Teasing out factors differentiating pathologic from benign pneumatosis intestinalis

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BACKGROUND: Pneumatosis intestinalis (PI) is a rare radiographic finding that can range from being a benign process to needing emergency surgery. Sufficiently powered studies are lacking, and recommendations for management remain unclear. The purpose of this study was to identify key predictors of pathologic PI using physical examination, laboratory, and radiographic findings.

METHODS: A retrospective cohort study was conducted at two quaternary academic centers (2010–2020). A total of 334 consecutive patients 18 years or older with radiographic evidence of PI were identified. Patients were excluded if they pursued comfort care or if there was concurrent radiographic evidence of vaso-occlusive process. Pathologic PI was defined as presence of ischemic and/or perforated bowel on exploratory laparotomy or death prior to planned surgery.

RESULTS: Of the 334 patients included in our study, 91 (27%) underwent exploratory laparotomy, of which 59 (65%) had ischemic and/or perforated bowel. These latter patients and 10 other patients who died before exploratory laparotomy defined the pathologic PI cohort. A stepwise model was created for predicting pathologic disease. Significant predictors were the presence of portal venous gas, multisegment PI, vasopressor use, peritonitis, increasing leukocyte count, and end organ injury, which were used to construct a nomogram for clinical use.

CONCLUSION: A nomogram score based on presence of portal venous gas, multisegment PI, vasopressor use, peritonitis, leukocytosis, and end organ injury may help predict the probability of pathologic PI and therefore can inform surgical decision making. (*J Trauma Acute Care Surg.* 2025;00: 00–00. Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Epidemiologic Study; Level III.

KEY WORDS: Pneumatosis intestinalis; nomogram; computed tomography.

Pneumatosis intestinalis (PI) is the rare radiographic finding of gas in the intestinal wall, which has implications that range from a benign process requiring no treatment to having life-threatening bowel ischemia and/or perforation in need of emergent operative intervention. While PI in neonates is more clearly worrisome for its association with necrotizing enterocolitis,[1] PI in adults is often found incidentally on imaging in an otherwise asymptomatic patient.[2] Thus, the true incidence of PI in adult patients is difficult to discern. A retrospective study by Morris et al.[3] in 2008 reviewing all abdominal computed tomography (CT) imaging performed during a 7-year period at one institution found that 0.37% scans identified the presence of PI. Others have tried to evaluate the proportion of patients with PI who had bowel ischemia and/or perforation on exploratory laparotomy; numbers range from 24% in the 2013 Pneumatosis Intestinalis Predictive Evaluation Study (PIPES) conducted by the Eastern Association for the Surgery of Trauma in 2013 to 44% at a single institutional study by Hawn et al. in 2004.[4,5] Notably, these data suggest that less than half of all PI patients taken for emergency exploratory laparotomy were found to have true bowel ischemia and/or perforation, demonstrating the difficulty in using this finding alone in surgical decision making.

The pathogenesis of PI is likely multifactorial. While a well-recognized cause of pathologic PI requiring surgical intervention is acute mesenteric ischemia,[4] it still remains unclear why some patients without radiographic evidence of mesenteric ischemia have PI. One possible cause is nonocclusive mesenteric ischemia, which is most often due to vasoconstriction. However, several nonischemic hypotheses have also been suggested: (1) mechanical, (2) immune, (3) bacterial, and (4) pulmonary.[6]

The mechanical theory describes a situation in which increased intraluminal pressure forces gas into the bowel wall, such as blunt abdominal trauma.[6–9] The immune theory attributes immune compromise of the mucosa to the introduction of gas into the bowel wall.[6] Examples include human immunodeficiency virus,[10] systemic lupus,[11] chemotherapy,[12–14] and inflammatory bowel disease.[15] The bacterial theory suggests that bacterial infection, such as necrotizing enterocolitis[6] or *Clostridium difficile* colitis,[16] can introduce gas into the bowel wall. Lastly, the pulmonary theory proposes that lung disease, such as asthma, chronic obstructive pulmonary disease, interstitial lung disease, cystic fibrosis, and pneumonia, can cause alveolar rupture, which forces gas into the retroperitoneum and mesenteric

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vasculature from the mediastinum.[17–19] However, other studies postulate that the association between lung disease and PI can be instead explained by the mechanical theory, via increased intra-abdominal pressure from coughing, and/or the immune theory, via immunosuppression from chronic steroid use.[20,21]

Given the wide variety of potential causes and rarity of the finding, sufficiently powered studies are lacking, and guidelines to determine the need for surgery remain elusive. Currently, PI has largely been managed on a case-by-case basis, which carries both the risk of performing unnecessary surgery and the risk of overlooking patients who require surgery. We thereby sought to examine potential predictors of pathologic PI without radiographic evidence of acute mesenteric ischemia for improved risk stratification and to develop a tool that informs surgical decision making.

