Prognostic and therapeutic importance of TROP-2 and MUC-1 in non-small cell lung cancer: A systematic review and meta-analysis

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Abstract. Non-small cell lung cancer (NSCLC) represents ~85% of all lung cancer and is a leading cause of cancer-related mortality worldwide. Trophoblast cell surface antigen-2 (TROP-2) and mucin-1 (MUC-1) have emerged as potential prognostic biomarkers and therapeutic targets. There are no reports of their combined impact as a biomarker in NSCLC. The present systematic review/meta-analysis aimed to evaluate the expression patterns and prognostic implications of TROP-2 and MUC-1 in NSCLC. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Population, Intervention, Comparison, and Outcome framework, 1,297 publications between 2019 and 2024 were systematically retrieved from PubMed, Scopus and EMBASE databases. A total of 12 studies (three for TROP-2 and nine for MUC-1) met the inclusion criteria and five (two for TROP-2 and three for MUC-1) were finally included in the final meta-analysis using fixed-effect models involving 1,159 patients. High TROP-2 [hazard ratio (HR) 1.43, 95% confidence interval (CI): 1.15-1.79; P=0.002] and MUC-1 (HR 2.25; 95% CI: 1.57-3.23, P<0.0001) were consistently overexpressed in NSCLC patient tissues. An exploratory pooled analysis of both biomarker groups demonstrated a significant association with poor clinical outcomes and short survival (HR 1.62; 95% CI: 1.34-1.96; P<0.00001), though this should not be interpreted as evidence of a true dual-biomarker effect. Mechanistically, both markers promote cancer cell proliferation, epithelial-mesenchymal transition, immune evasion and treatment resistance. In conclusion, TROP-2 and MUC-1 are valuable prognostic biomarkers in NSCLC. Their overexpression correlates with poor survival, supporting the development of targeted therapies in NSCLC.

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Abbreviations: TROP-2, trophoblast cell surface antigen-2; MUC-1, mucin-1; NSCLC, non-small cell lung cancer

Key words: trophoblast cell surface antigen-2, mucin-1, non-small cell lung cancer, prognostic value, biomarkers

Introduction

Lung cancer accounts for the highest number of cancer-related deaths worldwide, resulting in ~1.8 million deaths (18.7% of all cancer mortalities) (1). Non-small cell lung cancer (NSCLC), which comprises ~85% of all lung cancer cases, is the most common subtype (2). Conventional treatments, including chemotherapy, surgery and radiotherapy, are widely used for lung cancer (3). However, these approaches often have limited effectiveness, particularly for advanced NSCLC.

Targeted therapy and immunotherapy have gained significant attention as promising alternatives in pre-clinical and clinical studies over recent years (4) and selectively target cancer cells while minimizing damage to normal cells (5). Immunotherapy, in particular, enhances the immune system's ability to recognize and eliminate cancer cells, overcoming mechanisms of immune evasion, such as through the use of immune checkpoint inhibitors (6). These approaches mainly focus on precise binding to specific proteins on cancer cells, particularly those signaling pathways involved in the pathogenesis of NSCLC (7), making the selection of appropriate proteins crucial. Previous studies have identified multiple tumor-associated antigens (TAAs) that are upregulated in patients with NSCLC, including mesothelin, human epidermal growth factor receptor-2, epidermal growth factor receptor (EGFR), mesenchymal-epithelial transition factor and folate receptor α.

Trophoblast cell surface antigen-2 (TROP-2), encoded from tumor-associated calcium signal transducer 2, is a transmembrane glycoprotein that is primarily involved in cell signaling, adhesion, and proliferation (8). In normal tissues, TROP-2 is

expressed at low levels and plays a role in tissue regeneration and embryonic development (8). Notably, a recent review noted that TROP-2 is overexpressed in NSCLC, where it promotes tumor growth, invasion and metastasis by enhancing cell proliferation and survival (8). According to this review, high TROP-2 expression is associated with poor prognosis in patients with NSCLC (8). Additionally, a recent review highlighted transmembrane glycoprotein mucin-1 (MUC-1) as another tumor-associated antigen (TAA) in NSCLC (9). It normally covers the epithelial cells of the mucous membrane, providing lubrication and protection (9). However, aberrant expression of MUC-1 is involved in cancer development, invasion and metastasis (9). Upregulation of MUC-1 has been reported to be highly associated with the progression of different epithelial cancer types, including NSCLC (9). Given their individual roles in tumor progression, TROP-2 and MUC-1 represent promising targets for immunotherapeutic approaches (8,9). Recent evidence suggests that MUC-1 and TROP-2 may be co-regulated through galectin-3-MUC-1-mediated Specific protein 1 (Sp1) recruitment and leads to TROP-2 transcription (10). This provides a biological rationale for evaluating both TAAs as prognostic markers. To date, to the best of the authors' knowledge, no systematic review or meta-analysis has comprehensively evaluated the prognostic importance of TROP-2 and MUC-1 expression for their potential as immunotherapy targets in NSCLC.

The present systematic review and meta-analysis analyzed available evidence on the expression levels of TROP-2 and MUC-1 in NSCLC patients to evaluate their diagnostic, prognostic and therapeutic relevance. Immunohistochemical studies have revealed that both antigens are highly expressed in NSCLC tissues and are associated with reduced overall survival (OS) and disease-free survival (DFS). These findings are consistent with prior experimental and clinical studies suggesting that TROP-2 and MUC-1 contribute to tumor progression through mechanisms such as cancer cell invasion, epithelial-mesenchymal transition (EMT), and metastasis. Collectively, this meta-analysis supported the prognostic value of TROP-2 and MUC-1, individually and in combination, by exploratory pooled analysis in NSCLC, providing clinical support for the development of TROP-2 and MUC-1-directed therapeutic strategies to improve patient outcomes.

Materials and methods

Search strategy. The present study was conducted in the PubMed (pubmed.gov), Scopus (scopus.com) and EMBASE (embase.com) electronic bibliographic databases. To focus on contemporary treatment contexts and recent diagnostic methodologies, the search was restricted to studies published within 5 years of data collection (January 2019-December 2024). The MeSH term 'NSCLC' was combined with its synonymic terms (non-small cell lung carcinoma, NSCLC, Lung carcinoma (s), Lung cancer (s), Lung neoplasm (s), Lung tumo (ur, urs, s). The MeSH term 'TROP-2 or MUC-1' was also combined with their synonymous terms (Tumor-associated calcium signal transducer 2, TROP-2, Transmembrane glycoprotein Mucin 1, Mucin 1, MUC-1, CA 15.3 Antigen, Epithelial membrane antigen, EMA, Episialin, CD227). The present review was registered in PROSPERO ID: CRD42024597178. Population, Intervention, Comparison, and Outcome (PICO) details were Population: Patients diagnosed with NSCLC who exhibited levels of TROP-2 or MUC-1 expression with available clinicopathological parameters, OS or DFS, and values of hazard ratio (HR) with 95% confidence interval (CI). Intervention: The high levels of TROP-2 and MUC-1 expression in NSCLC. Comparator: A group of NSCLC patients with low levels of TROP-2 and MUC-1. Outcome was OS and DFS.

