



Acute vascular insufficiency of intestine: incidence highest in summer, outcomes worst in winter

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Abstract

Background The incidence of acute vascular insufficiency of intestine (AVII) is on the rise in the USA and is associated with significant morbidity and mortality. Seasonal variations have been observed in the onset of several gastrointestinal diseases. It is thus far unknown whether the incidence, in-hospital mortality rates, and length of hospital stay (LOS) of AVII vary in different seasons.

Aims The aims of this study were to study the seasonal variations in the (1) incidence, (2) in-hospital mortality, and (3) LOS of AVII in the USA.

Methods We used the Nationwide Inpatient Sample to identify patients aged ≥ 18 years hospitalized from the years 2000–2014. We used the Edwards recognition with estimation of cyclic trend method to study the seasonal variation of AVII hospitalizations and z test to compare the seasonal incidences (peak-to-low ratio), mortalities, and LOS.

Results A total of 1,441,447 patients were hospitalized with AVII (0.3% of all hospitalizations). Patients with AVII were older (69.0 ± 0.1 vs 56.9 ± 0.1) and more commonly females (65.4% vs 35.5%) than patients without AVII ($p < 0.001$). The incidence of AVII increased through the summer to peak in September (peak/low ratio 1.028, 95% CI 1.024–1.033, $p < 0.001$). Patients with AVII hospitalized in winter had the highest mortality (17.3%, $p < 0.001$) and LOS (9.2 ± 0.7 days, $p < 0.001$).

Conclusions The incidence of AVII in the USA peaks in late summer. The in-hospital mortality rates and LOS associated with AVII are the highest in winter. Physicians could be cognizant of the seasonal variations in the incidence, in-hospital mortality, and LOS of AVII.

Keywords Vascular insufficiency · Intestine · Incidence · Mortality · Seasonal

Introduction

Acute vascular insufficiency of the intestine (AVII) can affect the small or large intestine. Ischemic colitis is the most common type of gastrointestinal ischemia [1], with crude incidence of 7.2 per 100,000 person-years [2]. The incidence of ischemic colitis is on the rise in the USA [3, 4]. Colonic ischemia typically spontaneously resolves with supportive management; however, mortality rates range from 4 to 12%

as a considerable minority of patients may develop intestinal gangrene associated with adverse outcomes [1, 5]. Ischemia affecting the small intestine (mesenteric ischemia) is also being seen more commonly and associated with mortality rates of up to 50 to 70% [4, 6, 7]. The rising incidence of AVII may be due to an increased awareness amongst physicians, aging population with underlying risk factors for vascular diseases, and/or polypharmacy [8].

Seasonal variations have been observed in the onset of several gastrointestinal diseases [9]. Peptic ulcer disease is more commonly seen in the winter across several countries [10–12]. Patients with Crohn's disease often have onset of their gastrointestinal symptoms in spring to summer [13]. *Clostridium difficile* infections peak in spring, with lower incidence in summer and fall [14]. Hospitalizations from diverticulitis in the USA are more common in the summer [15]. Patients with colon cancer have also been shown to present more commonly to the hospitals in the summer [16]. In recent

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years, the authors have observed a higher number of patients hospitalized with ischemic colitis in the summer compared with winter. A single-center retrospective Japanese study ($n = 364$) also noted the same trend of less frequent hospitalizations from ischemic colitis in winter, but the seasonal differences in hospitalizations were not statistically different [17]. It is thus far unknown whether if the in-hospital mortality rates and length of hospital stay (LOS) of AVII vary in different seasons.

It is plausible that a study using a larger sample size may illicit clinically useful seasonal variations in the incidence, mortality, and LOS of AVII. The primary aims of this study were to study the seasonal variations in the (1) incidence, (2) in-hospital mortality, and (3) LOS of AVII in the USA using a large database. The secondary aims of this study were to assess the factors associated with higher incidence and mortality, and increased LOS in patients hospitalized with AVII.

