Volume 1, Issue 2, (2025)
1st August, 2025
DOI.org/10.71079/ASIDE.GI.1.2

ASIDE GASTROENTEROLOGY

HEALTHCARE

PUBLISHED BY
AMERICAN SOCIETY FOR INCLUSION, DIVERSITY, AND EQUITY IN HEALTHCARE (ASIDE)

ISSN (Print) 3066-4004
ISSN (Online) 3066-4012

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Editorial

Mycophenolate Mofetil Use for Inflammatory Bowel Disease

Ahmed Abomhya[1,*], Ahmed Elmoursi[2]

1-Department of Gastroenterology University of Kentucky Lexington, KY, USA
2-Division of Rheumatology, Allergy, and Immunology, Department of Medicine Massachusetts General Hospital; Harvard Medical School Boston, MA, USA

ARTICLE INFO

Article history:
Received 18 Mar. 2025
Received in revised form 06 Apr. 2025
Accepted 06 Apr. 2025
Published 14 Apr. 2025

Keywords:
Mycophenolate Mofetil
Inflammatory Bowel Disease
Ulcerative Colitis
Crohn's Disease
Immunosuppressive Therapy
Anti-inflammatory Agents
Immunomodulators
Gastrointestinal Inflammation
Mycophenolic Acid

EDITORIAL

Mycophenolate Mofetil (MMF) is a prodrug that gets converted to mycophenolic acid (MPA). MPA inhibits the Akt/mTOR and STAT5 pathways and has a reversible cytostatic effect on T and B lymphocytes [1].

MMF is FDA-approved for immunosuppressive therapy after solid organ transplantation. MMF has been used for multiple inflammatory/autoimmune conditions including psoriasis, dermatomyositis, autoimmune hepatitis, lupus erythematosus, myasthenia gravis, and Takayasu arteritis [2].

In this Editorial, we discuss the recently published systematic review and meta-analysis by Balassiano et al [3]. This systematic review and meta-analysis studied the use of MMF for the treatment of IBD patients. This review included both retrospective studies, case series, and clinical trials that evaluated the use of MMF in patients with IBD. Included patients were intolerant or unresponsive to Azathioprine. MMF was used in the included studies for induction and maintenance of remission, or as a steroid-sparing agent/immunomodulator. This study demonstrated MMF's efficacy in both induction and maintenance of remission in IBD patients. MMF was associated with added benefits for patients on steroids as well as those on anti-TNF therapy [3].

MMF has several boxed warnings in the United States, limiting its use outside FDA-approved indications. MMF should be prescribed only by healthcare providers experienced in immunosuppressive therapy and organ transplant management, with access to comprehensive laboratory and medical resources [4].

There is also a significant risk of infections associated with immunosuppression, including but not limited to opportunistic infections, which may result in significant morbidity and mortality. MMF use is associated with an increased risk of malignancy, including but not limited to lymphoma and skin cancers. There is also a boxed warning suggesting avoiding MMF use in pregnancy if alternative therapies are available, as its use is associated with congenital malformation and first-trimester pregnancy loss [5].

MMF has been associated with endoscopic findings that could be similar to acute colitis, IBD, ischemia, and graft-versus-host disease. Development of such side effects or endoscopic findings can lead to discontinuation of treatment, treatment interruption, or medication non-compliance [6, 7].

In this study, the pooled event rate for adverse events was 26.1% (20.3%-32.8%). The side effect profile is crucial in determining the role of MMF in IBD treatment. The IBD field is evolving around a patient-centered approach when it comes to therapeutic selection. IBDologists extensively discuss potential side effects and explore the patient's risk appetite. In general, more than one in four is considered a relatively high risk.

While side effects could constitute a major challenge for MMF use in IBD patients, their impact on treatment adherence, disease progression, and quality of life must be carefully weighed against MMF's potential benefits. The development of side effects has been associated with specific risk factors that increase the risk of developing side effects, which could open the door for drug adjustment and close monitoring that might allow its use. These risk factors include using a non-enteric-coated formulation, increased MMF blood levels, concomitant use of other immunosuppressant agents like calcineurin inhibitors, and female sex [8, 9, 10, 11].

MMF is relatively inexpensive compared to other IBD therapies. A dose price can range from as low as $0.32 for an oral dose to as high as $129.57 for an IV dose. This is cheaper compared to Azathioprine prices [12]. With the evolving widespread use of biosimilars, we are heading to an era with better accessibility to advanced IBD therapies, and this will allow gastroenterologists to adopt the recommended top-down approach in therapeutic selection [13].

The ACG guidelines for Crohn's disease recommend combining an immunomodulator with anti-TNF rather than using anti-TNF alone [14]. Hernandez-Camba et al. showed the added benefits of anti-TNF when combined with MMF [15]. This suggests potential benefits of MMF as an immunomodulator that could decrease anti-TNF immunogenicity and decrease the risk of secondary non-response.

* Corresponding author: Ahmed Abomhya, Department of Gastroenterology, University of Kentucky, Lexington, KY 40508, USA. Email: ahmedabdelsatar78@gmail.com

Citation: Abomhya A, Elmoursi A. Mycophenolate Mofetil Use for Inflammatory Bowel Disease. ASIDE GI. 2025;1(2):1-2, doi:10.71079/ASIDE.GI.04142552

The study has some significant limitations. The included studies had heterogeneous designs. The study lacked a control group and did not compare MMF to alternatives such as Azathioprine or Mercaptopurine.

The IBD therapies are expanding, and it's an evolving field with multiple advancements annually. Selection of therapy in patients with IBD is a multistep and complex process that involves close consideration of the disease stage, patient population, disease complications, medication history, prognostic factors, presence of extra-intestinal manifestations of IBD, potential side effects of medications, patients' preferences, and cost implications [14].

In conclusion, this study highlights the potential benefits of MMF as a steroid-sparing agent or as an immunomodulator in conjunction with ant-TNF. It provides evidence for the use of MMF as an alternative for those intolerant or unresponsive to Azathioprine and Methotrexate.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research

Funding Source

The authors declare that no specific grant or funding was received for this research from any public, commercial, or not-for-profit funding agency.

Acknowledgments

None

Institutional Review Board (IRB)

None

Large-Language Model

None

Authors' Contribution

All authors have contributed equally to the conception, drafting, review, and final approval of this manuscript. Each author has read and agreed to the final version for publication.

Data Availability

The data that support the findings of this study are openly available, as cited in the article.

References

1. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47(2-3):85-118. [PMID: 10878285, https://doi.org/10.1016/s0162-3109(00)00188-0].
2. Alakkas Z, Gari AM, Makhdoum S, AlSindi EA. Mycophenolate-induced colitis in a patient with lupus nephritis: a case report and review of the literature. J Med Case Rep. 2024;18(1):229. [PMID: 38689344, PMCID: PMC11061913, https://doi.org/10.1186/s13256-024-04539-7].
3. Balassiano N, Tidwell J, Abdelhalim O, Abusuliman M, Nassar M, Beran A, et al. Mycophenolate Mofetil for the Treatment of Resistant Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. ASIDE Gastroenterology. 2025;1(1):15-22. [https://doi.org/10.71079/aside.Gi.03132515].
4. Kim M, Rostas S, Gabardi S. Mycophenolate fetal toxicity and risk evaluation and mitigation strategies. Am J Transplant. 2013;13(6):1383-9. [PMID: 23617812, https://doi.org/10.1111/ajt.12238].
5. Pisoni CN, D'Cruz DP. The safety of mycophenolate mofetil in pregnancy. Expert Opin Drug Saf. 2008;7(3):219-22. [PMID: 18462179, https://doi.org/10.1517/14740338.7.3.219].
6. Calmet FH, Yarur AJ, Pukazhendhi G, Ahmad J, Bhamidimarri KR. Endoscopic and histological features of mycophenolate mofetil colitis in patients after solid organ transplantation. Ann Gastroenterol. 2015;28(3):366-73. [PMID: 26126799, PMCID: PMC4480174].
7. de Andrade LG, Rodrigues MA, Romeiro FG, Garcia PD, Contti MM, de Carvalho MF. Clinicopathologic features and outcome of mycophenolate-induced colitis in renal transplant recipients. Clin Transplant. 2014;28(11):1244-8. [PMID: 25142167, https://doi.org/10.1111/ctr.12452].
8. Arns W. Noninfectious gastrointestinal (GI) complications of mycophenolic acid therapy: a consequence of local GI toxicity? Transplant Proc. 2007;39(1):88-93. [PMID: 17275481, https://doi.org/10.1016/j.transproceed.2006.10.189].
9. Kiang TKL, Ensom MHH. Exposure-Toxicity Relationships of Mycophenolic Acid in Adult Kidney Transplant Patients. Clin Pharmacokinet. 2019;58(12):1533-52. [PMID: 31332670, https://doi.org/10.1007/s40262-019-00802-z].
10. Langone AJ, Chan L, Bolin P, Cooper M. Enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients experiencing gastrointestinal intolerance: a multicenter, double-blind, randomized study. Transplantation. 2011;91(4):470-8. [PMID: 21245794, https://doi.org/10.1097/TP.0b013e318205568c].
11. Meaney CJ, Sudchada P, Consiglio JD, Wilding GE, Cooper LM, Venuto RC, et al. Influence of Calcineurin Inhibitor and Sex on Mycophenolic Acid Pharmacokinetics and Adverse Effects Post-Renal Transplant. J Clin Pharmacol. 2019;59(10):1351-65. [PMID: 31062373, PMCID: PMC7375007, https://doi.org/10.1002/jcph.1428].
12. Tse KC, Tang CSO, Lam MF, Yap DYH, Chan TM. Cost Comparison Between Mycophenolate Mofetil and Cyclophosphamide-Azathioprine in the Treatment of Lupus Nephritis. The Journal of Rheumatology. 2009;36(1):76-81. [https://doi.org/10.3899/jrheum.080517].
13. Satsangi J, Nowak J, Kalla R, Colombel JF. Treatment strategies and biomarkers in Crohn's disease: the PROFILE trial. Lancet Gastroenterol Hepatol. 2024;9(7):591-2. [PMID: 38870964, https://doi.org/10.1016/S2468-1253(24)00082-7].
14. Lichtenstein GR, Loftus J E V, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. Correction: ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113(7):1101. [PMID: 29895986, https://doi.org/10.1038/s41395-018-0120-x].
15. Hernandez-Camba A, Arranz L, Vera I, Carpio D, Calafat M, Lucendo AJ, et al. Real-world use of mycophenolate mofetil in inflammatory bowel disease: Results from the ENEIDA registry. Dig Liver Dis. 2022;54(5):635-41. [PMID: 34862115, https://doi.org/10.1016/j.dld.2021.10.002].

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Original Article

Efficacy and Safety of Tofacitinib in Pediatric Ulcerative Colitis Patients: A Systematic Review

Abdelaziz A. Awad[1,*], Mohamed A. Aldemerdash[2], Ahmed Aldemerdash[2], Esraa Awad[3], Salma Allam[4], Ahmed L. Youseif[5], Alshimaa M. Abu alabbas[6], Nermin Elhossiny[7], Hazem Abosheaishaa[8]

1-Faculty of Medicine, Al-Azhar University, Cairo, Egypt
2-Faculty of Medicine, Sohag University, Sohag, Egypt
3-Internal Medicine Department,, Zagazig University, Zagazig, Egypt
4-Faculty of Medicine, Galala University, Suez, Egypt
5-Faculty of Medicine, Al-Azhar University, Damietta, Egypt
6-Faculty of Pharmacy, Egypt Japan University of Science and Technology, Alexandria, Egypt
7-Department of Clinical Pharmacy,, St Mary General Hospital, Passaic, NJ, USA
8-Internal Medicine Department,, Icahn School of Medicine at Mount Sinai / NYC Health + Hospitals Queens, New York, NY, USA

ARTICLE INFO

Article history:
Received 07 Jan. 2025
Received in revised form 11 Mar. 2025
Accepted 13 Mar. 2025
Published 21 Apr. 2025

Keywords:
Ulcerative Colitis
Inflammatory Bowel Disease
Crohn's disease
Tofacitinib
Janus kinase

ABSTRACT

Introduction: Ulcerative colitis (UC), an inflammatory Bowel Disease (IBD), is a chronic illness of unknown mechanism affecting the colonic mucosa, mainly causing diarrhea and bleeding. It can potentially disrupt the quality of life. Tofacitinib, a Janus Kinase inhibitor, showed a promising effect in inducing remission in IBD patients. In this study, we aim to assess the efficacy and safety of Tofacitinib in treating children with ulcerative colitis.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), we searched four electronic databases (PubMed, Scopus, Cochrane Library, Embase, and Web of Science) to identify eligible studies reported up to July 2024. We reported outcomes as frequencies and proportions in our study.

Results: We identified five studies encompassing 83 children diagnosed with IBD, of which 57 children had ulcerative colitis. The proportion of patients achieving a clinical response across one included study was 66.67%. The proportion of patients achieving clinical remission was 38.46%. Also, the proportion of patients achieving steroid-free remission across the three studies was 48.57%. The rate for serious adverse events was 25.53% across the three included studies.

Conclusion: Tofacitinib could be useful in achieving clinical remission in children with UC and reducing colectomy rates. Also, a low infection rate and the incidence of serious adverse events were observed. Future randomized controlled trials with larger samples and longer follow-up periods are needed to support these findings.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by inflammation of the colonic mucosa, leading to symptoms such as abdominal pain, diarrhea, and rectal bleeding that have a negative impact on the quality of life of affected individuals, including children. Management of UC in pediatric patients presents special challenges, as patients' growth, development, psychological health, and physical health [1, 2]. Numerous treatments, such as steroids, 5-aminosalicylic acid (5-ASA), azathioprine, and biologic therapy using anti-tumor necrosis factor (TNF) inhibitors, are currently authorized for use in juvenile UC patients. Many individuals have severe refractory illness, meaning that they do not respond to therapy and may need surgery, even with their effectiveness. Individuals with moderate-to-severe UC who don't respond to biological treatment can now use Tofacitinib [3].

Tofacitinib, an oral Janus kinase (JAK) inhibitor, has become a viable UC therapeutic option. It functions by specifically blocking JAK enzymes, which mediate immune response-related signaling pathways and are essential to the inflammatory process. Initially approved for the treatment of rheumatoid arthritis, Tofacitinib has demonstrated efficacy in adults with moderate to severe UC, providing rapid symptom relief and sustained remission in many cases. This success has prompted interest in its potential use for pediatric patients, who often have limited treatment options and may experience significant side effects from conventional therapies such as corticosteroids and immunomodulators [4].

Clinical trials and studies are increasingly focusing on the safety and efficacy of Tofacitinib in children and adolescents with UC. Early findings suggest that Tofacitinib may offer a well-tolerated and effective alternative, capable of inducing and maintaining remission with a favorable safety profile. As the understanding of

* Corresponding author: Abdelaziz A. Awad, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: awad.abdelaziz.0505@gmail.com

Published by the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print): 3066-4004, ISSN (Online): 3066-4012.

Citation: Awad AA, Mohamed A. Aldemerdash, Ahmed Aldemerdash, Esraa Awad, Salma Allam, Hazem Abosheaishaa. Efficacy and Safety of Tofacitinib in Pediatric Ulcerative Colitis Patients: A Systematic Review. ASIDE GI. 2025;1(2):3-8, doi:10.71079/ASIDE.GI.04212519

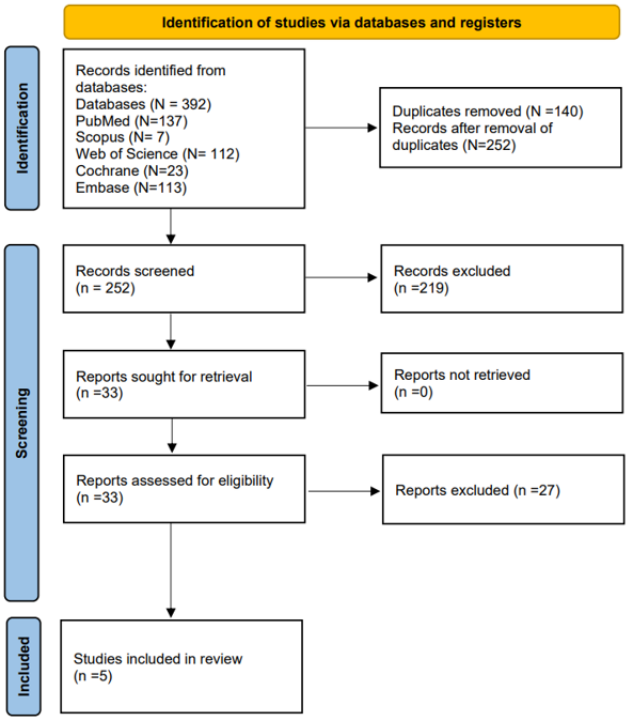

Figure 1: PRISMA flow chart diagram for our literature review results.

