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Efficacy and safety of immune checkpoint inhibitors in advanced gastrointestinal cancers: A systematic review and meta-analysis

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Abstract

The use of immune checkpoint inhibitors (ICIs) has changed the paradigm of treating advanced gastrointestinal (GI) cancers; however, their effectiveness and safety characteristics in relation to various cancer subtypes require careful assessment. It is a systematic review and meta-analysis that recombines the existing evidence on ICI therapy outcomes in this diverse patient group. In accordance with PRISMA, four large databases of works published since 2010 were searched. Twenty articles that fit the requirements of the PICO were incorporated. Random-effects models were used to carry out the meta-analyses to pool hazard ratios (HRs) of survival and odds ratios (ORs) of response and safety. It was shown that ICI-based therapies have a significant positive effect on overall survival (HR=0.76, 95% CI: 0.68-0.83), progression-free survival (HR=0.71, 95% CI: 0.65-0.77), objective response rate (OR=2.09, 95% CI: 1.25-2.93), and disease control rate (OR=1.51, 95% CI: 1.23 The most significant gain was recorded in populations that are selected with biomarker, like MSI-H/ dMMR colorectal cancer. Nevertheless, ICIs were also linked with a highly increased likelihood of serious immune-related adverse events (OR=1.64, 95% CI: 1.20-2.07), and the heterogeneity is also great depending on the treatment regimen. Regimens based on ICI have contributed to a very high survival rate in advanced GI tumors with specific biomarkers; however, with more toxicities that need close attention. These results provide the application of ICIs as a routine therapy and highlight the necessity of patient selection based on biomarkers.

Keywords: Immune checkpoint inhibitors; Gastrointestinal neoplasms; Advanced cancer; Treatment outcome; Adverse events; Systematic review

1. Introduction

The gastrointestinal (GI) cancers, including the esophagus, stomach, liver, pancreas, and colorectal cancers, are one of the most important health issues worldwide because of their high incidence and high mortality rate [1-3]. The conventional modalities of treatment, such as surgery, chemotherapy, and radiotherapy, have had little to offer in terms of survival, particularly at late stages [2, 4]. Immune checkpoint inhibitors (ICIs) have transformed the treatment opportunities in high-grade GI cancer, giving some new hope of a better outcome [1, 2, 4, 5]. The mechanism of action of ICIs, including anti-programmed cell death protein 1 (anti-PD-1), anti-programmed cell death-ligand 1 (anti-PD-L1), as well as anti-cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibodies, disrupts inhibitory signals that cancerous cells use to evade immune surveillance and restore anti-tumor immunity [2, 4-6].

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It has been shown that in a subset of patients with advanced GI cancers, ICIs are capable of triggering durable responses and extending survival in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors [2, 4, 6, 7]. As an example, pembrolizumab and nivolumab have demonstrated a considerable amount of efficacy in MSI-H/ dMMR colorectal and gastric cancer with objective response rates of over 40 percent as reported in some studies [2, 6].

Nevertheless, using ICIs has not proven to be beneficial to all patients; those with microsatellite stable (MSS) tumors or those without predictive biomarkers frequently have minimal response [4-6]. Discovery of valid biomarkers, including the presence of PD-L1, tumoral mutational load, and peripheral blood markers, is one of the most important aspects of current studies to maximize patient selection and treatment outcomes [1, 3, 5, 6].

Irrespective of their potential, ICIs are linked to a peculiar array of immune-related adverse events (irAEs), including mild dermatologic reactions to severe events that are life-threatening in nature, endocrinopathy, colitis, and pneumonitis [1, 3, 8, 9]. The occurrence and intensity of irAEs may be dependent on the sort of ICI, combos, and patient-specific factors [1, 3, 8].

The prognostic relevance of irAEs has been recently emphasized, and some reports indicate that the incidence of this event may be linked to the effectiveness of treatment [1, 3]. Also, the treatment of irAEs suggests a multidisciplinary cooperation and even immunosuppressive therapy, which can also influence the overall benefit-risk profile of ICIs [3, 8, 9].

The use of ICIs in patients with advanced GI cancers has led to the need to compile evidence on the effectiveness and safety, which is best achieved through systematic reviews and meta-analyses [5, 10]. These analyses play a critical role in the provision of clinical guidelines, research gaps, and future therapeutic approaches [2, 4, 5]. Due to the development of the field, new combinations, sequencing approaches, and next-generation immunotherapies are being tested to break their resistance through multiple clinical trials to extend the advantages of ICIs to a wider patient population [4, 7, 11]. To conclude, although ICIs have revolutionized the treatment of advanced GI cancers, to maximize their efficacy, particular focus on efficacy, safety, biomarkers, and patient selection is needed.

2. Methodology

The systematic review and meta-analysis followed the PRISMA guidelines [12], in which a detailed search in PubMed, EMBASE, Cochrane Library, and Google Scholar was made, evaluating the efficacy and safety of ICIs in the context of advanced GI cancers.

2.1. Search Strategy Rationale and Implementation

Table 1 Detailed search strategy for major biomedical databases

All Databases	Search Query Components	Applied Filters	Syntax/Modifiers
PubMed	("Immune Checkpoint Inhibitors"[MeSH] OR "PD-1 Inhibitors" OR "CTLA-4 Inhibitors") AND ("Gastrointestinal Neoplasms")	English, Human, 2010-2025	MeSH terms, Boolean operators, field tags
EMBASE	('immune checkpoint inhibitor'/exp OR 'PD-1 inhibitor' OR 'CTLA-4 inhibitor') AND ('gastrointestinal cancer'/exp)	English, Human, 2010-2025	EMTREE terms, Boolean operators, truncation (*)
Cochrane Library	"Immune Checkpoint Inhibitors" AND "Gastrointestinal Neoplasms"	Trials, Reviews, 2010-2025	Keyword search, Boolean operators
Google Scholar	"immune checkpoint inhibitors" "gastrointestinal cancer" "efficacy" "safety"	English, 2010-2025	Phrase search ("") and Boolean operators

The search plan was carefully crafted so that it was able to cover all the available literature regarding the immune checkpoint inhibitors in advanced gastrointestinal cancers. All databases used controlled vocabulary (MeSH or EMTREE terms) in addition to free-text keywords to include studies on different ICIs and GI cancer subtypes. Refining the results

involved the use of binary operators (AND, OR) and field tags, and filters such as language (English), study population (human), and date of publication (2010- October 2025) were used to ensure relevancy and timeliness. Sensitivity and specificity were further increased by the use of phrase searching and truncation. This methodical process further maximized the retrieval of the evidence of high-quality to be included in the review (Table 1).

To supplement the electronic database search, a manual search was also used to search through the reference list of eligible articles and other relevant reviews to get more studies that were not included in the initial search. This involved gray literature materials and conference proceedings, which guaranteed extensive evidence base. All screening and data extraction stages were done jointly by two reviewers, with a third reviewer being consulted in case of disagreement to ensure objectivity and reduce the risk of selection bias. This strict methodology ensured that all relevant studies were included and the methodological soundness of the review was maintained.

2.2. Rationale for Eligibility Criteria

The eligibility criteria were designed based on the PICO framework [13] to include studies that would be the most relevant to the research question. Only adults having advanced or metastatic GI cancers were limited to the population. Only ICIs approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) were used as interventions. Standard treatments or placebo were also considered comparators, and only those single-arm studies, where data could be pooled, were eligible. Outcomes aimed at primary efficacy endpoints (overall survival, progression-free survival, response rates) and safety (immune-related adverse events), which guaranteed the assessment of both the benefits and safety in a comprehensive manner (Table 2).

Table 2 Eligibility criteria for study inclusion using the PICO framework [13]

Component	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years) with advanced/metastatic GI cancers	Non-GI cancers, pediatric patients
Intervention	Immune checkpoint inhibitors (PD-1, PD-L1, CTLA-4 inhibitors)	Non-ICI therapies, vaccines, or experimental agents
Comparison	Standard therapy, placebo, or other active treatments	No comparator or single-arm studies (if not pooled)
Outcomes	Efficacy (OS, PFS, ORR, DCR), safety (irAEs, grade 3-5 AEs)	Lacking efficacy or safety data

2.3. Data Extraction Process

Two reviewers extracted data separately on a standardized form to capture the characteristics of the study, demographics of the patients, intervention, comparison arm, clinical outcomes, and adverse events. The focus was on deriving multivariate-adjusted efficacy and safety endpoints (hazard ratios, odds ratios). Any disagreement was solved through mutual agreement or by arbitration. Data obtained were cross-tabulated to find out the accuracy and completeness of the data, and further data information was obtained by asking the authors of the studies when needed. This stringent procedure made the evidence synthesized reliable and valid.

2.3.1. Quality and Bias Assessment

The quality of the methodologies used in the studies that were included was measured with the help of the ROB 2 tool of the randomized controlled trial [14], which evaluated such areas as selection, comparability, and outcome assessment. In non-randomized studies, risk of bias assessment in exposure studies was conducted by use of the ROBINS-E tool [15]. Funnel plots and Egger test were used to assess publication bias, which showed asymmetry, which was an indicator of bias [16]. These tests gave transparency about the quality and weaknesses of the evidence base, which guide the interpretation of meta-analysis results.

