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Global Hospitalization Trends for Crohn's Disease and Ulcerative Colitis in the 21st Century: A Systematic Review With Temporal Analyses

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Abbreviations used in this paper: **AAPC, average annual percentage change; CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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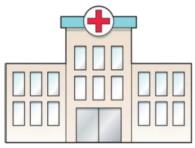
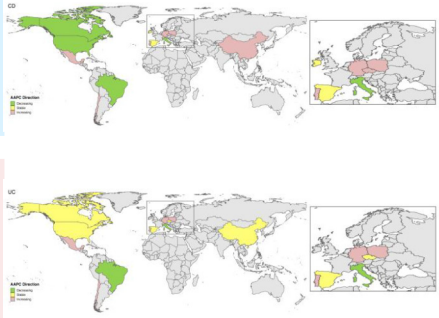
Global Hospitalization Trends for Crohn's Disease and Ulcerative Colitis in the 21st Century: A Systematic Review with Temporal Analysis

26 studies from 35 countries were analyzed for temporal trends in IBD hospitalization rates

Hospitalization rates for a primary IBD diagnosis are stabilizing in countries of the Western world experiencing compounding prevalence of IBD

In contrast, newly industrialized countries experiencing acceleration in incidence of IBD have rising average annual percentage change in hospitalization rates; IBD (+4.44%); CD (+8.34%); and UC (+3.90%).





Clinical Gastroenterology and Hepatology

BACKGROUND & AIMS: **The evolving epidemiologic patterns of inflammatory bowel disease (IBD) throughout the world, in conjunction with advances in therapeutic treatments, may influence hospitalization rates of IBD. We performed a systematic review with temporal analysis of hospitalization rates for IBD across the world in the 21st century.**

METHODS: **We systematically reviewed Medline and Embase for population-based studies reporting hospitalization rates for IBD, Crohn's disease (CD), or ulcerative colitis (UC) in the 21st century. Log-linear models were used to calculate the average annual percentage change (AAPC) with associated 95% confidence intervals (95% CIs). Random-effects meta-analysis pooled country-level AAPCs. Data were stratified by the epidemiologic stage of a region: compounding prevalence (stage 3) in North America, Western Europe, and Oceania vs acceleration of incidence (stage 2) in Asia, Eastern Europe, and Latin America vs emergence (stage 1) in developing countries.**

RESULTS: **Hospitalization rates for a primary diagnosis of IBD were stable in countries in stage 3 (AAPC, −0.13%; 95% CI, −0.72 to 0.97), CD (AAPC, 0.20%; 95% CI, −1.78 to 2.17), and UC (AAPC, 0.02%; 95% CI, −0.91 to 0.94). In contrast, hospitalization rates for a primary diagnosis were increasing in countries in stage 2 for IBD (AAPC, 4.44%; 95% CI, 2.75 to 6.14), CD (AAPC, 8.34%; 95% CI, 4.38 to 12.29), and UC (AAPC, 3.90; 95% CI, 1.29 to 6.52). No population-based studies were available for developing regions in stage 1 (emergence).**

CONCLUSIONS: **Hospitalization rates for IBD are stabilizing in countries in stage 3, whereas newly industrialized countries in stage 2 have rapidly increasing hospitalization rates, contributing to an increasing burden on global health care systems.**

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Hospitalization Rates; Epidemiology.

The inflammatory bowel diseases (IBDs), consisting of Crohn's disease (CD) and ulcerative colitis (UC), are chronic progressive or relapsing-and-remitting conditions characterized by inflammation of the gastrointestinal tract, which may result in hospitalization for diagnosis, relapse management, surgical intervention, or complications from active disease or therapy.[1,2] IBD affects a broad population including pediatrics, adults, and seniors, regardless of geographic region or ethnic background.[3,4]

Four epidemiologic stages of IBD have been proposed to explain the evolution of IBD across epidemiologic transition periods.[5] The 4 epidemiologic stages are as follows: (1) emergence, (2) acceleration of incidence, (3) compounding prevalence, and (4) prevalence equilibrium.[5] Countries in the Western world (ie, most countries in North America, Western Europe, and Oceania) are in stage 3 (compounding prevalence), where prevalence exceeds 0.5% and is as high as 0.75% in Canada and Scotland as of 2020.[6,7] In contrast, newly industrialized countries in Asia, Latin America, and the Middle East are in stage 2 (acceleration in incidence), which show low prevalence but rapidly increasing incidence.[8–10] With changes in the epidemiology of IBD throughout the world and disparities in access to advanced therapies including biologics and novel small-molecule therapies, hospitalization rates also vary by region.

