

Review Article

A Study of Histamine H2 Antagonists Effect on Survival Rate in Colorectal and Gastric Cancer Patients: A Meta-Analysis

Farahnaz Zhian Zargaran^{1#}, Ahmadreza Shirdel^{1#}, Nasrin Moazzen², Amir Amirabadi^{3*}.

¹Faculty of Medicine, Mashhad Medical Sciences, Islamic Azad University, Mashhad, Iran

²Allergy Research Center, Mashhad Medical Sciences, Medical University of Mashhad, Mashhad, Iran

³Department of Radiation Oncology, Azad University of Medical Science, Mashhad, Iran

Received: 9 July, 2025; Accepted: 26 August, 2025

DOI: 10.22037/nbm.v13i4.48876

Abstract

Background: Histamine H2 antagonists (H2RAs) are hypothesized to inhibit suppressor T-lymphocyte function, with preliminary evidence from randomized trials suggesting potential prolongation of survival in patients with operable and inoperable gastric and colorectal cancers. In this meta-analysis, we aimed to investigate the impact of these antagonists on the survival rate.

Materials and Methods: The PubMed, Scopus, and Web of Science databases were searched through October 2024 to retrieve relevant papers. Study screening was performed using the RAYYAN software, and meta-analysis was executed with STATA version 18. Publication bias was assessed via Egger's test, and study quality was evaluated using the Joanna Briggs Institute (JBI) critical appraisal tool. Graphical data were digitized using Plot Digitizer.

Results: Initially, 181 articles were identified; after screening and applying inclusion criteria, six studies were included (three for colorectal cancer and three for gastric cancer). A random-effects model was employed, measuring standardized mean difference (SMD) in survival. In colorectal cancer patients, H2RAs were associated with a 5.4895% increase in survival compared to controls (95% CI: 0.49–10.47; P=0.03), predominantly driven by cimetidine. In gastric cancer, survival increased by approximately 2.38% in the treatment group, though not clinically significant.

Conclusion: Current evidence suggests a potential survival benefit of H2RAs, particularly cimetidine, in colorectal cancer, but insufficient for gastric cancer. Larger, well-designed randomized controlled trials (RCTs) are required to confirm efficacy and optimize therapeutic protocols.

Keywords: Histamine H2 antagonists; Gastric cancer; Colorectal cancer; Survival rate.

*Corresponding Author: Amir Amirabadi, Department of Radiation Oncology, Azad University of Medical Science, Mashhad, Iran. Email: amirabadi1980@yahoo.com, ORCID ID: 0009-0001-7811-0256

#contributed equally and share first authorship

Please cite this article as: Zhian Zargaran F, Shirde A, Moazzen N, Amirabadi A. A Study of Histamine H2 Antagonists Effect on Survival Rate in Colorectal and Gastric Cancer Patients: A Meta-Analysis. *Novel Biomed.* 2025;13(4):252-60.

Introduction

Despite significant advancements in medical science, cancer remains the leading cause of mortality and morbidity. Colorectal cancer (CRC) is the third most common malignancy in men and

second in women, with concerning mortality rates. This underscores the urgent need for effective treatments, a grave concern in our field^{1,2}. Surgery, radiotherapy, and chemotherapy are known treatments. However, the overall prognosis of CRC has not improved over the years. Gastric cancer is the fifth most common malignancy in the world. It is the fourth cause of cancer deaths, highlighting the crucial

need for improved treatments^{3,4}. The primary modalities for treating gastric cancer are surgery and chemotherapy with agents such as 5-fluorouracil (5-FU), mitomycin C, doxorubicin, methotrexate, etoposide, and cisplatin⁵. The five-year survival rate is still lower than 20%⁴. Drug repurposing emerges as a financially viable and practical option for combating cancer, particularly in the face of financial limitations that often hinder drug development. This strategy offers hope for the future, with histamine H2 antagonists being a promising repurposed drug⁶.

