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Perspective

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The prognostic and clinical utility of circulating tumor DNA in diffuse large B-cell lymphoma: a systematic review and meta-analysis

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Circulating tumor DNA (ctDNA) provides a minimally invasive tool for assessing tumor burden and genetic evolution in diffuse large B-cell lymphoma (DLBCL). This systematic review and meta-analysis evaluated 53 studies reporting the association of ctDNA and survival outcomes. High ctDNA concentration at baseline was associated with increased progression risk (hazard ratio (HR): 2.50, 95% confidence interval (CI) 2.15–2.9). The prognostic power of ctDNA intensified during treatment, with end of treatment (EOT) positivity showing the strongest association (HR: 13.69, 8.37–22.39). In patients with a negative EOT positron emission tomography (PET) scan, positive ctDNA was highly specific (90.8%) for subsequent relapse. Critically, in patients with a positive EOT PET scan, a negative ctDNA result decreased the risk of relapse (negative likelihood ratio 0.15, 0.06–0.3). ctDNA concentration reliably reflects tumor burden and treatment response, refining PET findings. Future studies should standardize ctDNA protocols and assess the feasibility of ctDNA-based DLBCL management.

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL)[1] and demonstrates significant biological, molecular, and clinical heterogeneity[2]. Despite recent therapeutic advancements[3], variations in DLBCL pathophysiology among patients—affecting disease progression and treatment response—continue to pose significant challenges in the diagnosis, prognosis, and clinical management of this malignancy[4]. Conventional monitoring strategies (e.g., tissue biopsy and radiologic imaging) face inherent limitations, including invasiveness, insufficient sensitivity, and inability to dynamically assess tumor burden or capture DLBCL's unique genetic characteristics in individual patients[5,6]. Recent evidence indicates that established prognostic tools—such as molecular classification systems[7–10], the International Prognostic Index (IPI)[11,12], and total metabolic tumor volume[13,14] may have limited clinical utility in guiding personalized treatment strategies for DLBCL[5,6]. The challenges of dynamic monitoring and the practical infeasibility of repeated tissue biopsies underscore the urgent need for innovative, non-invasive approaches to precisely track therapeutic responses and enable early detection of progressive disease (PD)[15]. Circulating tumor DNA (ctDNA) has emerged as a promising minimally invasive biomarker, enabling dynamic and precise assessment of tumor burden while capturing evolving genetic diversity throughout treatment[16,17]. It represents the tumor-derived fraction of cell-free DNA (cfDNA), arising primarily from cellular breakdown processes of the tumor, such as apoptosis, necrosis, and/or phagocytosis[18].

Current literature highlights the potential of ctDNA for tumor surveillance across various solid and hematologic malignancies[19], emphasizing

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its diverse applications, including non-invasive tumor genotyping, diagnosis, dynamic minimal residual disease (MRD) assessment, early relapse detection, prognostic stratification, and survival prediction. Recently, the National Comprehensive Cancer Network (NCCN) recommended incorporating ctDNA-based MRD testing (ctDNA-MRD) in DLBCL patients with positive positron emission tomography (PET) scans at the end of treatment (EOT), particularly when biopsy is not feasible[20].

Immunoglobulin gene sequencing-based detection of ctDNA before starting the third cycle of dose-adjusted chemotherapy has demonstrated prognostic utility in predicting time to progression (TTP) in DLBCL patients. The ease of sample collection for ctDNA analysis allows for repeated testing, which could provide ongoing insights into tumor dynamics before and during therapy[17,21,22].

While ctDNA holds promise as an early clinical trial endpoint[23–26], its inconsistent diagnostic accuracy[27,28], prognostic significance, and predictive capacity for clinical outcomes in DLBCL patients—observed across studies evaluating baseline and interim ctDNA[17,25,29–31]—raise concerns regarding its effectiveness[32,33]. This inconsistency, characterized by variable sensitivity thresholds and contradictory survival correlations, hinders ctDNA's standardization and practical implementation as a robust clinical tool.

In this systematic review and meta-analysis, we comprehensively evaluated the literature to clarify the prognostic power of ctDNA in patients with DLBCL. Additionally, we assessed diagnostic accuracy, prognostic concordance with established biomarkers, and the capacity to monitor therapeutic responses through ctDNA assays. Furthermore, we assessed the utility of ctDNA in patients with positive and negative PET scans to assess whether it provides additional prognostic stratification for guidance of treatment. Ultimately, we aimed to provide clear, evidence-based guidance on whether ctDNA assays can effectively complement existing prognostic approaches, enhancing clinical decision-making and patient management in DLBCL.

Results

Search results and study selection

A total of 2159 publications were identified through our literature search across five databases: PubMed (295), Embase (1131), Cochrane Library[34], Scopus (321), and Web of Science (357). After removing 811 duplicate records, 1167 publications were excluded during title/abstract screening. Full-text evaluation excluded 131 studies that did not meet the inclusion criteria, yielding 41 eligible studies. An updated search on August 25, 2025, identified 152 additional articles, from which 26 underwent full-text review and 12 were included. The final systematic review comprises 53 studies, with 50 included in the meta-analysis. The PRISMA diagram illustrating the screening process is shown in Fig. S1, and quality assessments of the studies are reported in Table S2.

Characteristics of eligible studies

Among the included studies, 30 were prospective cohort studies, 13 were retrospective cohort studies, 7 were clinical trials, and 3 were case-control studies. The patient cohorts consisted primarily of newly diagnosed (37 studies) and relapsed/refractory (12 studies) populations. Four studies included a mixed cohort or did not specify the disease stage. The therapeutic approaches were diverse: 35 studies utilized R-CHOP-based regimens, eight focused on CAR T-cell therapy, six used targeted therapies, and two included autologous stem cell transplantation (ASCT). The specific R-CHOP-based regimens were themselves heterogeneous, as detailed in Table 1. A total of 47 studies evaluated cfDNA/ctDNA concentrations and variant allele frequencies (VAF), while three studies focused on methylation patterns. Additional studies explored copy number alterations, mutation-based scoring, and other molecular markers (Table S3). The detection techniques used were varied, with details provided in Table 1.

Prediction of disease progression

The risk of disease progression was evaluated using baseline ctDNA/cfDNA concentrations, classified as low or high. High baseline ctDNA/cfDNA levels were linked to increased progression risk (pooled HR: 2.50, 95% CI: 2.15–2.9, $I^2 = 0\%$, $p < 0.01$; Fig. 1A), across 22 studies involving 1081 patients below the cutoff and 861 above. Subgroup analyses found no significant differences in this association based on the analyte measured (cfDNA vs. ctDNA, $p = 0.47$), the ctDNA detection method ($p = 0.28$), or the line of treatment ($p = 0.11$) (Fig. S2A–C). In a focused analysis of three studies on advanced-stage disease, baseline cfDNA/ctDNA also strongly correlated with progression risk ($p < 0.01$) (Fig. S3A). (Fig. S3A).

Treatment response was defined either as a Molecular Response (changes in ctDNA levels from baseline) or as clearance of ctDNA (MRD) at a predefined time point.

In studies using chemoimmunotherapy, 12 assessed response at an interim time point (C1–C6; 380 responders vs. 203 non-responders), yielding a pooled HR for progression of 4.0 (95% CI: 3.01–5.31, $I^2 = 14.7\%$). Seven studies used an End-of-Treatment (EOT) collection (413 responders vs. 105 non-responders), which showed a pooled HR of 13.69 (95% CI: 8.37–22.39, $I^2 = 19.9\%$). The prognostic value of the EOT assessment was significantly higher than the interim assessment ($p < 0.01$) (Fig. 2A).

For the interim collection studies, there was no significant difference in prognostic value between those using molecular response (7 studies) and those using MRD (7 studies) ($p = 0.89$) (Fig. S4A). Among the seven molecular response studies, no difference was found between the 3 using CAPP-Seq and 4 using other hybrid capture-based methods ($p = 0.28$) (Fig. S5A), nor between the six collecting at C2 and two at C3. In the 7 MRD studies, no difference was seen by detection method (3 hybrid capture, 3 Ig-NGS, 1 PhasED-Seq; $p = 0.52$) (Fig. S5C) or by collection time (5 at C2, one at C3, three at C4). There was also no significant difference based on line of therapy ($p = 0.76$) (Fig. S6A).

