Alexandria Journal of Veterinary Sciences
www.alexjvs.com

AJVS. Vol. 57 (2): 58-71 April 2018.

DOI: 10.5455/ajvs.296449

Nonparametric and Semi-parametric Survival methods for Assessing days Open and Conception rates of Lactating cows

Sherif A. Moawed

Department of Animal Wealth Development, Biostatistics Division, Faculty of Veterinary Medicine, Suez Canal University, Ismailia 41522, Egypt.

Key words:
Survival analysis, Kaplan-Meier plots, log-rank test, Cox proportional hazard models, dairy cattle, days open

***Correspondence to:**
sherifstat@yahoo.com;
sherifmoawed@vet.suez.edu.eg

ABSTRACT

Evaluation of conception rates in dairy livestock requires specific statistical methods because of the followings: (i) some cows are still alive after the follow up period and their fate is not known, which means that records of these animals should be censored, (ii) the risk factors connected with fertility are not perform linearly and may vary with time, (iii) not all lactation records are normally distributed. Therefore, this study was undertaken to assess factors influencing days open (DO) and conception rates of dairy cattle, using nonparametric and semi-parametric survival functions. Parity, season of calving, milk yield levels (MYL), age at calving (AAC), days to first estrus (DFE), days to first insemination (DFI), number of inseminations per conception (NIPC) were significantly associated with days open for a number of 1980 lactation cows, of which 12.73 % were censored. The overall median of DO was 123 days (95 % CI = 119.55-126.44). For the first five parities studied, medians of DO were 111, 121, 128, 123 and 152 days; respectively. The Kaplan-Meier survivor functions and log-rank tests denoted highly significant differences ($p < 0.001$) among parities, seasons of calving and levels of milk yield in terms of time to conception. Proportions of pregnant cows were estimated at every postpartum time point alongside their cumulative probabilities. The overall percentages of pregnant cows were 0.5, 34.7, 67.2, 92.07 and 99.34 % at days 50, 100, 150, 200 and 250 postpartum. Cox PH models reveled significant contribution of all studied factors as hazards for conception. The hazard ratios (varied from 0.632 to 1.393) were used to quantify the exact differences between all categories. The present study has provided important survival functions that were used to identify and quantify the economic risk factors associated with days open length and conception rates of dairy cattle in Egypt.

1. INTRODUCTION

Measuring and quantifying factors associated with fertility in dairy cows is a complicated process, because the determinants of fertility are usually present at many scales, such as, cow management, feeding, estrus detection, experienced intervention for insemination at the first time, calving veterinary public health, genetics, and the diseases frequently attack the dairy herd (Bahonar et al., 2009). Among the potential outcomes that can be used to analyze these complex traits is the calving to conception interval, namely, days open (DO). The length of DO is considered as a monitor for routine assessment of cow's reproductive efficiency for further economic decisions in the herd, particularly culling of cows with low performance (Arthur et al., 2001). The main cause of culling in most of dairy herds is the reduced reproductive ability of cows (Swedish Dairy Association, 2002). Such poor fertility may be lead to low conception rate, increased inseminations, repeat breeding, elongated DO, increased culling and replacement cost (Royal et al., 2000; Roche et al., 2000; Lucy, 2001; Yusuf et al., 2010).

Positively speaking, there are a number of criteria that could be taken into account for a cow to be deemed with good fertility, such as, prominent signs of estrus, short calving to conception period, has an increased likelihood of being pregnant after insemination at the proper time and the profitability of the cow so that it can give a calve every year (Mark et al., 2005; Schneider et al., 2005; Taufik and Suriyasataphorn, 2008). To achieve this, Esslemont and Kossaibati (2000) have supplied breeders with a checklist for good fertility measures. For instances, the majority of cows should be inseminated after calving by adjusting the average calving to first insemination period to be less than 70 days, the overall estrus discovery must be more than half of the herd and the conception rate should exceed 50 %. For all the previously mentioned reasons, knowledge of factors potentially impacting cows' fertility and days open, in particular, is imperative for better management and improvement of dairy herds.

In term of statistical analysis and datasets assessment of dairy herds, a variety of linear and non-linear models have been investigated, such as, regression models, animal models, time series methods, general linear models, generalized linear models, least squares analysis. However, these methods cannot handle censored records, resulting in improper understanding of all available information, or at least lead us to biased estimates. Alternatively, survival analysis could be used for discovering time-related traits (Allore et al., 2001). Furthermore, the distribution of lactation or longitudinal data is skewed by time. Subsequently, normality based statistical methods have some limitations when dealing with survival data (Vukasinovic, 2016).

Survival analysis is an advanced statistical methodology used to analyze and model time to an outcome. This outcome is usually binary, involving either success or failure events. For the first time, survival analysis was incorporated in medicine to study time until death so that the survival time can be estimated (Ducroq et al., 2000; Lamuno et al., 2017). Survival analysis is hypothesized to be superior over other statistical approaches selected for analyzing the hazard or risk factors participated in determining the length of days open (Collett, 2003; Kleinbaum and Klein, 2005; Vukasinovic, 2016). This superiority is mainly attributed to the ability of survival analysis to benefits from incomplete or missed records of cows in the form of censoring. Taking the censored data into consideration denotes unbiased estimates and allows more inferences about the target population (Del et al., 2006). Moreover, survival analysis considers the non-normality and the skewed distribution of longitudinal data. Thus, it could be suited for continuous and discrete observations (Lamuno et al., 2017). Previous studies have attempted to examine the factors influencing days open in dairy herds (Farin et al., 1994; Harman et al., 1996; Meadows et al., 2006; Melendez and Pinedo, 2007). However, most of their researches have been conducted to handle factors such as parity, milk yield, diseases, body condition score, and season along with its impact on days open. Therefore, this study was conducted to benefit from different nonparametric and semi-parametric survival functions in recognizing factors connected with the length of days open and conception rates in dairy cows raised in Egypt. In addition, to quantify the expected hazard of conception at different parities, seasons of calving and milk yield levels.

2. MATERIALS AND METHODS

2.1. Data description and definition of censoring

Data of the present study were collected from a commercial dairy herd located in Damietta governorate, Egypt. The datasets consisted of 1980 lactation records covering the period from January 2008 to September 2017. The outcome variable of interest was the time interval form calving to conception which was called days open (DO, days). Cows had complete observations and experienced the event of interest, the conception, were considered uncensored observations. In contrast, some cows were culled, died or still not pregnant at the follow up period of this study. Such animals were treated as censored. Technically, all cows that had the event were coded one, while those with incomplete records were statistically coded as zero (i.e., pregnant cows = 1, and non-pregnant cows = 0). The main factors studied for comparing the risk of pregnancy in the current herd were parity (1-5), season of calving (summer, winter, autumn, and spring) and milk yield level (low, medium, and high). Cows were classified into the three categories of milk production on the basis of the empirical rule of normal distribution curve. Thus, the mean (μ = 6247 kg) and standard deviation (SD, σ = 2704 kg) of the studied population were first estimated, then the mean ± SD ($\mu \pm \sigma$) were calculated to represent the cows with medium yield (68 % of distribution was ranged from 3543 kg to 8951 kg). Also, the minimum and maximum values of milk yield were identified to be 440 kg and 14850 kg; respectively. Cows with milk yield < 3543 kg were considered those of low yield while cows with milk yield > 8951 kg were the high yielding. The other independent factors which treated as covariates in Cox model were age at calving (AAC, months), days to first estrus (DFE), and days to first insemination (DFI), number of inseminations per conception (NIPC).

