의학석사 학위논문

한국의 염증성 장질환 환자에서 문맥 혈전증의 특성과 결과

Characteristics and outcomes of portal vein thrombosis in patients with inflammatory bowel disease in Korea

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이 논문을 의학석사 학위 논문으로 제출함

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김기진의 의학석사학위 논문을 인준함

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Abstract

Objectives: Portal vein thrombosis (PVT) is known to occur frequently in patients with inflammatory bowel disease (IBD), particularly when compounded by factors such as abdominal infection, IBD flares, or intra-abdominal surgery. However, PVT can lead to diverse complications, causing acute issues like intestinal ischemia or necrosis and long-term problems such as portal hypertension, varices, and ascites. Nevertheless, there is a significant shortage of research regarding the characteristics and prognosis of PVT in the context of IBD. Particularly, with the rising prevalence of IBD patients in Asia, this study conducted an evaluation of clinical presentation and prognosis of PVT in IBD patients at a large tertiary hospital in South Korea.

Methods: This study is a retrospective study conducted at a single tertiary center in South Korea. It examined patients aged 18 and above diagnosed with inflammatory bowel disease (IBD) who had confirmed portal vein thrombosis (PVT) between June 1, 1989, and December 15, 2021. The study focused on investigating patient characteristics, PVT characteristics, treatment methods, and outcomes. The diagnosis and resolution of PVT were confirmed using enhanced CT imaging.

Results: A total of 78 patients met the inclusion criteria for this study. Only 21% (16/78) received oral anticoagulants, yet nearly all patients (96%; 75/78) achieved Complete Radiologic Resolution (CRR). When comparing baseline characteristics between the anticoagulation use group and the non-use group, a trend was observed with a higher utilization of anticoagulants in cases where the main portal vein was involved rather than only the left or right portal vein (p-value 0.006). However, when conducting multivariable analysis, no factors significantly influenced CRR, especially anticoagulant use and surgery status.

Conclusion: PVT concomitant with IBD demonstrated favorable outcomes regardless of anticoagulation use.

Keywords: inflammatory bowel disease, portal vein thrombosis, complete radiologic resolution, anticoagulation.

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Introduction

Portal vein thrombosis (PVT) can occur in various situations, with a higher prevalence primarily observed in patients with liver cirrhosis. However, PVT is also occasionally observed in patients without liver cirrhosis.[1] Factors contributing to PVT include intra-abdominal infections such as diverticulitis, cholecystitis, pancreatitis, abdominal malignancies, intra-abdominal surgery, trauma, thrombophilia, myeloproliferative neoplasm (MPN), and inflammatory bowel disease (IBD).[2]

IBD, in particular, has a higher incidence of venous thromboembolism compared to other digestive diseases.[3] The exact mechanism underlying the development of PVT in IBD is not yet well-defined. However, there is a hypothesis that chronic inflammation, along with intra-abdominal thrombophilia, may play a role.[2,4,5] Another theory suggests that translocation of intestinal bacteria into the portal venous system through ulcerations in the bowel mucosa can lead to portal pyelophlebitis and subsequent thrombosis.[6]

It is known that PVT is more likely to occur in IBD patients when additional factors, such as intra-abdominal infections, IBD flares, or intra-abdominal surgery, are present.[7-9] Patients who have used steroids before surgery or undergone emergency surgery are also at an increased risk of developing PVT.[10,11]

If PVT is left untreated and becomes chronic, it can lead to various complications. In the short term, it may cause intestinal ischemia or necrosis[12], while in the long term, it can result in portal hypertension, leading to complications such as varices and ascites.[2,13] Notably, the symptoms and signs associated with PVT in IBD are often nonspecific, and it is primarily incidentally discovered.[14,15]

PVT can be effectively treated with anticoagulation, and early initiation of treatment is crucial for preventing complications.[16] In cases where PVT is associated with liver cirrhosis, it is recommended to switch from low molecular weight heparin to warfarin or

direct oral anticoagulants (DOACs) after initiation.[17] Approximately half of the patients achieve complete recanalization[18], and the likelihood of spontaneous recanalization of the portal vein in acute PVT without anticoagulation is low.[19]