For the EOT collection, seven studies used clearance of ctDNA (MRD). No studies assessed molecular response by ctDNA at this time point; however, two studies that used molecular response defined by total cfDNA showed a significantly lower prognostic association ($p < 0.01$) and were therefore excluded from the main EOT analysis (Fig. S7A). In the remaining seven ctDNA MRD studies, no significant differences were found based on the detection method (3 used Ig-NGS, 2 used hybrid capture, one used PhasED-Seq, and 1 used mPCR-NGS; $p = 0.62$) (Fig. S5E) or line of treatment ($p = 0.49$) (Fig. S6C). Furthermore, a meta-regression of these EOT MRD studies using the assay detection limit as a covariate showed no significant influence on the results ($p = 0.97$) (Fig. S8).

In three studies of CAR T-cell therapy (2 using MRD and 1 using molecular response; 54 responders vs. 49 non-responders), the pooled HR for progression was 4.07 (95% CI: 1.61–10.26) (Fig. S9A).

Prediction of overall survival

Similar to its association with disease progression, high baseline cfDNA/ctDNA levels were a significant predictor of worse overall survival (OS). Across 20 studies (984 low vs. 649 high), elevated baseline concentrations were associated with a pooled HR for mortality of 2.67 (95% CI: 2.29–3.35, $I^2 = 16.1\%$, $p < 0.01$; Fig. 1B). Stratification by cfDNA/ctDNA type ($p = 0.73$), ctDNA detection method ($p = 0.45$), or line of treatments ($p = 0.27$) revealed no significant difference (Fig. S2B–D). In two studies exclusively focusing on advanced-stage patients, baseline cfDNA/ctDNA levels were significantly linked to OS ($p < 0.01$) (Fig. S3B).

Dynamic monitoring during chemoimmunotherapy also provided strong prognostic information for OS. In nine studies using interim collection (312 responders vs. 174 non-responders), a lack of response was associated with poorer survival (HR: 4.48, 95% CI: 2.78–7.22, $I^2 = 0\%$). Similarly, in five studies using EOT collection (226 responders vs. 64 non-responders), the association was even stronger (HR: 8.27, 95% CI: 4.54–15.06, $I^2 = 31\%$) (Fig. 2B). Although a trend towards a stronger prognostic value at EOT was observed, the difference between interim and EOT assessments did not reach statistical significance ($p = 0.12$).

In the interim studies, no significant differences were found between studies assessing MRD ($n = 5$) versus molecular response ($n = 5$) ($p = 0.51$) (Fig. S4B), nor by line of therapy ($p = 0.25$) (Figure S6B) or detection

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Table 1 | Basic characteristics and detection techniques of the included studies

	Country	Design	Population	Total	Age (years)	Male %	Stage (III, IV %)	Treatments	Measurement	Detection Technique
Hohaus et al.[16]	Italy	Prospective Cohort	DLBCL	63	58 (15–92)	51%	NA	R-CHOP, R-CHOP + R-MICmA consolidation + HCT + PBSCT, CVP, FND	cfDNA	qPCR
Kurtz et al.[55]	USA, Australia	Prospective Cohort	DLBCL, NOS (54), tDLBCL (13), PTLD (8)	75	58	58%	76%	DA-EPOCH-R, R-CHOP like, Modified Magrath, Other, none	ctDNA	lgNGS
Roschewski et al.[17]	USA	Retrospective Cohort	DLBCL, NOS (58), HIV-associated (24), MBL (44)	126	44 (14–85)	62%	56%	EPOCH w/wo Rituximab	ctDNA	lgNGS
Assouline et al.[56]	Canada	Clinical Trial	DLBCL (40)	40	60 (29–79)	53%	65%	Panobinostat w/wo Rituximab	ctDNA	CAPP-Seq & dPCR
Camus et al.[57]	France	Retrospective Cohort	DLBCL (11), PMBCL (3)	14	71	45%	78%	NA	ctDNA	mPCR-NGS & dPCR
Kristensen et al.[58]	Denmark	Retrospective Cohort	DLBCL (71)	71	60 (23–85)	53%	74%	Rituximab	cfDNA	Methylation (PCR pyrosequencing)
Li et al.[59]	China	Prospective Cohort	DLBCL (98)	98	NA	61%	57%	NA	cfDNA	qPCR
Kurtz et al.[29]	North America, Europe	Prospective Cohort	DLBCL (168), DLBCL, transformed low grade (25), PMBCL (24)	217	57	NA	68%	R-CHOP, DA-EPOCH-R, anthracycline and platinum-based regimen	ctDNA	CAPP-seq
Chiu et al.[60]	USA	Prospective Cohort	DLBCL (48)	48	58 (24–82)	63%	50%	R-CHOP, EPOCH-R, other	cfDNA	Methylation (5hmC-Seal)
Eskandari et al.[61]	Iran	Prospective Cohort	DLBCL (40)	40	NA	60%	50%	R-CHOP	cfDNA	qPCR
Sun et al.[62]	China	Retrospective Cohort	DLBCL (24)	24	NA	NA	NA	NA	cfDNA	Hybrid capture
Decazes et al.[63]	France	Prospective Cohort	DLBCL (27)	27	69 (20–93)	56%	74%	R-CHOP, R-CHOP-like	ctDNA	dPCR
Deng et al.[64]	USA	Prospective Cohort	DLBCL (16), tFL (6), PMBCL (2)	24	NA	NA	NA	CAR T-cell	cfDNA	Hybrid capture
Hur et al.[65]	South Korea	Prospective Cohort	DLBCL (51)	51	56 (18–83)	55%	63%	R-CHOP	cfDNA	nr
Bruscaggin et al.[66]	Switzerland	Clinical Trial	DLBCL (28)	28	61 (45–71)	68%	NA	Ibrutinib + Nivolumab	ctDNA	CAPP-Seq
Frank et al.[67]	USA	Prospective Cohort	DLBCL (49), tFL (17), PMBCL (6)	72	62 (19–79)	60%	72%	CAR T-cell	ctDNA	lgNGS
Rivas-Delgado et al.[68]	Spain	Prospective Cohort	DLBCL, NOS (63), HGBCL (16)	79	63 (20–94)	49%	78%	R-CHOP, Intensive chemoimmunotherapy, R-CVP/ R-GEMOX	ctDNA	Hybrid capture
Shimada et al.[30]	Japan	Prospective Cohort	IVLBCL (21)	21	70 ± 10	62%	100%	R-CHOP + HDMTX + ITCT, R-CHOP or R-CHOP-like w/wo ITCT by HCT	cfDNA	WES, Hybrid capture
Cherng et al.[69]	USA	Prospective Cohort	DLBCL (72), TIL (43), PMBCL (7)	122	61 (18–88)	71%	81%	CAR T-cell	cfDNA	lpWGS
Guan et al.[70]	China	Prospective Cohort	DLBCL (85)	85	NA	62%	62%	R-CHOP	ctDNA	Hybrid capture
Herrera et al.[39]	USA	Clinical Trial	R/R DLBCL (68), DLBCL (45)	113	70.5	66%	77%	Polatuzumab Vedotin + BR	ctDNA	CAPP-Seq
Li et al.[40]	China	Retrospective cohort	DLBCL (73)	73	57	47%	68%	R-CHOP, R-CHOP-like	ctDNA	Hybrid capture

Table 1 (continued) | Basic characteristics and detection techniques of the included studies

