

TROP2 Expression in Chinese Advanced NSCLC: Identification of an Optimal H-Score Cutoff and Association with Immunotherapy Resistance

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Background

Trophoblast cell surface antigen 2 (TROP2) is highly expressed in non-small cell lung cancer (NSCLC) and has emerged as a promising target for antibody-drug conjugates (ADCs). The Chinese-developed antibody-drug conjugate (ADC) sacituzumab tirumotecan has been approved for lung cancer. However, the optimal cutoff for TROP2 overexpression, its biological interplay with PD-L1 and driver genes, and its clinical implications for immunotherapy resistance remain incompletely defined.

Objective

This study aimed to investigate TROP2 expression in a cohort of Chinese patients with advanced NSCLC and to establish an optimal H-score cutoff for patient stratification. We further evaluated TROP2 expression heterogeneity between primary and metastatic sites, its co-occurrence patterns with key driver genes and PD-L1, and its association with immunotherapy outcomes.

Methods

This retrospective study analyzed 261 newly diagnosed advanced NSCLC patients (2014-2024). TROP2 expression was evaluated by immunohistochemistry (IHC) using the ENZ-ABS380-0100 antibody, quantified by H-score (intensity × percentage). The optimal H-score cutoff was determined by maximally selected rank statistics based on progression-free survival (PFS). TROP2 expression was further characterized by staining intensity components (1+, 2+, 3+) and compared between primary and metastatic specimens. UpSet plot analysis was applied to visualize co-occurrence patterns among TROP2, PD-L1, EGFR, TP53 mutations, and other key biomarkers.

Results

Among the enrolled patients, the histological subtypes were adenocarcinoma (n=153), squamous cell carcinoma (n=95), and others (n=13). Clinical stages included stage IIIB (n=96), IIIC (n=12), and IV (n=153). An H-score cutoff of 240 optimally stratified patients by PFS, with TROP2-high expression (≥240) observed in 15.3% of cases. TROP2-high was associated with significantly shorter PFS (median 8.9 vs. 18.8 months; P=0.013). Multivariate analysis, after adjustment for treatment modality and other confounders, identified clinical stage IV (HR 2.242, P=0.008) and treatment modality (overall P=0.008) as independent prognostic factors, whereas TROP2-high was not independently significant (P=0.238). Notably, metastatic lesions exhibited significantly lower 2+/3+ (P<0.001) and 3+ (P=0.009) expression compared to primary tumors. UpSet plot revealed that TROP2-high rarely coexisted with EGFR mutations, but showed partial overlap with high PD-L1 expression (TPS≥50%) , RET fusion andTP53 mutations. In immunotherapy-treated patients, the TROP2-high/PD-L1<1% subgroup had the shortest PFS, while the TROP2-low/PD-L1≥1% subgroup had the longest (P=0.014). Among patients treated with immunotherapy, TROP2-low achieved significantly higher ORR compared to TROP2-high (55.8% vs. 28.5%); in the PD-L1 TPS≥50% subset, the ORR was 62.5% vs. 11.1%.

Conclusion

This study establishes a prognostically relevant TROP2 H-score cutoff of 240 for advanced NSCLC, provides evidence of TROP2 expression heterogeneity between primary and metastatic sites, and delineates a distinct biomarker landscape in which TROP2-high was largely mutually exclusive with common driver alterations. High TROP2 expression predicts poor prognosis and resistance to immunotherapy, supporting its use for patient stratification and rationale for combining TROP2-targeted therapy with ICIs.

