

## Original Article

# Factors associated with bowel necrosis in patients with hepatic portal venous gas and pneumatosis intestinalis

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**Aim:** Historically, the presence of hepatic portal venous gas (HPVG) and pneumatosis intestinalis (PI) have been reported to be associated with bowel necrosis and fatal outcome. However, there are no criteria to judge whether bowel necrosis has occurred. We aimed to examine the factors associated with bowel necrosis in patients with HPVG and PI.

**Methods:** The study comprised 25 patients who were diagnosed as having HPVG and/or PI based on computed tomography (CT) findings in the Department of Emergency and Critical Care Medicine, Kansai Medical University Hospital (Osaka, Japan) between April 2013 and August 2017. We compared various factors, including clinical history, severity of present illness, laboratory data, and CT findings, and examined whether they were related to bowel necrosis.

**Results:** Both Sequential Organ Failure Assessment scores and total bilirubin levels were significantly higher in the necrosis group than those in the non-necrosis group ( $P = 0.03$  and  $P = 0.02$ , respectively). The quantity of portal venous gas observed on computed tomography was associated with bowel necrosis in patients with HPVG. In contrast, the presence of air-type PI, defined as PI with emphysema covering the total circumference of the intestine in the absence of wall edema, and the presence of free air were significantly higher in the non-necrosis group (both  $P < 0.01$ ).

**Conclusions:** This study showed that the quantity of HPVG was associated with bowel necrosis, whereas the presence of free air or air-type PI was associated with non-necrosis of the bowel.

**Key words:** CT findings, emphysema, free air, intestinal necrosis, SOFA score

## BACKGROUND

HEPATIC PORTAL VENOUS gas (HPVG) is defined as the presence of gas in the portal venous system,<sup>1</sup> and pneumatosis intestinalis (PI) is defined as the collection of gas within the bowel wall.<sup>2</sup> Historically, the presence of HPVG and PI have been reported to be associated with bowel necrosis and fatal outcome.<sup>3,4</sup> With the development of computed tomography (CT), more patients are being diagnosed as having HPVG and PI. However, bowel necrosis is not detected in some patients with HPVG or PI, despite surgical exploration. Recently, some reports on HPVG and

PI have shown that conservative treatment can lead to a favorable outcome in such cases.<sup>5,6</sup>

There are no criteria by which to judge whether HPVG and PI are accompanied by bowel necrosis. It is therefore difficult to determine the necessity of surgical treatment for patients with HPVG or PI, which can lead to confusion regarding a treatment strategy in the clinical setting. This study aimed to examine the factors associated with bowel necrosis in patients with HPVG and PI.

## METHOD

THIS RETROSPECTIVE OBSERVATIONAL study was carried out in a single emergency and critical care center. The study consisted of 25 patients who were diagnosed as having HPVG and/or PI based on CT findings at the Department of Emergency and Critical Care Medicine, Kansai Medical University Hospital (Osaka, Japan) between April 2013 and August 2017. There were no exclusion criteria.

Eighteen patients were diagnosed as having HPVG, 24 as having PI, and 17 as having both conditions. These patients

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Received 15 Nov, 2018; accepted 26 Apr, 2019; online publication 31 May, 2019

### Funding information

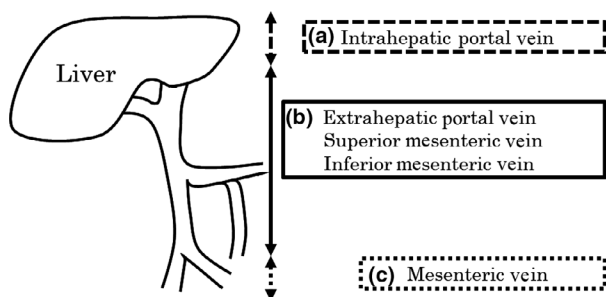
No funding information provided.

were divided into the necrosis group and non-necrosis group based on the presence or absence, respectively, of operative findings of bowel necrosis and on histopathological examination. Patients treated successfully by non-operative management and those who recovered without bowel resection after laparotomy were classified into the non-necrosis group.