JAK inhibitors in pediatric inflammatory diseases grows, Tofacitinib represents a beacon of hope for children with UC, offering a potential new avenue for management that could significantly improve their quality of life and long-term health outcomes [5, 6, 7]. Consequently, the goal of this study is to evaluate the effectiveness and safety of tofacitinib in pediatric patients.

2. Methods

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were adhered to in this systematic review and meta-analysis [8]. The Cochrane Handbook for Systematic Reviews of Interventions served as the primary reference for all steps of the study [9]. This study was registered with PROSPERO.

2.1. Data source and search terms

We searched PubMed, Web of Science (WOS), Scopus, Cochrane Library, and Embase databases until July 2024 for studies using Tofacitinib to treat children with ulcerative colitis. The applied search strategy is available in the supplementary file. Additionally, we reinforced our search by reviewing the references of our final included studies to include other relevant studies.

2.2. Eligibility criteria and study selection

We included observation studies evaluating the safety and efficacy of Tofacitinib, conducted on participants under 18 years old and published in English. The primary outcome was the clinical response, defined as a $\geq$ 20-point decrease in the Pediatric Ulcerative Colitis Activity Index. Secondary outcomes included clinical remission, steroid-free remission, colectomy rate, and adverse events. Animal studies and Studies published in other languages were excluded. After searching the mentioned databases, we imported the search results into Rayyan. Two researchers independently screened the titles and abstracts of all identified studies. Full-text articles of potentially eligible studies were sorted out and assessed for inclusion. Conflicts were resolved by discussion or by a third reviewer.

2.3. Data extraction

Data were extracted from each paper of the final included studies by two independent researchers into Microsoft Excel spreadsheets to ensure the accuracy of our data. Any conflicts were resolved by discussion or by a third reviewer. Extracted data included the following: (a) Summary of the included studies, (b) Baseline characteristics, and (c) Outcomes. Clinical response was our primary outcome. Our secondary outcomes included clinical remission, colectomy, and safety outcomes.

2.4. Risk of bias and quality assessment

We used the Newcastle Ottawa Scale (NOS) to assess the risk of bias for our observational included studies [10]. Two independent researchers assessed the quality using these NOS domains (Selection, Comparability, and Outcome). Any disagreements were resolved by consensus.

3. Results

3.1. Literature results

As shown in **(Figure 1)**, the systematic search identified 392 records from databases including PubMed, WOS, Scopus, Cochrane, and Embase. After removing 140 duplicates, 252 records were screened based on titles and abstracts. A total of 219 records were excluded as they did not meet the inclusion criteria. The remaining 33 full-text articles were assessed for eligibility. After further exclusions, 5 studies with a total of 83 participants with IBD met the inclusion criteria and were included in this review [5, 11, 12, 13, 6, 7].

Table 1: Summary of included studies

Study ID	Country	Study design	Total of Partici-pants	Study duration	Main inclusion criteria	Outcomes	Conclusion
Ryan 2023 [7]	Ireland	Retrospective cohort study	15	November 1, 2019, and June 30, 2022	All children with a confirmed diagnosis of IBD who were commenced on Tofacitinib either as monotherapy or in combination with another biological agent	The primary outcome was remission by 8 weeks, with other clinical outcomes being recorded to the maximum available follow-up.	Combining Tofacitinib with other biologics is effective in selecting children with refractory UC. Early responders were more likely to achieve a sustained response in week 16. Failure to achieve remission by week 16 of Tofacitinib therapy was strongly associated with progression to colectomy.
Constant 2022 [5]	USA	Retrospective cohort study	11	2018 to 2021	Patients were identified from departmental lists of patients initiating Tofacitinib and were eligible for inclusion if they were diagnosed with UC (per clinical, endoscopic, and histologic findings)	The primary outcome was 90-day colectomy-free survival. Secondary outcomes included colectomy-free clinical remission, corticosteroid independence, colectomy-free Tofacitinib drug persistence, Tofacitinib-related adverse events, and postoperative complications.	Tofacitinib may represent a new treatment option for hospitalized pediatric patients with corticosteroid- and anti-TNF-nonresponsive ulcerative colitis. Future research is essential in determining the optimal positioning of these therapies.
Moore 2021 [6]	USA	Retrospective cohort study	21	52 weeks	All patients 21 years and younger initiated on Tofacitinib because of active IBD despite biologic therapy being included.	The primary outcome measures were a clinical response to Tofacitinib at week 12, a time point corresponding to the end of the induction period, and at week 52. Secondary outcomes measured were clinical response at weeks 6 and 24 as well as adverse events (AEs). Specific AEs of interest included the development of thrombi, hyperlipidemia, and opportunistic infections.	There is limited experience with Tofacitinib in pediatric IBD. In this cohort, Tofacitinib induced a rapid clinical response with sustained efficacy in nearly half of the subjects. This study provides encouraging evidence for the efficacy and safety of Tofacitinib as part of the treatment paradigm for young individuals with moderate-to-severe IBD. Larger, well-powered, prospective studies are warranted.
Koubek 2023 [12]	USA	Retrospective cohort study	20	September 1, 2019, to September 30, 2021	Patients aged 0 to 18 years admitted to our institution for 2 years from September 1, 2019, to September 30, 2021, who received infliximab, adalimumab, Tofacitinib, Ustekinumab, and/or vedolizumab for the treatment of CD or UC	Outcomes are Readmission within 6 months, Colectomy, Biologic acceleration >7 days, Patients with new therapy, Infusion reaction, and Time to biologic administration.	The diversity of practice observed within our institution supports the need for guidelines to define the standard of therapy or guide the selection of second-line therapies based on patient-specific factors.
Dolinger 2021 [11]	USA	Retrospective cohort study	16	Part of an ongoing, single-center, pediatric IBD ob-servational registry, initiated in October 2014	All patients under the age of 18 years starting dual therapy were identified prospectively.	The primary outcome was steroid-free remission at 6 months, defined as a wPCDAI ≤12.5 for CD or pMS <2 for UC/IBD-U, and no form of corticosteroids for at least 4 weeks. Secondary outcomes included time to steroid-free remission, change in serum biomarkers (CRP and ESR) and albumin between baseline and 6 months, and adverse events. Safety reporting included infusion and injection reactions, in addition to any serious adverse events.	Our data suggest that dual therapy may be an option for patients with limited therapeutic options remaining. Safety concerns should always be at the forefront of decision-making, and larger studies are needed to help confirm the preliminary safety data observed.

UC, Ulcerative Colitis; IBD, Inflammatory Bowel Disease; CD, Crohn's disease; IBD-U, Indeterminate Inflammatory Bowel Disease; AEs, Adverse Events; TNF, Tumor Necrosis Factor; Retro., Retrospective; wPCDAI, Weighted Pediatric Crohn's Disease Activity Index; pMS, Pediatric Mayo Score; CRP, C-reactive Protein; ESR, Erythrocyte Sedimentation Rate

Table 2: Baseline characteristics of participants in included studies

Study ID	Age (Years), Mean (SD)	Gender (Female), N (%)	Diagnosis	Previous therapies							
				Infliximab	Adalimumab	Vedolizumab	Ustekinumab	5-ASA	Corticosteroids	Tofacitinib	Tacrolimus
Ryan 2023 [7]	12 (2.3)	10 (66.7)	UC = 15	15	5	5	2	-	-	-	-
Constant 2022 [5]	16 (1.8)	3 (27)	UC = 11	8	2	3	-	8	11	-	-
Moore 2021 [6]	17 (3.8)	7 (33.3)	UC = 14	20	9	13	2	-	-	-	-
			IBD-U = 4								
			CD = 3								
Koubek 2023 [12]	15 (1.6)	10 (50)	UC = 9	15	3	1	1	-	-	4	-
			CD = 11								
Dolinger 2021 [11]	15.4 (2.8)	8 (50)	UC = 8	16	3	8	10	-	10	4	-
			CD = 7								
			IBD-U = 1								

UC, Ulcerative Colitis; CD, Crohn's Disease; IBD-U, Inflammatory Bowel Disease-Unclassified; 5-ASA, 5-Aminosalicylic acid

Table 3: Summary of outcomes in included studies

Outcome	Number of studies	Event	Total	Proportion (%)
Clinical Response	1	10	15	66.667
Clinical Remission	2	10	26	38.46
Steroid-free remission	3	17	35	48.57
Colectomy	3	12	35	34.28
Infections	3	11	47	23.4
Serious adverse events	3	12	47	25.53

3.2. Characteristics of the included studies

A total of five studies encompassed 83 children diagnosed with IBD, of which 57 children had ulcerative colitis. Twenty-one patients (25.3%) were on corticosteroids before receiving Tofacitinib. Only eight patients (9.63%) were previously treated with 5-aminosalicylic acid. The summary and baseline characteristics of the included studies are shown in **(Table 1)** and **(Table 2)**, respectively.

3.3. Quality assessment of the included studies

We used the Newcastle Ottawa Scale to assess the risk of bias for included studies. All of the included cohort studies were of good overall quality [5, 11, 12, 13, 6, 7]. The detailed quality assessment is available in the supplementary material **(Supplementary Table 1)**.

3.4. Outcomes

One of our included studies reported a clinical response with a total of 15 from the total population. The proportion of patients achieving a clinical response was 66.67% (n=10) **(Table 3)**. We reported Clinical remission, steroid-free remission, colectomy, infections, allergies, and serious adverse events **(Table 3)**. Clinical remission was reported in two studies with a total population of 26 and a proportion of 38.46% (n=10). Steroid-free remission was reported in three studies with a total population of 35 and a proportion of 48.57% (n=17). Colectomy was reported in three studies, involving a total population of 35 and a proportion of 34.28% (n = 12). Infections were reported in three studies with a total population of 47 and a proportion of 32.4% (n=11). Serious adverse events were reported in three studies with a total population of 47 and a proportion of 25.53% (n=12).

4. Discussion

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that primarily affects the colon. In children, UC causes the inner lining of the colon to become inflamed and develop ulcers. Symptoms commonly include abdominal cramping, bloody diarrhea, fatigue, weight loss, loss of appetite, rectal bleeding, and an urgency to have a bowel movement. These symptoms can vary in severity and duration depending on the extent and duration of the disease. The exact cause of UC in children is not fully understood, but it is believed to involve a combination of genetic, environmental, and immune system

factors. The condition can significantly impact a child's growth, development, and overall quality of life. Treatment aims to reduce inflammation, manage symptoms, and induce and maintain remission. This can include medications such as aminosalicylates, corticosteroids, immunomodulators, and biologics, including tofacitinib, vedolizumab, and Ustekinumab. In some cases, surgery may be necessary [14].

Janus kinase inhibitors have gained growing popularity among gastrologists for several inflammatory conditions, especially when most other therapeutic options are exhausted [15]. Tofacitinib is an oral Janus kinase (JAK) inhibitor that targets JAK1 and JAK3 enzymes. Its mechanism of action involves inhibiting the JAK-STAT signaling pathway, which is crucial in the inflammatory

response. By blocking these kinases, Tofacitinib disrupts the downstream signaling that leads to inflammation; this inhibition reduces the activity of pro-inflammatory cytokines, thereby decreasing inflammation and halting the progression of the disease.

Tofacitinib has been studied for its pharmacokinetic profile in pediatric patients. The pharmacokinetics (PK) of the drug in children and adolescents with JIA have shown that it is well-absorbed orally, and its safety profile is consistent with that observed in adults. The PK parameters, such as absorption rate and plasma concentration, vary depending on the age and weight of the pediatric patients. These studies are crucial for determining appropriate dosing regimens to ensure both efficacy and safety in younger populations [16, 17, 18]. In this systematic review, we investigated the efficacy of Tofacitinib in Pediatric Inflammatory Bowel Disease in terms of clinical response. The primary efficacy outcome in our study. The results showed a clinical response proportion of 66.67% (10 out of 15), Ryan et al. 2023 [7]. For clinical remission, the proportion was 38.46% (10 out of 26). Regarding allergy, Koubek 2023 reported zero events, with a proportion of 0% (0 out of 20) [12].

Moving to serious adverse events, real-world safety data have associated Tofacitinib with higher incidences of venous thromboembolic events, herpes zoster reactivation, and serious infections. In our study, 15 % of children treated with Tofacitinib got an infection. However, these risks appear to be lower in the pediatric population [19]. Constant et al. 2021 stated that no serious adverse events were linked to Tofacitinib during follow-up [5]. On the other hand, the FDA has reported that adult patients with comorbidities who are taking higher doses of Tofacitinib face risks of pulmonary embolism and death, as well as cardiovascular events and cancers. Moore et al. 2021 declared that the majority of their subjects were on 10 mg BID for most of the study period, and there were no occurrences of thrombi, clinically significant hyperlipidemia, or other cardiovascular or oncologic adverse events [6]. Tofacitinib has shown benefits when used sequentially with or concomitantly to anti-TNF therapy. In the study, 4 out of 6 patients who received Tofacitinib after inpatient anti-TNF therapy remained colectomy-free at the last follow-up [15, 20]. Shimizu et al. 2021 used infliximab alone. Six patients (30%) underwent colectomy during the study period [21]. The colectomy rate was 3(21.5%) in Rohani et al. 2021 who used adalimumab and infliximab in the treatment of very early-onset ulcerative colitis.

Additionally, emerging research supports the use of Tofacitinib in combination with biological therapies like Ustekinumab or vedolizumab to achieve corticosteroid-free remission in medically refractory UC cases [22]. In the study of 16 biologically refractory pediatric IBD patients treated with dual biologics or biologics in combination with Tofacitinib, 75% (12 out of 16) achieved and maintained steroid-free remission after a median of 88 days. These children had previously failed to achieve steroid-free remission with at least 2 biological therapies and had a median disease duration of 3 years. The combination therapy allowed them to be safely weaned off steroids [11]. It can be considered as an add-on therapy as clinical and remission rates are < 50 %, which is low.

Although Tofacitinib has emerged as an adjunctive treatment in patients with refractory UC, the data in pediatric patients are limited, particularly regarding the effect of this agent in combination with TNF- inhibitors In pediatrics, use of the lowest effective dose is advised given a boxed warning noting an increased risk of pulmonary embolism observed in adult rheumatoid arthritis patients with additional risk factors. Further safety considerations should include dose-dependent herpes zoster infection rates and lipid abnormalities, as well as CYP3A4 drug interactions that may require empiric dose adjustment [23].

Overall, while the study demonstrates the efficacy of Tofacitinib, the five included studies provided data on a total of 83 participants and exhibited variations in design, sample size, and interventions. Despite the merits and strengths of our synthesis, there are important limitations. First, the lack of a comparator group and biases associated with retrospective studies. Second, the observed variability in the studies and outcomes highlights the need for further research to refine treatment protocols and understand the factors contributing to outcome differences. Third, the observational nature of the included studies and their small numbers of patients, lack of objective endoscopic data there was a lack of objective endoscopic data before and after Tofacitinib commencement, as well as a lack of calprotectin correlates of mucosal activity. Also, the study does not assess long-term outcomes, preventing conclusions about the efficacy and safety of specialty therapies over time. Additional studies with stronger evidence, extended follow-up periods, and more comprehensive data are necessary to reach more conclusive results.

