DETERMINING THE CORRELATION BETWEEN THE TP53 GENE AND KIDNEY CANCER SURVIVAL THROUGH THE COX PROPORTIONAL-HAZARDS REGRESSION MODEL

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January 31, 2021

ABSTRACT

Kidney cancer is among the most common and deadly forms of cancer and its incidence has spiked considerably in recent years. It contains a high propensity to rapidly spread to nearby organs, making swift and early diagnosis absolutely critical to ensuring optimal patient recovery. However, its subtle symptoms and manifestation in laboratory tests can make discerning its occurrence difficult. Predicting the probability of the carcinoma based upon various gene mutations has been previously explored, but this study specifically focuses on the TP53 mRNA and the effect its variants have. The Cox proportional-hazards regression technique, ubiquitously regarded as the most accurate method for survival modeling, is utilized to determine that there is a statistically significant difference in the renal cell carcinoma survival of patients with and without the TP53 gene expression. Specifically, possessing this gene, which itself encodes a tumor suppressor protein, correlates with a much higher survival rate from the carcinoma. This finding contains large implications for future exploration within the intersection of genomics and oncology and suggests the efficacy of gene prediction in carcinomas and other pathologies with hereditary predilections.

1 Introduction

1.1 Renal Cell Carcinoma

Renal cell carcinoma, the most common form of kidney cancer, has the highest mortality rate of the genitourinary cancers and has increase in incidence by 500% since 1971 [9]. Symptoms of afflicted patients can be diverse but generally consist of hematuria, pain, and a flank mass in advanced cases. It originates from uncontrolled cancer cell growth in the inner linings of the kidneys' tubules and often spreads to surrounding organs, including the lungs. Indicators of renal cell carcinoma include abdominal swelling and enlarged veins in the scrotal sac. Standard procedure for doctors to confirm the carcinoma diagnosis entails a complete blood count, CT scan, abdominal and kidney ultrasounds, urine examination, or a biopsy. Classifying the cancer from stage 1 to stage 4 (ordered by ascending severity) is performed through bone scans, PET scans, and chest X-rays [1]. Being an autosomal dominantly inherited disease, renal cell carcinoma can be predicted from an individual's gene expression profile using DNA microarrays.

1.2 TP53 mRNA

The TP53 gene encodes a tumor suppressor protein that contains oligomerization, DNA binding, and transcriptional activation domains [6]. This protein is capable of responding to a variety of cellular stresses in order to efficiently regulate the expression of target genes that induce changes in metabolism, DNA repair, senescence, apoptosis, and cell cycle arrest. Mutations in this gene tend to correlate with hereditary carcinomas such as Li-Fraumeni syndrome [3].

1.3 Semiparametric Models

Non-parametric models are often limited in their ability to model covariate effects while fully parametric models tend to overdo assumptions about the data [7]. As a semiparametric estimator, the Cox model's regression portion makes parametric assumptions regarding the effects predictors have on the hazard function; however, it doesn't make any assumptions concerning the hazard function itself [2].

1.3.1 Proportional-Hazards Regression

The proportional-hazards model, more commonly referred to as the Cox model, is one of the most frequently used methods for survival data analysis [4, 5]. It models the incidence or hazard rate, which is the number of new disease cases per population at-risk per unit time.

2 Methodology

2.1 The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) is the world's largest and most comprehensive collection of genomic data seeking to empower new discoveries relating to the underlying molecular basis for approximately two hundred different types of carcinomas [8]. Since its inception in 2005, the government funded project has generated nearly three petabytes of genomic, epigenomic, transcriptomic, and proteomic data. The publicly available database was accessed through the Genomic Data Commons Data Portal, supported by additional data processing, visualization, and computational tools.

2.2 Survival Function

The data was used to construct a series of survival time distributions.

2.3 Molecular Variable

The molecular variable is numeric; expression data often have skewed distributions, which is why gene expression and miRNA expression are transformed using the logarithmic scale.

2.4 Cox Regression

The molecular variable was interpreted as numeric in the Cox regression model.