Methods

We used the Nationwide Inpatient Sample, the largest publicly available all-payer inpatient care database in the USA to identify patients aged ≥ 18 years hospitalized from the years 2000 to 2014. Nationwide Inpatient Sample is sponsored by Healthcare Cost and Utilization Project, which is an undertaking of Agency for Healthcare Research and Quality [18]. It contains data from five to eight million inpatient hospital admissions from about 1000 hospitals across the USA and approximates a 20% sample of all US hospitals. We used the ICD-9-CM code 557.0 (acute vascular insufficiency of intestine) to identify patients with acute mesenteric ischemia and ischemic colitis. Seasons were defined as winter (January to March), spring (April to June), summer (July to September), and fall (October to December).

We used ICD-9-CM codes to assess for other comorbidities including hypertension (ICD-9-CM codes 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.0, 403.1, 403.9, 404.0, 404.1, 404.9, 405.0, 405.1, 405.9, 997.91), hypotension (458.0, 458.1, 458.21, 458.29, 458.8, 458.9), dyslipidemia (272.0, 272.1, 272.3), diabetes mellitus (250.0, 250.1, 250.2, 250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9), coronary artery disease (410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9, 411.0, 411.1, 411;81, 411;89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.2, 414.3, 414.4, 414.8, 414.9), congestive heart failure (428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9, 398.91), atrial fibrillation: (427.31, 427.32), peripheral vascular disease (443.0, 443.1, 443.2, 443.8, 443.9), chronic obstructive pulmonary disease (491.0, 491.1, 491.20, 491;21,

491.22, 491.8, 491.9, 492.0, 492.8), cirrhosis of liver (537.89, 571.2, 571.5, 571.6), portal hypertension (572.3), acute kidney injury (584, 584.5, 584.6, 584.7, 584.8, 584.9593.9), chronic kidney disease/end stage renal disease (403.0, 403.1, 403.9, 404.0, 404.1, 404.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, V45.11), systemic inflammatory response syndrome (SIRS)/sepsis/septic shock (995.90, 995.91, 995.92, 995.93, 995.94, 785.52), peritonitis (567.29, 567.90), ruptured abdominal aortic aneurysm/AAA (441.3), and thrombophilia/hypercoagulable state (289.81).

Statistical analysis

We used the Edwards recognition with estimation of cyclic trend method to study the seasonal variation of AVII hospitalizations. We used z test to compare the seasonal incidences (peak-to-low ratio), mortalities, and LOS. p value < 0.05 was considered statistically significant.

Results

A total of 1,441,447 patients were hospitalized with a diagnosis of AVII from 2000 to 2014 (0.3% of all hospitalizations). The mean age for patients with AVII was 69.0 ± 0.1 years, compared with 56.9 ± 0.1 years in hospitalizations without AVII ($p < 0.001$). Amongst AVII hospitalizations, 65.4% were females compared with 35.5% females in hospitalizations without AVII ($p < 0.001$). Majority of the patients hospitalized with AVII were Whites (79.4%), while other common races were African Americans (9%) and Hispanics (6.8%). Two-thirds (66.2%) of the patients were covered under Medicare. Over a third of the patients with AVII were hospitalized in the South (35.8%), followed by Northwest (24.6%), West (19.9%), and Northeast (19.9%). The comorbidities in patients hospitalized with AVII included hypertension (60.4%), dyslipidemia (28.9%), coronary artery disease (27.1%), diabetes mellitus (23.9%), acute kidney injury (23.3%), SIRS/sepsis (19.6%), atrial fibrillation (18%), chronic obstructive pulmonary disease (16.8%), congestive heart failure (16.1%), chronic kidney disease (14.1%), hypotension (7.5%), peripheral vascular disease (5.8%), peritonitis (5.2%), liver cirrhosis (2.4%), hypercoagulable state (1.2%), portal hypertension (1.1%), and ruptured abdominal aortic aneurysm (0.4%).

Seasonal variations in the incidence

Amongst all patients, the incidence of AVII increased steadily through the summer to peak on September 14 (peak/low ratio 1.028, 95% CI 1.032–1.043, $p < 0.001$, Fig. 1). The incidence of AVII was the lowest in the winter. Similar seasonal variations in the incidence of AVII were seen in the four geographical areas of the USA, where the peak incidences were seen

