

All-cause mortality of hospitalized inflammatory bowel disease patients: a multicenter study from Iran

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ABSTRACT

Aim: In this multicenter study, we investigated all causes of mortality in hospitalized inflammatory bowel disease (IBD) patients.

Background: The widespread use of biologics and immune suppressive treatments, along with the longer lifespan of patients with IBD, may have changed the cause of death in this population. Knowing this may lead to better preventive and therapeutic strategies for IBD patients.

Methods: This cross-sectional study reviewed records of 1926 IBD patients hospitalized in referral hospitals in Isfahan and Shiraz during 2013–2021. In nine years, 84 patients, 39 from Isfahan and 45 from Shiraz, died. We retrospectively gathered data on demographic, clinical, and laboratory information, as well as the cause of death. We extracted the cause of death from the death sheets and classified it using the International Classification of Diseases (ICD-10). Using the Kaplan-Meier model, we estimated the median survival time from disease diagnosis to death.

Results: Males accounted for 47 (55%) of the deceased patients. The mean age of the patients was 48.63 ± 18.7 years. The mortality rates among hospitalized UC and CD patients were 7.2% and 7.8%, respectively. The median duration of admission to death was 8 days, with 19 (22.6%) of IBD patients dying on the first day of their hospital admission. Half of the cohort of deceased IBD patients had survived for 8 years following their disease diagnosis. 32.7% of all recorded causes of death were due to certain infectious diseases. The second and third most common causes of death were diseases of the digestive system and diseases of the circulatory system, including pulmonary embolism, accounting for 30.1% and 14.2%, respectively.

Conclusion: According to this study from Iran, infectious diseases are the leading cause of death among hospitalized IBD patients. Prevention and clinical management of pulmonary embolism in IBD patients require more careful consideration. We strongly encourage population-based cohort studies to enhance the findings.

Keywords: Death, Inflammatory bowel disease, Iran, Pulmonary embolism, Infection

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Introduction

Inflammatory bowel disease (IBD), an inflammatory autoimmune disease of the intestine, manifests in two clinical forms: ulcerative colitis (UC) and Crohn's disease (CD) (1). The symptoms of IBD are related to the chronic inflammation of the mucosa of the gastrointestinal (GI) tract or the involvement of

extra-GI systems (2). The entire GI tract can be affected in CD, while UC often involves the colon and rectum (3). While Western countries have a higher prevalence of both types of IBD, there has been an increasing trend worldwide, including in Iran, in recent years (4, 5), which imposes high-cost burdens on both the health system and the patients (6-8).

The mortality rates of IBD patients have become a focus of research in recent years; however, the results are inconclusive and even contradictory. While some studies have reported that the mortality risk of IBD is increased

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compared to the general population (9, 10), others stated that the mortality risk is comparable to the general population (11). There are even pieces of evidence that reported the dissimilarity of outcomes for different subgroups of IBD, especially for UC and CD (12). Causes of death in patients with IBD are related to complications of multiple comorbidities, medical interventions, or surgical procedures (13), with some variations in different studies (9, 14). Generally, the causes of death could be categorized as general and cancer-specific deaths. Among the general category, infections, as well as cardiovascular, respiratory, digestive, and liver diseases, are the most commonly reported causes, while the highest rate of cancer-specific deaths is due to colorectal cancer (CRC) (14, 15).

Available epidemiological studies conducted in Iran are mainly focused on the description of the clinical features of IBD patients, while detailed causes of death were infrequently dedicated (5, 16, 17). An investigation by the current study's authors has demonstrated that the mortality risk of UC patients who underwent colectomy seems to be higher compared with the available global data (18). At the same time, there are limited studies to comprehend the causes of death of all IBD patients in Iran. The widespread use of biologics and immune suppressive treatments, combined with the increased longevity of IBD patients, may affect the mortality rate and cause of death in this population. Knowing this may lead to better preventive and therapeutic strategies for IBD patients. Therefore, this study aims to investigate all-cause mortality among hospitalized IBD patients in referral hospitals in Shiraz and Isfahan, two major provinces in Iran, from 2013 to 2021.

Methods

Study setting and data

This cross-sectional study was conducted in five referral hospitals in Shiraz and one in Isfahan, which provided care to IBD patients on March 21, 2013, and March 20, 2021. We collected information on all hospitalized IBD patients, including those who died, by reviewing the hospital records using relevant ICD-10 codes for IBD. We then separated the records of the deceased patients. Researchers re-examined the information in all IBD records (live and deceased) to confirm ICD-10 diagnoses and increase validity.