Table 1: Summary of survival type and patient number

Disease	Survival type	Patients	Time	Status	Time equals zero	Patients with valid data
KIRP	disease-free interval	291	107	107	1	183
KIRP	disease-specific survival	537	1	4	2	284
KIRP	overall survival	291	1	0	2	288
KIRP	progression-free interval	291	2	0	3	286
KIRC	disease-free interval	537	420	420	2	115
KIRC	disease-specific survival	537	0	12	2	523
KIRC	overall survival	537	0	0	2	535
KIRC	progression-free interval	537	2	0	2	533
KICH	disease-free interval	66	37	37	0	29
KICH	disease-specific survival	66	1	0	0	65
KICH	overall survival	66	1	0	0	65
KICH	progression-free interval	66	1	0	0	65

Figure 1: Survival status summary (0 denotes alive, 1 denotes death)

2.5 Kaplan-Meier

Patients were split into "High" and "Low" groups using the medium value as the cutoff.

3 Conclusion

The results of the Cox regression coupled with the Kaplan-Meier plots provide strong indications of a correlation between the presence of the TP53 gene and kidney cancer mortality. The model supported a lower mortality rate for patients possessing the TP53 gene, which likely stems for the gene being an encoder for the tumor suppressor protein responsible for initiating the biochemical reactions that hinder the growth of the carcinoma. This finding is a significant step towards being able to comprehensively screen and detect the occurrence of carcinomas in order to adequately treat them prior to their spread.

Figure 2: Survival time distribution

Figure 3: Molecular variable summary

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Table 2: Cox regression

Disease	Survival type	Num of samples	coef	Exp(coef)	Coxp	CoxpFDR
KIRP	disease-free interval	182	-0.4856	0.6153	0.2297	0.3445
KIRP	disease-specific survival	283	0.4822	1.62	0.1957	0.3355
KIRP	overall survival	287	0.2592	1.296	0.3954	0.4745
KIRP	progression-free interval	285	-0.09286	0.9113	0.7149	0.7149
KIRC	disease-free interval	115	0.636	1.889	0.3179	0.4239
KIRC	disease-specific survival	520	0.488	1.629	0.03938	0.1181
KIRC	overall survival	531	0.5097	1.665	0.006017	0.0722
KIRC	progression-free interval	529	0.4453	1.561	0.02255	0.1181
KICH	disease-free interval	29	4.318	75.05	0.03721	0.1181
KICH	disease-specific survival	65	-0.7893	0.4542	0.09426	0.2262
KICH	overall survival	65	-0.586	0.5566	0.1673	0.3346
KICH	progression-free interval	65	-0.2039	0.8156	0.6437	0.7022

Figure 4: Hazard ratio and 95% CI

2607(97)00043-6

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Table 3: Kaplan-Meier

Disease	Survival type	Num of samples	Var 1	Var 1 type	LRp	LRpFDR
KIRP	disease-free interval	182	TP53	mRNA	0.7398	0.8296
KIRP	disease-specific survival	283	TP53	mRNA	0.1034	0.2482
KIRP	overall survival	287	TP53	mRNA	0.03452	0.2036
KIRP	progression-free interval	285	TP53	mRNA	0.8296	0.8296
KIRC	disease-free interval	115	TP53	mRNA	0.8181	0.8296
KIRC	disease-specific survival	520	TP53	mRNA	0.06786	0.2036
KIRC	overall survival	531	TP53	mRNA	0.004817	0.0578
KIRC	progression-free interval	529	TP53	mRNA	0.223	0.446
KICH	disease-free interval	29	TP53	mRNA	0.05266	0.2036
KICH	disease-specific survival	65	TP53	mRNA	0.3116	0.5342
KICH	overall survival	65	TP53	mRNA	0.3847	0.577
KICH	progression-free interval	65	TP53	mRNA	0.6156	0.8208

Figure 5: TP53 mRNA with disease-free interval in kirp

Figure 6: TP53 mRNA with disease-specific survival in kirp

Figure 7: TP53 mRNA with overall survival in kirp

Figure 8: TP53 mRNA with progression-free interval in kirp

Figure 9: TP53 mRNA with disease-free interval in kirc

Figure 10: TP53 mRNA with disease-specific survival in kirc

Figure 11: TP53 mRNA with overall survival in kirc

Figure 12: TP53 mRNA with progression-free interval in kirc

Figure 13: TP53 mRNA with disease-free interval in kich

Figure 14: TP53 mRNA with disease-specific survival in kich

Figure 15: TP53 mRNA with overall survival in kich

Figure 16: TP53 mRNA with progression-free interval in kich