The advent of modern therapeutics, specifically monoclonal antibodies, occurred at the turn of the 21st century and revolutionized the medical management of IBD.[11,12] Moreover, paradigm shifts within management strategies, such as intensive disease activity monitoring, have fostered an explosion of clinical practice guidelines over the past 20 years.[13] Consequently, innovations in therapeutics and the adoption of clinical management algorithms largely have transitioned management of moderate to severe IBD from the hospital to outpatient settings in countries in the Western world in stage 3, leading to fewer hospitalizations over time.[14,15] In contrast, hospitalizations for IBD in newly industrialized countries outside the Western world in stage 2 may be increasing owing to rapidly increasing incidence in these regions and variable access to advanced medical therapies.[4,8] A prior study of IBD hospitalization rates observed these trends across different geographic regions. However, this study was limited to countries belonging to The Organisation for Economic Cooperation and Development, and did not stratify hospitalization by CD and UC.[16]

We hypothesize that regions in stage 2 will have significantly increasing hospitalization rates while countries in stage 3 will have stable or significantly decreasing hospitalization rates. Thus, we performed a systematic review with temporal analyses of hospitalization rates in the 21st century for population-based studies reporting hospitalizations for persons with IBD, CD, or UC. We compared hospitalization rates of IBD between regions in stage 2 with those in stage 3.

What You Need to Know

Background

Global trends in inflammatory bowel disease (IBD) hospitalization rates are divergent as a result of evolving epidemiologic patterns and advancements in care management.

Findings

This systematic review showed stable IBD hospitalization rates within countries in the Western world, whereas newly industrialized countries have rapidly increasing hospitalization rates. Population-based studies in developing countries are lacking.

Implications for patient care

Our data challenge clinicians and policy makers to address the increasing IBD burden and ensure health care systems optimize medical management with the goal of shifting care from hospitals to community.

Methods

Search Strategy

We conducted a systematic literature review of MEDLINE and EMBASE using IBD-specific and hospitalization-related terms for population-based studies published between January 1, 2000, and April 26, 2022 (Supplementary Table 1 and Supplementary Figure 1). No limitations on language or type of hospitalization (eg, in-patient procedures, elective procedures, or most responsible diagnosis) were placed on the search. When relevant (ie, in the case of previous hospitalization studies), we also performed a hand search of references to identify additional articles. The systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses and the Meta-analyses Of Observational Studies in Epidemiology checklists.

Selection Criteria

Two authors independently reviewed each abstract identified by the search. Studies identified as meeting general inclusion criteria by at least 1 reviewer underwent full-text review. During the full-text review stage, studies were assessed independently by 2 authors to ensure they met the following inclusion criteria: original full-text, population-based studies with human subjects that reported crude or adjusted hospitalization rates for IBD and/or its subtypes within a defined temporal period and geographic region. Population-based studies were defined as those capturing the entire population of a defined area, or a representative sample in a defined area (eg, using probability sampling). Studies were excluded if they were available as an abstract only, reported on only a subset of the population (eg, pediatric only), or for which a population denominator could not be ascertained. Studies whose cohorts preceded the year 2000 were excluded unless data from 2000 and beyond could be separated. Disagreements between reviewers were resolved by consensus through re-evaluation with an additional reviewer.

