

Development of a Polygenic Score to Predict Cisplatin-Induced Ototoxicity

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INTRODUCTION

Cisplatin is a major chemotherapeutic agent that is used in the treatment of many cancers, such as hematological malignancies and solid tumors. Unfortunately, **ototoxicity** (hearing loss) is one of the most common adverse drug reactions associated with cisplatin treatment. Up to 80% of patients treated with cisplatin develop hearing loss.¹

Genetics plays an important role in cisplatin-induced ototoxicity (CIO). Heritability studies have shown that 38-47% of the variability in the occurrence of CIO can be attributed to genetics.¹

HYPOTHESIS

Genomic data can be used to predict the occurrence of CIO.

RESULTS

Table 1. Associations between the two PGSs and CIO in the PanCareLife Cohort.

Polygenic Score	Number of Variants in PGS	R ² *	P-value
PGS _{HL}	2,753,914	0.021	3.85x10 ⁻³
PGS _{CIO}	158,032	0.062	6.02x10 ⁻⁷

*R²: proportion of variance explained by the PGS

Table 2. Associations between PGS_{CIO} and CIO in the SJMB Cohort, stratified by craniospinal irradiation (CSI) status.

Polygenic Score	CSI Status	Nagelkerke R ² *	P-value
PGS _{CIO}	No	0.031	4.85x10 ⁻²
	Yes	0.015	0.370
	Entire Cohort	0.0073	0.225

*Nagelkerke R²: proportion of the variance explained by PGS_{CIO}

CONCLUSION

To the best of our knowledge, **this is the first PGS developed to predict the risk of CIO using a biologically informed filter generated from cisplatin-treated murine inner ear single-nuclei RNA-sequencing data**. Although the PGS didn't significantly improve overall predictive performance, the study's novel data has enhanced our understanding of the genetic architecture underlying CIO, highlighting potential pathways and mechanisms.