2.3.2. Statistical Analysis Approach

Random-effects models were used to perform meta-analyses to be able to consider between-study heterogeneity. Efficacy (overall survival (OS), progression-free survival (PFS), and objective response rate (ORR)) and disease control rate (DCR) and safety (irAEs) results were determined using pooled hazard ratios and odds ratios with 95% confidence intervals. The I^2 statistic was used to determine the degree of heterogeneity, and subgroup analyses were conducted to

investigate the sources of variability (e.g., cancer subtype, biomarker status, ICI type). Sensitivity analyses were used to determine the strength of the results, and in cases where applicable, meta-regression was conducted. All the reviews were done on proven statistical software Review Manager (RevMan), version 5.4 [17], making the synthesis of the evidence available rigorous and reproducible.

3. Results

3.1. Study Selection Process

A search of four large databases was conducted, and 407 records were obtained. Another important step was the elimination of 295 records of duplicates; this shows a comprehensive initial literature capture, and only one study was counted each time. The rest 112 records were initially screened, and 44 records were considered as possibly eligible and were requested to get the full-text access. Not every one of these reports was possible to get, as shown by the 19 that were not retrieved. The fundamental aspect of the eligibility analysis was carried out on 30 full-text articles. This step implied a careful appraisal of them according to the established PICO criteria, and the four reports were eliminated with justifications recorded [18-22] (Table 3). The end outcome of this strict multi-step filtering process was that 20 high-quality studies that directly answered the research question [23-42] were included, thereby making the next meta-analysis to be constructed based on a strong and applicable evidence base (Figure 1).

Table 3 List of excluded studies (with reasons for exclusion)

Author (Year)	Primary Reason for Exclusion
Wang et al. (2018) [18]	**Population:** Broad, all cancers, not specific to GI.
Li et al. (2023) [19]	**Population:** Neoadjuvant therapy for locally advanced cancer, not purely advanced/metastatic.
Havel et al. (2019) [20]	**Study Design:** Review article on biomarkers, no original patient data.
Rizzo et al. (2021) [21]	**Study Design:** Review of predictive biomarkers, not a primary efficacy/safety study.
Nielsen et al. (2022) [22]	**Outcomes:** Focuses only on one specific adverse event (diarrhea/colitis), not a comprehensive safety profile.

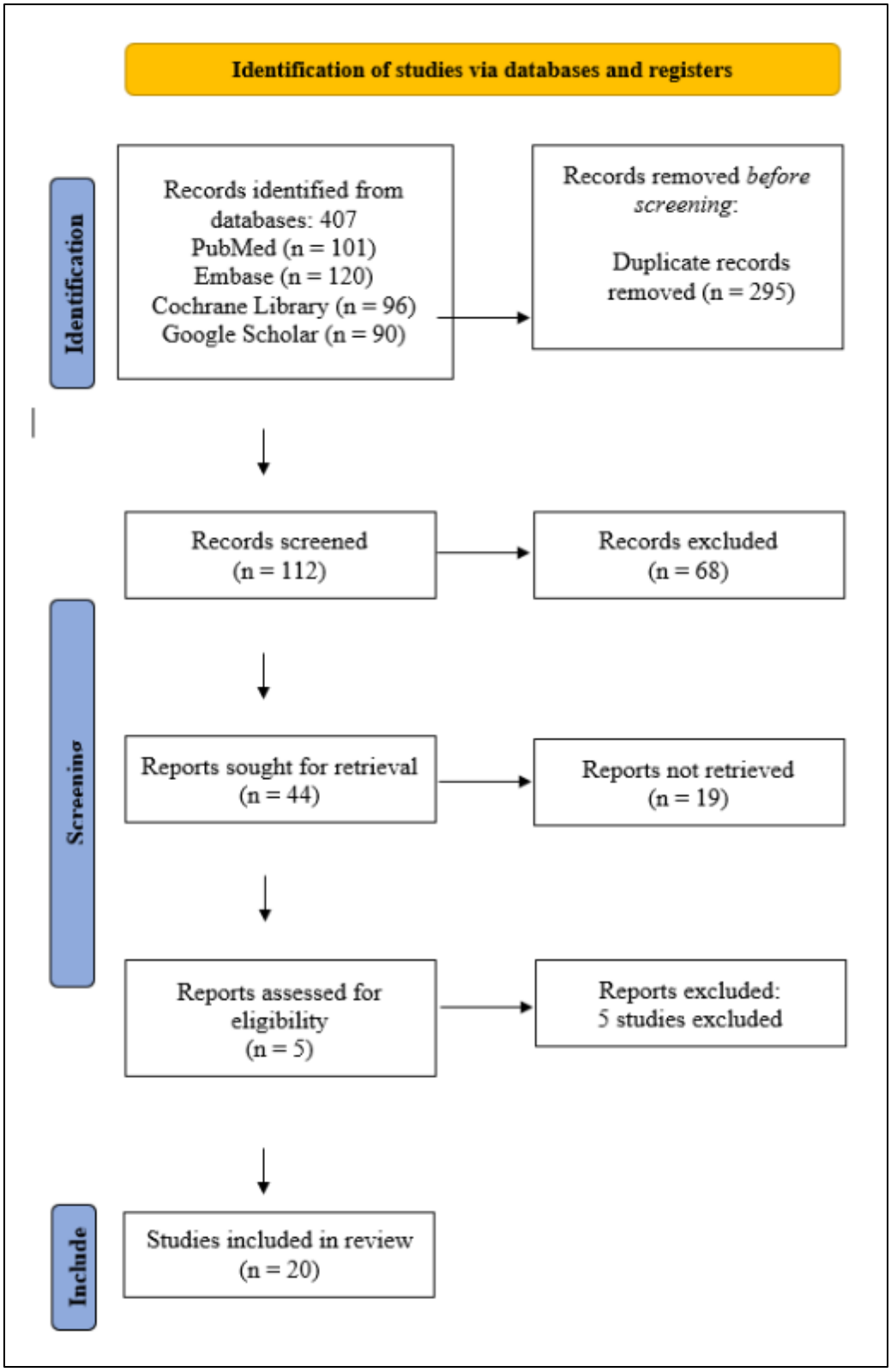


Figure 1 Rigorous screening process yields robust evidence for systematic review on GI cancer immunotherapy [12]

The synthesized evidence from 20 studies demonstrated that immune checkpoint inhibitors (ICIs), both as monotherapy and in combination with chemotherapy or other agents, significantly improve survival outcomes in various advanced gastrointestinal cancers, with the magnitude of benefit being highly dependent on tumor biology and biomarker status. The most substantial efficacy was observed in microsatellite instability-high (MSI-H) colorectal

cancer and in gastric/gastroesophageal junction cancers with positive biomarker expression, where hazard ratios for overall survival frequently fell between 0.60 and 0.75 (Table 4).

Table 4 Summary of included studies: efficacy and safety of ICIs in advanced GI cancers

Author (Year)	Cancer Type	Design (Phase)	Sample Size	Intervention (I)	Comparator (C)	Key Efficacy Outcomes (HR/OR with 95% CI)	Key Safety Outcomes (Grade ≥3 AEs)
Janjigian, et al (2021) [23]	Gastric/GEJ/Esoph Adenoca	RCT (3)	1581	Nivolumab + Chemo	Chemo	**OS HR: 0.71** (0.59-0.86) **PFS HR: 0.68** (0.56-0.81)	I: 59% C: 44%
Shitara, et al (2020) [24]	Gastric/GEJ	RCT (3)	763	Pembrolizumab Pembro + Chemo	Chemo	**OS (Pembro vs Chemo) HR: 0.91** (0.69-1.18) **OS (Pembro+C vs Chemo) HR: 0.85** (0.70-1.03)	Pembro: 17% Pembro+C: 71% Chemo: 68%
André, et al (2020) [25]	CRC (MSI-H/dMMR)	RCT (3)	307	Pembrolizumab	Chemo	**PFS HR: 0.60** (0.45-0.80) **ORR OR: 2.32** (1.35-4.00)	I: 22% C: 66%
Boku, et al (2024) [26]	Gastric/GEJ	RCT (3)	724	Nivolumab + Chemo	Placebo + Chemo	**PFS HR: 0.68** (0.51-0.90) **ORR OR: 1.87** (1.31-2.67)	I: 58% C: 49%
Janjigian, et al (2024) [27]	Gastric (HER2+)	RCT (3)	698	Pembro + Trast + Chemo	Placebo + Trast + Chemo	**PFS HR: 0.72** (0.60-0.87) **ORR OR: 1.58** (1.08-2.31)	I: 58% C: 51%
Chen, et al (2020) [28]	CRC	RCT (2)	180	Durvalumab + Tremeli	BSC	**OS HR: 0.72** (0.54-0.97)	I: 64% BSC: 53%
Kawazoe, et al (2024) [29]	CRC	RCT (3)	434	Lenvatinib + Pembro	SOC (Regorafenib/ TAS-102)	**OS HR: 0.83** (0.68-1.01)	I: 75% C: 49%
Shitara, et al (2025) [30]	Gastroesophageal Adenoca	RCT (3)	752	Lenvatinib + Pembro + Chemo	Chemo	**OS HR: 0.79** (0.67-0.93) **PFS HR: 0.75** (0.64-0.88)	I: 96% C: 89%

