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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

 WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Retrospective Study

Secondary angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease: Results from the nationwide inpatient sample

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Abstract

BACKGROUND
Chronic kidney disease is associated with angiodysplasia of gastrointestinal tract leading to increased risk of gastrointestinal bleeding.

AIM
To determine the nationwide prevalence, trends, predictors and resource utilization of angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease hospitalizations.

METHODS
The Nationwide Inpatient Sample database from 2009 to 2014, was utilized to conduct a retrospective study on patients with angiodysplasia associated-gastrointestinal bleeding and end-stage renal disease. Hospitalizations with end-

stage renal disease were included in the Nationwide Inpatient Sample database and a subset of hospitalizations with end-stage renal disease and angiodysplasia-associated gastrointestinal bleeding were identified with International Classification of Diseases, 9th revision, Clinical Modification codes for both end-stage renal disease (585.6) and Angiodysplasia (569.85, 537.83).

RESULTS
The prevalence of angiodysplasia-associated gastrointestinal bleeding was 0.45% (n = 24709) among all end-stage renal disease patients (n = 5505252) that were hospitalized. Multivariate analysis indicated that the following were significant factors associated with higher odds of angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease patients: an increasing trend from 2009-2014 ($P < 0.01$), increasing age ($P < 0.0001$); African American race ($P = 0.0206$); increasing Charlson-Deyo Comorbidity Index ($P < 0.01$); hypertension ($P < 0.0001$); and tobacco use ($P < 0.0001$). Diabetes mellitus ($P < 0.0001$) was associated with lower odds of angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease patients. In comparison with urban teaching hospitals, rural and urban nonteaching hospitals were associated with decreased odds of angiodysplasia associated-gastrointestinal hemorrhage.

CONCLUSION
Angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease patients showed an increasing trend from 2009-2014. Advanced age, African American race, overall high comorbidities, hypertension and smoking were significant factors for angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease hospitalized patients.

Key words: Angiodysplasia; Renal; Gastrointestinal; Hemorrhage

Core tip: There was an increasing trend of angiodysplasia associated-gastrointestinal bleeding among end-stage renal disease patients over the study period of 2009-2014. The likelihood of angiodysplasia associated-gastrointestinal bleeding significantly increased with advanced age with the highest likelihood occurring in patients above the age of 75 years. African American race, increased co-morbidities, hypertension and tobacco use were independent predictors of angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease hospitalized patients.

INTRODUCTION

Angiodysplasias, the most common vascular malformations of the gastrointestinal (GI) tract are vascular ectasias with an estimated prevalence of 0.82% in the general population[1]. GI Angiodysplasia are the underlying cause for nearly 6% of lower GI hemorrhage and 1.2%-8% of upper GI hemorrhage[1].

In the United States, the prevalence of chronic kidney disease (CKD) and subsequently end-stage renal disease (ESRD) has been on the rise. The United States Renal Data System 2018 Annual Data Report, showed that the prevalence of CKD was around 15% among adults[2]. CKD is associated with an increased risk of GI bleeding, mainly secondary to angiodysplasias and erosive esophagitis[2]. Suspected pathophysiological mechanisms include uremic platelet dysfunction and intermittent use of anticoagulants in dialysis[3,4].

Prior studies have shown that gastric and small bowel angiodysplasia are found to be the most common cause of obscure GI bleeds in patients with chronic renal

failure[5]. A study by Kalman *et al*[6] showed that angioectasia caused upper GI bleeding in 13% of the patients with CKD, however in comparison, 1.3% of patients with normal renal function were found to have angiodysplasia as a source of bleeding. Another study by Holleran *et al*[7] showed that 47% of CKD patients had small bowel angiodysplasia as compared to 17% of controls. The association between renal failure and angiodysplasia was first reported in 1981 and it remains a common cause of initial and recurrent upper GI bleeding in hemodialysis patients[8,9].

Angiodysplasia can be identified in any part of the GI tract but are particularly common in the cecum and ascending colon[10]. Endoscopic techniques (upper endoscopy, double-balloon enteroscopy, wireless capsule endoscopy, colonoscopy) remain the gold standard in the diagnosis of angiodysplasia[10]. The typical endoscopic appearance of an angiodysplastic lesion is that of an isolated, sub-centimeter, flat or raised bright red fernlike pattern of small dilated veins radiating from a central vessel[11]. Limited epidemiological data exists on the annual number of hospitalizations, patient characteristics and outcomes of angiodysplasia-associated GI bleeding in ESRD. The aim of this study was to determine nationwide prevalence, trends in inpatient hospitalizations, and predictors of hospitalization for patients with angiodysplasia-related GI bleeding in ESRD.

