Clinical Study

Hemodialysis Increases the Risk of Lower Gastrointestinal Bleeding and Angiodysplasia Bleeding: A Nationwide Population Study

Tzung-Jiun Tsai,1,2 Wen-Chi Chen,1,2 Yu-Tung Huang,3 Yi-Hsin Yang,4 I-Che Feng,5 Wen-Chieh Wu,6 Huang-Ming Hu,7 Deng-Chyang Wu,7 and Ping-I Hsu8

1Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
2National Yang-Ming University, Taipei, Taiwan
3Center for Big Data Analytics and Statistics, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan
4Center for Medical Informatics and Statistics, Kaohsiung Medical University, Kaohsiung, Taiwan
5Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan
6Division of GERD Center, Yuan Sheng Hospital, Changhua, Taiwan
7Division of Gastroenterology & Hepatology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
8Department of Medicine, An Nan Hospital, China Medical University, Taiwan

Correspondence should be addressed to Ping-I Hsu; williamhsup@yahoo.com.tw

Received 25 October 2019; Revised 30 January 2020; Accepted 15 February 2020; Published 3 March 2020

Academic Editor: Tatsuya Toyokawa

Copyright © 2020 Tzung-Jiun Tsai et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Patients with chronic kidney disease (CKD) with or without hemodialysis were considered to have bleeding tendency and higher risk for gastrointestinal (GI) bleeding. Previous studies had documented that hemodialysis may increase the gastroduodenal ulcer bleeding. Few studies evaluated the relationship between CKD and lower GI bleeding.

Methods. An observational cohort study design was conducted. The end-stage renal disease (ESRD) patients receiving regular hemodialysis (dialysis CKD), CKD patients without dialysis (dialysis-free CKD), and controls were selected from 1 million randomly sampled subjects in the National Health Insurance Research Database of Taiwan. These three group subjects were matched by age, sex, comorbidity, and enrollment time in a 1:2:2 ratio. The Cox proportional hazard regression models were used to identify the potential risk factors for lower gastrointestinal bleeding. Additional analyses were conducted to assess the relationship between CKD and lower GI bleeding in dialysis-free CKD patients and control subjects.

Results. Dialysis CKD patients (n = 574) had a higher incidence of lower GI bleeding than dialysis-free CKD patients (n = 1148) and control subjects (n = 1148) (12.9% vs. 3.6% and 2.8%; both P < 0.001). Multivariate analysis showed that extreme old age (age ≥ 85), male gender, dialysis-free CKD, and dialysis CKD were independent factors of lower GI bleeding. Additionally, dialysis CKD patients also had a higher incidence of angiodysplasia bleeding compared to dialysis-free CKD patients and control subjects (1.1% vs. 0.1% and 0.1%, respectively; both P = 0.003). Conclusion. Hemodialysis may have higher risk of lower GI bleeding and angiodysplasia bleeding.

1. Introduction

End-stage renal disease (ESRD) under regular renal replacement treatment, such as hemodialysis (HD), peritoneal dialysis, and transplantation, is a worldwide public health problem. The global prevalence of ESRD is 280 per million population [1]. According to the most recent United States Renal Data System (USRDS) database, the prevalence of CKD was 15%, and ESRD was 2160.7 per million in the United States populations [2]. The prevalence of chronic kidney disease (CKD) in Taiwan was 9.8-11.9% [3–6]. According to the most recent data, the prevalence of CKD in Taiwan increased from 11.9% in 2010 to 15.46% in 2018 [3, 7], and the incidence increase from 13.5/1000 person-years in 2003
The included subjects were extracted based on the International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM). Dialysis CKD patients were identified by ICD-9-CM code 585 and with a catastrophic illness card. The index date of the dialysis CKD group was the first appearance of catastrophic illness card. Patients who received the catastrophic card had chronic renal failure and had been receiving regular hemodialysis for at least 3 months. Subjects of dialysis-free CKD were identified by ICD-9-CM 582.0, 582.4, 582.8x, 586, 250.4x, 274.1, 403.x1, 404.x2, and 404.x3, which occurred in the hospitalization claims, or when their names were encountered in the outpatient department 3 times continuously when documents were examined [12]. This definition may correspond to CKD stages 4 and 5. The index date of this group was defined as the first-time diagnosis of CKD.

