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# Evaluation of Survival Analysis Models for Predicting Factors Infuencing the Time of Brucellosis Diagnosis

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## Abstract

**Background:** Brucellosis or Malta fever is one of the most common zoonotic diseases in the world. In addition to causing human suffering and dire economic impact on animals, due to the high prevalence of Brucellosis in the western regions of Isfahan province, this study aimed to analyze effective factors in the time of Brucellosis diagnosis using parametric and semi-parametric models and to evaluate the goodness of fit of these models.

**Methods:** This historical cohort study, 412 patients with Brucellosis in Fereydunshahr, Iran who had referred to hospital, rural & urban health centers and physicians' private clinics in Fereydunshahr between 2006 and 2016 were recruited through census sampling. The failure (or event) in this study, was diagnosis of Brucellosis based on positive immunologic tests (2-ME test ≥1:40 and Wright serology ≥1:80). In order to eliminate confounding variables, effective factors of the time of Brucellosis diagnosis were determined using univariate ($P \leq 0.20$) and multivariable ($P<0.05$) analysis according to Cox semi-parametric model and five parametric models (weibull, exponential, log-logic, log-normal and gompertz) and the best fitted model was identified. Data were analyzed using R software version 3.2.3.

**Results:** According to the results of this study, occupation (farmer and livestock breeder), place of residence (urban), having a history of direct contact with livestock, simultaneous infection in other family members, and the newness of the disease (vs. recurrence) were identified as predictors of early detection of the disease.

**Conclusion:** Despite the researchers' tendency to use Cox method in survival analysis, in this study, according to AIC, "Gopmpertz" parametric model was recognized as the best fitted regression model in the analysis of the effective factors in the definitive time of Brucellosis diagnosis.

## Introduction

Brucellosis or Malta fever is one of the most common zoonotic diseases in the world, which is found in many parts of the world, including Latin America, Middle East, Africa and Asia (1). Annually, more than 500,000 new human cases of brucellosis are reported in the world (2).

One of the most important advantages of survival methods in clinical sciences is their ability to manage such censored observations which are ignored by other methods (such as logistic or linear regression). Survival analysis is one of the statistical methods that was applied to study for the occurrence and time of occurrence of an event such as death, cancer survival, relapse, etc. (3, 4). There are 2 types of regression models for survival analysis; parametric models (like Exponential, Log-logistic, Weibull, Log-normal and Gompertz models) and cox semi-parametric proportional hazard model (5). Despite some limitations, Cox model is a common method in survival modeling, but parametric models have better efficiency (4, 6), under certain circumstances (6-10). The results of parametric models and cox regression were consistent in Rajaeefard *et al.* (11). In a survival analysis of patients with gastrointestinal cancer, log-logistic parametric model declared as the best-fitted model (12). Viswanathan *et al.* reported cox model as the best model in the study of risk factors of diabetic nephropathy (13). In medical sciences, semi-parametric survival analysis (such as cox model) is usually favored because, usually, data do not gratify the prerequisites of parametric survival analysis. Since models can produce different results depending on the extent of matching between the underlying assumptions of each model and the specific characteristics of the clinical-healthcare problem (14), we compared parametric and semi-parametric models.

Due to human suffering, and economic impact of Brucellosis in the animals, as well as the high prevalence of this disease in the western regions of Isfahan province, this study aimed to analyze effective factors in the time of Brucellosis diagnosis using parametric and semi-parametric models and to evaluate the goodness of fit of these models.

## Materials and Methods

In this historical cohort study, 412 patients with Brucellosis who had referred to Fereydunshahr hospital and its rural & urban health centers and physicians' clinics, between 2006 and 2016, were recruited through census method. They were followed for the diagnosis of Brucellosis. Data were extracted from patients' health-care records and have been presented in table 1. The failure (or event) in this study, according to the national and global protocol, was diagnosis of Brucellosis in patients based on positive immunologic tests (2-ME test ≥1:40 and Wright serology ≥1:80) and clinical symptoms (15-17). Studies have shown that after a 30-day delay in the diagnosis of the disease (after the onset of symptoms), the probability of occurrence of complications due to Brucellosis, increases (18-20). For this reason, in evaluating fitness of survival regression models, patients who had a definite diagnosis of the disease in less than 30 days after the first clinical symptoms of brucellosis were compared with those patients in whom, this period time was more than 30-days. Serum agglutination tests (based on 2-ME and Wright) were measured on blood samples and antibody titers were determined using an antigen kit from the Pasteur Institute (Pasteur Institute of IRAN, Tehran, IR Iran).

