A SURVIVAL ANALYSIS APPROACH TO GALLBLADDER CANCER PATIENTS

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Abstract

Gallbladder cancer, known for its formidable malignancy and poor prognosis, poses a challenging task in the field of oncology. This research aims to elucidate the intricate landscape of survival determinants among patients with gallbladder cancer by utilizing an integrated approach. Through the utilization of Cox Proportional Hazards (Cox PH) regression analysis, we conducted an exhaustive examination of a robust cohort comprising 644 patients diagnosed with gallbladder cancer. The present study evaluated the impact of critical variables, such as age, tumor stage, lymph node involvement, metastasis, treatment modalities, race, sex, and tumor grade, on patient survival. These Cox PH regression findings are supplemented by the visual clarity provided by Kaplan-Meier (KM) survival plots, which vividly illustrate the evolving survival dynamics of both the entire cohort and specific covariates. The findings

furnish a comprehensive foundation for clinical decision-making, personalized treatment strategies, and further research endeavors in the challenging realm of gallbladder cancer.

Key words: Survival, Hazard, Gallbladder Cancer, Cox PH, Kaplan-Meier AMS (2000) Subject Classification

1. INTRODUCTION

Gallbladder cancer (GBC) arises from the epithelial lining of the gallbladder and the cystic duct. Though a rare cancer worldwide, it is common in some geographical areas and some ethnic groups [4]. It is a highly aggressive malignancy [13]. The aggressive biologic behaviour and lack of sensitive screening tests for early detection are partly responsible for the poor prognosis of this cancer [3]. It is the sixth most common type of gastrointestinal malignancies worldwide [1]. Unlike other cancer types, GBC show extreme geographical and ethnic biases [5]. The GLOBOCON 2020 data revealed that GBC account for 84,695 deaths in 2020, which is 0.9% of the global cancer deaths and 115,949 new GBC cases diagnosed in the same year accounting for 0.6% of all the global cancer cases [12]. Existing literatures showed that the median age of GBC patients was 71 years [2]. Several studies have also shown that age is a risk factor for prognosis in patients undergoing surgery for gallbladder cancer [9]. Gallstones are the most important risk factor for the causation of gallbladder cancer. Long-standing gallstone disease increases the risk of gallbladder cancer. Hormonal factors play a role as gallbladder cancer is more common in females than males [6]. Higher intake of energy and carbohydrate possibly increase the risk of gallbladder cancer [10]. A recent study revealed that positive lymph nodes and tumor differentiation were found to be prognostic factors for survival in T1b/T2 gallbladder cancer patients [1]. Surgery is the

sole curative therapy for gallbladder cancer patients. Confronting an aging society, the demand to treat elderly patients with GBC is increasing [14].

Despite its infrequent occurrence, gallbladder cancer is often diagnosed at an advanced stage, limiting treatment options and contributing to its high mortality rate. One of the critical aspects in addressing the challenges posed by gallbladder cancer lies in understanding the factors that influence patient survival. It is a multifaceted disease influenced by various clinical, pathological, and demographic factors, each of which may play a role in determining patient outcomes. The existing literatures unrevealed that the factors can include the patient's age, the extent of tumor spread (staging), the involvement of nearby lymph nodes, the presence of metastasis to distant organs, the choice of treatment modalities, as well as patient-specific factors like race, sex, and tumor grade.

To shed light on this complex landscape, our research endeavours to employ an integrated approach that combines both statistical rigor and visual representation. Through Cox Proportional Hazards (Cox PH) regression analysis, we aim to quantify the impact of these critical variables on the survival of gallbladder cancer patients within a substantial and well-characterized cohort. This can aid clinicians in making informed decisions regarding patient care.

Keeping these aspects and facts in mind, our study focuses on the following objectives

- To assess the survival outcomes of gallbladder cancer patients.
- To identify significant prognostic factors associated with survival in gallbladder cancer patients.
- To provide valuable insights that can aid in the risk stratification and treatment decision-making for individuals diagnosed with gallbladder cancer.

2. METHODOLOGY

In this section, we explore and discuss the data, terminology and methodologies employed to conduct our research study.

The study data has been collected from the Surveillance, Epidemiology, and End Results (SEER) website. It is a program of the National Cancer Institute (NCI) in the United States that collects and publishes cancer incidence and survival data from various cancer registries across the country. The data contains the demographic, clinical and treatment related information of 644 patients who have been diagnosed with gallbladder cancer.

