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Inflammatory Bowel Disease Cause-specific Mortality: A Primer for Clinicians

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Background: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) is perceived to harbor significant morbidity but limited excess mortality, thought to be driven by colon cancer, compared with the general population. Recent studies suggest mortality rates seem higher than previously understood, and there are emerging threats to mortality. Clinicians must be up to date and able to clearly convey the causes of mortality to arm individual patients with information to meaningfully participate in decisions regarding IBD treatment and maintenance of health.

Methods: A MEDLINE search was conducted to capture all relevant articles. Keyword search included: "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," and "mortality."

Results: CD and UC have slightly different causes of mortality; however, malignancy and colorectal cancer–associated mortality remains controversial in IBD. CD mortality seems to be driven by gastrointestinal disease, infection, and respiratory diseases. UC mortality was primarily attributable to gastrointestinal disease and infection. *Clostridium difficile* infection is an emerging cause of mortality in IBD. UC and CD patients have a marked increase in risk of thromboembolic disease. With advances in medical and surgical interventions, the exploration of treatment-associated mortality must continue to be evaluated.

Conclusions: Clinicians should be aware that conventional causes of death such as malignancy do not seem to be as significant a burden as originally perceived. However, emerging threats such as infection including *C. difficile* are noteworthy. Although CD and UC share similar causes of death, there seems to be some differences in cause-specific mortality.

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Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, mortality, cause-specific mortality

Inflammatory bowel disease (IBD) refers to a common group of chronic inflammatory diseases of the intestine that includes Crohn's disease (CD) and ulcerative colitis (UC).[1,2] Although early literature suggests the overall excess mortality burden was negligible in UC and only marginally increased in CD compared with the general population, emerging data are challenging earlier perceptions of IBD-associated mortality.[3–5] A large Danish population-based IBD cohort and a recent meta-analysis are suggesting higher excess mortality in both CD and UC then previously reported.[6,7] Traditionally, clinicians have ascribed much of the excess morality in IBD to colorectal cancer (CRC); however, this may not be the primary driver of mortality, and practitioners managing IBD must be well versed in the landscape of threats that face patients today.[8–10] Addressing emerging threats such as venous thromboembolism (VTE) and *Clostridium difficile* infection (CDI),[8,9,11–19] navigating patient concerns over cardiovascular disease,[20] and addressing mortality concerns about new medical and surgical interventions are critical for the patient-centered practitioner. In an era of personalized medicine, this review assists clinicians in updating and summarizing the causes of mortality in IBD, to empower individual patients with information to participate in treatment decisions and inform them of early clinical warning signs that require immediate medical attention.

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METHODS

The literature was reviewed using MEDLINE database and included a keyword search using the terms: "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," and "mortality." Discussion with content experts was conducted to obtain key references. Furthermore, a recursive search of the bibliographies of all relevant articles was completed. Where possible, data have been presented as standardized mortality ratio (SMR), standardized incidence ratio (SIR) with 95% confidence intervals (CI), relative risk (RR), hazard ratio (HR), or adjusted odds ratio (aOR).

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OVERALL MORTALITY IN PATIENTS WITH IBD

Earlier meta-analyses have captured a summary estimate of overall morality in CD and UC.[3,5] In CD, Duricova et al[3] conducted a meta-analysis of 9 population-based studies totaling 5411 patients and found a significantly increased pooled SMR of 1.39 (95% CI, 1.30–1.49). In the same vein, Jess et al[5] performed a UC meta-analysis of 10 population-based inception cohorts totaling 10,443 patients with UC. They reported an overall pooled SMR of 1.1 (95% CI, 0.9–1.2) suggesting that the overall risk of death in UC was not different than the general population.[5] These divergent rates of mortality in CD and UC continue to be observed in a more recent population cohort. A Finish IBD cohort that included 1254 patients with UC and 550 patients with CD found an overall morality SMR of 1.14 (95% CI, 0.84–1.49) in CD and an SMR of 0.90 (95% CI, 0.77–1.06) in UC.[21] The rationale for the divergence in IBD mortality is not completely clear; however, smoking may have an important role because widely established smoking is more common among patients with CD.

Emerging literature is beginning to challenge the previously reported magnitude of mortality in IBD and in particular UC. Jess et al[6] assessed mortality of a Danish IBD population-based cohort with 36,080 patients with UC and 15,361 patients with CD over a 30-year time period. They found mortality was increased by approximately 10% in patients with UC and 50% among patients with CD compared with the general population. Specifically, patients with UC had a HR of 1.25 (95% CI, 1.22–1.28) and patients with CD had a HR of 1.73 (95% CI, 1.67–1.80).[6] A recent meta-analysis by Bewtra et al,[7] which did not include the large Danish IBD cohort, corroborated the modest excess in mortality in patients with UC and reported an all-cause mortality summary SMR of 1.19 (95% CI, 1.06–1.35). The all-cause mortality summary SMR for patients with CD was reported as 1.38 (95% CI, 1.23–1.55), which is in keeping with the previous meta-analysis.[3,7] Given the large Danish IBD population-based cohort that eclipses the previous meta-analysis sample size in the context of robust longitudinal follow-up, clinicians should be aware that the absolute mortality rate in both UC and CD might be higher than originally perceived. Although it is a modest increase in excess mortality, it remains meaningfully important to patients. This is highlighted by optics of mortality associated with diabetes, which also carries with it a modest excess risk of morality with the SMR for Type II diabetes 2.9 and Type I 1.8.[22]

