Arterial Stiffness in Inflammatory Bowel Disease: An Updated Systematic Review and Meta-Analysis

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Cite this article as: Lu Q, Shi R, Mao T, *et al*. Arterial stiffness in inflammatory bowel disease: An updated systematic review and meta-analysis. *Turk J Gastroenterol*. 2021; 32(5): 422-430.

ABSTRACT

Background: *This systematic review and meta-analysis were carried out on well-conducted and adequately powered studies to explore whether arterial stiffness was associated with inflammatory bowel disease (IBD).*

Methods: *The search for potential literature was conducted on PubMed, MEDLINE, Cochrane Library, and Embase from inception to February 15, 2020. The studies assessing arterial stiffness in IBD were reviewed and included.*

Results: *Conclusively, 17 eligible trials with a total of 2188 participants were in compliance with the inclusion criteria. Of the included 2188 participants, the cases for ulcerative colitis (UC) and Crohn's disease (CD) were 558 and 693, respectively. Altogether 10 studies were conducted to evaluate the carotid-femoral pulse wave velocity (CPWV) in overall IBD patients, which was significantly increased with the mean difference (MD) and 95% CI as 0.70 (0.48-0.92, P < .01). The pooled results for CPWV in patients with CD and UC were also faster than that of control groups with MD and 95% CI as 1.09 (0.45-1.72) and 0.57 (0.57-1.24), respectively. The CPWV in CD and UC groups was comparable with a MD of 0.07 (P = .74, 95% CI: −0.32 to 0.45).*

Conclusion: *Arterial stiffness had associations with the overall IBD, UC, and CD with a similar strength of association between UC and CD.*

Keywords: *Arterial stiffness, inflammatory bowel disease, Crohn's disease, ulcerative colitis, meta-analysis*

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), also known as inflammatory bowel disease (IBD), can directly diminish vital functions through their systemic inflammatory activity.[1] UC and CD, characterized as remission and exacerbation, represent the 2 major chronic courses regularly. However, the pathogenesis for IBD has not been fully illustrated.[2,3] Supported by extensive studies on C-reactive protein (CRP), systemic inflammation is an independent risk factor for cardiovascular diseases (CVD). Although IBD was generally featured as chronic systemic inflammation, the association between IBD and CVD risk remained uncertain. The strong association between carotid intima-media thickness and CVD risk was reported in a previous study; however, the causality for IBD cases has not been elucidated.[4] Increased arterial stiffness is reported as an independent CVD predictor by causing the pathological symptoms of vascular damage.[5] A recent study addressing the association between IBD and arterial stiffness enhanced the hypothesis of systemic inflammation, possibly playing a role in the pathogenesis of arterial stiffness, which is widely recognized as a crucial intermediate process of CVD.[6] In recent years, an arterial elastic property is increasingly used for stratifying the CVD risk.[7,8] Therefore, IBD might have an association with future cardiovascular events.

A systematic review and meta-analysis pooling results from 9 studies and focusing on the association between arterial stiffness and IBD suggested that carotid-femoral pulse wave velocity (CPWV) showed an increasing tendency among ulcerative UC and CD.[9] However, various studies[10-12] provided new evidence and suggested indeterminate strength of arterial stiffness and IBD. This systematic review and meta-analysis on well-conducted and adequately powered studies were carried out to explore the association of arterial stiffness with IBD.

METHODS

We conducted the study strictly following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (PRISMA) statement.[13] Two reviewers

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Received: **May 4, 2020** Accepted: **October 9, 2020** Available Online Date: **June 25, 2021**

DOI: **10.5152/tjg.2021.20293**

(2 authors) independently involved the targeted studies, extracted the data, and finished the quality assessment.

Literature Search

The search for the literature focusing on the association between arterial stiffness and IBD search was performed in PubMed, Medline, Cochrane Library, and Embase up to January 20, 2020. The individual and joint keywords "arterial stiffness", "pulse wave velocity", "inflammatory bowel disease", "Crohn's disease", and "ulcerative colitis" were used for the literature search.

Eligibility Criteria

The inclusion and exclusion criteria for potential studies were formulated by the investigative team. Studies fulfilling the following criteria were included: (1) studies investigating the association between arterial stiffness and IBD; (2) arterial stiffness was measured with well-validated devices or techniques; (3) studies provided either the necessary data or they can be calculated indirectly; (4) the full text of the studies were published in English; and (5) if the study population was reported in duplicate, the one providing more detailed data or recently published was included.

Non-original studies (reviews etc.), case reports or short reports, non-human, non-English studies, and those not available for extracting data were excluded from the analysis.

