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Multidisciplinary Management of Immune-Mediated Diarrhea and Colitis in Advanced Non-Small Cell Lung Cancer: Real-World Evidence

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ABSTRACT

Immune-related adverse events (irAEs) represent a major obstacle in treating solid tumors. This research collects real-world evidence on the frequency of immune-mediated diarrhea and colitis (IMDC) among patients with advanced non-small cell lung cancer (aNSCLC) undergoing immune checkpoint inhibitor (ICI) therapy, while examining how a multidisciplinary approach (MDA) influences IMDC handling and outcomes. Data were retrospectively compiled from sequential aNSCLC patients receiving ICIs alone or combined with chemotherapy from September 2013 through July 2022. For those who developed IMDC, colonic biopsy samples underwent blinded reassessment, and the effects of adopting an MDA were measured against established clinical metrics. Out of 607 enrolled patients, 84 (13.8%) presented with IMDC. Histology re-examination showed frequent microscopic colitis (28%), where collagenous features corresponded to extended symptom persistence (P = .01). IMDC appeared more often in women (P = .05) and those with PD-L1-positive tumors (P = .014), and it was associated with extended progression-free survival (17.0 vs 5.8, P < .001) as well as overall survival (28.3 vs 9.5, P < .001). Adopting the MDA led to higher utilization of diagnostic procedures, including fecal calprotectin assays (P < .001), colonoscopies (P < .001), and gastroenterologist consultations (P = .017), together with notable reductions in progression to grade 3 severity (P = .046) and relapse upon ICI rechallenge (P = .016). Hospital admissions fell from 17.2% to 3.8% (P: ns). The data emphasize the substantial clinical burden of IMDC and advocate integrating an MDA to refine management of this irAE, thereby advancing patient outcomes. A prospective study for confirmation is underway.

Keywords: Immune checkpoint inhibitors, Immune-related adverse events, Immune-mediated diarrhea and colitis.

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Introduction

Incorporating anti-PD-1/PD-L1 immune checkpoint inhibitors (ICIs) into therapy for advanced non-small cell lung cancer (aNSCLC) has substantially prolonged overall survival (OS) and improved quality of life for patients [1-5]. ICI treatment can provoke immune-related adverse events (irAEs) through broad immune stimulation and resulting organ damage, commonly targeting skin, endocrine organs, gastrointestinal system, and liver [6]. Despite low reported rates of particular irAEs in landmark trials [1-5, 7, 8] with mostly mild-to-moderate severity, successful handling necessitates early detection and adequate intervention to avert lasting, serious, or life-threatening consequences, often involving substantial hospital stays [9-13].

Additionally, participants in randomized controlled trials (RCTs) differ from routine clinical populations because of stringent inclusion rules related to age, performance status (PS), brain metastases, and concomitant illnesses [14], even as immunotherapy expands to vulnerable patients [15]. The growing application of these agents in

locally advanced or early-stage settings further stresses the need for effective irAE control, though targeted investigations are still needed.

Diarrhea stands out as a prevalent and potentially severe irAE, affecting 8-14% of patients (any grade) on anti-PD-1 therapies (nivolumab, pembrolizumab, atezolizumab) and nearing 30% when pembrolizumab is paired with chemotherapy. Severe (grades 3-4) diarrhea ranges from 1% to 4% with single-agent anti-PD-1 and reaches 5.2% in combinations [1-5, 16]. It typically signals underlying colitis, which may include abdominal discomfort, bloating, blood or mucus in stool. Together, these are designated immune-mediated diarrhea and colitis (IMDC) [17]. Symptom onset averages roughly 1 month after anti-CTLA-4 exposure but is delayed with PD-1/PD-L1 blockers [18, 19]. Current guidelines primarily recommend pausing ICIs, providing supportive therapy, and administering corticosteroids; expert multidisciplinary input is advised, but precise recommendations for restarting treatment after significant IMDC or managing corticosteroid-resistant cases remain unclear [17, 20-23]. Reliable predictive biomarkers for toxicity likelihood, intensity, or recurrence are also absent from routine practice [24].

This investigation seeks to outline the occurrence, clinical characteristics, pathology, treatment strategies, and results of IMDC in everyday practice via a sizable single-center series of aNSCLC cases managed with immunotherapy or chemo-immunotherapy. Furthermore, it explores the consequences of routinely applying multidisciplinary review on IMDC care and results, using set clinical parameters and economic evaluation.

Materials and Methods

Patients

This research encompassed a retrospective series of individuals diagnosed cytologically or histologically with advanced NSCLC (stage III ineligible for curative therapy, and stage IV per the eighth edition of the TNM Classification of Malignant Tumors) who received sequential treatment with anti-PD-1 or anti-PD-L1 agents in any line of therapy (as monotherapy or combined with chemotherapy) at the Veneto Institute of Oncology (Istituto Oncologico Veneto-IOV) between September 2013 and July 2022. From June 2017 onward, patients exhibiting PD-L1 $\geq$ 50% were administered first-line pembrolizumab. Starting January 2020, those with PD-L1 expression between 0% and 49% were treated with pembrolizumab combined with platinum-pemetrexed, in line with national recommendations. Every included patient had at least 3 months of follow-up.

All treatments followed standard clinical practice. Beginning in May 2021, thoracic oncologists at IOV began routinely consulting gastroenterologists and pathologists experienced in inflammatory bowel diseases and other immune-related gastrointestinal disorders for IMDC cases.