In term of the sample size required for survival analysis, Cleves et al. (2008) recommended that the minimum sample size needed for performing survival analysis is 1100 observations with a 95 % confidence degree. In other words, the estimates denoted by this sample size will be accurate enough with high percentage of certainty so that the analyzed lactation records significantly represent the true dairy herd.

2.2. Survival functions and methods

Survival technique is inferentially based on estimating two probability functions, the survival and hazard functions. Survival function or survivor, S (t), is the probability that a cow conceives beyond time t, and can be expressed as follows:

$$S(t) = P(T > t), \qquad 0 < t < \infty \quad \textbf{(1)}$$

Where $T \geq 0$ is a random variable denoted for the survival time (event of interest, or days open in this study). The cumulative survival function which is defined as the limit probability that failure event may happen between the time t and Δt, is associated with the survival function. It can be formulated as a density function F(t) as follows:

$$F(t) = \lim_{\Delta t \to 0} \frac{Prob(t \leq T < t + \Delta t)}{\Delta t} = -\frac{ds(t)}{dt} \quad \textbf{(2)}$$

The hazard function h(t) or $\lambda(t)$ is the probability that an animal which is under risk at a specific time t has the event of interest at that time. Thus, it is the immediate event proportion for animal that has survived to time t. Unlike the survival function, which is the probability of not having the event (cow is not-pregnant), the hazard function is the conditional probability that a cow having the event (pregnant) in the interval $(t, t + \Delta t)$, given it was non-pregnant at time t. The mathematical equation of hazard function is:

$$h(t) = \lambda(t) = \lim_{\Delta t \to 0} \frac{Prob(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \quad \textbf{(3)}$$

The survival functions are all inter-correlated and one function can be easily derived from another function (Kartsonaki, 2016). With regard of assumptions requested or not for conducting a statistical methodology, survival analysis can be classified into three main methods; non-parametric (Kaplan-Meier or product limit), semi-parametric (Cox proportional hazard regression models) and parametric (Weibull, exponential and log-logistic distributions), as reported by Lee and Wang (2003) and Kartsonaki (2016). This classification is dependent on the assumptions around the distribution of survival times.

2.3. Nonparametric survival method

2.3.1. Kaplan-Meier curve

Kaplan-Meier methodology is a non-parametric survival technique introduced for estimating the survival and cumulative survival probabilities. Formally, the Kaplan-Meier curve (Kaplan and Meier, 1958) portray the relationship between the survival function S(t) and the survival time (in the present study, the time was days open and the event of interest was the pregnancy occurrence). This method requires no assumptions about the shape and distribution of times of interest, hence, it can deals efficiently with skewed datasets. In addition, Kaplan-Meier approach allows all cows (censored and uncensored) in the herd to be significantly contributed in the estimation process. Therefore, the reliability of survival function estimates will be high so that more information could be gained (Clark et al., 2003). By estimating survival function and plotting it graphically with days from calving to conception (Days open), descriptive statistics, particularly the median of days open distribution can be determined, both for overall sample and for each level of studied factors.

The mechanism by which Kaplan-Meier estimation occurs can be done easily, particularly when studying survival curves of one factor. Assume that k dairy cows have the event of interest (i.e., conceived) in well-defined observed times, $t_1 < t_2 < t_3 < \ldots < t_k$ and n is the denoted sample size. Consider d_j is the number of cows that experienced the event at a given time t_j, where j = 1, 2, 3,… k, and p_j is the number of cows not experienced the event (i.e., censored) in the interval (t_j, t_j + 1). Therefore, n_j, the number of cows at risk before the time tj equals to $(p_j + d_j) + \ldots + (p_k + d_k)$. The non-parametric estimate of survival function by Kaplan-Meier method can be summarized as follows:

$$S(t) = \Pi \frac{n_j - d_j}{n_j} \quad \textbf{(4)}$$

Because it is assumed that the events in survival analysis are independent of each other's, the cumulative survival probability, which is defined as the probability of surviving from one time point to another, can be determined by multiplying the corresponding probabilities. In other words, the cumulative survival probability is expresses as follows:

$$S(t_j) = S(t_j\text{-}1) = S(t_j\text{-}1)\left(1-\frac{d_j}{n_j}\right) \quad \textbf{(5)}$$

Where, the proportion of non-pregnant cows S (t) at t_j, is estimated from $S(t_j\text{-}1)$, the probability of cows being pregnant-free at t_j-1, n_j is the number of cows still non-pregnant just before t_j, and d_j the number of pregnant cows at t_j. Moreover, The 100 % minus the cumulative survival functions denotes the proportions of pregnant cows throughout the corresponding days open. In a simple form, the probability or proportion of non-pregnant cows at any particular time is calculated by the following equation (Goel et al., 2010):

$$S(t)= \frac{\text{Number of cows not pregnant at the start - Number of pregnant cows}}{\text{Number of cows not pregnant at the start}} \quad \textbf{(6)}$$

2.3.2. Non-parametric tests for comparing survival curves (log-rank tests)

The comparison of days to conception among different parities was carried out using a non-parametric significance test of survival data, namely the log-rank test or Mantel-Haenszel test. The log-rank statistic tests the null hypothesis of equal survival functions or curves for the studied lactation numbers. This non-parametric test incorporates chi-square calculations with a degree of freedom equal to the number of factor levels minus one (Marubini and Valsecchi, 1995; Kartsonaki, 2016). Basically, the log-rank test estimate the weighted differences between the observed and expected events for each category or group (parities in this study). The statistical equation of log-rank test was expressed as follows:

$$\chi^2(\log\text{rank}) = \text{Log rank} = \frac{(O_1-E_1)^2}{E_1}+\frac{(O_2-E_2)^2}{E_2}+...+\frac{(O_K-E_K)^2}{E_K} \quad \textbf{(7)}$$

The null and alternative hypotheses behind the log-rank test were:

H_0: The survival times (or times to conception) in the studied categories are the same.

H_A: The survival times (or times to conception) in the studied categories are different.

2.4. Semi-parametric survival method

2.4.1. Cox proportional hazard regression (PHR) model

The non-parametric method of survival analysis provided useful information for summarizing and analyzing the time to event data (days open). Also, it allowed simple comparisons among one factor levels using survival curves and its estimated probabilities. However, this non-parametric intervention had some limitations, first, it cannot account for the explanatory variables associated with days open. Second, it does not determine specifically which parities are significantly different. Hence, a more prestigious survival method was needed to compensate the non-parametric deficiencies. In this context, regression-based survival models, called Cox proportional hazard regression models were used to quantify the potential effects of risk factors on days open.