Data Extraction

All potential studies searched from the databases mentioned above were reviewed independently by the 2 investigators (authors). Similarly, all the information was extracted independently using a standardized form. During the reviewing and extracting process, all inconsistent information was discussed, and a consensus was reached by the 2 reviewers. For studies meeting the inclusion criteria, the following data for each study were extracted: the authors, year for publishing, study design, the sample size of each research group, the mean age of the patients, sex ratio, characteristics of IBD, measurement, and device for arterial stiffness, results, and characteristics of arterial stiffness in different groups.

Pulse Wave Velocity Measurement

CPWV technique was employed to measure arterial stiffness and was defined as the speed at which the pressure wave generated by cardiac ejection was propagated along the arterial tree. CPWV was assessed by dividing the traveled distance (meters) by the time delay (seconds) between the arrival of the pulse wave at the common carotid artery and the common femoral artery.

Quality of Studies Assessment

The quality assessment for each included study was performed using the Newcastle–Ottawa Scale (NOS)[14] with an independent process and crosschecked by the 2 investigators. The methodological quality assessment for targeted studies was evaluated by the selection of the participants, comparability of the 2 research groups, and exposure of the factors. Each study was assessed for the following items: whether the patients were defined adequately, whether the study population could represent the target cases, how the study control was selected and defined if the cases and controls were comparable, exposure verifying, whether the cases and controls were ascertained by the same method, and nonresponse rate for each group.

The items for selection and exposure categories were awarded one star, and the comparability was awarded a maximum of 2 stars for the included studies. Therefore, for the current study, the NOSs for each study ranged from 2 to 9 stars. A scale of zero to 2 stars was defined as poor quality, 3 to 5 stars as fair quality, and more than 6 stars as high quality.

Statistical Analysis

Mean difference (MD) versus controls and 95% CIs of related variables were used to assess the associations between the control and patient groups.

The results of the included studies were pooled by inverse variance methods with random-effects. The I^2 statistic was used to assess heterogeneity. Heterogeneity was categorized into low, moderate, and high according to the values of I^2 by 25%, 50%, and 75%,[15] respectively. For the process with a higher heterogeneity, all the enrolled studies were sequentially excluded demonstrating the overall impact of individual study where $I^2 > 75\%$. Begg rank correlation[16] and Egger weighted regression methods[17] were used to assess the publication bias. Review Manager (5.3 version, The Cochrane Collaboration, Oxford, UK) was used for the pooling process. The Begg and Egger tests were assessed by STATA 15.0 (Stata Corporation, College Station, TX, USA). Significant for analysis was defined as a P value less than .05.

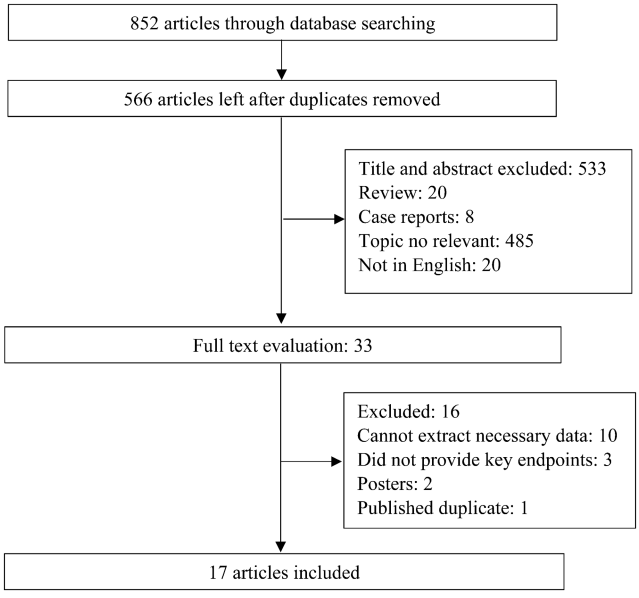

Figure 1. Flow chart of the study selection.

RESULTS

Study Selection

Altogether, 852 studies were found through the electronic database searches, and 286 were removed due to duplication. 533 studies were excluded by browsing titles or abstracts according to the eligibility criteria. Finally, 17 articles[10-12,18-31] were included for data extraction and meta-analysis after browsing 33 full-length manuscripts. The flow chart for the targeted study selection for the current meta-analysis is presented in Figure 1.

Study Characteristics

In total, 17 studies with 2188 participants were included. Of these, 558 were diagnosed as UC, and 693 as CD. A more detailed study and study population characteristics are presented in Supplementary Table 1 and Table 1. The included studies were published between 2012 and 2019. The sample size for each study was 25 and 334. There were 6 studies conducted in Turkey,[19,21,25,28] 4 in Italy,[11,12,23,30] 3 in Greece,[20,24,29] with one each in France,[18] Australia,[22] Switzerland,[31] and Croatia.[10]

Assessment of Study Quality

The study quality assessment following NOS is presented in Supplementary Table 2. All the 17 studies were assessed as high quality with 8 assessed as 6 stars and the other 9 as 7 stars.

