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Venous thromboembolism in IBD: Increased risk for women in CD?

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ABSTRACT

Although coagulation disturbances have been described in inflammatory bowel disease (IBD), it remains unclear how common venous thromboembolism (VTE) is in IBD, and what factors influence VTE frequency. We evaluated VTE in Crohn's disease (CD) and ulcerative colitis (UC) at LSUHSC-S, a southern US medical center with an approximately equal White: African-American (AA) (1.12:1) patient base. This retrospective study evaluated VTE as a co-morbidity in IBD as a function of age, gender and race based on ICD-10 coding (2011–2015.) Results. Of 276 IBD diagnostic records, 213 were for CD (77.17%) and 63 for UC (22.8%). 52% of the CD patients were white, 42% were AA, and 6% were other. 42% of CD patients were male, with 58% were female. 6.1% (13 patients) of the 213 CD patients had a VTE. Of these 13 CD patients, 9 had active disease and 4 were in remission. 9 of 13 were female and 4 were male, with 5 white patients and 4 A A patients. 63 patients were diagnosed with UC, 3.38-fold fewer cases than CD. 25 UC patients were white, 25 were AA and 13 were in other ethnic groups. Of 63 UC cases, 2 UC patients had a VTE, both with active disease. At our institution, VTE appears to be 3x more frequently associated with CD than UC and was more common in white female patients. The recognition of VTE risk in CD, particularly in women, may be an important observation which may guide therapy and limit potentially life-threatening consequences.

1. Introduction

Inflammatory bowel disease (IBD) patients are at an increased risk for developing venous thromboembolic (VTE) events as evidenced by several studies [1,2], suggesting that it represents an important pathologic co-morbid process associated with IBD. Thromboembolism in IBD is not limited to the intestine, (which does show increased incidence of mesenteric venous thrombosis) but rather influences the entire circulation, such that IBD patients are at a significantly increased risk for VTE than the general population [2]. VTE also remains an important cause of mortality in IBD [3].

This state of increased tendency towards coagulation in IBD appears to be triggered by several factors present in IBD which may predispose both CD and UC patients to increased risks for serious coagulopathic co-morbidity. VTE events are associated with three conditions (hypercoagulability, stasis and endothelial damage) which increase thrombus formation. This is known as 'Virchow's Triad' of hypercoagulability. Hypercoagulable states may reflect heritable factors which alter an abundance of components of the coagulation pathway, the state of activation of the vascular endothelium or acquired clinical risk factors such as cancer, pregnancy, chemotherapy, oral contraceptive use and obesity. The aforementioned list of acquired factors have by now been well studied in the literature and are generally accepted by physicians as risk factors for VTE.

In recent years, there have been several investigations into the possibility that inflammatory bowel disease (IBD) might be another such acquired factor which merits similar consideration. It has been reported by Miehsler et al. [4] that VTE appears to be uniquely associated with IBD as neither rheumatoid arthritis or celiac disease, which are also forms of chronic inflammation, are characterized by increased VTE risks [5].

This is an important clinical question as VTE are a significant source of morbidity in patients. The incidence of DVT in the general population is generally low [6,7], varying between 1–5 per 10,000

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people per year with equal distribution between males and females which also increases with age.

A review of the literature on VTE in IBD revealed several important trends. A cohort study in 2001 by Bernstein [8] showed that the incidence of DVT in CD was 31 in 10,000 person-years and PE in CD was 10.3 in 10,000 person-years, both substantially higher than the incidence reported in the general population. The same study also showed an increased risk in UC patients (30.0/10,000 person-years for DVT and 19.8/10,000 person-years for PE). These rates were highest for patients over 40 years old in both CD and UC as seen in the general population.

