Review Article

Relationship between Gut Microbiota and Gastric Cancer: A Systematic Review of Updated Evidence

Abdullah S. Alyami[1], Ghannam M. Sharif[2], Dhafer H. Alkhudhrah[3], Ammar A. Almakrami[4], Abdullah A. Almakrami[3], Abdulaziz N. Asiri[3], Khalid H. Al Agail[3], Awadh S. Alsaiari[3], Zayed A. Alghaythan[3], Sarah A. Alali [5], Fahad K. Al-Anezi[6]

[1]Consultant-internal medicine, King Khalid Hospital, Najran, KSA. [2]Internal medicine resident, King Khalid Hospital, Najran, KSA. [3]Medical Intern, College of Medicine, Najran University, KSA. [4]Medical Student, Najran University, KSA. [5]Hospital medicine fellow, King Abdulaziz Medical City MNGHA, Riyadh, KSA. [6]Eastern Health Cluster – Internship Training and Supervision Program, KSA.

ABSTRACT

Gastric cancer (GC) is an aggressive malignancy driven by genetics, environment, and microbes. Beyond H. pylori, the gut microbiota contributes via dysbiosis, inflammation, and metabolic changes. This review aims to synthesize evidence on gut microbiota–GC associations, microbial alterations, mechanisms, and clinical applications. A systematic review (PRISMA 2020) of PubMed, Scopus, Web of Science, Embase, and Cochrane was conducted for human and experimental studies using 16S rRNA sequencing, metagenomics, metabolomics, or genetic instrumental-variable data. Quality was assessed with the NOS, MR, or SYRCLE tools. GC patients show reduced alpha diversity and distinct beta diversity. Enriched taxa include Enterobacteriaceae, Streptococcus, Lactobacillus, Escherichia-Shigella, and Roseburia; depleted are Bifidobacterium, Bacteroides, and Faecalibacterium. Metabolomic shifts feature elevated glycylproline and reduced SCFAs. Mendelian randomization links GC to immune cells (NKT %T) and inflammatory proteins (CXCL1). Diagnostic models reach AUC 0.81–0.86. Microbiota-targeted therapies (probiotics, FMT) show promise. Metabolite indole-3-propionic acid promotes lymph node metastasis via AHR/CYP1A1-VEGFR3 signaling. Gut dysbiosis is strongly tied to GC via inflammation, immune modulation, and metabolic disruption. Microbial signatures hold potential as non-invasive biomarkers for early detection and monitoring. Microbiota interventions are promising adjuncts to standard care. Future work needs multi-ethnic cohorts, standardized methods, and interventional trials to enable precision oncology applications.

Keyword: Gastric cancer; Gut microbiota; Gastric microbiota; Dysbiosis; Helicobacter pylori; Microbial diversity; Carcinogenesis.

Introduction

Gastric cancer (GC) remains one of the most lethal malignancies and a leading cause of cancer mortality; despite diagnostic and therapeutic advances, advanced-stage prognosis remains poor [1]. GC develops through the multistep Correa cascade—chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and adenocarcinoma—driven by host genetics, environmental exposures, diet, and microbial factors [2]. The stomach was long considered sterile because of its acidity, but this was overturned by Helicobacter pylori (H. pylori), a Gram-negative gastric colonizer designated a group I carcinogen by WHO [3].

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Address for correspondence: Ghannam Mohammed Sharif, Internal medicine resident, King Khalid Hospital, Najran, KSA.
E-mail: ghannamsh94@gmail.com

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H. pylori is now recognized as the dominant microbial contributor to GC, accounting for an estimated 75% of global cases; it induces precancerous atrophy and intestinal metaplasia, with gastric microenvironmental alterations contributing to malignant transformation [4]. Metagenomics and high-throughput sequencing show that the stomach harbors a diverse, dynamic microbial ecosystem. The gut microbiota comprises trillions of bacteria, archaea, fungi, and viruses [5] and performs essential functions, including short-chain fatty acid production, vitamin synthesis, immune stimulation, nutrient absorption, and detoxification; its composition is individualized by genetics, age, diet, lifestyle, and environment [6]. Microbiota also contributes to homeostasis and diseases such as obesity, diabetes, allergy, and cancer. In GC, gut and gastric dysbiosis may promote tumor initiation, progression, and immune evasion [7], including decreased alpha diversity, bacterial overgrowth, and reduced abundance/homogeneity; H. pylori infection reduces gastric bacterial richness and evenness, and eradication restores some but not all diversity [8]. H. pylori interacts with commensals and strongly affects gastric microbiota. Clinical data show differences between H. pylori-positive subjects who progress to GC and those with gastritis, indicating that overall gastric microbiota contributes to cancer risk with H. pylori [9]. Diversity and abundance of taxa that modulate the tumor microenvironment are also associated with GC progression and immunotherapy success [7]. Mechanisms are multifaceted: chronic inflammation is modulated by microbes; bacteria can produce genotoxins causing DNA damage and impaired repair, activate abnormal signaling, and increase tumor hypoxia [4]; other mechanisms include altered short-chain fatty acids, raised bile acids, mucus barrier disruption, and increased N-nitrosamines and lactic acid. Microbiota also regulate immune responses, metabolic pathways, and direct interactions with tumor cells, with dysbiosis and systemic inflammation contributing to malignant transformation [8]. Clinically, anticancer therapies alter microbiota, which can change drug bioavailability and metabolism, affecting efficacy and side effects; increased Lactobacilli correlate with improved anti-PD-1/PD-L1 outcomes and longer PFS [2]. Antibiotic-induced dysbiosis reduces 5-fluorouracil efficacy, while probiotics and targeted microbiome modulation are emerging. Dietary changes, probiotics, synbiotics, prebiotics, and fecal microbiota transplantation are potential adjuncts to conventional cancer treatment [9]. This systematic review synthesizes updated evidence on gut microbiota and GC and characterizes consistent microbiota alterations associated with GC.