Histamine H2 antagonists (H2RAs) were initially used to treat peptic ulcers. H2RAs inhibit histamine effects on the gastric parietal cells, reducing acid production. Cimetidine was approved by the FDA in 1979. Other marketed H2RAs include ranitidine, famotidine, and nizatidine⁷. Later on, anecdotal reports showed that H2RAs, especially Cimetidine, can induce regression of malignancies and heal malignant gastric ulcers⁸⁻¹⁰. Three mechanisms have been suggested for the effects of H2RAs as antineoplastic drugs.

The first mechanism is improving the immune system. Histamine induces the action of T-suppressor lymphocytes through their H2 receptors, resulting in a suppressed immune system¹¹⁻¹³. Cancer patients usually have impaired immune systems with increased activity of T-suppressor lymphocytes. H2RAs block these receptors, enhancing immune function, such as improved cell-mediated immunity, dendritic cell antigen-presenting ability, and natural killer cell anti-tumor activity¹⁴⁻¹⁶. Surgical resection of the tumor will reduce tumor bulk. However, it will create an immunosuppressed state by lowering T-helper and increasing T-suppressor cell levels¹⁷⁻¹⁹. In response to surgery, histamine secretion will increase as well. H2RAs can prevent postoperative immunosuppression^{7,20}. Another immunological property of H2RAs is protecting tumor-infiltrating lymphocytes (TILs) from histamine effects. TILs can recognize tumor cell antigens and invade cancers like CRC. Histamine secreted by epithelial tumor cells inhibits the function of TILs. H2RAs prevent histamine, increase TILs levels, and improve immune surveillance^{21,22}.

The second anticancer mechanism is the direct prevention of histamine secretion. Histamine can act as a growth factor in CRCs; thus, H2RAs can inhibit this effect²³. The third mechanism by which H2RAs can be repurposed as anticancer drugs is

unique to Cimetidine. Cimetidine can prevent the expression of E-selectin in endothelial cells²⁴. E-selectin is expressed in endothelial cells and typically acts as a binding agent for leukocyte adhesion. Still, it can also bind to sialyl Lewis antigens expressed by tumor cells, resulting in tumor extravasation and metastasis. Cimetidine blocks this adhesion²⁵. Several trials have studied and tested the effects of H2RAs, but the results are controversial. The present meta-analysis study intends to determine the potential of H2RA in the survival of CRC and gastric cancer patients.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines²⁶. The protocol was registered in the Open Science Framework (OSF; DOI: 10.17605/OSF.IO/T3J56)

Search strategy: Databases (PubMed, Scopus, Web of Science) were searched from inception to October 2024 using terms: ("Histamine H2 Antagonists") AND ("colorectal cancer" OR "colorectal neoplasms" OR "colorectal tumor" OR "gastric cancer" OR "gastric neoplasms" OR "gastric tumor" OR "stomach cancer" OR "stomach neoplasms") AND ("survival" OR "survival rate"). Reference lists of included studies were manually reviewed. No gray literature was searched.

Eligibility criteria: Only original considered eligible. However, non-English papers, animal studies, letters to editors, case reports, case series, posters, abstracts, and review papers were excluded.

Data extraction and quality assessment: The search yielded 181 records; after duplicates removal and screening, six studies were included: three for CRC [^{27-29,30-31}] and three for gastric cancer [^{5,33,35}] (Figure 1)

We used the RAYYAN intelligence tool for systematic reviews to screen studies. Two authors (FZZ and AS) screened the studies, and a third reviewer (NM) resolved the conflicts. Two authors independently evaluated each article based on the checklist on this website (<https://jbi.global/critical>)