	Country	Design	Population	Total	Age (years)	Male %	Stage (III, IV %)	Treatments	Measurement	Detection Technique
Meriranta et al.[71]	Finland	Prospective Cohort	DLBCL (101)	101	(18 to 65)	NA	NA	R-CHOP, others	ctDNA	Hybrid capture + PhasED-Seq
Raman et al.[72]	Belgium	Prospective Cohort	DLBCL, NOS (61), EBV + DLBCL (4), PMBCL (10), HGBCL (2), THRLBCL (2), IVLBCL (1), plasmablastic lymphoma (1)	81	NA	NA	NA	R-CHOP	cfDNA	CNA-WGS
Shirouchi et al.[31]	Japan	Retrospective Cohort	DLBCL (66)	66	NA	50%	39%	R-CHOP-like	cfDNA	nr
Zhang et al.[73]	China	Prospective Cohort	DLBCL (33), PCNSL (3), PMBCL (1), tFL (1)	38	59 (25–71)	42%	69%	R-CHOP	ctDNA	cSMART
Bastos-Oreiro et al.[74]	Spain	Retrospective cohort	DLBCL (45), tFL (8), PMBCL (5)	58	NA	55%	22%	CAR T-cell	cfDNA	QuantiFluor dsDNA System
Cherng et al.[75]	USA	clinical trial	DLBCL (33)	33	NA	NA	NA	lenalidomide + obinutuzumab + CHOP	ctDNA	CAPP-Seq + PhasED-Seq
Desmots-Loyer et al.[25]	France	Clinical Trial	DLBCL (123)	123	50 (42–56)	61%	80%	R-CHOP, R-Chemo + ASCT	cfDNA	nr
Merryman et al.[37]	USA	Prospective Cohort	R/R DLBCL: DLBCL NOS (75), TIL (34), PMBCL (7)	116	59 (23–77)	59%	NA	ASCT	ctDNA	IgNGS
Sworder et al.[47]	USA	Prospective Cohort	R/R DLBCL: DLBCL (72), HGBCL (20), PMBCL (6), tFL (39), THRLBCL (1)	138	60.5 (49–72)	66%	69%	CAR T-cell	ctDNA	CAPP-Seq
Alcoceba et al.[76]	Spain	Prospective Cohort	DLBCL (68)	68	65 (34–85)	60%	78%	R-CHOP	ctDNA	Hybrid capture
Chen & Di et al.[77]	China	Retrospective Cohort	IVLCBL (34), DLBCL (37)	71	60 (41–75)	55%	87%	R-CHOP + Zanubrutinib, R-CHOP, R-CHOP + MTX, R-CHOP + Zanubrutinib + MTX, R-MTX	ctDNA	Hybrid capture
Diez-Feijóo et al.[78]	Spain	Retrospective Cohort	DLBCL, NOS (60), tLBCL (13), PMBCL (7), DLBCL, CNS (5), HGBCL (3)	88	67 (19–91)	58%	57%	R-CHOP, R-EPOCH-DA	cfDNA	mPCR-NGS
Duffles et al.[79]	Brazil	Prospective Cohort	DLBCL (18)	18	60 (24–84)	44%	64%	R-CHOP	cfDNA	mPCR-NGS
Elbordiny et al.[28]	Egypt	Case -Control	DLBCL (30)	30	(43–91)	NA	83%	NA	cfDNA	qPCR
Ghanem et al.[80]	Egypt	Case -Control	HCV-associated DLBCL (41), non-HCV associated DLBCL (30)	71	58 ± 9	NA	NA	R-CHOP	cfDNA	qPCR
Heger et al.[81]	Germany	Prospective Cohort	R/R DLBCL (12)	12	68 (44–79)	58%	92%	CAR T-cell, HCT-ASCT, CT + AlloSCT	ctDNA	IgNGS + dPCR
Melani et al.[82]	USA	Clinical Trial	R/R DLBCL: Non-GCB DLBCL, NOS (13), HGBCL (20), THRLBCL (5), GCB DLBCL, NOS (12)	50	61 (29–77)	66%	92%	VIPOR	ctDNA	IgNGS
Narkhede et al.[36]	USA	Retrospective Cohort	DLBCL (50)	50	59 (26–84)	44%	70%	R-CHOP, R-EPOCH, R-ICE, R-CHP-POLA, Other	ctDNA	mPCR-NGS
Soscia et al.[83]	multicenter	Prospective Cohort	DLBCL, NOS (49), HGBCL with rearrangements (10), tIL (8), HGBCL, NOS (6)	73	65 (19–85)	52%	56%	R-CHOP, R-CHOP-like regimens	ctDNA	IgNGS
Tabari et al.[84]	USA	Retrospective Cohort	DLBCL (310)	310	64 (18–86)	53%	75%	R-CHP, R-CHOP, R-obinutuzumab	ctDNA	CAPP-Seq

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Table 1 (continued) | Basic characteristics and detection techniques of the included studies

	Country	Design	Population	Total	Age (years)	Male %	Stage (III, IV %)	Treatments	Measurement	Detection Technique
Witzig et al.[85]	USA	Case -Control	DLBCL (100)	100	NA	NA	NA	CAR T-cell	cfDNA	Methylation (qPCR)
Zou et al.[15]	China	Prospective Cohort	DLBCL (14), HGBCL (5), tFL (4)	23	45 ± 24	74%	44%	CAR T-cell	ctDNA	Hybrid capture
Moia et al.[86]	multicenter	Prospective Cohort	DLBCL (166)	166	67 (53–76)	NA	71%	R-CHOP	ctDNA	CAPP-Seq
Zhang et al.[87]	China	Prospective Cohort	DLBCL (119)	119	NA	NA	NA	R-CHOP	cfDNA	Hybrid capture, methylation
Roschewski et al.[41]	USA	Prospective cohort	DLBCL (111), HGBCL (19), PMBCL (7)	137	62 (21–85)	53%	76%	Anthracycline-based	ctDNA	PhasED-Seq
Zhao et al. 2025 (R/R)[88]	Canada	Retrospective cohort	DLBCL NOS (49), HGBL (12), TCRBCL (1)	62	58 (25–75)	Nr	nr	ASCT, CAR-T	ctDNA	lpWGS
Zhao et al. 2025 (ND)[88]	Canada	Retrospective cohort	DLBCL NOS (94), HGBL (5), TCRBCL (1), PMBCL (1)	101	65 (19–90)	54%	47%	R-CHOP, R-mini-CHOP, R-CHOP/HD-MTX, DA-EPOCH-R	ctDNA	lpWGS
Wang et al.[89]	China	Retrospective cohort	DLBCL (33)	33	52 (39–78)	55%	77%	R-CHOP-based	ctDNA	lgNGS
Waltham et al.[90]	Australia	Prospective cohort	DLBCL (16), HGBCL (1)	17	53 (18–79)	65%	88%	R-CHOP-based, Dinaciclib + pembrolizumab	ctDNA	Hybrid capture
Song et al.[91]	Korea	Prospective cohort	DLBCL, PMBCL	52	70 (28–84)	59.6%	92.40%	R-CHOP	ctDNA	Hybrid capture
Leppä et al.[92]	Nordic countries	Clinical Trial	DLBCL NOS (102), HGBCL (14), THRLBCL (4), grade 3B FL (3)	123	55 (19–64)	57%	90%	R-CHOP + MTX	ctDNA	Hybrid capture
Dondolin et al.[93]	Italy	Prospective cohort	frontline DLBCL (NOS)	120	67 (51–76)	42%	73%	R-CHOP based	ctDNA	CAPP-Seq