5. Conclusions

In conclusion, our study may demonstrate the efficacy of Tofacitinib in inducing clinical response and remission. Still, due to the variability observed among included studies, the need for more robust, well-designed trials with more efficacy data is essential to confirm our findings. Additionally, while the safety profile of Tofacitinib was observed in the pediatric population, the small sample sizes and limited long-term data necessitate cautious interpretation. Further research is crucial to establish optimal dosing regimens, understand the long-term safety, and evaluate the potential of combining Tofacitinib with other therapies.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

Funding Source

The authors declare that no specific grant or funding was received for this research from any public, commercial, or not-for-profit funding agency.

Acknowledgments

None

Institutional Review Board (IRB)

None

Large-Language Model

The manuscript was language-edited using an LLM strictly to refine clarity, grammar, and readability. No new content was created or collected during this process, ensuring that the original scientific content remains unchanged.

Authors' Contribution

AAA: conceptualization and methodology. AAA, MA: investigation and data curation. AAA: formal analysis. AAA, SA, MA, NE,

AA, and ALY: Writing - Original Draft. HA: Supervision. AAA: Project administration. AAA and MA: Writing - Review & Editing. All authors read and approved the final content.

Data Availability

All data generated or analyzed during this study are included in this published article

References

1. Muller KE, Lakatos PL, Arato A, Kovacs JB, Varkonyi A, Szucs D, et al. Incidence, Paris classification, and follow-up in a nationwide incident cohort of pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2013;57(5):576-82. [PMID: 23820399, https://doi.org/10.1097/MPG.0b013e31829f7d8c].
2. Schechter A, Griffiths C, Gana JC, Shaoul R, Shamir R, Shteyer E, et al. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. Gut. 2015;64(4):580-8. [PMID: 24848266, https://doi.org/10.1136/gutjnl-2014-306999].
3. Alajmi R, Alabdulhadi M, Alali AA, Shehab M. Tofacitinib for a Child with Refractory Steroid-Dependent Ulcerative Colitis: A Case Report and Review of the Literature. Am J Case Rep. 2021;22:e934460. [PMID: 34767543, PMCID: PMC8596185, https://doi.org/10.12659/AJCR.934460].
4. Cordes F, Foell D, Ding JN, Varga G, Bettenworth D. Differential regulation of JAK/STAT-signaling in patients with ulcerative colitis and Crohn's disease. World J Gastroenterol. 2020;26(28):4055-75. [PMID: 32821070, PMCID: PMC7403801, https://doi.org/10.3748/wjg.v26.i28.4055].
5. Constant BD, Baldassano R, Kirsch J, Mitchel EB, Stein R, Albenberg L. Tofacitinib Salvage Therapy for Children Hospitalized for Corticosteroid- and Biologic-Refractory Ulcerative Colitis. J Pediatr Gastroenterol Nutr. 2022;75(6):724-30. [PMID: 36122389, https://doi.org/10.1097/MPG.0000000000003616].
6. Moore H, Dubes L, Fusillo S, Baldassano R, Stein R. Tofacitinib Therapy in Children and Young Adults With Pediatric-onset Medically Refractory Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2021;73(3):e57-62. [PMID: 34091545, https://doi.org/10.1097/MPG.0000000000003190].
7. Ryan N, Cooper S, Dominik A, Quinn S, Broderick A, Bourke B, et al. Outcomes of Tofacitinib Use in an Irish Pediatric Cohort. JPGN Rep. 2023;4(3):e332. [PMID: 37600624, PMCID: PMC10435039, https://doi.org/10.1097/PG9.0000000000000332].
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. [PMID: 33782057, PMCID: PMC8005924, https://doi.org/10.1136/bmj.n71].
9. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10(10):ED000142. [PMID: 31643080, PMCID: PMC10284251, https://doi.org/10.1002/14651858.ED000142].
10. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
11. Dolinger MT, Spencer EA, Lai J, Dunkin D, Dubinsky MC. Dual Biologic and Small Molecule Therapy for the Treatment of Refractory Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis. 2021;27(8):1210-4. [PMID: 33125058, https://doi.org/10.1093/ibd/izaa277].
12. Koubek DN, Pulk RA, Rosano JV. A Review of Therapeutic Escalation for Pediatric Patients Admitted for Inflammatory Bowel Disease Flares. J Pediatr Pharmacol Ther. 2023;28(7):649-57. [PMID: 38025147, PMCID: PMC10681080, https://doi.org/10.5863/1551-6776-28.7.649].
13. Ledder O, Dolinger M, Dubinsky MC, Stein R, Vellanki S, Buckuk R, et al. Tofacitinib in Pediatric Ulcerative Colitis: A Retrospective Multicenter Experience. Inflamm Bowel Dis. 2025;31(2):425-31. [PMID: 38828483, https://doi.org/10.1093/ibd/izae112].
14. Ferretti F, Cannatelli R, Monico MC, Maconi G, Ardizzone S. An Update on Current Pharmacotherapeutic Options for the Treatment of Ulcerative Colitis. J Clin Med. 2022;11(9):2302. [PMID: 35566428, PMCID: PMC9104748, https://doi.org/10.3390/jcm11092302].
15. Honap S, Agorogianni A, Colwill MJ, Mehta SK, Donovan F, Pollok R, et al. JAK inhibitors for inflammatory bowel disease: recent advances. Frontline Gastroenterol. 2024;15(1):59-69. [PMID: 38487554, PMCID: PMC10935522, https://doi.org/10.1136/flgastro-2023-102400].
16. Chang C, Vong C, Wang X, Hazra A, Diehl A, Nicholas T, et al. Tofacitinib pharmacokinetics in children and adolescents with juvenile idiopathic arthritis. CPT Pharmacometrics Syst Pharmacol. 2024;13(4):599-611. [PMID: 38298058, PMCID: PMC11015083, https://doi.org/10.1002/psp4.13104].
17. Ruperto N, Brunner HI, Zuber Z, Tzaribachev N, Kingsbury DJ, Foeldvari I, et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. Pediatr Rheumatol Online J. 2017;15(1):86. [PMID: 29282090, PMCID: PMC5745974, https://doi.org/10.1186/s12969-017-0212-y].
18. Vong C, Wang X, Hazra A, Mukherjee A, Nicholas T, Chang C. Fri0465Tofacitinib Population Pharmacokinetics in Children with Juvenile Idiopathic Arthritis: A Pooled Analysis of Data from Three Clinical Studies. Annals of the Rheumatic Diseases. 2020;79(Suppl 1):830-0. [https://doi.org/10.1136/annrheumdis-2020-eular.400].
19. Deepak P, Alayo QA, Khatiwada A, Lin B, Fenster M, Dimopoulos C, et al. Safety of Tofacitinib in a Real-World Cohort of Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2021;19(8):1592-601 e3. [PMID: 32629130, PMCID: PMC7779667, https://doi.org/10.1016/j.cgh.2020.06.050].
20. Sandborn WJ, Peyrin-Biroulet L, Sharara AI, Su C, Modesto I, Mundayat R, et al. Efficacy and Safety of Tofacitinib in Ulcerative Colitis Based on Prior Tumor Necrosis Factor Inhibitor Failure Status. Clin Gastroenterol Hepatol. 2022;20(3):591-601 e8. [PMID: 33684552, https://doi.org/10.1016/j.cgh.2021.02.043].
21. Shimizu H, Arai K, Takeuchi I, Minowa K, Hosoi K, Sato M, et al. Long-Term Durability of Infliximab for Pediatric Ulcerative Colitis: A Retrospective Data Review in a Tertiary Children's Hospital in Japan. Pediatr Gastroenterol Hepatol Nutr. 2021;24(1):7-18. [PMID: 33505889, PMCID: PMC7813568, https://doi.org/10.5223/pghn.2021.24.1.7].
22. Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. J Crohns Colitis. 2018;12(6):635-43. [PMID: 29370397, PMCID: PMC7189966, https://doi.org/10.1093/ecco-jcc/jjy004].
23. Inc P. XELJANZ® (tofacitinib) tablets, for oral use: prescribing information. Pfizer Inc.; 2018. [PMCID: PMCID].

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Original Article

Safety and Efficacy of Sodium Alginate and Mesna in Endoscopic Submucosal Dissection: A Systematic Review and Meta-analysis

Hazem Abosheaishaa[1], Abdallfatah Abdallfatah[2,*], Imad Samman Tahhan[3], Abdelmalek Abdelghany[2], Iyiad Alabdul Razzak[4], Mohamed A. M. Amer[5], Ahmed Y Azzam[6], Muhammed Amir Essibayi[7], Mahmoud Nassar[8], Omar Abdelhalim[1], Sherif Andrawes[9]

1-Internal Medicine Department Icahn School of Medicine at Mount Sinai / NYC Health + Hospitals Queens, New York, NY, USA
2-Internal Medicine Department October 6 University, Cairo, Egypt
3-Neurology and Neurosurgery Department Medical University of South Carolina, Charleston, SC, USA
4-Internal Medicine Department Alfaisal University, Riyadh, Saudi Arabia
5-Internal Medicine Department Menoufia University, Menoufia, Egypt
6-Visiting Assistant Professor, SNU Medical Big Data Research Center Seoul National University, Seoul, South Korea
7-Montefiore-Einstein Cerebrovascular Research Lab Albert Einstein College of Medicine, Bronx, New York, USA
8-Department of Medicine Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA
9-Gastroenterology Department Zucker School of Medicine at Hofstra/Northwell, Staten Island, New York, USA

ARTICLE INFO

Article history:
Received 02 Feb. 2025
Received in revised form 10 Mar. 2025
Accepted 11 Mar. 2025
Published 22 Apr. 2025

Keywords:
Endoscopic submucosal dissection
Solutions
Sodium Alginate
Na alginate
Mesna

ABSTRACT

Introduction: Sodium hyaluronate, commonly used in ESD, has drawbacks such as high cost and potential tumorigenesis. Sodium alginate (Na alginate) and Mesna offer promising alternative solutions with their viscoelastic and mucolytic properties. In this review, we aimed to evaluate the safety and efficacy of Na alginate and Mesna solutions in ESD.
Methods: A systematic search was conducted across multiple databases. Inclusion criteria were randomized controlled trials and observational studies assessing Na alginate and Mesna in ESD. The primary outcome included en bloc resection rates. Secondary outcomes included adverse events such as perforation and delayed bleeding, and procedural time.
Results: Eight studies involving 255 patients were included in this analysis. Overall en-bloc resection rate for sodium alginate was 97% [95% CI (93%-99%); I2: 0%]. En-bloc resection subgroup analysis revealed 97% [95% CI (93%-99%); I2: 0%] for 0.6% sodium alginate and 95% [95% CI (70%-99%); I2: 0%] for 0.4% sodium alginate. Moreover, the en-bloc resection rate for Mesna was 98% [95%CI (92%-100%); I2: 0%]. Delayed bleeding rates for sodium alginate were 5% [95% CI (1%-20%); I2: 65.2%]; however, after subgroup analysis delayed bleeding was 2% [95% CI (1%-6%); I2: 0%] for 0.6% sodium alginate and 22% [95% CI (8%-49%); I2: 0%] for 0.4% sodium alginate. Perforation rate for 0.6% sodium alginate was 1% [95% CI (0%-5%); I2: 0%].
Conclusion: Na alginate (0.6%) and Mesna are effective and safe alternatives to sodium hyaluronate for submucosal injection in ESD. These solutions offer potential cost-effective and safer options for clinical practice, with Na alginate (0.6%) showing particularly low rates of adverse events.

1. Introduction

The burden of gastrointestinal tumors is rapidly increasing worldwide and is associated with significant morbidity and mortality. Colorectal cancer ranks third in incidence and second in mortality worldwide, with esophageal cancer ranking as the eighth most diagnosed cancer [1, 2]. Endoscopic submucosal dissection (ESD) has gained increasing acceptance as a suitable approach for gastrointestinal cancers due to its low rate of local recurrence compared to endoscopic mucosal resection [3, 4, 5].

The submucosal injection is a critical step in ESD, as it forms a submucosal cushion fluid that facilitates the elevation and separation of the lesion from the muscularis propria. This enhances en bloc resection and decreases the risk of complications by creating a physical barrier protecting deep tissues [6, 7, 8]. The ideal submucosal injection solution should fulfill the following criteria: (1) Ensure an adequately thick submucosal fluid cushion; (2) it should be capable of long-term retention under the mucosa, minimizing the need for frequent submucosal injections; (3) It should be affordable, readily accessible, simple to store, and administer; (4) Minimizing the occurrence of adverse events during ESD, such as hemorrhage and perforation, and maintaining the integrity of excised specimens to ensure accurate pathological results [6]. Currently, sodium hyaluronate is one of the most common solutions used for ESD. However, it has been confirmed that it may stimulate tumor growth after ESD [9].

* Corresponding author: Abdallfatah Abdallfatah, Internal Medicine Department, October 6 University, Cairo, Egypt. Email: Abdallfatahofficial@gmail.com

Published by the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print): 3066-4004, ISSN (Online): 3066-4012.

Citation: Abosheaishaa H, Abdallfatah A, Samman Tahhan I, et al. Safety and Efficacy of Na Alginate and Mesna in Endoscopic Submucosal Dissection: A Systematic Review and Meta-analysis. ASIDE GI. 2025;1(2):9-15, doi:10.71079/ASIDE.GI.04222537

Mensa is a thiol compound commonly used as prophylaxis against some chemotherapy drugs to prevent hemorrhagic cystitis. Additionally, Mensa exhibits a mucolytic effect, which is utilized to facilitate sputum expectoration during respiratory distress. Due to its unique chemical property, Mesna can break down disulfide bonds that connect polypeptide chains, which soften connective tissue fibers between different anatomical planes. Several clinical surgical studies have shown that applying an aqueous solution of Mesna directly to the surgical area helped in smoother blunt dissection and led to shorter operation times, decreasing the risk of hemorrhage [10, 11, 12, 13, 14].

Na alginate (SA) has excellent water retention and viscoelastic properties. It is used in clinical settings to treat peptic ulcers or as a hemostatic agent [15, 16, 17]. SA has been used in Japan for more than 60 years as a protective agent for the digestive mucosa, typically at a 5% concentration. This extensive use has established the efficacy and safety of SA [18]. In 2018, Japan approved 0.6% SA for use as a submucosal injection solution in ESD [19]. We conducted this meta-analysis to evaluate the feasibility and safety of Na alginate and Mesna before endoscopic submucosal dissection.

2. Methods

2.1. Search Strategy and Data Extraction

A systematic search of relevant literature was conducted across multiple databases, including Embase, Scopus, Web of Science, Medline/PubMed, and Cochrane, from their inception to April 17, 2034. The search strategy utilized Boolean operators to combine terms related to "endoscopic submucosal dissection" or "submucosal dissection" or "ESD" AND "Mesna" AND "Na alginate". The search aimed to identify studies investigating the efficacy and safety of those two solutions for submucosal injection during endoscopic submucosal dissection (ESD) in patients with gastrointestinal adenomas and early-stage neoplastic lesions eligible for ESD treatment. Two independent reviewers screened titles, abstracts, and full-text articles for inclusion based on predefined eligibility criteria. Any discrepancies were resolved through discussion or consultation with a third reviewer. Data extraction was conducted independently by two co-authors using a standardized form, with discrepancies resolved through consensus. Our research adhered to the recommended guidelines for reporting systematic reviews and meta-analyses. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed to ensure transparency and completeness in reporting. Furthermore, we conducted systematic reviews and meta-analyses following the Cochrane criteria and the PRISMA checklist [20, 21]

2.2. Inclusion Criteria and Study Outcomes

Studies eligible for inclusion in this systematic review and meta-analysis were randomized controlled trials (RCTs) and observational studies focusing on patients with gastrointestinal adenomas and early-stage neoplastic lesions eligible for ESD treatment. The intervention of interest was the use of Mesna or Na alginate for submucosal injection during ESD procedures. Comparisons with other solutions were not applicable in this case. The primary outcomes of interest included procedural time, while secondary outcomes included en bloc complete dissection rate, amount of solution injected, and adverse events associated with those submucosal injection solutions. Procedural time refers to the duration of the ESD procedure. En bloc complete dissection rate indicates the proportion of cases where the lesion was completely removed in one piece. Adverse events encompass any undesirable effects related to the use of submucosal injection solutions, which include perforation, intra-operative bleeding, and post-operative delayed bleeding, which is defined as any bleeding after the patient leaves the operating room till one month later. Exclusion criteria comprised studies not written in English or with inadequate translation, case reports, editorials, letters, or conference abstracts without full-text availability, animal studies, or studies conducted on non-human subjects. Additionally, studies involving patients with contraindications or specific conditions that could significantly impact outcomes were excluded.

