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September 24, 2022

Dr. Lian-Sheng Ma
Editorial Office Director, Company Editor-in-Chief, Editorial Office
World Journal of Gastroenterology

Dear Dr. Ma,

Thank you for the opportunity to resubmit our manuscript entitled "Immune Checkpoint Inhibitor-Mediated Colitis Is Associated with Cancer Overall Survival" (manuscript number: 78536). The reviewers raised several important points, which we have fully addressed through the addition of new data analysis and revisions to the text, as discussed in point-by-point fashion below. We believe these changes have considerably strengthened the report, making it now suitable for publication in *World Journal of Gastroenterology*.

Reviewer #1: *The topic of this article is very interesting. The following issues deserve further discussion:*

1. The results showed that IMC was significantly associated with a higher OS, Whether this association effect is different between cancer types？For example, how does the occurrence of IMC affect the OS of melanoma?

We agree that understanding how OS compares between different types of malignancy is important to evaluate, given that potential differences in survival between different cancers may confound the effects of IMC. In Table 3, we have evaluated whether OS > 12 months within patients who developed IMC is associated with specific cancers. We do not find that any specific malignancy (including melanoma) is associated with OS > 12 months among this subset of our patients. In Table 2, we find that OS > 12 months

across all ICI users was significantly associated only with sarcoma within specific malignancies. It is unclear why this association is significant, but this may be related to the small number of patients with this malignancy included in the study (11), leading to increased statistical error.

2. In addition to IMC, what is the incidence of other irAEs in the two groups of patients, and does it affect cancer prognosis?

We agree that it is important to assess the incidence of irAEs besides IMC and their potential effect on cancer prognosis. We have added the incidence of prior non-IMC irAEs to Table 1, although this was not significantly different between our two cohorts. We did not find a significant association between OS > 12 months and non-IMC irAEs (OR 2.84, 95% CI 0.31-25.9, p = 0.356), and have added these data to Table 2.

Reviewer #2: *The article analyzes the literature factors of IMC in patients with malignant tumors after using ICI and its impact on PFS and OS, which has strong clinical guiding value.*

1. However, the number of cases included in the article is small, the statistical method needs to be refined, and the reliability of the results will be greatly reduced. It is suggested to expand the sample size.

We agree that our study is limited in size, which in turn is due to its limitation as a single-center study. Although the sample size cannot be increased in this case, we have emphasized this limitation in our discussion to make this point clear (lines 304-308).

Reviewer #3: *Despite ICI seem to have found their role in a plethora of hematological and solid malignancies, several questions remain unanswered. Among these, the lack of validated biomarkers of response represents an important issue since only a proportion of patients benefit from immunotherapy. Based on these premises, a greater understanding of the role of potential*

biomarkers including programmed death ligand 1 (PD-L1) expression, tumor mutational burden (TMB), microsatellite instability (MSI) status, gut microbiota and several others is fundamental. In addition, clinical trials on immunotherapy widely differed in terms of drugs, patients, designs, terms of study phases, and inconsistent clinical outcomes. Among predictors of response, also treatment-related adverse events should be considered, since a large number of reports has tried to assess this association. Based on these premises, the study assesses a current, timely topic. We recommend some changes:

1. We believe this article is suitable for publication in the journal although major revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides a clear answer, with some limitations. Certainly, the study is limited to a single-center experience with a very small sample size, and authors should further express this point.

As mentioned in our response to Reviewer #2, we agree that the single-center nature of our study (leading to a small sample size) is a noticeable limitation for our study. As above, we have emphasized this limitation in our discussion (lines 304-308).

2. Second, the study included a widely varied patient population from a single institution and the total number of patients analyzed was small. Thus, the authors should better highlight the limitations of the current paper.

Although the variety of the patient population could be considered a strength of our work, we agree that a low number of patients limits how powered our study can be for any single malignancy. We have emphasized this drawback in our discussion, along with highlighting the limited patient size as above (lines 304-308).

3. The background of the role of predictors of response to ICIs should be better discussed, and some recent papers regarding this topic should be included (PMID: 34429006; PMID: 34894318; PMID: 33714725).

This reviewer raises the excellent point that additional factors may contribute to survival in ICI use. Per their recommendation, we have added the recommended additional references and included discussion of several of these potential factors (lines 310-313).

4. Currently, the effect of immune-related adverse events (IrAEs) on survival of patients affected by advanced malignancies is uncertain. A plethora of recent retrospective studies have hypothesized that the development of IrAEs in cancer patients may correlate with durable response and survival benefit, although contradictory reports exist. Despite providing interesting data, several studies investigating this association should be interpreted with caution because of an inappropriate methodology. In particular, only a minority of these reports considered the effect of immortal time bias (ITB), a key element in determining the effective association between clinical outcomes and a time-dependent variable. Of note, ITB represents a key element regarding these kind of studies since patients who die or whose disease progresses earlier are less likely to develop toxicity; in fact, these patients probably have not stayed in the study long enough to develop adverse events, or because they discontinued treatment or died due to progressive disease. Conversely, included patients that stayed in the study for a longer time interval have an increased risk to experience toxicities. The authors should consider this point and discuss it, since it may represent a very important bias in this study. Major changes are necessary.

As this reviewer astutely notes, retrospective studies are often subject to immortal time bias (ITB). Indeed, in our study the number of ICI infusions is associated with OS > 12

months (Table 2), which is likely a key example of ITB – patients must survive for longer to receive additional infusions, creating a period of time where those patients are "immortal." However, greater numbers of infusions were not associated with IMC (Table 4). This suggests that the association between OS > 12 months and IMC is likely independent of the number of ICI infusions, limiting this as a source of ITB in our study. We have added this consideration to our discussion (lines 292-301).

All of the concerns raised have been addressed through our comments above, additional data analysis, and changes to the manuscript. We thank the editor and reviewers for their comments and careful review of our manuscript.