AmpliSeq amplicon sequencing, *ASCT* autologous stem cell transplantation, *BR* bendamustine & rituximab, *CAPP-Seq* cancer personalized profiling by deep sequencing, *CAR T-cell* chimeric antigen receptor t-cell, *cfDNA* cell-free DNA, CHO, cyclophosphamide, doxorubicin, vincristine, prednisone, *ctDNA* circulating tumor DNA, *CNA-WGS* copy number alteration whole-genome sequencing, *cSMART* circulating single-molecule amplification and re-sequencing technology, *CT* chemotherapy, *CVP* cyclophosphamide, vincristine, prednisone, *DA-EPOCH-R* dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab, *DLBCL* diffuse large b-cell lymphoma, *dPCR* digital polymerase chain reaction, *EBV* Epstein-Barr virus, *FND* fludarabine, mitoxantrone, and dexamethasone, *GCB* germinal center b-cell, *HCT* hematopoietic cell transplantation, *HDMTX* high-dose methotrexate, *HGBCL* high-grade b-cell lymphoma, *HIV* human immunodeficiency virus, *iBCL* indolent b-cell lymphoma, *IGK* immunoglobulin kappa, *lgNGS* immunoglobulin next-generation sequencing, *IQR* interquartile range, *ITCT* intrathecal chemotherapy, *IVLBCL* intravascular large b-cell lymphoma, *lpWGS* low-pass whole-genome sequencing, *mPCR* multiplex polymerase chain reaction, *NA* not available, *NOS* not otherwise specified, *PBSCT* peripheral blood stem cell transplantation, *PCNSL* primary central nervous system lymphoma, *PhasED-Seq* phased variant enrichment and detection sequencing, *PMBCL* primary mediastinal b-cell lymphoma, *POLA* polatuzumab vedotin, *qPCR* quantitative polymerase chain reaction, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, *R/R* relapsed/refractory, *RT* radiotherapy, *SD* standard deviation, *tFL* transformed follicular lymphoma, *THRLBCL* t-cell/histiocyte-rich large b-cell lymphoma, *TIL* transformed indolent lymphoma, *Vipor* venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide, *WES* whole-exome sequencing, *WGS* whole-genome sequencing, *w/wo* with or without, *5hmC* 5-hydroxymethylcytosine.

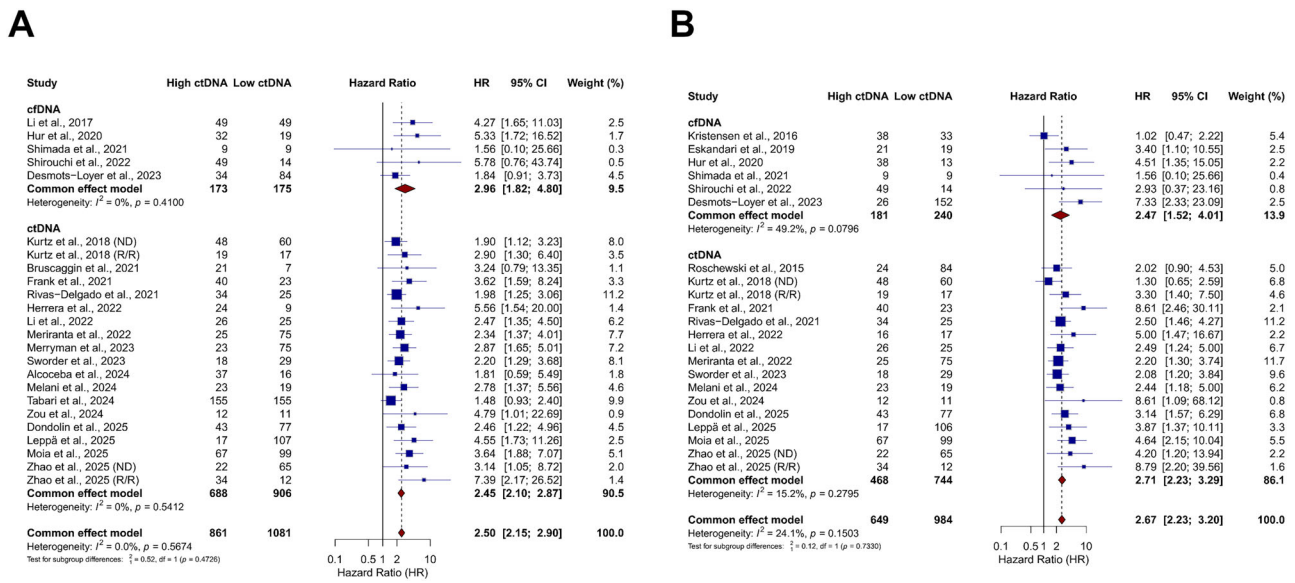

Fig. 1 | Prognostic value of baseline cfDNA/ctDNA. A Forest plots illustrating the association between high baseline cfDNA/ctDNA levels and pooled hazard ratios for disease progression stratified by ctDNA and cfDNA. **B** Pooled hazard ratios for overall survival.

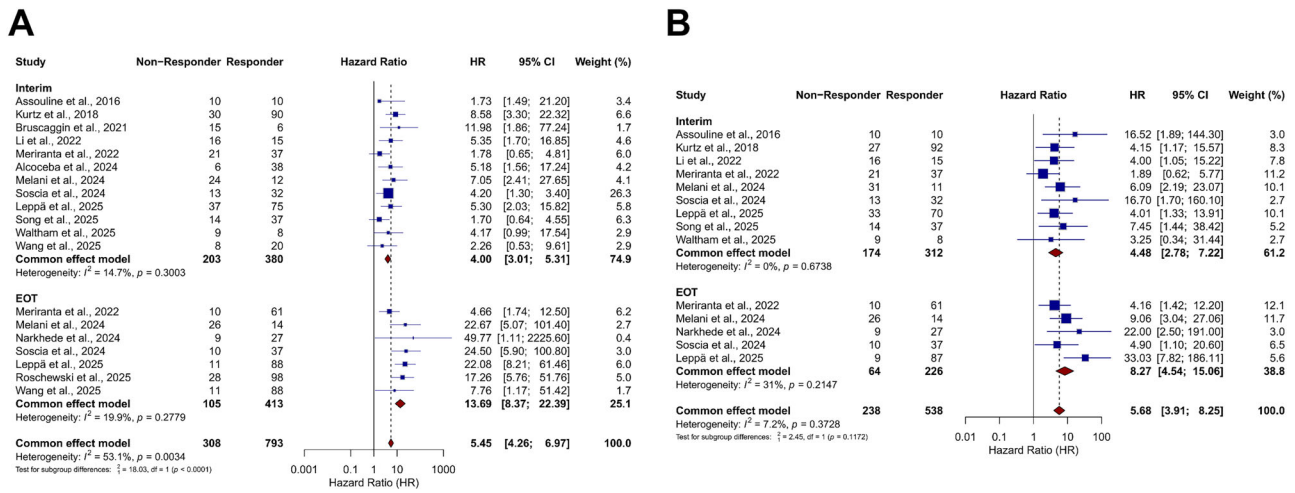

Fig. 2 | Prognostic value of dynamic ctDNA assessment during chemoimmunotherapy. Forest plots comparing the prognostic significance of ctDNA response assessment at interim versus end-of-treatment (EOT) timepoints. The plots show pooled HRs for (**A**) progression risk and (**B**) overall survival.

method (p = 0.38) (Fig. S5B). For the EOT studies, where all assessed MRD, the prognostic value was consistent across different lines of therapy (p = 0.84) (Fig. S6D) and detection methods (p = 0.65) (Fig. S5D).

Finally, in three studies assessing patients undergoing CAR T-cell therapy (54 responders vs. 49 non-responders), failure to achieve a response was also significantly associated with worse overall survival (HR: 4.20, 95% CI: 1.56–11.31) (Fig. S9B).

Over 30 studies have evaluated ctDNA dynamics throughout treatment and follow-up. Additional details on these studies, including key findings on treatment response, are summarized in Tables S4–S6.

EOT ctDNA MRD in PET/CT-negative patients

In patients who achieved a complete metabolic response (negative PET/CT scan) at the end of treatment, the concordance between a negative PET scan and a negative EOT MRD result was high, at 84% (95% CI: 78%–88%; 11 studies, I^2 = 0%). This concordance was not significantly influenced by the line of treatment (p = 0.27).

For predicting subsequent disease progression within this EOT PET-negative cohort (10 studies; 281 patients), the pooled sensitivity of ctDNA was 47.7% and the specificity was 90.8%. The analysis yielded a PLR of 5.5, a NLR of 0.6, and a DOR of 10.1. These performance metrics were consistent across different lines of treatment (p = 0.1). Projected predictive values across various disease prevalences are provided in Fig. 3A.