2.3. Risk of Bias Assessment

Two authors independently assessed the risk of bias and methodological quality of included studies. The Cochrane risk-of-bias tool for randomized trials (ROB 2) was used for RCTs, while for non-randomized clinical trials, the ROBINS-I tool was employed [22, 23]. Any discrepancies are resolved through discussion or consultation with a third reviewer.

2.4. Statistical Analysis

The forest plots illustrate the rates (shown by the black square) and 95% confidence interval (CI) shown by a horizontal line from non-comparative studies. The area of the black square is proportional to the specific study weight in the overall meta-analysis. The overall pool is visible in the middle of the red diamond shape representing the overall rate, and its width indicates the pooled 95% CI. For comparative studies, proportional variables were analyzed and mean differences (MD) with the corresponding 95% CI. All analyses were performed using Comprehensive Meta-analysis software [24].

3. Results

3.1. Study and patient characteristics

We ran a systematic search in our databases and identified 1130 studies, of which eight studies were included in our analysis [25, 26, 27, 28, 29, 30, 31, 19]. Detailed information about the selection of studies is shown in the PRISMA flow diagram **(Figure 1)**. A total of 415 patients were included in our analysis. 63% were men and 37% were women. The mean age ranged from 53 to 69 years **(Table 1)**.

3.2. Quality of included studies

Quality assessment of our included studies was assessed using the Cochrane RoB 2 tool for four RCTs. Two studies had a total low risk of bias status, and the other two had a Moderate risk of bias status. Non-randomized studies were assessed using the ROBINS-I tool. The four studies had a moderate risk of bias **(Table 2)**.

3.3. En-bloc resection

Five studies were pooled to evaluate the rates of en-bloc resection using 0.4% and 0.6% Na alginate, with an overall rate of 97% [95% CI (93%-99%); I2: 0%] **(Figure 2)**. Subgroup analysis with three studies pooled for the rates of en-bloc resection using Na alginate 0.6% with an overall rate of 97% [95% CI (93%-99%); I2: 0%] **(Figure 3)**. Two studies were pooled for the rates of en-bloc resection using Na alginate 0.6% with an overall rate of 95% [95% CI (70%-99%); I2: 0%] **(Figure 4)**. Three studies were pooled to evaluate the rates of en-bloc resection using Mesna with an overall rate of 98% [95% CI (92%-100%); I2: 0%] **(Figure 5)**.

3.4. Perforation, delayed bleeding, and procedural time

Two studies were pooled for the rates of Perforation for 0.6% Na Alginate with an overall rate of 1% [95% CI (0%-5%); I2: 0%] **(Supplementary figure 1)**. Five studies were pooled for the rates of

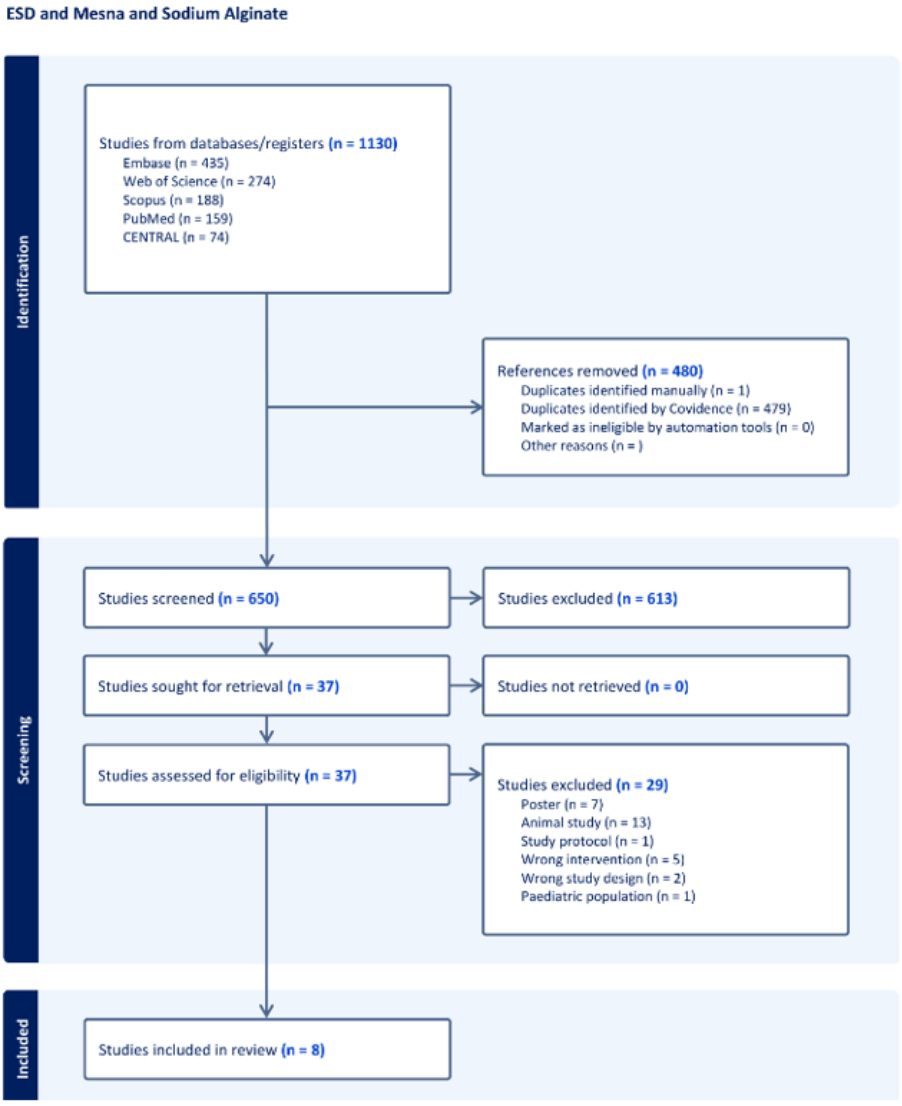

Figure 1: PRISMA flow chart diagram for our literature review results.

Delayed bleeding using Na alginate 0.6% and 0.4% with an overall rate of 5% [95% CI (1%-20%); I2: 65.21%] **(Supplementary figure 2)**. Three studies were pooled for the rates of Delayed bleeding using 0.6% Na alginate, with an overall rate of 2% [95% CI (1%-6%); I2: 0%] **(Supplementary Figure 3)**. Two studies were pooled for the rates of Delayed bleeding using Na alginate 0.4% with an overall rate of 22% [95% CI (8%-49%); I2: 0%] **(Supplementary figure 4)**.

Five studies were pooled to evaluate the mean Procedure time in minutes using Na alginate 0.4% and 0.6% [(Mean 60.86, 95% CI: 45.06 to 76.67); I2: 85.8%] **(Supplementary figure 5)**. Three studies were pooled to evaluate the mean Procedure time in minutes using Na alginate 0.6% [(Mean = 45.77, 95% CI: 32.94 to 58.59); I2: 80.7%] (Supplementary figure 6). Two studies were pooled to evaluate the mean Procedure time in minutes using Na alginate 0.4% [(Mean = 85.38, 95% CI: 61.29 to 109.47); I2: 24.8%] **(Supplementary figure 7)**. Three studies were pooled to evaluate the mean Procedure time in minutes using Mesna [(Mean = 28.54, 95% CI: 13.39 to 43.71); I2: 96.39%] **(Supplementary figure 8)**. The pooled results from two studies comparing Mesna and normal saline reporting the procedure time showed no significant difference between the two groups, [(MD: -6.55, 95% CI: -13.42 to 0.33; P=0.06); I2: 0%], as shown in **(Supplementary figure 9)**

4. Discussion

The high cost and potential tumorigenesis associated with sodium hyaluronate (SH) [25, 9], a widely used ESD submucosal injection solution, prompted the search for an alternative. In the early 2010s, Akagi et al. proposed Sodium alginate (SA) as a safe and effective submucosal injection solution. SA is a non-toxic natural polysaccharide polymer isolated from brown seaweed [25]. In addition to its low cost, SA is known for its safety, having been used in the treatment of peptic ulcer disease due to its protective and hemostatic properties on the mucosal membrane [15]. Lastly, the viscosity of SA helps in achieving reliable submucosal lift [9]. An early clinical experience with 3% SA in ESD was reported on 11 patients with early gastric cancer. The overall endoscopic en bloc resection rate was 100%. No major complications occurred with no tumor recurrence after a mean follow-up of 28 months [25].

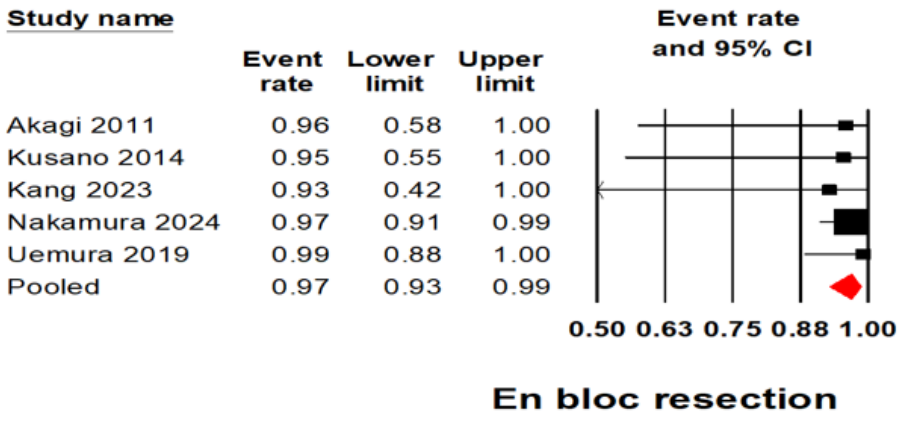

Figure 2: En-bloc resection rate (both 0.4% and 0.6% Na Alginate).

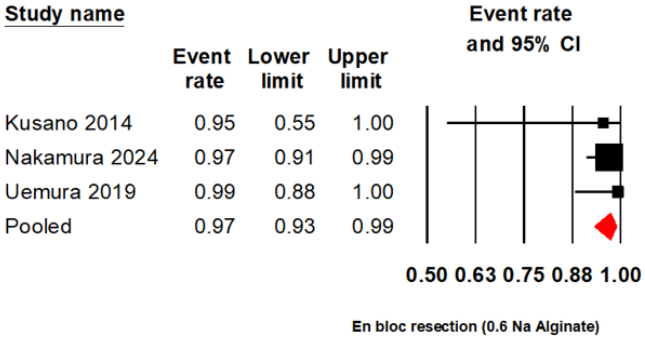

Figure 3: En-bloc resection (0.6% Na Alginate).

Later, the formulation of SA was improved to 0.6% to enhance injectability and facilitate uniform mucosal elevation [28].

A randomized controlled trial (RCT) compared the efficacy and safety of 0.6% SA to 0.4% SH in ESD for esophageal and gastric lesions. Efficacy was based on the en bloc complete resection rate in ESD and the formation and maintenance of mucosal elevation upon injection. SA was found to be non-inferior to SH. In addition, the mucosal resection time was similar between the two groups [19].

Table 1: Characteristics of included studies

Author	Country	Study design	Total participants (n)	ESD group Gender (female) N (%)	Used solution	Procedure location	Size of lesion (Mean ± SD), mm
Akagi, 2011 [25]	Japan	Clinical trial	11	2 (18)	0.4% Sodium alginate	Stomach	15.5±5.3
Kusano, 2014 [28]	Japan	Clinical trial	10	2 (20)	0.6% Sodium alginate	Stomach	16.21±5.8
Kang, 2023 [27]	Taiwan	RCT	12	8 (66)	0.4% Sodium alginate	Stomach, colon & esophagus	30.0±5.5
Nakamura, 2024 [29]	Japan	Cohort	100	40 (40)	0.6% Sodium alginate	Rectum and colon	20.89±8.8
Uemura, 2019 [19]	Japan	RCT	122	13 (21.7)	0.6% Sodium alginate	Stomach and esophagus	NA
Dobashi, 2015 [26]	Japan	RCT	40	1 (5)	Mesna	Esophagus	23.33±9.9
Sumiyama, 2010 [30]	Japan	Prospective cohort	20	NA	Mesna	Stomach	21.7±12.14
Sumiyama, 2014 [31]	Japan	RCT	100	9 (18)	Mesna	Stomach	19.49±11.74

RCT, Randomized Controlled Trial; ESD, Endoscopic Submucosal Dissection; SD, Standard Deviation; NA, Not Available; mm, Millimeter.

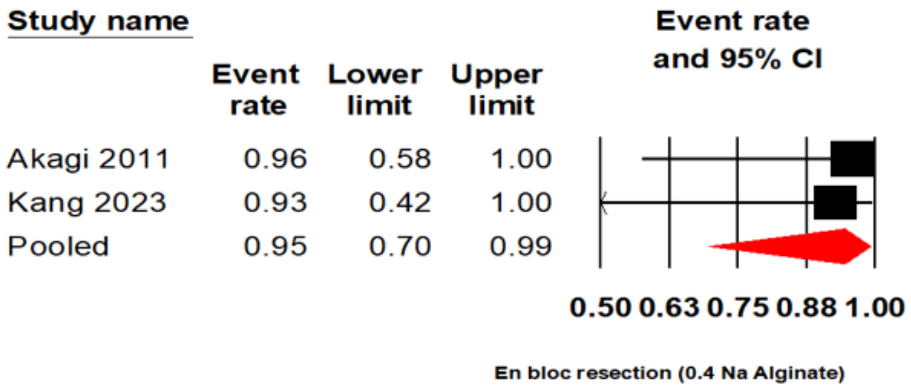

Figure 4: En-bloc resection (0.4% Na Alginate).

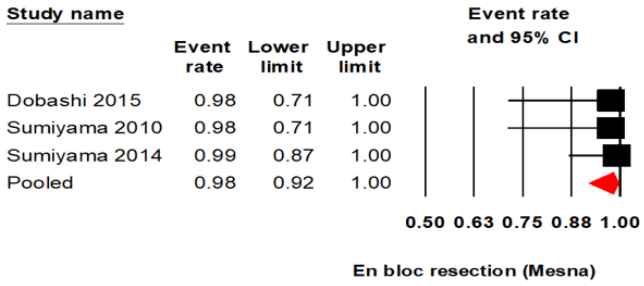

Figure 5: En-bloc resection (Mesna).

Table 2: Risk of bias assessment for included studies

Author name, year	Study design	Tool used	Overall ROB
Akagi, 2011 [25]	Clinical trial	ROBINS-I	Moderate
Kusano, 2014 [28]	Clinical trial	ROBINS-I	Moderate
Kang, 2023 [27]	RCT	Cochrane RoB 2	Low
Nakamura, 2024 [29]	Cohort	ROBINS-I	Moderate
Uemura, 2019 [19]	RCT	Cochrane RoB 2	Moderate
Dobashi, 2015 [26]	RCT	Cochrane RoB 2	Moderate
Sumiyama, 2010 [30]	Prospective cohort	ROBINS-I	Moderate
Sumiyama, 2014 [31]	RCT	Cochrane RoB 2	Low

RCT, Randomized Controlled Trial; ROB, Risk of Bias.