MATERIALS AND METHODS

This retrospective study utilized the Nationwide Inpatient Sample (NIS), 2009 to 2014[12,13]. Patients in the NIS database hospitalized during the study period with ESRD were included and a subset of ESRD hospitalizations with Angiodysplasia related GI bleeding hospitalizations were identified using International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes classified diseases according to primary diagnosis for inpatient admission. ESRD hospitalizations were identified based on the ICD-9 CM code - 585.6, and angiodysplasia associated-GI bleeding hospitalizations were identified based on the ICD-9 CM code 569.85 (Angiodysplasia of intestine with hemorrhage) or ICD-9 CM code 537.83 (Angiodysplasia of stomach and duodenum with hemorrhage). Other ICD-9 CM codes utilized in the study included: Hypertension ICD-9 code – 401.x-405.x, 642.0, 642.1, 642.2, 642.7, 642.9; Diabetes Mellitus (DM) ICD-9 code - 250.x (Includes Type 1 and Type II DM); and Tobacco use ICD-9 code - 305.1, V15.82.

Primary outcome was to estimate the prevalence, and predictors of hospitalization for ESRD patients with Angiodysplasia associated-GI bleeding. The secondary outcome was to examine the inpatient hospital-related total cost of care, length of stay (LOS), and inpatient mortality of Angiodysplasia-associated GI bleeding in patients with end stage renal disease hospitalizations. Inpatient hospital-related total cost of care was defined as, the amount the hospital received for the entire hospital stay. In-hospital cost was calculated using total weighted hospital charges and cost to charge ratios reported for participating hospitals. LOS was defined as the number of days the patient remained in the hospital with inpatient status. Inpatient mortality was defined as a binary (yes/no) variable. Other variables included age in years at admission (18 to ≤ 45, 45 to 65, > 65 to 75, and > 75), gender, race (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian Pacific Islander, Native American, Other), primary payer (Self-payer, Private payer, Medicaid, Medicare, Others), Charlson-Deyo Comorbidity Index (0, 1-2, 3-4, ≥ 5), presence of hypertension, DM, Obesity (Elixhauser comorbidity), tobacco use, Hospital location/teaching status (rural, Urban teaching, Urban non-teaching), Hospital region (Northeast, Midwest, South, West), and median household income quartile defined as: 1 ($1-$38999), 2 ($39000-$47 999), 3 ($48000-$62 999), 4 (≥ $63000).

Statistical analysis

All statistical analysis was done in SAS 9.4 (SAS Institute Inc., Cary, NC, United States) and utilized the SAS/STAT Survey Sampling and Analysis procedures. Univariate comparisons were made using the Rao-Scott Chi-Square test. The Rao-Scott Chi-Square test is similar to a Pearson Chi-Square tests and adjusts for the complex sampling design of the NIS. Multivariate predictive modeling was done using Logistic Regression for complex sampling data. Differences in LOS and total charges were computed using *t*-tests for complex sampling data. Proper variance estimation (strata, clustering, and domain analysis) were handled based on the recommendations provided by AHRQ[12,13].

All frequencies are displayed as weighted hospitalizations. Since data from both before and after 2012 was utilized, the data was weighted by the NIS Trend Weights. Pediatric cases (< 18 years at time of admission) were excluded from this analysis. The

Charlson-Deyo score was used to compute comorbidities[14]. A small proportion of patients were missing data on race, primary payer, median household income quartile, or hospital location/teaching status. These missing data points were either analyzed as their own "Unknown" group or were grouped with the "Other" group, whatever was most appropriate.

RESULTS

During the 2009-2014 study period, a total of 5505252 hospitalizations with an ESRD diagnoses were recorded in United States, hospitals. Angiodysplasia associated-GI bleeds were found in 24709 (0.45%) of ESRD hospitalizations. Baseline characteristics, demographics, risk factors, and complications comparisons of ESRD with and without GI angiodysplasia are displayed in Table 1. The prevalence of ESRD with GI angiodysplasia varied by year with the lowest annual rate in 2009 and the highest annual rate in 2013, respectively representing 0.33% and 0.52% of all ESRD hospitalizations ($P < 0.0001$). The greatest proportion of ESRD hospitalizations were in patients between ages 45-65 (40.25%) and the majority of hospitalizations were Non-Hispanic White (39.58%), followed by African Americans (32.26%). Medicare was the primary payor for the vast majority of ESRD hospitalizations (74.74%).

