



Received: 18 Aug 2026
Revised: 11 Sep 2026
Accepted: 21 Sep 2026
Published: 01 Oct 2026

Volume 12 Issue 10, 2026
Page No - 01-07
DOI - 10.55640/ijmsdh-12-10-01

Article Citation: Salem, Y. B., & Trabelsi, A. (2026). Integrative Predictive Modeling in Complex Pathology: Bridging Genetic Architectures, Clinical Biomarkers, and Statistical Nomograms for Multimodal Risk Stratification. *International Journal of Medical Science and Dental Health*, 12(10), 01-07. <https://doi.org/10.55640/ijmsdh-12-10-01>

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Integrative Predictive Modeling in Complex Pathology: Bridging Genetic Architectures, Clinical Biomarkers, and Statistical Nomograms for Multimodal Risk Stratification

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Abstract

Background: The stratification of patient risk in complex diseases—ranging from neurodegenerative disorders like Alzheimer’s Disease to vascular pathologies like Abdominal Aortic Aneurysm (AAA)—remains a significant challenge due to the heterogeneity of biological drivers. Traditional single-biomarker approaches often fail to capture the systemic nature of these conditions.

Methods: This study synthesizes a multimodal methodological framework, integrating insights from Genome-Wide Association Studies (GWAS) regarding shared genetic loci in Schizophrenia and Alzheimer’s, with clinical proteomic data and routine biomarkers such as Blood Urea Nitrogen (BUN). We further analyze the statistical application of regularized Cox regression and the construction of prognostic nomograms to translate these multidimensional data into clinically usable tools.

Results: Genetic analysis confirms significant overlap in risk loci between psychiatric and neurodegenerative traits, suggesting shared inflammatory pathways. Clinically, elevated BUN is identified as an independent predictor of mortality in AAA and sepsis, distinct from creatinine. The application of decision curve analysis (DCA) and time-dependent ROC curves demonstrates that nomogram-based models significantly outperform standard staging systems in predicting overall survival and disease-free survival.

Conclusion: Effective risk prediction requires a transition from isolated marker identification to integrative modeling. By combining genetic susceptibility scores with



dynamic clinical biomarkers through rigorous statistical nomograms, clinicians can achieve higher predictive accuracy and personalized patient management.

Keywords: Predictive Modeling, Genome-Wide Association Studies, Abdominal Aortic Aneurysm, Schizophrenia, Nomograms, Blood Urea Nitrogen, Decision Curve Analysis.

Introduction

The contemporary landscape of biomedical research is characterized by an unprecedented volume of data, ranging from the atomic resolution of single-nucleotide polymorphisms (SNPs) to the macroscopic observation of clinical outcomes. However, a persistent "translational gap" exists between the identification of these biological signals and their application in patient-specific risk assessment. Complex chronic diseases, particularly those affecting the neurological and vascular systems, are rarely the result of a single pathogenic factor. Instead, they emerge from a dynamic interplay of genetic susceptibility, proteomic dysregulation, and environmental stressors.

For instance, the genetic architecture of psychiatric disorders such as Schizophrenia has been elucidated through massive Genome-Wide Association Studies (GWAS), identifying over 100 associated genetic loci [1]. Yet, these genetic insights often remain siloed from clinical practice. Simultaneously, in the realm of vascular pathology, conditions like Abdominal Aortic Aneurysm (AAA) are managed through biomechanical metrics (aneurysm diameter), often ignoring systemic metabolic indicators like Blood Urea Nitrogen (BUN) or inflammatory states that significantly influence mortality [19, 20]. The challenge lies not in the discovery of new markers, but in the mathematical and statistical integration of existing ones into coherent predictive models.

The necessity for such integration is underscored by the overlapping etiologies of seemingly distinct diseases. Research has increasingly highlighted the "pleiotropic" nature of disease genes—where genetic variants influence multiple phenotypic traits. This is evident in the shared genetic risks between Schizophrenia, autoimmune diseases like Rheumatoid Arthritis, and neurodegenerative conditions like Alzheimer's Disease [6, 8]. To manage this complexity, the field of medical statistics has evolved beyond simple logistic regression. Techniques such as Mendelian Randomization [2], regularized Cox proportional hazards models [14], and the construction of graphical nomograms [15] have emerged as essential tools for distilling high-dimensional data into actionable clinical probability.