Inclusion and exclusion criteria. To be eligible for inclusion in the present study, the research must not be a review article, must involve only human subjects, be written in English, have full-text availability and be published within 5 years of the date of data collection.

Study selection. Two reviewers (PN and JL) independently evaluated all the studies retrieved using Covidence software (https://www.covidence.org) to ensure transparency and reproducibility in the selection process. Titles and abstracts were initially screened to exclude irrelevant articles, reviews, case reports and non-English publications. Full-text articles that met the inclusion criteria were then assessed for eligibility. Discrepancies between the reviewers were resolved through discussion and, when necessary, a third reviewer was consulted to reach consensus. The inclusion criteria focused on studies reporting TROP-2 and/or MUC-1 expression in NSCLC tissues and corresponding clinicopathological or survival data. The present study selection process was documented and summarized using a Reporting Items for Systematic Reviews and Meta-Analyses 2020 Version (PRISMA) flow diagram (https://www.prisma-statement.org).

Data extraction and quality assessment. Data extraction and quality assessment were independently reviewed by four reviewers (PN, JL, SL and CT). Data were extracted from each study on the first author's name, year of publication, total number of patients, the TROP-2 or MUC-1 expression levels in NSCLC patient tissues/serum/plasma/RNA sequencing data and progression of NSCLC patients using parameters such as median OS, DFS, progression free survival (PFS) and HR. The included studies used different criteria to define TROP-2 or MUC-1 positivity. To standardize the analysis, expression data were split into high vs. low groups according to the definitions provided by the original authors. The prognostic outcomes were extracted and systematically analyzed. The analysis relied primarily on the HR and CI reported by the original study authors, as these values had already been calculated using cut-off values that were pre-defined and specific to each individual study.

Risk of bias in individual studies. The results of the articles with the assessed risk of bias were selected using the revised Cochrane Risk-of-Bias Tool for Randomized Trials 2019 Version (ROB2 Tool) (https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2) for randomized controlled trial studies (Table I) and the Newcastle-Ottawa Scale (NOS) (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for cohort studies (Table II). Publication bias was not formally assessed because <10 studies were

included in the pooled analysis, which renders measures such as the Egger's or Begg's statistical tests unreliable.

Statistical methods. As no individual study simultaneously assessed the expression of TROP-2 and MUC-1 in the same patient cohort, the exploratory analysis was performed by pooling HRs derived from separate studies that investigated each biomarker independently. This approach aimed to provide an exploratory estimate of their overall prognostic relevance rather than a true patient-level dual-marker effect.

Pooled HRs and their 95% CIs were used to determine the association between either TROP-2 or MUC-1 expression and OS. The statistical analyses were performed using Review Manager (RevMan) version 5.4. Rationale for Exploratory pooled analysis (https://www.cochrane.org/products-and-services/review-writing-software): Given that both TROP-2 and MUC-1 are highly expressed TAAs in NSCLC and are mechanistically involved in promoting cancer cell invasion and metastasis, their combined expression was analyzed to investigate their overall prognostic relevance as independent biomarkers of OS. Heterogeneity among studies was assessed using the χ^2 test and I^2. A P-value of <0.1 or an I^2 statistic of >50% was indicative of significant heterogeneity between studies; in these cases, a random-effects model was used.

In the presence of low statistical heterogeneity (I^2<50%), a fixed-effect model was applied for the primary analysis. However, given the limited number of studies and limitations of the I^2 statistic in this context, an additional sensitivity analysis using a random-effects model was performed to assess the robustness of the pooled estimates. P<0.05 was considered to indicate a statistically significant difference. Sensitivity analysis was also performed using a leave-one-out approach to evaluate the influence of each study on the overall pooled HRs. The original HRs (95% CIs) were mathematically inverted by taking their reciprocals (1/HR) to ensure consistency in interpretation.

Results

Study selection and characteristics. A comprehensive systematic literature search across three databases, including PubMed, Scopus, and EMBASE, identified a total of 1,297 studies that were imported into Covidence to be screened. After removing 327 duplicate records, 970 unique citations were screened for title and abstract. This initial screening excluded 912 records that did not meet the inclusion criteria or were deemed irrelevant to the research question. The remaining 58 full-text articles were retrieved and assessed for eligibility. Following the full-text review, 46 studies were excluded for the following reasons: Seven studies did not involve human subjects, 15 studies had no full-text availability, one was identified as a review article and 23 studies were irrelevant to the specific research objectives. Ultimately, 12 studies met all inclusion criteria and were included in the present systematic review and meta-analysis. The present study selection process was conducted independently by two reviewers (PN and JL) and documented according to the PRISMA guidelines (Fig. 1). All included studies provided data on TROP-2 and/or MUC-1 expression in NSCLC patients with corresponding clinicopathological parameters and survival outcomes.

TROP-2 and prognostic value in NSCLC patients. Among the 12 studies, only three investigated the effect of TROP-2 on the progression of NSCLC (Table III). Bessede *et al* (11) conducted a randomized controlled trial involving 405 NSCLC patients to examine the association between TROP-2 expression and treatment outcomes with the atezolizumab anti-programmed cell death ligand 1 (PD-L1) drug. This study demonstrated that elevated TROP-2 expression was correlated with a poor prognosis. The patients were classified as high TROP-2 or low TROP-2 based on an optimized threshold obtained using maximally selected rank statistics from the maxstat R package (https://CRAN.R-project.org/package=maxstat). The result showed that patients with high TROP-2 expression had a median OS of 12.6 months compared with 16.3 months in those with low expression. The HR of OS of the low TROP-2 expression group of patients was 0.73 (95% CI: 0.57-0.92) with a statistical significance (P=0.007) and in PFS it was 0.69 (95% CI: 0.56-0.84) with a statistical significance (P<0.001; Table III).

Another study analyzed TROP-2 expression in 164 NSCLC patients by immunohistochemical staining and reported that 51.22% (84/164) exhibited high TROP-2 expressions, defined by a semi-quantitative histology score (H-score) of ≥130 (12). Moreover, the increase in TROP-2 expression was correlated with poor disease prognosis in patients treated with gefitinib. The log-rank χ^2 test for median OS between patients with high and low TROP-2 expression was 5.817, indicating statistical significance (P=0.016; Table III).

Mito *et al* (13) conducted a retrospective study in 331 NSCLC patients, including 228 with lung adenocarcinoma (ADC) and 103 with lung squamous cell carcinoma (SCC). The expression of TROP-2 was evaluated by immunohistochemical staining and used intensity (0-3) and proportion (0-3) scores to generate a summary score. The median summary scores were 4.5 in ADC and 5 in SCC. Cases with a total score >4.5 were classified into the high TROP2 expression group. The study demonstrated that high TROP-2 expression was found in 38% of total ADC samples and 35% of total SCC samples. Furthermore, the elevated TROP-2 level was markedly correlated with abnormal p53 nuclear expression and poor OS. Univariable analysis in ADC revealed a HR of OS was 2.05 (95% CI: 1.06-4.00) for high vs. low TROP-2 expression, with a statistical significance (P=0.0326), and HR of PFS was 1.40 (95% CI: 0.82-2.36) with no statistical significance (P=0.2175; Table III).