A meta-analysis by Papa [2] considered why IBD patients might be at risk for VTE. VTE risk factors such as hyperhomocysteinemia, dehydration, prolonged immobilization, infections, indwelling catheters, active disease burden and surgery. This study also stated that IBD patients had higher plasma levels of acute phase reactants and decreased levels of anticoagulants as well as reduced fibrinolytic activity. The same study also noted endothelial abnormalities in IBD patients, specifically suppression of endothelial protein C receptor which limits the conversion of protein C into its active form to increase the trend for coagulation as well as inflammation. We are aware that inflammatory and coagulation cascades are linked processes which can intensify each other. Inflammatory mediators, and the signaling pathways they activate, result in a hypercoagulable state in experimental colitis and in IBD patients. IL-1β, TNF-alpha, and IL-6 have been shown to increase tissue factor which leads to increased coagulation in mouse models of colitis [9–11]. Immunoblockade or genetic deletion of the receptors of these cytokines significantly decreased the onset of thrombus formation in colitis-prone mice. It was also demonstrated by Yoshida and Granger [12], that the hypercoagulable state in IBD reflects a relative inhibition of the fibrinolytic system, specifically protein C. In this setting, thrombin and tissue factor are known to promote inflammation, whereas, activated protein C and heparin are both anticoagulant and inflammatory. Yoshida et al. found that IBD patients had increased levels of pro-coagulants and decreased levels of the endogenous anticoagulants which could greatly intensify inflammation in IBD. The Papa et al., study found increased platelet activation and aggregation in IBD patients. An improved understanding of the interplay between the clotting cascade and the inflammatory state in IBD might yield important and novel therapeutic interventions (i.e. targeting IL-1β, TNF-α, and IL-6)

The meta-analysis by Papa et al. reported a 2–3 fold increased risk for development of VTE in IBD patients (approximately equal frequency between CD and UC) compared to the general population and also stated that VTE was more frequently in patients with active and extensive IBD compared to more well-controlled IBD patients. No link was found between gender and VTE in IBD patients.

A 2008 study by Nguyen [3] found that CD patients with *only* colonic disease had higher risks for VTE than those with small bowel disease. Nguyen et al., cited that this finding could be due to the fact that patients who are admitted with colitis are more likely to have hematochezia and therefore do not receive DVT prophylaxis on admission. They also hypothesized that patients with colonic or fistulizing disease might have more systemic inflammation which predisposes them to a greater thrombotic risk. Bryant et al. [13] document a similar potential link. Their study found UC patients with pancolitis and CD patients with colon involvement were at particular risk for VTE. Miehsler et al. [4] also described a similar trend with VTE in IBD patients with active disease, where IBD patients had higher risks for thromboembolic events if they had active disease along with complications such as stricturing, fistulization or abscesses. A 2018 study by Kim et al. [14], found when Korean IBD patients were analyzed, they found that proximal small bowel disease was associated with poor prognosis, specifically an increased need for surgery in these patients. In regards to UC disease location, Rubenstein et al. [15] reviewed 12 cases of UC-associated enteritis which found this condition to be exceedingly rare in UC.

This documentation of the increased risk of VTE in IBD sheds light on the fact that there are currently no clear guidelines for prophylactic anticoagulation in these patients. The consequences of developing VTE in these patients can include more frequent and prolonged hospitalizations, necessitating interruption of IBD therapy which can further intensify disease course and even increase mortality. It has also been well documented in the literature that patients with active and more severe disease have an increased risk for VTE. If we can better understand the connections between IBD and VTE, we may be able to more effectively control this serious additional risk. Risk for VTE likely reflects the overall health of the community including socioeconomic status, access to healthcare and diet. Despite these important observations on IBD and VTE, it is still unknown how gender, ethnic background, age at diagnosis or years with disease might influence the tendency to develop VTE.

Therefore, this study investigated the incidence of VTE among IBD patients at LSUHSC-S, with a division of these patients into UC and CD patients to evaluate these individual disease characteristics (e.g. Ethic background, age and gender). We also compared these trends to nationally reported statistics for IBD and VTE.

2. Methods

This was an IRB approved, single center, retrospective analysis of the epidemiology, patients' characteristics, management approach and IBD severity at the time of VTE event. This study examined the frequency of VTE events IBD patients seen at our institution. The study included patients between 11/01/2011 and 9/01/2015 who were between the ages of 18–80 years old and held a diagnosis of IBD (Ulcerative Colitis or Crohn's Disease) based on ICD-10 coding. (ICD codes for IBD include: 555, 555.0, 555.1, 555.2, 555.9, 556, 556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, and 556.9. ICD codes for VTE include: 453.40, 415.1, and 453). Data were collected retrospectively using our electronic medical record system in Shreveport, LA. Patients were given a unique patient identifier code to protect confidentiality. Medical charts were reviewed for demographics, severity of disease, endoscopic findings, current and past medications, reasons for hospitalization, presence of hypercoagulable state, and any thrombosis prophylaxis received during inpatient hospitalizations.