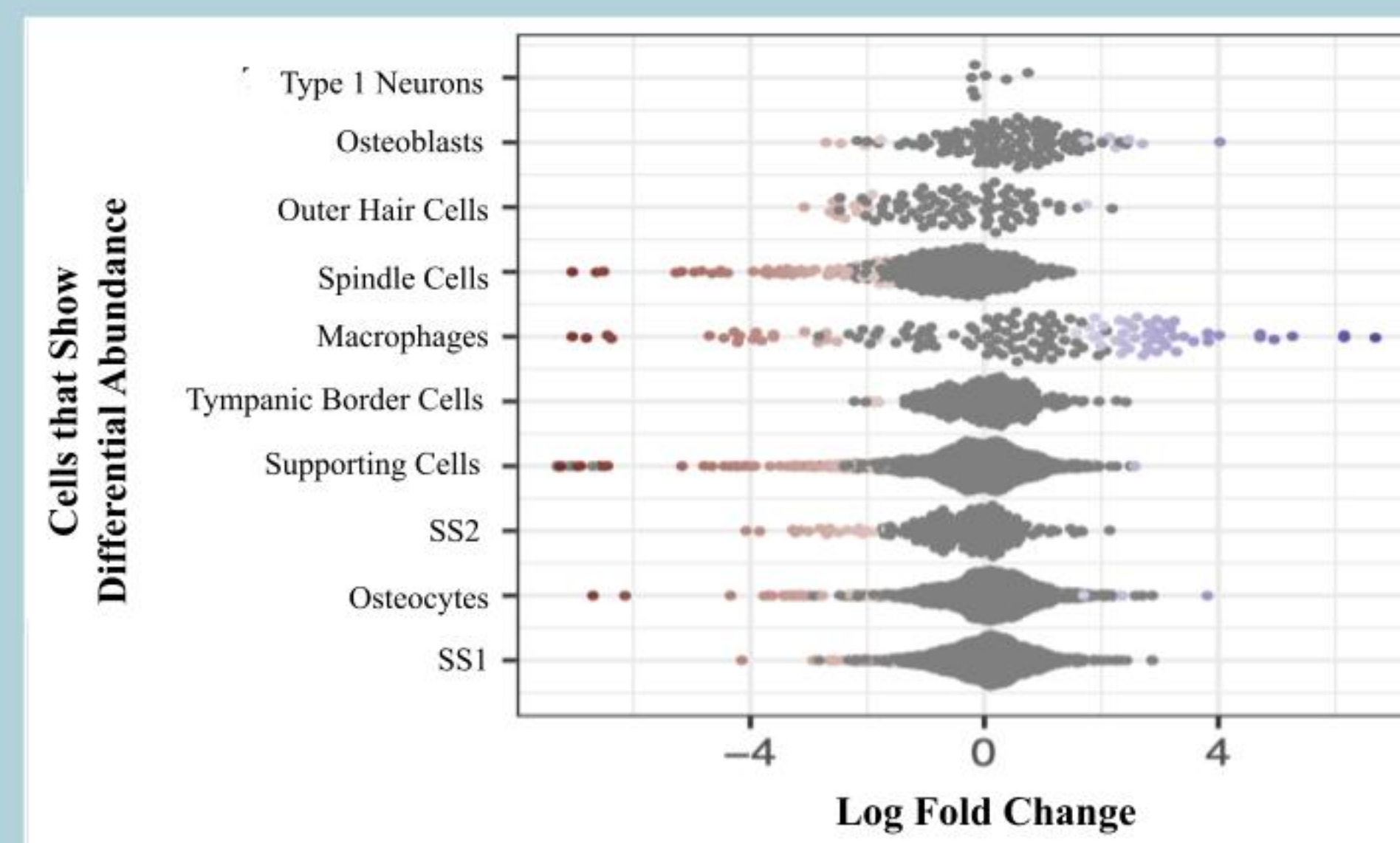
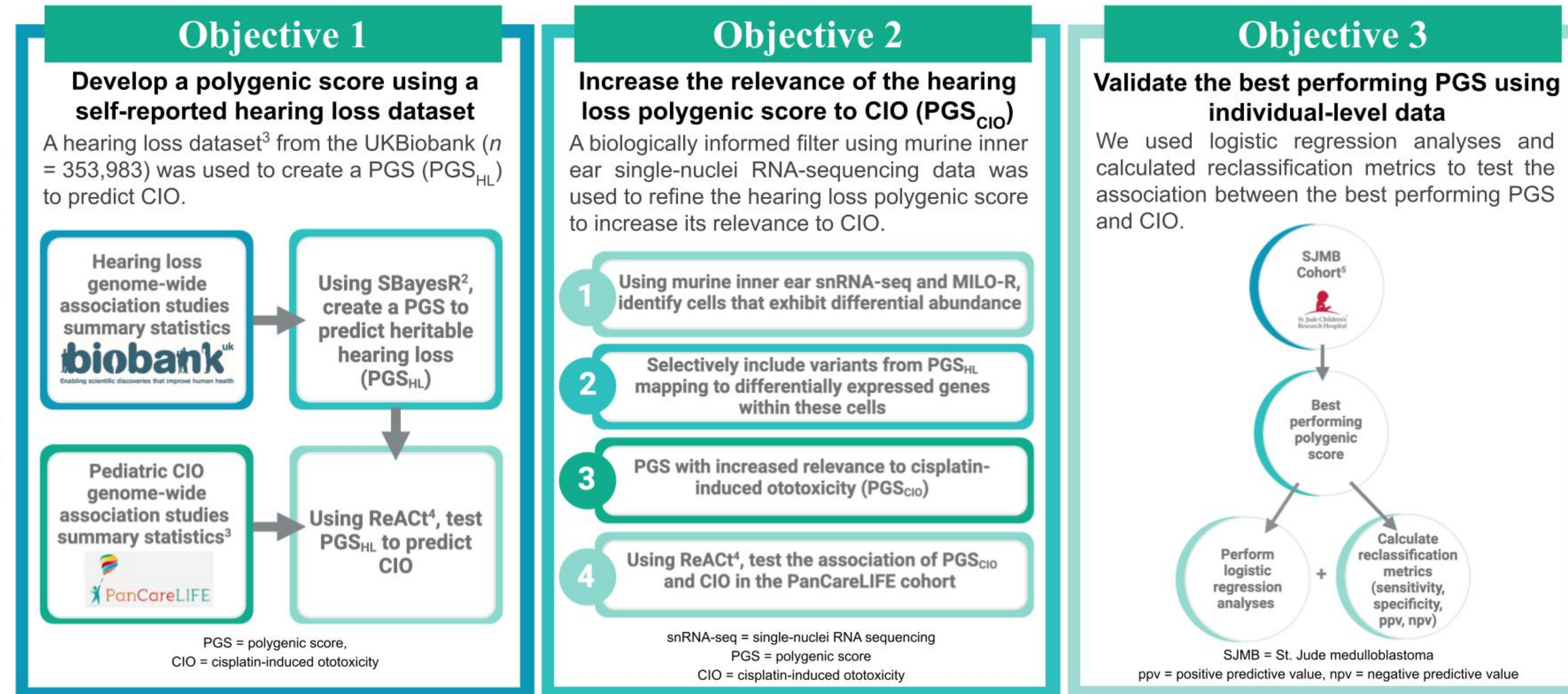


Figure 1. Beeswarm plot illustrating cochlear cells that show differential abundance four hours post-cisplatin treatment. Red indicates decreased abundance and blue indicates increased abundance of cells treated with cisplatin relative to controls.

