# *Mining NIH BTRIS Data for Drug Repurposing: A Case Study of Glioblastoma*

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2023 IEEE International Conference on Bioinformatics and Biomedicine (BIBM) | 979-8-3503-3748-8 /23/$31.00 USG | DOI: 10.1109/BIBM58861.2023.10385957

*Abstract*— **The purpose of drug repurposing is to identify alternative uses of FDA approved drugs, which significantly accelerates the drug development process. Meanwhile, clinical data illustrate the patterns and clinical outcomes of drug use, so they have been increasingly applied to support drug development, particularly for drug repurposing. The NIH Biomedical Translational Research Information System (BTRIS) is a resource which compiles deidentified patient data from clinical research done across NIH Institutes and Centers. In this study, we analyzed clinical data available from BTRIS to identify drug repurposing candidates, i.e., identifying drugs that were correlated with an increased survival rate for glioblastoma (GBM) patients. Specifically, we extracted all the administered drugs on GBM patients and fitted them to elastic-net penalized Cox proportional hazards (CPH) models, a regression model for investigating the association between the survival rate of patients and covariates (administered drugs in this study) . We were able to identify several potential drug candidates for GBM to be further evaluated with other data types and by performing biological experiments.**

***Keywords—Drug repurposing, clinical data, BTRIS, survival analysis***

## I. INTRODUCTION

The awareness and interest of the public, media and legislative bodies in the field of rare diseases has been growing consistently. Currently, there are about 10,000 rare diseases, together affecting 10% of the population. However, less than 6% of those rare diseases have an approved treatment option, highlighting the tremendous unmet needs in drug development in rare diseases. "Given cost effectiveness and a reduced timeline, the process of repurposing drugs for new indications represents an alternative method for finding rare disease treatments with compelling advantages over traditional drug development."[1]

The Biomedical Translational Research Information System (BTRIS) provides a single resource of clinical research data collected across NIH, including clinical data from NIH clinical center. Retrospective analysis of clinical data can generate real-world evidence (RWE) of drug effectiveness and safety in clinical settings for potential new repurposing indication signal detection. In this study, we explore clinical data from BTRIS for drug repurposing for glioblastoma (GBM), which is a grade IV brain tumor that is difficult to treat and no cure for GBM. Thus, there is an urgent need to identify effective treatment options for GBM.

## II. MATERIALS AND METHODS

### A. BTRIS data preparation for GBM

Four types of clinical data were obtained from BTRIS in January 2022 for GBM, including demographic, diagnostic, medication, and laboratory. In order to assess the clinical efficacy of medications for drug repurposing, we extracted medications administered on GBM patients after their diagnosis of GBM during 1997-2021. Some medications captured in BTRIS are in general form, such as, "Dry mouth treatment", without active ingredients attached to the medications, it is hard to further validation on identified drug candidates, thus, we excluded medications without active ingredients captured in BTRIS in this study.

### B. Identification of Drug Repurposing Candidates

Associations between treatments and the survival of GBM patients were assessed through a Penalized Cox regression model using the scikit-survival Python module[2]. The Elastic Net regularization method[3] was chosen due to its efficacy in feature selection when dealing with a substantial number of variables. Elastic Net regularization outperforms Ridge and Lasso in feature selection by balancing the complete inclusion of features (Ridge) and strict sparsity (Lasso). It is particularly advantageous in feature selection in high-dimensional datasets with correlated features. First, an Elastic Net regression model was constructed utilizing GBM patient treatment and survival data. To identify the optimal alpha, predictive performance was evaluated for each alpha value using a 5-fold cross-validation. Subsequently, treatments with positive coefficients in the model exhibiting the best predictive performance were extracted, and their potential as repurposing candidates was explored.

## III. RESULTS

### A. BTRIS data GBM patient distribution

Demographic information was gathered for a total of 1,151 patients, while diagnosis and survival data were available for 1,025 patients. Fig 1 illustrates the patient distribution regarding gender, race, and ethnicity. Additionally, medication history data was accessible for 426 patients. After further cleaning up the data, a cohort of 377

patients associated with 365 medications, were applied for survival analysis. The most frequently used drugs including central nervous system agents, gastrointestinal agents, anti-infectives, as shown in the Fig.2, are the common treatment options used for GBM.

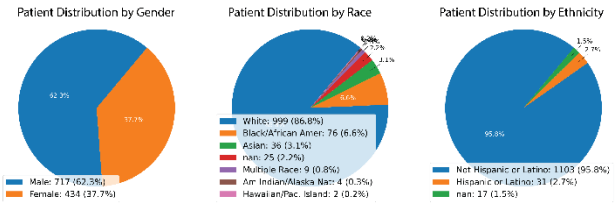


Fig. 1. Patient distributions based on demographic information, namely gender, race, and ethnicity.

