PROC (BAYL UNIV MED CENT)
2024;37(4):613–622

https://doi.org/10.1080/08998280.2024.2342723

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Immunotherapy-induced colitis in metastatic colorectal cancer: a systematic review and meta-analysis

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ABSTRACT

Colorectal cancer (CRC) presents significant mortality risks, underscoring the urgency of timely diagnosis and intervention. Advanced stages of CRC are managed through chemotherapy, targeted therapy, immunotherapy, radiotherapy, and surgery. Immunotherapy, while effective in bolstering the immune system against cancer cells, often carries toxic side effects, including colitis. This study aimed to evaluate the incidence of colitis in patients with metastatic CRC (mCRC) undergoing various immunotherapy treatments. Through a systematic search of Google Scholar and PubMed databases from inception until November 2023, nine relevant studies were identified. Subgroup analyses revealed a higher incidence of colitis, particularly in patients treated with anti-cytotoxic T-lymphocyte-associated molecule-4 (anti-CTLA-4) and combination therapies compared to monotherapy with programmed cell death receptor-1 (PD-1) or programmed cell death ligand receptor-1 (PDL-1) inhibitors. Notably, naive-treated metastatic CRC patients exhibited elevated colitis incidences compared to those previously treated. In conclusion, anti-CTLA-4 and combination therapies, such as nivolumab plus ipilimumab, were associated with increased colitis occurrences in metastatic CRC patients, highlighting the need for vigilant monitoring and management strategies, especially in immunotherapy-naive individuals.

KEYWORDS Anti-CTLA-4; anti-PD-1; anti-PDL-1; colitis; colorectal cancer; immunotherapy; incidence; metastatic colorectal cancer; toxic effects

Colorectal cancer (CRC) is the third-ranking cancer in incidence and the second in terms of mortality. In the year 2020, CRC accounted for 10.0% of all cancer incidences and 9.4% of all cancer-related mortalities.[1] In terms of gender, CRC is the third most common cancer in men (9%) after prostate and lung cancer, and in women, it is also the third most common (8%) after breast cancer and lung cancer. The etiology of colorectal cancer is very varied; most scientists have linked it to mutations in various genes, which is a common cause in most malignancies. Recent cancer statistics have shown an increased incidence of CRC in rapidly developing countries; this has led various scholars to link it to the adoption of Western culture, as it has been associated with increased cases of other CRC risk factors such as obesity.[1,2] Additionally, this incidence has been observed to increase in younger age groups and decrease in the older age group. These drastic changes have been attributed to the increased regular screening among older adults.[3] The risk factors for CRC include alcohol intake, long-term constipation, smoking, inadequate exercise, and eating diets high in fat and protein.[4,5]

The treatment and prognosis of CRC, like other malignancies, greatly depend on early diagnosis. Therefore, regular screening is essential. According to the American Gastroenterological Society, screening for CRC should be carried out in all average-risk individuals aged 45 to 75 years at least once every 10 years, depending on the specific diagnostic test.[6] Various diagnostic tests are used to screen for CRC, including colonoscopy, computed tomography

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The authors report no funding or conflicts of interest. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Received March 9, 2024; Revised March 27, 2024; Accepted March 28, 2024.

colonography, sigmoidoscopy, fecal immunochemical tests, and fecal DNA tests. Among these tests, colonoscopy is the most frequently used diagnostic tool.[7]

The relative overall 5-year survival for CRC patients is approximately 65%.[8] Among CRC patients, 33% present with metastatic CRC (mCRC) either at initial contact or during follow-up.[9] Deciding on the treatment options for mCRC is a multidisciplinary approach. The decision is always complex because of the heterogeneity of the patients and the molecular subtypes of the tumors they present with.[3] Furthermore, treatment choice depends on the tumor's staging and grading, the patient's general condition, and other prognostic factors.[10] Over the years, research on comprehensive treatment modalities for mCRC has been increasing, and combination therapy with a targeted agent is the main treatment modality for mCRC.[11] There are various treatments for mCRC; these modalities include chemotherapy, radiotherapy, surgery, immunotherapy, and other palliative interventions.