The primary utility of Mesna is to facilitate submucosal dissection by dissolving disulfide bonds, thereby softening the connective tissue fibers [30]. This also allows for less or no electrosurgical dissection, theoretically reducing the risk of perforation. In a pilot study, chemically assisted ESD with submucosal injection of Mesna led to a 100% en-bloc resection rate with a mean operation time of 21.17 ± 11.6 minutes [30]. Subsequently, a double-blind RCT comparing Mesna to saline submucosal injection in ESD for gastric cancer found no difference in submucosal dissection time between the two groups [31]. However, there were fewer time-consuming cases (more than 30 minutes) in the Mesna group (P=0.049). Additionally, the subjective difficulty of ESD was significantly lower in the Mesna group. Both groups had similar en-bloc resection rates (Mesna: 100%, Controls: 98.08%) and perforation rates (Mesna: 0%, Controls: 1.92%) [31].

As for the adverse events, we found that, in the aspect of perforation incidence, Na alginate was slightly safer than the standard used solution, sodium hyaluronate (1% in the Na alginate cases vs. 3% in the sodium hyaluronate in previous trials) [32]. When we compared the incidence of delayed bleeding between sodium hyaluronate and Na alginate solutions, it was found that Na alginate (with a pooled incidence of 5% for both 0.4% and 0.6% concentrations) is not as safe as sodium hyaluronate (with a pooled incidence of 1%). However, if we compare the two concentrations of Na alginate, the concentration of (0.6% Na Alginate) is much safer than (0.4% Na Alginate) (adverse event rates are 2% and 22%, respectively). This detail should guide future studies to focus more on the safer (0.6%) concentration in trials, maximizing the benefits of the new solution while minimizing the risk of adverse events. Our study has some limitations. First, it includes a small number of single-arm studies without comparative ones. Additionally, there are some variations in results during subgroup analysis. This persistent heterogeneity is likely attributable to differences in endoscopist skill levels and procedural efficiency across centers rather than the intervention itself. Variations in technique, experience, and procedural protocols

at different institutions inherently contribute to the observed discrepancies in procedure duration, making it a challenging factor to standardize across studies. Finally, all the studies are conducted in Asia with small sample sizes, which may limit the generalizability of our results. We suggest conducting randomized controlled trials to guide future directions, choices, and careful interpretation of results. Future enhancements should prioritize expanding network diversity, improving data validation mechanisms, and developing more sophisticated tools for bias mitigation.

5. Conclusion

Our study revealed that both Na alginate, especially Na alginate (0.6%), and Mesna are effective and safe alternatives to sodium hyaluronate for submucosal injection in endoscopic submucosal dissection. Na alginate (0.6%) achieved high en-bloc resection rates with notably low adverse event rates, making it a particularly promising option. Mesna also showed excellent en bloc resection rates and significantly reduced procedural times, highlighting its efficiency in ESD procedures. Both solutions offer cost-effective and safer options for clinical practice, addressing the limitations associated with sodium hyaluronate, such as high cost and potential tumorigenic risk. Future studies should focus on further validating these findings through larger randomized controlled trials and exploring the optimal concentrations and formulations for enhanced safety and efficacy.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

Funding Source

This project was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through CTSA award number: UM1TR004400. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Acknowledgments

None

Institutional Review Board (IRB)

None

Large-Language Model

None

Authors' Contribution

HA conceptualized the study; HA and AA developed the methodology; HA and IST conducted literature search; IAR and MAE performed screening; HA, IST, and IAR handled data extraction; MAMA and MAE validated the data; IST, AYA, and OA assessed risk of bias; AA conducted statistical analysis; MAMA provided statistical review; AA created data visualizations; HA and AA wrote the manuscript; AA, AYA, and MN reviewed and edited; AA, AJA, and SA supervised the project. All authors reviewed and approved the final manuscript.

Data Availability

This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. [PMID: 33538338, https://doi.org/10.3322/caac.21660].
2. Taylor PR, Abnet CC, Dawsey SM. Squamous dysplasia–the precursor lesion for esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2013;22(4):540-52. [PMID: 23549398, PMCID: PMC3681095, https://doi.org/10.1158/1055-9965.EPI-12-1347].
3. Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy. 2009;41(9):751-7. [PMID: 19693750, https://doi.org/10.1055/s-0029-1215053].
4. Higuchi K, Tanabe S, Azuma M, Katada C, Sasaki T, Ishido K, et al. A phase II study of endoscopic submucosal dissection for superficial esophageal neoplasms (KDOG 0901). Gastrointest Endosc. 2013;78(5):704-10. [PMID: 23680178, https://doi.org/10.1016/j.gie.2013.04.182].
5. Isomoto H, Yamaguchi N, Minami H, Nakao K. Management of complications associated with endoscopic submucosal dissection/ endoscopic mucosal resection for esophageal cancer. Dig Endosc. 2013;25 Suppl 1(S1):29-38. [PMID: 23368404, https://doi.org/10.1111/j.1443-1661.2012.01388.x].
6. Castro R, Libanio D, Pita I, Dinis-Ribeiro M. Solutions for submucosal injection: What to choose and how to do it. World J Gastroenterol. 2019;25(7):777-88. [PMID: 30809079, PMCID: PMC6385015, https://doi.org/10.3748/wjg.v25.i7.777].
7. Jung YS, Park DI. Submucosal injection solutions for endoscopic mucosal resection and endoscopic submucosal dissection of gastrointestinal neoplasms. Gastrointestinal Intervention. 2013;2(2):73-7. [https://doi.org/10.1016/j.gii.2013.09.003].
8. Uraoka T, Saito Y, Yamamoto K, Fujii T. Submucosal injection solution for gastrointestinal tract endoscopic mucosal resection and endoscopic submucosal dissection. Drug Des Devel Ther. 2009;2:131-8. [PMID: 19920900, PMCID: PMC2761197, https://doi.org/10.2147/dddt.s3219].
9. Matsui Y, Inomata M, Izumi K, Sonoda K, Shiraishi N, Kitano S. Hyaluronic acid stimulates tumor-cell proliferation at wound sites. Gastrointest Endosc. 2004;60(4):539-43. [PMID: 15472675, https://doi.org/10.1016/s0016-5107(04)01890-5].
10. Benassi L, Benassi G, Kaihura CT, Marconi L, Ricci L, Vadora E. Chemically assisted dissection of tissues in laparoscopic excision of endometriotic cysts. J Am Assoc Gynecol Laparosc. 2003;10(2):205-9. [PMID: 12732773, https://doi.org/10.1016/s1074-3804(05)60300-3].
11. Benassi L, Lopopolo G, Pazzoni F, Ricci L, Kaihura C, Piazza F, et al. Chemically assisted dissection of tissues: an interesting support in abdominal myomectomy. J Am Coll Surg. 2000;191(1):65-9. [PMID: 10898185, https://doi.org/10.1016/s1072-7515(00)00296-9].
12. Denaro V, Di Martino A, Longo UG, Costa V, Papalia R, Forriol F, et al. Effectiveness of a mucolythic agent as a local adjuvant in revision lumbar spine surgery. Eur Spine J. 2008;17(12):1752-6. [PMID: 18839224, PMCID: PMC2587676, https://doi.org/10.1007/s00586-008-0802-y].
13. Reinhart WH, Baerlocher GM, Cerny T, Owen GR, Meiselman HJ, Beer JH. Ifosfamide-induced stomatocytosis and mesna-induced echinocytosis: influence on biorheological properties of blood. Eur J Haematol. 1999;62(4):223-30. [PMID: 10227455, https://doi.org/10.1111/j.1600-0609.1999.tb01751.x].
14. Vincenti V, Mondain M, Pasanisi E, Piazza F, Puel JL, Bacciu S, et al. Cochlear effects of mesna application into the middle

ear. Ann N Y Acad Sci. 1999;884(1):425-32. [PMID: 10842611, https://doi.org/10.1111/j.1749-6632.1999.tb08659.x].
15. Daigo K, Wada Y, Yamada C, Yamaji M, Okuda S, Okada M, et al. [Pharmacological studies of sodium alginate. I. Protective effect of sodium alginate on mucous membranes of upper-gastrointestinal tract]. Yakugaku Zasshi. 1981;101(5):452-7. [PMID: 6793708, https://doi.org/10.1248/yakushi1947.101.5_452].
16. Daigo K, Yamaji M, Yamada C, Wada Y, Okuda S, Okada M, et al. [Pharmacological studies of sodium alginate. III. Acceleration of fibrin formation by sodium alginate]. Yakugaku Zasshi. 1981;101(5):464-9. [PMID: 7288587, https://doi.org/10.1248/yakushi1947.101.5_464].
17. Diago K, Yamada C, Yamaji M, Nakagiri N, Okada M, Komiya H, et al. [Pharmacological studies of sodium alginate. V. Effect of sodium alginate on platelet aggregation]. Yakugaku Zasshi. 1985;105(2):171-82. [PMID: 4009424, https://doi.org/10.1248/yakushi1947.105.2_171].
18. Daigo K, Yamada C, Wada Y, Yamaji M, Okuda S, Okada M, et al. [Pharmacological studies of sodium alginate. II. Hemostatic effect of sodium alginate on gastrointestinal bleeding]. Yakugaku Zasshi. 1981;101(5):458-63. [PMID: 6974775, https://doi.org/10.1248/yakushi1947.101.5_458].
19. Uemura N, Oda I, Saito Y, Ono H, Fujisaki J, Matsuhashi N, et al. Efficacy and safety of 0.6 Dig Endosc. 2019;31(4):396-404. [PMID: 30667557, PMCID: PMC6850280, https://doi.org/10.1111/den.13352].
20. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10(10):ED000142. [PMID: 31643080, PMCID: PMC10284251, https://doi.org/10.1002/14651858.ED000142].
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41. [PMID: 20171303, https://doi.org/10.1016/j.ijsu.2010.02.007].
22. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. [PMID: 31462531, https://doi.org/10.1136/bmj.l4898].
23. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. [PMID: 27733354, PMCID: PMC5062054, https://doi.org/10.1136/bmj.i4919].
24. Wallace BC, Lajeunesse MJ, Dietz G, Dahabreh IJ, Trikalinos TA, Schmid CH, et al. OpenMEE: Intuitive, open-source software for meta-analysis in ecology and evolutionary biology. Methods in Ecology and Evolution. 2017;8(8):941-7. [https://doi.org/10.1111/2041-210x.12708].
25. Akagi T, Yasuda K, Tajima M, Suzuki K, Inomata M, Shiraishi N, et al. Sodium alginate as an ideal submucosal injection material for endoscopic submucosal resection: preliminary experimental and clinical study. Gastrointest Endosc. 2011;74(5):1026-32. [PMID: 22032316, https://doi.org/10.1016/j.gie.2011.07.042].
26. Dobashi A, Goda K, Sumiyama K, Kobayashi M, Ohya TR, Kato M, et al. A feasibility study of chemically assisted endoscopic submucosal mechanical dissection using mesna for superficial esophageal squamous cell carcinomas. Surg Endosc. 2015;29(11):3373-81. [PMID: 25515984, https://doi.org/10.1007/s00464-014-4031-7].
27. Kang JW, Chen PJ, Chen CY, Riley G, Wang YS, Kuo HY, et al. Development of a hybrid hydrogel for submucosal injection in endoscopic resection of gastrointestinal neoplasm: From laboratory to clinical trial. Endosc Int Open. 2023;11(11):E1026-34. [PMID: 38835638, PMCID: PMC11148844, https://doi.org/10.1055/a-2161-2100].
28. Kusano T, Etoh T, Akagi T, Ueda Y, Shiroshita H, Yasuda K, et al. Evaluation of 0.6 Dig Endosc. 2014;26(5):638-45. [PMID: 24655031, https://doi.org/10.1111/den.12268].
29. Nakamura H, Morita R, Ito R, Sakurada A, Tomita N, Hirata Y, et al. Feasibility and safety of 0.6 DEN Open. 2024;4(1):e313. [PMID: 37927953, PMCID: PMC10625103, https://doi.org/10.1002/deo2.313].
30. Sumiyama K, Tajiri H, Gostout CJ, Kawamura M, Imazu H, Ohya TR, et al. Chemically assisted submucosal injection facilitates endoscopic submucosal dissection of gastric neoplasms. Endoscopy. 2010;42(8):627-32. [PMID: 20552541, https://doi.org/10.1055/s-0029-1244223].
31. Sumiyama K, Toyoizumi H, Ohya TR, Dobashi A, Hino S, Kobayashi M, et al. A double-blind, block-randomized, placebo-controlled trial to identify the chemical assistance effect of mesna submucosal injection for gastric endoscopic submucosal dissection. Gastrointest Endosc. 2014;79(5):756-64. [PMID: 24238308, https://doi.org/10.1016/j.gie.2013.09.027].
32. Iwashita C, Sakamoto H, Miura Y, Shinozaki S, Hayashi Y, Ino Y, et al. Esophageal endoscopic submucosal dissection using sodium hyaluronate is safe and effective. Minim Invasive Ther Allied Technol. 2018;27(3):171-6. [PMID: 28749205, https://doi.org/10.1080/13645706.2017.1356735].

ASIDE Gastroenterology

Original Article

Efficacy and Safety of Tislelizumab in Combination with Chemotherapy versus Placebo Plus Chemotherapy in Patients with Advanced Gastric Cancer or Gastroesophageal Junction Cancer: A Systematic Review of Randomized Controlled Trials

Ahmed Reda Bahr[1], Ahmed Magdy Hassan[2], Mohamed Wagdy[3,*], Mahmoud Abdelkader[4], Ahmed Samy Elgammal[2]

1-Faculty of Medicine, Alexandria University Alexandria, Egypt
2-Faculty of Medicine, Tanta University Tanta, Egypt
3-Faculty of Medicine, Modern University for Technology and Information Cairo, Egypt
4-Anesthesia, Intensive Care and Pain Management Department, Zagazig University Al-Sharqia, Egypt

ARTICLE INFO

Article history:
Received 21 Apr 2025
Received in revised form 15 May 2025
Accepted 15 May 2025

Keywords:
Immunotherapy
Immuno-oncology
Gastric cancer
Gastroesophageal junction cancer
Tislelizumab
Targeted therapy

ABSTRACT

Introduction Advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC) is an aggressive malignancy often having a poor prognosis. Despite current systemic therapies, GC/GEJC remains the third most common cause of cancer-related deaths worldwide. Tislelizumab, an anti-PD1 antibody, has shown promising results in treating various cancers. Therefore, this systematic review investigated the efficacy and safety of tislelizumab plus chemotherapy for patients with GC/GEJC.
Methods: Five databases were systematically searched until July 10, 2024. Articles identified in the screening process included two RCTs based on predefined inclusion criteria. We performed data extraction sheets and quality assessments using the Cochrane ROB2 tool.
Results: Out of the two randomized controlled trials (RCTs), 1646 patients were included in our systematic review. In Rational-306, efficacy outcomes improved, overall survival (OS) significantly improved from 10.6 months (95% CI 9.3–12.1) to 17.2 months (95% CI 15.8–20.1), and progression-free survival (PFS) from 5.6 months (4.9–6.0) to 7.3 months (6.9–8.3). Rational-305 also notably significantly improved.
Outcomes: improved OS from 12.9 months (12.1-14.1) to 15 months (13.6-16.5), and PFS from 6.2 months (5.6 to 6.9) to 6.9 months (5.7 to 7.2). The proportion of patients with any grade 3 or worse treatment-related adverse events was similar between treatment groups.
Conclusion: Compared with chemotherapy and placebo, Tislelizumab plus chemotherapy demonstrates superior efficacy with a similar safety profile in the two groups, encouraging the use of the tislelizumab group in patients with GC/GEJC.