EOT ctDNA MRD in PET/CT-positive patients

Among patients with a positive PET/CT scan post-treatment, the overall concordance with a positive EOT MRD result was 69% (95% CI: 50–82%; 8 studies), with significant heterogeneity (I^2 = 57.4%). This was driven by the patient population, as concordance was significantly lower in newly diagnosed patients (48.0%; 3 studies) compared to relapsed/refractory patients (80.0%; 5 studies).

In the PET-positive cohort (6 studies; 106 patients), ctDNA demonstrated high diagnostic performance for predicting disease progression, with a pooled sensitivity of 89.4% and a specificity of 73.5%. This resulted in an NLR of 0.15, a PLR of 3.5, and a DOR of 27. These metrics were not significantly influenced by the line of treatment (p = 0.4). Projected predictive values and detailed performance from individual studies are summarized in Fig. 3B, and Table 2.

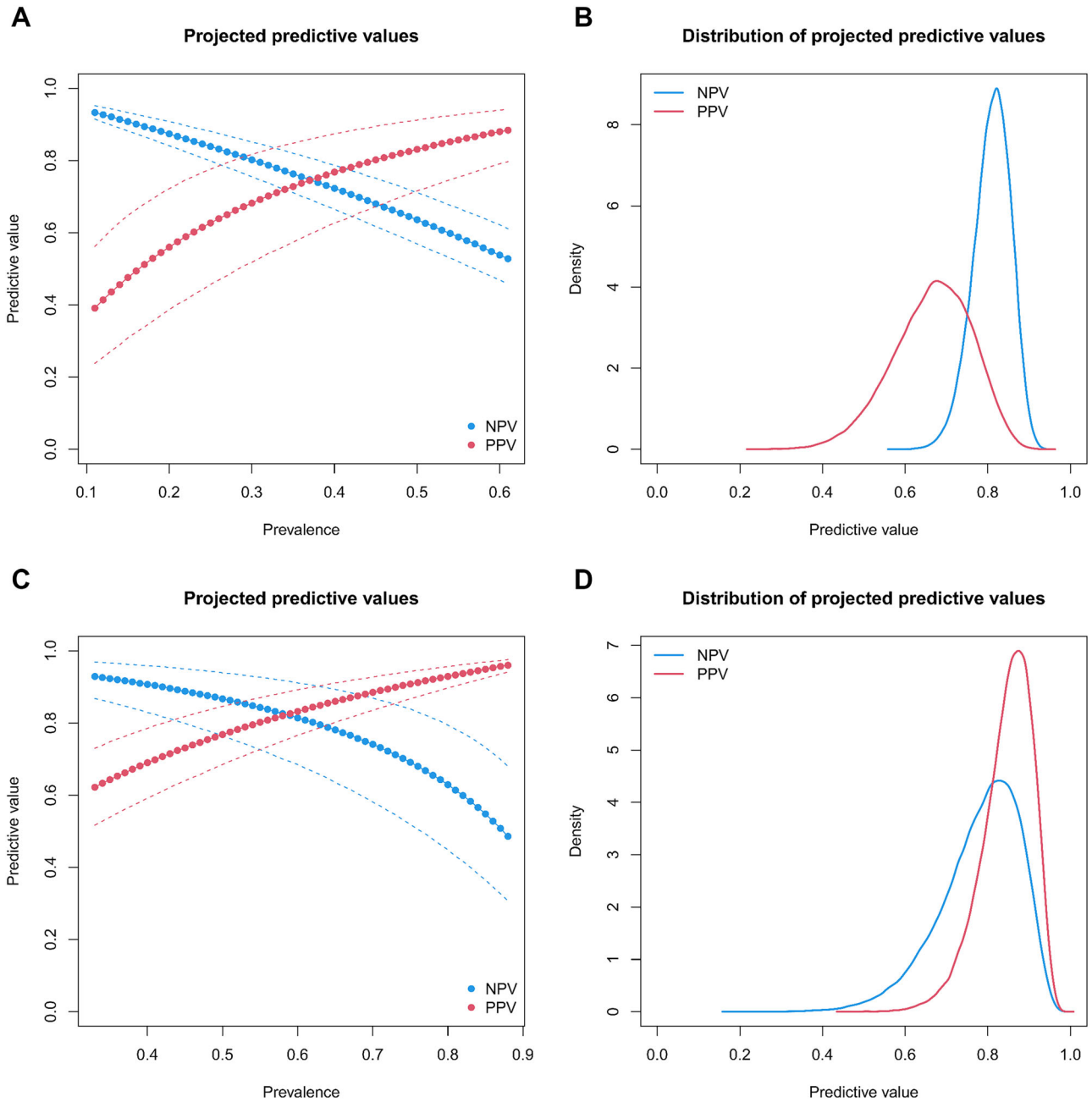

Fig. 3 | Predictive performance of EOT ctDNA in PET/CT-stratified patients. Projected positive and negative predictive values of end-of-treatment (EOT) ctDNA for disease progression across a range of disease prevalences. The analysis is stratified for patients who had (**A**, **B**) a negative PET/CT scan and (**C**, **D**) a positive PET/CT scan at the end of treatment.

Combined and comparative prognostic value of ctDNA and PET/CT

Five studies assessed the combined prognostic value of interim ctDNA and interim PET scans by stratifying patients into three risk groups: low-risk (ctDNA-negative/PET-negative), intermediate-risk (positive for one marker), and high-risk (ctDNA-positive/PET-positive).

Compared to the low-risk group, the intermediate-risk group had a significantly higher risk of progression (HR = 2.17, 95% CI: 1.28–3.66) and death (HR = 3.25, 95% CI: 1.03–10.25). The risk was substantially elevated for the high-risk group, which showed a pooled HR of 14.54 for progression and 22.18 for death when compared to the low-risk group. Furthermore, a direct comparison revealed that the high-risk group had a worse prognosis than the intermediate-risk group for both progression (HR: 6.70, 95% CI: 3.99–11.26) and death (HR: 6.82, 95% CI: 3.08–15.13) (Fig. 4A, B). The number of studies was too small to perform a similar analysis at the EOT timepoint.

To compare the prognostic power of the two modalities, we analyzed studies that reported outcomes for both. A preliminary analysis of reported HR showed a stronger association with progression for ctDNA compared to PET only at the EOT, while all other subgroups were non-significant (Table S7). Furthermore, the concordance index calculated from IPD for ctDNA and PET (available from six studies for progression and five for OS) is demonstrated in Fig. S11A, B.

Utility in differentiating DLBCL

Log-transformed cfDNA concentrations were significantly higher in DLBCL than in healthy controls ($p < 0.01$) (Fig. S12A). Compared to

Table 2 | Diagnostic Performance of EOT ctDNA for Disease Progression in PET/CT-Positive and Patients