MUC-1 and prognostic value in NSCLC patients. A total of nine studies investigated MUC-1 expression levels in NSCLC patients (Table IV). Of them, two studies analyzed data from genome databases and classified patients into high and low MUC-1 groups (14,15). Analysis of 136 NSCLC patients from The Cancer Genome Atlas had high MUC-1 mRNA expression (15). Its high expression was associated with poor clinical outcomes following osimertinib treatment (15). Tu *et al* (14) showed that MUC-1 mRNA expression increased in 50.03% of 1,925 NSCLC patients from the genome database. Prolonged OS was positively associated with MUC-1 expression, with a

Table I. Cochrane risk-of-bias tool for randomized trials (ROB2 Tool).

	Domain						
First author/s, year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the report result	Overall RoB Judgement	(Refs.)
Bessede *et al*, 2024	Low	Low	Low	Low	Low	Low	(11)

Table II. NOS for assessing the quality of cohort studies.

	Selection				Comparability	Outcome			Total Quality Score	Grading quality of the studies	(Refs.)
First author/s, year	S1	S2	S3	S4	C1	O1	O2	O3			
Sun *et al*, 2021	1	1	1	1	2	1	1	1	9	Good	(12)
Mito *et al*, 2020	1	1	1	1	2	1	1	1	9	Good	(13)
Tu *et al*, 2022	1	1	1	1	2	1	1	1	9	Good	(14)
Haratake *et al*, 2024	1	1	1	1	1	1	1	1	8	Good	(15)
Buyuk *et al*, 2023	1	1	1	1	2	1	1	1	9	Good	(16)
Xie *et al*, 2021	1	1	1	1	2	1	0	1	8	Good	(17)
Jiang *et al*, 2020	1	1	1	1	2	1	0	0	7	Good	(18)
Bes-Scartezini *et al*, 2022	1	1	1	1	2	1	1	1	9	Good	(19)
Kato *et al*, 2021	1	1	1	1	2	1	1	1	9	Good	(20)
Mohamadnia, *et al*, 2022	0	0	1	1	1	1	0	0	4	Fair	(21)
Pan *et al*, 2019	0	1	1	1	1	1	0	0	5	Fair	(22)

S1, representativeness of the exposed cohort; S2, selection of the non-exposed cohort; S3, ascertainment of exposure; S4, demonstration that outcome of interest was not present at start of study; C1, comparability of cohorts on the basis of the design or analysis; O1, assessment of outcome; O2, was follow-up long enough for outcomes to occur?; O3, adequacy of follow up of cohorts. Based on NOS scores, studies were categorized as good quality (7-9 points), fair quality (4 points), or poor quality (0-3 points). NOS, Newcastle-Ottawa Scale.

HR (95% CI) of 0.67 (0.59-0.76) and with statistical significance ($P=4.6x10^{-10}$); and high MUC-1 was markedly associated with worse DFS, with an HR of 1.5 (P=0.001), indicating a 50% higher risk of recurrence or progression compared with low MUC-1 expression.

Notably, three studies investigated the level of the MUC-1 protein in lung tissues and its relation to clinicopathological properties (16-18). A retrospective study conducted by Buyuk *et al* (16) indicated that 55.56% of ADC samples had a high immunoreactive score, and the increase of depolarized MUC-1 (characterized by expression on the entire cell surface or throughout the cytoplasm) was associated with lymphatic invasion, more advanced tumor stage and larger tumor size. Similarly, Xie *et al* (17) analyzed formalin-fixed paraffin-embedded (FFPE) lung tissue samples from 176 ADC patients at different stages and showed that 42% of samples exhibited high MUC-1 and a statistically significant correlation between MUC-1 expression levels and tumor stage. Jiang *et al* (18) studied 131 NSCLC patients using immunohistochemistry staining and found that 61.83% had high MUC-1 levels, particularly elevated in female and non-smoker patients with advanced ADC.

Two studies conducted retrospective cohort studies analyzing the correlation between MUC-1 level and clinical outcomes (19,20). Bes-Scartezini and Saad Junior (19) found that 50.60% of 112 NSCLC patients had high soluble MUC-1 levels (>25-30 UI/ml), which was associated with decreased overall survival (OS). The median OS for patients with low MUC-1 was 18.57 months, and 13.44 months for those with high MUC-1. The HR between these groups was 1.87 (95% CI: 1.13-3.10) with statistical significance (P=0.016). Kato *et al* (20) examined lung tissues from FFPE samples obtained via core needle biopsy and immunohistochemistry staining of MUC-1-Tn, which is an antigen that may be a novel epitope recognized by MUC-1-Tn epitope-defined antibody (MUC-1-Tn ED Ab). The authors found that 25.14% of samples had high MUC-1-Tn expression (>0.14), and MUC-1-Tn overexpression was associated with poor OS. The five-year OS rate was 87.9% in the low-to-moderate expression group and 69.3% in the high-expression group. The HR was 2.797 (95% CI: 1.579-4.956) with statistical significance (P<0.001).

Two studies investigated MUC-1 in the blood of NSCLC patients (21,22). Mohamadnia *et al* (21) compared MUC-1 levels in blood samples between 30 NSCLC patients and 30 healthy

