Characteristics and Outcomes of GLP-1 Receptor Agonist Therapy among Type 2 Diabetics with Primary Bone Sarcoma: Lower Early Complications and Improved Five-Year Survival After Resection

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INTRODUCTION:
Systemic metabolic dysregulation, including hyperglycemia, obesity, and chronic inflammation, has been linked to inferior oncologic outcomes in primary bone sarcoma. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve glucose control, reduce adiposity, and may exert anti-inflammatory and pro-apoptotic effects relevant to cancer. We investigated whether peri-operative GLP-1 RA exposure in type 2 diabetes mellitus (T2DM) modifies short-term morbidity and long-term oncologic outcomes following primary bone sarcoma resection.

METHODS:
This study utilized a global deidentified electronic health record network (TriNetX) to identify adults (≥18 years) with type 2 diabetes mellitus (T2DM) who underwent resection for a primary malignant bone tumor between 2015 and 2025. Patients with no prior history of other cancers and active GLP-1 RA treatment within 90 days before surgery constituted the GLP-1 RA(+) cohort. The GLP-1 RA(–) control cohort comprised patients with T2DM without GLP-1 RA exposure. One-to-one propensity score matching (caliper 0.1), balancing for age, sex, BMI, HbA1c, and prior diagnoses, yielded 280 matched pairs. Outcomes were assessed at 90 days (postoperative complications), 1 year, and 5 years (overall prognosis, quality of life, and healthcare utilization), with risk ratios (RR) and 95% confidence intervals (CI) calculated. A p-value <0.05 denotes statistical significance.

RESULTS:
90 days post-op: In the short term, GLP-1 RA(+) patients had reduced:
- All-cause Mortality (RR 0.44, p=0.006)
- Emergency-department visits (RR 0.61, p=0.004)
- Cardiac arrhythmias (RR 0.57, p=0.007

Higher incidence of Ketoacidosis (RR 1.96, p=0.001)

1 year post-op: GLP-1 users had lower:
- All-cause mortality (RR 0.56, p=0.013)
- Inpatient admission (RR 0.46, p=0.023)

No significant differences in neoadjuvant treatment, side effects, remission, or secondary metastasis.
Ketoacidosis rates were normalized.

5 years post-op: GLP-1 RA(+) therapy yielded lower:
- All-cause mortality (RR 0.51, p=0.001),
- Inpatient admissions (RR 0.44, p=0.016),
- Falls (RR 0.42, p=0.004)
- Mobility limitations (RR 0.38, p=0.005)

Consistently, lab results including Creatinine, BMI, and HbA1C were significantly elevated. Ketoacidosis rates were normalized.

DISCUSSION AND CONCLUSION:
Peri-operative GLP-1 RA exposure in T2DM patients undergoing primary bone sarcoma resection was associated with fewer early cardiometabolic complications and a nearly 50% relative reduction in five-year mortality. These protective effects may reflect improved metabolic control and favorable modulation of systemic inflammation or the tumor cellular environment. Randomized trials are warranted to evaluate GLP-1 RAs as an adjuvant metabolic intervention in musculoskeletal oncology.

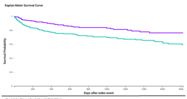

Figure 1. Kaplan-Meier overall-survival Curves for Matched Cohorts
5-year survival probabilities with time zero as the date of surgical excision of primary bone sarcoma. Five-year survival was 84.9% in the GLP-1 RA(+) cohort versus 70.4% in the controls.
The log-rank test revealed a significant difference between the curves (p<0.001), and Cox proportional-hazards modeling yielded a hazard ratio of 0.54 (95% CI 0.40–0.73), favoring GLP-1 RA exposure.

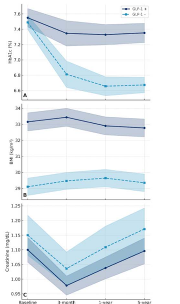

Figure 2: Long-term Lab trajectories in matched cohorts
Legend – Mean ± standard error for each lab parameter is plotted at baseline, 3 months, 1 year, and 5 years; dark-blue solid lines represent GLP-1 RA(+) patients, light-blue dashed lines represent GLP-1 RA(−) controls (matched n ranged from 114–245 per time-point).
Shaded ribbons denote ±1 SE; individual markers are offset horizontally for clarity.

HbA1c (A): Both groups showed early glycemic improvement, but the GLP-1 RA(−) cohort experienced the larger and more durable decline (−0.82% at 5y vs −0.20% in GLP-1 RA(+)), widening the between-group gap from 0.06% at baseline to 0.68% at 5 years.
Body-mass index (B): Weight fell in both cohorts; the control group lost roughly 1.8 kg m² by 5 years, whereas the GLP-1 RA(+) group decreased by 0.6 kg m², yielding a 1.1 kg m² relative advantage for controls.
Serum creatinine (C): Renal function remained stable overall, and differences between cohorts were insignificant.

