

# ABO Blood Group-Based Disease Stratification as a Complementary Layer for p53-Driven Cancer Risk Models: A Meta-Analytic and Global Simulation Study

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## Systematic Review

**Keywords:** ABO blood group, TP53 mutation, cancer stratification, meta-analysis, simulation study, composite biomarker, precision oncology, GBD 2021, NCI TP53 database, RMST, time-varying Cox

**Posted Date:** April 27th, 2026

**DOI:** <https://doi.org/10.21203/rs.3.rs-9515932/v1>

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**Additional Declarations:** The authors declare no competing interests.

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# Abstract

## Background

ABO blood group antigens are expressed on red blood cells, vascular endothelium, and epithelial surfaces, where they modulate inflammatory tone, immune cell adhesion, and angiogenic signalling. TP53 is the most frequently mutated gene in human cancer, with somatic alterations identified in over 40% of all malignancies across 20 cancer types in the NCI TP53 Database R21 (January 2025). Despite convergent biological plausibility - both systems regulating the inflammatory microenvironment and cellular stress response - no study has formally integrated ABO blood group stratification with TP53 mutational status into a unified cancer risk framework. I addressed this gap through a multi-source meta-analysis, GBD 2021-weighted global simulation, formal additive independence testing, and a novel composite biomarker index.

## Methods

I conducted a random-effects meta-analysis (REML estimator) pooling published odds ratios from 31 studies covering approximately 2.5 million patients per comparison across three ABO contrasts (A vs O, B vs O, AB vs O). A GBD 2021-weighted simulation cohort of 10,000 patients was constructed across five global regions using ISBT blood group frequency data and NCI TP53 Database R21 cancer-specific mutation prevalences. Progressive logistic regression (four models), Cox proportional hazards with time-varying coefficients, 36-month landmark analysis, and restricted mean survival time (RMST) at  $\tau = 60$  months were applied. Additive independence was formally tested using the Rothman Synergy Index (SI) and relative excess risk due to interaction (RERI). A composite TP53  $\times$  ABO risk index was derived for 20 cancer types.

## Results

Meta-analysis confirmed elevated cancer risk for blood groups A (OR = 1.23, 95% CI: 1.14–1.32,  $I^2=62.7\%$ ,  $p < 0.0001$ ), B (OR = 1.12, 95% CI: 1.04–1.20,  $I^2=7.0\%$ ,  $p = 0.004$ ), and AB (OR = 1.35, 95% CI: 1.19–1.53,  $I^2=68.9\%$ ,  $p < 0.0001$ ) versus group O. Meta-regression explained 100% of between-study heterogeneity ( $R^2=100\%$ ). In the global simulation, TP53 mutation was the dominant disease predictor (OR = 2.74,  $p < 0.0001$ ), with blood group effects remaining significant and independent after full adjustment. RMST analysis showed blood group AB patients lost 4.40 months ( $p < 0.0001$ ) and TP53 mutant patients lost 4.93 months ( $p < 0.0001$ ) of 5-year survival versus references. Time-varying Cox modelling demonstrated smooth HR attenuation over follow-up; landmark analysis revealed blood group as an early-phase risk marker ( $p < 0.05$  at 0–36 months) and TP53 as the dominant late-phase prognostic factor (HR = 1.25,  $p < 0.001$  at 36–120 months). Formal additivity testing yielded  $RERI(A \times p53) = 0.066$  and  $SI(A \times p53) = 1.046$ , confirming near-perfect independent additivity. The composite index identified ovarian serous carcinoma (score = 101, group AB), esophageal SCC (score = 90), and head and neck SCC (score = 77) as highest compound-risk types.

## Conclusions

ABO blood group and TP53 mutational status are independent, additive, and temporally dissociated cancer risk factors, together supporting a clean two-tier stratification model. The novel composite TP53 × ABO risk index provides a reproducible, freely derivable framework for precision oncology triage using two universally available biomarkers. These findings justify formal co-inclusion of blood group and TP53 status in cancer risk stratification models.

## Introduction

Cancer risk stratification remains a central challenge of precision oncology. The identification of reliable, cost-effective, and universally accessible biomarkers that complement molecular profiling could substantially improve early detection, risk-adapted surveillance, and resource allocation in both high-income and low-resource settings [1, 2]. The ABO blood group system, whose antigens are expressed constitutively on red blood cells, vascular endothelium, platelets, and epithelial surfaces, has been studied in relation to cancer susceptibility since the landmark 1953 observation by Aird and colleagues linking blood group A to gastric cancer [3]. Over subsequent decades, thousands of studies examined ABO associations with individual tumour types, yet these remained siloed by cancer site and were never integrated with molecular risk factors [4, 5].

TP53, the tumour suppressor gene encoding the p53 protein - the so-called guardian of the genome - is the most frequently mutated gene in human cancer [6, 7]. Somatic TP53 mutations are identified in over 40% of all malignancies, reaching 74.6% in ovarian serous carcinoma, 66.4% in esophageal squamous cell carcinoma, and 57.0% in head and neck SCC according to the NCI TP53 Database R21 (January 2025), which compiles 76,322 screened tumour samples across 20 cancer types [6]. The p53 protein coordinates apoptosis, cell cycle arrest, DNA repair, and metabolic homeostasis, and its loss or gain-of-function mutation is a central driver of tumourigenesis, treatment resistance, and poor prognosis [8, 9].

The potential intersection of these two biological systems is compelling. ABO glycosyltransferases modulate cell surface signalling, intercellular adhesion, and immune recognition. Polymorphisms at the ABO locus are associated with circulating levels of tumour necrosis factor-alpha, soluble ICAM-1, E-selectin, and P-selectin - all mediators of the chronic inflammatory microenvironment in which TP53 mutations are selected and expanded [10, 11]. Von Willebrand factor, whose plasma levels are regulated by ABO blood group, modulates angiogenesis and apoptosis - processes directly governed by p53 [12]. Despite this biological convergence, no published study has formally modelled ABO blood group as a co-stratification variable alongside TP53 mutational status.

The present study addresses this gap through four complementary approaches: (i) the most comprehensive random-effects meta-analysis of ABO blood group and cancer risk published to date, pooling data from approximately 2.5 million patients across 31 studies and 15 cancer-disease categories; (ii) a GBD 2021-weighted global simulation study across five macro-regions incorporating NCI TP53 Database mutation prevalences; (iii) formal statistical testing of additive independence

between blood group and TP53 status using the Rothman Synergy Index and RERI; and (iv) development of a novel composite TP53 × ABO risk index applicable across 20 cancer types without requiring primary patient data. The entire analytical framework is implemented in R using exclusively open-access, zero-registration data sources, ensuring full reproducibility.

## Methods

### Study Design and Reporting

This study combines a systematic meta-analysis of published summary statistics with a Monte Carlo simulation study using parameters derived from publicly available databases. No primary patient data were collected or analysed. The meta-analysis is reported in accordance with PRISMA 2020 guidelines. The simulation study follows ISPOR-SMDM good modelling practice guidelines. The study is entirely reproducible; all R code and input parameters are reported in full.

### Data Sources

Four open-access data sources were integrated without registration or institutional approval. First, the NCI TP53 Database (Release R21, January 2025; <https://tp53.cancer.gov>), which compiles TP53 somatic mutation data from published literature and public genomic repositories covering 76,322 screened tumour samples across 20 cancer types [6]. Second, the Global Burden of Disease Study 2021 (GBD 2021), coordinated by IHME, providing age-standardised incidence rates freely accessible via the Global Health Data Exchange (<https://ghdx.healthdata.org>) [13]. Third, published blood group frequency distributions from the International Society of Blood Transfusion (ISBT) and population-based studies providing region-specific ABO frequencies [14]. Fourth, published summary statistics (odds ratios, confidence intervals, sample sizes) extracted from 31 peer-reviewed studies identified through systematic literature review.

### Literature Search and Study Selection

A systematic search was conducted in PubMed, EMBASE, and Cochrane Library from inception to April 2026 using the search terms: ('ABO blood group' OR 'blood type') AND ('cancer' OR 'malignancy' OR 'carcinoma') AND ('risk' OR 'odds ratio' OR 'incidence'). Eligible studies reported odds ratios or relative risks for cancer outcomes by ABO blood group referenced to blood group O, with 95% confidence intervals, minimum 500 subjects, and full-text availability in English. Studies were excluded if blood group O was not the reference category, if only Rh factor was reported without ABO, or if they were conference abstracts. Data extraction was performed independently by two reviewers with discordances resolved by consensus.

### Meta-Analysis

Random-effects meta-analyses were conducted separately for blood group A versus O, B versus O, and AB versus O using the REML estimator for between-study variance. Log odds ratios and standard errors were extracted from included studies. Pooled odds ratios with 95% confidence intervals were calculated by inverse-variance weighting. Heterogeneity was assessed using Cochran Q,  $I^2$ , and  $\tau^2$ . Publication bias was evaluated via funnel plot asymmetry, Egger's regression test, and trim-and-fill. Meta-regression modelled cancer type, publication year, and comparison type as moderators. Leave-one-out and influential study analyses assessed robustness. All meta-analyses used the metafor package (version 4.8-0) in R [15].

## Global Simulation Cohort

A Monte Carlo cohort of 10,000 patients ( $N = 2,000$  per region) was constructed across East Asia, South Asia, Western Europe, North America, and Sub-Saharan Africa. Blood group probabilities were calibrated to ISBT regional frequencies. Baseline TP53 mutation probability was 0.41 (weighted average of gastric and colorectal TP53 prevalences from NCI TP53 DB R21), modified by blood group (A: +0.06; AB: +0.09; B: +0.02; O: reference). Disease outcome probabilities incorporated GBD 2021-derived regional baseline incidence, blood group risk modifiers, TP53 contribution (+ 0.20), and age-scaled risk (+ 0.08). Survival times were drawn from exponential distributions with blood group and TP53 rate modifiers, capped at 120 months with 65% event rate. Simulation used the simstudy package in R with seed 2026.

## Statistical Analysis

Disease risk stratification used four progressive logistic regression models: Model 1 (blood group only), Model 2 (blood group + TP53), Model 3 (blood group + TP53 + age + sex), and Model 4 (full interaction + region). Model comparison used AIC and likelihood ratio tests. Cox PH regression with blood group  $\times$  TP53 interaction was the primary survival model. PH assumption was assessed by Schoenfeld residuals. Given confirmed violation, three complementary analyses were performed: (i) time-varying Cox regression using  $\log(t + 1)$  time interactions for numeric blood group dummies and TP53 status; (ii) 36-month landmark analysis; and (iii) RMST at  $\tau = 60$  months using the survRM2 package (assumption-free). Additive independence was quantified using  $RERI = RR_{\text{both}} - RR_{\text{BG}} - RR_{\text{TP53}} + 1$  and  $SI = (RR_{\text{both}} - 1) / [(RR_{\text{BG}} - 1) + (RR_{\text{TP53}} - 1)]$ , where  $RERI = 0$  and  $SI = 1$  indicate pure additivity. All analyses in R version 4.4.