Carotid-Femoral Pulse Wave Velocity (CPWV) in Overall Inflammatory Bowel Disease Patients

A total of 10 studies were conducted to evaluate the CPWV in overall IBD patients. There were 607 patients with IBD and 529 controls included in the analysis. Moderate heterogeneity among groups (I^2 = 53%) was observed for pooled analysis with MD and 95% CI as 0.70 (0.48-0.92), suggesting the CPWV in IBD cases to be higher than the control group. The detailed data are presented in Figure 2.

CPWV in Patients With UC

Of the 17 studies, 10 provided the data on UC and included 363 patients in the group and 566 in the control group. The mean difference (MD) of CPWV in the UC and control group in each study ranged from –0.10 to 1.77, and according to the pooled result, the UC group had a faster velocity with a MD of 0.91 (P < .01, 95% CI: 0.57-1.24) with a moderate heterogeneity (I^2 = 72%). The data are presented in Figure 3.

CPWV in Patients With CD

Altogether 9 studies provided the data on CD patients with CPWV, and the pooled data are presented in Figure 4. The MD of the summarized result was 1.09 (P < .01, 95% CI: 0.45-1.72) with a higher heterogeneity (I^2 = 91%).

Comparison of CPWV in Patients With UC and CD

The pooled result on comparison of CPWV in cases with UC and CD is presented in Figure 5, and the results revealed that the CPWV in UC and CD cases was comparable with MD and 95% CI as 0.07 (P = .74, –0.32 to 0.45).

Heterogeneity Analyses

To explore the sources of the exciting heterogeneity for results on CPWV in patients with CD, a sensitivity analysis was performed. After excluding the study conducted by Aytac et al.,[27] the heterogeneity decreased to an acceptable level (I^2 = 42%) (Supplementary Figure 1).

Publication Bias

The publication bias assessed by the Begg rank correlation analysis and Egger weighted regression analysis indicated no publication bias (P > .05). The detailed P values for each analysis can be found in Supplementary Table 3.

DISCUSSION

In our current meta-analysis, the correlation between arterial stiffness and IBD was explored, where 17 studies