Sincerely,
Alexa Weingarden, MD, PhD, and John Gubatan, MD (on behalf of co-authors)

Journal: *World Journal of Gastroenterology*
Manuscript NO: 78536
Manuscript Type: ORIGINAL ARTICLE

Case Control Study

Immune Checkpoint Inhibitor-Mediated Colitis Is Associated with Cancer Overall Survival

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Gubatan J analyzed data; Weingarden AR, Gubatan J, Singh S, and Habtezion A wrote and edited the manuscript; all authors have read and approve the final manuscript.

Alexa R Weingarden was supported by NIH grant 5T32DK007056.

This study was reviewed and approved by the Stanford University Institutional Review Board at Stanford University (IRB 57125).

None of the authors have any potential conflicts of interest to disclose.

The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Core Tip (100 Words): Immune checkpoint inhibitor-mediated colitis (IMC) is a common adverse event following immune checkpoint inhibitor (ICI) therapy for cancer. We sought to determine the association of IMC with overall survival (OS) and progression-free survival (PFS) among cancer patients treated with ICI and identify clinical predictors of IMC. We performed a retrospective case-control study including 64 ICI users who developed IMC. In multivariate logistic regression analysis, IMC was significantly associated with a higher OS but not PFS. IMC was significantly associated with OS greater than 12 months. Vitamin D supplementation was associated with increased risk of IMC.

Abstract

BACKGROUND

Immune checkpoint inhibitor-mediated colitis (IMC) is a common adverse event following immune checkpoint inhibitor (ICI) therapy for cancer. IMC has been associated with improved overall survival (OS) and progression-free survival (PFS), but data are limited to a single site and predominantly for melanoma patients.

AIM

To determine the association of IMC with OS and PFS and identify clinical predictors of IMC.

METHODS

We performed a retrospective case-control study including 64 ICI users who developed IMC matched according to age, sex, ICI class, and malignancy to a cohort of ICI users without IMC, from May 2011 to May 2020. Using univariate and multivariate logistic regression, we determined association of presence of IMC on OS, PFS, and clinical predictors of IMC. Kaplan-Meier curves were generated to compare OS and PFS between ICI users with and without IMC.

RESULTS

IMC was significantly associated with a higher OS (mean 24.3 months versus 17.7, $p = 0.05$) but not PFS (mean 13.7 months versus 11.9, $p = 0.524$). IMC was significantly associated with OS greater than 12 months (Odds ratio [OR] 2.81, 95% confidence interval [CI] 1.17-6.77). Vitamin D supplementation was significantly associated with increased risk of IMC (OR 2.48, 95% CI 1.01-6.07).

CONCLUSION

IMC was significantly associated with OS greater than 12 months. In contrast to prior

work, we found that vitamin D use may be a risk factor for IMC.

Key Words: Immune checkpoint inhibitors; immune checkpoint inhibitor-mediated colitis; immune-related adverse events

Core tip: Immune checkpoint inhibitor-mediated colitis (IMC) is a common immune-related side effect of checkpoint inhibitor treatment for cancer. Prior work has suggested that IMC may be associated with increased survival from cancer. In this retrospective case-control study we found that IMC was significantly associated with increased overall survival. In contrast to prior work, however, we found that vitamin D supplementation was associated with increased risk of IMC. Our findings lend strength to the idea that IMC is associated with improved cancer outcomes with checkpoint inhibitor treatment and may suggest common immunologic underpinnings between IMC and the anti-tumor effects of these medications.

INTRODUCTION

Immune checkpoint inhibitors (ICI) have dramatically changed the landscape of cancer therapy. Early studies showed significantly prolonged survival in patients with metastatic melanoma compared to standard chemotherapy[1], and evidence now exists for improved outcomes in a variety of tumors ranging from lung cancers to urothelial carcinoma to breast cancer[2–5]. Although these are powerful treatments in our armamentarium against malignancy, ICI can cause immune-related adverse events (irAE) characterized by autoimmune-like inflammation in a variety of non-tumor organs, leading to increased morbidity for patients[6].

One of the most common irAE is immune checkpoint inhibitor-mediated colitis (IMC). IMC may occur in up to 40% of patients treated with ipilimumab, an antibody targeting CTLA-4, 11-17% of patients treated with antibodies against anti-PD-1 or anti-PD-L1, such as nivolumab, pembrolizumab, or atezolizumab, and around 32% of patients treated with a combination of anti-CTLA-4 and anti-PD-1[7]. Prior retrospective analyses of patients with IMC have attempted to identify characteristics associated with development of IMC, including type of malignancy, ICI class, dose of ICI, cancer stage, and vitamin D use[8–11]. Intriguingly, two prior studies have suggested that development of IMC may positively correlate with improved progression-free survival (PFS) and overall survival (OS)[9,10]. One of these studies controlled for confounding effects of ICI class via frequency matching, but was limited to patients with melanoma, hindering wider applicability of their findings[10]. These findings also conflict with data suggesting that use of steroids and the anti-TNF antibody infliximab in patients treated with ICI are associated with worse cancer outcomes[12,13]. These discrepancies represent a significant knowledge gap that impedes our ability to evaluate and manage IMC and ICI use.

Here we present data from a retrospective study of patients treated with ICI at our institution who developed IMC across malignancy types. We compare this cohort to a matched control cohort to determine whether IMC was associated with improved progression-free survival and overall survival. We also evaluate which clinical

characteristics increase the risk of developing IMC, including severe IMC.

MATERIALS AND METHODS

Study design and population

We conducted a retrospective case-control single-center study after obtaining approval from the Institutional Review Board at Stanford University (IRB 57125, approved 6/30/2020). Our primary aim was to determine the association of presence and severity of IMC on OS and PFS in ICI users. Our secondary aim was to identify clinical variables which predicted development of IMC in ICI users. We evaluated all patients over the age of 18 who had been treated with immune checkpoint inhibitors (ICI) for malignancy at Stanford Health Care from May 2011 to May 2020, including anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab), and anti-PD-L1 (atezolizumab, avelumab, durvalumab), with follow up through October 2020. Using the Stanford Research Repository (STARR) tool, we screened patients treated with ICI who were assigned International Classification of Diseases (ICD) 9 and 10 codes associated with non-infectious colitis and diarrhea (Supplemental Table 1). Each chart which passed the initial screen was further screened by review of clinic notes to confirm diagnosis of immune checkpoint inhibitor-related colitis by oncology providers. Any patient found to have other explanations for their clinical presentation was excluded from the study.