While it is crucial to screen for and administer anticoagulation in situations where PVT is expected to accompany IBD, research in this area has been somewhat limited, particularly in Asian regions. Given the rapidly increasing incidence and prevalence of IBD in Asia[20,21] and the noteworthy incidence of venous thromboembolism in Asian IBD patients compared to their Western counterparts[22], there is a strong need for studies that investigate the characteristics and prognosis of PVT in Asian IBD patients.

This study aimed to evaluate the clinical presentation and prognosis of PVT in IBD patients in a large tertiary hospital in South Korea.

Method

From June 1, 1989, to December 15, 2021, we identified patients aged 18 and above with a diagnosis of inflammatory bowel disease (IBD) at Asan Medical Center, a tertiary hospital in South Korea. Patients were selected if their imaging reports mentioned portal vein thrombosis (PVT), if they were prescribed anticoagulants, or if thrombophilia laboratory tests were conducted. Patient selection was confirmed through electronic medical records.

Exclusion criteria encompassed patients with a history of tumor thrombus, thrombolysis, or thrombectomy; those lacking baseline imaging at the time of PVT diagnosis; individuals without follow-up imaging performed a minimum of 3 months after diagnosis; and those exhibiting signs of chronic portal vein thrombosis. The identification of chronic portal vein thrombosis was based on radiological findings such as portal cavernomas and portal collaterals or clinical records.

Data collected from the selected patients included age at the time of PVT diagnosis, gender, type of IBD, the date of complete radiographic resolution (CRR) and the time taken to achieve resolution, the last follow-up date, the duration of follow-up from the time of diagnosis, the presence and specific constituents of oral anticoagulation, the existence and total duration of intravenous (IV) or subcutaneous (SC) bridging, the presence of venous thromboembolism (VTE) prophylaxis for patients diagnosed postoperatively, underlying issues present at the time of diagnosis (intra-abdominal infections, liver cirrhosis, pancreatitis, IBD flare), symptoms at the time of diagnosis (diarrhea, abdominal pain, constipation, anal pain, nausea, vomiting, fever, rectal bleeding), prior VTE history, myeloproliferative neoplasm (MPN), complications accompanying the diagnosis (bleeding, gut ischemia, portal hypertension, death), medications for IBD, laboratory results (leukocytosis, liver function tests, C-reactive protein), the performance and results of thrombophilia laboratory tests, surgical

procedures, the date of surgery, the type of surgery, and the reasons for surgery. The imaging modality, location, and degree of PVT, as well as the presence of inflammation on Computed Tomography (CT) scans, were also investigated.

Although fecal calprotectin is typically used to assess the disease activity of IBD[23], this parameter was not routinely measured in the subjects of this study and was therefore excluded from the analysis.

PVT location was categorized into two groups: "Main portal vein (PV) group" for those with involvement of the main PV and "Left or Right PV only group" for those without main PV involvement. PVT degree was divided into "occlusive" or "non-occlusive" based on whether total occlusion was present. IBD medications were categorized into 5-aminosalicylic acid (5-ASA), immunomodulatory, steroid, and biologics. (At present in South Korea, various biologics are being effectively used for both induction and maintenance therapies[24,25]. Although each of these biologics has different mechanisms of action, they were collectively grouped as 'biologics' for the purpose of statistical analysis.) For patients diagnosed postoperatively, surgery was further divided into "recent" surgery within 3 months and "remote" surgery more than 3 months post-diagnosis. In the statistical analysis, the "remote" surgery group was combined with the "no recent surgery" group. Since many patients did not use anticoagulants, the characteristics of patients who used anticoagulants were compared with those who did not. The primary outcome of interest was the complete radiographic resolution (CRR) of PVT.

