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Chinese research into severe ulcerative colitis has increased in quantity and complexity

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Abstract

AIM

To investigate the current state of research output from Chinese studies into severe ulcerative colitis (SUC) using a bibliometric analysis of publications.

METHODS

The contents of the Chinese periodical databases WANFANG, VIP, and China National Knowledge Infrastructure were searched for all papers regarding UC or SUC published in last the 15 years (from 2001 to 2015). The number of publications in each year was recorded to assess the temporal trends of research output. All SUC related publications were downloaded and the complexity of this research was evaluated with methods described previously. The number of patients with SUC reported each year was recorded and their clinical characteristics were analyzed using information available in the relevant papers.

RESULTS

There were 13499 publications regarding UC published in Chinese medical journals between 2001 and 2015, of which 201 focused on SUC. The number of publications increased rapidly with more than half of all papers being published in the most recent 5-year period. There was a significant increase in analytical

studies and clinical trials over the study period ($P < 0.01$), with research into the management of SUC, included pharmacotherapy, nutrition support as well as surgery, predominating. Almost half (46.2%) of the observational analytical studies and clinical trials focused on Traditional Chinese Medicine, with little research on the efficacy of cyclosporin and infliximab in disease management. About 6222 patients with SUC were reported in the 201 SUC relevant papers, with a ratio of male/female of 1.38. The number of patients reported in each 5-year period significantly increased. The colectomy rate and short-term mortality rate were 7.7% and 0.8% respectively. The most commonly employed operation was total proctocolectomy with ileal pouch-anal anastomosis.

CONCLUSION

The output and complexity of research related to SUC in China increased significantly over the previous 15 years, however few of these studies focused on salvage therapy.

Key words: Bibliometric analysis; Clinical trials; Salvage therapy; Complexity; Severe ulcerative colitis; Temporal trends; Traditional Chinese Medicine

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Core tip: Severe ulcerative colitis (SUC) is a potentially life-threatening condition. Our bibliometric analysis indicates that Chinese research into severe ulcerative colitis has increased in quantity and complexity over the previous 15 years. Research into the management of SUC, especially Traditional Chinese Medicine, predominates, with little research on salvage therapy. The number of SUC patients reported in Chinese publications also increased significantly, with male patients predominating in prevalence and a lower colectomy rate than western countries.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic inflammatory disease characterized by relapsing and remitting mucosal inflammation in the colon^[1]. About 15%-25% of all UC patients experience at least one severe exacerbation requiring hospitalization^[2]. Severe UC (SUC) is a potentially life-threatening condition which is defined as six or more bloody stools per day plus at least one of the following of Truelove and Witts' criteria: Fever

(temperature $> 37.8\text{ }^{\circ}\text{C}$); tachycardia (pulse rate $> 90\text{ bpm}$); anemia (hemoglobin $\leq 75\%$ of normal); and elevated erythrocyte sedimentation rate (ESR $> 30\text{ mm/h}$)^[2,3]. Intravenous corticosteroid remains the first-line therapy for SUC, having been reported to reduce the mortality rate from 24% to 7%^[4,5]. However, 30%-40% of patients have disease which is steroid-refractory, requiring more invasive treatment^[6,7]. The overall colectomy rate in SUC patients is higher than 30%, according to a cohort study^[8]. However, in cases that fail to respond to steroid therapy [stool frequency > 8 stools/d, or 3-8 stools/d together with a C-reactive protein (CRP) $> 45\text{ mg/L}$ on day 3], the colectomy rate is 85%^[9]. Salvage therapy with either infliximab or cyclosporin appears to improve clinical outcomes for cases of steroid therapy failure in randomized controlled trials^[10]. Patients who do not respond to intensive medical therapy or with severe complications including toxic megacolon, perforation and severe hemorrhage should be considered for timely surgery. Delayed surgery is associated with increased mortality and a higher risk of postoperative complications^[11,12]. Therefore it is of paramount importance to assess the response to therapy regularly, using standardized criteria, and to initiate optimal therapy options promptly. Above all, effective management of SUC remains a great challenge.

