The economic burden of moderate-to-severe ulcerative colitis in the EU5 Allie Cichewicz,¹ Tom Tencer,² Sonya Egodage,¹ Heather Burnett,¹ Jinender Kumar²

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Background

- Ulcerative colitis (UC) is an inflammatory bowel disease that causes inflammation and ulceration of the lining of the colon and rectum¹ • Over the past 50 years, the incidence of UC has risen from 8-14 to about 120-200 per 100,000 persons in Western countries.² Roughly 20% of that population experiences moderate disease activity and 1%-2% have severe disease,³ while 10%-30% of patients will require a colectomy
- The incidence of UC within France, Germany, Italy, Spain, and the United Kingdom (the EU5) ranges from 3.4 to 15.1 per 100,000 person-years, with the lowest incidence in France and highest in the United Kingdom⁴
- erate-to-severe disease are usually treated with corticosteroids followed by steroid-sparing agents with a thiopurine, anti-tumor necrosis factor (TNF) agent, or adhesion molecule inhibitor.⁵ The goal of medical treatment is to induce and maintain remission, improve the patient's health-related quality of life (HRQoL), and obtain mucosal healing⁶ as there is no cure for UC⁷
- The economic burden of moderate-to-severe UC and its management is substantial as it includes healthcare costs, healthcare resource utilization (HCRU), and societal impacts such as missed workdays

Objective

• To conduct a systematic literature review (SLR) on the economic burden of moderate-to-severe UC in the EU5 in terms of costs and HCRU based on real-world evidence

Study selection

Data sources

- Embase, MEDLINE, MEDLINE In-Process, EconLit, the Database of Abstracts of Reviews of Effects (DARE), and the National Health Service Economic Evaluation Database (NHS EED) were all searched via OvidSP from January 2010 to October 2021. Selection criteria are shown in **Table 1**
- Conference proceedings from the United European Gastroenterology Week (UEGW), Digestive Disease Week (DDW), European Crohn's and Colitis Organisation (ECCO), American College of Gastroenterology (ACG), Advances in Inflammatory Bowel Diseases (AIBD), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Academy of Managed Care Pharmacy, and Crohn's and Colitis Congress were searched for the last 3 years (2018 to 2021)

Screening process

• A 2-step screening process was performed: 1) titles and abstracts and 2) full texts were assessed by 2 independent reviewers, with discrepancies resolved by a third, senior reviewer, as needed

Table 1. PICOS selection criteria

Criteria	
Population	 Adults (≥18 years) with moderate-to-severe UC: When moderate-severe status was not defined, studies reporting data of interest for UC patients receiving biologics, those hospitalized, or those undergoing surgery were included
Interventions/ Comparators	Any or none required
Outcomes	 Total costs (direct + indirect) Direct costs (i.e., outpatient, hospitalization, ED, pharmacy, administration, diagnostics, and surgery) Indirect costs (i.e., productivity losses, absenteeism, presenteeism, and WPAI score) HCRU (i.e., healthcare visits, ED visits, hospitalizations, and LOS)
Study Design	Observational studies, including prospective and retrospective cohort studies and cross-sectional analyses
Time Limits	 Full-text articles: 2010 to 2021 Conference abstracts: 2018 to 2021
Geography	EU5 (France, Germany, Italy, Spain, United Kingdom)

ED, emergency department; HCRU, healthcare resource utilization; LOS, length of stay; PICOS, Population, Intervention, Comparison, Outcomes, and Study; UC, ulcerative colitis; WPAI, Work Productivity and Activity Questionnaire.

Overview of included studies

Included studies

- Twenty-two unique studies reported on the economic burden associated with moderate-to-severe UC (or prespecified proxy populations including patients with UC treated with biologics or surgery or who were hospitalized) in the EU5 (Figure 1)
- Most of the identified evidence was reported in full-text articles (19/22), was from studies done in Germany (9/22), and reported both costs and HCRU (8/22)

Figure 1. Study selection and characteristics



Availability of outcomes by type of UC population



Overview of medical costs (Table 2)

able 2. Medical costs associated with moderate-to-severe UC								
	Moderate-to-severe UC [n=2]	Biologic-treated UC [n=5]	Hospitalized with UC [n=3]	Surgically treated UC [n=2]				
Overall quality of evidence	Moderate	High	Low	Moderate				
Publication type	1 full text, 1 conference abstract	4 full texts, 1 conference abstract	3 full texts	2 full texts				
Country	Germany	France, Germany, UK	Germany, Spain, Italy	Germany, UK				
Total costs (direct + indirect)	<u>All-cause:</u> €37,449-€40,884 <u>UC-related:</u> €5,708-€8,655	Х	Х	X				
Total direct costs	<u>All-cause:</u> €30,425-€39,514 <u>UC-related:</u> €5,591-€8,140	<u>All-cause:</u> €16,532-€32,191 [n=3] <u>UC-related:</u> €13,678ª	€7,903	€3,336- €5276ª [n=2]				
Total medical costs	Х	Х	Х	Х				
Pharmacy costs	<u>All-cause:</u> €28,066-€37,369 [n=2] <u>UC-related:</u> €625-€30,132.69 [n=2]	<u>All-cause:</u> €13,429ª Biologics: €11,901-€26,463 [n=2]; Steroids: €131-€173; IS: €193-€219 <u>UC-related:</u> €13,197ª	€1,686	€110ª-€1,380 [n=2]				
Outpatient costs	<u>All-cause:</u> Outpatient visits: €503-€524; GP visits: €351-€392; GE visits: €185-€222 <u>UC-related:</u> Outpatient visits: €511; GP visits: €251-€288; GE visits: €118-€157	GP visits: €298-€344; GE visits: €168-€199	Х	Outpatient visits: €1,043ª GP visits: €488ª				
Hospitalization costs	<u>All-cause:</u> €1,621-€5,111 <u>UC-related:</u> €1,802-€3,417	€3,084-€4,177	€3,930	€1,800ª-€1,956 [n=2]				
ED visit costs	Х	€1,092-€1,764	Х	Х				