Data Extraction

Two reviewers performed data extraction independently. Yearly hospitalization rates for IBD, CD, and/or UC were calculated for 2 settings: hospitalization rates in the general population, which was reported as hospitalization rates per 100,000 persons; and hospitalization rates among the IBD-prevalent population, which was reported as rates per 100 IBD patients. Additional information was compiled, including study demographics (author and year); databases used; age range(s); country/region or specific center; study period; and whether hospitalization rates represented a primary diagnosis of IBD, all-cause hospitalizations, or were unclassified. A primary diagnosis was defined as studies that reported IBD, CD, and/or UC as the most

responsible diagnosis for the hospitalization, whereas all-cause hospitalizations represent hospitalizations resulting from any listed diagnosis of IBD, potentially including non–IBD-related conditions. For all-cause hospitalizations, coding of IBD by International Classification of Disease, 9th or 10th revision codes occurred at any diagnostic position. Unclassified studies were those that did not distinguish between primary and all-cause hospitalizations for IBD. We contacted corresponding authors in an attempt to clarify whether unclassified studies represented a primary diagnosis or all-cause hospitalization. Countries/regions were stratified by epidemiologic stage: stage 1 (emergence), including developing countries in Africa with a low incidence and prevalence of IBD; stage 2 (acceleration in incidence), including countries in Asia, Eastern Europe, and Latin America with rapidly increasing incidence but low prevalence of IBD; and stage 3 (compounding prevalence), including regions in North America, Western Europe, and Oceania with a high prevalence of IBD and predominantly stable incidence. A comprehensive description of the different epidemiologic stages and rationale for classification of countries is provided in Supplement A.

In cases in which hospitalization data were provided only in figures, data were extracted using OriginPro 2019b v.b9.5.5.409 (Northampton, MA). When data were provided for multiyear intervals, rates were treated as averages and coded as the value for the midpoint in the range. Crude hospitalizations were treated as being distributed evenly across the time span, allowing rates to be calculated for the population totals for the midpoint within the study range.

Quality assessment of the included articles was performed independently by at least 2 reviewers using the Newcastle–Ottawa Quality Assessment Scale and is reported in Supplementary Table 2.[17] We included an additional quality measure to differentiate studies that used the entire population sample vs a representative sample of the population.

Summarization of Data

Yearly IBD hospitalization rates were defined as the number of hospitalized cases in a population per 100,000 person-years. Annual population data were standardized to annual values provided by Worldbank.org, except in cases with single-center studies, which were included only if corresponding population values were provided in the article or available online. Yearly IBD hospitalization rates per prevalent IBD population were defined as the number of hospitalized cases in a population per 100 prevalent IBD patients. Annual data on hospitalization rates were categorized by IBD, CD, or UC. If multiple studies reported hospitalizations for the same country, a pooled estimate was calculated using the appropriate log linear model.

For temporal analysis, we used data from studies reporting at least 3 data points over a 5-year period to calculate the average annual percentage change (AAPC) in hospitalization rates with associated 95% confidence intervals (95% CIs), whereby CIs less than zero are significantly decreasing, CIs crossing zero are stable, and CIs greater than zero are significantly increasing. Temporal analysis was performed in Stata v16 (College Station, TX) using log linear models, Poisson regression, or negative binomial regression if the data displayed overdispersion. Studies that reported fewer than 3 data points after 2000 were not used in statistical analyses comparing regional trends but are included in Supplementary Table 3. If 2 or more studies had overlapping time periods from the same data source (eg, the National In-patient Sample), the study with the most recent data was used to prevent pooling of overlapping data. In cases in which studies reported both primary and all-cause hospitalization rates, only primary hospitalization rates were used for pooling of country-level data.

We stratified each study's AAPC in hospitalization rate for IBD, CD, and UC, and then pooled AAPCs were calculated for each country. Subsequently, we excluded studies that were unclassified by hospital type and stratified by primary diagnosis vs all-cause hospitalization. Random-effects meta-analyses were used to pool AAPCs with 95% CIs owing to heterogeneity between studies. Meta-analyses were performed using R version 4.0.3 (R Core Team, Vienna, Austria). Data were first stratified by United Nations Geoscheme Region (North America, Latin and South America, Oceania, Eastern Europe, Northern Europe, Western Europe, Southern Europe, Eastern Asia, Southeastern Asia, Southern Asia, Western Asia, and Africa)[18] to identify geographic trends. Country-level data then were pooled and stratified by epidemiologic stage 2 (accelerating incidence) or stage 3 (compounding prevalence) and shown as Forest plots. Statistical heterogeneity was assessed using the I^2 statistic. Cochran Q statistics and associated P values were calculated to determine any significant group differences between stage 2 or stage 3 countries—no population-based studies were available for any regions in stage 1 (emergence). Because of the low number of studies, a meta-analysis comparing trends in hospitalization rates per 100 IBD patients stratified by epidemiologic stage was not completed, but data on rates and trends are included in Supplementary Table 4.

