

Association between circulating tumor DNA and the prognosis of solid tumor patients receiving neoadjuvant therapy: a meta-analysis

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Abstract

Background

Circulating tumor DNA (ctDNA) has emerged as a promising noninvasive biomarker in solid tumors, yet its prognostic value following neoadjuvant therapy (NAT) warrants systematic validation.

Method

This study systematically searched databases such as PubMed, Embase, and the Cochrane Library, with a search period ranging from database establishment to October 2024. Two researchers independently screened the studies according to the inclusion/exclusion criteria, extracted data, and evaluated the quality of the included evidence, Stata 17.0 software (RRID:SCR_012763)

was used to assess the correlation between positive ctDNA status and disease-free survival (DFS)/relapse-free survival (RFS), overall survival (OS), progression-free survival (PFS), event-free survival (EFS). Subgroup analysis was performed stratified by study design, detection time, region, tumor type, immunotherapy, detection methods, and statistical approaches (univariate vs multivariate analyses). The hazard ratio (HR) was used to analyze survival outcomes. The quality of cohort studies was assessed using the NOS scale, RCT studies were evaluated using ROB 2.0, and non-RCT studies were rated using ROBINS-I. Publication bias was assessed using a combination of Begg's test and funnel plots. Sensitivity analysis was performed to evaluate the robustness of the results.

Results

Ultimately, 41 studies involving 3058 solid tumor patients were included in the analysis. The meta-analysis revealed a significant correlation between positive ctDNA status and worse survival outcomes, including DFS/RFS [HR = 8.60; 95% CI: 6.06–12.21], OS [HR = 7.00; 95% CI: 4.28–11.45], PFS [HR = 3.85; 95% CI: 2.35–6.30], EFS [HR = 3.40; 95% CI: 1.67–6.95]. In the subgroup analysis stratified by tumor type, ctDNA consistently predicted worse survival outcomes for patients with rectal cancer [DFS/RFS: HR = 9.23; 95% CI = 4.29–19.86; OS: HR = 9.72; 95% CI = 2.89–32.66], breast cancer [DFS/RFS: HR = 6.97; 95% CI = 4.20–11.56; OS: HR = 3.61; 95% CI = 1.76–7.40], esophageal cancer [DFS/RFS: HR = 10.83; 95% CI = 2.64–44.44; OS: HR = 2.85; 95% CI = 1.45–5.61], urothelial cancer [DFS/RFS: HR = 27.92; 95% CI = 12.16–64.09; OS: HR = 21.29; 95% CI = 10.51–43.11], lung cancer [DFS/RFS: HR = 4.59; 95% CI = 1.04–20.29; OS: HR = 25.00; 95% CI = 6.75–92.66], and pancreatic cancer [DFS/RFS: HR = 5.02; 95% CI = 1.23–20.51; OS: HR = 11.70; 95% CI = 1.26–108.88], colorectal liver metastasis [DFS/RFS: HR = 5.36; 95% CI = 2.63–10.90; OS: HR = 4.20; 95% CI = 1.50–11.78] receiving neoadjuvant therapy. However, in melanoma, ctDNA detection was not associated with DFS/RFS [HR = 10.8; 95% CI = 0.81–144.09]. In gastric cancer, ctDNA testing was associated with poor EFS [HR = 3.00; 95% CI = 1.30–6.91] but not with OS [HR = 7.17; 95% CI = 0.98–52.57]. Similarly, ovarian cancer was not associated with OS [HR = 2.46; 95% CI = 0.53–11.36]. Furthermore, subgroup analysis demonstrated that regardless of study design, detection time, region, immunotherapy, detection method, or univariate/multivariate analysis results, DFS/RFS, OS, PFS, and EFS were significantly poorer when ctDNA was detected positively.

Conclusion

These findings indicate that ctDNA is a reliable prognostic marker for DFS/RFS, OS, PFS and EFS in patients with solid tumors receiving NAT. ctDNA has significant implications for treatment strategy modification and prognosis prediction in these patients.

Introduction

Malignant tumors are the second leading cause of death worldwide after cardiovascular diseases(1). Despite major progress in cancer screening, treatment, and follow-up monitoring over the past decades, the incidence and mortality of malignant tumors has continued to increase in recent years (2018–2022) (1, 2). Aging population and lifestyle changes (such as smoking, alcohol consumption, and obesity) may be the main contributors to this trend(3). The integrated treatment approach is the main strategy for treating malignant tumors and includes combinations of surgery + radiotherapy + chemotherapy, surgery + targeted therapy/immunotherapy, or chemotherapy + targeted therapy/immunotherapy, which are based on cancer type, stage, and overall patient health, with the aim of maximizing therapeutic efficacy. NAT, a key component of the comprehensive treatment model, aims to reduce tumor burden through preoperative radiation, chemotherapy, or targeted therapy, allowing for downstaging surgeries and improving surgical success rates(4). NAT's unique advantage is its ability to dynamically assess changes in tumor size during treatment, enabling treatment strategy adjustments for precision medicine. It also offers unique translational research opportunities by comparing tumor biology at different stages: pretreatment, during treatment, and posttreatment(5). NAT significantly reduces the risk of local recurrence in locally advanced cancers(6), increases resectability in solid tumors, improves overall survival rates(4), and has been extensively used to treat most solid tumors(7–9). However, the prognosis of patients with malignant tumors treated with NATs remains challenging due to a lack of reliable biomarkers for clinical decision-making, prognostic assessment, and relapse risk prediction.

Owing to its advantages of minimal invasiveness, dynamic monitoring, and ability to reflect tumor heterogeneity, liquid biopsy has gained increasing attention in recent years and is commonly used as an alternative to traditional tissue biopsy methods(10). cfDNA, a key component of liquid biopsy, includes fragments from both healthy and tumor cells and mainly originates from necrosis and apoptosis(11). The cfDNA fragments that originate from tumors and carry cancer-related mutations are referred to as ctDNA(12). ctDNA provides greater sensitivity and specificity than traditional biomarkers do by detecting tumor-specific genetic changes (mutations, methylation, and copy number variations) (13). The value of ctDNA in various solid tumors, including precision medicine, treatment response evaluation, and prediction of recurrence and survival outcomes, has been confirmed by extensive research. ctDNA-based comprehensive treatment stratification strategies can aid in the personalized management of patients(14, 15). Ruiz's study indicated that ctDNA results can predict treatment response in prostate cancer patients, detect docetaxel resistance early, and guide the switch to more effective chemotherapy drugs(16). A study by Aparna R and colleagues revealed that ctDNA-based liquid biopsy is more sensitive to clinically relevant resistance changes and multiple resistance

mechanisms, with 78% of matching cases not detected in the tissue biopsy group(17). In patients with small cell lung cancer, the ctDNA variant allele frequency (VAF) and copy number alteration (CNA) were significantly correlated with OS(18). A ctDNA analysis involving 4037 advanced solid tumor patients revealed that ctDNA-guided treatment significantly improved survival outcomes in these patients(19). Several clinical trials have shown that ctDNA positivity is significantly associated with tumor recurrence, and in some cases, ctDNA levels in relapsed patients are significantly higher than those in nonrelapsed patients(20–23). However, whether changes in ctDNA can be a reliable indicator for adjusting treatment strategies during NAT has yet to be determined, and its role in deciding treatment escalation or de-escalation is still under exploration(24–26). Given that most current evidence focuses on single tumor types, a comprehensive meta-analysis exploring the relationship between ctDNA and prognosis after NAT in various solid tumors is needed for further development. To date, no research has integrated multiple solid tumors to explore the connection between ctDNA results and prognosis in NAT contexts, and a growing body of new evidence urgently needs evaluation and synthesis. Therefore, this study aims to elucidate the relationship between ctDNA and prognosis following NAT in solid tumors comprehensively.

Methods

With growing concerns over AI transparency in scientific research, we employed **the TITAN Guidelines 2025** to standardize AI reporting(27). No AI tools were used for data generation or analysis in this meta-analysis. This study adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) Guidelines(28, 29). This study has been prospectively registered in the PROSPERO database; the registration number will be disclosed after the peer review process.

Search strategy

An exhaustive search of the PubMed, Embase, and Cochrane Library databases was conducted from inception to October 2024. The following search terms were utilized: (solid cancer OR solid cancer OR cancer OR solid malignancy OR solid tumor OR tumor OR cancer OR malignancy OR cancer OR gastric cancer OR lung cancer OR breast cancer OR rectal cancer OR esophageal cancer OR ovarian cancer OR urothelial cancer OR pancreatic cancer) AND (neoadjuvant therapy OR neoadjuvant chemotherapy OR neoadjuvant immunotherapy OR neoadjuvant) AND (Circulating Tumor DNA OR ctDNA OR cell-free tumor DNA OR cell-free nucleic acids OR cell free tumor DNA OR liquid biopsy OR liquid biopsies) AND (prognosis OR survival OR recurrence OR relapse-free survival RFS OR disease-free survival OR DFS OR overall survival OR OS OR progression-free survival OR PFS OR event-free survival OR EFS OR metastasis-free survival OR MFS OR pathological complete response OR pCR). Two authors independently carried out study selection. Any disagreements were resolved through discussion with a third author.

