7%)	62 (71.3%)
Surgical complication	0.241	0.092	48 (55.2%)	44 (50.6%)
PDA	0.236	0.047	34 (39.1%)	36 (41.4%)
Cardiac anomalies	0.369	0.000	12 (13.8%)	12 (13.8%)
Peritoneal drain placement prior to ostomy creation	0.202	0.000	9 (10.3%)	9 (10.3%)
Indomethacin	0.224	0.000	7 (8.1%)	7 (8.1%)

closure than A1. The median post-operative length of stay for A2 and A1 respectively were 10 and 32 days. (See Fig. 2.)

2.5. Multivariate analysis modeling for modeling total cost and adjusted total cost

2.5.1. Total cost

Adjusting for the same covariates, A2 neonates had a 22% reduction in the average total cost compared A1 neonates (RR: 0.78; 95% CI for RR: 0.64–0.95; p-value = 0.014). The average total cost was \$245,742 for A2 neonates vs. \$315,052 for A1 neonates (p < 0.001).

2.5.2. Adjusted total cost

Adjusting for the same covariates, A2 neonates had a 24% reduction in the adjusted average total cost compared A1 neonates (RR: 0.76; 95% CI for RR: 0.62–0.93; p-value = 0.0085). The average adjusted total cost were \$235,994 for A2 neonates vs. \$310,518 for A1 neonates (p < 0.001).

3. Discussion

Our study differs from a large portion of the current literature for optimal timing of neonatal enterostomy closure because we specifically excluded neonates with NEC. The pathophysiology of IIP leads to a predictable pattern of bowel pathology, typically seen in the distal ileum with otherwise healthy surrounding bowel [15, 16]. The expected pathology allows for a more distal ostomy, decreasing the possibility of malabsorptive complications and dehydration. Therefore, neonates with IIP are able to tolerate a delayed enterostomy closure more than neonates with NEC. Comparison of long-term survival for IIP and NEC also shows the more favorable nature of IIP. Over the past 30 years, the long-term survival rate of neonates with IIP has improved with survival rates varying from 64% to 90%, compared to reported survival rates of 50% to 65% for certain neonates with NEC. [17–26]. The mortality rate in our study was even more favorable, 1.0%.

Surgical treatment options for IIP include primary peritoneal drain (PPD), exploratory laparotomy with enterostomy creation, and exploratory laparotomy with bowel resection and primary anastomosis [2, 15–20]. PPD is the most cost effective approach, however 20% to 64% of patients require a salvage laparotomy secondary to re-accumulation

of free air, sepsis, fistula, or bowel obstruction [2, 21, 25]. 13.3% of neonates in our study required laparotomy following PPD. Our study excluded neonates who had definitive treatment with either PPD or exploratory laparotomy with primary anastomosis. When enterostomy creation is required due to an inability to restore bowel continuity, the ideal treatment strategy is to optimize the timing of enterostomy closure while limiting surgical complications to obtain bowel continuity. As previously stated, the timing of enterostomy closure in neonates is dependent on both surgeon preference and the neonate's clinical status. Although our study excluded neonates with NEC, the timing of enterostomy closure in this population can shed insight into overall management of enterostomy closure. The disparities currently seen in timing of enterostomy closure specifically following NEC are reflective of the differences in published data. Historically, it was thought that neonates with NEC would have increased post-operative adhesions if enterostomy closure were performed before 6 weeks of its creation. One recommendation for enterostomy closure after NEC is to wait until at least 10 weeks because earlier closure negatively impacts post-operative course, including post-operative ventilation, duration of TPN, time until full enteral feeds, and length of hospital stay [27]. Conversely, another recommendation for enterostomy closure after NEC is to recreate bowel continuity within 6 weeks of the initial laparotomy as there was found to be no significant difference for medical costs between early and late closure as defined by 6 weeks [28]. The severity of NEC pathophysiology typically results in more significant bowel resection when compared to IIP and a more proximal ostomy. Therefore, neonates may require early enterostomy closure due to high ostomy output resulting in dehydration and failure to thrive, inability to achieve enteral independence, or surgical complications, and ultimately may not tolerate a delayed outpatient closure [4]. However, several other studies have shown no significant difference between early and late enterostomy closure in neonates with NEC [5, 28–30].