Age was associated with angiodysplasia associated-GI bleeding, where the highest rate occurred in those 75 years and older (0.69% of ESRD hospitalizations) ($P < 0.0001$). Non-Hispanic White patients had the highest rate of angiodysplasia associated-GI bleeding (0.48% of ESRD hospitalizations) while Medicare had the highest rate of Angiodysplasia associated-GI bleeding (0.50% of ESRD hospitalizations) (both $P < 0.05$).

The Charlson-Deyo Comorbidity Index score was predictive of angiodysplasia associated-GI bleeding with 0.35% of ESRD hospitalizations with a Charlson-Deyo Comorbidity Score of 1-2, 0.46% of ESRD hospitalizations with a Score of 3-4, and 0.50% of hospitalizations with a Score of 5 or more ($P \leq 0.0001$). Analyzed separately, hypertension and tobacco use were associated with angiodysplasia associated-GI bleeding (both $P < 0.0001$). Sex of the patient, DM, obesity, hospital location/teaching status, and hospital region all failed to demonstrate a statistically significant association with GI angiodysplasia (all $P \geq 0.05$).

Multivariate analysis of factors associated with ESRD and angiodysplasia associated-GI bleeding are reported in Table 2. From 2009 to 2014 for all ESRD hospitalizations, there were significantly increasing trend in the odds of concomitant angiodysplasia associated-GI bleeding with an ESRD hospitalization ($P < 0.0001$). Age independently influenced the odds of Angiodysplasia associated-GI bleeding. Compared to hospitalizations in patients between 18-44 years old, hospitalizations for 75+ patients had approximately 8 times greater odds of GI angiodysplasia (OR: 8.22, 95%CI: 5.87-11.5), followed by 7 times greater odds in those aged 65-74 (OR: 7.42, 95%CI: 5.27-10.4), and 4 times greater odds in those aged 45-65 (OR: 4.12, 95%CI: 3.05-5.57) (all $P < 0.0001$). The odds of angiodysplasia associated-GI bleeding were significantly greater for hospitalizations of African American patients (OR: 1.12, 95%CI: 1.02-1.23, $P = 0.0206$), but less for Asian Pacific Islander patients (OR: 0.77, 95%CI: 0.62-0.96, $P = 0.0194$) as compared to hospitalizations of Non-Hispanic White patients. While median household income quartile was not an independently predictive factor, Self-Pay hospitalizations had significantly lower odds of angiodysplasia associated-GI bleeding (OR: 0.32, 95%CI: 0.20-0.51, $P < 0.0001$) than Medicare patients.

The odds of angiodyslasia associated-GI bleeding increased with higher Charlson-Deyo Comorbidity Scores on multivariate analysis. When compared to Charlson-Deyo Scores between 1-2, Charlson-Deyo Scores of 5 or more represented the highest risk group for angiodysplasia associated GI-bleeding (OR: 1.26, 95%CI: 1.12-1.43, $P = 0.0002$), then followed by those with Charlson-Deyo Scores of 3-4 (OR: 1.15, 95%CI: 1.04-1.27, $P = 0.0047$). A DM co-morbidity decreased odds of having angiodysplasia associated-GI bleeding (OR: 0.79, 95%CI: 0.73-0.85, $P < 0.0001$); however, there were increased odds for Hypertension (OR: 2.01, 95%CI: 1.79-2.26) and tobacco use (OR: 1.26, 95%CI: 1.17-1.36) (both $P < 0.0001$). Rural (OR: 0.78, 95%CI: 0.66-0.93, $P = 0.0057$) and urban nonteaching hospitals (OR: 0.89, 95%CI: 0.80-0.98, $P = 0.0160$) had decreased odds of angiodysplasia associated-GI bleeds as compared to urban teaching hospitals. Hospital Region was not independently predictive of angiodysplasia associated-GI bleeds under multivariate analysis (all $P \geq 0.05$).

During the 2009-2014 study period, ESRD hospitalizations with angiodysplasia associated-GI bleeding had a significantly longer average LOS (8.71 d) than hospitalizations without angiodysplasia associated-GI bleeding (6.85 d) (p < 0.0001).