Gastroenterologists categorized patients with IBD into UC and CD based on clinical, endoscopic, and radiological findings (19).

Data collection forms consisted of four parts: demographic information, clinical presentations, laboratory findings, and cause of death. We recorded demographic information such as the date of admission, the date of death, sex, age, the age at diagnosis, the inhabitant status, and personal behavior. The following clinical data were included: disease subgroup (CD/UC), site of GI involvement (based on endoscopic assessments), extra-GI manifestations, presentation at the time of admission, presence of comorbidity, medication history at the time of hospitalization, primary surgery associated with IBD during hospitalization, laboratory data, and surgical information. We used the Crohn's Disease Activity Index (CDAI) and Mayo scores for CD and UC patients to assess the severity of their diseases, categorizing them into normal, mild, moderate, and severe groups (20). The Mayo scores ranged from 0 to 12; the highest indicated the most severe disease (21). We calculated partial Mayo scores when the endoscopy data was incomplete. The CDAI has a value between 150 and 450, of which 150 or less is associated with disease remission, and above indicates disease activity and numbers above 450 are associated with very severe disease activity (22). Laboratory findings included the last recorded hemoglobin level, albumin level, ESR, and CRP. We extracted the cause of death from death sheets and categorized it using the ICD-10 since the cause of death in patient records is not classified based on the standard. In certain situations, more than one cause of death was indicated, and all of them were retrieved.

Statistical analysis

We used SPSS software version 18 (USA, IL, Chicago, Inc.) to describe the data. We used the Kaplan-Meier model on deceased IBD patients to estimate the median survival time from disease initiation to death. We calculate the median survival time as the smallest survival time for which the survivor function is less than or equal to 0.5. We also used the log-rank test to compare two survival curves of deceased IBD patients whose age at diagnosis was less than 45 with IBD patients with age at diagnosis of 45 and more.

Results

From 2013 to 2021, 1,926 IBD patients were admitted, with 1,128 patients (733 UC and 395 CD) admitted to Shiraz hospitals and 798 (532 UC and 266 CD) to a hospital in Isfahan. Overall, in both cities, a total of 84 patients died. 53 (63%) of these patients had UC, and 31 (36%) had CD. 39 (46%) deaths occurred in Isfahan, and the majority of the deceased were men (55%). The mortality rate among hospitalized patients was 7.2% and 7.8% for UC and CD, respectively. The mean \pm standard deviation (SD) of the age of patients was 48.63 ± 18.7 , while the IBD was diagnosed for them at a mean \pm SD age of 38.85 ± 17.5 ; however, age at diagnosis was not available for 13 deceased patients. The diagnosis of IBD occurred in 44 (62%) and 27 (38%) individuals at ages less than 45 and 45 years and more, respectively. The median duration of admission was 8 days; this was 9 and 4 days for UC and CD, respectively.

None of the patients reported drinking alcohol at the time of admission. Table 1 presents the detailed characteristics of deceased IBD patients from 2013 to 2021. Table 2 details the clinical characteristics of deceased IBD patients. The most admitted IBD patients were categorized as moderate and severe; it seems that

CD patients had a more severe condition at the time of admission. Most of the deceased IBD patients were presented with abdominal pain and diarrhea. Five (9.4%) UC and six (19.3%) CD patients presented with extra-intestinal manifestation, primary sclerosing cholangitis, and fistula, respectively. Ten IBD patients reported a positive history of deep vein thrombosis as thromboembolic events. Corticosteroids and aminosalicylates were the most common medications used by patients at the time of admission. The extent of disease in deceased UC patients was extensive colitis, while in CD patients, it was both the small and large bowel (Table S1). Figure 1 presents Kaplan-Meier estimation of the overall survival function from disease diagnosis to in-hospital death, revealing that half of the deceased IBD patients had survived for 8 years after their disease diagnosis. The time from disease onset to death ranged from zero to thirty years. Figure S1 illustrates Kaplan-Meier's estimate of the overall survival function from disease diagnosis to in-hospital death by age less than 45 at diagnosis compared to 45 and more. The log-rank test was not significant for age at diagnosis in the less than 45 age group compared to 45 and more ($p=0.136$).

