Role of Circulating Tumor DNA Tumor Fraction in Advanced Non–Small Cell Lung Cancer and Its Impact on Patient Treatment Outcomes: A Prospective Real-World Study

Ben Man Fei Cheung, MBChB[1]; Elaine Yee-Ling Ko, BSc[2]; David Jen Hao Shih, PhD[3]; Jason Wing Hon Wong, PhD[3]; Matthew Kin-Liang Chiu, MD, PhD[2]; Gin Wai Kwok, MBBS[4]; Isaac Ho, MBBS[1]; Dennis Kwok-Chuen Leung, MBBS[1]; Anne Wing-Mui Lee, MD[2,5]; Victor Ho-Fun Lee, MBBS[2]; and Aya El Helali, MD, PhD, MRCP[2]

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ABSTRACT

PURPOSE Comprehensive genomic profiling (CGP) using targeted panel next-generation sequencing (TP-NGS) is pivotal in the clinical management of advanced non–small cell lung cancer (aNSCLC). Despite the limitations associated with tumor tissue sampling, circulating tumor DNA (ctDNA) presents a promising alternative. This study aims to assess the prognostic value of ctDNA tumor fraction (TF) in aNSCLC.

MATERIALS AND METHODS We conducted a multicenter prospective study in Hong Kong. Patients with aNSCLC provided blood samples within 31 days before treatment initiation, followed by CGP using a validated ctDNA assay.

RESULTS Among 878 patients, those with ctDNA TF ≥1% had significantly worse outcomes, with median progression-free survival (PFS) of 13.2 months and overall survival (OS) of 17.6 months compared with the ctDNA TF <1% group ($P < .05$). ctDNA TF demonstrated predictive capabilities for OS at various time points, with AUC values ranging from 0.65 to 0.75 for the overall population. The predictive strength of ctDNA TF in the epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) subgroup remained robust for OS at 24 months, achieving an AUC of 0.79. We validated a ctDNA TF threshold of 2.3% for inferior OS in the overall population, whereas a distinct threshold of 1.6% and 2.2% was validated for *EGFR* TKI and chemotherapy ± immunotherapy.

CONCLUSION Our findings establish ctDNA TF as a clinically relevant biomarker in aNSCLC, providing robust prognostic and predictive information. The findings support the integration of ctDNA TF quantification into routine clinical workflows, reinforcing its role in advancing precision oncology and improving risk stratification and outcomes for patients with aNSCLC.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

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INTRODUCTION

Comprehensive genomic profiling using targeted panel next-generation sequencing (TP-NGS) is the standard for molecular profiling in advanced non–small cell lung cancer (NSCLC)[1-3] but is often constrained by tumor location, heterogeneity, specimen adequacy, and prolonged turnaround times.[4-6] Although tissue remains the diagnostic gold standard,[1,7,8] circulating tumor DNA (ctDNA) offers a noninvasive alternative, enabling real-time detection of tumor-specific mutations.[9,10] Supported by the International Association for the Study of Lung Cancer, ctDNA has proven utility in identifying oncogenic drivers, monitoring tumor dynamics, detecting resistance mechanisms, and stratifying recurrence risk.[8,9,11] Despite its promise, the prognostic value of ctDNA as a biomarker in advanced NSCLC remains unvalidated in prospective studies, highlighting the need for further research to establish its clinical impact and integration into routine practice.[10]

Accurate prognostication is vital for optimizing treatment strategies in advanced NSCLC, yet current tools, such as the TNM staging system, fail to capture the heterogeneity within this population. For instance, patients with PD-L1 >50% may require tailored approaches, such as chemoimmunotherapy over immunotherapy alone, whereas others with favorable prognoses could benefit from localized interventions like stereotactic body radiotherapy.[12,13] Several prognostic models have been developed to address these challenges, including clinical nomograms that incorporate factors like

CONTEXT

Key Objective

To evaluate whether circulating tumor DNA (ctDNA) tumor fraction (TF) can be established as a definitive, treatment-agnostic biomarker for predicting survival, assessing metastatic burden, and guiding personalized treatment strategies in advanced non–small cell lung cancer (NSCLC). This study uniquely validates ctDNA TF as a prognostic and predictive biomarker in a real-world clinical context.

Knowledge Generated

The study demonstrates that higher ctDNA TF levels are strongly associated with worse survival outcomes and greater metastatic burden in advanced NSCLC. ctDNA TF serves as an independent measure of disease progression and treatment response, offering a valuable tool for precision oncology.

Relevance

By highlighting ctDNA TF as a practical and scalable biomarker, this research addresses a critical gap in clinical decision making. It supports its integration into routine workflows for risk stratification and personalized treatment planning, advancing the management of NSCLC in precision medicine.

performance status, metastatic burden, and surgical history. However, these nomograms are rarely used in clinical practice due to their complexity and lack of external and prospective validation.[14] In the absence of standardized guidelines or universally accepted biomarkers, clinical decisions often rely on judgment, underscoring the need for robust, evidence-based tools to guide treatment planning in advanced-stage NSCLC.

Advances in multi-omics and machine learning have led to the development of prognostic models that integrate genomics, radiomics, and clinical features, offering higher predictive accuracy.[15] However, their complexity, dependence on extensive feature sets, and frequent classification as black box models due to a lack of interpretability significantly limit their clinical applicability.[15] Additionally, these models often lack prospective and cross-institutional validation, further restricting their integration into routine practice. Many prognostic models are tailored to specific treatment subgroups, creating fragmentation and inefficiency in clinical workflows.[16-18] These limitations underscore the urgent need for a universal, interpretable, and clinically practical biomarker that can reliably predict outcomes across the diverse population of patients with advanced NSCLC.