PET	Study	Method of Detection (LOD)	Lines of therapy	TP	FN	TN	FP	Sensitivity	Specificity	NPV	PPV
PET-Negative	Meriranta et al.[71]	Hybrid capture (0.01%)	Newly diagnosed	1	6	34	0	14.3%	100.0%	85.0%	100.0%
	Li et al.[40]	Hybrid capture (0.1%)	Newly diagnosed	3	3	16	2	50.0%	88.9%	84.2%	60.0%
	Soscia et al.[83]	IgNGS (0.063%)	Newly diagnosed	8	5	27	0	61.5%	100.0%	84.4%	100.0%
	Roschewski et al.[41]	PhasED-Seq (0.00007%)	Newly diagnosed	9	2	81	4	81.8%	95.3%	97.6%	69.3%
	Waltham et al.[90]	Hybrid capture (0.2%)	Newly diagnosed	1	1	10	0	50.0%	100.0%	90.9%	100.0%
	Frank et al.[67]	IgNGS (0.01%)	Relapsed/Refractory	3	6	17	3	33.3%	85.0%	73.9%	50.0%
	Herrera et al.[39]	CAPP-Seq (0.0025%)	Relapsed/Refractory	2	6	4	1	25.0%	80.0%	40.0%	66.7%
	Melani et al.[82]	IgNGS (0.01%)	Relapsed/Refractory	1	3	12	0	25.0%	100.0%	80.0%	100.0%
	Zou et al.[15]	Hybrid capture (0.1%)	Relapsed/Refractory	2	0	4	0	100.0%	100.0%	100.0%	100.0%
	Heger et al.[81]	Hybrid capture, dPCR (NR)	Relapsed/Refractory	1	1	2	0	50.0%	100.0%	66.7%	100.0%
	Pooled Analysis: **Sensitivity**: 47.7% (95% CI: 33.3–62.6%); **Specificity**: 90.8% (95% CI: 84.0–94.8%); **NLR**: 0.6 (95% CI: 0.4–0.8); **PLR**: 5.5 (95% CI: 2.5–10.4); **DOR:** 10.1 (95% CI 3.4–23.6); **NPV**: 81.0% (95% CI: 71.2–88.9%); **PPV**: 66.5% (95% CI: 46.1–83.0%); **I²** (Zhou and Dendukuri): 0%.										
PET-Positive	Meriranta et al.[71]	Hybrid capture (0.01%)	Newly diagnosed	3	1	7	1	75.0%	87.5%	87.5%	75.0%
	Roschewski et al.[41]	PhasED-Seq (0.00007%)	Newly diagnosed	11	1	13	4	91.7%	76.5%	92.9%	73.3%
	Frank et al.[67]	IgNGS (0.01%)	Relapsed/Refractory	19	1	9	2	95.0%	81.8%	90.0%	90.5%
	Herrera et al.[39]	CAPP-Seq (0.0025%)	Relapsed/Refractory	8	0	1	1	100.0%	50.0%	100.0%	88.9%
	Zou et al.[15]	Hybrid capture (0.1%)	Relapsed/Refractory	6	0	6	3	100.0%	66.7%	100.0%	66.7%
	Heger et al.[81]	Hybrid capture, dPCR (NR)	Relapsed/Refractory	8	0	1	0	100.0%	100.0%	100.0%	100.0%
	Pooled Analysis: **Sensitivity**: 89.4% (95% CI: 78.1–95.2%); **Specificity**: 73.5% (95% CI: 59.8–83.7%); **NLR**: 0.15 (95% CI: 0.06–0.3); **PLR**: 3.5 (95% CI: 2.2–5.5); **DOR:** 27 (95% CI 8–68); **NPV**: 78.1% (95% CI: 55.3–92.5%); **PPV**: 84.6% (95% CI: 70.1–94.1%); **I²** (Zhou and Dendukuri): 2.2%.										

other NHL subtypes, DLBCL showed a trend toward higher cfDNA levels, reaching significance only against FL ($p < 0.01$), but not HL ($p = 0.20$) or MCL ($p = 0.08$) (Fig. S12B–D). Diagnostic accuracy of cfDNA for distinguishing DLBCL from healthy controls, assessed in seven studies, was notable (Pooled Sensitivity: 75.3% (70.9%–79.2%), Specificity: 88.3% (75%–95%), DOR: 26 (8.71–60.9), $I^2 = 0.1\%$, Fig. S13A). Using cfDNA concentration alone, results remained strong (Pooled Sensitivity: 73.5% (67.3%–79%), Specificity: 82.1% (62.1%–92.8%), DOR: 14.6 (4.6–35.3), $I^2 = 0.1\%$, Fig. S13B). Additional markers are detailed in Table S8.

Correlation of cfDNA/ctDNA levels and prognostic/clinical factors in DLBCL

Higher cfDNA/ctDNA levels were significantly associated with key DLBCL prognostic factors, including high IPI[3–5] ($p < 0.01$), advanced-stage disease ($p < 0.01$), elevated LDH ($p < 0.01$), and B symptoms ($p < 0.01$) (Fig. S14A–D). Extranodal involvement and non-GCB subtypes also correlated with elevated cfDNA/ctDNA levels ($p < 0.01$), with a non-significant trend for bone marrow involvement ($p = 0.12$) (Fig. S15A–C). Moderate to strong correlations between TMTV/MTV and cfDNA/ctDNA levels were also reported statistically significant (detailed findings in Table S9).

Assessment of publication bias, heterogeneity, and sensitivity analysis

Potential publication bias was evaluated using Funnel Plots and Galbraith Plots (Fig. S16A–F), and formally assessed with Egger's and Begg's tests. Significant publication bias was detected in the analyses of baseline cfDNA/ctDNA for both progression risk (Egger's: $p < 0.01$; Begg's: $p < 0.01$) and overall survival (Egger's: $p = 0.01$; Begg's: $p < 0.01$). In contrast, for the assessment of ctDNA response at the interim timepoint, neither Egger's test ($p = 0.85$) nor Begg's test ($p = 0.71$) indicated significant bias for the progression outcome.

To investigate potential sources of heterogeneity, a meta-regression analysis was performed, incorporating covariates such as NOS quality score, sample size, publication year, proportion of male patients, age, and study design.

Finally, a sensitivity analysis confirmed that the pooled estimates for progression and OS, based on baseline, interim, and EOT ctDNA levels, were robust and stable (Figs. S17–S22).

Discussion

In this systematic review and meta-analysis of 53 studies involving over 3700 patients, our findings demonstrate that ctDNA is a powerful and dynamic biomarker for risk stratification in DLBCL. ctDNA provides a critical layer of biological information that complements and refines the prognostic power of standard-of-care PET/CT imaging. By integrating ctDNA measurements before, during, and after treatment, clinicians can achieve a more precise assessment of disease burden, therapeutic response, and risk of progression.

At baseline, both total cfDNA and ctDNA concentrations are predictive of progression and survival. The slightly higher heterogeneity observed in cfDNA-based analyses may stem from non-specific physiological changes, as ctDNA constitutes only 5% of total cfDNA[35]. This suggests that while both are informative, ctDNA-specific assays may offer more reproducible risk assessment. Furthermore, multiple studies highlight that baseline ctDNA retains its prognostic power even after adjusting for established risk factors like the IPI and TMTV[36–40], thereby improving pretreatment risk stratification. Our findings, therefore, support additional prospective assessment of baseline ctDNA as a biomarker to improve the risk assessment delivered by these conventional tools.

Dynamic monitoring during chemoimmunotherapy reveals a dramatic amplification of ctDNA's prognostic signal over time. While failure to clear ctDNA as early as the second cycle is associated with a 4-fold higher risk of progression, this signal intensifies to nearly 14-fold risk for patients with detectable ctDNA at the end of treatment. This temporal dynamic is clinically informative, as an interim assessment provides an early identification of chemosensitivity, whereas ctDNA clearance by EOT signifies a deeper molecular remission, likely reflecting the eradication of resistant tumor clones necessary for cure[41]. Another key finding of our subgroup analyses is the consistency of ctDNA's prognostic hazard ratio across newly diagnosed and relapsed/refractory populations at all measured timepoints. Specifically, in the CAR T-cell therapy setting, despite a limited number of studies, ctDNA dynamics remained prognostic, suggesting that ctDNA is a