We excluded patients with renal transplantation, peritoneal dialysis, cirrhosis, GI tract malignancy, inflammatory bowel disease, coagulopathy, vascular insufficiency of the intestine, radiation gastroenteritis or colitis, a history of gastrointestinal bleeding one year before the index date, and a medication history of gastroprotective agents (PPI and H2B) and ulcerogenic agents (NSAID), which had been used for at least 4 weeks in the 8 weeks before the index date.

2.2. End Point. The primary endpoint was lower GI bleeding, which was identified by patients who with any admission diagnosis of ICD-9-CM 562.02, 562.03, 562.12, 562.13, 569.3, 578.1, 578.9, and 569.86, and angiodysplasia bleeding with ICD-9-CM 537.83 and 569.85. The bleeding-related mortality was defined as the last admission with a discharge diagnosis of GI bleeding and discharge due to death or in critical status, or patient’s withdrawal from the NHI. The incidences of all GI bleeding, lower gastrointestinal (LGI) bleeding, and angiodysplasia bleeding in patients with dialysis CKD, dialysis-free CKD, and the control groups were compared.

2.3. Statistical Analysis. The data were represented by frequency (percentage), and continuous variables were expressed as mean ± standard deviation. We compared continuous variables by Student’s t test and/or analysis of variance (ANOVA). Categorical variables were tested by chi-squared test or Fisher’s exact test. The time survival curve was evaluated by the Kaplan-Meier method to evaluate the cumulative incidence of lower GI bleeding. We compared the competing factors by log-rank test. Finally, we performed Cox proportional hazard regression analysis to evaluate the risk factor of lower GI bleeding. A two-sided P value of <0.05 was considered statistically significant.

3. Results

3.1. Demographic Data. A total of 574 dialysis CKD patients, 1148 dialysis-free CKD patients, and 1148 controls were selected from the one million NHIRD subjects (Figure 1). The demographic data of the dialysis CKD, dialysis-free CKD, and control groups are summarized in Table 1. The three study groups had comparable age, gender, and comorbidity. However, the dialysis CKD and dialysis-free CKD patients with CKD had higher incidences of upper GI bleeding [10, 11], peptic ulcer bleeding [12–14], and recurrent upper GI rebleeding [15–17] than those without CKD [18]. However, few studies investigate the exact incidence of lower GI bleeding and angiodysplasia bleeding in patients with CKD with or without hemodialysis. Most cohort studies for lower GI bleeding were from the West. Few Eastern countries’ studies were seen.

Lower GI bleeding is an emerging problem for medical doctors. A population-based epidemiological study from Spain demonstrated that the lower GI event rate was increasing from 1996 to 2005 though the upper GI bleeding, and perforation rates were decreasing [19]. The study also showed that lower GI events displayed a higher mortality rate, longer hospitalization, and higher resource utilization than upper GI bleeding [19]. In addition, another study by Patel et al. reported that lower GI bleeding increased mortality rate of in patients with coronary artery disease on triple antithrombotic therapy [20].

Angiodysplasia is an important cause of lower GI bleeding [21]. It is more common in patients with chronic renal failure, and its prevalence is related to the severity of the renal disease [22]. Angiodysplasia bleeding accounts for 19-32% of lower GI bleeding episodes in patients with chronic renal failure compared with 5-6% of bleeding episodes in general population [23, 24].

The aims of this study were to investigate the incidence of the lower GI bleeding in dialysis CKD and dialysis-free CKD patients and to identify the factors that are predisposing to the lower GI bleeding.

2. Materials and Methods

An observational cohort study design was conducted. The CKD patients receiving regular hemodialysis (dialysis CKD), CKD patients without hemodialysis (dialysis-free CKD), and controls were selected from 1 million randomly sampled subjects in the National Health Insurance Research Database (NHIRD) of Taiwan. The National Health Insurance (NHI) is the universal health insurance coverage more than 99% residents in Taiwan.

