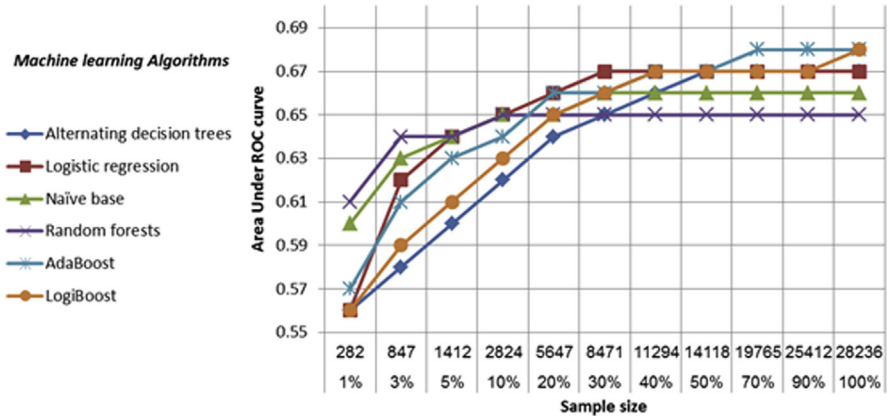

Figure 1. Predictive performance of TRM prediction models, adjusted for small size

100 TRM. A cohort of 28,236 acute leukemia, adult allogeneic HSCT recipients were analyzed. Twenty four variables were included. In the second phase, by applying a repetitive computerized simulation, factors necessary for optimal prediction were explored: algorithm type, size of data set, number of included variables, and performance in specific subpopulations. Models were assessed and compared on the basis of the area under the receiver operating characteristic curve (AUC).

We developed 6 ML based prediction models for day 100 TRM. Optimal AUCs ranged from 0.65-0.68. Predictive performance plateaued for a population size ranging from n=5647-8471, depending on the algorithm (Figure 1). A feature selection algorithm ranked variables according to importance. Provided with the ranked variable we data, discovered that a range of 6-12 ranked variables were necessary for optimal prediction, depending on the algorithm. Predictive performance of models developed for specific subpopulations ranged from an average of 0.59 to 0.67 for patient in second complete remission and patients receiving reduced intensity conditioning respectively.

In summary, we present a novel computational approach for prediction model development and analysis in the field of HSCT. Using data commonly collected on transplant patients, our simulation elucidates outcome prediction limiting factors. Regardless of the methodology applied, predictive performance converged when sampling more than 5000 patients. Few variables "carry the weight" with regard to predictive influence. Overall, the presented findings reveal a phenomenon of predictive saturation with data traditionally collected. Improving predictive performance will likely require additional types of input like genetic, biologic and procedural factors.

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Discovery Analysis of Associations Between MicroRNAs (MiRs) and Both Pre-Transplant Comorbidity Burden and Post-Transplant Mortality in Patients (Pts) with Acute Leukemia (AL) in Complete Remission (CR) Given Allogeneic Hematopoietic Cell Transplantation

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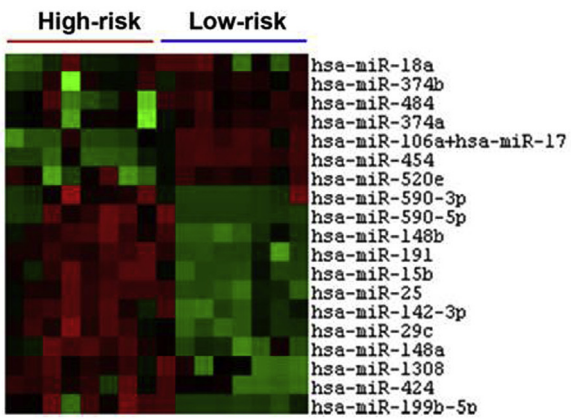
The HCT-comorbidity index (CI) was developed as a measure of health-status that could stratify risks of mortality after HCT. There is a great need for novel biomarkers that could explain the biologic link but also increase the objectivity of diagnosing pre-HCT comorbidities and increase the predictive power for post-HCT mortality. MiRs are a class of small non-coding RNAs (~22 nt) that negatively regulate gene expression. Studies have uncovered the functional role of miRs in diverse pathophysiological processes. Moreover, a single miR could be implicated in different pathological processes. To this end, we analyzed miRs as diagnostic for comorbidities before and as prognostic for mortality after HCT.

Peripheral blood mononuclear cell samples were previously collected from 36 pts within 30 days prior to HCT as a part of research repository. All samples were collected in EDTA tubes and processed and frozen at -80 Celsius degrees within 8 hours of draw. All pts were in CR before HCT. Low risk was defined as having HCTCI score of 0 before and surviving after HCT (median follow up 56 month, range 12.5-75.5), while high-risk pts had scores of 4-9 before HCT and none of them survived HCT (Table 1).