This article aims to synthesize these disparate domains. We review the biological basis of multimodal risk factors—spanning the genetic loci of neuro-psychiatric conditions to the

proteomic markers of dementia and vascular health. Furthermore, we provide a detailed examination of the statistical frameworks necessary to validate these models, specifically focusing on calibration measurements and decision curve analysis (DCA). By bridging the gap between molecular biology and clinical statistics, we propose a unified framework for predictive modeling in complex pathology.

Methods: A Framework for Integrative Analysis

To understand the predictive power of multimodal data, one must first establish the methodologies used to isolate signal from noise across different biological scales. This section outlines the integrative approach used to synthesize genetic, proteomic, and clinical data.

Genetic and Proteomic Data Integration

The foundation of modern risk prediction lies in the aggregation of summary data from GWAS. Traditional linkage analysis has been superseded by large-scale meta-analyses that allow for the fine-mapping of risk genes. For complex traits like Alzheimer's disease, integration involves not just the identification of risk loci (e.g., APOE, TREM2) but the application of Mendelian Randomization (MR) to infer causality [2, 13]. MR utilizes genetic variants as instrumental variables to assess the causal effect of a risk factor (e.g., plasma protein levels) on a disease outcome, thereby mitigating the confounding factors inherent in observational studies. Furthermore, the integration of expression quantitative trait loci (eQTL) data allows researchers to predict complex trait gene targets, linking static genetic code to dynamic protein expression [3].

Clinical Biomarker Selection

While genetics provides a static risk profile, clinical biomarkers offer a dynamic view of the patient's current physiological state. In the context of vascular and metabolic diseases, the selection of biomarkers must undergo rigorous screening for independence. For example, in analyzing mortality risks in sepsis or AAA, markers like BUN must be evaluated not just for their correlation with kidney function, but for their independent association with neuro-hormonal activation and catabolic states [19, 20]. The methodology for validating such markers involves multivariate regression analysis, adjusting for potential confounders such as age, hypertension, and medication use (e.g., ACE inhibitors or Beta-blockers) [21, 22].

Statistical Architecture of Prediction Models

The translation of these biological inputs into a risk score requires robust statistical modeling. The Cox proportional hazards model remains the cornerstone of survival analysis.



However, in the era of "omics" data, standard Cox models face the issue of overfitting due to high dimensionality.

To address this, regularization techniques such as the Lasso (Least Absolute Shrinkage and Selection Operator) are employed. As described by Simon et al., regularization paths for Cox models via coordinate descent allow for the selection of the most predictive variables while shrinking the coefficients of less relevant features to zero [14]. This prevents the model from capturing random noise in the training data.

Once a model is derived, it is often visualized as a nomogram—a graphical calculating device that assigns a relative point score to each predictor [15]. The construction of a nomogram requires the careful calibration of the underlying statistical model to ensure that the predicted probabilities align with observed outcomes. This validation process is critical and involves three key metrics:

- 1. Discrimination:** Measured by the C-index or Area Under the Curve (AUC), determining the model's ability to distinguish between patients who experience an event and those who do not.
- 2. Calibration:** Assessed via calibration plots and the Hosmer-Lemeshow test, ensuring the predicted risk matches the actual prevalence of the event [17].
- 3. Clinical Utility:** Evaluated using Decision Curve Analysis (DCA), which calculates the net benefit of using the model across a range of threshold probabilities [18].

Results: Biological Intersections and Model Performance

The application of the methodology described above reveals profound connections between distinct pathological domains and demonstrates the superior efficacy of integrative modeling.

Genetic Overlap in Neuro-Psychiatric Disorders

Analysis of large-scale genomic data has provided critical biological insights into the etiology of Schizophrenia and its connection to other systemic conditions. The Schizophrenia Working Group identified 108 schizophrenia-associated genetic loci, many of which are enriched in genes relevant to glutamatergic neurotransmission and immunity [1]. This immune component is further substantiated by epidemiological data linking schizophrenia with autoimmune diseases. Studies on the Swedish population have shown significant associations between schizophrenia and rheumatoid arthritis (RA), mediated by shared genetic risks and inflammatory pathways [6, 8].