Clinical characteristics and radiological scans for all enrolled patients were examined. Information was gathered on treatment delivery, clinical results, occurrence, severity, and handling of irAEs. For individuals experiencing diarrhea, data included presenting signs and symptoms, initial and peak diarrhea grade, timing of event onset and resolution, immunotherapy interruption and restart, as well as serological, stool, or procedural tests such as colonoscopy. Pathological details from colonic biopsies were compiled and independently reassessed by specialized gastrointestinal pathologists. Where applicable, the type, initial dose, highest dose, and length of corticosteroid or alternative immunosuppressive treatment were recorded. Attribution of symptoms to immune-mediated causes was verified by the study investigators, considering the treating physicians' diagnoses, documented clinical findings, diagnostic results, and therapies applied. As per institutional protocol, all patients in the study were advised to promptly report any new symptoms and provided direct contact options (telephone, email) to notify clinicians.

The investigation adhered to Good Clinical Practice guidelines and the Declaration of Helsinki. Participants provided signed informed consent in compliance with Regulation (EU) 2016/679 on data protection. Approval was obtained from the IOV Ethical Committee (292, 13 May 2019).

Pathological evaluation

All accessible colon-rectal endoscopic biopsies were re-evaluated by two dedicated gastrointestinal pathologists (V.A. and M.F.). Samples were fixed in 10% buffered formalin, paraffin-embedded, cut into 5 mm sections, and stained with hematoxylin and eosin. Available immunohistochemical stains were also examined when present. The evaluation determined the presence or absence of specific histopathological patterns: crypt atrophy/loss, crypt distortion, mucin depletion, apoptotic bodies, lamina propria expansion, crypt abscesses, subepithelial

macrophages, superficial erosion/ulceration, ischemic colitis-like changes, and Paneth cell metaplasia. Additional features were graded semiquantitatively: intraepithelial lymphocytes (absent; 0-2/100 enterocytes; 3-20/100 enterocytes; or >20/100 enterocytes), lymphomonocytic infiltration (absent, mild, moderate, or heavy), granulocytic infiltration (absent, mild, moderate, or heavy), and cryptitis (absent or focally present). An overall score was assigned reflecting the extent and intensity of colitis-related histopathological findings.

Statistical analyses

The main goals were to characterize the frequency and handling of IMDC in everyday clinical settings and to assess the effects of multidisciplinary consultation on diagnostic and therapeutic approaches.

Specific indicators were defined to summarize IMDC handling and results, enabling comparison before and after implementing multidisciplinary discussions. Outcome indicators included the highest IMDC grade documented, the proportion of cases progressing from grades 1-2 to grade ≥3, hospitalization rates due to IMDC, and symptom recurrence rates following immunotherapy resumption. "G3 conversion" denoted instances of worsening during ongoing management (post-onset), excluding those initially presenting as grade 3. Diagnostic and therapeutic process indicators comprised the percentage of patients undergoing endoscopy with biopsy, adoption of fecal calprotectin testing, rates of permanent ICI discontinuation due to irAEs, and frequency of ICI rechallenge post-irAE resolution.

Median progression-free survival (mPFS) was measured from treatment start to documented disease progression or death from any cause; median overall survival (mOS) was measured from treatment initiation to death from any cause. Tumor responses were assessed using RECIST version 1.1 criteria. Response rate (RR) represented the fraction achieving partial or complete response to immunotherapy. Disease control rate (DCR) included patients with partial response, complete response, or stable disease. irAE severity was classified per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Survival estimates employed the Kaplan-Meier method, while proportions were compared using chi-square or Fisher exact tests. Correlations involved chi-square, Mann-Whitney, Fisher exact tests, or multiple logistic regression. Analyses were conducted using Sigma-Plot (version 11; Systat Software, San Jose, CA).

A budget impact evaluation was undertaken to examine the financial consequences of the structural adjustments in handling IMDC. For every instance of this adverse reaction (spanning from initial appearance to full symptom clearance), the expenses tracked included: i) procurement charges for budesonide and/or immunomodulatory medications (infliximab/vedolizumab), ii) charges related to fecal calprotectin assays, iii) charges for colonoscopy examinations, and iv) cumulative hospitalization charges. Costs for hospital stays were computed using Italy's DRG-based reimbursement framework for inpatient services.

Cost comparisons were made across the phases prior to and following the adoption of multidisciplinary oversight for IMDC cases. The analysis covered the interval from January 2017 through May 2022, employing May 2021 as the dividing date.

Results and Discussion

Study population and outcomes

By the data lock date (August 2022), the analysis incorporated 607 individuals with advanced NSCLC who had received anti-PD-1/PD-L1 treatment.

Median patient age stood at 68.7 years, with males predominating (n = 389, 65.5%) and the bulk being active (n = 192, 31.6%) or ex-smokers (n = 307, 50.5%). The leading histological type was adenocarcinoma (394 patients, 64.9%). PD-L1 TPS data existed for the majority (n = 518, 85.3%), showing ≥50% levels in 219 (36.1%). Stage IV presentation dominated (n = 599, 98.7%), with under 3 metastatic locations in most (n = 467, 76.9%). ECOG-PS scores of 0-1 applied to 508 cases (83.7%).

Monotherapy with immune checkpoint inhibitors accounted for 483 patients (79.6%), pembrolizumab leading the list (n = 233, 38.4%). Half the cohort (50.7%) got ICIs frontline, split between standalone use (n = 184, 30.3%) and chemo combinations (n = 124, 20.4%).