Control patients were matched one to one with each IMC patient for sex, age, malignancy, type of ICI used, prior ICI exposure, and duration of ICI exposure (matched to number of doses from initiation of ICI to development of colitis in study cohort). Control patients were initially screened by those lacking the above ICD codes and were confirmed via direct evaluation of each chart to lack diarrhea and/or colitis ascribable to ICI per their treating oncologist.

We extracted clinical data on IMC and control patient charts including demographics (age at time of ICI initiation, sex, body mass index, race per patient report), medical history (presence of prior non-liver and non-upper gastrointestinal

disease, personal history of autoimmune disease, family history of autoimmune disease), and cancer history (type of malignancy, tumor stage at ICI initiation, prior chemotherapy, prior radiation therapy, type of ICI used, duration of ICI use, OS and PFS) (Supplemental Table 2). OS was determined as time from initiation of ICI to death, while PFS was determined as time from initiation of ICI to death or progression of disease as determined by oncology providers, based on radiographic evidence of progression. IMC severity was graded using commonly accepted determinants of IMC and irAE grading[14]. We specifically noted prior use of therapies designed to increase immune responses (interleukin [IL]-2, interferon [IFN]-γ, toll-like receptor [TLR]-9 agonist, tebentafusp, or anti-CD47 antibody). Vitamin D and non-steroidal anti-inflammatory (NSAID) use were defined as vitamin D supplement or NSAID medication, respectively, noted in the history of present illness or on the patient's medication list at the clinic visit closest to their date of ICI initiation.

We collected data on IMC diagnosis including number of patients who received endoscopy (flexible sigmoidoscopy or colonoscopy), findings on endoscopy, and fecal calprotectin (Supplemental Table 3). Data on management of IMC included treatment with anti-diarrheal medications, mesalamine, steroids (prednisone, budesonide, dexamethasone), infliximab, and vedolizumab.

Statistical analysis

The rate of the primary outcomes (OS > 12 months and PFS > 6 months among all ICI users, OS >12 months and PFS> 6 months in patients with IMC) and secondary outcomes (risks of IMC among patients with malignancy using ICI, IMC severity), predictive value of clinical variables on primary and secondary outcomes, odds ratio (OR) with its 95% confidence interval (CI), and P-values were calculated using Statistics/Data Analysis (Stata/IC 15.1 for Windows, College Station, TX). Dichotomous variables were analyzed for outcomes using the chi-squared test or the Fisher's exact test where appropriate, and continuous variables were analyzed using Student's T-tests if normally distributed, or the Wilcoxon signed-rank test for non-normal data. For our

multivariate analyses, model building was based on forward stepwise logistic regression, with a P-value of 0.05 required for entry, and known predictors were also included. We constructed Kaplan Meier curves for the outcomes of OS and PFS between patients with and without IMC and patients with mild versus severe IMC using GraphPad Prism (version 8.3; GraphPad Software, Inc., La Jolla, CA). All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Clinical characteristics associated with IMC

We identified a total of 314 patients treated with ICI at Stanford Health Care from May 2011 to May 2020 who had ICD codes matching our query (Supplemental Table 1). Of these, 64 had a diagnosis of IMC per review of Oncology providers' notes, after excluding patients with alternative diagnoses for their symptoms. 24 (37.5%) of these IMC patients underwent an endoscopy (colonoscopy or flexible sigmoidoscopy) during workup, of which seven (29.2%) had a normal endoscopic appearance, consistent with prior reports demonstrating that approximately one third of patients with IMC related to anti-PD-1 therapy have microscopic colitis[15] (Supplemental Table 3). An additional 14 patients (21.9%) had imaging findings suggestive of IMC while 3 patients (4.69%) without imaging or endoscopy had an elevated calprotectin or fecal lactoferrin.

These 64 patients were manually matched 1:1 with control patients based on age, sex, malignancy, type of ICI, whether or not the patient had prior ICI exposure, and duration of ICI use. We compared clinical characteristics of patients from the IMC cohort and the control cohort (Table 1). None of the matched characteristics were significantly different between the two cohorts. The mean age across the combined cohorts was 66.6 years, with an average age of 67.4 in the cohort with IMC compared with 65.8 in the control cohort (p=0.42). 57.81% of patients in each group were male (p=1.00). Patients were predominantly white in both groups, with 52 (81.25%) white individuals in the IMC cohort compared to 50 (78.13%) in the control group (p=0.66).

The most common malignancy in each group was melanoma (33 [51.56%] in both cohorts), followed by renal cell carcinoma (8 [12.5%] in the IMC cohort and 7 [10.94%] in the control cohort) and non-small cell lung cancer (6 [9.38%] in both cohorts). Both groups had similar numbers of patients with stage IV malignancy (56 [87.5%] in the IMC cohort and 58 [90.63%] in the control cohort, p = 0.778). Combination ipilimumab and nivolumab was the most commonly used checkpoint therapy (24 [37.5%] of patients in each cohort), followed by nivolumab monotherapy (19 [29.69%] of each cohort) and ipilimumab monotherapy (11 [17.19%] of each cohort).

Among the remainder of the clinical characteristics evaluated, personal history of autoimmune disease (including prior irAE) and family history of autoimmune disease were significantly more common in patients with IMC (p=0.037 and 0.048, respectively). Intriguingly, prior use of a therapy designed to increase immune responses was more common in the control cohort without IMC (p=0.027). In contrast to prior data[11], use of vitamin D supplementation at the time of first dose of ICI was significantly more prevalent in patients with IMC (p=0.020). Neither smoking status, NSAID use at time of ICI initiation, steroid use at the time of ICI initiation, nor recent vaccination were significantly more common in IMC patients compared to controls.

