Clinical and Peripheral Blood Immune Markers Predict Relapsed/Refractory Multiple Myeloma Prior to Autologous Stem Cell Transplant

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INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation within the bone marrow, leading to significant morbidity and mortality (Kumar et al., 2017). Despite significant advances in treatment, including the advent of immunotherapy modalities such as monoclonal antibodies and CAR T-cell therapy, relapse and disease progression remain major obstacles to long-term disease control (Anderson et al., 2020; Munshi et al., 2021). Early identification of patients at high risk for relapse or progression is critical for optimizing therapeutic strategies and improving survival outcomes (Rajkumar, 2020).

Clinical demographic features combined with laboratory assessments, such as complete blood count (CBC) and comprehensive metabolic panel (CMP), offer a readily accessible source of potential biomarkers for disease monitoring (Ludwig et al., 2019). Previous studies have demonstrated that certain laboratory parameters, including anemia, renal dysfunction, and elevated serum calcium, correlate with disease severity and prognosis in MM (Kyle & Rajkumar, 2004; Palumbo et al., 2011). However, reliable predictors of disease trajectory specifically in the context of immunotherapy remain incompletely characterized.

This research project aims to analyze clinical and laboratory data from MM patients receiving immunotherapy to identify markers predictive of relapse or progression by employing robust statistical analysis and modeling. Identification of such predictors holds promise for personalizing treatment approaches, improving early intervention strategies, and ultimately enhancing patient management and outcomes in multiple myeloma.

METHODS

Objective: Identify clinically meaningful biomarkers in baseline Complete Blood Count (CBC) and/or Comprehensive Metabolic Panel (CMP) prior to transplant to predict relapse/refractory Multiple Myeloma

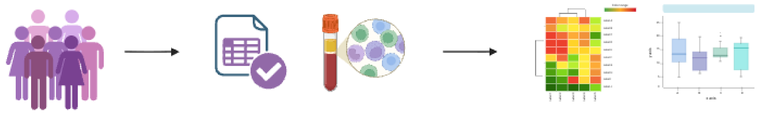

Figure 1: Methodology of pan-cancer immunotherapy response project

Random Forest Algorithm

Random Forest is a machine learning algorithm that builds an ensemble of decision trees to make predictions. Each decision tree is trained on a random subset of the data and a random subset of the predictors (features). The "forest" combines the predictions of all individual trees—by **majority vote** for classification tasks or averaging for regression tasks—to improve accuracy and reduce overfitting.

Key properties:

- **Non-parametric:** Makes no assumptions about the distribution of predictors.
- **Handles high-dimensional data:** Can include many correlated variables.
- **Captures complex relationships:** Can model nonlinear effects and interactions between predictors.
- **Robust:** Resistant to overfitting compared to a single decision tree.

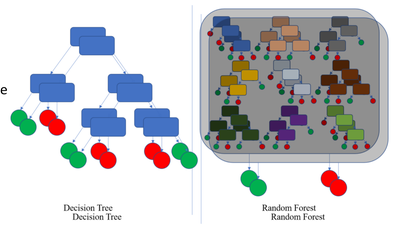

Figure 2: Visualization of Random Forest trees vs. decision tree

How Random Forest Determines Variable Importance

- **Gini Index:** Each decision tree splits nodes to increase "purity," meaning each branch is more homogeneous regarding the outcome (e.g., relapse vs no relapse). The Gini index measures impurity; lower is better.
- **Mean Decrease in Gini:** For each predictor, the algorithm calculates how much splitting on that variable decreases impurity across all trees in the forest.
  - A larger Mean Decrease in Gini means that variable is more important for correctly classifying the outcome.

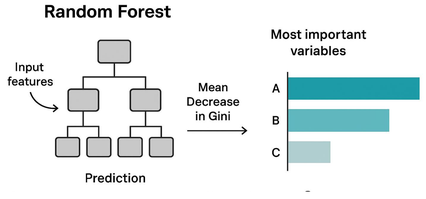

Figure 3: Random Forest algorithm workflow from input to output of MeanDecreaseGini

