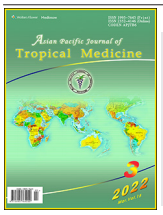

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Comparison of Cox proportional hazards model, Cox proportional hazards with time-varying coefficients model, and lognormal accelerated failure time model: Application in time to event analysis of melioidosis patients

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ABSTRACT

Objective: To compare the prognostic factors of mortality among melioidosis patients between lognormal accelerated failure time (AFT), Cox proportional hazards (PH), and Cox PH with time-varying coefficient (TVC) models.

Methods: A retrospective study was conducted from 2014 to 2019 among 453 patients who were admitted to Hospital Sultanah Bahiyah, Kedah and Hospital Tuanku Fauziah, Perlis in Northern Malaysia due to confirmed-cultured melioidosis. The prognostic factors of mortality from melioidosis were obtained from AFT survival analysis, and Cox's models and the findings were compared by using the goodness of fit methods. The analyses were done by using Stata SE version 14.0.

Results: A total of 242 patients (53.4%) survived. In this study, the median survival time of melioidosis patients was 30.0 days (95% *CI* 0.0-60.9). Six significant prognostic factors were identified in the Cox PH model and Cox PH-TVC model. In AFT survival analysis, a total of seven significant prognostic factors were identified. The results were found to be only a slight difference between the identified prognostic factors among the models. AFT survival showed better results compared to Cox's models, with the lowest Akaike information criteria and best fitted Cox-snell residuals.

Conclusions: AFT survival analysis provides more reliable results and can be used as an alternative statistical analysis for determining the prognostic factors of mortality in melioidosis patients in certain situations.

KEYWORDS: Cox proportional hazards; Time-dependent; Time-varying; Accelerated failure time survival analysis; Lognormal; Parametric model; Time-to-event; Melioidosis; Mortality

Significance

The current study applied the Cox proportional hazards regression analysis and accelerated failure time survival analysis in identifying the prognostic factors of mortality from melioidosis. The best model can be obtained by comparing the statistical methods, and it provides more precise results to contribute to the additional information of factors associated with mortality from melioidosis, which is underreported in Malaysia. AFT survival analysis was introduced in the study since its application is not common in medical research despite being easier to be interpreted than the Cox proportional hazards regression.

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1. Introduction

Melioidosis is an infectious disease that predominantly spreads in tropical climates like Southeast Asia and northern Australia. The study on melioidosis has been increasingly reported but still limited and underreported in the Malaysian context. The global burden of melioidosis was proven worldwide by increasing the number of deaths in this disease. From 2008 to 2014, only four deaths were reported in India because of melioidosis, but the incidence increased by around 100 deaths in the past five years[1]. There is a lack of alertness among healthcare personnel and the general public on this disease due to the problems and confines of fast and effective diagnosis[2].

The risk factors of mortality from melioidosis are identified using the multiple logistic regression reported in several studies in Malaysia[3–8]. However, the studies conducted on the risk factors of mortality using the applied multivariable analysis were still limited. The multiple logistic regression study to determine the prognostic predictors of mortality in melioidosis was reported in Kedah, Perlis, Kelantan, Kuala Lumpur, and Sarawak[3,4,6,9]. The recent study by Mardhiah *et al.* reported the prognostic factors of mortality from melioidosis using advanced Cox proportional hazards (PH) regression[10]. However, to the best of our knowledge, no published study in Malaysia reports the use of survival analysis in determining the prognostics factors of mortality by using the melioidosis data other than that study.

The unique ability of survival analysis is it can handle censored observations. As in analyzing the data with death events, it is normal to have incomplete cases called censored cases[11,12]. The clinician widely used the Cox PH model to analyze the time to event data, but it was reported that only an average of five percent of all studies checks the assumption for that analysis[13]. Not only that, the model is well known as robust when it can closely estimate the correct parametric model[14]. Furthermore, when the PH assumption is violated, the time-varying coefficients (TVC) method can be applied[12,14].

Alternatively, the accelerated failure time (AFT) model can be used. Several studies reported that the AFT models should lead to more efficient parameter estimates than the Cox PH model under certain situations[14,15]. Recently, parametric survival analyses like the AFT model attracted the clinician's attention because the PH assumption was not compulsory to fulfill in this analysis[16].

The parameters produced in the AFT model differ from the Cox PH models. Thus, to interpret the AFT model's result, the parameter used is time ratios (TR) rather than hazard ratios (HR) in the Cox PH model. The prognostic factors obtained from the AFT model compared the survival time between the group, while the Cox model compared the hazards between the groups[17,18]. The study was conducted to identify the best model in assessing the prognostic factors of mortality among melioidosis patients. The results of the Cox PH model and Cox PH-TVC model were also compared.

