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Efficacy and Safety of CAR-T Cell Therapy in Advanced Gastrointestinal Tumors: A Systematic Review and Hierarchical Bayesian Meta-Analysis

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Abstract

Background: CAR-T cell therapy has shown transformative efficacy in hematologic malignancies, but its role in gastrointestinal solid tumors remains under investigation.

Methods: Systematic review and meta-analysis of randomized and non-randomized clinical trials (PROSPERO: CRD42024629247). Searches were conducted in PubMed, Embase, LILACS, and Web of Science through November 2024. A Bayesian hierarchical binomial–logit model was used to pool proportions. Primary outcome was Objective Response Rate (ORR); secondary outcomes included cytokine release syndrome (CRS), ICANS, and grade ≥3 adverse events.

Results: Thirty-nine studies comprising 658 participants were included. The global pooled ORR was 13.2% (95% CrI: 6.1%–21.8%), with substantial heterogeneity. GCC+CD19 (ORR 31.8%) and CLDN18.2 (ORR 21.8%) were the most promising targets. Any-grade CRS occurred in 40.8% of patients, with a 3.0% absolute risk of grade ≥3 events. Most studies presented serious or critical risk of bias and small sample sizes.

Conclusions: CAR-T therapy shows initial effectiveness in gastrointestinal cancers, particularly for CLDN18.2 and GCC+CD19 targets. Well-powered controlled phase 2/3 trials are strongly needed.

Clinical Trial Registration: PROSPERO CRD42024629247.

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy consists of autologous T lymphocytes genetically modified to express a synthetic receptor capable of recognizing tumor-associated surface antigens, thereby promoting the elimination of malignant cells independently of MHC class[1]. The CAR receptor is structured into four main domains: the antigen-binding domain (scFv), the hinge region, the transmembrane domain, and the intracellular signaling and co-stimulatory domains, such as CD3ζ, CD28, and 4-1BB[2]. The generations of CAR-T cells have evolved structurally. First-generation CAR-T cells include only the CD3ζ signaling domain. Second-generation constructs incorporate a co-stimulatory domain (CD28 or 4-1BB) to enhance expansion and persistence. Third-generation CARs combine two co-stimulatory domains, while fourth-generation CAR-T cells, known as “armored CAR-T” or TRUCKs, include genes encoding cytokines or immunomodulatory proteins to overcome hostile tumor microenvironments[3].

Currently, clinical application is well established in hematologic malignancies, such as B-cell acute lymphoblastic leukemia, large B-cell lymphomas, and multiple myeloma, with six products approved by the FDA in the United States[5].The main therapeutic targets are CD19 for B-cell leukemias and lymphomas, and B-cell maturation antigen (BCMA) for multiple myeloma[6]. In patients with relapsed or refractory disease, complete remission rates are high: the ZUMA-1 study (axicabtagene ciloleucel) reported a 54% complete remission rate, the JULIET study (tisagenlecleucel) reported 39%, and the

CARTITUDE-1 study (ciltacabtagene autoleucel) reported 80% in multiple myeloma[7]. The clinical protocol begins with leukapheresis, followed by genetic modification, cellular expansion, and intravenous infusion[9]. Prior lymphodepleting chemotherapy, typically fludarabine (30 mg/m²/day) and cyclophosphamide (250–500 mg/m²/day) for two to three days, is essential to reduce endogenous lymphocytes, minimize anti-CAR immune responses, and enhance CAR-T cell expansion and persistence[10].

The main associated toxicities are cytokine release syndrome (CRS), characterized by fever, hypotension, and coagulopathy, and managed with tocilizumab and corticosteroids, and immune effector cell-associated neurotoxicity syndrome (ICANS), which presents with reversible neurological symptoms and is managed primarily with corticosteroids[12]. For solid tumors, targets such as mesothelin, EGFR, and HER2 are under investigation but have not yet achieved clinical approval. This is due to challenges such as antigen heterogeneity, which increases the risk of on-target/off-tumor toxicity, and physical barriers such as dense stroma and extracellular matrix that impair cellular infiltration[14]. In the gastrointestinal tract, tumors such as pancreatic adenocarcinoma exhibit an immunosuppressive tumor microenvironment (TME), characterized by hypoxia, acidic pH, suppressive cell populations (MDSCs and Tregs), and inhibitory cytokines such as TGF-β[16] Next-generation strategies to overcome these barriers include armored CAR-T cells that secrete cytokines (e.g., IL-12, IL-18), logic-gated CAR systems, and combination therapies with checkpoint inhibitors such as anti-PD-1 to enhance persistence and tumor infiltration[17, 18]. Although several narrative reviews have addressed CAR-T therapy in solid tumors broadly, no systematic review with meta-analysis has specifically synthesized the available evidence for gastrointestinal malignancies. Given the rapid expansion of early-phase trials investigating novel antigenic targets and next-generation CAR constructs in this setting, a quantitative synthesis is warranted. Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy and safety of CAR-T cell therapy in adults with gastrointestinal solid tumors (Population: adults with confirmed gastrointestinal cancers; Intervention: CAR-T cell therapy targeting any tumor-associated antigen; Comparator: no comparator required, or treatment of physician's choice when present; Outcomes: objective response rate as the primary endpoint, and cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and other grade ≥ 3 adverse events as secondary safety outcomes).

Methods

Protocol and Reporting Standards

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. The study protocol was prospectively registered in the PROSPERO database under the identifier CRD42024629247.

Search Strategy and Databases

A systematic search was performed across the PubMed, Embase, LILACS, and Web of Science electronic databases. The primary search was executed on November 9, 2024, without restrictions regarding language or publication date. The search strategy was developed with the assistance of a research librarian and utilized the following terms across Title/Abstract, Medical Subject Headings (MeSH), and Publication Type fields: ((Digestive System Neoplasms OR Biliary Tract OR Gastrointestinal OR Esophageal OR Intestinal OR Stomach OR liver OR Hepatic OR Pancreatic OR Peritoneal) AND (neoplasm OR cancer) AND (Immunotherapy, Adoptive OR Chimeric Antigen Receptor Therapy) AND (randomized controlled trial OR controlled clinical trial) NOT (animals NOT humans). Identification of additional studies was further supplemented through citation searching. Full search strategies for all databases are provided in Supplementary Material.