IMC significantly increases overall survival

As IMC has previously been associated with increased overall survival (OS) and progression-free survival (PFS) in cancer patients[9,10], we evaluated whether this association was seen in our study. We found that OS was significantly longer in patients who developed IMC compared to those who did not, with a mean OS of 24.3 months in patients with IMC and 17.7 months in control (p=0.05, Table 1). OS at 12 months following ICI initiation was significantly higher in patients who developed IMC compared to those who did not (p = 0.02, Figure 1). However, in contrast to prior findings, our study did not find a significant difference in PFS between IMC patients and controls, with a mean PFS 13.7 months in IMC patients and 11.9 months in controls (p=0.524) (Table 1). PFS also did not differ between patients who developed mild versus

severe IMC (p = 0.690, Supplemental Table 5).

Across both cohorts, we identified clinical characteristics significantly associated with OS greater than 12 months and PFS greater than 6 months, which are correlated with cancer outcomes in patients treated with ICI[16] (Tables 2-3, Supplemental Tables 4-5). IMC was significantly and independently associated with OS > 12 months in the multivariate model (OR 2.81, 95% CI 1.17-6.77, p=0.021) (Table 2). Number of ICI infusions was also positively associated with OS > 12 months (OR 1.23, 95% CI 1.09-1.40), while sarcoma as underlying malignancy was significantly associated with OS < 12 months (OR 0.17, 95% CI 0.029-0.947). Within the IMC cohort, nivolumab use was associated with OS < 12 months in the univariate analysis (OR 0.09, 95% CI 0.01-0.83), while only age was associated with OS < 12 months in multivariate analysis (OR 0.93, 95% CI 0.88-0.99) (Table 3). No individual malignancy was significantly associated with OS > 12 months within the IMC cohort (Table 3).

Significant risk factors for developing IMC and severe IMC

As certain clinical characteristics were significantly more common in patients with IMC compared to controls, we evaluated whether any of these clinical characteristics were associated with risk of developing IMC (Table 4). In univariate analysis, history of autoimmune disease and vitamin D use were both significantly associated with increased risk of IMC (OR 2.45, 95% CI 1.04-5.78, p=0.040 for autoimmune disease; OR 2.51, 95% CI 1.14-5.54, p=0.022 for vitamin D use). Interestingly, the use of vitamin D supplementation has previously been associated with a decreased risk of IMC, in contrast to our findings here[11]. Prior use of an immune-enhancing therapy (Supplemental Table 2) was associated with a significantly decreased risk of IMC (OR 0.20, 95% CI 0.04-0.95, p=0.043). In the multivariate model which incorporated these characteristics, only the use of immune-enhancing therapy remained significantly associated with decreased risk of IMC, with an OR of 0.20 (95% CI 0.04-1.00, p=0.050).

We next determined if any variables were associated with an increased risk of

severe IMC. Consistent with prior studies of irAE in ICI[17–19], we defined grade 1-2 IMC as mild and grade 3 or higher IMC as severe. In our study, 38 of the 64 patients (59.4%) had severe IMC (Supplemental Table 3). In the univariate model, ipilimumab and vitamin D supplementation were significantly associated with development of severe IMC (OR 8.93, 95% CI 1.07-74.8, p=0.043 for ipilimumab; OR 3.33, 95% CI 1.10-10.14, p=0.034 for vitamin D) (Supplemental Table 6). Combination therapy (ipilimumab plus nivolumab) trended towards an increased risk of severe IMC but did not reach significance (p=0.053). In contrast, pembrolizumab was significantly associated with a decreased risk of severe IMC (OR 0.26, 95% CI 0.09-0.81, p=0.020). In the multivariate model no characteristic reached significance for association with severe IMC, although both combination therapy and ipilimumab monotherapy approached significance for increased risk of severe IMC (p=0.058 and 0.060, respectively).

DISCUSSION

In our study, development of IMC following ICI use was associated with improved overall survival, although not improved progression-free survival, compared to ICI users without IMC. This is similar to findings at another center demonstrating both improved OS and PFS in patients with IMC[9,10]. We also found that vitamin D supplementation at the start of ICI treatment is a risk factor for developing IMC, in contrast to other research suggesting vitamin D use is associated with lower risk of IMC[11]. Our results, therefore, provide critical additional information on these previous associations and present a need for prospective studies.

Both publications showing improved survival in patients with IMC were retrospective analyses performed at the same center[9,10]. One study noted that ICI class was significantly associated with development of IMC[9], a finding that has been demonstrated several times in retrospective work[8,17,18,20–23]. However, unlike our work, this study did not match control patients to account for this likely confounder, as ICI class has been associated with differences in PFS in some malignancies[24,25]. The second study at this center examined survival in melanoma patients with IMC, compared to

our work across multiple malignancies, although frequency matching was performed to account for use of different ICI classes[10]. Since our study is the first to examine survival in patients with IMC at a different center, our work here reinforces that IMC may be associated with increased overall survival and prompts a need for prospective studies.

The only other independent factor in our study positively associated with OS > 12 months was number of ICI doses. This finding may be due to trivial length-time bias, as patients who survive longer are more likely to receive more doses of ICI. It is also possible that patients who required cessation of ICI due to IMC had worse outcomes, although prior work has suggested that patients still derive equivalent long-term benefit from ICI even if stopped due to irAE[26]. Type of underlying malignancy (sarcoma) was independently associated with OS < 12 months in our study. These findings are not unexpected, as most advanced soft tissue sarcomas have a median OS of less than one year[27].

In contrast to prior work, we found a positive association between vitamin D supplementation and development of IMC[11]. It is unclear if this is related to low serum vitamin D levels or negative impact of the supplementation itself, as vitamin D levels near the time of ICI initiation were not recorded in most patients. Additionally, the prior report on vitamin D in IMC was in melanoma patients only, which may partially account for discrepancies with our study. As this association did not remain significant in our multivariate analysis, it is possible that another confounding factor may explain the association between vitamin D supplementation and IMC in our study.

In addition to challenging existing findings, we report here on additional novel risk factors for IMC. We are the first to report that prior use of immune-enhancing medications prior to ICI, such as IL-2 or interferon-γ, is significantly and independently associated with decreased risk of IMC. Much more work should be done to evaluate the relationship between these medications and future risk of IMC.