For a single covariate (independent variable), the Cox proportional hazard model can be written as:

$$h_i(t; x) = h_0(t)\exp^{\beta X} \quad \textbf{(8)}$$

Where $h_i(t, x)$ is the hazard function for a cow i at a time point t, $h_0(t)$ is the baseline hazard function (the hazard function when the independent variable is zero), exp is the exponent function, X is the covariate, β is the parameter or coefficient estimated by the model denoting the effect of covariate(s) on days open. The term $\exp^{\beta X}$ is a linear function of the covariates raised to the exponential function (e). Cox model is a semi-parametric method because it involves non-parametric and parametric components. The non-parametric portion of the model is that it makes no distributional assumptions on the hazard function, while the parametric part is associated with the parameter estimates of the effect of predictors on the hazard. The equation (8) of the Cox model was used for studying single covariate, thus, more than one factor can be incorporated in the model to account for the effects of other variables. Therefore, the multiple Cox proportional hazard model assumes the following form:

$$h_i(t; x_1, x_2, \ldots x_k) = h_0(t)\exp^{\beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k} \quad \textbf{(9)}$$

The baseline hazard for multiple Cox model is the hazard for a cow when all covariates equal to zero. To interpret the effect of any covariate X in multiple Cox model, it was assumed that for each unit increase in the X, holding all covariates fixed, the hazard is multiplied by $\exp^{\beta_k}$.

2.4.2. Hazard ratio and proportionality

The assumption that should be fulfilled by the Cox model is the proportionality, which means that the ratio of hazards in any two groups or two categories remains constant over time (Van Dijk et al., 2008). This ratio is called the hazard ratio or the relative risk, which is a measure of effect size for the effect of the covariates on days open. The proportionality assumption was examined using the log minus log survival plot. Non crossing (parallel) curves are a good indication and verification of proportional hazard assumption. For qualitative covariates, such as parity, milk yield categories, the hazard ratios were compared versus the baseline or reference category. The hazard ratio of quantitative variables (such as age at calving) implies that for each unit change in the X variable, the hazard of the event is multiplied by e^{β}. All statistical analyses were carried out using the commercial copies of statistical softwares, SPSS, SAS and MedCalc.

3.1. Kaplan-Meier curves and nonparametric survival estimates

The number of censored or incomplete observations as well as the number of cows experienced the event of interest (verification of conception), alongside with their corresponding percentages are presented in Table 1. Out of 1980 total examined cows, there were 646 (87.06 %), 428 (85.77 %), 354 (90.31 %), 147 (88.55 %), and 153 (84.53 %) cows that showed pregnancy in first, second, third, fourth, and fifth parities, respectively. The overall conception rate for dairy cows in the current study was 87.27 % as denoted by the Kaplan-Meier survival analysis. The nonparametric estimations of survival functions for days open (or the interval from calving to conception) have been carried out considering the effects of parity, milk yield levels and calving season, separately. Table 2 showed means and medians and other descriptive statistics for postpartum times until conception so that cows enrolled in the first five parities can be evaluated. The means of days open were 120.48, 127.19, 133.71, 130.21 and 145.85 days for parities 1 to 5; respectively. The same trend of days open was noticed from a lactation number to another based on the median estimates. Median days open for the studied parities were 111, 121, 128, 123 and 152 days; respectively. The shortest days open was observed for the first lactation while the largest time interval required for cows to be pregnant was recorded for the fifth lactation.

3. RESULTS AND DISCUSSION

Table (1): Summary of censored and uncensored cows distributed in the five parities

Parity	Total N	N of Events (pregnant cows)	Censored observations (cows not experienced conception)	
			N	Percent
First	742	646	96	12.94 %
Second	499	428	71	14.23 %
Third	392	354	38	9.69 %
Fourth	166	147	19	11.44 %
Fifth	181	153	28	15.46 %
Overall	1980	1728	252	12.73 %

A number of reasons make the median estimates of survival functions are more powerful and reliable when compared with the corresponding means (Van Dijk et al., 2008). First, the estimates are outcome of a nonparametric methodology, so no restrictions are made on the shape of data distribution. Second, estimation of means of censored observation is a complicated process, because we do not know when and if a censored cow will be pregnant or not at the end of follow up period. Third, survival times are usually skewed. Therefore, the median becomes more advantageous than the mean in such situations. Fourth, in datasets where there was no censoring, the mean calculation requires the observer to wait until all cows show the event, which may extend for a long time period. Finally, observation of median on the Kaplan-Meier plot is well-defined once the survival curve reaches 50 % of the distribution.

Table (2): Survival function estimates as denoted by the Kaplan-Meier method for days open distributed on the five parities

Means and Medians of days open according to parity or lactation number								
Parity	Mean[a] (days)				Median (days)			
	Estimate	SE	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			From	To			From	To
1	120.480	1.560	117.423	123.537	111.000	2.325	106.443	115.557
2	127.196	2.179	122.926	131.466	121.000	3.723	113.703	128.297
3	133.714	2.353	129.103	138.326	128.000	2.798	122.517	133.483
4	130.211	4.288	121.807	138.614	123.000	5.424	112.368	133.632
≥ 5	145.851	3.800	138.403	153.298	152.000	3.802	144.548	159.452
Overall	128.212	1.076	126.104	130.321	123.000	1.758	119.555	126.445

a. Estimation is limited to the largest survival time if it is censored.

Table 3 showed the distribution of days open for cows according the level of milk production. The medians of days open for cows with low, moderate and high milk yield were 95, 130 and 151days; respectively. This table revealed that low yielding cows had the shortest time from calving to conception as compared to cows with medium and high milk yield. A similar recent study was conducted by Nemeckova et al. (2015) who evaluated the effect of milk yield levels on the length of fertility measures using records of first to fourth parity. They found that high milk yield (> 9500 kg) was associated with poor fertility and longer length of days open in relation to cows with low milk production. The present findings are in accordance with those reported by previous authors (Stadnik and Louda, 1999; Lucy, 2001; Lopez-Villalobos et al., 2005; Stadnik et al., 2009; Walsh et al., 2011) who mentioned that cows with high yield showed irregular estrus cycles, low levels of progesterone and longer postpartum-pregnancy times.

Table (3): Survival function estimates as denoted by the Kaplan-Meier method for days open distributed on different milk yield levels

Means and Medians of days open according to milk yield levels								
Milk yield	Means [a]				Medians			
	Estimate	SE	95% Confidence Interval		Estimate	SE	95% Confidence Interval	
			From	To			From	To
Low (< 3543 kg)	100.83	1.38	97.34	104.34	95.0	1.79	92.29	97.71
Medium (3543-8951 kg)	130.54	1.34	127.92	133.16	130.0	2.03	126.03	133.97
High (> 8951 kg)	148.78	2.59	143.71	153.86	151.0	4.54	142.11	159.89
Overall	128.212	1.076	126.104	130.321	123.000	1.758	119.555	126.445

a. Estimation is limited to the largest survival time if it is censored.