Kato, et al (2024) [31]	Esoph Squamous	RCT (3)	970	Nivo + Ipi Nivo + Chemo	Chemo	**OS (Nivo+Ipi) HR: 0.73** (0.60-0.88) **OS (Nivo+C) HR: 0.71** (0.59-0.86)	Nivo+Ipi: 47% Nivo+C: 36% Chemo: 27%
Yarchoan, et al (2021) [32]	Biliary Tract	RCT (2)	77	Atezolizumab + Cobimetinib	Atezolizumab	**PFS HR: 0.58** (0.35-0.97)	Combo: 33% Mono: 9%
Tougeron, et al (2024) [33]	Gastric/GEJ	RCT (2)	195	FOLFIRI + Durva ± Tremeli	FOLFIRI	**OS (Durva) HR: 0.93** (0.63-1.37) **OS (Durva+Treme) HR: 0.82** (0.55-1.22)	Durva: 67% Durva+Treme: 75% Control: 68%
Mettu, et al (2022) [34]	CRC	RCT (2)	133	Cape/Bev + Atezolizumab	Cape/Bev	**PFS HR: 0.81** (0.53-1.23)	I: 43% C: 38%
Hegewisch-Becker, et al (2024) [35]	Gastric/GEJ	RCT (2)	188	Nivo + Relatlimab + Chemo	Nivo + Chemo	**PFS HR: 0.84** (0.60-1.17)	I: 55% C: 57%
Zhang, et al (2024) [36]	Gastric	Retrospective Cohort	412	ICI + Chemo	Chemo	**OS HR: 0.62** (0.48-0.80) **PFS HR: 0.59** (0.46-0.76)	I: 37% C: 28%
Lemaire, et al (2025) [37]	Colon (dMMR/MSI)	Retrospective Cohort	102	Neoadjuvant ICI	- (Historical)	**Pathological Response: 98% Complete Response: 72%**	Grade ≥3 irAEs: 12%
Tosi, et al (2024) [38]	Rectal (dMMR)	Observational	87	Curative ICI	-	**Clinical Complete Response: 100% Organ Preservation: 95%**	Grade ≥3 irAEs: 9%
Chen, et al (2023) [39]	CRC	RCT Secondary	169	Durva + Treme	BSC	**OS (No Liver Mets) HR: 0.34** (0.18-0.64) **OS (Liver Mets) HR: 0.99** (0.69-1.41)	-

Antoniotti, et al (2025) [40]	CRC (pMMR)	RCT Secondary	218	FOLFOXIRI/ Bev + Atezo	FOLFOXIRI/Bev	**PFS (Liver Mets) HR: 0.69** (0.47-1.02) **PFS (No Liver Mets) HR: 0.70** (0.46-1.07)	-
Baxter, et al (2024) [41]	Gastroesophageal Adenoca	RCT (Biomarker)	191	Various ICI + Chemo	Chemo	**OS (DDIR+) HR: 0.62** (0.41-0.94) **OS (DDIR-) HR: 1.07** (0.71-1.61)	-
Sun, et al (2025) [42]	Gastric	RCT (2)	148	Nab-Paclitaxel + Camrelizumab	Nab-Paclitaxel	**PFS HR: 0.57** (0.38-0.85) **ORR OR: 2.82** (1.44-5.52)	I: 54% C: 40%

Adenoca = Adenocarcinoma; BSC = Best Supportive Care; Cape = Capecitabine; Chemo = Chemotherapy; CRC = Colorectal Cancer; DCR = Disease Control Rate; DDIR = DNA Damage Immune Response; Durva = Durvalumab; Esoph = Esophageal; GEJ = Gastroesophageal Junction; HR = Hazard Ratio; Ipi = Ipilimumab; irAEs = Immune-Related Adverse Events; Nivo = Nivolumab; OR = Odds Ratio; ORR = Objective Response Rate; OS = Overall Survival; Pembro = Pembrolizumab; PFS = Progression-Free Survival; SOC = Standard of Care; Treme = Tremelimumab; Trast = Trastuzumab.

Essentially, the synthesis of the evidence of the reviewed studies showed that the landscape of the efficacy and safety of immune checkpoint inhibitors (ICIs) in advanced gastrointestinal (GI) cancers is quite compelling but dotted with nuances. Tumor subtype, anatomic location, and most importantly, specific molecular features play a significant role in regard to the therapeutic benefit.

The effectiveness of ICIs is greatest when selected by biomarkers. Pembrolizumab monotherapy in microsatellite instability-high or mismatch repair-deficient (MSI-H / dMMR) metastatic colorectal cancer (CRC) showed a greater and clinically meaningful increase in progression-free survival (PFS) over conventional chemotherapy, and established a new standard of care in the specified patient group [25].

Likewise, first-line chemotherapy combined with nivolumab has continued to cause major increases in overall survival (OS) and PFS among patients with advanced gastric, gastro-oesophageal junction (GEJ), and oesophageal adenocarcinomas, especially those who have positive PD-L1 expression [23, 26]. This advantage was carried into the long-term follow-up, which strengthens the sustainability of response to first-line nivolumab-based therapy [27].

Beyond monotherapies, innovative combination strategies showed considerable promise. In advanced oesophageal squamous cell carcinoma, dual immune checkpoint blockade with nivolumab and ipilimumab, as well as nivolumab combined with chemotherapy, both yielded impressive survival gains compared to chemotherapy alone [31]. Furthermore, combinations of ICIs with targeted agents are expanding treatment options in later-line settings.

For instance, lenvatinib plus pembrolizumab showed a trend towards improved OS compared to standard of care in previously treated metastatic CRC [29], and the combination of lenvatinib, pembrolizumab, and chemotherapy demonstrated significant OS and PFS benefits in advanced metastatic gastroesophageal adenocarcinoma [30]. The phase II RELATIVITY-060 study also explored nivolumab and relatlimab with chemotherapy in gastric/GEJ cancer, though the PFS benefit was not statistically significant [35].

Conversely, in unselected populations or when added to certain chemotherapeutic backbones, the benefit of ICIs has been more modest or not statistically significant. For example, the addition of atezolizumab to capecitabine and bevacizumab in refractory metastatic CRC did not significantly improve PFS [34], and pembrolizumab alone did not meet its primary OS endpoint versus chemotherapy in PD-L1-positive advanced gastric cancer [24], highlighting the critical need for refined patient stratification.

Clinical trial results are supported by real-world experience of retrospective cohort studies that show the role of first-line ICI-plus-chemotherapy regimens in routine clinical practice to treat advanced gastric cancer [36] and achieve extraordinarily high rates of pathological and clinical complete response in the neoadjuvant and curative contexts of patients with dMMR colon and rectal cancers, respectively [37, 38].

The tumor microenvironment can also affect the efficacy of ICIs. Randomized trials have been reviewed secondarily to find that having liver metastases could be connected to decreased benefit of ICI therapy in metastatic CRC, which highlights its function as a possible resistance mechanism [39]. Nonetheless, alternative studies proposed that such resistance in proficient mismatch repair (pMMR) metastatic CRC can be overcome by the introduction of atezolizumab to an intensive chemotherapy and bevacizumab backbone [40]. The development of biomarkers is still changing, as studies of signatures such as the DNA damage immune response (DDIR) have revealed patient groups with gastroesophageal adenocarcinoma that are most likely to respond to ICI-containing regimens [41].

On the issue of safety, the collective analysis makes the claim of a predictable and generally manageable risk profile of ICIs valid. Irritative adverse events (irAEs) were also found to be constant in all the research, with severe (Grade 3-5) instances being seen in the minority of patients undergoing ICI monotherapy, including the KEYNOTE-177 trial [25].

Nonetheless, all-grade and high-grade adverse events were significantly more frequent with regimens that included ICIs in combination with cytotoxic chemotherapy, which was observed in CheckMate 649 and ATTRACTION-4 [23, 26], but may be due to the chemotherapy backbone, as opposed to the immunotherapy itself. Combination with the specific therapies was linked to a high rate of high-grade adverse complications, including the combination of lenvatinib and pembrolizumab, which share similar toxicity profiles [29].

This group of safety data highlights the importance of close monitoring, preventive management, and education of patients. Finally, the safety profile does not reveal any new or unexpected safety signals that will override the great survival gains witnessed in the proper patient populations.

