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Sağkalım ve Cox Regresyon Analizi: Hayvancılık Alanında Bir Uygulama

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ÖZ

Bu çalışmanın amacı, sağkalım analiz yöntemlerinden Kaplan-Meier (K-M) ve Cox regresyon yöntemlerini teorik ve uygulamalı olarak incelemektir. Bu amaçla hayvancılık alanına ait veriler kullanılmıştır. İlk veri seti, iki farklı kümese ait yumurta tavuklarının ölüm kayıtlarını, ikinci sayısal örnek ise tedavi ve kontrol gruplarındaki farelere ait ölüm kayıtlarını içermektedir. Elde edilen sonuçlara göre, Kümes 6b'deki tavukların ortalama sağkalım süresi (22.7 hafta), Kümes 6a'ya (22.5 hafta) göre daha uzundur. Kümes 6a'daki tavukların, Kümes 6b'ye kıyasla %73.7 daha yüksek risk altında olduğu tespit edilmiştir (p=0.000). Farelerde, tedavi grubundaki tümör insidansı kontrol grubuna göre 2.193 kat daha yüksek bulunmuş ve bu durum tümör oluşum riskini %119.3 artırmıştır (p=0.011). Ayrıca, erkek farelerde olay oluşma oranı dişi farelere göre %95.3 daha düşük bulunmuştur. Bu bulgular, tedavi ve cinsiyetin olay oluşum oranı üzerinde önemli bir etkisi olduğunu göstermektedir. Bu çalışmanın, hayvancılık alanında çalışan araştırmacılara yol gösterici olması ve bahsi geçen yöntemlerin hayvancılık alanında kullanımının yaygınlaşmasına katkıda bulunması umut edilmektedir.

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ABSTRACT

The aim of this study is to examine the Kaplan-Meier (K-M) and Cox regression methods, which are survival analysis techniques, both theoretically and practically. For this purpose, data from the field of animal husbandry were used. The first dataset consists of mortality records of laying hens from two different poultry houses, while the second data set includes mortality records of rats in treatment and control groups. According to the results, the mean survival time of chickens in Coop 6b (22.7 weeks) was slightly longer than in Coop 6a (22.5 weeks). Chickens in Coop 6a faced a 73.7% higher risk compared to those in Coop 6b (p=0.000). In rats' data, the tumour incidence was 2.193 times higher in the treatment group than in the control group, indicating a 119.3% increased risk of tumour formation (p=0.011). Additionally, the event rate was 95.3% lower in male rats compared to females, highlighting the significant effects of treatment and gender on event occurrence. It is hoped that this study will guide researchers working in the field of animal husbandry and contribute to the wider application of these methods in the field.

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1. Introduction

The origins of survival analysis can be traced to the 17th century when Edmund Halley created the first life table between 1687 and 1691. In the 20th century, survival analysis was used to evaluate the life expectancy of military vehicles during World War II (Bulut, 2011). The field advanced with the introduction of the Kaplan-Meier method in 1958, Cox's Proportional Hazard Model in 1972, and Miller's application of nonparametric methods in 1981 (Tuncay, 2005).

Survival analysis is a statistical method used to assess the probability of an event, such as mortality, occurring over time. While originally applied to medical outcomes, it is also used in areas like engineering, insurance, and economics, where it is often referred to as failure analysis, event-time analysis, or time-to-event analysis. The method can assess not only mortality but also events like recovery, treatment response, or task completion. Its dual objectives are to estimate the probability of an event within a specified time and to identify factors influencing that probability (Kaygısız, 2010).

The term "survival time" refers to the duration until an event of interest occurs, which can vary from unemployment duration to machine part failure or drug efficacy (İnceoğlu, 2013; Şimşek, 2013). Some data may be censored, meaning the event is not observed within the study period, often due to unrelated factors (Yetkin, 2006).

