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| **Number** | **scRNA-seq dataset** | **Bulk dataset** | **MAD Metric** | **SDES Metric** | **MiRNA Metric** | **MiRNA + SDES Metric** | **MiRNA + MAD Metric** | **MAD Metric + Tumor Stage** | **SDES Metric + Tumor Stage** | **MiRNA Metric + Tumor Stage** | **MiRNA + SDES Metric + Tumor stage** | **MAD Metric + Tumor Stage + N Stage** | **SDES Metric + Tumor Stage + N Stage** | **MiRNA Metric + Tumor Stage + N Stage** | **MiRNA + SDES Metric + Tumor Stage + N Stage** | **KM p-value from MAD** | **KM p-value from SDES** | **KM p-value from MiRNA** | **Km p-value from MiRNA + SDES** | **MiRNA + SDES Significant KM?** | **Km p-value from SDES + Tumor Stage + N Stage** | **Km p-value from MiRNA + Tumor Stage + N Stage** | **Km p-value from MiRNA + SDES + Tumor Stage + N Stage** | **MiRNA + SDES + Tumor Stage + N Stage Significant KM?** | **Does Tumor Stage + N Stage Information Improve KM separation?** |
| 1. | GSE81861\_CRC\_tumor | TCGA-COAD | 0.5845 (0.02282) [15] | 0.6048 (0.02239) [5] | 0.6530 (0.02389) [27] | 0.6393 (0.02233) [216] | 0.6536 (0.01900) [114] | 0.6453 (0.02845) [28] | 0.6844 (0.02101) [6] | 0.6972 (0.02698) [33] | 0.7012 (0.02854) [31] | 0.6860 (0.01953) [3] | 0.7111 (0.01852) [7] | 0.7077 (0.01881) [34] | 0.7132 (0.01908) [31] | 3.805e-01 | 6.675e-04 | 3.805e-01 | 6.675e-04 | Y | 8.552e-06 | 3.253e-02 | 6.147e-08 | Y | Y |
| 2. | GSE81861\_Cell\_line\_hct116 | TCGA-COAD | 0.6095 (0.02860) [18] | 0.6033 (0.02201) [17] | 0.6006 (0.02415) [21] | 0.6405 (0.02450) [17] | 0.6097 (0.02640) [29] | 0.6871 (0.03665) [18] | 0.6723 (0.01432) [26] | 0.6812 (0.02436) [12] | 0.7017 (0.02945) [13] | 0.7054 (0.02255) [5] | 0.7012 (0.01887) [7] | 0.6956 (0.01771) [13] | 0.7086 (0.01757) [7] | 7.115e-02 | 1.322e-02 | 7.115e-02 | 1.322e-02 | Y | 7.643e-06 | 1.09e-01 | 3.209e-06 | Y | Y |
| 3. | GSM1599500\_K562 | TCGA-DLBC | 0.5286 (0.05483) [2] | 0.4524 (0.13398) [18] | 0.4905 (0.06461) [13] | 0.7036 (0.0284) [21] | 0.6024 (0.10184) [7] | NA | NA | NA | NA | NA | NA | NA | NA | 1.827e-01 | 2.965e-02 | 1.827e-01 | 2.965e-02 | Y | NA | NA | NA | NA | NA |
| 4. | GSE57872\_GBM | TCGA-GBM | 0.6394 (0.02363) [36] | 0.6119 (0.02084) [155] | 0.6162 (0.02152) [18] | 0.6265 (0.02039) [9] |  | NA | NA | NA | NA | NA | NA | NA | NA | 1.735e-01 | 5.871e-03 | 1.735e-01 | 5.871e-03 | Y | NA | NA | NA | NA | NA |
| 5. | GSE81861\_Cell\_line\_a549 | TCGA-LUAD | 0.6264 (0.04558) [98] | 0.5277 (0.04795) [52] | 0.6236 (0.05074) [2] | 0.6041 (0.02826) [199] |  | 0.6643 (0.03068) [125] | 0.4899 (0.03839) [47] | 0.6297 (0.04861) [189] | 0.6312 (0.05185) [200] | 0.6711 (0.03123) [133] | 0.5245 (0.03584) [38] | 0.6272 (0.03658) [58] | 0.6335 (0.05608) [198] | 2.767e-01 | 4.647e-02 | 2.767e-01 | 4.647e-02 | Y (but low risk performs worse than high risk) | 5.295e-01 | 6.693e-01 | 9.54e-03 but low risk performs worse than high risk | Y (but low risk performs worse than high risk) | Y (but low risk performs worse than high risk) |
| 6. | GSE69405\_PROCESSED\_GENE\_TPM\_ALL | TCGA-LUAD | 0.6321 (0.04074) [94] | 0.6194 (0.03758) [15] | 0.5930 (0.03443) [1] | 0.6194 (0.03758) [15] |  | 0.6374 (0.03704) [104] | 0.6159 (0.03242) [2] | 0.5930 (0.03443) [1] | 0.6159 (0.03242) [2] | 0.6375 (0.03701) [104] | 0.6137 (0.03191) [28] | 0.5917 (0.02658) [82] | 0.6137 (0.03191) [28] | 1.631e-01 | 5.911e-01 | Just one risk group (can’t calculate) | 3.282e-01 | N | 5.833e-01 | 5.76e-01 | 3.885e-02 | Y | Y |
| 7. | GSE81861\_CRC\_tumor | TCGA-READ | 0.6116 (0.05349) [14] | 0.5746 (0.07579) [2] | 0.6737 (0.04465) [45] | 0.6670 (0.05563) [42] | 0.6784 (0.05313) [52] | 0.6464 (0.07234) [3] | 0.5941 (0.04097) [58] | 0.6957 (0.05405) [49] | 0.7076 (0.06931) [53] | 0.6464 (0.07234) [3] | 0.5718 (0.02965) [73] | 0.6863 (0.07178) [61] | 0.7293 (0.05247) [59] | 2.759e-01 | 7.608e-01 | 2.759e-01 | 7.608e-01 | N | 2.842e-03 | 6.456e-01 | 2.842e-03 | Y | Y |
| 8. | GSE81861\_CRC\_tumor | TCGA-COAD + TCGA-READ | 0.6423 (0.02819) [124] | 0.5919 (0.03622) [22] | 0.6108 (0.02962) [290] | 0.6414 (0.01870) [265] | 0.6513 (0.02306) [153] | 0.6527 (0.02661) [2] | 0.6567 (0.02359) [125] | 0.6433 (0.02611) [7] | 0.6596 (0.01954) [198] | 0.6898 (0.02192) [3] | 0.6883 (0.02290) [3] | 0.6702 (0.02458) [5] | 0.6883 (0.02290) [3] | 3.506e-01 | 3.651e-02 | 3.506e-01 | 3.651e-02 | Y | 1.588e-08 | 1.588e-08 | 1.588e-08 | Y | Y |