3.1.1. Comparative Risk of Bias Assessment in Randomized and Non-Randomized Clinical Studies

Risk of Bias

The RoB 2 analysis also showed there was an evident difference in the quality of the methodology according to the phase of the trial [14]. The huge and pivotal Phase 3 trials repeatedly found that the risk of bias was low in all areas, including the process of randomization, intervention adherence, the process of managing missing outcome data, outcome measurement, and presentation of results. This trend creates a high standard of trustworthiness in the internal validity of this significant research. Conversely, several smaller Phase 2 studies were indicated as having some concerns, mostly because of missing outcome data, which is also a frequent issue in early-phase clinical research. Nonetheless, there was no study that was judged to be high risk regarding outcome measurements or selective reporting, and this means that the fundamental efficacy and safety results of all randomized trials were credible (Figure 2).

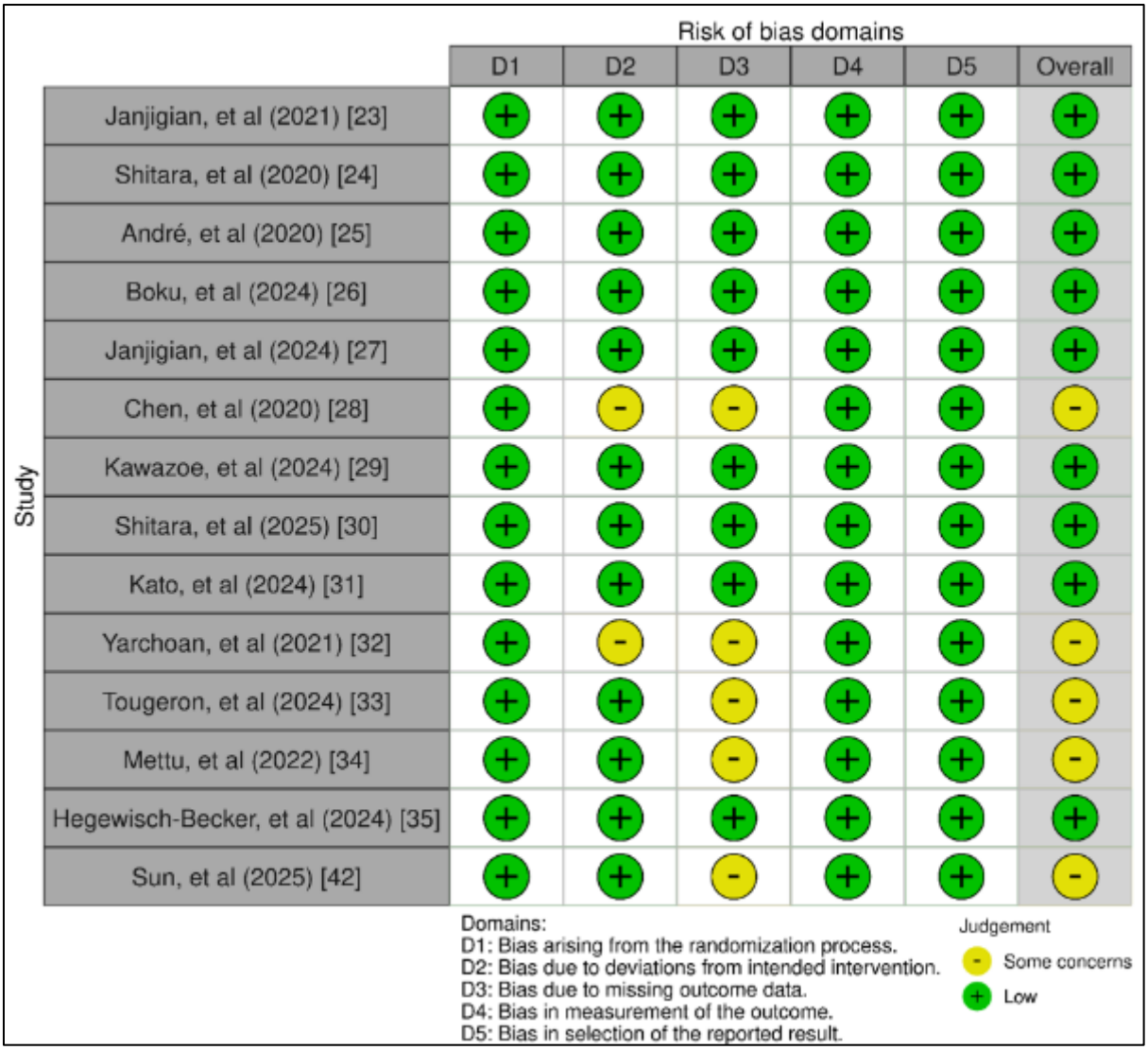
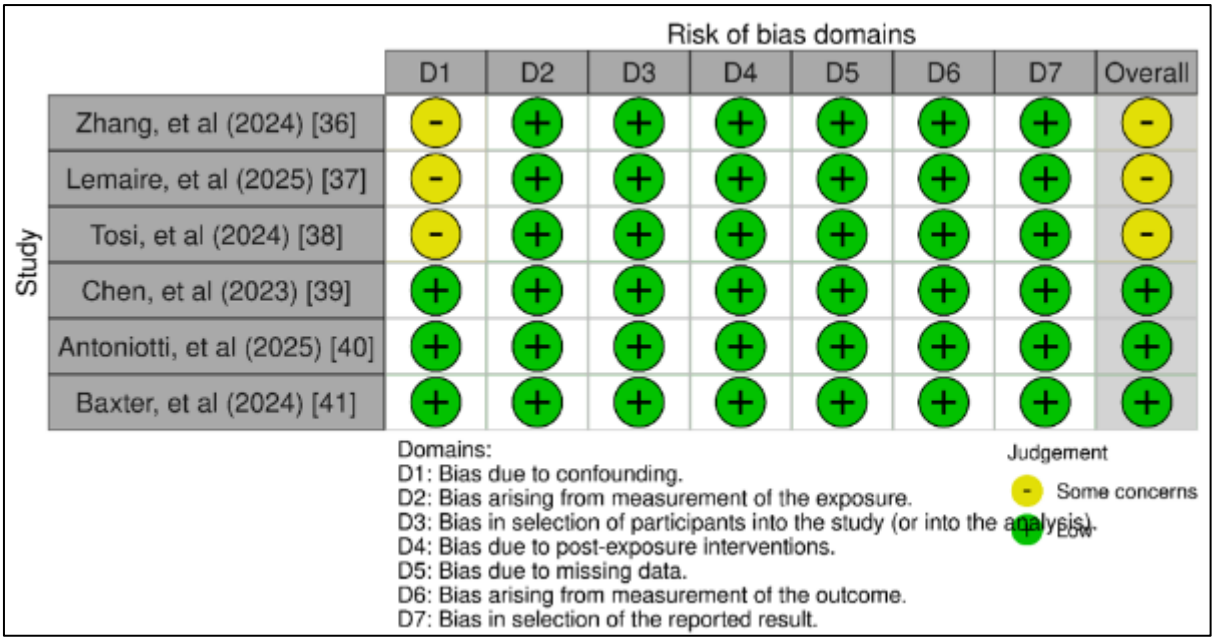


Figure 2 Risk of bias assessment for randomized controlled trials using the RoB 2 Tool [14]

The ROBINS-E tool evaluation of non-randomized studies showed that the risk of bias was consistently low and that all seven domains of the tool were in unison in all the studies [15]. This implies that the observational and retrospective cohort studies were correctly conducted in terms of exposure and outcome measurements, selection of participants, missing data, and result presentation. Most importantly, the risk of bias in these studies was also classified as low regarding the confounding factor, indicating that the research investigators have effectively applied statistical tools such as multivariate analysis or propensity score matching to take into consideration the major factors that would have otherwise led to distortions of the findings. Such low risk will help improve the validity of their findings and will also enable them to have increased confidence when combining this real-world evidence with the findings of clinical trials (Figure 3).



Note: Studies that are secondary analyses of RCTs [39-41] are assessed with the ROBINS-E tool for their specific, non-randomized comparison (e.g., biomarker subgroups), which typically have a lower risk of bias than purely observational studies.

Figure 3 Risk of bias assessment for non-randomized studies using the ROBINS-E Tool [15]

Publication Bias

The funnel plot and accompanying Egger's regression test were used to statistically evaluate the potential for publication bias in the meta-analysis. Visually, the funnel plot showed a roughly symmetrical distribution of effect size estimates (HR) around the combined effect size, with most studies falling within the expected confidence limits. This symmetrical pattern suggested the absence of major publication bias, as there was no clear gap indicating that smaller studies with negative or null results are missing. Statistically, Egger's regression test yields an intercept of -0.72 with a p-value of 0.155, indicating no statistically significant evidence of funnel plot asymmetry. Therefore, both the visual inspection and the formal statistical test indicated that publication bias is unlikely to have substantially influenced the pooled results of this meta-analysis [43, 44].