Across all, ICIs produced a 30% response rate (95% CI 26.4-33.8) alongside 59.5% disease control (95% CI 55.5-63.4). Frontline responses proved markedly superior, whether monotherapy (n = 79, 49.2%, 95% CI 35.7-50.4%, P < .001) or chemo-combined (n = 96, 50.8%, 95% CI 41.7-59.9, P < .001). Median follow-up reached 8.8 months

(IQR 3.5-17.7), delivering cohort-wide mPFS of 7.7 months (95% CI 6.6-8.9) and mOS of 10.9 months (95% CI 9.4-12.4). Frontline ICI recipients showed clear advantages in PFS (P < .001) and OS (P < .001).
Variables linked to PFS/OS among ICI recipients encompassed PD-L1 levels, metastatic burden at baseline, and performance status. Adenocarcinoma linked to enhanced OS without influencing PFS post-ICI.

Incidence and clinico-pathological features associated with IMDC in a real-world setting
Among participants, any-grade diarrhea emerged in 111 (18.3%). Of these, 84 (75.7%) qualified as immune-mediated per trajectory (onset timing, persistence, improvement) plus ruled-out infection via routine testing. Non-immune diarrhea uniformly cleared in ≤3 days sans immunosuppressants or ICI holds. Chemo-ICI arms saw IMDC in 19/124 (15.3%), versus 65/483 (13.5%) on solo ICI (P = .696).
Diarrhea typically started at median 3.3 months (IQR 1.530-7.32). Initial grading was 1-2 for 77 (91.7%), though escalation to 3-4 hit 14 (16.7%). Co-occurring issues affected 34 patients (40.5%): abdominal discomfort (n = 26, 31.0%), hematochezia (n = 6, 9.4%), pyrexia (n = 2, 2.4%), emesis/nausea (n = 8, 12.5%), weight reduction (n = 7, 8.3%), upper abdominal ache (n = 5, 7.3%).
Higher IMDC rates tied to women (P = .002), PD-L1 ≥1% (P = .019), favorable PS (P = .002), and adenocarcinoma (P = .049). Multivariable modeling pinpointed female sex (OR 0.478, 95% CI 0.286-0.798, P = .005) plus PD-L1 positivity (OR 0.475, 95% CI 0.262-0.861, P = .014) as standalone IMDC drivers **(Table 1).**

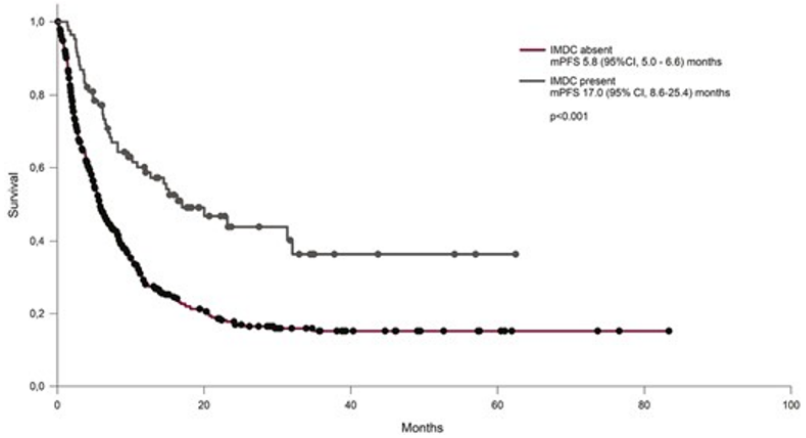
Table 1. Clinico-pathological features associated with immune-mediated diarrhea and colitis (IMDC)

Variable	Total Population N (%)	IMDC N (%)	No IMDC N (%)	Univariate Analysis P / OR (95% CI)	Multivariate Analysis P / OR (95% CI)
Number of cases	607 (100)	84 (100)	523 (100)	–	–
Age					
<68 years (median)	283 (46.6)	39 (46.4)	244 (46.7)	0.937 / 0.991 (0.624–1.573)	–
>68 years (median)	324 (53.4)	45 (53.6)	279 (53.3)	–	–
Gender					
Male	398 (65.6)	42 (50)	356 (68.1)	0.002 / 0.469 (0.295–0.747)	0.005 / 0.478 (0.286–0.798)
Female	209 (34.4)	42 (50)	167 (31.9)	–	–
Smoking status					
Never smokers	92 (15.1)	17 (20.2)	75 (14.3)	0.217 / 1.516 (0.844–2.723)	–
Former/current smokers	515 (84.9)	67 (79.8)	448 (85.7)	–	–
Histology					
Adenocarcinoma	394 (64.9)	63 (75.0)	331 (63.3)	0.049 / 1.740 (1.030–2.941)	0.108 / 1.621 (0.899–2.924)
Squamous & other carcinoma	213 (35.1)	21 (25.0)	192 (36.7)	–	–
Number of metastatic sites					
0–1	264 (43.5)	43 (51.2)	221 (42.3)	0.157 / 1.433 (0.903–2.274)	–
>1	343 (56.5)	41 (48.8)	302 (57.7)	–	–
Lumbo-sacral RT					
Yes	70 (11.5)	11 (13.1)	59 (11.3)	0.735 / 1.203 (0.602–2.403)	–
No	537 (88.5)	73 (86.9)	464 (88.7)	–	–
PS ECOG at treatment start					
0–1	510 (84.0)	77 (91.7)	433 (82.8)	0.002 / 2.132 (1.338–3.396)	0.087 / 2.065 (0.901–4.730)
>1	97 (16.0)	7 (8.3)	90 (17.2)	–	–
PD-L1					

<1%	180 (29.7)	16 (19.0)	164 (31.4)	0.019 / 0.483 (0.268–0.868)	0.014 / 0.475 (0.262–0.861)
≥1%	339 (55.8)	57 (67.9)	282 (53.9)	–	–
Not valuable	88 (14.5)	11 (13.1)	77 (14.7)	–	–

Abbreviations: N, number of cases; PD-L1, programmed death-ligand 1; PS, performance status; ECOG, Eastern Cooperative Oncology Group; ICIs, immune-checkpoint inhibitors; RT, radiotherapy.