The study protocol was approved by the Institutional Review Board in Kaohsiung Veterans General Hospital, with the number 17-CT8-04 (170627-1).

2.1. Study and Control Group. The more than 20-year-old dialysis CKD patients were selected from the NHIRD as the study group between 2000/1/1 and 2012/12/31. And then using the dialysis CKD data in 1:2:2 to matched by age, gender, comorbidity, and enrollment time with dialysis-free CKD and controls from the same dataset and time periods.
groups had higher Charlson scores than that of the control group (1.7 ± 1.5 and 1.5 ± 1.4 vs. 1.4 ± 1.3; P < 0.001). There were also no differences in the frequencies of antithrombotic agent use among the three study groups (Table 1).

3.2. The Rate of GI Bleeding. During a mean follow-up of 6.4 years, a total of 175 patients (30.5%) in the dialysis CKD group suffered from GI bleeding episodes and needed hospitalization, with 126 (11.0%) in dialysis-free CKD, and 93 (8.1%) in the control group. Both dialysis CKD and dialysis-free CKD groups had higher incidences of GI bleeding than the control group (P < 0.001 and P = 0.019, respectively). In lower GI bleeding, dialysis CKD group also had higher rate compared to dialysis-free CKD and control groups (12.9% vs. 3.6% and 2.8%; both P < 0.001; Table 2). There were no differences in the incidence of lower GI bleeding between the dialysis-free CKD group and control group. Kaplan-Meier survival analysis showed that dialysis CKD group exhibited a higher incidence of lower GI bleeding than dialysis-free CKD and control group. 

3.3. Risk factors for Lower GI bleeding. Table 3 lists the independent clinical factors influencing the incidence of lower GI bleeding. Multivariate analysis disclosed that extreme old age (age ≥ 85), male gender, dialysis CKD, and dialysis-free CKD were independent risk factors for lower GI bleeding with adjusted hazard ratios of 61.47 (95% confidence interval (CI): 2.68-1412.10), 3.14 (95% CI: 1.45-6.78), 29.09 (95% CI: 9.66-87.63), and 6.61 (95% CI: 2.27-19.23), respectively.

4. Discussion

In the nationwide population-based cohort study, we investigated the impact of CKD on the incidence of lower GI bleeding and assessed the incidences of angiodysplasia bleeding in patients with CKD and general population. The data clearly demonstrated that dialysis CKD patients had a higher incidence of lower gastrointestinal bleeding than dialysis-free CKD patients and control subjects (12.9% vs. 3.6% and 2.8%; both P < 0.001). Multivariate analysis documented that both CKD under hemodialysis and CKD without hemodialysis were independent factors predicting lower GI bleeding. Additionally, dialysis CKD patients also had a higher incidence of angiodysplasia bleeding than dialysis-free CKD patients and control subjects.
Table 1: Demographic characteristics and comorbidities of CKD-HD, CKD dialysis-free, and control groups.