The quantification of tumor fraction (TF) in ctDNA is a widely recognized biomarker that measures tumor DNA released into the bloodstream. Recent findings indicate that the TF of ctDNA serves as a potentially reliable biomarker for forecasting overall survival (OS) across different cancer types.[19] Reichert et al[19] retrospectively showed plasma ctDNA TF is predictive of survival in advanced NSCLC, prostate cancer, breast cancer, and colorectal cancer. Despite previous efforts, there have been no prospective validations of ctDNA TF until now. In this study, we prospectively assessed ctDNA TF as a versatile, treatment-independent biomarker for advanced-stage NSCLC.[20] To our knowledge, this is among the largest prospective genomic studies investigating the prognostic significance of ctDNA TF for advanced-stage NSCLC in real-world scenarios.

The TF of ctDNA, a measure of the amount of ctDNA as a fraction of total cell-free DNA in blood, is emerging as a potentially important prognostic biomarker pan-cancer.[19] Despite its potential, prospective validation of ctDNA TF has been notably absent, limiting its clinical utility. In this study, we present the first prospective evaluation of ctDNA TF as a robust, treatment-agnostic biomarker for advanced NSCLC. To our knowledge, this represents one of the largest prospective genomic investigations into the prognostic utility of ctDNA TF in real-world clinical settings, establishing its potential as a universal tool for risk stratification and personalized care.

MATERIALS AND METHODS

Study Population

Participants included advanced-stage nonsquamous NSCLC as part of an ongoing territory-wide, multicenter prospective Precision Oncology Program for advanced NSCLC in Hong Kong, which commenced in January 2021.

For more comprehensive methods and materials, see Supplementary Methods.

Optimal Threshold Selection and Cross-Validation

To establish a clinically relevant TF threshold that predicts OS, we first used data from the treatment-naïve cohort. The data were split into two parts: 70% for optimal threshold

determination and 30% for internal validation. Thresholds of TF were identified using maximally selected rank statistics from the maxstat package (v0.7.25). This approach evaluates all possible thresholds and selects those that maximize the separation of survival outcomes.

Threshold selection was tuned by varying the minimal proportion of observations from 10% to 50%. The robustness of the thresholds was evaluated using a 5-fold cross-validation process on the training set, with Kaplan-Meier analyses performed to assess outcome separation. The threshold with the minimum mean *P* value across all folds was selected as the optimal cutoff.

To ensure reliability, the optimal threshold was validated using the internal validation set. Additionally, we tested the threshold on data from patients with disease progression to confirm its applicability across different clinical contexts.

RESULTS

Patient Recruitment

Between January 2021 and May 2025, 878 patients with metastatic NSCLC of adenocarcinoma histology underwent blood-based TP-NGS. Of these, 257 patients were excluded for various reasons, including failed NGS quality control (n = 8), nonadenocarcinoma NSCLC histology (n = 9), insufficient follow-up duration (n = 84), loss to follow-up (n = 33), and the adoption of best supportive care as the treatment plan (n = 123). This resulted in a final study cohort of 621 patients. Blood biopsies were collected either before treatment initiation in 280 patients or at the time of first disease progression in two patients, ensuring robust data for analysis (Data Supplement, Fig S1).

Patient Genomic and Clinical Characteristics

Treatment-naïve blood samples were collected within 31 days before treatment, with a median follow-up of 21.4 months (range, 6.2-49.5 months). Of the 279 patients, 112 (40%) received epidermal growth factor receptor (*EGFR*)–targeted therapy, 122 (43.6%) chemotherapy ± immunotherapy, and 33 (11.8%) immunotherapy alone (Data Supplement, Table S1).

A total of 169 patients (60.4%) had ctDNA TF ≥1% (Table 1). Clinical characteristics, including age, sex, PD-L1 status, previous radiotherapy, and Eastern Cooperative Oncology Group (ECOG) performance scores, were similar between groups. However, distant metastases were more frequent in the ctDNA TF ≥1% group, including brain (26.6%, *P* = .058), bone (57.4%, *P* < .0001), and liver (23.1%, *P* < .0001; Table 1).

Key mutations, such as *EGFR* (46.1% *v* 31.5%, *P* < .0001), *KRAS* (16.0% *v* 5.6%, *P* = .012), *TP53* (75.2% *v* 22.3%, *P* < .0001), and *STK11* (20.0% *v*. 6.3%, *P* = .0016), were more frequent in the ctDNA TF ≥1% group (Table 1). Tumor mutational burden was also higher (3.79 *v* 1.26 mutations/Mb, *P* < .0001; Table 1). Alterations in *BRAF*, *ERBB2*, *MET*, *KEAP1*, *RET*, *ROS1* fusion, and microsatellite instability high were comparable, whereas *ALK* fusion was slightly more common in the ctDNA TF <1% group (2.7% *v* 0.6%; Table 1).

These findings highlight distinct genomic profiles between the ctDNA TF ≥1% and ctDNA TF <1% groups, with the former group displaying higher frequencies of driver mutations and markers of genomic instability, which may contribute to their poorer clinical outcomes.

ctDNA Tumor Fraction as a Prognostic Biomarker in Treatment-Naïve Advanced-Stage NSCLC

We evaluated the impact of ctDNA TF on survival outcomes. The median progression-free survival (mPFS) was shorter in the ctDNA TF ≥1% group (13.2 months) compared with the ctDNA TF <1% group (18.1 months; *P* = .02; hazard ratio [HR], 1.6 [95% CI, 1.1 to 2.3]; Fig 1A). Similarly, the ctDNA TF ≥1% group had significantly worse OS, with a median OS (mOS) of 17.6 months (95% CI, 13.6 to 24.3) versus an unreached mOS in the ctDNA TF <1% group (*P* = .00019; HR, 2.1 [95% CI, 1.4 to 3.1]; Fig 1B).