Study selection

Inclusion criteria:

1) Studies including patients pathologically diagnosed with a single primary solid tumor or metastatic solid tumor (rectal cancer, breast cancer, esophageal cancer, urothelial cancer, pancreatic cancer, colorectal liver metastasis, gastric cancer, or ovarian cancer); 2) case–control studies, cohort studies, or randomized controlled trials; 3) studies providing complete survival or pathological data, including at least one of the following: disease-free survival (DFS)/relapse-free survival (RFS), overall survival (OS), progression-free survival (PFS), event-free survival (EFS); 4) ctDNA data derived from plasma samples; and 5) patients receiving NAT.

Exclusion criteria:

1) Studies with insufficient survival data; 2) patients without a confirmed diagnosis of solid tumors; 3) other types of studies, such as systematic reviews, meta-analyses, case reports, or conference abstracts; 4) patients not receiving neoadjuvant therapy; 5) insufficient ctDNA detection data and 6) Inadequate studies for meta-analysis.

Data extraction

Two researchers independently extracted the following data: 1) study characteristics: author, publication year, region, study design, and sample size; 2) population information, including: sex, age, cancer type, and tumor stage; 3) NAT information: neoadjuvant chemotherapy regimen and neoadjuvant immunotherapy regimen; 4) ctDNA information: detection method, detection time, gene target, and cutoff; and 5) survival and pathological outcomes, including DFS/RFS, PFS, OS, and EFS corresponding HRs with 95% CIs.

Quality assessment

The quality of randomized controlled trials (RCTs) was assessed via the Cochrane Risk of Bias Tool (RoB 2.0)(30), which evaluates seven domains of bias, including bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurements, and selection of the reported result. Each domain was rated as "low risk," "some concerns," or "high risk". The Newcastle–Ottawa Scale (NOS) (31) was used for cohort studies, including prospective and retrospective studies. This tool assesses studies across three categories: participant selection, group comparability, and outcome assessment. Scores range from 0 to 9, with higher scores indicating a lower risk of bias. Nonrandomized controlled trials (non-RCTs) were appraised via the ROBINS-I tool(32). This comprehensive framework examines seven domains of bias, including confounding, selection, and outcome reporting, assigning ratings of 'low,' 'moderate,' 'serious,' or 'critical' risk of bias.

Statistical analysis

The meta-analysis was conducted via Stata 17.0 software (RRID:SCR_012763). HRs were used to assess the prognostic effects of ctDNA on clinical outcomes, including DFS/RFS, PFS, OS and EFS. Natural logarithm-transformed HRs (lnHR), along with their standard errors (selnHR), were utilized to standardize effect estimates across studies. All P values were two-sided, with $P < 0.05$ considered statistically significant. Statistical heterogeneity among studies was assessed via the I^2 statistic and Cochran's Q test, with $I^2 \geq 50\%$ or $P < 0.05$ recognized as indicating significant heterogeneity. A random-effects model was used to pool effect sizes regardless of heterogeneity level, accounting for interstudy variability. Subgroup analyses were performed to explore sources of heterogeneity considering factors such as study design, detection time, region, tumor type, immunotherapy, detection methods, and statistical approaches (univariate vs multivariate analyses). Sensitivity analyses were conducted by sequentially excluding individual studies to assess the robustness of the results. The results are presented as forest plots. Publication bias was evaluated via a funnel plot and Begg's test.

Results

Study selection and basic characteristics

A total of 11,225 records were identified, and after removing irrelevant studies ($n = 10,798$), studies without relevant data ($n = 217$), nonclinical research studies ($n = 50$), studies on nonsolid tumors ($n = 33$), studies with insufficient ctDNA data ($n = 43$), studies not involving neoadjuvant therapy ($n = 41$), inadequate studies for meta-analysis($n = 1$), and 41 studies (3058 solid tumor patients) that met the criteria were confirmed for inclusion in the analysis (Fig. 1). Patient characteristics and study design variables of the included studies are summarized in Table 1. Between 2017 and 2024, 41 studies spanning 13 countries included 3058 patients with 10 types of solid tumors: breast cancer(33–44) ($n = 12$), rectal cancer(45–54) ($n = 10$), esophageal cancer(55–58) ($n = 4$), colorectal liver metastases(59, 60) ($n = 2$), lung cancer(61–64) ($n = 4$), pancreatic cancer(65, 66) ($n = 2$), melanoma(67) ($n = 1$), urothelial cancer(68–70) ($n = 3$), ovarian cancer(71) ($n = 1$), and gastric cancer(72, 73) ($n = 2$). Among them, 33 studies were prospective or retrospective cohort studies, whereas 8 were RCTs or nonrandomized controlled trials (non-RCTs). All patients received NAT, and seven studies included neoadjuvant immunotherapy. Next-generation sequencing (NGS) (36/41) and digital polymerase chain reaction (dPCR) (5/41) were the main ctDNA sequencing methods used, with six studies employing whole-exome sequencing (WES) and two studies applying whole-genome sequencing (WGS), categorized as NGS, whereas four studies utilizing droplet digital polymerase chain reaction (ddPCR) were categorized as dPCR. In our analyses, the gene targets for mutation detection were varied. For the NGS and dPCR methods, the common targets included driver genes such as TP53, APC, PIK3A, and KRAS. Additionally, WES primarily detects single nucleotide variants (SNVs) and small InDels in coding regions, whereas WGS provides comprehensive genome-wide coverage to identify variants such as SNVs, copy number variants (CNVs), and structural variants (SVs). Supplementary Table 1 provides the concept biomarkers investigated in each study, along with their respective roles in prognostic prediction, including the associated HRs. Two studies have reported dynamic changes in ctDNA. Sixteen studies targeted non-Asian populations, and 25 studies focused on Asian populations. The main clinical outcome was DFS/RFS (29/41), followed by OS (16/41), PFS (10/41), EFS (6/41).

Table 1
The basic characteristic and experimental design variab

Author	Year	Country	Study design	Cancer Type	Tumor Stage	Neoadjuvant chemotherapy
Murahashi	2020	Japan	prospective	Rectal cancer	II,III	CapeOx, Bmab FOLFOX+Bmab(+ CRT) CapeOx (+ SRT) CRT + Tegafur/Gimeracil/Oteracil Potassium
Deutsch	2023	USA	prospective	Lung cancer	IIB-IIIA	nivolumab + platinum-doublet chemotherapy platinum-doublet chemotherapy
Wang	2023	China	prospective	Colorectal liver metastases	IV	mFOLFOX6 FOLFIRI FOLFOXIRI+bevacizumab/cetuximab
Cavallone	2020	Canada	prospective	Breast cancer	I,II,III	Anthracyclines +Taxanes Taxanes+Anthracyclines Taxanes alone Taxanes-Anthracyclines
Rothé	2019	Belgium	RCT	Breast cancer	0,I	HER2-targeted alone HER2-targeted + Taxol
Stecklein	2023	USA	prospective	Breast cancer	I,II,III	Anthracycline ± taxane Anthracycline/taxane/platinum Taxane/platinum Taxane
Pazdirek	2024	Czechia	prospective	Rectal cancer	II,III	50.4Gy of radiation and concomitant administration of Xeloda™ (capecitabine)
Magbanua	2023	USA	prospective	Breast cancer	II,III	paclitaxel + AC endocrine therapy+chemotherapy HER2-targeted drugs +chemotherapy pembrolizumab
Magbanua	2021	USA	prospective	Breast cancer	II,III	paclitaxel paclitaxel + MK-2206(AKT inhibitor) anthracycline regimens
Morimoto	2023	Japan	prospective	Esophageal cancer	I,II,III,orIVESCCincludingcT4bandcM1	CF (Cisplatin + 5-FU) DCF (Docetaxel + CF)

CRT, chemoradiotherapy; SRT, stereotactic radiotherapy; MAF, mutant allele frequency; VAF, variant allele frequency; ctDNA, circulating tumor DNA; ddPCR, d sequencing; WGS, whole genome sequencing; USA, United States of America; UK, United Kingdom; NR, not reported; DFS, disease-free survival; RFS, relapse

Author	Year	Country	Study design	Cancer Type	Tumor Stage	Neoadjuvant chemotherapy
Zhou	2021	China	prospective	Breast cancer	IIB,III,IV	docetaxel/epirubicin/cyclophosphamide (TEC) docetaxel/carboplatin/trastuzumab (TCbH)
Chen	2017	China	RCT	Breast cancer	NR	Cisplatin Cisplatin+ Rucaparib→ Rucaparib maintance
Cailleux	2022	Belgium	prospective	Breast cancer	II,III	NR
McDuff	2021	USA	prospective	Rectal cancer	II,III	capecitabine; infusional fluorouracil (5FU)
Liu	2022	China	RCT	Rectal cancer	II,III	capecitabine plus oxaliplatin regimen long-course chemoradiotherapy (2 Gy x 25 with capecitabine)
Zhang	2023	China	prospective	Gastric cancer	II,III	S-1 plus oxaliplatin(SOX) NACT programmed cell death 1 (PD-1) inhibitors and CAR-T administration
Provencio	2022	Spain	RCT	Lung cancer	IIIA	paclitaxel and carboplatin plus nivolumab
Liu	2023	China	RCT	Lung cancer	IIA,IIB,IIIA,IIIB	mono-nivolumab (N) or nivolumab + nabpaclitaxel+ carboplatin (N/C) based on PD-L1 expression
Schou	2017	Denmark	prospective	Rectal cancer	II,III	ICT with capecitabine + oxaliplatin long-course CRT comprising concomitant capecitabine ± oxaliplatin
Lindskrog	2023	Denmark	prospective	Urothelial Carcinoma	NR	NR
CRT, chemoradiotherapy; SRT, stereotactic radiotherapy; MAF, mutant allele frequency; VAF, variant allele frequency; ctDNA, circulating tumor DNA; ddPCR, d sequencing; WGS, whole genome sequencing; USA, United States of America; UK, United Kingdom; NR, not reported; DFS, disease-free survival; RFS, relapse						