The static map depicting AAPC directions by country for IBD, CD, and UC was created in R version 4.1.2 (R Core Team) using the ggplot2 and rnaturalearth packages.[19,20] Hospitalization rates and AAPC data are available to view in an open-access, online interactive dashboard (https://kaplan-gi.shinyapps.io/hospitalization) created in R using the shiny and leaflet packages.[21,22] The application allows users to view and manipulate maps, and obtain country- and region-specific hospitalization rates and AAPCs based on their selections.

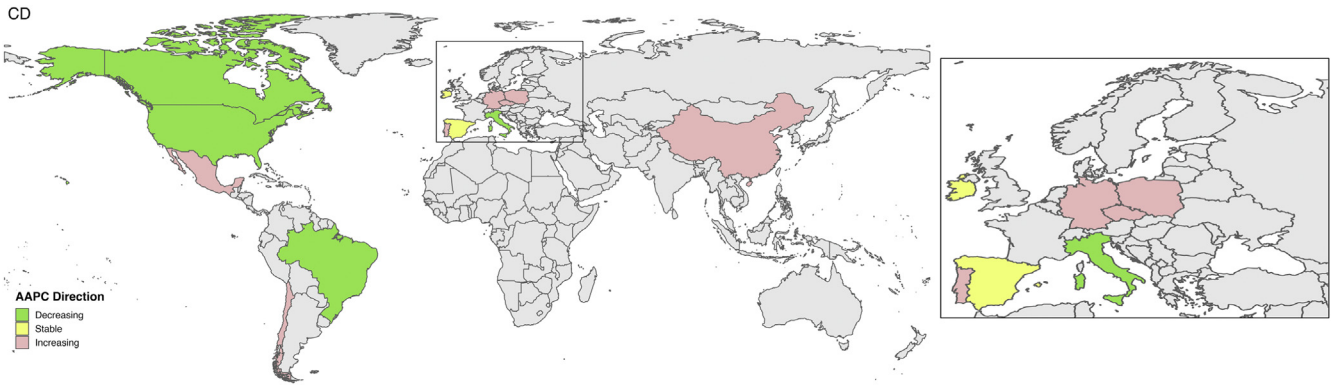


Figure 1. World map of the average annual percentage change (AAPC) direction (decreasing, stable, or increasing) for primary hospital discharge rates from 2000 to 2018 among persons with Crohn's disease (CD). If primary diagnosis data were unavailable, all-cause or unspecified data were reported (*gray countries* represent insufficient or no data available). An online interactive map reporting country-specific hospitalization rates is available: https://kaplan-gi.shinyapps.io/hospitalization.

Results

Of the 12,686 citations reviewed, the systematic review identified 84 studies providing hospitalization rates for IBD from 42 countries/regions: Australia, Austria, Bahrain, Brazil, Belgium, Canada, Chile, China, the Czech Republic, Denmark, England, Finland, France, Germany, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, San Marino, Scotland, the Slovak Republic, Slovenia, Spain, South Korea, Sweden, Switzerland, Turkey, the United Kingdom, and the United States. A summary of the data taken from each of the included studies and organized by Geoscheme Region and country is provided in Supplementary Table 3 and in an online interactive map: https://kaplan-gi.shinyapps.io/hospitalization.

Of the 42 countries for which hospitalization rates for IBD were found, temporal analyses could be performed on data from 27 studies, encompassing 35 countries or regions. Of the 84 studies identified, 6 reported or enabled the calculation of hospitalization rates per 100 IBD, CD, or UC patients (Supplementary Table 4). The pooled AAPC with 95% CIs from all countries and regions stratified by UN Geoscheme is reported in Supplementary Table 5. Figures 1 and 2 show global maps of countries with significantly increasing, decreasing, or stable hospitalization rates, stratified by CD and UC, respectively. Supplementary Figure 2 shows countries with significantly increasing, decreasing, or stable IBD hospitalization rates.