Similar to evaluations for enterostomy closure in NEC, studies have shown conflicting results and conclusions when evaluating optimal timing of enterostomy closure in IIP [3, 5, 27–30]. Lee et al. showed that the only significant risk factor in developing complications following enterostomy closure was a weight under 2660 g [3]. Other authors investigated if enterostomy closure at weight <2500 g was associated with increased morbidity and found that only incisional hernia was

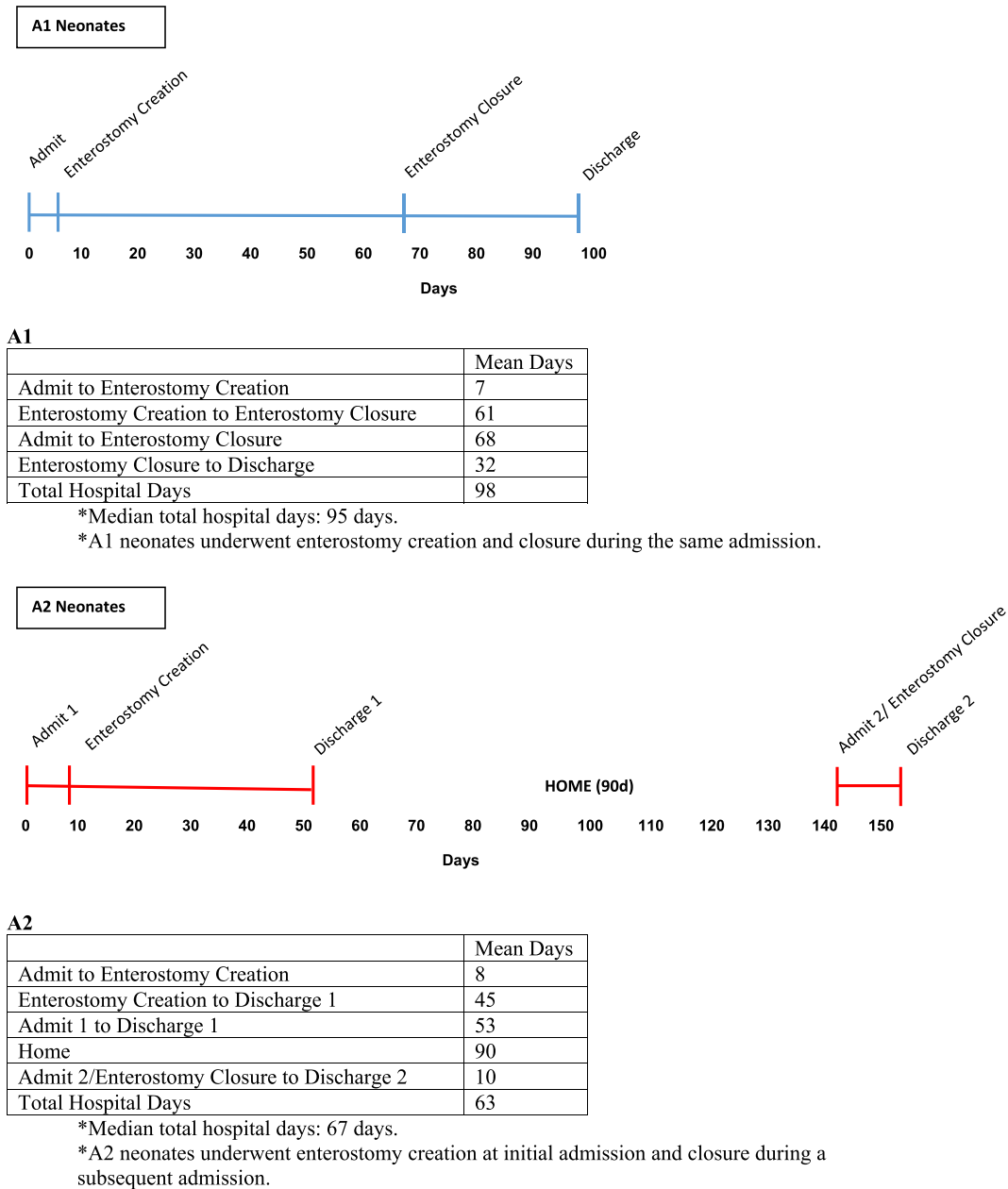


Fig. 2. Comparison of various time periods after A1 neonates were matched to A2 neonates in a 1:1 ratio using propensity score matching (n = 87 pairs).

significantly different as a complication between weight groups [4]. Justifying these results, a recent review of the NSQIP database for enterostomy closure in premature neonates concluded that weight should not be a primary determinant in closure and that comorbidities, predominantly pulmonary, are the key determinants of the safety of enterostomy closure in premature neonates [31].

Enterostomy-related complications occur in 40% of neonates and more commonly occur in neonates with low birth weight and low gestational birth age [5]. Functional and mechanical complications can occur early or late in the hospital course which can influence surgical variability in closure timing. Enterostomy complications, which included infection, functional complications, and mechanical complications, occurred in 18% (74/420) of the neonates reviewed in this study prior to matching. Anastomotic leak and enterocutaneous fistula, specific complications highlighted in other studies known to complicate enterostomy closure time, occurred in 1% of our study's population.