| Variables                        | Dialysis CKD group (N = 574) | Dialysis-free CKD group* (N = 1148) | Control* (N = 1148) | P value |
|----------------------------------|------------------------------|-------------------------------------|---------------------|---------|
|                                  | n                            | %                                  | n                   | %       | n                   | %       |       |         |
| **Age (mean ± SD)**              | 61 ± 13.0                    | 62 ± 13.4                           | 61 ± 13.5           | 0.61    |
| 20-44                            | 57                           | 9.9%                                | 93                  | 8.1%    | 114                 | 9.9%    |       |
| 45-64                            | 277                          | 48.3%                               | 559                 | 48.7%   | 554                 | 48.3%   |       |
| 65-74                            | 146                          | 25.4%                               | 308                 | 26.8%   | 284                 | 24.7%   | 0.80  |
| 75-84                            | 78                           | 13.6%                               | 163                 | 14.2%   | 165                 | 14.4%   |       |
| ≥85                              | 16                           | 2.8%                                | 25                  | 2.2%    | 31                  | 2.7%    |       |
| **Gender**                       |                              |                                     |                     |         |                     |         |       |         |
| Male                             | 318                          | 55.4%                               | 653                 | 56.9%   | 636                 | 55.4%   | 0.74  |
| Female                           | 256                          | 44.6%                               | 495                 | 43.1%   | 512                 | 44.6%   |       |
| **Comorbidities**                |                              |                                     |                     |         |                     |         |       |         |
| Alcoholic liver disease and alcoholism | 4                        | 0.7%                                | 6                   | 0.5%    | 11                  | 1.0%    | 0.47  |
| Cirrhosis                        | 0                            | 0.0%                                | 0                   | 0.00%   | 0                   | 0.00%   | —     |
| Stroke                           | 57                           | 9.9%                                | 109                 | 9.5%    | 87                  | 7.6%    | 0.15  |
| Diabetes mellitus                | 363                          | 63.2%                               | 739                 | 64.3%   | 714                 | 62.2%   | 0.56  |
| Hypertension                     | 363                          | 63.2%                               | 718                 | 62.5%   | 812                 | 70.7%   | <0.001*|
| Ischemic heart disease           | 130                          | 22.7%                               | 263                 | 22.9%   | 276                 | 24.0%   | 0.75  |
| Congestive heart failure         | 26                           | 4.5%                                | 55                  | 4.8%    | 56                  | 4.9%    | 0.95  |
| Chronic lung disease             | 91                           | 15.9%                               | 185                 | 16.1%   | 215                 | 18.7%   | 0.17  |
| **Charlson score**               |                              |                                     |                     |         |                     |         |       |         |
| 0                                | 140                          | 24.4%                               | 281                 | 24.5%   | 284                 | 24.7%   |       |
| 1                                | 152                          | 26.5%                               | 404                 | 35.2%   | 451                 | 39.3%   | <0.001*|
| 2                                | 119                          | 20.7%                               | 218                 | 19.0%   | 232                 | 20.2%   |       |
| ≥3                               | 163                          | 28.4%                               | 245                 | 21.3%   | 181                 | 15.8%   |       |
| **Charlson score (mean ± SD)**    | 1.7 ± 1.5                    | 1.5 ± 1.4                           | 1.4 ± 1.3           | <0.001* |
| **Medication**                   |                              |                                     |                     |         |                     |         |       |         |
| Aspirin                          | 189                          | 32.9%                               | 389                 | 33.9%   | 394                 | 34.3%   | 0.85  |
| Steroids                         | 70                           | 12.2%                               | 143                 | 12.5%   | 165                 | 14.4%   | 0.30  |
| Warfarin                         | 7                            | 1.2%                                | 18                  | 1.6%    | 14                  | 1.2%    | 0.73  |
| Clopidogrel                      | 11                           | 1.9%                                | 17                  | 1.5%    | 16                  | 1.4%    | 0.70  |
| Ticlopidine                      | 7                            | 1.2%                                | 12                  | 1.1%    | 8                   | 0.7%    | 0.51  |

*Match (1:2 ratio) with age, sex, comorbidities, and enrollment time. CKD: chronic kidney disease; SD: standard deviation.

Table 2: The gastrointestinal bleeding and bleeding-related mortality in dialysis CKD and dialysis-free CKD and control groups during a 6.4-year follow-up period.

| Variables                        | A: dialysis CKD group (N = 574) | B: dialysis-free CKD group (N = 1148) | C: control group (N = 1148) | P value |
|----------------------------------|---------------------------------|---------------------------------------|------------------------------|---------|
|                                  | n                              | %                                     | n                            | %       | n                    | %       | A vs. B | A vs. C | B vs. C |
| All GI bleeding, hospitalized    | 175                            | 30.5%                                 | 126                          | 11.0%   | 93                   | 8.1%    | <0.001*| <0.001* | 0.019*  |
| Lower GI bleeding                | 74                             | 12.9%                                 | 41                           | 3.6%    | 32                   | 2.8%    | <0.001*| <0.001* | 0.27    |
| Angiodysplasia bleeding          | 6                              | 1.1%                                  | 1                            | 0.1%    | 1                    | 0.1%    | 0.003*| 0.003*  | 1.00    |
| Bleeding related mortality       | 14                             | 2.4%                                  | 13                           | 1.13%   | 0                    | 0       | 0.0040| <0.001 | 0.0003  |