Various factors were compared to examine their relationship to bowel necrosis, including clinical history (age, sex, abdominal symptoms, abdominal pain, blood pressure [BP], heart rate [HR], and Glasgow Coma Scale [GCS]), evaluation of severity (disseminated intravascular coagulation [DIC] score,<sup>7</sup> Sequential Organ Failure Assessment [SOFA] score,<sup>8</sup> and Acute Physiology and Chronic Health Evaluation [APACHE] II score<sup>9</sup>), laboratory data (white blood cell count, platelets, C-reactive protein, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total bilirubin (T-BIL), creatine kinase, lactate, pH, and base excess), and CT findings. The DIC scores were calculated according to the DIC scoring system of the Japanese Association for Acute Medicine.<sup>10</sup> The CT findings included gas distribution, the presence of free air or ascites, and thinning of the bowel wall. Hepatic portal venous gas was classified into three groups according to the distribution of portal venous gas: (a) the intrahepatic portal vein; (b) the extrahepatic portal vein (EPV), superior mesenteric vein, and inferior mesenteric vein; and (c) the mesenteric vein (Fig. 1).

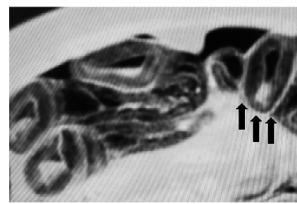
Pneumatosis intestinalis was classified into two patterns: (i) air type (air infiltration rush: emphysema completely covers the entire circumference of the intestine, absent of wall edema); (ii) bubble type (air bubbles are detected in the edematous intestinal wall) (Fig. 2). Computed tomography findings were diagnosed by an intensivist or a radiologist.

The local ethics committee reviewed the study protocol and the study was granted institutional review board approval.

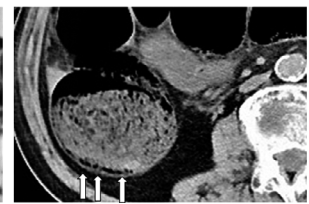


**Fig. 1.** Distribution of hepatic portal venous gas (HPVG) was classified into three regions: (a) the intrahepatic portal vein; (b) the extrahepatic portal vein, superior mesenteric vein, and inferior mesenteric vein; and (c) the mesenteric vein.

**(A) Air type**



**(B) Bubble type**



**Fig. 2.** Pneumatosis intestinalis (PI) was classified into two patterns based on computed tomography findings. A, In this example of air-type PI (air infiltrates rigidly), emphysema continuously covers the entire circumference of the intestine without wall edema. Black arrows indicate emphysema in the intestinal wall. B, In this example of bubble-type PI, air bubbles are present in the edematous intestinal wall (white arrows).

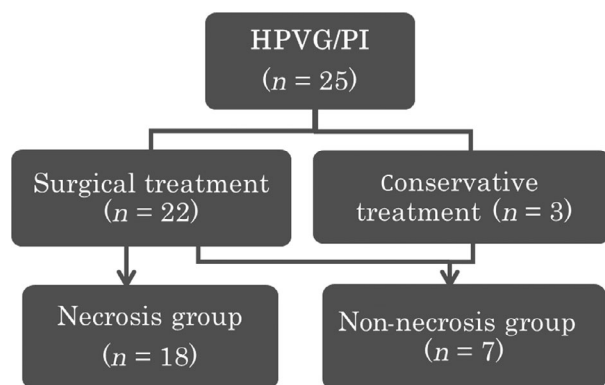
All statistical analyses were undertaken using SPSS 25 (IBM Corp., Armonk, NY, USA). A *t*-test and the Mann–Whitney *U*-test were used to compare differences between the necrosis and non-necrosis groups. *P*-values were determined by the Chi-square test and Fisher's exact test, with *P*-values <0.05 indicating statistical significance.

## RESULTS

**T**HE MEAN AGE of the 25 patients with HPVG/PI was 74 (range, 47–92) years, and sex distribution of the patients was nearly equal (48% male and 52% female). The treatments included laparotomy ( $n = 22$ ; 88%) and conservative treatment ( $n = 3$ ; 12%). Of the 22 patients who underwent laparotomy, 18 showed bowel necrosis and four did not. These four patients and the three patients who were cured with conservative treatment were therefore classified into the non-necrosis group (Fig. 3).