PATIENTS AND METHODS

Patients

All patients aged 18 years or older with radiographic evidence of PI on abdominal/pelvic CT between January 1, 2010, and December 31, 2020, who received care at either Brigham and Women's Hospital or Massachusetts General Hospital were identified using the Mass General Brigham Research Patient Data Registry. This study was approved by the Massachusetts General Brigham Institutional Review Board. Patients were excluded if they exhibited concurrent radiographic evidence of a vaso-occlusive process, as PI together with vaso-occlusion is highly indicative of ischemic bowel[22] and therefore does not present as a similar management dilemma as those with only PI. Unlike prior analyses on pathologic PI,[4,5,23–26] our study also excluded patients who pursued comfort measures, as this care pathway involved cessation of not only subsequent evaluations needed to confirm benign versus pathologic PI but also the surgical decision-making process as a whole (Fig. 1).

Variables

The outcome of interest was pathologic PI, defined as (1) radiographic evidence of PI with ischemic and/or perforated bowel confirmed on exploratory laparotomy or (2) radiographic evidence of PI with patient death prior to planned exploratory laparotomy. Extensive chart review was performed to collect information regarding patient demographics, initial presentation, past medical and surgical history, physical examination and laboratory values on the surgical history and presentation or consult note, radiographic findings, medications, operative events, and complications.

"Peritonitis" was identified by documentation of peritoneal signs such as involuntary guarding and rebound tenderness.[27] "Sepsis" was verified using surgery documentation and when patient vital signs and laboratory values indicated systemic inflammatory response syndrome.[28] Acute kidney injury (AKI) was defined as an increase in serum creatinine at or above 1.5 times that of either patient baseline or the hospital laboratory's upper limit of normal in the event that baseline values were not known.[29] "Multisystem organ failure" was identified if the term was written on surgery documentation or if all three of the following were concurrently documented: AKI, acute lung injury/mechanical ventilation, and acute transaminitis. "Hypotension with vasopressor use" was defined as having a systolic blood pressure below 90 mmHg that failed to improve with fluid administration alone, requiring vasopressor medication to raise blood pressure to goal.

Statistical Analysis

Descriptive analyses compared the number and percentage of patients with certain characteristics, treatments, and outcomes in benign versus pathologic PI. χ^2 tests of proportion were used to test for the statistical significance of differences in patients with benign versus pathologic PI. Variables with a p value of <0.05 on χ^2 analysis were then included in our univariable and full multivariable regression models to determine whether they were independently associated with pathologic PI. Missing data were omitted from analysis.

Given our extensive list of variables, we elected to use more parsimonious regression models to improve statistical power by selecting for the most significant independent predictors of pathologic PI.[30] To do this, all variables with a p value of <0.05 on χ^2 analysis were entered into a stepwise backward logistic regression model with a threshold of $p < 0.1$ and a least absolute shrinkage and selection operator (LASSO) regression model.[31] The stepwise backward logistic regression model is an iterative statistical model of sequentially eliminating the least statistically significant variable until each variable remaining is statistically significant. The stepwise model is a commonly used model in medical literature because of its user-friendliness and efficiency; of the four previous studies on PI that have used more parsimonious regression models to select independent predictors, all used this method.[4,23,25,26] However, the stepwise model has, in recent years, received growing criticism, as it does not

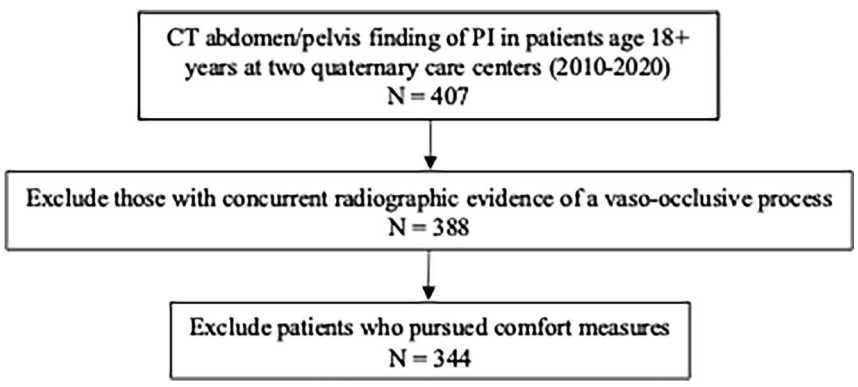

Figure 1. Consolidated Standards of Reporting Trials diagram.

consider all possible combinations and prioritizes individual fit over group fit.[32]

The LASSO model, on the other hand, has become a more often preferred model in many other fields, such as genetics, environmental science, and finance. This machine learning algorithm chooses predictors by minimizing the residual sum of squares while also adding regularization, thus circumventing the problem in stepwise.[31] However, the LASSO model can struggle with collinear variables by arbitrarily selecting one instead of another; it can also be less reproducible and interpretable by being too sensitive to slight variations in different datasets.[33]

