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High Risk Multiple Myeloma Cases Are Identified In An MMRC Led Study By The SKY92 Gene Signature (MMprofiler)

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Introduction

Multiple Myeloma is not a single disease. There is increasing support for risk classification in combination with treatment decision making because of its impact on clinical outcomes. Here we demonstrate additional evidence of the prognostic value of SKY92 signature, an established genetic marker of high risk Multiple Myeloma in a data evaluation study of a multicenter collection of samples with undisclosed treatments.

Materials and Methods

A public, 114 cases GEP dataset (MMRC, MMGI portal) of untreated Multiple Myeloma was used for SKY92 [1], UAMS70 [2], IFM15 [3], Centrosome Index (CI) [4], Proliferation index (PI) [5], and Cancer Testis Antigen (CTA) [6] signature high risk prediction. In collaboration with MMRC, OS data (with a minimum of at least 2 year follow-up) was collected for 91 of those 114 cases for the purpose of this analysis. Gene expression data had been obtained from CD138-positive plasma cells, total RNA extraction and subsequent gene expression profiling on Affymetrix HG-U133 Plus2.0 GeneChips. The 91 cases represented 9 different clinical sites. Baseline characteristics in Table 1.

Results

SKY92 resulted in 19 high risk (20.9%) versus 72 standard risk (79.1%) cases in the unselected 91 case-cohort.. The OS analysis (Figure 1A) shows that the high risk cases have significantly shorter survival (Hazard Ratio 8.2, p = 1.2 x 10-8). Table 1 shows that high risk cases had more elevated B2M (26.3% vs 13.9%), more low albumin (26.3% vs 16.7%) and more high creatinine (26.3% vs 11.0%). There was no difference between high and standard risk groups in diagnosis dates (not shown). Cause of the 16 (84.2%) deaths among the high risk cases, and 21 (29.1%) deaths among the standard risk cases indicates that high risk contains less disease progression deaths (57.1% vs 31.3%), and more unknown deaths (56.3% vs 23.8%). Five other signatures were also applied (Figure 1), revealing HRs ranging from 1.9 to 4.3. Signatures differ in the cases that are identified as high risk, see Figure 2. All but the Centrosome Index reached univariate significance and only SKY92 and IFM15 reached multivariate significance (with all six signatures), of HR 6.4 and 2.3, respectively (see Table 2).