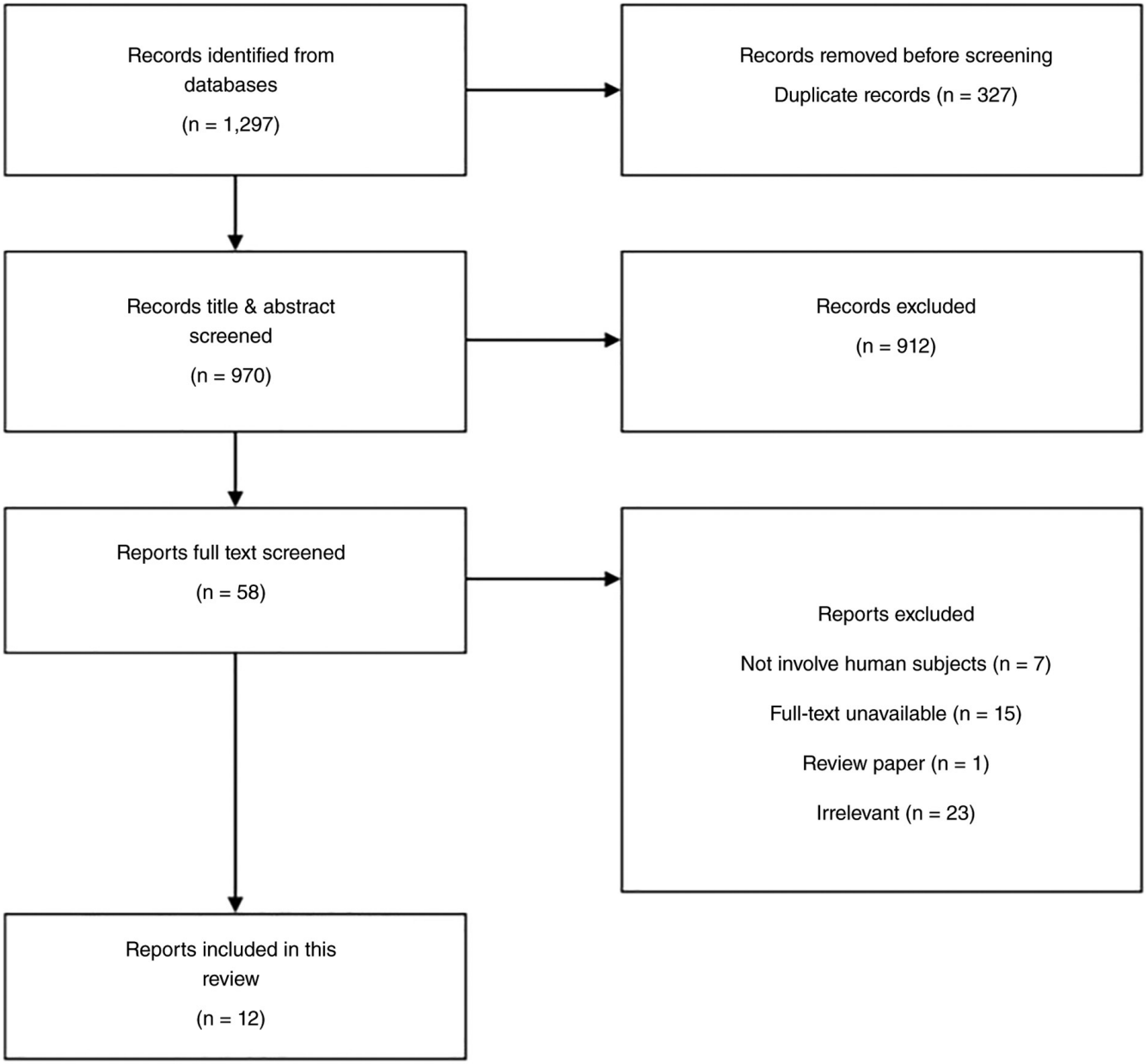

Figure 1. A Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the number articles included in the present study.

subjects. High MUC-1 was observed in 63.3% of NSCLC patients and 17% of healthy subjects, showing a 2.64-fold increase in NSCLC patients with statistical significance (P=0.031). Pan *et al* (22) measured MUC-1 exosomes in plasma using electrochemiluminescence immunoassay analysis in 27 NSCLC patients and 16 healthy subjects. The mean exosome levels were 1.55±0.16 in NSCLC patients and 1.05±0.06 in healthy subjects. The study concluded that exosomal MUC-1 might be valuable in distinguishing NSCLC patients from healthy controls, with a diagnostic value Area under the curve (AUC) (95% CI)=0.685 (0.526-0.818) and statistical significance (P=0.0234).

Meta-analysis of TROP-2 and MUC-1 expression and OS. Forest plot analysis demonstrated distinct prognostic patterns for TROP-2 and MUC-1 in NSCLC patients (Fig. 2). Elevated TROP-2 expression was markedly associated with poor OS, with an HR of 1.43 (95% CI: 1.15-1.79; P=0.002) based on two studies comprising 736 patients (Fig. 2A). Heterogeneity among TROP-2 studies was low (I^2=20%; χ^2=1.26; P=0.26), indicating consistency across studies. The two included studies showed concordant directional effects, which, after reciprocal calculation, Bessede *et al* (11) (2024; n=405) reported HR of 1.37 (95% CI: 1.08-1.74) and Mito *et al* (13) (2020; n=331) reported HR of 2.05 (95% CI: 1.06-3.98).

Similarly, increased MUC-1 expression demonstrated a significant correlation with worse OS (HR=2.25; 95% CI: 1.57-3.23; P<0.0001) across three studies with 423 patients (Fig. 2B). Low heterogeneity was observed, indicating consistency between the included studies (I^2=0%; χ^2=1.10; P=0.58). Three included studies showed consistent outcomes, with Bes-Scartezini and Saad Junior (19) (2022; n=112) reporting HR of 1.87 (95% CI: 1.13-3.10), Haratake *et al* (15) (2024; n=136) reporting HR of 2.49 (95% CI: 0.70-8.86) and Kato *et al* (20) (2021; n=175) reporting HR of 2.80 (95% CI: 1.58-4.96).

Table III. Summary of TROP-2 expression and clinical outcomes in NSCLC patients.

First author/s, year	Population	Treatment	Expression (%)	Median OS (negative vs. positive)	HR of OS (95% CI)	P-value	HR of PFS (95% CI)	P-value	Conclusion	(Refs.)
Bessede *et al*, 2024	Randomized Phase II POPLAR and Phase III OAK trials (n=405)	Atezolizumab (IV/1,200 mg/ q 3 weeks)	N/A	16.3 vs. 12.6	1.37[a] (1.09-1.75)	0.007	1.45[a] (1.19-1.79)	<0.001	High TROP-2 level was associated with worse outcomes in NSCLC patients treated with atezolizumab.	(11)
Sun *et al*, 2021	NSCLC patients (n=164)	Gefitinib	51.22%	Log-rank χ^2=5.817	N/A	0.016	N/A	N/A	High TROP-2 level in NSCLC patients with EGFR mutations was associated with earlier drug resistance and poor OS during gefitinib treatment.	(12)
Mito *et al*, 2020	Retrospective study (n=331; ADC=228 and SCC=103)	N/A	38% in ADC; 35% in SCC	N/A	ADC 2.05 (1.06-4.00)	0.0326	ADC 1.40 (0.82-2.36)	0.2175	Increased TROP-2 level was markedly associated with a poor clinical course in ADC patients, but not in those with SCC.	(13)

N/A, Not assessed; [a]The original HR (95% CI) were mathematically inverted to ensure consistency in interpretation. TROP-2, trophoblast cell surface antigen-2; NSCLC, non-small cell lung cancer; IV, intravenous; OS, overall survival; PFS, progression-free survival; q, every; ADC, lung adenocarcinoma; SCC, lung squamous cell carcinoma.

Table IV. Summary of MUC-1 expression and clinical outcomes in NSCLC patients.