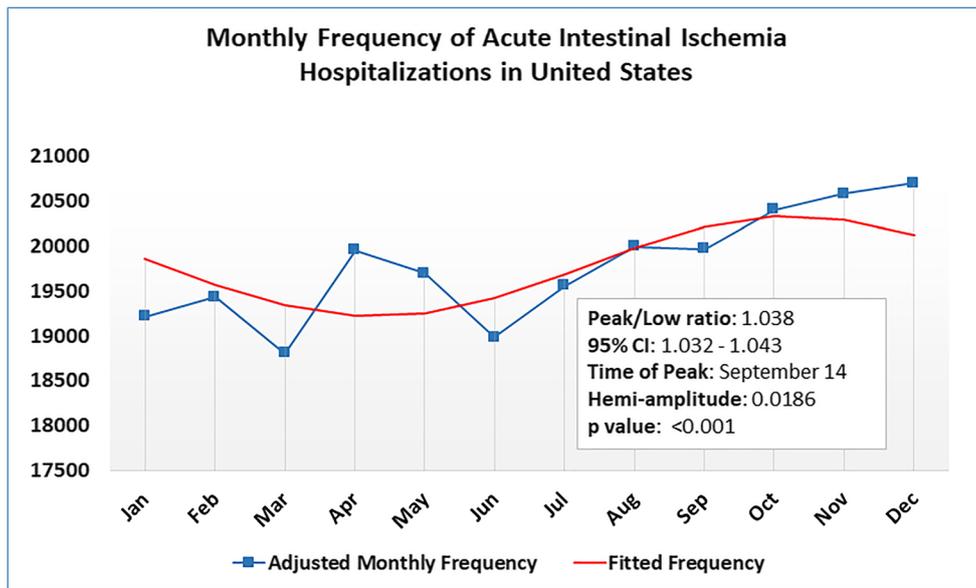


Fig. 1 Seasonal variations in the incidence of acute vascular insufficiency of the intestine in the USA from 2000 to 2014

between mid-summer to early-fall (Figs. 2, 3, 4 and 5). The incidence of AVII peaked on July 24 in Midwest, September 11 in South, September 14 in West, and October 25 in Northeast.

Seasonal variations in the mortality

The average in-hospital mortality of all patients hospitalized with AVII was 15.9%. Patients hospitalized in winter had a higher mortality (17.3%) compared with spring (15.7%), summer (14.9%), and fall (15.7%, $p < 0.001$, Table 1). The higher mortality rates in winter were noted across Northeast, Midwest, South, and West.

Seasonal variations in the length of hospital stay

Mean LOS for AVII hospitalizations for all patients was 9.0 ± 0.1 days (Table 1). Patients hospitalized in winter had a longer LOS (9.2 ± 0.1 days) compared with spring (8.9 ± 0.1), summer (8.8 ± 0.1), and fall (9.0 ± 0.1 days, $p < 0.001$). The longer LOS in winter was seen in all four geographical areas of the USA.

Factors associated with higher incidence

On multivariate analysis, females had a higher risk of AVII (OR 1.66, Table 2). African Americans (OR 0.68) and Hispanics (OR 0.85) had lower odds of hospitalizations for AVII. The

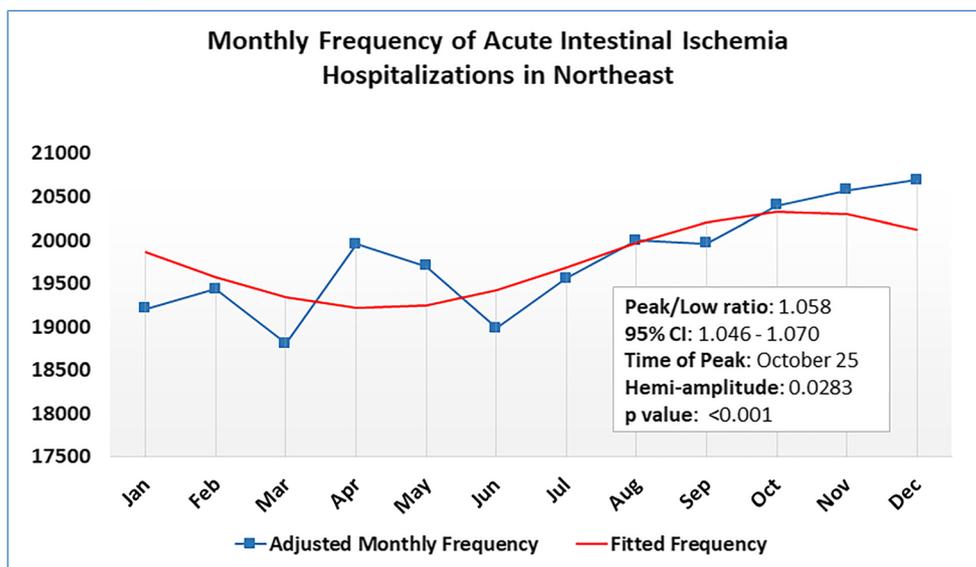


Fig. 2 Seasonal variations in the incidence of acute vascular insufficiency of the intestine in the Northeastern United States