While survival analysis is primarily applied in medicine (Başar, 2013; Karal, 2014; Cao et al., 2015; Du et al., 2020; Nagy et al., 2021; Lundgreen et al., 2021), it is also used in insurance (Kılık, 2019; Hidayat et al., 2022), engineering (Thijssens and Varhagen, 2020), economics (Göktaş et al., 2012; Karasoy et al., 2015), and construction (Showkat and Singh, 2022). However, its use in agriculture and animal husbandry (Caetano et al., 2013; Grseziak et al., 2022), particularly in Turkish literature, remains limited.

This paper investigates the use of survival analysis on animal science data, providing a useful reference for scholars on this subject. It demonstrates the practical use of the K-M and Cox regression methods.

This study is of significance in that it draws attention to the potential of survival analysis methods that are seldom employed in the fields of animal husbandry and agriculture. Survival analyses afford researchers who are engaged in work with time-oriented data the opportunity not only to ascertain the probability of an event occurring, but also to analyse the factors affecting this probability. These methods, which are of paramount importance for risk management and strategic decision-making processes in the agriculture and livestock sectors, permit a more comprehensive analysis of data and more reliable results. In this context, the objective of this study is twofold: firstly, to provide a theoretical explanation of the K-M and Cox regression models of survival analysis; and secondly, to offer a practical illustration of these models using two different data set relating to animal science.

2. Material and Method

The study used mortality records from two laying hen coops of a private poultry farm and a rat data set provided by Mantel et al. (1977), available in the R software data archive. The rat data included

categorical variables for tumor development, sex, and treatment groups (drug-treated vs. control), with 300 rats observed over 104 weeks. The poultry sample comprised 5344 chickens from two coops, A and B, observed for 23 weeks. In both data sets, the first level was used as the reference category.

2.1. Laying Hen Data set

The laying hen data set, detailed in Table 1, includes information from 5344 breeder hens observed over 23 weeks in two coops. Mortality events are marked as 1, while other instances are marked as 0. Coop 6a had 2224 chickens, with 108 deaths and 2116 censored observations. Coop 6b had 3120 chickens, with 88 deaths and 3032 censored observations (Table 1).

Table 1. Number of laying chickens, event and censored data

	Number of chickens	Event (Death)	Censored data	
			Number of chickens	%
Coop 6a (Reference)	2224	108	2116	95.1
Coop 6b	3120	88	3032	97.2
Toplam	5344	196	5148	96.3

2.2. Rat Data set

Kaplan-Meier and Cox regression analyses were performed on the rat data, with the results presented below. Tumor development was tracked weekly for 300 rats, with tumor emergence coded as 1 (event) and other conditions as 0 (censored). The treatment group was coded as 1 and the control group as 0. For gender, female was coded as 0 and male as 1. Table 2 provides descriptive statistics: the control group had 200 observations with 21 tumors and 179 without, while the treatment group had 100 observations with 21 tumors and 79 without.

Table 2. Number of rats, event and censored data by treatment status

	Number of rats	Event	Censored data	
			Number of rats	%
Control group	200	21	179	89.5%
Treatment group	100	21	79	79.0%
Total	300	42	258	86.0%

2.3. Survival Analysis

Survival analysis examines the time until an event, such as death, illness, or failure, occurs. This time is referred to as “failure time”, “event occurrence time” or “survival time” (Yay et al., 2007). The term “survival time” refers to the period between the start of observation and the occurrence of death. The primary focus of survival analysis is the observed duration of survival or life expectancy, making it crucial to clearly define this variable. To measure it, a clear starting point and a consistent time scale must be established for each unit or individual, ensuring the precise moment of failure is recorded (Sertkaya et al., 2005).

2.3.1. Data types used in survival analysis

A key feature of survival analysis is the presence of censored data, which distinguishes it from other statistical methods. In survival analysis, data distribution, particularly for disease progression and mortality, is typically asymmetrical and positively skewed. Censoring occurs under three conditions: (1) the study concludes without the event occurring, (2) the individual stops being observed or is removed from the study, or (3) the event is removed from observation due to unrelated reasons (Kleinbaum and Klein, 2012). Censored data can be categorized into three types (Kleinbaum and Klein, 2012; Oralhan, 2015). Right censoring occurs when the event has not yet occurred but is unobserved, making it the most common form. Left censoring refers to cases where the event's exact time is unknown but occurred within a specific time interval.