The Kaplan-Meier estimates and survivor functions of days open in term of calving season were given in Table 4. The median estimates of DO were 144, 116, 123 and 78 days for summer, winter, autumn and spring seasons, respectively. The results revealed that cows calved in winter months had shorter DO than those calved in summer and hot months. This finding is in consistence with those reported by other studies (Muller et al., 2014; Zewdu et al., 2015; Soydan and Kuran, 2017) who revealed that cows that calved in winter months had more chance to become pregnant than those calved in summer. Jordan (2003) reported that when dairy cows are exposed to heat stress, their reproductive performance declines along with uncontrolled estrus. In overall, the median days open in the present study was found to be medium (123 days), according to the levels recognized by Lee et al. (2013). That is, half (50 %) of cows in the current herd were likely to became pregnant at the day 123 postpartum. In addition, time interval from calving to conception for Holstein cows of this study, in overall, was lower than those estimated in a similar study reported by Taufik and Suriyasataphorn (2008), but it was relatively close to those observed by Punyapornwithaya and Teepatimakorn (2004).

Table (4): Survival function estimates as denoted by the Kaplan-Meier method for days open distributed on seasons of calving

Means and Medians for days open according to season of calving								
	Mean[a]				Median			
Season	Estimate	SE	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			From	To			From	To
Summer	140.686	2.423	135.936	145.435	144.000	3.287	137.557	150.443
Winter	120.611	1.427	117.815	123.407	116.000	2.290	111.512	120.488
Autumn	132.280	1.955	128.449	136.111	123.000	2.897	117.321	128.679
Spring	118.630	2.424	109.300	127.960	78.000	4.760	69.685	86.315
Overall	128.212	1.076	126.104	130.321	123.000	1.758	119.555	126.445

a. Estimation is limited to the largest survival time if it is censored.

The nonparametric significance tests concerned with testing equality of survival functions and distributions of Days open at different levels of parity, milk yield and season were showed in Table 5. The log-rank (Mantel-Cox) test result showed highly significant differences (chi-square = 47.239, df = 4, p = 0.0001) among different parities in term of interval from calving to conception. The Kaplan-Meier plot (Figure 1) showed the proportions of non-pregnant cows that were estimated by the cumulative survival probabilities at any time point after calving. This figure started with all cows directly after calving and each descend in the curve represents a failure (no conception). For each parity, the 50 % of non-pregnant cows correspond to the median values of time to conception (days open). Inversely, the Kaplan-Meier curve (Figure 2) portrayed the proportions of pregnant cows as 100 % minus cumulative survival probabilities. In Figure 2, each ascend in the curve represents a success (conception) so that we can determine time form calving at which all cows become pregnant, for each lactation. Any vertical line from the Kaplan-Meier curve toward the X-axis represents the median days open where 50 % of cows have been conceived. The log-rank test also showed highly significant differences among different levels of milk yield (chi-square = 217.321, df = 2, p = 0.0001) and calving seasons (chi-square = 70.068, df = 3, p = 0.0001). Log-rank test is preferred to other nonparametric tests described in Table 5 for comparing survival curves because this test takes into account the whole follow up time period, while other tests compare only the cumulative survival at specific time points (Zhao, 2008). However, log-rank test has some limitations; it cannot adjust for the confounding factors such as age of cows at calving, study the effect of a single factor only, it cannot determine which level is significantly different, if any, from other factor levels. In other words, log-rank test provided the overall significance among parities, milk yield levels and seasons of calving.

Table (5): Nonparametric significance tests for overall comparison of days open among the five parities and milk yield categories

Nonparametric comparisons of days open with regard to parity (lactation No)			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	47.239	4	0.0001
Breslow (Generalized Wilcoxon)	43.371	4	0.0001
Tarone-Ware	47.921	4	0.0001
Nonparametric comparisons of days open with regard to milk yield levels			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	217.321	2	0.001
Breslow (Generalized Wilcoxon)	219.956	2	0.001
Tarone-Ware	236.651	2	0.001
Nonparametric comparisons of days open with regard to calving season			
Log Rank (Mantel-Cox)	70.068	3	0.001
Breslow (Generalized Wilcoxon)	58.303	3	0.001
Tarone-Ware	60.188	3	0.001

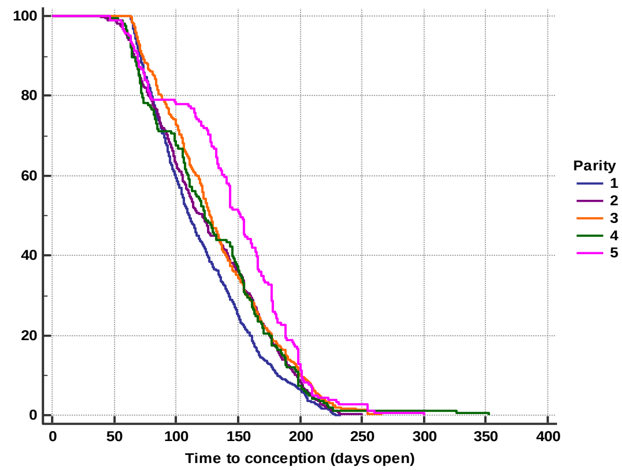

Fig. 1: Kaplan-Meier plot showing the proportion of non-pregnant cows in the form of cumulative survival probability on the Y-axis along with the time to pregnancy occurrence (days open) on the X-axis.

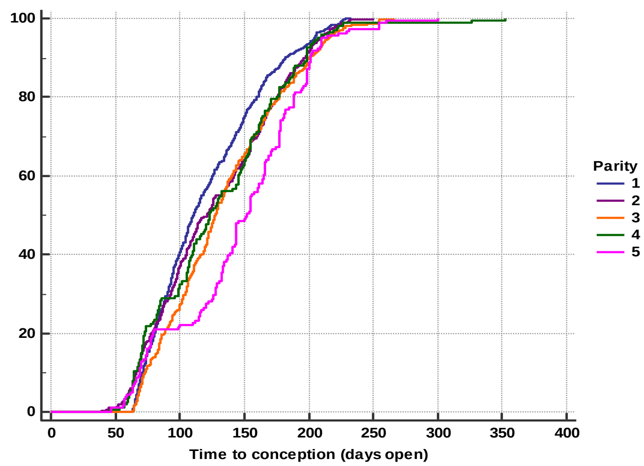

Fig. 2: Kaplan-Meier plot showing the proportion of pregnant cows in the form of 100 % minus cumulative survival probability on the Y-axis along with the time to pregnancy occurrence (days open) on the X-axis.