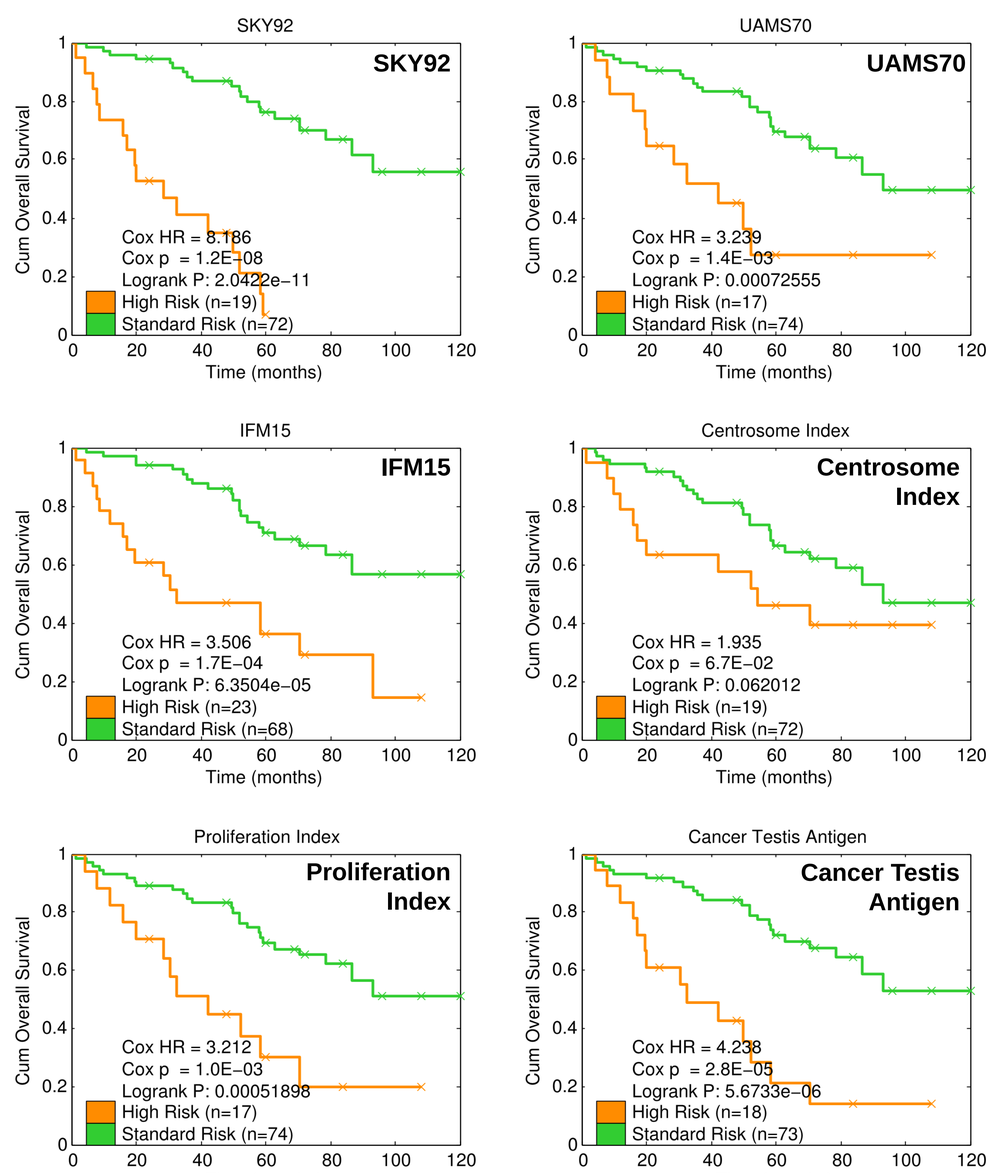

Figure 1. Kaplan-Meier curves for six classifiers;

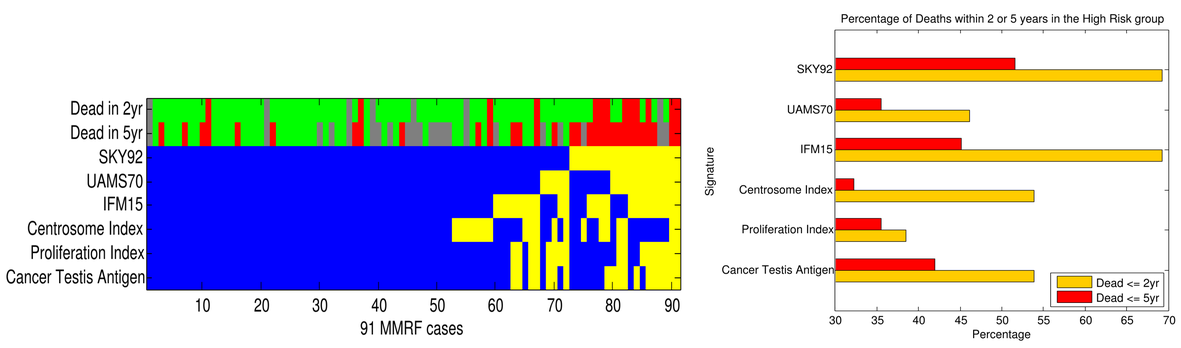

Figure 2. A) Overlap between High Risk cases (yellow) as classified by the various classifiers across all 91 cases analyzed. Red, deceased; Grey, censored, Green, alive. B) Percentage of the deaths at 2y and at 5y predicted by each of the six classifiers.

Table 1. Baseline patients' characteristics.

Characteristic		SKY92 Standard Risk	SKY92 High Risk
SKY92 results	n (% of total)	72 (79.1)	19 (20.9)
Deaths	Within 2 years; n (% of total)	4 (30.8)	9 (69.2)
	All; n (% of total)	21 (56.8)	16 (43.2)
Cause of Death	Progression; n (% of deaths)	12 (57.1)	5 (31.3)
	Other; n (% of deaths)	4 (19.0)	2 (12.5)
	Unknown; n (% of deaths)	5 (23.8)	9 (56.3)
Age [yrs]	Mean (range)	62.5 (36 - 86)	67.1 (50 - 89)
Sex	Male; n (%)	46 (63.9)	11 (57.9)
B2M level [mg/L]	> 3.5; n (%)	10 (13.9)	5 (26.3)
	Mean (range)	3.4 (0.02 - 11.3)	3.8 (0.05 - 9.2)
Serum albumin [g/dL]	< 3.5; n (%)	12 (16.7)	5 (26.3)
	Mean (range)	3.9 (2.3 - 5.4)	3.7 (2.7 - 4.6)
	Data missing; n (%)	5 (6.9)	1 (5.3)
ISS (% calculated excl. n.d. cases)	I; n (%)	33 (55.9)	6 (42.9)
	II; n (%)	16 (27.1)	3 (21.4)
	III; n (%)	10 (16.9)	5 (35.7)
Serum creatinine [mg/dL]	> 2; n (%)	8 (11.0)	5 (26.3)
	Mean (range)	1.27 (0.7 - 10)	1.89 (0.6 - 10.9)
M-spike [g/dL]	Mean (range)	3.1 (0.13 - 7.3)	2.9 (0 - 6.5)

Table 2. Multivariate Cox Proportional Hazards Model

			95% CI	
Signature	HR	p	lower	upper
SKY92*	**6.5958**	**1.40E-05**	2.8161	15.4483
UAMS70	0.5704	0.3849	0.1608	2.0237
IFM15	1.7653	0.1730	0.7795	3.9980
Centrosome Index	1.1753	0.6862	0.5368	2.5735
Proliferation Index	1.1361	0.8559	0.2866	4.5032
Cancer Testis Antigen	2.3226	0.2174	0.6087	8.8616

***Significant**

Conclusions

The SKY92 classifier identified 21% (19/91) of the cases predicting 69% of all deaths within 2 years, recapitulating earlier results [1]. In summary, the SKY92 has a higher HR compared with the other signatures, and is the only significant signature in multivariate analyses.

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