China and other Asian countries are experiencing an increasing incidence and prevalence of UC^[13]. A long-term follow-up study from Hong Kong reported a sixfold increase in the incidence of UC (from 0.3 per 100000 in 1986-1988 to 1.8 per 100000 in 2004-2006)^[14]. Wang *et al*^[15] analyzed 3100 UC patients hospitalized in 23 hospitals in mainland China from 1990-2003, and noted a steady increase in the number of cases. 21.7% of these patients (654/3100) were identified as severe. Bibliometric analyses and literature reviews of scholarly publications in Chinese periodical databases provide more epidemiological information. For example, a comprehensive search of the Chinese Biomedical Literature database retrieved 3384 articles relating to inflammatory bowel disease (IBD) published in Chinese medical journals between 1989 and 2013, in which 140114 cases of UC were reported with the number of reported cases steadily increasing annually^[16]. According to Jiang *et al*^[17], there were 1560 Chinese papers regarding UC published from 1981 to 2000 where 10218 patients with UC were reported. Given this dramatic increase in UC, further database surveys and publication analyses are required to collate the available information about the recent epidemiology and treatment efficacy of UC and SUC in China.

In addition to epidemiological information, bibliometric analyses provide a perspective of research hotspots. For example, according to Ouyang *et al*^[18], articles of basic research on IBD in China rapidly increased and predominantly focused on immunological mechanisms. Moreover, bibliometric analysis of indicators including publication output and research complexity is

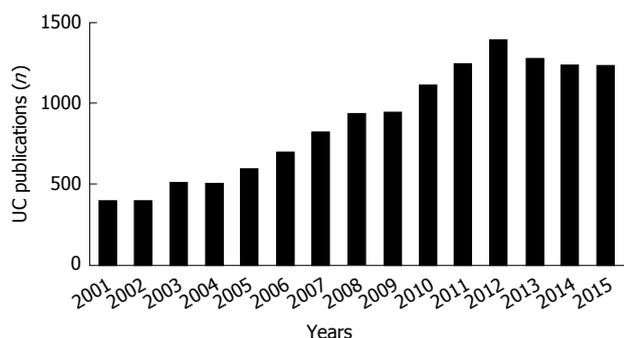


Figure 1 Number of Chinese publications regarding ulcerative colitis published in each year from 2001 to 2015. About 13499 ulcerative colitis related articles were published in Chinese medical journals from 2001 to 2015. The annual increase is statistically significant ($r = 0.94$, $P < 0.01$). Almost half of the overall papers (6447/13499) were published in the last 5 years (2011-2015). UC: Ulcerative colitis.

widely used to assess the performance of the research programs of institutions and/or countries^[19,20]. As mentioned above, China has witnessed an increasing incidence and prevalence of UC. Furthermore, China's population accounts for 20% of the total world population. A comprehensive study of the quantity and quality of SUC-related Chinese publications is desperately needed. This study aims to perform a bibliometric analysis to determine the temporal trends in the number of Chinese publications on UC and SUC between 2001 and 2015, and to assess the SUC research performance. This study also aims to provide a review of the data on treatment type and efficacy in SUC patients that has been reported in Chinese medical journals. In addition, such a study can more broadly provide insight into improving UC and SUC treatment worldwide.

MATERIALS AND METHODS

Database searching

We conducted searches of the Chinese periodical databases WANFANG, VIP, and China National Knowledge Infrastructure (CNKI) on August 1, 2016 using the search terms "ulcerative colitis" or "severe ulcerative colitis" in the Article Title or Keywords. Results were limited to those published in the years from 2001 to 2015. Publications from 2016 were excluded since only partial data was available for this year. The number of UC related publications in each year as defined by the WANFANG database was recorded, however only the SUC related publications were downloaded to obtain information about publication year, type, topic, study design, and sample size.

Literature review

All SUC publications were retrieved and reviewed. Publications were classified as original research articles, case reports and case series, reviews and others (conference papers, graduation theses and papers published in journals on nursing practice). The topic of each paper was recorded and only those that were

clinical in nature were included in the assessment of the complexity of SUC research. According to the methods described by Scott *et al.*^[20], the study design of clinical papers was grouped into one of three categories: Descriptive studies (case reports, cases series and cross sectional studies), observational analytical studies (case-control and cohort studies) and clinical trials. The proportion of the total within each group was compared in every 5-year period from 2001 to 2015. The characteristics of the patient treatment and disease activity reported in all SUC related publications were recorded in Excel for further analysis.

Statistical analysis

All statistical analyses were performed using SPSS Statistics 22.0. Spearman's rank correlation coefficient was calculated to study trends over time. The statistical significance of differences between proportions was compared with Chi-squared test. A P -value of < 0.05 was considered as statistically significant.

