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Parenteral nutrition prolongs hospital stay in children with nonoperative blunt pancreatic injury: A propensity score weighted analysis☆,☆☆

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ABSTRACT

Background: Blunt pancreatic injury is frequently managed nonoperatively in children. Nutritional support practices – either enteral or parenteral – are heterogeneous and lack evidence-based guidelines. We hypothesized that use of parenteral nutrition (PN) in children with nonoperatively managed blunt pancreatic injury would 1) be associated with longer hospital stay and more frequent complications, and 2) differ in frequency by trauma center type.
Methods: We conducted a retrospective cohort study using the National Trauma Data Bank (2007–2016). Children (≤18 years) with blunt pancreatic injury were included. Patients were excluded for duodenal injury, mortality <4 days from admission, or laparotomy. We compared children that received versus those that did not receive PN. Logistic regression was used to model patient characteristics, injury severity, and trauma center type as predictors for propensity to receive PN. Treatment groups were balanced using the inverse probability of treatment weights. Outcomes included hospital length of stay, intensive care unit days, incidence of complications and mortality.
Results: 554 children with blunt pancreatic injury were analyzed. PN use declined in adult centers from 2012 to 2016, but remained relatively stable in pediatric centers. Propensity-weighted analysis demonstrated longer median length of stay in patients receiving PN (14 versus 4 days, rate ratio 2.19 [95% CI: 1.97, 2.43]). Children receiving PN also had longer ICU stay (rate ratio 1.73 [95% CI: 1.30, 2.30]). There was no significant difference in incidence of complications or mortality.
Conclusions: Use of PN in children with blunt pancreatic injury that are managed nonoperatively differs between adult and pediatric trauma centers, and is associated with longer hospital stay. Early enteral feeding should be attempted first, with PN reserved for children with prolonged intolerance to enteral feeds.
Level of evidence: III, Retrospective cohort.

Blunt pancreatic injury (BPI) is relatively rare in pediatric trauma patients, occurring in less than 1% of children presenting with traumatic injury [1]. While many children with BPI may require surgical intervention, nonoperative management is frequently attempted when immediate need for surgery is not evident [2]. Nonoperatively managed children may experience intolerance to enteral feeds or have feeding withheld altogether, creating a challenge in achieving nutritional goals. Pediatric patients who are unable to meet caloric goals via enteral feeding are often placed on parenteral nutrition (PN) in hopes to prevent hypoglycemia, muscle catabolism, and malnutrition [3].

Retrospective data from adult trauma patients have demonstrated that early use of PN is associated with increased infectious complications [4]. Randomized studies in both adult and pediatric mixed intensive care unit (ICU) populations found that early PN is associated with an increased risk for infections, longer ICU and hospital length of stay, and longer duration of mechanical ventilation [5,6]. Despite the

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known potential for harm associated with PN use, a recent multicenter study reported 68% of children with high grade BPI were treated with PN [7]. There are no consensus guidelines for nutritional management in children with BPI, which may lead to heterogenous practices among physicians and institutions. Nutritional care trends in centers that treat adult and pediatric patients may differ from those that treat children alone. We hypothesized that use of PN in children with nonoperatively managed BPI would 1) be associated with longer hospital stay and more frequent complications, and 2) differ in frequency by trauma center type.

1. Methods

1.1. Cohort selection

Institutional Review Board approval was obtained from the Children's Hospital Los Angeles prior to conducting this study. We obtained a retrospective cohort from the National Trauma Data Bank (2007–2016). We included all pediatric patients (age ≤ 18 years) with a diagnosis of pancreatic injury as defined by Abbreviated Injury Scale (AIS) coding, excluding those with a penetrating mechanism of injury, those receiving surgical intervention on the pancreas, and those receiving laparotomy (Fig. 1). We also excluded patients that were treated at a nontrauma center (defined by State or American College of Surgeons [ACS] designation), patients with mortality <4 days from admission (to minimize survival bias), and patients with concomitant duodenal injury (to minimize PN treatment bias). Patients were additionally excluded if they were treated at a center that never reported PN use. This last exclusion was meant to address potential reporting bias related to PN use, which might result in erroneous assignment of patients into the wrong treatment group and represent a threat to internal validity.