Table 1. Characteristics of 84 deceased inflammatory bowel disease patients between 2013 and 2021

		Ulcerative colitis (53)	Crohn's disease (31)	Total
Yearly mortality	2013-2015	24 (70.58%)	10 (29.41%)	34 (40.47%)
	2016-2018	20 (57.14%)	15 (42.85%)	35 (41.66)
	2019-2021	9 (60%)	6 (40%)	15 (17.85)
Male		26 (55.31%)	21 (44.68%)	47 (55%)
Age (year)		49.17 ± 19.97	48.09 ± 16.69	48.63 ± 18.7
Age at diagnosis (year)*		38.39 ± 17.84	39.32 ± 17.45	38.85 ± 17.5
Duration of admission (day)		13.5 ± 17.1	10.9 ± 12.9	12.6 ± 15.7
Duration of admission (categorized)	1 day	12 (22.6%)	7(22.6%)	19 (22.6%)
	1 to 7 days	9(17%)	9(29%)	18(21.4%)
	8 days and more	32(60.4%)	15(48.4)	47(56%)
Hospital*	1- Esfahan	24 (61.53%)	15 (38.46%)	39 (46%)
	2-Shiraz	16 (72.72%)	6 (27.27)	22 (26%)
	3-Shiraz	3 (75%)	1 (25%)	4 (4%)
	4- Shiraz	0 (0.0%)	0 (0.0%)	0 (0.0%)
	5- Shiraz	0 (0.0%)	0 (0.0%)	0 (0.0%)
	6- Shiraz	10 (52.63%)	9 (47.36%)	19 (22.61%)
Inhabitant status	Metropolis	30 (71.42%)	12 (28.57%)	44 (52%)
	Non-metropolis and village	21 (52.5%)	19 (47.5%)	40 (48%)
Current smoker		5 (55.55%)	4 (44.44%)	9
Opium/ drug addiction		3 (33.33%)	6 (66.66%)	9

N (%) for qualitative and mean \pm standard deviation (SD) for scale data

* Age at diagnosis was not available for 13 patients.

**Hospitals numbered 4 and 5 had no death during the study period.

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Table 2. Clinical characteristics of 84 deceased inflammatory bowel disease patients between 2013 and 2021

		Ulcerative colitis (53)	Crohn's disease (31)	Total (84)
Severity score of disease ^I n (%)	Normal	9 (100%)	0 (0)	9 (11%)
	Mild	11 (92%)	1 (8%)	12 (14%)
	Moderate	22 (76%)	7 (24%)	29 (35%)
	Severe	11 (32%)	23 (68%)	34 (40%)
Presenting symptoms in last hospitalization ^{II}	Fever	11 (57.89%)	8 (42.1%)	19 (23%)
	Abdominal pain	27 (57.44%)	20 (42.5%)	47 (56%)
	Diarrhea	15 (65.21%)	8 (34.78%)	23 (27%)
	Vomiting	4 (57.14%)	3 (42.85%)	7 (8%)
	Jaundice/Ascites	11 (84.61%)	2 (15.38%)	13 (15%)
	Rectal bleeding	11 (73.33%)	4 (26.66%)	15 (18%)
	bloody vomiting	2 (100%)	0 (0)	2 (2%)
	Wight loss	1 (100%)	0 (0.0%)	1 (1%)
	Weakness	6 (60%)	4 (40%)	10 (12%)
	Decreased levels of consciousness	6 (60%)	4 (40%)	10 (12%)
	Dyspnea	4 (66.66%)	2 (33.33)	6 (7%)
	Extra-intestinal manifestation ^{III}	Primary sclerosing cholangitis	5 (100%)	0 (0.0%)
Fistula		0 (0.0%)	6 (100%)	6 (7%)
Perianal abscess		0 (0.0%)	1 (100%)	1 (1%)
Joint involvement		0 (0.0%)	1 (100%)	1 (1%)
Aphthous oral ulcer		0 (0.0%)	1 (100%)	1 (1%)
Deep vein thrombosis		2 (20%)	8 (80%)	10 (12%)
Positive history of thromboembolic events	Cardiovascular disease	15 (71.42%)	6 (28.57%)	21 (25%)
	Cancer	5 (45.45%)	6 (54.55%)	11 (13%)
	Psychiatric disease	4 (80%)	1 (20%)	5 (6%)
	Rheumatologic disease	0 (0.0%)	2 (100%)	2 (2%)
	Kidney disease	10 (66.66%)	5 (33.33%)	15 (18%)
	Liver disease	12 (80%)	3 (20%)	15 (18%)
Surgery in current hospitalization	No surgery	35 (41.7%)	14 (17.9%)	50 (60%)
	Colectomy/ Small bowel resection	8 (9.5%)	9 (10.7%)	17 (20%)
	Other	9 (10.7%)	8 (9.5%)	17 (20%)
Last lab data results	Hemoglobin	8.03 ± 2.47	7.75 ± 2.37	7.88
	Albumin	2.4 ± 0.63	2.26 ± 0.5	2.33
	ESR	28.8 ± 32.67	33.1 ± 25.12	30.95
	CRP	72.6 ± 73.32	122 ± 156.57	97.3
Medications ^V	Corticosteroid	28 (68.29%)	13 (31.71%)	41 (49%)
	Aminosalicylates	29 (65.9%)	15 (34.1%)	44 (52%)
	Azathioprine	5 (50%)	5 (50%)	10 (12%)
	Methotrexate	0 (0.0%)	2 (100%)	2 (2%)
	Infliximab	1 (33.33%)	2 (66.66%)	3 (4%)
	Adalimumab	1 (14.28%)	6 (85.72%)	7 (8%)
	Mycophenolate mofetil	1 (50%)	1 (50%)	2 (2%)