The underlying diseases in the necrosis group ( $n = 18$ ) were non-occlusive mesenteric ischemia (NOMI,  $n = 17$ ) and amyloid deposition ( $n = 1$ ). The causative diseases in the non-necrosis group ( $n = 7$ ) included enteritis ( $n = 6$ ) and gas-producing bacteria ( $n = 1$ ). Table 1 shows the clinical characteristics of the necrosis and non-necrosis groups. There were no significant differences between the two groups regarding age, sex, abdominal distention, abdominal pain, or vital signs (BP/HR). Although the difference did not reach statistical significance, the GCS scores of the patients in the necrosis group tended to be lower than those of the patients in the non-necrosis group.

Among the evaluations of severity, the SOFA scores of the patients in the necrosis group were significantly higher than those in the non-necrosis group ( $P = 0.03$ ). Although the difference did not reach statistical significance, the APACHE II scores of the patients in the necrosis group



**Fig. 3.** Clinical history of 25 patients with hepatic portal venous gas/pneumatosis intestinalis (HPVG/PI). The treatments included laparotomy ( $n = 22$ ) and conservative treatment ( $n = 3$ ). Among the 22 patients who underwent laparotomy, 18 showed bowel necrosis, and four did not. These four patients and the three patients cured with conservative treatment were therefore classified into the non-necrosis group.

tended to be higher in comparison with those in the non-necrosis group.

Among the laboratory data, the T-BIL levels of the patients in the necrosis group were significantly higher than those in the non-necrosis group ( $P = 0.02$ ). No significant differences were observed the two groups in the other measured values. Of the 18 patients in the bowel necrosis group, 12 had HPVG and 17 had PI. Of the seven patients in the bowel non-necrosis group, six had HPVG and seven had PI.

The CT findings of the two groups can be compared in Table 2. A statistically significant difference was observed in the case of HPVG distribution ( $n = 18$ ) between regions (b), (a) + (b), (a) + (c), and (a) + (b) + (c). In comparison to only one region ( $n = 5$ ), distribution to more than two regions ( $n = 13$ ) was associated with bowel necrosis ( $P = 0.02$ ). Additionally, air-type PI was not associated with necrosis ( $P = 0.01$ ).

Although the incidence of ascites and thinning of the bowel wall in the two groups did not differ to a statistically significant extent, the frequency of free air was significantly higher in the non-necrosis group ( $P < 0.01$ ). The patients with PI and free air had a significantly lower level of T-BIL in comparison to the patients with the absence of free air ( $P < 0.01$ ). In addition, despite the lack of statistical significance, the APACHE II score, SOFA score, and C-reactive protein level of patients with PI and free air tended to be lower compared to patients with PI and the absence of free air. Furthermore, the incidence of air-type PI was greater in patients with free air than in those with the absence of free air ( $P < 0.01$ ).

## DISCUSSION

HEPATIC PORTAL VENOUS gas was first described in 1955,<sup>11</sup> whereas PI was first reported in 1754 and then later in 1952 by Koss.<sup>12</sup> The presence of HPVG and PI have been reported as signs associated with a poor prognosis.<sup>2,13</sup>

The mechanism underlying the development of HPVG has not been uncovered; however, two theories have been proposed. The first proposed mechanism is mechanical: bowel gas invades a vein through an ulcer or necrosis stemming from damage to the bowel wall mucosa.<sup>14</sup> The causes of disease in patients with bowel necrosis include NOMI, superior mesenteric artery obstruction, necrotizing enteritis, and strangulated bowel obstruction. The causes of disease in patients without bowel necrosis include simple bowel obstruction, perforation of the lower gastrointestinal tract, and infectious enteritis. In our study, a mechanical mechanism was found to apply to patients with NOMI or enteritis. The second proposed mechanism is bacterial: gas-forming bacteria invade the mucosal barrier and produce gas within the bowel wall.<sup>15</sup>