Author	Year	Country	Study design	Cancer Type	Tumor Stage	Neoadjuvant chemotherapy
Vidal	2021	Spain	RCT	Rectal cancer	NR	ICT with aflibercept + mFOLFOX6 → CRT with capecitabine. ICT with mFOLFOX6 alone → CRT with capecitabine
Cabalag	2022	Australia	prospective	Esophageal adenocarcinoma	NR	5-FU/Cisplatin and 50.4 Greys or CROSS protocol
Yue	2022	China	prospective	Lung cancer	IB–IIIA	chemotherapy (IO+Chemo) dual immunotherapy (IO + IO) chemotherapy alone (Chemo)
Hofste	2023	Netherlands	prospective	Rectal cancer	NR	capecitabine and oxaliplatin (CAPOX)
Tie	2020	Australia	prospective	Colorectal liver metastases	NR	FOLFOX or CAPOX
Khakoo	2019	UK	prospective	Rectal cancer	I,II,III	capecitabine
Hofste	2022	Netherlands	prospective	Esophageal cancer	IB,IIA,IIB,IIIA,IIB	carboplatin and paclitaxel
Wang	2021	China	prospective	Rectal cancer	IIIB,IIIC	FOLFOX(5-FU + Leucovorin + Oxaliplatin);CAPOX(Capecitabine + Oxaliplatin)
Lin	2021	China	prospective	Breast cancer	II,III	trastuzumab/pertuzumab
Kim	2023	Korea	RCT	Breast cancer	II,III	anthracycline, cyclophosphamide (AC), carboplatin,taxane, paclitaxel
CRT, chemoradiotherapy; SRT, stereotactic radiotherapy; MAF, mutant allele frequency; VAF, variant allele frequency; ctDNA, circulating tumor DNA; ddPCR, d sequencing; WGS, whole genome sequencing; USA, United States of America; UK, United Kingdom; NR, not reported; DFS, disease-free survival; RFS, relapse						

Author	Year	Country	Study design	Cancer Type	Tumor Stage	Neoadjuvant chemotherapy
Kitahata	2021	Japan	prospective	Pancreatic cancer	NR	gemcitabine plus nab-paclitaxel
Magbanua	2021	USA	prospective	Breast cancer	II,III	Paclitaxel -and anthracycline ,MK-2206 (AKT inhibitor)
Tie	2018	Australia	prospective	Rectal cancer	II,III	fluoropyrimidine
Chan	2024	Australia	prospective	melanoma	III	ipilimumab nivolumab
Nordentoft	2024	Denmark	prospective	Urothelial cancer	NR	NR
Cecchini	2024	USA	N-RCT	Pancreatic cancer	NR	mFOLFIRINOX
Ng	2023	China	prospective	Esophageal cancer	II,III	NR
Garcia-Murillas	2024	UK	prospective	Breast cancer	NR	NR
Kfoury	2024	France	prospective	Ovarian cancer	III,IV	NR
Leal	2020	USA	prospective	Gastric cancer	IB–IVA	Epirubicin, cisplatin or oxaliplatin + capecitabine

CRT, chemoradiotherapy; SRT, stereotactic radiotherapy; MAF, mutant allele frequency; VAF, variant allele frequency; ctDNA, circulating tumor DNA; ddPCR, d sequencing; WGS, whole genome sequencing; USA, United States of America; UK, United Kingdom; NR, not reported; DFS, disease-free survival; RFS, relapse

Author	Year	Country	Study design	Cancer Type	Tumor Stage	Neoadjuvant chemotherapy
Christensen	2019	Denmark	prospective	Urothelial cancer	T1-T4b	Gemcitabin, Carboplatin / Etoposide
CRT, chemoradiotherapy; SRT, stereotactic radiotherapy; MAF, mutant allele frequency; VAF, variant allele frequency; ctDNA, circulating tumor DNA; ddPCR, d sequencing; WGS, whole genome sequencing; USA, United States of America; UK, United Kingdom; NR, not reported; DFS, disease-free survival; RFS, relapse						

Quality evaluation of the included literature

The quality of the 33 cohort studies was predominantly high, one study scoring 6 points, 10 studies scored 7 points, 16 studies scored 8 points, and six studies scoring 9 points. Among the seven RCTs, five were rated as “some concerns” due to deviations from the intended interventions. One non-RCT was at moderate risk of bias. Figure 2 presents a comprehensive overview of the quality assessment of the included studies.

Associations between ctDNA and the prognosis of patients with solid cancer after NAT

Forty-one studies have evaluated the association between ctDNA status and prognostic outcomes in solid tumor patients receiving NAT. Statistical analysis revealed that, compared with ctDNA-negative patients, ctDNA-positive patients were significantly associated with all poor survival outcomes, including DFS/RFS [HR = 8.60; 95% CI: 6.06–12.21; $I^2=55.8\%$, $P < 0.001$] (Fig. 3A), OS [HR = 7.00; 95% CI: 4.28–11.45; $I^2=61.9\%$, $P < 0.001$] (Fig. 3B), PFS [HR = 3.85; 95% CI: 2.35–6.30; $I^2=0.0\%$, $P = 0.686$] (Fig. 3C), EFS [HR = 3.40; 95% CI: 1.67–6.95; $I^2=51.9\%$, $P = 0.065$] (Fig. 3D). To further explore the impact of ctDNA positivity across different tumor types, a subgroup analysis was performed. In rectal cancer, ctDNA positivity was associated with poor DFS/RFS [HR = 9.23; 95% CI = 4.29–19.86; $I^2=70.4\%$] and OS [HR = 9.72; 95% CI = 2.89–32.66; $I^2=66.9\%$] (Fig. 4A). In breast cancer, ctDNA positivity was associated with poor DFS/RFS [HR = 6.97; 95% CI = 4.20–11.56; $I^2=48.5\%$] and OS [HR = 3.61; 95% CI = 1.76–7.40; $I^2=0.0\%$] but was not significantly correlated with EFS [HR = 4.84; 95% CI = 0.93–25.15; $I^2=75.0\%$] (Fig. 4B). In esophageal cancer, ctDNA positivity was associated with poor DFS/RFS [HR = 10.83; 95% CI = 2.64–44.44; $I^2=0.0\%$] and OS [HR = 2.85; 95% CI = 1.45–5.61; $I^2=0.0\%$] (Fig. 4C). In urothelial cancer, ctDNA positivity was associated with poor DFS/RFS [HR = 27.92; 95% CI = 12.16–64.09; $I^2=17.8\%$] and OS [HR = 21.29; 95% CI = 10.51–43.11; $I^2=0.0\%$] (Fig. 4D). In lung cancer, ctDNA positivity was associated with poor DFS/RFS [HR = 4.59; 95% CI = 1.04–20.29; $I^2=NA$] and OS [HR = 25.00; 95% CI = 6.75–92.66; $I^2=NA$] but was not significantly correlated with EFS [HR = 2.96; 95% CI = 0.78–11.26; $I^2=49.6\%$] (Fig. 4E). In pancreatic cancer, ctDNA positivity was associated with poor DFS/RFS [HR = 5.02; 95% CI = 1.23–20.51; $I^2=NA$] and OS [HR = 11.70; 95% CI = 1.26–108.88; $I^2=NA$] (Fig. 4F). In colorectal liver metastasis, ctDNA positivity was associated with poor DFS/RFS [HR = 5.36; 95% CI = 2.63–10.90; $I^2=0.0\%$] and OS [HR = 4.20; 95% CI = 1.50–11.78; $I^2=NA$] (Fig. 4G); however, in melanoma, ctDNA positivity was not associated with DFS/RFS [HR = 10.8; 95% CI = 0.81–144.09; $I^2=NA$] (Fig. 4H). In gastric cancer, ctDNA positivity was associated with poor EFS [HR = 3.00; 95% CI = 1.30–6.91; $I^2=NA$], but there was no association with OS [HR = 7.17; 95% CI = 0.98–52.57; $I^2=71.8\%$] (Fig. 4I). Similarly, ovarian cancer was not associated with OS [HR = 2.46; 95% CI = 0.53–11.36; $I^2=0.0\%$] (Fig. 4J).

