Clinically Relevant Effects of GLP-1 Agonists in Myelodysplastic Syndromes: Unveiling Therapeutic Benefits Beyond Glycemic Control – A Global Propensity Score-Matched Analysis

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Introduction

- Emerging evidence indicates that glucagon-like peptide-1 receptor agonists (GLP-1a) reduce the risk of myelodysplastic syndromes (MDS) in patients with type 2 diabetes mellitus and autoimmune disorders, potentially due to GLP-1a's anti-inflammatory and cytostatic activities
- GLP-1a, initially developed for glycemic control, exhibit antineoplastic properties by inhibiting PI3K/AKT/mTOR and ERK/MAPK pathways, inducing G2/M cell cycle arrest, modulating JAK/STAT pathway and reducing glucose uptake in neoplastic cells. Furthermore, activation of GLP1 receptor in monocytes, macrophages, and neutrophils has been shown to suppress NF-κβ signaling, limit NLRP3 inflammasome priming, and mitigate oxidative stress.
- This study investigates the effects of GLP-1a on leukemia progression, clinical outcomes, and overall survival in patients with MDS.

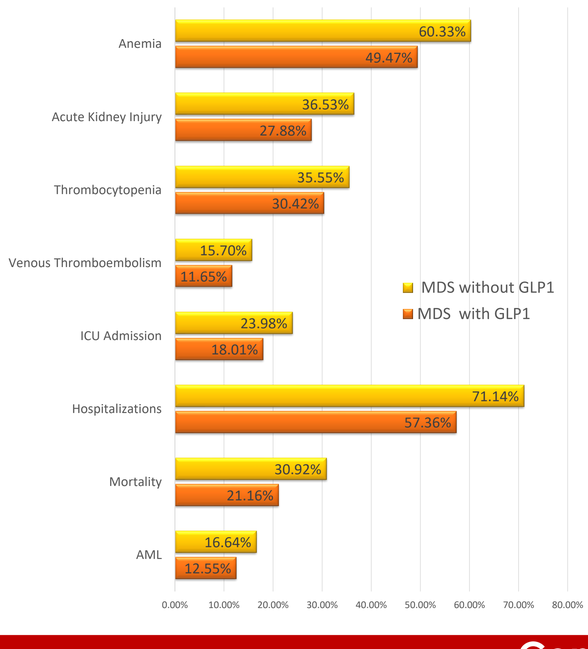
Methods

- We conducted a retrospective, propensity score-matched (PSM) cohort study using the **TriNetX Analytics Network database,** including MDS patients ≥18 years with GLP-1a (n=2,864) and matched controls without GLP-1a (n=127,018) from 2015 to 2021.
- PSM (1:1) was applied using a greedy nearest-neighbor method with a caliper of 0.1 pooled standard deviations, and adjusting for demographics, therapy for MDS, comorbidities, laboratory values, and cardiovascular medications. **Primary outcomes** were progression to acute myeloid leukemia (AML), all-cause mortality, and ICU admissions.
- **Secondary outcomes** included all-cause hospitalizations, anemia, thrombocytopenia, acute kidney injury (AKI), and venous thromboembolism (VTE). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated **over 3 years**.

Results

- After PSM, 2,765 matched pairs (mean age 70.4±12.4 years for GLP-1a users and mean age 71.2±14.7 years for nonusers in each group) were analyzed
- Mean time for patients on GLP-1 a therapy was 241.72 ± 207.04 days