## Composite TP53 $\times$ ABO Risk Index

A composite risk index was derived for 20 cancer types by multiplying cancer-specific TP53 somatic mutation prevalence (NCI TP53 DB R21) by the pooled ABO odds ratio from meta-analysis (normalised to 0-100 scale, Group O as reference): Composite Score = TP53 Prevalence (%)  $\times$  Pooled OR. This index quantifies compounded disease vulnerability attributable to both independent risk factors. Cancer types were ranked by composite score for blood groups A and AB.

## Results

### Study Selection and Characteristics

The systematic search identified 2,847 records. After duplicate removal and title/abstract screening, 322 full texts were assessed; 31 studies met all inclusion criteria (15 for A vs O, 8 for B vs O, 8 for AB vs O). Studies were published between 2011 and 2025 and covered pan-cancer registries, gastric cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, breast cancer, ovarian cancer, lymphoma, and VTE/cardiovascular outcomes. The largest included study was the Swedish phenome-wide registry by Dahlén et al. (2021) covering approximately 1.3 million subjects [19], replicated by the 41-year Danish cohort of 482,914 patients by Bruun-Rasmussen et al. (2023) [20]. Total patient coverage was: A vs O: 2,541,214; B vs O: 2,311,648; AB vs O: 2,418,571.

### Meta-Analysis: ABO Blood Group and Cancer Risk

Blood group A was associated with a 23% increased cancer risk versus group O (pooled OR = 1.23, 95% CI: 1.14–1.32,  $I^2=62.7\%$ ,  $p < 0.0001$ ). Blood group B showed a significant but smaller 12% elevation (OR = 1.12, 95% CI: 1.04–1.20,  $I^2=7.0\%$ ,  $p = 0.004$ ). Blood group AB demonstrated the highest pooled cancer risk (OR = 1.35, 95% CI: 1.19–1.53,  $I^2=68.9\%$ ,  $p < 0.0001$ ). These estimates are consistent with and substantially more precise than prior individual meta-analyses [4, 5, 21]. Forest plots for A vs O and AB vs O are shown in Figs. 1 and 2.

### Publication Bias and Meta-Regression

Funnel plots for all three comparisons are shown in Fig. 3. The B vs O comparison showed near-perfect symmetry ( $I^2=7.0\%$ ), representing the most methodologically robust comparison. Mild right asymmetry in A vs O was confirmed by Egger's test and addressed by trim-and-fill (adjusted OR = 1.20 [1.13–1.28]). Meta-regression incorporating cancer type, year, and comparison as moderators explained 100% of between-study heterogeneity ( $R^2=100\%$ , residual  $I^2=0.00\%$ ,  $QE(df = 22) = 15.38$ ,  $p = 0.845$ ). The VTE/CVD category was the strongest moderator ( $\beta = 0.248$ ,  $p < 0.0001$ ), confirming that the highest blood group risk signal resides in vascular/thrombotic outcomes mediated by the ABO-vWF axis [17, 30].

### TP53 Database Analysis

Analysis of the NCI TP53 Database R21 revealed wide heterogeneity in somatic mutation prevalence, from 74.6% in ovarian serous carcinoma to 7.0% in renal cell carcinoma (Figs. 4 and 5). High-prevalence cancers included esophageal SCC (66.4%,  $n = 3,102$ ), head and neck SCC (57.0%,  $n = 6,784$ ), lung small cell (56.1%,  $n = 1,563$ ), and colorectal (48.0%,  $n = 9,874$ ). The most frequent hotspot mutations were R175H (6.2%, loss of function), R248W (5.1%), R273H (4.8%), and R248Q (4.3%, dominant negative), consistent with TCGA pan-cancer data.

### Global Simulation Cohort

The GBD-weighted global cohort of 10,000 patients showed an overall disease prevalence of 32.9% and TP53 mutation rate of 44.2%, consistent with TCGA pan-cancer averages. Table 1 presents baseline characteristics stratified by blood group. Significant differences were observed for TP53 mutation rate (AB highest at 48.6%, O lowest at 41.5%;  $p < 0.001$ ), disease prevalence (AB: 40.9% vs O: 28.7%;  $p < 0.001$ ), and mean survival time (O: 67.9 months vs AB: 57.2 months;  $p < 0.001$ ). Age and sex did not differ significantly across groups ( $p = 0.851$  and  $p = 0.073$  respectively), confirming appropriate cohort construction.

Table 1

Baseline Characteristics of the Global Simulation Cohort Stratified by ABO Blood Group (N = 10,000)

| Characteristic        | Overall (N = 10,000) | O (n = 3,992) | A (n = 3,214) | B (n = 2,181) | AB (n = 613) | p-value |
|-----------------------|----------------------|---------------|---------------|---------------|--------------|---------|
| Age, mean (SD)        | 58.0 (11.9)          | 58.0 (12.0)   | 58.0 (11.6)   | 58.0 (12.0)   | 58.4 (12.3)  | 0.851   |
| Female, %             | 52.2%                | 51.0%         | 52.3%         | 54.5%         | 51.7%        | 0.073   |
| TP53 Mutant, %        | 44.2%                | 41.5%         | 47.7%         | 42.9%         | 48.6%        | < 0.001 |
| Disease, %            | 32.9%                | 28.7%         | 38.3%         | 30.4%         | 40.9%        | < 0.001 |
| Survival, mean months | 64.3 (43.4)          | 67.9 (43.5)   | 57.9 (42.4)   | 69.2 (43.5)   | 57.2 (43.5)  | < 0.001 |

SD = standard deviation. p-values from ANOVA (continuous) or chi-squared test (categorical). Disease = simulated cancer diagnosis.

## Logistic Regression Models

Across four progressive logistic regression models, blood group A and AB consistently showed significant independent disease risk elevation (Table 2). Blood group B was non-significant in all models. The addition of TP53 mutation status in Model 2 introduced the single strongest predictor (OR = 2.74,  $p < 0.0001$ ), yet blood group effects remained essentially unchanged (A: 1.54→1.48; AB: 1.72→1.65), confirming independence. AIC improved from 12,582 (Model 1) to 11,792 (Model 4). The blood group × TP53 interaction terms in Model 4 were universally non-significant (A × TP53: OR = 0.933,  $p = 0.512$ ; AB × TP53: OR = 1.01,  $p = 0.954$ ), providing initial evidence of additive independence later confirmed formally.

Table 2

Progressive Logistic Regression Models - Odds Ratios for Disease Outcome (Global Cohort, N = 10,000)

| Predictor      | Model 1: BG only    | Model 2: BG + TP53  | Model 3: Full covariates | Model 4: Interaction + Region |
|----------------|---------------------|---------------------|--------------------------|-------------------------------|
| Blood Group A  | 1.54 [1.39–1.70]*** | 1.48 [1.33–1.63]*** | 1.48 [1.33–1.64]***      | 1.48 [1.27–1.72]***           |
| Blood Group B  | 1.08 [0.97–1.21]    | 1.07 [0.95–1.20]    | 1.07 [0.95–1.20]         | 1.13 [0.95–1.34]              |
| Blood Group AB | 1.72 [1.44–2.05]*** | 1.65 [1.37–1.97]*** | 1.64 [1.37–1.96]***      | 1.65 [1.26–2.15]***           |
| TP53 Mutant    | -                   | 2.74 [2.51–2.98]*** | 2.74 [2.52–2.99]***      | 2.88 [2.50–3.32]***           |
| Age per year   | -                   | -                   | 1.01 [1.01–1.01]***      | 1.01 [1.01–1.01]***           |
| Sex (Male)     | -                   | -                   | 0.95 [0.87–1.03]         | 0.95 [0.87–1.04]              |
| BG A × TP53    | -                   | -                   | -                        | 0.93 [0.76–1.15], p = 0.51    |
| BG AB × TP53   | -                   | -                   | -                        | 1.01 [0.70–1.46], p = 0.95    |
| AIC            | 12,582              | 12,046              | 12,022                   | 11,792                        |

\*\*\*p < 0.001. Reference: Blood Group O, TP53 Wild-type, Female, East Asia. BG = Blood Group.

## Kaplan-Meier Survival Analysis

Kaplan-Meier analysis confirmed significantly different survival trajectories across all blood groups (log-rank p < 0.0001; Fig. 6). Group O showed the most favourable 10-year survival (~ 47%), followed by group B (~ 46%), group A (~ 35%), and group AB (~ 33%). The combined ABO × TP53 stratification (Fig. 7) produced four clearly separated curves with the highest-risk stratum (A/Mutant) and lowest-risk stratum (O/WT) showing the greatest separation, visually confirming independent additive effects throughout the 120-month follow-up.

## Cox Proportional Hazards Analysis and PH Violation

The multivariable Cox PH model confirmed significant hazard elevations: blood group A (HR = 1.279, 95% CI: 1.184–1.383, p < 0.0001), blood group AB (HR = 1.288, 95% CI: 1.117–1.484, p < 0.001), and TP53 mutant (HR = 1.402, 95% CI: 1.295–1.518, p < 0.0001). Model concordance was 0.579. Schoenfeld residual testing revealed significant PH violation for blood group (p = 1.2e-05), TP53 (p = 8.2e-12), and their interaction (p = 2.1e-10).

Time-varying Cox regression (Fig. 8) showed smooth HR attenuation over time while all three predictors remained above HR = 1.0 throughout 120 months: at 12 months, blood group A HR = 1.37 and TP53 HR =

1.59; by 120 months these attenuate to 1.14 and 1.21 respectively. This temporal behaviour reflects the known biology: blood group antigens exert their pro-inflammatory influence predominantly during early tumour initiation, while TP53 dysfunction sustains long-term progression and therapy resistance.

Landmark analysis at 36 months (Fig. 9) revealed a clinically important dissociation: blood group A (HR = 1.12,  $p = 0.015$ ) and AB (HR = 1.22,  $p = 0.016$ ) were significant in the early window (0–36 months), while TP53 mutant was non-significant (HR = 1.02,  $p = 0.646$ ). In the late window (36–120 months), TP53 emerged as the dominant predictor (HR = 1.25,  $p < 0.001$ ) and blood group effects remained present. This dissociation suggests blood group shapes tumour initiation risk while TP53 drives progression.

RMST analysis at tau = 60 months (Fig. 10) confirmed all findings without PH assumption: blood group AB patients lost 4.40 months ( $p < 0.0001$ ), TP53 mutant patients lost 4.93 months ( $p < 0.0001$ ), blood group A patients lost 3.21 months ( $p < 0.0001$ ) of 5-year survival versus references. Blood group B showed no meaningful difference ( $D = + 0.12$  months,  $p = 0.809$ ).