RESULTS

Temporal trends in UC and SUC publications

The defined search of the WANFANG database retrieved 13499 UC related papers that were published between 2001 and 2015. The annual number of publications was compared with a significant increase from 409 in 2001 to 1245 in 2015 ($r = 0.94$, $P < 0.01$), shown in Figure 1. Almost half of the overall papers (6447/13499) were published in the last 5 years (2011-2015).

To determine if the same temporal changes occurred in SUC publications, we repeated the search process in the WANFANG, VIP and CNKI databases with the search terms "severe ulcerative colitis" in the Article Title or Keywords. About 510 papers were retrieved from these three databases when the publication year was limited to the most recent 15 years (2001-2015). Removal of duplicates resulted in 201 individual papers on SUC during this time (shown in Figure 2). A fivefold increase was observed in the number of papers (from 6 in 2001 to 31 in 2015, $r = 0.86$, $P < 0.01$), more than half of all papers (112/201) were published in the last 5 years (2011-2015), shown in Figure 3.

Complexity of SUC research in China

The 201 publications in Chinese journals on SUC comprised 96 original research articles (47.8%), 29 case reports and case series (14.4%), 18 reviews (9%), 25 conference papers, 7 graduation thesis and 26 papers that were published in journals of nursing. Of the 96 original articles, 65 (67.8%) have reported the adopted diagnostic criteria for SUC, which are diagnostic criteria in "Consensus on the Diagnosis and Management of Inflammatory Bowel Disease" that were developed and revised by Chinese Society Of Gastroenterology in 1978, 1993, 2000, 2007, or 2012. In these consensuses, SUC is diagnosed according to Truelove and Witts' criteria (six or more bloody stools per day plus at least one of

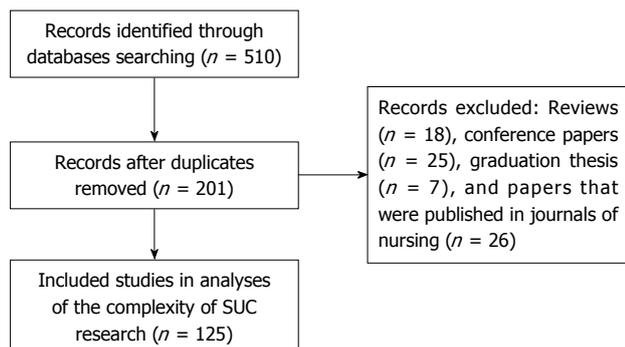


Figure 2 Flowchart of study selection. The search of WANFANG, VIP and CNKI databases with the search terms “severe ulcerative colitis” in the Article Title or Keywords retrieved 510 papers when the publication year was limited to the most recent 15 years (2001-2015). Removal of duplicates resulted in 201 individual papers on severe ulcerative colitis (SUC) during this time. We included original research articles and case reports/case series in our analyses of the complexity of SUC research ($n = 125$).

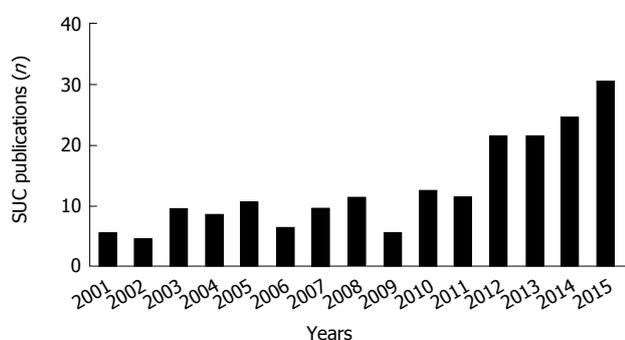


Figure 3 Annual number of Chinese publications where the prime focus was severe ulcerative colitis from 2001 to 2015. There were 201 severe ulcerative colitis related publications from 2001 to 2015. The increase in the number of publications in each year is statistically significant ($r = 0.86$, $P < 0.01$). SUC: Severe ulcerative colitis.

the following: temperature $> 37.8\text{ }^{\circ}\text{C}$; pulse rate > 90 bpm; hemoglobin $\leq 75\%$ of normal; ESR > 30 mm/h). Above all, the severity of UC was judged according to Truelove and Witts’ criteria in these Chinese hospitals, consistent with the criteria applied in Western countries.

We included original research articles and case reports/case series in our analyses of the complexity of SUC research in each 5-year period, as described by Scott *et al.*^[20]. Articles on basic research were excluded to ensure that all articles included in our study were clinical in nature. The resulting 125 papers were classified into three groups (descriptive studies, observational analytical studies, and clinical trials). There was a significant increase in observational analytical studies and clinical trials, especially in the most recent 5 year period ($P < 0.05$) (Figure 4). The proportion of descriptive studies decreased from 71.8% in 2001-2005 and 64.3% in 2006-2010, to 41.5% in 2011-2015, while the proportion of clinical trials increased 1.5 fold (from 18.8% in 2001-2005 to 35.4% in 2011-2015).