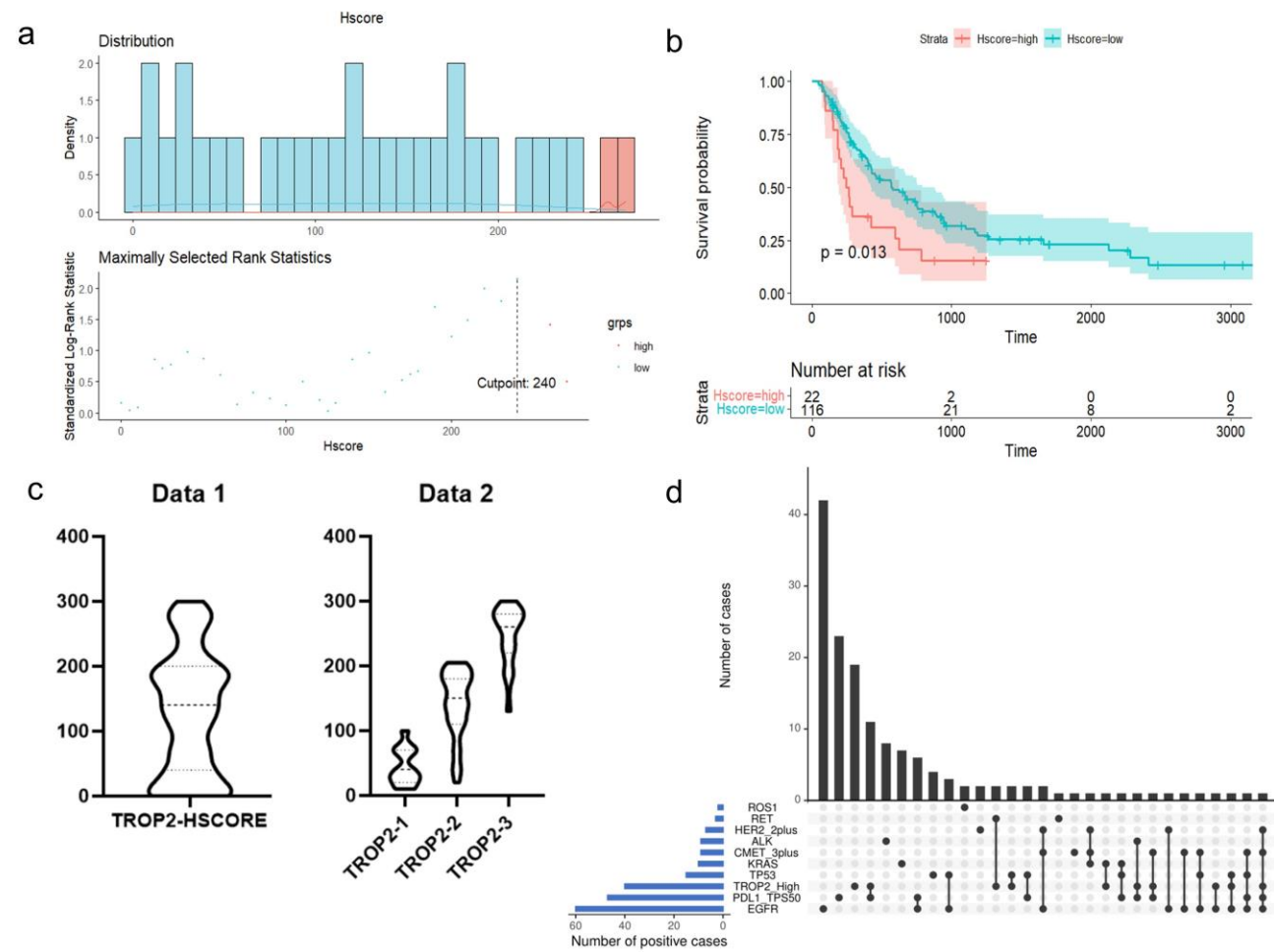


Figure 1. (a)(b) The optimal H-score cut-off was determined by the maximum rank test, and PFS Kaplan-Meier curves are shown for the stratified groups. (c) Violin plot showing the distribution of TROP2 H-scores in the overall cohort and the distributions of staining intensity components (1+, 2+, 3+) (d) UpSet plot depicting the co-occurrence and mutual exclusivity patterns of key biomarkers.

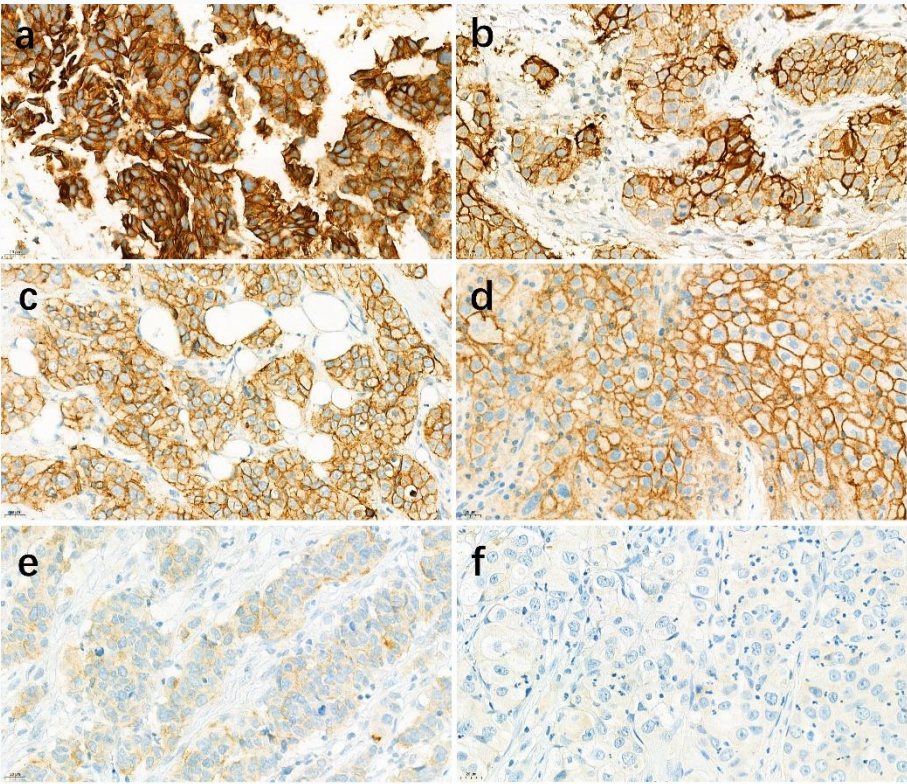


Figure 2. Representative Pathological Images of Different TROP2 Staining Intensities (a)Adenocarcinoma, 3+;(b) Squamous cell carcinoma, 3+;(c) Adenocarcinoma, 2+; (d) Squamous cell carcinoma, 2+;(e) 1+;(f) 0.