*P < 0.05. CKD: chronic kidney disease; GI: gastrointestinal.
The dialysis CKD group had a higher cumulative incidence of lower GI bleeding than dialysis-free CKD and control groups (12.9% vs. 3.6% and 2.8%). Multivariate analysis revealed that ESRD was an independent risk factor for lower GI bleeding with an adjusted hazard ratio of 29.1 (95% CI: 9.7-87.6). The promising data presented here are consistent with an independent work in a USA community-based study [26] showing a higher incidence of lower GI bleeding in patients with eGFR (ml/min per 1.73 m²) \(< 30\). The work revealed that the hazard ratios of lower GI bleeding in patients with eGFR \(\geq 90\), 60-80, 30-59, and <30 were 1, 1.5, 2.3, and 10.8, respectively.

In the Cox regression analysis, Table 3, we had 15 control variables. According to rule of thumb, Cox model outcome events (at least 10 events per variable (EPV)), we need at least 150 events to get stable estimates of the regression coefficients. In our data, we found 147 lower GI bleeding events, and a little lower than the EPV recommendation. Further result interpretation should be cautious. But in our data, we reported the rare event rates in the real would.

Angiodysplasia is a common and important cause of GI bleeding, especially in patients with CKD. Angiodysplasia bleeding was reported to be associated with chronic renal failure, Von Willebrand’s disease, aortic stenosis, cirrhosis, and pulmonary disease, but the actual etiology is unknown [23]. Currently, the pathophysiological mechanisms contributing the development of angiodysplasia and consequent bleeding in patients with chronic renal failure are unclear. Several possible causes including uremic platelet dysfunction [27, 28] and use of anticoagulants [29] have been proposed to explain the increased risk of bleeding in uremic patients. Further studies are warranted to investigate the pathogenesis of the development of angiodysplasia bleeding in patients with ESRD.

In addition to CKD and hemodialysis, extreme old age, and male gender were independent risk factors predicting lower GI bleeding. Previous studies reported that the prevalence of diverticular disease bleeding and angiodysplasia bleeding increases with age [30], which might explain why old age is associated with higher risks of LGI bleeding. The actual cause of males having a higher risk of lower GI bleeding is unclear. According to previous literature review, males are at higher risk of GI bleeding [19, 31]. Further study is needed to confirm the reason for this.

Anticoagulant and antiplatelet agents are reported to be the risk factors for lower GI bleeding [32, 33], but still some authors stated that antiplatelet agents were not associated with LGI bleeding [34]. In our study, we found that LGI bleeding had no association with antiplatelet agents and anticoagulants.

There were some limitations to this study. First, this was a retrospective cohort study, and immortal time bias and selection bias might be present in this study. Nonetheless, we have conducted multivariate analysis to identify the independent risk factors predicting lower GI bleeding. Because some patients had CKD and progression to ESRD with or without dialysis for a long time, immortal time bias might exist in this condition. Second, our study was
based on the ICD-9-CM code. If the doctors did not input a correct or accurate ICD code for CKD, lower GI bleeding, or angiodysplasia bleeding, we might have missed the case or the clinical events. Third, the stage of CKD could not be well classified because no laboratory data were available in the NHIRD database.

In conclusion, dialysis CKD patients have higher risks of lower GI bleeding and angiodysplasia bleeding than the non-CKD subjects and dialysis-free CKD patients. Hemodialysis, dialysis-free CKD, extreme old age, and male gender were independent risk factors for lower GI bleeding. Further prospective well-designed study is warranted.

Data Availability

Raw data were generated at the Center for Medical Informatics and Statistics, Kaohsiung Medical University, Kaohsiung, Taiwan. Derived data supporting the findings of this study are available from the corresponding author on request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] A. Grassmann, S. Gioberge, S. Moeller, and G. Brown, “ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends,” *Nephrology, Dialysis, Transplantation*, vol. 20, no. 12, pp. 2587–2593, 2005.