Subgroup analysis based on study design

Subgroup analysis based on study design indicated that in prospective cohort studies, positive ctDNA status was significantly correlated with worse DFS/RFS [HR = 9.39; 95% CI: 6.35–13.89; Supplementary Fig. 1A], OS [HR = 5.44; 95% CI: 3.24–9.13; Supplementary Fig. 1B], EFS [HR = 3.90; 95% CI: 1.65–9.19; Supplementary Fig. 1C], and PFS [HR = 3.68; 95% CI: 2.14–6.31; Supplementary Fig. 1D]. In RCTs, ctDNA positivity was not significantly associated with EFS [HR = 2.56; 95% CI: 0.44–14.94; Supplementary Fig. 1C]. However, ctDNA positivity was significantly associated with worse survival outcomes [DFS/RFS: HR = 5.60; 95% CI: 2.57–12.22; Supplementary Fig. 1A; OS: HR = 22.94; 95% CI: 9.94–52.94; Supplementary Fig. 1B; PFS: HR = 3.85; 95% CI: 1.06–14.00; Supplementary Fig. 1D].

Subgroup analysis based on ctDNA detection timing

Sixteen studies examined the association between postoperative ctDNA testing and DFS/RFS [HR = 14.88; 95% CI: 9.48–23.34; Supplementary Fig. 2A]; 10 studies examined the association between preoperative ctDNA testing and DFS/RFS [HR = 5.65; 95% CI: 4.06–7.85; Supplementary Fig. 2A]; three studies examined the association between baseline ctDNA testing and DFS/RFS [HR = 2.69; 95% CI: 1.66–4.37; Supplementary Fig. 2A]; four studies examined the association between preoperative ctDNA testing and EFS [HR = 3.90; 95% CI: 1.65–9.19; Supplementary Fig. 2B]; one study examined the association between baseline ctDNA testing and EFS [HR = 1.10; 95% CI: 0.30–4.10; Supplementary Fig. 2B]; one study examined the association between postoperative ctDNA testing and EFS [HR = 6.67; 95% CI: 1.37–32.39; Supplementary Fig. 2B]; nine studies examined the association between preoperative ctDNA testing and OS [HR = 5.23; 95% CI: 2.87–9.54; Supplementary Fig. 2C]; one study examined the association between baseline ctDNA testing and OS [HR = 13.21; 95% CI: 2.74–63.61; Supplementary Fig. 2C]; six studies examined the association between postoperative ctDNA testing and OS [HR = 9.92; 95% CI: 4.08–24.12]; four studies examined the association between preoperative ctDNA testing and PFS [HR = 3.22; 95% CI: 1.90–5.46; Supplementary Fig. 2D]; and three studies examined the association between postoperative ctDNA testing and PFS [HR = 13.10; 95% CI: 3.28–52.27; Supplementary Fig. 2D].

Subgroup analysis based on region

In both Asian and non-Asian populations, ctDNA positivity is associated with poor clinical outcomes. For DFS/RFS, the association was significant in Asian [HR = 8.30; 95% CI = 4.66–14.77; Supplementary Fig. 3A] and non-Asian populations [HR = 8.86; 95% CI = 5.61–13.98; Supplementary Fig. 3A]. Similarly, ctDNA positivity was linked to poor OS in Asian [HR = 3.61; 95% CI = 1.58–8.28; Supplementary Fig. 3B] and non-Asian populations [HR = 7.86; 95% CI = 4.51–13.70; Supplementary Fig. 3B]. For EFS, the association remained significant in Asian [HR = 6.67; 95% CI = 1.37–32.39; Supplementary Fig. 3C] and non-Asian populations [HR = 3.11; 95% CI = 1.40–6.92; Supplementary Fig. 3C]. For PFS, ctDNA positivity was significant in Asian [HR = 4.05; 95% CI = 2.24–7.31] and non-Asian populations [HR = 3.42; 95% CI = 1.39–8.41; Supplementary Fig. 3D].

Subgroup analysis based on neoadjuvant immunotherapy

In 22 cohort studies of patients who did not receive neoadjuvant immunotherapy, ctDNA detection was associated with poor DFS/RFS [HR = 8.67; 95% CI = 5.64–13.34] (Fig. 5A). In five cohort studies of patients who received immunotherapy, ctDNA detection was associated with poor DFS/RFS [HR = 5.11; 95% CI = 3.19–8.18] (Fig. 5A). In 10 cohort studies of patients who did not receive immunotherapy, ctDNA detection was associated with poor OS [HR = 5.25; 95% CI = 3.06–8.99] (Fig. 5B). In three cohort studies of patients who received immunotherapy, ctDNA detection was associated with poor OS [HR = 6.01; 95% CI = 1.75–20.67] (Fig. 5B). In four cohort studies of patients who received immunotherapy, ctDNA detection was associated with poor EFS [HR = 2.73; 95% CI = 1.25–5.97] (Fig. 5C). In two cohort studies of patients who did not receive immunotherapy, ctDNA detection was not significantly associated with poor EFS [HR = 9.88; 95% CI = 0.62–158.16] (Fig. 5C). In five cohort studies of patients who did not receive immunotherapy, ctDNA detection was associated with poor PFS [HR = 3.68; 95% CI = 2.14–6.31] (Fig. 5D). In one cohort study of patients who received immunotherapy, ctDNA detection was associated with poor PFS [HR = 3.85; 95% CI = 1.06–14.00] (Fig. 5D).

Subgroup analysis based on ctDNA detection methods

In 27 cohort studies where NGS was used for ctDNA detection, it was associated with poor DFS/RFS [HR = 8.93; 95% CI = 6.19–12.88; Supplementary Fig. 4A]. In two cohort studies where dPCR was used for ctDNA detection, it was associated with poor DFS/RFS [HR = 4.28; 95% CI = 1.39–13.23; Supplementary Fig. 4A]. In two cohort studies in which dPCR was used for ctDNA detection, it was associated with poor OS [HR = 3.15; 95% CI = 1.41–7.00; Supplementary Fig. 4B]. In 14 cohort studies in which NGS was used for ctDNA detection, it was associated with poor OS [HR = 7.95; 95% CI = 4.61–13.72; Supplementary Fig. 4B]. In five cohort studies in which NGS was used for ctDNA detection, it was associated with poor EFS [HR = 4.12; 95% CI = 1.99–8.57; Supplementary Fig. 4C]. In one study using dPCR for ctDNA detection, no significant association with EFS was found [HR = 1.10; 95% CI = 0.30–4.10; Supplementary Fig. 4C]. In two studies in which dPCR was used for ctDNA detection, it was associated with poor PFS [HR = 4.55; 95% CI = 1.66–12.48; Supplementary Fig. 4D]. In five studies, the use of NGS for ctDNA detection was associated with poor PFS [HR = 3.64; 95% CI = 1.96–6.77; Supplementary Fig. 4D].

Subgroup analysis based on statistical approaches

Regardless of univariate or multivariate analysis, ctDNA detection was consistently associated with poor survival outcomes: DFS/RFS [multivariate: HR = 8.34, 95% CI = 4.59–15.14; univariate: HR = 8.79, 95% CI = 5.63–13.74; Supplementary Fig. 5A], OS [multivariate: HR = 2.86, 95% CI = 1.16–7.05; univariate: HR = 7.57, 95% CI = 4.52–12.67; Supplementary Fig. 5B], EFS [multivariate: HR = 6.67, 95% CI = 1.37–32.39; univariate: HR = 3.11, 95% CI = 1.40–6.92; Supplementary Fig. 5C], and PFS [multivariate: HR = 2.78, 95% CI = 1.13–6.83; univariate: HR = 4.43, 95% CI = 2.45–7.99; Supplementary Fig. 5D].

Publication bias and sensitivity analysis

The results of the sensitivity analysis revealed that after the systematic exclusion of individual studies, there were no significant changes in the primary survival outcomes, indicating the stability of the meta-analysis results (Fig. 6A-B). Detailed changes in pooled effect estimates after each study exclusion were provided in Supplementary Table 2. Funnel plot and Begg's tests were used to assess publication bias in studies related to DFS/RFS and OS, and no significant bias was observed (Fig. 6C-F).

Discussion

This meta-analysis aims to explore the prognostic significance of ctDNA in patients with solid tumors receiving NAT and innovatively performs the following: (1) To our knowledge, this represents the most comprehensive meta-analysis in the field, encompassing 41 studies and 3,058 patients - the largest pooled cohort reported to date; (2) Our study is the first to integrate NAT in examining the relationship between ctDNA and prognosis across various solid tumors within the context of NAT; (3) We performed a comprehensive subgroup analysis to identify factors that may influence the association between ctDNA and study outcomes; (4) We included 20 high-quality studies with an impact factor (IF) ≥ 10 , such as *Nature Medicine*, *Nature Communications*, *JAMA Surgery*, *European Urology*, *Journal of Clinical Oncology*, *Gut*, and *Annals of Oncology*, enhancing the reliability and relevance of our findings. Therefore, our study is the most recent and comprehensive meta-analysis to date, surpassing the limitations of previous relevant studies and elucidating the prognostic significance of ctDNA in solid tumor patients receiving NAT. The findings clearly show a strong link between ctDNA positivity and worse survival outcomes. This indicates that ctDNA has the potential to be a reliable biomarker for predicting DFS, RFS, OS, PFS and EFS in patients with different solid tumors receiving NAT.

ctDNA enters the bloodstream via several mechanisms, including tumor cell apoptosis and necrosis, exosomes derived from tumor cells, tumor shedding, tumor angiogenesis, primary tumor metastasis, therapeutic interventions, and immune responses(74). In recent years, advances in NGS and dPCR technologies have greatly enhanced the sensitivity and accuracy of detecting ctDNA(75). Testing for gene mutations and epigenetic changes in ctDNA has shown a clear link to worse prognosis across several solid tumors, including breast cancer (76, 77), esophageal cancer(78, 79), rectal cancer (80–82), and urothelial cancer(83, 84). In addition to prognosis, the results of the first phase III clinical trial (CheckMate-816) of neoadjuvant immunotherapy combined with chemotherapy in lung cancer patients also demonstrated that ctDNA clearance is related to pCR(85). Having a comprehensive summary of the latest research in this area is essential for understanding the role of ctDNA in patients with solid tumors who are undergoing NAT.