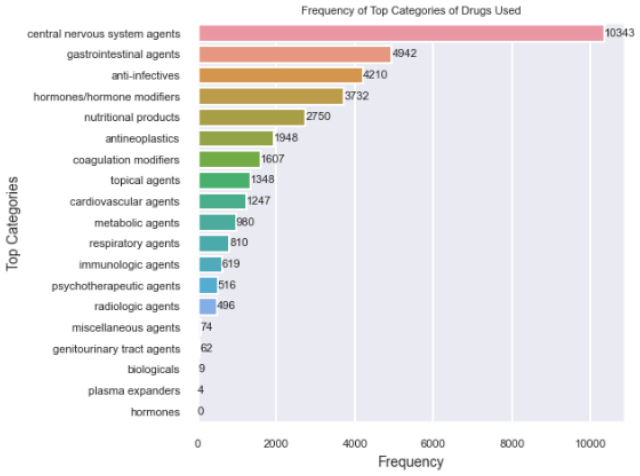


Fig.2. The drug categories ranked by their use frequency.

### *B. Identification of Drug Repurposing Candidates*

Within the optimal-performing Cox model, eight treatments exhibited non-zero predictive coefficients with survival rate after the Elastic Net penalty, four of which possessed positive coefficients to indicate patients on those drugs with high survival rate. Among these four medications, Selinexor, an FDA-approved nuclear export inhibitor employed in the treatment of multiple myeloma and relapsed or refractory diffuse large B-cell lymphoma, illustrated the highest coefficient, which suggests a positive association between Selinexor administration and the survival duration of GBM patients. A Phase II clinical trial study (NCT01986348) has demonstrated the capacity of Selinexor to induce a response rate and prolong progression-free survival in recurrent glioblastoma patients[4]. Moreover, Selinexor is currently under investigation in three ongoing clinical trials for its therapeutic potential in the management of glioblastoma or high-grade glioma (NCT05432804, NCT04216329, NCT05099003). Carvedilol as a beta blocker used for heart diseases, shows relatively high positive correlation to survival duration of GBM patients. There are several studies under investigation on the use of Carvedilol for GBM,[5, 6] and one early phase 1 clinical trial (NCT03861598) to study Carvedilol with chemotherapy in second line GBM and response of circulating tumor cells, although this clinical study was terminated due to covid.

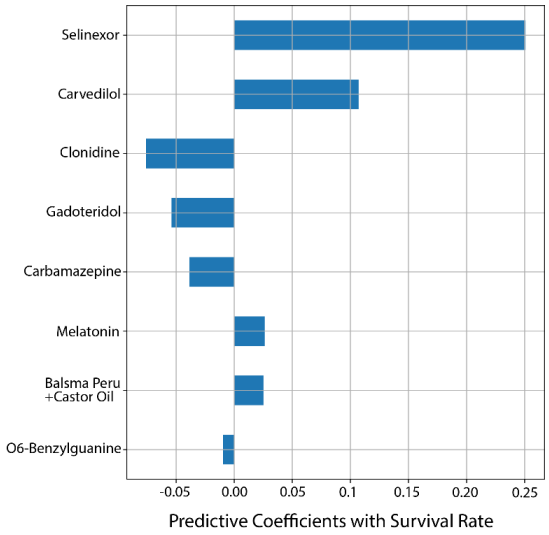


Fig. 3. Identified drug repurposing candidates with their predictive coefficient with survival rate

## IV. Discussion

In this study, we applied clinical data from NIH BTRIS for an application of drug repurposing in GBM, where we demonstrated the capability of BTRIS data for identifying potential drug repurposing candidate signals. Since this is our preliminary study as a proof-of-concept, cofounders such as, medical history, demographic information have not been considered to stratify the Cox hazard model for refined predictions, which will be applied in our future study. The focus of this study was to identify drug repurposing signals, which can direct other studies for further investigation. As a next step, we will incorporate this study with other drug repurposing projects for drug repurposing candidate evaluation.


## Acknowledgment

We thank the BTRIS team to prepare the data for us. This project was supported by the intramural program (ZIA TR000410-05) at NCATS.


## References


1. Roessler HI, Knoers NV, van Haelst MM, van Haaften G. Drug repurposing for rare diseases. Trends in pharmacological sciences. 2021;42(4):255-67.
2. Pölsterl S. scikit-survival: A Library for Time-to-Event Analysis Built on Top of scikit-learn. The Journal of Machine Learning Research. 2020;21(1):8747-52.
3. Zou H, Hastie T. Regularization and variable selection via the elastic net. Journal of the Royal Statistical Society Series B: Statistical Methodology. 2005;67(2):301-20.
4. Lassman AB, Wen PY, van den Bent MJ, Plotkin SR, Walenkamp AME, Green AL, et al. A Phase II Study of the Efficacy and Safety of Oral Selinexor in Recurrent Glioblastoma. Clinical Cancer Research. 2022;28(3):452-60.

5. Erguven M, Yazihan N, Aktas E, Sabanci A, Li CJ, Oktem G, et al. Carvedilol in glioma treatment alone and with imatinib in vitro. International journal of oncology. 2010;36(4):857-66.

6. Tewarie IA, Senders JT, Hulsbergen AF, Kremer S, Broekman ML. Beta-blockers and glioma: a systematic review of preclinical studies and clinical results. Neurosurgical Review. 2021;44:669-77.