RESULTS

Kappa-Restricted

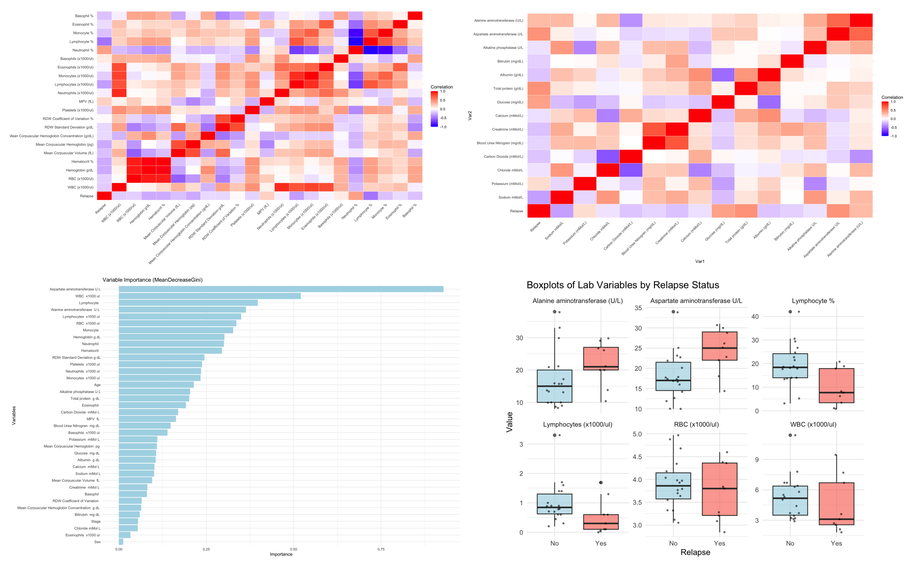

Figure 4: A: Heatmap of CBC lab markers and Relapse **B:** Heatmap of CMP lab markers and Relapse **C:** Variable Importance Plot of CBC/CMP variables as determined by Random Forest **D:** Boxplots of top six CBC/CMP lab variables by relapse status.

Lambda-Restricted

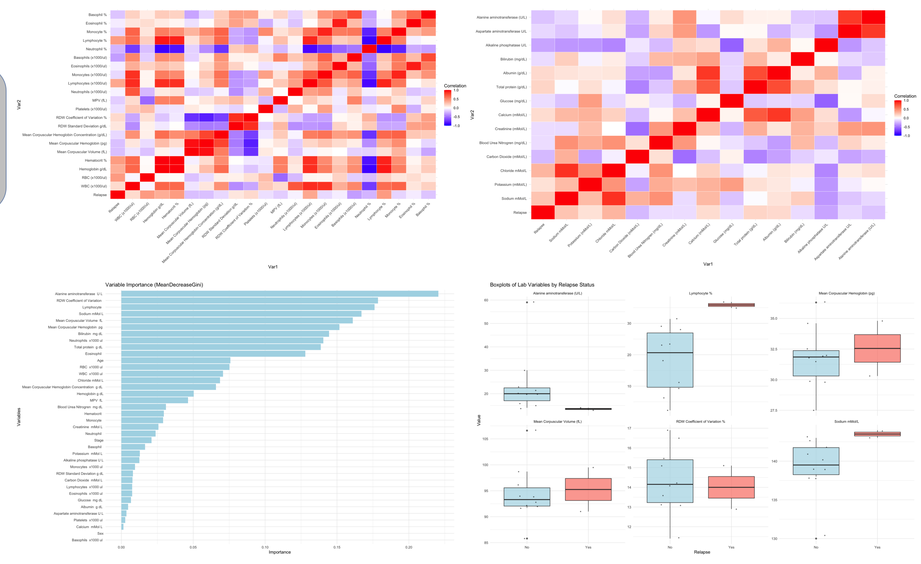

Figure 5: A: Heatmap of CBC lab markers and Relapse **B:** Heatmap of CMP lab markers and Relapse **C:** Variable Importance Plot of CBC/CMP variables as determined by Random Forest **D:** Boxplots of top six CBC/CMP lab variables by relapse status.