Eligibility Criteria

Population: The review included studies involving adults (≥ 18 years) with confirmed diagnoses of gastrointestinal solid tumors, specifically involving the esophagus, stomach, liver, pancreas, gallbladder, small intestine, colon, and rectum. Intervention: Eligible interventions comprised chimeric antigen receptor T (CAR-T) cell therapies targeting tumor-associated antigens, regardless of the specific CAR construct or transfection method utilized. Study Design: Both randomized and non-randomized clinical trials were eligible for inclusion, while case reports, cohort studies, and reviews were excluded.

Outcomes

Although the study protocol originally pre-specified comparative measures of effect, such as relative risks (RR), odds ratios (OR), and hazard ratios (HR) for survival outcomes, the absence of included studies utilizing control groups or comparators precluded the use of these original metrics. Consequently, a single-arm meta-analysis of proportions was performed to synthesize clinical activity. Overall Response Rate (ORR) was designated as the primary outcome for quantitative analysis because it was the most consistently reported endpoint across the included trials.

Study Selection

The study selection process followed a structured PRISMA workflow. A total of 1,206 records were identified through database searches, with an additional 9 records identified via citation searching. Following the removal of 98 duplicate records, 1,108 reports were screened. Ultimately, 15 published studies and 26 reports met the eligibility criteria and were included in the final review.

Data Extraction

Data were extracted independently by two pairs of reviewers (H.D.P, H.C, D.S, G.S). Disagreements during the screening and extraction phases were resolved through discussion between the reviewers; if

consensus was not achieved, an independent reviewer (R.V.P.) made the final decision. The Rayyan software was utilized for the study selection process. Extracted data points included study design, participant characteristics, intervention details, and all pre-specified clinical outcomes.

Risk of Bias Assessment

Methodological quality was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials and the ROBINS-I tool for non-randomized studies. The assessment covered seven specific domains: bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. Risk levels were categorized as low, moderate, serious, critical, or no information, as visualized in the summary and traffic light plots. Risk of bias assessments were conducted independently by two reviewers (H.D.P, R.D.P).

Statistical Analysis

A Bayesian hierarchical binomial–logit generalized linear mixed model was used to estimate pooled response proportions while accounting for anticipated clinical and methodological heterogeneity across studies. Analyses were conducted in R using the brms package with the Stan (rstan interface). The model specified a binomial likelihood with a logit link, allowing direct modeling of event counts and inclusion of zero-event studies without continuity corrections.

For the primary efficacy analysis, the hierarchical structure included random intercepts for both study and antigen molecular target, enabling multi-level variance decomposition and partial pooling. This approach produced shrinkage estimates, improving stability for targets supported by limited data. Weakly informative priors were prespecified to regularize estimation: a Normal (0, 2.5) prior for the intercept and half-Student-t (3, 0, 1) priors for variance parameters.

Posterior inference was performed using Markov Chain Monte Carlo (MCMC) sampling with four chains of 5,000 iterations each, including 1,500 warmup iterations (14,000 post-warmup samples). Sampling was parallelized across four cores with a fixed random seed (123). To improve sampling efficiency, adapt_delta was set to 0.97 and max_treedepth to 12. Convergence was assessed using the Gelman–Rubin statistic ($\hat{R} < 1.01$), trace plots, and effective sample sizes, and model adequacy was evaluated through posterior predictive checks.

Results are reported as posterior means transformed to the probability scale using the inverse-logit function, with uncertainty summarized by 95% Bayesian credible intervals (CrI). Between-target heterogeneity was quantified using the intraclass correlation coefficient (ICC). Target-specific pooled response proportions were estimated within the hierarchical framework, and 95% Bayesian prediction intervals (PI) were calculated to reflect the expected range of true effects in future studies. Model fit and predictive performance were assessed using leave-one-out cross-validation with Pareto k diagnostics,

and leave-one-study-out analyses were conducted to evaluate the influence of individual studies. Posterior ranking probabilities were calculated to estimate the likelihood that each antigen target achieved the highest response, along with probabilities of exceeding clinically relevant thresholds (10%, 20%, and 30%).

To evaluate safety outcomes, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and grade ≥ 3 adverse events, we performed Bayesian single-arm meta-analyses of proportions using the same binomial–logit framework. The models incorporated random intercepts by study to account for between-study heterogeneity. For the global intercept, a weakly informative Normal(0, 2.5) prior was specified. Heterogeneity parameters (τ) were regularized using half-Student-t(3, 0, 1) priors for standard analyses, while Exponential(1) priors were used for the nested toxicity models to ensure stable estimation of conditional risks. Posterior estimation was conducted using MCMC with four chains of 4,000 iterations (1,000–2,000 warmup iterations), and convergence was assessed using $\hat{R}$ and trace plots.

For CRS and ICANS, a nested Bayesian model was implemented to jointly estimate the probability of any-grade events and the conditional probability of grade ≥ 3 toxicity, allowing derivation of absolute risks from the joint posterior distribution.

For comparison, frequentist random-effects meta-analyses were conducted using generalized linear mixed models with logit transformation and Hartung–Knapp adjustments via the meta package. In this framework, heterogeneity was quantified using I^2 and τ^2. Frequentist results are presented alongside Bayesian estimates for contextual comparison.

