Immunotherapy and Vertebral Compression Fractures

Alicia Chang [3] Dahlia Sukaik [1] Ellie Lee [2] Vincent Nguyen [1] Yoav Noiman [1]

[1]California State University, Fullerton [2]University of California, Irvine [3]Cypress College

Abstract

In conjunction with chemotherapy and other cancer treatments, cancer patients may also take Immunotherapy, a class of treatments that assists the body in targeting and destroying neoplasms via strengthening the immune response typically administered by injection. One possible side effect is Vertebral Compression Fractures (VCFs) [1]. VCFs may occur in cancer patients or those without cancer but mainly occur when individuals have a lower bone mass density or increased physical strain on the vertebrae. To determine the risk of VCF with Immunotherapy, we are using Multinomial Logistic Regression, and the results indicate an increase in odds for age, gender, treatment duration in days, and treatment drugs Pembrolizumab and Durvalumab.

Background Information and Scientific Goal

From 2011-2022, various patients were checked into UC Irvine Health facilities, and their data was recorded and anonymized for this project.

- Immunotherapy - A type of cancer treatment that increases the immune response to cancer cells. This significantly benefits patients because it reduces the harm to healthy cells. This type of treatment is used alongside radiation therapy and chemotherapy to increase the likelihood of survival [2].
- Vertebral Compression Fracture - VCF is a fracture in the spine due to physical stress or lower bone mass density, which can lead to severe pain, deformity, and loss of height [4].
- Neoplasm - Abnormal growths that are more commonly known as tumors and may be malignant (spreads), which are cancerous, or benign (static) [3].

The objective is to find if immunotherapy has a significant association with the rate of VCFs.

Data Structure and Wrangling

Our data is from pre-wrangled datasets extracted from the LDS OMOP RDW (Limited Data Set Observational Medical Outcomes Partnership Relational Data Warehouse) Database located on the UCI Health Protected Virtual Computing Environment (PVCE). The data includes various information such as basic demographics, the type of immunotherapy the patient received, the treatment duration, and the number of treatments received.

The 61 patients in the datasets have the following characteristics:

- The patients range in age from 5 to 88, with 29 females and 32 males.
- Each patient could have fractures pre-treatment and/or post-treatment.
- Each patient had neoplasms and received immunotherapy and radiation therapy.

	After Treatment		
Before Treatment	0	1	≥2
0	0	23	17
1	14	1	1
≥2	3	0	2

Table 1. Contingency Table of Number of VCFs Before Treatment and After Treatment

We wrangled the data by each unique patient (61 rows), and we created new variables that correlate to the number of VCFs before and after treatment. The contingency table above shows the counts of patients in each category of number of VCFs before and after treatment.

Exploratory Data Analysis

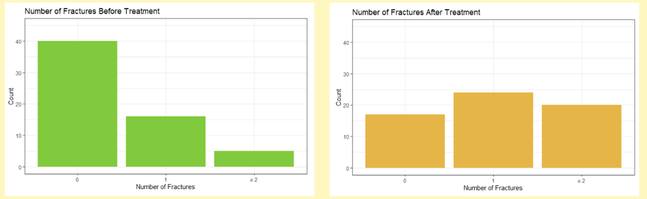
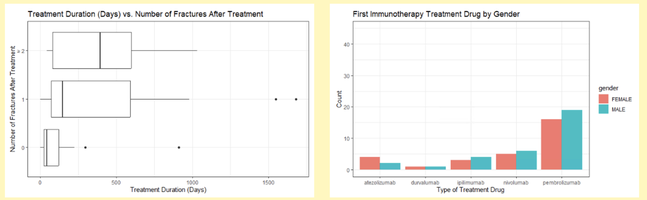


Figure 1. Number of Fractures Before Treatment (left) vs. Number of Fractures after Treatment (right)



(a) (b)

Figure 2. (a) Box plot of Treatment Duration in Days vs. Number of Fractures After Treatment; (b) Bar Graph of First Immunotherapy Drug by Gender

1. Number of VCFs Before and After Treatment The majority of patients have 0 fractures before treatment, while the number of patients with 0, 1, and ≥ 2 fractures after treatment is relatively uniform. The plots show a lot of skewness due to most patients having only one fracture.
2. Treatment Duration in Days vs. Number of Fractures After Treatment The box plots show that the number of treatment days in relation to the number of fractures is skewed right.
3. First Immunotherapy Drug by Gender The bar graph displays that gender doesn't appear to play a role in which immunotherapy a person takes, while also displaying that the most taken immunotherapy is Pembrolizumab and the least taken is Durvalumab.