Earlier meta-analyses explored cause-specific mortality. Specifically, CD mortality seemed to be driven by gastrointestinal (GI) disease (SMR, 6.76; 95% CI, 4.37–10.45), which the authors speculated might be explained by increased pancreatitis and cholelithiasis-associated deaths, although these were not specifically coded.[3] Furthermore, CD had increased risk of dying from genitourinary diseases (SMR, 3.28; 95% CI, 1.69–6.35), which the authors speculated was secondary to smoking-associated bladder cancer, although this was not specifically coded either.[3] Mortality associated with respiratory diseases also potentially linked to smoking such as chronic obstructive pulmonary disease (2.55; 95% CI, 1.19–5.47) and pulmonary malignancy (SMR, 2.72; 95% CI, 1.35–5.45) were also increased in patients with CD.[3] The large Danish IBD population-based cohort largely emphasizes similar CD-related mortality-associated etiologies including GI disease (HR, 5.71; 95% CI, 5.28–6.19) and respiratory diseases (HR, 2.05; 95% CI, 1.86–2.27), although infection was noteworthy (HR, 3.23; 95% CI, 2.64–3.94).[6] However, UC mortality was driven by pulmonary embolism (PE) (SMR, 4.0; 95% CI, 1.5–8.7), nonalcoholic liver disease (SMR, 4.0; 95% CI, 2.5–6.5), and pneumonia (SMR, 3.1; 95% CI, 2.0–4.6).[5] Interestingly, the above Danish IBD cohort noted slight differences in causes of mortality in patients with UC. UC mortality was driven by GI disease (HR, 3.06; 95% CI, 2.88–3.25) and infection (HR, 2.21; 95% CI, 1.93–2.53), although PE was not specifically captured in the coding process.[6] In the same study, Jess et al found that the mortality greatly increased in the first year after being diagnosed with IBD (UC: HR, 2.43; 95% CI, 2.31–2.57 versus CD: HR, 3.69; 95% CI, 3.41–3.99). This was primarily driven by infection (UC: HR, 9.17; 95% CI, 7.19–11.69; CD: HR, 10.19; 95% CI, 6.88–15.11) and GI disease (UC: HR, 13.27; 95% CI, 11.87–14.82; CD: HR, 23.02; 95% CI, 19.69–26.92).[6] Overall mortality fell dramatically during the 2- to 4-year period after diagnosis in both UC (HR, 1.14; 95% CI, 1.09–1.19) and in CD (HR, 1.53; 95% CI, 1.43–1.63).[6] Interestingly, those diagnosed with UC in childhood or adolescence had a 2.15-fold higher mortality than those diagnosed at age 60 to 70 years.[6] In CD, mortality was 62% higher in patients diagnosed at age 0 to 19 years versus those diagnosed with CD at age of 60 to 79 years.[6]

Ananthakrishnan et al[23] recently reported on the impact of primary sclerosing cholangitis (PSC) on mortality in IBD. In this multicenter cohort of 5506 patients with CD and 5522 patients with UC, 224 (2%) were diagnosed with IBD-PSC and had higher mortality than those with IBD alone (OR, 3.51; 95% CI, 2.30–5.36).[23] Those with IBD-PSC also had increased risk of cancers versus those with IBD alone (OR, 4.36; 95% CI, 2.99–6.37). This was primarily driven by excess risk of cancer of the digestive tract (OR, 10.40; 95% CI, 6.86–15.76), pancreatic (OR, 11.22; 95% CI, 4.11–30.62), CRC (OR, 5.00; 95% CI, 2.80–8.95), and cholangiocarcinoma (OR, 55.31; 95% CI, 22.20–137.80).[23]

Cause-specific mortality data from meta-analyses must be interpreted with caution given methodological limitations. Etiologies of cause-specific mortality frequently only had a few studies to generate a pooled SMR. Accordingly, studies may be underpowered, and generalizability to clinicians and clinical practice may not be appropriate. This is particularly important when cause-specific pooled SMRs are driven by a single geographic-specific cohort. Additionally, it seems that heterogeneity was significant in the UC meta-analysis ($\chi^2 = 54$, $P < 0.001$) and not reported in the CD meta-analysis and thus one must be cautious when interpreting subgroup cause-specific mortality results.[3,5] See Table 1 for a summary of statements regarding cause-specific mortality in IBD.