osts converted from GBP (1 GBP = lote: Costs assumed to be all-cause if not explicitly stated as UC related and are reported as mean annual costs. The number of studies contributing to each data point or range was n=1 unless otherwise stated. X indicates that no data were identified. ED, emergency department; GE, gastroenterology; GP, general practice; IS, immunosuppressant; UC, ulcerative colitis; UK, United Kingdom.

Overview of healthcare system use (Table 3)

	Unit	Moderate-to-severe UC [n=6]	Biologic-treated UC [n=2]	Hospitalized UC [n=3]	Surgically treated UC [n=2]
Overall quality of evidence	NA	Moderate	High	Low	Moderate
Publication type	NA	5 full texts, 1 conference abstract	2 full texts	3 full texts	2 full texts
Country	NA	France, Germany, UK	France, Germany	Germany, Spain	Germany, UK
	Proportion of patients	Outpatient visits: 100% GP visits: 82.9% Specialist visits: 57.9%-59.1%	GP visits: 97%-98% GE visits: 66%-69%	Х	X
Outpatient visits	Mean # visits	<u>All-cause:</u> GP visits: 5.7-5.9; GE visits: 2.1-2.3; Specialist visits: 6.6-6.7 <u>UC-related:</u> GP visits: 2.5-2.9; GE visits: 1.3-1.8	GP visits: 13.11-16.24 GE visits: 5.27-7.11	Х	2.7-7.2 [n=2]
Hospitalizations	Proportion of patients	<u>All-cause:</u> 43% <u>UC-related:</u> 22.2%-32% [n=2]	30%-43% At least 1 hospitalization over 18 months: 36%	100%	<u>All-cause:</u> 53.9% <u>UC-related:</u> 32.9%
	Mean # admissions	<u>UC-related:</u> 0.3-0.6 [n=2]	0.56-0.89	UC-related: 18.5	<u>All-cause:</u> 0.38-1.2 [n=2] <u>UC-related:</u> 0.127
LOS	Mean # days	<u>All-cause:</u> 14.8-19.2 [n=2] <u>UC-related:</u> 8.5-11.5	5.09-10.3	8.4-12.6 [n=3]	<u>All-cause:</u> 2.4-3.9 [n=2] <u>UC-related:</u> 1.4
ED visits	Proportion of patients	65%-76%	15%-25%	Х	Х
	Mean # visits	X	0.18-0.39	Х	Х

Most HCRU data were reported for populations with disease defined explicitly as moderate-to-severe, while cost outcomes were most frequently reported for UC patients treated with biologics (Figure 2)

Impact of biologics on medical costs and healthcare system use



Key findings on direct medical costs and healthcare system use

- Total annual direct UC-related healthcare costs ranged from €5,591—€13,678 per patient per year (PPPY) and were largely driven by GP visits (83%—98%; €298—€488 PPPY), hospitalizations (22%—33%; €1,802—€4,177 PPPY), and prescriptions (up to 100%; €110—€30,132 PPPY)
- Initiation of biologic therapy was associated with increases in the use of hospital and emergency services and their associated costs in the first year, with subsequent reductions in costs and services observed in the second year. However, use of biologics was not associated with the baseline cost burden, and prescription costs remained the main driver of direct costs⁸
- UC-related costs and resource use accounted for more than half of the total burden of direct medical costs and healthcare services used by patients with moderate-to-severe UC

Key findings on indirect costs

- Only 4 studies (3 full texts, 1 conference abstract) reported on indirect costs
- Patients in the EU5 with active disease newly initiating biologic therapy (n=1,037) experienced significantly higher proportions of impairments than those in remission (**Figure 4**)⁹
- The PPPY costs associated with sick leave in Germany were higher among patients with active disease/steroid dependency took long-term sick leave⁸

Figure 4. Impact of remission status on productivity and daily living among UC patients treated with biologics in the EU5 (n=1,037)



Disease activity was found to greatly impact indirect costs to UC patients, with significant impairments across work and non-work-related activities among those with active disease

compared to those without (€515 vs €118, 2013-2017 Euros).¹⁰ Of German patients taking sick leave (n=145), as many as 38 (26.2%)