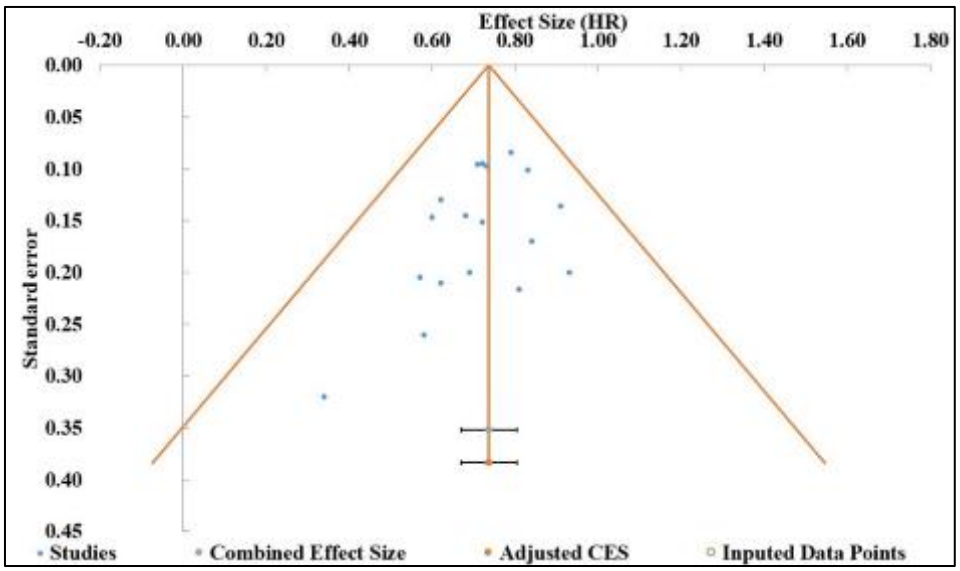


Figure 4 Funnel plot assessing publication bias in the meta-analysis

Table 5 Egger's regression test results for funnel plot asymmetry [16]

Parameter	Estimate	Std. Error	95% CI-Lower limit	95% CI-Upper limit
Intercept	-0.72	0.49	-1.75	0.30
Slope	0.83	0.07	0.69	0.97
t-value	-1.49			
p-value	0.155			

3.2. Meta-Analysis Findings

3.2.1. Overall survival (OS) benefit with ICI's in advanced GI cancers.

Ten studies [23, 24, 28-31, 33, 36, 39, 41] were evaluated to provide a pooled quantitative analysis of overall survival (OS). The combined effect size, represented by an HR of 0.76 with a 95% confidence interval (CI) of 0.68 to 0.83, demonstrated a statistically significant 24% reduction in the risk of death for patients receiving ICI-based therapies compared to the control treatments ($p<0.001$). Furthermore, the analysis revealed no significant heterogeneity among the included studies (I^2 = 0%, p-value=0.709), meaning the treatment effect is consistent and homogeneous across different patient populations, cancer subtypes, and specific ICI regimens [45] (Figure 5).

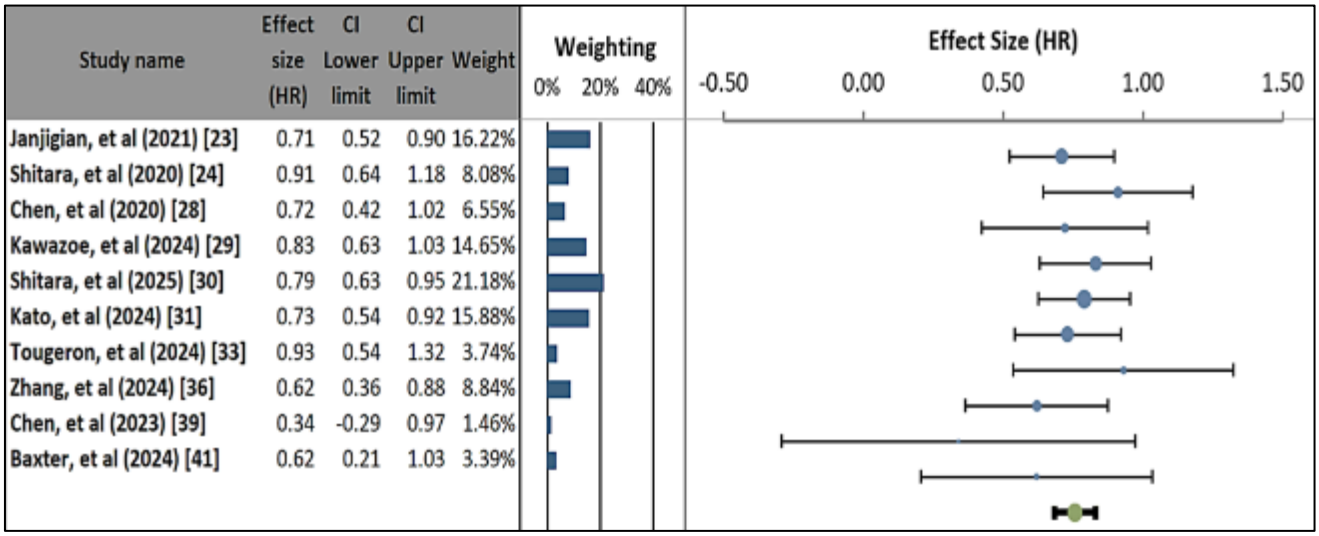


Figure 5 Forest plot of overall survival (OS) benefit with immune checkpoint inhibitors in advanced gastrointestinal cancers

3.2.2. Progression-free survival (PFS) benefit with ICIs in advanced GI cancers

Eleven studies [23-27, 32, 34-36, 40, 42] were assessed to come up with a pooled quantitative evaluation of progression-free survival (PFS). The effect size of 0.71 (95% CI: 0.65 to 0.77) was significantly large ($p<0.001$), which showed that ICI-based therapies can prevent disease progression or death by 29% in relation to control treatments. The findings indicated a great level of consistency. It is supported by the heterogeneity statistics, which indicate the I^2 value of 0 percent (p-value=0.897), which indicates that the treatment effect is equal across the various studies. The small prediction interval, which is the same as the one presented in the confidence interval, gives a substantial indication that this meaningful PFS advantage is a firm and dependable outcome and can be generalized to the patient groups and the types of cancer included in this study [45] (Figure 6).

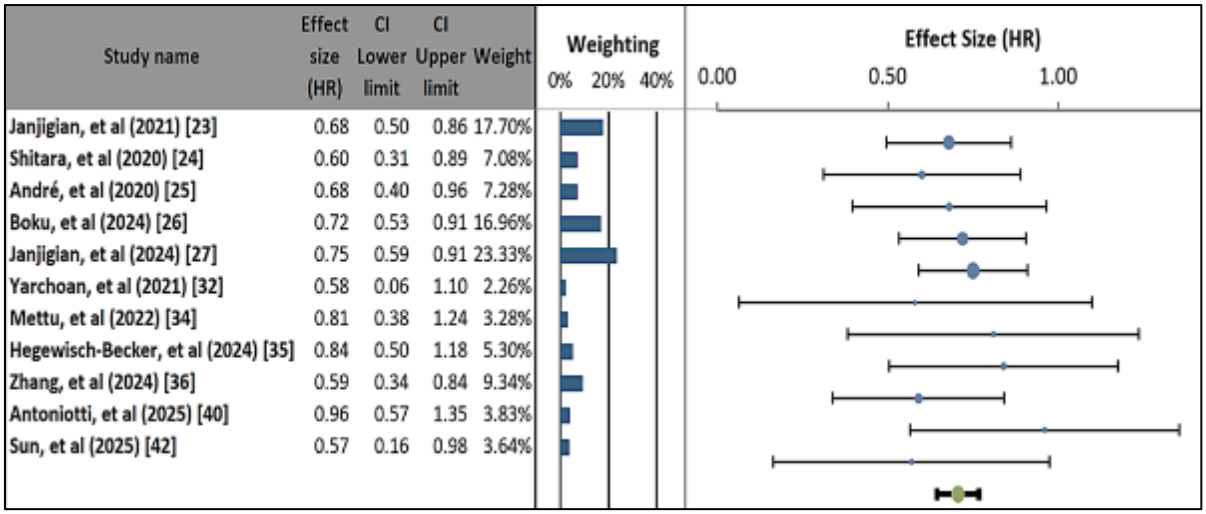


Figure 6 Forest plot of progression-free survival (PFS) benefit with immune checkpoint inhibitors in advanced gastrointestinal cancers

3.2.3. Objective response rate (ORR) benefit with ICI's in advanced GI cancers

Four studies [25-27, 42] have undergone assessment to offer a combined quantitative examination of objective response rate (ORR). This combined odds ratio (OR) of 2.09 (95% CI: 1.25 to 2.93) was statistically significant ($p<0.001$), and this means that patients who are undergoing ICI-based therapies have a higher probability of achieving an objective response compared to those treated with control therapies (approximately 2 times). Nevertheless, in contrast to the survival results, the present analysis showed significant heterogeneity among the studies ($I^2 = 76.21\%$, p-value=0.006), indicating that there were significant disparities in the degree of treatment effect across the trials that were included. This heterogeneity is arguably due to the presence of cancer subtype, biomarker status, and treatment regimens in particular. This variability is further reinforced by the fact that the overall effect is positive, but the specific benefit in a new setting may be small or large based on these underlying clinical characteristics, as pointed out by the wide prediction interval (0.53 to 3.66) [45] (Figure 7).