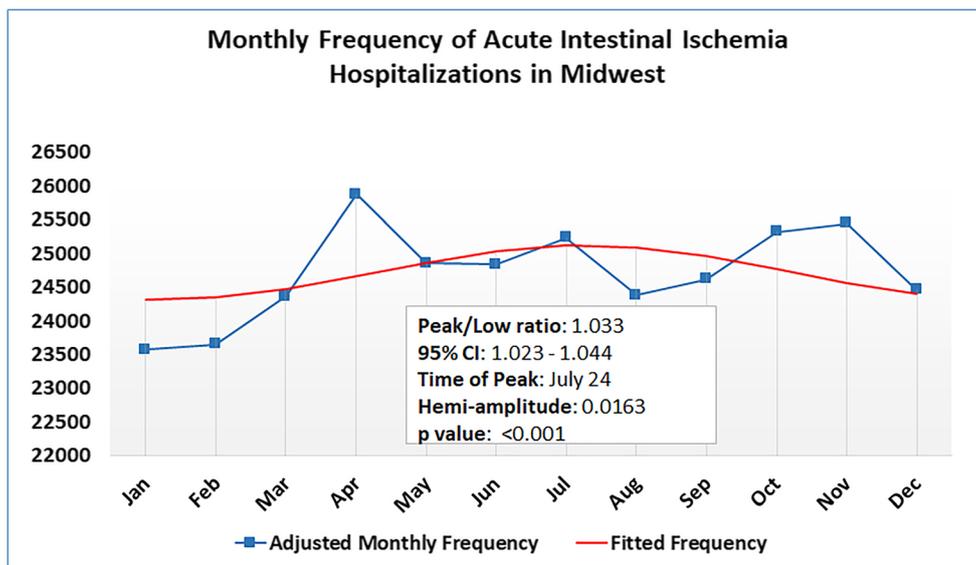


Fig. 3 Seasonal variations in the incidence of acute vascular insufficiency of the intestine in the Midwestern United States

comorbidities associated with the highest odds of AVII included ruptured abdominal aortic aneurysm (OR 10.1), hypercoagulable states (OR 3.62), SIRS/sepsis (OR 3.25), acute kidney injury (2.13), portal hypertension (OR 1.68), peripheral vascular disease (1.55), and hypotension (1.45).

Factors associated with higher mortality

Females had a lower mortality from AVII in our study (OR 0.86, Table 3). Higher mortality was seen in African Americans (OR 1.27) and Hispanics (OR 1.09) hospitalized for AVII, compared with Whites. The comorbidities associated with higher mortality in patients with AVII included SIRS/sepsis (OR 6.92), ruptured AAA (OR 4.20), acute kidney injury (OR 2.35), liver cirrhosis (OR 1.94), hypotension (OR 1.53), atrial fibrillation (OR 1.39),

coronary artery disease (OR 1.34), chronic obstructive pulmonary disease (OR 1.27), congestive heart failure (OR 1.24), peripheral vascular disease (OR 1.21), and chronic kidney disease (OR 1.13). Lower mortality was seen in patients with hypertension (OR 0.69), dyslipidemia (OR 0.62), and diabetes mellitus (OR 0.91).

Factors associated with longer length of hospital stay

On multi-variable analysis, females had a shorter LOS (OR 0.91, Table 4) from AVII than males. African Americans had longer LOS (OR 1.55) than Whites. The comorbidities associated with increased LOS included hypercoagulable state (OR 2.59), peritonitis (OR 1.96), acute kidney injury (OR 1.61), congestive heart failure (OR 1.30), and hypertension (OR 1.18).

