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QBIO 490
Midterm
10/14/22

PIK3CA Mutation Correlation and Effects on HER2- and HER2+ Patients

Introduction:

The Cancer Genome Atlas (TCGA) is a cancer genomics database that includes genomic, transcriptomic, epigenomic, and proteomic data from 33 different cancer types. TCGA is incredibly important because it is a huge genome database for use throughout the research community, giving cancer researchers a huge amount of information to study. Using data from TCGA, researchers can analyze a problem from a “multi-omic” perspective, meaning they address a problem from a genomic, transcriptomic, epigenomic, and proteomic perspective. This often leads to realizations that could not have been possible if a researcher was simply looking at just the genome. From TCGA, we can extract clinical data, radiation data, and gene mutation data. This data will often be “cleaned up” to focus on a specific feature, which means clearing out NA values, among other things. This data can then be used in statistical analyses and survival plots. According to Pinto et. al, breast cancer is the most common cancer in the world for women. Through using TCGA data to link certain multi-omic features to a phenotypic response can help in uncovering the best-suited treatments. This investigation looked into whether PIK3CA mutations were more common in HER2- or HER2+ patients, and if this could have any effect on the survival rates of these patients. The R package ggplot and maftools were used to graph Kaplan-Meier survival plots, oncoplots, and MAF survival curves, among other things. These analyses showed that there was not quite enough data to tell the effect of PIK3CA mutations on HER2- patients.

Methods:

Breast cancer clinical data was accessed from TCGA using code “TCGA-BRCA”. HER2 immunohistochemistry level results were sorted into two categories: positive and negative. All positive values were “3+”, while the negative values were “1+” or “0”. All NA values and

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“borderline” values (with an immunohistochemistry result of “2+”) were removed, leaving only HER2-positive and HER2-negative patients. Using the clinical data of “days to death” and “days to the last follow-up”, a survival time dataset was created. Then, a death event dataset was created using each patient's vital status. A Kaplan-Meier survival plot based off of a patient’s HER2 status was then made with the R package ggplot, using the survival time and death event datasets to calibrate it. Then, breast cancer MAF data was accessed from TCGA using code “TCGA-BRCA”. Using the R package maftools, an oncoplot based off of HER2 status was created. After creating a list of the positive and negative patients' barcodes respectively, a co-oncoplot was created, again based off of HER2 status. Using the same package, a lollipop plot was created based off of HER2 status and the PIK3CA gene. The PIK3CA gene was chosen because our first oncoplot showed that it had the most mutations when sorted by HER2-patients. Finally, a death event and survival time dataset were created using the MAF data, and then used for a survival plot based on PIK3CA mutations.

Figures:

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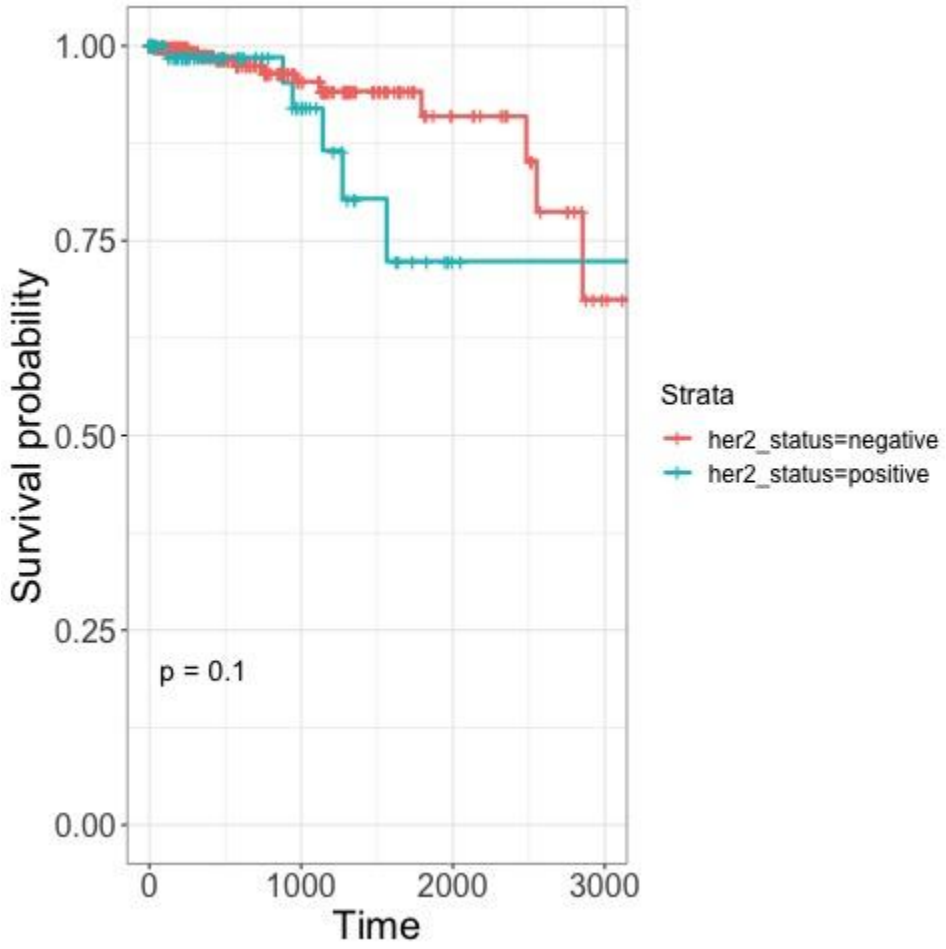