All analyses were conducted in R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Frequentist meta-analyses were implemented using metafor (4.8-0) and meta (8.2-1), employing random-effects models with restricted maximum likelihood estimation on the logit scale. Bayesian hierarchical modeling was performed using brms (2.23.0) with a Stan backend, with posterior inference conducted using posterior (1.6.1), tidybayes (3.0.7), and loo (2.9.0). Visualization was performed using ggplot2 (4.0.2), complemented by ggdist (3.3.3), ggridges (0.5.7), ggrepel (0.9.7), and scales (1.4.0).

Sensitivity Analysis

Sensitivity analyses were conducted to evaluate the robustness of the primary Bayesian findings and the impact of individual studies on the pooled estimates. A frequentist random-effects meta-analysis was performed using restricted maximum likelihood and a generalized linear mixed model with logit-transformed proportions to provide a non-Bayesian methodological comparator. The robustness of the Bayesian framework was further examined through a comprehensive prior sensitivity analysis, testing a range of alternative distributions for the global intercept and alternative priors for heterogeneity (τ). Finally, a leave-one-out influence analysis was executed by iteratively refitting the model with one study removed to quantify the delta change in the pooled mean and the between-study standard deviation.

Publication bias / small-study effects

Publication bias and small-study effects were evaluated for the objective response rate (ORR) outcome. Potential asymmetry was initially investigated via visual inspection of a funnel plot. Statistical evaluation for funnel plot asymmetry was conducted using the Egger regression test (utilizing the standard error as a predictor) and the Begg rank correlation test. To adjust the pooled estimates for potential bias, the trim-and-fill method by Duval & Tweedie was applied. Additionally, precision-based meta-regressions were implemented: the PET (Precision Effect Test) using the standard error as a moderator and the PEESE (Precision Effect Estimate with SE) using the variance. A Bayesian small-study model was also implemented using the brms package to estimate a bias-adjusted pooled proportion. This model incorporated the inverse square root of the sample size as a predictor to estimate the adjusted pooled ORR at the limit of an infinite sample size.

Results

Study Selection

The systematic search identified a total of 1,206 records through database searching and 9 additional records through citation searching. After the removal of 98 duplicate records, 1,108 reports were screened. Following title and abstract screening, 1,074 records were excluded. A total of 41 reports (32 from databases and 9 from citations) were assessed for eligibility. Three reports were excluded (one in-vitro study, one trial protocol, and one with overlapping data), resulting in the inclusion of 38 reports in the final review (Figure Ia). While the systematic review identified 38 reports that met the clinical inclusion criteria for gastrointestinal malignancies, the quantitative meta-analysis was restricted to 24 reports that provided the complete numerical data required for Bayesian hierarchical modeling. The remaining 14 reports, which lacked specific primary or secondary outcome metrics such as objective response counts or granular safety data, were retained for qualitative synthesis and discussion only.

Study Characteristics

A total of 39 studies were included, comprising 658 participants (Table I). Study designs included randomized controlled trials, non-randomized trials, and pilot studies conducted between 2015 and 2024 in China, the United States, South Korea, Belgium, Japan, the United Kingdom, and Singapore. The studies predominantly enrolled patients with advanced or metastatic gastrointestinal malignancies refractory to multiple prior lines of systemic therapy, including hepatocellular carcinoma, colorectal cancer, gastric and gastroesophageal junction adenocarcinoma, pancreatic adenocarcinoma, biliary tract cancers, esophageal cancer, and neuroendocrine tumors. Sample sizes ranged from 2 to 156 participants. Interventions included chimeric antigen receptor T-cell therapy targeting GPC3, CLDN18.2, CEA, GCC, mesothelin, NKG2D, EGFR, HER2, CD133, TAG-72, PSCA, CDH17, MAGE-A4, KRAS G12V, and HBsAg. Technological modifications included armored CAR constructs (e.g., IL-18, RUNX3, IL-7/XCL1 expression), logic-gated/Tmod systems designed to mitigate off-tumor toxicity, and CoupledCAR platforms intended to enhance expansion and persistence. Most studies were early-phase (Phase I or

I/II), single-arm, open-label studies without a comparator; when present, comparators included treatment of physician's choice.

Risk of Bias Assessment

Methodological quality was assessed using the ROBINS-I tool for non-randomized studies (Supplementary Fig I and Figure Ib). The overall risk of bias was predominantly judged as serious or critical. Regarding specific domains, nearly all studies exhibited serious or critical risk bias due to confounding (D1). Bias in the selection of participants (D2) was mostly moderate or low, while bias in the classification of interventions (D3) was consistently low. Bias due to deviations from intended interventions (D4) and bias due to missing data (D5) showed a mix of low, moderate, and serious risks. Bias in the measurement of outcomes (D6) was largely moderate, and bias in the selection of the reported result (D7) ranged from low to serious.

Primary Bayesian Hierarchical Meta-analysis

The primary Bayesian hierarchical binomial–logit model estimated a global pooled Objective Response Rate (ORR) of 0.132 (95% CrI 0.061–0.218)(Figure IIa). Substantial between-study heterogeneity was observed, with a standard deviation of 1.27 (95% CrI 0.73–2.14), When antigen targets were included in a hierarchical model, the between-target standard deviation (σ target) of 1.13 (95% CrI 0.18–2.45) and a residual between-study standard deviation (τ) of 0.843 (95% CrI 0.347–1.744). The intraclass correlation coefficient (ICC) was 0.26 (95% CrI 0.006–0.603), indicating that antigen targets accounted for a modest proportion of the total variability in response rates. However, when considering only the variability modeled by the random effects, the proportion attributable to antigen targets increased to 0.66 (95% CrI 0.019–0.957).

Target-Specific Analysis and Ranking

Analysis of individual molecular targets showed varying response rates (Figure IIb). The highest pooled ORRs were observed for GCC+CD19 (0.318; 95% CrI 0.095–0.603), GCC (0.307; 95% CrI 0.058–0.734), and CLDN18.2 (0.218; 95% CrI 0.074–0.424). Conversely, lower response rates were found for CEA (0.048; 95% CrI 0.001–0.166).

