**Shot Communication**
Volume 11:2, 2020
DOI: 10.37421/jbmbs.2020.11.439

Journal of
Biometrics & Biostatistics

ISSN: 2155-6180 Open Access

# Short Prognostic APP for Multiple Myeloma

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## Abstract

We briefly describe methods pertaining to the development of a prognostic tool for Multiple Myeloma and direct readers to detail published clinical and methods manuscripts. This short communication provides a simpler combined version of nomograms for predicting early and late survival in the context of Multiple Myeloma.

**Keywords:** Prognostic model • Nomogram • Multiple myeloma

## Introduction

A simplified app for small computing devices, which is being considered for possible development with a Bristol Myers Squibb patent pending [1], uses the detailed early and late survival prognostic nomograms in Terebelo et al. [2,3], also in our patent specifications in Srinivasan and Elion-Mboussa [1], is described here. The methods for the predictions are published as well in a study [4]. In the Terebelo publications a study [1], 7 attributes were predictive of early mortality 10 attributes were predictive of late mortality. The two sets were overlapping, leading to a total of 11 attributes in our simple combined version in Figure 1. The short version of the prediction nomogram provides the early death prediction and the estimated probabilities of survival beyond 2, 3, 4 and 5 years. The reported probabilities are identical to those deriving from the early and late prediction nomogram when information on all attributes of a patient are available at diagnosis. The short version allows a "Not Provided" alternative for the attributes and re-computes predictions assuming equal likelihood of the patient having each of the levels of the attribute for which information is unavailable. The screen-shot of the APP in the figure below, for instance, has a prediction for a patient for whom EQ-5D mobility information and DEL 17p cytogenetic abnormality is not available. The patient presents with ISS stage III disease, thrombocytopenia, and a history of diabetes. Probabilities of surviving more than two years, given standard of care like those available to the patients in the registry, is estimated at about 40%. It is noted that the predictions of such probabilities are aggregate assessments. The prediction is meaningful when we consider, say, 100 patients having the same patient profile. Amongst those about 40 will survive beyond 2 years, and about 15 beyond 4 years, with 95% confidence range of about 30 to 50 surviving beyond 2 years, and about 8 to 22 surviving beyond 4 years. These predictions, as noted earlier, presume standard of care like those available to the patients in the registry, during the registry follow up period. The utility of the prediction matrix tool in Srinivasan et al. [4] and this short form app is in providing a differential prognosis at diagnosis and can possibly have the patient and provider consider therapy alternatives to improve outcomes, or address drug toxicity through dose modifications or longer interruptions when the patient's prognosis permits (Figure 1).

| Attributes | User Inputs (select category from drop down menu) |
|---|---|
| Age Group | <=75 |
| Mobility | Not provided |
| Del 17P | Not provided |
| ISS Stage | III |
| Platelet Count X10^9/L | <=150 |
| Solitary Plasmacytoma | Yes |
| ECOG Status | <2 |
| History of Diabetes | Yes |
| Serum Creatinine in mg/DL | <=2 |
| Triplet Therapy at Induction | No |
| Hypertension History | No |

| Predicted Probabilities | | |
|---|---|---|
| Death within 180 days | | 12% |
| Survival | > 2 years | 40% |
| | > 3 years | 25% |
| | > 4 years | 15% |
| | > 5 years | 10% |

**Figure 1.** Prediction Matrices Short App Version.

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**Received** 06 March 2020; **Accepted** 08 April 2020; **Published** 15 April 2020

## Additional Details on Methods

The methods to derive the logistic and survival-based models from which the predictions are obtained, are described in [4]. We treated early mortality (within 6 months) as a discrete endpoint and used logistic models for predicting this. For long term survival, we used Cox regression models. Briefly, analysis methods in both contexts used an initial screening step, and modeling and variable selection using multiple imputation [5] to address missing data. Predictions from the logistic and Cox models were placed in a heat-map prediction matrix. The prediction matrix placed less favorable outcomes in the bottom left corner and more favorable outcomes towards the top right corner of the matrix. The predictive attributes at diagnosis were placed in the column and row headers of the matrix to help direct the user of the nomograms navigate to the cell containing the prediction. The nomogram format, while requiring some effort in navigation to a cell, do bring out visually, a quick read to a user of attributes and combinations which we have assessed as likely to lead to poor or good prognosis. This effect was achieved through color shading as well as the placement and ordering of the variables along rows and columns depending on their relative effect on survival. The short calculator lacks the quick holistic visual read of the prediction model. It extracts information in one panel which however, is easier on the user. It has the additional functionality of estimating survival probabilities when the user does not have information on one or more attributes in the calculator. A excel version of the calculator is available in supplementary materials as Supplementary for Apps for Prediction Matrix. xlsx.(Now Attached as Appendix A)

The predictions were based on analyses of the first cohort of the 1493 enrolled subjects in the MM-Connect newly diagnosed multiple myeloma registry. Results have been internally and externally validated using the Harrel's Concordance Index [6], which is the probability that a randomly selected pair of patients, one with a poorer survival outcome than the other, will be correctly differentially identified. This probability was around 70% for the internal and external validations for the early and late mortality models. An index well above 50% is considered clinically useful. Statistically significant predictors of death within 180 days were the EQ5D Mobility Item, ECOG Performance Status ≥2, Platelet Count ($\times 10^9$/L) ≤150, Hypertension History, ISS staging of III vs. I or II, Age > 75 years, and Serum Creatinine (mg/dL) > 2. The predictors of survival beyond 3 years did not include Hypertension History and additionally included Del 17P, Solitary Plasmacytoma, Diabetes History and Triplet therapy at induction (Yes vs.

No). ISS Stage was used in the model in lieu of Albumin (≤3.5 vs. >3.5 g/dL) and Beta 2 Microglobulin (≥5.5 mg/L). ISS Staging and cytogenetics were used in lieu of IMWG risk.

Other factors considered but screened out in univariate screening or in multivariate model selection were Body mass index, History of VTE, T(4;14), History of MGUS, History of Smoldering Multiple Myeloma, LDH (≤300 vs. >300 g/dL), IgG (<5 vs. ≥5 g/dL), Myeloma Bone Involvement, Hypercalcemia (Serum Calcium ≥ 11.5 mg/dL), Anemia (Hemoglobin < 10 g/dL or >2 below LLN), ANC ≤ 1.5 × $10^9$/L and Self-care from EQ5D.

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**How to cite this article:** Shankar Srinivasan and Lihua Yue. Short Prognostic APP for Multiple Myeloma. *J Biom Biostat* 11 (2020) doi: 10.37421/jbmbs.2020.11.439