Figure 1. Kaplan-Meier survival plot shows that HER2- patients have an overall higher survival rate than HER2+ patients. All borderline HER2 immunohistochemistry results were excluded.

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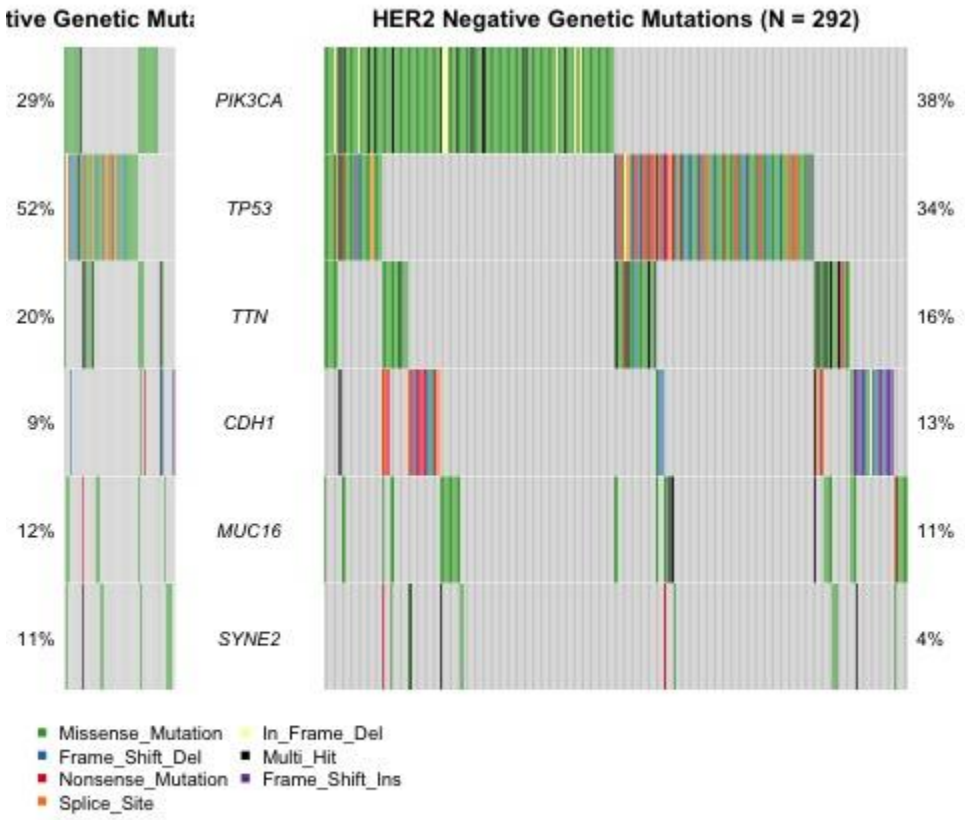

Figure 2. Oncoplots show that HER2- patients have the most PIK3CA mutations, while HER2+ patients have the most TP53 mutations. Left side is HER2+ patients.