1.2. Covariates for the propensity score model

Covariates were selected in developing our propensity score model based on our expectation that they would impact the probability of a child receiving PN. We also aimed to include covariates that reflect overall injury severity, including known independent predictors of mortality in trauma patients [8]. These variables included patient-level characteristics of age, gender, race, ethnicity, transfer status, emergency department vital signs, Glasgow Coma Scale (GCS) motor score, AIS scores by body region (head, face, neck, chest, abdomen, spine, lower extremity, upper extremity, and external), intraabdominal organ injury (categorized by liver, spleen, kidney, or gastrointestinal tract), pancreatic injury grade, transfusion, craniotomy, endoscopic retrograde cholangiopancreatography (ERCP); and hospital-level characteristics including trauma center type, State or ACS level 1 designation, and presence of PICU. Injuries and procedures were defined by International Classification of Diseases, Clinical Modification codes (ICD-9-CM and ICD-10-CM), except for pancreatic injury grade — which could only be determined by AIS codes (Appendix A). Presence of hypotension, tachycardia, and bradycardia was determined using age-adjusted systolic blood pressure (SBP) and heart rate based on Pediatric Advanced Life Support (PALS) normative values [9]. We converted GCS motor to simplified motor score (SMS) [10–12] and AIS scores were dichotomized into severe (≥3) or not severe (<3).

1.3. Parenteral nutrition exposure

Use of parenteral nutrition was defined by ICD-9-CM and ICD-10-CM procedure coding. Any patient with a procedure code for PN was classified in the exposure group. Duration of PN exposure is not coded in the NTDB, and as such, was not analyzed.

1.4. Definition of outcomes

The primary outcome of this study was hospital length of stay. Secondary outcomes included mortality, ICU length of stay, and in-hospital complications reported to the NTDB (catheter-related blood stream infection, sepsis, DVT/PE, ARDS, UTI, and pneumonia). Patients treated at a hospital that never reported complications to the NTDB were categorized as 'missing' for all complications to prevent reporting bias [13].

1.5. Statistical analysis

Multiple imputation specifying a multivariate imputation by fully conditional specification methods was used to impute missing SBP (n = 26), heart rate (n = 13), and GCS motor (n = 35). The multiple

