Elastic-Net Modeling of Serum Proteomics for Treatment Failure Prediction in Advanced High-Grade Serous Ovarian Carcinoma

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Background

- High-grade serous ovarian carcinoma (HGSOC) remains a challenging and deadly disease for oncologists within and outside the Military Health System (MHS).
- Most patients present with advanced-stage disease, experience disease progression and platinum-resistance, and >80% die from their disease.
- Current clinicopathologic factors incompletely identify patients at highest risk for treatment failure.
- Machine-learning analysis of pretreatment serum proteomics may improve precision risk stratification before systemic therapy begins and survival outcomes.

Objective

- Determine whether serum biomarkers and elastic-net machine learning applied to pretreatment serum proteomics improves prediction of progression, survival, and platinum-taxane resistance beyond conventional clinical variables.

Why This Matters to the MHS

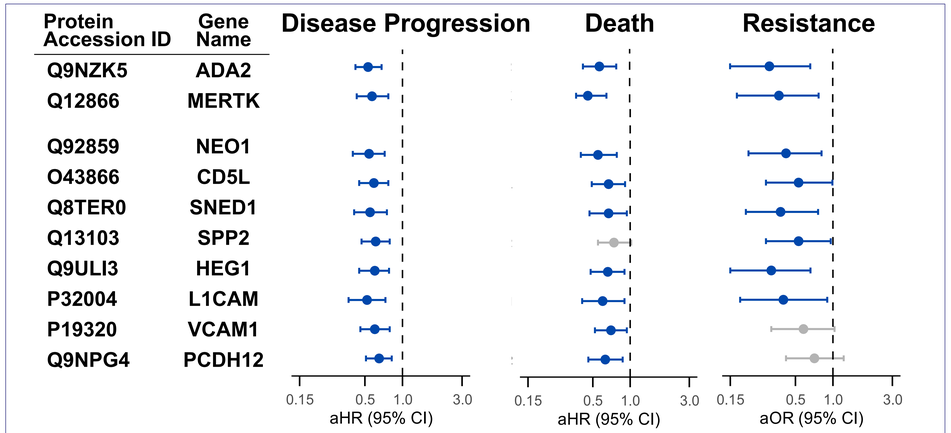
- Integrates machines with clinical and proteomic data to improve individualized risk prediction.
- Provides a scalable framework for future deployment across OCUNS and UCONUS Military Health System facilities.

Methods

- **Study Design**
  - Multisite cohort of stage III-IV HGSOC (2012-2021) from the prospective Tissue and Data Acquisition Network.
  - Patients underwent primary debulking surgery followed by platinum-taxane chemotherapy and salvage therapy as needed.
- **Biospecimen and Proteomic Analysis**
  - Pre-treatment serum was collected prior to surgery and therapy.
  - Immunodepletion followed by TMT-based quantitative LC-MS/MS proteomics quantified 791 serum proteins for analysis.
  - Elastic-net regularized Cox regression used for feature selection and development of a multivariable prognostic risk score.
  - Model performance was evaluated using multivariable Cox modeling and ROC/AUC analysis.
- **Endpoints**
  - Progression-Free Survival (PFS), Overall Survival (OS), and Platinum-Taxane Resistance with a drug free interval ≤182 days.
- **Statistical Analysis**
  - Cox modeling with hazard ratio (HR) and 95% confidence interval (CI for disease progression or death).
  - Logistic regression odds ratio (OR) and 95% CI for platinum-taxane resistance.
  - Multivariable models adjusted for age, stage, and residual disease.

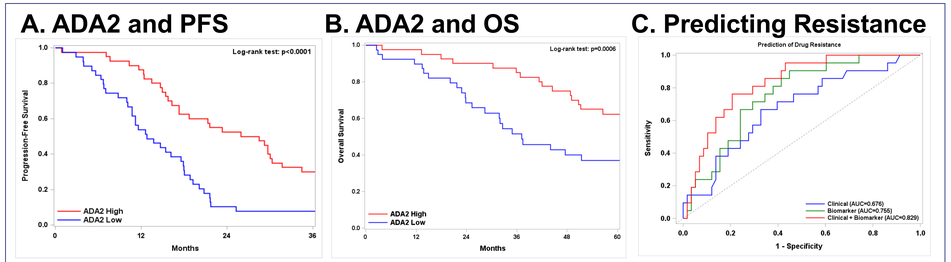
Results: Serum-Based Proteomic Profiling and Machine Learning Identify Clinically Relevant Biomarkers for Aggressive and Deadly Cancer

Figure 1. Outcomes Risk for the Top 10 Favorable Prognostic Serum Biomarkers



Serum proteins and reduced adjusted risk of disease progression, death, and resistance in HGSOC.