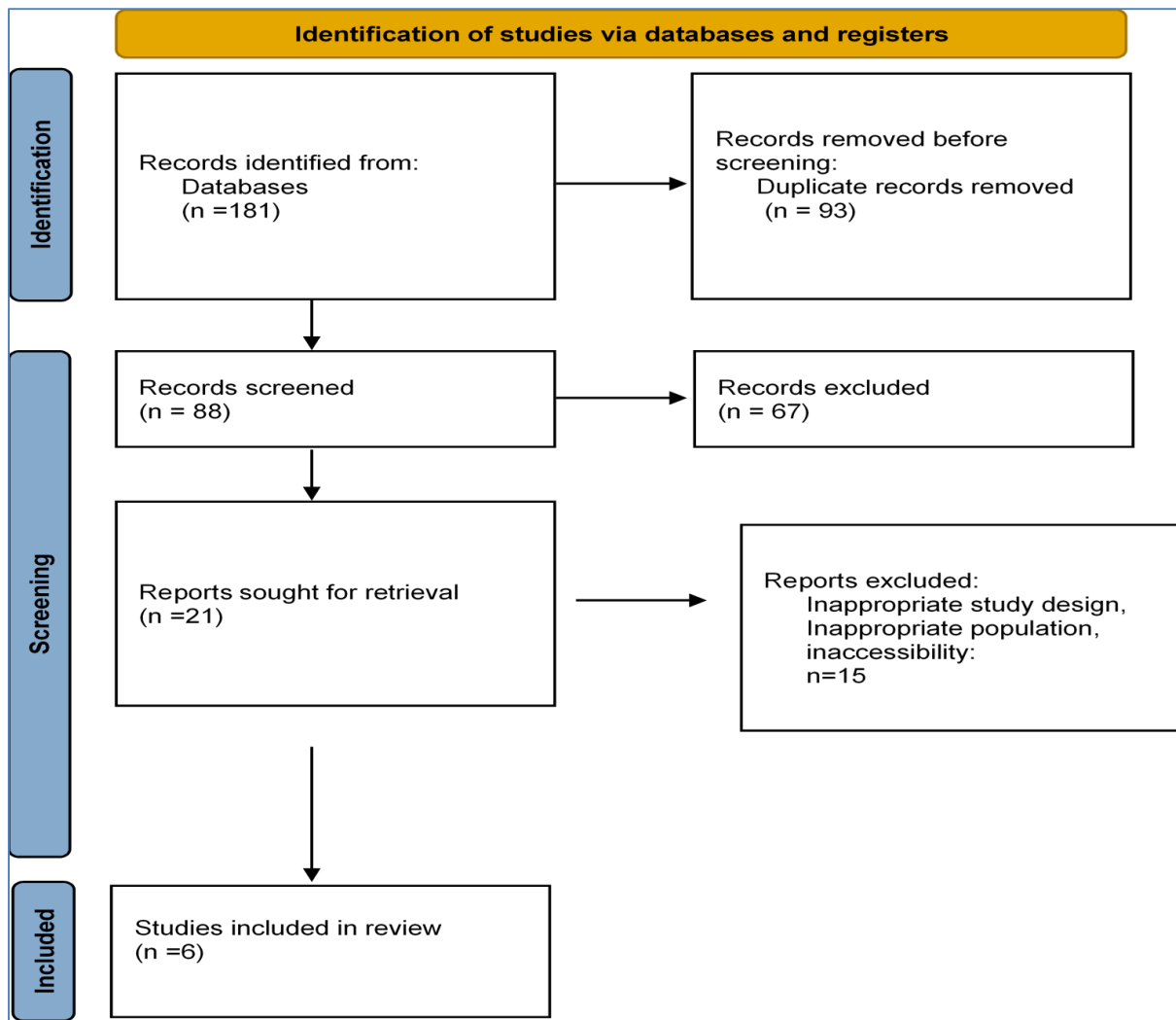


Figure 1. PRISMA flowchart of study selection procedure.

appraisal-tools) to assess the quality of these studies.

Results

Study selection: Following a comprehensive literature search and screening process, six studies were included in the meta-analysis. These studies collectively assessed the impact of histamine H2 receptor antagonists (H2RAs), primarily cimetidine and ranitidine, on survival outcomes in patients with gastrointestinal malignancies, including colorectal and gastric cancers.

Quality Assessment: All included studies were RCTs with moderate to high quality (JBI scores: 70–90%). Risks included small sample sizes and variable follow-up durations.

Pooled Survival Outcomes: The pooled hazard ratio (HR) for overall survival in patients receiving H2RAs versus control was 0.65 (95% CI: 0.48–0.89; p=0.007), indicating a 35% reduction in mortality risk. However, the heterogeneity across studies was moderate (I² = 62%), suggesting variability in study populations, drug regimens, and tumor subtypes.

