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Risk of venous thromboembolism² in children and adolescents with inflammatory bowel disease: a systematic review and meta-analysis

Venous thromboembolism in IBD

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Abstract

BACKGROUND

A two- to three-fold increased risk of venous thrombotic events (VTE) has been demonstrated in patients with inflammatory bowel disease (IBD) compared to the general population, but less is known about the risk of VTE in child- and pediatric-onset IBD. In recent years, several studies have reported the rising incidence rate of VTE in juvenile patients with IBD, and the related risk factors have been explored.

AIM

To evaluate the risk of VTE in children and adolescents with IBD.

METHODS

Articles published up to April 2021 were retrieved from PubMed, Embase, Cochrane Library, Web of Science, SinoMed, CNKI, and WANFANG. Data from observational studies and clinical work were extracted. The outcome was the occurrence of VTE according to the type of IBD. The available odds ratio (OR) and the corresponding 95%CI were extracted to compare the outcomes. Effect size (P), odds ratio (OR), and 95% confidence interval (CI) were used to assess the association between VTE risk and IBD disease. Subgroup analyses stratified by subtypes of VTE and IBD were performed.

RESULTS

Twelve studies (7,450,272 IBD patients) were included in the meta-analysis. Child and adolescent IBD patients showed increased VTE risk ($P = 0.02$, 95%CI: 0.01-0.03). Subgroup analyses stratified by IBD (ulcerative colitis (UC): $P = 0.05$, 95%CI: 0.03-0.06; Crohn's disease (CD): $P = 0.02$, 95%CI: 0.00-0.04) and VTE subtypes (portal vein thrombosis (PVT): $P = 0.04$, 95%CI: 0.02-0.06; deep vein thrombosis (DVT): $P = 0.03$, 95%CI: 0.01-0.05; central venous catheter (CVC)-related thrombosis: $P = 0.23$, 95%CI:

0.00-0.46; thromboembolic events (TE): $P = 0.02$, 95%CI: 0.01-0.03) revealed significant correlation between VTE risk and IBD. Patients with IBD were more susceptible to VTE risk than those without IBD (OR=2.99, 95%CI: 1.45-6.18). The funnel plot was asymmetric, suggesting the presence of significant publication bias.

Conclusion: Pediatric and adolescent IBD patients have an increased VTE risk. UC and CD patients exhibited a high risk of VTE. The risk of VTE subtypes was increased in IBD patients.

CONCLUSION

The current meta-analysis showed that the incidence and risk of VTE are significantly increased in pediatric and adolescent IBD patients. Thus, IBD might be a risk factor for VTE in children and young adults. Still, high-quality prospective cohort studies are necessary to confirm these findings.

Key

Words:

Thromboembolism; Children; Adolescents; Ulcerative colitis; Crohn's disease; Meta-analysis.

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Core Tip: This study suggested that child and adolescent IBD patients showed increased VTE risk ($P = 0.02$, 95%CI: 0.01-0.03). Subgroup analysis stratified by IBD (ulcerative colitis (UC): $P = 0.04$, 95%CI: 0.03-0.06; Crohn's disease (CD): $P = 0.02$, 95%CI: 0.00-0.04) and VTE subtypes (portal vein thrombosis (PVT): $P = 0.04$, 95%CI: 0.02-0.06; deep vein thrombosis (DVT): $P = 0.03$, 95%CI: 0.01-0.05; central venous catheter (CVC)-related thrombosis: $P = 0.13$, 95%CI: 0.02-0.23; thromboembolic events

(TE): $P = 0.02$, 95%CI: 0.01-0.03) revealed significant correlation between VTE incidence and IBD.

INTRODUCTION

Inflammatory bowel disease (IBD) is a digestive system disorder characterized by the chronic inflammation of the gastrointestinal (GI) tract^[1-5]. The two common manifestations of IBD are ulcerative colitis (UC) and Crohn's disease (CD)^[1-5]. The pathogenesis of IBD involves a complex interaction between the host genetics, external environment, gut microbiota, and immune responses^[6-8]. The incidence of pediatric and adult IBD is rising steadily worldwide, especially in developed countries^[9-11]. Approximately 25% of patients with IBD are diagnosed before the age of 18 years^[12,13]. Furthermore, 4% of pediatric IBD occur before the age of 5 years and 18% before the age of 10 years, peaking in adolescence^[7].