Similarly, the mechanism underlying the development of PI has yet to be uncovered; however, four theories have been proposed. The first proposed mechanism is mechanical: increased intraluminal pressure derived from an ileus. In our study, this would apply to patients with NOMI. The second proposed mechanism is pulmonary: specifically, pulmonary alveolar rupture resulting from pulmonary disease. The third proposed mechanism is bacterial: the invasion of gas-forming bacteria into the mucosal barrier and the production of gas within the bowel wall. In one of our patients, we identified group A *Streptococcus*, which can be gas-forming bacteria. The fourth proposed mechanism is chemical: specifically,  $\alpha$ -glucosidase inhibitors.<sup>16</sup>

Hepatic portal venous gas and PI are thought to be generated through similar mechanisms, and it has been reported that HPVG and PI represent different phases of the same pathophysiological condition.<sup>17</sup> In fact, 17 of the 25 patients in our study had both HPVG and PI. Based on these reports, we examined the common factors associated with bowel necrosis in the 17 patients with both conditions.

Regarding clinical history, the presence of abdominal pain was reported to be associated with bowel necrosis in a previous study;<sup>18</sup> however, this association was not observed in our study. Eight of 18 patients with bowel necrosis complained of abdominal pain; the remaining 10 patients did not complain of symptoms due to disorders of consciousness or poor communication. Thus, there was no way to accurately ascertain whether these patients had abdominal pain. In fact, the GCS scores of the necrosis group tended to be lower in

**Table 1.** Comparison of the clinical characteristics between the necrosis and non-necrosis groups of patients with hepatic portal venous gas (HPVG) and pneumatosis intestinalis (PI)

	Necrosis group (n = 18)	Non-necrosis group (n = 7)	P-value
Baseline characteristics			
Age, years	74.5 ± 2.6	79.0 ± 2.8	0.13
Sex, male	11 (61)	1 (14)	0.07
Abdominal distension	15 (83)	5 (71)	0.91
Abdominal pain	8 (44)	4 (57)	0.67
BP, mmHg	98.0 ± 8.1	120.0 ± 8.9	0.25
HR, /min	103.0 ± 5.6	94.0 ± 4.9	0.26
GCS	8.5 ± 1.1	15.0 ± 0.4	0.06
Evaluation of severity			
DIC score	4.0 ± 0.5	3.0 ± 0.7	0.26
SOFA score	9.0 ± 1.2	4.0 ± 1.0	0.03*
APACHE II score	20.0 ± 1.6	17.0 ± 2.7	0.25
Laboratory data			
WBC, /μL	11,800 ± 1,788	10,200 ± 2,084	0.87
PLT, /μL	18.4 ± 2.3	14.0 ± 3.5	0.85
CRP, mg/dL	11.6 ± 6.0	5.1 ± 1.6	0.05
BUN, mg/dL	39.0 ± 2.8	24.0 ± 4.7	0.11
Cr, mg/dL	1.7 ± 0.3	1.0 ± 0.3	0.18
AST, U/L	54 ± 18	43 ± 134	0.97
ALT, U/L	23 ± 7	49 ± 44	0.38
LDH, U/L	345 ± 262	375 ± 102	0.67
T-BIL, mg/dL	2.7 ± 0.6	0.6 ± 0.3	0.02*
CK, IU/L	158 ± 1,155	38 ± 681	0.20
Lactate, mg/dL	38.0 ± 6.3	16.0 ± 9.9	0.10
pH	7.40 ± 0.05	7.40 ± 0.03	0.23
Base excess, mmol/L	-3.3 ± 1.3	-0.4 ± 1.9	0.13
HPVG	12 (67)	6 (86)	0.63
PI	17 (94)	7 (100)	1.00

\*P-values <0.05.

Data are shown as n (%) or median ± standard error (Mann–Whitney U-test).

ALT, alanine aminotransferase; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CK, creatine kinase; Cr, creatinine; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; GCS, Glasgow Coma Scale; HR, heart rate; LDH, lactate dehydrogenase; PLT, platelet; SOFA, Sequential Organ Failure Assessment; T-BIL, total bilirubin; WBC, white blood cell count.

comparison to those of the non-necrosis group. These findings suggest that the predominant symptoms of seriously ill patients were unclear and unreliable.