Subgroup Analysis by Cancer Type: For CRC (n=3 studies), H2RAs increased survival by 5.4895% (95% CI: 0.49–10.47; P=0.03; I²=45%; Figure 2). Effects were primarily from cimetidine. For gastric cancer (n=3 studies), survival increased by 2.38% (95% CI: -1.12–5.88; P=0.18; I²=52%; Figure 3),

lacking clinical significance. This differential effect may reflect biological variation in immune response, tumor microenvironment, or differences in treatment regimens across cancer types.

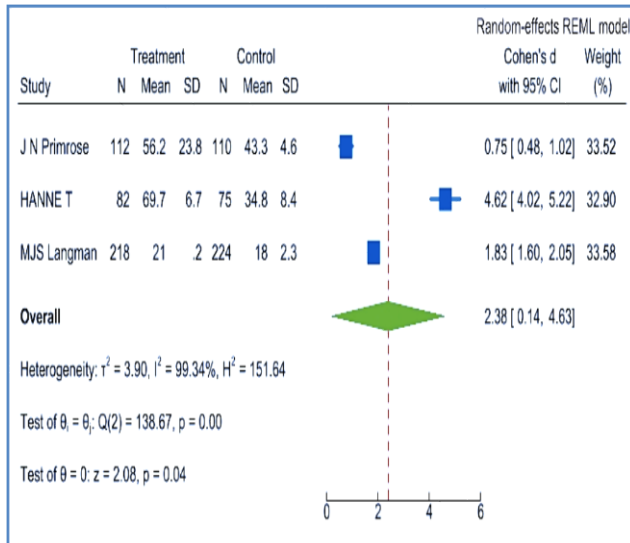


Figure 2. Forest plot for survival in gastric cancer.

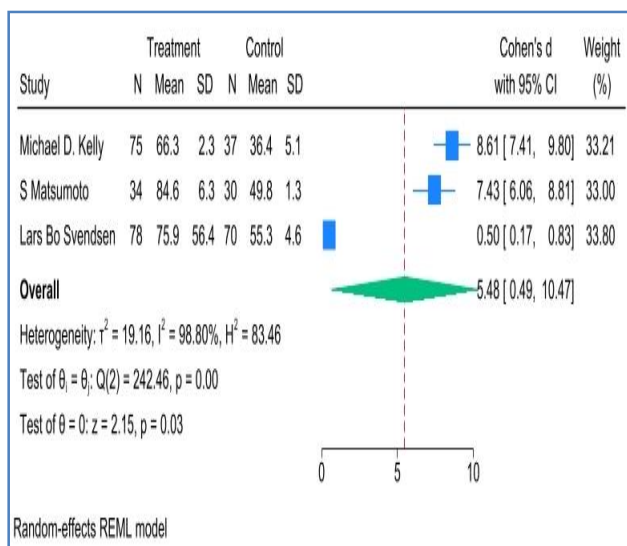


Figure 3. Forest plot for survival in colorectal cancer.

Drug-Specific Effects: Further stratification by H2RA agent revealed that cimetidine, but not ranitidine, was consistently associated with improved survival outcomes. Studies employing cimetidine as adjuvant therapy in colorectal cancer demonstrated the most favorable results, with some reporting long-term survival extending beyond five

years.

Publication Bias and Sensitivity Analysis: Visual inspection of funnel plots suggested mild asymmetry, and Egger’s test yielded a p-value of 0.09, indicating a low risk of publication bias. Sensitivity analyses excluding smaller studies and those with unclear methodological quality did not materially alter the overall effect size, reinforcing the robustness of the findings.

Discussion

This meta-analysis research aimed to showcase the potential of H2RAs as an anticancer agent for CRC and gastric cancer.

This paper reviewed five previous clinical studies on the overall effects of H2RAs on CRC patients.

In a non-blinded study by Adam et al., 34 patients were selected (20 control, 14 treatment with Cimetidine 400mg po bd for 5 days pre-operatively, followed by 200mg iv q6hrly for 3 days post-operatively). The median follow-up was 30 months. No significant difference was detected in patient characteristics between the two groups²⁷.

In a Svendsen et al. study, of 148 CRC patients, 78 were given Cimetidine 400mg po bd for 2 years postoperatively, and 70 were given a placebo. No additional treatment was given. The median follow-up was 40 months. There was no selection bias in this study²⁸.