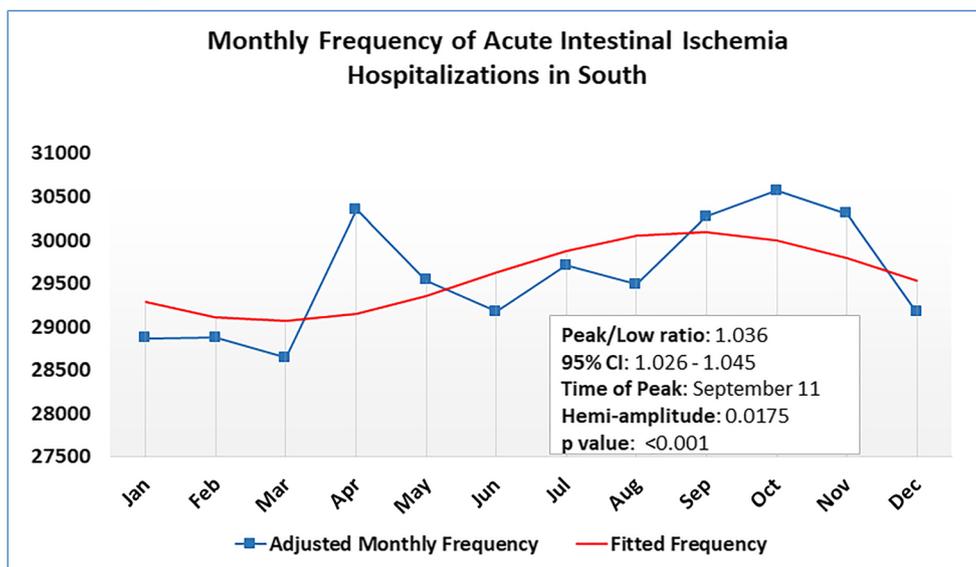


Fig. 4 Seasonal variations in the incidence of acute vascular insufficiency of the intestine in the Southern United States

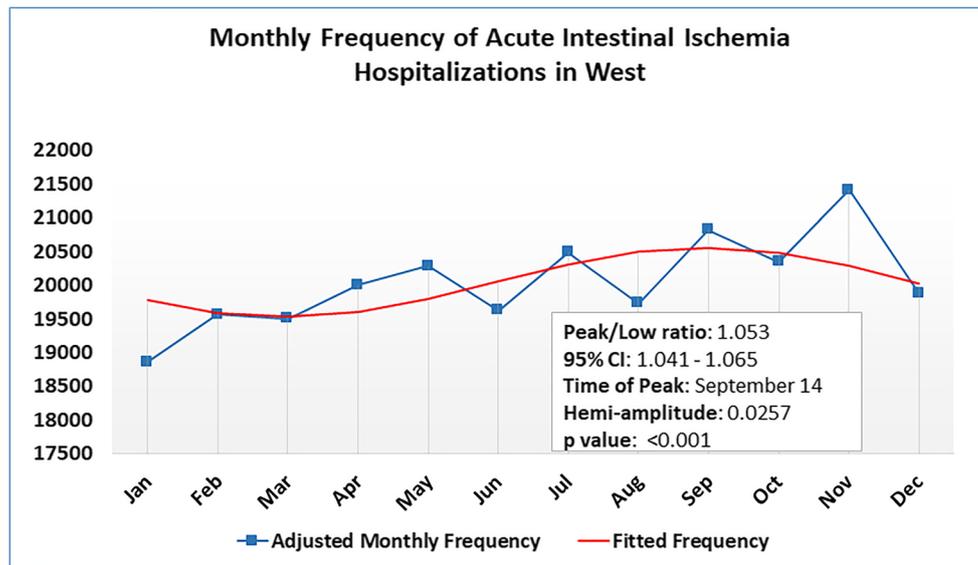


Fig. 5 Seasonal variations in the incidence of acute vascular insufficiency of the intestine in the Western United States

Discussion

In this study, we assessed the seasonal variations in the incidence, mortality, and length of hospital stay of patients hospitalized in the USA with acute vascular insufficiency of the intestine using the Nationwide Inpatient Sample. The incidence of AVII peaked in late summer and reached its nadir in winter. The in-hospital mortality rates and LOS associated

with AVII were the highest in winter. These seasonal variations in the incidence, mortality, and LOS were seen in all four geographical regions of the USA.