N (%) for qualitative and mean ± standard deviation (SD) for scale data. ^I Mayo, and partial Mayo score for ulcerative colitis, CDAI for Crohn's disease. ^{II} more than one Presenting symptom in the last hospitalization is possible. ^{III} Extra-intestinal manifestations at the admission time. ^{IV} comorbid diseases unrelated to IBD complications or extra-intestinal manifestations: diabetes, heart disease, cancer, mental illness, rheumatologic diseases, kidney disease, and liver disease. ^V More than one medication might be used.

Cause of death

Out of 84 IBD patients, 60 (71.4%) had one recorded cause of death, 19 (22.6%) had two causes,

and 5 (6%) had three causes of death. [Table S2](#), which is supplementary material, details the causes of death of 84 IBD patients. However, Table 3 categorizes the

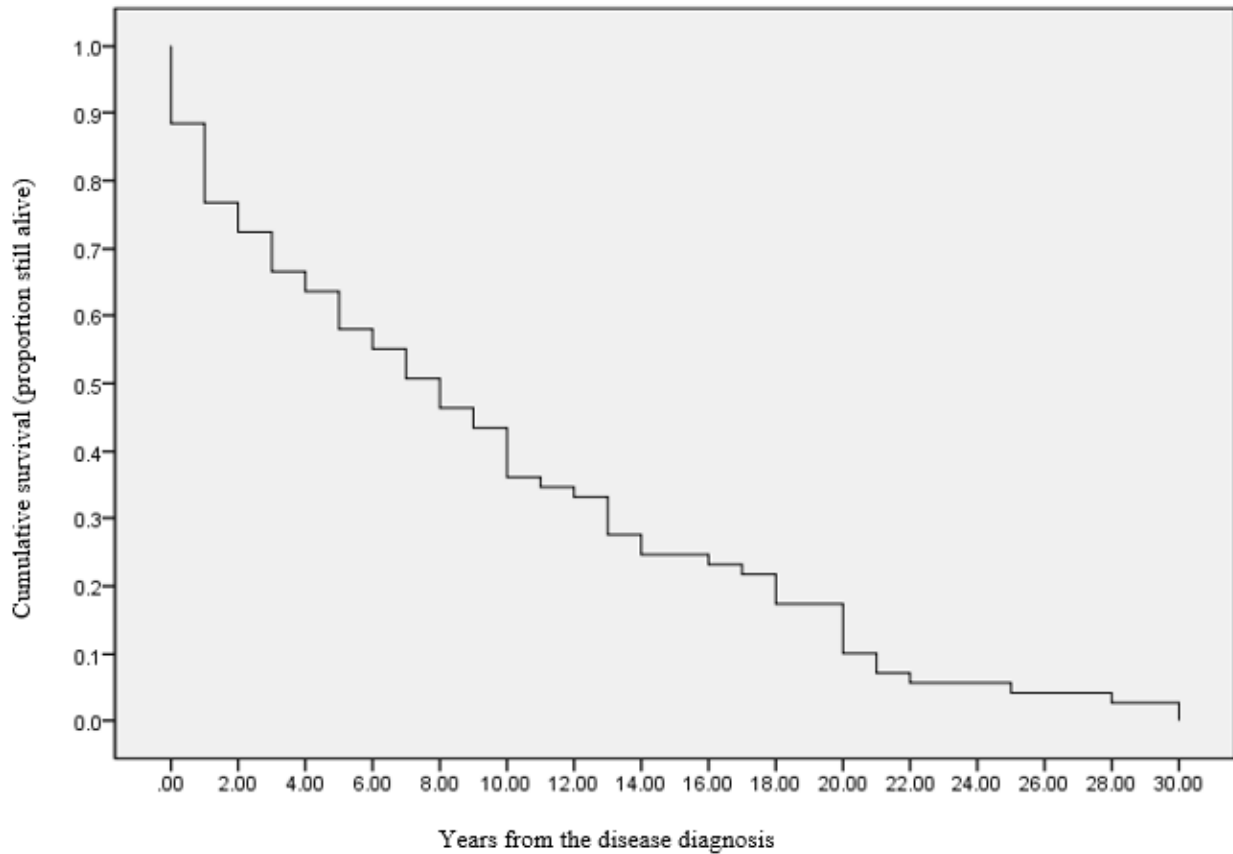


Figure 1. Kaplan-Meier estimation of the overall survival function from disease diagnosis to in-hospital death over a 30-year period

causes of death into nine different ICD-10 categories. Notably, in cases where more than one cause from one main category of ICD-10 was listed on the death sheet, only the main category of reasons is shown in Table 3. As shown in Table 3, certain infectious diseases, including parasitic diseases, accounted for 32.7% of all recorded causes of death. Diseases of the digestive system were the second most common cause of death, accounting for 30% of deaths. In this category, acute and sub-acute hepatic failure, acute peritonitis, gastrointestinal hemorrhage, and acute vascular disorders of the intestine were the main records.

Diseases of the circulatory system account for the third cause of death among IBD patients, with pulmonary embolism emerging as the leading cause in this category for 10 patients (7 UC and 3 CD). It is noteworthy to mention that 4 IBD patients (2 UC and 2 CD) who were categorized by codes for special purposes had coronavirus disease 2019 (COVID-19) recorded as the cause of death.

One patient who was referred for colostomy closure died due to cardiac arrest during surgery. This was categorized as the main category of injury, poisoning, and other consequences of the external cause category of ICD-10.

Discussion