Methods

This systematic review was conducted and reported per PRISMA 2020 guidelines [10]. The review question used the PECO framework: Population (gastric cancer patients, human-derived datasets, or validated animal models), Exposure (gut microbiota composition, dysbiosis, or genetically predicted microbiota), Comparison (healthy controls, non-cancer gastric pathologies, different cancer stages, or control conditions), and Outcomes (microbial diversity, taxonomic profiles, functional pathways, metabolites, diagnostic performance, and clinical associations). Because eligible evidence was heterogeneous—cross-sectional studies, prospective cohorts, Mendelian randomization (MR), bioinformatic/metagenomic investigations, animal experiments, and a clinical trial—methods captured human observational and complementary mechanistic/genetic evidence. Search Strategy: We searched PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library for publications from 2021 to 2026, combining MeSH terms and free-text keywords for gut microbiota (“gut microbiota,” “gastrointestinal microbiome,” “intestinal flora,” “dysbiosis,” “16S rRNA sequencing,” “metagenomics,” “metabolomics”) and gastric cancer (“gastric cancer,” “gastric carcinoma,” “stomach neoplasms”) with Boolean operators. Reference lists of eligible studies and relevant reviews were hand-screened. Study Selection: Records were imported into Rayyan QCRI (https://www.rayyan.ai/) for duplicate removal and initial screening. Two independent reviewers screened titles/abstracts against eligibility criteria; disagreements were resolved by discussion or a third reviewer. Potentially eligible records underwent full-text assessment, with exclusion reasons documented. The workflow is summarized in the PRISMA flow diagram (Figure 1). Eligibility Criteria: Studies were eligible if they: (1) presented original research; (2) investigated gut microbiota in relation to gastric cancer; (3) included confirmed human gastric cancer for clinical/observational studies, human GWAS summary statistics for MR, human-derived metagenomic datasets for bioinformatic studies, or validated animal models for mechanistic experiments; (4) compared gastric cancer patients with healthy controls, non-cancer gastric pathologies, different cancer stages, or relevant controls; (5) provided

primary microbiome data from 16S rRNA sequencing, metagenomics, metabolomics, or genetic instrumental-variable data; (6) were published in English between 2021 and 2026; and (7) for human observational/clinical studies, included ≥5 participants per group (no minimum for MR, bioinformatic, or animal studies). Exclusions were: reviews/editorials/case reports/conference abstracts; studies of gastric microbiota only without gut/fecal samples; clinical therapeutic intervention studies lacking baseline microbiota–cancer data; insufficient data; overlapping populations; other gastrointestinal cancers without gastric cancer subgroup analysis; non-English publications; and publications outside the date range. Data Extraction: Two reviewers independently extracted data using a standardized form pilot-tested on three studies; discrepancies were resolved by consensus or a third reviewer. Data included bibliographic details, location, design, sample size, demographics, specimen type, clinical characteristics, microbiome methods, diversity indices, taxonomic composition, relative abundances with p-values, functional pathways, metabolites, clinical correlations, effect sizes, and diagnostic metrics (AUC, sensitivity, specificity). For MR, instrumental variables, sensitivity analyses, and pleiotropy assessments were extracted; for animal experiments, species, model, intervention, and outcomes; for bioinformatic studies, database source, pipeline, and validation approach. Quality Assessment: Two reviewers independently appraised quality using design-appropriate instruments: adapted Newcastle–Ottawa Scale (NOS) for cross-sectional studies (maximum 10 stars; 7–10 low risk, 5–6 moderate, ≤4 high), standard NOS for cohorts (maximum 9 stars), a specialized MR checklist (relevance, independence, exclusion restriction, non-genetic confounders, population heterogeneity), SYRCLE for animal experiments, modified NOS for bioinformatic studies, and Cochrane Risk of Bias 2 for clinical trials where applicable. Disagreements were resolved by consensus. Data Synthesis: Given heterogeneity in designs, populations, specimens, and outcomes, a narrative synthesis followed Cochrane Non-Randomised Studies Methods Group guidance. Findings were organized into: (1) microbial diversity (alpha and beta); (2) taxonomic composition; (3) functional pathways and metabolites; and (4) clinical applications (biomarkers, diagnostics, therapeutics). Microbial enrichment/depletion patterns were identified across studies; MR causal estimates (odds ratios, mediation proportions) and diagnostic performance metrics (AUC) were summarized descriptively. Subgroup analyses by H. pylori status, histological subtype, cancer stage, and geographic region were planned but constrained by data availability. Reporting followed the PRISMA 2020 checklist [10].

Results

Study Selection: (Figure 1) shows that a systematic search across databases and registers initially retrieved 320 records. Following duplicate removal, 172 records were excluded, leaving 148 for title and abstract screening. Of these, 86 records were discarded based on eligibility criteria. Among the 62 reports sought for full-text retrieval, 32 were unobtainable, resulting in 30 reports undergoing full-text eligibility assessment. At this stage, 7 reports were excluded for the following reasons: incorrect outcomes (n=3), inappropriate population (n=2), and abstract-only publications (n=2). Ultimately, 23 studies satisfied all inclusion criteria and were incorporated into the final systematic review. Study Characteristics: (Table 1) provides a comprehensive overview of the demographic and methodological characteristics of the 23 included studies. The evidence base initially triangulates cross-sectional stool-based human observations from Finland [11] and India [12] with a public-SRA bioinformatic/metagenomic analysis [13] and a European GWAS-based Mendelian randomization (MR) investigation [14]. It subsequently extends to a Chinese prospective cohort across the gastric precancerous cascade [15] and a multi-cohort MR causal analysis [16], followed by a SIRI-stratified cohort [17], a clinical trial of chemotherapy-induced cachexia [18], and an integrated MR–pilot cohort evaluating sdLDL-mediated effects [19]. A Chinese cross-sectional fecal study [20] precedes three mechanistically oriented animal/in vitro investigations of modified Gexia-Zhuyu Tang with FMT [21], ShenXia KuanZhong Decoction with molecular docking and dynamics simulations [22], and high-capsaicin/TRPV1/FMT modulation [23]. Subsequent cross-sectional human analyses from China [24] and Japan [25] are followed by an MR analysis incorporating immune cell traits [26], a diagnostic model development/validation study [27], a treatment-naïve HPBC/GC assessment [28], an MR analysis incorporating inflammatory proteins [29], and a prospective longitudinal pre-/post-gastrectomy study [30]. The table concludes with high-altitude Chinese metabolomic and 16S rDNA investigations [31], [32] and a final cross-sectional analysis of lymph node metastasis [33]. Microbial Diversity: Findings