Table 1. Characteristics of the Included Studies

Study Included	Cases		Controls	Active Diseases (%)	Anti-TNFα Therapy (%)	BMI (mean ± SD, kg/m²)		SBP/DBP (mean ± SD mmHg)		Carotid-femoral pulse wave velocity (mean ± SD, m/s)			
	CD	UC				IBD	Controls	IBD	Controls	CD	UC	All	Controls
Zanoli et al., 2012	16	16	32	12	13	23.5 ± 3.6	24.3 ± 2.8	115 ± 10/66 ± 10	113 ± 11/68 ± 8	6.5 ± 1.5	6.8 ± 1.3	6.6 ± 1.4	6.0 ±0.8
Akdogan et al., 2013	0	37	30	100	5	27.0 ± 4.4	27.5 ± 4.1	NA	NA	NA	8.9 ±2.9	8.9 ± 2.9	7.2 ± 1.7
Theocharidou et al., 2013	43	23	44	26	44	23.7 (16.5-37.2) [a]	24.3 (18.3-34.2) [a]	86 (62-107) [a]	86 (41-113) [a]	6.8 ± 1.3	6.3 ± 1.1	6.6 ± 1.3	6.1 ± 0.9
Fan et al., 201437	25	17	73	NA	14	26.9 ± 6.1	25.6 ± 3.8	125 ± 17/74 ± 10	118 ± 14/67 ± 10	NA	NA	13.8 ±2.6	13.5 ± 2.6
Zanoli et al., 2014	34	40	80	28	19	24.2 ± 4.8	24.7 ± 4.3	118 ± 12/70 ± 11	115 ± 12/70 ± 9	8.0 ± 1.6	7.8 ± 1.7	7.9 ± 1.7	7.0 ± 1.1
Alkan et al., 2014	17	23	40	0	0	23.7 ± 1.9	23.7 ± 1.6	118 ± 10/74 ± 8	117 ±10/71 ±7	7.2 ± 0.7	7.1 ± 0.8	7.2 ± 0.9	6.0 ± 0.5
Korkmaz et al., 2014a	18	84	74	100	≤5	25.3 ± 3.5	26.8 ± 3.1	107 ± 6/75 ± 7	104 ±10/72 ±9	NA	NA	6.6 ± 1.0	6.0 ± 1.3
Korkmaz et al., 2014b	18	84	74	0	≤3	26.6 ± 2.6	26.8 ± 3.1	105 ± 9/74 ± 8	104 ± 10/72 ± 9	NA	NA	6.4 ± 1.3	6.0 ± 1.3
Aytac et al., 2015	25	30	25	0	NA	24.0 [b]	25.4 ± 1.9	121[b]/75[b]	108 ±10/59 ± 7	9.6 ± 1.4	9.3 ± 1.3	NA	7.6 ±0.3
Ozturk et al., 2015	52	74	68	38	5	23.7 [b]	23.6 ± 2.8	119[b]/72[b]	117 ± 12/70 ± 8	8.2 ± 1.7	8.1 ± 1.6	NA	6.9 ±1.0
Aslan et al., 2016	16	56	50	NA	NA	27.6 ± 4.5	27.0 ± 3.5	121 ± 12/75 ± 9	118 ± 11/74 ± 8	8.0 ± 1.3	8.0 ± 1.5	8.0 ±1.4	10.6 ±2.3
Theocharidou et al., 2016	29	15	44	28	20	23.7 (16.5-37.4) [a]	24.3 (18-36.3) [a]	86 ±12	87.2 ± 121	7.6 ± 1.2	6.3 ± 1.2	6.8 ±1.2	6.4 ±0.9
Cappello et al., 2017	45	23	38	28	NA	22.5 ± 3.8	23.9 ± 4.4	NA	NA	8.6 ± 1.3	9.1 ± 1.4	8.7 ± 1.3	8.0 ± 1.2
Lurz et al., 2017	10	15	NA	75	48	18.4 (17.2-19.7) [a]	NA	NA	NA	4.2 (3.5-4.8) [a]	4.6 (4.0-5.2) [a]	4.4 (4.0-5.2) [a]	NA
Prijić et al., 2018	60	29	73	14	NA	NA	NA	124 ± 17/73 ± 8	NA	7.6 ± 1.6	8.0 ± 1.9	7.7 ± 1.8	NA
Zanoli et al., 2018	45	45	45	NA	NA	CD: 24.0 (19.0-30.0) [a] UC: 25.0 (21.0-35.0) [a]	26.0 (20.0-36.0) [a]	NA	NA	8.6 (6.9-10.5) [a]	8.5 (5.9-10.2) [a]	NA	7.5 (5.6-9.3) [a]
Zanoli et al., 2019	85	82	167	CD: 33 UC: 28	CD: 8 UC: 27	CD: 24.0 ± 4.0 UC: 24.0 ± 0.5	Controls: 25.0 ± 5.0	CD: 120 ± 14/73 ± 12 UC: 117 ± 20/72 ± 10	118 ± 13/71 ± 11	7.9 ± 2.0	7.8 ± 2.0	NA	7.1 ± 1.4

SD, strand deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; NA, not available.

[a]Means and range.

[b]Means.

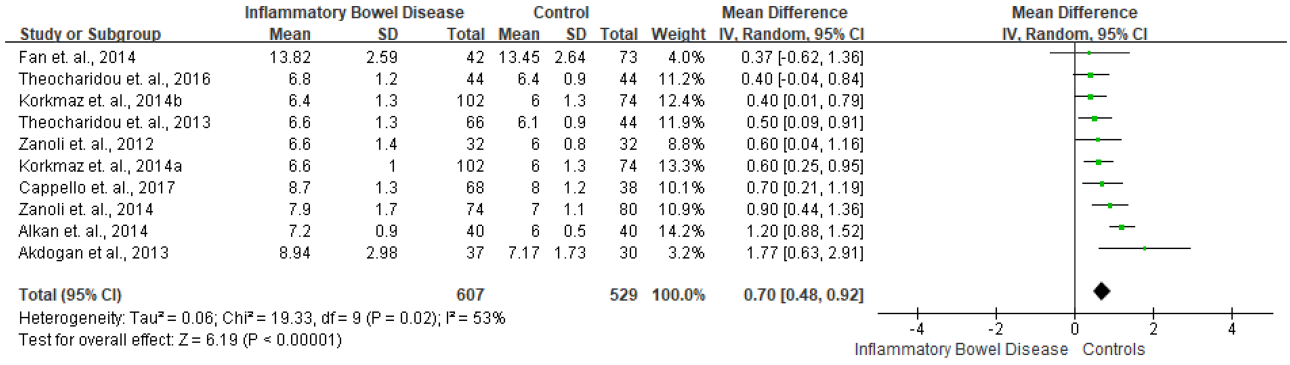

Figure 2. Summarized carotid-femoral pulse wave velocity in the overall inflammatory bowel disease patients.

