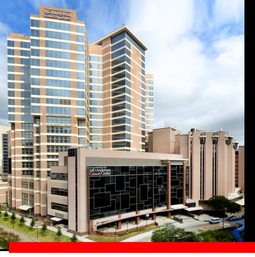

Prognostic Utility of Glycemic Trends in Patients with Hematologic Malignancy and Mucormycosis

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Background

- MCR is an uncommon but aggressive fungal infection in patients with HM and HSCT, and carries with it high morbidity and mortality in this population[1,2].
- In addition, MCR causes disease in patients with several other underlying predisposing conditions, especially diabetes mellitus (DM), diabetic ketoacidosis (DKA), penetrating trauma, and more recently patients with COVID-19 receiving glucocorticoid therapy.
- Research on the pathogenesis of MCR showed that impaired cellular immunity and conditions that that favor both fungal adhesion and invasion are critical, especially in patients with DKA.
- Similar pathways of pathogenesis may apply to non-diabetic patients who experience hyperglycemia from corticosteroid use[3].
- Differences in mortality have been demonstrated in previous studies based underlying disease, with patients for whom DM is the primary predisposing condition having more favorable prognosis compared to those with HMs or HSCT[4].
- However, little research exists exploring the interplay of predisposing factors in patients with both hyperglycemia and HM or HSCT.
- In this study, we sought to further elucidate the specific effects of hyperglycemia and the receipt of anti-hyperglycemic therapies on outcomes of MCR in the HM and HSCT populations

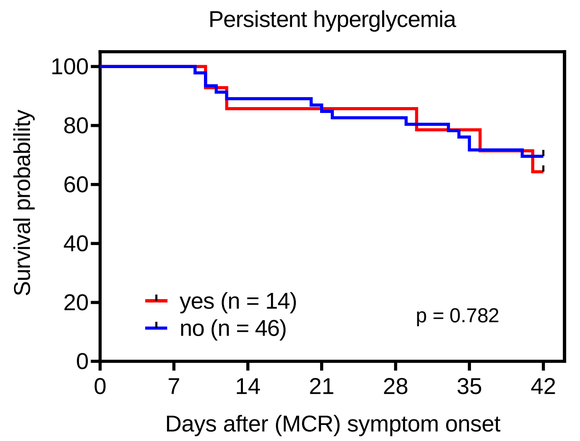
Methods

- **Design:** This was a retrospective cohort from MD Anderson Cancer Center, a 710-bed oncologic center located in Houston, TX
- **Inclusion Criteria:** Proven or probable MCR (EORTG/MSG criteria)[6].
- **Exclusion Criteria:** De novo infection or infection that started while on fluconazole prophylaxis, insufficient data on fasting sGL levels at time of diagnosis or at 28 days prior to diagnosis.
- **Data Collected:** Demographics, type and status of HM, HSCT status, presence and status of graft-versus host disease (GvHD), clinical presentation, absolute neutrophil count (ANC) at time of MCR diagnosis, mold-active prophylaxis and treatment regimens, surgical treatments for MCR, site/type of MCR and specific organism of MCR, immunosuppressive medications, history of DM, insulin and/or metformin prescription, serum fasting glucose levels (sGL) within 7 days of symptom onset and at 28 days prior to symptoms, ICU admission at diagnosis, and hospice care and mortality.
- **Definitions:** Neutropenia was defined as absolute neutrophil count (ANC) </= 500 cells/µL. Corticosteroid use was defined as prednisone 600 mg or dose-equivalent received in the 30 days preceding diagnosis of MCR. Persistent hyperglycemia was defined as having both an average fasting sGL >126 mg/dl in the five most recent measurement prior to symptom onset and a value of >126 for the fasting sGL closest to 28 days prior to symptom onset. Severe hyperglycemia was defined as any recorded fasting sGL > 180. Diagnosis of known DM was based on the patients' problem list and diagnoses in the EHR and in the most most recent discharge note prior to index admission and H+P at time of index admission.
- **Statistical Analyses:** The primary outcome was 42-day all-cause mortality from time of symptom onset. Categorical variables were compared by chi-squared test. Continuous variable were compared by Wilcoxon rank sum test. Univariate time-dependent survival analysis of the primary outcome was performed for the main variables of interest using Kaplan-Meier curves.
- Multivariate logistic regression analysis was used to identify independent risk factors for the primary outcome.

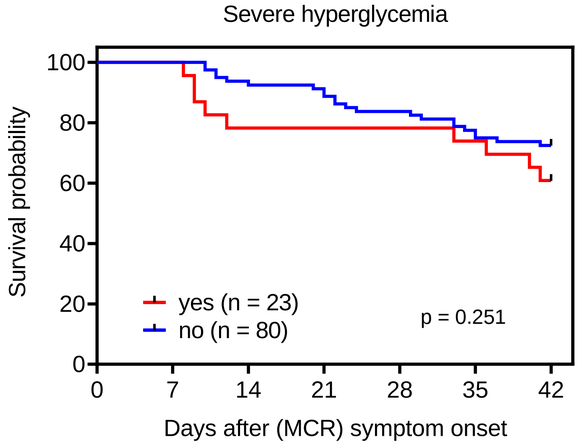
Table 1: Baseline Cohort Characteristics