Among the important information denoted by the Kaplan-Meier survival function estimates was its ability to determine the percentages of pregnant (conception rate) and non-pregnant cows at any time point after parturition. As shown in Table 6, the overall percentages of pregnant cows increased with postpartum time proceeding so that 99.34 % of cows became pregnant at the day 250. The overall proportions of pregnant cows at days 50, 100, 150, 200 and 250 postpartum were 0.5 %, 34.7 %, 67.2 %, 92.07 % and 99.34 %; respectively. These cumulative probabilities could also be estimated using Kaplan-Meier curves (Figure 2). The percentages of non-pregnant cows (Table 6 and Figure 1) for all parities and in overall were estimated. The present findings are in accordance with the results shown by previous studies (Taufik and Suriyasataphorn, 2008; Yusuf et al., 2011). It was observed that the conception rates were higher in early lactations than the fifth one, for most of time points. This may suggest the idea that cows with older ages suffered from fertility related problems so that days open length could be prolonged (Elmetwally et al., 2016). Reaching the day 250 postpartum, nearly all uncensored cows became pregnant, with a conception rate greater than 95 %. In summary, 50 % of cows were pregnant at the day 123, which was the overall median (can be estimated graphically using Kaplan-Meier plot, Figure 2) of days open estimated by nonparametric survival functions

Table (6): The estimated proportion of non-pregnant cows (cumulative survival probability) and proportion of pregnant cows (100 % minus cumulative survival probability) at time points samples (days) following calving, as given by survival functions of different parities

Postpartum days	Proportion of cows (%)	1st parity	2nd parity	3rd parity	4th parity	5th parity	Overall
Zero point	Non-pregnant	100	100	100	100	100	100
	Pregnant	0	0	0	0	0	0
50	Non-pregnant	100	98.8	100	99.2	98.9	99.5
	Pregnant	0	1.2	0	0.8	1.1	0.5
100	Non-pregnant	59.3	62.9	72.7	68.7	77.9	65.3
	Pregnant	40.7	37.1	27.3	31.3	22.1	34.7
150	Non-pregnant	24.8	37.3	34.4	36.1	50.8	32.8
	Pregnant	75.2	62.7	65.6	63.9	49.2	67.2
200	Non-pregnant	6.2	8.22	9.69	6.63	11.0	7.93
	Pregnant	93.8	91.78	90.31	93.37	89	92.07
250	Non-pregnant	0	0	1.28	0	0	0.66
	Pregnant	Nearly 100	Nearly 100	98.72	Nearly 100	Nearly 100	99.34

3.2. Cox PHR model and semi-parametric survival estimates

Despite the nonparametric survival intervention of the current livestock data provided fruitful information about the reproductive profitability of dairy cows, however, there was a gap connected with absence of confounding (interrelationships among some considered variables) factors potentially impacted the length of days open other than parities, milk yield levels or even the calving season. Such confounders have been considered in another approach, statistically based on regression functions, the Cox proportional hazard regression model (Bahonar et al., 2009). Another advantage of the Cox model was its flexibility when dealing with different types of covariates. In a word, all types of data (continuous, discrete, or categorical) could be used as a covariate in Cox models (Hallan et al., 2006). Furthermore, the effect size or the quantity of effect for each confounder was estimated in Cox model. The assumption of proportional hazards was verified as shown in Figure 3. The log minus log survival plot showed parallel and not crossed lines representing the days open lengths for the five parities. The same interpretations were noticed by using proportionality plots for milk yield levels and calving seasons. The results of Cox model for testing the impact of a single covariate, the parity, on the time interval from calving to conception was given in Table 7. Parties 2 to 5 were compared versus the first parity which was fitted as a reference category. In general, the effect of parity number on days open was very significant (Wald Chi-square statistic = 45.789, df = 4, $p < 0.001$). To quantify the difference of days open for cows calved in any parity with those calved in the first parity, the hazard ratios (HR) were estimated in this context. The hazard ratio for 2nd parity versus the 1st parity was 0.836, which implied that cows calved in 2nd parity were 1.19 (1 / 0.836) times lower (HR < 1, beta was negative) than those of 1st parity becoming pregnant. Similarly, the hazard ratios for 3rd, 4th and 5th parities versus 1st parity were 0.749, 0.792 and 0.609; respectively. These estimates means that the risk or the probabilities of conception for cows in 2nd to 5th parities were 1.34, 1.26 and 1.64 times lower than cows calved in 1st parity; respectively. In addition, these chances of conception were all significant ($p < 0.001$) based on the values of Wald test results presented in Table 7. These results were different with the findings of Taufik and Suriyasataphorn (2008) who reported that cows with lactation number 2 and more had 1.54 times greater chance to be pregnant in comparison with cows of the first lactation. However, their finding of hazard ratio was statistically not significant ($p > 0.05$). On the contrary, the present findings were in agreement with those reported by Punyapornwithaya and Teepatimakorn (2004) and Bahonar et al. (2009). The later estimated the hazard ratios as 0.95, 0.90 and 0.86 for 2nd, 3rd and 4th parities; respectively, versus the 1stlactation number.

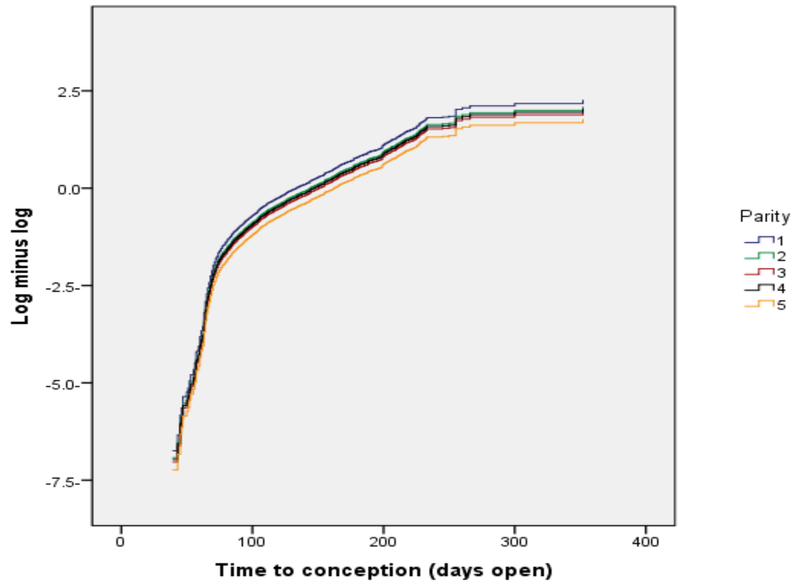

Fig. 3: Log minus log plot for visual displaying of the proportional hazard assumption of the Cox regression model. The chart showed the log minus log survival function for days open of parities 1-5.

Table (7): Cox proportional hazard regression survival model for the effect of parity on days open (model with single covariate).

Covariate	β	SE (β)	Wald $[\beta / SE(\beta)]^2$	df	Sig.	Exp(β) Hazard ratio	95.0% CI for Exp(β)	
							Lower	Upper
Parity			45.789	4	0.0001**			
2	- 0.179	0.058	9.506	1	0.002**	0.836	0.746	0.937
3	- 0.289	0.063	21.225	1	0.0001**	0.749	0.662	0.847
4	- 0.233	0.087	7.160	1	0.007**	0.792	0.668	0.940
≥ 5	- 0.496	0.084	35.121	1	0.0001**	0.609	0.517	0.718