IMDC's influence on prognosis underwent review. Those with immune-triggered colitis enjoyed extended PFS (mPFS 17.0 months, 95% CI 8.6-25.4 vs 5.8 months, 95% CI 5.0-6.6, P < .001) and OS (mOS 28.3 months, 95% CI 18.7-37.8 vs 9.5 months, 95% CI 8.2-10.8, P < .001) over non-affected counterparts **(Figure 1)**. Multivariable results flagged PD-L1, histology, baseline metastases, PS, and IMDC as standalone PFS/OS correlates. A 12-week landmark review (restricted to progression-free survivors) confirmed patterns: mPFS (n = 412, 23.2 vs 10.1 months, IMDC vs none, P < .001; HR 0.54 [95% CI 0.38-0.77], P < .001) and mOS (n = 489, 28.4 vs 12.9 months, P = .001; HR 0.50 [95% CI 0.35-0.70], P = .001).



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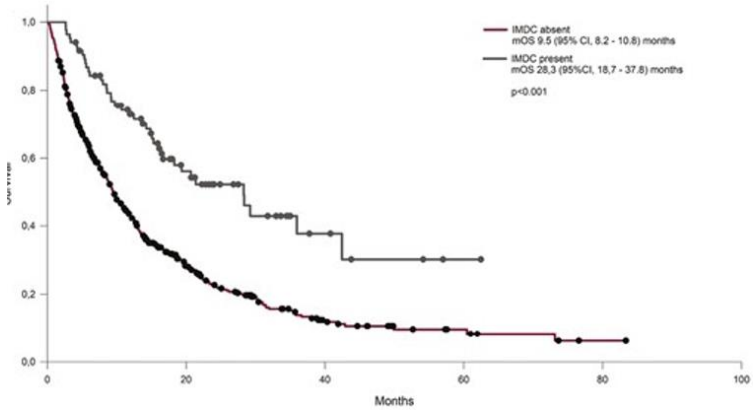


b)

Figure 1. Survival outcomes in patients receiving ICIs stratified by the occurrence of immune-mediated diarrhea, showing progression-free survival (PFS, a) and overall survival (OS, b).

IMDC management

Diarrhea led to temporary treatment discontinuation in 59 patients (70.2%). Corticosteroids were administered to 68 of the 84 patients (81.0%), with 10 (11.9%) receiving them intravenously; all untreated patients had only grade 1 diarrhea. Additional intravenous supportive care was required in 22 patients (25.0%). The median duration of corticosteroid therapy was 122.5 days (IQR 75.0-252.0). One patient (1.2%) required biologic treatment (vedolizumab) for symptom control following 182 days of steroid use. Colonoscopy for diagnostic purposes was conducted in 30 cases (30.7%), at a median of 1.9 months after symptom onset (IQR 0.9-4.2).

Notably, 11 patients (13.1%) were admitted to hospital due to diarrhea complications, with a median length of stay of 15.5 days (IQR 9.0-17.0). Reasons for admission included severe symptoms in 7 cases (63.6%),

diverticulitis in 1 (9.0%), dehydration in 1 (9.0%), and bone fracture after near-syncope in 1 (0.9%). No fatalities related to toxicity occurred.

By the data cutoff, symptom resolution was documented in 81 of 84 cases (96.4%), with a median resolution time of 48 days (IQR 38.7-59.3). Patients on combined chemo-immunotherapy showed a non-significant trend toward prolonged symptoms compared to monotherapy (median 59 vs 45 days, P = .174). Following resolution, immunotherapy was restarted in 30 patients (35.7%), among whom 7 (23.3%) had previously experienced grade 3 diarrhea. Only 2 patients (6.0%) restarted treatment after progressing on prior therapy. The median interval to restarting therapy was 4.9 months (95% CI −0.4, 10.2). Diarrhea recurred in 19 of the 30 restarted cases (63.3%), with a median onset of 2.1 months after resumption (95% CI 1.1-3.0).

In this series, temporary treatment interruption had no impact on PFS or OS.

Comparison of clinical characteristics and management between monotherapy and combination regimens revealed no significant differences.

Impact of introducing a multidisciplinary team on diagnostic-therapeutic pathways and outcomes

From May 2021 onward, IMDC cases were reviewed through email and virtual meetings with gastroenterologists expert in inflammatory bowel disease and other immune-related gastrointestinal conditions. Biopsy cases were additionally reviewed by two specialized gastrointestinal pathologists. In-person gastroenterology consultations were reserved for selected patients.

The effects of multidisciplinary review on IMDC handling were assessed using established process indicators **(Table 2 and Figure 2).**

Table 2. Management of immune-mediated diarrhea and colitis (IMDC) before and after the introduction of multidisciplinary team.