The full, stepwise, and LASSO models were then compared using Akaike information criterion (AIC) divided by sample size and adjusted R^2 to determine the best fit model for prediction. The model with the lowest AIC and highest R^2 was selected as our final model to be implemented in a nomogram that would calculate a patient's probability of pathologic PI. All analyses were performed using Stata, version 17.0 (StataCorp LLC, College Station, TX). This study was written in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology checklist (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/E238).[34]

RESULTS

Between 2010 and 2020, 388 patients 18 years or older with radiographically confirmed non–vaso-occlusive PI were identified. Fifty-four patients pursued comfort measures; thus, 344 patients were ultimately included in our analyses. The median age was 60.8 years (interquartile range [IQR], 52.5–70.1 years). Fifty-eight percent of our cohort was male; 84% was White. Ninety-one patients (26%) underwent exploratory laparotomy, of which 59 (65%) had ischemic and/or perforated bowel. These latter patients and 10 other patients who died before planned exploratory laparotomy defined the pathologic PI cohort of 69 patients, which formed 20% of the total PI cohort (Table 1). Meanwhile, 23 patients (7%) died within 30 days of radiographic findings of PI but were included in the benign PI cohort because of confirmation on exploratory laparotomy, clinical and/or radiographic improvement or resolution, death from non–PI-related cause, and/or lack of abdominal symptoms throughout admission.

Of all clinical variables evaluated, the following were significantly associated with pathologic PI on χ^2 analysis: peritonitis (40% vs. 5%, $p < 0.001$), lack of ability to evaluate symptoms because of intubation and/or altered mental status (22% vs. 11%, $p = 0.01$), hypotension with vasopressor requirement (52% vs. 8%, $p < 0.001$), sepsis (48% vs. 11%, $p < 0.001$), AKI (59% vs. 20%, $p < 0.001$), acute lung injury/ventilation use (44% vs. 10%, $p < 0.001$), and multisystem organ failure (33% vs. 4%, $p < 0.001$). Interestingly, hypotension without vasopressor requirement (15% vs. 14%, $p = 0.85$) was not a statistically significant variable.

In terms of laboratory and imaging characteristics, patients with higher serum lactate (median [IQR], 2.4 [1.4–4.2] vs. 1.4 [0.9–2.0]), higher serum white blood cell (WBC) count (median [IQR], 14.5 [10.1–20.1] vs. 9.2 [5.0–13.8]), and lower serum bicarbonate (median [IQR], 22.0 [19.0–26.0] vs. 24.0 [21.0–27.0]) were significantly associated with pathologic PI. There was no location of PI on CT that was found to be more associated with pathologic PI. Multisegment PI on CT was significantly associated with pathologic PI (54% vs. 40%, $p = 0.04$), while foci of pneumatosis on CT were significantly associated with benign PI (7% vs. 17%, $p = 0.04$). Other CT findings that were significantly associated with pathologic PI were presence of portal venous gas (51% vs. 17%, $p < 0.001$) and ascites (46% vs. 30%, $p = 0.009$).

Patients with concurrent pneumonia (25% vs. 13%, $p = 0.01$), preexisting lung disease (42% vs. 20%, $p < 0.001$), or lupus (3% vs. 0.4%, $p = 0.05$) were significantly associated with pathologic PI. Meanwhile, patients with solid organ cancer (20% vs. 39%, $p = 0.003$), with metastatic cancer (4% vs. 15%, $p = 0.02$), or on chemotherapy within the past 30 days (12% vs. 34%, $p < 0.001$) were significantly associated with benign PI.

Variables with a p value of <0.05 on χ^2 analysis were included in our univariable logistic regression model (Table 2). When the aforementioned statistically significant variables were included in a full multivariable logistic regression model, serum WBC count (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.01–1.11), peritonitis (OR, 7.43; 95% CI, 2.71–20.35), and hypotension with vasopressor use (OR, 3.13; 95% CI, 1.07–9.17) remained statistically significant (Table 3).

In the stepwise backward logistic regression model, six variables were selected as independent predictors, with the ORs of five of the predictors proving statistically significant: WBC count (OR, 1.05; 95% CI, 1.00–1.10), peritonitis (OR, 11.14; 95% CI, 4.62–26.87), hypotension with vasopressor use (OR, 4.59; 95% CI, 1.79–11.80), end organ injury (OR, 1.74; 95% CI, 1.16–2.61), and portal venous gas (OR, 2.20; 96% CI, 1.02–4.78).

In the LASSO model, 10 variables were selected as independent predictors, with the ORs of four of the predictors proving statistically significant: WBC count (OR, 1.05; 95% CI, 1.01–1.10), peritonitis (OR, 9.85; 95% CI, 3.93–24.69), hypotension with vasopressor use (OR, 3.77; 95% CI, 1.39–10.21), and end organ injury (OR, 1.65; 95% CI, 1.07–2.54).