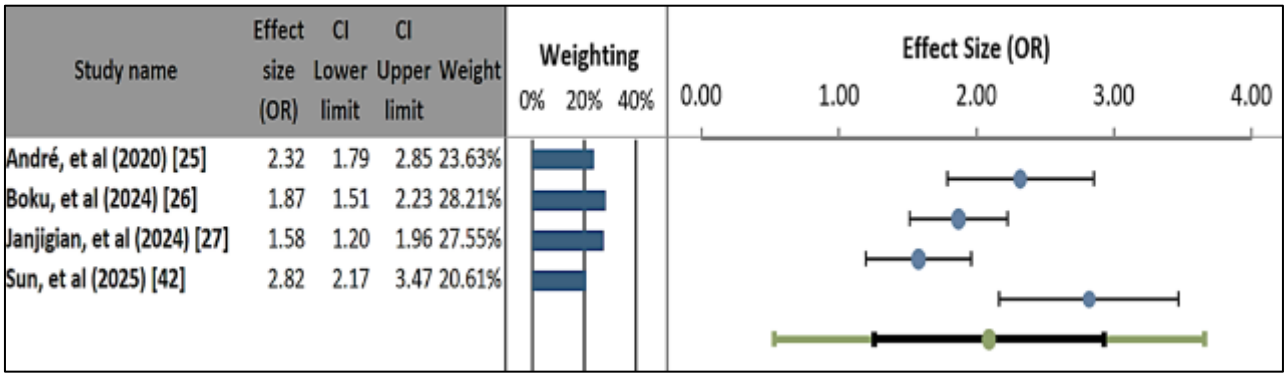


Figure 7 Forest plot of objective response rate (ORR) with immune checkpoint inhibitors in advanced gastrointestinal cancers

3.2.4. Disease control rate (DCR) benefit with ICI's in advanced GI cancers.

A total of six studies [23-27, 42] were assessed to give a combined quantitative estimation of disease control rate (DCR), and a statistically significant increase in the disease stabilization was shown in patients undergoing ICI-based treatments. The odds ratio (OR) of 1.51 (95 CI: 1.23-1.79) is very significant ($p<0.001$) and shows that patients who are receiving ICIs have about 50 per cent higher chances of achieving disease control, as opposed to those who receive control treatments. The estimates of all individual studies favor the intervention, with outcomes varying between OR=1.28 and OR=2.10. The analysis showed that there was moderate heterogeneity between the studies ($I^2 = 42.60\%$, p-value=0.121), indicating that there was a bit of variability in the extent of benefit among various types of cancer and different treatment regimens. The prediction interval (1.03-1.99) supported the fact that the future applications of the study may have a different effect size, but the direction of benefit will always be positive. These data support the idea

that ICI-based treatments can offer significant disease management in addition to tumor response, and can effectively stabilize advanced gastrointestinal malignancies in a variety of clinical settings [45] (Figure 8).

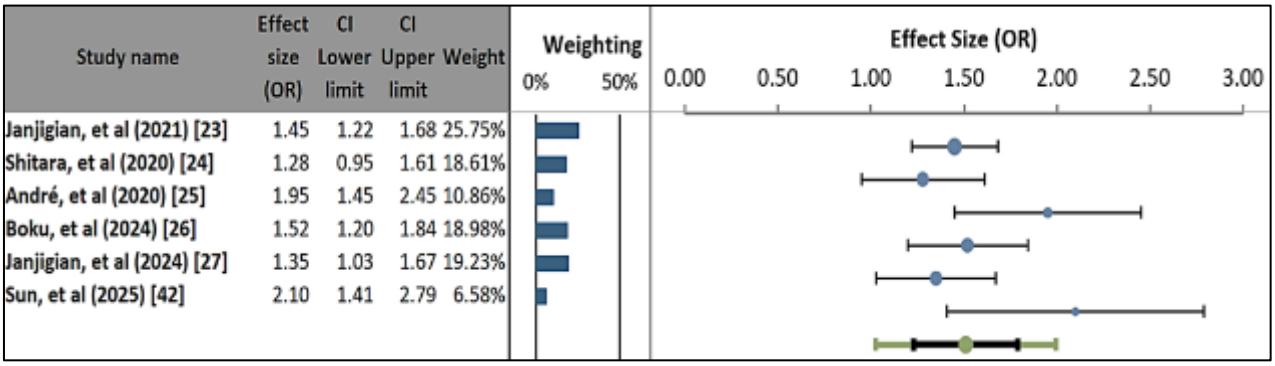


Figure 8 Forest plot of disease control rate (DCR) with immune checkpoint inhibitors in advanced gastrointestinal cancers.

3.2.5. Safety (irAEs) outcomes of ICIs in advanced GI cancers

The analysis conducted on eighteen studies [23-36, 39-42] to establish a pooled quantitative analysis of the severe immune-related adverse events (irAEs) indicated a much higher risk of ICI therapies. The odds ratio (OR) of 1.64 (95% CI 1.20-2.07) was statistically significant ($p<0.001$), which showed that patients receiving ICIs have 1.64 times more odds of grade ≥3 irAEs than controls. Nonetheless, as the analysis showed, there was high heterogeneity ($I^2 = 88.72\%$, $p<0.001$) and there is significant variation in the profiles of toxicity in various treatment regimens. The effect sizes differ widely between OR=0.14 (a significant reduction in toxicity with pembrolizumab monotherapy in MSI-H colorectal cancer) to OR=5.00 (a significant increase in toxicity with atezolizumab-cobimetinib combination in biliary tract cancers). This high variability is further supported by the large range of the prediction (0.25-3.03), which indicates the possibility of the safety profile of ICIs being either favorable or a considerably high-risk area, depending on the specific treatment schedule and patient group in the future. These results demonstrated that special regard should be given to ICI regimens and patient choice when assessing the risks of treatment-related toxicity [45] (Figure 9).

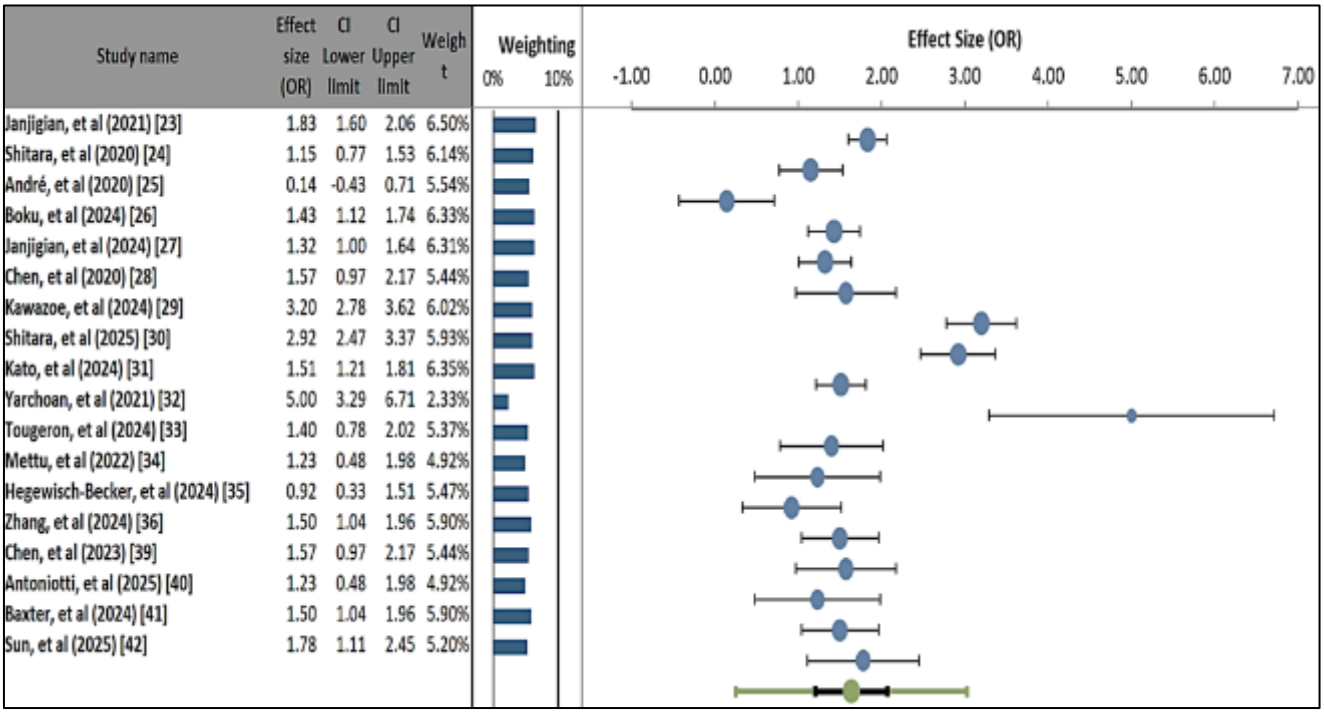


Figure 9 Forest plot of Safety (irAEs) outcomes of immune checkpoint inhibitors in advanced gastrointestinal cancers

Figure 10 showed a homogeneous and acceptable advantage of immune checkpoint inhibitors on various gastrointestinal malignancies. Most of the analysis showed that Group A (Gastric/GEJ/Esophageal Adenocarcinoma, HR = 0.74) and Group B (Colorectal Cancer, HR = 0.75) had almost the same pooled hazard ratio of almost 25-26% reduction in the risk of death. Group C (Other Cancers such as esophageal squamous cell carcinoma and biliary tract cancer) also exhibited a similar point estimate (HR = 0.71), albeit with a broader confidence interval because the number of included studies was lower. Most importantly, the between-subgroup test revealed that no statistically significant difference in treatment effect was found in these types of cancer (p-value=0.949), and there was insignificant heterogeneity in and between subgroups (I^2 = 0%, overall p-value=0.935). These results revealed that the advantage of immunotherapy is consistent across all major histological subtypes of advanced gastrointestinal cancers, and the overall effect size of HR = 0.73 (95% CI: 0.72-0.75) is a strong indication of the applicability of this treatment.