DISCUSSION

Variables of Highest Importance in Predicting Relapse (via Random Forest)

	Kappa-Restricted	Lambda-Restricted
CBC	WBC (x1000/ul) Lymphocyte (x1000/ul) Lymphocyte % RBC (x1000/ul)	Lymphocyte % Mean Corpuscular Volume (fL) Mean Corpuscular Hemoglobin (pg) RDW Coefficient of Variation %
CMP	Alanine aminotransferase (U/L) Aspartate aminotransferase (U/L)	Alanine aminotransferase (U/L) Sodium mMol/L

The application of random forest modeling to baseline laboratory parameters in Kappa- and Lambda-restricted Multiple Myeloma (MM) patients prior to autologous stem cell transplant (ASCT) has identified distinct sets of hematologic and biochemical predictors associated with relapse risk. For Kappa-restricted MM, the most important predictors—white blood cell count (WBC), lymphocyte count and percentage, red blood cell (RBC) count, and liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST])—reflect both immune status and potential organ function interplay relevant to disease biology and prognosis. Elevated or altered lymphocyte populations might indicate tumor-immune interactions influencing relapse, consistent with prior evidence linking lymphocyte metrics to survival outcomes in MM (Palumbo et al., 2011; Paiva et al., 2015). The inclusion of liver enzymes may reflect systemic inflammation or subclinical organ involvement; however, their direct mechanistic role warrants further investigation.

In Lambda-restricted MM patients, the top predictors include lymphocyte percentage, erythrocyte indices such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW) coefficient of variation percentage, ALT, and sodium. Although these markers differ somewhat from those identified in Kappa-restricted patients, they similarly emphasize immune cell proportions and red cell morphology, which have been variably associated with prognosis in hematologic malignancies (Wan et al., 2019; Zhao et al., 2020). Of note, the Lambda-restricted analysis is limited by a small sample size and low relapse incidence, which may reduce the reliability and generalizability of variable importance rankings in this subgroup.

These findings suggest subtype-specific baseline hematologic and biochemical profiles predictive of relapse risk in MM that could aid early risk stratification prior to ASCT. However, given the limited Lambda-restricted cohort and reliance on single-center data, validation in larger, independent cohorts is imperative. Moreover, integrating these laboratory variables with established clinical and molecular prognostic factors (such as cytogenetics and minimal residual disease status) could enhance predictive accuracy (Munshi et al., 2017).

FUTURE DIRECTIONS

- **Validation in Larger Cohorts**
  - Conduct prospective studies with increased sample sizes, especially for Lambda-restricted MM patients, to confirm the predictive value of the identified baseline CBC and CMP variables for relapse risk post-ASCT.
- **Integrative Prognostic Modeling**
  - Combine these laboratory predictors with established clinical, cytogenetic, and molecular markers (e.g., cytogenetic risk stratification, minimal residual disease status) to develop comprehensive, multimodal relapse prediction models.
- **Exploration of Erythrocyte Indices**
  - Study alterations in red blood cell parameters (MCV, MCH, RDW) in MM patients to assess their relationship with disease progression.
- **Application of Advanced Machine Learning:**
  - Utilize more complex to improve predictive accuracy and uncover novel biomarkers of relapse.
- **Development of Clinical Decision Support Tools**
  - Translate predictive models into user-friendly platforms for individualized risk assessment and treatment planning in ASCT-eligible MM patients.

References

Anderson KC, et al. Immunotherapies for multiple myeloma. Nat Rev Clin Oncol. 2020;17(9):509–526.
Kumar SK, et al. Multiple myeloma. Nat Rev Dis Primers. 2017;3:17046.
Kyle RA, Rajkumar SV. Multiple myeloma. Blood. 2008;111(6):2962-2972.
Ludwig H, et al. Current concepts in the diagnosis and management of multiple myeloma. Nat Rev Clin Oncol. 2019;16(3):139-154.
Munshi NC, et al. CAR T-cell therapy for multiple myeloma: where are we now? Nat Rev Clin Oncol. 2021;18(5):271-274.
Palumbo A, et al. Revised International Staging System for Multiple Myeloma. J Clin Oncol. 2015;33(26):2863-2869.
Paiva, B., et al. (2015). "Minimal residual disease monitoring in multiple myeloma: the new standard for hematologic malignancies." *Leukemia*, 29(10), 2119-2128.
Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk stratification and management. Am J Hematol. 2020;95(5):548-567.
Wan, T., et al. (2019). "Red blood cell distribution width as a prognostic factor in hematologic malignancies: a systematic review and meta-analysis." *Cancer Medicine*, 8(14), 6359-6367.
Zhao, D., et al. (2020). "Prognostic value of lymphocyte count and lymphocyte-to-monocyte ratio in patients with multiple myeloma: A systematic review and meta-analysis." *Journal of Clinical Laboratory Analysis*, 34(6), e23261.

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