Furthermore, the genetic architecture of Alzheimer's disease (AD) shares surprising commonalities with these psychiatric traits. Meta-analyses of diagnosed AD have implicated genes involved in lipid processing, tau pathology, and immunity [10]. Notably, white matter integrity studies suggest a structural connection between the neurodegenerative processes in Schizophrenia and AD, potentially driven by alpha-7 nicotinic receptor dysfunction [4, 5]. These findings underscore that "brain health" is not compartmentalized but is influenced by a pleiotropic genetic background affecting immunity and lipid metabolism.

Proteomics and Vascular Mortality

Moving from the genome to the proteome, the integration of plasma proteomics has identified markers capable of predicting dementia risk years before symptom onset [11, 12]. However, the utility of blood-based biomarkers extends beyond neurology into vascular survival.

In the context of Abdominal Aortic Aneurysm (AAA) and severe sepsis, Blood Urea Nitrogen (BUN) has emerged as a potent independent marker of mortality [19, 20]. While traditionally viewed merely as an indicator of renal function, elevated BUN in the absence of corresponding creatinine spikes suggests a state of neuro-hormonal activation and protein catabolism. Studies investigating the efficacy of Renin-Angiotensin-Aldosterone System (RAAS) inhibitors versus Beta-blockers in aneurysm repair have further highlighted how modulating these metabolic and hemodynamic pathways can significantly alter survival outcomes [21, 22]. The data indicates that BUN serves as a composite proxy for both renal perfusion and systemic metabolic stress.

Superiority of Nomogram-Based Stratification

When these genetic and clinical factors are combined into prognostic nomograms, the predictive accuracy surpasses that of traditional staging systems. In hepatocellular carcinoma (HCC) and vascular surgery cohorts, machine learning models utilizing time-series data (Dynamic-DeepHit) and standard nomograms consistently achieved C-indices greater than 0.75, significantly higher than single-variable models [16].

The calibration measurements for these models generally show high concordance between predicted and observed survival. Crucially, time-dependent ROC curve analysis demonstrates that the sensitivity and specificity of these integrative models remain robust over long-term follow-up (3, 5, and 10 years) [16]. This confirms that learning "rich features"—whether they are complex genetic risk scores or composite clinical markers—without necessarily requiring new "labels" (diagnoses) allows for better stratification of sub-clinical risk.



Statistical Expansion: The Rigor of Nomogram Construction and Validation

To fully appreciate the validity of the results presented, it is necessary to expand upon the statistical mechanics governing the construction and validation of prognostic nomograms. As the bridge between raw data and clinical application, the rigorous development of these tools is paramount. This section details the mathematical and logical frameworks of Regularization, Calibration, and Decision Curve Analysis (DCA), which ensure that predictive models are not only mathematically sound but clinically safe.

1. Regularization in High-Dimensional Survival Analysis

In the era of multi-omics, the number of potential predictors (p) often exceeds the number of observations (n), or at least approaches a magnitude where traditional regression fails. Standard Maximum Likelihood Estimation (MLE) in Cox Proportional Hazards models becomes unstable in these scenarios, leading to high variance and overfitting. Overfitting occurs when a model learns the "noise" of the training data rather than the underlying signal, resulting in poor performance on external validation.

To mitigate this, we utilize regularization methods, specifically the Lasso (Least Absolute Shrinkage and Selection Operator) and Elastic Net. As detailed by Simon et al. [14], these methods introduce a penalty term to the likelihood function. The Cox partial likelihood $L(\beta)$ is modified to maximize:

$$\log L(\beta) - \lambda \sum |\beta_j|$$

Here, λ is the tuning parameter. As λ increases, the coefficients (β) of less informative variables are shrunk toward zero. The Lasso penalty has the unique property of forcing some coefficients to become exactly zero, effectively performing variable selection. This is crucial when integrating GWAS summary data [3] or plasma proteomic panels [12], where thousands of proteins may be measured, but only a handful (e.g., specific inflammatory cytokines or lipid transporters) are causally linked to the outcome.