First author/s, year	Population	Treatment	Expression (%)	Median OS (neg vs. pos)	HR of OS (95% CI)	P-value	HR of DFS (95% CI)	P-value	Conclusion	(Refs.)
Tu *et al*, 2022	KM plotter from genome database (n=1925)	N/A	50.03%	Low<high	0.67 (0.59-0.76)	4.6E-10	1.5 (n=962)	0.001	Increased MUC-1 mRNA expression is associated with favorable OS but worse DFS.	(14)
Haratake *et al*, 2024	The Cancer Genome Atlas (n=136)	Osimertinib	60.30%	22.4 vs. 16.6[a] 66.4 vs. 6.9[b]	2.49 (0.70-8.87)	0.1	4.17 (1.60-10.82)	0.0015	High MUC-1 expression in EGFR-mutant NSCLCs was associated with poor clinical outcomes.	(15)
Buyuk *et al*, 2023	Retrospective cohort study ADC (n=99)	N/A	55.56%	N/A	N/A	N/A	N/A	N/A	Depolarized MUC-1 expression was associated with lymphatic invasion, more advanced tumor stage, and larger tumors.	(16)
Xie *et al*, 2021	Prospective cohort ADC (n=176)	Radical surgery and systematic nodal dissection	42.00%	N/A	N/A	N/A	N/A	N/A	MUC-1 expression in patients was related to differentiation and TNM stage.	(17)
Jiang *et al*, 2020	NSCLC patients (n=131)	N/A	61.83%	N/A	N/A	N/A	N/A	N/A	MUC-1-C expression was highly expressed in NSCLC especially in female, non-smoker patients with advanced-stage ADC.	(18)
Bes-Scartezini *et al*, 2022	Retrospective cohort study non-SCC (n=112)	N/A	50.60%	18.57 vs. 13.44	1.87 (1.13-3.10)	0.016	N/A	N/A	High pre-treatment levels of MUC-1 were correlated with decreased survival in non-SCC.	(19)
Kato *et al*, 2021	Retrospective cohort study ADC (n=175)	N/A	High: 25.14%	5-year OS rate Low to Moderate: 87.9% High: 69.3%	2.797 (1.579-4.956)	<0.001	N/A	N/A	Overexpression of MUC-1-Tn was strongly associated with EMT potential and poor survival in patients with ADC.	(20)

Table IV. Continued.

First author/s, year	Population	Treatment	Expression (%)	Median OS (neg vs. pos)	HR of OS (95% CI)	P-value	HR of DFS (95% CI)	P-value	Conclusion	(Refs.)
Mohamadnia, *et al*, 2022	NSCLC patients (n=30)	N/A	63.3%	N/A	N/A	N/A	N/A	N/A	NSCLC patients and healthy controls show significant difference in marker positivity.	(21)
Pan *et al*, 2019	NSCLC patients (n=27)	N/A exosomes patients= 1.55±0.16	Mean	diagnostic value AUC= 0.685 (0.526-0.818)	N/A	N/A	N/A	N/A	Exosomal MUC-1 might be valuable in distinguishing NSCLC patients from healthy controls.	(22)

N/A, Not assessed; [a]after diagnosis, [b]after initiation of osimertinib. MUC-1, mucin-1; NSCLC, non-small cell lung cancer; SCC, lung squamous cell carcinoma; ADC, lung adenocarcinoma; DFS, disease-free survival; OS, overall survival; AUC, area under curve.

A sensitivity analysis was performed using a random-effects model to assess the robustness of the pooled estimates given the limited number of included studies. As shown in Table V, the pooled HRs from the random-effects model were comparable to those derived from the fixed-effects model. The direction and statistical significance of the associations remained unchanged for TROP-2, MUC-1 and the exploratory pooled analysis, indicating that the results were generally robust despite the small number of studies. When both markers were evaluated together, high expression of TROP-2 and MUC-1 was markedly associated with short OS (HR 1.62; 95% CI 1.34-1.96; P<0.00001; Fig. 2C). Heterogeneity remained low (I^2=40%; χ^2=6.67; P=0.15).

Discussion

The present study conducted a systematic review and meta-analysis of 12 eligible studies carefully selected from 1,297 publications, comprising three studies on TROP-2 and nine on MUC-1. The two groups concluded that elevated TROP-2 and MUC-1 levels were observed in NSCLC patients. Analysis of the correlation between TROP-2 or MUC-1 expression levels and clinical outcomes revealed that high expression levels were markedly associated with poor clinical outcomes and short survival. Notably, the exploratory pooled analysis of TROP-2 and MUC-1 expression suggests a potential association with an unfavorable prognosis, although this should not be interpreted as evidence of a true dual-biomarker effect. These findings underscore the prognostic value of TROP-2 and MUC-1 and their potential as therapeutic targets for personalized treatment strategies in NSCLC.

The NSCLC patients with high TROP-2 expression were markedly associated with reduced survival and aggressive tumor behaviors (11-13). Several mechanisms may underlie these associations (Fig. 3). TROP-2 overexpression may induce T-cell apoptosis due to its immunoregulatory role, although the precise mechanism remains unclear (23) (Fig. 3E). High TROP-2 was markedly correlated with p53 mutations, which then promoted the production of transforming growth factor-beta (TGF-β) (24,25). This pathway induces cancer metastasis by inhibiting Smads/p63 signaling, which specifically suppresses epithelial differentiation and enhances the EMT, a crucial step in metastasis via the reduction of E-cadherin and the increase of mesenchymal markers such as vimentin and N-cadherin (24,25) (Fig. 3A) that facilitates cytoskeletal reorganization, cell detachment and invasive behavior. The loss of p63 also allows tumor cells to escape normal growth control and acquire stem cell-like properties (24). Additionally, TROP-2 contributed to resistance against gefitinib by facilitating NSCLC cell migration and proliferation through the insulin-like growth factor 2 (IGF2)/insulin-like growth factor receptor (IGF1R)/Akt signaling axis, which is crucial for drug resistance and tumor microenvironment (TME) remodeling in NSCLC (12) (Fig. 3D).

For MUC-1, a two-sample binomial test comparing its positivity in NSCLC patients and healthy subjects revealed a significant difference between the two groups. The average initial copy number of this marker in patients was 2.64 times higher than in healthy subjects (21). Additionally, another study suggested that plasma exosomal MUC-1 has potential as a diagnostic marker for NSCLC, as its levels were