Patients reported in 201 Chinese SUC related publications
 There were 6222 patients with SUC reported in the total

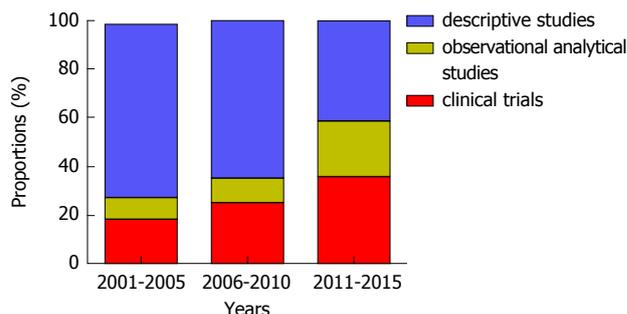


Figure 4 Relative proportions of descriptive studies, observational analytical studies, and clinical trials in every 5-year period from 2001 to 2015. There was a significant increase in observational analytical studies and clinical trials, especially in the most recent 5 years ($P < 0.05$).

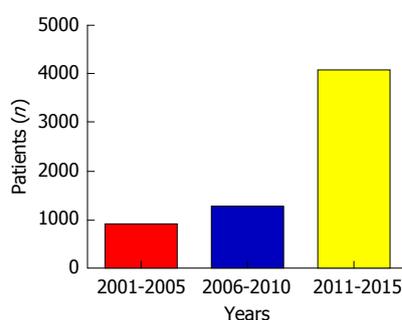


Figure 5 Number of severe ulcerative colitis patients reported in Chinese publications from 2001 to 2015 (shown with each 5-year period). There were 6222 patients reported in 201 severe ulcerative colitis related publications with a significant increase in the number of patients over the time period ($r = 0.83$, $P < 0.01$).

of 201 papers on SUC (the number of patients reported in each 5-year period is presented in Figure 5). The overall increase in the annual number of patients (from 113 in 2001 to 1605 in 2015) was greater than 10-fold. Temporal trends in the number of patients are similar to the data for the number of publications ($r = 0.83$, $P < 0.01$). Where the patient gender was reported, 3105 were males and 2243 were females, resulting in a ratio of male/female of 1.38.

The clinical manifestations of 912 SUC patients were reported in 17 articles, with blood in stool (87.70%), abdominal pain (82.9%), diarrhea (73.2%), and fever (40.8%) being the most common symptoms. Of the 997 patients reported in 15 articles with information about clinical type, 487 (48.8%) were classified as chronic recurrence type, 203 (20.4%) chronic persistent type, 268 (26.9%) initial onset type, and 39 (3.9%) acute fulminant type. Only 4 articles recorded the inducement of onset, in which 72 of 201 patients reported mental stress as the trigger for symptoms, 43 physical strains, 28 improper diets, 18 infections, and there are 37 patients without known predisposing factors.

To roughly estimate the incidence of serious complications in patients with SUC, the number of cases with toxic megacolon, intestinal perforation, severe hemorrhage, intestinal obstruction, colorectal cancer was

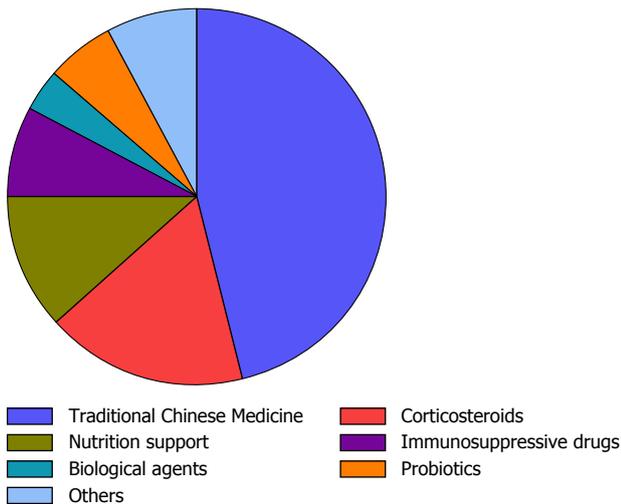


Figure 6 Relative proportions of research topics in medical management. About 16 of the 21 observational analytical studies and all of the 36 clinical trials focused on the medical management of severe ulcerative colitis, almost half (46.2%) of them are about Traditional Chinese Medicine.

recorded to be 40 (0.64%), 30 (0.48%), 25 (0.40%), 10 (0.16%), and 8 (0.13%) respectively. The colectomy rate in the 6222 SUC patients was 7.7% (480 cases of colectomy were reported in 201 papers); while the mortality rate calculated with our data was 0.8%, since 50 deaths were reported from a total 6222 patients.