Statistical analysis was conducted as follows. Continuous variables were summarized as medians and interquartile ranges (IQR), while categorical variables were presented as N (%). A comparison of patient characteristics between groups who used anticoagulants and those who did not used the Mann-Whitney test for continuous variables and Pearson's test and Fisher's exact test for categorical variables. Multivariable analysis for CRR of PVT was performed using the Cox Proportional-Hazards Model to determine odds ratios.

Subgroup analysis based on anticoagulant drug components was considered, but the small number of patients using anticoagulants made the results unreliable, and therefore, subgroup analysis was not performed.

Results

1. Baseline Characteristics

Among patients aged 18 or older with a diagnosis of inflammatory bowel disease (IBD), a total of 438 individuals met the inclusion criteria, as they had mentions of portal vein thrombosis in radiological reports, a history of anticoagulant prescriptions, or had undergone thrombophilia laboratory tests. Out of these, only 78 patients satisfied the inclusion criteria (70 with Crohn's disease (CD), 8 with ulcerative colitis (UC)) as depicted in Figure 1. The patients were followed up for an average duration of 109 months, and their baseline characteristics are summarized in Table 1.

Some patients with portal vein thrombosis (PVT) diagnosis had not received IBD therapy within 3 months of the PVT diagnosis (9%; 7/78). Additionally, patients were categorized based on the treatment they received, with 28% (22/78) using 5-aminosalicylic acid (5-ASA), 31% (24/78) receiving immunomodulatory agents, 23% (18/78) prescribed steroids, and 9% (7/78) treated with biologics. Notably, only one patient (1%; 1/78) among this cohort had liver cirrhosis, and no patients had a prior history of venous thromboembolism (VTE) or were diagnosed with myeloproliferative neoplasms (MPN).

2. Presenting Characteristics

Laboratory findings, symptoms, and signs at the time of PVT diagnosis are summarized in Table 1. Approximately one-third of patients had concomitant abdominal infections (37%; 29/78), and a similar proportion were judged by gastroenterologists to have IBD

flares (28%; 22/78). Presenting symptoms were nonspecific, with abdominal pain (71%; 55/78) and diarrhea (45%; 35/78) being the most common, while fever (13%; 10/78) and rectal bleeding (9%; 7/78) were relatively less common. Laboratory results at the time of diagnosis were also nonspecific, with elevated C-reactive protein being the most common abnormal finding (73%; 57/78), followed by leukocytosis (23%; 18/78), while elevated liver function tests were uncommon (12%; 9/78). Eighty-one percent of patients (63/78) underwent surgery within three months, with the majority having bowel surgery related to IBD, although one patient had a Cesarean section, and another underwent living donor liver transplantation.

3. Diagnosis and Workup

The diagnosis of PVT was confirmed exclusively through CT imaging, with chronic PVT cases excluded (those with a previous PVT history or radiographic features suggesting chronic PVT, such as cavernous transformation). Occlusive PVT was observed in only one patient (1%), with the majority affecting the left or right portal vein without involvement of the main portal vein (95%; 74/78). PVT was incidentally discovered in all cases, with evidence of active bowel inflammation observed in 23% (18/78). Thrombophilia testing was performed in 18% of patients (14/78), as shown in Table 2, and no cases of primary thrombophilia were identified.

4. Management

Oral anticoagulants were used in only 21% (16/78) of patients, with 10 receiving warfarin and 6 receiving rivaroxaban. The majority of patients (14 out of 16) underwent bridging therapy with IV heparin or SC enoxaparin before starting oral anticoagulants,

and the average duration of oral anticoagulant use was 165 days (IQR 90–279). Characteristics of all patients, as well as comparisons between those who received anticoagulants and those who did not, are summarized in Table 3. A trend was observed where ulcerative colitis (UC) patients tended to receive more anticoagulants than Crohn's disease (CD) patients (p-value 0.008), and patients with involvement of the main portal vein were more likely to receive anticoagulants than those with left or right portal vein involvement (p-value 0.006). There were no significant differences in other baseline characteristics between the anticoagulant-treated and untreated groups.