regarding alpha diversity were inconsistent across studies. Several studies reported significantly lower diversity in gastric cancer patients compared to healthy controls [15, 24], while others found no significant difference [11, 30]. Notably, Sarhadi et al. [11] reported lower alpha diversity that did not reach statistical significance. In contrast, Chen and Chen [27] paradoxically observed increased microbial richness (Chao1 index, $P < 0.05$) in gastric cancer patients. Miao et al. [15] demonstrated reduced diversity across four groups (superficial gastritis, atrophic gastritis, gastric mucosal atypical hyperplasia, and gastric cancer), while Yang et al. [24] reported significantly decreased diversity, particularly at the G3 atrophy stage. Matoba et al. [25] found higher diversity in healthy individuals compared to advanced gastric cancer patients. In contrast to alpha diversity, beta diversity analyses consistently demonstrated significant compositional differences between cancer patients and controls across multiple studies [11, 13, 24, 27, 28, 33]. Sarhadi et al. [11] reported significant compositional differences between gastric cancer subtypes and controls. Nath and Natarajan [13] found significant sex-based beta diversity differences among gastric cancer, gastritis, and healthy groups. Yang et al. [24] observed compositional shifts along the Correa sequence using LEfSe analysis. Chen and Chen [27] demonstrated distinct compositions via PCoA. Daly et al. [28] reported significant compositional differences between hepato-pancreatico-biliary/gastric cancer patients and controls. Wang M et al. [33] found drastically different compositions between gastric cancer patients with and without lymph node metastasis. Taxonomic Composition: Regarding specific taxa, several genera were repeatedly found to be increased in gastric cancer patients, including Enterobacteriaceae [11], Streptococcus [18, 25, 27, 28], Lactobacillus [25, 28], Escherichia-Shigella [17, 30], and Roseburia [14, 16, 20]. Conversely, genera such as Bifidobacterium [12, 25], Bacteroides [12, 24, 28], and Faecalibacterium [24, 28] were consistently decreased. However, important exceptions and context-dependent findings warrant consideration. Zhang J et al. [16] reported that Enterobacteriaceae (family) exhibited a protective role, contrary to other studies. Wu J et al. [18] found that Bacteroides, Streptococcus, and Prevotella were increased in the specific context of chemotherapy-induced cachexia, alongside Enterotoxigenic Bacteroides fragilis (ETBF), which drives cachexia through intestinal mucosal barrier disruption and M1 macrophage recruitment. Li S et al. [32] identified Prevotella_9, Streptococcus, and Lactobacillus as differential taxa in plateau-area gastric cancer patients, with directions that varied by metabolite correlations. Devi et al. [12] reported that Dialister was increased and Bifidobacterium spp. were extremely low in H. pylori-positive patients with aggressive gastric diseases. Additional taxa identified as enriched in gastric cancer included Akkermansia, Gammaproteobacteria, and Veillonella, with Desulfobacteriota and Synergistota reported for the first time in gastric cancer by Nath and Natarajan [13]. Miao et al. [15] identified Scardovia and Halomonas as new genera associated with gastric cancer. Yang et al. [24] found Actinobacteria (phylum), Peptostreptococcaceae, and Lachnoclostridium enriched, while Matoba et al. [25] identified Odoribacter as enriched. Zou et al. [17] reported Escherichia-Shigella enrichment alongside elevated N-acetylcadaverine and epsilon-caprolactam. Regarding post-surgical changes, He et al. [30] found that after gastrectomy, Campylobacter, Actinobacteria (phylum), and Bacillota were increased, while Bacteroidota, Synergistota, Verrucomicrobia, Bacteroides, Faecalibacterium, and Blautia were decreased, with significant structural changes but no overall diversity change. Functional Pathways and Metabolites: Metabolomic analyses revealed distinct profiles in cancer patients. Elevated metabolites included glycylproline [31, 32], glycine [31], hydroxyisocaproic acid [31], and indole-3-propionic acid (3-IPA) [33], alongside decreased metabolites such as short-chain fatty acids (SCFAs) [24], cytidine [31], 5'-methylthioadenosine [31], and trehalose [31]. Zhu et al. [31] additionally reported positive correlation with serum albumin and negative correlations with HDL, LDL, and AFP. Li S et al. [32] identified Proteobacteria (phylum) enrichment alongside desulfo-biotin, glycylproline, tyramine, and betaine in plateau-area patients. Functional pathway analyses highlighted enriched butanoate and pyruvate metabolism in healthy individuals, whereas cancer patients showed enrichment in pathways related to ABC transporters and ribosomes [25]. Miao et al. [15] reported enrichment in genetic information processing and circulatory system pathways. Matoba et al. [25] demonstrated that functional pathway clustering clearly classified patients from healthy individuals better than flora-based clustering. Several MR studies established causal relationships between specific taxa and gastric cancer risk [14, 16, 19, 26, 29]. Chang et al. [14] identified Roseburia and Eubacterium brachy group as risk taxa, with Clostridium sensu stricto 1,