To comprehensively clarify the association between ctDNA and prognosis in patients with solid tumors receiving NAT, we performed subgroup analyses on the basis of study design, detection time, region, tumor type, immunotherapy, detection methods, and statistical approaches (univariate vs multivariate analysis). We found that ctDNA demonstrated good consistency in prediction across different subgroups, especially in terms of detection methods, study design, region and statistical approaches. Additionally, ctDNA positivity was associated with worse survival in solid tumor patients following immunotherapy, suggesting that ctDNA has the potential to serve as a biomarker for neoadjuvant immunotherapy in solid tumors.

Subgroup analysis of tumor type revealed that ctDNA positivity was correlated with unfavorable OS and DFS/RFS in rectal cancer, breast cancer, esophageal cancer, urothelial cancer, lung cancer, pancreatic cancer and colorectal liver metastasis patients. These results are consistent with those of previously published meta-analyses. Papakonstantinou et al(77) systematically analyzed 11 studies on early breast cancer patients receiving NAT and reported a correlation between ctDNA positivity and worse RFS and OS. Sullivan et al(86) found that in cases of locally advanced rectal cancer, patients who tested positive for ctDNA after NAT had a notably higher risk of worse RFS. A meta-analysis conducted by Gögenur et al.(87) reviewed 10 studies encompassing 727 patients with rectal, breast, gastric, and bladder cancers receiving NAT. The analysis found that baseline, preoperative, and postoperative ctDNA positivity was significantly associated with cancer recurrence. We also find some negative evidence. In melanoma, ctDNA positivity was not statistically associated with DFS/RFS [HR = 10.8; 95% CI = 0.81–144.09]. The limited sample size and the disparity in the number of patients—only 4 positive cases compared to 36 negative ones—emphasize needing additional research with a larger group to obtain more reliable insights. Furthermore, gastric cancer patients [HR = 7.17; 95% CI = 0.98–52.57] and ovarian cancer patients [HR = 2.46; 95% CI = 0.53–11.36] had no significant associations with OS. This outcome may be partly due to the limited sample size, with small samples leading to broad confidence intervals. In addition, gastric and ovarian cancers are often diagnosed at advanced stages, with lower overall five-year survival rates(88, 89), and the short-term prognosis of advanced-stage patients may obscure the potential link between early ctDNA levels and long-term OS. No significant associations were found between ctDNA and EFS in lung cancer or breast cancer patients, which may be related to the multiple molecular subtypes and different treatment regimens used for these cancers. For example, breast cancer encompasses hormone receptor-positive, HER2-positive, and triple-negative subtypes, each with distinct biological behaviors and responses to therapy, potentially confounding the relationship between ctDNA and clinical outcome(90).

Our temporal stratification analysis confirms the superior prognostic capacity of postoperative ctDNA detection. Across multiple endpoints—DFS/RFS (HR = 14.88 vs 5.65 preoperative), OS, and PFS—postoperative assessment revealed stronger associations with disease recurrence than baseline or preoperative testing. This underscores two critical insights: First, the temporal context recalibrates ctDNA's clinical utility. While preoperative ctDNA reflects initial tumor shedding, postoperative detection captures established micrometastatic burden(91), explaining its enhanced predictive power for relapse monitoring. Second, the marked effect gradient between timepoints (postoperative > preoperative > baseline) revealed ctDNA's role in dynamic risk assessment. Serial postoperative monitoring can instruct adjuvant therapy decisions, transforming liquid biopsy from a static snapshot to a real-time surveillance tool during the critical treatment response window.

In conclusion, our meta-analysis revealed that ctDNA positivity is associated with poor DFS/RFS, OS, PFS, and EFS and can serve as a marker for relapse detection and survival prediction in NAT patients with rectal cancer, breast cancer, esophageal cancer, urothelial cancer, lung cancer, pancreatic cancer, and colorectal liver metastasis. However, its role in melanoma, gastric cancer, and ovarian cancer needs further investigation with larger sample sizes.

In the context of NAT, ctDNA has demonstrated considerable potential as a noninvasive biomarker, assisting in the evaluation of treatment response, prognosis prediction, and disease progression monitoring. Compared with traditional tissue biopsy, the continuous improvement in the sensitivity and specificity of ctDNA testing has made it a key monitoring tool for cancer patients, especially those receiving NAT, particularly for patients who cannot tolerate or are unsuitable for invasive surgery. Changes in ctDNA levels can dynamically reflect the tumor burden and treatment response. High preoperative ctDNA levels typically indicate a poor prognosis, whereas postoperative ctDNA negativity is associated with better survival outcomes. The half-life of ctDNA clearance in the blood is between 15 minutes and 2 hours, enabling real-time monitoring(92). Beyond its prognostic significance, ctDNA also contributes to surgical decision-making following neoadjuvant therapy. Pretreatment analysis of ctDNA in locally advanced cancers offers key insights into tumor biology and helps guide neoadjuvant therapy decisions(14, 17). By identifying patients likely to respond, it supports personalized treatment planning. During therapy, response can be tracked through changes in ctDNA levels, providing early evidence of tumor downstaging. This strategy has been shown to improve R0 resection rates, which are essential for achieving long-term cure(93). While neoadjuvant therapy carries known toxicities, surgery performed afterward typically has complication rates similar to immediate resection(94, 95). In some cases, it may even be technically easier due to tumor shrinkage. Importantly, patients receiving neoadjuvant treatment tend to experience better disease-free and overall survival outcomes. Postoperative ctDNA monitoring, usually starting around four weeks after surgery, offers a sensitive method to detect minimal residual disease(14). It also enables more accurate risk stratification, helping to inform decisions on further treatment and long-term surveillance. Furthermore, ctDNA analysis can also provide guidance for targeted therapy and immunotherapy, further enhancing the precision of treatment decisions on the basis of genetic mutations or copy number alterations in ctDNA. In terms of patient stratification, ctDNA monitoring can enable more refined management on the basis of the molecular characteristics and disease risks of patients, leading to more targeted and efficient treatment, avoiding excessive intervention in low-risk patients, and reducing side effects. Currently, the major challenges hindering the clinical application of ctDNA include the absence of standardized risk stratification thresholds and a lack of unified testing standards (96). To address these challenges, future research should prioritize the development of standardized ctDNA testing protocols tailored to tumor types, advancing the application of ctDNA in clinical settings.

The limitations of this study should also be acknowledged. First, although we performed multiple subgroup analyses and sensitivity analyses, the significant heterogeneity of the included studies and the small sample sizes of some subgroups may affect the stability and generalizability of the results.

Future studies should aim for larger, well-designed RCTs to strengthen the evidence supporting these findings. Second, the heterogeneity in ctDNA detection techniques and target selection poses a significant challenge for standardization and comparability across studies. Even when the same sequencing technology is employed, different cancer types often necessitate distinct gene panels. Also, the criteria for defining ctDNA positivity vary among studies,

further limiting interstudy comparability. For example, some studies define positivity as the detection of more than one ctDNA alteration(36), whereas others use a threshold variant allele frequency (VAF), such as ≥ 8 percentages(71). Additional approaches include defining positivity on the basis of the presence of single nucleotide variants (SNVs) (58)or an average VAF change exceeding 50%(59). These inconsistencies emphasize the urgent need for standardized methodologies and a consensus on ctDNA positivity criteria to increase the reproducibility and clinical application of ctDNA-based prognostic assessments. Third, current studies on the associations between ctDNA and prognosis in patients with gastric cancer, ovarian cancer, pancreatic cancer and melanoma receiving NAT are limited. The scarcity of relevant studies and the reliance on small sample sizes result in unstable and insufficient data analyses, hindering the ability to draw reliable conclusions. Further large-scale, high-quality studies are essential to better evaluate the role of ctDNA in predicting outcomes and therapeutic responses in these tumor types.

Conclusion

In conclusion, our meta-analysis revealed that ctDNA is an important prognostic biomarker for patients with solid tumors receiving NAT and effectively predicts survival outcomes such as DFS/RFS, OS, PFS and EFS. However, factors such as tumor type, treatment regimens, and the use of immunotherapy may influence the predictive ability of ctDNA. Future studies should further explore the prognostic role of ctDNA in different treatment contexts and enhance its clinical application.