2. Materials and methods

2.1. Data collection and selection of patients

Data on patients with melioidosis admitted to Hospital Sultanah Bahiyah (HSB) and Hospital Tuanku Fauziah (HTF) were obtained from the hospital registry of Malaysia. The selection of the patients was from 1st January 2014 to 31st December 2019. All patients with culture-confirmed melioidosis admitted to HSB and HTF within this period of time were included in the study. Patients that died before 24 hours of admission and aged below 15 years were excluded from the study. There were 453 patients qualified for this retrospective study.

2.2. Definitions

2.2.1. Type of melioidosis distribution

The culture-confirmed melioidosis was determined in all patients and was categorized according to the existence of the bacteria in the blood. The bacteremic melioidosis was defined as patients with blood culture positive for *Burkholderia pseudomallei*. In contrast, non-bacteremic melioidosis was patients with positive *Burkholderia pseudomallei* when the organism was isolated from other blood cultures.

2.2.2. Survival time

The time to event for this study was the survival time (in days) of melioidosis patients. The survival time was the subtraction between the date of diagnosis from melioidosis and death from melioidosis.

2.2.3. HR

The *HR* is defined as the ratio of the hazard rates of occurring the event for the set point of time[12].

2.2.4. TR

TR is defined as the progression time or the speed of time to experience the event in a specific period[19].

2.3. Statistical analysis

The prognostic factors of mortality from melioidosis were determined by using the AFT and Cox PH model. The study performed the lognormal AFT model as it is the most suitable AFT model for the short gestation period disease[20]. The graphical method that used to check the normality assumption for log-normal distribution is by plotting $\Phi^{-1}[1-\tilde{S}(t)]$ *versus* $\log(t)$[21].

The univariate analysis was applied to find the important variables. In this step, only variables with a *P*-value less than 0.25 and clinically importance were included in multivariate analysis (variable selection). In the variables selection step, the preliminary main effect model of mortality from melioidosis was obtained.

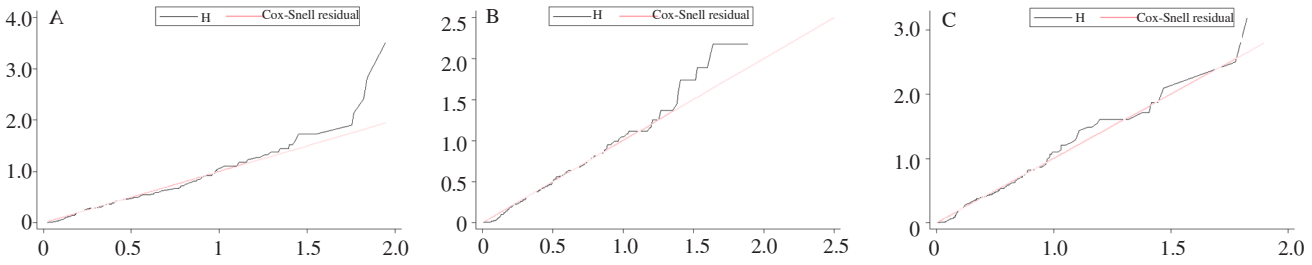

Figure 1. The Cox-Snell residuals plots. (A) The Cox-Snell residuals plot in the considered Cox proportional hazards (PH) model, (B) The Cox-Snell residuals plot in the considered Cox PH with time-varying coefficient (TVC) model, and (C) The Cox-Snell residuals plot in the considered accelerated failure time (AFT) model.

Methods of variable selection have proceeded whereby forward selection automatically entered the important variables into the model, meanwhile backward elimination automatically removed unimportant variables from the model. All the stepwise methods in selecting the variables were applied, and the most parsimonious model was selected.

Then, the PH assumption were checked using graphical (hazard function plot, a log-minus-log plot, scatter plot of scaled Schoenfeld residuals) and mathematical approach (scaled and unscaled Schoenfeld residuals test and C-statistics). The time-varying coefficients would be applied to the Cox PH model if the PH assumption was violated.

The regression diagnostic was applied by plotting the martingale residuals, Cox-Snell residuals, deviance residuals, and influential residuals for both models. Cox-Snell residuals were used to identify the best-fitted model. Martingale, deviance, and influential residuals were applied to check the outliers and influential observations in the model.

The performance of the final model was compared by using Akaike information criteria (AIC). All analyses were conducted using the STATA/SE 14.0 for Windows (SAS Institute, Inc., Cary, NC). The *P*-value less than 0.05 was set as significant.