Survival analysis which is a statistical technique used in medical, biological, and social sciences to analyze the time until an event of interest occurs. The event of interest in our case is 'death' due to gallbladder cancer. Survival time, also known as time to event, is the primary variable of interest in survival analysis. It represents the time elapsed from a specific starting point (year of diagnosis in our case) until the occurrence of the event (year of death). Survival function $S(t)$ gives the probability that an individual will survive beyond a certain time t without experiencing the event of interest. The hazard function $h(t)$ measures the risk of the event happening at a specific moment in time, given that the individual has survived up to that point. The hazard ratio (HR) is a ratio of hazard rates between two groups or conditions. It quantifies the relative risk of experiencing the event for one group compared to another. When HR is 1, it suggests that there is no difference in risk among the groups, while an HR greater than 1 indicates an increased risk and an HR less than 1 indicates a reduced risk for the same.

In survival analysis, some individuals may not experience the event by the end of the study or may be lost to follow-up before experiencing the event. These individuals are said to be "censored". Censoring is a crucial aspect of survival analysis, and it provides information about the time at which individuals were last observed without experiencing the event.

Now that we have introduced the basic concepts of survival and hazard, we can delve into the explanations of the Kaplan-Meier (KM) plot method and the Cox Proportional Hazards (Cox PH) method, which are two essential tools in survival analysis.

2.1. The Kaplan-Meier Approach

The Kaplan-Meier approach, also known as the Kaplan-Meier estimator or product limit estimator, is a non-parametric method used in survival analysis and medical research to estimate the probability of an event occurring over time. It makes no assumptions about the underlying distribution of event times, making it a valuable tool for analyzing survival data in situations where such assumptions cannot be met. This approach is particularly useful when studying time-to-event data, where the event of interest can be anything from a medical condition's onset to the failure of a mechanical component.

Let us consider,

$t_1, t_2, \ldots, t_k$ as the distinct event times, where $t_1 < t_2 < \cdots < t_k$

d_i as the number of events (deaths) that occurred at time t_i

n_i as the number of subjects at risk just before time t_i where subjects are considered 'at risk' if they have not experienced the event or been censored before t_i

c_i as the number of censored observations at time t_i

Then the Kaplan-Meier estimator for survival probability $S(t)$ at time t is given by the following equation

$$S(t) = \prod_{i:t_i \le t} \left(1 - \frac{d_i}{n_i}\right) \quad (1)$$

2.2. Cox Proportional Hazard Model

The Cox Proportional Hazard Model is a semi-parametric, meaning it combines parametric and non-parametric elements statistical method for analyzing survival data in medical research and other fields. It assumes that the hazard rate i.e., the risk of an event occurring for an individual at any given time is a product of two components:

(i) The baseline hazard function, denoted as $h_0(t)$, which represents the hazard for an individual with covariates set to zero (the reference or baseline level)

(ii) The exponential of a linear combination of covariates, often referred to as the hazard ratio, denoted as $exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k)$

where,

$X_1, X_2, \ldots, X_k$ are the covariates and $\beta_1 + \beta_2 + \cdots + \beta_k$ are the coefficients associated with these covariates.

Hence, the formula for the Cox Proportional Hazard Model is given by

$$h(t) = h_0(t) exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k) \quad (2)$$

3. RESULTS AND DISCUSSIONS

This section gives a detailed explanation of the results obtained by our comprehensive analysis. Firstly, it gives a pictorial view of the survival and hazard curves obtained by the Kaplan Meier approach.