Actinomycetales, Selenomonadales, Negativicutes, and Rikenellaceae as protective. Zhang J et al. [16] identified Prevotella 7, Roseburia, Ruminococcaceae UCG014, Ruminococcaceae UCG004/UCG009, and Enterobacteriales as risk taxa, with Enterobacteriaceae (family), Allisonella, and Lachnospiraceae FCS020 as protective. Wang C et al. [26] identified one risk taxon and two risk bacterial pathways, with four protective taxa and five protective pathways. Mediation analyses identified immune cells (particularly NKT %T cells) [26], inflammatory proteins such as C-X-C motif chemokine 1 (CXCL1) [29], and metabolites like sdLDL [19] as potential mediators. Yu et al. [29] found that Ruminococcaceae UCG014 mediates gastric cancer risk through downregulation of CXCL1, with a mediation ratio of 7.79%. Wang C et al. [26] demonstrated that immune cells, particularly NKT %T cells, mediate the genetic effect of gut microbiota on gastric cancer. Ji et al. [19] delineated a partial causal pathway from gut microbiota to gastric cancer mediated through sdLDL, accounting for 4.31% of the total effect. Wang M et al. [33] furnished robust mechanistic evidence indicating that gut microbiota-derived indole-3-propionic acid (3-IPA) facilitates lymph node metastasis in gastric cancer via the AHR/CYP1A1-VEGFR3 signaling cascade, establishing a direct mechanistic connection between a specific microbial metabolite and malignant progression. Clinical Applications: Diagnostic and Prognostic Biomarkers: Several studies proposed novel biomarkers. Nath and Natarajan [13] identified Akkermansia, Gammaproteobacteria, and Veillonella as potential noninvasive biomarkers, while also identifying Desulfobacteriota and Synergistota for the first time in gastric cancer. Chen and Chen [27] developed a random forest classifier utilizing 20 diagnostically relevant genera, achieving an AUC of 0.81, which improved to 0.86 when integrated with conventional tumor biomarkers. Yang et al. [24] reported that Actinobacteria achieved an AUC of 0.935 for discriminating gastric cancer. Wu J et al. [18] constructed a random forest model based on the six most abundant genera to predict chemotherapy-associated gastric cancer cachexia, attaining an AUC of 93.5% with specificity and accuracy exceeding 75%. Wang M et al. [33] identified 3-IPA as a prognostic biomarker for lymph node metastasis in gastric cancer. Zhu et al. [31] and Li S et al. [32] identified plateau-specific microbe-metabolite associations with potential biomarker utility. Zou et al. [17] proposed SIRI-associated microbial and metabolic features as non-invasive risk markers. Daly et al. [28] demonstrated that increases in pathogens and decreases in beneficial bacteria support early biomarker potential. Therapeutic Implications: Therapeutic strategies targeting the gut microbiota are increasingly recognized as promising adjuncts to conventional gastric cancer treatments. Zhao and Yu [21] demonstrated that modified Gexia-Zhuyu Tang suppressed gastric cancer tumor growth and induced pyroptosis through modulation of the gut microbiota, a finding corroborated by fecal microbiota transplantation (FMT) assays. Zhou et al. [22] showed that ShenXia KuanZhong Decoction alleviated gastric cancer by modulating gut microbial communities—including Lactobacillus plantarum and Akkermansia muciniphila—and suppressing TNF signaling. Deng et al. [23] demonstrated that high capsaicin intake promotes gastric cancer metastasis through upregulation of TRPV1 expression and concomitant shifts in gut microbial communities—notably increased Firmicutes and Clostridiales—leading to elevated peripheral 5-hydroxytryptamine (5-HT) levels. Regarding chemotherapy interactions, Wu J et al. [18] identified ETBF as a pivotal driver of chemotherapy-induced cachexia through disruption of the intestinal mucosal barrier and recruitment of M1 macrophages. He et al. [30] demonstrated that surgery significantly alters microbial structure but not overall diversity, with increases in Campylobacter, Actinobacteria, and Bacillota, and decreases in Bacteroidota, Synergistota, Verrucomicrobia, Bacteroides, Faecalibacterium, and Blautia. (Table 3) presents the risk-of-bias assessment for all 23 included studies, conducted using design-appropriate tools.

Discussion

Our findings confirm consistent gut microbial dysbiosis in GC, though signatures vary by population, stage, and treatment. Reduced alpha diversity was reported in GC, especially diffuse adenocarcinoma and advanced stages [11,15,24], aligning with Zhang et al. [34], who found lower Shannon index in GC. Progressive diversity decline along the Correa sequence [24] suggests loss of microbial complexity may be early; Miao et al. [15] identified atrophy (G3) as a metabolic breakpoint, consistent with evidence that dysbiosis disrupts homeostasis and fuels chronic inflammation [8]. Heterogeneity in alpha diversity—no difference [11,30] or increased richness [27]—reflects confounders such as H. pylori, antibiotics, diet, and geography; Wu et al. [35] similarly noted context-dependent diversity changes. Beta diversity consistently showed compositional differences between GC and controls [11,13,24,27,28,33],