5. Outcomes

During the follow-up period, no patients died, but 2 patients (3%) required major bleeding-related blood transfusions. Nearly all patients (96%; 75 out of 78) achieved Complete Radiographic Resolution (CRR). Only 3 patients progressed to chronic portal vein thrombosis (PVT).

The Kaplan-Meier curve in Figure 2 illustrates the CRR for patients in the anticoagulant use group and those in the non-use group. To identify potential determinants of CRR, a multivariable analysis was conducted, and the results are presented in Table 4. Ultimately, no factors were found to significantly influence CRR. CRR was observed in the majority of patients, regardless of whether anticoagulants were used or not, and it was unrelated to whether the patients were postoperative or not.

The 3 patients who did not achieve CRR were all postoperative cases, and two of them had used anticoagulants (one on warfarin and one on rivaroxaban). Importantly, during the follow-up period, there were no documented PVT complications, such as gut ischemia or portal hypertension, in any of the patients, including the 3 with chronic PVT.

Figure 1. Research schematic diagram

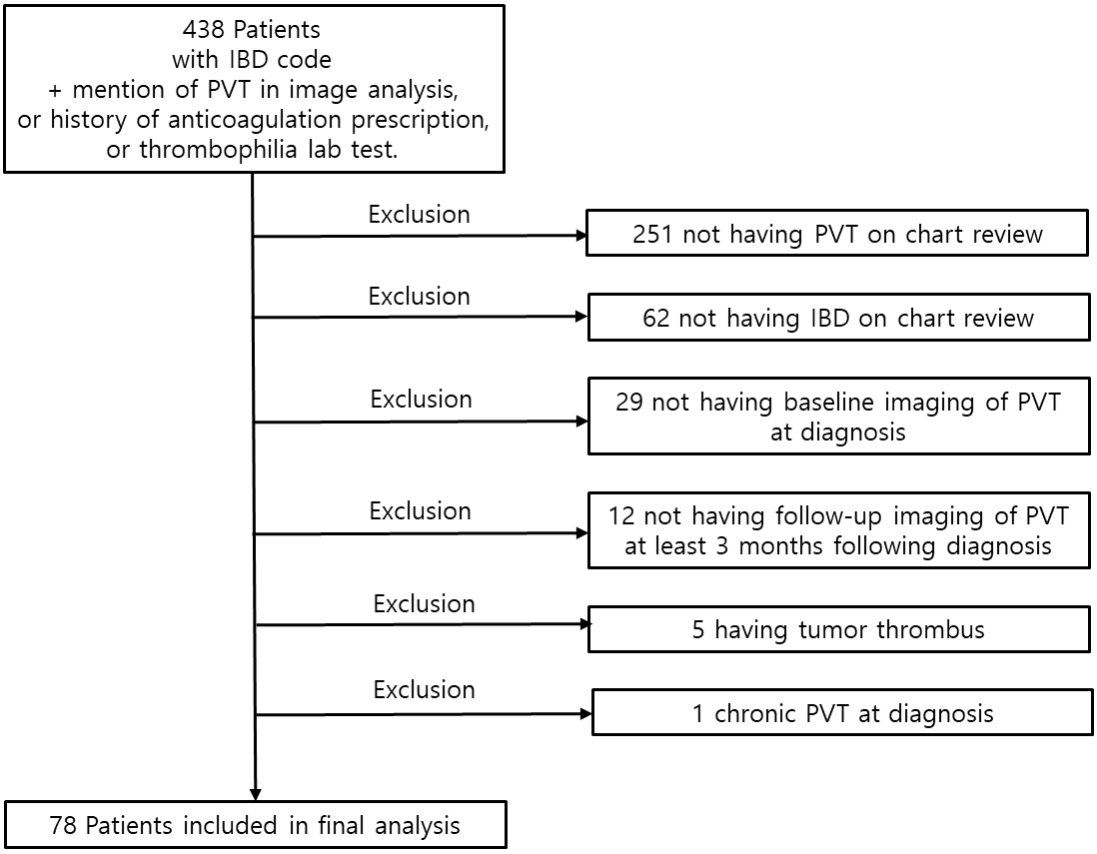

Table 1. Baseline Characteristics

Variable	
Age, median years (IQR)	31.0 (24 – 38)
Male	51 (65)
IBD type	
Crohn's disease	70 (90)
Ulcerative colitis	8 (10)
Follow up duration, months (IQR)	109 (72 – 141)
Oral anticoagulation	16 (21)
Abdominal infection	29 (37)
Cirrhosis	1 (1)
IBD flare	22 (28)
Bowel involvement	18 (23)
Associated symptoms	
Diarrhea	35 (45)
Abdominal pain	55 (71)
Constipation	1 (1)
Anal pain	4 (5)
Nausea or vomiting	8 (10)
Fever	10 (13)
Rectal bleeding	7 (9)
Major bleeding after diagnosis	2 (3)
IBD specific therapy	29 (94)
No therapy	7 (9)
5-Aminosalicylic acid	22 (28)
Immunomodulator	24 (31)
Steroid	18 (23)
Biologics	7 (9)
Laboratory findings at diagnosis	
White blood cell, median counts/microliter (IQR)	6300 (5000 – 9000)
Leukocytosis	18 (23)
Asperate aminotransferase, median IU/mL (IQR)	18 (13 – 23)
Alanine aminotransferase, median IU/mL (IQR)	13 (8 – 22)