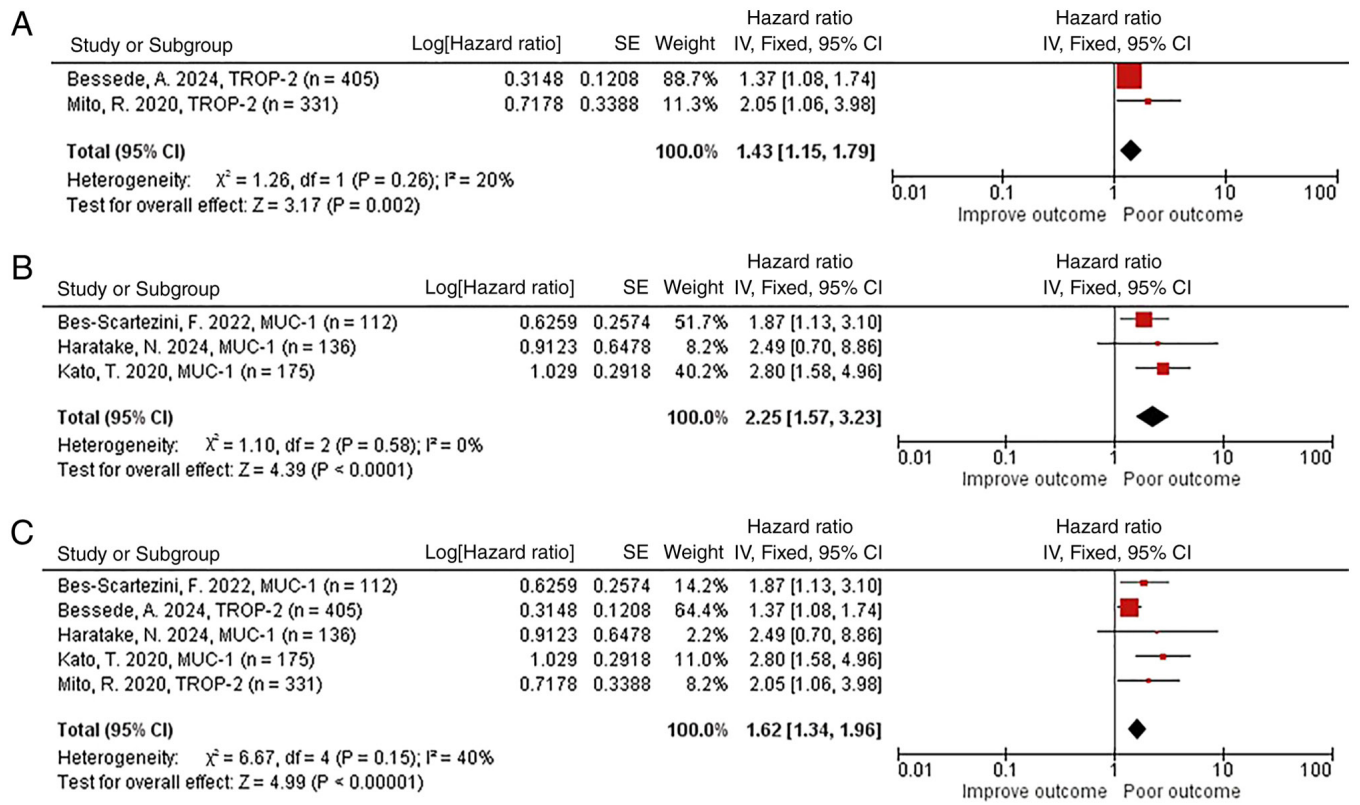

Figure 2. Forest plots of TROP-2 and MUC-1 associations with overall survival in NSCLC. Forest plots of HR and 95% CI for the association of TROP-2 and MUC-1 with OS in NSCLC patients. (A) TROP-2 expression and OS, (B) MUC-1 expression and OS, (C) The exploratory pooled analysis of TROP-2 and MUC-1 levels and OS. TROP-2, trophoblast cell surface antigen-2; MUC-1, mucin-1; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; OS, overall survival.

markedly elevated in NSCLC patients compared with healthy controls (22). High MUC-1 levels were associated with cancer progression, poor clinical outcomes, low OS and increased resistance to therapy. However, increased MUC-1 mRNA expression was associated with favorable OS, but shorter DFS, indicating possible context-dependent effects (14).

MUC-1 can regulate the progression of cancer in several ways (Fig. 3). The C-terminal of MUC-1 (MUC-1-C) interacts with NF-κBp65 or C-MYC on the PD-L1 promoter, inducing PD-L1 activation, leading to T-cell exhaustion and immune evasion (26,27). These lead to T-cell suppression, contributing to worse clinical outcomes and greater resistance to immunotherapy (26,27) (Fig. 3H). This effect, which has been demonstrated in studies of treatment with evodiamine, specifically targets MUC-1-C and disrupts its interaction with NF-κB and C-MYC, leading to downregulation of the MUC-1-C/PD-L1 axis and resulting in improved clinical outcomes (26). Moreover, binding of the Tn antigen on MUC-1 to macrophage galactose-type C-type lectin (MGL) on immune cells leads to immunosuppressive effects, facilitating immune evasion and cancer metastasis (28-30) (Fig. 3B). Therefore, high MUC-1 levels were markedly associated with decreased patient OS and were correlated with tumor extension and pleural invasion (19,20). It has been suggested that MUC-1 acts as a signaling molecule involved in the regulation of apoptosis through its interaction with the BAX protein (31) (Fig. 3G). The C-terminal of MUC-1 interacts with EGFR and other receptor tyrosine kinases (RTKs), leading to downstream signaling activation that promotes EMT, cancer stem cell formation and inflammatory memory. These mechanisms contributed to resistance to osimertinib, although there are additional pathways that explain this drug resistance. For example, the WNT/β-catenin, NF-κB and JAK1/STAT3 pathways, which induce EMT, stemness, and inflammatory signaling and engage RTK-RAS effectors such as PI3K and GRB2/SOS to enhance proliferative and survival signaling. These molecules also recruit chromatin remodeling complexes polycomb repressive complex 1 and 2 (PRC1/2) and SWItch/sucrose non-fermentable (SWI/SNF) that cooperate with JUN/AP-1 to promote pluripotency factors, lineage plasticity and drug resistance (32) (Fig. 3C).

Exosomal MUC-1 was preferentially found in NSCLC cells, suggesting a role in shaping the TME and evading immunity (22). Its level was nearly nine times higher than the total cellular membrane-associated MUC-1. The elevated plasma exosomal MUC-1 levels distinguished NSCLC patients from healthy individuals more accurately than total plasma MUC-1, highlighting its promising noninvasive biomarker (22). Cell-surface and exosomal MUC-1 both contributed to tumor progression, therapeutic resistance and immune modulation (18).

Subtype-specific differences were observed in NSCLC. Subgroup meta-analyses according to tumor subtype were planned. However, the limited number of eligible studies precluded a meaningful quantitative synthesis. Therefore, these differences were described narratively. Mito *et al* (13)

Table V. Sensitivity analysis comparing fixed-effect and random-effects models.

	Fixed-effect model		Random-effect model	
Study	HR	95% CI	HR	95% CI
TROP-2 expression	1.43	(1.15, 1.79)	1.48	(1.08, 2.02)
MUC-1 expression	2.25	(1.57, 3.23)	2.25	(1.57, 3.23)
Exploratory pooled analysis of TROP-2 and MUC-1	1.62	(1.34, 1.96)	1.83	(1.35, 2.48)

TROP-2, trophoblast cell surface antigen-2; MUC-1, mucin-1; HR, hazard ratio; CI, confidence interval.