3. Results

In our study, 213 patients were diagnosed with CD and 63 diagnosed with UC over the 4 year study period based on ICD-10 coding. Each patient's chart record was reviewed and age, sex, race, weight, onset and severity of disease findings collected. Complications and surgeries as a result of their IBD were recorded, and past treatment regimens and presence of VTE (based on imaging results) evaluated. We also documented what, if any, VTE prophylaxis these patients had been administered during inpatient hospitalizations. We also investigated into any histories of malignancy or coagulation disorders to illuminate possible confounding factors for hypercoagulability.

Information on the severity of disease was determined based on the most recent Gastroenterology progress note and was given a score from 0 to 3, where '0′ meant no active disease (endoscopic remission), '1′ indicated mild disease, '2′ indicated moderate '3′ indicated severe disease; patients without documentation of disease severity were not included.

Of 213 CD patients, 13 (6.1%) had experienced a VTE (Fig. 2, left). Nine of these patients (69%) had active disease flares at the time of diagnosis of the VTE. Only one of these patients was found to have

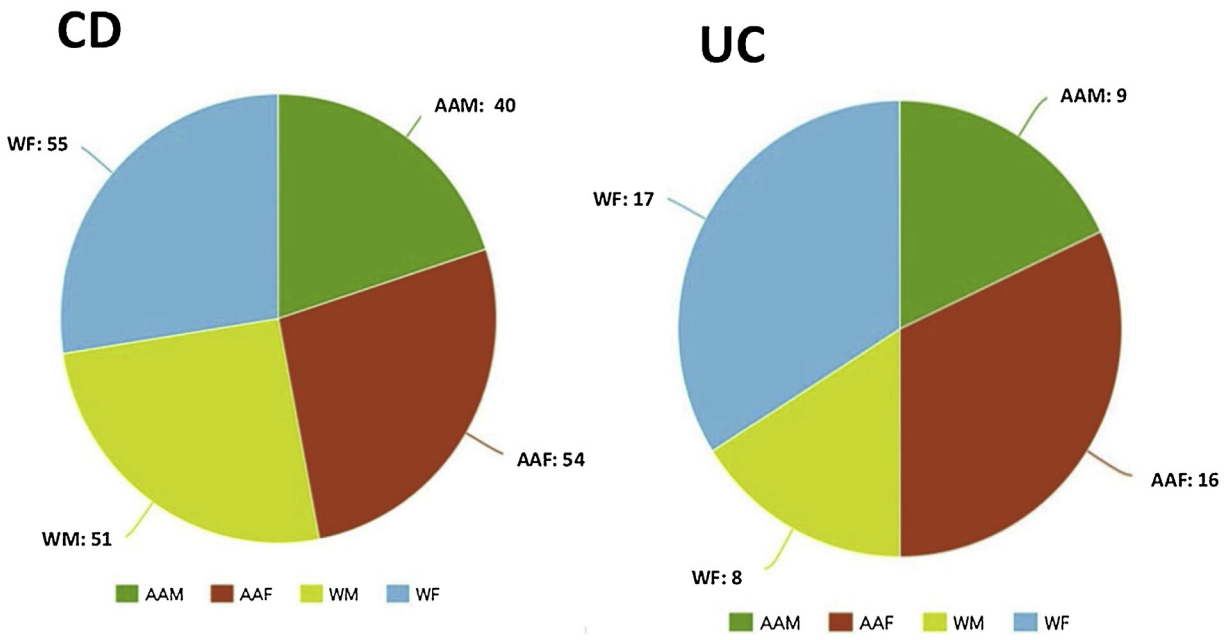

Fig. 1. Pie chart showed gender and race contributions in CD and UC.

an arterial thrombus, the rest had venous thromboembolic events (including DVT and PE). The remaining 4 patients with VTE in the CD patient group had non-active CD at the time of the VTE event. One patient was diagnosed with anti-phospholipid syndrome, and two patients in the CD group who had VTE also had a known history of malignancy.

Considering the ethnic background of these patients, of 213 CD patients, 111 of these patients were white (52%), 89 were AA (42%), and 13 were in other racial/ethnic groups (6.1%). We also noted that 58% of CD patients in our institution were female (123/213) and 42% were male (90/213). Interestingly, those 13 CD patients who had a thromboembolic event, 9 were female (69%) and 4 were male (31%). Similar numbers of VTE were detected in female patients when divided into race (5 patients were white and 4 were AA).