As a retrospective observational study, there are inherent limitations to the study design. The PHIS data source may have incorrect data entry,

missing data, or incomplete covariates. This is a common limitation when administrative databases are used instead of clinical data acquisition or intelligent chart review. PHIS is specifically limited by its use of ICD-9 and ICD-10 diagnosis codes and risks coding errors, which have been shown to range from 2% to 4% [31, 32]. While we were unable to control for this error, the low percentage in similar retrospective studies suggests it is unlikely to account for a significant difference in our conclusion. Second, performing propensity score model matching on this retrospective observational study accounts for observed variables that were collected in this data. This type of matching lacks the ability to include the effect of the potential unmeasured confounding variables on the significance of the observed treatment effect. In our dataset, matching excluded lower birthweight unmatched patients which could create a group of patients for comparison that is different from the overall cohort. Third, there is the possibility of institutional bias or surgeon preference for timing of enterostomy closure. This analysis did not control for surgical decision-making. Reasons for enterostomy closure including both mechanical (enterostomy appliance with poor

seal, skin excoriation) and functional (high output) are not included in the indications for the ostomy closure procedure provided by this dataset; however, enterostomy complications were included in the surgical complications. The propensity score matching attempted to address this limitation by ensuring both groups (A1 and A2) had comparable complications. Moreover, some neonates in the A1 may undergo enterostomy closure either due to unavailability of homecare by insurance or discomfort by family members caring for the enterostomy appliance. The inability to control for surgeon decision-making remains the major limitation of this study. Future studies will need to be performed in a prospective, randomized manner comparing early enterostomy closure versus delayed enterostomy closure with discharge eligibility determined by tolerance of enteral nutrition. By randomizing the two treatment arms, it will eliminate the variable of surgeon preference and hospital protocol. Fourth, the distinction between NEC versus IIP may be incorrect from the dataset as this can be difficult to determine. Additional costs for home nursing visits, transfer to another inpatient ward or lower tier children's care facility, enterostomy supplies, or follow up clinic visits are not included in the cost analysis as it only includes costs for the neonate as an inpatient. The data does not provide information regarding wound or enterostomy complications while at home.

The current data concerning enterostomy closure for neonates with IIP shows conflicting results that have no difference in morbidity but a 28 day shorter hospital length of stay, \$75,000 or 24% lower total hospital costs, and a 22 day shorter post-operative course following enterostomy closure when enterostomy creation and closure is performed on separate admissions. While these results are statistically different, factors at a local hospital level could cause clinical variation between two groups. Our study utilized propensity score matching to demonstrate a benefit for neonates who undergo enterostomy closure after being discharged during a subsequent admission.

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Appendix A. Surgical complications prior to matching

Complication	Pre-Match Total N (%)	A1	A2	After Match	A1	A2
Iatrogenic PTX	1 (0.24%)	1	0		0	0
Acute Lung Edema	1 (0.24%)	1	0		1	0
Acute Respiratory Failure	17 (4.05%)	13	4		4	3
Pulmonary insufficiency	3 (0.71%)	1	2		0	2
Other Respiratory complication					1	2
Gastrostomy						
Infection	1 (0.24%)	1	0		1	0
Mechanical complication	4 (0.95%)	3	1		2	1
Other complication	4 (0.95%)	2	2		3	2
Post-gastric surgery syndrome	18 (4.29%)	16	2		3	2
Digestive system						
Post-op GI functional disorder	1 (0.24%)	1	0		1	0
Complication	1 (0.24%)	1	0		1	0
Other	33 (7.86%)	22	11		4	10
Enterostomy						
Infection	3 (0.71%)	3	0		1	0
Mechanical complication	10 (2.38%)	7	3		1	2
Other complication	61 (14.52%)	44	17		12	14
Post-op nonabsorption	49 (11.67%)	39	10		11	9

(continued)

Complication	Pre-Match Total N (%)	A1	A2	After Match	A1	A2
Vascular device						
Infection	5 (1.19%)	5	0		1	0
Mechanical complication	11 (2.62%)	10	1		3	1
Other complication	22 (5.24%)	16	6		0	0
CVC infection	3 (0.71%)	1	2		1	0
NSGY device						
Infection	2 (0.48%)	1	1		0	1
Mechanical complication	3 (0.71%)	1	2		0	2
Surgical complication	1 (0.24%)	1	0		0	0
Other complication	1 (0.24%)	1	0		0	0
Surgical complication heart	1 (0.24%)	1	0		0	0
Ventilator associated PNA	4 (0.95%)	4	0		1	0
Intra-op/Post-op						
Hemorrhage	8 (1.90%)	6	2		1	1
Hematoma	1 (0.24%)	1	0		0	0
Seroma	2 (0.48%)	2	0		0	0
Accidental laceration	12 (2.86%)	8	4		3	3
Wound disruption	3 (0.71%)	2	1		0	1
Internal	5 (1.19%)	2	3		0	3
External	23 (5.48%)	19	4		6	4
Post-op infection	53 (12.62%)	41	12		15	8
Post-op fistula	4 (0.95%)	2	2		0	1
Bloodstream infection	16 (3.81%)	12	4		3	3

Not included: Post-procedural fever, mechanical complication device graft, other post-op complication, extravasation vesicant agent, transfusion reaction, complication of medical care.

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