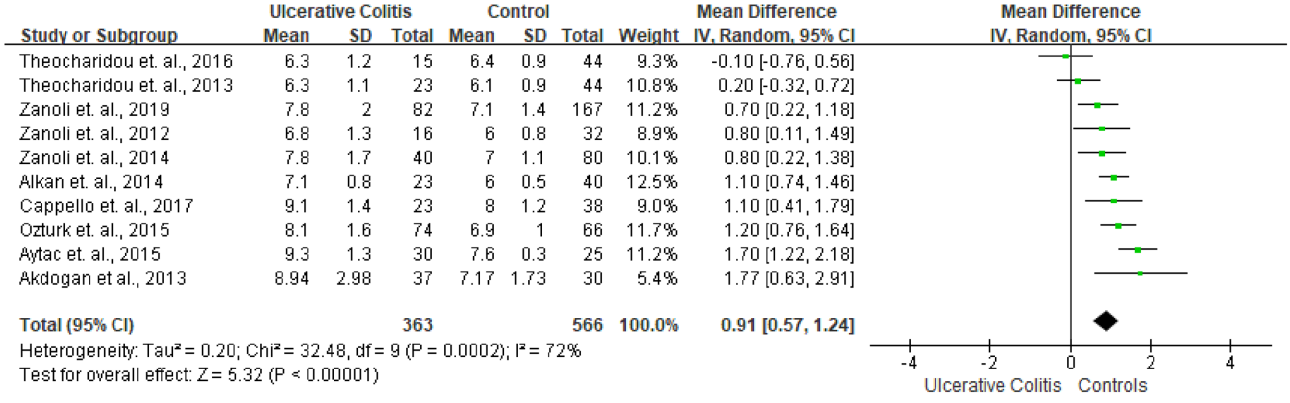

Figure 3. Summarized carotid-femoral pulse wave velocity in patients with ulcerative colitis.

with 558 UC patients, and 693 CD patients were included and summarized. A total of 10 studies were conducted to evaluate the CPWV in overall IBD patients, and the pooled result revealed an association of IBD with arterial stiffness. Similarly, the pooled result indicated the association of both UC and CD with arterial stiffness. Moreover, the strength of the association of arterial stiffness between UC and CD was comparable.

CPWV, the speed at which the pressure wave generated by cardiac ejection is propagated along the arterial tree, was deemed as the gold standard for arterial stiffness assessments. The most recent previous meta-analyses,[9] including 234 CD and 342 UC patients, concluded an increase in CPWV in both UC and CD patients. In our current meta-analysis with the enlarged sample of 558 UC and 693 CD patients, similar results of increased

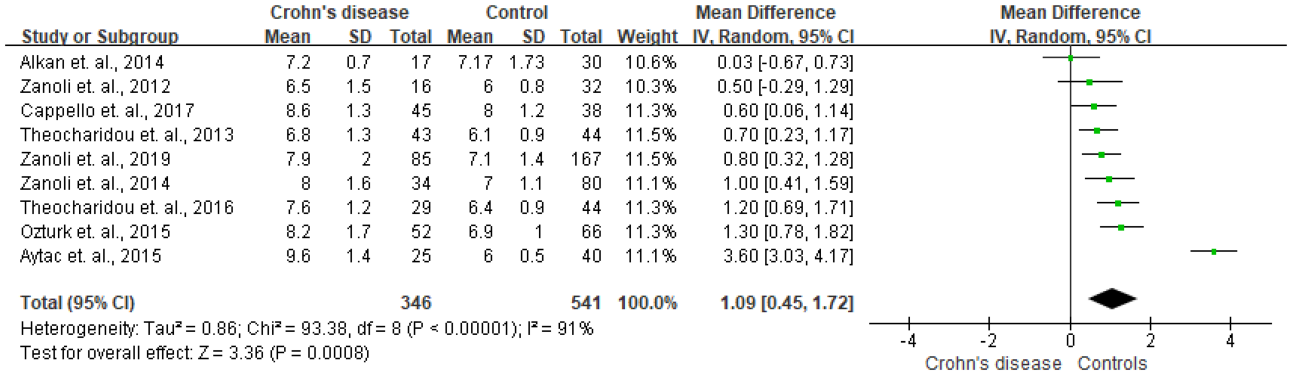

Figure 4. Summarized carotid-femoral pulse wave velocity in patients with Crohn's disease.