Multivariable Cox regression analysis confirmed ctDNA TF ≥1% as an independent predictor of shorter PFS (HR, 2.2 [95% CI, 1.1 to 4.3]; *P* = .029; Fig 2A). For OS, ECOG performance score >1 was the only independent factor associated with poorer outcomes (HR, 3 [95% CI, 1.6 to 5.6]; *P* < .001; Fig 2B). These findings were consistent with univariable analyses, which also showed higher risks of progression (HR, 2 [95% CI, 1.4 to 3]; *P* < .001; Data Supplement, Fig S2A) and death (HR, 2 [95% CI, 1.4 to 3]; *P* < .001; Data Supplement, Fig S2B) in the ctDNA TF ≥1% group.

ctDNA TF as a Biomarker Across Distant Metastasis Sites

The prognostic significance of ctDNA TF was evaluated in relation to distant metastasis (DM) sites (brain, bone, or liver) and survival outcomes. Patients with ctDNA TF <1%, regardless of DM status, had the most favorable PFS (*P* = .0023; Data Supplement, Fig S3A) and OS (*P* = .0043; Data Supplement, Fig 3B). ctDNA TF was independently prognostic for PFS (HR, 2.18 [95% CI, 1.44 to 3.31]; *P* < .001; Data Supplement, Fig S3A) and OS (HR, 2.03 [95% CI, 1.35 to 3.05]; *P* < .001; Data Supplement, Fig S3B).

When stratified by DM sites, ctDNA TF ≥1% consistently predicted worse outcomes. In brain metastases, ctDNA TF <1% was linked to better OS (not reached [NR] *v* 13.4 months; *P* = .0053) and PFS (NR *v* 13.4 months; *P* = .002; Data Supplement, Table S2). For bone metastases, ctDNA TF <1% correlated with superior OS (31.5 *v* 15.9 months; *P* = .0044) and PFS (31.5 *v* 8.0 months; *P* = .00081; Data Supplement, Table S3). In liver metastases, ctDNA TF <1% was associated with improved OS (31.5 *v* 14.2 months; *P* = .0014) and PFS (31.5 *v* NR; *P* = .0052; Data Supplement, Table S4).

TABLE 1. Clinical and Genomic Characteristics of Metastatic Treatment-Naïve Non–Small Cell Lung Cancer With Blood-Based NGS Grouped by ctDNA TF

	ctDNA TF ≥1%, No. (%)	ctDNA TF <1%, No. (%)	
Clinical Characteristic	169 (60.4)	111 (39.6)	*P*
Sex			
Female	69 (40.8)	55 (49.5)	.19
Male	100 (59.2)	56 (50.5)	
Age at metastatic stage diagnosis (years), median (range)	64 (32-92)	68 (32-89)	.064
Smoking status: Ever smoker	74 (44.0)	44 (40.4)	.63
PD-L1			
High	44 (50)	26 (43.3)	.66
Low	33 (37.5)	24 (40)	
Negative	11 (12.5)	10 (16.7)	
Brain metastases	45 (26.6)	18 (16.2)	.058
Bone metastases	97 (57.4)	33 (29.7)	<.0001
Liver metastases	39 (23.1)	5 (4.5)	<.0001
Radiation therapy before blood biopsy	33 (19.5)	20 (18.0)	.87
Previous adjuvant therapy	2 (22.2)	10 (47.8)	.25
ECOG performance score >1	40 (25.6)	21 (21.2)	.51
Genomic biomarker			
ALK fusion	1 (0.6)	3 (2.7)	.3
BRAF	14 (8.3)	12 (10.8)	.53
EGFR	78 (46.1)	35 (31.5)	<.0001
ERBB2	19 (11.2)	5 (4.5)	.052
KRAS	27 (16.0)	6 (5.6)	.012
MET	16 (9.5)	9 (8.1)	.83
RET fusion	3 (1.8)	2 (1.8)	1
ROS1 fusion	2 (1.2)	2 (1.8)	.64
TP53	109 (75.2)	23 (22.3)	<.0001
STK11	34 (20)	7 (6.3)	.0016
KEAP1	12 (7.1)	4 (3.6)	.3
TMB (mut/Mb), median (range)	3.79 (0-51.8)	1.26 (0-15.2)	<.0001
Microsatellite instability high	1 (0.6)	0 (0)	1

NOTE. Percentages were presented for patients with complete data.
Abbreviations: ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; *ERBB2*, Erb-B2 Receptor Tyrosine Kinase 2; *KEAP1*, Kelch-like ECH-associated protein 1; *KRAS*, Kirsten rat sarcoma virus; *RET*, rearranged during transfection; *STK11*, serine/threonine kinase 11; TF, tumor fraction; TMB, tumor mutational burden; *TP53*, tumor protein p53.

ctDNA Tumor Fraction as a Predictive Marker for Response to Treatment

Patients were stratified by treatments received, demonstrating that ctDNA TF is a predictive biomarker for response to chemotherapy ± immunotherapy and EGFR tyrosine kinase inhibitors (TKIs). ctDNA TF was significantly associated with PFS (HR, 1.9 [95% CI, 1.1 to 3.1]; $P = .01$) and OS (HR, 2.6 [95% CI, 1.5 to 4.4]; $P < .001$; Data Supplement, Table S5). Similarly, for EGFR TKIs, ctDNA TF correlated with poorer PFS (HR, 3.1 [95% CI, 1.1 to 8.2]; $P = .03$) and OS (HR, 3.5 [95% CI, 1.4 to 9.1]; $P = .009$; Data Supplement, Table S5).

Among 122 patients treated with chemotherapy ± immunotherapy, those with ctDNA TF <1% had better median PFS (mPFS; 11.8 *v* 6 months; $P < .001$; Data Supplement, Fig S4A) and OS (NR *v* 12.1 months; $P < .001$; Data Supplement, Fig S4B). For the 33 patients who received immunotherapy alone, no significant differences in PFS or OS were observed between ctDNA TF groups due to the small sample size (Data Supplement, Figs S5A and S5B).

In the EGFR TKI cohort (112 patients), ctDNA TF <1% was associated with superior PFS ($P = .013$; Data Supplement, Fig S6A) and OS ($P = .012$; Data Supplement, Fig S6B).