The higher incidence of ACII in summer may theoretically be due to heat-associated intravascular volume depletion causing hypoperfusion of the organs [19]. In our study, females were more likely to be hospitalized for AVII (OR 1.66) which is consistent with the prior literature showing female preponderance for ischemic colitis [17, 20, 21]. While the cause of higher prevalence of ischemic colitis in females is not completely understood, females do experience constipation more commonly, and a fourth of patients with ischemic colitis report constipation in the month before suffering from ischemic colitis [20, 22]. Over a third (35.8%) of patients with AVII were hospitalized in the Southern states of the USA, with the lowest proportion of AVII hospitalizations in the Northeast (19.7%). This is consistent with the distribution of general US population, with 38.1% of the population living in the South in 2018 and 17.2% in the Northeast [23].

The patients hospitalized with AVII had a considerable mortality (15.3%) and length of hospital stay (9 days). African Americans and Hispanics were less likely to be hospitalized for AVII, but had a higher mortality compared with Whites. Racial minorities have a lower socioeconomic status in the USA and often receive poorer quality of care, leading to higher mortality rates [24]. On multivariate analysis, the factors associated with higher mortality in patients with AVII included male gender, SIRS/sepsis, ruptured AAA, acute kidney injury, liver cirrhosis, hypotension, atrial fibrillation, coronary artery disease, chronic obstructive pulmonary disease, and congestive heart failure which is consistent with the prior literature [3, 25–29]. The mortality and LOS for AVII were the highest in winter compared with the other seasons across all four geographical regions of the USA. Some of the

Table 1 Seasonal variations in the mortality and length of hospital stay for acute vascular insufficiency of the intestine in the USA

Seasonal variations in the mortality					
Region	Overall	Winter	Spring	Summer	Fall
All USA	15.3%	16.8%	15.3%	14.5%	15.2%
Northeast	16.3%	17.6%	16.2%	15.1%	16.3%
Midwest	14.3%	16%	14%	13.2%	14.1%
South	15.8%	17%	15.7%	14.9%	15.6%
West	15.4%	16.7%	15.3%	14.6%	14.8%
Seasonal variations in the length of hospital stay					
Region	Overall	Winter	Spring	Summer	Fall
All USA	9.0 ± 0.1	9.2 ± 0.1	8.9 ± 0.1	8.8 ± 0.1	9.0 ± 0.1
Northeast	9.6 ± 0.1	9.7 ± 0.2	9.6 ± 0.2	9.3 ± 0.2	9.6 ± 0.2
Midwest	8.3 ± 0.1	8.6 ± 0.1	8.1 ± 0.1	8.2 ± 0.2	8.3 ± 0.2
South	9.0 ± 0.1	9.2 ± 0.1	8.8 ± 0.1	8.9 ± 0.1	8.9 ± 0.1
West	8.8 ± 0.1	9.0 ± 0.2	8.8 ± 0.2	8.6 ± 0.2	8.8 ± 0.2

Footnote: Length of hospital stay in days, expressed as mean ± SEM. *p* value calculated using *z* test to compare the seasonal variations in the mortality and length of hospital stay for acute intestinal ischemia (peak-to-low ratio) < 0.001 for all USA and the four geographic areas

Table 2 Factors associated with incidence of acute vascular insufficiency of the intestine in the USA

Demographics, insurance status, tobacco use, comorbidities	OR	95% CI	<i>p</i> value
Age	1.02	1.02–1.02	< 0.001
Gender (female)	1.66	1.65–1.68	< 0.001
Race ¹			
African American	0.68	0.66–0.69	< 0.001
Hispanics	0.85	0.82–0.87	< 0.001
Others	0.91	0.88–0.94	< 0.001
Insurance ²			
Medicaid	0.77	0.75–0.79	< 0.001
Private insurance	1.05	1.03–1.06	< 0.001
Self-pay	0.79	0.76–0.81	< 0.001
Other	0.81	0.77–0.85	< 0.001
Tobacco use	1.10	1.08–1.12	< 0.001
Comorbidities			
Hypertension	1.13	1.12–1.14	< 0.001
Dyslipidemia	1.02	1.00–1.03	0.007
Coronary artery disease	1.01	0.99–1.02	0.052
Diabetes mellitus	0.78	0.77–0.79	< 0.001
Acute kidney injury	2.13	2.10–2.16	< 0.001
SIRS/Sepsis	3.25	3.20–3.31	< 0.001
Atrial fibrillation	1.06	1.05–1.08	< 0.001
Chronic obstructive pulmonary disease	0.98	0.96–0.99	0.002
Congestive heart failure	0.72	0.71–0.73	< 0.001
Chronic kidney disease	0.89	0.87–0.90	< 0.001
Hypotension	1.45	1.42–1.47	< 0.001
Peripheral vascular disease	1.55	1.52–1.59	< 0.001
Peritonitis	7.93	7.72–8.14	< 0.001
Liver cirrhosis	0.97	0.93–1.00	0.077
Hypercoagulable state	3.62	3.46–3.80	< 0.001
Portal hypertension	1.68	1.58–1.78	< 0.001
Ruptured abdominal aortic aneurysm	10.1	9.22–11.01	< 0.001