Finally, our study is the first to examine risk factors for severe IMC. In addition to increasing risk for IMC overall, we find that vitamin D supplementation may also be a risk factor for severe IMC. Similarly, our results suggest that the use of ipilimumab

may be associated with increased risk of severe IMC, while pembrolizumab may be associated with decreased risk of severe IMC in patients who develop this syndrome. As ipilimumab has previously been associated with increased risk of IMC overall, while anti-PD-1, including pembrolizumab, are associated with lower risk of IMC overall[8,9], these findings emphasize that ICI class may affect severity of IMC.

Our findings may significantly impact clinical practice by identifying novel risks for IMC and severe IMC that clinicians, including oncologists and gastroenterologists, should be aware of, while also potentially providing reassurance to physicians and patients that development of IMC may be a positive prognosticator for cancer survival. Neither prior work nor ours found that treatment of IMC, including steroids or infliximab, negatively impacts OS[9,10], and therefore appropriate treatment of IMC should be pursued early on to minimize morbidity and mortality. Both steroid and infliximab use have been suggested to worsen survival in ICI users[12,13], but all current evidence suggests that use of these medications for IMC specifically does not impair cancer outcomes. Our work also cautions against supplementation with vitamin D in ICI users, as this may increase risk of IMC and severe IMC, although carefully designed studies with vitamin D measurements should be performed.

Our work has several strengths. We performed robust cohort matching to minimize confounding effects of ICI class and malignancy. This is also the first study to explore risk factors associated with severe IMC. However, there are limitations to our work. As a retrospective, observational study, it is subject to recall bias and cannot evaluate causation, and may also be subject to immortal time bias (ITB). Patients may have longer exposure to checkpoint inhibitors before developing IMC, compared to patients who do not manifest this irAE, leading to a period where they must survive for long enough to develop IMC and are therefore "immortal"[28]. We found that OS > 12 months was significantly associated with greater numbers of ICI infusions (Table 2), which is likely due to ITB. However, greater numbers of infusions were not associated with IMC (Table 4). This suggests that the association between OS > 12 months and IMC is likely independent of the number of ICI infusions, limiting this as a source of

ITB in our study.

Other weaknesses of our work include selection of patients based on clinical criteria for IMC, including those who did not undergo endoscopy or other objective testing for intestinal inflammation, and therefore may not have had a true colitis. Like prior work, this is also a single-center study, and our results may not be widely generalizable, particularly since we identified fewer patients compared to prior work and our patient population is highly variable, including individuals with several different underlying malignancies. We did not exclude patients with prior non-GI irAEs in either group, although the presence of these was not independently associated with increased OS in our study. We also have not accounted for other factors which may be potential predictors of ICI response, including tumor PD-L1 expression burden, tumor mutational burden, gut microbial composition, proton pump inhibitor use, and combination treatment with tyrosine kinase inhibitors[29–34].

CONCLUSION

In conclusion, our findings suggest presence of IMC is associated with improved OS in cancer patients when cases were matched closely to controls. We also found that vitamin D supplementation was significantly associated with development of both IMC and severe IMC, while immune-enhancing medications were significantly associated with decreased risk of IMC. Future work should focus on broader populations to resolve the discrepancies raised in our work, and to confirm the association between IMC and increased cancer survival. Closely involving gastroenterologists with the workup and management of IMC will be crucial to ensuring the best care possible for these patients.

ARTICLE HIGHLIGHTS

Research background

Immune checkpoint inhibitor-mediated colitis (IMC) is a common immune-related side effect (irAE) of checkpoint inhibitor treatment for cancer. Prior work has suggested that

IMC may be associated with increased survival from cancer.

Research motivation

We sought to determine if IMC was associated with increased overall survival (OS) in a cohort of patients at our institution. These findings could expand existing data on IMC and cancer outcomes and might suggest a common immunological underpinning between the efficacy of checkpoint inhibitors and certain irAEs.

Research objectives

We aimed to investigate if IMC was significantly correlated with increased OS in our cohort, and whether specific clinical factors were associated with either IMC or increased OS.

Research methods

We performed a retrospective case-control study of individuals treated with immune checkpoint inhibitors at our institution who developed IMC, closely matched to a cohort of patients treated with checkpoint inhibitors without IMC. Using univariate and multivariate logistic regression, we determined significant clinical predictors of IMC and the association of presence of IMC on OS.

Research results

We found that IMC was significantly associated with a higher OS as well as OS greater than 12 months. In contrast to previous findings, vitamin D supplementation was significantly associated with development of both IMC and severe IMC. However, prior treatment with immune-enhancing medications was significantly associated with decreased risk of IMC.

Research conclusions

Our findings lend strength to the idea that IMC is associated with improved cancer

363 outcomes with checkpoint inhibitor treatment. This may suggest common immunologic
364 underpinnings between IMC and the anti-tumor effects of checkpoint inhibitors. These
365 results also emphasize the importance of involving gastroenterologists with the
366 management of IMC.
367
368 ***Research perspectives***
369 Future research in this area should seek to expand current knowledge of the
370 relationship between IMC and cancer survival. In particular, future work should focus
371 on broadening the type and number of patients treated with immune checkpoint
372 inhibitors and on tracking patients prior to initiating checkpoint inhibitors to determine
373 if this relationship remains significant prospectively.