Surgery is the primary treatment modality for most CRC patients. Surgical management of CRC includes complete resection of the bowel with the tumor and the intermediate lymph nodes and vessels (radical resection).[12] Radical resection is only performed on patients who do not have distant metastasis; in cases of distant metastasis, i.e., mCRC, surgery is only used to control the complications of the tumors, such as perforation, bleeding, and intestinal obstruction.[13,14] Chemotherapy, on the other hand, is used as adjuvant therapy to surgery. The chemotherapeutic agents for CRC patients are 5-fluorouracil and capecitabine, which are usually administered together with oxaliplatin. These drugs improve survival and reduce the risk of CRC recurrence in patients with stage III cancer.[15] Neoadjuvant radiotherapy is usually administered preoperatively. Some trials have reported a complete pathological response with chemoradiation in about 15% of patients, and this rate increases to about 30% when it is combined with chemotherapy.[16]

Immunotherapy is a recent treatment modality that has been used increasingly in solid tumor treatment. It has achieved major curative effects in tumors such as non–small cell lung cancer and melanoma.[17,18] Some patients have obtained long-lasting benefits and a better prognosis after undergoing ICI therapy. For example, in a recent trial, the mean overall survival (mOS) of advanced melanoma improved to 72.1 months for patients receiving ipilimumab and nivolumab treatment, compared to 36.9 and 19.9 months for patients receiving monotherapy of nivolumab or ipilimumab.[19] These agents have, therefore, been approved as the first-line treatment for advanced solid tumors.[20] However, therapy with programmed death (PD-1) and programmed cell death-ligand 1 (PD-L1) inhibitors has had minimal effects in the treatment of mCRC.[21–23] For CRC, in the late 20th century, only 5-fluorouracil was used as an alternative therapy, with a mOS of <1 year. Later on, oxalipitin and irinotecan, together with fluoropyrimidine, were approved by the Food and Drug Administration to be used in treating mCRC, almost doubling the mOS. These drugs were then combined with a targeted drug, which resulted in the mOS of mCRC patients improving exceedingly over 2 years.[24] However, in a phase III clinical trial, it was found that chemotherapy, when combined with two targeted drugs, did result in a further increase in the mOS but resulted in intolerable toxicity.[25,26] Recently, the Food and Drug Administration has approved pembrolizumab and nivolumab to be used in the treatment of mCRC.[27,28] ICI therapy is further recommended for mCRC patients with mismatch repair-deficient or microsatellite-instability-high mutations.[29] However, caution must be observed since 45% to 60% of mCRC patients with these mutations develop resistance to ICI therapy.[30]

Cancer treatment modalities are associated with various toxicities and side effects. These symptoms, including nausea, paresthesia, and lack of energy, occur within a few days of treatment administration. The severity of these symptoms varies widely according to gender, age, type of treatment, and performance status.[31] These side effects have resulted in patient refusal of treatment, reduced treatment compliance, and therapy delays, which eventually result in poor patient outcomes. The adverse effects caused by immunotherapeutic agents, also known as immune-related events (irAEs), are different from those induced by chemotherapeutic agents.[32] Immunotherapeutic agents such as immune checkpoint inhibitors (ICIs) have unique characteristics in terms of organ involvement, toxicity, severity, and onset of symptoms.[33] ICI induces an immune response by interfering with different stages of T-cell activation; this results in distinct and partially overlapping toxicities of different drugs.[34] The toxicity severity also varies across different types of ICI drugs, with anti-PD-1 having a lower incidence of toxicity (16%) and anti-CTLA-4 having toxicities as high as 27%. When all the irAEs are combined for all the drugs, they can be as high as 55%.[35] Multiple randomized controlled trials (RCTs) have defined pulmonary, gastrointestinal, skin, hepatic, endocrine, and skin toxicities.[36–38] Some irAEs, such as colitis, can be fatal and life-threatening when they develop complications. Colitis is among the most common irAE of the gastrointestinal system. It has been an emerging issue for specialists dealing with cancer patients receiving immunotherapy.[39]

Although there has been increasing research on colitis and other irAEs in different patients, very few reviews have focused on specific types of cancer and identified the incidence of irAEs. This review aimed to achieve three objectives regarding mCRC cancer patients receiving immunotherapy:

1. Determine the incidence of colitis among patients receiving immunotherapy.
2. Identify the class of immunotherapy drugs associated with increased incidence of colitis.
3. Determine the incidence of colitis in treatment-naive and previously treated patients.

METHODOLOGY

This systematic review and meta-analysis is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[40]

Search strategy

To identify all published articles describing the incidence of colitis in mCRC patients receiving immunotherapy, we performed a detailed search on PubMed and Google Scholar for all articles published from inception until November 2023 using two strategies. The first strategy utilized the following keywords in the online search: ("Colitis" OR "Immune-related adverse events" OR "Immunotherapy" OR "Immune checkpoint inhibitors" OR "Immune checkpoint blockade" AND "Toxicity" OR "Toxicities" AND "Colorectal cancer" OR "metastatic colorectal cancer"). After identifying the relevant articles, a second strategy was utilized, wherein we manually searched each article's list of references and identified additional articles. This strategy enabled us to identify all the relevant articles available.

Eligibility criteria

Two reviewers independently assessed all the articles retrieved from the electronic databases using the exclusion and inclusion criteria. Studies were included in the analysis if they met the following inclusion criteria:

1. Was published in the English language
2. Reported colitis as the toxicity of mCRC immunotherapy
3. Was either an RCT, nonrandomized clinical trial, or cohort observational study
4. Had more than 10 patients. This criterion aided in improving the statistical power of our meta-analysis.