When all three multivariable regression models were compared to determine the best fit model, the stepwise model was found to have the largest adjusted R^2 and smallest AIC adjusted for sample size, indicating that it had the best fit regression. The areas under the curve for all three models remained above 0.8 (Fig. 2).

A nomogram based on the six independent predictors identified by the stepwise model was created to predict the probability of pathologic PI (Fig. 3). Each predictor was assigned points based on their effect size in the regression model.[35] The total score, the sum of points for each individual predictor variable, would range from 0 to 40 and correspond to a risk for having pathologic PI. The probability of pathologic PI was found to be less than 5% for those with fewer than 4 points and greater than 99% for those with more than 35 points.

DISCUSSION

Pneumatosis intestinalis can be a concerning radiographic finding in the adult patient with life-threatening complications. It can be associated with bowel ischemia and/or perforation in need of emergency operative intervention. However, PI is also commonly seen as an incidental finding in an otherwise asymptomatic patient who is clinically well. The clinical significance of PI depends on a patient's clinical context. Therefore, a study

TABLE 1. Patient Characteristics, Treatments, and Outcomes, Benign Versus Pathologic PI

	No. Patients, n (%)			
	Total	**Benign PI**	**Pathologic PI**	***p***
Total patients	334	265 (79.3)	69 (20.7)	NA
Patient characteristics				
Age, median (IQR), years	60.8 (52.5–71.3)	59.5 (51.0–70.1)	66.1 (61.3–75.0)	<0.001*
Sex, male	193 (57.8)	158 (59.6)	35 (50.7)	0.18
Race				
White	280 (83.8)	217 (81.9)	63 (91.3)	0.08
Black	22 (6.8)	17 (6.4)	5 (7.3)	
Asian	11 (3.4)	11 (4.2)	0 (0.0)	
Other	21 (6.4)	20 (7.6)	1 (1.5)	
Presenting symptoms				
Diarrhea	95 (28.4)	77 (29.1)	18 (26.1)	0.63
Constipation	61 (18.3)	45 (17.0)	16 (23.2)	0.24
Unable to evaluate (e.g., intubated)	43 (12.9)	28 (10.6)	15 (21.7)	0.01*
Laboratories, median (IQR)				
Lactate	1.5 (1.0–2.5)	1.4 (0.9–2.0)	2.4 (1.4–4.2)	<0.001*
WBC count	10.2 (6.1–16.0)	9.2 (5.0–13.8)	14.5 (10.1–20.1)	<0.001*
CO_2	24.0 (21.0–26.7)	24.0 (21.0–27.0)	22.0 (19.0–26.0)	0.02*
K	4.0 (3.6–4.4)	3.9 (3.6–4.3)	4.3 (3.9–5.1)	<0.001*
Platelet	235 (155–333)	230 (150–321)	250 (179–345.5)	0.12
Presenting signs				
Distension, no peritonitis	129 (43.4)	105 (41.5)	24 (54.6)	0.11
Peritonitis	41 (12.5)	14 (5.3)	27 (40.3)	<0.001*
Heme-positive stool	25 (7.5)	19 (7.2)	6 (8.8)	0.65
Hypotension, no vasopressors	38 (13.7)	33 (13.5)	5 (14.7)	0.85
Hypotension, with vasopressors	56 (16.8)	21 (7.9)	35 (51.5)	<0.001*
Sepsis	63 (18.9)	30 (11.3)	33 (47.8)	<0.001*
AKI	95 (28.4)	54 (20.4)	41 (59.4)	<0.001*
Acute lung injury	56 (16.8)	26 (9.8)	30 (43.5)	<0.001*
Transaminitis	36 (10.8)	25 (9.5)	11 (16.2)	0.11
Multisystem organ failure	34 (10.2)	11 (4.2)	23 (33.3)	<0.001*
Radiographic findings				
Gastric PI	20 (6.0)	16 (6.0)	4 (5.8)	0.88
Small bowel PI	147 (44.1)	112 (42.4)	35 (50.7)	0.41
Right colon PI	157 (47.1)	122 (46.2)	35 (50.7)	0.70
Transverse colon PI	71 (21.3)	55 (20.8)	16 (23.2)	0.80
Left colon PI	51 (15.3)	43 (16.3)	8 (11.6)	0.55
Rectum PI	6 (1.8)	5 (1.9)	1 (1.5)	0.85
Foci of PI	51 (15.3)	46 (17.4)	5 (7.3)	0.04*
Isolated segment PI	140 (41.9)	115 (43.4)	25 (36.2)	0.28
Multisegment PI	142 (42.5)	105 (39.6)	37 (53.6)	0.04*
Bowel wall thickening	100 (29.9)	75 (28.3)	25 (36.2)	0.20
Portal venous gas	81 (24.3)	46 (17.4)	35 (50.7)	<0.001*
Free air	40 (12.0)	33 (12.5)	7 (10.1)	0.60
Ascites	111 (33.2)	79 (29.8)	32 (46.4)	0.009*
Concurrent infection	123 (36.8)	91 (34.3)	32 (46.4)	0.07
Pneumonia	50 (15.0)	33 (12.5)	17 (24.6)	0.01*
UTI	29 (8.7)	22 (8.3)	7 (10.1)	0.63
C. diff colitis	20 (6.0)	16 (6.0)	4 (5.8)	0.94
Bacteremia	39 (11.8)	31 (11.8)	8 (11.6)	0.97
Other	42 (12.6)	34 (12.8)	8 (11.6)	0.78
Comorbidities				
Prior PI	16 (4.8)	13 (4.9)	3 (4.4)	0.85