Elevated liver function test	9 (12)
Total bilirubin, median mg/dL (IQR)	0.6 (0.4 – 0.8)
Hyperbilirubinemia	3 (4)
C-reactive protein, median mg/dL (IQR)	1.6 (0.6 – 6.2)
Elevated C-reactive protein	57 (73)
Operative status	
No	10 (13)
Recent (<3 months)	63 (81)
Remote (>3 months)	5 (6)
PVT location	
Left or Right vein only	74 (95)
Main with left or right vein	2 (3)
Main with superior mesenteric vein	1 (1)
Main with superior mesenteric and splenic vein	1 (1)
Occlusive PVT	1 (1)

NOTE. Data are presented as number of patients (%) unless otherwise indicated.
IQR; interquantile range. IBD; inflammatory bowel disease. PVT; portal vein thrombosis

Table 2. Thrombophilia Testing

Test	Percentage Testing Positive
Protein C deficiency*	0% (0/13)
Protein S deficiency*	0% (0/12)
Antithrombin III deficiency*	0% (0/12)
Lupus anticoagulant	0% (0/12)
Anticardiolipin antibodies	0% (0/8)
Beta-2 glycoprotein I antibodies	0% (0/8)
JAK2V617F mutation	0% (0/3)
Paroxysmal nocturnal hemoglobinuria	0% (0/3)

The results of thrombophilia testing among our cohort are described above.

*Tests were excluded if sent in the context of acute thrombosis or while a patient was on warfarin (for proteins C and S).

Table 3. Patient Characteristics by AC Used

	all patients n=78	no anticoagulant n=62	anticoagulant n=16	p-value
1. Median age (IQR)	31.0 (24 - 38)	30.2 (24 - 38)	33.0 (27 - 40)	0.4
2. Sex				0.786
Male	51 (65.4%)	41 (66.1%)	10 (62.5%)	
Female	27 (34.6%)	21 (33.9%)	6 (37.5%)	
3. Location of PVT				0.006
Left or Right PV only	74 (94.9%)	61 (98.4%)	13 (81.3%)	
Main PV	4 (5.1%)	1 (1.6%)	3 (18.7%)	
4. Degree of PV occlusion				0.205
Nonocclusive	77 (98.7%)	62 (100%)	15 (93.8%)	
Occlusive	1 (1.3%)	0 (0%)	1 (6.2%)	
5. Type of IBD				0.008
UC	8 (10.3%)	3 (4.8%)	5 (31.3%)	
CD	70 (89.7%)	59 (95.2%)	11 (68.7%)	
6. Recent abdominal surgery				0.069
No recent surgery	15 (19.2%)	9 (14.5%)	6 (37.5%)	
Recent surgery	63 (80.8%)	53 (85.5%)	10 (62.5%)	
7. Median follow-up time in months (IQR)	109 (72 - 141)	114 (86 - 144)	82 (29 - 123)	0.068
8. Resolution time in days (IQR)	197 (105 - 495)	198 (105 -662)	157 (107 - 343)	0.283