1. Introduction

Gastrointestinal (GI) cancers account for more than 25% of newly diagnosed cancers worldwide, with incidence reaching up to more than 4 million cases per year [1]. In 2020, Gastroesophageal junction cancers (GEJCs) ranked 7th globally in incidence and 6th in mortality rate [2]. Although GEJCs are rare [3], their diagnosis is still poor until metastasized [4, 5]. GEJC poses significant therapeutic challenges due to its complex location where the stomach and esophagus meet and its tendency to present at advanced stages [6]. Surgical intervention remains the only definite treatment, even though high recurrence may occur in poorly differentiated tumors [7], with 5-year survival rates averaging around 30% with surgery alone [8]. Therefore, there is a revolution of immunotherapy use as a potential treatment in a neoadjuvant setting before the surgery, hoping to minimize surgery and tumor recurrence. Immune evasion occurs when PD-1 binds to its ligand, programmed death-ligand 1 (PD-L1), in turn inhibiting T-cell activity and establishing an immunosuppressive environment. [9, 10]. Targeting the PD-1/PD-L1 pathway has shown good antitumor activity and safety in gastroesophageal junction cancer [11, 12]. Tislelizumab (BGB-A317), a humanized immunoglobulin G4 variant, is an anti-PD-1 monoclonal antibody [13]. It shows superior clinical efficacy in multiple types of cancer, including non-small cell lung cancer (NSCLC) [14], nasopharyngeal carcinoma (NPC) [15], unresectable hepatocellular carcinoma (uHCC) [16], and upper tract urothelial carcinoma (UC) [17]. In March 2024, the FDA approved Tislelizumab in esophageal squamous cell carcinoma (ESCC) compared to chemotherapy based on the RATIONALE-302 trial as a second-line setting for patients who have not previously received any PD-1/PD-L1 inhibitors. Also, in December 2024, the FDA approved Tislelizumab in combination with chemotherapy as a first-line setting for advanced gastric cancer and gastroesophageal junction cancer (GC/GEJC) based on the RATIONALE-305, which

* Corresponding author: Mohamed Wagdy, Faculty of Medicine, Modern University for Technology and Information Cairo, Egypt. Email: tamerwagdyali79@gmail.com

Published by the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print): 3066-4004, ISSN (Online): 3066-4012 – See front matter

Citation: Bahr AR, Magdy Hassan A, Wagdy M, Abdelkader M, Samy Elgammal A. Efficacy and Safety of Tislelizumab in Combination with Chemotherapy versus Placebo Plus Chemotherapy in Patients with Advanced Gastric Cancer or Gastroesophageal Junction Cancer: A Systematic Review of Randomized Controlled Trials. ASIDE GI. 2025;1(2):16-20. doi:10.71079/ASIDE.GI.06052577

is included in our systematic review. This systematic review investigated the efficacy and safety of tislelizumab plus chemotherapy compared to placebo and chemotherapy in GC/GEJC, trying to shed light on this combination as a first-line setting for GC/GEJC patients.

2. Methods

We established this systematic review with the standards of the Cochrane Handbook for Systematic Reviews of Interventions 2019 and the preferred reporting items for systematic reviews and meta-analysis 2020. Our protocol is registered on Prospero with the ID number CRD42024616507.

2.1. Literature Search

We performed a comprehensive literature search on five databases: PubMed, Cochrane Library, Scopus, Ovid, and Embase, to identify the relevant studies for our systematic review. The retrieval cutoff date was July 10, 2024. Our strategy was based on Medical Subject Headings (MeSH terms), other medical synonyms, and search strategies in advanced gastric cancer or gastroesophageal junction adenocarcinoma (GC/GEJC). A part of our literature search is ("Tislelizumab") OR ("BGB-A317") AND ("Chemotherapy") AND ("Gastroesophageal Junction Adenocarcinoma").

2.2. PICO and Eligibility Criteria

Our specific PICO represents patients with advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC) aged 18 years or more without restrictions to tumor grade. They were randomized to receive either tislelizumab, an intravenous PD-1-targeted inhibitor, combined with chemotherapy or chemotherapy plus placebo, measuring overall survival (OS) as the primary outcome, and progression-free survival (PFS), objective response rate (ORR), time to progression, duration of response (DoR), and adverse events (AEs) as the secondary outcomes. We determined specific inclusion criteria as follows: (a) included all randomized controlled clinical trials (RCTs) that assessed the efficacy and safety of tislelizumab plus chemotherapy versus placebo plus chemotherapy in patients with advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC). (b) We only included RCTs written in English. Exclusion Criteria: (a) Excluded all study designs rather than RCTs (literature reviews, case reports, and cohorts). (b) Excluded other combinations, either with tislelizumab or chemotherapy in patients with advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC). (c) Excluded chemotherapy combined with tislelizumab in patients with other types of cancer. (d) Excluded animal studies or preclinical studies.

2.3. Data Extraction

We created a spreadsheet to extract data from the included RCTs. Two independent reviewers extracted the following data from each study: study characteristics, including study ID, authors' names, year of publication, country of the study, and study design; patients' demographic characteristics, including the number of patients in intervention and control groups, age, gender distribution, race, number of metastases, PDL expression, TAP score, interventions, dosage of the combined interventions, and duration of the treatment; and outcome characteristics including Overall survival (OS), Progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events (AES).

2.4. Quality Assessment

To assess the risk of bias (RoB) in included RCTs and minimize the potential of bias, two independent authors used the Cochrane Risk of Bias (RoB2) version. They evaluated the five domains in the ROB2 tool: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The overall RoB for each study was determined based on the judgments made for each of the five domains. Each domain is assessed for RoB 2 as either low, with some concerns, or high. The two authors followed the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions to assess the RoB 2 in included RCTs. More details about ROB2 results are provided in **(Figure 1)**.

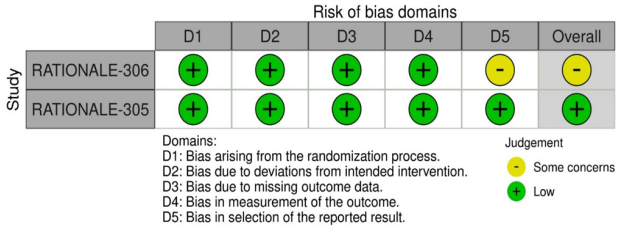

Figure 1: Risk of Bias Assessment of Included Trials

3. Results

3.1. Study Selection

The initial search identified 1,880 studies. After removing 558 duplicates, 1,322 unique records were screened by title and abstract. Of these, 1,303 records were excluded for not meeting the inclusion criteria, leaving 19 full-text articles for detailed evaluation. Among these, five were excluded as protocol-only publications, nine as abstracts, one as an editorial, and two as single-arm. Ultimately, only two studies met the eligibility criteria and were included in this systematic review. The PRISMA flow diagram **(Figure 2)** details the study selection process.

3.2. Study Characteristics

The included studies were large-scale randomized controlled trials published between 2023 and 2024, investigating the efficacy and safety of Tislelizumab, a monoclonal antibody targeting programmed cell death-1 (PD-1), in combination with chemotherapy versus placebo and chemotherapy for patients with locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) and gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. The trials, conducted globally, enrolled HER2-negative patients aged 18 or older with advanced or unresectable disease. Key exclusion criteria included HER2-positive tumors, active leptomeningeal disease, uncontrolled brain metastasis, and prior anti-PD-1/PD-L1 therapy. In all trials, patients were randomized to receive 200 mg of Tislelizumab or a matching placebo every three weeks, along with chemotherapy regimens tailored to each study. Frequently used agents included capecitabine, oxaliplatin, and cisplatin, administered as initial cycles or maintenance therapy until disease progression or unacceptable toxicity. Baseline characteristics and demographics were balanced across treatment groups. Specific endpoints included survival outcomes, progression metrics, and objective response rates **(Table 1)**.

3.3. Efficacy outcomes

3.3.1. Overall Survival (OS)

The study by Qiu et al. (2024) found that Tislelizumab-treated patients had a median OS of 15.0 months (range: 13.6–16.5)

Table 1: Baseline Characteristics of Included Randomized Controlled Trials

Study ID	Country	Study Design	Year	No. of Patients	Age, median (range), years	No. Male
Miao-Zhen Qiu, 2024 (Rational-305)	China	RCT (randomized, double-blind, phase 3 trial)	2024	997	60.0 (53.0–66.0)	692
Jianming Xu, 2023 (Rational-306)	China	RCT (randomized, double-blind, phase 3 trial)	2023	649	64.0 (59.0–69.0)	563

Table 2: Efficacy Outcomes of Included Randomized Controlled Trials

Study ID	Median Overall Survival (months, CI)	Median Progression-free Survival (months, CI)	Median Objective Response Rate (CI)	Median Disease Control Rate (CI)
Miao-Zhen Qiu, 2024 (Rational-305)	15.0 (13.6–16.5) vs 12.9 (12.1–14.1)	6.9 (5.7–7.2) vs 6.2 (5.6–6.9)	90 (87–92) vs 83 (80–86)	48 (43–52) vs 41 (36–45)
Jianming Xu, 2023 (Rational-306)	17.2 (15.8–20.1) vs 10.6 (9.3–12.1)	7.3 (6.9–8.3) vs 5.6 (4.9–6)	89% (85–92) vs 80% (75–84)	63% (58–69) vs 42% (37–48)

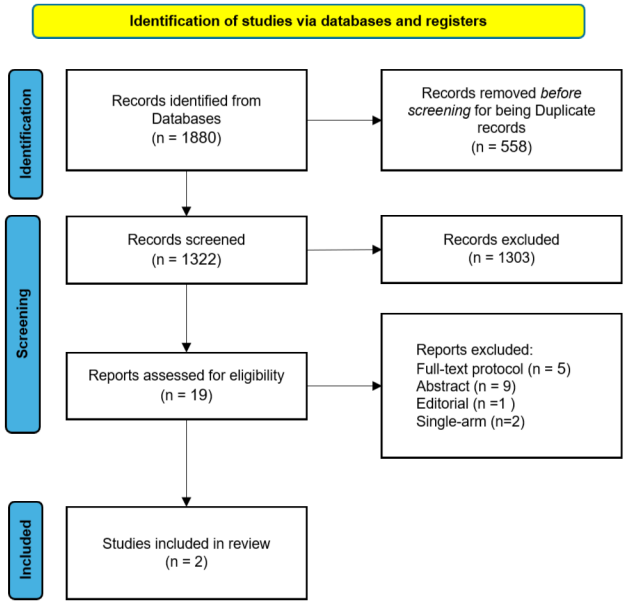

Figure 2: PRISMA Flow Diagram of Study Selection

compared to 12.9 months (range: 12.1–14.1) in the control group. In the study by Xu et al. (2023), Tislelizumab-treated patients had a median OS of 17.2 months (range: 15.8–20.1), which was significantly longer than the 10.6 months (range: 9.3–12.1) in the control group. Both studies showed a clear survival benefit with Tislelizumab **(Table 2)**.

CI, confidence interval; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate.

3.3.2. Progression-Free Survival (PFS)

Qiu et al. (2024) reported a median PFS of 6.9 months (range: 5.7–7.2) for Tislelizumab-treated patients compared to 6.2 months (range: 5.6–6.9) in the control group. The study by Xu et al. (2023) showed a median PFS of 7.3 months (range: 6.9–8.3) for Tislelizumab-treated patients, compared to 5.6 months (range: 4.9–6.0) in the control group. In both studies, Tislelizumab demonstrated a benefit in PFS **(Table 2)**.

3.3.3. Disease Control Rate (DCR)

In the study by Qiu et al. (2024), Tislelizumab-treated patients achieved a DCR of 90% (range: 87–92%) compared to 83% (range: 80–86%) in the control group. Xu et al. (2023) reported a DCR of 89% (range: 85–92%) for Tislelizumab-treated patients versus 80% (range: 75–84%) in the control group. Both studies showed a higher DCR in the Tislelizumab-treated group **(Table 2)**.

3.3.4. Objective Response Rate (ORR)

The study by Qiu et al. (2024) found that 48% of Tislelizumab-treated patients achieved an ORR (range: 43–52%), compared to 41% (range: 36–45%) in the control group. In the study by Xu et al. (2023), Tislelizumab-treated patients showed a higher ORR of 63% (range: 58–69%) compared to 42% (range: 37–48%) in the control group **(Table 2)**.

3.3.5. Adverse Events (AEs)

Across both RATIONALE-306 and RATIONALE-305, nearly all treatment-emergent adverse events were low grade: most adverse events were Grade 1–2, and no Grade 5 events occurred in either arm. This implies that adding Tislelizumab to chemotherapy has meaningful safety besides its high efficacy compared to a placebo with chemotherapy. For instance, Grade 1–2 rates for decreased appetite were 33.53% vs. 34.07% in Tislelizumab and placebo groups, respectively in RATIONLE 306 and 32.82% vs 33.44% in RATIONALE-305. Nausea, vomiting, fatigue, hypoesthesia, asthenia, and a few hematologic events (e.g., anemia, decreased WBC, peripheral sensory neuropathy) showed only mild differences in the two groups Tislelizumab and placebo groups. The sole notable imbalance was hypothyroidism, which was modestly higher with Tislelizumab (10.78% vs 2.42% in RATIONALE-306 and 9.51% vs 4.33% in RATIONALE-305).

4. Discussion

In this systematic review, we found that the combination therapy of Tislelizumab and chemotherapy was superior to placebo with chemotherapy in all efficacy measurements: overall survival (OS), progression-free survival (PFS), objective response rate (ORR),

and disease control rate (DCR), in turn, it represents a potent targeted therapy for GC/GEJC. Importantly, this combination therapy maintained an acceptable and manageable profile of adverse effects that was consistent with the adverse events associated with the usage of anti-PD-1 drugs. Multiple studies have investigated the safety and efficacy of tislelizumab alone or combined for the treatment of gastroesophageal junction cancer: adenocarcinoma and ESCC. A phase I study by Desai et al. has demonstrated an acceptable safety profile for tislelizumab in the treatment of advanced solid tumors, including esophageal cancer (EC) and gastric cancer (GC) [18]. A phase II study by Xu et al. has shown that tislelizumab plus chemotherapy had durable responses and a manageable safety profile in patients with advanced GEJ adenocarcinoma [19]. In the RATIONALE-302 phase III study, Ajani et al. found that tislelizumab monotherapy had better overall survival rates and safety profile than mono-chemotherapy [20]. Another study by Kim et al. found that Asian patients with ESCC who received tislelizumab monotherapy had better health-related quality of life and ESCC symptoms compared to patients who received chemotherapy alone [21]. However, and to the best of our knowledge, no RCTs have directly compared tislelizumab monotherapy to combination therapy of tislelizumab plus chemotherapy. In the TD-NICE phase II study, Yan et al. found that the combination therapy of tislelizumab plus chemotherapy demonstrated a promising antitumor activity [22]. Moreover, Xu et al. found that adding tislelizumab to chemotherapy could be a new first-line treatment for advanced ESCC and GEJ adenocarcinoma [23]. Tislelizumab plus chemotherapy has shown superiority to pembrolizumab plus chemotherapy in KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 [24]. In addition, Tislelizumab plus chemotherapy is superior to other combinations such as Nivolumab plus chemotherapy in ATTRACTION-4 [23] and Sintilimab plus chemotherapy in ORIENT-16 [25]. Our results from RATIONALE-305, and RATONALE-306 imply that Tislelizumab may yield better results for patients with higher PD-L1 TAP scores. However, due to the limited amount of RCTs and the challenges associated with multiple PD-L1 scoring methods across different studies, future studies should further investigate the relationship between PD-L1 TAP score status and their ability to predict treatment efficacy with PD-L1 inhibitors such as tislelizumab for patients with ESCC or GEJ adenocarcinoma.

In addition to its novelty, a notable strength of this paper is that both RCTs included in our review were conducted globally, involving numerous medical centers across Asia, Europe, Oceania, and North America. However, the study has limitations, including two RCTs and the potential concerns regarding the risk of bias in one of the included RCTs. Despite the limitations, the results of our systematic review confirm the safety and efficacy of tislelizumab when used in conjunction with chemotherapy for treating gastroesophageal junction adenocarcinoma or esophageal squamous cell carcinoma. These findings also emphasize the need for further RCTs investigating this topic.

