

BACKGROUND

Non-small cell lung cancer (NSCLC) in adolescent and young adult (AYA) patients shows distinct clinical and molecular features compared with older patients, but large-scale, age-stratified genomic and immune data remain limited.

Objective: Evaluate age-associated differences in actionable genomic alterations and tumor immune profiles in a real-world NSCLC cohort.

14,246 real-world NSCLC patients

Labcorp database, comprehensive genomic & immunologic profiling

770 (5.4%) 13,476 (94.6%)
AYA, ages 20–54 Older, ages ≥55

METHODS

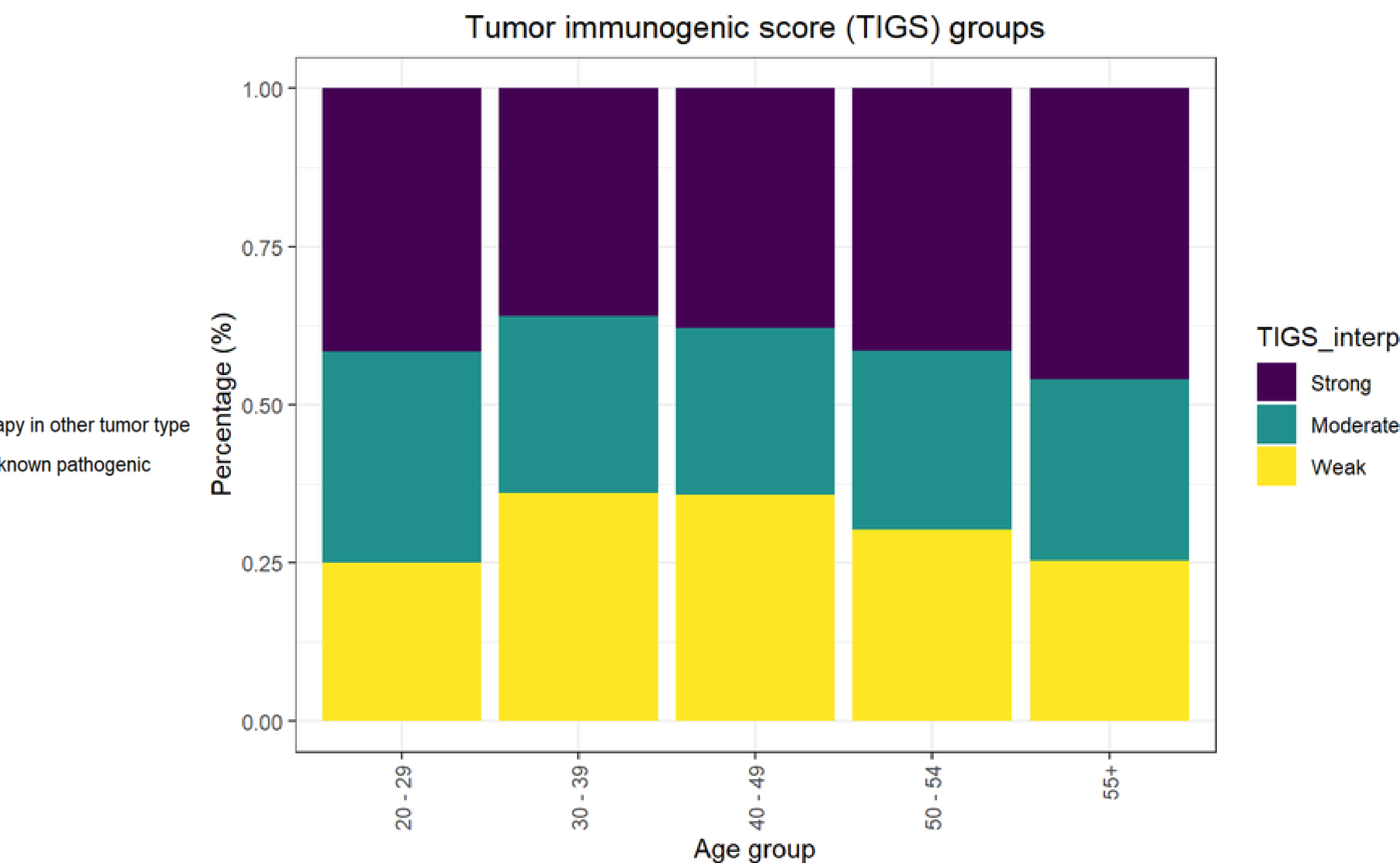
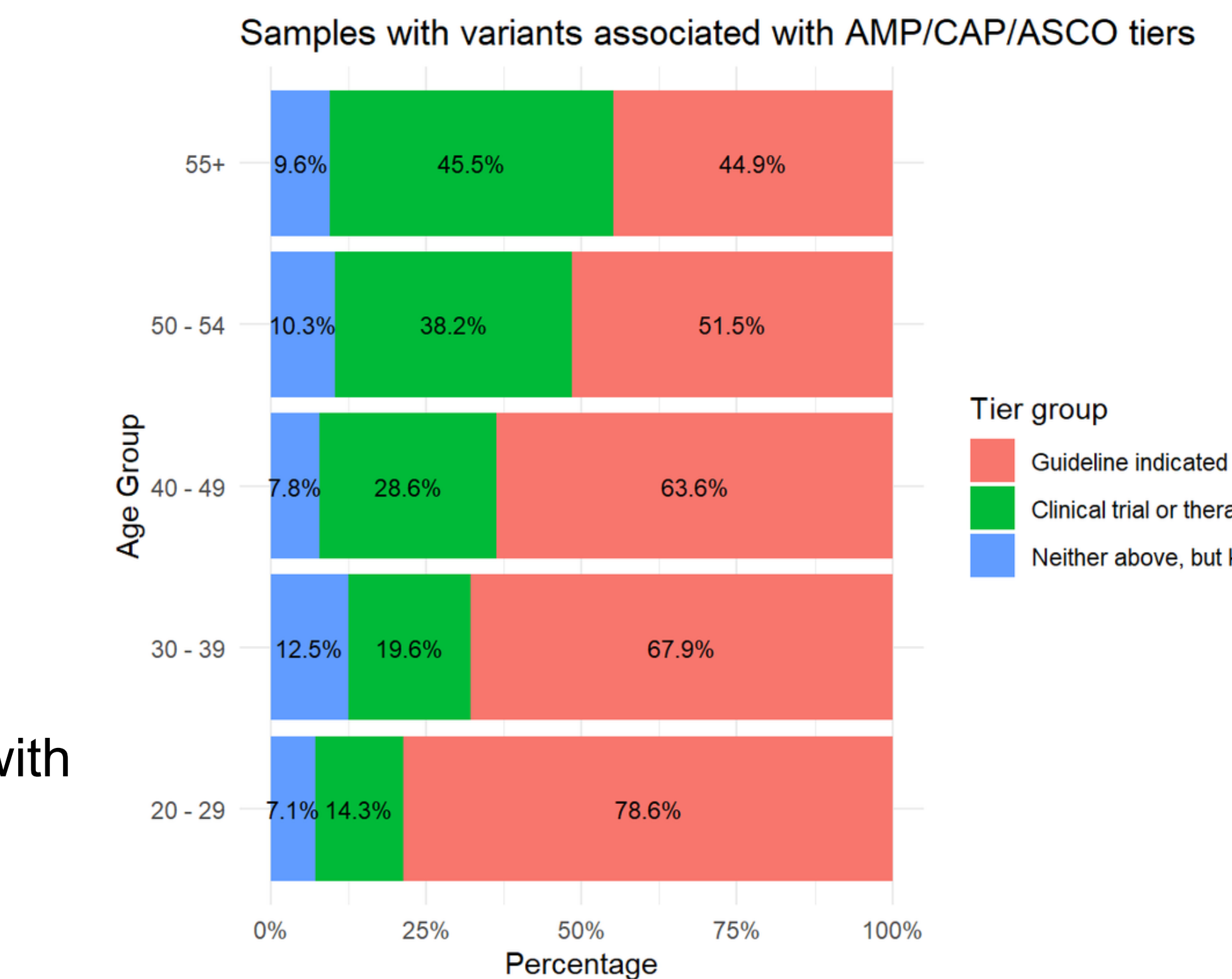
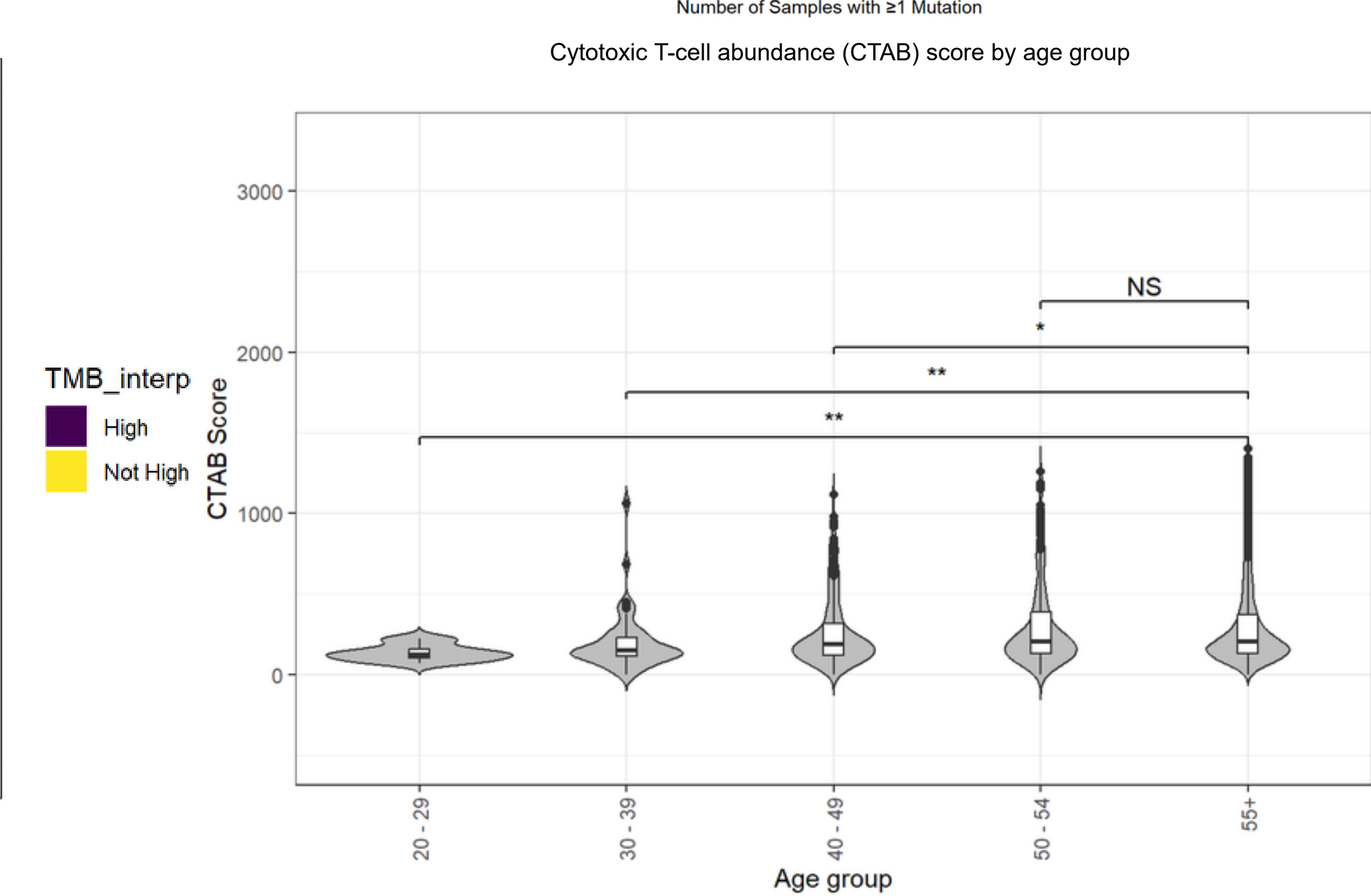
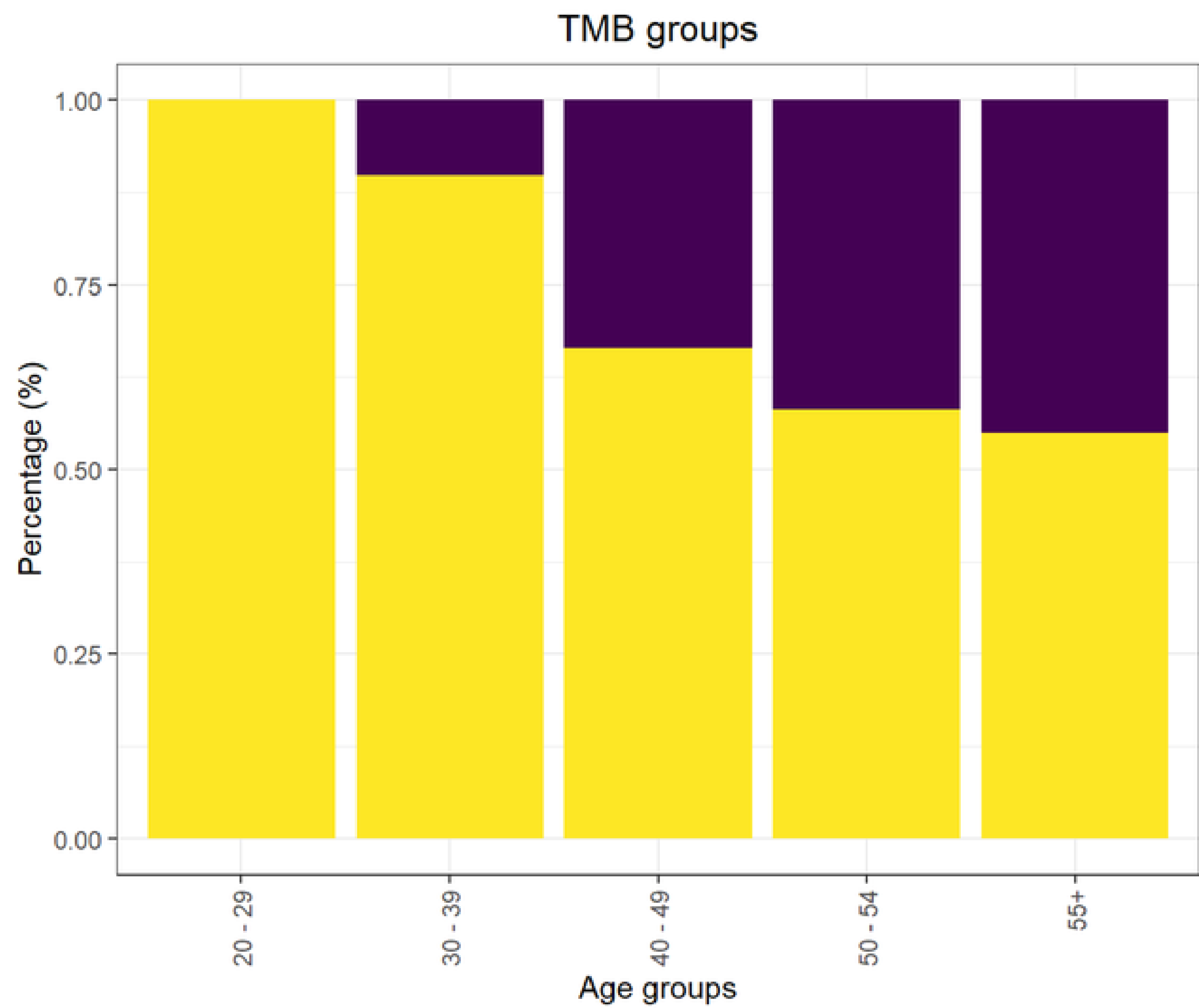
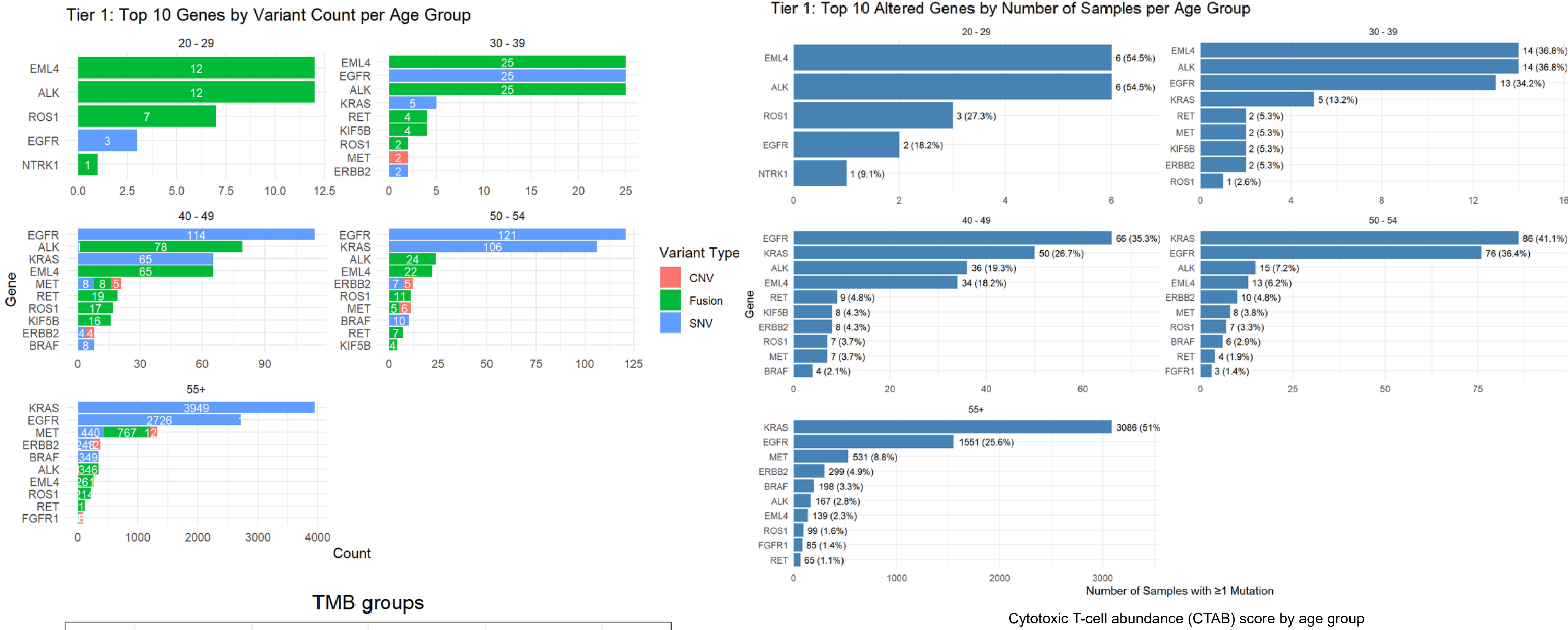
- Retrospective analysis of NSCLC patients undergoing comprehensive genomic and immunologic profiling; stratified as AYA (20–54y) vs. older (55y), with additional decade-level analyses
- Primary endpoint: age-based distribution of actionable genomic alterations by AMP/CAP/ASCO tier
- DNA sequencing** – SNVs, CNVs, gene fusions, tumor mutational burden (TMB; high 10 mut/Mb)
- RNA sequencing** – immune/proliferation signatures (CTAB, TIGS) and immune checkpoint expression (LAG3, TIGIT)
- Genomic-inferred ancestry (GIA) grouped into 6 categories to assess population-level differences
- Associations evaluated with chi-square and Wilcoxon rank-sum tests