2.4. Survival Functions

2.4.1. Survival function

The term "survival time" refers to the period between the start of observation and the occurrence of event (death, disease, incidence etc.). The variable T, representing survival time, is a random variable ranging from zero to infinity ($0 \leq T \leq \infty$). The survival data $t_1, t_2, \ldots, t_n$ are observations of the positive random variable T. The probability density function *f(t)* of T is the cumulative distribution function *F(t)*, which represents the probability of being less than or equal to a given value t.

$$F(t) = P\ (T \leq t) = \int_0^t f(u)du \quad (1)$$

The survival function is;

S(t) =1-F(t).

Hence, it has shown as:

$$S(t) = P\ (T > t) = \int_t^\infty f(u)du \quad (2)$$

2.4.2. Hazard (Risk) function

The hazard function, h(t), represents the instantaneous mortality rate, or the risk of dying within a small-time interval t+Δt. It focuses on failure and may be constant, increasing, decreasing, or following a more complex pattern (Saygı, 2007; Bulut, 2011; Kleinbaum and Klein, 2012).

$$h(t) = \lambda = \lim_{\Delta t \to 0}\left[\frac{P(t \leq T < t+\Delta t\ |\ T \geq t)}{\Delta t}\right] \text{ and provides } h(t) \geq 0 \text{ and } \int_t^\infty h(t)dt = \infty \quad (3)$$

The cumulative hazard function (H(t)) represents the accumulated failure rates over a given time period t. Mathematically, it is the integral of the hazard function between integration limits of 0 and t. Its formulation is as follows;

$$H(t) = \int_0^t h(x)dx \quad (4)$$

2.5. Survival analysis methods

In survival analysis, non-parametric and semi-parametric techniques are used to assess whether and how specific variables affect survival times. This study employs Kaplan-Meier method, a non-parametric approach for deriving survival curves and confidence limits, alongside the semi-parametric Cox regression method to evaluate the impact of the parameters under investigation (Göktaş et al., 2012).

2.5.1. Kaplan-Meier (K-M) method

K-M analysis is a non-parametric method used to predict time-related events and evaluate statistical significance between survival curves for different conditions. It calculates survival times in the presence of censored data. The construction of Kaplan-Meier estimations involves the establishment of time intervals according to the occurrence of events in an ascending order.

The Kaplan-Meier estimate of the survival function is presented below;

$$\hat{S}(t) = \prod_{t_i \le t} (1 - \frac{d_i}{n_i}) \quad (5)$$

In the formula (5),

$\hat{S}(t)$ = The estimated survival probability at time *t,*

t_i: The time points where events (e.g., death, failure) occur,

d_i: The number of events (e.g. deaths) occurring at time t_i,

n_i: The number of the subjects at risk just prior to time t_i. Besides, $\frac{d_i}{n_i}$ represents the probability of the event occuring at t_i and $1 - \frac{d_i}{n_i}$ is the probability of surviving (not experienced the event) at t_i (Özdemir, 1994; Türe et al., 2009).

2.5.1.1. Log-rank test

The Kaplan-Meier method provides an overview of survival functions across groups but does not assess the statistical significance of observed differences. The log-rank test evaluates these differences by testing the null hypothesis of no difference between survival functions. The log-rank test statistic follows a $\chi^2_{1,\alpha}$ distribution with 1 degree of freedom under the null hypothesis. For the two groups, significance is determined by comparing the test statistic to the chi-square critical value for 1 degree of freedom at the α level (Kleinbaum and Klein, 2012; Şimşek, 2013). The log-rank statistic is calculated by taking the square of the difference between the summed observed and expected scores for one group—for example group 2—and dividing it by the variance of that summed difference (Kleinbaum and Klein, 2012). It is formulated as follows;

$$Log-rank=\frac{\left(O_2-E_2\right)^2}{Var(O_2-E_2)} \quad (6)$$

2.5.2. Cox regression method

The Cox regression method aims to determine the effect of variables on the occurrence of an event within a defined time interval and predicts life expectancy by mathematically modeling these effects (Kaygisiz, 2010). It calculates the influence and direction of variables on survival time (Çekçeki, 2007; Ata et al., 2008).