In the UC population, (Fig. 2, left) of 63 patients, only 2 were found to have had a thromboembolic event (3.17%). Both UC patients had active disease at the time of their VTE events. Of note in our UC patients, 25 patients were white (39%), 25 were AA (39%) (Fig. 1). 13 UC patients were in other racial/ethnic groups (20%). Twenty-five of these patients were male (39%) and 38 were female (60%). Of the two patients with a thromboembolic event, 1 was male and 1 was a female. In the UC patients, 1 patient with VTE was given sequential compression devices (SCDs) and the other given no VTE prophylaxis.

By comparison, upon reviewing the CD patients who experienced a thromboembolic event, it was noted that 5 of the 13 patients were given VTE prophylaxis with Lovenox, 5 were given SCDs and 3 were given no prophylaxis. Two of the CD patients with VTE carried a diagnosis of malignancy and 1 carried a diagnosis of a coagulation disorder (antiphospholipid syndrome). Neither of the UC patients with VTE had malignancy or any other coagulopathy.

We also noted that white males and white female patients with IBD (UC and CD) had longer-standing disease than their AA counterparts (13.529 ± 0.80 years vs. 11.291 ± 0.83 years, $p = 0.055$, Kruskal-Wallis, Dunn's Multiple Comparisons Test. Fig. 3A) When considered individually, black males with CD had fewest years since their diagnosis than their white counterparts, (BM = 9.0 ± 1.29 years vs. WF = 14.02 ± 1.28 years, $p < 0.05$, WM = 13.54 ± 1.205 years, $p < 0.05$, Fig. 3D) With respect to years since diagnosis, BF were found to be not significantly different from BM, WM or WF. There were no differences among the number of years since diagnosis among UC patient groups.

Considering the age at diagnosis within UC, there were no significant differences among WF, WM, BM or BF; neither were there any difference between the ages at diagnosis in CD among these groups. We did find that for WF, the age at diagnosis for CD occurred at earlier than for UC (CD = 31.8 ± 1.77 years vs. UC = 38.41 ± 3.11 years, $p = 0.051$, Fig. 3D).

When our data were analyzed with regard to disease location, we found that 7 of 13 patients (53.8%) in the CD VTE group had small bowel disease involvement. Specifically, we knew that 3 of these 7 patients with small bowel disease had terminal ileal disease. 3 of the 13 patients had *only* small bowel disease; 4 of them had both small bowel and colon disease; 3 had colon involvement only. Two patients in this group were in endoscopic remission at the time their VTE was found. One of the CD patients, we did not identify disease location.

When we compared this trend to the disease location in our entire population of CD patients, we found that 89 of our 213 patients (41.8%) had small bowel and colon involvement - this made up the majority. 59 patients (27.7%) had only colon disease with 15 of them having pan-colitis. 35 (16.4%) had only small bowel disease and 16 of this group specifically had disease confined to the terminal ileum. 20 patients (9.4%) were in remission and disease location was unknown in 10 patients (4.7%).

We further analyzed disease location with regard to gender in the CD-VTE group and found that 5 of the 7 (71.4%) patients with small bowel involvement were women and only 2 (28.6%) were men.

In our UC patients with VTE, one had only rectal disease and one had disease spanning from the rectum to the transverse colon; one was male and one was female. When our entire UC population was analyzed, we found that a substantial subset (18 patients, 28.6%) had rectal to descending colon involvement. 14 of these (22.2%) had rectum to ascending colon disease, 4 (6.3%) had rectum to transverse colon disease, and 9 (14.3%) had only rectal involvement. 6 (9.5%) were in remission and 12 (19.1%) had disease whose extent was unknown.