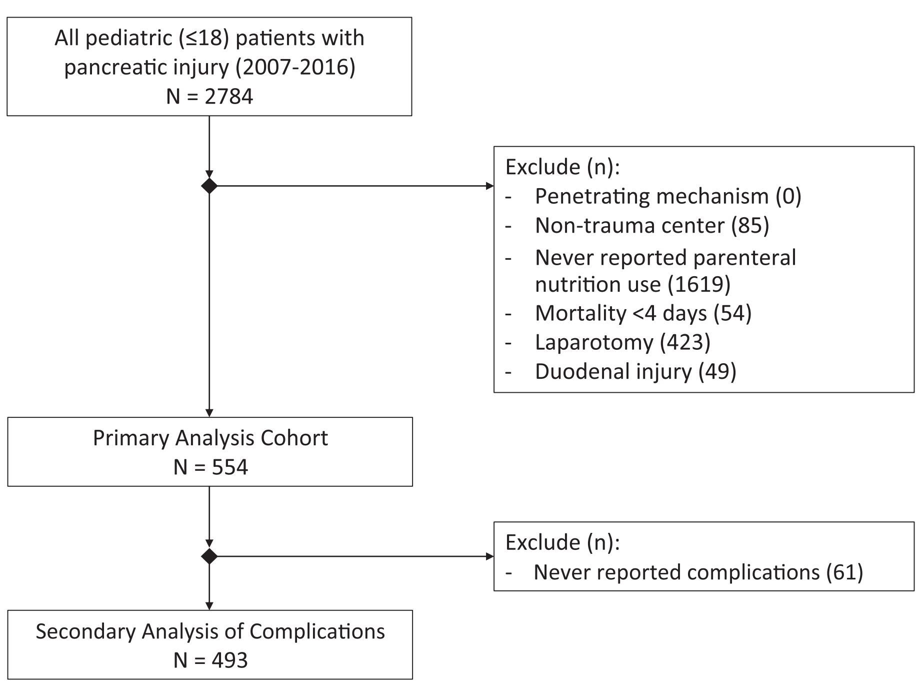

Fig. 1. Flow diagram demonstrating cohort selection from National Trauma Data Bank.

Table 1
Characteristics of pediatric (<19 years) with blunt pancreatic injury treated nonoperatively from 2007 to 2016.

Characteristics[a]	No PN (N = 489)	PN (N = 65)	Unadjusted p-value	IPTW adjusted p-value
	Median (IQR)	**Median (IQR)**		
Age	10 (5, 15)	7 (3, 11)	<0.01	0.98
	N (%)	**N (%)**		
Gender			0.66	0.75
Male	306 (62.8)	39 (60.0)		
Female	181 (37.2)	26 (40.0)		
Race			0.13	0.94
African American	116 (24.5)	21 (36.8)		
White	296 (62.6)	30 (52.6)		
Other	61 (12.9)	6 (10.5)		
Ethnicity			0.38	0.27
Hispanic or Latino	62 (12.7)	10 (15.4)		
Not Hispanic or Latino	342 (69.9)	48 (73.9)		
Not specified	85 (17.4)	7 (10.8)		
Trauma Center Type			0.08	0.92
ATC	148 (30.3)	11 (16.9)		
PTC	143 (29.2)	23 (35.4)		
MTC	198 (40.5)	31 (47.7)		
Level I designation (any)	397 (81.2)	62 (95.4)	<0.01	0.65
Presence of PICU	417 (85.3)	65 (100.0)	<0.01	---
Transfer	240 (49.1)	38 (58.5)	0.16	0.85
ED Hypotension	27 (5.8)	2 (3.3)	0.56	0.69
ED Tachycardia	102 (21.3)	12 (19.1)	0.68	0.77
ED Bradycardia	24 (5.0)	0 (0)	0.10	---
Simplified Motor Score				
0	62 (13.5)	2 (3.3)	<0.01	0.90
1	9 (2.0)	4 (6.7)		
2	388 (84.5)	54 (90.0)		
	N (%)	**N (%)**		
Severe Injury (AIS ≥3)[b]				
Head	76 (15.5)	6 (9.2)	0.18	0.33
Face	4 (0.8)	1 (1.5)	0.47	---
Neck	2 (0.41)	0 (0)	>0.99	---
Chest	123 (25.2)	11 (16.9)	0.15	0.76
Abdomen	192 (39.3)	44 (67.7)	<0.01	0.85
Spine	16 (3.3)	0 (0)	0.24	---
Lower Extremity	11 (2.3)	0 (0)	0.63	---
Upper Extremity	45 (9.2)	5 (7.7)	0.69	---
External	1 (0.2)	0 (0)	>0.99	---
Intraabdominal Injury				
Liver	142 (29.0)	21 (32.2)	0.59	0.62
Spleen	90 (18.4)	6 (9.2)	0.07	0.63
Kidney	50 (10.2)	6 (9.2)	0.80	0.55
Gastrointestinal	17 (3.5)	4 (6.2)	0.29	0.47
	Median (IQR)	**Median (IQR)**		
Pancreatic Injury Grade	1 (1, 1)	2 (1, 4)	<0.01	0.88
	N (%)	**N (%)**		
Transfusion	43 (9.0)	10 (15.4)	0.10	0.13
Craniotomy	13 (2.7)	0 (0)	0.38	---
ERCP	11 (2.3)	7 (10.8)	<0.01	0.62

[a] Missing data: 2 missing gender, 24 missing race, 26 missing hypotension, 13 missing tachycardia, 13 missing bradycardia, and 35 missing for GCS motor.
[b] Not mutually exclusive.

imputation model included gender, age, race, transfer status, GCS motor score, severe AIS (head, chest, and abdomen), heart rate, and SBP by vital interactions. A total of five imputed data sets were produced. Analysis from the imputed data was pooled to produce the results.