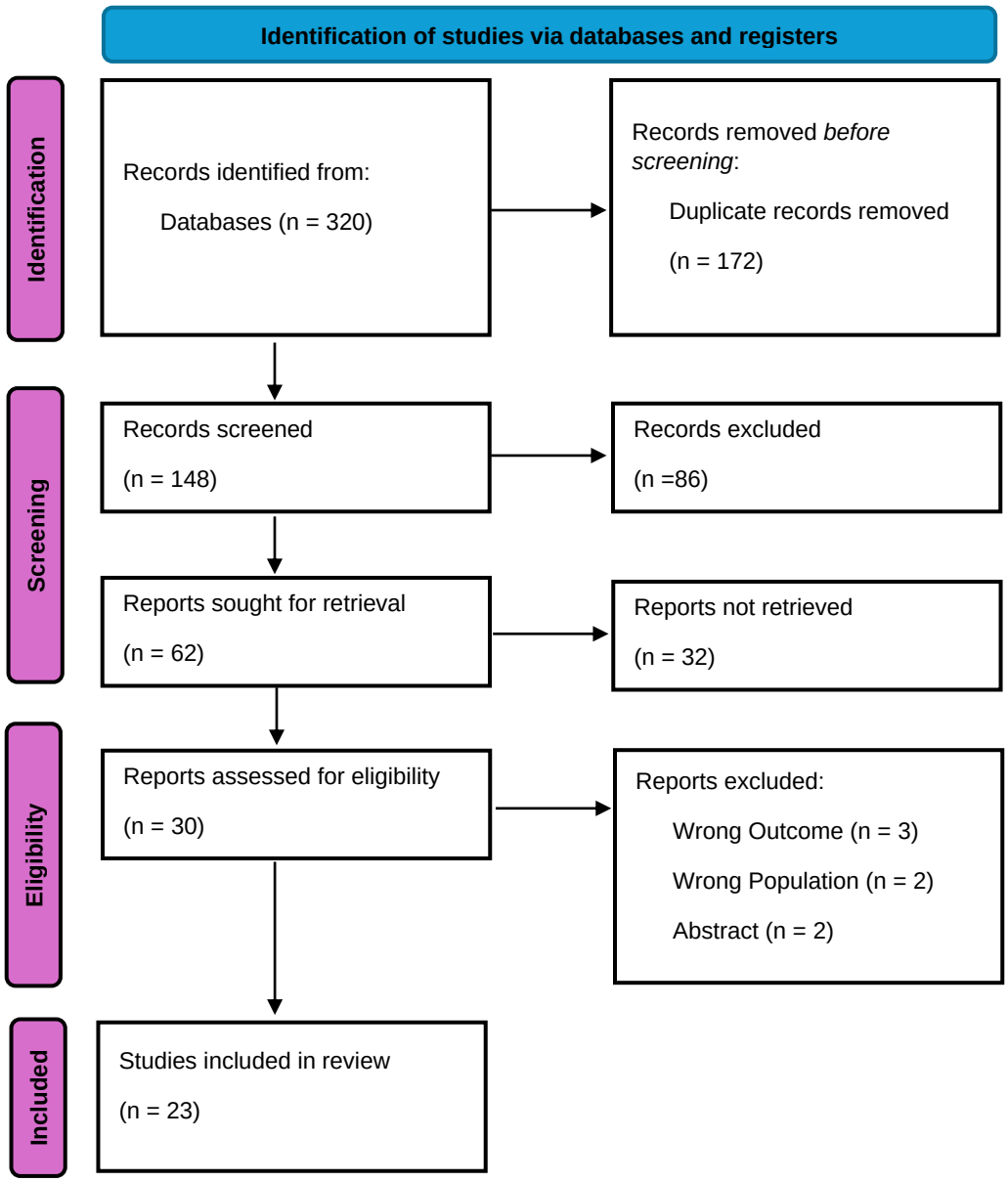

Figure 1: PRISMA 2020 Flow Diagram of Study Selection Process.

Table 1: Characteristics of Included Studies.

Study (Author, Year [Ref.])	Location	Study Design	Sample Size (GC / Total)	Sample Type	Key Clinical Features / Stratification
Sarhadi et al., 2021 [11]	Finland	Cross-sectional	NR / (GC subtypes + GIST + controls)	Stool	Histological subtypes (diffuse, intestinal) & GIST
Devi et al., 2021 [12]	India (Trivandrum)	Cross-sectional	NR / 375 (H. pylori+ & H. pylori−)	Stool (lower gut)	H. pylori infection status & virulence genes (vacAs1i1m1cagA+)
Nath & Natarajan, 2024 [13]	Public database (SRA)	Bioinformatic / Metagenomic	NR / (GC, gastritis, healthy)	Fecal	Sex-based diversity comparison
Chang et al., 2024 [14]	European (GWAS)	Mendelian Randomization	476,116 (GC GWAS) / 8,956 (Microbiome GWAS)	Genetic data (IVs)	GWAS summary statistics from MiBioGen & GC datasets
Miao et al., 2022/2024 [15]	China	Prospective cohort	15 advanced GC / 51	Feces	Histological stages: SG, AG, GMAH, GC
Zhang J et al., 2024 [16]	Multi-cohort (GWAS)	Mendelian Randomization	NR	Genetic data	Causal association from summary statistics
Zou et al., 2025 [17]	China	Cohort	276 (high SIRI) + 219 (low SIRI) / 495	Stool (45 patients for omics)	Stratified by Systemic Inflammation Response Index (SIRI) threshold 2.6
Wu J et al., 2024 [18]	China	Clinical trial (ChiCTR2200064547)	NR	Stool	Chemotherapy-induced cachexia development
Ji et al., 2026 [19]	Multi-cohort (GWAS) + Pilot	MR + Pilot cohort	5/group (pilot)	Fecal (pilot)	Mediation analysis via metabolite met-c-926 (sdLDL)
Chen C et al., 2022 [20]	China	Cross-sectional	157 GC / 314	Fecal	Surgery, chemotherapy, lymph node metastasis, Ki67/HER2 expression
Zhao & Yu, 2024 [21]	China	Animal experiment (In vivo)	Mouse xenograft (MFC cell line)	Fecal (mouse)	Modified GZT low/high dose treatment & FMT assay
Zhou et al., 2025 [22]	China	Animal experiment + In vitro	Mouse model / AGS cells	Fecal (mouse)	SXKZD treatment, molecular docking, MD simulations
Deng et al., 2023 [23]	China	Animal experiment + In vitro	Xenograft mouse & zebrafish models	Fecal (mouse)	High capsaicin diet, TRPV1 expression, FMT
Yang J et al., 2026 [24]	China	Cross-sectional	NR / (5 groups: G1 normal, G2 gastritis, G3	Fecal & gastric tissue	Correa sequence (CS) stages

			atrophy, G4 erosion, G5 GC)		
Matoba et al., 2026 [25]	Japan	Cross-sectional	475 advanced GC / 581 (106 healthy controls)	Stool	Advanced GC, prior gastrectomy (55.5%), relapse (37%)
Wang C et al., 2024 [26]	European (GWAS)	Mendelian Randomization	NR	Genetic data	Mediation analysis via 731 immune cell traits
Chen C & Chen C, 2025 [27]	China	Cross-sectional / Diagnostic	153 GC / 455 (100 HC, 43 non-neoplastic, 159 validation)	Fecal	Non-invasive diagnostic model building & validation
Daly et al., 2026 [28]	Europe (inferred)	Cross-sectional	37 HPBC/GC / 84 (47 age-matched controls)	Stool	Treatment-naïve, newly diagnosed patients
Yu C et al., 2026 [29]	European (GWAS)	Mendelian Randomization	NR	Genetic data	Mediation analysis via 91 inflammatory proteins
He et al., 2024 [30]	China	Prospective longitudinal	60 GC / 60 (120 specimens)	Fecal	Pre- and post-gastrectomy (during hospitalization)
Zhu et al., 2025 [31]	China (Qinghai, high-altitude)	Cross-sectional	30 GC / 60 (30 healthy controls)	Stool + Serum	High-altitude residents; serum proteins, lipids, AFP
Li S et al., 2026 [32]	China (Qinghai, high-altitude)	Cross-sectional	30 GC / 60 (30 healthy controls)	Fecal	High-altitude; 16S rDNA + untargeted metabolomics
Wang M et al., 2026 [33]	China	Cross-sectional	NR / (GC with LN metastasis vs. without)	Fecal	Lymph node metastasis (GC-LM vs. GC-non-LM)