Respectively, studies were excluded if they met the following exclusion criteria:

1. Was not published in the English language
2. Was a case report, review article, or letter to the editor
3. Did not report colitis as one of the toxicities
4. Used combined therapy of immunotherapy and other chemotherapeutic agents. This criterion helped in reporting only irAEs related to immunotherapy only.
5. Involved an incomplete trial

Data extraction

Two reviewers independently extracted the data for all the articles. For each study, the following data were obtained: Author ID; study design; study name; sample characteristics including sample size and sex distribution; follow-up period; immunotherapy characteristics including the agent, type, and dosage; number of patients who developed colitis of any grade and grade III; and type of mCRC subjected to immunotherapy. The study characteristics are presented in *Table 1*.

Quality assessment

The studies' quality was measured using the Cochrane risk of bias tool provided by the Review Manager (RevMan 5.4.1). The basis of the assessment involved the following elements: performance, selection, reporting, and attrition bias. The elements were assigned as 'high risk,' 'low risk,' or 'unclear risk.' High risk was assigned when an element was inadequately addressed or not addressed. On the other hand, an unclear risk of bias was assigned when no clear judgment was made on an element by the reviewers. In the risk of bias summary, a high risk of bias was assigned a red color, a low risk of bias was assigned a green color, and an unclear risk was not given any color.

Statistical analysis

The comprehensive meta-analysis software was utilized to carry out the statistical analysis. The analysis was conducted for the various event rates reported across different studies. Furthermore, a subgroup meta-analysis was done to determine the rates of colitis and severe colitis across the different types of immunotherapy agents (anti-CTLA-4, anti-PD-L1, and anti-PD-1). Another subgroup analysis was carried out to determine the rates of colitis and severe colitis depending on the type of patient group, either treatment-naive or previously treated patients.

RESULTS

The online search yielded 489 articles. These articles were analyzed, 240 duplicates were removed, and automation tools removed five additional studies. As a result, 245 records were screened, and 172 were excluded based on their titles and abstracts. Therefore, 72 articles were retrieved and screened according to our eligibility criteria. Finally, nine articles were included in the data analysis,[27,41–48] and the remaining 63 articles were excluded as follows: 15 were not published in English, 2 were incomplete trials, 9 were case reports, 18 were review articles, and 28 combined immunotherapies with other forms of treatment. The search flow chart is presented in *Figure 1*.

Risk of bias outcomes

The risk of bias graph is presented in *Figure 2*, while the risk of bias summary is shown in *Figure 3*.

Study characteristics

The nine studies—published between 2010 and 2023—provided data from 734 patients with mCRC treated with immunotherapy only. Among these patients, 54.4% were male and 45.6% were female. Furthermore, among the studies selected, three were RCTs, five were nonrandomized trials, and one was a retrospective cohort study. The mean follow-up period across the studies ranged from 2.3 to 32.4 months. The type of immunotherapy the patients received varied widely across the studies; one trial reported the effects of anti-PDL-1 therapy, five studies reported on anti-PD-1 therapy, one study reported on anti-CTLA-4, and two

Table 1. The characteristics of the studies included in the meta-analysis

Author ID	Study design	Study name	Characteristics of mCRC patients treated with immunotherapy only		Follow-up period (months)	Immunotherapy characteristics			Comparator therapy	Number of patients with colitis		Type of mCRC subjected to immunotherapy
			Size	M/F		Agent	Dose	Type		Any grade	Grade ≥3	
Eng et al[41]	Multicenter open-label phase III RCT	IMblaze370	90	59/31	7.3	Atezolizumab	1200 mg every 3 weeks IV	PDL – 1	Atezolizumab plus cobimetinib OR regorafenib	1	NR	Previously treated
Chung et al[42]	Single-arm, multicenter phase II RCT	NR	47	29/18	2.3	Tremelimumab	15 mg/kg IV on day 1 of every 90-day cycle	Anti-CTLA-4	None	3	1	Previously treated
Le et al[43]	Multicenter open-label phase II non-randomized trial	KEYNOTE-164	124	69/55	31.3	Pembrolizumab	200 mg every 3 weeks IV up to 35 cycles	PD-1	None	2	1	Previously treated
Lenz et al[44]	Multicenter open-label multicohort phase II non-randomized trial	CheckMate 142	45	23/22	29	Nivolumab plus ipilimumab	3 mg/kg nivolumab once every 2 weeks and low-dose ipilimumab 1 mg/kg once every 6 weeks	PD-1 and anti-CTLA-4	None	4	2	Naive
Andre et al[27]	Multicenter open-label phase III RCT	KEYNOTE-177	153	71/82	32.4	Pembrolizumab	200 mg every 3 weeks IV	PD-1	Chemotherapy	10	5	Naive
Morse et al[45]	Multicenter open-label multicohort phase II non-randomized trial	CheckMate 142	119	70/49	13.4	Nivolumab plus ipilimumab	3 mg/kg nivolumab and low-dose ipilimumab 1 mg/kg once every 3 weeks for four doses followed by nivolumab 3 mg/kg every until disease progression	PD-1 and anti-CTLA-4	None	3	3	Previously treated
Overman et al[46]	Multicenter open-label multicohort phase II non-randomized trial	CheckMate 142	74	44/30	12	Nivolumab	3 mg/kg IV until disease progression	PD-1	None	1	1	Previously treated
Saberzadeh-Ardestani et al[47]	Multicenter retrospective cohort study	NR	41	12/29	23	Pembrolizumab	200 mg every 3 weeks IV	PD-1	None	2	1	Naive
Le et al[48]	Multicenter open-label phase II non-randomized trial	NR	41	22/19	8.7	Pembrolizumab	10 mg/kg every 2 weeks	PD-1	None	0	0	Previously treated