Multinomial Logistic Regression

We are utilizing **multinomial logistic regression** to predict if the number of VCFs after treatment (η_{ij}) is 0 ($j = 1$), 1 ($j = 2$), or ≥ 2 ($j = 3$). Our explanatory variables (β_i) are age ($i = 1$), gender ($i = 2$), treatment duration (days) ($i = 3$), total number of treatments ($i = 4$), type of immunotherapy treatment drug ($i = 5, 6, 7, 8$), and number of fractures before treatment (0, 1, ≥ 2) ($i = 9, 10$).

$$\eta_{ij} = \log\left(\frac{P(Y_{i=j}|X_i)}{P(Y_{i=1}|X_i)}\right) = \beta_{0j} + \sum_{i=1}^{10} \beta_{ij} X_i \text{ for } j = 1, 2$$

Odds Ratio

To interpret an effect of an explanatory variable, we examine the Odds Ratio (OR), which, in our model, represents the change in odds of having either 1 or ≥ 2 fractures after treatment relative to having no fractures after treatment, given a one-unit change in the explanatory variable. An odds ratio of 1 indicates no effect, while > 1 indicates an increase, and < 1 indicates a decrease.

Results

The following table shows the estimated ORs for going from 0 to 1 VCF after treatment and 0 to ≥ 2 VCFs after treatment.

Variable	OR ($j = 1$ to 2)	OR ($j = 1$ to 3)
X_1: Age	1.062	1.032
X_2: Gender	5.273	1.281
X_3: Treatment Duration	1.007	1.01
X_4: Number of Treatments	0.978	0.964
X_5: Treatment Drug (Durvalumab)	376046.5	578509.4
X_6: Treatment Drug (Ipilimumab)	0.00	0.00
X_7: Treatment Drug (Nivolumab)	0.005	0.006
X_8: Treatment Drug (Pembrolizumab)	> 100000	> 100000
X_9: Number of VCF Before Trt. (1)	0.00	0.00
X_{10}: Number of VCF Before Trt. (≥ 2)	0.00	0.00

Table 2. Estimated Odd Ratios of Model Coefficients ($e^{\beta_{ij}}$).

As observed in Table 2, a unit increase in **age, gender, treatment duration, and treatment drugs (Pembrolizumab and Durvalumab)** show an **increased** estimated odds ratio of having 1 or ≥ 2 VCFs after treatment as opposed to having 0 VCFs after treatment. However, age and treatment duration show only slight increases in effects on the estimated odds ratio. Number of treatments shows a slight decrease in estimated odds ratio, while treatment drugs Ipilimumab, Nivolumab, and number of VCFs before treatment show large decreases in effect on the estimated odds ratio.

Future Work

Our research can be further improved with access to additional cancer patients who haven't taken any immunotherapy, then we could set a control group baseline and compare the rates of VCF between cancer patients who have taken immunotherapy and those that haven't. In addition, comprehensive data on the days each treatment occurred would facilitate a timeline of events directly between the time a treatment is taken and when a VCF occurs.

Acknowledgments

We wish to express gratitude to Dr. Jessica Jaynes, Dr. Sam Behseta, Dr. Roberto Pelayo, Dr. Babak Shahbaba, Dr. Mine Dogucu, Professor Alma Castro and our two TAs, Brian Schetzsle and Zahra Moslemi for their guidance. We want to thank our PI, Dr. Joyce Keyak, and UCI Health for providing data. We are grateful for the awards 2123366, 2123380, and 2123384 provided by the National Science Foundation HDR Data Science Corps that made this project possible.

References

[1] Filippini, Daria Maria, et al. "Bone Fracture as a Novel Immune-Related Adverse Event with Immune Checkpoint Inhibitors: Case Series and Large-Scale Pharmacovigilance Analysis." International Journal of Cancer, 1 Aug. 2021, www.ncbi.nlm.nih.gov/pmc/articles/PMC8251715/.

[2] "What Is Immunotherapy?" Cancer.Net, 26 May 2022, www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/what-immunotherapy.

[3] professional, Cleveland Clinic Medical. "Malignant Neoplasm: What It Is, Types amp; Factors." Cleveland Clinic, my.clevelandclinic.org/health/diseases/22319-malignant-neoplasm. Accessed 27 July 2023.

[4] "Vertebral Compression Fractures." AANS, www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Vertebral-Compression-Fractures. Accessed 27 July 2023.