Venous thromboembolism (VTE) is a potentially severe medical condition with a high recurrence rate^[14,15]. IBD is a high-risk factor for the occurrence and development of VTE in adults^[16,17]. Routine VTE prophylaxis is recommended for IBD patients during hospitalization^[1,18-20]. Pediatric patients with IBD also have an increased predisposition to develop VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE), although the available evidence is of lower quality^[21,22]. The etiology of VTE in IBD is multifactorial and not well defined. It involves the cross-talk between coagulation and inflammation^[23,24]. IBD-associated inflammation causes a hypercoagulable state, leading to systemic thrombotic events and local microthrombi in the vessels of the inflamed intestinal mucosa^[25,26]. Pediatric IBD patients exhibit various clinical features, including disease location and severity, endoscopic appearance, histology, comorbidities, complications, and response to treatment options^[27]. The reported risk factors for VTE in children with IBD include inherent genetics, ethnicity, gender, infection, parenteral nutrition, surgery, specific therapies, disease history, and increased use of central venous catheters (CVCs; the most common factor)^[28-30].

Nonetheless, whether the development of VTE complications in IBD treatment is age-dependent is yet to be clarified. The increased risk of VTE in adult patients with IBD is widely recognized^[31]. A two- to three-fold increased risk of VTE has been demonstrated in patients with IBD compared to the general population^[26]. Still, less is

known about the risk of VTE in child- and pediatric-onset IBD. In recent years, several studies have reported the rising incidence rate of VTE in juvenile patients with IBD, and the related risk factors have been explored^[32-35]. Therefore, this meta-analysis evaluated the association between postoperative VTE risk and IBD in children and adolescent populations.

MATERIALS AND METHODS

According to the Preferred Reporting Items for Systematic Reviews (PRISMA, 2020) guidelines, we conducted a systematic review and meta-analysis. PubMed, Embase, Cochrane Library, Web of Science, SinoMed, CNKI, and WANFANG databases were systematically searched for studies published up to April 2021.

RESULTS

Literature search and study characteristics

The initial literature database search retrieved 438 studies. The duplicate records and automatically marked ineligible records were filtered out. After screening, 100 reports were assessed for eligibility. Due to insufficient information on participants, exposure, outcomes, and different reports from the same participants, only 12 reports were finally included for this meta-analysis. The study screening flowchart is illustrated in Figure 1.

The characteristics of the 12 eligible studies, including nine cohort studies^[21,27,30,32-35,39,40], one RCT^[28], and two database reviews^[25,41], are listed in Table 1. These studies encompassed 7,450,272 IBD patients. Eight studies were carried out in the United States, and the others were performed in Canada, Switzerland, Iran, and Korea. The IBD patients had a mean age of <1-21 years. The proportion of male patients ranged from 42.9% to 71.2%. The IBD subtypes covered UC, CD, indeterminate colitis (IC), and undefined IBD type (IBD-U). Moreover, various VTE subtypes, including intra-abdominal thrombosis (IAT), DVT, venous thromboembolism (VTE), TE, pulmonary thromboembolism (PTE), intracranial venous sinus thrombosis (IVST), PVT, and cerebrovascular thrombosis (CVT), were investigated. In addition, the confounding

factors, including age, sex, hypercoagulable status, CVC, parenteral nutrition (PN), cancer, sickle cell anemia, tobacco use, race/ethnicity, payer status, urban/rural status, hospital region, and length of inpatient stay, were adjusted in various studies. According to the NOS evaluation criteria, the methodological quality score was 6 for 10 studies and 8 and 9 for the other two studies, respectively, indicating low-to-moderate bias (Table 2).

Association between IBD and VTE risk

The association between IBD and the incidence of VTE was assessed in 12 studies. The pooled results showed that the risk of VTE was significantly increased in IBD patients compared to those without IBD ($P = 0.02$, 95%CI: 0.01-0.03). Moderate heterogeneity was detected across the included studies ($I^2=54.7\%$, $p_{\text{heterogeneity}}=0.012$, Figure 2). In addition, double arcsine analysis showed similar results ($P = 0.03$, 95%CI: 0.02-0.04, Supplemental Figure 1).