RESULTS

- AYA tumors were more often **adenocarcinoma** (69% vs 61%) and less often squamous (14% vs 25%), with more metastatic disease at profiling (30% vs 22%)
- Tier 1** actionable alterations were more common in AYA (57.8% vs 44.9%), while **Tier 2** alterations were more frequent in patients 55y (45.5% vs 32.7%)
- AYA tumors were strongly enriched for targetable fusion drivers (ALK, ROS1) and for EGFR alterations; older patients were KRAS/STK11-dominant

Immune & Ancestry Biology

- Older patients show a KRAS-dominant immune-genomic phenotype, with higher TMB and elevated LAG3/TIGIT expression
- TP53 was the most frequent mutation overall, except East & Central Asian ancestry (EGFR predominated); fusions enriched in AYA, KRAS/STK11 in older –consistent across ancestry groups



KEY FINDING

Gene fusions (ALK, ROS1) and EGFR alterations are markedly enriched in AYA NSCLC, driving a higher rate of Tier 1 actionable alterations than in older patients.

Table 1. Age-Stratified Genomic & Immune Landscape of NSCLC

Measure	AYA (20–54y) N=770	Older (≥55y) N=13,476
Guideline-indicated actionable alterations	445 (57.8%)	6,052 (44.9%)
Most Common Mutations by Ancestry (GIA)		
African	TP53 (78), EGFR (25)	TP53 (859), KRAS (308)
American	TP53 (44), EGFR (35)	TP53 (371), EGFR (195)
European	TP53 (209), KRAS (107)	TP53 (4,852), KRAS (2,248)
East & Central Asian	EGFR (38), TP53 (28)	EGFR (336), TP53 (255)
South Asian / Middle Eastern	TP53 (11), EGFR (8)	TP53 (83), KRAS (31)
Immune Landscape & Biomarkers – Median (IQR)		
TIGS	55.0 (38.1–69.1)	59.5 (42.6–73.5)
Checkpoint score (CP)*	35.0 (17.2–53.2)	30.9 (14.8–50.7)
CTAB Score*	194 (120–276)	205 (131–369.2)
TMB*	6.3 (3.1–13.6)	8.7 (4.7–14.8)
LAG3*	46.0 (21.0–76.0)	56.0 (31.0–79.0)
TIM3 (ns)	52.0 (29.0–74.0)	54.0 (30.0–77.0)
TIGIT*	60.0 (31.5–80.0)	69.0 (44.0–86.0)
Ki67*	30.0 (12.0–51.0)	27.0 (10.0–48.0)

*p<0.05 vs. AYA; ns = not significant (TIM3 only)

CONCLUSIONS

- NSCLC shows age-associated divergence in both genomic drivers and tumorimmune biology, reflecting a biologic continuum across age
- NSCLC in AYAs is predominantly fusion-driven and enriched for highly actionable alterations
- Older patients exhibit KRAS/STK11-enriched tumors with an immune-activated yet potentially resistant phenotype
- Age is an important determinant of tumor biology – comprehensive genomic profiling is especially valuable in younger patients

TAKE-HOME MESSAGE

Incorporating age into biomarker interpretation and treatment selection may improve precision oncology care across the NSCLC population.