Propensity scores for receiving PN were estimated using a multivariable logistic regression model with 20 different covariates (age, gender, race, ethnicity, trauma center, level 1 designation, transfer, hypotension, tachycardia, SMS, AIS head, AIS chest, AIS abdomen, liver injury, spleen injury, kidney injury, gastrointestinal injury, pancreatic injury grade, transfusion, and ERCP). The final covariates were selected based on our expectation that they might confound the association between PN use and outcomes. The inverse probability of treatment weights (IPTW) were derived from the propensity scores using average treatment effect for the treated (ATT) weights. Balance between PN exposure groups was assessed adjusting for the weights.

Descriptive analyses were performed to report the frequency counts and percentages for categorical variables. Median and interquartile ranges were reported for continuous data that were not normally distributed. A chi-square or Fisher's exact test (for counts <5) was used for categorical data and Wilcoxon–Mann–Whitney test for continuous variables. An IPTW-weighted logistic regression was used to produce the odds ratio and 95% confidence intervals (CI) for dichotomous outcomes. An IPTW-weighted Poisson regression was used to estimate the rate ratio and 95% CI for continuous outcomes. All significance tests were two-tailed, with $\alpha = 0.05$. All analyses were performed using SAS software v. 9.4 (SAS Institute Inc.).

2. Results

The analysis cohort included 554 children with blunt pancreatic injury treated nonoperatively from 2007 to 2016 (Fig. 1). Twelve percent of the population was treated with parenteral nutrition. Children exposed to PN were younger (median [IQR]: 7 [3, 11] years), when compared to the PN-unexposed group (10 [5, 15] years, $p < 0.01$, Table 1). A simplified motor score of 0 was less frequent in children treated with PN (3.3% vs 13.5%, $p < 0.01$). Patients exposed to PN were more

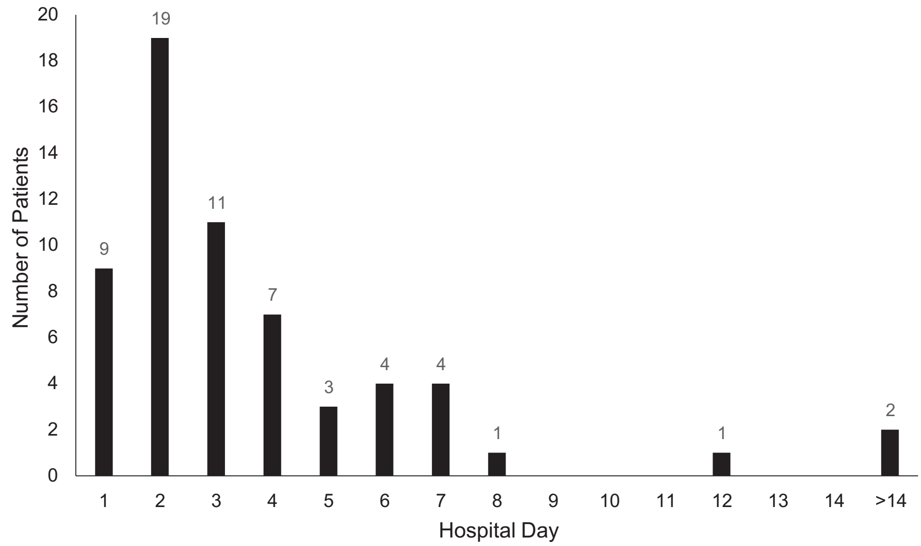

Fig. 2. Hospital day of parenteral nutrition initiation in children with blunt pancreatic injury from 2007 to 2016 (N = 61).