In this study, to eliminate confounding variables and to identify the best fitted model, effective factors in the time of Brucellosis diagnosis were determined using univariate and multivariable analysis according to Cox semi-parametric model and five parametric models (weibull, exponential, log-logic, log-normal and gompertz). Researchers often prefer cox model to the parametric models due to its less assumptions. Although some studies showed that parametric models estimate the variables more efficiently than cox model (4). Since models can produce different results depending on the extent of matching between the underlying assumptions of each model and the specific characteristics of the clinical-healthcare problem (14), we compared these 5 models. After univariate analysis, variables with statistical significance ($P \leq 0.20$) were entered in a multiple regression model ($P<0.05$) and analyzed using Back-ward: LR stepwise method.

Risk Ratio (RR) was calculated in Cox and Gompertz models as Hazard Ratio (HR), as well as, in weibull, exponential, log-logic and log-normal models as Time Ratio (TR) (Tables 2 & 3). HR and RR have similar interpretation, but HR gives instantaneous risk at a particular time and RR gives cumulative risk over a time span. HR is the probability of an event at a particular time, provided that intended event has not occurred, before that time. HR>1 shows that the group is more high risk for the occurrence of the event versus the reference group.

In this study, Kaplan-Meier's nonparametric approach was used to compare two survival functions using Mantel-Cox Log Rank Test. This test compares the number of observed final outcomes in each group with the number of expected final outcomes (similar to Chi-square test and rejection of the zero hypothesis with $P<0.05$) (21).

Also, we used Akaike's information criterion AIC (Akaike's Information Criterion) and standardized variation of parameters to evaluate the goodness of fit (22). The goodness of fit of a statistical model describes how well it fits a set of observations. This criterion was formulated by the statistician "Hirotugu Akaike" (1974) in the following equation; given a set of candidate models for the data, the preferred model is the one with the minimum AIC value. Thus, AIC rewards goodness of fit (as assessed by the likelihood function), but it also includes a penalty that is an increasing function of the number of estimated parameters (4):

$$AIC = -2\times \log(\text{likelihood}) + 2\times (a + c)$$

In this formula, "a" is the number of parameters, and "c" is a constant factor (for example, equals 0 in the cox model, equals 1 in the exponential model and equals 2 in the Weibull, log-logistic and log-normal models) (22).

## Results

A total of 412 patients entered the study, of whom 148 (35.9%) were female and 264 (64.1%) were male (Table 1). Mean age of subjects was 30.41±0.91 years (ranged from 1 to 89 years and median age of 25 years). Non-parametric Kaplan-Meier approach showed that the mean of diagnosis time of brucellosis was 19.00±1.30 days after the first clinical symptoms [95% CI: 16.46-21.54]. According to the results, the time of diagnosis has been less than 30-days in 62.4% of patients (N=257) and the rest of patients were considered as censored observations.

**Table 1.** Frequency distribution of demographic variables and risk factors of patients with brucellosis

| Variable | | n | % | Variable | | n | % |
|---|---|---|---|---|---|---|---|
| **Age** | <10 years | 37 | 9.0 | Disease status | New | 382 | 92.7 |
| | 10-19 y | 97 | 23.5 | | Relapse | 30 | 7.3 |
| | 20-29 y | 105 | 25.5 | Contact with animals | Yes | 366 | 88.8 |
| | 30-39 y | 61 | 14.8 | | No | 46 | 11.2 |
| | 40-49 y | 37 | 9.0 | Type of unpasteurized dairy products | Milk | 216 | 52.4 |
| | 50-59 y | 33 | 8.0 | | Cheese | 18 | 4.4 |
| | ≥60 years | 42 | 10.2 | | Milk + Cheese | 90 | 21.9 |
| **Gender** | Male | 264 | 64.1 | | Other | 3 | 0.7 |
| | Female | 148 | 35.9 | | Not used | 85 | 20.6 |
| **Job** | Farmer | 57 | 13.8 | Time between onset of symptoms and diagnosis | <1 month | 257 | 62.4 |
| | Stockbreeder | 107 | 26.0 | | ≥1 month | 155 | 37.6 |
| | Housewife | 120 | 29.1 | Livestock vaccination | Yes | 306 | 74.3 |
| | Student | 58 | 14.1 | | No | 71 | 17.2 |
| | Child | 26 | 6.3 | | Without livestock | 35 | 8.5 |
| | Other | 44 | 10.7 | Season of the event of disease | Spring | 133 | 32.3 |
| **Education** | Illiterate | 173 | 42.0 | | Summer | 190 | 46.1 |
| | Elementary | 105 | 25.5 | | Fall | 51 | 12.4 |
| | middle school | 95 | 23.0 | | winter | 38 | 9.2 |
| | Diploma or high | 39 | 9.5 | Keeping livestock at home | Yes | 376 | 91.3 |
| **Habitat** | Urban | 74 | 18.0 | | No | 36 | 8.7 |
| | Rural | 201 | 48.8 | Ethnicity | Lor | 305 | 74.0 |
| | Tribal | 137 | 33.2 | | Turk | 69 | 16.8 |
| **Infection of family members** | Yes | 163 | 39.6 | | Georgian | 31 | 7.5 |
| | No | 249 | 60.4 | | Fars | 7 | 1.7 |