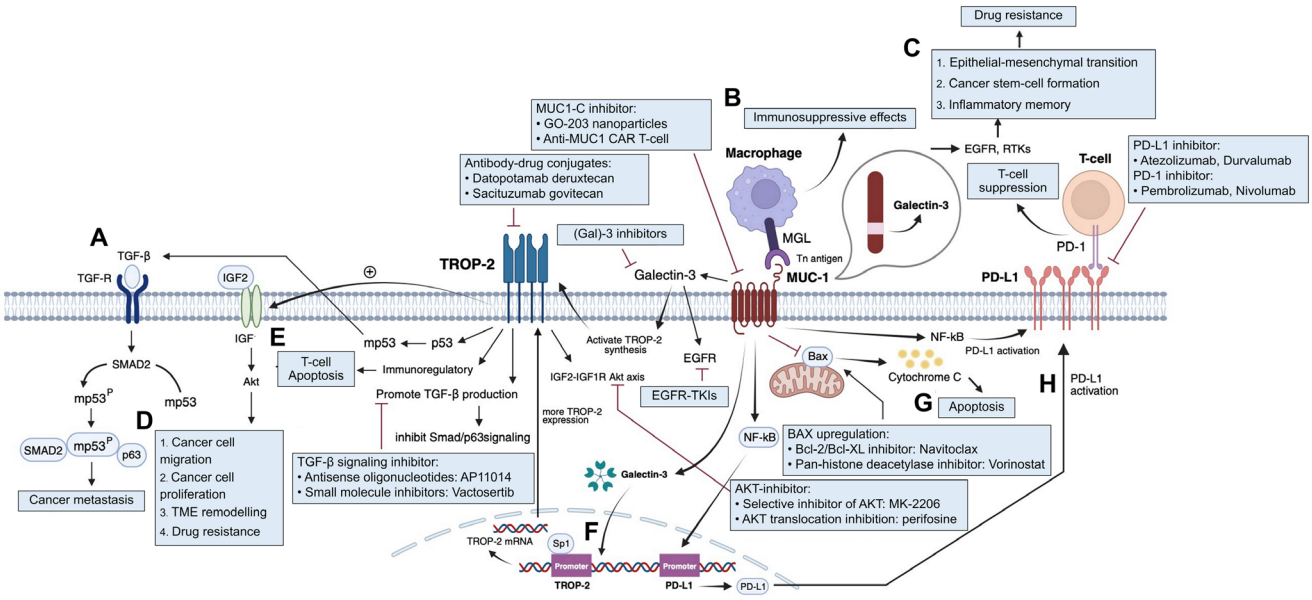

Figure 3. Proposed schematic mechanisms by which TROP-2 and MUC-1 overexpression contribute to poor NSCLC patient clinical outcomes through promoting immune evasion, metastasis, and drug resistance. TROP-2 induces T-cell apoptosis, enhances TGF-β-driven metastatic signaling linked to p53 alterations, and activates the IGF2/IGF1R/Akt axis to support proliferation, migration, and gefitinib resistance. MUC-1, particularly MUC-1-C, upregulates PD-L1 via NF-κB and c-MYC, suppresses immunity through Tn-MGL interactions, and modulates apoptosis through BAX. It also cooperates with EGFR and other RTKs to drive EMT, stemness, and resistance to osimertinib, while galectin-3 further amplifies TROP-2 expression to reinforce oncogenic signaling. (A) High TROP-2 expression is linked to p53 mutations, increasing TGF-β production and suppressing Smads/p63 signaling to promote metastasis. (B) The Tn antigen on MUC-1 binds MGL on immune cells, driving immunosuppression and metastasis. (C) MUC-1 cooperates with EGFR and other RTKs to activate signaling that promotes EMT, stemness, and resistance to osimertinib. (D) TROP-2 enhances migration, proliferation, and gefitinib resistance via the IGF2/IGF1R/Akt pathway. (E) TROP-2 induces T-cell apoptosis through immunoregulatory activity. (F) Galectin-3 binding to MUC-1 recruits Sp1 to the TROP-2 promoter, increasing TROP-2 expression and reinforcing oncogenic signaling. (G) MUC-1 regulates apoptosis through interaction with BAX, and (H) MUC-1-C activates PD-L1 transcription through NF-κB or c-MYC, leading to T-cell suppression. Figure was created with BioRender.com. Akt, protein kinase B; BAX, BCL2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; c-MYC, cellular myelocytomatosis; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; IGF1R, insulin-like growth factor receptor; IGF2, insulin-like growth factor 2; MUC-1, mucin-1; mp53, mutant p53; NF-κB, nuclear factor kappa B; NSCLC, non-small cell lung cancer; p63, tumor protein 63; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RTKs, receptor tyrosine kinases; SMAD2, mothers against decapentaplegic homolog 2; Sp1, specificity protein 1; TGF-β, transforming growth factor-beta; TGF-R, transforming growth factor receptor; TKI, tyrosine kinase inhibitor; Tn-MGL, Tn antigen-macrophage galactose-type C-type lectin; TROP-2, trophoblast cell surface antigen-2.

reported that high TROP-2 expression was markedly correlated with poor clinical outcomes in ADC patients, but not in SCC patients (13). The researchers suggested that SCC is more resistant to the immune system due to its mutations, which may explain the different outcomes. Similarly, Jiang *et al* (18) found that high expression of MUC-1-C was predominantly observed in women, non-smokers, ADC (but not SCC) and patients with advanced-stage ADC (27). The mechanism for this finding may involve MUC-1-C activating oncogenic pathways such as PI3K/AKT/mTOR, NF-κB, and Wnt/β-catenin, which enhance proliferation, metastasis, and immune evasion and are more active in ADC than in SCC (8,30).

Notably, the expression of MUC-1 stimulates the expression of TROP-2 through an interaction between galectin-3, an endogenous ligand, and MUC-1 (27). This binding attracts Sp1 and promotes binding between Sp1 and the TROP-2 promoter, resulting in an increased TROP-2 expression (10) (Fig. 3F). Therefore, there is a high potential that cancer cells that have a high MUC-1 may also have high TROP-2. The preliminary data in our cohort containing 109 NSCLC cases depicted 80% of total cases had high expression of both antigens.

Mechanistically, cancer cells with high levels of both TROP-2 and MUC-1 have more aggressive tumorigenic properties to invade and metastasize (8,9). Hence, the co-regulation of TROP-2 and MUC-1 through galentin-3 may provide a biological rationale for why both markers, when evaluated together in an exploratory pooled analysis, were associated with poor survival outcomes in NSCLC patients.