More randomized clinical trials are necessary to compare tislelizumab plus chemotherapy and placebo plus chemotherapy in GC/GEJC. In addition, we need clinical trials to compare tislelizumab plus chemotherapy versus tislelizumab as monotherapy in GC/GEJC since this approach has not yet been studied. Tislelizumab plus chemotherapy has shown promising results in GEJC and NSCLC; in turn, it should be investigated in new solid tumors treated with PD-1 inhibitors like breast cancer and colorectal. In addition, Tislelizumab plus chemotherapy should be more investigated in GC/GEJC, HCC, NSCLC, and nasopharyngeal carcinoma, as there are still few trials about this combination, which requires more trials to be clearly understood.

5. Conclusion

Compared with chemotherapy and placebo, Tislelizumab plus chemotherapy demonstrates superior efficacy with a similar safety profile in the two groups, encouraging the use of the tislelizumab group in patients with GC/GEJC. More clinical is necessary to compare tislelizumab plus chemotherapy to chemotherapy and placebo and to use tislelizumab with chemotherapy in more solid tumors, which are now treated with PD-1 inhibitors as first or second lines.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

Funding Source

None

Acknowledgements

None

Institutional Review Board (IRB) approval

None

Large Language Model Statement

None

Authors Contribution Statement

ARB conceptualized the study; ARB and AMH developed the methodology; ARB, MA, and MW conducted literature screening; MA and AMS performed quality assessment; MA and ARB handled data extraction; ARB, MA, MW, and AMS wrote the manuscript; ARB and AMS reviewed and edited; All authors reviewed and approved the final manuscript and ensured its accuracy and integrity.

Data Availability Statement

This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

References

1. S Zhang, H Orita, T Fukunaga. Current surgical treatment of esophagogastric junction adenocarcinoma. World J Gastrointest Oncol. [PMCID: PMC6700029, https://doi.org/10.4251/wjgo.v11.i8.567].
2. D J Uhlenhopp, E O Then, T Sunkara, V Gaduputi. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. Clin J Gastroenterol. [https://doi.org/10.1007/s12328-020-01237-x].
3. Cancer Council. Oesophageal cancer; 2022. Available from: https://www.cancer.org.au/cancer-information/types-of-cancer/oesophageal-cancer.
4. H Sung, J Ferlay, R L Siegel, M Laversanne, I Soerjomataram, A Jemal, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. [https://doi.org/10.3322/caac.21660].

5. T Lerut, W Coosemans, G Decker, P De Leyn, P Nafteux, D Van Raemdonck. Cancer of the esophagus and gastro-esophageal junction: potentially curative therapies. Surg Oncol. [https://doi.org/10.1016/s0960-7404(01)00027-5].
6. M Abdullah, A A Karim, K L Goh. Late presentation of esophageal cancer: observations in a multiracial South-East Asian population. J Dig Dis. [https://doi.org/10.1111/j.1751-2980.2009.00410.x].
7. J A Ajani, J Lee, T Sano, Y Y Janjigian, D Fan, S Song. Gastric adenocarcinoma. Nat Rev Dis Primers. [https://doi.org/10.1038/nrdp.2017.36].
8. B Njei, T R McCarty, J W Birk. Trends in esophageal cancer survival in United States adults from 1973 to 2009: A SEER database analysis. J Gastroenterol Hepatol. [PMCID: PMC4885788, https://doi.org/10.1111/jgh.13289].
9. A K Nowak, R A Lake, A L Marzo, B Scott, W R Heath, E J Collins, et al. Induction of tumor cell apoptosis in vivo increases tumor antigen cross-presentation, cross-priming rather than cross-tolerizing host tumor-specific CD8 T cells. J Immunol. [https://doi.org/10.4049/jimmunol.170.10.4905].
10. W J Lesterhuis, C J Punt, S V Hato, D Eleveld-Trancikova, B J Jansen, S Nierkens, et al. Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice. J Clin Invest. [PMCID: PMC3148725, https://doi.org/10.1172/JCI43656].
11. J Xu, H Jiang, Y Pan, K Gu, S Cang, L Han, et al. Sintilimab Plus Chemotherapy for Unresectable Gastric or Gastroesophageal Junction Cancer: The ORIENT-16 Randomized Clinical Trial. JAMA. [PMCID: PMC10698618, https://doi.org/10.1001/jama.2023.19918].
12. Y K Kang, N Boku, T Satoh, M H Ryu, Y Chao, K Kato, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. [https://doi.org/10.1016/S0140-6736(17)31827-5].
13. L Shen, J Guo, Q Zhang, H Pan, Y Yuan, Y Bai, et al. Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. J Immunother Cancer. [PMCID: PMC7304812, https://doi.org/10.1136/jitc-2019-000437].
14. A Daei Sorkhabi, M ZareDini, A Fazlollahi, A Sarkesh, A Naseri, S E Mousavi, et al. The safety and efficacy of tislelizumab, alone or in combination with chemotherapy, for the treatment of non-small cell lung cancer: a systematic review of clinical trials. BMC Pulm Med. [PMCID: PMC10704633, https://doi.org/10.1186/s12890-023-02755-3].
15. H Sun, F Bu, L Li, X Zhang, X Xin, J Yan, et al. Efficacy and Safety of Immune Checkpoint Inhibitors Combined With Chemotherapy as First-line Treatment for Recurrent or Metastatic Nasopharyngeal Carcinoma: A Network Meta-analysis of Randomized Controlled Trials. Ann Pharmacother. [https://doi.org/10.1177/10600280231188171].
16. S Qin, M Kudo, T Meyer, Y Bai, Y Guo, Z Meng, et al. Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Phase 3 Randomized Clinical Trial. JAMA Oncol. [PMCID: PMC10557031, https://doi.org/10.1001/jamaoncol.2023.4003].
17. P Quan, L Zhang, B Yang, H Hou, N Wu, X Fan, et al. Effectiveness and safety of adjuvant treatment of tislelizumab with or without chemotherapy in patients with high-risk upper tract urothelial carcinoma: a retrospective, real-world study. Clin Transl Oncol. [https://doi.org/10.1007/s12094-024-03659-2].
18. J Desai, S Deva, J S Lee, C C Lin, C J Yen, Y Chao, et al. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. J Immunother Cancer. [PMCID: PMC7295442, https://doi.org/10.1136/jitc-2019-000453].
19. J Xu, Y Bai, N Xu, E Li, B Wang, J Wang, et al. Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma. Clin Cancer Res. [https://doi.org/10.1158/1078-0432.CCR-19-3561].
20. J Ajani, F El Hajbi, D Cunningham, M Alsina, P Thuss-Patience, G V Scagliotti, et al. Tislelizumab versus chemotherapy as second-line treatment for European and North American patients with advanced or metastatic esophageal squamous cell carcinoma: a subgroup analysis of the randomized phase III RATIONALE-302 study. ESMO Open. [PMCID: PMC10837773, https://doi.org/10.1016/j.esmoop.2023.102202].
21. S B Kim, E Van Cutsem, J Ajani, L Shen, G Barnes, N Ding, et al. Tislelizumab in advanced/metastatic esophageal squamous cell carcinoma: health-related quality of life in Asian patients. Curr Med Res Opin. [https://doi.org/10.1080/03007995.2023.2270894].
22. X Yan, H Duan, Y Ni, Y Zhou, X Wang, H Qi, et al. Tislelizumab combined with chemotherapy as neoadjuvant therapy for surgically resectable esophageal cancer: A prospective, single-arm, phase II study (TD-NICE). Int J Surg. [https://doi.org/10.1016/j.ijsu.2022.106680].
23. B Gafton, S Morarasu, G Dimofte. Role of immunotherapy in gastric cancer with liver metastasis. World J Clin Oncol. [PMCID: PMC11514424, https://doi.org/10.5306/wjco.v15.i11.1383].
24. S Y Yan, J G Fan. Application of immune checkpoint inhibitors and microsatellite instability in gastric cancer. World J Gastroenterol. [PMCID: PMC11185298, https://doi.org/10.3748/wjg.v30.i21.2734].
25. X M Zhang, T Yang, Y Y Xu, B Z Li, W Shen, W Q Hu, et al. Effectiveness and tolerability of programmed cell death protein-1 inhibitor + chemotherapy compared to chemotherapy for upper gastrointestinal tract cancers. World J Gastrointest Oncol. [PMCID: PMC11037061, https://doi.org/10.4251/wjgo.v16.i4.1613].

ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Original Article

Evaluating Biliary Complications in Jaundiced Patients with Alcohol-Related Hepatitis: A Retrospective Study

Junaid Khan[1], Qamar Iqbal[1], Gajendra Acharya[1], Mubasshar Shahid[1], Safana Ismail[1], Umme Ferdaush[1], Christina Gomez[2], Osama Kaddourah[3,*]

1-Department of Internal Medicine, TidalHealth Peninsula Regional Salisbury, Maryland, USA
2-Department of Internal Medicine, St Luke's Hospital Kansas City, Missouri, USA
3-Department of Gastroenterology, TidalHealth Peninsula Regional Salisbury, Maryland, USA

ARTICLE INFO

Article history:
Received 16 Mar. 2025
Received in revised form 13 May 2025
Accepted 22 May 2025
Published 24 Jun. 2025

Keywords:
Alcoholic hepatitis
Jaundice
Biliary complications
Common bile duct dilation
Alcohol-Related Hepatitis

ABSTRACT

Introduction: This study aims to differentiate whether jaundice in patients with alcoholic hepatitis (AH) is due to alcohol-related liver disease or underlying biliary pathology, including choledocholithiasis, primary sclerosing cholangitis, primary biliary cholangitis, benign strictures, cholangiocarcinoma, or pancreatic cancer. Accurate differentiation is crucial for appropriate treatment decisions.

Methods: A non-interventional retrospective study examined patients admitted to our institute for presumed alcohol-related hepatitis management from 2016 to 2023. The primary outcome was the occurrence of biliary processes, whether benign or malignant, in patients managed for alcohol-related hepatitis within 90 days. Secondary outcomes assessed bilirubin level trends over seven days to evaluate steroid effects on alcohol-related hepatitis and predict underlying biliary processes. Variables were analyzed using bivariate and multivariate logistic regression with biliary process as the dependent variable.

Results: Our study revealed that patients with alcohol-related hepatitis and jaundice who had dilated common bile duct (CBD) or pancreatic duct (PD) on cross-sectional imaging were more likely to have biliary processes regardless of cholecystectomy history p-value 0.007 (CI 0.03-0.242) OR 7.5 and p-value 0.001 (CI 0.58-1.34), OR 1.2 respectively. However, there was no correlation between biliary process incidence and various demographic or clinical factors.

Conclusion: Cross-sectional imaging should be routinely used to evaluate biliary tree conditions in alcohol-related hepatitis patients with jaundice who have dilated CBD, particularly those with previous cholecystectomy or gallstones on imaging studies. This systematic approach enables early identification of underlying biliary issues and facilitates prompt, appropriate management decisions.

1. Introduction

Alcohol use disorder (AUD) and alcohol-related liver disease (ALD) are on the rise in the US. The average yearly prevalence of AUD was 9.4% of ED visits (9.3 million visits) between 2014 and 2018, and it gradually rose to 30% [1]. Alcohol-related cirrhosis rose by 43% during the same period, especially in young adults and women [2]. This coincided with an increase in mortality from alcohol-related liver disease along with improved screening for AUD [3]. AUD was further exacerbated by the COVID-19 pandemic in 2020. Alcohol sales rose from 7 billion dollars to 9 billion dollars [4]. This was believed to be due to a traumatic experience from the pandemic, financial insecurity, job loss, and lack of group support meetings like Alcoholics Anonymous (AA). ALD soon followed the trend with an increase in hospitalizations by 50% and an increase in mortality by 25% in many states [5, 6]. There is no unique presentation of ALD, and it can mimic many other liver disease presentations. Alcohol-related hepatitis (AH) per se can be present with few symptoms, with the distinct histopathological finding of alcohol steatohepatitis. American Association for the Study of Liver Disease (AASLD) provides guidance for diagnosis that categorizes patients into three groups: biopsy-proven AH, probable AH, and possible AH. Diagnosis criteria include pieces of patient history (high and long-term alcohol intake, recent development of jaundice) and labs consistent with AH (AST/ALT ratio > 1.5, Bilirubin > 3). Symptoms and signs of alcohol-related disease can overlap with drug-induced liver injury, viral hepatitis, ischemic hepatitis, and an autoimmune process [7]. Among the differentials are malignant and benign biliary obstruction with painless jaundice that is subacute. This includes exocrine pancreatic adenocarcinoma or cholangiocarcinoma, while benign causes may include choledocholithiasis, primary sclerosing cholangitis, or primary biliary cirrhosis. While alcohol abuse can suggest an alcohol-related process, this picture can be complicated by an increased risk of malignancy in alcohol users. Bile duct dysplasia was noted in native explanted livers in patients with either hepatitis C, alcohol, or both. This included low-grade and high-grade dysplasia, typically multifocal and more papillary than flat [8]. Also, alcohol liver disease was implicated in intrahepatic

* Corresponding author: Osama Kaddourah, Department of Gastroenterology, TidalHealth Peninsula Regional, Salisbury, Maryland, USA. Email: Osama.kaddourah@tidalhealth.org

Published in collaboration with the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print): 3066-4004, ISSN (Online): 3066-4012

Citation: Khan J, Iqbal Q, Acharya G, et al. Evaluating Biliary Complications in Jaundiced Patients with Alcohol-Related Hepatitis: A Retrospective Study. ASIDE GI. 2025;1(2):21-25, doi:10.71079/ASIDE.GI.06242551

cholangiocarcinoma (ICC) development [9]. Specifically, Alcohol use > 80 grams daily was linked with a higher incidence of cholangiocarcinoma [10]. Tyson et al. demonstrated an association between intrahepatic and extrahepatic cholangiocarcinoma ECC [11]. A study in Italy of patients with Intrahepatic cholangiocarcinoma showed that the mean age was 65, 80% males, and 38% had cirrhosis, 23% reported alcohol use > 80 grams daily, but no significant association [12]. An increased risk of pancreatic cancer has also been associated with various types of hepatitis. Active HBV infection is linked with an increased risk of developing pancreatic cancer [13]. Low to moderate alcohol use was not strongly associated with pancreatic cancer risk; however, heavy use might be associated with increased risk [14]. In our study, we evaluated factors associated with malignant and benign biliary obstruction in patients who presented with painless jaundice in the setting of alcoholism. This will guide the need for a more thorough biliary workup in patients managed for suspected alcohol-related hepatitis.

2. Methods

2.1. Study design and patient cohort

This is a non-interventional retrospective study of all patients in the TidalHealth system located in Salisbury, Maryland, who were admitted and managed for presumed alcohol-related hepatitis from 2016 to 2023 (January until December). The Institutional Review Board (IRB) exempted the study in December 2023 with IRB review 1-1722687-1. Patient information was collected via an EPIC specialist who pulled the database. Specific diagnoses used were "alcoholic hepatitis" and "alcoholic liver disease". Our cohort included 186 patients who met our criteria based on AASLD guidelines. We excluded patients with missing data. We also excluded patients with alcohol liver disease but no active hepatitis after reviewing the charts.

2.2. Data collection

We gathered data from multiple variables that, in our opinion, reflect their comorbidities, risk factors for malignancy, their workup while admitted, including labs and imaging studies, steroid use while admitted, and finally, the incidence of benign biliary process and biliary cancer. This included data on age, gender, smoking history (any), chronic pancreatitis diagnosis, cirrhosis diagnosis, hepatitis B, and hepatitis C at baseline. Labs (serum bilirubin (day 0, 7), platelet count, serum alkaline phosphatase). Imaging (type of imaging, presence of dilated common bile duct CBD and pancreatic duct PD, presence of mass, presence of choledocholithiasis). Incidence of the biliary process (i.e., choledocholithiasis, PSC, PBC, benign strictures) and biliary cancer or related (cholangiocarcinoma, pancreatic adenocarcinoma, liver metastasis).