	Before Matching				After Matching			
Demographics	GLP1RA(+)	GLP1RA(−)	P-Value	Std diff.	GLP1RA(+)	GLP1RA(−)	P-Value	Std diff.
Age at Index	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
White	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Black or African American	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Unknown Race	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
American Indian or Alaska Native	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Asian	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Native Hawaiian or Other Pacific Islander	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Other Race	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diagnoses								
Essential (primary) hypertension	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dyslipidemia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Sleep Disorders (Apnea, Insomnia)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Anemias	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Obesity	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ischemic heart disease	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diabetic Neuropathy	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diabetic Nephropathy	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diabetic Retinopathy	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hypothyroidism	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Anxiety Disorder	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Bone Density Disorders	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cardiac arrhythmias	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Atrial fibrillation and flutter	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Asthma	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hypertensive chronic kidney disease (stage 1 - 4)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hypertensive chronic kidney disease (stage 5)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hernia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Chronic obstructive pulmonary disease	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Acute myocardial infarction	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Coronavirus as the cause of diseases classified elsewhere	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Major depressive disorder, recurrent	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Other peripheral vascular diseases	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cerebral infarction	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Osteoarthritis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dorsopathies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Arthropathies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Pathological fracture, not elsewhere classified	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Procedures								
Arthrocentesis, aspiration and/or injection, major joint or bursa	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Level I - Surgical pathology, gross examination only	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Level II - Surgical pathology, gross and microscopic examination	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Level III - Surgical pathology, gross and microscopic examination	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Level IV - Surgical pathology, gross and microscopic examination	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Level V - Surgical pathology, gross and microscopic examination	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Level VI - Surgical pathology, gross and microscopic examination	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Physical Medicine and Rehabilitation Evaluations	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Medications								
Metformin	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Insulin	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Labs								
Creatinine	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hemoglobin A1c	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
BMI	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 1. Baseline Cohort Characteristics
Legend – Continuous variables are reported as mean ± SD; categorical variables as n (%). RD=risk difference. RR=risk ratio. CI=95% confidence interval. Std diff.<0.10 indicates adequate post-match balance. Abbreviations: BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; SD, standard deviation.
Demographic, comorbidity, procedure, medication, and laboratory variables before and after one-to-one matching.

Outcome (90 days)	Risk (GLP1+) (n=280)	Risk (GLP1-) (n=280)	Risk Difference (95% CI)	Risk Ratio (95% CI)	P-Value
Cardiac arrhythmias	**0.111**	**0.193**	**−0.082 (−0.141, −0.023)**	**0.574 (0.381, 0.865)**	**0.007**
ED visits	**0.154**	**0.25**	**−0.096 (−0.162, −0.030)**	**0.614 (0.436, 0.865)**	**0.004**
Embolism	0.054	0.086	−0.032 (−0.074, 0.010)	0.625 (0.335, 1.166)	0.135
In-patient admission	0.036	0.071	−0.036 (−0.073, 0.001)	0.500 (0.238, 1.049)	0.061
Ketoacidosis	**0.357**	**0.182**	**0.175 (0.103, 0.247**	**1.961 (1.462, 2.630)**	**0.001**
Mortality	**0.05**	**0.114**	**−0.064 (−0.109, −0.019)**	**0.438 (0.239, 0.802)**	**0.006**
Respiratory complication	0.079	0.079	0.000 (−0.045, 0.045)	1.000 (0.567, 1.763)	1
Surgical infections	0.154	0.204	−0.050 (−0.113, 0.013)	0.754 (0.527, 1.081)	0.122
UTIs	0.057	0.104	−0.046 (−0.091, −0.002)	0.552 (0.307, 0.993)	0.143

Table 2. Short-term (90-day Outcomes After Operative Treatment
Legend – Risk = proportion of patients with the outcome. RD=risk difference. RR=risk ratio. CI=95% confidence interval. Boldface denotes p<0.05. Abbreviations: ED, emergency department; DKA, diabetic ketoacidosis
90 days after surgery, GLP users were associated with significantly fewer arrhythmias, ED visits, and deaths, but higher DKA rates.