frequently cared for at a center with a PICU (100% vs 85%, $p < 0.01$) and level I trauma center designation (95% vs 81%, $p < 0.01$). Use of PN was more frequently associated with severe abdomen AIS (68% vs 39%, $p < 0.01$) and use of ERCP (11% vs 2%, $p < 0.01$). The median pancreatic injury grade was higher in the PN group (2 [1,4] vs 1 [1], $p < 0.01$). After adjusting for IPTW weights, there were no statistically significant differences in covariates between the two groups.

Among children receiving PN, initiation of PN occurred most frequently on hospital day two (31%) and 93% were started on PN before hospital day 8 (Fig. 2). The temporal trend of PN use appeared to differ by trauma center type (Fig. 3). Parenteral nutrition use peaked in adult trauma centers in 2009 (29%), with a subsequent decline to 0% in both 2015 and 2016. In contrast, use of PN did not decline in pediatric or mixed trauma centers over the course of the study (17% and 14% in 2016, respectively).

After adjusting for IPTW, PN use was independently associated with longer hospital stay (RR: 2.19 [1.97, 2.43]) and ICU stay (RR: 1.73 [1.30, 2.30], Table 2). There was no significant difference in the odds of complications or mortality between the two groups. Odds ratios for catheter-related bloodstream infection, sepsis, and pneumonia were not calculated as no patients in the PN group had these complications; but these complications were rare in the no-PN group (0.5%, 0.5%, and 1.2% respectively).

3. Discussion

This propensity-weighted, retrospective cohort study examined the impact of PN in nonoperatively managed BPI in children, finding a dramatic decline in PN use at adult trauma centers, but no decrease in PN use in freestanding pediatric trauma centers. When PN is used, it is

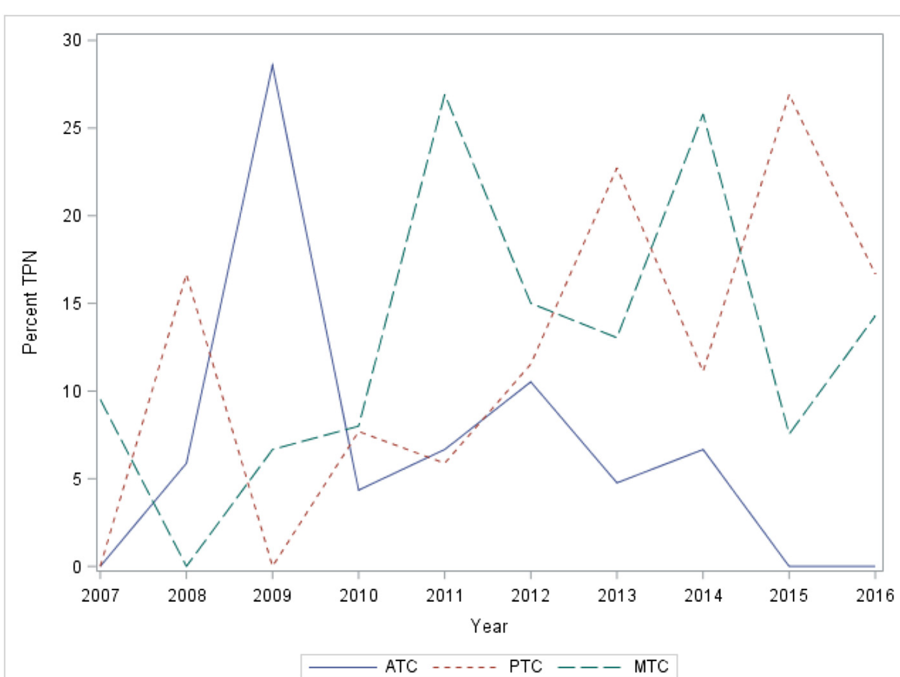

Fig. 3. Temporal trend of annual parental nutrition use, comparing trauma center type, for children with blunt pancreatic injury treated nonoperatively from 2007 to 2016 (N = 554).