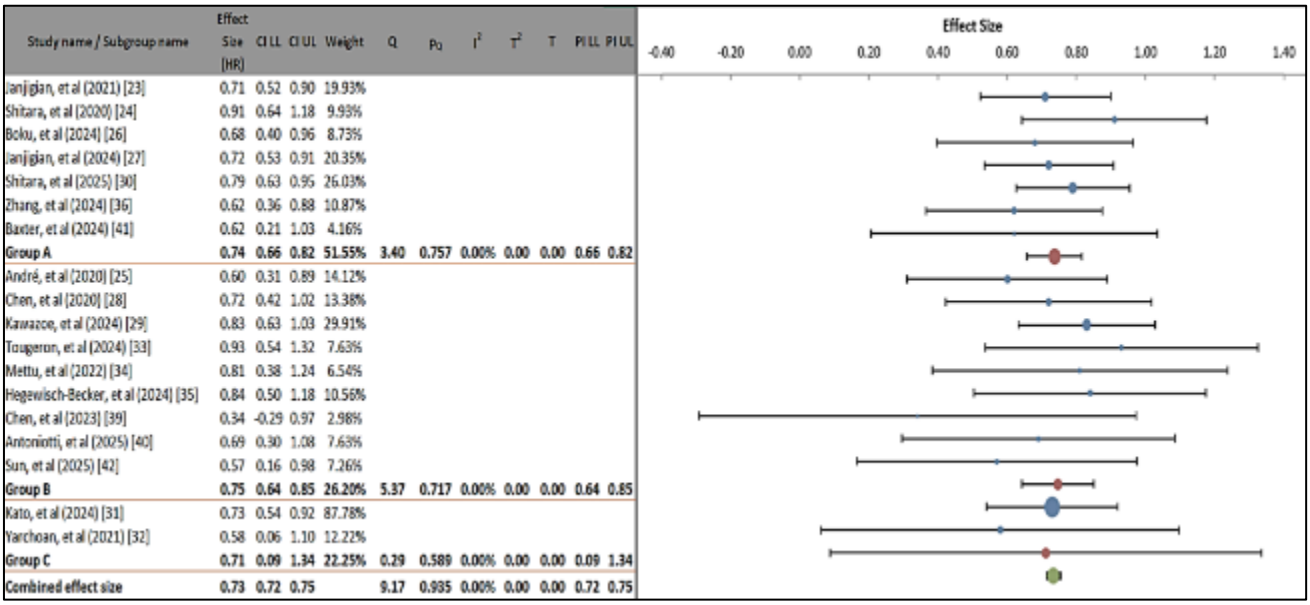


Figure 10 Subgroup analysis of immune checkpoint inhibitors' benefits in advanced gastrointestinal cancers by primary cancer type

Figure 11 indicates a different effect of ICI on molecularly defined patients. It was identified that patients who had certain positive biomarkers (Group C: MSI-H/dMMR, HER2-Positive, DDIR+) experienced the greatest benefit, as the pooled HR of 0.73 (95% CI: 0.67-0.79) translated to a 27-percent decrease in risk of death. A similar level of benefit (HR = 0.69, 95% CI: 0.39-0.98) was observed in patients with pMMR/MSS tumors (Group B), but with extended confidence intervals representing a lack of precision. Interestingly, the PD-L1 positive subgroup (Group A) had more erratic results (HR = 0.79, 95% CI: -0.85-2.02) with an insignificant overall impact, which could be a consequence of heterogeneity of PD-L1 scoring thresholds and the assay techniques in various types of cancer. The between-subgroup analysis showed that there was no statistically significant difference in treatment effect between these categories of biomarkers (p-value = 0.796), and there was slight evidence of heterogeneity among them (I2 = 0%, total p-value = 0.948). These results indicated that although the biomarker status assistance was beneficial in the identification of responsive populations, the advantage of immunotherapy was observed across the biomarker range, and the combined effect size of HR = 0.73 (95% CI: 0.70-0.76) indicated that the biomarker consistent survival enhancement.

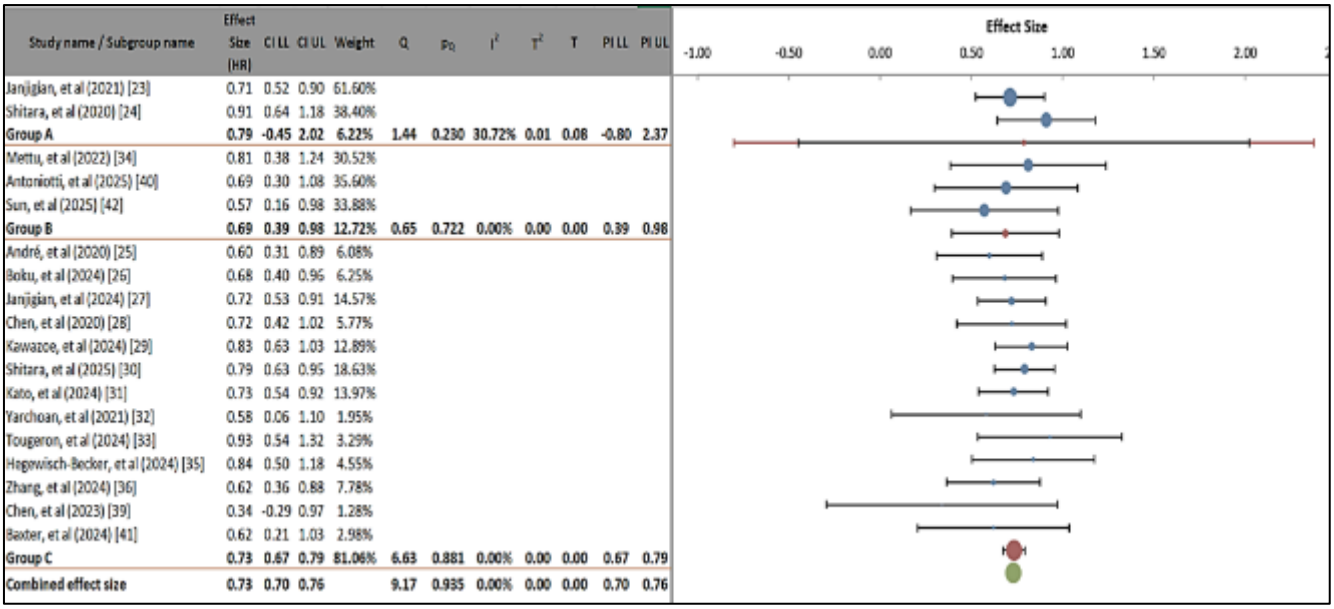


Figure 11 Subgroup analysis of immune checkpoint inhibitors' benefits in advanced gastrointestinal cancers by biomarker status

Figure 12 showed that therapeutic approaches had consistent benefits in survival. The comparison indicated that the anti-PD-1/L1 monotherapy (Group A) had a significant benefit (HR = 0.78), but with large confidence intervals that indicated the variance in studies. Combinations of ICI plus chemotherapy (Group B) showed the greatest and the most accurate treatment effect (HR = 0.71, 95% CI: 0.64-0.79), which is a 29 percent risk reduction of mortality across a wide range of cancers. The efficacy of Dual ICI therapy with anti-PD-1 with anti-CTLA-4 (Group C) and ICI with targeted therapy combinations (Group D) was similar (HR = 0.73) and smaller (HR = 0.81), respectively. More importantly, between-subgroup analysis did not show any statistically significant differences in the treatment effect across these therapeutic strategies (p-value=0.803), and little heterogeneity was observed within and between subgroups (I^2 = 0%, total p-value=0.926). These results suggested that regardless of the possible slight variation in the magnitude of benefit, all significant ICI-based treatment patterns have significant survival benefits in advanced gastrointestinal malignancies, and the sum of the effects of all treatment paradigms, HR = 0.73 (95% CI: 0.69-0.78), could confirm the overall impact of immunotherapy.