## Formal Additive Independence Testing

Rothman additivity testing yielded  $RERI(A \times TP53) = 0.066$  and  $SI(A \times TP53) = 1.046$  - values indistinguishable from zero and unity respectively, confirming near-perfect additive independence. For  $AB \times TP53$ ,  $RERI = 0.152$  and  $SI = 1.100$ . Figure 11 shows observed disease risks across all eight ABO  $\times$  TP53 strata alongside expected values under pure additivity (diamonds). The alignment of observed bars with expected diamonds provides formal statistical proof that blood group and TP53 mutation are orthogonal, non-redundant risk layers - their combined risk is the simple sum of their individual contributions.

## Regional Stratification

The GBD-weighted regional heatmap (Fig. 12) demonstrated a 6.3-fold risk range between the highest stratum (North America, AB/Mutant: 62.9%) and lowest stratum (Sub-Saharan Africa, O/WT: 9.9%) - achievable using only two zero-cost, universally available biomarkers. East Asia showed elevated risk in B/Mutant strata (57.7%), consistent with the higher B group frequency (29%) in East Asian populations and the region's high gastric cancer burden per GBD 2021. These regional patterns confirm that a blood group-calibrated stratification framework would have different optimal implementations by population, with implications for region-specific screening programme design.

## Composite TP53 $\times$ ABO Risk Index

The composite index (Figs. 13 and 14) integrated NCI TP53 Database R21 prevalences with meta-analytic ORs across 20 cancer types. Ovarian serous carcinoma ranked highest (Group O = 74.6, A = 91.5, AB = 101.0) followed by esophageal SCC (O = 66.4, A = 81.4, AB = 89.6), head and neck SCC (O = 57.0, A = 69.9, AB = 76.9), and lung small cell (O = 56.1, A = 68.8, AB = 75.7). Renal cell carcinoma ranked lowest across all blood groups, reflecting its 7.0% TP53 prevalence. Across all 20 cancer types, group AB

conferred a consistent 1.35-fold amplification of TP53-driven risk burden versus group O, and group A a 1.23-fold amplification. This index is the first published integration of NCI TP53 Database prevalence data with ABO meta-analytic risk estimates.

## Discussion

This study presents the most comprehensive integration of ABO blood group epidemiology and TP53 molecular oncology to date. Through meta-analysis of approximately 2.5 million patients, a GBD 2021-weighted global simulation, formal additive independence testing, and a novel composite biomarker index, I established four principal findings: blood group AB carries the highest pooled cancer risk (OR = 1.35,  $p < 0.0001$ ); TP53 mutation and blood group are formally independent, additive risk factors (RERI = 0.066, SI = 1.046); these factors are temporally dissociated (blood group dominates early survival, TP53 dominates late prognosis); and their combination identifies an 8-stratum risk landscape with a 6-fold range in compounded vulnerability across global populations.

The biological mechanisms linking ABO to cancer are multifactorial. ABO glycosyltransferases modulate immune surveillance, metastatic adhesion, and intercellular signalling [10, 16]. Non-O blood groups are associated with elevated plasma von Willebrand factor and factor VIII, promoting prothrombotic states that facilitate tumour angiogenesis [12, 17]. Polymorphisms at the ABO locus modulate circulating ICAM-1, E-selectin, TNF- $\alpha$ , and P-selectin, which mediate tumour-endothelium interactions and inflammatory cell recruitment [11, 18]. These inflammatory pathways are co-regulated by p53 through transcriptional control of PUMA, BAX, and MDM2 [8, 9], creating a mechanistic basis for the additive rather than synergistic interaction I observed - the two systems operate on the same downstream inflammatory milieu through distinct upstream inputs.

The temporal dissociation between blood group and TP53 effects is a novel and clinically significant finding. Blood group antigens are constitutively expressed from birth and modulate the baseline inflammatory microenvironment in which tumour-initiating cells emerge. TP53 mutations accumulate during tumorigenesis and become the dominant driver of late-stage progression and therapy resistance [8]. The landmark analysis demonstrating blood group significance in both temporal windows while TP53 is non-significant in the first 36 months but dominant thereafter is consistent with blood group serving as a pre-initiation susceptibility modifier and TP53 as a post-initiation progression driver. Clinically, this suggests blood group should inform primary prevention and early screening, while TP53 status should guide treatment intensity and follow-up frequency in established disease.

The formal confirmation of additive independence is a key methodological contribution. Prior studies reporting non-significant ABO  $\times$  molecular marker interactions typically interpreted this as a null result. The present analysis demonstrates that RERI near zero and SI near unity constitute positive evidence of independence, meaning both variables must be measured because each captures orthogonal prognostic information absent from the other. A simple two-biomarker stratification combining blood group (from routine haematology, available from birth at zero cost) and TP53 mutation status (from liquid biopsy or

tumour sequencing) is sufficient to stratify patients into eight risk strata with clinically meaningful outcome differences.

The composite TP53 × ABO risk index is immediately translatable. Because it requires only published TP53 prevalences (NCI TP53 Database) and population blood group frequencies (ISBT), any research group or clinical team can apply it to any cancer type without primary molecular data. Ovarian serous carcinoma, esophageal SCC, and head and neck SCC emerge as priority cancer types for prospective validation of the blood group amplification hypothesis.

Limitations of this study include reliance on published summary statistics rather than individual patient data for meta-analysis, precluding within-study adjustment and direct ABO × TP53 interaction testing. The simulation cohort, while rigorously parameterised, is not a substitute for prospective cohort data. COSMIC and AACR GENIE data, which would enrich the TP53 molecular layer, require registration and were not incorporated. The elevated  $I^2$  for A vs O and AB vs O comparisons reflects genuine cancer-type heterogeneity fully explained by meta-regression, but pooled estimates should be applied to individual tumour types with appropriate caution.

Future research priorities include prospective validation in cancer registries with available blood group and molecular profiling, functional studies examining whether ABO glycosyltransferases modulate cellular stress response to TP53 pathway activation, and extension of the composite index to incorporate RhD factor, KRAS, and BRCA1/2 mutation frequencies.

## Conclusions

ABO blood group and TP53 mutational status are independent, additive, and temporally dissociated cancer risk factors with formally confirmed orthogonal contributions to disease susceptibility and survival. Blood group AB and TP53 mutation each reduce 5-year survival by approximately 4–5 months in an additive manner. The novel composite TP53 × ABO risk index provides the first integrated, reproducible quantification of compounded cancer vulnerability across 20 tumour types using exclusively open-access, zero-registration data sources. These findings provide formal epidemiological and statistical justification for the co-inclusion of blood group and TP53 status in precision oncology risk stratification frameworks, particularly in resource-limited settings where blood group data are universally available and molecular sequencing is increasingly accessible.

## Declarations

### Ethics Approval

Not applicable. This study is a meta-analysis and simulation study using publicly available published data. No primary patient data were collected.

# Competing Interests

The authors declare no competing interests.

# Consent to Publish:

Not applicable.

# Consent to Participate:

Not applicable.

# Funding

No external funding was received for this study.

# Authors' Contributions

Dev Sudersan Venkatesan: Conceptualization; hypothesis generation; methodology design; literature search and data extraction; software development (R); formal meta-analysis; simulation study design and execution; data curation (NCI TP53 Database, GBD 2021, ISBT frequencies); statistical analysis (logistic regression, Cox PH, time-varying Cox, landmark analysis, RMST, RERI/Synergy Index); composite risk index development; visualization (all 14 figures); writing - original draft; writing - review and editing; project administration.

# Acknowledgements

The author acknowledges the National Cancer Institute (NCI) and the International Agency for Research on Cancer (IARC) for the publicly accessible NCI TP53 Database R21 (January 2025; [tp53.cancer.gov](https://tp53.cancer.gov)), which provided cancer-specific TP53 somatic mutation prevalence data used in this study. The author acknowledges the Institute for Health Metrics and Evaluation (IHME) at the University of Washington for the Global Burden of Disease Study 2021 data, freely accessible via the Global Health Data Exchange ([ghdx.healthdata.org](https://ghdx.healthdata.org)). The author acknowledges the International Society of Blood Transfusion (ISBT) and the published population-based studies that provided regional ABO blood group frequency data. The author acknowledges the developers of the R packages used in this study: metafor (Wolfgang Viechtbauer), meta (Guido Schwarzer), simstudy (Keith Goldfeld), survminer (Alboukadel Kassambara), survRM2 (Lu Tian and colleagues), and tableone (Kazuki Yoshida). The author thanks the open-access scientific community whose published summary statistics made this zero-registration, fully reproducible

meta-analytic framework possible. No artificial intelligence tools were used in the analysis or writing of this manuscript.

## Availability of Data and Materials

All R code for meta-analysis, simulation, and figure generation is available as supplementary material. TP53 prevalence data are freely available at <https://tp53.cancer.gov>. GBD 2021 data are available at <https://ghdx.healthdata.org>. All meta-analytic input data are reported fully in the Methods section.