Table 2
Outcomes adjusted by inverse probability of treatment weights, comparing parental nutrition use in children with blunt pancreatic injury treated nonoperatively from 2007 to 2016.

Outcomes[a]	No PN (N = 489)	PN (N = 65)	IPTW adjusted data
	Median (IQR)	**Median (IQR)**	**Rate Ratio (95% CI)**
Hospital days	4 (2, 8)	14 (10, 25)	2.19 (1.97, 2.43)
ICU days	3 (2, 5)	4 (3, 7)	1.73 (1.30, 2.30)
	N (%)	**N (%)**	**Odds Ratio (95% CI)**
Catheter-related blood stream Infection	2 (0.5)	0 (0)	---
Sepsis	2 (0.5)	0 (0)	---
DVT/PE	4 (0.9)	1 (1.7)	3.13 (0.04, 238.07)
ARDS	6 (1.4)	1 (1.7)	2.04 (0.04, 101.48)
UTI	2 (0.5)	1 (1.7)	2.09 (0.05, 86.42)
Pneumonia	5 (1.2)	0 (0)	---
Mortality	6 (1.4)	1 (1.5)	23.93 (<0.01, 1,322,955.93)

[a] Missing data: Complications (n = 61), Mortality (n = 54).

often started early — suggesting this is done per routine and in the absence of attempting enteral feeding first. We demonstrated an independent association between PN use and prolonged hospital and ICU stay, which is intuitive as receiving PN generally requires inpatient admission — even if asymptomatic from the pancreatic injury. Use of PN was not significantly associated with incidence of complications or mortality. These findings suggest that PN use may not confer a clinical benefit to children with nonoperative BPI, and should be avoided unless prolonged oral feed intolerance occurs.

The management of pancreatic injury in children can be challenging. Owing to the rarity of pancreatic injury in the pediatric population, there is a paucity of data currently available to arrive at evidence-based guidelines. Consensus indications for operative versus nonoperative treatment have not been clearly established. Whether surgical intervention is required or not, nutritional support strategies in children with pancreatic injury are particularly heterogeneous. A survey of pediatric surgeons found that 53% based their decision to initiate oral feeds on improvement in epigastric tenderness, while others placed emphasis on normalization of pancreatic enzyme levels or a combination of the two [14]. If enteral feeds are withheld, many clinicians may consider the use of PN. A multicenter study of children with high-grade pancreatic injury found 77% of patients were exposed to PN [7] — a much higher rate of PN use than our study reports, which likely reflects our inclusion of all pancreatic injury grades (low-grade injuries are less likely to require PN). This high rate of PN use may reflect an opportunity for improvement in the management of this rare injury. Based on the results of our study, PN use does not improve outcomes and may actually prolong recovery as it may delay the initiation of enteral feeds and therefore delay discharge to home.

Historic nonoperative management of pancreatic injury has relied upon prolonged fasting. In theory, withholding enteral feeds may limit pancreatic stimulation, inflammation and exacerbation of injury. Simultaneous use of PN may prevent catabolism and hypoglycemia. However, there are little data to support these theories. Routine use of PN has been associated with increased complications and mortality in adults with acute pancreatitis, and early enteral feeding is considered the gold standard for nutrition in both adult and pediatric pancreatitis patients [15–17]. While we must be careful in comparing medical pancreatitis to traumatic pancreatic injury, limitation of prolonged fasting may be favorable in both populations. Early enteral feeds may prevent gut mucosal atrophy and improve the immunologic response to pancreatic injury [18]. The benefit of maintaining gut mucosal integrity may overshadow any potential risk of pancreatic injury exacerbated by early enteral feeding.