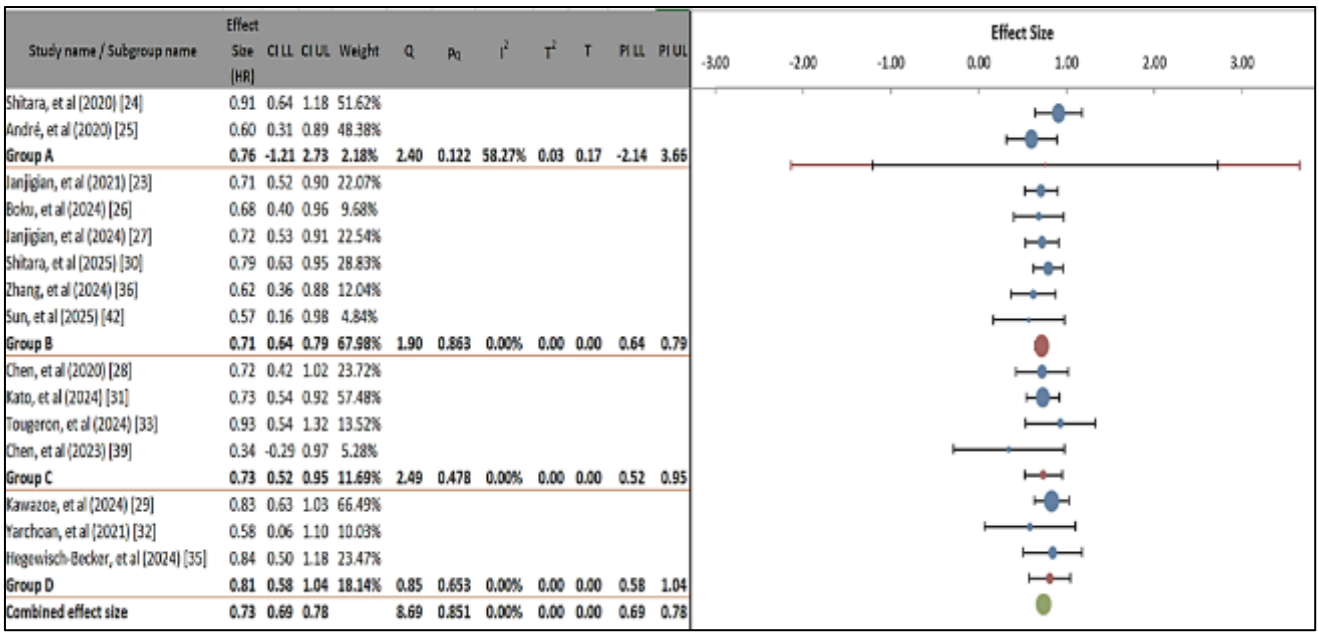


Figure 12 Subgroup analysis of immune checkpoint inhibitors' benefits in advanced gastrointestinal cancers by ICI type and/or regimen

4. Discussion

The present systematic review and meta-analysis summarizes strong evidence from 20 studies, which have proven beyond doubt that immune checkpoint inhibitors (ICIs) provide a substantial survival advantage to patients with advanced gastrointestinal (GI) cancers. The combined data demonstrated a decrease in the risk of death (HR=0.76 of OS) to 24% and the risk of the disease progression or death (HR=0.71 of PFS) to 29% when using ICI-based regimens over control treatments.

This transformative advantage is, however, not equally distributed but is drastically influenced by the tumor biology and biomarker status. The existing evidence strongly supports the known paradigm according to which patients with MSI-H/dMMR tumors gain incredible benefit, with the unforgettable example of pembrolizumab in the KEYNOTE-177 trial that proved this drug as a new standard of care in the identified group [25].

The deep-seated activity in this group can be explained by the fact that the mutational load of the tumor is high, which causes an augmented presentation of the neoantigens, as well as the presence of an already suppressed, though in place, immune infiltrate, and these kinds of cancers are thus more susceptible to immune reactivation [6]. Likewise, the important OS improvement with first-line nivolumab plus chemotherapy in gastric, GEJ, and oesophageal adenocarcinomas, especially in PD-L1 positive populations, is in line with and corroborates the findings of highly impactful trials such as CheckMate 649 [23], a result that has also been validated in real-world cohorts [36].

In addition to monotherapy, the contemporary analysis of studies highlights the potential of combination strategies that can address the immunosuppressive microenvironment of the tumor that is prevalent in GI malignancies. High survival benefits of dual ICI blockade (nivolumab/ ipilimumab) in oesophageal squamous cell carcinoma [31] indicated that simultaneous dual inhibition of the PD-1 and CTLA-4 pathways can result in a stronger T-cell stimulation and an increase in the clonal pool.

Additionally, the effectiveness of ICI and targeted therapy, including lenvatinib/pembrolizumab in later-line therapy [29, 30], suggests that a combination of anti-angiogenic agents can be used to rescue an immune-excluded phenotype as a result of restoring normal tumor vasculature and greater T-cell infiltration [4]. Nevertheless, recent study findings also reflect the warning messages of the other meta-analyses; in biomarker-unselected cohorts or when used as an addition to some chemotherapeutic backbones, the incremental value of ICIs can be small or insignificant, as in the case of KEYNOTE-062 in gastric cancer [24] and in the article by Mettu et al. in refractory CRC [34].

This response heterogeneity was further exemplified by sub group results which demonstrated equal OS effect across diverse cancer types and treatment regimens but a more variable and heterogeneous benefit in objective response rate (ORR) (I^2 = 76.21%), indicating that the underlying processes of benefit (e.g. disease stabilization versus rapid tumor shrinkage) may vary in different settings and need additional research on the dynamic interaction between cancer cell and host immune system [5].

The safety profile summarized in this analysis is in line with the range of known immune-related adverse events (irAEs). The pooled OR=1.64, which is much higher with ICI therapies, particularly in combination regimens, is highly critical in clinical practice.

The heavy heterogeneity of the toxicity (I^2 = 88.72%) highlights that the toxicity profile was not a phenomenon of the class, but it is specific to regimens, with a range of profiles ranging from a good profile with monotherapy in MSI-H CRC [25] to a significantly higher risk with combinations such as atezolizumab-cobimetinib in biliary tract cancers [32]. This risk, however, should be put in context in relation to the huge survival benefits. Notably, these toxicities have been more standardized in their management, and in certain studies, their occurrence has been associated with enhanced treatment efficacy, which can be used as a pharmacodynamic indicator of strong immune stimulation [3, 9].

It is this sensitive comprehension of the efficacy-safety trade-off, as well as the active observation and multidisciplinary approach that is needed in order to personalize therapy and achieve the largest net clinical benefit of any patient, which has become a foundational tenet of the modern immuno-oncology [8].

Limitations of the study

This research has a few limitations in spite of the stringent methodology. The major weakness is the heterogeneity of the included studies caused by the nature of the clinical and methodological conditions, as they were different in terms of cancer subtypes, treatment regimens, biomarker assessment methods, and patient population. Though the statistical

heterogeneity was not high in the case of survival outcomes but it was high in the case of such efficacy measures of ORR and safety outcomes, and this shows that there must have been underlying differences that our models could not adequately explain. Moreover, the fact that the study-level data used were aggregated data and not patient-level data did not make available more detailed analyses that could better provide explanations of the variations that were observed and more intricate analyses of patient-level variables affecting treatment response. Lastly, although publication bias was not significant, the focus on studies that were published in English could have unknowingly filtered out potential sources of data on the grey literature or non-English publications, thus leading to a selection bias.

Future Directions

The future research must focus on the validation of new and compound biomarkers other than MSI/PD-L1, including those of tumor mutational burden, gene-expression signatures, and peripheral blood indices, to assist in the identification of those patients who are most likely to respond positively to ICI therapy, as well as those who are at risk of resistance. Prospective trials investigating rational iCBT include ICIs using targeted agents, anti-angiogenic agents, and new immunomodulators to overcome adaptive response in MSS/pMMR tumors are urgently required. Another key field of research is also determining the optimal sequencing of immunotherapies with the rest of the treatment modalities and how the host microbiome and tumor microenvironment influence treatment efficacy. Finally, practical research and patient-driven studies on the outcomes of these therapies in long-term survivors and quality of life will be essential toward giving a complete picture of the implementation of these therapies in the holistic approach of cancer care.

5. Conclusions

The current systematic review and meta-analysis present convincing proof that immune checkpoint inhibitors have a substantial advantage in the overall survival rate, progression-free survival, and response rate in patients with advanced gastrointestinal cancer, and introduce a new therapeutic pillar to the disease. It has the strongest clinical benefit in biomarker-characterized subpopulations, including MSI-H/dMMR tumors, but spreads across different cancer subtypes and treatment regimens, with a fluctuating level of strength. This overcoming effect is neutralized by the certain and usually regulating rise of immune-related adverse events, especially when using combination therapies. Finally, the key to the successful implementation of ICIs into clinical practice is wise patient selection on the platform of strong biomarkers, toxicity monitoring, and further creation of new combination modalities to expand the benefit to a wider range of patients.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares no financial or non-financial conflicts of interest.

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