The selection of the optimal λ is typically achieved through K-fold cross-validation, where the data is partitioned into K subsets. The model is trained on $K-1$ subsets and validated on the remaining one, ensuring that the selected predictors are robust across different data cuts. This process transforms a "black box" of thousands of genetic loci into a manageable set of significant predictors suitable for a clinical nomogram.

2. The Architecture of the Nomogram

A nomogram is a geometric representation of a mathematical formula. In the context of the Cox model, the hazard function is $h(t|X) = h_0(t) \exp(\beta_1 X_1 + \dots + \beta_k X_k)$. The nomogram linearizes this relationship. Each predictor (X_i) is assigned a scale based on its regression coefficient (β_i).

- **Points Scale:** The variable with the largest absolute coefficient effect is assigned 100 points. All other variables are scaled relative to this.
- **Total Points:** The points for each patient's values are summed to calculate a "Total Score."
- **Probability Scale:** The total score is mapped to a probability axis (e.g., "3-Year Survival Probability") via a transformation of the baseline hazard function.

The beauty of the nomogram, as implemented in software packages like R [15], is that it demystifies the risk calculation. For a patient with an Abdominal Aortic Aneurysm, a clinician can locate the patient's age on one axis, their BUN level [19] on another, and their genetic risk score on a third. By manually or digitally summing these points, the clinician derives a personalized mortality estimate. This transparency fosters trust in AI and statistical systems, which is often lacking in "deep learning" black-box approaches.

3. Calibration and Discrimination: The Dual Pillars of Accuracy

A common pitfall in predictive modeling is confusing discrimination with accuracy.

- **Discrimination** (C-index) measures the model's ability to rank patients correctly. If Patient A dies before Patient B, the model should assign a higher risk score to Patient A. A C-index of 0.5 suggests random chance, while 1.0 is perfect prediction.
- **Calibration**, however, measures how close the predicted risk is to the absolute reality. If a model predicts a 20% risk of death for a group of 100 patients, exactly 20 of them should die.

As Huang et al. [17] describe, calibration is best visualized using a calibration plot. The x-axis represents the predicted probability, and the y-axis represents the observed frequency (estimated via Kaplan-Meier). A perfectly calibrated model aligns with the 45-degree diagonal line. Deviations indicate bias: curves below the diagonal suggest overestimation of risk (causing unnecessary anxiety or treatment), while curves



above suggest underestimation (missing opportunities for intervention).

For example, in models predicting Alzheimer's risk using plasma proteomics [11], high discrimination is insufficient if the model consistently overestimates risk in older populations. Calibration techniques, such as bootstrapping, correct for this "optimism" bias in the training set.

4. Decision Curve Analysis (DCA): Assessing Clinical Net Benefit

Traditional metrics like ROC curves and p-values do not account for the clinical consequences of a false positive versus a false negative. This is where Decision Curve Analysis (DCA), as championed by Zhao et al. [18], becomes essential.

DCA calculates the "Net Benefit" of a model across a range of threshold probabilities (P_t). The threshold probability is the point at which a patient or clinician would opt for intervention. For instance, if the side effects of a prophylactic drug for Rheumatoid Arthritis are severe, the threshold for treatment might be high (e.g., 40% risk).

The formula for Net Benefit is:

$$\text{Net Benefit} = \frac{\text{True Positives}}{N} - \frac{\text{False Positives}}{N} \times \frac{P_t}{1 - P_t}$$

DCA plots the Net Benefit (y-axis) against the Threshold Probability (x-axis). The model is compared to two default strategies: "Treat All" (assuming everyone has the disease) and "Treat None." A model is clinically useful only if its decision curve lies above both the "Treat All" and "Treat None" lines.

In the context of the Schizophrenia and autoimmune overlap [7], DCA helps determine if screening schizophrenia patients for autoimmune markers yields a net benefit compared to universal screening or symptom-based screening. It quantifies the value of the "rich features" extracted from the data, answering the pragmatic question: "Does this model actually improve patient outcomes?"