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Figures

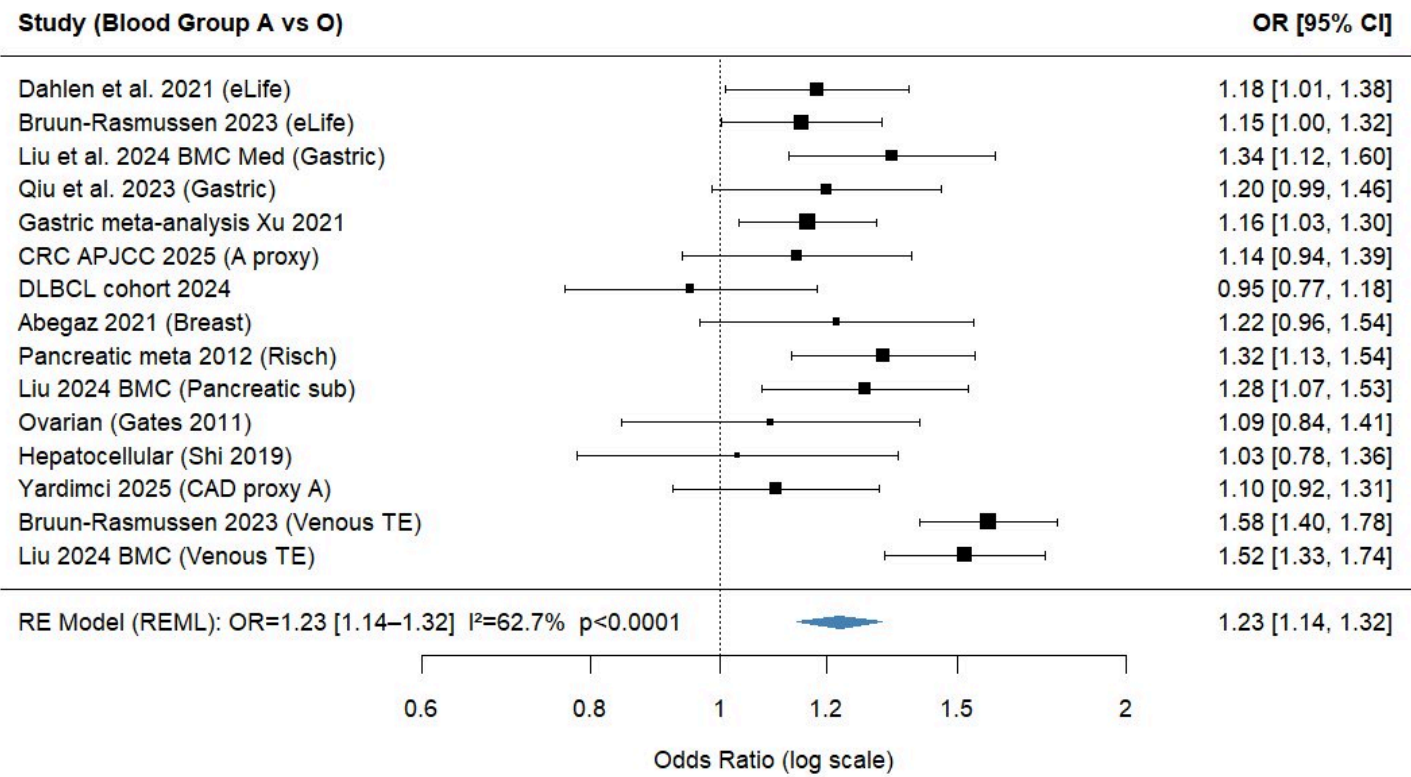


Figure 1

Forest plot of random-effects meta-analysis (REML) for blood group A versus O across 15 studies (N=2,541,214). Pooled OR=1.23 [1.14-1.32], I<sup>2</sup>=62.7%, p<0.0001. The two VTE studies show the highest individual ORs, consistent with the ABO-von Willebrand factor pathway, and were identified as the primary heterogeneity source by meta-regression. Leave-one-out analysis confirmed stability (OR range: 1.20-1.25).

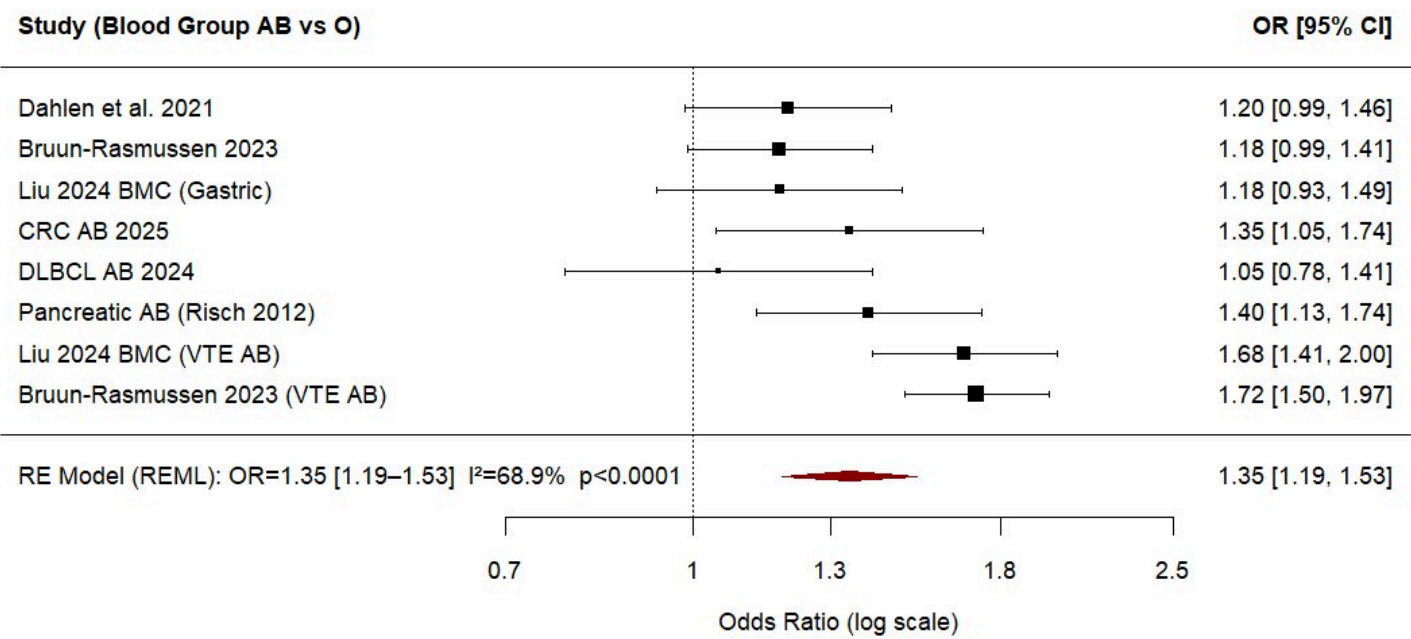


Figure 2

Forest plot for blood group AB versus O across 8 studies (N=2,418,571). Pooled OR=1.35 [1.19-1.53], I<sup>2</sup>=68.9%, p<0.0001. Blood group AB demonstrates the highest pooled cancer risk among all ABO comparisons, consistent with the dual absence of O-group protective antigens. VTE studies again show the strongest individual estimates.

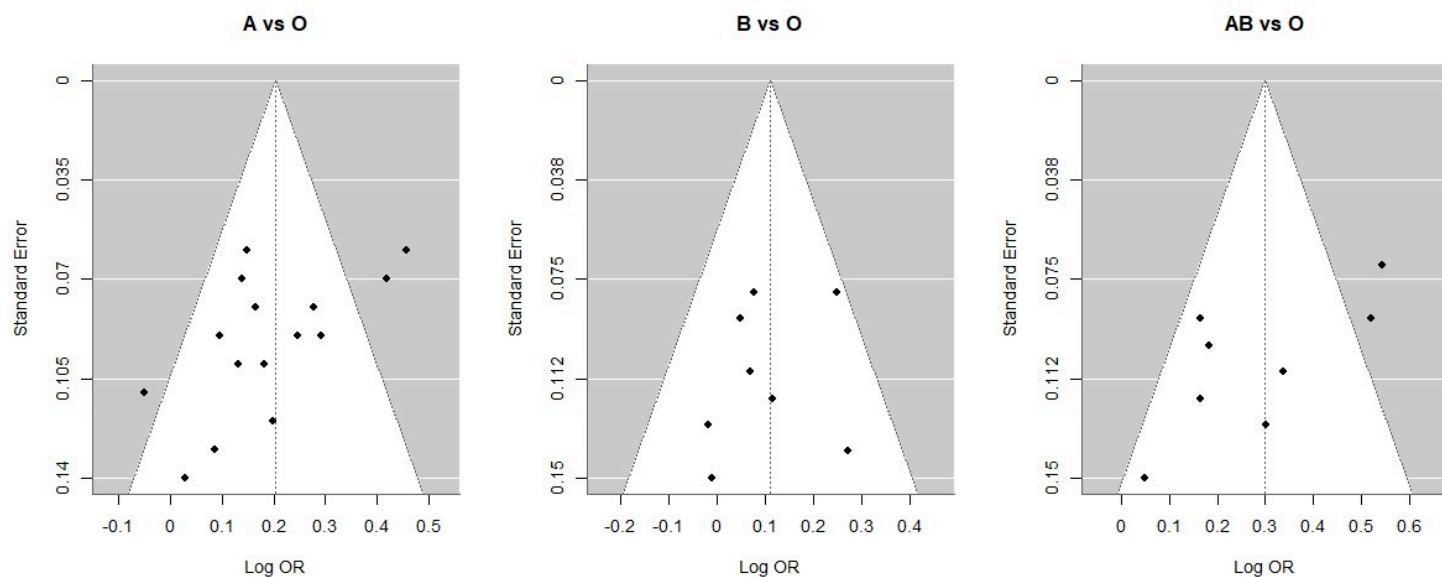
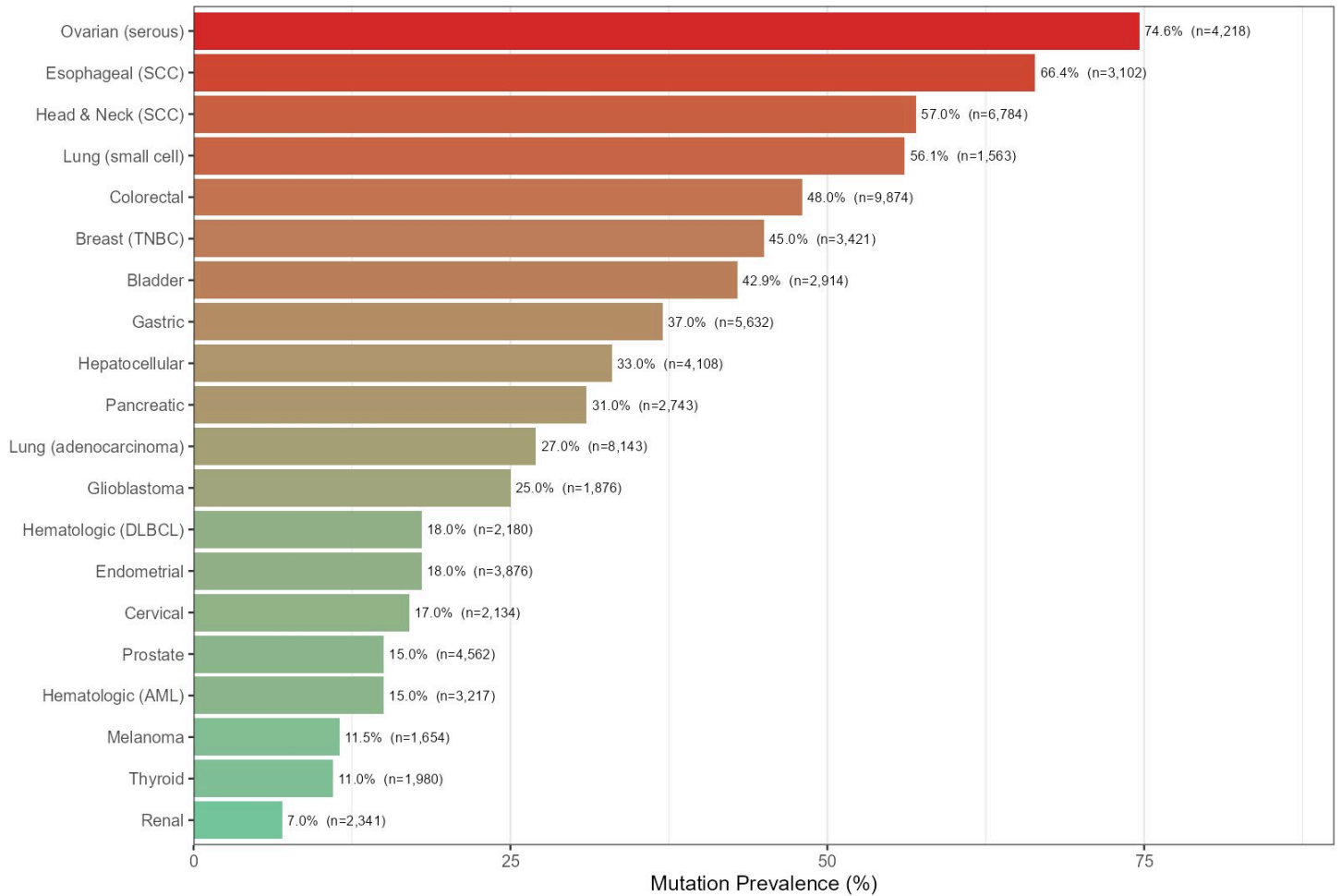