Figure 2. Elevated Serum ADA2 and Improved Outcomes and Resistance Prediction

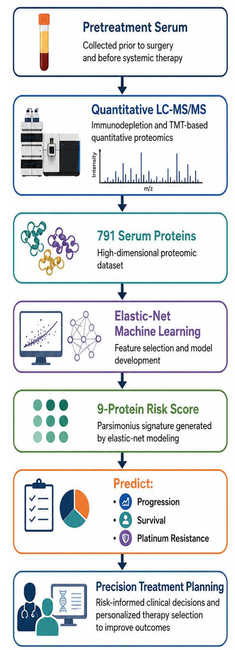


Higher serum ADA2 independently predicts improved PFS (A), OS (B), and resistance (C) in HGSOC.

MHS Impact

- Enables identification of patients at high risk for treatment failure before initiation of chemotherapy.
- Supports precision treatment planning and enrollment into biomarker-directed clinical trials.
- Advances Military Health System goals for data-driven, personalized oncology while potentially reducing ineffective therapy and associated toxicity.
- Provides minimally invasive serum biomarkers for future deployment across Military Health System treatment facilities.
- Demonstrates how serum biomarkers may support earlier therapeutic decision making using minimally invasive testing.

Figure 3. Elastic Net-Derived Optimal Predictive Protein Combination for Unfavorable Prognosis

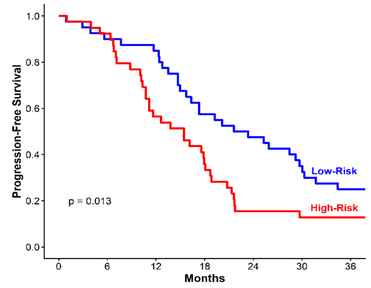


A. Proteomic Risk Score

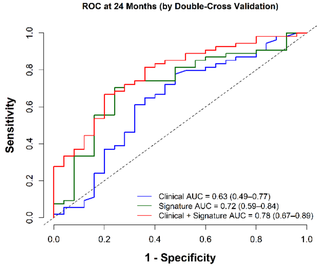
Gene Name	Coefficient
ADA2	-0.16539
IL1RAP	-0.10158
CRP	0.034116
BMP1	-0.03378
CD5L	-0.01793
NEO1	-0.01591
CPN2	-0.0137
SPP2	-0.0077
EGFR	-0.00064

Algorithm derived using elastic-net Cox model based on 791 proteins

B. High Risk Score Worse PFS



C. Risk Score Accuracy



D. Independent Risk Score

	Adj. HR (95% CI)	p-value
Risk of Progression		
Risk-Score (continuous)	1.40 (1.08-1.82)	0.011
High vs. Low Risk-Score	1.90 (1.16-3.11)	0.011
Risk of Death		
Risk-Score (continuous)	1.59 (1.16-2.18)	0.004
High vs. Low Risk-Score	1.86 (1.04-3.31)	0.037

Elastic-Net Machine Learning Identifies a Nine-Protein Independent Prognostic Signature for Progression & Death.

Take-Home Message: Elastic-net machine learning identified a clinically meaningful serum proteomic signature that improves prediction of progression, survival, and platinum resistance beyond traditional clinical factors, minimizes overfitting, and selects a parsimonious signature suitable for clinical translation, supporting future precision oncology implementation across the Military Health System.

Conclusions

- The top-ranked serum proteins identified by machine learning represent clinically relevant circulating biomarkers warranting external validation.
- Adenosine deaminase 2 (ADA2) and tyrosine-protein kinase Mer (MERTK) demonstrate consistent associations as continuous and categorized variables across all three endpoints: PFS, OS, and resistance.
- Integration of serum ADA2 with conventional clinical variables substantially improved predictive performance (AUC 0.829), demonstrating added value beyond standard clinicopathologic assessment.
- Elastic-net modeling reduced 791 quantified serum proteins to a parsimonious nine-protein prognostic signature independently associated with progression and survival, and a strong AUC (0.78) with clinical covariates.

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