p value calculated using multivariate logistic regression

CI confidence interval, *OR* odds ratio, *SIRS* systemic inflammatory response syndrome

¹ Reference Whites

² Reference Medicare

comorbidities associated with higher mortality rates in patients with AVII in our study (such as coronary artery disease, congestive heart failure, and atrial fibrillation) are known to cause higher mortality in the winter [30–32], possibly due to stimulation of sympathetic nerves from low temperatures [33]. Hypertension was associated with higher incidence but lower mortality in patients with AVII. Our data suggests that amongst patients hospitalized with AVII, hypotension is associated with higher mortality that corroborates the findings of Lee et al. [34]. In a recent preliminary report, use of beta-blockers was associated with higher odds of ischemic colitis [35]; this may be due to hypotension caused by these medications. Hypercoagulable states may play an important role in

the pathogenesis of AVII. In a study by Koutroubakis, 72% of the patients with colonic ischemia tested positive for thrombophilia on serological screening [36]. In our study, hypercoagulable state was associated with a higher prevalence (OR 3.62) but lower mortality (OR 0.59) from AVII.

Our study has some limitations. We assessed the factors associated with higher mortality in patients with AVII, but from the data, we cannot tell the primary causes of mortality in these patients. From our data, we cannot explain the reasons for lower incidence and mortality from AVII in patients with diabetes mellitus seen in our study. However, our findings are consistent with a recent report showing lower inpatient mortality in diabetics hospitalized with AVII [4]. Huerta et al. also

Table 3 Factors associated with mortality in patients with acute vascular insufficiency of the intestine in the USA

Demographics, insurance status, tobacco use, comorbidities	OR	95% CI	<i>p</i> value
Age	1.03	1.03–1.03	< 0.001
Gender (female)	0.86	0.84–0.89	< 0.001
Race ¹			
African American	1.27	1.21–1.34	< 0.001
Hispanics	1.09	1.02–1.17	0.008
Others	1.08	1.01–1.15	0.018
Insurance ²			
Medicaid	1.21	1.13–1.29	< 0.001
Private insurance	0.88	0.83–0.92	< 0.001
Self-pay	1.37	1.24–1.51	< 0.001
Other	1.38	1.23–1.55	< 0.001
Tobacco use	0.92	0.87–0.97	0.002
Comorbidities			
Hypertension	0.69	0.67–0.71	< 0.001
Dyslipidemia	0.62	0.60–0.64	< 0.001
Coronary artery disease	1.34	1.29–1.38	< 0.001
Diabetes mellitus	0.91	0.88–0.93	< 0.001
Acute kidney injury	2.35	2.28–2.43	< 0.001
SIRS/Sepsis	6.92	6.69–7.16	< 0.001
Atrial fibrillation	1.39	1.34–1.44	< 0.001
Chronic obstructive pulmonary disease	1.27	1.22–1.32	< 0.001
Congestive heart failure	1.24	1.20–0.29	< 0.001
Chronic kidney disease	1.13	1.08–1.17	< 0.001
Hypotension	1.53	1.46–1.61	< 0.001
Peripheral vascular disease	1.21	1.14–1.28	< 0.001
Peritonitis	0.97	0.91–1.02	0.219
Liver cirrhosis	1.94	1.77–2.13	< 0.001
Hypercoagulable state	0.59	0.50–0.70	< 0.001
Portal hypertension	0.93	0.81–1.07	0.322
Ruptured abdominal aortic aneurysm	4.20	3.37–5.24	< 0.001

p value calculated using multivariate logistic regression

CI confidence interval, *OR* odds ratio, *SIRS* systemic inflammatory response syndrome