Continued next page

TABLE 1. *(Continued)*

	No. Patients, n (%)			
	Total	**Benign PI**	**Pathologic PI**	***p***
Ileus	29 (8.7)	26 (9.8)	3 (4.4)	0.15
Bowel obstruction	65 (19.5)	55 (20.8)	10 (14.5)	0.24
Lung disease (e.g., COPD, asthma, PF, CF)	81 (24.3)	52 (19.6)	29 (42.0)	<0.001*
IBD	23 (6.9)	23 (8.7)	0 (0.0)	0.01*
Enteritis	14 (4.2)	11 (4.2)	3 (4.4)	0.94
Diverticulitis	13 (3.9)	8 (3.0)	5 (7.3)	0.11
Peptic ulcer disease	4 (1.2)	0 (0.0)	4 (5.8)	<0.001*
GI bleed	29 (8.7)	22 (8.3)	7 (10.1)	0.63
Gallbladder disease	29 (8.7)	22 (8.3)	7 (10.1)	0.63
Pancreatitis	18 (5.4)	14 (5.3)	4 (5.8)	0.87
Cirrhosis	19 (5.7)	15 (5.7)	4 (5.8)	0.97
Lupus	3 (0.9)	1 (0.4)	2 (2.9)	0.05*
Amyloidosis	3 (0.9)	3 (1.1)	0 (0.0)	0.38
Sarcoidosis	1 (0.3)	1 (0.4)	0 (0.0)	0.61
HIV/AIDS	1 (0.3)	1 (0.4)	0 (0.0)	0.61
CKD	25 (7.5)	17 (6.4)	8 (11.6)	0.15
ESRD	27 (8.1)	18 (6.8)	9 (13.0)	0.09
Transplant	34 (10.2)	28 (10.6)	6 (8.7)	0.65
Hematologic cancer	4 (1.3)	3 (1.2)	1 (1.5)	0.87
Solid organ cancer	119 (35.7)	105 (39.8)	14 (20.3)	0.002*
Metastatic cancer	42 (12.6)	39 (14.7)	3 (4.4)	0.25
Recent procedure (within past 30 days)				
EGD	27 (8.1)	20 (7.6)	7 (10.1)	0.48
Laparoscopy	17 (5.1)	17 (6.4)	0 (0.0)	0.03*
Open abdominal surgery	37 (11.1)	29 (10.9)	8 (11.6)	0.88
Treatment				
Antibiotics	226 (67.7)	166 (62.6)	60 (87.0)	<0.001*
Exploratory laparotomy	91 (27.3)	32 (12.1)	59 (85.5)	<0.001*
Outcomes				
Radiographic improvement or resolution	100 (70.0)	80 (76.9)	20 (51.3)	0.003*
Initially asymptomatic	14 (4.2)	13 (4.9)	1 (1.5)	<0.001*
Clinical improvement or resolution	159 (74.7)	145 (88.4)	14 (28.6)	<0.001*
Death within 30 days of diagnosis	48 (14.4)	23 (8.7)	25 (36.8)	<0.001*

*$p < 0.05$.

C. diff, *Clostridium difficile*; CF, cystic fibrosis; CKD, chronic kidney disease; CO_2, bicarbonate; COPD, chronic obstructive pulmonary disease; EGD, esophagogastroduodenoscopy; ESRD, end stage renal disease; GI, gastrointestinal; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IBD, inflammatory bowel disease; K, potassium; NA, not applicable; PF, pulmonary fibrosis; UTI, urinary tract infection.

meant to identify risk factors for harboring pathologic as opposed to benign PI demands thorough chart review. As PI is also a rare entity,[3] very few clinical groups have had both a sufficiently large sample size and full access to patients' clinical information required to make meaningful conclusions about the implications of such a radiographic finding, let alone construct a predictive tool for future clinical use.

Our data spanning a decade of experience managing PI patients from two high-volume quaternary care centers in the United States and gathered from extensive chart review indicate that select physical examination, laboratory, and radiographic data may meaningfully predict a patient's risk for having pathologic PI in need of surgical intervention. We are also the only study to exclude patients with concurrent evidence of occlusive mesenteric ischemia and/or comfort care status to gear our predictive tool toward surgical candidates with an unclear operative need.