The adjustment of baseline factors related to days open was carried out using the extended or expanded Cox model, where multiple covariates were incorporated (Table 8). When the model was adjusted for the potential confounders such as age at calving, days to first estrus, days to first insemination, days in milk, number of inseminations per conception, dry period length, the effects of parity, milk yield levels and calving season on days open were also highly significant ($p < 0.001$). However, slight and non significant changes were obtained connected with the values of hazard ratio. The adjustment for confounders involved the effect of certain covariate (such as parity, season of calving or milk yield level) on days open, with other covariates held fixed. Overall, the effect of parity on the interval from calving to conception was highly significant (Wald chi-square = 33.223, df = 4, $p < 0.001$) as revealed by the adjusted Cox model (Table 8). The hazard ratio of 2nd parity relative to the 1st parity was 1.046, indicating that cows in 2nd lactation had slight superiority for becoming pregnant than those in earlier one. However, this result was non-significant (Wald = 0.494, df = 1, $p > 0.05$). The 3rd parity had cows with a 1.43 times lower chance of becoming pregnant than those of the 1st parity (HR = 0.699). This difference was statistically significant (Wald = 18.514, df = 1, $p < 0.001$). The hazard ratio of 4th parity versus 1st parity was 0.862, which implied that 4th parity's cows had a non-significant (Wald = 1.539, df = 1 , $p > 0.05$) lower probability of conception than 1st parity. The greatest difference with 1st parity was observed for the 5th parity with a HR = 0.632, which means that cows calved in their 5th parity had 1.58 times lower conception rate than those in early reproductive stage (Wald = 11.45, df = 1, $p < 0.001$). The present outcomes are in agreement with the findings reported by previous studies (Pollot, 2011; Muller et al., 2014; Zewdu et al., 2015) who reported in separate studies that the lactation number or order had a significant impact on the length of days open. In addition, they also concluded that the significant impact of parity on fertility measures may be attributed to management, environmental conditions and diseases associated with parities and age of cows. In conclusion, cows in the 2nd parity had a 4.6 % higher expected hazard of conception than those in 1st parity, holding other factors constant. In contrast, the hazards rates of conception for cows calved in their 3rd, 4th and 5th parities were 30.1 %, 13.8 % and 36.8 %; respectively, lower than cows calved for the first time, given all other confounders were constant.

The results of adjusted Cox model showed a highly significant effect of milk yield levels on days open (Table 8). Compared to cows with low milk yield, cows with medium milk production had 1.32 times lower hazard of becoming pregnancy (hazard ratio = 0.757, Wald chi-square = 15.01, df = 1, $p < 0.001$). Moreover, the higher milk yields the longer length of days open. This indication was emphasized by the hazard ratio (0.655) of high yielding cows relative to those yielded little milk quantities. That is, high yielding cows had 1.53 times lower chance of conception than low milk yielding cows. This result was statistically significant (Wald chi-square = 13.70, df = 1, $p < 0.001$). Within average, longer days open (40 days) were observed for cows yielded more than 8950 kg. This result came in accordance with those reported by Nemeckova et al. (2015) who conducted a similar study and detected that high yielding cows (> 9500 kg) had longer (38 days) calving-conception interval. Previous studied have reported that higher milk yield was connected with longer time to recurrence of ovarian activity and subsequently longer postpartum fertility intervals (Stadnik and Louda, 1999; Lucy, 2001; Lopez-Villalobos et al., 2005) as a result of lower progesterone levels (Stadnik et al., 2009), or irregular estrous cycles in cows selected for their high milk yield (Stadnik et al., 2002; Walsh et al., 2011). To interpret and summarize the hazard ratios in the form of incidence rates, the present study revealed that cows with medium milk yield had a 24.3 % smaller hazard of experiencing pregnancy than those with low milk yield. Similarly, cows with high milk production were expected to have a 34.5 % lower incidence of pregnancy rates than low yielding cows.

The adjusted Cox proportional hazard model revealed overall model significant differences between seasons and months of calving in term of the times when cows may experience the event of conception (Wald chi-square = 35.703, df = 3, $p < 0.001$) as summarized in Table 8. According to the hazard ratios estimated, cows that calved in winter , autumn and spring seasons had greater chance of 1.367, 1.328 and 1.393 times of becoming pregnant than those calved in summer; respectively. These differences were statistically significant ($p < 0.05$). These findings have confirmed the estimates of survival functions generated by the Kaplan-Meier method (Table 4), where the medians of days open for all seasons were shorter than those of summer. These findings agreed with the reports of other researchers (Farin et al., 1994; Muller et al., 2014; Zewdu et al., 2015; Soydan and Kuran, 2017) who concluded that high temperatures and heat stress adversely affect the reproductive efficiency of dairy cattle. In practice, it can be concluded that, cows calved in winter had a 36.7 % higher hazard of conception than cows calved in summer. Moreover, cows that gave birth in autumn had a 32.8 % higher incidence in the expected hazard of conception when compared to those calved in summer. Additionally, the expected hazard of conception rate was 39.3 % higher for calving in spring season as compared to summer months. These conclusions were applicable, holding the other covariates constant.

The other quantitative covariates considered as risk determinant for days open in this study were, age of cows at calving, interval from calving to first estrus, interval from calving to first insemination, number of inseminations per conception, days in milking and dry period length (Table 8). Age at calving has a significant effect on days open (Wald chi-square value = 8.87, df = 1, $p < 0.001$). Taking all studied factors into account, the hazard ratio estimate (0.993) for age at calving (month) showed that the hazard of conception was decreased by 0.7 % $[(1 – 0.993) * 100]$ for every one month increase in the age at calving. This result was highly significant ($p < 0.001$). The parameter estimate ($\beta = - 0.007$) represent the decrease in the expected log of the relative hazard for every one unit increase in the predictor, holding other factors constant (Zhao, 2008). The negative sign of the Cox model coefficient indicated the negative association between age of cows at calving and the risk of pregnancy (i.e., there was decreased risk or incidence of conception for older cows. The number of inseminations per conception

(NIPC) was proved to be an important index for evaluating the cow fertility. Results (Table 8) showed that NIPC significantly ($p < 0.001$) affected days open with a hazard ratio of 0.645. There was a 35.5 % [(1-0.645) * 100] decrease in the expected hazard of conception for each one additional insemination. The model parameter ($\beta = - 0.438$) was negative, indicating a negative association between NIPC and occurrence of conception. In other words, the expected hazard of pregnancy was 1.55 (1 / 0.645) times lower for a cow that has received one insemination higher than another cow, holding other covariates constant. Moreover, the effect of days to first estrus on days open and fertility is shown in Table 8. The hazard ratio for DFE which was equal to 0.997 revealed that there was a 0.3 % decrease in the expected hazard of conception relative to one day increase in the time interval from calving to first estrus. This result was highly significant (Wald chi-square = 9.25, $p < 0.001$). Accordingly, the hazard rate of conception decreased 1.2 % for every one day increase in the interval from calving to first insemination (DFI). This effect was statistically significant (HR = 0.988, Wald statistic = 44.92, $p < 0.001$). The current findings are in agreement with those reported by other studies (Gurcan and Akcay, 2007; Yusuf et al., 2011; Mohammed, 2014) who showed a significant effect of NIPC, DFE and DFI on cows' fertility along with their impact on the conception rates.

Table (8): Adjusted Cox proportional hazard regression survival model for the effect of all studied risk variables on days open (model with many covariates).