Table 1 Prevalence and distribution of demographics, severity of disease, and covariate of patients hospitalized with a diagnosis of end-stage renal disease and angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease hospitalizations, 2009-2014

	End-stage renal disease hospitalizations (*n* = 5505252), *n* (%)	End-stage renal disease with angiodysplasia associated-gastrointestinal bleeding (*n* = 24709), *n* (%)	End-stage renal disease withoutangiodysplasia (*n* = 5480543), *n* (%)	*P* value
Year				
2009	876373 (15.92)	2886 (0.33)	873488 (99.67)	< 0.0001
2010	905614 (16.45)	3845 (0.42)	901768 (99.58)	
2011	975245 (17.72)	4273 (0.44)	970972 (99.56)	
2012	911325 (16.55)	4450 (0.49)	906875 (99.51)	
2013	909080 (16.51)	4715 (0.52)	904365 (99.48)	
2014	927615 (16.85)	4540 (0.49)	923075 (99.51)	
Sex				
Female	2598705 (47.20)	11792 (0.45)	2586913 (99.55)	0.5452
Male	2906547 (52.80)	12917 (0.44)	2893630 (99.56)	
Age category				
18-44	805556 (14.63)	646 (0.08)	804909 (99.92)	< 0.0001
45-64	2215958 (40.25)	7632 (0.34)	2208326 (99.66)	
65-74	1266923 (23.02)	7996 (0.63)	1258927 (99.37)	
75+	1216815 (22.10)	8435 (0.69)	1208381 (99.31)	
Race/ethnicity				
Caucasian	2179234 (39.58)	10509 (0.48)	2168725 (99.52)	0.0149
African American	1776081 (32.26)	8051 (0.45)	1768030 (99.55)	
Hispanic	796930 (14.48)	3240 (0.41)	793690 (99.59)	
Asian Pacific Islander	174118 (3.16)	610 (0.35)	173507 (99.65)	
Native American	53624 (0.98)	188 (0.35)	53436 (99.65)	
Others/Unknown	525265 (9.54)	2111 (0.40)	523155 (99.60)	
Primary payor				
Self-Payor	86637 (1.58)	78 (0.09)	86559 (99.91)	< 0.0001
Private Payor	606394 (11.01)	2114 (0.35)	604280 (99.65)	
Medicaid	595160 (10.81)	1528 (0.26)	593632 (99.74)	
Medicare	4114876 (74.74)	20728 (0.50)	4094148 (99.50)	
Others/Unknown	102185 (1.86)	261 (0.26)	101924 (99.74)	
Median Household Income Quartile				
1st Quartile (Lowest)	2042427 (37.10)	9105 (0.45)	2033322 (99.55)	0.2426
2nd Quartile	1344796 (24.43)	5844 (0.43)	1338952 (99.57)	
3rd Quartile	1147171 (20.84)	5170 (0.45)	1142001 (99.55)	
4th Quartile (Highest)	831706 (15.11)	4052 (0.49)	827653 (99.51)	
Unknown	139152 (2.52)	538 (0.39)	138615 (99.61)	
Charlson-Deyo Comorbidity Index				
Score 1-2	1024375 (18.61)	3617 (0.35)	1020758 (99.65)	< 0.0001
Score 3-4	2918273 (53.01)	13289 (0.46)	2904984 (99.54)	
Score 5+	1562604 (28.38)	7803 (0.50)	1554801 (99.50)	
Hypertension				
Yes	4234181 (76.91)	21756 (0.51)	4212425 (99.49)	< 0.0001
No	1271071 (23.09)	2953 (0.23)	1268118 (99.77)	
Diabetes mellitus				
Yes	3119720 (56.67)	13648 (0.44)	3106072 (99.56)	0.1309
No	2385532 (43.33)	11061 (0.46)	2374471 (99.54)	
Tobacco use				
Yes	1124816 (20.43)	6004 (0.53)	1118812 (99.47)	< 0.0001
No	4380436 (79.57)	18705 (0.43)	4361731 (99.57)	
Obesity				