NR: Not reported; GC: Gastric Cancer; GIST: Gastrointestinal Stromal Tumor; MR: Mendelian Randomization; FMT: Fecal Microbiota Transplantation; SIRI: Systemic Inflammation Response Index; SG: Superficial Gastritis; AG: Atrophic Gastritis; GMAH: Gastric Mucosal Atypical Hyperplasia; HPBC: Hepato-Pancreatico-Biliary Cancer; IVs: Instrumental Variables; LN: Lymph Node; HC: Healthy Control; AFP: Alpha-Fetoprotein.

Table 2: Microbiome, Metabolite, and Functional Findings (Outcomes & Mechanisms).

Study (Author, Year [Ref.])	**Alpha Diversity (GC vs. Control)**	**Beta Diversity (GC vs. Control)**	**Increased Taxa / Metabolites in GC**	**Decreased Taxa / Metabolites in GC**	**Functional Pathways / Mediators**	**Key Findings & Biomarkers**
Sarhadi et al., 2021 [11]	Lower (non-significant)	Significant differences in composition	Enterobacteriaceae (both adenocarcinoma subtypes)	Bifidobacteriaceae (diffuse); Oscillibacter (intestinal)	NR	Higher Enterobacteriaceae abundance as marker for all gastric malignancies
Devi et al., 2021 [12]	NR	NR	Dialister (in H. pylori+ group)	Bifidobacterium spp. (in H. pylori+ group)	NR	Extremely low Bifidobacterium linked to

						aggressive H. pylori-related diseases
Nath & Nataraj an, 2024 [13]	Significant (GC/gastritis/h ealthy; male vs. female)	Significan t (sex-based)	Akkermansia, Gammaproteoba cteria, Veillonella; Desulfobacteriot a, Synergistota (first report)	NR	Metageno mic prediction (KEGG correlation)	First-time reporting of Desulfobacter iota & Synergistota in GC
Chang et al., 2024 [14]	MR (genetic causal inference)	MR (genetic causal inference)	Risk: Roseburia, Eubacterium brachy group	Protective: Clostridium sensu stricto 1, Actinomycetales, Selenomonadales, Negativicutes, Rikenellaceae	Causal (MR-IVW)	Genetically confirmed protective vs. risk taxa
Miao et al., 2022/2 024 [15]	Reduced among four groups	Altered communit y dissimilari ty	Scardovia, Halomonas (new genera associated with GC)	NR	Genetic informatio n processing; Circulatory system	Stage-specific microbial compositional changes from SG to advanced GC
Zhang J et al., 2024 [16]	MR (no direct)	MR (no direct)	Risk: Prevotella 7, Roseburia, Ruminococcace ae UCG014, Ruminococcace ae UCG004/UCG0 09, Enterobacteriale s	Protective: Enterobacteriaceae (family), Allisonella, Lachnospiraceae FCS020	Causal (MR-IVW)	Enterobacteri aceae shows protective role (contrary to other studies)
Zou et al., 2025 [17]	NR	NR	Escherichia-Shigella; N-Acetylcadaverin e, Epsilon-caprolactam	Blautia, Klebsiella; S-(PGA2)-glutathione	Multi-omics integrative correlation	SIRI-associated microbial/met abolic features as non-invasive risk markers
Wu J et al., 2024 [18]	Decreased (post-chemotherapy)	NR	Bacteroides, Streptococcus, Prevotella; Enterotoxigenic B. fragilis (ETBF)	NR	Intestinal mucosal barrier via M1 macrophag e attraction	ETBF drives cachexia; RF prediction model (AUC 93.5%)
Ji et al., 2026 [19]	Pilot cohort (non-significant stability)	Pilot cohort (divergent shifts)	14 taxa significantly associated (specifics NR)	14 taxa significantly associated (specifics NR)	Mediation via sdLDL (met-c-926) accounting for 4.31%	Ruminococcu s subgroup shifts; genetically anchored evidence chain
Chen C et al.,	NR	NR	Surgery-group: Enterococcus,	NR	Correlation with Ki67	Blautia, Ruminococcu

2022 [20]			Megasphaera, Corynebacterium, Roseburia, Lachnospira		& HER2 expression	s, Oscillospira (Ki67); Prevotella, Lachnospira, Eubacterium, Desulfovibrio (HER2)
Zhao & Yu, 2024 [21]	Increased species abundance & diversity (GZT-treated)	NR	NR	NR	Pyroptosis (NLRP3, ASC, caspase-1 dependent); TNF-α, IL-1β, IL-18	Modified GZT promotes pyroptosis via gut microbiota modulation (confirmed by FMT)
Zhou et al., 2025 [22]	NR	NR	Lactobacillus plantarum, Akkermansia muciniphila (modulated by SXKZD)	NR	TNF & IL-17 signaling pathways	Ginsenoside Rh2 & 3-Indolepropionic acid bind TNF; enhances anti-tumor immunity
Deng et al., 2023 [23]	NR	NR	Firmicutes (phylum), Clostridiales (order); peripheral 5-hydroxytryptamine (5-HT)	NR	TRPV1 channel elevation	High capsaicin promotes metastasis via gut microbiota shift & 5-HT increase
Yang J et al., 2026 [24]	Decreased significantly (especially at G3 atrophy)	Compositional shifts (LEfSe)	Actinobacteria (phylum), Peptostreptococcaceae, Lachnoclostridium	Bacteroides, Faecalibacterium; SCFAs	Metabolic reprogramming (amino acid, lipid)	Atrophy (G3) is the metabolic "breakpoint"; Actinobacteria AUC 0.935
Matoba et al., 2026 [25]	Higher diversity in healthy individuals	Cluster analysis (pathway-based better than flora-based)	Streptococcus, Lactobacillus, Odoribacter	Bifidobacterium, Anaerostipes, Parabacteroides	Butanoate & pyruvate (healthy); ABC transporters & ribosomes (GC)	Functional pathway clustering clearly classifies patients from healthy
Wang C et al., 2024 [26]	MR (no direct)	MR (no direct)	1 taxon (risk); 2 bacterial pathways (risk)	4 taxa (protective); 5 bacterial pathways (protective)	Mediation via NKT %T cell (immune cells)	Immune cells mediate the genetic effect of GM on GC
Chen C & Chen C,	Increased richness (Chao1 index, $P<0.05$)	Distinct composition (PCoA)	31 GC-enriched genera (e.g., Streptococcus)	19 HC-enriched genera (e.g., Bacteroides)	Diagnostic modeling (Random Forest)	RF model AUC 0.81; combined with tumor