Overall, it seems that surgeons were able to identify patients with pathologic PI who were surgical candidates, as they operated on 59 (86%) of the pathologic PI cohort, with 10 (14%) dying prior to surgery. However, they were not always able to identify all patients with benign PI, as they also operated on 32 (12%) of the benign PI cohort.

Our analyses indicate that the presence of portal venous gas, multisegment PI, vasopressor requirement, peritonitis, leukocytosis, and end organ injury are independent predictors for having ischemic and/or perforated bowel or for dying prior to planned operative exploration. Using these variables, we were able to quantify the relative risk of each variable and create a more nuanced prediction tool to help guide surgical decision making and patient/family discussions.

Our data are consistent with prior work demonstrating associations between peritonitis, vasopressor requirement, and end

TABLE 2. Odds of Pathologic PI, Univariable Analysis

	OR	95% CI	*p*
Age, years	1.03	1.01–1.05	0.001*
Laboratories			
Lactate, continuous	1.6	1.32–1.93	<0.001*
WBC count, continuous	1.08	1.05–1.12	<0.001*
CO_2, continuous	0.94	0.89–0.99	0.03*
K, continuous	1.17	0.92–1.48	0.2
Presenting symptoms			
Unable to evaluate (e.g., intubated)	2.35	1.18–4.70	0.02*
Presenting signs			
Peritonitis	11.96	5.78–24.73	<0.001*
Hypotension, with vasopressors	12.32	6.42–23.65	<0.001*
Sepsis	7.18	3.92–13.17	<0.001*
End organ injury (1, AKI or acute lung injury; 2, AKI and acute lung injury; 3, multisystemic organ failure)	2.86	2.16–3.78	<0.001*
Radiographic findings			
Multisegment PI	1.76	1.03–3.00	0.04*
Foci of PI	0.37	0.14–0.98	0.04*
Portal venous gas	4.90	2.77–8.66	<0.001*
Ascites	2.04	1.18–3.50	0.01*
Concurrent infection			
Concurrent pneumonia	2.30	1.19–4.44	0.01*
Active treatment use (within past 30 days)			
Chemotherapy	0.26	0.12–0.56	0.001*
Comorbidities			
Lung disease (e.g., asthma, COPD, PF, CF)	2.97	1.69–5.23	<0.001*
Lupus	7.88	0.70–88.22	0.09
Solid organ cancer	0.47	0.29–0.77	0.002*

*$p < 0.05$.
CF, cystic fibrosis; CO_2, bicarbonate; COPD, chronic obstructive pulmonary disease; K, potassium; PF, pulmonary fibrosis.

organ injury and the incidence of pathologic PI. Vasopressor requirement and end organ injury likely indicate septic shock secondary to bowel ischemia and/or perforation. The 2013 PIPES study revealed that peritonitis, vasopressor requirement, AKI, and acute lung injury were associated with pathologic PI on multivariable analysis.[4] Other smaller investigations such as Hawn et al.,[5] Duron et al.,[36] Lee et al.,[25] Ferrada et al.,[26] and Rieser et al.[23] identified similar variables to be of statistical significance on either univariable or multivariable analysis. Of note, Ferrada et al.[26] remains the only prospective study on predictive factors of pathologic PI to this date. Peritoneal signs in particular have long been known to be a concerning physical examination finding; it is thought to indicate inflammation of the parietal peritoneum, which may occur secondary to perforated bowel contents or necrotic tissue irritating the lining.[35] Pneumatosis intestinalis on imaging with peritonitis on examination would therefore be reasonably suggestive of pathologic PI.

However, our analyses also highlighted certain variables not previously consistently associated with pathologic PI and questioned the relevance of others. While we found portal venous gas, multisegment PI, and WBC count to be independent predictors of pathologic PI, their statistical significances in previous studies are much more varied. Presence of portal venous gas, associated with severe necrotizing enterocolitis in neonates, was found to be significantly associated with pathologic PI on univariable analysis in many previous studies[4,23,25,26,34,37–41] those that also conducted multivariable analysis did not continue to find statistical significance.[4,23,25,26,34,37] Presence of multisegment PI, which theoretically could have a higher risk of pathologic PI than those confined in a single intestinal segment, was found to have statistical significance on univariable analysis only in the 2013 PIPES study and Lee et al.,[4,25] while Ferrada et al.[26] did not find statistical significance on either univariable or multivariable analysis. Statistical significance of WBC count, while consistent with the bacterial theory, was especially varied, with Greenstein et al.[37] finding statistical significance on multivariable analysis, several studies finding statistical significance only on univariable analysis,[4,23,26] and Duron et al.[36] finding no statistical significance on either analysis.

Meanwhile, unlike many previous studies, [4,5,23,26,34] our study did not find elevated serum lactate to be an independent predictor of PI on multivariable analysis, although we did find statistical significance on univariable analysis.