The 95% prediction intervals (PI) for future studies within each target were wide, reflecting the residual heterogeneity: GCC+CD19 (0.341 95% PI 0.030–0.792), GCC (0.329 95% PI 0.020–0.836), CLDN18.2 (0.248 95% PI 0.022–0.681), and CEA (0.067 95% PI 0.001–0.356). Bayesian ranking probabilities identified GCC+CD19 and GCC as having the highest probability of being the most effective targets (P-best), followed by CLDN18.2 and HBsAg.

Probability of Exceeding Thresholds

The posterior probability that the global ORR exceeded clinically relevant thresholds was 59% for the 10% threshold, 5% for the 20% threshold, and 2% for the 30% threshold (Figure IIIa). For specific targets,

GCC+CD19, GCC, and CLDN18.2 showed the highest probabilities of exceeding the 20% ORR threshold, with values of 79%, 65% and 54%, respectively.

Sensitivity and Influence Analyses

A frequentist random-effects GLMM (REML) yielded a pooled ORR of 0.13 (95% CI 0.05–0.54), with a heterogeneity index I2 of 77.4% ($p < 0.001$), consistent with the Bayesian primary model (Supplementary Fig. 2). Substantial shrinkage toward the global mean was observed, particularly for targets with small sample sizes or extreme observed proportions. The observed proportion for GCC decreased from 57.1% to 30.8% (− 26.3 percentage points), whereas targets with zero observed responses, such as TAG-72 and Mesothelin, were assigned non-zero response probabilities (7.3%). Estimates for well-represented targets, such as CLDN18.2, showed minimal change (22.0% vs. 21.9%). Study-specific results indicated that Qi et al. (2021)[22] and Keenan et al. (2024)[23] reported the highest individual response proportions. Although a formal leave-one-out analysis was executed, the exclusion of these studies did not alter the global model's robustness. The Bayesian results for the pooled proportion and heterogeneity remained robust across a range of alternative weakly informative and informative prior distributions.

Safety and Adverse Events

The safety of CAR-T cell therapy was evaluated across five key toxicity endpoints using both Bayesian and frequentist frameworks. The primary Bayesian models provided robust estimates of pooled incidence, with results consistent with the frequentist GLMM comparators (Supplementary Fig. 3). The pooled incidence of any-grade CRS was estimated at 40.8% (95% CrI 7.7%–82.4%). Within a nested model framework (Figure IIIb), the conditional probability of developing grade ≥ 3 CRS, given the presence of any-grade CRS, was 8.0% (95% CrI 0.9%–25.5%). This resulted in a global absolute risk of grade ≥ 3 CRS of 3.0% (95% CrI 0.2%–9.5%) across the entire treated population. For neurotoxicity, the pooled incidence of any-grade ICANS was notably lower at 4.7% (95% CrI 1.0%–10.4%). While the conditional risk of severe neurotoxicity among patients experiencing any ICANS was 41.1% (95% CrI 5.4%–87.9%), the overall absolute risk for grade ≥ 3 ICANS was estimated at 1.9% (95% CrI 0.1%–5.6%). The overall incidence of grade ≥ 3 adverse events (including hematological and non-hematological toxicities) was 11.5% (95% CrI 1.0%–38.1%). Consistent with the efficacy findings, individual study estimates for safety outcomes showed varying degrees of shrinkage toward the global mean, particularly in trials with limited sample sizes or extreme observed proportions. Posterior density plots for the nested models confirmed the stability of these estimates across the sampled MCMC chains. Detailed forest plots comparing Bayesian and frequentist estimates for all safety outcomes are provided in the Supplementary Material.

Model Diagnostics

All model parameters achieved convergence, with R-hat values < 1.01. The model adequacy was confirmed via posterior predictive checks. Predictive performance metrics included an Expected Log Predictive Density (ELPD-LOO) of -45.40 and a Leave-One-Out Information Criterion (LOOIC) of 90.80.

The inclusion of tumor location as a covariate did not substantially improve the overall model fit compared to the base target-only model (ΔELPD = -2.1, SE = 1.1; ΔLOOIC = 4.18), suggesting that tumor site is not a primary driver of response variability in this dataset.

Publication bias / small-study effects

Visual inspection of the funnel plot suggested potential asymmetry, indicating possible small-study effects (Supplementary Fig. 4). This impression was partially supported by formal testing: the Egger regression test detected significant asymmetry (p = 0.004), whereas the Begg rank correlation test was not statistically significant (p = 0.10). Adjustments for small-study effects yielded a wide range of pooled estimates compared with the original REML estimate (ORR 0.20, 95% CI 0.14–0.29). The trim-and-fill method imputed seven potentially missing studies, increasing the pooled ORR to 0.26 (95% CI 0.18–0.36). Regression-based corrections produced higher estimates, with ORRs of 0.49 (95% CI 0.25–0.73) using PET and 0.36 (95% CI 0.23–0.51) using PEESE. In contrast, the Bayesian small-study model showed weaker evidence for asymmetry. The estimated slope was positive but highly uncertain (β = 0.10, 95% CrI − 0.67 to 0.78; P[β > 0] = 0.61). The corresponding bias-adjusted pooled ORR, extrapolated to an infinitely large study, was 0.115 (95% CrI 0.039–0.223) and was consistent with the primary Bayesian hierarchical estimate (0.116).