Variable	Before MDT Collaboration (before May 2021) N (%)	After MDT Collaboration (after May 2021) N (%)	P-value
All cases	58 (100)	26 (100)	–
Treatment			
ICI + Chemotherapy (first line)	10 (17.2)	9 (34.6)	0.105
ICI monotherapy	48 (82.8)	17 (65.4)	–
Fecal calprotectin test			
Yes	7 (12.0)	17 (65.4)	<0.001
No	51 (87.9)	9 (34.6)	–
Colonoscopy			
Yes	13 (22.4)	17 (65.4)	<0.001
No	45 (75.9)	9 (34.6)	–
Gastroenterological visit			
Yes	9 (15.5)	11 (42.3)	0.017
No	49 (84.5)	15 (57.7)	–
Grade at onset			
G1–G2	54 (93.1)	23 (88.5)	0.671
G3	4 (6.9)	3 (11.5)	–
Maximum grade			
G1	30 (51.7)	10 (38.4)	0.374
G2	17 (19.3)	13 (50.1)	–
G3	11 (19.0)	3 (11.5)	–
Conversion from G1–G2 to G3			
No	50 (86.2)	26 (100.0)	0.046
Yes	8 (13.8)	0 (0.0)	–
Symptoms duration (days)	Median (IQ range)	51.0 (24.0–91.0)	47.0 (24.0–89.8)
Time to colonoscopy (days)	Median (IQ range)	82.0 (34.5–160.0)	55.0 (26.8–120.0)
Budesonide treatment			
Yes	3 (5.1)	15 (57.7)	<0.001
No	55 (94.8)	11 (42.3)	–

Steroid treatment			
Yes	46 (79.3)	22 (84.6)	0.766
No	12 (20.7)	4 (15.4)	–
Steroid duration (days)	Median (IQ range)	111.5 (58.0–247.0)	139.5 (84.5–286.5)
Systemic steroid duration (days)	Median (IQ range)	98.5 (43.0–170.0)	121.0 (81.0–198.0)
Hospitalization			
Yes	10 (17.2)	1 (3.8)	0.160
No	48 (82.8)	25 (96.2)	–
Treatment interruption			
Yes	38 (65.5)	21 (80.8)	0.248
No	20 (34.5)	5 (19.2)	–
Treatment resumption			
Yes	22 (37.9)	8 (30.8)	0.118
No	16 (27.6)	13 (50.0)	–
Not applicable	20 (34.5)	5 (19.2)	–
Recurrence			
Yes	16 (27.6)	1 (3.8)	0.016
No	6 (10.3)	7 (26.9)	–
Not applicable	36 (62.0)	18 (69.2)	–
Biological drug use			
Yes	0 (0.0)	1 (3.8)	0.310
No	58 (100)	25 (96.2)	–

Abbreviations: MDT, multidisciplinary team; N, number; ICI, immune checkpoints inhibitors; ChT, chemotherapy, G, grade; IQ, inter-quartile. *In conversion to G3 group were included cases experiencing worsening of symptoms during active management.

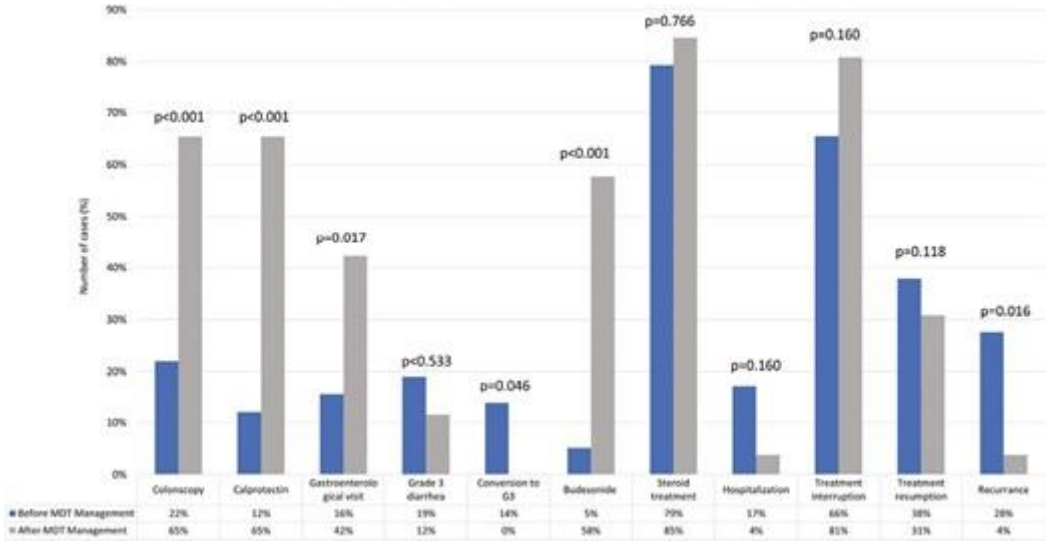


Figure 2. The figure illustrates modifications in the handling and results of immune-mediated diarrhea and colitis (IMDC) following implementation of multidisciplinary review. *In conversion to G3 group were included cases experiencing worsening of symptoms during active management.

Following the establishment of the specialized multidisciplinary team, significant increases were observed in the use of diagnostic modalities, including fecal calprotectin testing (12.0% vs 65.4%, P < .001), colonoscopy (22.4% vs 65.4%, P < .001), and gastroenterology consultation (15.5% vs 42.3%, P = .017) **(Figure 2).**

Although the peak grade distribution showed no significant change, post-implementation there were no instances of symptom escalation during treatment, with all grade 3 events present at initial presentation (P = .046). A notable decrease in recurrence upon therapy resumption was also seen (3.8% vs 27.6%, P = .016) **(Figure 2 and Table 2).**

These enhancements in diagnostic and treatment processes likely enabled more tailored approaches. Specifically, ICI rechallenge was guided by fecal calprotectin monitoring, and in 20% of rechallenged patients, only topical (non-systemic) steroids were continued at the time of restart.