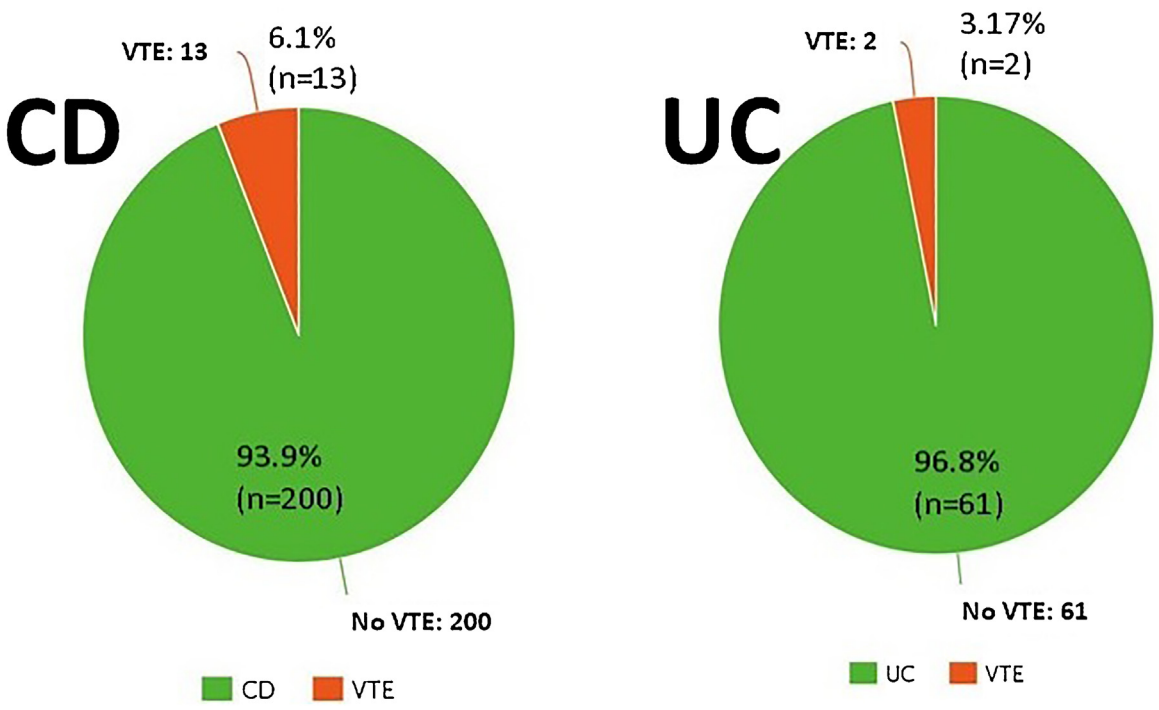

Fig. 2. Pie chart shows relative fraction of VTE in CD vs UC patients. Of 200 patients with CD, 6.1% had VTE whereas only 3.17% had VTE in UC.