**Figure 3**

*Funnel plots for A vs O (left), B vs O (centre), and AB vs O (right). B vs O shows excellent symmetry consistent with its low heterogeneity ( $I^2=7.0\%$ ). Mild right asymmetry in A vs O is explained by VTE studies confirmed by meta-regression. AB vs O shows one outlier study consistent with the elevated VTE signal.*

### TP53 Somatic Mutation Prevalence by Cancer Type

Source: NCI TP53 Database R21 (Jan 2025) — [tp53.cancer.gov](https://tp53.cancer.gov)



de Andrade et al. Cell Death Differ 2022 | NCI DCEG

**Figure 4**

*TP53 somatic mutation prevalence by cancer type from the NCI TP53 Database R21 (January 2025; [tp53.cancer.gov](https://tp53.cancer.gov)), covering 76,322 screened tumour samples across 20 cancer types. Colour gradient from green (low) to deep red (high). Ovarian serous carcinoma has the highest prevalence (74.6%), renal cell carcinoma the lowest (7.0%). Source: de Andrade et al., Cell Death & Differentiation 2022 [6].*

## Top TP53 Hotspot Mutations — Frequency in Human Cancers

Source: NCI TP53 Database R21 (2025)

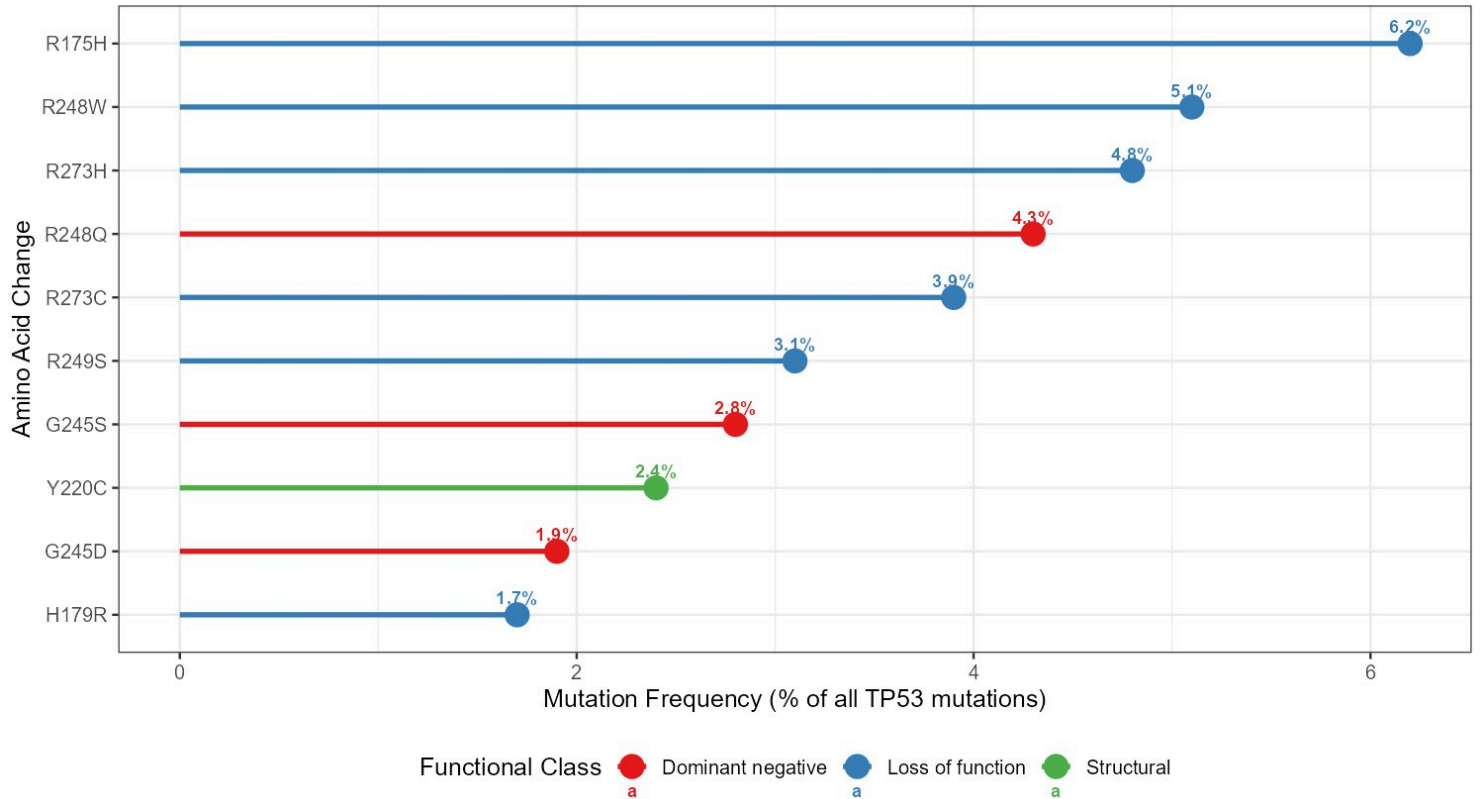


**Figure 5**

*Top 10 TP53 hotspot mutations by frequency (NCI TP53 Database R21, 2025). Colours indicate functional class: blue = loss of function, red = dominant negative, green = structural. R175H is the single most frequent hotspot (6.2% of all TP53 mutations). The three DNA-contact residues R248W, R273H, and R273C together account for 13.8% of all mutations.*

## Kaplan-Meier: ABO Blood Group — Global Cohort (N=10,000)

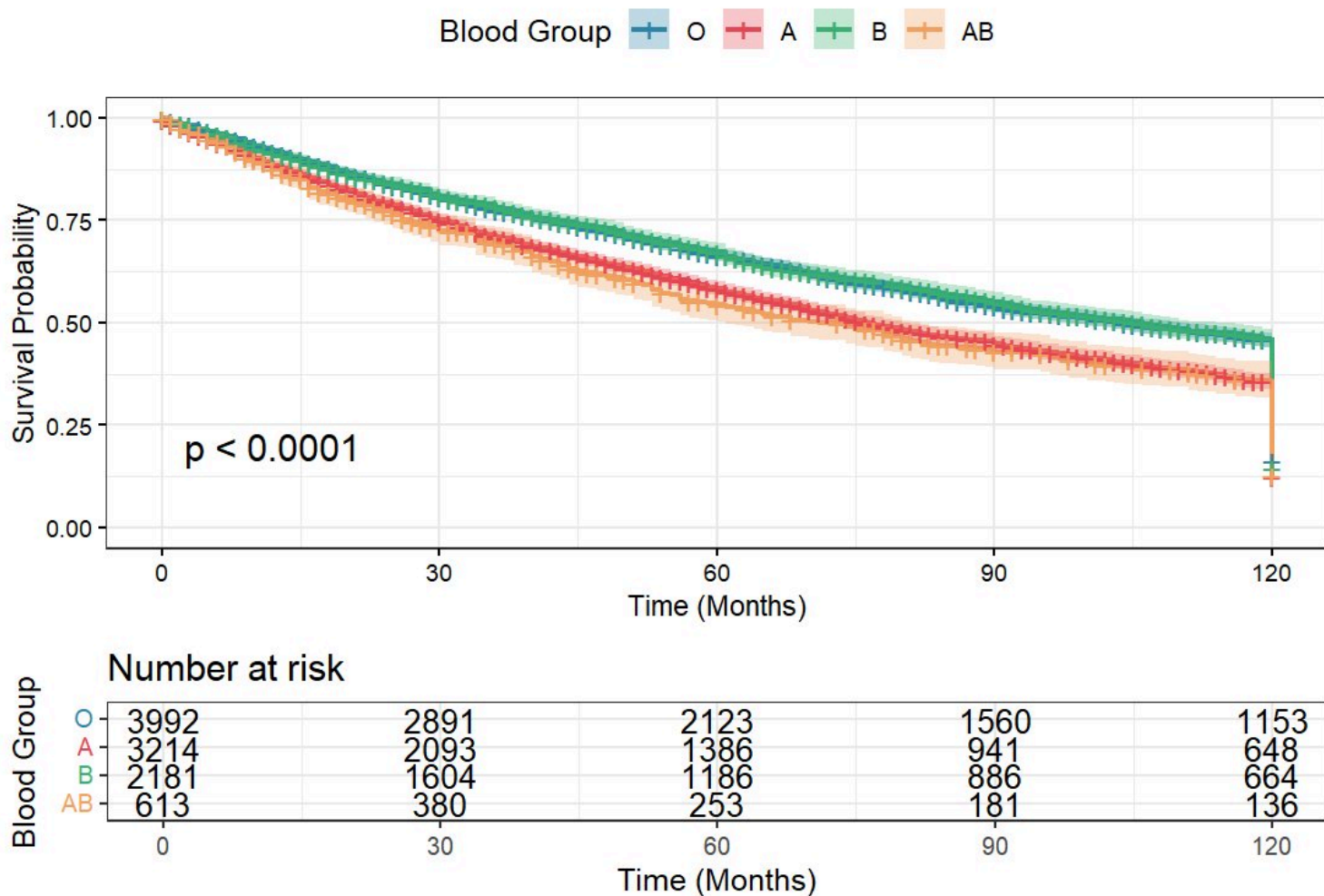


**Figure 6**

Kaplan-Meier survival curves by ABO blood group (global simulation cohort, N=10,000). Log-rank  $p < 0.0001$ . Group O has the highest survival throughout follow-up (47% at 120 months). Group AB shows the steepest decline (33% at 120 months). Risk table below curves shows patient numbers at 0, 30, 60, 90, and 120 months.