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THROMBOSIS-ASSOCIATED MORTALITY IN IBD

Inflammation is thought to play a major role in the development of thromboembolic phenomenon, such as VTE. IBD is associated with a >3-fold increased risk of thromboembolic disease with risk exceeding 15-fold during an IBD flare.[16,17,24] An Austrian prospective cohort study also suggested that this risks extends into recurrent VTE with a HR of 2.5 (95% CI, 1.4–4.2) in patients with IBD.[17] Interestingly, arterial thrombotic events may also be increased in IBD. A large American retrospective cohort study reported that patients with IBD had a marked increase in risk of acute mesenteric ischemia (HR, 11.2; $P < 0.001$), although they did not find an increased risk in other arterial thrombotic events.[25] Overall, the impact of thromboembolic disease is significant as the incidence of systemic thromboembolic events has been reported as high as 7.7% in some clinical studies.[26–28]

The risk of thromboembolic phenomenon has also been explored within CD and UC; however, the VTE study results are not congruent. A Canadian population-based study of hospitalized patients with IBD highlighted a slightly higher burden of deep venous thrombosis and PE in CD. Specifically, in patients with CD, the incidence rate ratio (IRR) for deep venous thrombosis was 4.7 (95% CI, 3.5–6.3) and for PE 2.9 (95% CI, 1.8–4.7), whereas in the UC group, the IRR for deep venous thrombosis was 2.8 (95% CI, 2.1–3.7) and for PE 3.6 (95% CI, 2.5–5.2).[29] However, a large American population-based study of hospitalized patients with IBD suggests VTE was more prevalent among patients with UC compared with CD (OR, 1.32; 95% CI, 1.17–1.48). Specifically, UC had an OR of 1.84 (1.70–2.01) for VTE, whereas CD had an OR of 1.48 (1.35–1.62) compared with non-IBD patients.[30]

Importantly, there is a paucity of data on mortality-associated with VTE within IBD. Nguyen and Sam found that VTE was associated with an increased risk of mortality in patients with IBD after adjustment for demographic, hospital, and clinical factors compared with non-VTE patients with IBD (aOR, 2.50; 95% CI, 1.83–2.43).[30] Additionally, they observed that after adjusting for confounding factors, patients with IBD with VTE had a 2.1-fold increase in mortality compared with non-IBD patients with VTE (95% CI, 1.6–2.9; $P < 0.0001$).[30] Between 1991 and 2000, Solem et al[31] observed a VTE-related mortality rate of 22% after a median follow-up of 1.8 years in their IBD group. Interestingly, this is in accordance with the reported mortality rate reported in the same institution from 1970 to 1980.[26] The differences between VTE mortality in CD and UC have not been extensively evaluated. Nguyen and Sam did suggest patients with UC were more likely to have VTE-associated mortality. They reported UC to have more VTE-associated morality (37.4 versus 9.9 cases per 1000 hospitalizations, $P < 0.001$) compared with CD (17.0 versus 4.2 cases per 1000 hospitalizations, $P < 0.0001$).[30] Overall, the exact increase in risk of death from thromboembolic disease is still unclear. Additional studies are required to assess the precise burden of mortality of VTE in IBD and delineate if CD or UC are particularly at risk.

CARDIOVASCULAR DISEASE-ASSOCIATED MORTALITY IN IBD

Some chronic inflammatory diseases have been linked to accelerated atherosclerosis, and preliminary studies have alluded to endovascular dysfunction in IBD.[32] This relationship was further explored in the context of IBD by Bernstein et al[9] who used the Manitoba IBD administrative database to compare results with a matched cohort. They found an increased risk for coronary artery disease in patients with IBD (IRR 1.26; 95% CI, 1.11–1.44); however, this risk was not significant when IBD was stratified by IBD classification: CD (1.50; 95% CI, 0.91–2.46) and UC (1.11; 95% CI, 0.65–1.89).[9] Additionally, only patients with CD displayed an increased risk for cerebrovascular disease (IRR, 1.32; 95% CI, 1.05–1.66). Although this study concluded that patients with IBD were more likely to develop coronary artery disease, the authors did not directly assess mortality associated with coronary artery disease.

Cardiovascular (CV) mortality in IBD was assessed by Dorn and Sandler[33] in a meta-analysis of 11 studies capturing 4532 patients with CD and 9533 patients with UC. The SMR point estimates ranged from 0.7 to 1.5 for patients with CD and 0.6 to 1.1 for patients with UC; however, the meta-SMR for CD was 1.0 (95% CI, 0.8–1.1) and the meta-SMR for UC was 0.9 (95% CI, 0.8–1.0).[33] Thus, these authors concluded that IBD is not associated with increased CV-associated mortality.[33] This result is in accordance with other meta-analyses that suggest that the risk of CV-associated mortality was not increased in CD or UC versus the general population.[3,34] Interestingly, a recent study did observe a slightly elevated HR for CV-associated mortality in CD (1.39; 95% CI, 1.28–1.51) and UC (1.20; 95% CI, 1.14–1.26), and some reports have questioned if there may be a subgroup of patients with IBD that are more susceptible.[6,35] Although a Dutch study did not find that patients with IBD had a significantly increased risk of CV-related mortality, they observed that individuals with colonic CD were more likely to die of cardiovascular disease (SMR, 3.5; 95% CI, 1.1–8.2).[35] Another study suggests women older than 40 years with IBD were at increased risk for myocardial infarction (HR, 1.6; $P < 0.05$) and women younger than 40 years were shown to have an increased risk of stroke (HR, 2.4; $P = 0.04$).[25] Although the IBD type, gender, and age differences are interesting, one must interpret the results with caution because the role of smoking on the vascular burden may in fact be the most important factor, and the overall risk of myocardial infarction in patients with IBD was not significantly increased.[25] Ultimately, the current body of literature does not support a strong link to CV-associated mortality in IBD, and although subgroups may be at risk, it remains unclear if this risk may be predominately driven by established environmental factors, such as smoking.