Studies about mortality rates in IBD patients have shown differing data; some studies have reported increased mortality for both patients with UC and CD (10), while others have shown that the risk of mortality is comparable to the general population (23, 24). In this study, we investigated the all-cause mortality of hospitalized IBD patients in two large provinces of Iran during 2013-2021. We demonstrated a decrease in hospital mortality for both CD and UC from 2013 to 2021, similar to other countries (25). This may result from improved medical therapy in recent years with the introduction of anti-TNF α that modified the natural

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Table 3. Cause of in-hospital death* of 84 inflammatory bowel disease patients between 2013-2021

Cause of death (ICD-X) n (%)	Ulcerative colitis (53)	Crohn's disease (31)	Total (84)
Certain infectious and parasitic diseases (A41.9)	20 (29.4)	17 (37.8)	37 (32.7)
Neoplasms (C18.9, C78.7)	1 (1.5)	1 (2.2)	2 (1.8)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D65)	3 (4.4)	3 (4.4)	6 (5.3)
Diseases of the circulatory system (I26, I46.1, I46.9, I50.9, 98.3*)	11 (16.2)	5 (11.1)	16 (14.2)
Diseases of the respiratory system (J69.0, J18, J44.1)	2 (2.9)	2 (4.4)	4 (3.5)
Diseases of the digestive system (K55.0, K72.0, K59.3, K65.0, K92.2, K63.1, K92.0, K91.8, K59.3, K63.1)	22 (32.4)	12 (26.7)	34 (30.1)
Codes for special purposes (U07 /U07.1)	2 (2.9)	2 (4.4)	4 (3.5)
Diseases of the genitourinary system (N39.0)	1 (1.5)	0 (0)	1 (0.9)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R57.2, R57.0)	5 (7.4)	3 (6.7)	8 (7.1)
Injury, poisoning, and certain other consequences of external causes (T81.8)	1 (1.5)	0 (0)	1 (0.9)
Total	68 (60.2)	45 (39.8)	113 (100)

All data are presented as N (%).

* More than one cause of death is possible

course of IBD and recognized and treated the early clinical warning signs of the disease.

The mortality rate among hospitalized patients was 7.2% and 7.8% for UC and CD, respectively, similar to other studies that showed higher mortality in CD patients (23, 25).

Half of the cohort of deceased IBD patients had survived for eight years following their disease diagnosis (median survival). In a study in Shiraz on the survival of UC patients who underwent colectomy, all the deceased patients underwent the procedure more than ten years after definite diagnosis. Also, all deaths occurred within six years after colectomy (26). There is a lack of updated data on the survival of IBD patients, especially in a cohort of IBD patients, as well as population-based studies that have reported standard mortality rates for different age groups.