No population-based studies were available for developing regions in stage 1 (emergence). Table 1 reports the pooled AAPC for hospitalization of IBD, CD, and UC stratified by epidemiologic stage: stage 3 (compounding prevalence) vs stage 2 (acceleration of incidence). Since 2000, for all studies (including primary diagnosis, all-cause, and unclassified hospitalizations), countries in stage 3 show stable hospitalization rates for IBD (AAPC, −0.32%; 95% CI, −0.95 to 0.30), CD (AAPC, 1.12%; 95% CI, −2.13 to 4.37), and UC (AAPC, 0.71%; 95% CI, −2.28 to 3.71) (Table 1). Since 2000, newly industrialized countries in stage 2 have significantly increasing hospitalization rates for IBD (AAPC, 4.67%;

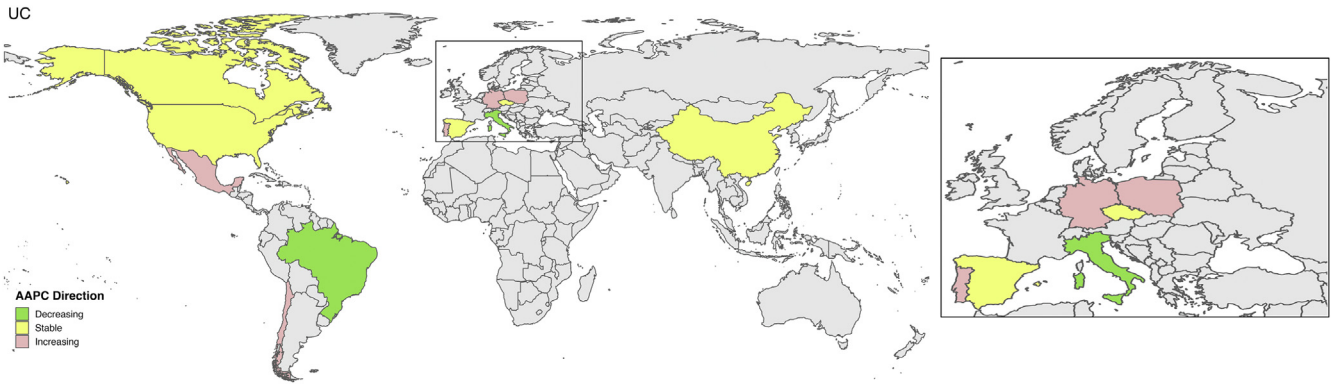


Figure 2. World map of the average annual percentage change (AAPC) direction (decreasing, stable, or increasing) for primary hospital discharge rates from 2000 to 2018 among persons with ulcerative colitis (UC). If primary diagnosis data were unavailable, all-cause or unspecified data were reported (*gray countries* represent insufficient or no data available). An online interactive map reporting country-specific hospitalization rates is available: https://kaplan-gi.shinyapps.io/hospitalization.

Table 1. Comparison of AAPCs in countries from North America, Western Europe, and Oceania in Epidemiologic Stage 3 (Compounding Prevalence) Compared With Countries in Epidemiologic Stage 2 (Acceleration in Incidence)

Hospitalization type	Disease type	Third epidemiologic stage AAPC (95% CI)	Second epidemiologic stage AAPC (95% CI)	Between-group difference, *P* value[a]
All studies (n = 26)	IBD	−0.32% (-0.95 to 0.30)	4.67% (2.63 to 6.72)[b]	<.0001
	CD	1.12% (−2.13 to 4.37)	7.28% (3.62 to 10.94)[b]	.0185
	UC	0.71% (−2.28 to 3.71)	2.60% (−0.06 to 5.26)	.3553
Primary diagnosis (n = 16)	IBD	0.13% (−0.72 to 0.97)	4.44% (2.75 to 6.14)[b]	<.0001
	CD	0.20% (−1.78 to 2.17)	8.34% (4.38 to 12.29)[b]	<.0001
	UC	0.02% (−0.91 to 0.94)	3.90% (1.29 to 6.52)[b]	.0060
All-cause (n = 10)	IBD	3.23% (0.85 to 5.61)[b]	8.28% (5.55 to 11.00)[b]	.0062
	CD	4.57% (0.60 to 8.54)[b]	10.24% (6.18 to 14.31)[b]	.0505
	UC	3.20% (−0.36 to 6.76)	3.30% (−3.65 to 10.25)	.9803