INFECTION-ASSOCIATED MORTALITY IN IBD

Advances in IBD therapeutics have facilitated an increase in use of agents that confer systemic immunosuppression and lead to

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increases in overall rates of infection.[36] Recent studies have highlighted the burden of infection-associated mortality in IBD. Jess et al[6] reported the HR for infection-associated mortality was 3.23 (95% CI, 2.64–3.94) in CD and 2.21 (95% CI, 1.93–2.53) in UC. Again, as noted above, mortality due to infection was dramatically increased during the first year after IBD diagnosis (UC: HR, 9.17; 95% CI, 7.19–11.69; CD: HR, 10.19; 95% CI, 6.88–15.11).[6]

Ananthakrishnan and McGinley[37] reported that patients with IBD with infection-related hospitalizations had significantly greater risk of mortality compared with those without (OR, 4.8; 95% CI, 3.67–5.23). Specifically, they noted the highest rates of excess mortality was associated with sepsis (OR, 15.18; 95% CI, 12.39–16.61) and pneumonia (OR, 3.61; 95% CI, 2.92–4.47).[37] Enteric infections (OR, 2.58; 95% CI, 2.06–3.22) and urinary tract infections (OR, 1.39; 1.13–1.72) also were associated with excess mortality, whereas interestingly viral infections, abdominal abscesses, candida, and postoperative infections did not seem to carry any excess mortality.[37] The mortality burden of nosocomial infections such as CDI and Methicillin-resistant *Staphyloccoccus aureus* (MRSA) in IBD has been particularly significant.

The emergence of CDI in IBD is well established with a rise in CDI prevalence and recognition that patients with IBD are vulnerable despite the absence of conventional risk factors.[18,38–40] This trend has been accompanied by a significant CDI-associated mortality. In the United States Nationwide Inpatient Sample, CDI-associated mortality in the IBD cohort increased dramatically from 1993 to 2003 with an overall in-hospital mortality for patients with IBD with CDI of 5.7%.[18] The CDI-associated mortality was higher in UC (7.7%) than in CD (2.4%).[18] Also, the associated operative mortality for CDI was higher in UC (25.7%) than CD (4.6%).[18] Another recent study found that from 1998 to 2007, CDI in hospitalized patients with IBD doubled (1.4%–2.9%), and there was an increase in absolute CDI-associated mortality (5.9%–7.2%) leading to speculation around the emergence of hypervirulent CDI strains as a possible etiologic consideration.[41] Nguyen et al[42] also showed a near doubling of the incidence of CDI in UC with a corresponding increase in mortality risk compared with patients with UC alone (OR, 3.79; 95% CI, 2.84–5.06). More recently, a study suggests that CDI is among the leading causes of infection-associated mortality in IBD (OR, 3.23; 95% CI, 2.55–4.03).[37] Furthermore, Ananthakrishnan et al[43] recently reported that host genetics may influence susceptibility to CDI in IBD. They found that 6 documented IBD risk polymorphisms were associated with an increased risk of CDI, and 2 were inversely associated.[43] Overall, CDI has rapidly become a major cause of morbidity and mortality in IBD, but clinicians must be specifically aware that patients with UC may be most vulnerable to CDI-associated adverse outcomes.

MRSA is a major cause of nosocomial infections worldwide; however, there has been speculation that patients with IBD may be at greater risk given risk factor profiles.[44,45] Nguyen et al,[44] compared the prevalence and in-hospital mortality of MRSA infections among IBD, non-IBD GI, and general medical patients using the United States Nationwide Inpatient Sample between 1998 and 2004. The authors concluded that patients with IBD were at increased risk for MRSA infection compared with non-IBD GI (aOR, 1.61; 95% CI, 1.33–1.96) and general medical inpatients (aOR, 1.36; 95% CI, 1.11–1.66). Also, they found that patients with IBD had an increased in-hospital mortality (aOR, 7.61; $P = 0.001$) compared with non-IBD GI (aOR, 3.20; 95% CI, 2.46–4.18) and general medical patients (aOR, 2.15; 95% CI, 1.57–2.93) with MRSA infections.[45] With the exponential global rise of nosocomial infections such as MRSA and CDI, clinicians must be aware of the susceptibility of nosocomial infections and conventional infections in their vulnerable IBD patient population.

Infection-mediated macrophage activation syndrome (MAS) in IBD has recently gained recognition. MAS is a clinical syndrome characterized by fevers, peripheral blood cytopenias, hepatosplenomegaly, and a constellation of laboratory abnormalities including elevated serum ferritin, triglycerides, soluble interleukin-2 receptor, in the context of decreased NK-cell activity. A recent systematic review identified 50 cases of MAS in IBD with a mortality rate of 30%.[46] Infection seemed to be a main trigger particularly with associated cytomegalovirus or Epstein–Bar virus infections, although bacterial infections seemed to be a potential trigger in some cases. Given the high burden of mortality with MAS in IBD, clinicians must be aware to facilitate early diagnosis, especially in high-risk patients, such as those on thiopurine therapy.[46]