CTLA-4 indicates cytotoxic T-lymphocyte associated protein 4; IV, intravenous; mCRC, metastatic colorectal cancer; NR, not reported; PD-1, programmed death receptor-1; PDL-1, programmed cell death receptor ligand-1; RCT, randomized controlled trial.

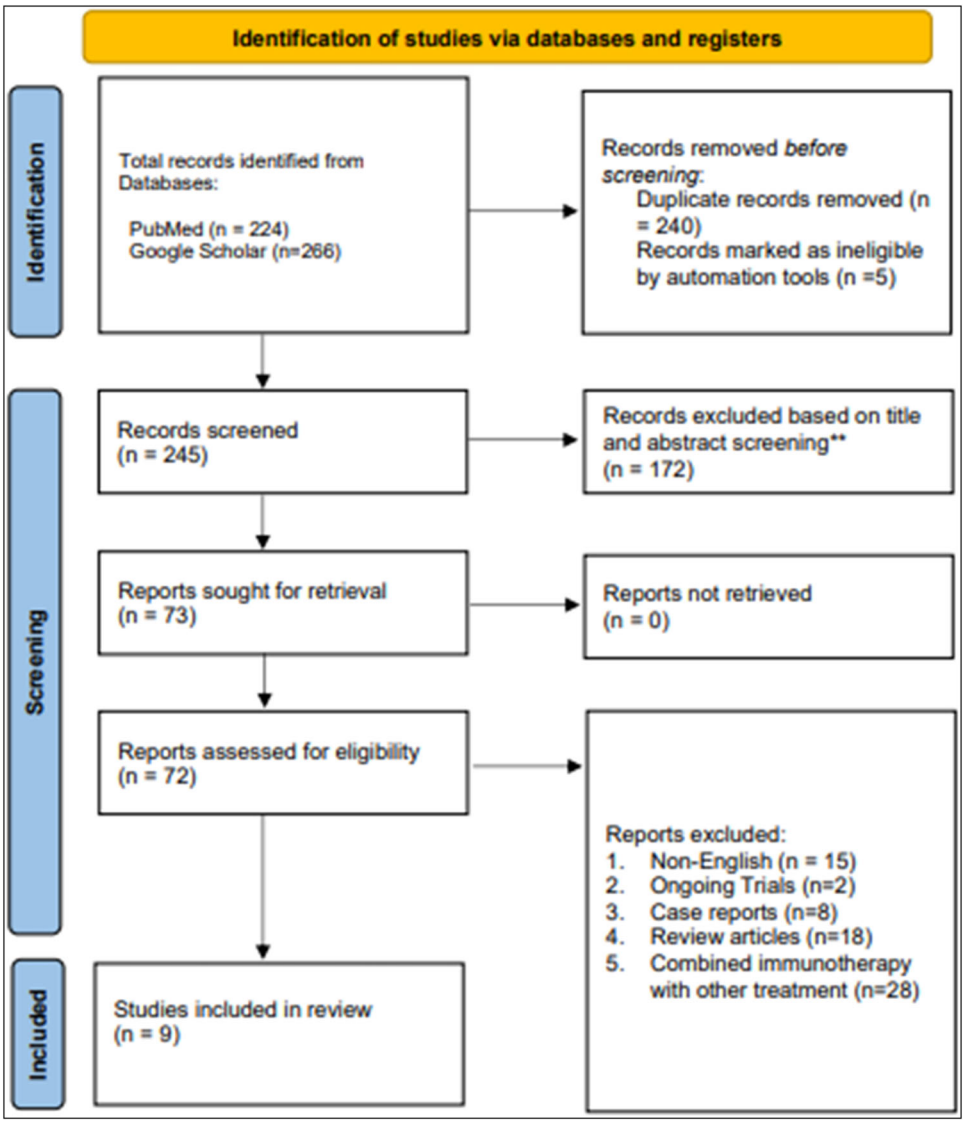

Figure 1. A PRISMA flow diagram illustrating the search results.

