KENNESAW STATE UNIVERSITY
COLLEGE OF COMPUTING AND SOFTWARE ENGINEERING
*School of Data Science and Analytics*

HEALTH ECONOMICS AND OUTCOMES RESEARCH:

# Multiple Myeloma, where are you hiding?

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## INTRODUCTION

Multiple Myeloma is a rare form of bone marrow cancer where plasma cells accumulate in your blood stream attacking your skeletal system and nervous system, as well as your kidneys. This disease has been known to primarily affect males and more specifically African American males. In the early years of Multiple Myeloma's diagnosis, the disease was termed a death sentence by various physicians. However, in recent years, treatments have been developed to prolong the quality of life of individuals living with this disease.

Using a study of 203 Multiple Myeloma patients from Algeria diagnosed during the period of 2008-2019, specific biomarkers were sought to predict the most aggressive stage of Multiple Myeloma (Stage 3). Then using the concepts of health economics and outcomes research, the cost comparisons were made between the biomarkers that predict Multiple Myeloma versus the definitive diagnostic test of a bone marrow biopsy.

To measure the effects of Multiple Myeloma on the kidneys, the blood markers of kidney stress were investigated: Creatinine Clearance, Blood Urea Nitrogen (BUN), and Proteinuria. In addition, the presence of bone lesions and the diagnosis stage of Multiple Myeloma were noted. Actions that reduce kidney stress as well as strengthen bones were researched to determine ways to prolong the patient's quality of life with the disease.

Twenty-one variables were considered as predictors for Multiple Myeloma.

- Mean Corpuscular Hemoglobin Concentration (MCHC)
- Albumin (alb)
- Prothrombin (TP)
- Creatinine Clearance (clair_creat)
- Hemoglobin (HGB )
- White Blood Cells (WBC)
- Mean Corpuscular Volume (MCV)
- Hematocrit (HCT)
- Sedimentation rate (VS)
- Potassium (k)
- Calcium (ca)
- Sodium (na)
- Blood Urea Nitrogen (BUN)
- Proteinuria (24h_prot)
- Osteolytic Lesions (ost_les)
- High Blood Pressure (HBP)
- Diabetes (diabete)
- Tobacco Use (tobacco)
- Chronic Diseases (chron_disea)
- Anemia
- Multiple Myeloma Stage

## METHODS

***Logistic Regression*** was used to determine whether Multiple Myeloma Stage 3 can be predicted by 21 blood tests including the significant predictors: MCHC, Creatinine Clearance, and Albumin.

***Odds-Ratio Table*** was used to calculate the relationship between the predictor variables and the likelihood of a Multiple Myeloma patient having Stage 3.

***ROC Curve*** displays the probability of distinguishing the chances of a patient having Stage 3 Multiple Myeloma vs having Stage 1 or 2.

***Welch ANOVA Test on Ranks*** for heterogeneous and non-normal data was used to determine whether the Multiple Myeloma Stages predicted the patient's median MCHC.

***Levene Test*** was used to determine MCHC level variability for the different stages of Multiple Myeloma.

***Two-mean t-Test*** was used to determine if Creatinine Clearance can be predicted by High Blood Pressure.

***Wilcoxon Rank Sum Test*** was used to determine if the Proteinuria (presence of protein in the urine) predicts Blood Urea Nitrogen Levels.

**Chi-Square Test of Independence** was used to determine whether a relationship exists between (1) Osteolytic Lesions and (2) Stage of Multiple Myeloma.

**LinkedIn** | **GitHub CODE**

Table 1. Parameter Estimates for Best Predictor Variables of Stage 3 Multiple Myeloma

| Analysis of Maximum Likelihood Estimates | | | | | |
|---|---|---|---|---|---|
| Parameter | DF | Estimate | Standard Error | Wald Chi-Square | Pr > ChiSq |
| Intercept | 1 | -11.3985 | 3.5854 | 10.1071 | 0.0015 |
| MCHC | 1 | 0.2412 | 0.1030 | 5.4870 | 0.0192 |
| Clair_creat | 1 | 0.0103 | 0.00542 | 3.5912 | 0.0581 |
| Alb | 1 | 0.0440 | 0.0278 | 2.5046 | 0.1135 |