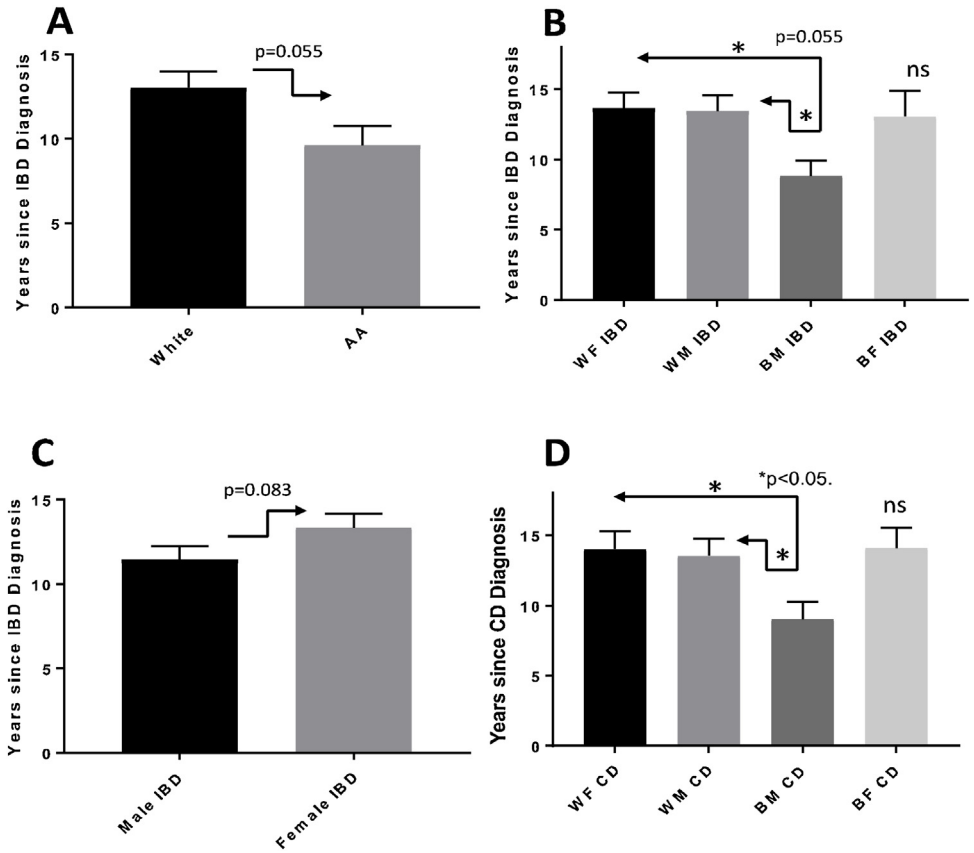

Fig. 3. A: Years since diagnosis by ethnicity: AA IBD patients had fewer years since IBD diagnosis ($p = 0.055$) than white IBD patients. Fig. 3B. Years since diagnosis in individual groups in all IBD cases. Fig. 3C. Years since IBD diagnosis by gender: Female patients with IBD showed more years since their IBD diagnosis than males ($p = 0.083$). Student's t-test, two-tailed, average ± SEM. Fig. 3D. AA males had significantly fewer years since their diagnosis than white males ($p < 0.05$). AA male years since diagnosis were not different from AA females (ns). (Kruskal-Wallis, Dunn's test, average ± SEM.).

4. Discussion

Although trends in IBD indicate that CD and UC suggest that UC is more common than CD (238 cases/100,000 CD vs. 201 cases/100,000 UC) [16], we found at our institution that CD is diagnosed more than 3 times more frequently than is expected based on national trends. Further, Kappelman et al., found that IBD was relatively less common in Southern US regions.

In our previous study on IBD, (Veluswamy et al., 2010), we found that at our institution, CD was diagnosed 2.3 times more often than UC. In our current study, we have again found that CD is more common than UC; this time with 3.38 times more CD than UC diagnoses, an increase in CD cases in the past decade. VTE is a serious comorbidity associated with IBD, and our study indicates that IBD patients appear to be at higher risk for developing VTE compared to the general population. To our knowledge, prior to this study, the risk of VTE had not been separated into CD and UC groups in a population with equal white and AA makeup.

Disease activity and early onset of disease have been reported to be factors which increase the risk of IBD patients to develop VTE [3]. Our investigation here shows that most VTE events occurred in patients with poorly controlled or active disease. In our current study of IBD patients, those with CD patients appear to display VTE three times more often than UC patients, even adjusting for the fact that CD is diagnosed 3.38 times more often at our institution than UC.

Furthermore, female patients with CD appear to be at increased risk for developing a VTE. VTE in CD was found mainly in female patients, 5 of whom were white and 4 of whom were AA. Our analysis did not determine whether these female patients were taking oral contraceptives (OCP) which could increase VTE risk. However, based on the ages of these female patients with VTE diagnosis, most were peri-/post-menopausal age (average/SE = 53.7 ± 3.8) reducing the likelihood that OCP use contributed to this finding. Future analysis should investigate further into post-menopausal status at the time of diagnosis of VTE in IBD to determine if this could play an important role in the development of hypercoagulability as an IBD co-morbid state.

Male CD patients with VTE were all white and younger than female CD VTE patients (average/SE = 45.7 ± 2.6). It is interesting to note that the average age of the female IBD patient was 44.08 ± 1.169 which was significantly older than the male IBD patient (40.49 ±1.219, $p < 0.05$). Apart from consumption of pro-coagulant medications we also assume that increasing age increases risk for VTE in IBD. This trend has been described in several population based studies, particularly Bernstein [8] who found rates of VTE diagnosis increased with age in both UC and CD patients.

In our study, it was noted that white patients with IBD had longer standing disease than their AA counterparts (13.529 ± 0.80 years vs. 11.291 ± 0.83 years, $p = 0.055$). However, there was no significant difference seen for age at diagnosis between W and AA patients. When considering the influence of gender, we saw that among UC or CD patient groups. A larger proportion of IBD cases were female, Fig. 3C, $p = 0.083$) and white ($p = 0.055$, Fig. 3C) There was no difference between the ages at IBD diagnosis between men and women.