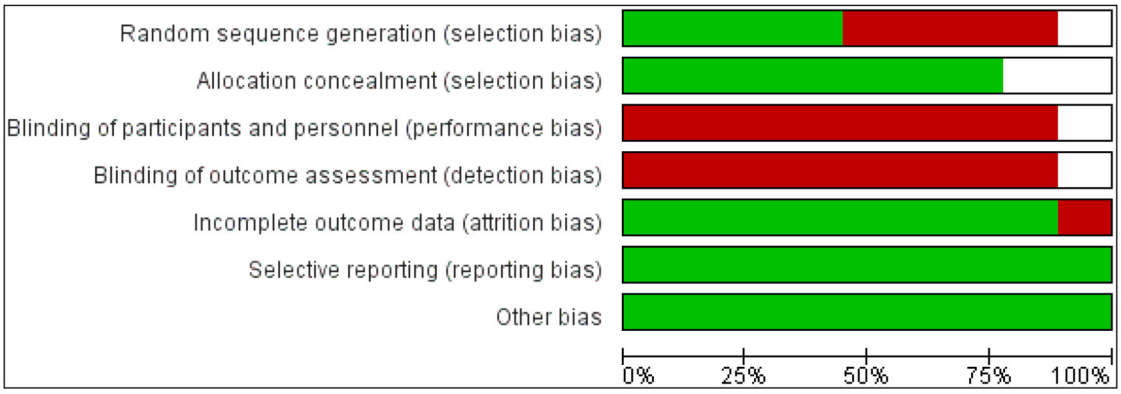

Figure 2. A risk of bias graph of the selected studies. Green indicates a low risk of bias; red, a high risk of bias; white, unclear risk of bias.

studies reported on combined therapy of anti-CTLA-4 and anti-PD-1. Furthermore, three studies reported findings of patients with naive mCRC, while six reported findings of patients who had previously treated mCRC (*Table 1*).

Incidence of colitis of any grade according to the class of immunotherapy

The subgroup analysis indicated a higher incidence of any grade colitis in mCRC patients treated with anti-CTLA-4 antibodies and combined therapy of

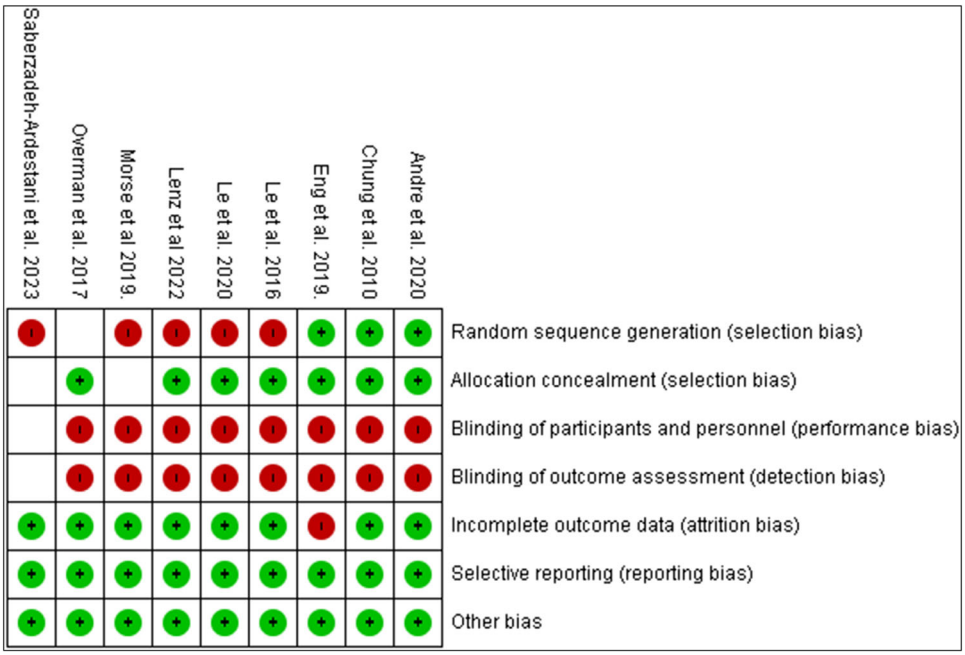

Figure 3. The risk of bias summary of the individual studies.[27,41–48]