IQR; interquantile range. PVT; portal vein thrombosis. PV; portal vein
IBD; inflammatory bowel disease. UC; ulcerative colitis. CD; Crohn's disease

Figure 2. Kaplan-Meier curve for the primary outcome of CRR of PVT by anticoagulation.

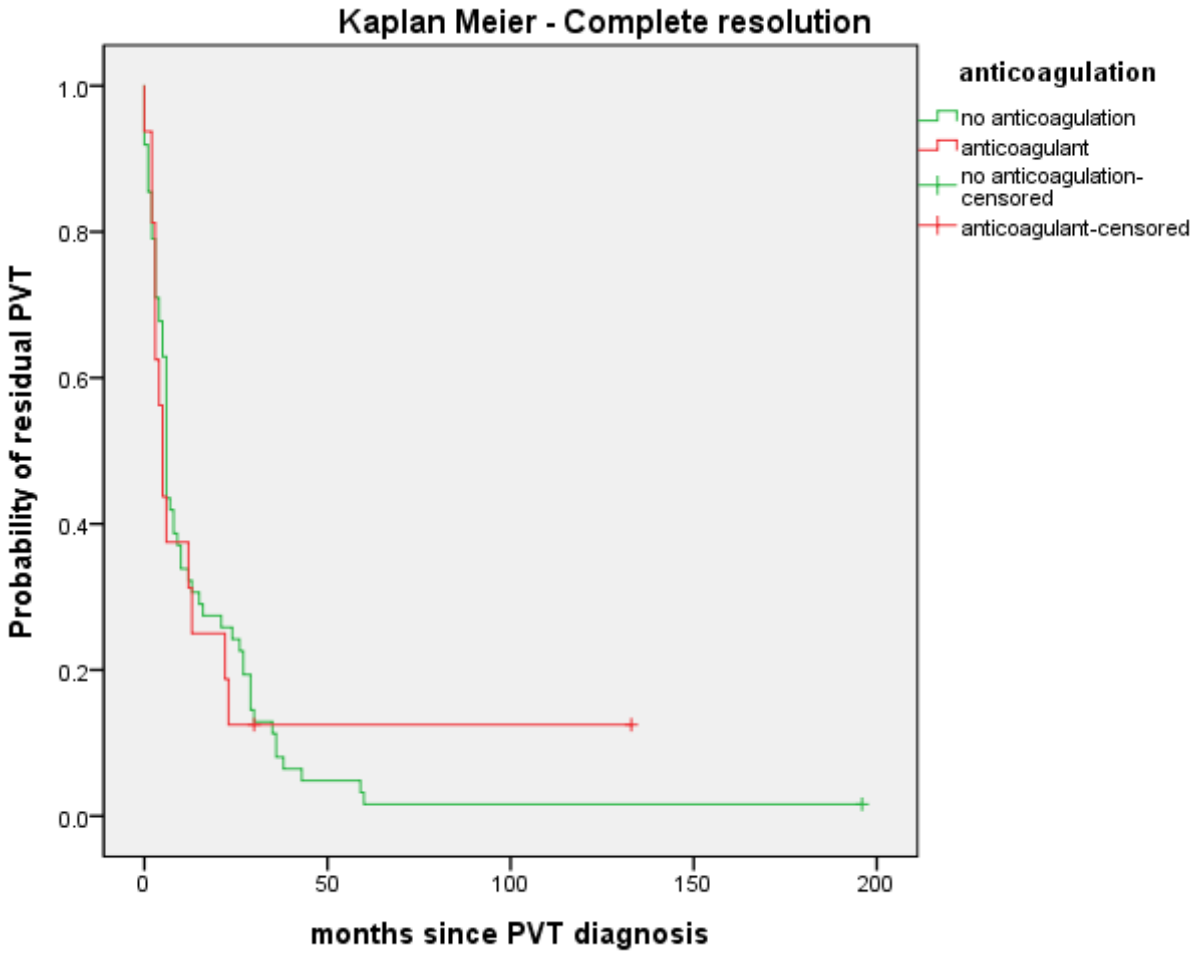

Table 4. Multivariable Analysis for CRR of PVT

Reference		OR	p-value
1. age			0.74
2. sex			
male	female	0.698	0.193
3. anticoagulant			
none	anticoagulant	0.943	0.857
4. PVT location			
Left or Right PV	Main PV	0.68	0.584
5. baseline occlusion			
no occlusion	occlusion	5.407	0.186
6. IBD type			
UC	CD	0.452	0.095
7. recent surgery			
no recent surgery	recent surgery	1.364	0.335

PVT; portal vein thrombosis. PV; portal vein
IBD; inflammatory bowel disease. UC; ulcerative colitis. CD; Crohn's disease

Discussion

Portal vein thrombosis (PVT) is known to frequently co-occur in patients with Inflammatory Bowel Disease (IBD)[2,4], especially when associated with intra-abdominal surgery, intra-abdominal infection, or IBD flare.[7] Acute PVT often presents with non-specific symptoms and is typically discovered incidentally.[14,15] While acute PVT itself can lead to complications such as intestinal ischemia[12], chronic PVT can cause conditions like portal hypertension, varices, and ascites[2,13]. Prompt anticoagulation is essential for treating PVT, and the prognosis is generally favorable with anticoagulant therapy.[16]

Although there has been relatively little research on the characteristics and prognosis of PVT in IBD patients, a 2021 study reported promising results. In this study of 63 IBD patients with PVT, 92% received anticoagulation, and 71% achieved Complete Radiographic Resolution (CRR). It was also noted that Direct Oral Anticoagulants (DOACs) demonstrated higher CRR rates (96% vs. 55%) and shorter treatment durations (median 3.9 months vs. 8.5 months) compared to warfarin. Notably, patients who did not receive anticoagulation had a much lower CRR rate (20%).[26]