MEDICAL TREATMENT-ASSOCIATED MORTALITY IN IBD

There has been growing concerns about treatment-related mortality related to anti-tumor necrosis factor (TNF) therapy and immunomodulator agents. Accordingly, a number of studies have attempted to describe the mortality profile of these core therapeutic interventions. In a study by Zabana et al[47] assessing 152 patients (121 CD, 24 UC, 7 indeterminate colitis) treated with infliximab, the mortality rate was 3% over a 9-year period. In the larger TREAT Registry database of 6253 patients with CD, 3179 received infliximab (5519 patient-years), and the mortality rates were not different between those who received infliximab and patients with CD who did not (RR, 1.24; 95% CI, 0.73–2.10).[48] A study pooled the primary safety data across 10 IBD trials that compared infliximab with placebo and found no increase in malignancy or infections, including those classified as serious.[49,50] More recently, a Dutch cohort of 469 patients with CD on infliximab reported a mortality of only 1.9% (0.39/100 patient-years).[51] Similarly, Colombel et al[52] reviewed the safety data from 6 international clinical trials of patients with CD treated with adalimumab and found that these patients had a decreased SMR of 0.44 (95% CI, 0.12–1.12).

Although anti-TNF therapy seems to have a tolerable safety profile, there seems to be some discrepancy about immunomodulators, such as 6-mercaptopurine, azathioprine, and methotrexate. Lichtenstein et al suggest that in patients with UC, but not CD, immunomodulator treatment is associated with a higher

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incidence of infection although no increase in mortality compared with placebo.[49,50] Additionally, they suggest that in patients with CD, but not UC, immunomodulator treatment is associated with a higher incidence of malignancy but again no increase in mortality compared with placebo.[49,50] In contrast to this study, the TREAT Registry data suggest immunomodulators are correlated with a trend towards a decreased risk of death although this was not statistically significant (aOR, 0.731; 95% CI, 0.398–1.340).[48] Additionally, the TREAT Registry data highlighted that prednisone, and narcotic analgesics were independent risk factors for serious infection (OR, 2.21; 95% CI, 0.64–1.54 and OR, 2.38; 95% CI, 1.56–3.63, respectively) and most importantly that prednisone was the only factor associated with increased mortality risk (OR, 2.10; 95% CI, 1.15–3.83).[48]

Recently, Pasternak et al[53] reported on the use of azathioprine and the risk of cancer in patients with IBD. This large study from Denmark found that azathioprine use was associated with an overall increase in cancers (HR, 1.41; 95% CI, 1.15–1.74) but no change in those previously exposed (HR, 1.02; 95% CI, 0.83–1.25).[53] The only significant increases were the risk of developing lymphoid tissue cancers and urinary tract cancers but no significant increases in CRC or skin cancers in those taking or previously exposed to azathioprine.[53] The risk of skin cancer in IBD is discussed further below. Overall, clinicians must be cautious with their use of prednisone and narcotic in the treatment of IBD; however, anti-TNF treatments seem to have a tolerable safety profile based on the current literature.

SURGERY-ASSOCIATED MORTALITY IN IBD

Postoperative mortality is an important factor in the survival of patients with CD given the prevalence of surgery among this patient population. It is estimated that up to 70% to 90% of patients with CD will require surgery at some point in their disease course.[54] In the cohort study by Jess et al,[34] the 10-year probability of intestinal resection during the first decade after diagnosis was 63% to 65% with no significant change from cohort 1 (1962–1987) to cohort 2 (1991–1993). More recently, Kaplan's group reported in a systematic review and meta-analysis that surgery rates for CD and UC have decreased over the last 6 decades.[55] Risk of surgery 1, 5, and 10 years after diagnosis of CD was 16.3% (95% CI, 11.4%–23.2%), 33.3% (95% CI, 26.3%–42.1%), and 46.6% (95% CI, 37.7%–57.7%), respectively.[55] The risk of surgery 1, 5, and 10 years after diagnosis of UC was 4.9% (95% CI, 3.8%–6.3%), 11.6% (95% CI, 9.3%–14.4%), and 15.6% (95% CI, 12.5%–19.6%), respectively.[55]

Muhe et al[56] reported on 155 patients who underwent intestinal resection for CD, with an operative mortality rate of 8.4% with 12 of 13 deaths related to perioperative sepsis. Subsequent studies have reported significantly lower mortality rates. In a study of 282 patients who underwent a total of 331 intestinal resections, the mortality rate was 1.2% with all cases attributed to perioperative intra-abdominal sepsis.[57] A nationwide study in the United States compared laparoscopic surgical approach versus traditional open approaches in 396,911 patients admitted for CD, of whom 49,609 (12%) underwent surgery reported a low mortality rates in both arms.[58] The mortality rate was 0.2% in the laparoscopic group versus 0.9% in the open surgery group.[58] In a recent smaller study comprising 124 patients who underwent laparoscopic ileocolonic resection, there were no surgical-related deaths reported.[59] Overall, advances in the field of surgery have led to surgical mortality rates falling significantly in CD over the last 25 years.

Similarly, perioperative mortality in UC is an important issue given the prevalence of surgical procedures among this patient population. Approximately, 15% to 30% of patients with UC will undergo colectomy at some point during the course of the disease.[34,55,60] The 2 most common surgical procedures associated with UC include total proctocolectomy with ileal pouch anal anastomosis and total abdominal colectomy with ileostomy. Jess et al[5] found that the probability of proctocolectomy in patients with UC, during the first decade after diagnosis, was similar in the 3 cohorts studied (1962–1987, 1991–1993, and 2003–2004) with a 10-year probability of 24%. Similarly, Hefti et al[60] reported that 97 (17.3%) of 561 patients with UC underwent colectomy in a study with a 21.4-year median follow-up period.