Abbreviations

ctDNA
circulating tumor DNA
NAT
neoadjuvant therapy
DFS
disease-free survival
RFS
relapse-free survival
OS
overall survival
PFS
progression-free survival
EFS
event-free survival
HR
hazard ratio
CI
confidence interval
NGS
next-generation sequencing
dPCR
digital polymerase chain reaction
ddPCR
droplet digital polymerase chain reaction
WES
whole-exome sequencing
WGS
whole-genome sequencing
pCR
pathological complete response.

Declarations

Ethics approval and consent to participate

Not applicable. This study is a meta-analysis of previously published literature and does not involve direct human or animal subjects, nor the collection of primary patient data.

Consent for publication

Not applicable. This manuscript does not contain any individual person’s data, images, or clinical details that would require consent for publication.

Competing Interests

There are no conflicts of interest.

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Author Contribution

T. J. and E. D. contributed equally to the study. T.J. and K.Y. conceived and designed the study. T.J. and E.D. participated in acquisition and analysis of data. T.J., E.D., and K.Y. wrote the manuscript. T.J., E.D., X.F., Y.C., P.L., and Y.G. interpreted the data and revised the manuscript. All authors conducted final manuscript approval.

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Not applicable.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files. The original studies included in the meta-analysis are publicly available from the databases as cited in the reference list.

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Figure 1 Flow chart of the selection of studies and specific reasons for exclusion

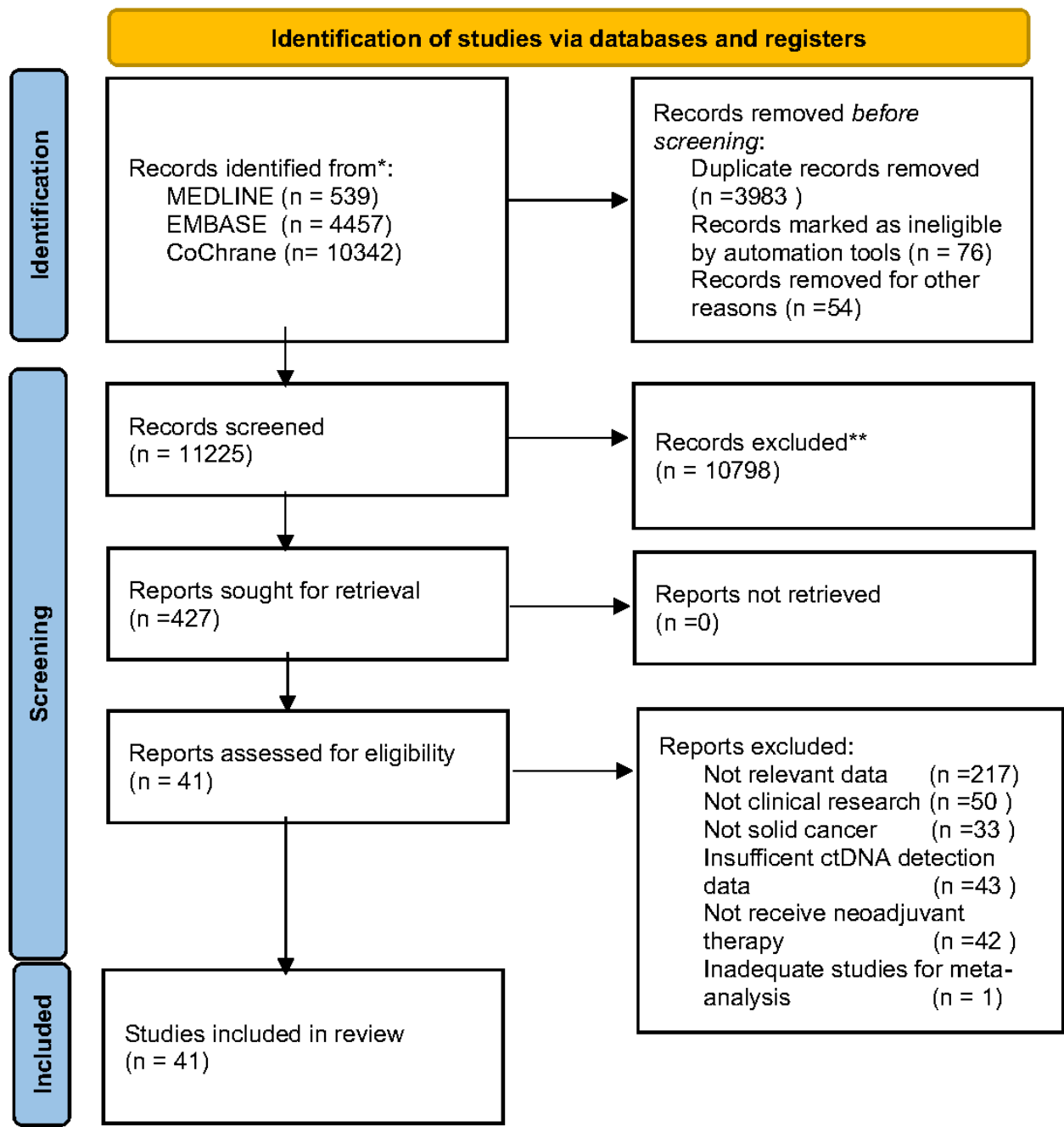


Figure 1

Flow chart of the selection of studies and specific reasons for exclusion

Figure 2 – Quality assessment of the eligible literatures

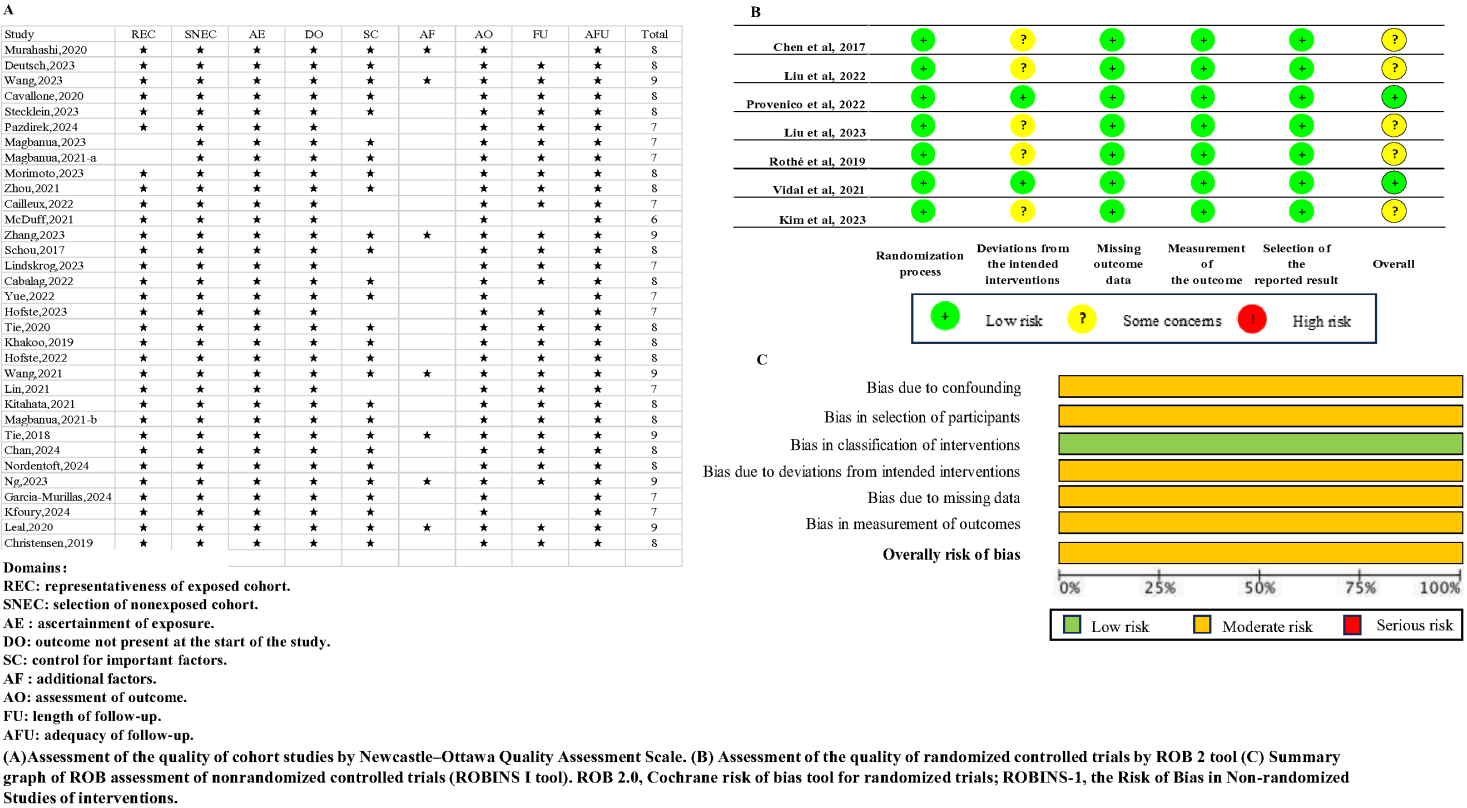
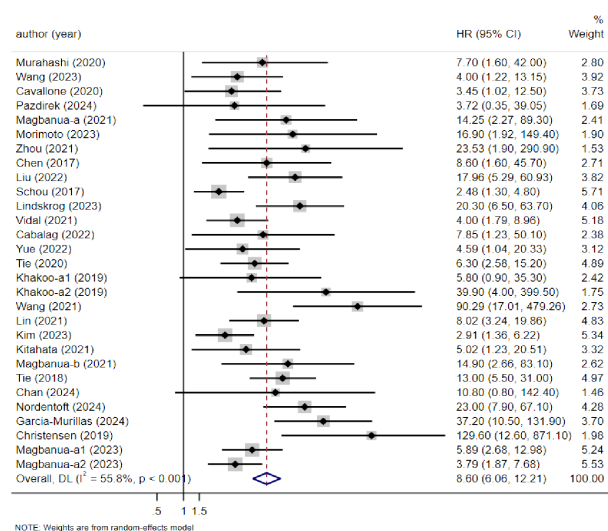