In the current study, we also did not find a significant difference in the survival of deceased IBD patients who were less than 45 years old at the initiation of the disease versus patients 45 years and older. The mean age of deceased patients was 49 years in our study, while in other studies, mortality was significantly higher in older patients (9, 11, 25, 27). Further studies are necessary to understand the reasons behind the lower mortality rate of IBD patients in Iran, but it appears that hospitalized patients in our area are

relatively young. The mean age of the hospitalized patient was 35 years, according to a recent study in Shiraz from 2015 to 2018 (20).

We found a predominance of IBD in-hospital mortality in men, as in the Ananthakrishnan et al. study in the United States (28) and Guedes et al.'s publication from Brazil in 2022 (29).

Among the deceased IBD patients, the median duration of admission to death was 8 days, and 19 (22.6%) of IBD patients died on the first day of their hospital admission. The major causes of hospitalizations in UC patients who died were abdominal pain and diarrhea with or without rectal bleeding, which are symptoms of disease activity. The majority of patients had moderate to severe disease severity upon admission. Analyses of the admissions of patients with IBD in a tertiary hospital in Germany for one year with 91 patients found that most cases (29 patients, 31.8%) had moderate-to-severe flare-ups on admission (30). This indicates the importance of more intensive disease control and earlier IBD patient assessment.

Although the majority of deceased CD patients in this study were admitted with severe diseases, perianal complications, particularly fistulas, were the most common presentation. Fistula is a severe complication of CD, which is associated with increased morbidity

and impairment in quality of life, but it appeared that it was not a factor of mortality (25).

Consistent with other recent studies, we found an increased incidence of certain infectious diseases, including parasitic diseases, digestive system diseases (acute and sub-acute hepatic failure, acute peritonitis, and acute vascular disorders of the intestine), and circulatory system diseases, including pulmonary embolism, as the main causes of death for both UC and CD (11, 25, 31). In a study in the US, IBD patients were more likely to die prematurely of a gastrointestinal etiology (23). A meta-analysis examining cause-specific mortality in IBD revealed a statistically significant increase in colorectal cancer, pulmonary disease, and nonalcoholic liver disease for UC and a statistically significant increase in pulmonary disease and nonalcoholic liver disease for CD. However, neither UC nor CD showed increased mortality due to cardiovascular disease (32). Collectively, infectious diseases, which were the most important cause of death in this study, were rarely referenced among the most common causes of IBD death in recently published pieces of literature (10). It is worth noting that, in this study, the second most common cause of death was digestive system diseases; it comprised some infectious causes, including peritonitis and toxic megacolon. Although infectious diseases in IBD patients can be effectively controlled, they need timely and appropriate management. Increasing the clinical suspicion for infection diagnosis in IBD patients admitted during a disease flare, reducing the use of corticosteroids, and transitioning to steroid-sparing agents could potentially address this issue. Underuse of vaccinations in adults may also contribute to the higher rate of infectious causes of mortality in our series.

Corticosteroids, aminosalicylates, and azathioprine were the most common medications used among the patients. While the use of immunomodulators appears to alter the course of IBD, the interpretation of this finding remains unclear due to potential associations with infections, lymphatic and hematopoietic cancers, septicemia, and respiratory diseases. In a cohort study in the USA, exposure to Anti TNF recent use of prednisolone and narcotics were associated with increased risk of pneumonia and pneumonia-related hospitalization, and anti-TNF and prednisolone increased

risk of mortality (33). Care providers for IBD patients should consider a balanced view of the benefits of the use of immunomodulators and corticosteroids, as well as their possible effects on complications such as infection.

Diseases of the circulatory system were the third cause of death among IBD patients in this study, with pulmonary embolism as the leading cause in this category in 10 patients. This aligns with a Taiwanese study that identified pulmonary embolism as a risk factor for mortality in UC (25). The risk of pulmonary embolism increases in patients with active IBD disease, flare-ups, surgery, steroid treatment, and hospitalization (25, 34-37) and is associated with significant morbidity and mortality, making pulmonary embolism imperative in the clinical management of IBD patients (38).

While this is among the first multicenter studies in our area for evaluating the cause of death in hospitalized IBD patients, it will assist clinicians in better understanding the risk factors for mortality in these patients. However, using records may limit the confirmation of characteristics such as disease extent and extraintestinal manifestation. It is necessary to conduct population-based cohort studies on the causal effect of biologic agents, comorbidities, and malignancies on morbidity due to the study's retrospective nature on only two cities and the unclear percentage of deaths occurring in hospitals vs. other locations in Iran. Furthermore, population-based cohort studies, which employ legitimate statistical approaches, will shed light on the survival rate of IBD patients and the variables influencing this rate.