In contrast, our study, conducted at a large tertiary hospital in South Korea, revealed somewhat different results. Most of the patients had Crohn's Disease (CD) (90%), and PVT primarily involved the main portal vein in a relatively low percentage of cases (5%). Moreover, only 21% of patients received anticoagulation therapy, yet nearly all patients (96%) achieved CRR. Although there were some slight differences in baseline characteristics between the anticoagulation use group and non-use group (with a tendency for more UC patients to use anticoagulants and more main portal vein involvement in the anticoagulation group), multivariable analysis did not identify any factors significantly affecting CRR (including anticoagulant use and surgery).

The differences observed can be attributed to the characteristics of patients where the majority had PVT involving the right or left portal vein only (95%). It is likely that in

cases where PVT extends to the main portal vein, there is a higher tendency to administer anticoagulation, potentially leading to an overall increase in CRR rates. The high proportion of right or left portal vein-only involvement can be explained by the fact that most patients were postoperative cases (81%), and PVT was more frequently discovered at an early stage with right or left portal vein involvement when incidentally detected during routine postoperative imaging.

Considering these findings, it may be possible to expect complete remission regardless of anticoagulation for PVT involving only the right or left portal vein, particularly when it is incidentally found during routine postoperative imaging. In addition, many IBD patients undergo periodic imaging follow-up for postoperative relapse monitoring[27], which may allow for a relatively short duration of anticoagulation.