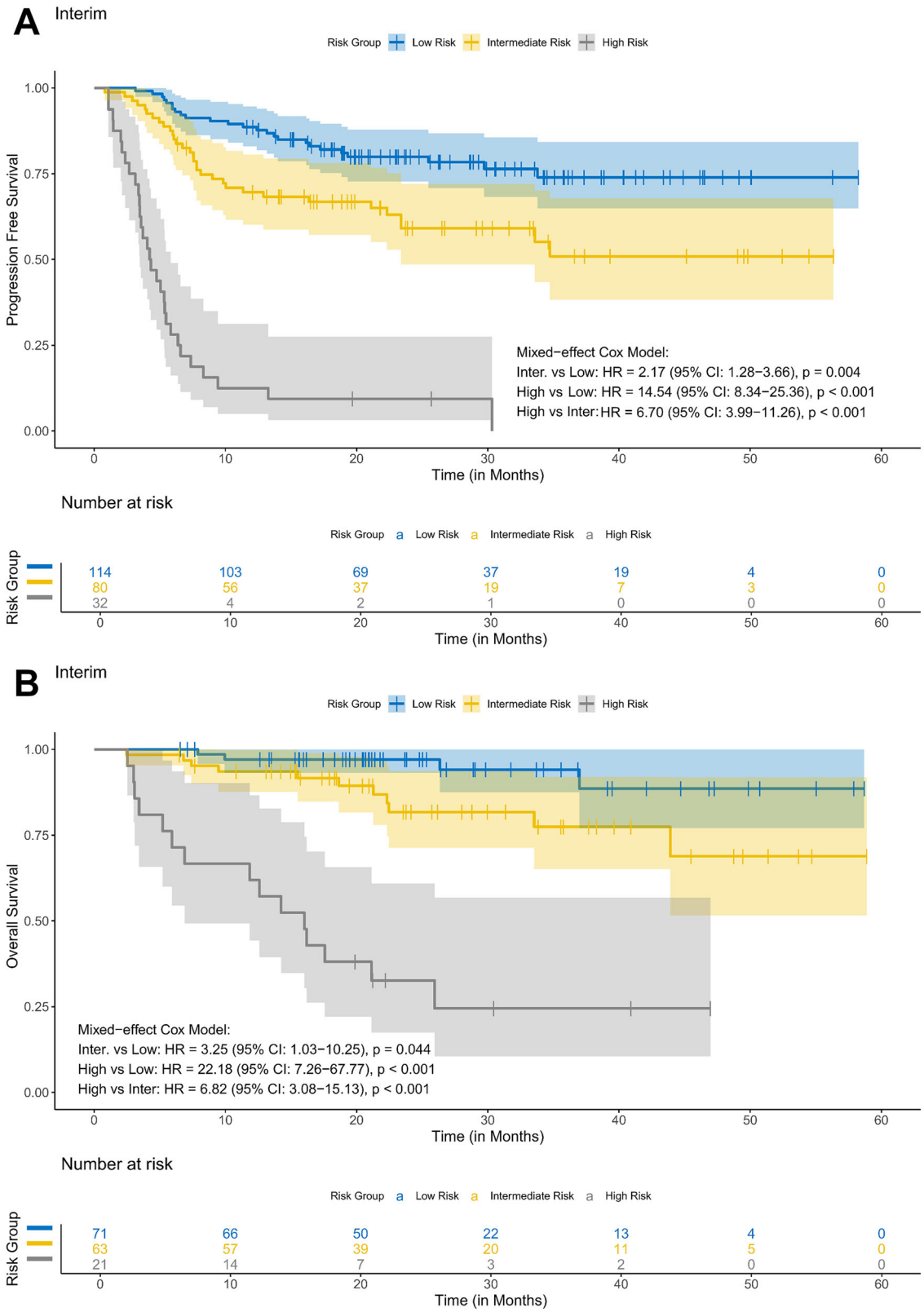

Fig. 4 | Combined prognostic value of interim ctDNA and interim PET/CT. Forest plots showing the combined prognostic value of interim ctDNA and PET/CT scans. Patients were stratified into low-risk (both negative), intermediate-risk (one positive), and high-risk (both positive) groups. The plots display the hazard ratios for (**A**) progression risk and (**B**) overall survival.

robust indicator of biological risk that is widely applicable in the management of DLBCL. Overall, these findings support the rationale for formally investigating ctDNA as a surrogate endpoint in clinical trials for DLBCL[29].

The clinical utility of ctDNA is most evident when integrated with PET/CT imaging, particularly as prior studies have shown that treatment modulation efficacy based on PET/CT scans is limited by residual avidity ambiguity and relapses despite complete metabolic response[42,43]. In patients with a negative EOT PET/CT scan, a positive ctDNA result is associated with a high probability of progression (PLR: 5.5, 95% CI: 2.5–10.4), identifying a high-risk cohort that is otherwise indistinguishable by imaging and who might benefit from more intensive surveillance or consolidative therapy. Minimally invasive serial monitoring with ctDNA in these patients may indicate residual disease several months before imaging or clinical symptoms develop[17]. However, the modest sensitivity (47.7%) in this cohort highlights that a negative ctDNA result does not reliably preclude future progression. This may reflect disease burdens below the assay's limit of detection or relapse driven by subclones not captured by the specific assay panel, underscoring the need for continued routine clinical monitoring regardless of the negative ctDNA result[44].

Conversely, in patients with a positive EOT PET/CT scan, a negative ctDNA result is associated with a low probability of progression (NLR: 0.15, 95% CI: 0.06–0.3). This finding is consistent with recent studies demonstrating that PET avidity in the absence of detectable ctDNA is often not associated with an increased risk of relapse, potentially allowing patients to avoid unnecessary consolidative therapies or invasive biopsies[41,45]. These finding suggests that some instances of residual PET avidity represent non-viable tumor or inflammation rather than active lymphoma[46]. Crucially, in patients with residual disease after therapy or during surveillance for whom tumor biopsy is not accessible, ctDNA offers the benefit of tracking clonal evolution and identifying resistance mechanisms over PET/CT, in addition to lymphoma burden assessment, which can be used to inform subsequent personalized therapeutic approaches[47,48].

While our analysis suggests a practical algorithm where ctDNA can refine management in both PET-positive and PET-negative patients, these findings are based on a limited number of studies incorporating assays with various sensitivities. Especially, data in PET/CT-negative patients suggest a potential for suboptimal sensitivity, considering that assays with a detection limit above 1 part per million might not have adequate sensitivity for detecting minimal residual disease after treatment[44]. This is in contrast to highly sensitive assays like PhasED-seq, which demonstrate a sensitivity exceeding 80% for the detection of relapse in PET-negative patients[41]. The validation of these findings in larger, prospective trials should be considered a research priority.

We acknowledge several limitations in this study. First, reliance on aggregated data precluded patient-level adjustments, and the estimation of HRs from digitized curves may introduce bias. Moreover, since HRs provide insights into relative risks across groups, the inference of absolute risks should be avoided. Second, to address the significant clinical heterogeneity in the included studies, we performed extensive subgroup analyses at all timepoints, which confirmed that the prognostic value of ctDNA was robust across newly diagnosed and relapsed/refractory patients. Third, in contrast to previous comparative studies[44], our subgroup analyses and meta-regressions did not detect a significant performance difference among various ctDNA assays. The findings may be limited by insufficient power or variability across studies, and do not negate the potential for specific assays to demonstrate superior performance in defined settings, especially in the detection of MRD. Fourth, our therapeutic subgroups were broadly defined (CAR T-cell therapy vs. chemoimmunotherapy), and some studies included a small minority of patients with other lymphoma subtypes (e.g., PMBCL), which may slightly affect findings.

Despite these limitations, our study is the first to systematically synthesize the extensive recent evidence on ctDNA utility in DLBCL. By using hazard ratios and conducting comprehensive subgroup analyses, we provide robust insights into the impact of timing, treatment context, and PET/CT status. Our findings provide a framework for integrating ctDNA dynamics with imaging to better inform clinical management. This integration of a biological biomarker with anatomical and metabolic imaging enhances prognostic precision, with the potential to improve both treatment decision-making and patient quality of life[49].

In conclusion, in this systematic review and meta-analysis, we demonstrated that ctDNA levels are elevated in DLBCL patients and correlate with established prognostic markers in DLBCL, including IPI score, LDH levels, and disease stage. We demonstrate that dynamic ctDNA assessment, before, during, and especially at the end of treatment, serves as a robust predictor of progression and survival. When integrated with standard imaging, ctDNA refines prognostication in both PET-positive and PET-negative patients. Overall, the evidence supports the integration of ctDNA into clinical practice as a complementary tool that can enhance prognostic precision, minimize unnecessary interventions, and improve quality of life. Future research must focus on the standardization of ctDNA methodologies, including pre-processing protocols and analytical thresholds. Clinical trials are required to determine whether patient outcomes can be improved through ctDNA-guided treatment modification and to assess the cost-effectiveness of implementing these assays in standard clinical practice.