NOTE. Analyses were stratified by hospitalization type: IBD was the primary diagnosis vs all-cause hospitalizations for IBD. Studies that did not classify data as primary or all-cause discharge diagnoses were included in an analysis of all studies. The AAPC with 95% CIs were compared using a random-effect meta-analysis, and Q statistics tested group differences.

AAPC, average annual percentage change; CD, Crohn's disease; 95% CI, 95% confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis.

[a]Group difference between stage 2 and stage 3 *P* value calculated using Q statistics.

[b]Statistically significant increase at $P < .05$.

95% CI, 2.63 to 6.72) and CD (AAPC, 7.28%; 95% CI, 3.62 to 10.94), but hospitalization rates for UC were stable (AAPC, 2.60%; 95% CI, −0.06 to 5.26) (Table 1).

Forest plots of pooled AAPCs stratified by stage 2 and stage 3 are shown in the Supplementary Figures for IBD (Supplementary Figure 3), CD (Supplementary Figure 4), and UC (Supplementary Figure 5). Heterogeneity between countries within each epidemiologic stage was observed. For example, in Northern Europe (stage 3), Scandinavian countries showed decreasing hospitalization rates for IBD, whereas hospitalization rates were increasing in the United Kingdom (Supplementary Figures 2 and 3, Supplementary Table 5). In Latin America (stage 2), hospitalization rates for CD were increasing in Chile (AAPC, 6.22%; 95% CI, 5.35 to 7.10) and Mexico (AAPC, 5.21%; 95% CI, 3.07 to 7.39), whereas rates were decreasing in Brazil (AAPC, −3.22%; 95% CI, −5.24 to −1.15) (Figure 1, Supplementary Table 5, Supplementary Figure 4).

Table 1 reports pooled AAPCs of countries that provided hospitalization rates for primary diagnosis (ie, most responsible diagnosis) and/or all-cause diagnosis (ie, hospitalization with IBD listed in any diagnostic position). Hospitalization rates for a primary diagnosis of IBD were stable in countries in stage 3 (AAPC, 0.13%; 95% CI, −0.72 to 0.97), CD (AAPC, 0.20%; 95% CI, −1.78 to 2.17), and UC (AAPC, 0.02%; 95% CI, −0.91 to 0.94) (Table 1, Supplementary Figures 6–8). In contrast, hospitalization rates were increasing in countries in stage 2 (AAPC, 4.44%; 95% CI, 2.75 to 6.14), CD (AAPC, 8.34%; 95% CI, 4.38 to 12.29), and UC (AAPC, 3.90%; 95% CI, 1.29 to 6.52) (Table 1 and Supplementary Figures 6–8). Pooled AAPCs for countries in stages 2 and 3 showed increasing hospitalization rates for all-cause hospitalizations for IBD and CD, but not for UC (Table 1 and Supplementary Figures 9–11). However, low precision may result in a stable hospitalization rate for UC because the 95% CIs were wide.

Discussion

This article comprises a comprehensive review of global hospitalization trends for IBD. Hospitalization rates in the 21st century vary by the epidemiologic stage of each region; countries embedded in stage 3 (compounding prevalence) predominantly show stabilizing hospitalization rates, including those in North America and Northern Europe.[5] These data suggest that advances in the management of IBD are shifting the care of IBD from the hospital to the community.[23] In contrast, hospitalization rates are increasing rapidly in newly industrialized countries currently in stage 2 (acceleration of incidence), including those in Asia, Latin America, and the Middle East.[4] The increased hospitalization trends mirrored the increasing incidence of IBD observed in these regions.[10] Collectively, these data offer insight into a differential health care burden that IBD may pose across the world.