In Cox regression, the independent variables are not required to be normally distributed and correlated. The model assumes a proportional relationship between variables, known as the proportional hazard model (Yetkin, 2006). As a semi-parametric model, the Cox regression does not assume a specific probability distribution for the survival time (Işık, 2007). For a single independent variable, the hazard function can be expressed as follows:

$$\text{h (t, X)} = h_0(t).e^{\beta x} \quad (7)$$

In the event that there are multiple independent variables, the hazard function is presented as follows;

$$\text{h (t, X)} = h_0(t)\ .\ e^{(\beta_1X_1+\beta_2X_2+\cdots+\beta_PX_P)} \text{ or } h_0(t)\ .\ e^{\sum_{i=1}^{p}\beta_iX_i} \quad (8)$$

The Cox model states that the hazard at time *t* is the product of two quantities: the baseline hazard function ($h_0(t)$) and the exponential of the linear sum of β_iX_i for *p* explanatory variables (Kleinbaum and Klein, 2012). The Cox regression model relies on four key assumptions: (i) the effects of explanatory variables on the hazard function are log-linear, (ii) there is a multiplicative relationship between the log-linear function of explanatory variables and the hazard function, (iii) the hazard ratio between any two individuals remains constant over time, and (iv) explanatory variable values are recorded at the study's start. Thus, the ratio of mortality functions for units with different explanatory variables is time-independent, though their hazard ratios are proportional (Karal, 2014).

The effects of explanatory variables are estimated through the β-coefficients, and their influence on the hazard is quantified using the hazard ratio (e^{β}). The baseline hazard function ($h_0(t)$) does not require direct estimation for the regression model, as the Cox model relies on relative hazards rather than the explicit form of $h_0(t)$. Coefficient estimates are obtained using the maximum likelihood method through the maximization of the partial likelihood function, which focuses on the order of event times rather than their exact values. The function is formulated as (Collet, 2003);

$$L(\beta)=\prod_{j=1}^{r}\frac{\exp\left(\beta' x_{(j)}\right)}{\sum_{I\in R(t_{(j)})}\exp(\beta' x_I)} \quad (9)$$

The likelihood function in Cox regression incorporates censored data and evaluates the order of event occurrences. Notably, the Cox model does not depend on a specific distribution; rather, it relies on the

order of event occurrences (Kleinbaum and Klein, 2012). Maximum likelihood estimates of β-coefficients are obtained by maximizing the log-likelihood function using the Newton-Raphson algorithm through successive iterations (Collet, 2003; Karal, 2014).

3. Results and Discussion

The K-M and Cox regression methods were applied to analyze survival data from two different data sets. Initially, these analyses were conducted on the laying hen data set, with results interpreted accordingly. Subsequently, the same analyses were applied to the rat data set.

The mean survival times are presented in Table 3. K-M estimator is a commonly used approach for analyzing survival data and comparing different groups of individuals (Grzesiak et al., 2022). K-M analysis shows that the mean survival time for Coop 6a is 22.5 weeks, while for Coop 6b it is 22.7 weeks, indicating a longer survival time in Coop 6b.

Table 3. Descriptives of survival times of coops

	Mean survival time (week)	Standard error	95% Confidence interval	
			Lower bound	Upper bound
Coop 6a	22.496	0.051	22.396	22.596
Coop 6b	22.669	0.041	22.589	22.749
Total	22.597	0.032	22.534	22.660

Figure 1 illustrates the survival function, showing that Coop 6b has a longer survival time compared to Coop 6a.