[2] R. Saran, B. Robinson, K. C. Abbott et al., “US renal data system 2017 annual data report: epidemiology of kidney disease in the united states,” *American Journal of Kidney Diseases*, vol. 71, 3, Supplement 1, pp. A7–A8, 2019.

[3] S. J. Hwang, J. C. Tsai, and H. C. Chen, “Epidemiology, impact and preventive care of chronic kidney disease in Taiwan,” *Nephrology*, vol. 15, Supplement 2, pp. 3–9, 2010.

[4] C. P. Wen, T. Y. Cheng, M. K. Tsai et al., “All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan,” *The Lancet*, vol. 371, no. 9631, pp. 2173–2182, 2008.

[5] J. Y. Guh, H. C. Chen HC, J. F. Tsai, and L. Y. Chuang, “Herbal therapy is associated with the risk of CKD in adults not using analgesics in Taiwan,” *American Journal of Kidney Diseases*, vol. 49, no. 5, pp. 626–633, 2007.

[6] C. C. Hsu, S. J. Hwang, C. P. Wen et al., “High prevalence and low awareness of CKD in Taiwan: a study on the relationship between serum creatinine and awareness from a nationally representative survey,” *American Journal of Kidney Diseases*, vol. 48, no. 5, pp. 727–738, 2006.
C. C. Kuo, H. W. Kuo, I. M. Lee, C. T. Lee, and C. Y. Yang, “Incidence, prevalence, and duration of chronic kidney disease in Taiwan: results from a community-based screening program of 106, 094 individuals,” Nephron, vol. 140, no. 3, pp. 175–184, 2018.

H. W. Kuo, S. S. Tsai, M. M. Tiao, and C. Y. Yang, “Epidemiological features of CKD in Taiwan,” American Journal of Kidney Diseases, vol. 49, no. 1, pp. 46–55, 2007.

R. Hägendorf, N. Farkas, Á. Vincze et al., “The risk of upper gastrointestinal bleeding in patients treated with hemodialysis: a meta-analysis,” World Journal of Gastroenterology, vol. 23, no. 47, pp. 8415–8425, 2017.

C. C. Kuo, H. W. Kuo, I. M. Lee, C. T. Lee, and C. Y. Yang, “The risk of upper gastrointestinal bleeding in patients treated with hemodialysis: a population-based cohort study,” BMC Nephrology, vol. 14, no. 1, 2013.

H. Wasse, D. L. Gillen, A. M. Ball et al., “Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients,” Kidney International, vol. 64, no. 4, pp. 1455–1461, 2003.

J. C. Luo, H. B. Leu, K. W. Huang et al., “Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis,” Canadian Medical Association Journal, vol. 183, no. 18, pp. E1345–E1351, 2011.

K. W. Huang, H. B. Leu, J. C. Luo et al., “Different peptic ulcer bleeding risk in chronic kidney disease and end-stage renal disease patients receiving different dialysis,” Digestive Diseases and Sciences, vol. 59, no. 4, pp. 807–813, 2014.

P.-C. Wu, C.-J. Wu, C.-J. Lin, and V.-C. Wu, “Long-term risk of upper gastrointestinal hemorrhage after advanced AKI,” Clinical Journal of the American Society of Nephrology, vol. 10, no. 3, pp. 353–362, 2015.

J. Cheung, A. Yu, J. LaBossiere, Q. Zhu, and R. N. Fedorak, “Peptic ulcer bleeding outcomes adversely affected by end-stage renal disease,” Gastrointestinal Endoscopy, vol. 71, no. 1, pp. 44–49, 2010.

C. Y. Wu, M. S. Wu, K. N. Kuo, C. B. Wang, Y. J. Chen, and J. T. Lin, “Long-term peptic ulcer rebleeding risk estimation in patients undergoing haemodialysis: a 10-year nationwide cohort study,” Gut, vol. 60, no. 8, pp. 1038–1042, 2011.

C. C. Liang, S. M. Wang, H. L. Kuo et al., “Upper gastrointestinal bleeding in patients with CKD,” Clinical Journal of the American Society of Nephrology, vol. 9, no. 8, pp. 1354–1359, 2014.