Medical management of SUC in China

Management is the prime focus of SUC related clinical research. Sixteen of the 21 observational analytical studies and all of the 36 clinical trials focused on the medical management of SUC (median sample size of 64). Treatment types included Traditional Chinese Medicine (46.2%), corticosteroid therapy (17.3%), enteral or parenteral nutrition support (11.5%), immunosuppressive drugs (7.7%), biological agents (3.8%), probiotics (5.7%) and others (7.7%) (Figure 6). Adjunctive therapy with Traditional Chinese Medicine was studied in 55.6% (20/36) of clinical trials with the effective rates ranging from 73% to 97%, with 12 articles reporting an effective rate of more than 90%. The most commonly used herbs were *Radix Pulsatillae*, *Radix Scutellariae*, *Rhizoma Coptidis*, *Radix Paeoniae Rubra*, and *Radix Puerariae* and the most commonly used formulation was a modified Pulsatilla decoction.

Intravenous corticosteroids treatment remains the first-line therapy; however, the assessment of response to therapy remains a great challenge. Predictors and predictive indices for the failure of steroid therapy and the subsequent need for colectomy have been widely studied. Nine of the 96 original research articles focused on corticosteroid treatment, in which 800 patients with SUC received corticosteroids as the principal therapy. Three of these 9 articles reported both outcome and predictors of therapy failure, while 6 only reported outcomes. The effective rate of steroid treatment ranged from 58.3% to 90%, with a pooled effective rate

of 67.3%. Previous severe attack and onset with stool frequency $\geq 10/d$ are associated with increased rates of steroids failure. Further predictors of steroid treatment failure include: A stool frequency $\geq 6/d$, obvious bloody stool, severe hypoalbuminemia, and an elevated platelet count after 3 d of intravenous steroids.

We found few publications on research into salvage therapy. No clinical trials for cyclosporin were available and only 2 retrospective studies were retrieved, including 29 and 7 cyclosporin treatment cases respectively. Side effects were reported for 15 of these cases (8 cases of hypertension, 4 hepatic dysfunction, 2 hypertrichosis, and 1 hyperlipidemia). There were only 2 studies on the treatment efficacy of biological agents (1 case-control study and 1 randomized controlled trial), in which 33 SUC patients received infliximab as salvage therapy, resulting in 4 cases of nonresponse, 4 cases of transfusion reaction, 2 upper respiratory tract infections. The disease response rates were found to be 82.3% and 87.5% respectively, with the rates of adverse effects being 17.6% and 25.0%.

Surgical management of SUC in China

Our publication search retrieved 8 original research articles focused on surgical management in SUC patients, in which 200 SUC patients who received surgical intervention were studied. Two articles investigated the predictors for the need for colectomy, using the Oxford index, Swedish index, Edinburgh index, and Seo index^[21]. The Oxford index, also known as the Travis index, was developed in 1996 and has been validated in cohort studies. According to this index, patients with a stool frequency of more than 8 per day, or 3-8 stools per day plus an elevated CRP (> 45 mg/L) at day 3 of corticosteroid therapy, have a 85% chance of colectomy. The Swedish index is calculated using the algorithm: "number of stools per day + 0.14 x CRP (mg/L)", with scores > 8 indicating a high risk of requiring colectomy. The Edinburgh index is also known as the Ho score, in which scores for stool frequency (1-4 points), hypoalbuminemia < 3 mg/dL (1 point) and radiological evidence of colonic dilation (4 points) are summed, and scores greater than 4 are predictive for failure of corticosteroid therapy and subsequent need for colectomy. The Seo index is calculated using the mathematical formula: "60 x frequency of bloody stool + 13 x bowel movements + 0.5 x ESR (mm/h) - 4 x hemoglobin (g/dL) - 15 x albumin (g/dL) + 200"; where scores greater than 200 predicting the need for colectomy. These 2 articles reported that the either the Oxford and Swedish indices are superior to the Edinburgh and Seo indices in predicting medical failure and the subsequent need for surgical intervention.