Methods

Overview and search strategy

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[50] and was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews, ID: CRD42024620521). A comprehensive literature search was performed across five major online databases: PubMed, Embase, Cochrane Library, Scopus, and Web of Science.

The initial literature search was conducted on December 27, 2024, using a controlled vocabulary (*Medical Subject Headings [MeSH]*) and keywords related to "B-cell lymphoma," "Diffuse Large B-Cell Lymphoma (DLBCL)," "Circulating Tumor DNA (ctDNA)," "cell-free tumor DNA (cfDNA)," "plasma DNA," and "liquid biopsies." An updated search was performed on August 25, 2025, to capture newly published studies.

All English publications available through the database were retrieved without any restriction on country of origin, study population, or dates of assessment. All database-specific search strategies (PubMed, Embase, etc.) are detailed in Table S1. Newly identified records were compared against initial results, and duplicates were removed using EndNote (version 22.3) with automated deduplication. To ensure comprehensiveness, the reference lists of included studies were manually reviewed to identify further relevant studies.

Study selection

Following duplicate removal, the remaining studies underwent a two-stage screening process. First, two investigators (S.F. and M.K.) independently assessed titles and abstracts to exclude non-relevant studies. Subsequently, full-text articles of potentially eligible studies were evaluated based on predefined inclusion/exclusion criteria. In case of disagreement, a third investigator (R.S.) was consulted for the final decision. To ensure the independence of observations, a rigorous screening of author affiliations, study periods, and patient cohorts was conducted to identify and exclude publications with potentially overlapping patient data.

Studies included in this review met the following criteria: (1) Case-controls, retrospective or prospective cohort studies, or randomized controlled trials; (2) Studies involving patients diagnosed with Large B-cell lymphoma (LBCL) and DLBCL; (3) Studies that measured ctDNA or cfDNA concentration, either as the proportion of ctDNA-positive (ctDNA +) versus ctDNA-negative (ctDNA-) patients, or as mean/median ctDNA/cfDNA concentration, mutational patterns, or methylation status, (4) Studies reporting one or more of the following: (1) Survival outcomes, including progression-free survival (PFS), event-free survival (EFS), TTP, or overall survival (OS), expressed as hazard ratios (HRs) or

Kaplan-Meier estimates; (2) Diagnostic performance in distinguishing DLBCL from healthy subjects or other lymphoma subtypes; (3) Prognostic factors such as the IPI, disease stage, lactate dehydrogenase (LDH) levels, and presence of B symptoms; (4) Treatment response assessment using ctDNA/cfDNA.

The following studies were excluded: (1) Studies on non-DLBCL/LBCL lymphomas, primary central nervous system lymphoma (PCNSL) or primary mediastinal B-cell lymphoma (PMBCL); (2) Case reports, case series, reviews, commentaries, systematic reviews, conference abstracts, and preclinical studies; (3) Studies with duplicate database entries, incomplete/unavailable data on mentioned oucomes; (4) Investigations limited to single-gene mutations or methylation patterns without composite mutational/methylation scores.

Data extraction

Before data extraction, a standardized Excel template was developed to ensure consistency. Two researchers (A.S. and SH.F.) independently extracted data, with discrepancies resolved through consensus discussion. The following variables were systematically recorded: (1) Study characteristics: first author, publication year, country, study design, sample size, population type, mean/median age, male percentage, advance stage (III-IV) prevalence, treatment regimen, ctDNA/cfDNA collection time points, detection/quantification methods, number of genes assessed, and most frequent mutations (percentage); (2) Diagnostic performance: sensitivity, specificity, true positives (TP), false positives (FP), false negatives (FN), true negatives (TN), Mean ± standard deviation (SD) of ctDNA/cfDNA concentrations in DLBCL patients, healthy controls, Hodgkin lymphoma (HL), follicular lymphoma (FL), and mantle cell lymphoma (MCL); (3) Survival outcomes: PFS, OS, EFS, and TTP, with HRs and 95% confidence intervals (CIs) for baseline, molecular response, and MRD; (4) Treatment response: TP, FP, FN, and TN for MRD and molecular response assessments, stratified by complete response (CR), partial response (PR), stable disease (SD), or PD; (5) Prognostic factors: P-values, correlation coefficients (R), and mean ± SD of ctDNA/cfDNA concentrations for IPI, LDH levels, disease stage, B symptoms, total metabolic tumor volume (TMTV), bone marrow involvement, extranodal involvement, and germinal center B-cell (GCB) classification.

Quality assessment

Study quality was evaluated using the Newcastle-Ottawa Scale (NOS)[51] by two researchers (S.F. and M.K.) independently, with discrepancies resolved through consensus discussion among all researchers. For this analysis, clinical trials were categorized as prospective cohort studies to align with NOS criteria.

Statistical analysis

This meta-analysis employed R software (version 4.4.2) using the meta (version 8.0-2) and mada (version 1.0.3) packages for statistical analysis and forest plots. Hazard ratios (HRs) for overall survival (OS), progression-free survival (PFS), event-free survival (EFS), and time to progression (TTP) were extracted or estimated from Kaplan-Meier curves using the method described by Guyot et al.[52]. Pooled HRs were calculated, and subgroup analyses were performed based on the line of treatment (newly diagnosed vs. relapsed/refractory), cfDNA vs. ctDNA, type of response (MRD vs. molecular response), time of response (Interim vs. end-of-treatment (EOT)), and the detection methodology (e.g., Ig-NGS, CAPP-Seq, hybrid capture). cfDNA refers to the total DNA fragments found in the bloodstream, released from all cell types. ctDNA is the specific subset of cfDNA that originates only from lymphoma cells and carries lymphoma-specific mutations[53]. MRD is defined as ctDNA clearance at the end of a treatment cycle or at the completion of treatment, and molecular responses are defined as significant changes in ctDNA/cfDNA levels from baseline.

The diagnostic accuracy of ctDNA for predicting disease progression was evaluated by stratifying patients based on EOT PET/CT status: PET-negative (complete response) versus PET-positive (partial response, stable disease, or progressive disease). Summary receiver operating characteristic (sROC) curves were generated to estimate the pooled sensitivity, specificity, Positive and Negative Likelihood Ratios (PLR/NLR), and the Diagnostic Odds Ratio (DOR). Positive and Negative Predictive Values (PPV and NPV) were calculated using the progression prevalence reported in the included studies, with projected values also generated across various prevalences.

To assess the relationship between ctDNA/cfDNA concentrations and prognostic factors, mean and SD values were derived from patient data or digitized plots using WebPlotDigitizer (version 4.8). Medians and IQRs were converted to means and SDs using Wan et al.'s method (2014)[54]. Log-transformed ctDNA/cfDNA concentrations were analyzed, and the ratio of means (ROM) was calculated. All ctDNA/cfDNA concentrations were log-transformed when necessary, using the EpiNow2 (version 1.7.1) package in R, and the ratio of means ROM was calculated. Heterogeneity was evaluated using Cochran's Q test and the I^2 statistic (Zhou, Dendukuri approach for diagnostic accuracy), categorized as low ($I^2 < 25\%$), moderate ($25\% \leq I^2 \leq 50\%$), or high ($I^2 > 50\%$)[34]. When significant heterogeneity was detected, random-effects models were applied. Publication bias was evaluated through Egger's test, Begg's test, and funnel/Galbraith plots. Subgroup and sensitivity analyses, including meta-regression, were performed to explore potential sources of heterogeneity.

Data availability

All data generated or analyzed during this study are included in this article and its supplementary information files. The data supporting the findings of this systematic review and meta-analysis are available from the original publications, which are cited in the reference list.

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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