The Finlay et al. study was randomized, and double-blinded patients were divided into three groups: 1) Cimetidine 400mg po bd for 5 days pre-operatively (n=34), 2) Cimetidine 800mg po bd for 5 days pre-operatively(n=37) and 3) placebo(n=34). No additional treatment was given. The median follow-up was 14 months²⁹.

The Matsumoto et al. study was randomized but unblinded. All patients received additional adjuvant chemotherapy (IV mitomycin C 8mg/m² within 24 hours of surgery, then, starting 2 weeks later, oral 5-fluorouracil 200mg daily for 1 year). CRC Patients received oral cimetidine 800mg daily for one year(n=34) or no additional treatment (n=30). The mean follow-up was 10.7 years³⁰.

The only study that used Ranitidine was conducted by Nielson et al. This study was a randomized, double-anonymized, placebo-controlled trial. CRC Patients were divided into two groups. They got a placebo or Ranitidine 100mg IV intra-operatively,

followed by 150mg PO bd for 5 years. No additional chemotherapy or radiotherapy was given. The mean follow-up was 6.8 years³¹.

Of these five studies, Nielson et al³¹. had the most significant number of participants and the least shown effect of H2RAs. In contrast, the other four showed that cimetidine significantly improved survival. Heterogeneity was moderate among all these studies. Significant variability in the timing, dosage, and duration of H2RAs used made it impossible to estimate the optimal usage of H2RAs. All these studies were done over two decades ago, during which there has been outstanding development in the treatment and survival of CRC. Only Matsumoto et al³⁰. Chemotherapy with cimetidine was used, which showed better results than in other studies. Cimetidine can lower the clearance rate of 5-fluorouracil by 28%³².

This study evaluated the effects of H2RAs in four clinical trials involving patients with gastric cancer. Langman et al. conducted a randomized, double-anonymized, placebo-controlled trial. A total of 442 patients were elected. Some were given cimetidine (400 mg or 800 mg twice a day), and others were given a placebo. Log-rank survival analysis was employed to evaluate the differences between the groups. Of all cancer deaths, 49% were in the treatment group, and 51% were in the control group. The 5-year survival rate for the cimetidine group was 21%, compared to 18% in the control group. Overall, there were no noticeable differences between the two groups or the different doses of cimetidine⁵.

The Primrose et al. study was a multicenter prospective randomized, double-anonymized trial involving 222 patients. Of these, 110 were given a placebo, while the remaining 112 received ranitidine 150 mg twice daily. The participants either underwent surgery or were considered inoperable. The media survival of the treatment group was 331 days compared to 187 days in the control group. There was no significant improvement in the survival rate of patients³³.

Wotherspoon et al. conducted a prospective, randomized, double-anonymized, placebo-controlled trial involving 159 patients. All of them underwent laparotomy for gastric cancer. Patients were either in the placebo group(n=80) or the treatment group(n=79). The treatment group received ranitidine 150 mg/cont IV at op and peri-op, then 150 mg for 2 yrs. Log-rank survival analysis was conducted. Patients were similar in

age, sex, weight, site of the tumor, and type of surgery in both groups. The median survival was 280 days in the ranitidine group compared to 344 days in the control group. This study showed no noticeable effects of H2RAs³⁴.

Tonnensen et al. performed a randomized, double-anonymized study involving 181 patients. Patients were either post-op or inoperable. Eighty-two patients were given cimetidine (400 mg twice daily for two years or until death), and 72 patients received a placebo. The median survival of the cimetidine group was 450 days compared to 316 days in the placebo group. The relative survival rates (cimetidine/placebo) were 45%/28% at 1 year, 22%/13% at 2 years, 13%/7% at 3 years, 9%/3% at 4 years, and 2%/0% at 5 years³⁵.

Of these four studies, two used ranitidine, which resulted in no significant difference^{33,34}. The other two studies that used cimetidine have opposite results^{5,35,36}, which the number of participants could explain. Again, these studies were done nearly twenty years ago.