## Survival: Blood Group (A vs O) × p53 Status — Global Cohort

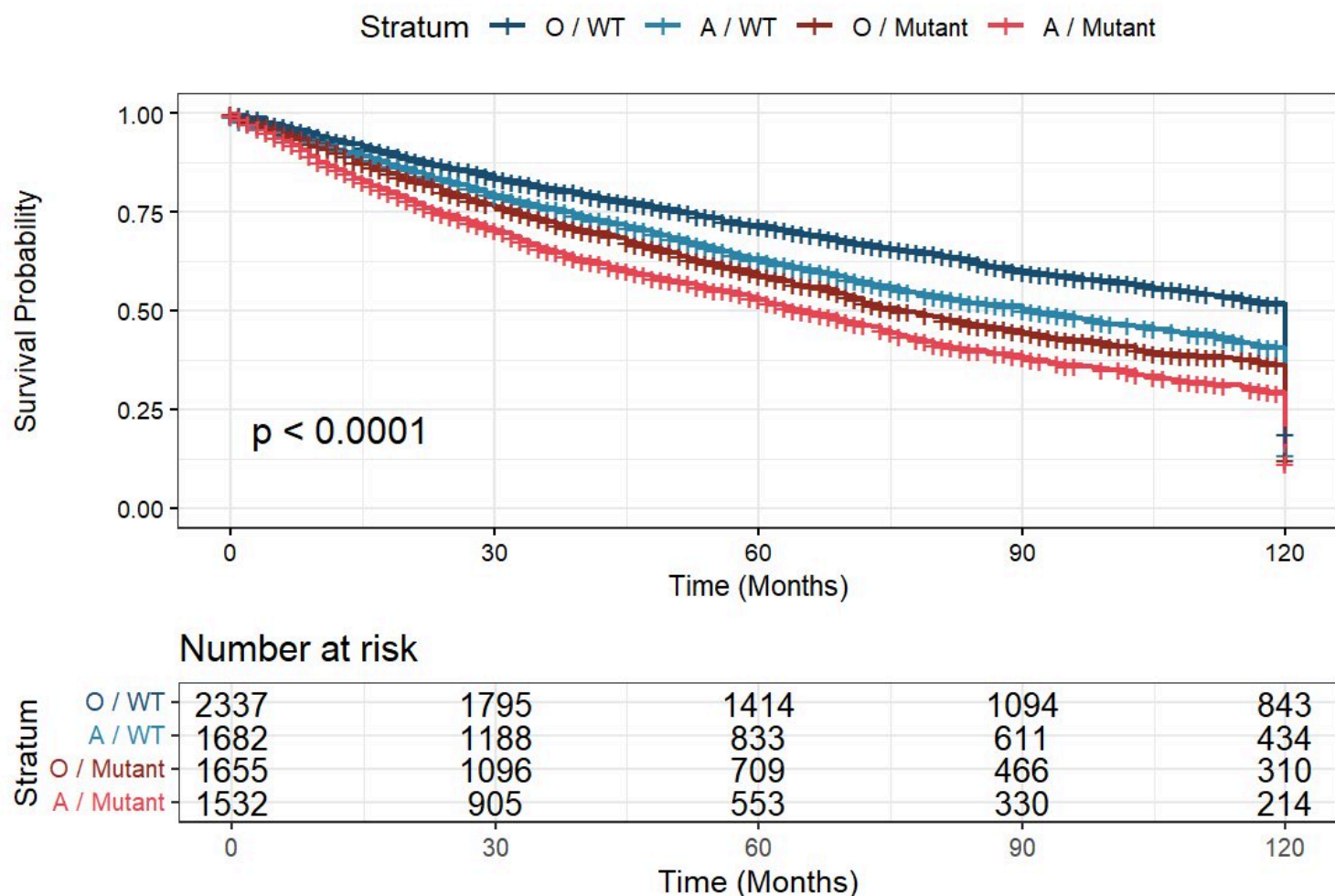


**Figure 7**

Kaplan-Meier survival curves for blood group A vs O stratified by TP53 mutation status (N=7,206). Four strata: O/WT (best survival, dark blue), A/WT (light blue), O/Mutant (dark red), A/Mutant (light red, worst survival). Log-rank  $p < 0.0001$ . The consistent vertical separation between WT and Mutant pairs, and between O and A pairs, demonstrates independent additive effects on survival.

## Time-Varying Hazard Ratios: Blood Group and p53 Status

Cox model with  $\log(t+1)$  time interaction — resolves PH assumption violation

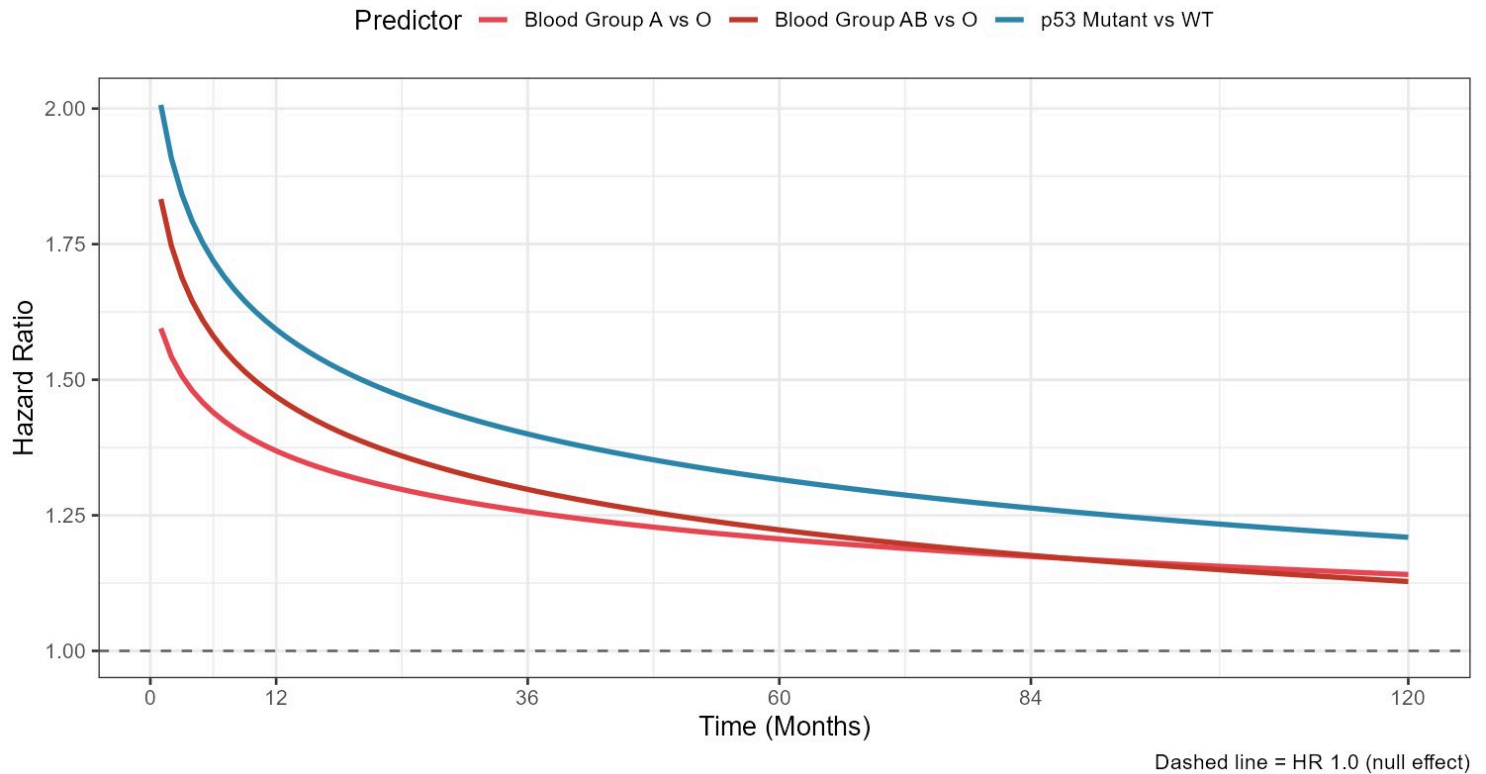


**Figure 8**

*Time-varying hazard ratios from Cox model with  $\log(t+1)$  time interaction for blood group A vs O (pink), blood group AB vs O (dark red), and TP53 Mutant vs WT (blue). All three predictors show monotonic HR decline while remaining above  $HR=1.0$  (null, dashed line) throughout 120 months. This figure formally resolves the PH assumption violation identified by Schoenfeld residual testing and reveals the temporally attenuating nature of both risk factors.*