Yes	642352 (11.67)	2569 (0.40)	639783 (99.60)	0.1030
No	4862900 (88.33)	22140 (0.46)	4840760 (99.54)	
Hospital location/teaching status				
Rural	362509 (6.58)	1419 (0.39)	361090 (99.61)	0.1437
Urban Nonteaching	2047397 (37.19)	8858 (0.43)	2038539 (99.57)	
Urban Teaching	3053214 (55.46)	14248 (0.47)	3038965 (99.53)	
Unknown	42132 (0.77)	184 (0.44)	41949 (99.56)	
Hospital region				
Northeast	993923 (18.06)	4742 (0.48)	989181 (99.52)	0.1104
Midwest	1149456 (20.88)	5388 (0.47)	1144068 (99.53)	
South	2289246 (41.58)	10245 (0.45)	2279002 (99.55)	
West	1072627 (19.48)	4334 (0.40)	1068292 (99.60)	

Similarly, angiodysplasia associated-GI bleeding hospitalizations also had higher average total charges ($82340 *vs* $64579) (*P* < 0.0001). The mortality rate in ESRD hospitalizations with angiodysplasia associated-GI bleeding was 3.41% while the mortality rate in ESRD hospitalizations without angiodysplasia associated-GI bleeding was 5.01% (*P* < 0.0001). The comparison of hospitalization mortality, total charges, and LOS averages between ESRD hospitalizations with and without Angiodysplasia-associated GI bleeding is shown in Table 3.

DISCUSSION

A significant number of patients with ESRD develop GI angiodysplasia during the disease course and hence our study renders valuable information about an important patient cohort. To our knowledge, this is the first population-based study that looks at hospitalization rates, associated factors and outcomes of angiodysplasia related GI bleeding in renal failure patients. Our study showed that over a 5-year period from 2009-2014, there were a total of 5505252 hospitalizations with the diagnoses of ESRD. Of these 0.45% (24709) had angiodysplasia associated-GI hemorrhage. The incidence of Dieulafoy lesions, angiodysplasia and cancers as etiology of upper GI bleeding has been on the rise. Our study also showed a similar trend towards increasing hospitalizations for angiodysplasia related bleeding in ESRD patients from 2009-2014. During the study period, the hospitalization rate of angiodysplasia related hemorrhage in renal failure patients increased by 6.7%. This finding mirrors that of the study by Abougergi *et al*[15], who showed that the hospitalization rate of angiodysplasia in general increased by 32% from 2002-2012. Despite the introduction of newer and innovative treatment options which are successful in achieving short-term hemostasis, recurrent hemorrhage still remains an important problem in angiodysplasia and neoplasm induced hemorrhage[15].

The results of our study showed that elderly patients had a higher tendency of having bleeding angiodysplastic lesions and hence advanced age was noted to be a significant risk factor in our study[16]. This is compatible with the previously known epidemiology of the angiodysplastic lesions[17,18]. No sex differences in patients with angiodysplasia related GI bleeding and ESRD were seen in our study. However, it was found that hypertension was one of the comorbidities associated with increased risk of GI bleeding in patients with ESRD. Holleran *et al*[7] (2013) on multivariate analysis demonstrated that hypertension was positively associated with small bowel angiodysplasia. One possible reason for it might be that old age is associated with increased prevalence of hypertension as a result of decreased arterial compliance[19] and old age was noted to be the single, strongest and independent risk factor for GI angiodysplasia. It is speculated that aging causes vascular fragility which may lead to dysplastic changes of blood vessels and subsequent bleeding.

Results of our multivariate analysis showed that African-American population is associated with an increased risk of developing angiodysplasia related GI bleeding. This finding may reflect a higher prevalence of CKD among African-Americans[20]. Choi *et al*[21], in his study demonstrated higher risk of ESRD and associated mortality among African American individuals when compared to whites. Plausible reasons for this disparity include inadequately controlled diabetes, hypertension and proteinuria in African Americans compared to their white counterparts[21].

Previous studies by Kim *et al*[17] (2015) and Nishimura *et al*[22] (2016) demonstrated that the DM was not associated with bleeding from GI angiodysplasia. Our analysis