Table 2 shows the results of multivariable analysis of parametric and semi-parametric models for significant variables. Table 3 shows the result of univariate analysis.

We used Kaplan-Meier's nonparametric approach to compare two survival functions. Figures 1 & 2 show comparison of two significant variables (type of disease and direct contact with animal) based on non-parametric Kaplan-meier method. For example Kaplan–Meier survival analysis showed that the event time of brucellosis was shorter in new cases compared to recurrence cases. This time was shorter in patients who had direct contact with animal than in patients without contact (figure 1 & 2).

**Table 2.** Comparison of the final results of cox and parametric models in multivariable analysis for the diagnosis of brucellosis (P<0.05)

| Variables | Log-Normal Reg. | | | | Weibull Reg. | | | | Log-Logistic Reg. | | | | Gompertz Reg. | | | | Exponential Reg. | | | | Cox Regression | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TR | 95% CI | | P | HR | 95% CIyy | | P | TR | 95% CI | | P | HR | 95% CI | | P | HR | 95% CI | | P | HR | 95% CI | | P |
| Occupation | No significance | | | | 1.13 | 1.04 | 1.22 | 0.003 | No significance | | | | 1.09 | 1.00 | 1.17 | 0.04 | 1.15 | 1.06 | 1.24 | 0.0001 | No significance | | | |
| place of residence | No significance | | | | No significance | | | | No significance | | | | No significance | | | | No significance | | | | 1.88 | 1.03 | 3.44 | 0.40 |
| Contact with livestock | 1.87 | 1.05 | 3.35 | 0.03 | 1.71 | 1.11 | 2.65 | 0.02 | 1.90 | 1.05 | 3.45 | 0.03 | 1.56 | 1.01 | 2.42 | 0.04 | No significance | | | | 1.58 | 1.01 | 2.47 | 0.04 |
| Infection in family | 1.63 | 1.14 | 2.34 | 0.008 | 1.48 | 1.14 | 1.94 | 0.004 | 1.56 | 1.08 | 2.23 | 0.02 | 1.37 | 1.05 | 1.79 | 0.02 | 1.59 | 1.22 | 2.07 | 0.001 | 1.30 | 1.00 | 1.69 | 0.05 |
| Type of the disease | 6.66 | 3.17 | 14.0 | 0.0001 | 5.23 | 2.65 | 10.3 | 0.0001 | 8.41 | 3.55 | 19.9 | 0.0001 | 2.83 | 1.45 | 5.53 | 0.002 | 9.02 | 4.60 | 17.7 | 0.0001 | 3.00 | 1.54 | 5.86 | 0.001 |

**Table 3.** Comparison of the final results of cox and parametric models in univariable analysis for diagnosis of brucellosis (P≤0.20)