Kaplan et al[61] assessed postoperative mortality after colectomy for UC in the United States using a Nationwide Inpatient Sample Database of 7108 patients (1995–2005) and found an overall mortality rate of 2.3%.[61] Specifically, the mortality rate was the lowest in those undergoing a pouch procedure (0.15%) and the highest in patients with UC undergoing colectomy, ileostomy, and rectal stump surgery (5.5%). Furthermore, in-hospital mortality was higher in patients admitted emergently (aOR, 5.40; 95% CI, 3.48–8.40), in those older than 60 years of age (aOR, 8.70; 95% CI, 3.30–22.92), and in those with Medicaid healthcare insurance (aOR, 4.29; 95% CI, 2.13–8.66). There was also an increased mortality rate for patients with UC undergoing colectomy after an emergent or urgent admission, with a mortality rate of 5.7% compared with 0.7% in those admitted electively.[61] These rates have also been observed in a more recent Danish cohort study.[62] They found that patients with IBD undergoing total emergency colectomy had a 30-day mortality of 5.3% compared with 1% for elective procedures and that patients with UC fared slightly better than patients with CD in the context of emergency total colectomy (5.3% versus 8.1% mortality, respectively).[62] Ikeuchi et al[63] reported on surgical outcomes and mortality in a Japanese study of 1000 patients over a 24-year period. Ileal pouch anal anastomosis was performed in 944 patients, with 79% of all cases performed electively. They reported 20 postoperative deaths with 35% attributable to pneumonia, 25% due to sepsis, and 15% secondary to advanced CRC as the major etiologies.[63] Overall, surgical mortality is rare in UC but it still remains an important area of patient interest given the prevalence of colectomy in this patient population.[64]

LATE-ONSET IBD AND MORTALITY

Recent evidence has shown decreased survival and more complicated course in late-onset IBD.[19,65–72] It is established that

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approximately 10% to 15% of the patients with IBD are diagnosed older than 60 years with 50% of those being diagnosed between 60 and 70 years of age.[71,73] Ananthakrishnan and Binion[19] found that patients with IBD older than 65 years accounted for 25% of all hospitalizations, with a higher proportion of admissions among patients with UC (UC, 33.7% and CD, 20.3%). Furthermore, in-hospital mortality was significantly higher in the group aged 65 or older (OR, 3.91; 95% CI, 2.5–6.11), even after adjusting for comorbidities. Generally, the disease course is more severe in elderly patients with UC, and the in-hospital mortality rates are approximately 3 to 5 times higher in both UC and CD patients older than 65 years, when compared with younger groups.[72] Although CRC is responsible for 15% of deaths in IBD, the difference in mortality between early and late-onset IBD is not entirely accounted for by CRC rates.[74] Overall, clinicians must be aware that late-onset IBD carries it with a higher mortality particularly in UC and may require a lower threshold for therapeutic escalation.

MALIGNANCY-ASSOCIATED MORTALITY IN IBD

Malignancy-associated mortality in IBD has developed into an important area of IBD research both in terms of all-cause malignancy and CRC-associated malignancy. Despite previous perceptions, a recent study has suggested that patients with IBD do not have a significantly elevated risk of malignancy-associated mortality compared with the general public.[6] They do suggest that patients with CD may have a slightly increased risk (HR, 1.45; 95% CI, 1.35–1.56) compared with patients with UC (HR, 1.07; 95% CI, 1.02–1.12) but this was modest at the best.[6] They also noted that the risk of dying of CRC has decreased (2000–2010 versus 1990–1999 and 1982–1989) with the largest decline seen in the UC population 2000–2010 versus 1982–1989 (HR, 0.69; 95% CI, 0.49–0.98).[6] Interestingly, Romberg-Camps et al[35] reported that mortality risk from all cancers was actually reduced in IBD compared with the general population with a SMR of 0.5 for both UC (95% CI, 0.2–0.9) and CD (95% CI, 0.1–1.3) although the rationale is elusive at present. This interesting observation was also found in a study from Winther et al[75] who reported mortality from all cancers was significantly lower than expected in patients with UC (SMR, 0.70; 95% CI, 0.52–0.93).[75] Additionally, a recent meta-analysis did not find a significant increase in mortality risk from CRC in patients with CD (SMR, 1.34; 95% CI, 0.54–3.33).[3] Recent cohort studies remain divided on CRC-associated mortality in IBD.[76,77] Although patients with CD had an increased risk of dying from GI malignancy (SMR, 4.7; 95% CI, 1.7–10), their relative risk of CRC was not significantly different from that expected (RR, 1.9), and the cumulative risk of CRC was 2.4% after 25 years of CD.[78] Pancreatic and small bowel tumors accounted for the majority of non-CRC GI malignancy-related deaths.[78] Similarly, the meta-analysis by Duricova et al[3] found an overall increased risk of death from all cancers (SMR, 1.50; 95% CI, 1.18–1.92), but the main drivers of this was pulmonary cancer (SMR, 2.72; 95% CI, 1.35–5.45) and malignant melanoma (SMR, 10.0; 95% CI, 1.21–36.1).