2.3. Outcome

The primary outcome measured was the occurrence of biliary events, benign or malignant, in patients who were managed for presumed alcohol-related hepatitis within 90 days of their first presentation. This was assessed based on cross-sectional imaging and liver biopsies collected from patient charts within 90 days of admission. Our secondary outcome was a bilirubin level trend over 7 days from admission to assess predictors of bilirubin improvement and whether that is related to a combination of biliary processes rather than merely alcohol-related hepatitis.

2.4. Statistical analysis

The statistical program SPSS 29.0 was used to analyze the data and find pertinent associations. Descriptive data were first assembled to determine the prevalence of different variables in the general population. The incidence of biliary processes was then used as the dependent variable in bivariate and multivariate logistic regression analyses. Furthermore, bilirubin levels were also used as the dependent variable in our study. 95% confidence intervals were generated, along with corresponding p-values. A two-tailed p-value of less than 0.05 was deemed statistically significant. We conducted a Mantel-Haenszel analysis using the incidence of biliary processes as the dependent variable. We evaluated the correlation with dilated CBD while stratifying for a history of cholecystectomy (CCY). Cholecystectomy can lead to physiological dilation of the CBD, so it was important to account for this as a confounding factor. Additionally, we performed a similar analysis stratified by both a history of stone disease and a history of CCY.

3. Results

3.1. Baseline Characteristics

A total of 186 patients with clinical jaundice and a history of significant alcohol use were included between 2016 and 2023. The mean age of the cohort was 50 years (range: 25–91 years), and 67% were male. A considerable percentage had comorbidities pertinent to hepatobiliary pathology: 72% were former smokers, and 44% suffered from cirrhosis. Roughly a third of the patients (33.9%) exhibited thrombocytopenia. Chronic hepatitis C occurred in 10% of cases, while chronic hepatitis B was present in 1.1% of cases. Cholecystectomy had been performed on only 13% of the individuals. Upon presentation, the average serum bilirubin level was 5.4 ± 6.5 mg/dL, showing minimal change after 7 days (5.3 ± 6.7 mg/dL), which reflects the mixed causes of jaundice. The average value of alkaline phosphatase was 161 ± 173 IU/L. Imaging showed that 14% of patients had a dilated CBD, whereas PD dilation was uncommon, occurring in only 1% of cases. Variables are described in **(Table 1)**.

3.2. Incidence of biliary process benign or malignant in patients with jaundice and alcoholism

We ran logistic regression and risk analysis with the incidence of the biliary process as a cause of jaundice as a dependent variable. This correlated with dilated CBD (CBD 6mm) with p-value 0.007 (CI 0.03 – 0.242) OR 7.5 and dilated PD 0.001 (CI 0.58 – 1.34) OR 1.2. However, no correlation with age p-value 0.445, gender p-value of 0.09, history of smoking p-value 0.58, cirrhosis status p-value of 0.81, history of cholecystectomy p-value 0.75, weight loss p-value 0.83, serum bilirubin on presentation p-value 0.28, platelets p-value 0.99, chronic hepatitis C p-value 0.08, serum alkaline phosphatase p-value 0.63, bilirubin response in one-week p-value 0.47. It is also described in **(Table 2)**.

3.3. Incidence of biliary process, benign or malignant, in correlation with dilated CBD stratified by whether the patient had a cholecystectomy

Using Chi-square and the Mantel-Haenszel formula, we found that a history of cholecystectomy increases the risk of biliary process in patients with dilated CBD by an odds ratio of 7, p-value 0.019.

3.4. The incidence of biliary process, benign or malignant, in correlation with dilated CBD, was stratified by whether the patient had CCY or a finding of stones on imaging (both suggest stone disease or a history of it in these patients)

Using Chi-square and the Mantel Haenszel formula, we found that a history of cholecystectomy or observing gallbladder stones on

Table 1: Baseline Characteristics of Study Subjects

Variable	Description
Age (mean, years)	50 (25–91)
Gender (male)	125 (67%)
Smoking (any history)	134 (72%)
Cirrhosis (present)	82 (44%)
Hx of CCY (present)	24 (13%)
Bilirubin (mg/dl) (day 0)	5.4 ± 6.5
Bilirubin (mg/dl) (day 7)	5.3 ± 6.7
Thrombocytopenia (present)	63 (33.9%)
Hepatitis C (chronic, present)	19 (10%)
Hepatitis B (chronic, present)	2 (1.1%)
Chronic pancreatitis (present)	4 (2.2%)
Alkaline phosphatase (IU/L) (day 0)	161 ± 173
Imaging studies (US, CS)	53 (28.5%), 109 (58.6%)
Dilated CBD (present)	26 (14%)
Dilated PD (present)	2 (1%)
Presence of stone disease	39 (21%)
Use of steroids (present)	21 (11.3%)
Malignant biliary process	2 (1.1%)

CCY, Cholecystectomy; US, Ultrasound; CS, Cross-sectional; CBD, Common bile duct; PD, Pancreatic duct.

imaging raises the risk of biliary pathology in patients with dilated CBD by an odds ratio of 6.9, p-value 0.03. The discovery of stones on imaging alone raised the risk of biliary processes in patients with dilated CBD, with an odds ratio of 5.8 and a p-value of 0.05. There was no correlation between the bilirubin trend between days 0 and 7 from presentation and steroid administration for alcohol-related hepatitis or with the incidence of an underlying biliary process. Our analysis did not show any significant correlation with steroid administration. This goes with current literature that failed to show significant improvement in clinical parameters in patients with severe alcohol-related hepatitis receiving steroids [15]. Our analysis also did not show any significant correlation between bilirubin improvement and incidence of a separate biliary etiology of jaundice (benign biliary processes (i.e., biliary stones) or malignant (i.e., cholangiocarcinoma)). This did not support our theory of the likelihood of a biliary process rather than alcohol-related hepatitis as a cause of jaundice in patients with sudden improvement in bilirubin or, conversely, failure to respond to steroids. The bilirubin trend, whether favorable or unresponsive to steroids, does not predict the likelihood of a biliary process.

4. Discussion

According to our research, patients suffering from alcohol-related hepatitis and jaundice, as well as those with a dilated CBD or PD, are more prone to have biliary processes, regardless of their history of cholecystectomy. These patients may require cross-sectional for further evaluation. Our study examined the relationship between

Table 2: p-values for Association Between Clinical and Laboratory Variables and Biliary Process

Variable	p-value
Age	0.445
Gender	0.09
History of smoking	0.58
Cirrhosis	0.81
Cholecystectomy	0.75
Weight loss	0.83
Serum bilirubin on presentation	0.28
Platelets	0.99
Chronic Hepatitis C	0.08
Serum alkaline phosphatase	0.63
Bilirubin response in 1 week	0.47

age, smoking status, gender, presence of cirrhosis, weight loss, hepatitis C and hepatitis B, and serum levels of platelets, serum alkaline phosphatase, and serum bilirubin with the occurrence of biliary processes. The absence of correlation between the incidence of biliary processes and various demographic and clinical factors presents noteworthy findings for our understanding of biliary pathophysiology. This is especially true for age. With increasing age, prior research indicates a higher occurrence of biliary diseases like gallstones. Various studies showed rates reaching up to 30% among women aged over 50, and a similar pattern was seen in aging men [16]. CBD dilation could be pathological. Determining the cause of CBD dilation is recommended in all symptomatic patients [17]. However, the approach to CBD dilation in asymptomatic patients is far from uniform in clinical practice. It is especially challenging in ALD, given underlying abnormal liver enzymes and elevated bilirubin, along with risk factors for developing biliary and pancreatic malignancy, mainly long-term alcohol intake. There are many obstructive (gallstones, malignancies) and non-obstructive (advanced age, opiate use, and prior cholecystectomy) etiologies of CBD dilation [18]. CCY has been a known cause of CBD dilation in some patients since 1887, as postulated by Oddi [19]. Residual or newly formed gallstones remain the most common long-term complication of cholecystectomy, as reported by Latenstein et al. [20]. Our study evaluated the significance of cholecystectomy, which leads to CBD dilation in alcohol-related hepatitis patients. Our analysis showed an odds ratio (OR) of 7 (p=0.019) in finding biliary pathology in alcohol-related hepatitis patients who had prior cholecystectomy with CBD dilation versus the same population with an intact gallbladder. This could be because patients with a history of cholecystectomy likely had gallbladder stone disease in the past, and they still carry the same risk factors to develop more stones. We recommend keeping a high clinical suspicion for concomitant biliary pathology in alcoholic hepatitis patients, even with a history of cholecystectomy.

We further analyzed patients with dilated CBD by stratifying them into subgroups differentiated by their CCY status or the presence of gallstones on imaging. We chose those two conditions to indicate these patients' potential stone disease history or current issues. Our analysis suggested that patients with a history of CCY or those with gallstones on imaging have a significantly increased risk of biliary

processes, as above. Such findings can increase the yield of further imaging to assess for any biliary complications in alcohol-related hepatitis patients. The main limitations of our study stem from its retrospective nature, which restricted our control over variables that could have influenced the observed associations. For instance, the decision to pursue imaging might have been biased by clinician judgment rather than patient presentation alone. The study included only 186 patients over seven years, limiting our findings' generalizability and statistical power, especially in multivariate analyses or subgroup stratifications. This small sample size may also increase the risk of Type II errors, where significant associations could be missed. Lastly, selection bias is a concern, as we only included patients with a presumed diagnosis of alcohol-related hepatitis based on coding. This may have inadvertently excluded patients with overlapping features or included those inaccurately diagnosed due to similar clinical and laboratory results.

5. Conclusion

The results of our research suggest that for patients with alcohol liver disease and jaundice who have dilated CBD, it is advisable to use cross-sectional imaging techniques to assess the condition of the biliary tree. This recommendation holds particularly true for those who have a medical history of cholecystectomy or for individuals with gallstones identified in imaging studies. This method enables early identification of underlying problems, which allows timely intervention and treatment.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

Funding Source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgment

None

Institutional Review Board (IRB)

This study was a non-interventional retrospective review of patients admitted for presumed alcohol-related hepatitis at TidalHealth Peninsula Regional, Salisbury, Maryland, from 2016 to 2023. The Institutional Review Board (IRB) of TidalHealth exempted this study in December 2023 (IRB review 1-1722687-1).

Large Language Model

None

Authors Contribution

QI and GA collected and interpreted data and drafted the manuscript; SI, JK, MS, UF, and CG interpreted data and drafted the manuscript; OK planned and conducted the study, collected and interpreted data, and drafted the manuscript. All authors reviewed and approved the final manuscript.

Data Availability

The data supporting this study's findings are available from TidalHealth Peninsula Regional, but restrictions apply. These data were used under license for the current study and are not publicly available. However, data are available from the authors upon reasonable request and with permission of the TidalHealth Institutional Review Board (IRB).

References

1. Suen LW, Makam AN, Snyder HR, Repplinger D, Kushel MB, Martin M, et al. National Prevalence of Alcohol and Other Substance Use Disorders Among Emergency Department Visits and Hospitalizations: NHAMCS 2014-2018. J Gen Intern Med;2022:2420. PMID: 34518978,. [PMID: 34518978, https://doi.org/10.1007/s11606-021-07069-w].
2. Mellinger JL, Shedden K, Winder GS, Tapper E, Adams M, Fontana RJ, et al. The high burden of alcoholic cirrhosis in privately insured persons in the United States. Hepatology;2018:872. PMID: 29579356,. [PMID: 29579356, https://doi.org/10.1002/hep.29887].
3. Moon AM, Yang JY, ASt B, Bataller R, Peery AF. Rising Mortality From Alcohol-Associated Liver Disease in the United States in the 21st Century. Am J Gastroenterol;2020:79. PMID: 31688021,. [PMID: 31688021, https://doi.org/10.14309/ajg.0000000000000442].
4. Lee BP, Dodge JL, Leventhal A, Terrault NA. Retail Alcohol and Tobacco Sales During COVID-19. Ann Intern Med. 2021: 1027 [PMID: 33646843,. [PMID: 33646843, https://doi.org/10.7326/M20-7271].
5. Gonzalez HC, Zhou Y, Nimri FM, Rupp LB, Trudeau S, Gordon SC. Alcohol-related hepatitis admissions increased 50 Liver Int;2022:762. PMID: 35094494,. [PMID: 35094494, https://doi.org/10.1111/liv.15172].
6. Deutsch-Link S, Jiang Y, Peery AF, Barritt AS, Bataller R, Moon AM. Alcohol-Associated Liver Disease Mortality Increased From 2017 to 2020 and Accelerated During the COVID-19 Pandemic. Clin Gastroenterol Hepatol;2022:2142. PMID: 35314353,. [PMID: 35314353, https://doi.org/10.1016/j.cgh.2022.03.017].
7. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. Hepatology;2020:306. PMID: 31314133,. [PMID: 31314133, https://doi.org/10.1002/hep.30866].
8. Torbenson M, Yeh MM, Abraham SC. Bile duct dysplasia in the setting of chronic hepatitis C and alcohol cirrhosis. Am J Surg Pathol;2007:1410. PMID: 17721197,. [PMID: 17721197, https://doi.org/10.1097/PAS.0b013e318053d122].
9. Gupta A, Dixon E. Epidemiology and risk factors: intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr:101. PMID: 28503557,. [PMID: 28503557, https://doi.org/10.21037/hbsn.2017.01.02].
10. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. Hepatology;2011:173. PMID: 21488076,. [PMID: 21488076, https://doi.org/10.1002/hep.24351].
11. Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol;2007:1221. PMID: 17689296,. [PMID: 17689296, https://doi.org/10.1016/j.cgh.2007.05.020].
12. Donato F, Gelatti U, Tagger A, Favret M, Ribero ML, Callea F, et al. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case-control study in Italy. Cancer Causes Control;2001:959. PMID: 11808716,. [PMID: 11808716, https://doi.org/10.1023/a:1013747228572].
13. Luo G, Hao NB, Hu CJ, Yong X, Lu MH, Cheng BJ, et al. HBV infection increases the risk of pancreatic cancer: a meta-analysis. Cancer Causes Control;2013:529. PMID: 23306552,. [PMID: 23306552, https://doi.org/10.1007/s10552-012-0144-2].
14. Brown LM. Epidemiology of alcohol-associated cancers. Alcohol;2005:161. PMID: 16054977,. [PMID: 16054977,

https://doi.org/10.1016/j.alcohol.2005.03.008].

15. Forrest E, Mellor J, Stanton L, Bowers M, Ryder P, Austin A, et al. Steroids or pentoxifylline for alcoholic hepatitis (STOPAH): study protocol for a randomised controlled trial. Trials;2013:262. PMID: 23958271,. [PMID: 23958271, https://doi.org/10.1186/1745-6215-14-262].
16. Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. Lancet:230. PMID: 16844493,. [PMID: 16844493, https://doi.org/10.1016/S0140-6736(06)69044-2].
17. Rizvi A, Sethi A, Poneros J, Visrodia KH. Does incidentally detected common bile duct dilation need evaluation? Cleve Clin J Med;2022:315. PMID: 35649563,. [PMID: 35649563, https://doi.org/10.3949/ccjm.89a.21029].
18. Smith I, Monkemuller K, Wilcox CM. Incidentally Identified Common Bile Duct Dilatation: A Systematic Review of Evaluation, Causes, and Outcome. J Clin Gastroenterol;2015:810. PMID: 26302495,. [PMID: 26302495, https://doi.org/10.1097/MCG.0000000000000394].
19. Oddi R, Rosciano G. Sulla esistenza di speciali gangli nervosi in prossimità dello sfintere del coledoco. Monitore Aoologico Italiano;1894:216 7.
20. Latenstein CSS, Wennmacker SZ, Jong JJ, Laarhoven C, Drenth JPH, Reuver PR. Etiologies of Long-Term Postcholecystectomy Symptoms: A Systematic Review. Gastroenterol Res Pract;2019:4278373. PMID: 31110517,. [PMID: 31110517, https://doi.org/10.1155/2019/4278373].