Conclusion

Infectious diseases are the most common cause of death in IBD patients in this series from Iran. Infectious diseases in hospitalized IBD patients should be strongly considered, and effective preventive measures should be considered, including appropriate vaccination and limiting the dose of steroids. Prevention and clinical management of pulmonary embolism in IBD patients need to be more considered. Further population-based cohort studies are highly recommended for the fortification of the results.

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Ethics approval

Anonymity for deceased IBD patients was guaranteed, and the study protocol was approved by the Ethical Committee of Shiraz University of Medical Sciences with Reg. No: IR.SUMS.REC.1400.274. The study protocol followed the ethical guidelines of the 2013 Declaration of Helsinki.

Conflict of interests

The authors declare that they have no competing interests.

References

1. Kaser A, Martínez-Naves E, Blumberg RS. Endoplasmic reticulum stress: implications for inflammatory bowel disease pathogenesis. *Curr Opin Gastroenterol* 2010;26:318.
2. Ramos GP, Papadakis KA, editors. Mechanisms of disease: inflammatory bowel diseases. *Mayo Clinic Proceedings*; 2019: Elsevier.
3. Kóvári B, Pai RK. Upper gastrointestinal tract involvement in inflammatory bowel diseases: histologic clues and pitfalls. *Adv Anat Pathol* 2022;29:2-14.
4. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020;5:17-30.
5. Olfatifar M, Zali MR, Pourhoseingholi MA, Balaii H, Ghavami SB, Ivanchuk M, et al. The emerging epidemic of inflammatory bowel disease in Asia and Iran by 2035: A modeling study. *BMC Gastroenterol* 2021;21:204.
6. Ghahramani S, Shojaadini H, Akbarzade A, Sadeghi F, Hajianpour V, Nozaie F, et al. Hospital cost of inflammatory bowel disease and its determinants in a multicenter study from Iran. *Middle East J Dig Dis* 2023;15:167-74.
7. Pakdin M, Zarei L, Bagheri Lankarani K, Ghahramani S. The cost of illness analysis of inflammatory bowel disease. *BMC Gastroenterol* 2023;23:21.
8. Lankarani KB, Ghahramani S, Hadipour M, Pourhashemi M, Mahmoodi A, Zeraatpishe M, et al. Determinants of hospital costs of inflammatory bowel disease. *Govareh* 2019;24:230-7.
9. Chu TPC, Moran GW, Card TR. The pattern of underlying cause of death in patients with inflammatory bowel disease in England: a record linkage study. *J Crohn's Colitis* 2016;11:578-85.
10. Follin-Arbelet B, Cvancarova Småstuen M, Hovde Ø, Jelsness-Jørgensen L-P, Moum B. Mortality in patients with inflammatory bowel disease: results from 30 years of follow-up in a Norwegian inception cohort (the IBSEN study). *J Crohn's Colitis* 2022;17:497-503.
11. Nocerino A, Feathers A, Ivanina E, Durbin L, Swaminath A. Mortality risk of inflammatory bowel disease: a case-control study of New York state death records. *Dig Dis Sci* 2019;64:1604-11.
12. Olén O, Askling J, Sachs MC, Neovius M, Smedby KE, Ekblom A, et al. Mortality in adult-onset and elderly-onset IBD: a nationwide register-based cohort study 1964–2014. *Gut* 2020;69:453-61.
13. Rönblom A, Ljunggren Ö, Karlsson U. Complications and adverse effects related to surgical and medical treatment in patients with inflammatory bowel disease in a prospectively recruited population-based cohort. *Scand J Gastroenterol* 2021;56:1296-303.
14. Li F, Ramirez Y, Yano Y, Daniel CR, Sharma SV, Brown EL, et al. The association between inflammatory bowel disease and all-cause and cause-specific mortality in the UK Biobank. *Ann Epidemiol* 2023;88:15-22.
15. Kassam Z, Belga S, Roifman I, Hirota S, Jijon H, Kaplan GG, et al. Inflammatory bowel disease cause-specific mortality: a primer for clinicians. *Inflamm Bowel Dis* 2014;20:2483-92.
16. Gheibipour H, Ahmadi A, Rahimian G. Epidemiology and clinical characteristics of ulcerative colitis in Chaharmahal and Bakhtiari Province, Iran. *Arch Hyg Sci* 2020;9.
17. Malekzadeh MM, Sima A, Alatab S, Sadeghi A, Daryani NE, Adibi P, et al. Iranian registry of Crohn's and colitis: study profile of first nation-wide inflammatory bowel disease registry in Middle East. *Intest Res* 2019;17:330.
18. Ghahramani S, Papisabet M, Sayari M, Hosseini SV, Lankarani KB. Colectomy in ulcerative colitis: trends in southern Iran in a decade. *Arch Iran Med* 2021;24:665.
19. Jameson JL, Kasper DL, Fauci AS, Hauser SL, Longo DL, Loscalzo J. Harrison's principles of internal medicine: McGraw-hill education; 2018.
20. Ghahramani S, Tamartash Z, Sayari M, Vahedi H, Karimiyan F, Heydari S, et al. Risk factors affecting 90-day readmission of patients with inflammatory bowel disease. *Middle East J Dig Dis* 2022;14:34-43.
21. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to