Recent concerns about increased risk of skin cancers have been raised in IBD. Bernstein's group in Manitoba found that patients with IBD had an increased risk of nonmelanoma skin cancers (NMSC) (HR, 1.25; 95% CI, 1.09–1.43) and that the use of thiopurines increased the risk of squamous cell carcinomas (HR, 5.40; 95% CI, 2.00–14.56).[79] Similarly, a recent French study by Peyrin-Biroulet showed that current (HR, 5.9; 95% CI, 2.1–16.4) and past (HR, 3.9; 95% CI, 1.3–12.1) thiopurines use markedly increased the risk of NMSC in those with IBD.[80] Long et al[81] studied a United States database with the largest cohort of patients with IBD to date and also found an increased risk of NMSC in those taking thiopurines (OR, 4.27; 95% CI, 3.08–5.92). Although smaller studies failed to show a significant increase in NMSC in patients with IBD taking thiopurines (RR, 1.67; 95% CI, 0.86–3.21[53]; OR, 0.99; 95% CI, 0.35–2.81[82]; HR, 0.85; 95% CI, 0.51–1.41[83]), the above larger more comprehensive studies are strong evidence for increased risk.

The risk of melanoma has also been shown to be increased in IBD[84] and has been found to be higher in CD (HR, 1.28; 95% CI, 1.00–1.64), and the use of biologic therapies increased the risk (OR, 1.88; 95% CI, 1.08–3.29).[85] Duricova et al[3] found a marked increased risk of patients with CD dying from melanoma (SMR, 10.0; 95% CI, 1.21–36.1). However, a recent study with 49,735 patient-years of follow-up did not show an increased risk of melanoma in patients with IBD compared with the general population (SIR, 0.64; 95% CI, 0.17–1.63), and the risk was not increased with thiopurines (SIR, 0; 95% CI, 0–3.11) or anti-TNF therapy.[86] Interestingly, in a large study of rheumatoid arthritis (29,555 patients), psoriasis (1298 patients), psoriatic arthritis (2498 patients), and IBD (6357 patients), anti-TNF therapy was recently shown not to increase the risk of any of the top 10 cancers or NMSC compared with other therapies.[87] More studies are required to further assess the risk patient with IBD on anti-TNF therapy developing either NMSC or melanoma. It seems that patients with IBD may have an increased risk of developing skin cancers, and they should be counseled on protection against sun exposure and consult with a dermatologist for screening on a regular basis, especially those on thiopurines.[88]

Singh et al[89] recently published a systematic review and meta-analysis on the risk of melanoma in IBD. They assessed 12 studies that included 172,837 patients with IBD that included 179 IBD-melanoma cases and found IBD was associated with a 37% increased risk of melanoma.[89] The risk was higher in patients with CD (RR, 1.80; 95% CI, 1.17–2.75) versus UC (RR, 1.23; 95% CI, 1.01–1.50), and the risk was higher before introduction of biologic therapy in 1998 (7 studies; RR, 1.52; 95% CI, 1.02–2.25) but not in studies performed after 1998 (only 2 studies; RR, 1.08; 95% CI, 0.59–1.96).[89]

The risk of CRC in IBD seems much more controversial in the literature. Early studies suggested that those with UC had significantly increased risk of CRC than those with CD.[90–93] However, subsequent studies suggested that patients with CD with colonic involvement also had an increase risk of CRC, potentially more than the risk observed in UC.[94–97] These assertions have

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TABLE 1. Cause-specific Mortality in IBD Statements, Clinical Impact, and Risk Estimates

Statement	Clinical Impact (++: Agree; −−: Disagree)	Highest Risk Estimate	Lowest Risk Estimate
Overall Mortality			
UC is associated with increased mortality	+	HR, 1.25 (95% CI, 1.22–1.28)[6]	Pooled SMR, 1.1 (95% CI, 0.9–1.2)[5]
CD is associated with increased mortality	++	HR, 1.73 (95% CI, 1.67–1.80)[6]	SMR, 1.14 (95% CI, 0.84–1.49)[21]
Thrombosis			
Patients with IBD are more likely to die from VTE then non-IBD patients	++	SMR, 4.0 (95% CI, 1.5–8.7)[5,a]	aOR, 2.1 (95% CI, 1.6–2.9)[30]
Cardiovascular disease			
Patients with CD are more likely to die from CV disease than the general population	−	SMR, 3.5 (95% CI, 1.1–8.2)[35,b]	Meta-SMR 1.0 (95% CI, 0.8–1.1)[33]
Patients with UC are more likely to die from CV disease than the general population	−−	SMR, 1.20 (95% CI, 1.14–1.26)[35]	Meta-SMR, 0.9 (95% CI, 0.8–1.0)[33]
CDI			
Patients with UC are more likely to die from CDI than non-IBD patients	++	OR, 3.79 (95% CI, 2.84–5.06)[42]	OR, 3.23 (95% CI, 2.55–4.03)[37,c]
Patients with CD are more likely to die from CDI than non-IBD patients	+	OR, 3.23 (95% CI, 2.55–4.03)[37,c]	OR, 1.66 (95% CI, 0.75–3.66)[42]
Anti-TNF therapy			
Patients with CD are more likely to die on anti-TNF therapy compared with patients with CD not on anti-TNF treatment	−−	RR, 1.24 (95% CI, 0.73–2.10)[48,d]	SMR, 0.44 (95% CI, 0.12–1.12)[52,e]
Melanoma			
Patients with IBD are at risk for melanoma	+/−	SMR, 10 (95% CI, 1.21–36.1)[3,f]	SIR, 0.64 (95% CI, 0.17–1.63)[86,g]
CRC			
Patients with CD are more likely to die of CRC compared with the general population	+/−	SMR, 3.12 (0.04–17.4)[100]	Meta-SMR, 1.34 (0.54–3.33)[3]
Patients with UC are more likely to die of CRC compared with the general population	+/−	Meta-SMR, 1.9 (95% CI, 1.0–3.8)[5]	SMR, 0.70 (95% CI, 0.52–0.93)[75]