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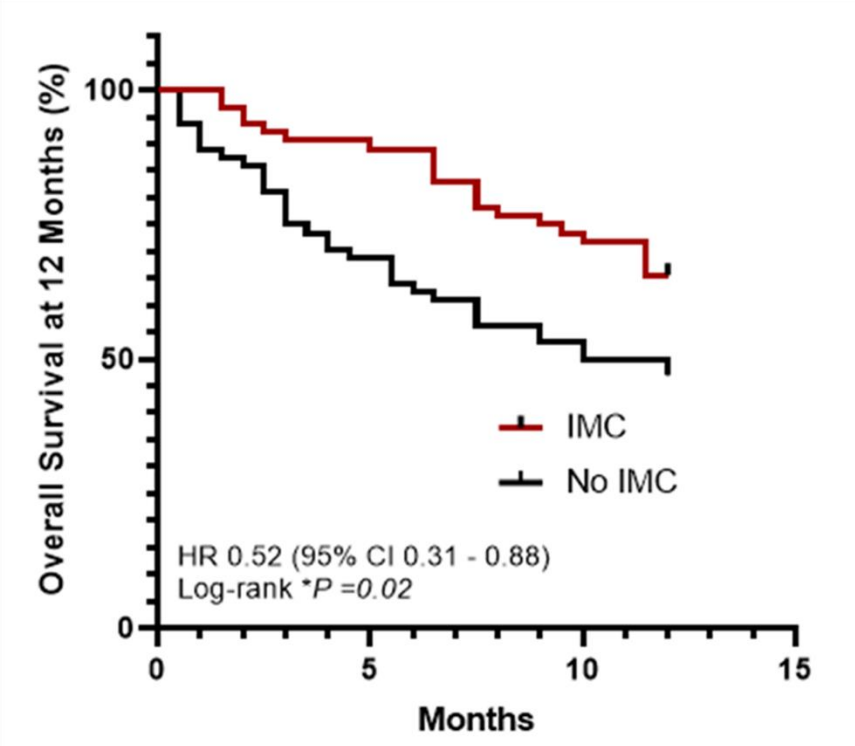
Figures

Figure 1. Overall survival at 12 months in patients with and without IMC. Kaplan-Meier curve of overall survival (OS) at 12 months in patients with IMC (red) and without IMC (black). IMC, immune checkpoint inhibitor-mediated colitis. HR, hazard ratio.



Tables

Table 1. Baseline Characteristics of Patients with Immune Checkpoint Inhibitor (ICI) Use

Clinical Variables	All Patients (N= 128)		Patients with IMC (N= 64)		Patients without IMC (N= 64)		P-Value
Age, years (mean ± SD)*	66.6 (± 11.5)		67.4 (±11.7)		65.8 (± 11.3)		0.420
Sex*							
Male, no. (%)	74	57.81%	37	57.81%	37	57.81%	1.000
Female, no. (%)	54	42.19%	27	42.19%	27	42.19%	
Race							
White, no. (%)	102	79.69%	52	81.25%	50	78.13%	0.660
Black, no. (%)	4	3.13%	2	3.13%	2	3.13%	1.000
Asian, no. (%)	9	7.03%	4	6.25%	5	7.81%	0.730
Type of Malignancy*							
Melanoma, no. (%)	66	51.56%	33	51.56%	33	51.56%	1.000
RCC, no. (%)	15	11.72%	8	12.50%	7	10.94%	0.783
NSCLC, no. (%)	12	9.38%	6	9.38%	6	9.38%	1.000
Sarcoma, no. (%)	11	8.59%	5	7.81%	6	9.38%	0.752
Head and neck SCC, no. (%)	7	5.47%	3	4.69%	4	6.25%	0.697
Other, no. (%)	17	13.28%	9	14.06%	8	12.50%	0.795

Stage IV malignancy, no. (%)	114	89.07%	56	87.50%	58	90.63%	0.778
Type of Immune Checkpoint Inhibitor*							
Ipilimumab plus nivolumab, no. (%)	48	37.50%	24	37.50%	24	37.50%	1.000
Ipilimumab, no. (%)	22	17.19%	11	17.19%	11	17.19%	1.000
Nivolumab, no. (%)	12	9.38%	6	9.38%	6	9.38%	1.000
Pembrolizumab, no. (%)	38	29.69%	19	29.69%	19	29.69%	1.000
Atezolizumab, no. (%)	8	6.25%	4	6.25%	4	6.25%	1.000
Number of Infusions[a] (mean ± SD)*	6.91 (± 8.4)		6.09 (± 7.2)		7.73 (± 9.4)		0.268
Dose of ICI (mg/kg) (mean ± SD)	2.47 (± 1.3)		2.63 (± 1.6)		2.31 (± 1.0)		0.318
Prior ICI use*	19	14.84%	10	15.63%	9	14.06%	0.500
Medical History, no. (%)							
Non-liver, non-upper GI disease[b], no. (%)	28	21.88%	18	28.13%	10	15.63%	0.087
Personal history of autoimmune disease[b], no. (%)	30	23.44%	20	31.25%	10	15.63%	0.037

Prior irAE[b], no. (%)	8	12.50%	7	10.90%	1	1.56%	0.062
Family history of autoimmune disease[b], no. (%)	10	7.81%	8	12.50%	2	3.13%	0.048
Prior immune-enhancing therapy[b], no. (%)	11	8.59%	2	3.13%	9	14.06%	0.027
Prior interferon-γ therapy, no. (%)	7	5.47%	1	1.56%	6	9.38%	0.115
Vitamin D use, no. (%)	38	29.69%	25	39.06%	13	20.31%	0.020
Smoking (current or prior), no. (%)	61	47.66%	33	51.56%	28	43.75%	0.376
NSAID use, no. (%)	21	16.41%	10	15.63%	11	17.19%	0.811
Any vaccine, no. (%)	25	19.53%	9	14.06%	16	25.00%	0.119
Flu vaccine, no. (%)	19	14.84%	7	10.94%	12	18.75%	0.214
Pneumonia vaccine, no. (%)	11	8.59%	4	6.25%	7	10.94%	0.344
Other vaccine, no. (%)	2	1.56%	1	1.56%	1	1.56%	1.000
Weight at start of ICI (kg) (mean ± SD)	78.1 (± 17.4)		79.4 (± 16.9)		76.8 (± 17.9)		0.396
Medications							
Steroid at start of ICI, no. (%)	20	15.63%	11	17.19%	9	14.06%	0.626
Steroid Duration (days)	N/A		107.7 (± 164.2)		N/A		