Table 2. Odds Ratio Estimates for Each Variable in the Logistic Regression Model

| Odds Ratio Estimates | | | |
|---|---|---|---|
| Effect | Point Estimate | 95% Wald Confidence Limits | |
| MCHC | 1.273 | 1.040 | 1.557 |
| Clair_creat | 1.010 | 1.000 | 1.021 |
| Alb | 1.045 | 0.990 | 1.104 |

Figure 2. ROC Curve for the Best Model

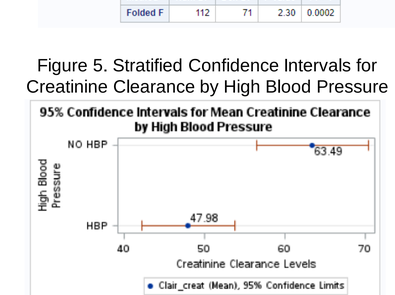
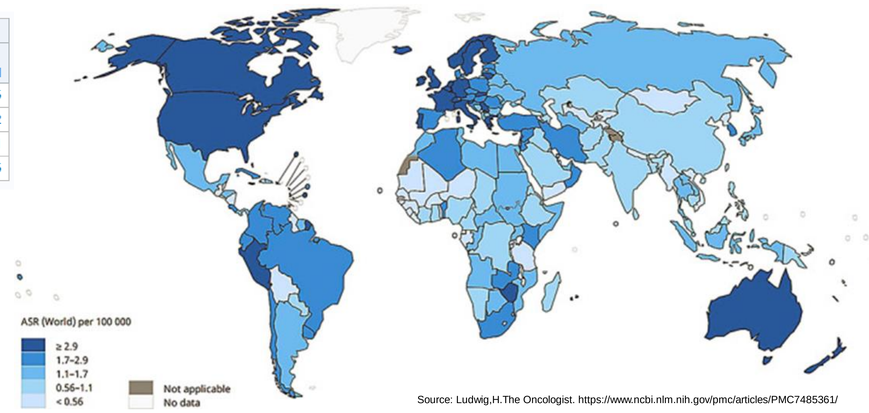



Figure 1. Multiple Myeloma Global Incidence Rate




Source: Ludwig,H.The Oncologist. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7485361/

Table 3. Welch ANOVA Test on MCHC Ranks by Multiple Myeloma Stage

The GLM Procedure

| Welch's ANOVA for MCHC_RANKS | | | |
|---|---|---|---|
| Source | DF | F Value | Pr > F |
| Multiple Myeloma Sta | 2.0000 | 4.38 | 0.0207 |
| Error | 32.7101 | | |

Figure 3. MCHC Ranks by Multiple Myeloma Stage

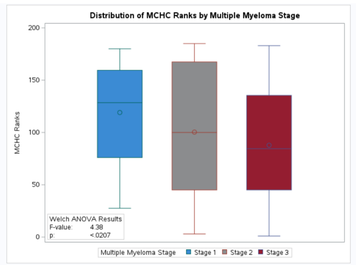



Table 4. Levene Test on MCHC by Multiple Myeloma Stage

| Levene's Test for Homogeneity of MCHC Variance ANOVA of Squared Deviations from Group Means | | | | | |
|---|---|---|---|---|---|
| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
| Multiple Myeloma Sta | 2 | 425.3 | 212.6 | 6.11 | 0.0027 |
| Error | 182 | 6335.7 | 34.8115 | | |

Figure 4. MCHC by Multiple Myeloma Stage

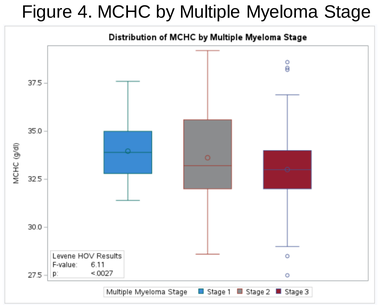



Table 5. T-Test for Creatinine Clearance based on Whether the Patient has High Blood Pressure