Discussion

CAR-T cells (chimeric antigen receptor T-cells) represent a revolutionary innovation in cancer immunotherapy, consisting of genetically modified T lymphocytes engineered to express chimeric receptors that recognize specific tumor antigens [5, 24, 25]. Although they have demonstrated remarkable success in hematologic malignancies, CAR-T cells are now emerging as a promising strategy for solid tumors of the gastrointestinal tract ([24, 26] [24][27]. Target antigens include CLDN18.2, CEA, GCC, HER2, and EpCAM [28, 29]. The first randomized clinical trial of CAR-T therapy in solid tumors demonstrated that CLDN18.2-targeted CAR-T cells (satri-cel) significantly improved progression-free survival in patients with advanced gastric cancer (3.25 vs. 1.77 months), with objective response rates of 48–57% [26, 24, 27]. Despite these advances, the application still faces substantial challenges, including an immunosuppressive tumor microenvironment, antigen heterogeneity, barriers to cellular infiltration, and toxicities such as cytokine release syndrome [17, 27, 30, 31, 32].

General presentation

The synthesis of the studies reveals substantial heterogeneity in the magnitude of therapeutic effect, varying according to the antigenic target and CAR-T construct technology. The most robust evidence derives from a phase 2 randomized clinical trial, which demonstrated that satri-cel (CT041), targeting Claudin-18 in patients with gastric or gastroesophageal junction adenocarcinoma, achieved an ORR of 22% (95% CI: 15–31), compared to 4% (95% CI: 0–13) in the investigator's choice group. The precision of this effect is reinforced by a 63% reduction in the risk of progression (HR 0.37; p < 0.0001) and an

improvement in overall survival (mOS 7.92 months vs. 5.49 months; HR 0.69; p = 0.0416), establishing a milestone of clinical superiority in the third-line setting.

In metastatic colorectal cancer (mCRC), the CoupledCAR platform targeting GCC + CD19 showed clinically meaningful efficacy signals, with an ORR of 80% at dose level 2 and reports of complete metabolic and pathological responses. However, these findings are derived from very small samples (n = 5 to n = 9), implying substantial imprecision. Conversely, other first-generation CAR constructs or those targeting different antigens, such as TAG-72, failed to demonstrate objective radiological responses (ORR 0%), highlighting that the absence of co-stimulatory domains, high receptor immunogenicity, and tumor escape limit cellular persistence and clinical benefit.

From a benefit–harm perspective, safety interpretation suggests a manageable toxicity profile, although not devoid of serious risks. Cytokine release syndrome (CRS) is frequent but predominantly low grade (G1/G2), as reported by Qi et al. 2025 (95% of patients) ([22, 24] and Keenan et al. 2025 (100%)[23]. However, long-term safety remains uncertain due to isolated fatal events, including one death from multiorgan failure following grade 5 CRS and another from grade 5 fungal sepsis. On-target, off-tumor toxicities specific to the affected organ - such as severe diarrhea (grade 3/4 in 47.6% in Xiao, 2023) and gastrointestinal bleeding (grade 2–3 in Feng, 2018 and Qi, 2025) - reflect physiological antigen expression (GCC and CLDN18.2) in normal gastrointestinal tissues. Therefore, continuous refinement of therapeutic platforms is imperative, aiming not only to optimize cytotoxic potency but also to develop robust strategies to mitigate immune escape mechanisms and ensure sustained clinical responses.

The results address the review question by indicating that, although CAR-T therapy in gastrointestinal solid tumors still faces critical barriers to infiltration and persistence, next-generation strategies (“armored” or logic-gated CARs) are beginning to translate biological activity into measurable progression-free survival. According to Cochrane standards, confidence in the estimates is moderate for the CLDN18.2 subgroup due to the randomized design, but remains low or inconclusive for other targets. Data comparing CAR-T directly with conventional chemotherapy for targets other than CLDN18.2 are insufficient for this analysis.

Limitations

Most studies present a Critical or Serious risk of bias, particularly in domain D1 (bias due to confounding), which is severely compromised due to the non-randomized nature of studies and lack of contemporary control groups. Additionally, domains D5 (missing data) and D7 (selective reporting) frequently lack adequate information, compromising transparency in reporting secondary outcomes and adverse events.

Statistical imprecision, driven by extremely small sample sizes, prevents the construction of narrow and reliable confidence intervals. From an evidence-based medicine perspective, the “leap of faith” required to generalize these findings is excessively large, as certainty is downgraded not only by imprecision but also by inconsistency arising from critical risks of bias in measurement domains. Some studies report

biological activity but are limited by Critical risk in D1 and Serious risk in D2, suggesting that survival outcomes may be overestimated due to intensive clinical management and selection of patients with better baseline prognosis. Overall, the limitations of current evidence downgrade most findings to low or very low certainty, with the exception of Qi et al. 2025 [24], which stands out for its lower risk of bias.

Limitations of the review process

The limitations of the systematic review process, from a statistical methodology perspective and in accordance with Cochrane guidelines, lie at the intersection between the fragility of primary data and the residual uncertainty of Bayesian estimates. The applicability of findings to clinical practice is hindered by observed statistical imprecision. This high-risk-of-bias profile directly impacts the reliability of Bayesian parameters, as statistical uncertainty is compounded by methodological uncertainty.

From a statistical standpoint, the major limitation is the magnitude of prediction intervals (PI), which are markedly wide across nearly all therapeutic targets, indicating limited knowledge of the true effect in future clinical settings and rendering the current evidence insufficient for definitive recommendations.The figure IVa analysis shows that smaller studies with lower precision undergo considerable shrinkage toward the global mean, which corrects overestimation but also highlights instability in effect estimates for sparsely studied targets.

Additionally, probability distributions in the figure Ib reveal substantial overlap across ranks, indicating that the proposed efficacy hierarchy lacks statistical stability. Systematic absence of information in key domains, such as missing data (D5) and reporting bias (D7), further limits the robustness of the Bayesian synthesis. Thus, the observed heterogeneity (I^2 = 76.2%), combined with methodological bias, reduces the certainty of evidence (GRADE), limiting conclusions to a predominantly exploratory nature for future phase 3 research.