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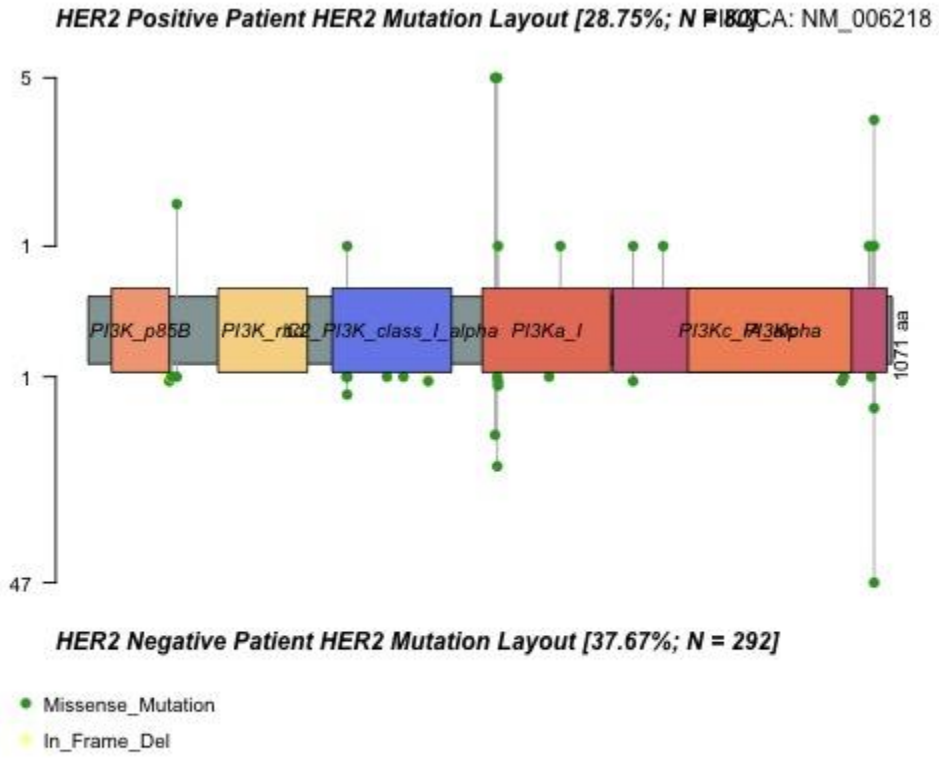

Figure 3. Lollipop plot shows that most mutations were missense mutations, and song HER2- and HER2+ patients, the mutations fell in the same place. More HER2- patients than HER2+ patients.