Characteristics	All patients (n=103)
Age (years), median (range)	52 (18-76)
Sex, male	67 (65)
Race	
White	72 (70)
Balck	11 (11)
Asian	6 (6)
Hispanic	14 (14)
Type of cancer	
Lymph/MM	11 (11)
Leuk/MDS	92 (89)
Status of cancer	
Remission	23 (22)
Active	80 (78)
HCT	50 (49)
Allo HCT	50/50 (100)
Type of allo HCT	
Matched related	20/50 (40)
Matched unrelated	24/50 (48)
Mismatched related	2/50 (4)
Mismatched unrelated	1/50 (2)
Haploidentical	2/50 (4)
Double cord	1/50 (2)
GVHD	40/50 (80)
Status of GVHD	
Active	23/40 (58)
Chronic	17/40 (43)
HCT within 1 year prior to treatment	38 (37)
Surgery	46 (45)
Steroid use pred≥ 600mg in 1 month	36 (35)
Duration of ANC< 500 prior to collect date (days), medain (IQR)	13 (0-37)
ANC at diagnosis, median (IQR)	40 (0-2660)
Neutropenia (ANC< 500)	65 (63)
ANC < 100	56 (54)
ALC at diagnosis, median (IQR)	120 (0-530)
APACHE II score at diagnosis, median (IQR)	14 (12-17)
ICU at diagnosis	13 (13)
Malnutrition (Alb ≤ 3)	88 (85)
Fasting BG closest to symptom onset, median (IQR)	125 (105-150)
Average Blood Glucose (BG) from 5 samples closest to symptom onset, median (IQR)	124 (107-156)
Fasting BG 28 days prior to symptom,	117 (99-147)
DM	15/102 (15)
Metformin at admission	12/102 (12)
Insulin at admission	16/101 (16)
Persistent hyperglycemia	14 (23)
Severe hyperglycemia	23 (22)
MCR classification	
Proven	81 (79)
Probable	22 (21)

42 Day Survival of Patients with MCR with and without Persistent Hyperglycemia



42 Day Survival of Patients with MCR with and without Severe Hyperglycemia



42 Day Survival of Patients with MCR with and without Insulin Use

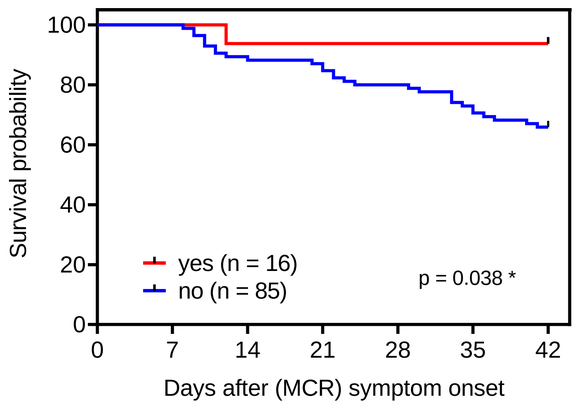


Table 2: Multivariate Logistic Regression Model of Predictors of 42-day Mortality

Independent predictor	OR	95% CI	p-value
ANC at diagnosis (every increase of 100)	0.97	0.93 to 0.996	0.024
ICU at diagnosis	5.65	1.95 to 39.16	0.0001
Insulin at admission	0.22	0.03 to 0.78	0.009
Surgery	0.41	0.19 to 0.79	0.005

Analysis

- The median fasting sGL closest to symptom onset was 125, and the median fasting sGL 28 days prior to symptoms onset was 117.
- Twenty three patients (22%) met criteria for severe hyperglycemia with at least one fasting sGL of >180.
- Of the patients with sufficient sGL measurements for analysis (N=60), 14 (23%) met criteria for persistent hyperglycemia
- Sixteen patients (16%) received insulin prior to index admission, and 12 (12%) were on metformin.42 day all-cause mortality occurred in 31 (30%) of patients in the overall cohort.
- Neither severe (p=0.251) nor persistent hyperglycemia (p=0.782) were associated with all-cause 42-day mortality on univariate analysis
- Use of insulin prior to admission was associated with decreased all-cause 42 day mortality on univariate (p=0.038) and multivariate (OR=0.22, p=0.009) analysis.
- Other factors associated with all-cause 42 day mortality included ANC at diagnosis (OR 0.97, p=0.024), ICU at diagnosis (OR=5.65, p<0.001), and surgical intervention (OR=0.42, p=0.005).

Discussion/Conclusions

- In a setting of high crude mortality, neither severe nor persistent hyperglycemia were found to be associated with excess mortality in patients with MCR and HMs or HSCT.
- Interestingly, insulin use prior to index admission was found to be associated with decreased all-cause 42 day mortality
- The exact mechanism for the protective effects of insulin in this setting remain unclear, but previous research on MCR pathogenesis and immunity provides compelling hypotheses.
- Experimental models have supported a role for insulin in macrophage mediated immunity. Specifically, deletion of molecules involved in insulin signaling in macrophages leads to decreased secretion of pro-inflammatory factors upon stimulation[7].
- Further study and validation of the protective role of exogenous insulin administration in terms of outcomes of MCR in HM and HSCT patients is needed.

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