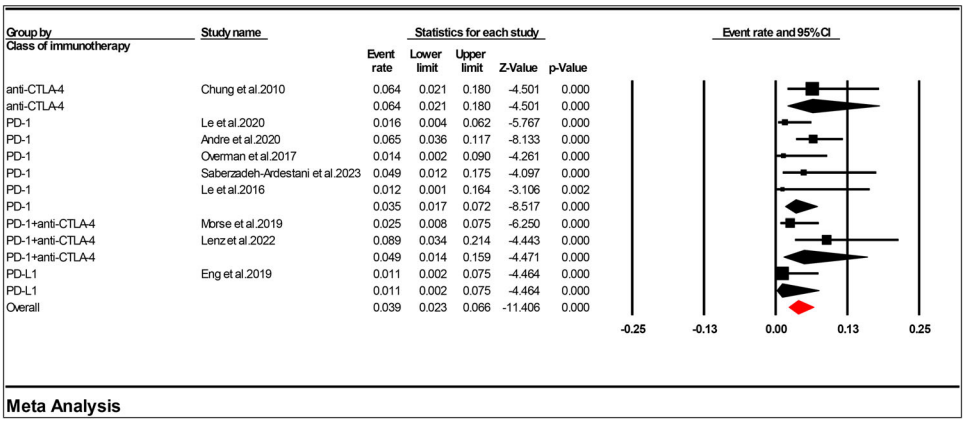

Figure 4. Incidence of colitis of any grade according to class of immunotherapy ($P < 0.05$).[27,41–48]

anti-CTLA-4 and PD-1 inhibitors with event rates of 6.4% (95% confidence interval [CI] [2.1%, 18%]) and 4.9% (95% [1.4%, 15.9%]), respectively, compared with PD-1 and PDL-1 monotherapy, which had event rates of 3.5% (95% CI [1.7%, 7.2%]) and 1.1% (95% CI [0.2%, 7.5%]), respectively (*Figure 4*). The overall incidence of any grade colitis was 3.9% (95% CI [2.3%, 6.6%]) (*Figure 4*). Furthermore, the difference in incidence rate among the different classes of immunotherapy was statistically significant ($P < 0.05$).

Incidence of grade ≥3 colitis according to the class of immunotherapy

The subgroup analysis indicated a higher incidence of severe colitis (grade ≥3) in patients receiving combined therapy of anti-CTLA-4 antibodies and PD-1 inhibitors, with an event rate of 3.2% (95% CI [1.3%, 7.4%]) than in patients receiving monotherapy of anti-CTLA-4 antibodies and PD-1 inhibitors, with event rates of 2.1% (95% CI [0.3%, 13.6%]) and 2.3% (95% CI [1.2%, 4.4%]), respectively (*Figure 5*). The overall incidence of severe colitis was 2.5% (95% CI [1.5%, 4.2%]) (*Figure 5*). Furthermore, the difference in incidence rate among the different classes of immunotherapy was statistically significant ($P < 0.05$).

Incidence of colitis of any grade according to CRC treatment

The subgroup analysis indicated a higher incidence of any grade colitis in treatment-naive patients, with an event rate of 6.8% (95% CI [4.2%, 10.6%]), than in previously treated patients, with an event rate of 2.5% (95% CI [1.4%, 4.6%]) (*Figure 6*). The overall incidence of any grade colitis was 4.6% (95% CI [3.1%, 6.6%]) (*Figure 6*). Furthermore, the difference in incidence rate between the two groups of patients was statistically significant ($P < 0.05$).

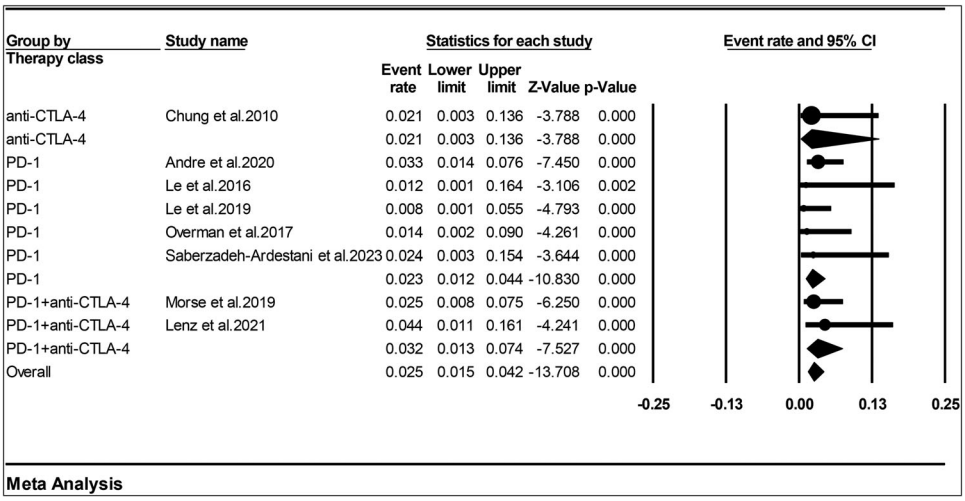

Figure 5. Incidence of grade ≥3 colitis according to class of immunotherapy ($P < 0.05$).[27,41–48]