The TTEST Procedure

Variable: Clair_creat

| HBP | Method | N | Mean | Std Dev | Std Err | Minimum | Maximum |
|---|---|---|---|---|---|---|---|
| NO HBP | | 113 | 63.4883 | 37.3780 | 3.5162 | 0.4900 | 260.4 |
| HBP | | 72 | 47.9800 | 24.6237 | 2.9019 | 2.4700 | 95.4600 |
| Diff (1-2) | Pooled | | 15.5083 | 33.0198 | 4.9791 | | |
| Diff (1-2) | Satterthwaite | | 15.5083 | | 4.5591 | | |

| HBP | Method | Mean | 95% CL Mean | | Std Dev | 95% CL Std Dev | |
|---|---|---|---|---|---|---|---|
| NO HBP | | 63.4883 | 56.5214 | 70.4553 | 37.3780 | 33.0585 | 43.0061 |
| HBP | | 47.9800 | 42.1937 | 53.7663 | 24.6237 | 21.1554 | 29.4630 |
| Diff (1-2) | Pooled | 15.5083 | 5.6844 | 25.3322 | 33.0198 | 29.9556 | 36.7878 |
| Diff (1-2) | Satterthwaite | 15.5083 | 6.5132 | 24.5035 | | | |

| Method | Variances | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|
| Pooled | Equal | 183 | 3.11 | 0.0021 |
| Satterthwaite | Unequal | 182.77 | 3.40 | 0.0008 |

| Equality of Variances | | | | |
|---|---|---|---|---|
| Method | Num DF | Den DF | F Value | Pr > F |
| Folded F | 112 | 71 | 2.30 | 0.0002 |

Figure 5. Stratified Confidence Intervals for Creatinine Clearance by High Blood Pressure




Table 6. Wilcoxon Rank Sum Test for BUN Levels based on Presence of Proteinuria

The NPAR1WAY Procedure

| Wilcoxon Scores (Rank Sums) for Variable BUN Classified by Variable 24h_prot | | | | | |
|---|---|---|---|---|---|
| 24h_prot | N | Sum of Scores | Expected Under H0 | Std Dev Under H0 | Mean Score |
| Present | 40 | 1482.50 | 1300.0 | 72.082955 | 37.062500 |
| Not Present | 24 | 597.50 | 780.0 | 72.082955 | 24.895833 |
| Average scores were used for ties. | | | | | |

| Wilcoxon Two-Sample Test | | | | | |
|---|---|---|---|---|---|
| | | | | t Approximation | |
| Statistic | Z | Pr < Z | Pr > \|Z\| | Pr < Z | Pr > \|Z\| |
| 597.5000 | -2.5249 | 0.0058 | 0.0116 | 0.0071 | 0.0141 |
| Z includes a continuity correction of 0.5. | | | | | |

Figure 6. Stratified Boxplots for BUN by Presence of Protein in the Urine

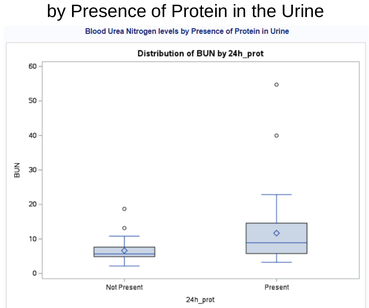
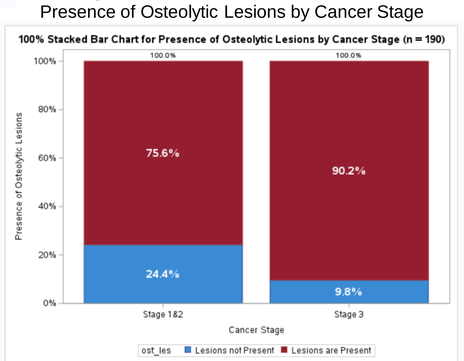



Table 7. Chi Square Test of Osteolytic Lesions by Multiple Myeloma Stage

Statistics for Table of ost_les by Multiple Myeloma Stage

| Statistic | DF | Value | Prob |
|---|---|---|---|
| Chi-Square | 1 | 5.6697 | 0.0173 |
| Likelihood Ratio Chi-Square | 1 | 5.0975 | 0.0240 |
| Continuity Adj. Chi-Square | 1 | 4.4797 | 0.0343 |
| Mantel-Haenszel Chi-Square | 1 | 5.6351 | 0.0176 |
| Phi Coefficient | | 0.1859 | |
| Contingency Coefficient | | 0.1828 | |
| Cramer's V | | 0.1859 | |

Figure 7. 100% Stacked Bar Charts for Presence of Osteolytic Lesions by Cancer Stage




## RESULTS

**LOGISTIC REGRESSION:** In Table 1, three variables: MCHC, Creatinine Clearance, and Albumin are in the best stepwise model. Creatinine Clearance and Albumin are retained in the best model because of their clinical importance, not because of their p-value.