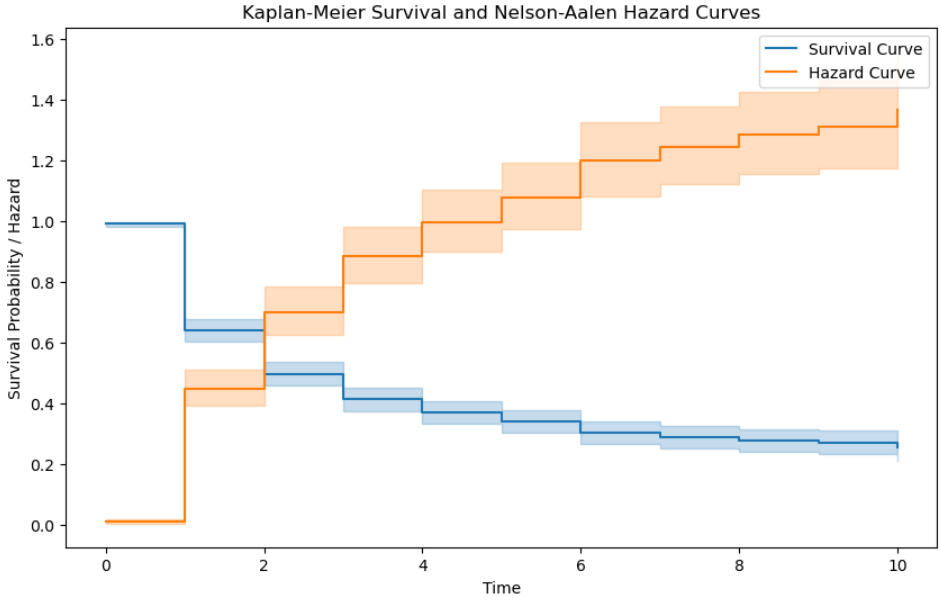

Fig. 1: Survival Probability and Hazard vs Survival Time (in years)

INTERPRETATION

From **Fig.1**, it very clear that the patients diagnosed with gallbladder cancer have a decreasing survival rate and an increasing hazard rate. Meaning that the chance of surviving decrease with time while the probability of failing all of a sudden increase with time.

In the next part (**Fig.2 to Fig.9**), the Kaplan Meier curves with respect to various factors are given.