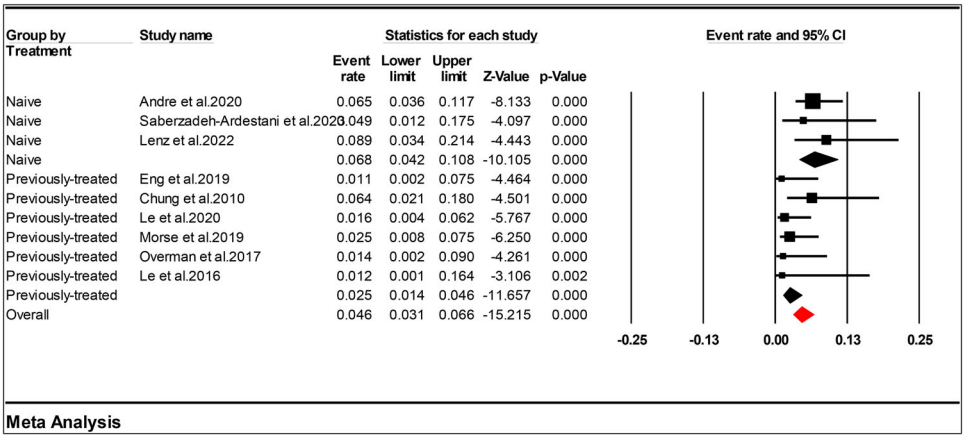

Figure 6. Incidence of colitis of any grade according to colorectal cancer treatment ($P < 0.05$).[27,41–48]

Incidence of colitis of grade ≥3 according to CRC treatment

The subgroup analysis of eight studies indicated a higher incidence of severe colitis in treatment-naive patients with an event rate of 3.4% (95% CI [1.7%, 6.7%]) than in previously treated patients (1.8% 95% CI [0.8%, 3.8%]) (*Figure 7*). The overall incidence of severe colitis was 2.5% (95% CI [1.5%, 4.2%]) (*Figure 7*). Furthermore, the difference in incidence rate between the two groups of patients was statistically significant ($P < 0.05$).

DISCUSSION

irAEs of the gastrointestinal system include a myriad of symptoms that range from mild diarrhea to severe colitis, which may be complicated by perforation, peritonitis, and death. As a common irAE of the gastrointestinal system, colitis has emerged as one of the common clinically relevant and highly morbid irAEs. This review examined the incidence of colitis in mCRC patients undergoing immunotherapy. To our knowledge, this is the first meta-analysis to assess the rates of immunotherapy-related colitis among mCRC patients.

Colitis rate according to class of immunotherapy drugs

Importantly, there were higher rates of colitis in any grade in anti-CTLA-4 therapy (6.4%) and when it was combined with anti-PD-1 agents (4.8%). Similarly, in a review analyzing the incidence of colitis related to immunotherapy of solid tumors, Wang et al reported a higher incidence of colitis with the anti-CTLA-4 drug ipilimumab compared to anti-PD-1 and anti-PD-1 agents.[49] The higher incidence of colitis in anti-CTLA-4 agents can be attributed to their crucial role in immune regulation. Since activation of CTLA-4 receptors increases the activity of T-regulatory (Treg) cells and downmodulates the activity of T-helper cells, the blockade of these receptors inhibits Treg cell–dependent immunosuppression and activation of T-helper cell–dependent immune responses.[50] Unfortunately, during this activation process, some cross-reactive T cells that bind to both tumor and normal tissue receptors are also activated. It is, therefore, easy to appreciate that irAEs

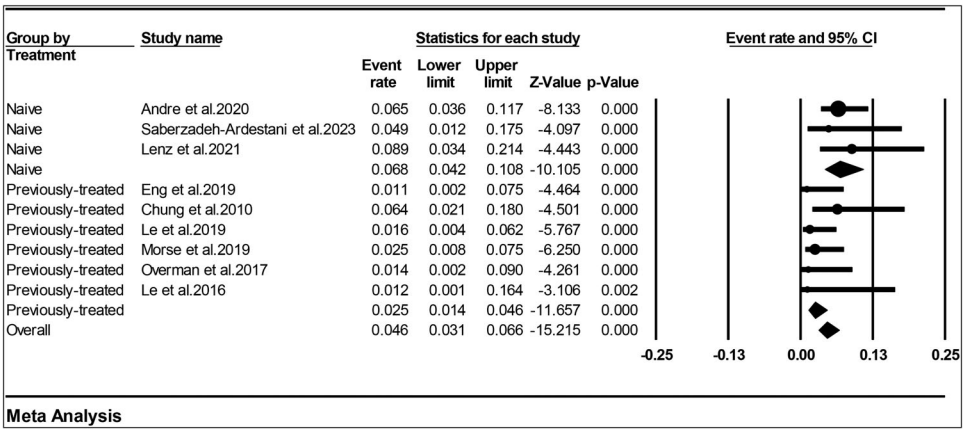

Figure 7. Incidence of colitis of grade ≥3 according to colorectal cancer treatment.[27,41–48]