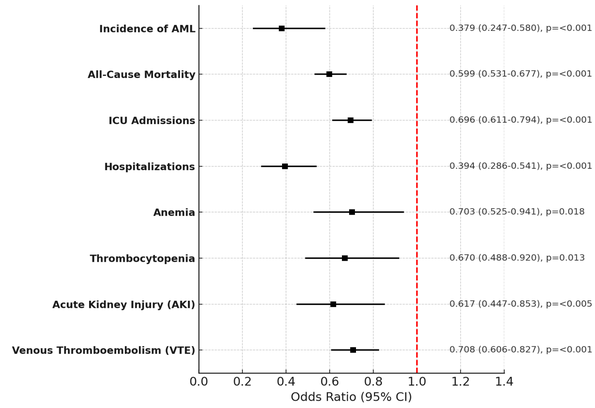
Number of Events %



Patient Characteristics

Characteristic	GLP-1a Users n=2,765	GLP-1a Non-users n=2,765	Std Diff.
Demographics			
Age (years), mean ± SD	70.4 ± 12.4	71.2 ± 14.7	0.062
Age at Index (years), mean ± SD	67.1 ± 12.3	68.0 ± 14.9	0.062
White	2,018 (73.0)	2,061 (74.5)	0.035
African American	345 (12.5)	345 (12.5)	<0.001
Asian	84 (3.0)	80 (2.9)	0.009
Hispanic/Latino	144 (5.2)	146 (5.3)	0.003
AIAN	12 (0.4)	13 (0.5)	0.005
API	10 (0.4)	10 (0.4)	<0.001
Unknown Race	219 (7.9)	186 (6.7)	0.046
Female	1,380 (49.9)	1,294 (46.8)	0.062
Male	1,318 (47.7)	1,410 (51.0)	0.067
Diagnosis			
Hypertension	2,041 (73.8)	2,072 (74.9)	0.026
Cardiomyopathy	249 (9.0)	260 (9.4)	0.014
Dyslipidemia	1,900 (68.7)	1,914 (69.2)	0.011
Ischemic Heart Disease	1,038 (37.5)	1,031 (37.3)	0.005
Obesity	1,296 (46.9)	1,280 (46.3)	0.012
Heart Failure	726 (26.3)	728 (26.3)	0.002
Neoplasms	1,920 (69.4)	1,922 (69.5)	0.002
CKD Stage 3	761 (27.5)	783 (28.3)	0.018
COPD	408 (14.8)	412 (14.9)	0.004
Stroke	170 (6.1)	176 (6.4)	0.009
Hepatic Fibrosis	51 (1.8)	49 (1.8)	0.005
PAD	343 (12.4)	357 (12.9)	0.015
ESRD	148 (5.4)	161 (5.8)	0.020
Coagulation Disorders	903 (32.7)	891 (32.2)	0.009
Sleep Apnea	763 (27.6)	800 (28.9)	0.030
Atrial Fibrillation	521 (18.8)	514 (18.6)	0.006
Nicotine Abuse	322 (11.6)	324 (11.7)	0.002
Alcohol Disorders	93 (3.4)	95 (3.4)	0.004
Diabetes Mellitus	2,078 (75.2)	2,102 (76.0)	0.020
Bone Marrow Transplantation	127 (4.6)	108 (3.9)	0.034
Medications			
Antilipemic Agents	1,866 (67.5)	1,909 (69.0)	0.033
Insulin	1,560 (56.4)	1,582 (57.2)	0.016
Aspirin	1,115 (40.3)	1,130 (40.9)	0.011
Azacitidine	63 (2.3)	62 (2.2)	0.002
Decitabine	40 (1.4)	39 (1.4)	0.003
Cedazuridine	13 (0.5)	12 (0.4)	0.005
Epoetin Alfa	171 (6.2)	173 (6.3)	0.003
Darbepoetin Alfa	154 (5.6)	166 (6.0)	0.019
Filgrastim	142 (5.1)	138 (5.0)	0.007
Luspatercept	13 (0.5)	10 (0.4)	0.017
Laboratory			
LDL Cholesterol	75.3 ± 36.8 (n=1,710)	71.4 ± 35.2 (n=1,700)	0.108
Hemoglobin A1c	7.1 ± 1.8 (n=1,884)	6.5 ± 1.6 (n=1,893)	0.374

Forest Plot



Outcomes

Outcomes	Odds Ratio (OR)	95% (CI)	P-value
Incidence of AML	0.379	0.247 - 0.580	<0.001
All-Cause Mortality	0.599	0.531 - 0.677	<0.001
ICU Admissions	0.696	0.611 - 0.794	<0.001
Hospitalizations	0.394	0.286 - 0.541	<0.001
Anemia	0.703	0.525 - 0.941	0.018
Thrombocytopenia	0.670	0.488 - 0.920	0.013
AKI	0.617	0.447 - 0.853	<0.005
VTE	0.708	0.606 - 0.827	<0.001

Conclusion

- GLP-1 agonist therapy in MDS patients was associated with significantly reduced risks of **progression to AML**, all-cause mortality, ICU admissions, and other critical complications.
- Notwithstanding the limitation of registery database, these findings highlight the potential of GLP-1 agonists as a promising therapeutic strategy, offering both antineoplastic and anti-inflammatory benefits in MDS, warranting further investigation in prospective trials

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References:

1. Wang, Lindsey et al. "Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes." *JAMA network open* vol. 7,7 e2421305. 1 Jul. 2024, doi:10.1001/jamanetworkopen.2024.21305.
2. Lin, Anqi et al. "Glucagon-like peptide 1 receptor agonists and cancer risk: advancing precision medicine through mechanistic understanding and clinical evidence." *Biomarker research* vol. 13,1 50. 27 Mar. 2025, doi:10.1186/s40364-025-00765-3

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