Differences between our findings and those of previous studies can be partly explained by variations in sample size and regression analyses. Our study, apart from the 2013 PIPES study of 500 patients, has the largest sample of PI cases to date. Smaller sample sizes may lead to wider fluctuations in statistical significance. Many previous studies also did not conduct regression analyses on as many variables as included in the present study. For example, most studies did not analyze the association between extent of PI on imaging and pathologic PI.[5,23,34,37]

TABLE 3. Comparison of Multivariable Regression Models for Pathologic PI

	Full Model (n = 264)			Stepwise Model (n = 322)			LASSO Model (n = 322)		
Odds of Pathologic PI	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age, continuous, years	1.00	0.97–1.03	0.93				1.02	0.99–1.04	0.22
Laboratories									
Lactate, continuous	1.24	0.95–1.61	0.11						
WBC count, continuous	1.06	1.01–1.11	0.02*	1.05	1.00–1.10	0.02*	1.05	1.01–1.10	0.02*
CO_2, continuous	1.02	0.94–1.1	0.65						
Presenting symptoms									
Unable to evaluate (e.g., intubated)	1.53	0.48–4.92	0.48				1.44	0.53–4.01	0.49
Presenting signs									
Peritonitis	7.43	2.71–20.35	<0.001*	11.14	4.62–26.87	<0.001*	9.85	3.93–24.69	<0.001*
Hypotension, with vasopressors	3.13	1.07–9.17	0.04*	4.59	1.79–11.80	0.002*	3.77	1.39–10.21	0.01*
Sepsis	1.67	0.6–4.66	0.33				1.33	0.51–3.48	0.56
End organ injury	1.54	0.93–2.54	0.09	1.74	1.16–2.61	0.01*	1.65	1.07–2.54	0.02*
Radiographic findings									
Multisegment PI	2.06	0.86–4.94	0.11	1.91	0.92–3.96	0.08	1.86	0.89–3.89	0.10
Foci of PI	0.68	0.15–3.11	0.62						
Portal venous gas	1.88	0.76–4.63	0.17	2.20	1.02–4.78	0.05*	2.05	0.93–4.48	0.07
Ascites	0.86	0.35–2.13	0.74						
Concurrent infection									
Pneumonia	0.96	0.33–2.78	0.94						
Active treatment use (within 30 days)									
Chemotherapy	1.86	0.75–4.59	0.18						
Comorbidities									
Lung disease (asthma, COPD, PF, CF)	0.90	0.22–3.63	0.88				1.61	0.73–3.57	0.24
Solid organ cancer	0.60	0.18–1.98	0.41						
Constant	0.01	0.00–0.16	0.001*	0.02	0.01–0.05	<0.001*	0.01	0.00–0.05	<0.001*
Measures of fit									
Adjusted R^2		0.31				0.33		0.32	
AIC divided by n		0.74				0.68		0.69	

*$p < 0.05$.
CO_2, bicarbonate; COPD, chronic obstructive pulmonary disease; PF, pulmonary fibrosis; CF, cystic fibrosis.

Furthermore, our patient selection criteria are uniquely tailored to guide the surgical decision-making process. All previous studies included patients with concurrent evidence of vaso-occlusive process,[4,5,23–26,34] which is a known etiology of bowel ischemia, and therefore does not present the same level of operative uncertainty.[42,43] Most previous studies also chose to not only include patients who pursued comfort measures in their study but also to count them as pathologic PI patients.[4,5,23–26] These differences in patient population can potentially skew the pathologic PI cohorts in previous studies toward a more severe clinical picture. Morris et al.[3] in 2008, for example, found that the median serum lactate value of PI patients was higher in those who pursued comfort care (median, 6.1; IQR, 2.0–9.1) than both the operative (median, 2.9; IQR, 1.5–3.3) and nonoperative groups (median, 1.3; IQR, 0.8–1.6). Lactic acidosis, in the right clinical context, can increase concern for bowel ischemia and/or perforation[44,45] but can also be a general reflection a severely ill patient nearing the end of their life. Therefore, our exclusion of patients who pursued comfort measures ensures that variables identified in our analysis may be especially helpful in teasing pathologic from benign PI in cases that would otherwise be unclear.

Limitations

Our study results must be taken with consideration of sample size and missing variables. First, while it is one of the

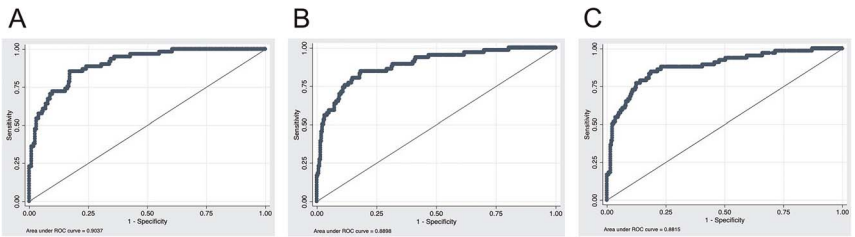

Figure 2. Areas under the curve of different regression models. (*A*) Full model. (*B*) LASSO model. (*C*) Stepwise model.