Current guidelines for adult pancreatic trauma issued by Eastern Association for the Surgery of Trauma (EAST) and Western Trauma Association (WTA) provide indications for operative versus nonoperative management, with no mention of nutritional care [19,20]. Nutritional support guidelines provided by the American Society of Parenteral and Enteral Nutrition (ASPEN) recommend early enteral nutrition for critically ill adult and pediatric patients, and withholding PN until 1 week if enteral goals are not met [21,22]. Providers may be hesitant to apply ASPEN guidelines to pediatric patients with pancreatic trauma, however, as our data revealed that 93% of PN was initiated within 1 week of admission. There has been some attempt at creating guidelines specific to the management of pediatric pancreatic trauma. Naik et al. proposed an algorithm for nonoperative management of children with pancreatic injury which recommends obtaining baseline serum pancreatic enzyme levels on admission and initiating oral feeds when abdominal pain/tenderness improves [7]. While this algorithm does begin to establish consensus guidelines, it was based on management strategies used in >50% of cases in their retrospective review, and not based on outcomes-level evidence. We ultimately need more prospective, well-designed studies to support impactful recommendations for pediatric patients with pancreatic injury.

There are many limitations to this study, primarily those of unmeasured confounding — which cannot be adjusted for in our model. First, we were unable to determine whether a child received enteral feeds (nor how much was given), as these data are not captured by the NTDB. It is possible that enteral feed intolerance resulted in the use of PN for many children in this study — in which case the enteral feed intolerance would be the main culprit for prolonged length-of-stay, and not PN exposure (resulting in type I error). However, enteral feed intolerance does not fully explain the tendency towards early initiation of PN demonstrated in our study, suggesting that many children were started on PN before enteral feeding was adequately attempted. Dose and duration of PN exposure are also not reported in the NTDB and therefore were not captured — obviating the option to analyze PN as a continuous variable and determine whether a dose-dependent effect existed. Provider and institutional-level trends in caring for children with BPI were not analyzed, representing a potential source of confounding as providers that favor early use of PN may also favor longer inpatient monitoring. While our analysis accounted for injury severity and physiologic data on admission, we did not account for day-to-day patient factors indicative of critical illness such as use of vasopressors or mechanical ventilation. This may have also resulted in unmeasured confounding, as sicker patients may be more likely to receive PN and require longer hospital stay. An additional limitation of this study was the relatively small sample size of children that received PN, which likely resulted in an underpowered comparison of complications (potentially leading to type II error). In comparison to previous studies on pediatric pancreatic trauma [7,14,23,24], however, the sample size in our study was actually quite large. The low frequency of PN use in our study (12%) is not surprising because we included all grades of pancreatic injury (providers are less hesitant to enterally feed a low-grade pancreatic injury). The primary strength of this study was the use of a propensity-weighted design which allowed for a balanced comparison based on those confounders that we could measure, and thus limited treatment bias inherent to retrospective research.

4. Conclusions

In summary, we found that PN use is independently associated with longer hospital and ICU stay in children with nonoperative blunt pancreatic injury without a demonstrable benefit in outcome. There also appears to be practice variation in PN use by trauma center type. While more data may be needed to establish consensus guidelines for nonoperative management of blunt pancreatic trauma in children, we suggest that early enteral feeding should be attempted first and PN should be reserved for patients with prolonged intolerance to enteral feeds.

Conflict of interest disclosures

The authors report no conflicts of interest.

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Appendix A. Covariate definitions.

Variable	Definition
Pancreatic injury grade	AIS scores for pancreatic injury: Grade 1: 542810.2, 542812.2, 542820.2, 542822.2 Grade 2: 542814.3 Grade 3: 542824.3 Grade 4: 542826.4, 542828.4, 542830.4 Grade 5: 542832.5
Gastrointestinal injury	ICD-9-CM OR ICD-10-CM diagnostic codes for injuries to: - esophagus - stomach - duodenum - small intestine - colon - rectum

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