Infliximab Use, no. (%)	N/A		10	15.63%	N/A		
Vedolizumab Use, no. (%)	N/A		1	1.56%	N/A		
Malignancy Outcomes							
Mean Progression-Free Survival (PFS) (months)	12.8 (± 15.3)		13.7 (± 14.9)		11.9 (± 15.8)		0.524
Progression-Free Survival > 6 months, no. (%)	63	49.22%	35	54.69%	28	43.75%	0.216
Overall Survival (OS) (months)	21.0 (± 18.9)		24.3 (± 19.4)		17.7 (± 18.0)		0.050
Overall Survival > 12 months, no. (%)	72.0	56.25%	42	65.63%	30	46.88%	0.025
Death, no. (%)	20	15.63%	6	9.38%	14	21.88%	0.051

IMC, immune checkpoint inhibitor-mediated colitis. SD, standard deviation. RCC, renal cell carcinoma. NSCLC, non-small cell lung cancer. SCC, squamous cell carcinoma. irAE, immune related adverse event. *Variable matched between cases and controls. [a]Number of infusions of ICI prior to IMC diagnosis (cases) or total (controls). [b]See Supplemental Table 2.

Table 2. Univariate and Multivariate Predictors of Overall Survival > 12 Months Among Patients with Malignancy Using ICI (N=128)

	Univariate Predictors			Multivariate Predictors		
Clinical Variables						
	Odds Ratios (OR)	**95% CI**	**P-Value**	**Odds Ratios (OR)**	**95% CI**	**P-Value**
Demographics						
Age (years)	1.00	0.97 - 1.03	0.970			
Male	0.92	0.45 - 1.87	0.822			
Female	1.08	0.53 - 2.20	0.822			
Race						
White	1.37	0.58 - 3.25	0.473			
Black	2.39	0.24 - 23.6	0.456			
Asian	0.97	0.25 - 3.79	0.965			
Other	0.45	0.14 - 1.45	0.181			
Type of Malignancy						
Melanoma	0.87	0.43 - 1.74	0.688			
RCC	1.65	0.53 - 5.12	0.390			
NSCLC	2.52	0.65 - 9.80	0.181			
Sarcoma	0.15	0.03 - 0.72	0.018	0.17	0.03 -	0.043

					0.95	
Head and Neck SCC	1.04	0.22 - 4.84	0.961			
Other	1.50	0.52 - 4.35	0.453			
Presence of IMC	2.16	1.06 - 4.41	0.034	2.81	1.17 - 6.77	0.021
Presence of high grade IMC	0.47	0.16 - 1.38	0.167			
Stage IV malignancy	0.48	0.14 - 1.61	0.233			
Type of Immune Checkpoint Inhibitor						
Ipilimumab plus Nivolumab	1.32	0.30 - 5.77	0.714			
Ipilimumab	0.74	0.29 - 1.85	0.517			
Nivolumab	1.63	0.46 - 5.70	0.448			
Pembrolizumab	2.93	1.27 - 6.73	0.011	1.06	0.38 - 2.98	0.911
Atezolizumab	1.32	0.30 - 5.77	0.714			
Number of ICI Infusions[a]	1.19	1.08 - 1.32	0.001	1.23	1.09 - 1.40	0.001
Dose of ICI (mg/kg)	1.33	0.86 - 2.05	0.198			
Prior ICI use	0.51	0.19 - 1.37	0.183			
Medical History						
Non-liver, non-upper GI disease[b]	0.87	0.38 - 2.02	0.747			
Personal history of	1.47	0.63 - 3.40	0.373			

autoimmune disease[b]						
Family history of autoimmune disease[b]	1.03	0.32 - 4.41	0.804			
Prior irAE	2.84	0.31 – 25.9	0.356			
Prior immune-enhancing therapy[b]	0.62	0.18 - 2.15	0.454			
Vitamin D use	0.60	0.28 - 1.29	0.190			
Smoking (current or prior)	0.74	0.37 - 1.50	0.410			
NSAID use	1.04	0.41 - 2.69	0.928			
Any vaccine	0.36	0.14 - 0.89	0.026	1.03	0.16 - 6.70	0.972
Flu vaccine	0.22	0.08 - 0.67	0.007	0.30	0.04 - 2.31	0.248
Pneumonia vaccine	0.41	0.11 - 1.48	0.175			
Other vaccine	0.77	0.05 - 12.66	0.858			
Weight at start of ICI (kg)	0.99	0.97 - 1.01	0.207			
Medications						
Steroid at start of ICI	0.74	0.29 - 1.93	0.541			
Steroid Duration (days)	1.00	0.997 - 1.01	0.368			
Infliximab Use	0.76	0.21 - 2.77	0.226			
Vedolizumab Use	1.00	0.99 - 1.01	1.000			

IMC, immune checkpoint inhibitor-mediated colitis. SD, standard deviation. RCC, renal cell carcinoma. NSCLC, non-small cell lung cancer. SCC, squamous cell carcinoma. irAE, immune

related adverse event. [a]Number of infusions of ICI prior to IMC diagnosis (cases) or total (controls). [b]See Supplemental Table 2.

Table 3. Univariate and Multivariate Predictors of Overall Survival > 12 Months Among Patients with Immune Checkpoint Inhibitor Colitis (N= 64).

	Univariate Predictors			Multivariate Predictors		
Clinical Variables						
	Odds Ratios (OR)	**95% CI**	**P-Value**	**Odds Ratios (OR)**	**95% CI**	**P-Value**
Demographics						
Age (years)	0.96	0.92 - 1.01	0.103	0.93	0.88 - 0.99	0.023
Male	0.82	0.29 - 2.32	0.711			
Female	1.22	0.43 - 3.44	0.711			
Race						
White	0.87	0.23 - 3.27	0.835			
Black	1.00	0.90 - 1.34	0.996			
Asian	0.54	0.07 - 4.10	0.550			
Other	1.07	0.97 - 1.11	0.912			
Type of Malignancy						
Melanoma	1.26	0.45 - 3.51	0.654			
RCC	0.51	0.12 - 2.28	0.381			
NSCLC	0.53	0.10 - 2.85	0.456			
Sarcoma	2.38	0.25 - 22.65	0.451			
Head and Neck SCC	1.05	0.89 - 1.10	0.865			