NA means that no tumor stage or N stage information is available from TCGA for that dataset. The c-index and KM performance is based solely on gene signatures for these datasets. It appears that the SDES metric is the most important metric across datasets in regard to KM curve separation, but it is also clear that the MiRNA + SDES metric is the most important for the c-index performance. Given that we are looking for a comprehensive view of how both of these metrics can improve patient outcomes [especially in a big data, multi-variate model context] it is clear to me that our MiRNA metric provides meaningful new information for improving prediction when paired with the SDES metric. Each block of color is to delineate different conditions that I tested and how I assessed which metric ‘won’ for each dataset. The entries highlighted in green in each block had either the best c-index or KM value for that dataset across the different combinations of metrics.

For the red block our combined method has the highest c-index 4/7 times and our MiRNA metric has the highest c-index 1/7 times. The MAD metric has the highest c-index 2/7 times. Overall, our MiRNA metric or our combination metric have the highest c-index for 5/7 datasets (71.4%). Note, the red block contains no patient metadata like tumor stage or n stage included for either the c-index calculation or the KM curve p-values calculated in the purple block. It is based strictly on gene expression alone. In terms of KM p-values our combined method ties with the SDES method in all 7 datasets and is able to separate the survival in 6/7 (85.7%). Note, that the TCGA-LUAD dataset has separation of KM curves but the low-risk group performs worse than the high-risk group.

Despite this it is clear to me that we should be using the combination metric as we are using high dimensional data and the cox-model c-index is a much better metric to assess model performance in a large, multivariate analysis and we have clear improvements in c-index performance when using our MiRNA metric with the SDES metric.

We have improvement in KM curve separation when including tumor stage and N stage clinical information along with the gene signatures. It separates survival in all 5 relevant datasets including the renal cancer dataset which could not be separated by gene signatures alone. Note, it has the same issue with the lung cancer dataset that we had with strictly just gene signatures (of low-risk group performing worse than high risk group)