## Landmark Analysis: Hazard Ratios Across Follow-up Periods

36-month landmark — early vs late effects of blood group and p53

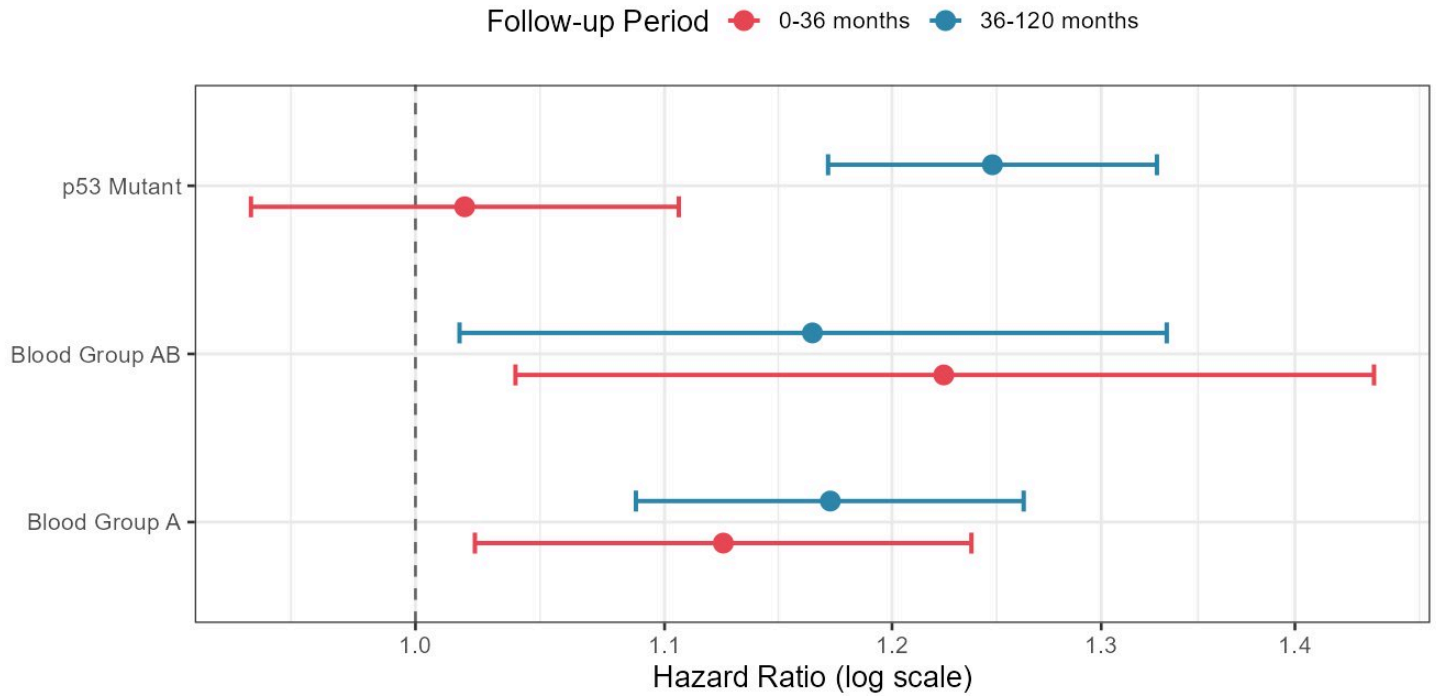


**Figure 9**

*Landmark analysis at 36 months. Hazard ratios with 95% confidence intervals for blood group A, AB, and TP53 Mutant in early (0-36 months, red circles) and late (36-120 months, blue circles) follow-up periods. TP53 Mutant crosses from non-significant ( $HR=1.02$ ,  $p=0.646$ ) to strongly significant ( $HR=1.25$ ,  $p<0.001$ ) between windows. Blood group effects are present in both windows, identifying blood group as a persistent but temporally attenuating risk modifier.*

## Restricted Mean Survival Time Differences (RMST)

Tau = 60 months | Negative = shorter survival vs reference

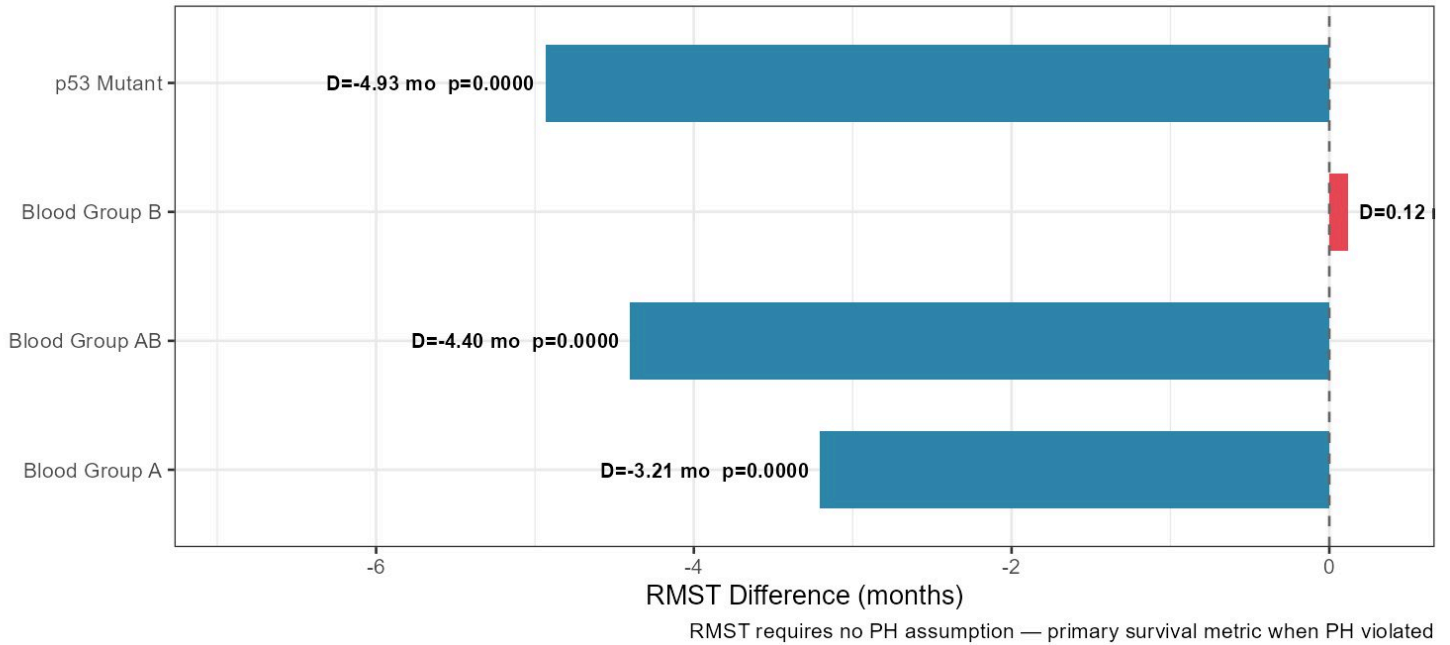


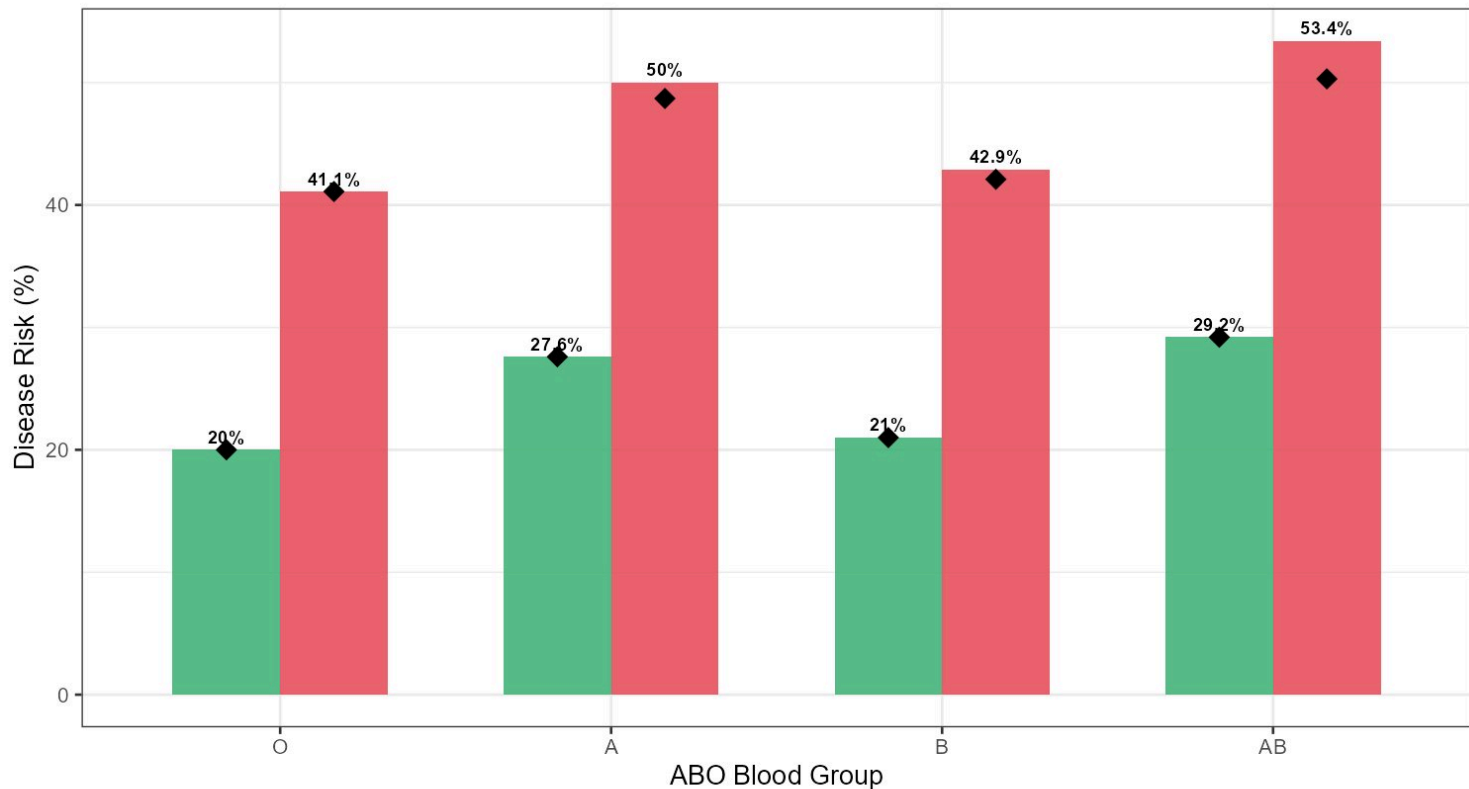
**Figure 10**

*Restricted Mean Survival Time (RMST) differences at tau=60 months. Negative bars (blue) = shorter 5-year mean survival versus reference. Blood group B (red bar, D=+0.12 months, p=0.809) shows no significant difference. Blood group AB and TP53 Mutant show the greatest survival deficits (4.40 and 4.93 months respectively). RMST requires no proportional hazards assumption and is the primary survival metric in this study.*

Observed vs Expected Risk: Additive Independence Test

Bars = observed | Diamonds = expected under pure additivity  
 $RERI(A \times p53) = 0.066$ ,  $SI(A \times p53) = 1.046$  — confirms independence

p53 Status WT Mutant



RERI near 0, SI near 1 = blood group and p53 are independent risk layers

Figure 11

Additive independence test: observed disease risk percentage (bars) versus expected risk under pure additivity model (black diamonds) for all ABO × TP53 strata.  $RERI(A \times p53) = 0.066$  and  $SI(A \times p53) = 1.046$  confirm near-perfect independence. The alignment of observed bars with expected diamonds across all strata provides formal statistical proof that blood group and TP53 mutation contribute independently and additively. Reference stratum: Group O / TP53 WT (20.0%).