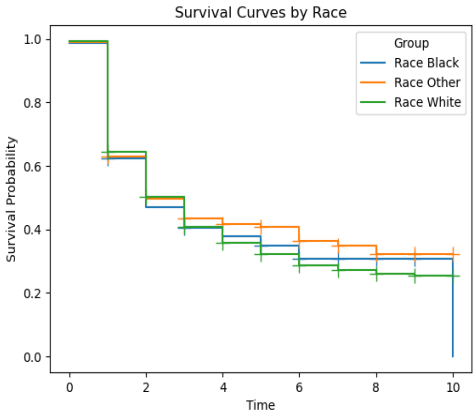

Fig. 2: Survival probability vs Race

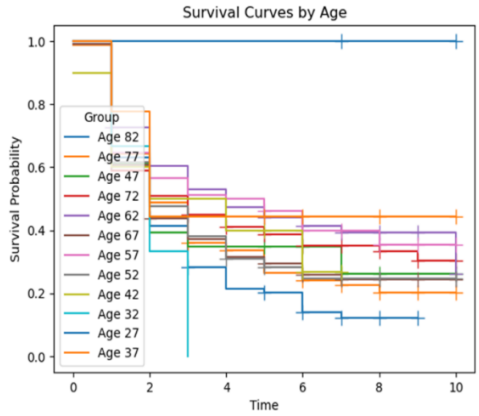

Fig. 3: Survival probability vs Age

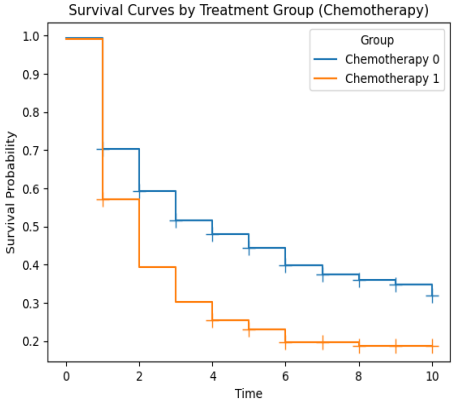

Fig. 4: Survival probability vs Chemotherapy

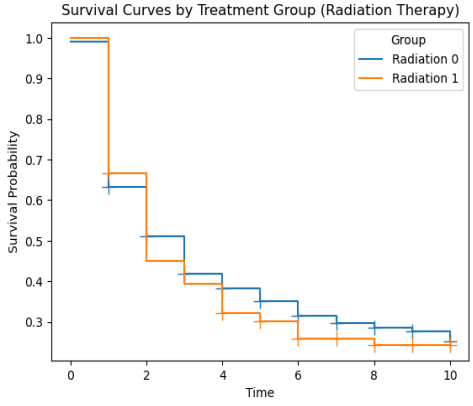

Fig. 5: Survival probability vs Radiation

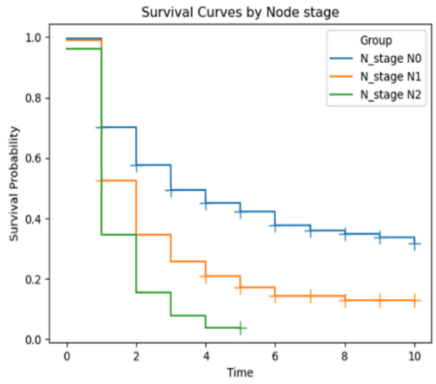

Fig. 6: Survival probability vs Node Stage

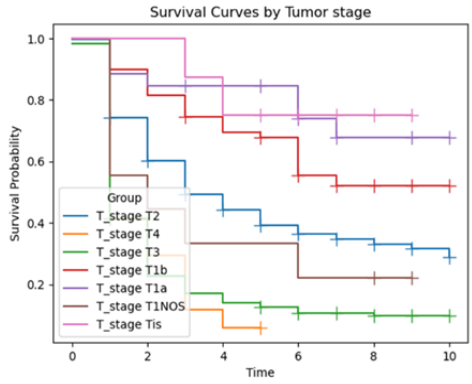

Fig. 7: Survival probability vs Tumor Stage

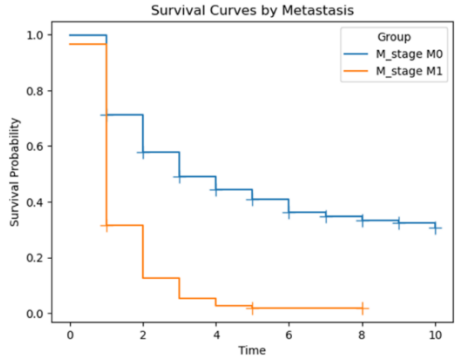

Fig. 8: Survival probability vs Metastasis

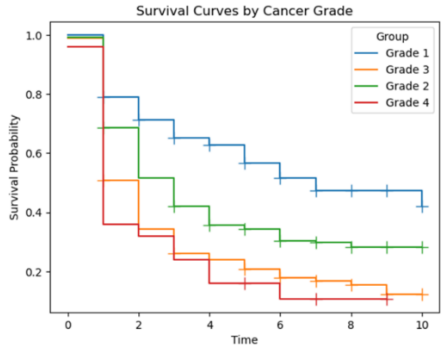

Fig. 9: Survival probability vs Cancer Grade

INTERPRETATION

In this study analyzing the survival outcomes of patients with gallbladder cancer, we observed distinct patterns in the Kaplan-Meier survival curves in terms of various factors like age, race, stages, treatments etc.

Fig. 2 suggests that the survival probability of the patients belonging to the White race are higher than that of the Blacks and that of the others. In case of age, as depicted by **Fig. 3**, the chance of survival of the patients diagnosed with gallbladder cancer decreases with the increase in age. Interestingly, the survival probability of the patients who had not undergone proper treatments like chemotherapy and radiation therapy are found to be high as shown in **Fig. 4** and **Fig. 5**. This means that the patients go for the treatments when the cancer is in the advanced stage. **Fig. 6** and **Fig. 7** shows that the chance of dying from gallbladder cancer increases with the advancement of the node as well as the tumor sizes. The metastatic patients are having a lower survival probability as expected which is represented in **Fig. 8**. Regarding the grades of the gallbladder cancer, the patients are observed to have a higher chance of survival while it becomes almost impossible to recover from a gallbladder cancer that has reached grade 4 as depicted by **Fig. 9**.