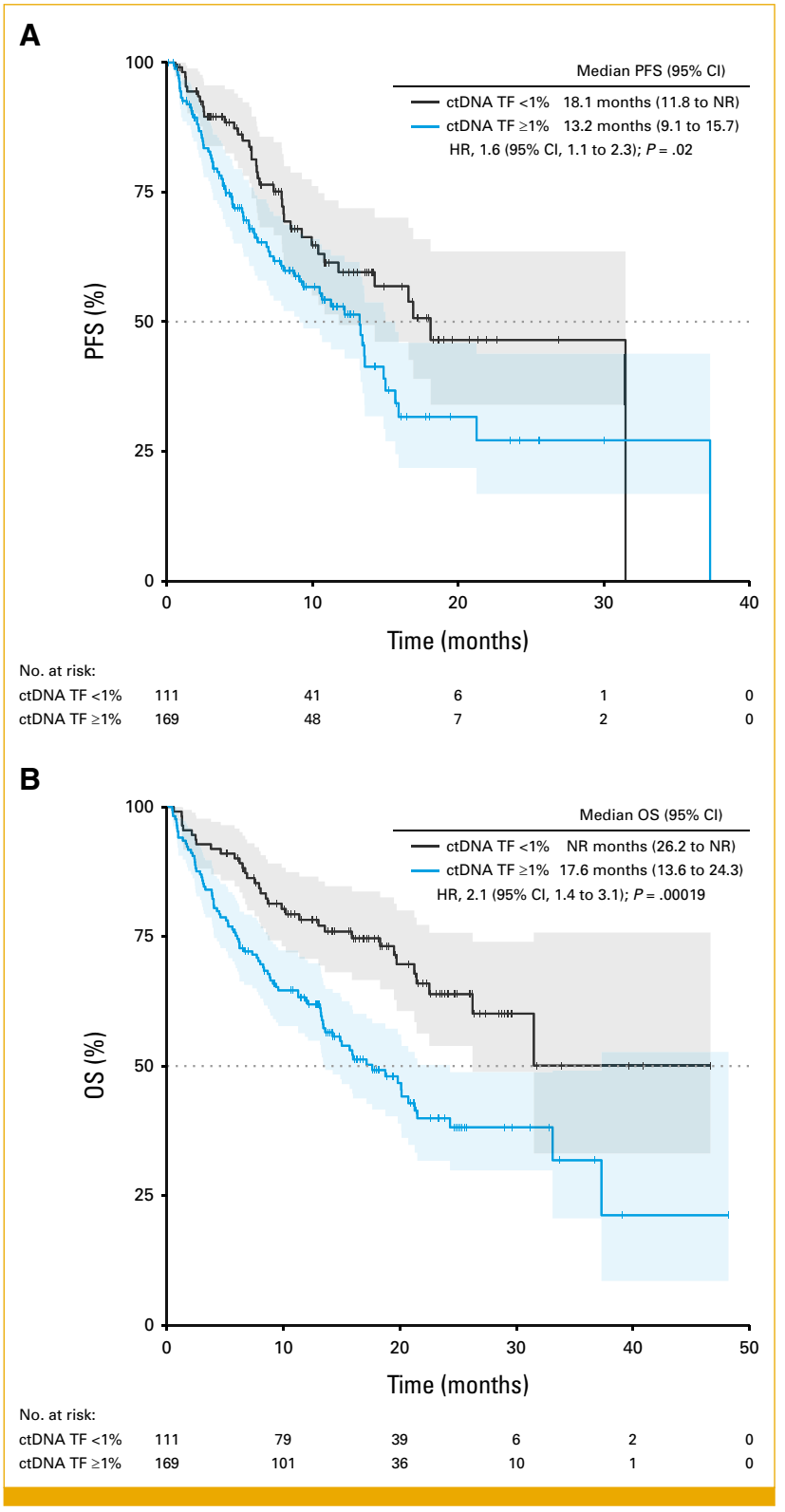

FIG 1. Comparisons of ctDNA TF ≥1% and <1%: The survival analysis of patients between ctDNA ≥1% and <1% was analyzed using Kaplan-Meier estimates. In all, 280 treatment-naïve patients were included in the analysis. (A) PFS in months and (B) OS. Median PFS and OS with 95% CI and log-rank test *P* value were reported. The shading represents the 95% CI. ctDNA, circulating tumor DNA; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; TF, tumor fraction.

Validating the Impact of ctDNA Tumor Fraction as a Predictive Biomarker at Disease Progression

The predictive utility of ctDNA TF was analyzed in 256 patients with TP-NGS performed at first disease progression. Clinical characteristics are detailed in the Data Supplement (Table S6). Patients with ctDNA TF ≥1% had significantly worse PFS after first-line (PFS1) and second-line (PFS2) therapies compared with those with ctDNA TF <1%. For first-line therapy, the median PFS1 (mPFS1) was 10.9 months (95% CI, 9.5 to 13.1) in the ctDNA TF ≥1% group versus 13.4 months (95% CI, 9.5 to 16.7) in the ctDNA TF <1% group (P = .0075; HR, 1.4 [95% CI, 1.1 to 1.8]; Fig 3A). In second-line therapy, the ctDNA TF ≥1% group had a median PFS2 of 6.1 months (95% CI, 4.5 to 8.6) compared with 14.0 months (95% CI, 9.3 to NR) in the ctDNA TF <1% group (P = .0056; HR, 1.9 [95% CI, 1.2 to 3]; Fig 3B). Additionally, ctDNA TF ≥1% was strongly associated with inferior OS, with an HR of 2.1 (95% CI, 1.4 to 3.1; P = .00013; Fig 3C).

Optimizing the Threshold for ctDNA TF

The optimal threshold for ctDNA TF was determined to maximize its prognostic utility. In the overall population, a threshold of 2.3% was associated with significantly worse OS (P = .00046; Fig 4A, Data Supplement, Table S7). Subgroup analyses revealed treatment-specific thresholds: 1.6% for EGFR TKIs (P = .011; Fig 4B, Data Supplement, Table S8) and 2.2% for chemotherapy ± immunotherapy (P = .00081; Fig 4C, Data Supplement, Table S9). These thresholds highlight ctDNA TF as a predictive biomarker tailored to specific treatment modalities.