Covariates	β	SE (β)	Wald $[\beta / SE(\beta)]^2$	df	Sig.	Exp(β) Hazard ratio	95.0% CI for Exp(β)	
							Lower	Upper
AAC (month)	- 0.007	0.002	8.870	1	0.003**	0.993	0.989	0.998
DFE (days)	- 0.003	0.001	9.251	1	0.002**	0.997	0.995	0.999
DFI (days)	- 0.013	0.002	44.916	1	0.0001**	0.988	0.984	0.991
NIPC	- 0.438	0.021	453.076	1	0.0001**	0.645	0.620	0.672
Parity:			33.223	4	0.0001**			
2	0.045	0.064	0.494	1	0.482NS	1.046	0.923	1.186
3	- 0.358	0.083	18.514	1	0.0001**	0.699	0.594	0.823
4	- 0.149	0.120	1.539	1	0.215NS	0.862	0.681	1.090
≥ 5	- 0.459	0.136	11.452	1	0.001**	0.632	0.484	0.824
Milk yield (MY)			21.769	2	0.0001**			
Medium yield	- 0.279	0.072	15.010	1	0.0001**	0.757	0.657	0.871
High yield	- 0.422	0.114	13.70	1	0.0001**	0.655	0.614	0.689
Season of calving			35.703	3	0.0001**			
Winter	0.313	0.148	4.427	1	0.0352*	1.367	1.015	1.509
Autumn	0.284	0.075	14.136	1	0.0001**	1.328	1.113	1.550
Spring	0.332	0.086	14.661	1	0.0001**	1.393	1.254	1.543

DFE: Days to first estrus; DFI: Days to first insemination; AAC: Age at calving; NIPC: Number of inseminations per conception.
Parity: the first parity was fitted as a reference category, with which all other parities were compared.
Milk yield: cows with low milk yield were fitted as the reference group, with which the other categories were compared.
Calving season: summer season was the reference category, with which all other seasons were compared.
NS = non-significant ($p > 0.05$), * = significant ($p < 0.05$), ** = highly significant ($p < 0.01$).

4. CONCLUSION

The present investigation has provided important evidences to positively speaking that, survival analysis is the method of choice for evaluating time interval from calving to conception in dairy herds. The first evidence was derived from the ability of Kaplan-Meier nonparametric survivors alongside the log-rank test to generate and compare median estimates of days open in the studied grouping variables such as different lactations, calving seasons and milk yield scales. Secondly, the outcome of cumulative survival functions regarding the proportions of pregnant and non-pregnant cows, at any postpartum time point, could be used for fertility assessment of dairy cows, allowing proper interventions for maximizing the reproductive efficiency of lactating cows. The third and most important proof has been emphasized by Cox proportional hazard models that could be incorporated to estimate the hazard ratios for risk factors linked with days open and cow's fertility. Such hazard ratios were used to identify and quantify the exact differences between covariates so that factors influencing days open and conception hazards can be easily treated. The biological value of the current results indicate that factors such as parity number, calving season, cow's milk yield level, age at calving, interval from calving to first estrus, days to first insemination and the number of inseminations per conception should be carefully managed in order to optimize dairy herd's conception rates.

5. REFERENCES

Allore, H.G., Warnick, L.D., Hertl, J., Grohn, Y.T. 2001. Censoring in survival analysis: A simulation study of the effect of milk yield on conception. Prev. Vet. Med. 46: 223–234.

Arthur, G., Noakes, D., Pearson, H., Parkinson, T. 2001. Veterinary Reproduction and Obstetrics. 8thEdn. In: Saunders, W.B. et al. (Eds.). London, England, pp: 520.

Bahonar, A.R., Azizzadeh, M., Stevenson, M.A., Vojgani, M., Mahmoudi, M. 2009.Factors Affecting Days Open in Holstein Dairy Cattle in KhorasanRazavi Province, Iran; A Cox Proportional Hazard Model. J. Anim. Vet. Advan. 8 (4): 747-754.

Clark, T.G., Bradburn, M.J., Love, S.B., Altman, D.G. 2003. Survival Analysis Part I: Basic concepts and first analyses. British J. Cancer. 89: 232–238.

Cleves, M., Gould, W., Gutierrez, R., Marchenko, Y.2008. An Introduction to Survival Analysis usingStata. 2nd Edn. Stata Press, College Station, TexasUSA, pp: 372.

Collett, D. 2003. Modeling Survival Data in Medical Research. Chapman and Hall/CRC London. 2nd Edn. pp: 251-271.

Del, P. Schneider, M., Strandberg, E., Ducrocq, Roth, A. 2006. Survival analysis applied to genetic evaluation for female fertility in dairy cattle. J. Dairy Sci. 88: 2253–2259.

Ducrocq, V., Besbes, B., Protais, M. 2000. Genetic improvement of laying hen's viability using survival analysis. Genet. Selec. Evol. 32: 23-40.

Elmetwally, M.A., Montaser, A., Elsadany, N., Bedir, W., Hussein, M., Zaabel, S. 2016. Effects of Parity on Postpartum Fertility Parameters in Holstein Dairy Cows. IOSR J. Agricult. Vet. Sci. 9(8): 91-99.

Esslemont, R.J., Kossaibati, M.A. 2001. The use of databases to mange fertility. Anim. Reprod. Sci. 60(61):725-741.

Farin, P.W., Slenning, B.D., Correa, M.T., Brit, J.H. 1994. Effects of calving season and milk yield on pregnancy risk and income in North Carolina Holstein cows. J. Dairy Sci. 77: 1848-1855.

Goel, M.K., Khanna, P., Kishore, J. 2010. Understanding survival analysis: Kaplan-Meier estimate. Internat. J. Ayurveda Res. 1(4): 212-216.

Gurcan, I.S., Akcay, A. 2007. Survival analysis oncalving interval and gestation length in Simmental xSouth Anatolian Red F X B crossbred cows.Ankara, Üniv. Vet. Fak. Derg. 54: 219-222.

Hallan, S., de-Mutsert, R., Carlsen, S. 2006. Obesity, smoking, and physical inactivity as risk factors for CKD: are men more vulnerable. Americ. J. Kidney Diseas. 47: 396–405.

Harman, J.L., Groehn, Y.T., Erb, H.N.,Casella, G. 1996. Event time analysis of the effect of 60-day milk production on the parturition-to-conception interval in dairy cows. Americ. J. Vet. Res. 57: 634–639.

Jordan, E.R. 2003. Effect of heat stress on reproduction. J. Dairy Sci. 86: 104–114.

Kaplan, E.L., Meier, P.1958. Nonparametric estimation from incomplete observations. J. Americ. Stat. Assoc. 53: 457–481.

Kartsonaki, C. 2016. Introduction to survival analysis. Mini-symposium in medical statistics. Diagnos. Histopath. 22(7):263-270.

Kleinbaum, D., Klein, M. 2005. Survival Analysis. 2ndEdn. A Self Learning Text. Springer-Verlag New York**,** USA. pp: 83-225 ISBN-13:978-0387-23918-7.

Lamuno, D., Mészáros, G., Ellen, E.D., Sölkner, J. 2017. Survival Analysis of White Leghorn Laying Hens in the Early and Late Production Period. Agricult. Conspec. Scientif. 82(2): 179-183.

Lee, E.T., Wang, J.W. 2003. Statistical methods for survival data analysis. A wiley-Interscience publication, John Wiley and Sons, Inc. 3rd Ed., Ch., 1, P. 1, Ch. 2, P.8.

Lee, S.C., Lee, T.H., Jeong, J. 2013. Effect of the interval from calving to first insemination and days open on the subsequent reproductive performance in dairy cows. J. Vet. Clinics. 30(6): 435-441.