RNA was isolated from PBMC using previously described methods (Xie LN et al, Clinical Transplant. 2014; 28:314). For discovery of relevant miRs, we used NanoString nCounter miR assay as previously described (Knouf EC et al, 2013. PLoS ONE 8: e69630) comprising 654 endogenous miRs. Analysis of miR raw data was done using nSolver™ 2.0 Software (NanoString Technologies, Inc.) applying standard quality control tests. All samples contributed to the discovery analysis. MiRs

Table 1

Characteristics		%	
		Low risk (n=18)	High risk (n=18)
Donor	Related	17	28
	Unrelated	83	72
AL	Myeloid	78	67
	Lymphoid	22	33
CR#	1st	67	61
	2nd	33	39
Conditioning	High-dose	50	39
	Reduced-intensity	50	61



miR-	Fold change	P value
18a	-2.01	0.071
374b	-2.38	0.039
484	-1.59	0.085
374a	-1.62	0.058
106a + 17	-2.0	0.099
454	-2.38	0.039
520e	-2.72	0.064
590-3p	2.49	0.008
590-5p	4.69	0.047
148b	1.33	0.082
191	1.57	0.011
15b	1.5	0.0188
25	1.36	0.08
142-3p	1.81	0.05
29c	1.48	0.039
148a	1.47	0.051
1308	3.19	0.014
424	3.0	0.031
199b-5p	2.3	0.036

Figure 1.

were filtered to include only those expressed with at least 50 counts for the NanoString abundance analyses. MiR raw data was normalized using the geometric mean of top 100 miRs (probes with highest 100 counts) as recommended by the manufacturer. Fold change was calculated with partitioning by the low- *vs* high-risk groups computing two-tailed t-test on the log transformed normalized data that assumes unequal variance. We used p-value cut-off of <0.1 to identify relevant miRs. Heat-map analysis used z-score transformation on samples computing Spearman correlation of the median between samples.

Among 654 tested miRs, 7 were under-expressed and 12 were over-expressed among the high- *vs* low-risk group (Table provided with figure). Agglomerative cluster "heat-map" analysis of 16 samples representative of both groups is shown in Figure.

We identified a group of MiRs as biomarkers for pre-transplant relevant comorbidities and increased post-transplant mortality. Validation of findings and determination of gene associations in a larger dataset is under way.

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Outcomes of Allogeneic Stem Cell Transplantation for Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

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Introduction: Philadelphia chromosome (PH) positive (+) acute lymphoblastic leukemia (ALL) is incurable without undergoing allogeneic hematopoietic stem cell transplant (HCT). Ideally patients should be in complete remission (CR) prior to HCT without minimal residual disease (MRD). Center for International Blood and Marrow Research data shows that ALL patients $\geq$20 years of age receiving matched sibling HCT between 2001-2011, the 3-year survival probabilities were 53% $\pm$ 1%, 32% $\pm$ 2%, and 23% $\pm$ 2% for patients with early, intermediate, and advanced disease, respectively. Corresponding probabilities among the 3,929 recipients of unrelated donor HCT were 50% $\pm$ 1%, 34% $\pm$ 2%, and 18% $\pm$ 2%. Recognizing that patients with PH + ALL have aggressive disease we questioned if there were factors that would predict relapse or prevent relapse post HCT in this cohort.

Methods: The HCT database at Mayo Clinic Arizona was used to identify patients with Ph + ALL undergoing transplant from January 1994 through December 2013. 20 PH+ patients were identified. Demographic and HCT data were taken from this database. Data on tyrosine kinase inhibitor (TKI) use and chimerism were obtained retrospectively from the patient record.

Results: 6 (30%) patients relapsed and 5 died from their disease. 1 patient died from transplant related mortality. 5 year survival rate was 59.5%. Of the 6 patients who relapsed none were MRD positive pre HCT, 3 had 100% donor chimerism at day 100 and 3 started a TKI post HCT. The 3 who started a TKI did so at day 80, 169 and 172. Conditioning regimen for these 6 patients consisted of: Fludarabine/ Melphalan/Busulfan (2), Fludarabine/Melphalan (1), Etoposide/Cyclophosphamide/Total Body Irradiation (1) and Cyclophosphamide/Total Body Irradiation (1). At HCT 2 patients were in CR1, 1 in CR2 and 1 in CR3. 1 patient came to HCT in relapse but did not relapse after. 15 of the 20 patients were placed on a TKI post HCT. No statistically significant factor was detected to impact relapse or overall survival.

Discussion: PH + ALL is a disease with a poor prognosis. This study shows a 60% overall survival at 5 years post HCT which is better than has been reported. We had hypothesized that if patients were not started on a TKI, had PH + MRD pre or post HCT, did not reach 100% chimerism at day 100 or did not receive radiation as part of the conditioning regimen it would impact relapse. Though this is a small descriptive study it is notable that there were no trends observed. In the era where we have many TKIs to choose from perhaps our outcomes in PH positive ALL are improving. Future research should focus on conditioning regimen for ALL (full versus reduced intensity, radiation versus no radiation), optimal time to start a TKI post HCT and does MRD by PCR pre and post HCT matter. Certainly in this study of 20 patients none of these factors was statistically significant. Future study of a larger population would be prudent.

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Bendamustine-Brentuximab: Bridging to Transplant

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