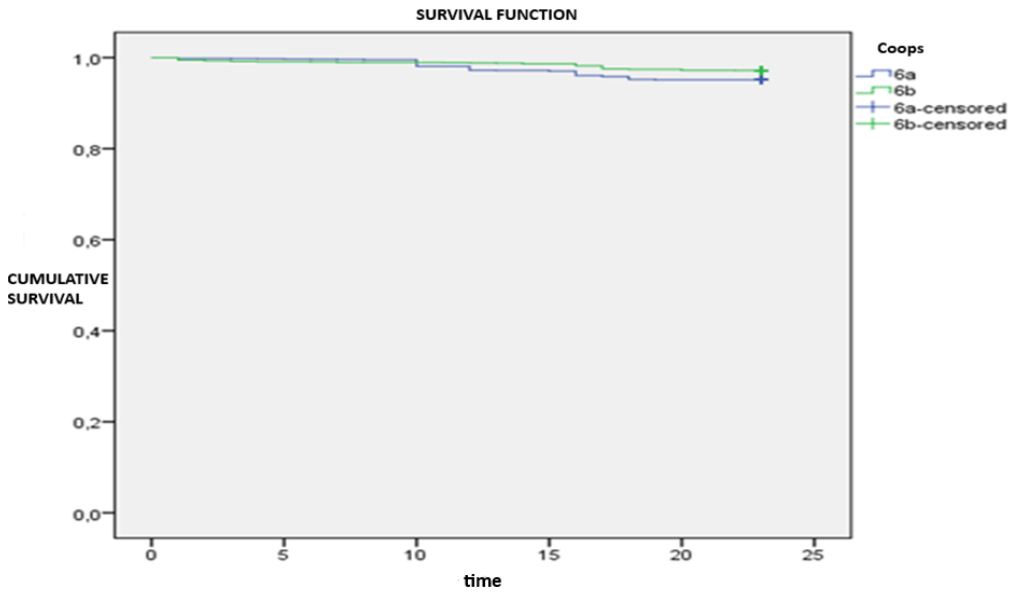

Figure 1. Survival function for both coops (K-M Curve)

Kaplan-Meier analysis tracks the likelihood of an event over time but does not assess the significance of differences between survival curves. The log-rank test, used to compare survival probabilities, is presented in Table 4. The results indicate a statistically significant difference between Coop 6a and Coop

6b ($p<0.01$). In a study conducted at two poultry farms in Kenya, Ngolo et al. (2018) found no significant difference in the survival rates of the broilers on the two farms.

Table 4. Log-rank results

	Chi-Square	P value
Log Rank (Mantel-Cox)	15.212	0.000**

**p<0.01

Cox regression analysis examines the hazard rate of an event in relation to independent variables. Applied to the laying hen data, the results are shown in Table 5. Here, the dependent variable is survival time in weeks, and the independent variable is the type of coop. The Exp(β) value, or hazard ratio, indicates the relative risk compared to the reference category. A positive β coefficient signifies a higher risk, while a negative β coefficient indicates a lower risk (Özşen, 2006; Bulut, 2011; Şimşek, 2013).
The interpretation of positive and negative estimates of the regression coefficients using the Cox model is that they intensify or reduce the effect on the risk function, respectively (Caetano et al., 2013). Table 5 shows a positive coefficient (0.552), suggesting that hens in Coop 6a have a shorter lifespan than those in Coop 6b. Specifically, the hazard ratio (Exp(β)) indicates that the event occurs 1.737 times more frequently in Coop 6a, reflecting a 73.7% higher risk for chickens in Coop 6a compared to those in Coop 6b.

Table 5. Results of Cox reggression

	β	S. error	Wald	Sd	p value	Exp(β)	95% confidence interval	
							Lower bound	Upper bound
Coop	0.552	0.144	14.770	1	0.000	1.737	1.311	2.301

-2Likelihood= 3343.53, χ^2= 15.14, p=0.000

Table 6 presents the mean tumor development times: 100.4 weeks for the control group and 98.5 weeks for the treatment group. The shorter tumor development time in the treatment group indicates an effect of the treatment and the log-rank test confirms this difference is statistically significant (p=0.018).