2025 [27]						biomarkers AUC 0.86
Daly et al., 2026 [28]	Trend towards decreased diversity with stage	Significant compositional differences	Enterococcus, Enterobacter, Streptococcus, Lactobacillus	Lachnospiraceae, Ruminococcaceae_UCG014, Bacteroides, Faecalibacterium	Predictive functional profiling (PICRUSt)	Increase in pathogens & decrease in beneficial bacteria supports early biomarker potential
Yu C et al., 2026 [29]	MR (no direct)	MR (no direct)	3 genera (increased risk)	8 genera (protective role)	Mediation via C-X-C motif chemokine 1 (CXCL1) downregulation (7.79%)	Ruminococcaceae UCG014 mediates GC risk through inflammatory protein CXCL1
He et al., 2024 [30]	No significance change (post-surgery)	Significant structural change (post-surgery)	Post-op: Campylobacter, Actinobacteria (phylum), Bacillota; Campylobacter, Porphyromonas (genus)	Post-op: Bacteroidota, Synergistota, Verrucomicrobia; Bacteroides, Faecalibacterium, Blautia	NR	Surgery significantly alters microbial structure but not overall diversity
Zhu et al., 2025 [31]	NR	NR	Metabolites: glycylproline, glycine, hydroxyisocaproic acid	Metabolites: cytidine, 5'-methylthioadenosine, trehalose	Microbiota-metabolism-serum axis	Positive correlation with serum albumin; negative with HDL, LDL, AFP
Li S et al., 2026 [32]	Significant difference ($P<0.001$)	NR	Proteobacteria (phylum); desulfo-biotin, glycylproline, tyramine, betaine	Prevotella_9, Streptococcus, Lactobacillus (differential)	Multi-omics correlation ($P<0.05$)	Plateau-specific microbe-metabolite associations provide potential biomarkers
Wang M et al., 2026 [33]	NR	Drastically different (GC-LM vs. non-LM)	Indole-3-propionic acid (3-IPA) in feces of GC-LM	NR	AHR/CYP1A1-VEGFR3 signaling axis	3-IPA promotes lymph node metastasis via AHR pathway; serves as prognostic biomarker

NR: Not reported; NS: Non-Significant; RF: Random Forest; AUC: Area Under the Curve; SCFAs: Short-Chain Fatty Acids; ETBF: Enterotoxigenic Bacteroides fragilis; 5-HT: 5-Hydroxytryptamine; 3-IPA: Indole-3-Propionic Acid; AHR: Aryl Hydrocarbon Receptor; LM: Lymph Node Metastasis; HC: Healthy Control; PCoA: Principal Coordinates Analysis; LEfSe: Linear Discriminant Analysis Effect Size; PICRUSt: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States;

KEGG: Kyoto Encyclopedia of Genes and Genomes; IVW: Inverse Variance Weighted; MR: Mendelian Randomization; GZT: Gexia-Zhuyu Tang; SXKZD: ShenXia KuanZhong Decoction; AFP: Alpha-Fetoprotein.

Table 3: Risk of Bias Assessment of Included Studies.

Study (Ref.)	**Study Design**	**Assessment Tool**	**Selection Bias**	**Comparability / Confounding**	**Outcome / Assumptions**	**Overall Risk of Bias**
Sarhadi et al. [11]	Cross-sectional	NOS (Cross)	3/5	1/2	2/3	Moderate
Devi et al. [12]	Cross-sectional	NOS (Cross)	3/5	1/2	2/3	Moderate
Nath & Natarajan [13]	Bioinformatic / Metagenomic	Modified NOS	3/5	1/2	2/3	Moderate
Chang et al. [14]	Mendelian Randomization	MR Checklist	Low	Low	Low (Sensitivity robust)	**Low**
Miao et al. [15]	Prospective Cohort	NOS (Cohort)	3/4	1/2	2/3	Moderate
Zhang J et al. [16]	Mendelian Randomization	MR Checklist	Low	Low	Low (Sensitivity robust)	**Low**
Zou et al. [17]	Cohort (SIRI-based)	NOS (Cohort)	3/4	2/2	2/3	Moderate
Wu J et al. [18]	Prospective Cohort / Clinical Trial	NOS (Cohort)	3/4	1/2	2/3	Moderate
Ji et al. [19]	Mendelian Randomization + Pilot	MR Checklist	Low	Low	Low (Sensitivity robust)	**Low**
Chen C et al. [20]	Cross-sectional	NOS (Cross)	4/5	2/2	2/3	**Low**
Zhao & Yu [21]	Animal Experiment (In vivo)	SYRCLE	Unclear	Unclear	Unclear	Unclear
Zhou et al. [22]	Animal Experiment (In vivo)	SYRCLE	Unclear	Unclear	Unclear	Unclear