Hospitalization rates declined numerically after multidisciplinary implementation (17.2% vs 3.8%, P = .16). Logistic regression, adjusted for gender, PD-L1 status (≥1%), treatment type (ICI monotherapy vs combination), performance status, and peak toxicity grade, showed no significant association with reduced hospitalization risk (OR 0.82, 95% CI 0.14-4.94). Nonetheless, the OR direction hints at a potential benefit from multidisciplinary review (data not shown). Additional information is provided in **Table 2.**

Endoscopic and pathological findings

A total of 30 patients (30.7%) proceeded to colonoscopy: 6 (20%) after grade 3 IMDC, 13 (43.3%) with grade 2, and 11 (36.7%) despite grade 1. Visible mucosal changes were noted in 11 individuals (36.7%); the other 19 (63.3%) still underwent multiple random biopsies despite unremarkable endoscopic appearance.

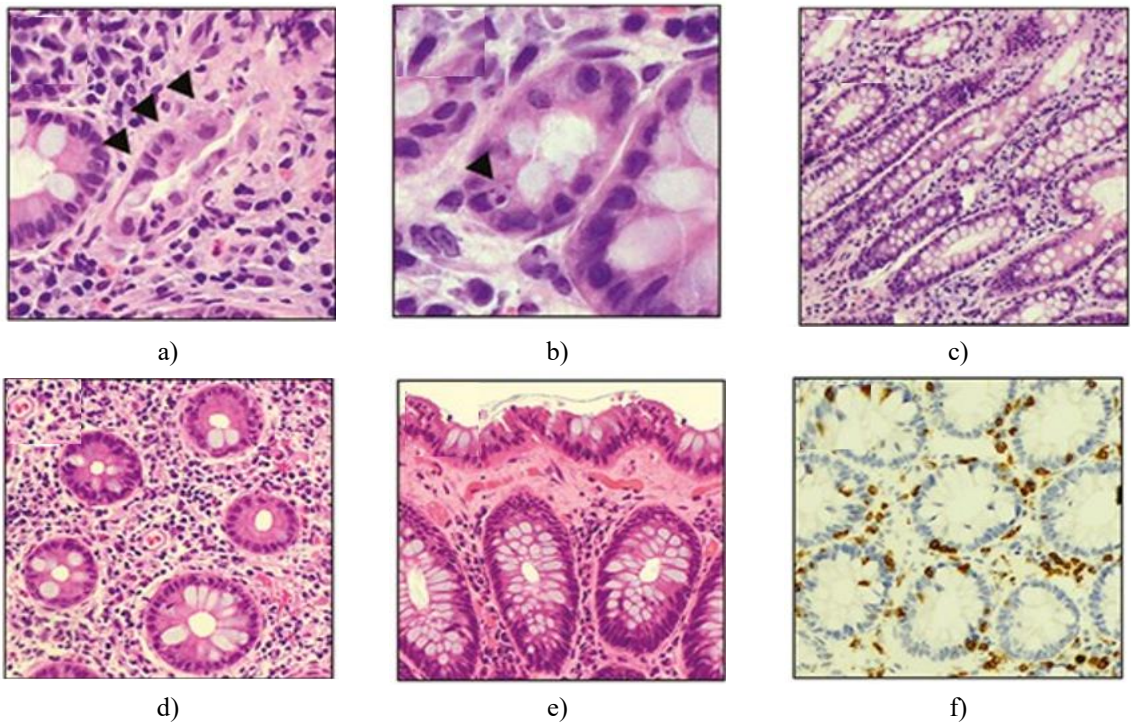
Histological results from the 25 patients (83.3%) yielding adequate biopsy specimens for reassessment are presented in **Table 3.**

Table 3. Microscopic characteristics observed in biopsies from patients with immune-mediated diarrhea and colitis.

Histopathological Feature	N (%)
Number of cases	25 (100.0)
Crypt atrophy/loss	
Present	12 (48.0)
Absent	13 (52.0)
Crypt distortion	
Present	15 (60.0)
Absent	10 (40.0)
Mucin depletion	
Present	20 (80.0)
Absent	5 (20.0)
Apoptotic bodies	
Present	19 (76.0)
Absent	6 (24.0)
Lamina propria expansion	
Present	21 (84.0)
Absent	4 (16.0)
Collagenous band	
Absent	16 (64.0)
Focal	5 (20.0)
Extensive	4 (16.0)
Intraepithelial lymphocytes	
Absent	1 (4.0)
0–2/100 enterocytes	11 (44.0)
3–20/100 enterocytes	13 (52.0)
>20/100 enterocytes	0 (0.0)
Lymphomonocytic infiltrate	
Absent	0 (0.0)
Mild	8 (32.0)
Moderate	17 (68.0)
Heavy	0 (0.0)
Granulocyte infiltrate	
Absent	13 (52.0)
Mild	11 (44.0)
Moderate	1 (4.0)
Heavy	0 (0.0)
Cryptitis	

Absent	20 (80.0)
Focally present	5 (20.0)
Crypt abscess	
Present	2 (8.0)
Absent	23 (82.0)
Subepithelial macrophages	
Present	6 (24.0)
Absent	19 (76.0)
Superficial erosion/ulceration	
Present	5 (20.0)
Absent	20 (80.0)
Ischemic colitis–like features	
Present	6 (24.0)
Absent	19 (76.0)
Paneth cell metaplasia	
Present	7 (28.0)
Absent	18 (72.0)
Global histology score	
1	9 (36.0)
2	9 (36.0)
3	7 (28.0)

Every available colonic biopsy from the center was independently re-assessed. Histology led to a diagnosis of microscopic colitis in 7 of 25 specimens (28%) **(Figure 3),** including collagenous colitis in 4 cases (16%). Full descriptions of the microscopic patterns across reviewed samples appear in **Table 3.**