Outcome (1-year)	Risk (GLP1+) (n=280)	Risk (GLP1-) (n=280)	Risk Difference (95% CI)	Risk Ratio (95% CI)	P-Value
Antineoplastic Drugs	0.175	0.147	0.028 (0.011, 0.315)	1.192 (0.947, 1.224)	0.463
Antineoplastic Drugs: Side Effects	0.044	0.05	-0.006 (−0.016, 0.014)	0.886 (0.671, 0.995)	0.756
ED visits	0.228	0.254	−0.025 (−0.097, 0.046)	0.900 (0.669, 1.211)	0.486
Falls	0.04	0.036	0.004 (−0.028, 0.036)	1.100 (0.475, 2.548)	0.824
Functional Status: Mobility problems	0.041	0.046	−0.005 (−0.041, 0.031)	0.894 (0.387, 2.066)	0.793
Functional Status: Pain	0.207	0.152	0.054 (−0.010, 0.118)	1.357 (0.945, 1.949)	0.096
Functional Status: Weakness	0.14	0.147	-0.007 (−0.009, 0.002)	0.952 (0.712, 1.141)	0.811
In-patient admission	**0.04**	**0.087**	**−0.047 (−0.088, −0.007)**	**0.458 (0.229, 0.917)**	**0.023**
Mortality	**0.087**	**0.156**	**−0.069 (−0.123, −0.015)**	**0.558 (0.349, 0.894)**	**0.013**
Pathological Fracture	0.036	0.043	−0.007 (−0.040, 0.025)	0.833 (0.366, 1.897)	0.663
Prosthesis & Implant Complications	0.049	0.053	−0.004 (−0.040, 0.033)	09.33 (0.459, 1.898)	0.845
Radiation Therapy	0.035	0.036	0	0.989	0.981
Radiation Therapy: Side Effects	0.035	0.036	0	0.996	0.994
Remission	0.119	0.1	0.019 (−0.037, 0.074)	1.189 (0.713, 1.981)	0.507
Secondary metastasis	0.067	0.047	0.020 (−0.023, 0.063)	1.426 (0.661, 3.074)	0.362

Table 3. One-Year Outcomes After Operative Treatment
Legend – Risk = proportion of patients with the outcome. RD=risk difference. RR=risk ratio. CI=95% confidence interval. Boldface denotes p<0.05. Abbreviations: ED, emergency department; DKA, diabetic ketoacidosis
At 1 year, GLP-1 RA(+) patients had lower inpatient admission and all-cause mortality, with no differences in antineoplastic-drug utilization or functional mobility.

Outcome (5-year)	Risk (GLP1+) (n=280)	Risk (GLP1-) (n=280)	Risk Difference (95% CI)	Risk Ratio (95% CI)	P-Value
Antineoplastic Drugs	0.218	0.195	0.023 (-0.059, 0.106)	1.119 (0.749, 1.670)	0.583
Antineoplastic Drug: Side Effects	0.052	0.056	-0.005 (-0.044, 0.034)	0.912 (0.449, 1.853)	0.8
Chronic Opioid Use	0.821	0.832	-0.011 (-0.062, 0.041)	0.987 (0.903, 1.080)	0.68
Diabetic Nephropathy	0.039	0.037	0.002 (-0.030, 0.035)	1.063 (0.450, 2.511)	0.89
Diabetic Neuropathy	**0.196**	**0.121**	**0.075 (0.015, 0.135)**	**1.618 (1.091, 2.399)**	**0.015**
Diabetic Retinopathy	0.057	0.036	0.021 (-0.013, 0.056)	1.600 (0.739, 3.464)	0.228
ED visits	**0.329**	**0.425**	**-0.096 (-0.176, -0.017)**	**0.773 (0.623, 0.959)**	**0.019**
Falls	**0.05**	**0.118**	**-0.068 (-0.113, -0.022)**	**0.424 (0.232, 0.775)**	**0.004**
Functional Status: Mobility	**0.041**	**0.107**	**-0.066 (-0.112, -0.020)**	**0.383 (0.189, 0.777)**	**0.005**
Functional Status: Pain	0.271	0.2	0.071 (0.001, 0.141)	1.357 (1.003, 1.837)	0.056
Functional Status: Weakness	0.193	0.261	-0.068 (-0.137, 0.001)	0.740 (0.542, 1.009)	0.055
In-patient admission	**0.039**	**0.089**	**-0.050 (-0.090, -0.010)**	**0.440 (0.221, 0.877)**	**0.016**
Mortality	**0.15**	**0.296**	**-0.146 (-0.214, -0.079)**	**0.506 (0.363, 0.705)**	**0.001**
Pathological Fracture	0.036	0.054	-0.018 (-0.052, 0.016)	0.667 (0.305, 1.458)	0.306
Prosthesis & Implant Complications	0.061	0.107	-0.046 (-0.050, -0.025)	0.571 (0.301, 0.992)	0.054
Radiation therapy	0.036	0.036	0.000 (-0.031, 0.031)	0.996 (0.421, 2.356)	0.993
Radiation-therapy Side Effects	0.036	0.036	0.000 (-0.031, 0.031)	0.996 (0.421, 2.356)	0.993
Remission	0.166	0.189	-0.023 (-0.091, 0.044)	0.877 (0.599, 1.285)	0.5
Secondary metastasis	0.104	0.135	-0.032 (-0.090, 0.027)	0.766 (0.467, 1.257)	0.29

Table 4. Five-Year Outcomes After Operative Treatment
Legend – Risk = proportion of patients with the outcome. RD=risk difference. RR=risk ratio. CI=95% confidence interval. Boldface denotes p<0.05. Abbreviations: ED, emergency department; DKA, diabetic ketoacidosis.
Long-term GLP-1 RA therapy remained protective against ED visits, falls, mobility limitations, hospital admissions, and mortality, although diabetic neuropathy incidence was higher in the treated cohort.