Implications of the results

The evidence synthesized in this systematic review, from an evidence-based medicine perspective, suggests an encouraging scenario for CAR-T therapy in gastrointestinal solid tumors, with direct implications for clinical practice and health policy. Bayesian ranking analysis indicates that the GCC + CD19-targeted intervention has the highest probability of clinical success, with approximately a 28% chance of being the most effective strategy in terms of pooled ORR. This finding is supported by clinically meaningful outcomes, including pathological complete response and an ORR of 80% at higher dose levels.[23] There is also a high posterior probability that the overall ORR exceeds minimal thresholds of biological efficacy; however, this probability declines as more stringent clinical response criteria are applied.

Confidence in applicability is strengthened when therapeutic benefit is considered alongside methodological rigor. The CLDN18.2 target stands out as high-confidence evidence, as the pivotal satricel study demonstrated low risk of bias across most ROBINS-I domains. Findings from Keenan et al. 2025 [23, 24] and Qi et al. 2025 [24] provide proof of concept that barriers imposed by the solid tumor

microenvironment can be overcome. For oncologists, the immediate practical implication is the consideration of CAR-T therapy as a viable and promising option for patients with refractory gastric and colorectal cancers, provided that rigorous biomarker screening (GCC and CLDN18.2) is performed and treatment is delivered in specialized centers capable of managing specific toxicities.

From a health policy perspective, the data support the need to develop access programs that account for manufacturing feasibility, with reported success rates of 98–100% in U.S. and Chinese cohorts. For future research, efforts should focus on reducing uncertainty through well-designed phase 2/3 controlled trials, particularly for targets such as GCC and HBsAg, aiming to elevate the certainty of evidence to the level achieved for Claudin 18.2. Although effect estimates are encouraging, final clinical decisions must balance observed biological benefit against potential harms. Therefore, the future of the field lies in optimizing “armored” and logic-gated CAR technologies to expand the therapeutic window and consolidate systemic safety of these innovative therapies.

Declarations

Additional Information:

Authors' contributions

Henrique Ritter Dal-Pizzol contributed to conceptualization, formal analysis, methodology, software, visualization, and writing of the original draft. Humberto Cardoso Alves contributed to conceptualization, formal analysis, methodology, software, visualization, and writing of the original draft. Daví Enrique Salini contributed to conceptualization, formal analysis, methodology, software, visualization, and writing of the original draft. Gabriel Signori contributed to conceptualization, formal analysis, methodology, software, visualization, and writing of the original draft. Rafael Piccon contributed to conceptualization, project administration, supervision, and writing – review & editing. All authors read and approved the final manuscript.

Data availability

This systematic review was prospectively registered in PROSPERO. The data supporting the findings of this study were generated by the authors through systematic searches conducted in PubMed, Embase, LILACS, and Web of Science up to February 2026. The extracted data are publicly available in the following OSF projects:10.5281/zenodo.21919511.

Competing interests

The authors declare no competing interests.

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Table

Table 1 is available in the supplementary files section

Figures

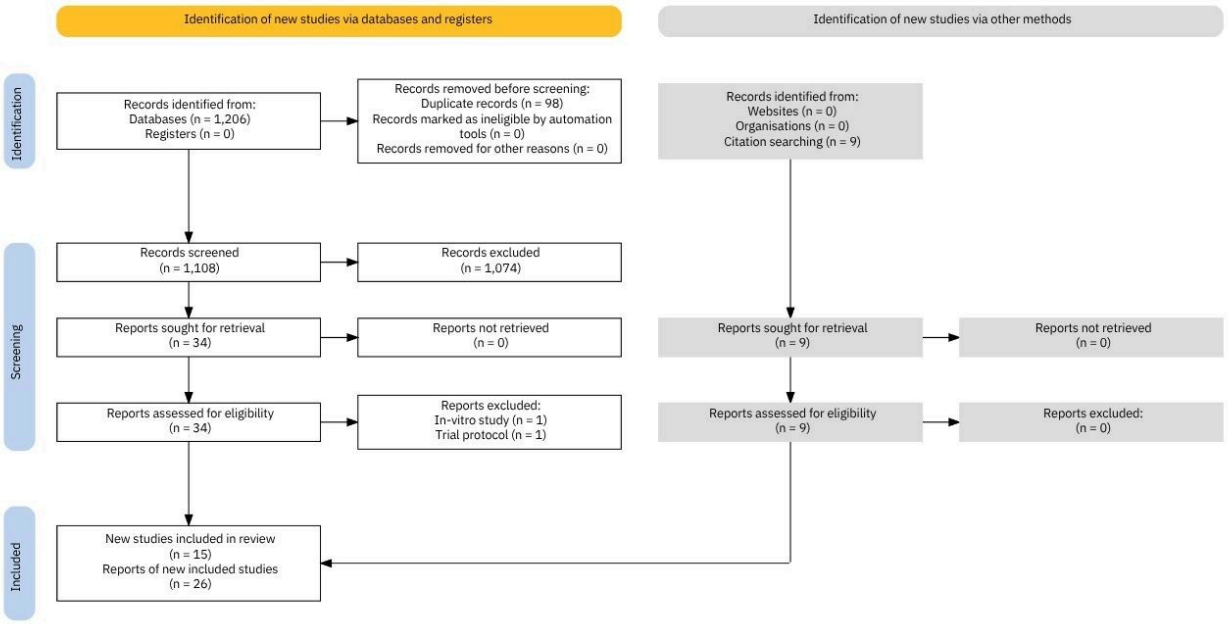


Figure Ia: PRISMA 2020 flow diagram of study identification, screening, and selection.