Table 2 Multivariable analyses of factors associated with Angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease hospitalizations, 2009-2014		
	Adjusted odds ratio (95%CI)	***P* value**
Year		
2010	1.27 (1.07, 1.52)	0.0071
2011	1.28 (1.08, 1.53)	0.0045
2012	1.43 (1.23, 1.66)	< 0.0001
2013	1.51 (1.30, 1.76)	< 0.0001
2014	1.39 (1.19, 1.61)	< 0.0001
2009	Reference	
Sex		
Male	0.99 (0.93, 1.06)	0.8053
Female	Reference	
Age category		
45-64	4.12 (3.05, 5.57)	< 0.0001
65-74	7.42 (5.27, 10.4)	< 0.0001
75+	8.22 (5.87, 11.5)	< 0.0001
18-44	Reference	
Race/ethnicity		
African American	1.12 (1.02, 1.23)	0.0206
Asian Pacific Islander	0.77 (0.62, 0.96)	0.0194
Hispanic	1.08 (0.89, 1.30)	0.4459
Native American	0.93 (0.61, 1.42)	0.7335
Others/unknown	0.98 (0.86, 1.12)	0.7289
Caucasian	Reference	
Primary payor		
Others/Unknown	0.69 (0.52, 0.90)	0.0072
Medicaid	0.84 (0.69, 1.01)	0.0669
Private Payor	0.96 (0.83, 1.10)	0.5551
Self-Payor	0.32 (0.20, 0.51)	< 0.0001
Medicare	Reference	
Median Household Income Quartile		
2nd Quartile	0.96 (0.86, 1.06)	0.4205
3rd Quartile	0.97 (0.88, 1.08)	0.6124
4th Quartile (Highest)	1.00 (0.89, 1.12)	0.9335
Unknown	0.96 (0.76, 1.20)	0.7065
1st Quartile (Lowest)	Reference	
Charlson-Deyo Comorbidity Index		
Score 3-4	1.15 (1.04, 1.27)	0.0047
Score 5+	1.26 (1.12, 1.43)	0.0002
Score 1-2	Reference	
Hypertension		
Yes	2.01 (1.79, 2.26)	< 0.0001
No	Reference	
Diabetes mellitus		
Yes	0.79 (0.73, 0.85)	< 0.0001
No	Reference	
Tobacco use		
Yes	1.26 (1.17, 1.36)	< 0.0001
No	Reference	
Hospital location/teaching status		
Rural	0.78 (0.66, 0.93)	0.0057
Unknown	1.20 (0.77, 1.86)	0.4205
Urban Nonteaching	0.89 (0.80, 0.98)	0.0160
Urban Teaching	Reference	

Hospital region		
Midwest	0.99 (0.89, 1.10)	0.8082
Northeast	0.97 (0.85, 1.10)	0.6453
West	0.93 (0.80, 1.09)	0.3770
South	Reference	

suggested that diabetes was associated with reduced risk of bleeding from angiodysplastic lesions[17,22]. However, it is unknown whether glycemic control was a contributory factor to bleeding from angiodysplasia. Hypothetically, hyperglycemia could be important because of reactive oxygen species mediated oxidative stress[23]. It is essential to elucidate whether DM affects the risk of hemorrhage from angiodysplasia and whether strict glycemic control can lower the bleeding risk. Hence, further studies are required before any definitive conclusions can be drawn.

Our study found smoking to be a significant risk factor promoting angiodysplasia related bleeding in renal failure patients. Kaplan *et al*[24], in his study reported that smokers had a high risk of hospitalizations for upper GI bleed compared to non-smokers. Proposed mechanism involves inhibition of prostaglandins in the upper GI tract induced by smoking. This leads to vasoconstriction of the overlying mucosa and possible ischemia. This effect may be aggravated in ESRD patients who have pre-existing microvascular disease and hence are at increased risk of developing GI bleeding compared to the general population[25,26].

It was also noted in our study that presence of other comorbidities was also significantly associated with bleeding from angiodysplasia in ESRD patients. These comorbidities included peripheral vascular disease, cerebrovascular disease, chronic lung disease, rheumatological disease, peptic ulcer disease, liver disease, DM, cancer and AIDS. We utilized the Charlson Comorbidity Index because it is a well validated score for measuring comorbidity in many different contexts[14]. Many potential mechanisms for this observed association are hypothesized for example decreased oxygen levels in chronic lung disease, malnutrition in many diseases (such as chronic liver disease) or micro-and macrovascular complications in diabetes. Hence, a cumulative effect rather than a single mechanism is involved. This highlights the fact that it is imperative to know the burden of comorbidities of the patient since early recognition will help guide management particularly in cases where modifiable GI risk factors are absent[27].