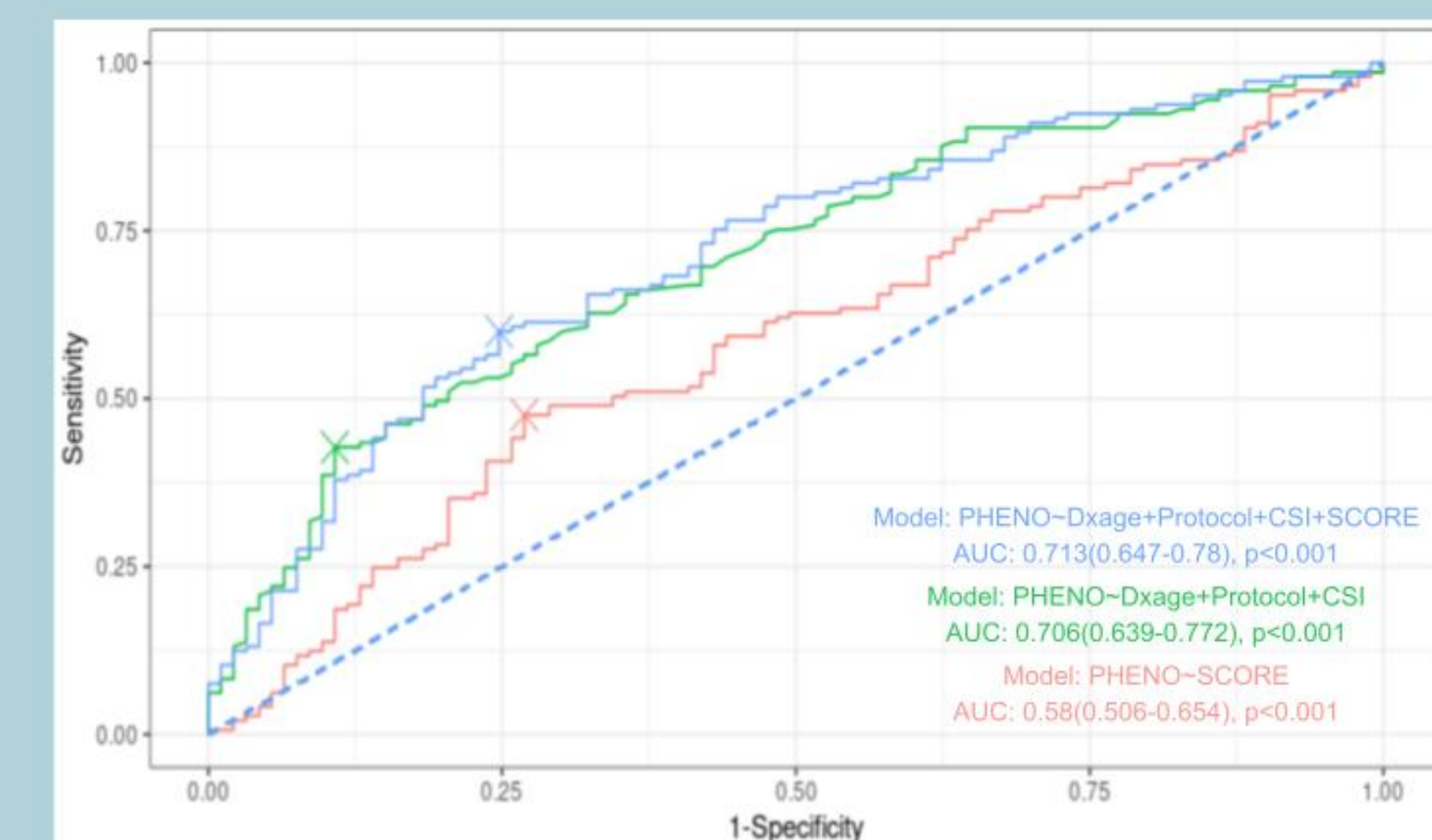


Figure 2. Comparison of different logistic regression models (PGS_{CIO}, only clinical predictors and PGS_{CIO}+clinical predictors) based on the receiver operating characteristic (ROC) curves and area under the curve (AUC) values.

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