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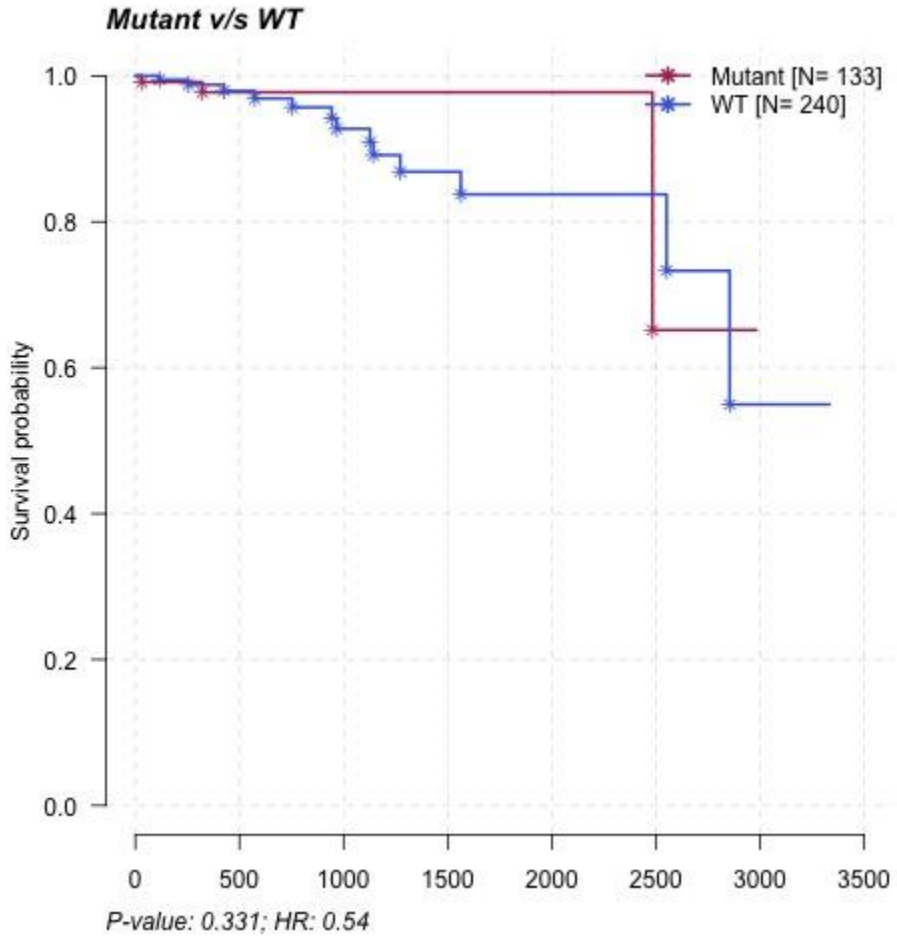

Figure 4. MAF survival plot attempts to show that mutated PIK3CA patients have a higher survival rate than the wild-type patients. Mutated N=133, WT N=240.

Results:

The Kaplan-Meier survival plot shows us that, while HER2+ and HER2- patients start similarly, HER2- patients have a much higher survival rate throughout time (Figure 1). However, this survival rate takes a steep decline near the end, eventually dipping below HER2+ patients, while the HER2+ patients' survival rate seems to plateau at about 74%. The first co-oncoplot created shows that 38% of HER2- patients have a mutated PIK3CA gene, with most of those mutations being missense mutations (Figure 2). This lines up with Pinto et. al, who described a similar number of missense mutations for PIK3CA in HER2 patients. The co-lollipop plot,

however, shows that PIK3CA mutations in HER2+ and HER2- patients happen in, largely, the same spots (Figure 3). Finally, the MAF survival plot based on PIK3CA seems to say that PIK3CA mutations have a higher survival rate than the wild-type, but there was also not much data to support this, as is visible by the lack of data points in the mutant line (Figure 4).

Discussion:

While it is clear that HER2- patients have lots of mutated PIK3CA and have a higher survival rate then HER2+ patients, there is not enough data about PIK3CA mutated HER2+ patients to tell whether or not PIK3CA mutations adversely effect survival prognosis. PIK3CA is responsible for transmitting signals from oncogenic receptors, including HER2 (Rasti et. al, 2022). In fact, HER2 signaling is done almost exclusively though the PIK3CA pathway (Goel and Krop, 2016). It seems like HER2+ patients should all have mutated PIK3CA, but this does not agree with out results, where 38% of HER2- patients had mutated PIK3A and only 29% of HER2+. However, this ambiguity is apparent in Elwy et. al, who references several studies that show more mutated PIK3CA in HER2- patients and several studies that show the opposite. For instance, Azim et. al, one of the former studies, says PIK3CA cannot be a predictive marker of HER2- patients because it lacks clinical relevance, despite a statistically significant difference than HER2+ patients. HER2+ patients have a poor survival rate, which likely coupled with PIK3CA mutations will lower that survival rate. As HER2+'s exclusive pathway to tumorigenesis, mutated PIK3CA should lower HER2+ patients' survival rates, especially because it interferes with anti-HER2 therapy (Pinto et. al). This leads to the possibility of future investigation into how PIK3CA interacts with TP53, which is mutated in 52% of HER2+ patients.

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Works Cited:

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