In-hospital mortality of ESRD patients with angiodysplasia related GI bleeding was found to be lower compared to inpatient mortality of population with end stage renal disease without angiodysplasia (3.41% *vs* 5.01%). This particular finding can potentially be explained by the fact that the reduction in mortality rate could be due to improvements in treatment modalities which include not only medications such as proton pump inhibitors (PPI) and octreotide, but also various hemostatic techniques utilized during endoscopy as well as surgical interventions. This is supported by a study published in 2015, which showed that at the same time that the in-hospital mortality rates have been declining, the rate of in-hospital endoscopy, endoscopy within 24 h of admission and endoscopic therapy for patients with non-variceal upper GI bleeding increased during 1989-2009[28]. There has also been advances in diagnostic testing, provision of better care in the intensive care units and general health care delivery. Effective nonsurgical therapies are currently in place for patients undergoing dialysis and hence they have better chances of survival even in cases of massive, acute upper GI bleeding. Better outpatient management and treatment with erythropoiesis stimulating agents and intravenous iron therapy might have translated into the observed better outcomes as a result of higher hemoglobin targets and an increased "hematocrit reserve"[29]. Yang *et al*[29], by utilizing the NIS database from 2002-2012 similarly showed that the mortality rate for all of the different causes of non-variceal upper GI hemorrhage declined over the study period. Prior studies have demonstrated that the in-hospital mortality of upper GI hemorrhage has been gradually decreasing since 1989.

The total length of hospital stay and hospital charges were noted to be higher in patients with angiodysplasia related bleeding compared to those patients who had only ESRD without angiodysplasia, as a result of more complicated disease course in the former group. This is in line with another study published in 2015, which showed that healthcare burden as well as the median individual hospital charges have increased sharply for upper non-variceal GI hemorrhage, over the past 20 years. The cause for this increase is possibly multifold and include not only more frequent use of expensive therapies such as medications, blood transfusions and endoscopic techniques but also possibly due to changes in reimbursement models[28].

Table 3 Comparison between inpatient mortality, mean hospitalization cost of care, and mean length of stay between end-stage renal disease and angiodysplasia associated-gastrointestinal bleeding, and end-stage renal disease hospitalizations, 2009-2014

	Mortality		Total charges		Length of stay	
	Odds ratio (95%CI)	*P* value	Difference (95%CI)	*P* value	Difference (95%CI)	*P* value
Angiodysplasia	0.67 (0.58, 0.78)	< 0.0001	$17761 ($12550, $22973)	< 0.0001	1.86 (1.40, 2.32)	< 0.0001
No Angiodysplasia	Reference		Reference		Reference	

The NIS is an administrative database hence coding errors and selection bias are unavoidable. In our study the diagnosis of GI hemorrhage related to angiodysplasia and ESRD might be limited by the accuracy and comprehension of the ICD-9 codes. Laboratory parameters are unavailable which is a significant limitation since it is not possible to determine the severity of anemia or CKD without hemoglobin and creatinine[30]. Similarly, the use of medications (PPI, octreotide) during the hospital stay is not included in the NIS.

Information regarding outpatient follow-up, readmission, and the bleeding rates cannot be estimated after hospitalizations since the data is limited to only inpatient stay. For the same reason overall mortality rates cannot be measured due to unavailability of out of hospital mortality rates. Despite these limitations, the NIS database has many strengths including its unprecedented size and the fact that it is a uniform, inpatient administrative database. Due to these reasons, the epidemiological data and outcomes obtained by utilizing it are comprehensive and generalizable[31].

This study highlighted a clear trend in the rising number of hospitalizations of patients with ESRD-related GI angiodysplasia. Advanced age, African American race, overall comorbidities and specifically hypertension and smoking were significantly associated with angiodysplasia-related GI hemorrhage. In addition, patients admitted with GI bleed in the setting of angiodysplasia experienced an increase in their LOS and hospital charges. A unique finding of this study was that compared to ESRD patients without angiodysplasia related bleeding, patients with angiodysplasia related GI hemorrhage were noted to have lower inpatient mortality rate which may reflect better outpatient care and availability of advanced endoscopic hemostatic techniques.

Nonetheless, recurrent hemorrhage remains an important problem in ESRD patients with angiodysplasia leading to increased inpatient encounters. Hence, further studies must continue to identify and formulate long term management plans which aim to stop and prevent repeated episodes of GI bleeding in this particular patient population.

ARTICLE HIGHLIGHTS

Research background
Gastrointestinal (GI) angiodysplasia are commonly occurring vascular malformations in the GI tract and account for approximately 6% of lower GI bleeding and up to 8% of upper GI bleeds. Chronic kidney disease and subsequent end-stage renal disease (ESRD) have been associated with increased development and risk of hemorrhage from GI Angiodysplasia.