Other	5.33	0.62 - 45.68	0.127			
Stage IV malignancy	0.60	0.11 - 3.26	0.554			
Presence of high grade IMC	0.91	0.32 - 2.57	0.855			
Type of Immune Checkpoint Inhibitor						
Ipilimumab plus Nivolumab	0.95	0.31 - 2.88	0.922			
Ipilimumab	0.98	0.25 - 3.77	0.974			
Nivolumab	0.09	0.01 - 0.83	0.033	0.13	0.01 - 1.43	0.096
Pembrolizumab	2.74	0.78 - 9.58	0.114	3.46	0.84 - 14.19	0.084
Atezolizumab	1.74	0.17 - 17.73	0.641			
Number of ICI Infusions[a]	0.28	0.04 - 1.82	0.183			
Dose of ICI (mg/kg)	1.88	0.36 - 9.83	0.457			
Prior ICI use	0.46	0.12 - 1.80	0.265			
Medical History						
Non-liver, non-upper GI disease[b]	1.67	0.51 - 5.49	0.397			
Personal history of autoimmune disease[b]	0.78	0.26 - 2.31	0.648			
Family history of autoimmune disease[b]	0.93	0.20 - 4.29	0.922			
Prior immune-enhancing therapy[b]	0.55	0.03 - 9.23	0.678			

Prior interferon-g therapy	1.00	0.99 - 1.10	0.976			
Vitamin D use	2.45	0.80 - 7.46	0.116	2.77	0.75 - 10.20	0.124
Smoking (current or prior)	1.66	0.59 - 5.65	0.334			
NSAID use	2.55	0.49 - 13.16	0.265			
Any vaccine	5.33	0.62 - 45.68	0.127			
Flu vaccine	1.46	0.26 - 8.19	0.668			
Pneumonia vaccine	1.00	0.99 - 1.05	0.995			
Other vaccine	1.00	1.00 - 1.01	0.941			
Weight at start of ICI (kg)	1.02	0.98 - 1.05	0.329			
Medications						
Steroid at start of ICI	0.98	0.25 - 3.77	0.974			
Steroid Duration (days)	1.00	1.00 - 1.01	0.736			
Infliximab Use	2.55	0.49 - 13.16	0.265			
Vedolizumab Use	1.00	1.00 - 1.01	0.936			

IMC, immune checkpoint inhibitor-mediated colitis. SD, standard deviation. RCC, renal cell carcinoma. NSCLC, non-small cell lung cancer. SCC, squamous cell carcinoma. irAE, immune related adverse event. [a]Number of infusions of ICI prior to IMC diagnosis (cases) or total (controls). [b]See Supplemental Table 2.

Table 4. Univariate and Multivariate Predictors of IMC Among Patients Using ICI (N=128).

	Univariate Predictors			**Multivariate Predictors**		
Clinical Variables						
	Odds	95% CI	P-	Odds	95% CI	P-

	Ratios (OR)		Value	Ratios (OR)		Value
Demographics						
Age (years)	1.01	0.98 - 1.04	0.417			
Male	1.00	0.50 - 2.02	1.000			
Female	1.00	0.50 - 2.02	1.000			
Race						
White	1.21	0.51 - 2.88	0.661			
Black	1.00	0.14 - 7.33	1.000			
Asian	0.79	0.20 - 3.07	0.730			
Other	0.84	0.27 - 2.66	0.770			
Type of Malignancy						
Melanoma	1.00	0.50 - 2.00	1.000			
RCC	1.16	0.40 - 3.42	0.784			
NSCLC	1.00	0.30 - 3.28	1.000			
Sarcoma	0.82	0.24 - 2.83	0.753			
Head and Neck SCC	0.74	0.16 - 3.44	0.698			
Other	1.15	0.41 - 3.18	0.795			
Stage IV malignancy	0.72	0.24 - 2.22	0.572			
Type of Immune Checkpoint Inhibitor						
Ipilimumab plus	1.00	0.49 - 2.05	1.000			

nivolumab						
Ipilimumab	1.00	0.40 - 2.51	1.000			
Nivolumab	1.00	0.30 - 3.28	1.000			
Pembrolizumab	1.00	0.47 - 2.13	1.000			
Atezolizumab	1.00	0.24 - 4.18	1.000			
Number of Infusions[a]	0.98	0.93 - 1.02	0.273			
Dose of ICI (mg/kg)	1.23	0.82 -1.84	0.327			
Medical History						
Non-liver, non-upper GI[b]	2.11	0.89 - 5.03	0.091			
Autoimmune disease[b]	2.45	1.04 - 5.78	0.040	1.87	0.74 - 4.74	0.186
Prior irAE	7.74	0.92 - 64.82	0.059			
Family history of autoimmune disease[b]	4.43	0.90 - 21.74	0.067	3.98	0.74 - 21.38	0.107
Prior immune-enhancing therapy[b]	0.20	0.04 - 0.95	0.043	0.19	0.04 - 1.01	0.052
Prior interferon-γ therapy	0.15	0.018 - 1.31	0.087			
Vitamin D use	2.51	1.14 - 5.54	0.022	2.48	1.01 - 6.07	0.047
Smoking (current or prior)	1.37	0.68 - 2.74	0.377			
NSAID use	0.89	0.35 - 2.28	0.811			
Any vaccine	0.49	0.20 - 1.21	0.123			
Flu vaccine	0.53	0.19 - 1.45	0.219			
Pneumonia vaccine	0.54	0.15 - 1.95	0.350			
Other vaccine	1.00	0.06 - 16.34	1.000			
Weight at start of ICI	1.01	0.99 - 1.03	0.393			

(kg)						

ICI, immune checkpoint inhibitor. IMC, immune checkpoint inhibitor-mediated colitis. RCC, renal cell carcinoma. NSCLC, non-small cell lung cancer. SCC, squamous cell carcinoma. irAE, immune related adverse event. [a]Number of infusions of ICI prior to IMC diagnosis (cases) or total (controls). [b]See Supplemental Table 2.