Only one of these 8 articles reported the rate of colectomy. According to Pan *et al.*^[22], there were 412 patients with UC admitted to the West China Hospital (Sichuan, China) from 1996 to 2008, of which 162 patients (39.3%) were identified as having severe disease with the colectomy rate in these patients being

17.9% (29/162). Five articles reported the indications for surgery, which included medically refractory disease and severe complications (toxic megacolon, colonic perforation, massive hemorrhage and colorectal carcinoma). Six of these articles reported the specific operative approaches adopted to treat these cases. The most commonly employed operations were total proctocolectomy with ileal pouch-anal anastomosis (IPAA) (45%), total proctocolectomy with ileostomy (19%), total proctocolectomy with ileoanal anastomosis (IAA) (15%), and total colectomy with ileorectal anastomosis (IRA) (14%). The most common late complication of IPAA was pouchitis with an incidence of ranging from 7.7% to 50%, as reported in 4 articles^[23]. Two articles reported a high frequency of post-surgical bowel movements in patients that underwent IAA, between 20-30 per day in the first month and decreasing to 6-10 per day in the third month. Among the 21 patients who underwent IRA following total colectomy, 67% experienced disease recurrence in the rectum, however no cases of rectal dysplasia and/or cancer was reported after a median 3-year follow-up.

DISCUSSION

Bibliometric analysis is widely used to assess the performance of the research programs of institutions and/or countries. Research productivity and research influence are important bibliometric indicators that can be measured by the number of publications and subsequent citations^[24]. We performed a bibliometric analysis of Chinese SUC research using both quantitative and qualitative approaches. The number of publications about UC and SUC both experienced a significant increase over the 15 year study period. This temporal change is similar to the trends in IBD publications archived in PubMed between 1993 and 2011, as reported by Weintraub *et al.*^[25]. This may be attributable to the increased prevalence of UC, improved diagnostic methods, physician awareness of the disease, increased interest, and the spread of internet access^[26,27]. Accompanied with the increasing output of SUC research, we also observed a significant increase in the number of analytical studies and clinical trials, which are more complex in study designs and are stronger in terms of the strength of evidence than descriptive studies^[20]. Above all, this study has demonstrated that there has been a significant increase in publication output and research complexity on SUC in Chinese scholarly journals. This implied that there was a correlated increased in the prevalence of UC and SUC disease resulting in a subsequent increase in UC/SUC associated research in China.

There was a more than tenfold increase in the number of SUC patients reported in Chinese medical journals over the most recent 15 years. A male predominance in SUC incidence was observed in our data, with a male to female ratio of 1.38, similar to the value of 1.34 reported by a multi-centre study in China^[15]. However, male and female patients were reported to be equally affected in

10218 UC patients reported in Chinese medical literature from 1981 to 2000, with a male to female ratio of 1.09^[17]. A similar gender distribution for disease has also been noted in other Asian and western countries^[26]. One hypothesis for this observation is that male patients with UC may have a more severe disease course since male gender has been reported as a risk factor for colectomy^[8,28]. Further, more detailed, population-based studies are required to validate these data.

These data also indicate that management is the prime focus of SUC research in China, since almost all analytical studies and clinical trials were found to focus on management regimes, including pharmacotherapy, nutrition support and surgery. While intravenous corticosteroid treatment remains the first-line therapy for SUC, the low rate of efficacy, 67.3% reported in our pooled analysis is consistent with the high refractory rate of 31%-35% reported by Seah *et al.*^[2]. Prompt and objective assessment of the failure of steroid therapy plays an important role in the management of SUC^[29]. However, only 3 of the 201 articles reported predictive factors for steroids failure, consequently it is hard to obtain a unified index with high sensitivity and specificity. Further studies are required to establish homogenous predictors and unified methods for predicting steroid treatment failure and the subsequent requirement for salvage therapy or surgery.

Cyclosporine and infliximab are commonly used as salvage therapy in patients that fail to enter remission after corticosteroid treatment. Cyclosporine treatment has improved the outcome of steroids-refractory disease in SUC patients and achieved an immediate response rate of 64%-82%^[2]. There is a lack of randomized controlled trials and long-term follow-up studies focused on cyclosporine treatment in China, two retrospective studies with small sample size have reported a high rate of side effects. Treatment with infliximab was also reported to reduce the colectomy rate in SUC patients, but our search determined that publications on infliximab therapy in Chinese SUC patients did not appear until 2013. The 2 studies regarding infliximab treatment both reported a response rate greater than 80%, with rates of adverse effects of 17.6% and 25%. More evidence is required to evaluate the benefit and safety of both cyclosporine and infliximab treatment in Chinese SUC patients.