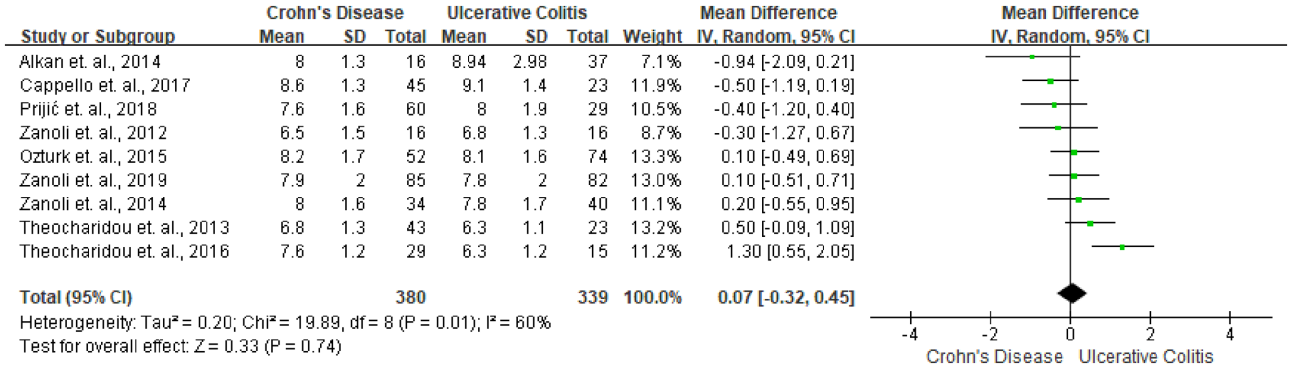

Figure 5. Summarized comparison of carotid-femoral pulse wave velocity in patients with ulcerative colitis and Crohn's disease.

CPWV in both CD and UC patients were observed. Similar results were reported in hypertensive patients and chronic inflammatory disorders by various studies.[32,33] Another measure of wave reflection, augmentation index, was observed to be significantly increased in patients with IBD in another meta-analysis.[34] The findings from our study and previous meta-analysis might explain the reason for IBD cases obtaining higher cardiovascular risk despite the low prevalence of traditional CVD risk factors. IBD was also deemed as a thrombotic state. Therefore, IBD cases with increased stiffness might obtain a higher incidence of thrombotic complications, and a 2- to 3-fold increased risk was reported for IBD patients compared to the general population.[35,36] However, further pooling of the results on thromboembolic complications could not be done due to the limited number of included studies.

The patients with chronic inflammatory disorders and comorbidity as arterial stiffness might have a strong association with the disease duration of atherosclerosis.[20] The frequent clinical feature for inflammatory diseases was the early stage of atherosclerosis. A long-term intervention experiment reported immunomodulatory therapy effectively decreasing the aortic stiffening in IBD.[23] Another study published by Angel et al.[37]reported long-term anti-TNF-α therapy improved aortic stiffness and carotid intima-media thickness progression in patients with IBD. In the current study, the majority of the studies included cases treated with anti-TNF-α therapy. A meta-analysis evaluating anti-TNF use reported medications influencing disease activity and CVD in patients with IBD.[38] A study focusing on this topic found improvement with long-term anti-TNF therapy suggesting a reduction of inflammation leading to improvement in endothelial dysfunction.[12] However, in our current study, none of the studies provided specific data on patients treated with anti-TNF-α therapy.

Traditional risk factors for CVD are age family, history of coronary artery disease (CAD), obesity, hypertension, diabetes, tobacco and alcohol use, and chronic kidney disease.[39] However, IBD cases tend to obtain lower body mass iindex and no significant lipid abnormality.[40] Multiple studies reported more occurrence of CVD in women and younger patients with IBD as compared to the general population.[41] However, the association of CVD with IBD is disputable.[32,33,42-50] A meta-analysis reported that IBD might not increase the risk of CVD and relevant mortalities[51]. In 2018, another updated meta-analysis[52] included 27 articles and reported a positive association between IBD and a higher risk of CVD incidence, particularly in females. In 2016, the European guidelines on CVD prevention in clinical practice systematically identified CVD-related risk factors and the evidence-based prevention strategies based on the general population level to reduce the prevalence of CVD .[53] IBD was not a well-identified risk factor in the guidelines. However, all the conclusions from the studies support the hypothesis that a well-organized anti-inflammatory intervention on IBD cases aiming to prevent atherosclerosis could be effective, and more studies are needed in the future to further enhance the association of IBD and CVD. Moreover, previous studies reported a lower prevalence of traditional cardiovascular risk factors among IBD cases compared with the general population, including diabetes (6.18%), obesity (15.45%), and hypertension (20.51%).[40] Additionally, in this long-term case-cohort study, these risk factors had a lower impact on CAD development in the IBD group.