Treatment with biologics was associated with significant improvements (P<0.0001) from baseline after 3 months in work productivity and the capacity for daily activities. Further improvements were maintained up to 2 years following treatment initiation for all WPAI domains (Figure 5)^{11,1}



Overview of surgery and diagnostic test utilization (Table 4)

	Unit	Moderate-to-severe UC [n=3]	Biologic-treated UC [n=1]	Hospitalized v [n=2]
Overall quality of evidence	NA	Low	Moderate	Low
Publication type	NA	3 full texts	1 full text	2 full tex
Country	NA	France, UK	Germany	Spain
Surgery	Proportion of patients	Colectomy: 21.6%-57% [n=2]	Surgery (not specified): 19%-38%	Surgery (not spec
	Rates of surgery	Х	0.26-0.86	UC-related colec
Diagnostic tests	Proportion of patients	At baseline: Abdominal imaging: 25.9%-31.5% [n=2]; Lower GI endoscopy: 81.2%; Upper GI endoscopy: 17.1%-23.8%; Fecal pathogen test: 31.5%-35.9%	Х	X
	Mean # tests	CRP: 2.9-3.0	Х	Х

HCRU was assumed to be all-cause if not explicitly stated as UC-related and is reported as annual rates. The number of studies contributing to each data point or range was n=1 unless otherwise stated. X indicates that no data were identified. CRP, C-reactive protein; GI, gastrointestinal; HCRU, healthcare resource utilization; NA, not applicable; UC, ulcerative colitis

Key findings on surgical and diagnostic costs and utilization

Costs of surgical interventions have been found to increase over time; however, more intense biologic regimens may reduce colectomy rates and associated costs

- The majority of the evidence on surgical and diagnostic costs and utilization were of low quality; data were heterogeneous and reported by very few studies
- Patients in France treated with infliximab (IFX) monotherapy received fewer diagnostic tests (e.g., abdominal imaging, endoscopy, fecal pathogen tests) than those treated with IFX combination therapies¹³ • The average cost of surgical interventions among German patients newly initiated on biologics increased from €1,047 at baseline to
- €3,542 over 12 months of follow-up⁸
- In propensity score-matched groups of UK patients with steroid-refractory acute severe UC (n=29 per group), an accelerated dosing regimen of IFX had significantly (P<0.05) lower rates of short-term colectomy compared with the standard regimen (**Figure 6**)¹⁴ • No EU5 studies were identified reporting on costs related to UC diagnosis

Figure 6. Colectomy rates by infliximab regimen among patients with steroid-refractory acute severe UC in the UK







Limitations

- Most evidence on the cost and HCRU impact of moderate-to-severe UC for the EU5 was from Germany (19/25 studies), with results based on study periods prior to 2000 (range of study years: 1997-2019)
- Many of the included studies focused more broadly on UC or inflammatory bowel disease, with only subgroup data for moderate-tosevere UC or proxy populations
- The inclusion of patients hospitalized with UC or those treated with surgery may not reflect the true economic burden of moderate-to-severe disease
- The types of data reported were heterogeneous across studies, resulting in wide ranges that limited the utility and interpretation of finding
- Costs reported by economic studies were poorly contextualized; they lacked costing year, units for costs (i.e., per-patient-permonth or annual), or definitions
- HCRU outcomes were often reported by a single study and also varied with regard to units, follow-up period, etc.
- One quarter of the evidence base came from conference abstracts with limited details and data available

Evidence gaps

- Only 1 study was identified from Italy, 2 from Spain, 2 from the United Kingdom, and 5 from France
- No studies provided a comprehensive look at the impact of more than 1 type of biologic therapy and comparisons across biologics for costs and resource use over time
- Very few studies reported on the costs related to diagnostic testing and surgeries
- Four studies reported on the indirect costs, most of which focused specifically on outcomes related to disease activity
- No studies reported on the burden to caregivers of patients with moderate-to-severe UC
- Cost or resource use data stratified by previous biologic use (naïve vs experienced) were limited
- The impact of route of administration of biologics on the economic burden of UC was scarcely reported

Conclusions

- Moderate-to-severe UC has a significant impact on direct healthcare costs (i.e., outpatient, hospitalization, and prescription) and indirect work-related costs (i.e., absenteeism, presenteeism, and work productivity)
- Limited, but mixed evidence was identified on the impact of biologic treatments on the direct costs associated with UC. However, 1 study suggested initial increases in costs and resource use associated with treatment initiation in the first year followed by a subsequent reduction in hospitalization rates and use of emergency services as well as associated costs in the second year of treatment that remained higher than the pre-biologic burden
- In contrast, significant improvements from baseline in indirect costs were observed as quickly as 3 months after biologic initiation and were maintained over 2 years of treatment
- The findings from this SLR demonstrated that despite availability of various biologics, there remains an unmet need for therapies that can reduce the healthcare burden and impact on society
- Due to inadequate availability of evidence, there is also a need for more robust studies evaluating costs and HCRU for moderate-to-severe disease

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