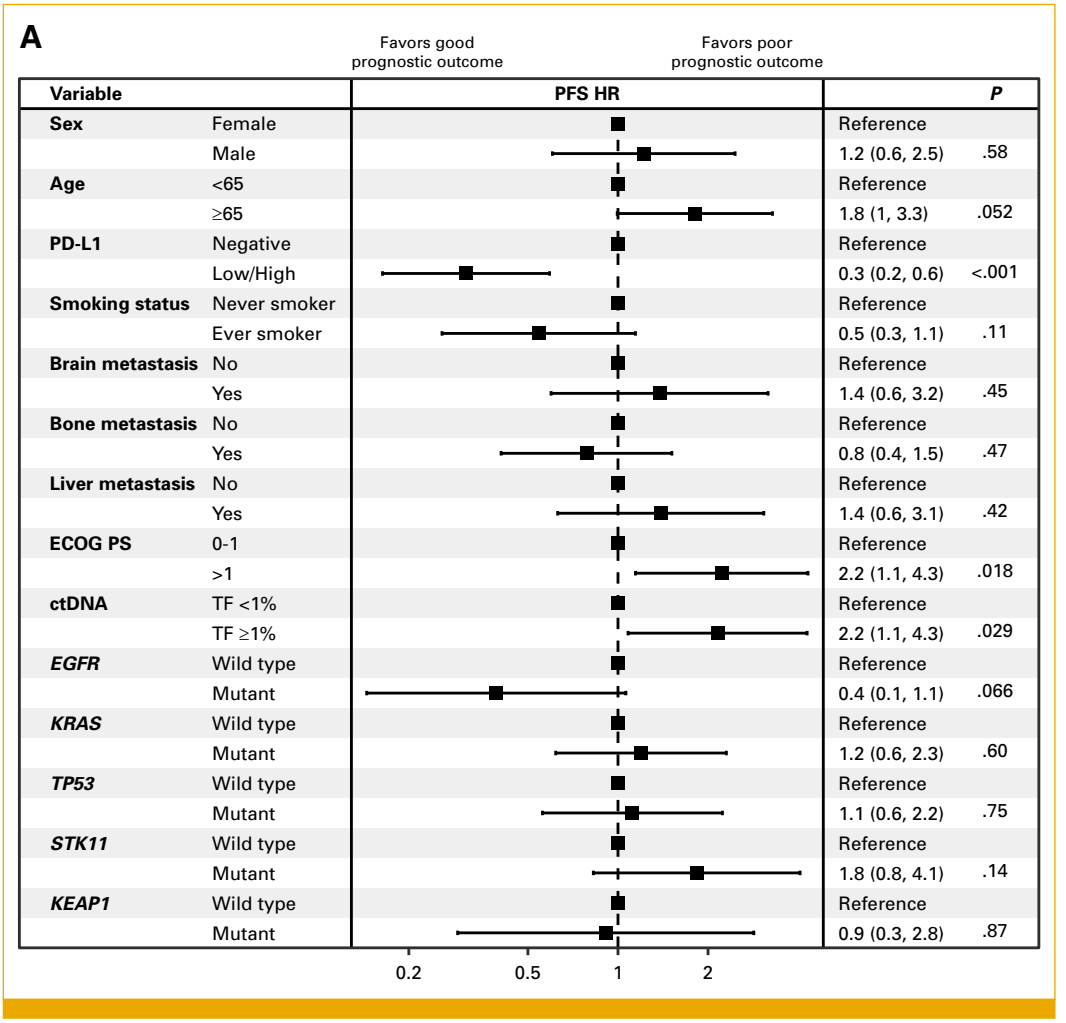

FIG 2. Multivariable Cox proportional hazard models demonstrated ctDNA TF ≥1% was associated with poor survival outcome in treatment-naïve patients. (A) Forest plot for multivariable Cox regression of PFS. (B) Forest plot for multivariable Cox regression of OS. Data derived from multivariable Cox regression of ctDNA TF and other clinical factors. The HR with 95% CI and P value of each variable were reported in the table right to each graph. ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group Performance Score; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TF, tumor fraction. (continued on following page)