- moderately active ulcerative colitis. *N Engl J Med* 1987;317:1625-9.
22. Best WR, Beckett JM, Singleton JW, Kern Jr F. Development of a Crohn's disease activity index: National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;70:439-44.
23. Nocerino A, Feathers A, Ivanina E, Durbin L, Swaminath A. Mortality risk of inflammatory bowel disease: a case-control study of New York state death records. *Dig Dis Sci* 2019;64:1604-11.
24. Bitton A, Vutcovici M, Sewitch M, Suissa S, Brassard P. Mortality trends in Crohn's disease and ulcerative colitis: a population-based study in Quebec, Canada. *Inflamm Bowel Dis* 2016;22:416-23.
25. Lin W-C, Weng M-T, Tung C-C, Chang Y-T, Leong Y-L, Wang Y-T, et al. Trends and risk factors of mortality analysis in patients with inflammatory bowel disease: a Taiwanese nationwide population-based study. *J Transl Med* 2019;17:1-10.
26. Ghahramani S, Papisabet M, Sayari M, Hosseini SV, Bagheri Lankarani K. Colectomy in ulcerative colitis: trends in southern Iran in a decade. *Arch Iran Med* 2021;24:665-9.
27. Schwartz J, Stein DJ, Lipcsey M, Li B, Feuerstein JD. High rates of mortality in geriatric patients admitted for inflammatory bowel disease management. *J Clin Gastroenterol* 2022;56.
28. Ananthakrishnan AN, McGinley EL, Binion DG. Does it matter where you are hospitalized for inflammatory bowel disease? A nationwide analysis of hospital volume. *Am J Gastroenterol* 2008;103:2789-98.
29. Guedes ALV, Lorentz AL, Rios LFDAR, Freitas BC, Dias AGN, Uhlein ALE, et al. Hospitalizations and in-hospital mortality for inflammatory bowel disease in Brazil. *World J Gastrointest Pharmacol Ther* 2022;13:1.
30. Suarez Ferrer C, Poza Cordon J, Cerpa Arencibia A, Sanchez Azofra M, Martin Arranz E, Jacuotot Herranz M, et al. Hospitalization in inflammatory bowel disease: current perspective. *Gastroenterol Hepatol* 2018;41:350-2.
31. Hutfless SM, Weng X, Liu L, Allison J, Herrinton LJ. Mortality by medication use among patients with inflammatory bowel disease, 1996-2003. *Gastroenterology* 2007;133:1779-86.
32. Bewtra M, Kaiser LM, TenHave T, Lewis JD. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. *Inflamm Bowel Dis* 2013;19:599-613.
33. Khan N, Patel D, Trivedi C, Pernes T, Kavani H, Xie D, et al. The impact of IBD medications on risk of pneumonia and pneumonia-related hospitalization: a nationwide cohort study of 56,410 IBD patients. *Aliment Pharmacol Ther* 2022;55:64-72.
34. Gala D, Newsome T, Roberson N, Lee SM, Thekkanal M, Shah M, et al. Thromboembolic events in patients with inflammatory bowel disease: a comprehensive overview. *Disease* 2022;10:91.
35. Faye AS, Lee KE, Dodson J, Chodosh J, Hudesman D, Remzi F, et al. Increasing rates of venous thromboembolism among hospitalised patients with inflammatory bowel disease: a nationwide analysis. *Aliment Pharmacol Ther* 2022;56:1157-67.
36. Coremans L, Strubbe B, Peeters H. Venous thromboembolism in patients with inflammatory bowel disease: review of literature and practical algorithms. *Acta Gastroenterol Belg* 2021;84:79-85.
37. Yuhara H, Steinmaus C, Corley D, Koike J, Igarashi M, Suzuki T, Mine T. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;37:953-62