| | Log-Normal Reg. | | | | Weibull Reg. | | | | Log-Logistic Reg. | | | | Gompertz Reg. | | | | Exponential Reg. | | | | Cox Regression | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TR | 95% CI | | P | TR | 95% CI | | P | TR | 95% CI | | P | HR | 95% CI | | P | TR | 95% CI | | P | HR | 95% CI | | P |
| Age | No Significance | | | | | | | | | | | | | | | | | | | | 1.70 | 1.04 | 2.79 | 0.20 |
| Sex | 1.40 | 0.96 | 2.06 | 0.08 | 1.73 | 1.12 | 2.69 | 0.01 | 1.46 | 1.00 | 2.15 | 0.05 | 1.29 | 0.99 | 1.68 | 0.06 | 1.57 | 1.21 | 2.05 | 0.0001 | 1.25 | 0.96 | 1.63 | 0.09 |
| Occupation | 1.12 | 1.00 | 1.25 | 0.05 | 1.18 | 1.05 | 1.34 | 0.01 | 1.12 | 1.01 | 1.25 | 0.04 | 1.08 | 1.00 | 1.16 | 0.05 | 1.18 | 1.09 | 1.27 | 0.0001 | 1.61 | 1.06 | 2.45 | 0.20 |
| Habitat | No Significance | | | | | | | | | | | | | | | | | | | | 1.23 | 0.87 | 1.73 | 0.18 |
| Ethnicity | 1.31 | 1.01 | 1.69 | 0.04 | 1.44 | 1.08 | 1.91 | 0.01 | 1.30 | 1.02 | 1.67 | 0.04 | 1.17 | 0.99 | 1.39 | 0.06 | 1.42 | 1.19 | 1.69 | 0.0001 | 1.49 | 0.28 | 1.63 | 0.16 |
| Contact with livestock | 1.47 | 0.82 | 2.65 | 0.20 | 1.63 | 0.81 | 3.29 | 0.17 | 1.55 | 0.85 | 2.83 | 0.16 | 1.32 | 0.87 | 2.02 | 0.19 | No Significance | | | | 1.33 | 0.87 | 2.02 | 0.18 |
| consuming unpasteurized dairies | 1.41 | 0.90 | 2.19 | 0.13 | 1.70 | 1.05 | 2.77 | 0.03 | 1.39 | 0.90 | 2.14 | 0.13 | 1.24 | 0.93 | 1.66 | 0.15 | 1.76 | 1.31 | 2.36 | 0.0001 | 1.25 | 0.94 | 1.68 | 0.13 |
| Infection in family | 1.75 | 1.21 | 2.54 | 0.003 | 2.05 | 1.34 | 3.15 | 0.001 | 1.75 | 1.20 | 2.54 | 0.003 | 1.42 | 1.10 | 1.84 | 0.01 | 1.76 | 1.35 | 2.28 | 0.0001 | 1.39 | 1.07 | 1.79 | 0.01 |
| Type of the disease | 7.52 | 3.55 | 15.9 | 0.0001 | 14.7 | 5.29 | 40.7 | 0.0001 | 10.2 | 4.19 | 24.8 | 0.0001 | 3.09 | 1.59 | 6.03 | 0.001 | 10.3 | 5.29 | 20.0 | 0.0001 | 3.07 | 1.58 | 5.98 | 0.001 |