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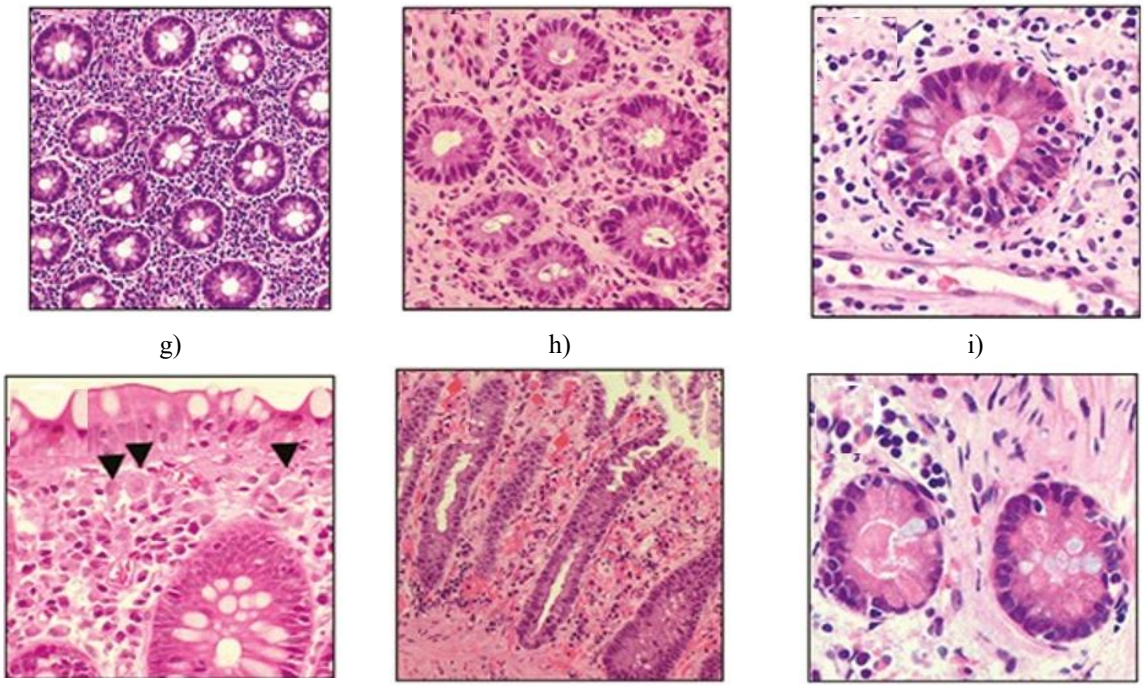

g) h) i)

j) k) l)

Figure 3. Examples of typical microscopic abnormalities identified in colonic tissue from individuals on immune checkpoint inhibitors. (a) Crypt atrophy. (b) Apoptotic bodies within a gland. (c) Mild crypts' distortion. (dD) Lamina propria expansion and mucin depletion. (e) Collagenous band. (f) CD3 immunostaining showing moderate intraepithelial lympho-monocitic infiltrate. (g) Lympho-monocitic and plasmacellular infiltrate within the lamina propria. (h) Granulocytic infiltrate within the lamina propria associated with cryptitis. (i) Cryptic abscess. (j) Subepithelial macrophages. (k) Ischemic-like colitis features and superficial erosion. (l) Paneth metaplasia.

Among those showing endoscopic evidence of colitis, hospitalization was required in 3 of 11 (27.3%), versus 1 of 19 (5.3%) with normal endoscopy (P = .126).

Symptom persistence was substantially greater in cases featuring microscopic collagenous colitis than in others (median 200.5 days, IQR 118.5-292.0 versus 54.0 days, IQR 30.0-101.5, P = .011).

Budget impact

Implementation of multidisciplinary IMDC assessment resulted in a net decrease in overall expenditure for handling these events. The primary driver was a marked drop in hospitalization-related costs **(Table 2).** In contrast, spending surged for budesonide (up 400%) and fecal calprotectin assays (up 143%), more than doubling those items. Colonoscopy expenses rose more modestly (up 31%). Despite these increases, yearly totals fell around 20% (from 7.200 to 5.935 euros), while per-patient costs declined by roughly 60%.

Encountering immune-related adverse events (irAEs) represents a major challenge in the clinical management of advanced non-small cell lung cancer (NSCLC). Although international guidelines primarily draw from clinical trial data and emphasize the value of a multidisciplinary approach, analyses of real-world experience are crucial for enhancing patients' quality of life and outcomes in everyday practice [20, 22, 25-28].

We conducted a retrospective review of a large consecutive cohort of patients with advanced NSCLC who received immune checkpoint inhibitors (ICIs) either as monotherapy or combined with chemotherapy, with a particular focus on the clinical management and outcomes of immune-mediated diarrhea and colitis (IMDC). In our real-world setting, the incidence and outcomes aligned closely with published literature, particularly for ICI monotherapy [1, 3-5, 29-31] and, consistent with prior reports, the occurrence of IMDC was linked to a greater likelihood of extended progression-free survival (PFS) and overall survival (OS) in patients receiving immunotherapy [24, 32-34]. Interpreting these findings accurately may be complicated by potential biases, including suboptimal diagnostic accuracy in identifying irAEs and immortal-time bias [35, 36]. To mitigate the latter in part, we performed a landmark survival analysis at 12 weeks following the initial ICI dose, which yielded results congruent with those of the overall cohort.

Regarding IMDC management, we observed a comparatively low frequency of colonoscopy procedures and a prolonged interval between symptom onset and endoscopic evaluation, despite recent evidence underscoring its importance and showing that early colonoscopy (within 7 days) correlates with improved outcomes [17, 37]. Additionally, the duration of steroid therapy in our series tended to exceed recommendations in international guidelines, which advocate tapering over 4-6 weeks, alongside restricted utilization of second-line immunosuppressive agents—many of which remain off-label in several European nations, including Italy.