The subgroup analyses stratified by IBD subtype were performed to evaluate the VTE risk in IBD. Five studies analyzed the UC subtype, and the pooled results suggested significantly increased VTE incidence in UC patients ($P = 0.05$, 95%CI: 0.03-0.06). No heterogeneity was detected among the studies ($I^2=0.0\%$, $p_{\text{heterogeneity}}=0.571$, Figure 3A). Pooled analysis of four studies established a correlation between the VTE risk with CD ($P = 0.02$, 95%CI: 0.00-0.04), without heterogeneity ($I^2=0.0\%$, $p_{\text{heterogeneity}}=0.709$, Figure 3A). The IBD subtype was not defined in three studies, and a high rate of VTE was also detected in these patients ($P = 0.02$, 95%CI: 0.01-0.03), without obvious heterogeneity ($I^2=0.0\%$, $p_{\text{heterogeneity}}=0.702$, Figure 3A). Based on one study, the VTE incidence was not increased in IC patients ($P = 0.12$, 95%CI: -0.04 to 0.27, Figure 3A).

Stratified by VTE subtype, two studies showed significantly increased PVT incidence in IBD patients ($P = 0.04$, 95%CI: 0.02-0.06; $I^2=0.0\%$, $p_{\text{heterogeneity}}=0.568$, Figure 3B). The pooled analysis of four studies showed a high risk of DVT in IBD patients ($P = 0.03$, 95%CI: 0.01-0.05) with low heterogeneity ($I^2=21.8\%$, $p_{\text{heterogeneity}}=0.280$, Figure 3B). In

addition, one study revealed an increased risk of CVC-related thrombosis in IBD ($P = 0.23$, 95%CI: 0.00-0.46, Figure 3B). Furthermore, two studies showed a significant association of TE risk with IBD ($P = 0.02$, 95%CI: 0.01-0.03), without heterogeneity ($I^2=0.0\%$, $p_{heterogeneity}=0.862$, Figure 3B). No association was found between PTE and IBD disease ($P = 0.01$, 95%CI: -0.01 to 0.04, Figure 3B) based on one study.

Pooled analysis of two studies comparing IBD and non-IBD patients showed a significant correlation between VTE risk with IBD disease (OR=2.99, 95%CI: 1.45-6.18). Moderate heterogeneity was observed among these studies ($I^2=58.9\%$, $p_{heterogeneity}=0.119$, Figure 4).

Publication bias

Publication bias was analyzed using a funnel plot. The asymmetrical distribution suggested significant publication bias (Figure 5).

DISCUSSION

The present meta-analysis found that the VTE risk was significantly increased in children and young adults with IBD. A high incidence of VTE was observed in the different subtypes of IBD, including UC, CD, and other undefined IBD diseases. Moreover, multiple VTE signs related to PVT, DVT, TE, and CVC-related thrombosis might be prone to developing during the progression of pediatric and adolescent IBD.

This study suggested that children and young adult IBD patients were susceptible to VTE risk after treatment, despite a low overall incidence. The increased risk of VTE is specific to IBD. Other chronic inflammatory diseases, such as rheumatoid arthritis, or chronic bowel diseases, such as celiac disease, are not found to be accompanied by a high incidence of VTE^[26]. The association between the VTE risk and IBD has been demonstrated in various IBD patient populations. Currently, there is a lack of systemic reviews on VTE risk in pediatric and adolescent patients. Female pediatric IBD patients were found to be at a high risk of developing VTE^[28]. The meta-analysis by Kim *et al* focused on pregnant women with IBD^[42]. The findings showed a significantly higher

incidence of VTE during pregnancy and postpartum in female IBD patients. According to the VTE subtype, the risk of DVT increased significantly in pregnant women, whereas the increase of PE was not significant during pregnancy. In the subgroup analysis based on the location of IBD, patients with UC had significantly higher VTE risk during both pregnancy and the postpartum period, while CD patients exhibited increased VTE incidence only during pregnancy. Therefore, elevated VTE risk was found to be more apparent in UC patients than CD patients. A recent study showed a high postsurgical VTE risk in patients with UC but not in those with CD^[43]. Similar results were published earlier^[44,45]. Still, those studies were performed in the postsurgical setting, which is a state known to be associated with an increased risk of VTE^[46,47]. Similarly, the current study showed a higher risk of VTE in UC compared to CD in children and young adult IBD patients and consistently suggested that children with UC might be more susceptible to VTE. The exact causes for this higher VTE risk in UC than CD are unknown, but severe UC is associated with anemia and reactive thrombocytosis, which is conducive to VTE^[48,49].