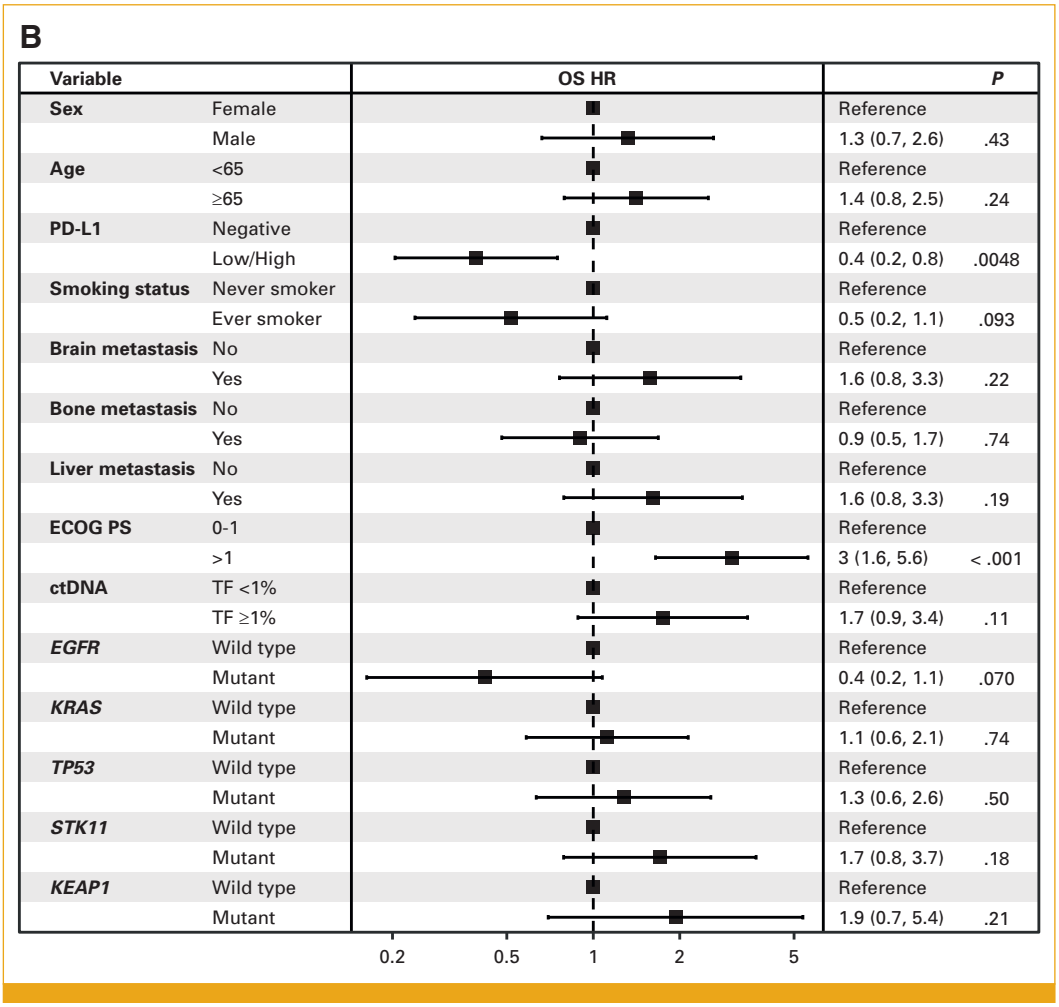

FIG 2. (Continued).

The prognostic value of ctDNA TF for OS was further evaluated across the overall population and treatment subgroups. In the overall cohort, ctDNA TF demonstrated consistent prognostic significance, with AUC values ranging from 0.65 to 0.70 at various time points (Fig 5A). Within the EGFR TKI subgroup, ctDNA TF showed strong predictive capability for OS, with AUC values ranging from 0.68 to 0.79, reaching 0.79 at 24 months (Fig 5B). In the chemotherapy ± immunotherapy subgroup, ctDNA TF had a predictive AUC of 0.73 for OS at 18 months (Fig 5C).

DISCUSSION

This prospective study establishes ctDNA TF as a robust, treatment-agnostic predictive and prognostic biomarker for advanced-stage NSCLC, specifically in the adenocarcinoma subtype. To date, this is one of the largest real-world genomic studies validating ctDNA TF in this context.

Although retrospective studies have linked elevated ctDNA TF with poor outcomes pan-cancer,[19,21-23] our findings provide critical prospective validation of its prognostic significance in advanced NSCLC. Patients with ctDNA TF ≥1% had a median OS of 17.6 months, whereas OS was NR for those with ctDNA TF <1%. Higher ctDNA TF levels consistently correlated with worse survival outcomes, reinforcing its value as a biomarker of tumor burden and metastatic spread. Furthermore, ctDNA TF ≥1% was significantly associated with synchronous distant metastases and was prognostically independent of metastatic site, highlighting its role as a refined marker of metastatic load. These findings align with previous evidence linking ctDNA to tumor burden, such as metabolic tumor volume in NSCLC.[16,23]

Our results position ctDNA TF as a universal and versatile biomarker for risk stratification, survival prediction, and disease monitoring in advanced NSCLC, with significant potential to guide personalized treatment strategies.

This study highlights ctDNA TF as a potential biomarker applicable across diverse treatment strategies and therapy lines in advanced NSCLC. ctDNA TF <1% levels were strongly

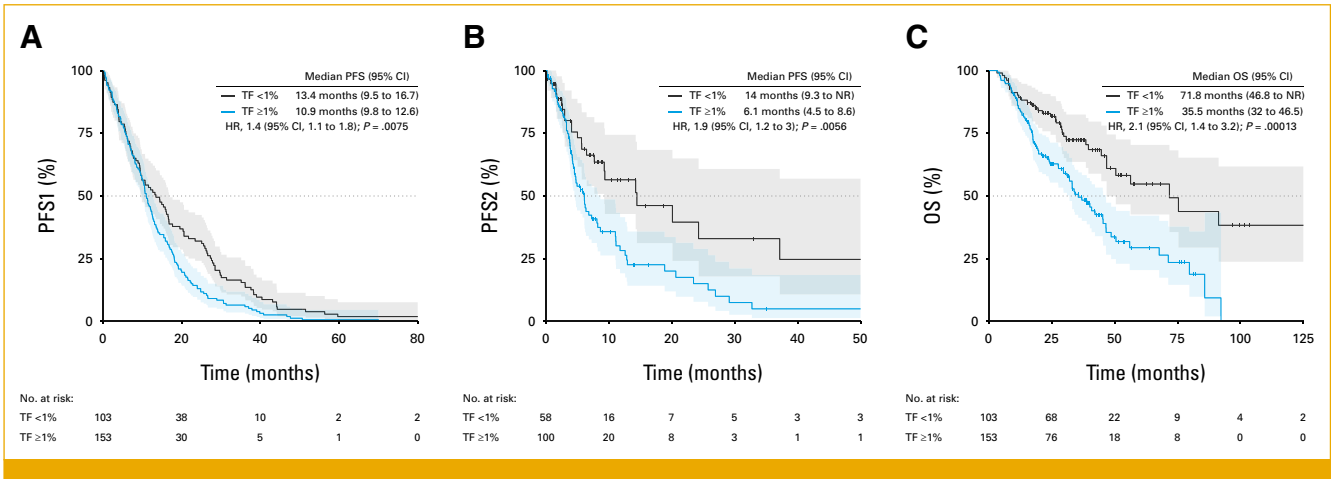

FIG 3. Comparisons of ctDNA TF ≥1% and <1% at progression: The survival analysis of patients between ctDNA ≥1% and <1% was analyzed using Kaplan-Meier estimates. In all, 256 patients who had blood biopsy at progression were included. (A) PFS1; before blood biopsy, (B) PFS2; after blood biopsy, and (C) OS. Median PFS and OS with 95% CI and log-rank test *P* value were reported. The shading represents the 95% CI. ctDNA, circulating tumor DNA; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; PFS1, PFS of first line of treatment; PFS2, PFS of second line of treatment; TF, tumor fraction.

associated with improved PFS and OS in patients treated with chemotherapy-immunotherapy combinations or EGFR TKIs. Importantly, ctDNA TF proved reliable in both first- and second-line treatments, offering a quantitative tool to predict outcomes in heterogeneous patient populations and enhancing its utility in clinical practice.