Figure 2

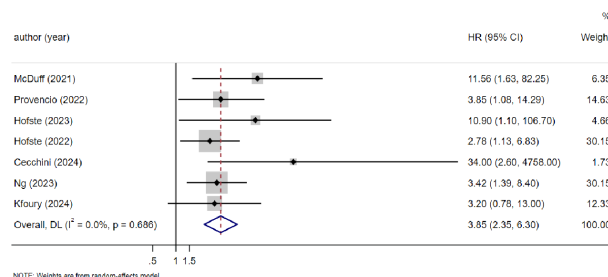
Quality assessment of the eligible literatures. (A)Assessment of the quality of cohort studies by Newcastle–Ottawa Quality Assessment Scale. (B) Assessment of the quality of randomized controlled trials by ROB 2 tool (C) Summary graph of ROB assessment of nonrandomized controlled trials (ROBINS I tool). ROB 2.0, Cochrane risk of bias tool for randomized trials; ROBINS-1, the Risk of Bias in Non-randomized Studies of interventions.

Figure 3

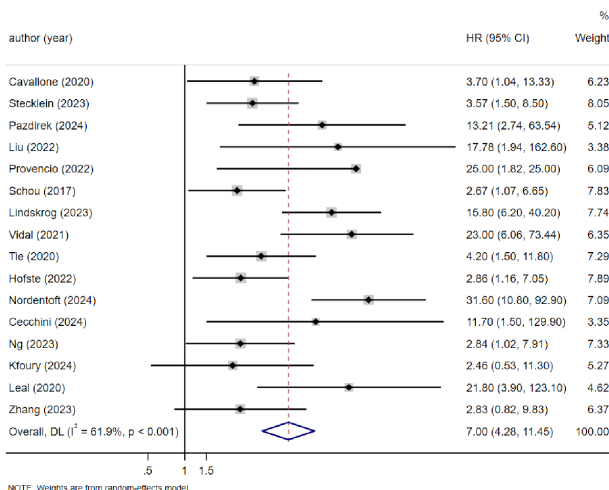
A DFS/RFS



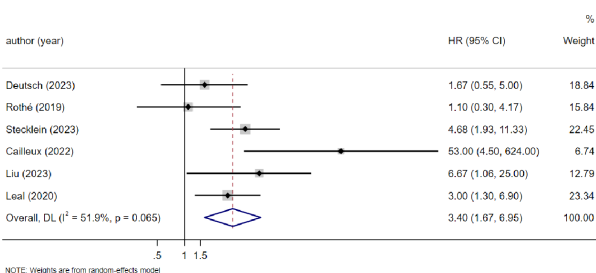
C PFS



B OS



D EFS



Forest plots of studies demonstrating the association between circulating tumor DNA positivity and survival outcomes in solid cancer patients who received neoadjuvant treatment. (A) Disease-free survival/recurrence-free survival. (B) Overall survival. (C) Progression-free survival. (D) Event-free survival. DFS/RFS, disease-free survival/recurrence-free survival; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; HR, Hazard ratio.

Figure 3

Forest plots of studies demonstrating the association between circulating tumor DNA positivity and survival outcomes in solid cancer patients who received neoadjuvant treatment. (A) Disease-free survival/recurrence-free survival. (B) Overall survival. (C) Progression-free survival. (D) Event-free survival. (E) Metastasis-free survival. DFS/RFS, disease-free survival/recurrence-free survival; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; HR, Hazard ratio.

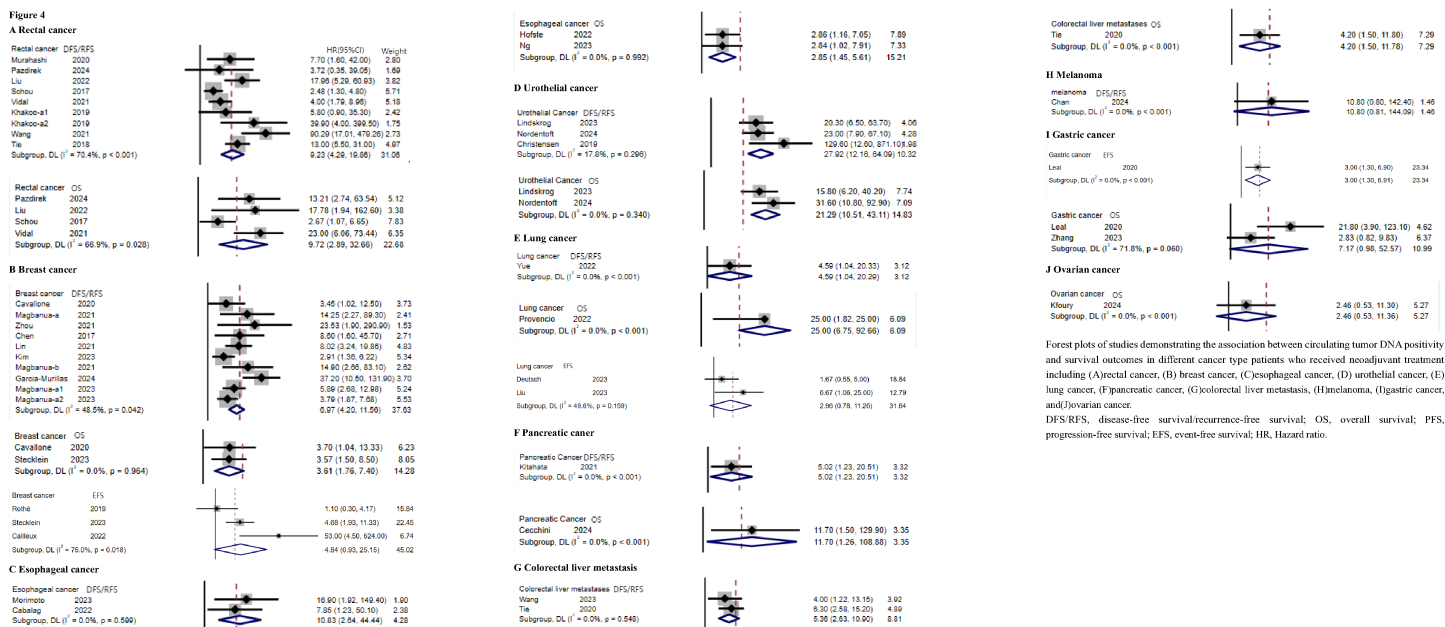
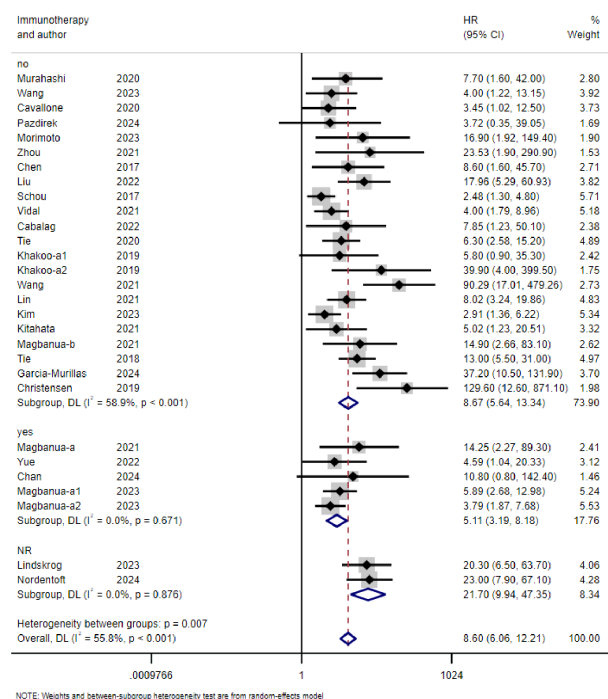


Figure 4

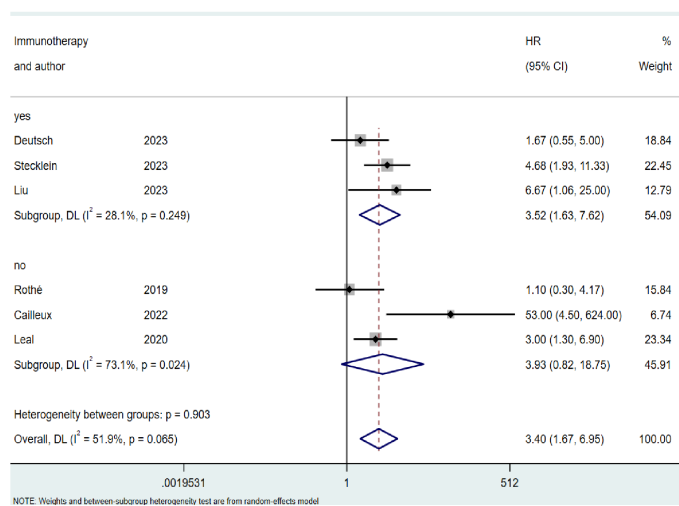
Forest plots of studies demonstrating the association between circulating tumor DNA positivity and survival outcomes in different cancer type patients who received neoadjuvant treatment including (A)rectal cancer, (B) breast cancer, (C)esophageal cancer, (D) urothelial cancer, (E) lung cancer, (F)pancreatic cancer, (G)colorectal liver metastasis, (H)melanoma, (I)gastric cancer, and(J)ovarian cancer. DFS/RFS, disease-free survival/recurrence-free survival; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; HR, Hazard ratio.