Traditional Chinese Medicine is one of the most developed complementary and alternative medicine approaches used in the treatment of IBD^[30]. Extracts or decoctions of herbs are administered by oral intake or retention enema combined with 5-aminosalicylic acid or corticosteroid therapy as treatment for severe or refractory UC. The underlying mechanisms involve anti-oxidation, anti-inflammation, and alteration of gut microbiota^[30,31]. In our study, more than half of the analytical studies and clinical trials related to SUC focused on Traditional Chinese Medicine, with most reporting an efficacy rate greater than 90%. The most commonly used formulation was found to be a modified

Pulsatilla decoction, which has been proven to attenuate experimental colitis in mice by inhibiting the activation of nuclear factor- κ B signal pathway, reducing the production of pro-inflammatory cytokines, and repairing the colonic epithelial barrier^[32]. A review of Chinese articles regarding IBD therapy also reported a higher proportion of articles (60.9%) that focus on Traditional Chinese Medicine and less use of immunosuppressants and biological agents^[18]. Although the popularity of Traditional Chinese Medicine has increased both in China and some western countries, further studies are required to validate its efficacy and safety.

The colectomy rate in our study was found to be 7.7%, while the colectomy rate in hospitalized SUC patients reported by the West China Hospital is 17.9%, both are lower than the 20%-40% reported in United Kingdom^[8]. It is assumed that the indications of surgery are more conservative in China than in Western Countries such as the United Kingdom^[22]. Lower colectomy rates were also reported in UC cohorts in other Asian countries like Japan and Korea^[26,28]. The most commonly employed operation was total proctocolectomy with IPAA since it avoids the requirement for a permanent stoma, has a lower risk of disease recurrence and/or rectal carcinoma, and has excellent long-term functional results with good quality of life^[33]. However, almost 20% of patients experienced pouch failure due to pouchitis or pouch dysfunction after IPAA^[33]. The incidence of pouchitis ranged from 7.7% to 50% as reviewed in this study. According to our data, the short-term mortality rate of SUC is 0.8%, lower than the 1.2% reported in western countries^[15,28]. These results are consistent with that reported by Wang *et al.*^[16], who observed a relatively milder clinical course and lower rate of complications in Chinese UC patients. UC is associated with an increased risk of colorectal cancer. The severity of histological inflammation correlates with colorectal cancer risk^[34]. The incidence of colorectal cancer among SUC patients is 0.13% in our study, lower than the values of 0.4% and 3%-5% reported by Wang *et al.*^[15] and in western studies respectively. Further studies are required to confirm the hypothesis that Asian UC patients have a milder disease course and a lower risk of colectomy, colorectal cancer, and mortality.

There are some limitations about this study. Firstly, we only included literature published from 2001 to 2015 and performed the bibliometric analysis in each 5-year period. Publications since 2016 were not included since only partial data of these publications were available online when the database search was performed. As it is well known that the mode of treatment is continuously changing day by day, here we repeated the database search with published year limited to 2016 and 2017. We retrieved 33 publications, included 23 original articles, 6 case reports, 2 reviews, and 2 papers published in journals of nursing. In these 23 original articles, 21 were focused on the management of SUC, including traditional Chinese medicine (17.4%), corticosteroid therapy (8.7%), immunosuppressive drugs (4.3%), biological agents (26.1%), and probiotics

(17.4%). There is an increase in articles about biological agents than before.

Secondly, biological agents have been widely suggested and used in developed countries, but in our study, it's found that biological agents had been prescribed for patients in 3.8% publications regarding SUC from 2001 to 2015. This might be due to the fact that biological agents such as infliximab was approved just a few years ago in China, and this kind of medication is so expensive that some patients who met the indications could not afford it. This situation may be changed with the passage of time and the development of economy. As discussed above, biological agents have been prescribed more frequently in the last two years than before.

Thirdly, we only reviewed the 201 papers with a prime focus of SUC, the patients with SUC that reported in articles regarding inflammatory bowel disease might be omitted. We also failed to calculate the incidence of SUC since this study is not an epidemiological study, and furthermore, the total number of patients with UC is unavailable.