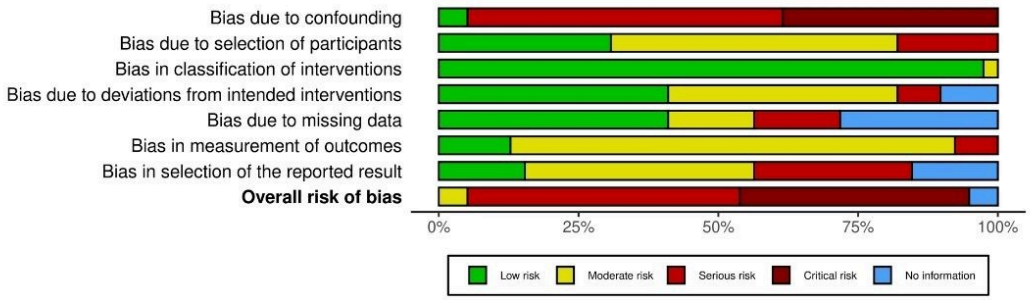


Figure Ib: Summary bar chart of risk of bias judgements across all domains and studies.

Figure 1

See image above for figure legend.

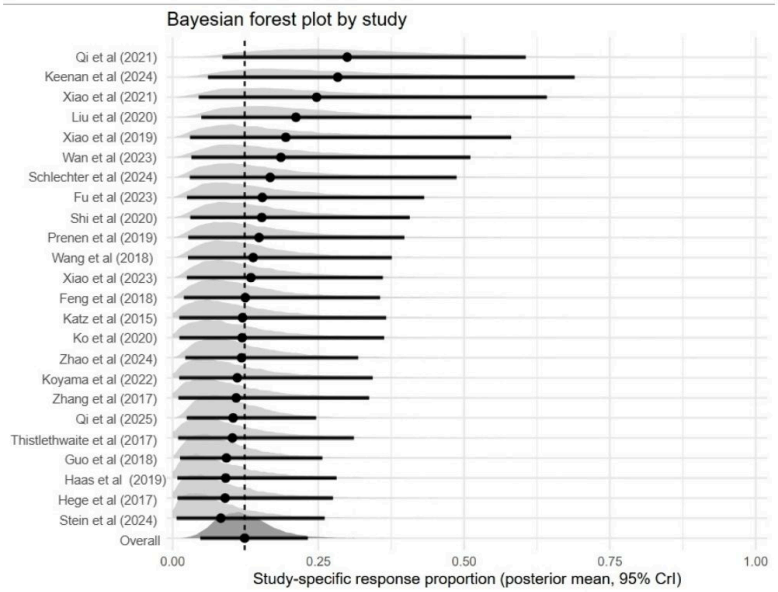


Figure IIa: Bayesian forest plot of study-specific ORR proportions (posterior mean, 95% CrI).

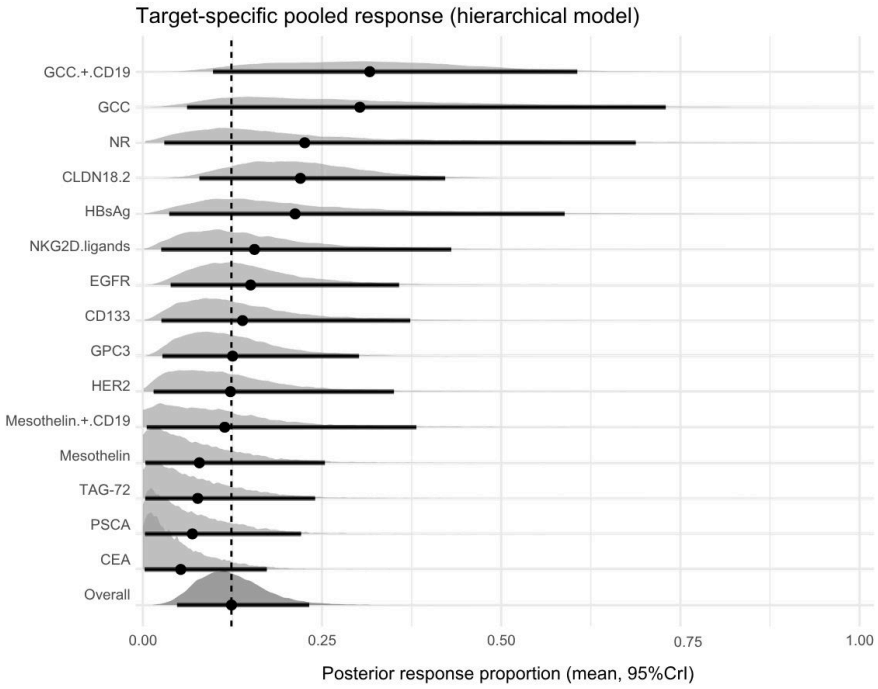


Figure IIb: Target-specific pooled ORR estimates from a Bayesian hierarchical model, by CAR-T antigen target.

Figure 2

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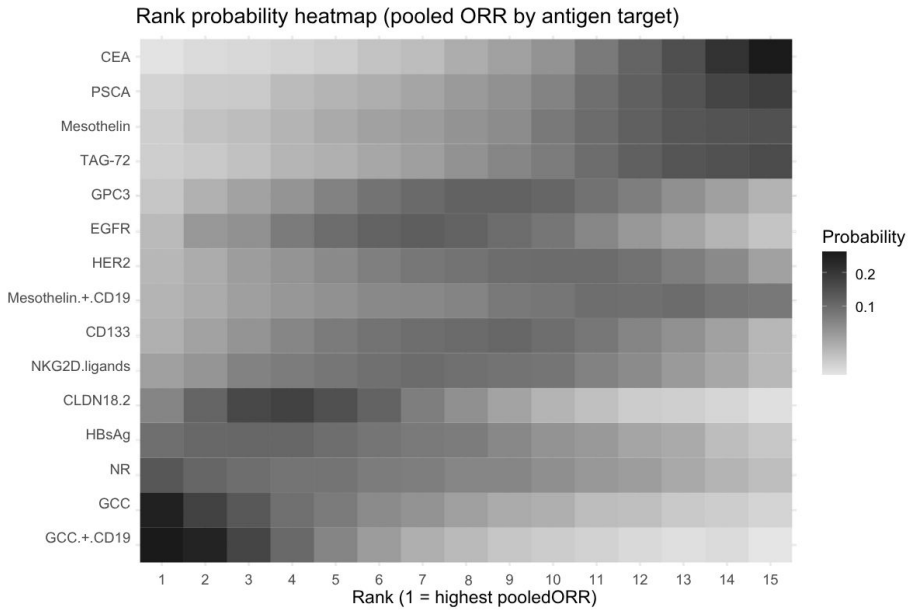


Figure IIIa: Rank probability heatmap of antigen targets by pooled ORR (rank 1 = highest).