+, some evidence for agreement; ++, strong evidence for agreement; −, some evidence for disagreement; −−, strong evidence for disagreement; +/−, conflicting evidence.
[a]Pulmonary embolism-associated mortality in UC.
[b]CV disease-associated mortality in colonic CD.
[c]CDI-associated mortality in hospitalized patients with IBD; no delineation between CD and UC.
[d]Infliximab-associated mortality in CD.
[e]Adalimumb-associated morality in CD.
[f]Melanoma-associated morality in CD.
[g]No increased risk of melanoma in IBD population compared with general population, and in turn, melanoma-associated morality is a nonfactor.

largely been refuted because many large studies have not reported increased CRC-associated mortality.[5,75,78] Additionally, although some cohorts suggest an elevated SIR for CRC, a recent meta-analysis did not find a significant increase in mortality risk from CRC in patients with CD (SMR, 1.34; 95% CI, 0.54–3.33).[3] Recent cohort studies seem to support this suggestion.[76] Although patients with CD had an increased risk of dying from GI malignancy (SMR, 4.7; 95% CI, 1.7–10), their relative risk of CRC was not significantly different from that expected (RR, 1.9) and the cumulative risk of CRC was 2.4% after 25 years of CD.[78] Larsen et al[98] compared 100 CRC patients with CD with 71, 438 CRC patients without CD. They found that patients with CD developed CRC at a younger age (57.7 versus 71.2 yr) and were more often female (57% versus 51%).[98] Although the stage of CRC at diagnosis was similar between those with and without CD, those with CD had reduced survival.[98] CRC is equally controversial in UC patient population. Jess et al[34] also found no increased risk of CRC in patients with UC in their Danish cohort, with only 14 patients having developed CRC compared with expected 13 (SIR, 1.1; 95% CI, 0.6–1.8). A more recent study by Jess et al[99] found the risk of CRC among patients with UC was comparable with the general population (RR, 1.07; CI, 0.95–1.21). Those with UC diagnosed in childhood or adolescence, those with long duration of disease (13 or more yr), and those with PSC were at increased risk.[99] Interestingly, they found that the risk of CRC in UC decreased markedly from 1979 to 1988 (RR, 1.34; 95% CI, 1.13–1.58)

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compared with 1999 to 2008 (RR, 0.57; 95% CI, 0.41–0.80).[99] The risk of CRC in CD was 0.85 (95% CI, 0.67–1.07) and did not change over the above time periods.[99] The same group recently completed a meta-analysis of population-based cohort studies (based on review of meeting abstracts from 2006 to 2011) assessing the risk of CRC in UC, and they found that UC increases the risk of CRC (SIR, 2.4; 95% CI, 2.1–2.7).[4] Men with UC had a greater risk of CRC (SIR, 2.6; 95% CI, 2.2–3.0) than women (SIR, 1.9; 95% CI, 1.5–2.3).[4] They also found that young age at diagnosis and extensive colitis increased the risk.[4]

Overall, it seems from the body of literature that the rates of IBD-associated CRC and associated mortality are falling, and although some associated excess CRC related mortality may exist, it is not as high as commonly perceived.

LIMITATIONS

There are several limitations that must be considered when interpreting the data from this review. A major drawback of epidemiology studies observing mortality is that many lack the power necessary to detect a difference because of the low event rate of death. Furthermore, there is a significant amount of heterogeneity in the characteristics of the study populations. Some of the studies are population-based, whereas others were recruited from hospitals, leading to selection bias. Population-based studies have inherent challenges linked to coding terminology and definitions including misclassification bias. Determining the precise cause-specific mortality of nonspecific codes, such as GI disease, is challenging and leads to speculation. Follow-up periods established in the majority of studies are likely still too short to allow for a better understanding of mortality in patients with IBD. Importantly, many studies, particularly those determining SMR, did not control important confounders with smoking being by far the most important. Smoking is known to increase the risk of CD, while decreasing the risk of UC and is associated with increased mortality from CV disease, pulmonary disorders, and many malignancies. Given these limitations, one must be cautious in the interpretation of mortality data in IBD.

CONCLUSIONS

Robust emerging literature is challenging previous data regarding the magnitude of mortality in IBD. Although traditional causes of death such as CRC may still be factor in IBD-associated mortality, there are emerging threats that are likely to have a larger impact on CD and UC patients. Thus, clinicians should be aware of emerging new threats to patients with IBD and be able to clearly convey the evidence-based risks to empower patients. Overall, an evidence-based approach will allow early recognition of mortality threats, which will translate into better patient outcomes.

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