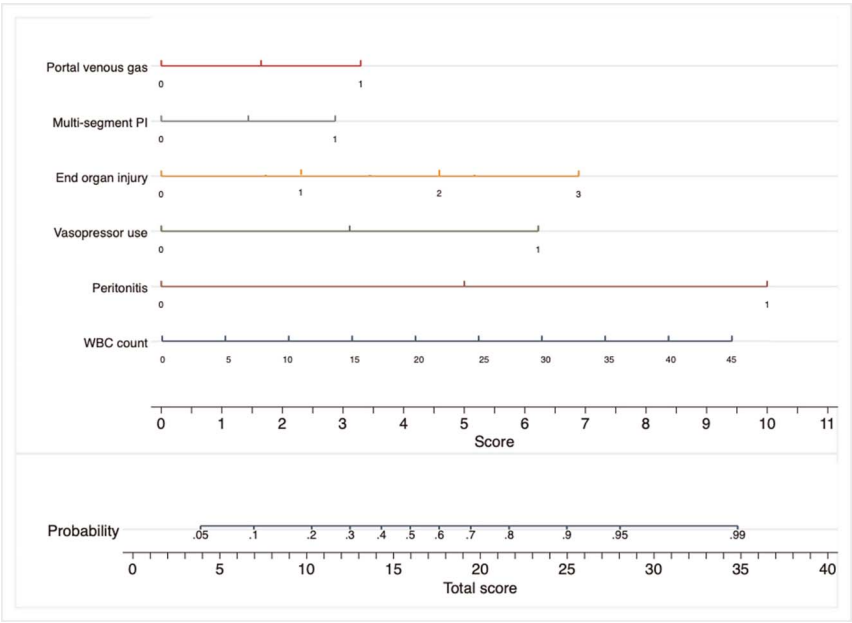

Figure 3. Nomogram predicting probability of pathologic PI. This nomogram provides a method to calculate probability of a patient having pathologic PI based on our identified predictors. To use, choose "0" or "1" depending on whether a patient has portal venous gas on CT; draw a line straight down to the points axis to establish the score associated with portal venous gas. Repeat for the five predictors. Of note, a score of "0" for end organ injury refers to no evidence of injury to kidney, lung, or other organs; a score of "1" refers to evidence of AKI or acute lung injury; a score of "2" refers to evidence of both AKI and acute lung injury; and a score of "3" refers to evidence of not only AKI and acute lung injury but also of injury to at least one other organ. Add the scores for each predictor together and locate the total score on the points axis. Draw a line straight down from the total score to obtain the probability of pathologic PI.

largest studies on PI to this date, our sample size still required more parsimonious models to tease out the statistical significance of our independent predictors on multivariable analysis given that our pathologic PI cohort had only 69 patients. Second, variability in clinical decision making within our hospital system can introduce biases in the data. For example, serum lactate was not routinely collected and therefore was missing in 19% of our cohort. While it was not found to be an independent predictor of PI in our analysis, more consistent testing in future prospective studies can further evaluate whether this laboratory value can be useful in surgical decision making. Third, other potential confounders such as frailty and socioeconomic status were not measured, which could introduce biases in clinical decision making ranging from diagnosis to evaluation of surgical candidacy, to health outcomes and follow-up. Fourth, our predictive tool has not been validated with a separate patient cohort. Our next step is to validate our nomogram in a prospective study to test our independent predictors of pathologic PI identified in this. This prospective study would not only be able to validate our nomogram in a separate cohort but also minimize missing data and account for possible confounders that were not controlled in this retrospective study.

CONCLUSION

This study is one of the largest studies examining the difference between benign and pathologic PI in existing literature. Furthermore, it is the only study looking at patients not pursing comfort care with PI without evidence of vaso-occlusive mesenteric ischemia to focus on patients who require more nuanced surgical judgment. Our analyses reveal that the presence of peritonitis, portal venous gas, multisegment PI, leukocytosis, vasopressor requirement, and end organ injury were independent predictors of pathologic PI. These predictors were used to develop a nomogram to calculate the likelihood that a patient with PI would benefit from surgical intervention. Future efforts to validate our predictive tool via larger retrospective studies and prospective trials may further elucidate optimal guidelines and counsel patients and their family on managing PI.

AUTHORSHIP

B.Z. and R.A. conceived the study idea. J.S., B.Z., M.C.-A., T.D., and R.A. developed the study design. J.S., B.Z., D.M., and M.S. collected data. J.S. analyzed the data, designed the tables/figures, and drafted the manuscript with consultation from B.Z. and R.A. R.A. supervised the study. All authors read and approved the final manuscript.

DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E239). Membership: Reza Askari, MD, FACS, is a member of the American Association for the Surgery of Trauma and Eastern Association for the Surgery of Trauma.

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