Figure 5

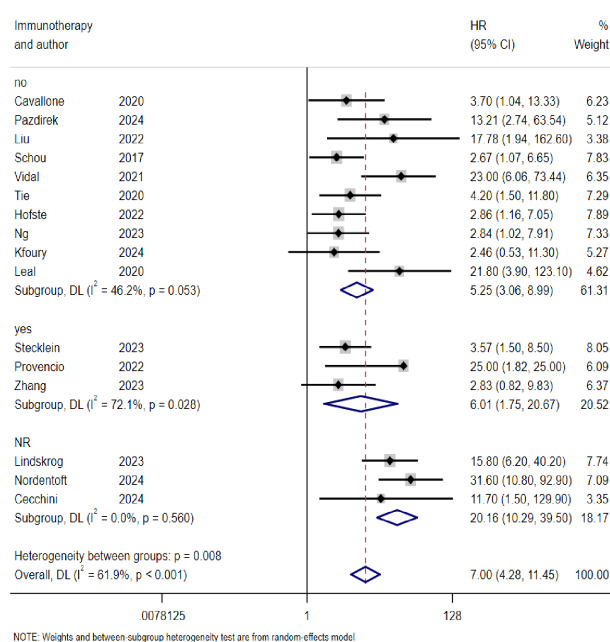
A DFS/RFS



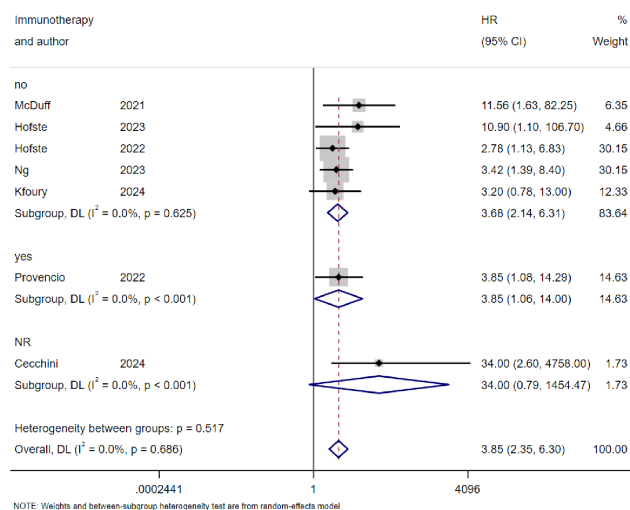
C EFS



B OS



D PFS

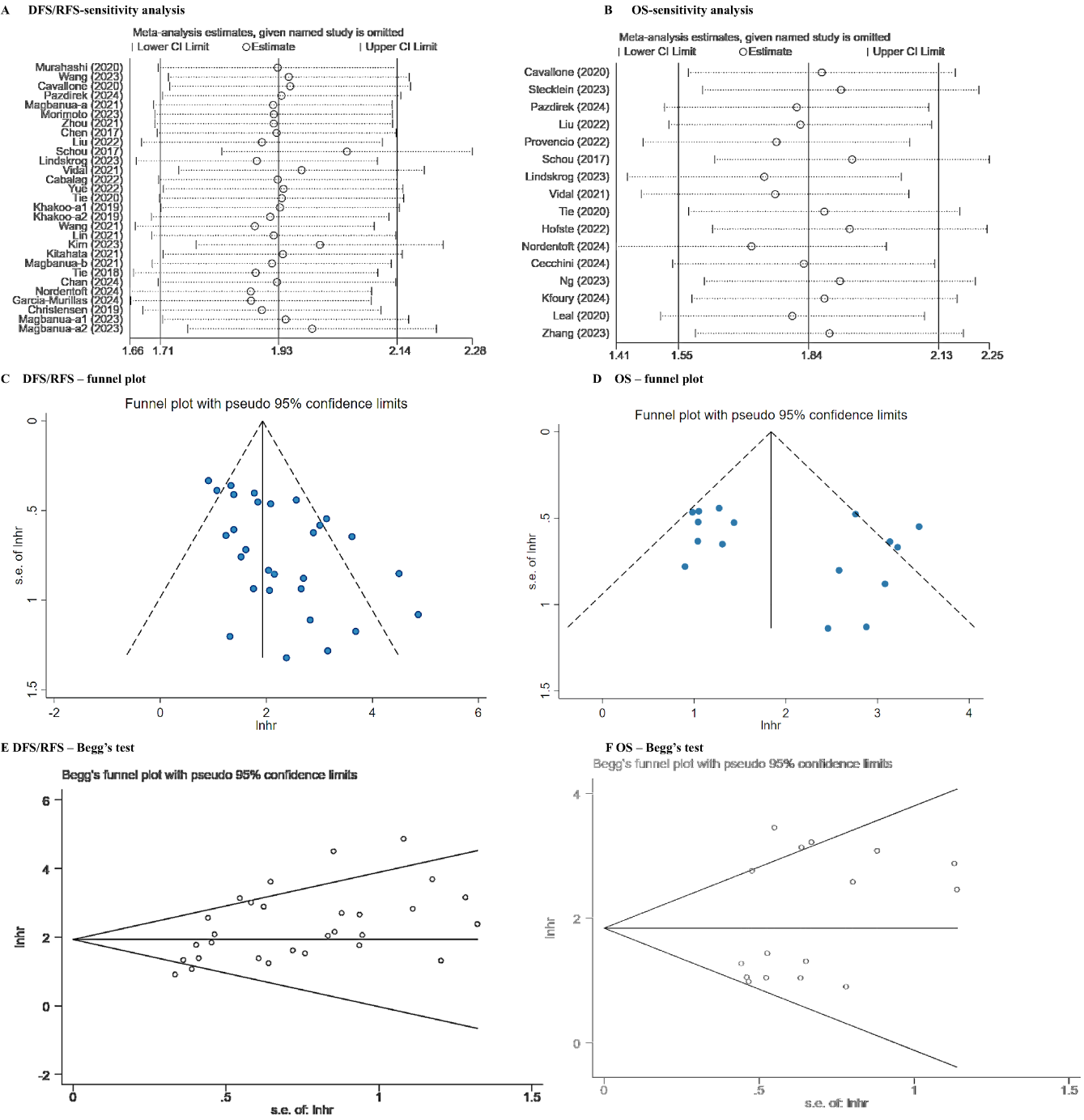


Forest plots of studies demonstrating the association between circulating tumor DNA positivity and survival outcomes in solid cancer patients who received neoadjuvant immunotherapy. (A) Disease-free survival/recurrence-free survival. (B) Overall survival. (C) Event-free survival. (D) Progression-free survival. DFS/RFS, disease-free survival/recurrence-free survival; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; HR, Hazard ratio; NR, not reported.

Figure 5

Forest plots of studies demonstrating the association between circulating tumor DNA positivity and survival outcomes in solid cancer patients who received neoadjuvant immunotherapy. (A) Disease-free survival/recurrence-free survival. (B) Overall survival. (C) Event-free survival. (D) Progression-free survival. DFS/RFS, disease-free survival/recurrence-free survival; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; HR, Hazard ratio; NR, not reported.

Figure 6 Publication bias and sensitivity analysis



The publication bias for the meta-analysis of ctDNA for disease-free survival/recurrence-free survival and overall survival was assessed using various methods. These included (A) DFS/RFS - sensitivity analysis, (B)OS - sensitivity analysis, (C)DFS/RFS – funnel plot, (D)OS – funnel plot; (E)DFS/RFS - Begg's test, and (F)OS - Begg's test. DFS/RFS, disease-free survival/recurrence-free survival; OS, overall survival.

Figure 6

The publication bias for the meta-analysis of ctDNA for disease-free survival/recurrence-free survival and overall survival was assessed using various methods. These included (A) DFS/RFS - sensitivity analysis, (B)OS - sensitivity analysis, (C)DFS/RFS – funnel plot, (D)OS – funnel plot; (E)DFS/RFS - Begg's test, and (F)OS - Begg's test. DFS/RFS, disease-free survival/recurrence-free survival; OS, overall survival.

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