5. Handling Time-Dependency in Prognosis

Static models often fail in chronic diseases where risk factors change over time. The association between Beta-blocker use and AAA mortality [22] may vary depending on when the medication was started relative to the surgical repair. Time-dependent ROC analysis [16] addresses this by evaluating the model's accuracy at specific time points (e.g., 1-year, 3-year, 5-year AUC).

Furthermore, dynamic prognostication (as seen in the Dynamic-DeepHit models) updates the risk prediction as new data becomes available. If a patient's BUN levels rise over six months, the survival probability is recalculated. This moves the field from a static "snapshot" prediction to a continuous monitoring framework, essential for managing long-term conditions like dementia and cardiovascular disease.

By adhering to these rigorous statistical standards—regularization for feature selection, calibration for accuracy, and DCA for utility—we ensure that the integration of multimodal data translates into reliable, actionable clinical intelligence.

Discussion

The integration of high-dimensional biological data with robust statistical modeling represents a paradigm shift in the management of complex diseases. This review has highlighted the utility of combining genetic susceptibility (GWAS) with dynamic clinical biomarkers (proteomics, metabolic indices) to refine risk stratification.

The Biological Continuum

The findings discussed regarding the genetic overlap between Schizophrenia, Alzheimer's, and autoimmune disorders [1, 10] challenge the traditional nosology of disease. The presence of shared risk loci implies common molecular pathways—likely involving inflammation and lipid metabolism—that manifest differently based on environmental triggers or secondary genetic modifiers. This supports the use of "pleiotropy-informed" prediction models, where a family history of autoimmune disease might increase the pre-test probability of psychiatric or neurodegenerative conditions in a risk model [7].

Similarly, the identification of BUN as a mortality marker in vascular disease [19] points to the systemic nature of focal pathologies. An abdominal aneurysm is not merely a mechanical failure of the aorta but a reflection of systemic vascular health, renal perfusion, and catabolic stress. Therefore, predictive models that focus solely on local anatomy (aneurysm size) are inherently limited.

Clinical Implications of the Nomogram

The primary contribution of the statistical frameworks reviewed here is the democratization of complex data. A nomogram condenses the complexity of a Cox regression model into a user-friendly tool. For the clinician, this means that the insights from a 108-loci GWAS or a comprehensive plasma proteomic panel can be distilled into a simple point score. The superiority of these models over standard staging, as evidenced by higher C-indices and better calibration [16], argues for their broader adoption in clinical guidelines.



However, the implementation of such models requires caution. As highlighted by the section on calibration, a model developed in a Swedish cohort (e.g., the schizophrenia-RA study [8]) may not be perfectly calibrated for an Indonesian or American population due to differences in baseline risk and genetic background. External validation remains the gold standard before clinical deployment.

Limitations

Despite the promise of multimodal AI and statistical modeling, several limitations persist. First, the "missing heritability" in GWAS suggests that we are still only capturing a fraction of the genetic risk. Second, most integrative studies are retrospective. While they establish correlation and prediction, they do not prove that acting on the prediction improves survival—a gap that only randomized controlled trials using these models as inclusion criteria can fill. Finally, the complexity of proteomic interactions [11, 13] poses a computational challenge, requiring ever-more sophisticated regularization techniques to avoid false discoveries.

Future Directions

The future of predictive modeling lies in "Dynamic Precision Medicine." Moving beyond static nomograms, we envision real-time risk calculators integrated into Electronic Health Records (EHR) that update automatically as new biomarker data (like serial BUN measurements or repeat proteomic screens) becomes available. Furthermore, the application of Mendelian Randomization [2] should be expanded to screen potential drug targets, using nature's own genetic randomization to predict the efficacy of therapeutic interventions.

Conclusion

Learning rich features from the vast, unlabeled ocean of biological data requires more than just powerful algorithms; it requires a structured statistical and biological framework. By rigorously integrating genetic insights with clinical phenotypes through calibrated nomograms and decision curve analysis, we can achieve a more nuanced, accurate, and actionable understanding of patient risk in complex diseases.

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