Lopez-Villalobos, N., McNaughton, L.R., Spelman, R.J. 2005. The relationship between lactation persistency and reproductive performance in New Zealand dairy cattle, Session 35 CPh6. 4 in Proc. The 56th Annual Meeting of the EAAP. June 5-8, Uppsala, Sweden.

Lucy, M.C. 2001. Reproductive loss in high-producing dairy cattle: where will it end. J. Dairy sci. 84: 1277-1293.

Mark, T., Nielsen, U.S., Poso, J., Gundel, M., Svendsen, M. 2005. Genetic relationships among functional traits in the Nordic Holstein populations. Interbull Bull. 27: 64–67.

Marubini, E., Valsecchi, M.G. 1995. Analyzing survival data from clinical trials and observational studies. ISBN: 978-0-471-93987-0, PP, 1-430.

Meadows, C., Rajala-Schultz, R., Frazer, G. Meirin, R. Hoblet, K. 2006. Evaluation of a contract breeding management program in selected Ohio dairy herds with event-time analysis I. Cox proportional hazards models. Prev. Vet. Med. 77: 145-160.

Melendez, P., Pinedo, P. 2007. The association between reproductive performance and milk yield in Chilean Holstein cattle. J. Dairy Sci. 90: 184-192.

Mohamed, M.A. 2014. Survival analysis by using Cox regression model with application. Internat. J. Scient. Technol. Res. 3(11): 314-320.

Muller, C.J.C., Potgieter, J.P., Cloete, S.W.P., Dzama, K. 2014. Non-genetic factors affecting fertility traits in South African Holstein cows. South Afric. J. Anim. Sci. 44 (1): 54-53.

Němečková, D., Stádník, L., Čítek, G. 2015. Associations between milk production level, calving interval length, lactation curve parameters and economic results in Holstein cows. Mljekarstvo. 65 (4): 243-250.

Pollot, G.E. 2011. Short communication: Do Holstein lactations of varied lengths have different characteristics. J. Dairy Sci. 94: 6173-6180.

Punyapornwithaya, V.,Teepatimakorn, S. 2004. Reproductive efficiency of dairy cows in the northern part of Thailand. Chiang Mai Vet. J. 2: 3-8.

Roche, J.F., Mackey, D., Diskin, M.D. 2000. Reproductive management of postpartum cows. Anim. Reprod. Sci. 60(61): 703-712.

Royal, M.D., Darwash, A.O., Flint, A.P.F., Webb, R., Woolliams, J.A., Lamming, G.E. 2000. Decling fertility in dairy cattle: changes in traditional and endocrine parameters of fertility. Anim. Sci. 70: 487-501.

Schneider, M., Strandberg, E., Ducrocq, V., Roth, V. 2005. Survival analysis applied to genetic evaluation for female fertility in dairy cattle. J. Dairy Sci. 88: 2253–2259

Soydan, E., Kuran, M. 2017. The effect of calving season on reproductive performance of Jersey cows. Mljekarstvo. 67 (4): 297-304.

Stadnik, L., Louda, F. 1999. The effect of genetic parameters of sire in France on the performance and reproduction of daughters imported to the Czech Republic and calving here. Czech J. Anim. Sci. 44 (10): 433-439.

Stadnik, L., Louda, F., Jezkova, A. 2002. The effect of selected factors at insemination on reproduction of Holstein cows. Czech J. Anim. Sci. 47 (5): 169-175.

Stadnik, L., Jezkova, A., Louda, F. 2009. The Relationships among Recovery of Ovarian Functions after Calving, Level of Progesterone in Milk and Reproduction Results in Dairy Cows, Reproduction in Domest. Anim. 44: 126-126.

Swedish Dairy Association. 2002. Husdjursstatistik (cattle statistics). SvenskMjolk, Eskilstuna, Sweden.

Taufik, E., Suriyasataphorn, W. 2008. Survival Analysis of the Effect of Season at Calving, Lactation Number and Breeding on Days Open in Dairy Cattle. Indon. J. Anim. Vet. Sci. 13(3): 214-220.

Van Dijk, P.C., Jager, K.J., Zwinderman, A.H., Zoccali, C., Dekker, F.W. 2008.The analysis of survival data in nephrology: basic concepts and methods of Cox regression. Kidney Internat. 74: 705–709.

Vukasinovic N. 2016. Application of survival analysis in breeding for longevity. J. Anim. Breed. Genet. 4 (2): 1-8.

Walsh, S.W., Williams, E.J., Evans, A.C.O. 2011. A review of the causes of poor fertility in high milk producing dairy cows. Anim. Reprod. Sci. 123: 127-138.

Yusuf, M., Nakao, T., Ranasinghe, R.M., Gautam, G., Long, S.T., Yoshida, C., Koike, K., Hayashi, A. 2010. Reproductive performance of repeat breeders in dairy herds. Theriogen. 73: 1220-1229.

Yusuf, M., Nakao, T., Yoshida, C., Long, S.T., Gautam, G., Ranasinghe, B.K., Koike, K., Hayashi, A. 2011. Days in milk at first AI in dairy cows; its effect on subsequent reproductive performance and some factors influencing it. J. Reprod. Develop. 57 (5): 643-649.

Zhao, G.M.A. 2008. Nonparametric and parametricsurvival analysis of censored data with possibleviolation of method assumptions. Published MasterThesis. Faculty of TheGraduateSchool at theUniversity of North Carolina at Greensboro.

Zewdu, W., Thombre, B.M., Bainwad, D.V. 2015. Studies on some non-genetic factors affecting reproductive performance of HolseienFreeisian X Deoni crossbred cows. Afric. J. Agricult. Res. 10(12): 1508-1516.

nephrology: basic concepts and methods of Cox regression. Kidney International, 74: 705–709.

Vukasinovic N. 2016. Application of survival analysis in breeding for longevity. J. Anim. Breed. Genet.4 (2): 1-8.

Walsh, S.W., Williams, E.J., Evans, A.C.O. 2011. A review of the causes of poor fertility in high milk producing dairy cows. Animal Reproduc. Sci. 123: 127-138.

Yusuf, M., Nakao, T., Ranasinghe, R.M., Gautam, G., Long, S.T., Yoshida, C., Koike, K., Hayashi, A. 2010. Reproductive performance of repeat breeders in dairy herds. Theriogenology, 73: 1220-1229.

Yusuf, M., Nakao, T., Yoshida, C., Long, S.T., Gautam, G., Ranasinghe, B.K., Koike, K., Hayashi, A. 2011. Days in milk at first AI in dairy cows; its effect on subsequent reproductive performance and some factors influencing it. J. Reprod. and Develop., 57 (5): 643-649.

Zhao, G.M.A. 2008. Nonparametric and parametricsurvival analysis of censored data with possibleviolation of method assumptions. Published MasterThesis. Faculty of TheGraduateSchool at the University of North Carolina at Greensboro.

Zewdu, W., Thombre, B.M., Bainwad, D.V. 2015. Studies on some non-genetic factors affecting reproductive performance of HolseienFreeisian X Deoni crossbred cows. African J. Agricult. Res., 10(12): 1508-1516.