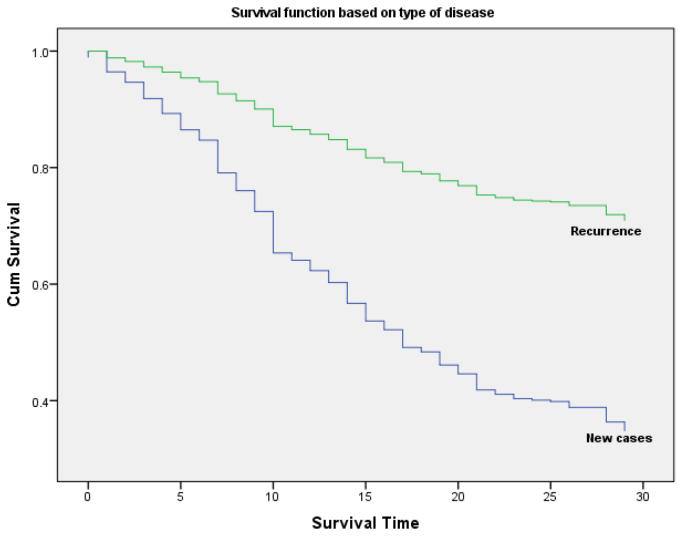


**Figure 1.** Cumulative survival function in patients with brucellosis in accordance with the type of disease

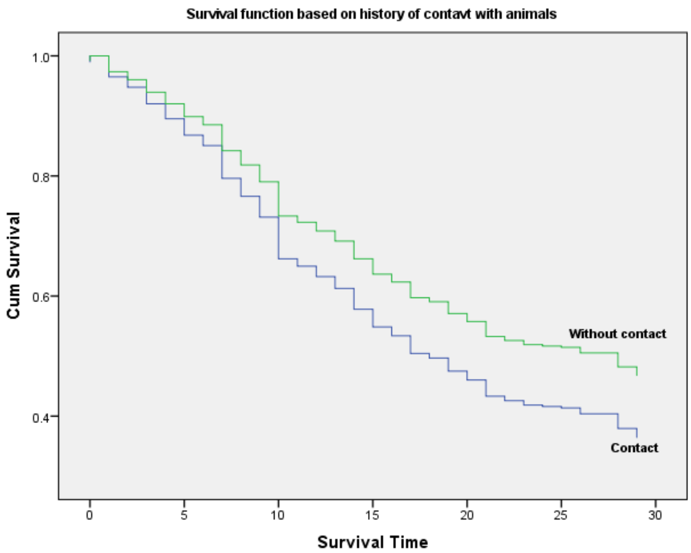


**Figure 2.** Cumulative survival function in patients with brucellosis in accordance with direct contact with livestock

Although univariate analysis results were not different between parametric and semi-parametric models, based on AIC, parametric models showed a preferable fit to our data than semi-parametric Cox model (Table 4). The "Gompertz parametric model" with the lowest AIC's value, provided the excellent goodness of fit to the data.

**Table 4.** Comparison of fitness of models based on AIC

| Model | -2 × Log Likelihood | AIC |
|---|---|---|
| **Cox** | 2895.45 | 2903.45 |
| **Exponential** | 1383.70 | 1391.70 |
| **Weibull** | 1296.13 | 1308.13 |
| **Log-logistic** | 1229.67 | 1239.67 |
| **Log-normal** | 1224.18 | 1234.19 |
| **Gompertz** | 1145.37 | 1153.37 |

AIC: Akaike information criterion

## Discussion

The main purposes of this study were investigating effective factors in the definitive time of Brucellosis diagnosis using semi-parametric and parametric models, and, compare the fitness of these models based on AIC.

According to the results of this study, direct contact with livestock was one of the effective factors on the detection of brucellosis. Other studies have pointed Contact with livestock as an important reservoir for the disease (23, 24). One study in Iran showed that exposure to animals increases the chance of developing this disease (23). Cash-Goldwasser et al. showed association between livestock and brucellosis (24). Our findings showed simultaneous presence of infection in the other family members as an effective factor in determining time of brucellosis diagnosis. El-Koumi et al. showed that 45% of children with brucellosis had a positive family history of the disease (25). Contrary to our study, in some studies, the family history of the disease has not been associated with the disease (23).

In this study, time of diagnosis in 62.4% of patients (N=257) was less than 30-days. According on non-parametric Kaplan-Meier approach, the median time of brucellosis diagnosis was 19.00±1.30 days after the first clinical symptoms [95% CI: 16.46-21.54]. Also, "Gompertz model" provided the excellent goodness of fit to our data. In order to minimize selection bias and external validity increase, we used census method in this study.

A number of studies have been directed to compare several survival models, which some suggested semi-parametric models as the most appropriate modeling method (13, 26), and some implied parametric models (4, 27).

In this study, parametric models had a better fitness than Cox model. Several studies parallel with this study showed that fitness of parametric methods were better than cox regression. Kargarian *et al.* (4) evaluated log-normal model in survival analysis of event time of neuropathy in patients with type 2 diabetes. Roshany *et al.* assessed Weibull model as the best-fitted model in the application of parametric, semi-parametric and nonparametric approaches in survival analysis of patients with acute myocardial infraction (27). However, in some studies, the results of data analysis were approximately similar in both Cox model and parametric models(11). In contrast with our study, some studies such as a study on diabetes-related lower-extremity amputation by Lacle *et al.* (26) and a study about risk factors associated with the development of overt nephropathy in type 2 diabetes patients by Viswanathan *et al.* (13) showed a better fitness for Cox model than parametric models. We did not find any study about survival analysis of Brucellosis to compare with our study.

Based on the results of this study, in case of existing a patient in a family, education about the transmission ways of the disease to other members of family, and more importantly, referring the patient with clinical symptoms to a specialist are highly recommended. Since women, especially in rural areas, are the main pillar of the family in the process of keeping animals, milking and preparing dairy products, we emphasize on the training of those housewives who have contact with animals.

## Conclusion

Despite the researchers' tendency to use Cox method in survival analysis, parametric models have more precise results than Cox model, especially, when fewer censored data are presented. In this study, according to AIC, “Gopmpertz” parametric model, was recognized as the best fitted regression model in the analysis of the effective factors in the definitive diagnosis time of Brucellosis.

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Nil

## Conflicts of interest

The authors have no conflicts of interest.

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