Stage 3 (compounding prevalence) is denoted by stabilization of incidence, but steadily increasing prevalence as a result of the incidence of IBD exceeding mortality.[5] Despite the increasing prevalence, hospitalization rates remained largely stable or decreasing in North America and Northern Europe. Heterogeneity between countries exists, with some countries reporting decreasing hospitalization rates for IBD (eg, Canada, −3.01% per year, Italy: −1.09% per year) and others reporting increasing hospitalization rates for IBD (the Netherlands, +3.25% per year, Portugal, +1.92% per year) (Supplementary Table 5).[16] Although our study was not designed to explain the factors driving

hospitalization trends, heterogeneity likely is explained by clinical, health system, and methodologic factors that differ between countries and studies.

Several clinical factors have influenced hospitalization rates in countries of the Western world in stage 3 during the 21st century. The advent of biological therapies revolutionized the medical management of IBD, leading to a reduction in the need for hospital-based care and surgery for intestinal resections.[11,24–28] The majority of studies included in our systematic review reported hospitalization trends in the first 15 years of the new millennium as anti–tumor necrosis factor (TNF) therapies were introduced and increased in utilization; however, few periods extended long enough to subsequently capture the impact of novel biologicals and small molecules.[29–32] In addition, in the early years of anti-TNF use, the learning curve necessary to optimize its use may have blunted the impact of biologic therapy on hospitalizations.[29]

In contrast, hospitalization rates were increasing consistently in newly industrialized countries in Asia and Latin America that were classified as stage 2 (acceleration in incidence), which was denoted by rapidly increasing incidence but low prevalence. Because of the low prevalence of IBD, the magnitude of hospitalization rates was numerically lower than regions in stage 3. However, the AAPCs in hospitalization rates were considerably greater in newly industrialized countries. Temporal trends were increased across disease types (IBD, CD, and UC), as well as definitions of hospitalization (primary diagnosis vs all-cause). Multiple factors may explain the increasing rates in newly industrialized countries, with the most likely explanation being the rapid increase in annual diagnoses of IBD. Often, the first year after diagnosis is associated with the highest risk of hospitalization for IBD.[14,33] Furthermore, barriers to accessing expensive medications such as biological therapies may lead to worse disease severity, which results in hospital-based management.

Prior studies have correlated increasing incidence, and in turn hospitalization, of IBD to societal and economic factors. Both increased population density, such as a shift from rural to urban living, and economic advancement are associated with an increasing incidence of IBD in newly industrialized countries.[34] In part, economic advancement increases access to health care systems, electronic surveillance systems, specialists, and infrastructure such as endoscopic procedures. In turn, the ability to detect patients with IBD in these regions has improved. In contrast, insurance coverage is disparate in many newly industrialized countries, leading to some residents with IBD receiving care in private hospitals, which may lead to better outcomes. Although hospitalization rates were increasing consistently throughout Asia and Latin America, recent data from Brazil have shown that hospitalization rates are trending downward after increased penetration of biological therapies over the past decade.[8] More population-based studies in Latin American countries are needed to better understand hospitalization trends within this region.[8]

Moreover, a plethora of guidelines have been published in the past decade that have advanced clinical management paradigms of IBD beyond medical therapeutics alone. Notable examples include risk stratification, allowing for the earlier introduction of advanced therapies and an increased focus on proactive monitoring of persons with IBD, which includes the use of therapeutic drug level testing, evolving treatment targets beyond symptoms, and treat-to-target approaches using biomarkers aimed at achieving deeper remission beyond symptoms alone.[35–37]

Despite advances in the ambulatory management of IBD, health system and societal factors also vary by geography and between individuals.[38–40] Differential access to health care and medications may be driven by variation in health insurance.[41] For example, regions such as the United States that lack universal health care may have impediments to routine access of ambulatory care, leading to the hospital/emergency department being the primary point of care.[40–42] Even when health insurance is available, regulations may impede timely access to biologics and IBD-trained gastroenterologists. Similarly, heterogeneity of outcomes may be especially obvious in newly industrialized countries where access to maintenance biological therapies is variable. Furthermore, personal factors such as socioeconomic status or mental health may reduce access to optimal ambulatory-based care of IBD.[40,43,44] Moreover, even with universal access to health care, increased hospitalization rates have been observed in those of lower socioeconomic status.[40] Systemic biases, often driven by sex, race, or ethnicity, increasingly are recognized in patients with IBD, which may lead to differential hospitalization rates.[45–47]