Research motivation
There are few epidemiology studies exploring the association between angiodysplasia-related GI bleeding in renal disease patients. With increasing burden of chronic kidney disease, prevalence of nearly 15% in United States adults, the proportion of GI bleeding attributed to Angiodysplasia in renal disease patients is expected to increase. Studies need to be carried out to determine the burden and epidemiology, clinical presentation, diagnosis, management and outcomes of angiodysplasia-associated GI bleeding in renal disease patients. Such efforts would help guide clinicians to be watchful and prevent major bleeding in susceptible renal disease patients, improve outcomes and reduce hospitalization costs, especially in the elderly and chronic disease patients.

Research objectives
The main objectives of this study were to determine nationwide prevalence, hospitalization trends, and risk factors of hospitalization for angiodysplasia-associated GI hemorrhage in ESRD patients in the United States. Secondary objectives that were realized included length of stay, average total inpatient charges and mortality rate. The nationwide objectives achieved in this study provide baseline estimates for future research, the prevalence and risk factors identified should guide prevention and lead to improved management and outcomes in such patients.

Research methods

This retrospective study utilized the Nationwide Inpatient Sample, database from 2009 to 2014. International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes, were used to identify all patients nationwide with ESRD hospitalizations during the study period, and a subset of ESRD hospitalizations with angiodysplasia associated-GI bleeding were identified and compared. Independent variables (risk factors) included hospitalization year (2009-2014), gender, age category, race, primary payor, median household income quartile, Charlson Deyo-comorbidity index, hypertension, diabetes mellitus, tobacco use, obesity, hospital location (rural, urban, urban teaching), and hospital region. Multivariable regression modelling was performed to determine the risk factors associated with angiodysplasia associated-GI hemorrhage in ESRD hospitalized patients.

Research results

Angiodysplasia-associated GI hemorrhage in ESRD patients had a prevalence of 0.45% (*n* = 24709) among all ESRD hospitalizations (*n* = 5505252). Multivariable regression analysis showed that higher odds of angiodysplasia associated-GI hemorrhage in ESRD hospitalized patients occurred with increasing year trend from 2009-2014; increasing age; African American race; increasing Charlson-Deyo Comorbidity Index; hypertension; and tobacco use. And lower odds were associated with rural and urban nonteaching hospitals in comparison to urban teaching hospitals. ESRD hospitalizations with Angiodysplasia associated-GI bleeding had mean length of stay of 8.71 d, total average inpatient charges of $82340, and mortality rate of 3.41%.

Research conclusions

To our knowledge this is the first nationwide study that has determined baseline epidemiology estimates, hospitalization trends, risk factors and outcomes of angiodysplasia-associated GI bleeding in renal failure (ESRD) hospitalized patients. During the study period of 2009-2014, the hospitalization rate of angiodysplasia-associated GI bleeding in (ESRD) hospitalized patients increased by 6.7%, which indicates that recurrent hemorrhage in such patients should be expected. Clinical implications include patient communication to ESRD patients to immediately seek medical care if they have any signs of GI bleeding. Elderly ESRD patients had the strongest association for angiodysplasia-associated GI bleeding and such patients should be carefully observed for any signs and symptoms of GI bleeding. Hypertensive ESRD patients also had high risk and since elderly patients are frequently hypertensive, the risk for angiodysplasia-associated GI bleeding gets compounded. African American ESRD patients also had increased odds of angiodysplasia-associated GI bleeding that could be attributed to inadequate control of chronic conditions (e.g. hypertension, diabetes mellitus). Further studies need to be carried out to determine if there is a genetic predisposition in ESRD African American patients for angiodysplasia-associated GI bleeding. This study is the first one to report that Diabetes mellitus in ESRD patients was associated with decreased odds of angiodysplasia-associated GI bleeding. The biological mechanisms of diabetes mellitus and glycemic control being a protective factor for angiodysplasia-associated GI bleeding in renal disease patients needs to be elucidated in future studies.

Research perspectives

With increasing burden of renal disease, angiodysplasia-associated GI bleeding in ESRD patients has shown a rising trend. Elderly age group, African American race, overall co-morbidities, hypertension and smoking were significant risk factors for angiodysplasia-associated GI bleeding in ESRD patients. The role of diabetes mellitus in this study showed decreased odds of angiodysplasia-associated GI bleeding in renal disease patients. Future translational studies should look at the underlying biological mechanisms of hyperglycemia being a protective factor for angiodysplasia-associated GI bleeding in renal disease patients.

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