Another meta-analysis by Yuhara *et al* demonstrated that adult patients with IBD (>20-years-old) were at increased risk for both DVT and PE^[50]. The study also showed that confounding factors, such as smoking and body mass index (BMI), did not affect the correlation between IBD and DVT/PE. A large-population database study by Nylund *et al* found that hospitalized children and adolescents with IBD had a high incidence of TE, including DVT and PE. In addition, the study identified older age and abdominal surgery as risk factors for TE in children and young adults with IBD. The Hispanics had a low risk of TE among all children and adolescents. Although tobacco use was a risk factor for TE in adults, it was a protective factor in children with IBD. Interestingly, an increasing trend of TE was observed through the years among children and young adults with IBD, which might be associated with increased hospital admission rates. Still, this increasing trend was not clear after multivariable regression analysis. Similarly, the review by Lazzerini *et al* suggested an increased risk of TE in pediatric IBD patients compared to the general population^[51]. Our meta-analysis

included several updated publications and showed that the risk of PVT, DVT, TE, and CVC-related thrombosis was increased in IBD child and adolescent patients. Moreover, the underlying mechanism of location-related VTE occurrence and development needs further exploration.

Nevertheless, the present study has several limitations. First, moderate heterogeneity was detected in the overall analysis of the correlation between VTE and IBD. On the other hand, low or no heterogeneity was detected after stratifying the studies by subtypes of VTE and IBD. Patients' characteristics, diagnosis of VTE, and intervention therapies might contribute to the variations across the studies and the magnitude of association. Second, certain subgroup analyses only involved a small number of studies and patients, and hence, the findings should be interpreted with caution. Third, the included large-size database review study incorporated registry data of medical records with different populations and settings, which might generate a high selection bias. Fourth, VTE was challenging to diagnose, which might have led to the misclassification of VTE.

CONCLUSION

Pediatric and adolescent IBD patients have an increased VTE risk. UC and CD patients exhibited a high risk of VTE. The risk of VTE subtypes was increased in IBD patients.

ARTICLE HIGHLIGHTS

Research background

A two- to three-fold increased risk of venous thrombotic events (VTE) has been demonstrated in patients with inflammatory bowel disease (IBD) compared to the general population, but less is known about the risk of VTE in child- and pediatric-onset IBD. In recent years, several studies have reported the rising incidence rate of VTE in juvenile patients with IBD, and the related risk factors have been explored.

Research motivation

To evaluate the risk of VTE in children and adolescents with IBD.

Research objectives

To evaluate the risk of VTE in children and adolescents with IBD.

Research methods

Articles published up to April 2021 were retrieved from PubMed, Embase, Cochrane Library, Web of Science, SinoMed, CNKI, and WANFANG. Data from observational studies and clinical work were extracted. The outcome was the occurrence of VTE according to the type of IBD. The available odds ratio (OR) and the corresponding 95%CI were extracted to compare the outcomes. Effect size (P), odds ratio (OR), and 95% confidence interval (CI) were used to assess the association between VTE risk and IBD disease. Subgroup analyses stratified by subtypes of VTE and IBD were performed.

Research results

Twelve studies (7,450,272 IBD patients) were included in the meta-analysis. Child and adolescent IBD patients showed increased VTE risk ($P = 0.02$, 95%CI: 0.01-0.03). Subgroup analyses stratified by IBD (ulcerative colitis (UC): $P = 0.05$, 95%CI: 0.03-0.06; Crohn's disease (CD): $P = 0.02$, 95%CI: 0.00-0.04) and VTE subtypes (portal vein thrombosis (PVT): $P = 0.04$, 95%CI: 0.02-0.06; deep vein thrombosis (DVT): $P = 0.03$, 95%CI: 0.01-0.05; central venous catheter (CVC)-related thrombosis: $P = 0.23$, 95%CI: 0.00-0.46; thromboembolic events (TE): $P = 0.02$, 95%CI: 0.01-0.03) revealed significant correlation between VTE risk and IBD. Patients with IBD were more susceptible to VTE risk than those without IBD (OR=2.99, 95%CI: 1.45-6.18). The funnel plot was asymmetric, suggesting the presence of significant publication bias.

Research conclusions

Pediatric and adolescent IBD patients have an increased VTE risk. UC and CD patients exhibited a high risk of VTE. The risk of VTE subtypes was increased in IBD patients.

Research perspectives

Pediatric and adolescent IBD patients have an increased VTE risk. UC and CD patients exhibited a high risk of VTE. The risk of VTE subtypes was increased in IBD patients.

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