P. Sood, G. Kumar, R. Nanchal et al., “Chronic kidney disease and end-stage renal disease predict higher risk of mortality in patients with primary upper gastrointestinal bleeding,” American Journal of Nephrology, vol. 35, no. 3, pp. 216–224, 2012.

A. Lanas, L. A. Garcia-Rodriguez, M. Polo-Tomás et al., “Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice,” The American Journal of Gastroenterology, vol. 104, no. 7, pp. 1633–1641, 2009.

P. Patel, N. Nigam, and N. Sengupta, “Lower gastrointestinal bleeding in patients with coronary artery disease on antithrombotics and subsequent mortality risk,” Journal of Gastroenterology and Hepatology, vol. 33, no. 6, pp. 1185–1191, 2018.

S. S. Sami, S. A. Al-Araji, and K. Ragunath, “Review article: gastrointestinal angiodyplasia - pathogenesis, diagnosis and management,” Alimentary Pharmacology & Therapeutics, vol. 39, no. 1, pp. 15–34, 2014.

N. Chalasani, G. Cotsonis, and C. M. Wilcox, “Upper gastrointestinal bleeding in patients with chronic renal failure: role of vascular ectasia,” The American Journal of Gastroenterology, vol. 91, no. 11, pp. 2329–2332, 1996.

P. G. Foutch, “Angiodyplasia of the gastrointestinal tract,” The American Journal of Gastroenterology, vol. 88, no. 6, pp. 807–818, 1993.

H. Kaaroud, L. B. Fatma, S. Beji et al., “Gastrointestinal angiodyplasia in chronic renal failure,” Saudi Journal of Kidney Diseases and Transplantation, vol. 19, no. 5, pp. 809–812, 2008.

M. M. Sood, S. E. Bota, E. McArthur et al., “The three-year incidence of major hemorrhage among older adults initiating chronic dialysis,” Canadian Journal of Kidney Health and Disease, vol. 1, p. 21, 2014.

J. Ishigami, M. E. Grams, R. P. Naik, J. Coresh, and K. Matsushita, “Chronic kidney disease and risk for gastrointestinal bleeding in the community: the atherosclerosis risk in communities (ARIC) study,” Clinical Journal of the American Society of Nephrology, vol. 11, no. 10, pp. 1735–1743, 2016.

P. Boccardo, G. Remuzzi, and M. Gallussera, “Platelet dysfunction in renal failure,” Seminars in Thrombosis and Hemostasis, vol. 30, no. 5, pp. 579–589, 2004.

A. L. Weigert and A. I. Schafer, “Uremic bleeding: pathogenesis and therapy,” The American Journal of the Medical Sciences, vol. 316, no. 2, pp. 94–104, 1998.

M. K. Kringsen, S. Narum, I. Lygren et al., “Reduced platelet function and role of drugs in acute gastrointestinal bleeding,” Basic & Clinical Pharmacology & Toxicology, vol. 108, no. 3, pp. 194–201, 2011.

K. Buttenschoen, D. C. Buttenschoen, R. Odermath, and H. G. Beger, “Diverticular disease-associated hemorrhage in the elderly,” Langenbeck’s Archives of Surgery, vol. 386, no. 1, pp. 8–16, 2001.

S. Hernandez-Diaz and L. A. Rodriguez, “Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s,” Archives of Internal Medicine, vol. 160, no. 14, pp. 2093–2099, 2000.

W. C. Chen, K. H. Lin, Y. T. Huang et al., “The risk of lower gastrointestinal bleeding in low-dose aspirin users,” Alimentary Pharmacology & Therapeutics, vol. 45, no. 12, pp. 1542–1550, 2017.

A. Lanas, P. Carrera-Lasfuentes, Y. Arguedas et al., “Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants,” Clinical Gastroenterology and Hepatology, vol. 13, no. 5, pp. 906–912.e2, 2015.

N. Nagata, R. Niikura, T. Aoki et al., “Lower GI bleeding risk of nonsteroidal anti-inflammatory drugs and antiplatelet drug use alone and the effect of combined therapy,” Gastrointestinal Endoscopy, vol. 80, no. 6, pp. 1124–1131, 2014.