Although a ctDNA TF cutoff of 1% is commonly recommended, our findings underscore the need for personalized thresholds tailored to specific therapies. For NSCLC, we propose a clinically significant cutoff of 2.3% for the overall population, with subgroup-specific thresholds of 2.2% for chemotherapy ± immunotherapy and 1.6% for EGFR TKIs. These refined cutoffs reflect the variability in ctDNA shedding and tumor biology across treatments, emphasizing the inadequacy of a universal threshold. The biological mechanisms underlying these differences warrant further investigation. Therefore, establishing a definitive ctDNA TF cutoff is imperative for forthcoming clinical trials. The analysis of ctDNA TF with appropriate cutoffs may be used as a criterion in future trials to elucidate the optimal patient selection strategy.

Personalized treatment strategies, including escalation and de-escalation, are gaining traction, yet patient selection criteria remain unclear. Trials like FLAURA2[24] have shown

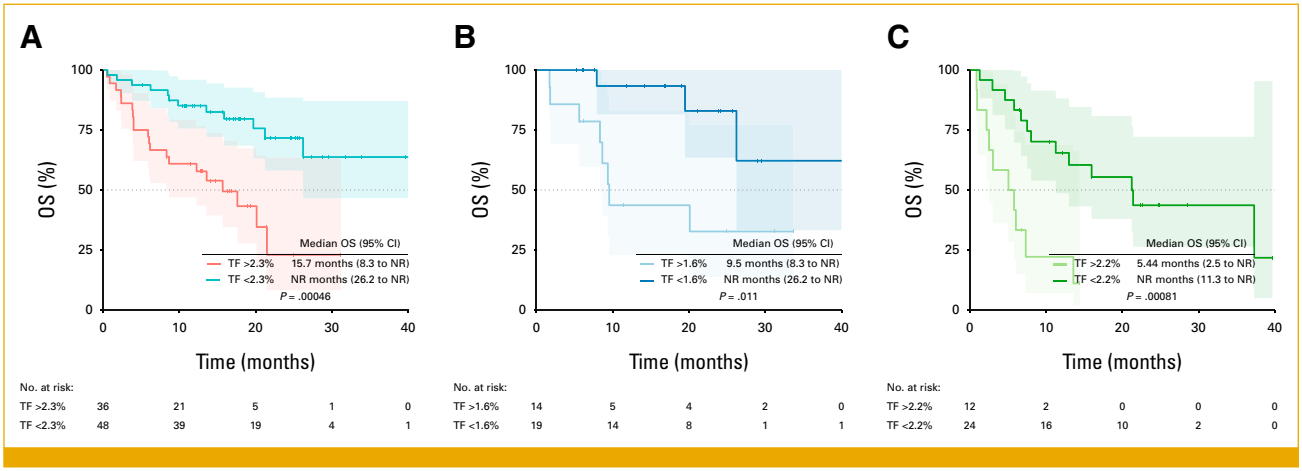

FIG 4. Clinically significant cutoff of ctDNA in advanced NSCLC: The optimal cutoff of ctDNA TF of treatment-naïve patients was used to determine maximally selected rank statistics. Kaplan-Meier analysis using the optimal thresholds for ctDNA TF was performed. (A) Cutoff at 2.3% determined by OS. (B) Cutoff at 1.6% in EGFR TKI. (C) Cutoff at 2.2% in chemotherapy ± immunotherapy. ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; NR, not reached; NSCLC, non–small cell lung cancer; OS, overall survival; TF, tumor fraction; TKI, tyrosine kinase inhibitor.

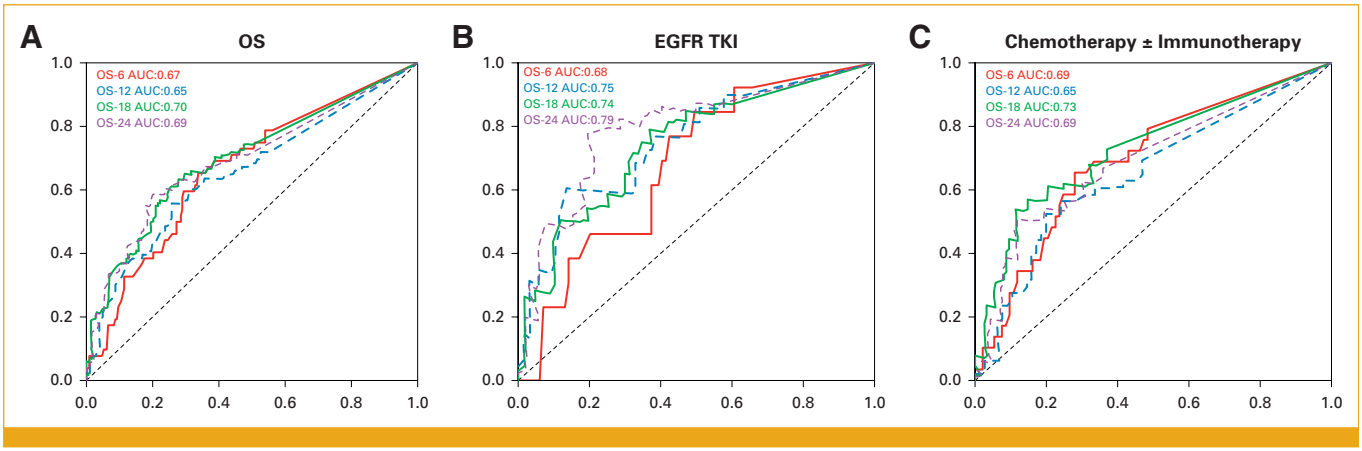

FIG 5. Time-dependent ROC curve: The time-dependent ROC curves were estimated from overall survival data using the Kaplan-Meier method. The AUC is estimated across predicted time and was reported on the top left of each graph. (A) All treatment-naïve patients (n = 280). (B) EGFR TKI. (C) Chemotherapy ± immunotherapy subgroups. EGFR, epidermal growth factor receptor; OS, overall survival; ROC, receiver operating characteristics; TKI, tyrosine kinase inhibitor.