Total bilirubin levels were associated with bowel necrosis in our study, a finding that has not been described in any of the previous reports. We presume that the reasons for this were the inflow of gases from necrotic tissue to the portal system and infection, which could lead to the development of liver damage and cholestasis. However, the aspartate aminotransferase and alanine aminotransferase levels in the patients with and without bowel necrosis did not differ to a statistically significant extent. Moreover, no other studies have

reported this. Further research is thus required to better understand the relationship between HPVG/PI and T-BIL levels.

Koami *et al.*<sup>19</sup> reported three risk factors as diagnostic criteria of bowel necrosis in patients with HPVG, namely lower systolic BP, higher lactate dehydrogenase level, and the presence of intestinal pneumatosis. Their criteria were not easily applicable to our 18 patients with HPVG, probably because the severity of our patients differed from that of their patients. In fact, our rates of mortality and shock were lower than their rates.

We attempted to estimate the quantity of portal venous gas based on gas distribution in the portal venous system.

**Table 2.** Comparison of computed tomography findings between the necrosis and non-necrosis groups of patients with hepatic portal venous gas (HPVG) and pneumatosis intestinalis (PI)

	Necrosis group	Non-necrosis group	P-value
HPVG	12/18 (67)	6/7 (85)	
(a)	11/12 (92)	4/6 (67)	0.24
(b)	10/12 (83)	1/6 (17)	0.01
(c)	10/12 (83)	3/6 (50)	0.27
(a) + (b)	10/12 (83)	0/6 (0)	<0.01
(a) + (c)	9/12 (75)	1/6 (17)	0.04
(b) + (c)	8/12 (67)	1/6 (17)	0.13
(a) + (b) + (c)	8/12 (67)	0/6 (0)	0.01
More than two regions	11/12 (92)	2/6 (33)	0.02
PI	17/18 (94)	7/7 (100)	
Only air type	0/17 (0)	3/7 (43)	0.01
Both air type and air bubble type	2/17 (12)	2/7 (29)	0.55
Only bubble type	15/17 (88)	5/7 (71)	0.07
Free air	1/18 (5.5)	5/7 (71)	<0.01
Ascites	15/18 (83)	6/7 (85)	0.88

Data are shown as *n* (%).

Distribution of portal venous gas: (a) intrahepatic portal vein; (b) extrahepatic portal vein, superior mesenteric vein, and inferior mesenteric vein; (c) mesenteric vein.

The results showed that the number of gas-containing portal venous regions was associated with bowel necrosis. Some studies supported this result. Faberman and Mayo-Smith<sup>20</sup> reported that large quantities of HPVG were associated with a poor prognosis and bowel infarction.

With regard to portal venous gas distribution, the presence of gas in the EPV was associated with bowel necrosis in our study. This might suggest that gas in the EPV is indicative of the presence of a large quantity of gas overall.

According to our results, air-type PI was not associated with bowel necrosis. Although a definite conclusion cannot be drawn from this single study, it is reasonable to hypothesize that a CT finding of air-type PI is indicative of non-necrosis.

Among the five HPVG/PI patients with free air, one had bowel necrosis, but bowel perforation was not present. The remaining four cured patients had no bowel necrosis. Thus, free air is not necessarily an indication that surgery should be undertaken in patients with HPVG/PI. We hypothesize that free air with HPVG/PI could be attributed to spontaneous pneumoperitoneum caused by the rupture of serosal

and subserosal cysts in the bowel wall. When patients with free air are accompanied by air-type PI and a low level of T-BIL, it is necessary to also consider non-necrosis of the bowel.

Our study has several limitations. It is a retrospective, single-center study, and the number of patients was small. Furthermore, there is bias in terms of the causes of disease in our hospital. However, our findings could be useful to better understand the mechanisms by which bowel necrosis develops in patients with HPVG and PI.

We examined the factors associated with the presence and absence of bowel necrosis in patients with HPVG and PI. In conclusion, this study indicated that the number of sites of HPVG was associated with bowel necrosis. In addition, the presence of free air or air-type PI was associated with the absence of bowel necrosis in patients with HPVG/PI.

## DISCLOSURE

Approval of the research protocol: The present study was approved by the institutional ethics committee of Kansai Medical University.

Informed consent: The Ethics Committee waived the requirement for informed consent due to the retrospective nature of the study.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None declared.

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