Conversely, the rate of IMDC recurrence following ICI rechallenge appeared somewhat lower than figures documented in the literature [23].

The infrequent administration of biologic therapies and the extended steroid courses observed in our cohort highlight the pressing need for dedicated diagnostic and therapeutic protocols tailored to IMDC and irAEs broadly, as well as the potential development of specialized regulatory approval processes.

Building on these real-world observations, we examined the influence of multidisciplinary management by stratifying our data based on the implementation of formal multidisciplinary team (MDT) discussions at our Cancer Institute, incorporating expert gastroenterologists and pathologists. We defined key indicators of diagnostic-therapeutic pathways informed by existing literature and consensus on IMDC [26, 28]. Following MDT introduction, there was a statistically significant rise in the performance of colonoscopies and fecal calprotectin testing. These elements are believed to substantially affect outcomes, supported by literature on IMDC, with the role of colonoscopy recently emphasized and its association with prognosis robustly established [38, 39]. In contrast, the use of fecal calprotectin to guide the timing of ICI resumption has seen limited exploration in routine practice but warrants further assessment based on our findings, as a fecal biomarker for tracking IMDC progression [40]. Concurrently, post-MDT implementation, we began employing non-systemic steroids, which may reduce steroid-associated toxicity and ultimately enhance patient quality of life, as noted previously [41]. Additional prospective studies are required to determine the optimal formulation, dosage, and duration of systemic steroids when combined with budesonide.

Within this project, we also conducted a blinded re-evaluation of histological biopsies and identified a notably high prevalence of microscopic colitis relative to expectations in inflammatory bowel disease and even in IMDC [27, 28, 40, 41]. No statistically significant relationship emerged between macroscopic endoscopic inflammatory findings and symptom duration, aligning with a recent retrospective analysis across various solid tumors [28]. Notably, the referenced series similarly found no meaningful link between diarrhea grade and endoscopic appearances, and many published cohorts examining endoscopic and histopathologic characteristics of IMDC involved patients treated with anti-CTLA-4 agents, which are typically linked to more severe colitis [17, 27, 28, 38, 42-44].

Upon reassessing microscopic biopsy features, we detected a clinically meaningful association between collagenous patterns and symptom duration, implying that distinct histopathologic subtypes may predict steroid resistance irrespective of initial symptom severity and reinforcing the importance of comprehensive biopsy sampling during endoscopy. The potential for early identification of grade 2 "steroid-refractory" cases could meaningfully influence patient care, supporting the recommendation for colonoscopy in grade 2 IMDC as per international guidelines [21, 41, 45-47].

We assessed the changes in outcome indicators following the implementation of multidisciplinary discussion, and the most notable finding was a decrease in the relapse rate after resumption of ICIs. In these instances, we tailored management based on clinical assessment and fecal calprotectin testing, and in certain cases, continued budesonide without systemic steroids at the time of ICI rechallenge (20% of cases). Importantly, after the adoption of multidisciplinary discussion, we recorded no instances of symptom grade escalation following IMDC diagnosis. Although not reaching statistical significance—likely owing to the limited number of hospitalizations across the entire cohort—we documented 10 hospitalizations among 58 cases prior to multidisciplinary discussion, compared to just one case out of 26 IMDC events thereafter.

Although the sample size and retrospective study design preclude definitive conclusions, we posit that the observed improvements in outcome indicators stem from overall enhancements in management. In particular, we suggest that employing fecal calprotectin testing to monitor patients after ICI discontinuation and the utilization of non-systemic steroids contribute to the lower relapse rate, while the absence of grade worsening may be attributable to vigilant monitoring and individualized management guided by diagnostic tools alongside clinical findings.

Future studies, including prospective assessments of diagnostic-therapeutic pathways and the effects of multidisciplinary discussion, are planned to examine long-term outcomes and the relationship between improvements in these pathways and long-term results, including the evaluation of steroid-related adverse effects. This study has several strengths, as it describes a substantial real-world cohort of patients with advanced NSCLC managed in routine clinical practice. By concentrating on IMDC clinical management, we were able to gather comprehensive clinical data on this significant irAE, review histological specimens from endoscopies, and translational analyses are presently underway.

We recognize certain limitations, including the retrospective and single-center design, which may introduce biases in documenting irAE-related symptoms, diagnostic procedures, and management decisions in complex and heterogeneous clinical situations. Furthermore, our patients received treatment starting from the initial introduction of ICIs into clinical practice and prior to the establishment of current diagnostic and management guidelines. Accordingly, we noted generally suboptimal use of diagnostic modalities such as calprotectin testing and endoscopy, which was partly addressed following the introduction of MDT discussion. Given the patient numbers and the concurrent changes in multiple diagnostic pathway indicators, we were unable to isolate the independent contribution of each indicator—including fecal calprotectin testing and colonoscopy rates—to outcome measures. Moreover, we have not yet established formal institutional boards for the multidisciplinary management of immune-related toxicities, as reported in other experiences [11, 48-50].

Conclusion

In summary, this study presents a large real-world cohort of patients with advanced NSCLC managed in routine clinical practice. By emphasizing IMDC clinical management, we were able to acquire data on microscopic features in patients treated with anti-PD-1/L1 agents and assess the influence of multidisciplinary discussion in everyday practice. The primary limitations arise from its retrospective design, encompassing potential variability in toxicity reporting and diagnostic planning. Nonetheless, the effect of multidisciplinary discussion—even without a formalized tumor board—is substantial and strongly supports the necessity to transform our clinical strategy for IMDC and irAEs overall.

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