Heterogeneity in hospitalization rates between studies also may be explained by methodologic factors. The primary factor differentiating studies on hospitalization rates is the definition used to identify those with IBD within administrative databases. Some studies focused only on hospitalizations with IBD as the primary diagnosis, whereas others accepted an IBD code listed in any diagnostic position. The former approach focuses on hospitalizations for a flare of IBD, whereas the latter is all-cause hospitalization, which includes flaring patients and those with IBD as a comorbidity in remission but hospitalized for alternate reasons (eg, a cardiac event). A primary diagnosis for flaring reflects disease burden resulting from disease activity; in contrast, all-cause hospitalizations report the overall burden of IBD to the health system.

All studies included in the systematic review reported hospitalization rates of IBD relative to the number of people living in the general population (ie, cases per 100,000), but only 6 reported or enabled the calculation of hospitalization rates per 100 IBD-prevalent population (Supplementary Table 4). The prevalence of IBD is

increasing at a faster rate than the growth of the general population in stage 3 countries.[6,7] For example, provincial all-cause hospitalization rates for IBD in Alberta, Canada, increased from 2002 to 2018 when the denominator was the general population (AAPC, 1.56%; 95% CI, 1.32 to 1.80); however, rates decreased when the denominator was the IBD-prevalent population (AAPC, −4.18%; 95% CI, −4.69 to −3.66).[48] Similarly, primary hospitalization rates for CD in Catalonia, Spain, increased from 2011 to 2017 when the denominator was the general population (AAPC, 5.34%; 95% CI, 4.07 to 6.62); however, rates decreased when the denominator was the IBD-prevalent population (AAPC, −4.38%; 95% CI, −5.50 to −3.25).[49] However, this pattern is not ubiquitous. For example, regional primary cause hospitalization rates for IBD in Lothian, Scotland, decreased at similar rates from 2010 to 2019 when both denominators were used (general population: AAPC, −6.73%; 95% CI, −8.26 to −5.18; IBD-prevalent population: AAPC, −6.75%; 95% CI, −7.93 to −5.55) (Supplementary Tables 3 and 4).[50] Future studies that focus on a primary diagnosis of IBD and with the prevalent IBD, CD, or UC population as the denominator may provide better estimates of the temporal trends in hospital-based care of IBD in regions in stage 3.

Limitations of this systematic review are driven primarily by the quality of identified studies. Although the quality assessment showed a low risk of bias, many studies lacked information on important clinical criteria associated with hospitalization such as phenotype, disease severity, and drug utilization. Because of the population-based nature of the data, selection bias was minimized; however, misclassification error may have led to over-reporting of hospitalization rates for IBD. For stage 2 countries, only data from Bahrain and China were available for the all-cause UC hospitalization rates in the meta-analysis. Therefore, the number of studies within the stage 2 strata are limited, resulting in lower precision as evident from the wider 95% CIs. Unfortunately, hospitalization rates from regions in stage 1 (eg, Africa) were not identified so our analysis can compare only stage 2 and stage 3 regions. Future population-based studies on the epidemiology of IBD in stage 1 developing countries are needed. Because of the scarcity of data, we were not able to assess hospitalization rates as a proportion of total hospitalizations in a defined region. Reporting bias was assessed qualitatively and was not evident, whereas publication bias was not assessed statistically.[51]

This systematic review provides global hospitalization trends for IBD during the 21st century. Countries in the Western world in stage 3 (compounding prevalence) predominantly are reporting stable hospitalization rates, particularly for primary hospitalizations—when the hospitalization is for a relapse of IBD. With the increasing incidence of IBD in newly industrialized countries in stage 2 (acceleration in incidence), hospitalization rates have followed suit. These countries will need to address the increasing burden of IBD to ensure their health care systems optimize medical management with the goal of shifting care from the hospital to the community. Future studies should explore hospitalization rates in the era of novel mechanistic medications beyond anti-TNF therapy and stratify based on primary vs all-cause hospitalization rates.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.06.030.

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Data Availability Statament

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