Deng et al. [23]	Animal Experiment (In vivo)	SYRCLE	Unclear	Unclear	Unclear	Unclear
Yang J et al. [24]	Cross-sectional	NOS (Cross)	4/5	2/2	3/3	**Low**
Matoba et al. [25]	Cross-sectional	NOS (Cross)	4/5	1/2	2/3	Moderate
Wang C et al. [26]	Mendelian Randomization	MR Checklist	Low	Low	Low (Sensitivity robust)	**Low**
Chen C & Chen C [27]	Cross-sectional (Diagnostic)	NOS (Cross)	4/5	2/2	3/3	**Low**
Daly et al. [28]	Cross-sectional	NOS (Cross)	3/5	1/2	2/3	Moderate
Yu C et al. [29]	Mendelian Randomization	MR Checklist	Low	Low	Low (Sensitivity robust)	**Low**
He et al. [30]	Prospective Longitudinal	NOS (Cohort)	3/4	1/2	2/3	Moderate
Zhu et al. [31]	Cross-sectional	NOS (Cross)	3/5	1/2	2/3	Moderate
Li S et al. [32]	Cross-sectional	NOS (Cross)	3/5	1/2	2/3	Moderate
Wang M et al. [33]	Cross-sectional	NOS (Cross)	3/5	2/2	2/3	Moderate

NOS (Cross-sectional): maximum 10 stars — 5 selection, 2 comparability, 3 outcome. 7–10 = low; 5–6 = moderate; ≤4 = high. NOS (Cohort): maximum 9 stars — 4 selection, 2 comparability, 3 outcome. 7–9 = low; 5–6 = moderate; ≤4 = high. **MR Checklist:** addresses relevance, independence, exclusion restriction, non-genetic confounders, and population heterogeneity. "Low (sensitivity robust)" = all three instrumental-variable assumptions met and sensitivity/pleiotropy analyses supported the estimate. **SYRCLE:** covers selection, performance, detection, attrition, and reporting biases. "Unclear" = insufficient reporting to permit a definitive judgment. **Modified NOS:** adapted for database-derived bioinformatic analyses. **Abbreviations:** NOS, Newcastle–Ottawa Scale; MR, Mendelian randomization; SYRCLE, Systematic Review Centre for Laboratory Animal Experimentation; SIRI, Systemic Inflammation Response Index.

indicating disrupted community structure even when richness is unchanged. Recurring taxa were enriched (Enterobacteriaceae [11,16], Streptococcus [18,25,27,28], Lactobacillus [25,28], Escherichia-Shigella [17,30], Roseburia [14,16,20]) or depleted (Bifidobacterium [12,25], Bacteroides [12,24,28], Faecalibacterium [24,28]). Enterobacteriaceae enrichment across tumor types [11] is notable because it includes opportunistic pathogens promoting inflammation/genotoxicity. Bifidobacterium depletion [12,25], especially B. adolescentis and B. longum in aggressive disease [12], suggests a protective role in homeostasis/immune surveillance. Depletion of butyrate producers such as Faecalibacterium and Oscillibacter [11,24,28] is concerning given SCFA anti-inflammatory/anticancer properties [36]. Mechanisms are multifactorial: chronic inflammation, immune modulation, genotoxic metabolites, and barrier disruption. MR studies consistently show causal links between taxa and GC risk [14,16,19,26,29]. Ruminococcaceae UCG014 may increase risk via CXCL1 downregulation (7.79% mediation) [29]; immune cells, especially NKT %T cells, mediate microbiota effects [26]. Metabolites contribute: sdLDL mediated 4.31% of the effect [19], and microbiota-derived indole-3-propionic acid (3-IPA) promotes lymph node metastasis via AHR/CYP1A1-VEGFR3 [33], positioning 3-IPA as a prognostic/therapeutic candidate. Gastric microbiota-driven immune remodeling involving Streptococcus, Lactobacillus, and Bacteroides affects CD8+ T cells, macrophages, dendritic cells, and Tregs [37]. Diet also matters: high capsaicin promoted metastasis via TRPV1 and microbial shifts (Firmicutes, Clostridiales) with elevated 5-HT [23], consistent with microbiome–inflammation–nutrition interactions in GI malignancies [38]. Microbiota show translational promise as non-invasive biomarkers. A 20-genera random forest classifier achieved AUC 0.81, rising to 0.86 with conventional biomarkers [27], supporting augmentation of early detection. AI/ML review found Random Forest most common (44.4%), with AUCs 0.88–0.97 but external validation in only 33.3% [39], highlighting validation needs. A six-genera model predicted chemotherapy-associated cachexia (AUC 93.5%; specificity/accuracy >75%), with ETBF driving cachexia via mucosal barrier disruption and M1 macrophages [18]. Preoperative microbiota, especially Escherichia shigella, predicted postoperative delirium in elderly GC patients (AUC 0.75) [40]. Therapeutic targeting is promising. Modified Gexia-Zhuyu Tang suppressed tumor growth and induced pyroptosis via microbiota modulation, corroborated by FMT [21]. ShenXia KuanZhong Decoction alleviated GC by modulating Lactobacillus plantarum and Akkermansia muciniphila and suppressing TNF signaling [22]. Microbiome-guided precision oncology review examined interactions with surgery, chemotherapy, radiotherapy, immunotherapy, and viroimmunotherapy, and microbiota-targeted interventions (probiotics, prebiotics, FMT, metabolites) [41]. Limitations: heterogeneity across 23 studies (design, sample size, methods) limits definitive conclusions; MR provides genetic causal evidence while observational studies are confounded by H. pylori and diet, inconsistently controlled. Demographic reporting, especially age/sex, was inconsistent, precluding pooled comparison; East Asian predominance limits generalizability. Cross-sectional designs prevent temporal inference; animal studies carry risk of bias; one bioinformatic study relied on limited datasets, limiting confounder adjustment; publication bias may favor significant findings.

Conclusion

Gut dysbiosis is strongly associated with GC, with enriched Enterobacteriaceae, Streptococcus, and Lactobacillus and depleted Bifidobacterium, Bacteroides, and Faecalibacterium. Mechanisms include inflammation, immune modulation, and barrier disruption, with causal links from MR. Microbiota signatures are promising non-invasive biomarkers with high diagnostic accuracy. Microbiota-targeted therapies (probiotics, FMT) require validation. Future research should use multi-ethnic cohorts, standardized protocols, and rigorous trials for precision oncology.

Conflict of Interest

None

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None

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