The overall meta-analysis suggested a statistically significant association between biomarker overexpression and poorer survival outcomes. Leave-one-out sensitivity analysis demonstrated that exclusion of any single study did not materially alter the pooled effect estimates and the overall associations remained statistically significant, supporting the reliability of the findings. However, the limited number of included studies due to the PICO inclusion criteria combined with the existing survival statistics, particularly for TROP-2 (n=2) and MUC-1 (n=3), warrants careful interpretation of the results. Although statistical heterogeneity was low in the individual biomarker analyses (I^2=20% for TROP-2 and I^2=0% for MUC-1), the small number of studies may limit the interpretability of the I^2 statistic and may not fully capture potential between-study variability. Therefore, an additional sensitivity analysis using a random-effects model, which accounts for both within-study and between-study variability, was performed. The results were consistent with those obtained using the fixed-effect model, with no changes in the direction or statistical significance of the associations (Table V). For the exploratory pooled analysis of TROP-2 and MUC-1, moderate heterogeneity was observed (I^2=40%), which may reflect biological and methodological differences between studies evaluating the two biomarkers. Notably, because no included study simultaneously assessed TROP-2 and MUC-1 within the same patient cohort, this analysis should not be interpreted as evidence of a dual-biomarker effect or co-expression.

Clinically, both TROP-2 and MUC-1 have emerged as actionable targets. TROP-2 has been applied as a targeted therapy in the form of antibody drug conjugates, such as datopotamab deruxtecan, a TROP-2-directed monoclonal antibody covalently linked to a topoisomerase I inhibitor (Fig. 3). In phase 3 of the clinical trial, this antibody drug conjugate was found to markedly improve PFS compared with docetaxel (33). Moreover, sacituzumab govitecan, another TROP-2 antibody drug conjugate that selectively delivers SN-38 (an active metabolite of irinotecan), also showed numerically improved OS with favorable tolerability (34). Other therapeutic strategies include TGF-β inhibitors (such as vactosertib) and Akt inhibitors (such as MK-2206 and perifosine), which target downstream TROP-2 pathways. TGF-β production, which inhibits Smad/p63 signaling, has been targeted using TGF-β signaling inhibitors such as antisense oligonucleotides and small-molecule inhibitors such as vactosertib (25) (Fig. 3). The IGF2/IGF1R/Akt axis has been targeted using Akt inhibitors, including the selective Akt inhibitor (MK-2206) and the Akt translocation inhibitor (perifosine) (35).

For MUC-1, therapeutic approaches include Chimeric antigen receptor T-cells (CAR T-cells). A study by Wei *et al* (36) developed prostate stem cell antigen-redirected CAR T-cells and MUC-1-redirected CAR T-cells and found antitumor activity; a synergistic effect was observed when used as combined therapy. Moreover, the aforementioned mechanism pathways of MUC-1 have also been applied as targeted therapies. NF-κB-induced PD-L1 activation, which leads to T-cell exhaustion, has been targeted using PD-L1 inhibitors such as atezolizumab and durvalumab (37,38), and PD-1 inhibitors such as pembrolizumab and nivolumab (39,40) (Fig. 3). Since MUC-1 interacts with the BAX protein involved in apoptosis regulation, BAX upregulation has been used for treatment, for example, navitoclax (Bcl-2/Bcl-xL inhibitor) (41), and vorinostat (pan-histone deacetylase inhibitor) (42). MUC-1 interacts with EGFR and other RTKs, which have been widely used as targets of therapy, particularly EGFR inhibitors such as EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and osimertinib (43). One component of MUC-1 is Galectin-3, which can activate pathways of other RTKs and induce TROP-2 synthesis. Galectin-3 has been targeted using galectin-3 inhibitors, which can block tumor growth and modulate T-cell function. Furthermore, synergistic antitumor activity has been observed when galectin-3 inhibitors are combined with PD-L1 blockade (44) (Fig. 3).

The present systematic review and meta-analysis offered insights into the prognostic role of TROP-2 and MUC-1 in NSCLC. However, several limitations should be considered. The limited number of studies (n=12) were included, and the potential specific search term use may have resulted in the omission of relevant studies, leading to publication bias. Therefore, the findings should be interpreted cautiously. In addition, although several studies (21,22) were rated as fair quality according to the NOS, they still met the predefined inclusion criteria and reported relevant outcome data. Their findings were consistent with those of lower risk of bias studies, and their inclusion did not meaningfully affect the pooled estimates.

Several important limitations must be considered when interpreting the results of the present study. First, no included study simultaneously evaluated the expression of TROP-2 and MUC-1 within the same patient cohort. Therefore, the present pooled analysis should not be interpreted as evidence of a true dual-biomarker effect and further prospective studies are needed to evaluate both biomarkers in the same population to clarify their potential combined prognostic value. Furthermore, there is considerable clinical and methodological heterogeneity among the included studies. The studies differed substantially in specimen types (including tumor tissue, blood/plasma, exosomes and RNA-based datasets), detection methods and cut-off definitions, all of which may affect the comparability of reported hazard ratios. Clinical characteristics, such as NSCLC histological subtype, disease stage and treatment backgrounds, also varied widely. Consequently, while the present pooled analysis provided an overall estimate of prognostic significance, these findings do not originate from a homogeneous clinical setting and must be generalized and interpreted with caution.

Future studies should place greater emphasis on the evaluation of longitudinal and dynamic assessment of biomarkers. Adequately designed prospective studies are needed that incorporate serial measurements, paired pre- and post-treatment tissue samples and standardized detection techniques to improve the characterization of treatment-related changes

in TROP-2 and MUC-1 expression over time. Additionally, integrating dynamic biomarker data into prognostic models can enhance risk stratification and treatment selection. Importantly, studies that evaluate both biomarkers simultaneously within the same patient cohorts are necessary to validate their combined prognostic and predictive value and to enhance the clinical and translational applicability of these markers in NSCLC.

In conclusion, the present systematic review and meta-analysis suggested that elevated expression of either TROP-2 or MUC-1 in NSCLC is associated with poorer survival and more aggressive clinicopathological features. Furthermore, an exploratory pooled analysis of both biomarker groups indicates a potential association between biomarker expression and worse survival outcomes, highlighting the need for further investigation of their prognostic value as a dual biomarker strategy. Future studies that simultaneously assess TROP-2 and MUC-1 expression within the same patient cohorts are warranted to validate whether their co-expression provides additional prognostic information beyond individual biomarker assessment. While the potential for a dual assessment of TROP-2 and MUC-1 to enhance risk stratification requires further validation through prospective studies, existing mechanistic evidence supports a potential role for their coordinated involvement in tumor progression, immune escape and resistance to therapy. Together, these preliminary findings provide a clinical suggestion for further investigating TROP-2 and MUC-1 as potential therapeutic targets. Continued exploration of directed strategies, including antibody-drug conjugates, CAR T-cell approaches, and pathway-focused inhibitors, is warranted to determine if they can ultimately improve the precision of treatment for patients with NSCLC.

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Availability of data and materials

Not applicable.

Authors' contributions

PN, JL, NS and KS performed the data curation (including literature search, study selection, data extraction and quality assessment), conducted the formal analysis and wrote the original draft of the manuscript. RW, PT, RK and CT contributed to the writing, reviewing and editing of the manuscript. RW and RK performed the validation of the present study. CT was responsible for conceptualization, the formal analysis and the final revision of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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