For hypertensive patients and chronic inflammatory disorders, arterial stiffening could be an independent factor for the presence of atherosclerosis and has an association with the disease duration.[44] Several studies have revealed strong correlations between the severity

of arterial stiffness and homocysteine, together with the inflammatory markers, such as the white blood cell count, neutrophil/lymphocyte ratio, adhesion molecules, fibrinogen, CRP, cytokines, microRNAs, and cyclooxygenase-2, in patients with a broad variety of diseases, including IBD.[54,55] However, limited by the number of the included sample size and the information from the included studies, the relationship between disease duration and the presence of atherosclerosis in IBD patients could not be further analyzed. In 2016, the first European Crohn's and Colitis Organization (ECCO) consensus guideline addressing extra-intestinal manifestations in IBD was published,[56] which established the European consensus guidelines for the treatment of IBD. ECCO summarized the current evidence on the medical management of patients and aimed to guide the clinicians' decisions with the best evidence available. The risk factors summarized by previous studies, along with IBD treatment guidelines, would significantly improve the outcome of such cases.

When interpreting the conclusions from the current study, the limitations should be considered. First, most included studies had a limited sample size. Therefore, limited by a smaller number of participants of each study, more subgroups analyses cannot be conducted, which could be an obstacle for interpreting the results. Second, a majority of the included studies did not match the objects by age, sex, and severity of the cases. Therefore, the mean age and the sex ratio of each included study largely varied, causing heterogeneity and reducing the comparability between the patient and control group. Third, the measures for testing CPWV in each included study were complex, causing heterogeneity of the results. Fourth, potential language bias might exist as only the studies published in English were included.

CONCLUSION

Our current study systemically assessed the association of arterial stiffness and IBD and demonstrated the association of arterial stiffness with the overall IBD, UC, and CD. The strength of the association of arterial stiffness between UC and CD was similar. In the future, outcomes of increased stiffness (cardiovascular or cerebrovascular manifestations) could justify screening for arterial stiffness in IBD patients. To strengthen the results and conclusions in the current study, larger sized studies matched for age, sex, and severity of the patients are required to address the issue.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer Review: Externally peer-reviewed.

Author Contributions: Design – Q.Q.L., R.S.; Writing Manuscript – Q.Q.L., R.S.; Data Collection – T.Y.M, Z.B.W.; Data Analysis – T.Y.M, Z.B.W.; Literature Search – Z.M.S., X.T., Y.W.; Edit – J.X.L.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This research was supported by the National Natural Science Foundation of China No. 81874386. Stat-notch signaling pathway was used to study the regulation mechanism of qingchang wen on the polarization balance of M1/M2 type macrophages in ulcerative colitis rats.

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Supplementary Table 1. Study participants' characteristics of the included studies

Study included	Country	Gender (% of males)	Age (mean±SD, years)	Disease duration (mean±SD, years)	Measurement	Device
Zanoli et al., 2012	France	IBD: 59 Controls: 59	CD: 29.0±9.0 UC: 31.0±8.0 Controls: 31.0±7.0	63.0±61.0[b]	Subtracted	SphygmoCor system
Akdogan et al., 2013	Turkey	IBD: 57 Controls: 30	IBD: 48.0±15.0 Controls: 45.0±8.0	NA	Subtracted	SphygmoCor system
Theocharidou et al., 2013	Greece	NA	NA	NA	Direct	SphygmoCor system
Fan et al., 2014	Australia	IBD: 45 Controls: 46	IBD: 50.0±10.0 Controls: 51.0±10.0	11.5±10.7	Direct	Colin VP-1000 Plus
Zanoli et al., 2014	Italy	NA	UC: 38.0±14.0 CD: 36.0±14.0 Controls: 38.0±13.0	UC: 5.9±5.6 CD: 7.0±6.2	Direct×0.8	SphygmoCor system
Theocharidou et al., 2014	Greece	IBD: 50 Controls: 50	IBD:36.1±10.3 Controls: 37.2 ±10.7	8.4±7.2	Direct	SphygmoCor system
Alkan et al., 2014	Turkey	IBD: 55 Controls: 55	IBD: 38.4±6.5 Controls: 38.25±6.4	52.2±48.7[b]	Subtracted	SphygmoCor system
Korkmaz et al., 2014	Turkey	IIBD: 65.6 AIBD: 63.1 Controls: 62.1	IIBD: 43.0±13.1 AIBD: 45.4±9.9 Controls: 44.6±11.3	IIBD: 42.0 (13.8–72.0)[a,b] AIBD: 48.0 (3.0–96.0)[a,b]	Direct	Mobil-O-Graph
Aytac et al., 2015	Turkey	NA	UC: 44.7±11.5 CD: 38.9±10.1 Controls:42.1±6.6	NA	Direct	Complior
Ozturk et al., 2015	Turkey	UC: 73 CD: 82.7 Controls: 68.2	UC: 32.9±8.4 CD: 29.9±8.9 Controls: 30.9±7.0	UC: 4.1±3.9 CD: 4.2±3.5	Subtracted	Tensomed
Aslan et al., 2016	Turkey	IBD: 46/26 Controls: 29/21	IBD: 41.6±11.7 Controls: 39.9±7.9	68.2±18.7[b]	Subtracted	Vingmed System 7
Theocharidou et al., 2016	Greece	IBD: 50 Controls: 50	IBD: 36.1±10.3 Controls: 37.2±10.7	8.4±7.2	Subtracted	SphygmoCor
Cappello et al., 2017	Italy	IBD: 35 Controls: 18	IBD: 31.6±8.1 Controls: 30.4±6.3	5.0±4.3	Subtracted	SphygmoCor
Lurz et al., 2017	Switzerland	UC: 50 CD: 60	UC: 10.3(7.9–11.8)[a] CD: 14.4(11.7–16.4)[a]	2.8	Direct×0.8	Vicorder™ device
Prijić et al., 2018	Croatia	IBD: 58.4 Controls: 56.1	IBD: 20.0-64.0 Controls: 20.0-69.0	122.0±10.2[b]	Subtracted	Medexpert
Zanoli et al., 2018	Italy	NA	NA	NA	Subtracted	SphygmoCor
Zanoli et al., 2019	Italy	UC: 55 CD: 61 Controls: 57	UC: 37.0±11.0 CD: 39.0±13.0 Controls: 38.0±12.0	NA	Direct×0.8	SphygmoCor

Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; IIBD, inactive inflammatory bowel disease; AIBD, active inflammatory bowel disease; IBD, inflammatory bowel disease; PWV, pulse wave velocity; SD, strand deviation; NA, not available.

[a], means and range.

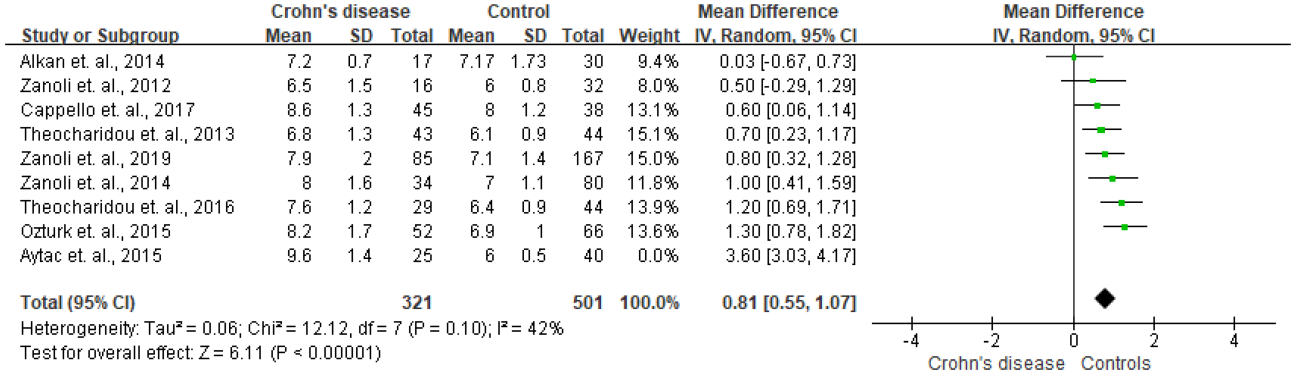
[b], per month.

Supplementary Table 2. Quality assessment of included studies by Newcastle-Ottawa Scale

Study included	Overall quality score
Zanoli et al., 2012	6
Akdogan et al., 2013	6
Theocharidou et al., 2013	7
Fan et al., 2014	7
Zanoli et al., 2014	7
Theocharidou et al., 2014	7
Alkan et al., 2014	7
Korkmaz et al., 2014	7
Aytac et al., 2015	6
Ozturk et al., 2015	7
Aslan et al., 2016	6
Theocharidou et al., 2016	7
Cappello et al., 2017	6
Lurz et al., 2017	7
Prijić et al., 2018	6
Zanoli et al., 2018	6
Zanoli et al., 2019	6

Supplementary Table 3. Publication bias of summarized outcomes

Outcomes	Begg (*P* value)	Egger (*P* value)
Summarized carotid-femoral pulse wave velocity in overall inflammatory bowel disease patients	.60	.51
Summarized carotid-femoral pulse wave velocity in patients with ulcerative colitis	.29	.14
Summarized carotid-femoral pulse wave velocity in patients with Crohn's disease.	.84	.70
Summarized comparation of carotid-femoral pulse wave velocity in patients with ulcerative colitis and Crohn's disease.	.54	.47
Heterogeneity analyses on carotid-femoral pulse wave velocity in patients with Crohn's disease.	.62	.48



Supplementary Figure 1. Heterogeneity analyses of carotid-femoral pulse wave velocity in patients with Crohn's disease.