Table 6. Mean tumour development time by treatment status

	Mean survival time (week)	Standard error	95% Confidence interval	
			Lower bound	Upper bound
Control group	100.380	0.824	98.764	101.996
Treatment group	98.550	1.430	95.748	101.352
Total	99.780	0.729	98.351	101.210

Log-rank (Mantel Cox) χ^2 =5.549, p=0.018

Figure 2 shows that the survival time for the control group is longer compared to the treatment group.

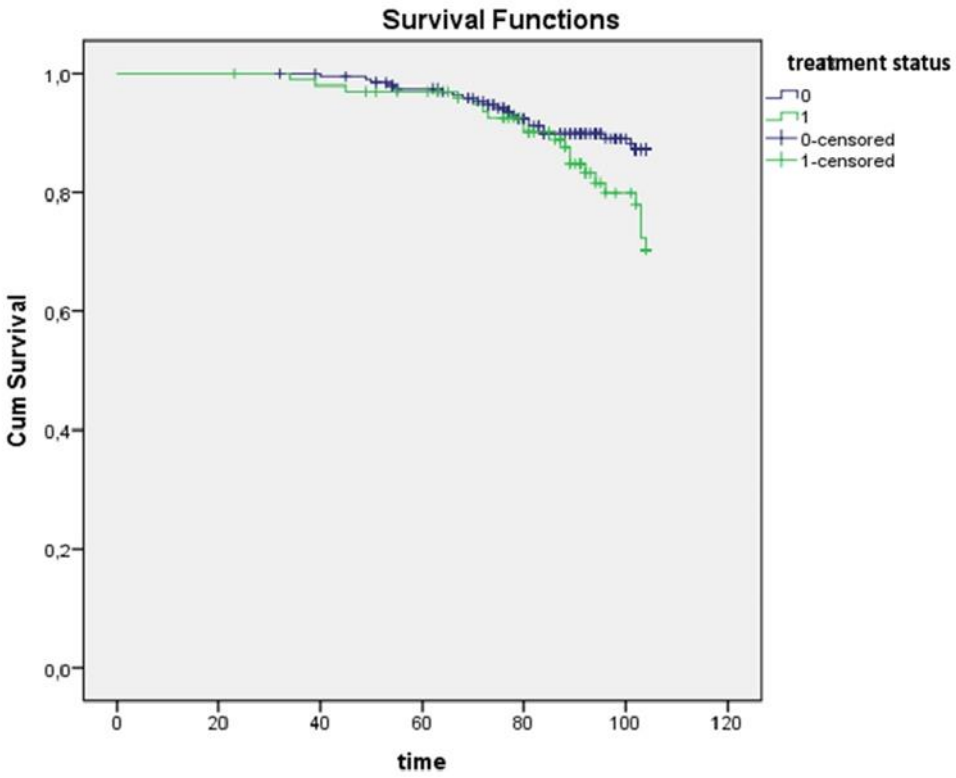

Figure 2. Survival function according to treatment status (K-M Curve)

Table 7 shows that out of 300 observations, 150 were female and 150 were male. Tumor development occurred in 40 females (110 without tumors) and 2 males (148 without tumors).

Table 7. Number of rats, event and censorship data by gender

	Number of rats	Event (Tumour)	Censored data	
			Number of rats	%
Female	150	40	110	73.3
Male	150	2	148	98.7
Total	300	42	258	86.0

Upon examination of the average tumour development time of the observations by sex, it was found that males exhibited a greater tumour development time than females (Table 8). As illustrated, the average tumour development time of males was 103.52 weeks, while the average development time of females was 96.20 weeks. The log-rank test results demonstrated that the difference was statistically significant (p=0.000).

Table 8. Mean tumour development time by gender

	Mean survival time (week)	Standart error	95% Confidence interval	
			Lower bound	Lower bound
Female	96.202	1.329	93.597	98.806
Male	103.525	0.334	102.871	104.179
Total	99.780	0.729	98.351	101.210

Log-rank (Mantel Cox) χ^2=35.907, p=0.000

Figure 3 illustrates the survival function graph of gender status. As evidenced by the Figure 3, tumour development in female rats occurred in a shorter time frame than in male rats.