**ROC CURVE:** In Figure 2, the ROC Curve displays the concordance index of .6543, which means that the model is able to distinguish 65.43% of the time between whether patients have Stage 3 versus Stage 1 and 2.

**LOGISTIC BETA COEFFICIENTS:** Table 1 shows the best predictors of Stage 3 Multiple Myeloma. Creatinine Clearance and Albumin are retained in the best model because of their clinical importance. By exponentiating the coefficients, the relationships of the predictors with Stage 3 Multiple Myeloma are discovered for each variable in the presence of the other two variables in the model:

- **MCHC:** The odds of having Stage 3 Multiple Myeloma increase 1.27 times for each one g/dL decrease in MCHC. Lower patient MCHC levels are more indicative of them having Stage 3 Multiple Myeloma.
- **Creatinine Clearance:** The odds of having Stage 3 Multiple Myeloma increase 1.01 times for each one ml/min decrease in Creatinine Clearance.
- **Albumin:** The odds of having Stage 3 Multiple Myeloma increase 1.04 times for each one g/dL decrease in Albumin.

**COST SAVINGS:** Using the global incidence rate of 2.9 people per 100,000 in Figure 1 paired with the Algerian population size of 44.9 million, we expect that approximately 1,302 Algerians have Multiple Myeloma. Using MCHC as a highly predictive, inexpensive, and non-invasive biomarker, fewer people could be subjected to the bone marrow biopsy surgery saving 235,147 Algerian dinar ($1734 USD) per person if their MCHC does not warrant a biopsy.

**MULTIPLE MYELOMA STAGE PREDICTS MCHC VARIABILITY:** The Levene Test in Table 4 shows a significant difference in the variability of the MCHC blood levels for patients with Stage 1 Multiple Myeloma. The MCHC blood levels for Stage 1 are more consistent than for other stages.

**MCHC LEVELS DEPEND ON MULTIPLE MYELOMA STAGE:** In Table 3 the MCHC blood markers were not normal and not homogeneous, so the Welch Test on Ranks was used to show that the median MCHC levels tend to be lower for patients with Stage 3 and Stage 2. This is also shown with the stratified box plots in Figure 3.

**HIGH BLOOD PRESSURE PREDICTS CREATININE CLEARANCE:** Table 5 displays the Two-mean t-Test results, which are that there is a significant difference in a multiple myeloma patient's creatinine clearance based on whether the patient has high blood pressure. The stratified confidence intervals in Figure 5 show that the creatinine clearance is higher for patients without high blood pressure.

**PROTEINURIA PRESENCE PREDICTS BUN LEVELS:** In Table 6, the Wilcoxon Rank Sum Test shows that the mean score BUN levels are significantly higher for patients with the presence of protein in their urine. Figure 6 displays the original BUN scores, not ranks. The BUN levels are higher for patients with the presence of protein in their urine.

**OSTEOLYTIC LESIONS PREDICTS MULTIPLE MYELOMA STAGE:** The Chi Square Test in Table 7 shows a significant relationship between the presence of Osteolytic Lesions and whether the patient has Stage 3 versus Stage 1 and 2. Figure 7 shows that a higher percent of lesions are associated with Stage 3 Multiple Myeloma.

## RECOMMENDED ACTIONS

To help support kidney function as long as possible:
- Lower your blood pressure by (1) reducing your salt intake, (2) including potassium in your diet, and (3) lowering your alcohol consumption.
- Cut back on protein to lower the risk of having protein in your urine.

To help strengthen your bones:
- Get regular exercise.
- Take vitamin D supplements.

To raise MCHC Levels:
- Consume iron rich foods.
- Include vitamin B12 and folate as well as Vitamin A and C to help with your iron absorption.

Building your support system to include friends and family while living with this disease helps you to gain the strength to keep living as normally as you can to prolong the longevity of your life.