the impact of escalation, whereas PACE-LUNG demonstrated the potential of ctDNA parameters to guide treatment adjustments.[25] Consequently, we emphasize that treatment escalation or de-escalation may be effectively addressed by integrating ctDNA TF into the treatment methodology. Our findings indicate that the ctDNA TF cutoff is crucial, depending on the treatment strategy adopted. Therefore, establishing a definitive ctDNA TF cutoff is imperative for forthcoming clinical trials. The analysis of ctDNA TF with appropriate cutoffs may be used as a criterion in future trials to elucidate the optimal patient selection strategy.

This study underscores the potential of ctDNA TF as a prognostic and predictive biomarker in advanced NSCLC, but its successful clinical implementation requires addressing several real-world challenges. Key barriers include regulatory approval, cost, turnaround time, and technical limitations. Liquid biopsy, although less invasive and potentially more cost effective than tissue biopsy, faces hurdles such as the lack of standardized protocols for ctDNA TF reporting and cutoff thresholds. High upfront costs of TP-NGS assays and the need for advanced bioinformatics support further limit accessibility, especially in resource-constrained settings.

Health care systems must assess the cost-effectiveness of ctDNA TF, factoring in its potential to reduce unnecessary treatments, mitigate side effects, and improve patient outcomes. Economic models that highlight these benefits could strengthen the case for integrating ctDNA TF into routine care. Additionally, variability in ctDNA TF sensitivity based on tumor type, stage, and burden may lead to false-negative results, necessitating further validation to establish universal or context-specific thresholds. Preanalytical factors, including sample collection, handling, and storage, also need standardization to ensure consistent ctDNA yield and quality.

Prevailing clinical guidelines currently lack comprehensive protocols for quantifying and reporting TFs, highlighting the need for revisions to incorporate these advances.[26] Emerging evidence, including findings from this study, strongly supports ctDNA TF as a critical biomarker. We advocate for updating guidelines to fully integrate ctDNA TF, enabling its effective use to enhance personalized oncology and improve outcomes for patients with advanced NSCLC.

This study has limitations, notably the absence of longitudinal tracking of ctDNA TF. Although ctDNA was assessed at baseline and first progression, continuous monitoring throughout the treatment journey is necessary for a deeper understanding of patient outcomes. This ongoing prospective real-world study aims to address these limitations by including more comprehensive patient data and detailed genomic insights in future updates. Despite these challenges, integrating ctDNA TF into routine practice has the potential to revolutionize personalized oncology.

In conclusion, our research highlights ctDNA TF as both a prognostic and predictive biomarker for advanced NSCLC, carrying substantial implications for clinical practice. This study fills existing gaps in understanding the prognostic and predictive importance of longitudinally measured ctDNA TF, reinforcing its value in guiding treatment decisions. The integration of ctDNA TF quantification into disease monitoring presents a vital opportunity to enhance patient outcomes through personalized, data-informed care approaches for advanced NSCLC.

AFFILIATIONS

[1]Department of Clinical Oncology, Queen Mary Hospital, Hong Kong SAR, China
[2]Department of Clinical Oncology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, Hong Kong SAR, China
[3]School of Biomedical Science, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
[4]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China
[5]Department of Clinical Oncology, Shenzhen Key Laboratory for Cancer Metastasis and Personalized Therapy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

CORRESPONDING AUTHOR

Aya El Helali, MD, PhD, MRCP; e-mail: ahelali@hku.hk.

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The raw sequencing data originated from Foundation Medicine, Inc. The derived data supporting this study's findings are available upon reasonable request from the authors.

AUTHOR CONTRIBUTIONS

Conception and design: Ben Man Fei Cheung, Elaine Yee-Ling Ko, Dennis Kwok-Chuen Leung, Anne Wing-Mui Lee, Victor Ho-Fun Lee, Aya El Helali
Administrative support: Anne Wing-Mui Lee, Aya El Helali
Provision of study materials or patients: Aya El Helali
Collection and assembly of data: Ben Man Fei Cheung, Elaine Yee-Ling Ko, Dennis Kwok-Chuen Leung, Victor Ho-Fun Lee, Aya El Helali
Data analysis and interpretation: All authors
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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Matthew Kin-Liang Chiu
Honoraria: Novartis, MSD
Consulting or Advisory Role: Daiichi Sankyo/Astra Zeneca, MSD
Travel, Accommodations, Expenses: Novartis, Astellas Pharma, Daiichi Sankyo/Astra Zeneca, Johnson & Johnson/Janssen

Anne Wing-Mui Lee
Research Funding: Roche

Victor Ho-Fun Lee
Honoraria: Roche, Lilly, Pfizer, Amgen, AstraZeneca/MedImmune, Boston Scientific, Takeda, Merck, Merck Serono, Novartis, AQUILAB, Accuray
Consulting or Advisory Role: Lilly, Pfizer, Bristol Myers Squibb, TopAlliance BioSciences Inc, Merck, BeiGene, Varian Medical Systems
Research Funding: AstraZeneca/MedImmune
Travel, Accommodations, Expenses: Novartis, AstraZeneca

Aya El Helali
Honoraria: Chimerix (Inst), Roche (Inst), Zai Lab (Inst)
Research Funding: Pfizer
Travel, Accommodations, Expenses: Zai Lab, Roche Hong Kong Limited

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