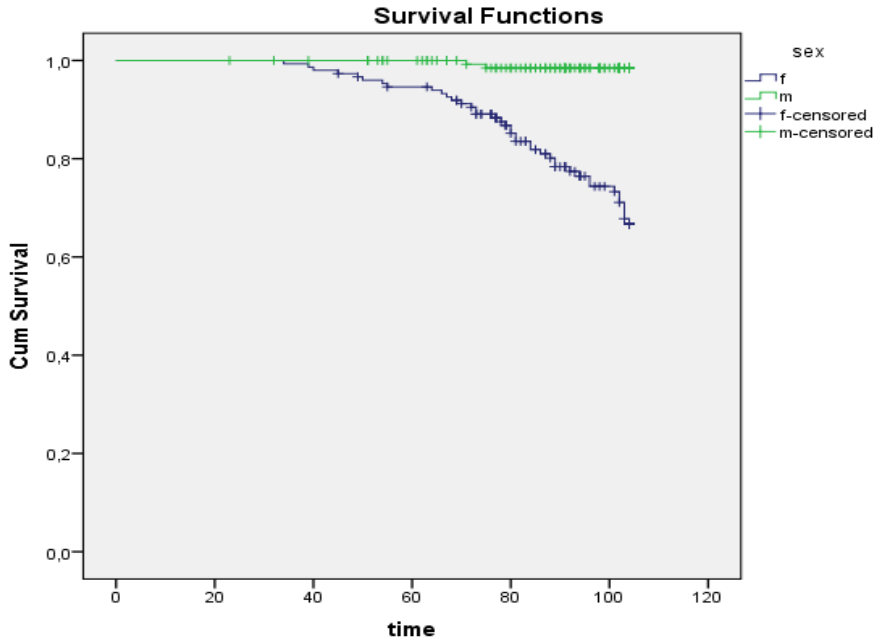

Figure 3. Survival Function by gender (K-M Curve)

The results of the Cox regression analysis are presented in Table 9. The results indicated that the incidence of tumours was 2.193 times higher in the treatment group than in the control group. This indicates that the drug elevated the risk of tumour formation by 119.3 percent ((2.193-1= 1.193) *100), i.e. 119.3 per cent) (p=0.011). A negative β value indicates that the event occurrence rate is lower in males than in females. The results indicate that the tumour occurrence rate is 95.3 per cent lower in males than in females (1 – 0.047 = 0.953, i.e. 95.3 percent reduction). These findings demonstrate that treatment and gender significantly influence the rate of occurrence of the event. The treatment group (those receiving treatment) is at a higher risk, while male rats are at a lower risk.

Table 9. Results of cox regression

	β	Standard error	Wald	p value	Exp (β)	95% confidence interval	
						Lower bound	Upper bound
Treatment	0.785	0.309	6.446	0.011	2.193	1.196	4.020
Gender	-3.063	0.725	17.865	0.000	0.047	0.011	0.193

-2LogLikelihood= -445.49, χ^2= 5.197, p= 0.023

4. Conclusion

The objective of this study was to provide a theoretical and practical guide for the utilisation of K-M and Cox regression analyses in livestock research. Despite the dearth of studies in the extant literature, the deployment of survival analyses in livestock data holds considerable promise, particularly in research that requires long-term observation.

The K-M analysis demonstrated the influence of the observation period on survival probabilities, while the Cox regression analysis facilitated the investigation of the factors contributing to these probabilities. The results of the analyses provided crucial insights into the identification and management of risk factors in the livestock sector. It is anticipated that the methodologies employed will inform the decision-making processes of both researchers and sector professionals.

One of the principal constraints of this study is the restricted scope of the data sets employed. The incorporation of larger and more heterogeneous data sets for survival analyses would enhance the generalisability of the findings.

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Conflict of Interest Statement: The authors declare that they have no conflict of interest.

Authors' Contribution Declaration

Authors declare that they have contributed equally to the article.

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