In conclusion, our study documents that significant progress has occurred in SUC research within the Chinese medical research community, as reflected by the increased output and complexity of publications. Although Traditional Chinese Medicine has been widely used as a complementary therapy for SUC, rigorous experiments and careful analysis of the resulting experimental data are required to validate the benefit and safety of this type of treatment. The relatively few publications into salvage therapy suggest that more research into the efficacy of treatment with cyclosporin or infliximab in Chinese SUC patients is required. We reported a male predominance in SUC incidence and a lower colectomy rate in Chinese SUC patients compared to western countries based on literature review. Data of clinical characteristics obtained from our literature review should be verified and extended by further well-designed and detailed population-based studies.

ARTICLE HIGHLIGHTS

Research background

Severe ulcerative colitis (SUC) is a potentially life-threatening condition and its effective management remains a great challenge. China is experiencing an increasing incidence and prevalence of UC. However, data about the state of SUC related research outputs are unavailable and thus, a comprehensive study on the SUC-related Chinese publications is desperately needed. A bibliometric analysis and literature review of the SUC-related publications in Chinese periodical databases would provide more epidemiological information and provide a perspective of research hotspots.

Research motivation

The SUC research performance in China can be evaluated by the number of publications and the complexity of research designs presented with these manuscripts. Bibliometric analysis will provide information about the temporal trends of the number of publications and the change in complexity of the research described. Further, a literature review will provide information about the number of patients reported each year, the clinical characteristics, and the state of the management of SUC patients. Such a study can provide information

useful for the design of new treatment programs for SUC patients worldwide.

Research objectives

The aim of this study is to perform a bibliometric analysis to determine the temporal trends in the number of Chinese publications on UC and SUC (2001-2015), to assess the overall SUC research performance; to provide a review of the data on treatment type and efficacy in SUC patients that has been reported in Chinese medical journals. Such a study can provide an understanding of the current state of research output from Chinese studies into SUC, a perspective of research hotspots, and provide information for SUC patient treatment worldwide.

Research methods

We retrieved the Chinese publications related to SUC published between 2001 to 2015 in the Chinese periodical databases (WANFANG, VIP, and China National Knowledge Infrastructure). The number of publications for each year was recorded after the duplicates were removed. The topic of each paper was recorded and only those that were clinical in nature were included in the assessment of the complexity of SUC research. The complexity of SUC research was evaluated according to the methods described by Scott *et al.* The proportion of the total within each group was compared in every 5-year period (2001-2015). The statistical significance of the differences between proportions was compared using a Chi-squared test where a *P*-value of < 0.05 was considered as statistically significant. The number of SUC patients reported in each year, the clinical characteristics of these patients, the treatment and efficacy reported were recorded and analyzed.

Research results

There were 201 publications regarding SUC published in Chinese medical journals between 2001 and 2015. The number of publications increased rapidly. Significant increase was found in analytical studies and clinical trials over the study period, with research into the management of SUC, included pharmacotherapy, nutrition support as well as surgery, predominating. About 46.2% of the observational analytical studies and clinical trials focused on Traditional Chinese Medicine, with little research on the efficacy of cyclosporin and infliximab in the disease management. About 6222 SUC patients were reported in 201 relevant papers (ratio of male/female patients: 1.38). The number of patients reported in each 5-year period significantly increased. The colectomy rate and short-term mortality rate were 7.7% and 0.8% respectively. Total proctocolectomy with ileal pouch-anal anastomosis was the most commonly employed operation.

Research conclusions

This study documents that significant progress has occurred in Chinese SUC research, as reflected by the increased output and complexity of publications available in research databases. The complexity of publications was evaluated with the new methods described by Scott *et al.* The number of patients reported significantly increased. The information on the clinical characteristics of SUC in Chinese patients obtained from our literature review should be verified and extended by further well-designed and detailed population-based studies. Although Traditional Chinese Medicine has been widely used as a complementary therapy for SUC, rigorous experiments and careful analysis of the resulting experimental data are required to validate the benefit and safety of this type of treatment. More research into the efficacy of treatment with cyclosporin or infliximab in Chinese SUC patients is required.

Research perspectives

Chinese research into severe ulcerative colitis has increased in quantity and complexity according to our bibliometric analysis. The methods previously described by Scott *et al.* could be used to evaluate the complexity of publications for SUC and other diseases. We also reported an increase in the number of SUC patients, a male predominance in SUC incidence, and a lower risk of colectomy for Chinese patients compared with SUC outcomes worldwide. Further well-designed population-based studies are required to validate these results. In addition, more research into the efficacy of treatment with cyclosporin or infliximab in Chinese SUC patients is required.

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