Table 1: Results of Cox Proportional Hazards regression

Covariates		Coefficient	Hazard Ratio	95 % CL	*p*-value
Age		0.02	1.02	1.01-1.03	<0.005
Sex	Male	0.02	1.02	0.84-1.25	0.84
	Female (ref)				
Race	White	-0.06	0.94	0.70-1.28	0.71
	Other	-0.12	0.89	0.62-1.27	0.51
	Black (ref)				
Tumor Stage	T1a	-1.11	0.33	0.11-0.98	0.05
	T1b	-0.58	0.56	0.23-1.36	0.20
	T1NOS (ref)				
	T2	-0.09	0.92	0.41-2.05	0.83
	T3	0.66	1.93	0.86-4.31	0.11
	T4	0.54	1.71	0.67-4.37	0.26
	Tis	-1.30	0.27	0.06-1.34	0.11
Node Stage	N0 (ref)				
	N1	0.29	1.34	1.07-1.68	0.01
	N2	0.78	2.19	1.42-3.37	<0.005
Metastasis	M0 (ref)				
	M1	0.79	2.20	1.72-2.82	<0.005
Treatment	Beam Radiation	-0.18	0.83	0.65-1.07	0.16
	No Radiation (ref)				
	Chemotherapy	-0.03	0.97	0.76-1.25	0.84
	No Chemotherapy (ref)				
Grade	1 (ref)				
	2	0.33	1.40	1.05-1.86	0.02
	3	0.49	1.64	1.21-2.22	<0.005
	4	1.00	2.71	1.63-4.50	<0.005

INTERPRETATION

From the **Table 1**, we come across the following observations.

For the variable age, the positive coefficient of 0.02 with a hazard ratio of 1.02 suggests that for each one-year increase in age, the hazard (risk) of an event (likely death in this case) increases by 2% among gallbladder cancer patients. This effect is statistically significant (p-value < 0.005), indicating that older age is associated with a higher risk of the event.

The coefficient for sex (male) of 0.02 and a hazard ratio of 1.02 indicate that, among gallbladder cancer patients, being male is not significantly associated with a different risk of the event compared to being female. The confidence interval includes 1, and the p-value is 0.84, suggesting no statistically significant difference based on gender.

Neither White nor Other race categories show statistically significant differences in the risk of dying of gallbladder cancer compared to the reference category Black in this analysis. The hazard ratios for both groups are close to 1, and their confidence intervals include 1, indicating no statistically detectable effect on survival in this analysis.

Among the different tumor stages, T1a is associated with a significantly lower risk of death compared to T1NOS. T1b shows a lower risk compared to T1NOS, but this difference is not statistically significant. T2, T3, T4, and Tis do not show statistically significant differences in risk compared to T1NOS in this analysis.

Node Stage N1 is associated with a significantly higher risk of death compared to N0, with a 34% increase in hazard. In the same way, Stage N2 is associated with a significantly higher risk, with a 119% increase in hazard compared to N0.

The presence of metastases (Metastasis M1) in gallbladder cancer patients is associated with a significantly higher risk of death compared to patients without distant metastases (Metastasis M0). The hazard ratio of 2.20 indicates a substantial increase in the risk of death in patients with metastases. This finding underscores the importance of metastasis status as a strong predictor of prognosis and survival in gallbladder cancer patients.

However, the analysis suggests that neither Beam Radiation nor Chemotherapy has a statistically significant impact on the risk of dying in gallbladder cancer patients, as the hazard ratios are close to 1, and the confidence intervals include 1. These treatments do not appear to have a strong, statistically detectable effect on survival in this analysis. However, it's essential to consider that the lack of statistical significance in this analysis does not necessarily mean that these treatments have no effect; other factors and study limitations may be at play.

The positive coefficients for Grade 2 (0.33), Grade 3 (0.49), and Grade 4 (1.00) suggest that higher tumor grades are associated with higher risks of death compared to Grade 1, which is the reference category.

These findings can provide valuable insights for clinicians and researchers working with gallbladder cancer patients, helping them understand which factors are associated with higher or lower risks of adverse events and potentially guiding treatment and management decisions.

4. CONCLUSION

The study on gallbladder cancer survival outcomes has revealed distinct patterns influenced by various factors. Notably, age emerges as a significant predictor, with each year increasing the risk of adverse events by 2%, highlighting the importance of

age in prognosis. Gender, however, does not significantly affect survival. Race does not exhibit statistically significant differences, emphasizing the need for equitable care.

Tumor stage and node involvement play pivotal roles, with specific stages carrying higher risks of adverse events. The presence of metastases significantly increases the risk of death, underscoring its prognostic importance. Surprisingly, chemotherapy and radiation therapy do not exhibit a statistically significant impact on survival, warranting further investigation.

Lastly, tumor grade shows a clear association, with higher grades correlating with increased risks. These findings offer valuable guidance for clinicians and researchers, aiding in treatment decision-making and enhancing our understanding of gallbladder cancer prognosis.

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