Conducting this meta-analysis had some limitations. We only used three databases, which may have resulted in missing some relevant research. The sample size of some selected studies was small, which can render the actual effects of H2RAs on gastric and colorectal cancers. The timing, dosage, and duration of treatment were so vast that estimating optimum usage would be impossible.

Exciting data on cost-benefit and well-tolerated drugs like H2RAs can provide a valuable basis for their future use as an effective adjuvant treatment for colorectal and gastric cancer. This potential has been largely overlooked.

Clinical Relevance of Findings in Colorectal Cancer: Clinically, the observed survival benefit of cimetidine in colorectal cancer patients is particularly compelling in perioperative contexts. As colorectal surgery often induces transient immunosuppression, the immunomodulatory effects of cimetidine, such as enhancement of TILs and suppression of histamine-mediated T-cell inhibition, could mitigate postoperative recurrence risks. For surgical oncologists and multidisciplinary cancer teams, this suggests that perioperative cimetidine could be a simple, adjunctive intervention that leverages immune support without added toxicity or cost burden.

Implications for Oncology Practice in Low-Resource Settings: From a translational perspective, histamine H2 receptor antagonists offer a unique opportunity to

enhance oncologic care in low-resource or LMIC settings. Unlike biologics or immune checkpoint inhibitors, H2RAs like cimetidine are inexpensive, widely available, and orally administered. If validated in modern RCTs, these drugs could be rapidly integrated into existing chemotherapy protocols, particularly in hospitals where immunotherapy access remains limited.

Personalized Oncology: Stratifying Beneficiaries: The variability in outcomes across cancer types and between cimetidine and ranitidine underscores the need for patient stratification. Integrating biomarkers such as MSI status, TIL density, or sialyl Lewis antigen expression could help identify patients most likely to benefit. This aligns with the growing emphasis in oncology on tailoring treatment based on tumor microenvironment and molecular profile.

Bridging to Current Immunotherapy Paradigms: Notably, the immunostimulatory mechanisms of cimetidine may synergize with current immune checkpoint inhibitors. There is potential for H2RAs to augment anti-tumor immunity by preserving TIL function and modulating dendritic cell activation. These features warrant exploration in combination regimens, potentially enhancing response rates in otherwise non-responding microsatellite-stable tumors.

Future Directions and Clinical Implications: The findings of this meta-analysis support the potential repurposing of histamine H2 receptor antagonists, particularly cimetidine, as adjuvant agents in gastrointestinal oncology, especially for colorectal cancer. Given their affordability, safety profile, and widespread clinical use for non-oncologic indications, H2RAs represent an accessible therapeutic candidate for immunomodulatory support in cancer treatment.

However, critical gaps remain. Future clinical trials should be designed to:

Clarify optimal dosing regimens, timing (perioperative vs. postoperative), and duration of therapy;

Differentiate drug-specific effects between cimetidine and other H2RAs such as ranitidine or famotidine;

Stratify patient populations by tumor histology, microsatellite instability status, and immune infiltration profiles;

Incorporate immune biomarkers and tumor microenvironment analysis to elucidate mechanistic pathways, including effects on TIL density and E-

selectin expression.

Clinically, if validated in contemporary randomized trials, cimetidine could serve as a low-cost adjunct to immunotherapy or chemotherapy, particularly in settings with limited access to advanced biologics. These insights also open avenues for investigating other non-oncology drugs with potential immunologic or anti-metastatic properties, reinforcing the value of drug repurposing in precision oncology.

Conclusion

This meta-analysis provides evidence that histamine H2 receptor antagonists, particularly cimetidine, may offer a survival benefit in patients with gastrointestinal cancers, most notably those with colorectal malignancies. The pooled data indicate a statistically significant reduction in mortality, especially when cimetidine is used in the perioperative or adjuvant setting. While heterogeneity across studies exists, the consistency of benefit in colorectal cancer and the favorable safety profile of H2RAs warrant further clinical investigation. Future randomized trials with standardized dosing protocols and stratification by cancer subtype are essential to validate these findings and to clarify the therapeutic role of H2RAs in modern oncologic care.

Acknowledgment

None.

Conflict of Interest

The authors further declare that they have conflict of interest.

Funding

None.

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