may also occur as a result.[51] However, the exact pathophysiological mechanism of how colitis results is unclear.

Grade ≥ 3 colitis incidence according to class of immunotherapy drugs

Our subgroup meta-analysis of the rate of colitis of grade ≥3 according to the class of immunotherapy used showed the highest rate of colitis in those patients who received combined therapy of anti-PD-1 and anti-CTLA-4 (2.5%). Additionally, there was a higher incidence of colitis in those patients who received anti-PD1 therapy (2.3%) than in those who received anti-CTLA-4 therapy (2.1%). Contrary to our results, two other systematic reviews reported a higher incidence of grade 3 or higher colitis in the patients receiving anti-CTLA-4 therapy (4.1% to 6.8%) compared to anti-PD-1 agents (0.0% to 0.9%).[49,52] The difference in the results may be attributed to the difference in the sample sizes and the number of studies included. Our review had fewer studies since it focused specifically on CRC and excluded other solid tumors, unlike the other reviews. However, since most chemotherapeutic and immunotherapeutic drugs' mechanism of action is systemic, it is most likely that the mechanism of irAEs is similar across patients with different malignancies, thus making the results of the other reviews relevant. It is also important to note that the crude rate of anti-PD-1 colitis was higher in our review (2.3%) than in the other reviews (0% to 0.9%).[49,52] Although it is presumed that the mechanism of irAEs is similar across different malignancies, research has indicated that the risk of colitis is different across various malignancies. Our review has shown that the risk of developing severe colitis is greater in CRC patients compared to renal cell carcinoma, non–small cell carcinoma, and melanoma.[49,52] However, these results cannot be generalized since no single review has directly compared rates of severe colitis related to immunotherapy in CRC patients vs patients with different malignancies.

Any grade colitis incidence according to type of treatment

The rates of colitis in any grade were higher in patients who had never received any type of immunotherapy (6.8%) compared to patients who had received treatment previously (4.6%). Similarly, the rate of severe colitis in treatment-naive patients (3.4%) was higher than that of previously treated patients (2.5%). A meta-analysis by Thompson et al also found that treatment-naive patients with metastatic melanoma undergoing ipilimumab therapy had a higher incidence of colitis compared to those with previously treated metastatic melanoma.[53] Although the exact mechanism for the higher incidence of irAEs such as colitis in treatment-naive patients lacks a clear explanation, many clinical trials and reviews have reported similar results across different patients receiving immunotherapy. For example, Khunger et al reported a higher incidence of all grades of irAEs, such as pneumonitis, colitis, and hepatitis, among treatment-naive non–small cell lung cancer patients receiving PD-1 and PDl-1 inhibitors.[54]

Limitations

There are various limitations to our study. First, due to the specificity of our research on CRC, limited studies were used compared to another previous meta-analysis. Consequently, the sample size of our study was relatively small compared to other reviews. Therefore, we recommend more studies focusing specifically on the irAEs in CRC patients receiving immunotherapy to increase the available data for review. Second, very few studies reported colitis as an irAE in anti-CTLA-4 therapy; this resulted in only one study, which included anti-CTLA-4 therapy, thus limiting the statistical ability of the result. We therefore recommend that additional studies focusing on specific drugs, such as anti-CTLA-4 agents, be carried out. Another limitation of the review was that various studies did not report specific characteristics of patients who experienced the irAEs, such as gender and age. It was, therefore, impossible to identify any confounding factor related to patients who may have been predisposed to the observed irAEs and draw meaningful conclusions. Lastly, since most of the studies were open-label trials, there was a significantly high risk of bias in the performance and detection elements. We therefore

recommend, if possible, blinding in future trials to increase their internal and external validity.

CONCLUSIONS

This study has demonstrated an increased incidence of colitis in patients receiving anti-CTLA-4 therapy compared to other drugs, such as anti-PDL-1 and anti-PD-1 agents. Additionally, patients receiving anti-CTLA-4 had a higher incidence of severe colitis grade $\geq$3 compared to other therapies. When treatment naive patients were compared with patients previously treated for mCRC, there was a higher incidence of any grade colitis and severe colitis in the naive group.

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