It was noted that BM had fewest years since their IBD diagnosis than WM or WF (WF 13.6 + 1.1, WM 13.4 + 1.1, BM 8.8 + 1.0, BF 13 + 1.1. When considering the years since diagnosis of CD, we also found that BM had significantly fewer years since their diagnosis than WF or WM. Although not statistically significant, we noted that WF were the oldest in both CD and UC in regards to age at diagnosis. It is also interesting that the age at diagnosis for WF patients with CD was younger than for WF with UC ($p = 0.051$). Therefore, IBD occurs more in whites, in females with WF with CD having been diagnosed earlier. The risk of VTE in this population does not appear to parallel absolute age.

Because white patients had longer records of clinically recognized IBD than their AA counterparts, this might indicate more severe disease in whites. With respect to the age at diagnosis, WF with CD were 6.6 years younger than WF with UC, suggesting that WF with CD have the earliest onset and might have more active disease. However, when disease severity was evaluated in CD, WF had the least severe disease (1.42 ± 0.134 W F vs. 1.45 ± .149 BM, 1.588 ± 0.145 BF or 1.6 ± 0.127 WM, avg. ± SE). Therefore, disease severity at the time of presentation may not necessarily reflect overall VTE risk.

Interestingly, no AA males with IBD (neither CD nor UC) had any VTE records in our study. It is possible that the relatively shorter disease duration in AA males (years since diagnosis, Fig. 3D) could decrease VTE risk. Alternatively, AA males may be diagnosed with IBD later than their white counterparts and associations with VTE are being missed. It is also possible that male AA IBD patients may be protected from VTE which could be a point for future analysis.

With regard to the potential importance of disease location, since 54% of our CD patients with VTE events had at least some small bowel involvement, small bowel disease may increase the risk for VTE compared to other areas of the GI tract. These studies contrast with those by Nguyen [3] and Bryant et al. [13] who described CD patients with colonic disease as having higher risks development of VTE. However, it is important to note that a large portion of our CD patient population (41.8%) had both small bowel and colon involvement. Based solely on the fact that this is our largest group could explain why more of these CD patients had VTE. As we have previously stated, white women seem to be at higher risk for developing VTE in our CD population. When we analyzed disease location in these women with CD-VTE, we found that 5 of 7 patients (71.4%) had small bowel involvement.

In our UC-VTE patients, it is interesting to note that the 2 patients who had VTE events showed either only rectal involvement or rectal to transverse colon and not more extensive disease or pancolitis.

5. Conclusion

Based on these findings, we believe that IBD patients should be evaluated for, and provided with VTE prophylaxis at the time of hospital admission. We further found that CD patients had higher rates of VTE than in UC, and that women, especially white women, were at an apparently increased risk for VTE. Although our analysis did not find VTE to be age-dependent, we did see that VTE events appear to increase proportionately with years since diagnosis. We also found that a majority of our CD patients had evidence of at least some small bowel involvement; therefore we would recommend that VTE prophylaxis should always be considered for these 1patients. We recommend that all hospitalized IBD patients, especially those with CD, receive DVT prophylaxis to protect them against VTE events, as several studies confirm their elevated risk. Aspirin might be considered for DVT prophylaxis, however, it carries risk and increased severity in CD as it may be more useful in the prevention of *arterial*, rather than venous thromboemboli. Other choices to limit VTE might include prophylactic dosing with heparin or lovenox (in the inpatient setting.) Patients should also be asked for signs and/or symptoms of VTE during outpatient clinic visits and screening be performed if present. The recognition of increased risk of VTE in CD, particularly in women, irrespective of age may be an important observation which could guide therapy and limit potentially life-threatening consequences of coagulation disorders in IBD.

Ethics approval and consent to participate

This was an IRB approved retrospective study of our institutional IBD patients. All patient data was collected anonymously and adheres to the HIPAA protocol associated with ethical handling of patient data.

Consent to publish

In our IRB proposal it was stated that data would be submitted for poster, oral presentation and for publication in National Gastroenterology Journals and meetings.

Disclosures

All authors declare that they have no disclosures.

Author contributions

Dr. Kelli Morgan: Acquisition of data, analysis and interpretation of data, drafting of the manuscript.

Dr. Moheb Boktor: Study concept, IRB protocol and study design, critical revision of the manuscript.

Carey Ford: Critical revision of the manuscript.

Dr. Ly Pham: Critical revision of the manuscript.

Dr. Urska Cvek and Dr. Marjan Trutschl contributed to the analysis of the data and critical revision of the manuscript.

Dr. J. Steven Alexander: Study concept and design, analysis of data, critical revision of the manuscript for important intellectual content, administrative support.

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