However, this study has several limitations, primarily due to its retrospective design. Various biases may exist, particularly among patients in whom anticoagulation was not administered, as there may be multiple variables at play, and the study sample size might not have been large enough to detect statistically significant differences. Furthermore, since the study included a limited number of patients who received anticoagulation, it was not possible to compare CRR between warfarin and DOACs. Given the potential benefits of DOACs demonstrated in other studies[26], additional research is warranted. The study is also limited as it is a single-center study conducted in a tertiary hospital, potentially not representing the entire population of IBD patients in South Korea.

Nonetheless, the study boasts several strengths. It is among the largest studies to describe the clinical presentation and prognosis of IBD patients with PVT, and in light of the rising trend of IBD patients in Asia, this research holds significant value. Moreover, the high incidence of partial thrombosis involving only the right or left portal vein, even in non-anticoagulation patients, who mostly achieved CRR, suggests a potential shift in the current guideline's recommendation to initiate anticoagulation immediately upon detecting portal vein thrombosis. This finding can offer valuable insights for postoperative patients, particularly in terms of bleeding risk awareness and management.

Conclusion

This study analyzed the characteristics and prognosis of concurrent Portal Vein Thrombosis (PVT) in South Korean Inflammatory Bowel Disease (IBD) patients and is of significance due to the favorable outcomes observed regardless of anticoagulation use. While current guidelines recommend anticoagulation therapy upon PVT confirmation, it may be worth considering modifications to the treatment guidelines, taking into account individual patient factors and PVT characteristics. Further research is needed to facilitate this potential revision in clinical guidelines.

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국문요약

배경 및 목적 : 염증성 장질환 환자에서는 간문맥혈전증이 잘 발생하며, 복부내 감염이나 염증성 장질환의 악화 또는 복부 수술 등의 요인들이 더해지면 간문맥혈전증이 더 호발하는 것으로 알려져 있다. 그러나 간문맥 혈전증은 다양한 합병증을 유발할 수 있는데, 급성기로는 장허혈이나 괴사를 유발할 수 있고, 장기적으로는 문맥고혈압을 유발하여 정맥류나 복수 등의 합병증을 동반할 수 있게 된다. 그러나 염증성 장질환에 동반된 간문맥혈전증에 대한 특성이나 예후에 대한 연구가 많이 부족한 상황인데, 특히 아시아권의 염증성 장질환 환자가 점차 증가하는 가운데, 이 연구는 한국의 대규모 3차병원에서 염증성 장질환 환자에서의 간문맥혈전증 발생에 대한 임상양상과 예후를 평가하였다.

대상 및 방법 : 이 연구는 한국의 단일 3차 센터에서 실시된 후향적 연구이다. 18세 이상의 염증성 장질환 환자 중 1989.06.01부터 2021.12.15까지 간문맥 혈전증이 확인된 환자들을 대상으로, 환자와 간문맥 혈전증의 특성 및 치료방법과 결과에 대해 조사하였다. 간문맥 혈전증의 진단 및 추적관찰은 조영증강 전산화 단층촬영(CT)을 통해 확인하였다.

결과 : 78명의 환자들이 본 연구의 선정 기준에 부합하였고, 경구 항응고제는 21%(16/78)만이 사용되었으나, 거의 대부분의 환자(96%; 75/78)가 완전한 방사선학적 해소에 도달하였다. 항응고제 사용군과 비사용군간의 기본 특성들을 비교하였을 때, 왼쪽 또는 오른쪽 간문맥만을 침범한 군보다는 주간문맥(main portal vein)을 침범한 군에서 항응고제를 더 많이 사용하는 경향(p-value 0.006)이 있었으나, 다변량 분석을 시행하였을 때, 어떠한 요소들도 완전한 방사선학적 해소에 영향을 주는 요소는 아니었고, 특히 항응고제의 사용 여부와 수술 여부와도 관계없었다.

결론 : 염증성 장질환에 동반된 간문맥 혈전증은 항응고제 사용 여부와 관계없이 좋은 결과를 보였다.

중심단어 : inflammatory bowel disease, portal vein thrombosis, complete radiologic resolution, anticoagulation.