¹ Reference Whites

² Reference Medicare

did not find an association of diabetes with colonic ischemia, though diabetes was associated with higher risk of small bowel ischemia [37]. Because of the same ICD-9 code for ischemic colitis and acute mesenteric ischemia, we could not separately analyze patients with small and large intestinal ischemia. We cannot tell how many of the patients in our study had recurrence of AVII and whether those recurrences affected the seasonal variations observed in our study. About 8 to 15% of the patients with ischemic colitis experience recurrence; however, these patients often tend to have the recurrence in the same season [3, 17].

In conclusion, patients with acute vascular insufficiency of the intestine are most commonly hospitalized in the

summer in the USA. However, patients with AVII hospitalized in winter seem to have the worst outcomes, with a significantly higher mortality rates compared with the other seasons. Physicians could be cognizant of the variations in the incidence and outcomes of AVII in different seasons. Physicians may need to caution patients with underlying risk factors for intestinal ischemia of the higher incidence of AVII in summer. Encouraging adequate hydration in these high-risk patients in hotter climate may decrease the risk of intravascular volume depletion and possible subsequent AVII. In addition, physicians caring for patient hospitalized with AVII in winter may need to observe these patients more vigilantly to promptly

Table 4 Factors associated with length of hospital stay in patients with acute vascular insufficiency of the intestine in the USA

Demographics, insurance status, tobacco use, comorbidities	OR	95% CI	<i>p</i> value
Age	1.01	0.99–1.01	0.202
Gender (female)	1.32	1.16–1.51	<0.001
Race ¹			
African American	1.55	1.18–2.02	0.001
Hispanics	1.17	0.92–1.51	0.207
Others	0.97	0.79–1.42	0.705
Insurance ²			
Medicaid	1.16	0.86–1.55	0.336
Private insurance	0.92	0.76–0.11	0.372
Self-pay	0.79	0.56–1.10	0.157
Other	0.78	0.52–1.16	0.225
Tobacco use	0.91	0.76–1.09	0.302
Comorbidities			
Hypertension	1.18	1.02–1.37	0.023
Dyslipidemia	1.03	0.89–1.18	0.690
Coronary artery disease	1.02	0.87–1.19	0.849
Diabetes mellitus	0.94	0.81–1.09	0.405
Acute kidney injury	1.61	1.31–1.99	<0.001
SIRS/Sepsis	0.92	0.74–1.14	0.429
Atrial fibrillation	1.09	0.89–1.34	0.398
Chronic obstructive pulmonary disease	1.09	0.90–1.32	0.392
Congestive heart failure	1.30	1.03–1.64	0.025
Chronic kidney disease	1.04	0.84–1.28	0.728
Hypotension	1.00	0.78–1.27	0.994
Peripheral vascular disease	0.83	0.64–1.07	0.148
Peritonitis	1.96	1.30–2.96	0.001
Liver cirrhosis	0.68	0.46–1.01	0.056
Hypercoagulable state	2.59	1.15–5.81	0.021
Portal hypertension	1.10	0.62–1.96	0.739
Ruptured abdominal aortic aneurysm	0.97	0.24–3.94	0.964

p value calculated using multivariate logistic regression

CI confidence interval, *OR* odds ratio, *SIRS* systemic inflammatory response syndrome

¹ Reference Whites

² Reference Medicare

recognize and manage deterioration in their clinical status. Additional studies assessing the benefits of these interventions to reduce the incidence and improve outcomes of patients with AVII may be useful.

Authors' contributions Asad Jehangir helped in the study planning, data interpretation, literature review, and writing the manuscript. Rashmi Dhital helped in data collection, statistical analysis, and writing the manuscript. Anam Qureshi helped in the literature review and writing the manuscript. Eugene P. York planned the study and did literature review and critical revision of the manuscript for important intellectual content. All the authors approve the final version of the manuscript.

An abstract of this study was presented at the Digestive Disease Week® at the San Diego Convention Center, San Diego, CA, on May 21, 2019 and nominated as the Poster of Distinction.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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