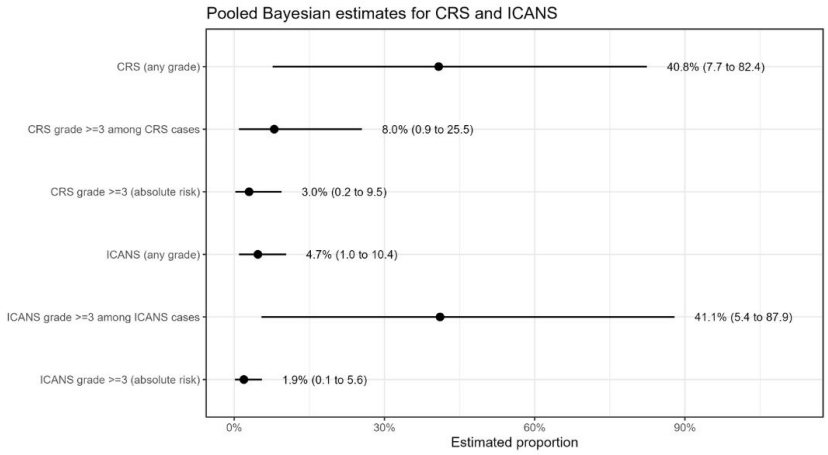


Figure IIIb: Pooled Bayesian estimates for any-grade and grade ≥3 CRS and ICANS (95% CrI).

Figure 3

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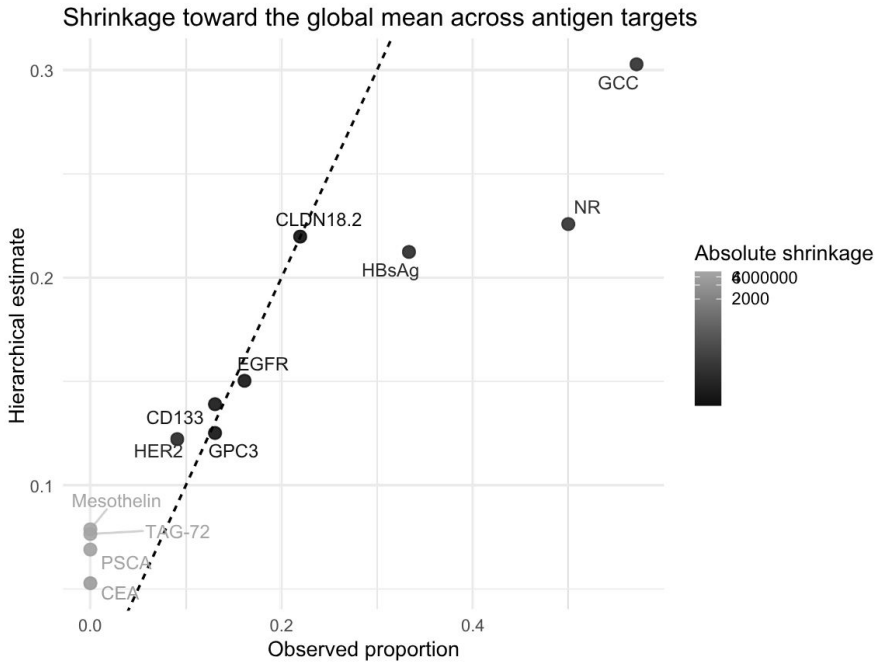


Figure IVa: Bayesian shrinkage of observed ORR proportions toward the global mean, by antigen target.

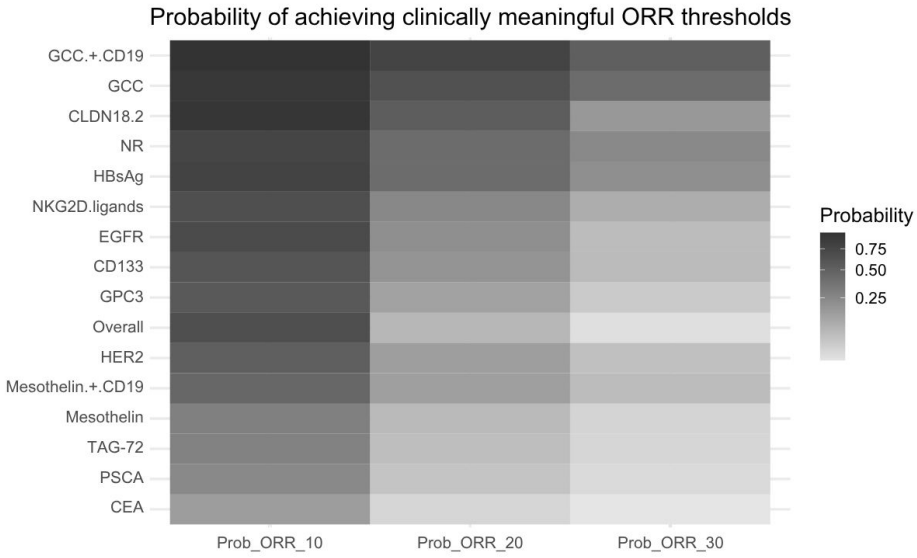


Figure IVb: Posterior probabilities of achieving ORR thresholds of ≥10%, ≥20%, and ≥30% by antigen target.

Figure 4

See image above for figure legend.

Supplementary Files

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