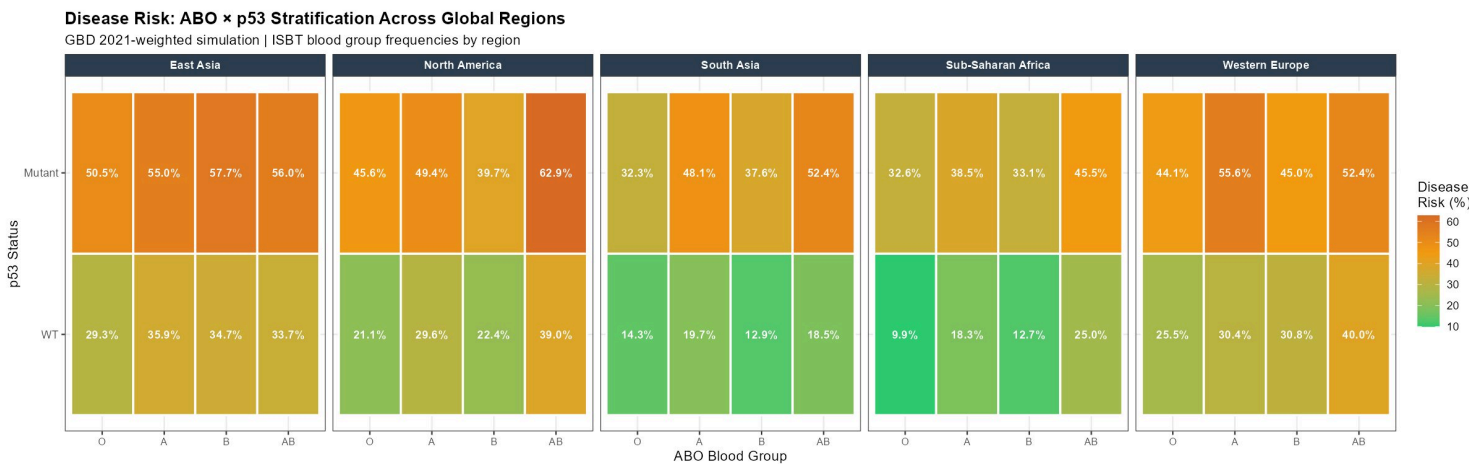


Figure 12

Disease risk heatmap across ABO blood groups, TP53 mutation status, and five global regions (GBD 2021-weighted simulation). Colour scale from green (low) to deep orange-red (high risk). The highest compound-risk stratum is North America AB/Mutant (62.9%) and the lowest is Sub-Saharan Africa O/WT (9.9%), a 6.3-fold range using two universally available biomarkers. Consistent with published GBD 2021 and ISBT regional data.

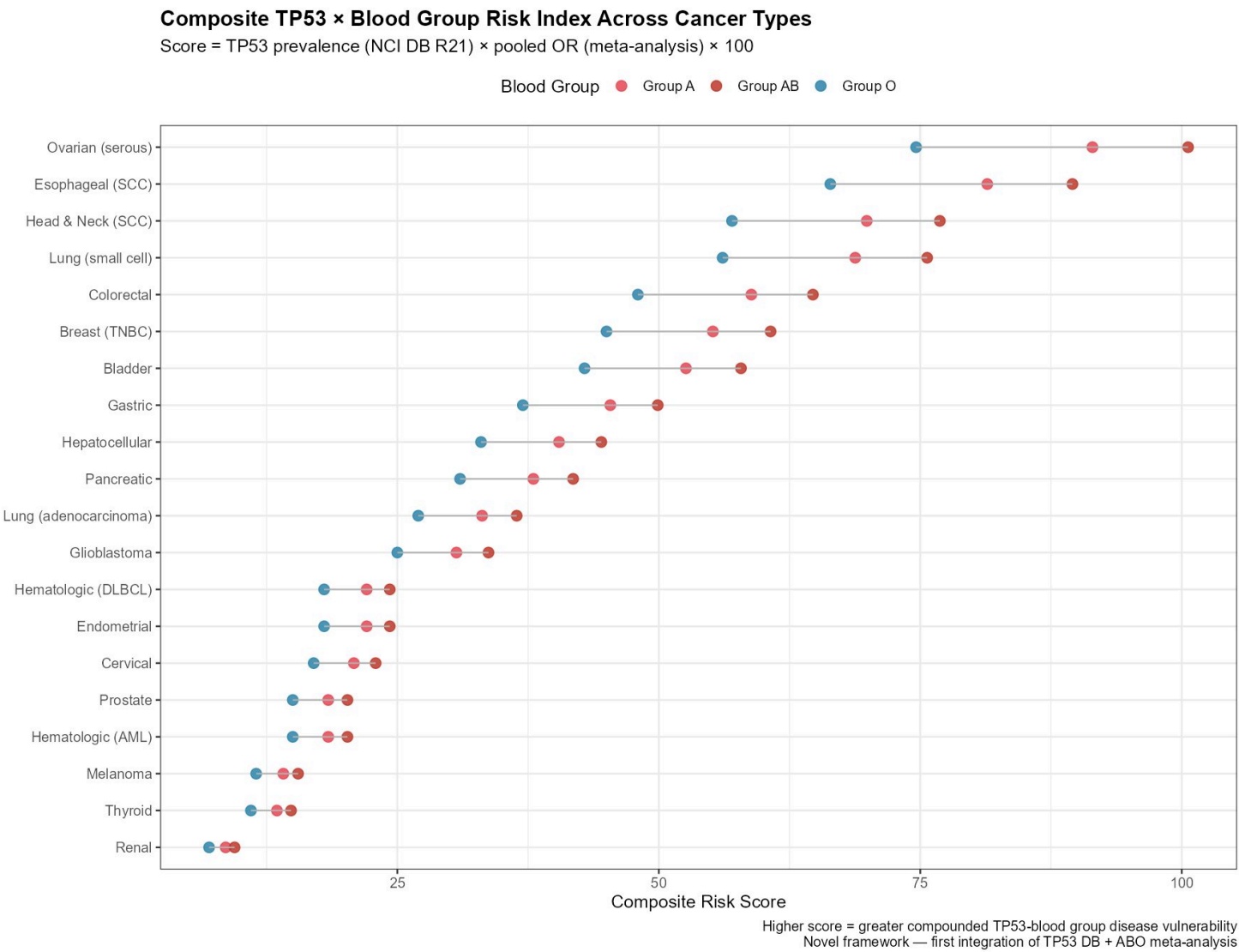


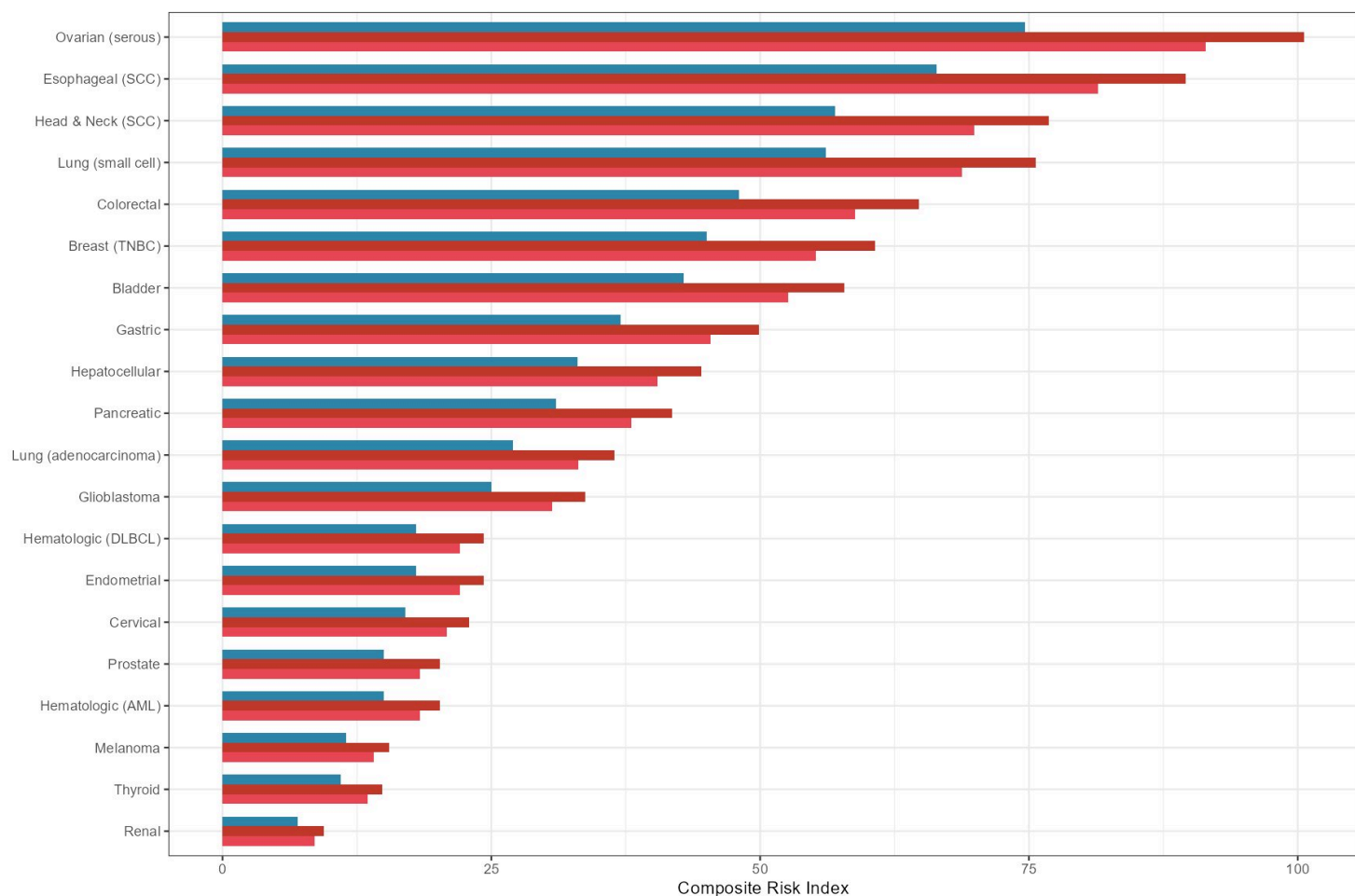
Figure 13

Composite TP53 × ABO risk index (Score = TP53 prevalence × pooled OR × 100) across 20 cancer types, shown as dot plot with connecting lines between blood group O (blue, reference), A (light pink), and AB (dark red). Cancers ranked by maximum composite score. Ovarian serous carcinoma has the highest compounded vulnerability (AB score=101). The consistent rightward shift from O to A to AB confirms uniform blood group amplification of TP53-driven risk across all cancer types. Novel framework - first integration of NCI TP53 Database with ABO meta-analysis.

# Joint TP53 × Blood Group Risk Score by Cancer Type

TP53 prevalence (NCI DB R21) × Blood group OR (meta-analysis pooled)

Blood Group    Group A    Group AB    Group O (ref)



Higher values = greater compound disease vulnerability

**Figure 14**

*Joint TP53 × Blood Group risk score as grouped bar chart for all 20 cancer types, showing Group O (blue, reference), Group A (pink), and Group AB (dark red) composite risk indices. The consistent ordering  $O < A < AB$  across all cancer types confirms the additive blood group amplification of TP53-driven cancer vulnerability across the spectrum of solid tumours and haematologic malignancies.*