3. Results

Table 1 showed descriptive statistics of covariates in melioidosis patients admitted to HSB and HTF. A total of 453 patients with culture-confirmed melioidosis were studied retrospectively. Out of 453 patients, 211 (46.6%) died from melioidosis. The overall median survival time for melioidosis patient admitted to HSB and HTF were 30.0 days. The age of patients was (51.9±15.3) years old (mean±SD). Based on the study, 384 (84.8%) patients had bacteremic melioidosis. A total of 350 (77.3%) patients had received antibiotics throughout the hospital admission. The most common presenting comorbid among melioidosis patients was diabetes mellitus (71.3%), hypertension (33.6%), and chronic renal failure (13.5%).

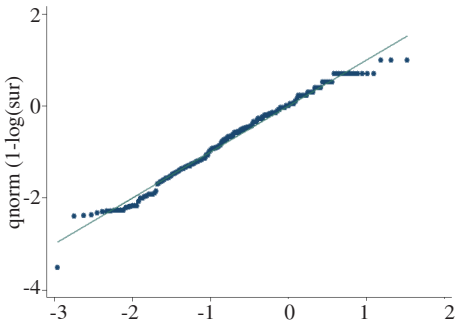

Figure 2. Graphical check of accelerated failure time (AFT) assumption for log-normal distribution.

Figure 1 compared between the models (Cox PH, Cox PH-TVC, and AFT) to identify the best-fitted model to the data with melioidosis. It can be concluded that the AFT model provides a better fit to the study data than the Cox PH and Cox-PH TVC models as the Cox-Snell residual showed the closer jagged line towards the reference line. The graph was in accordance with the AIC values. The AIC values of the AFT model (937.95) were the smallest compared to Cox PH (2 373.66) and Cox PH-TVC (1 563.79) model after including all the significant predictors in the model. In other words, when comparing these three models based on the data, the AFT model is considered the best-fitted model. The plot (Figure 2) showed a straight line approaching the origin, indicating that the AFT model was fit.

The statistically significant variables in univariate analysis for Cox models were age, antibiotic received, type of melioidosis distribution, chronic lung disease, asthma, pneumonia, systolic blood pressure, diastolic blood pressure, platelet count, urea level, creatinine level, albumin, AST level, ALT level, and cough. The variables that were statistically significant in univariate analysis for AFT model were age, antibiotic received, type of melioidosis distribution, chronic lung disease, pneumonia, systolic blood pressure, diastolic blood pressure, platelet, urea, creatinine, albumin, AST level, ALT level, and cough.

Table 2 shows the final model of comparison of coefficient and changes in hazard and survival time between the models based

Table 1. Descriptive statistics of covariates in melioidosis patients (*n*=453).

Covariates	Data, *n* (%)	Covariates	Data, *n* (%)
Age (years)▽	51.9±15.3	Chronic lung disease	
Systolic blood pressure▽	127.3±24.9	No	437 (96.5)
Diastolic blood pressure▽	72.8±13.6	Yes	16 (3.5)
Pulse rate▽	108.3±22.8	Hypertension	
Haemoglobin▽	11.4±2.7	No	301 (66.4)
White blood cell▽	14.3±9.2	Yes	152 (33.6)
Platelet▽	233.9±132.5	Asthma	
Urea▽	13.2±11.9	No	440 (97.1)
Creatinine*	113.5 (183.0)	Yes	13 (2.9)
Hepatic function		IHD	
Albumin▽	23.7±7.7	No	438 (96.7)
AST*	106.8 (169.0)	Yes	15 (3.3)
ALT*	55.5 (66.0)	Gout	
ALP*	157.0 (147.0)	No	448 (98.9)
Gender		Yes	5 (1.1)
Male	351 (77.5)	Dyslipidemia	
Female	102 (22.5)	No	419 (92.5)
Race		Yes	34 (7.5)
Malay	399 (88.1)	Chronic liver disease	
Chinese	19 (4.2)	No	449 (99.1)
Indian	24 (5.3)	Yes	4 (0.9)
Others	11 (2.4)	Pneumonia	
Nationality		No	266 (58.7)
Malaysian	447 (98.7)	Yes	187 (41.3)
Non-Malaysian	6 (1.3)	Fever	
Occupation		No	68 (15.0)
Unknown	180 (39.7)	Yes	385 (85.0)
High risk	55 (12.1)	Cough	
Low risk	218 (48.1)	No	239 (52.8)
Smoking status		Yes	214 (47.2)
Unknown	420 (92.7)	Sputum	
Yes	17 (3.8)	No	360 (79.5)
No	16 (3.5)	Yes	93 (20.5)
Type of melioidosis distribution		Hemoptysis	
Bacteremic	384 (84.8)	No	442 (97.6)
Non-bacteremic	69 (15.2)	Yes	11 (2.4)
Previous history of melioidosis		Abdominal pain	
Yes	14 (3.1)	No	386 (85.2)
No	439 (96.9)	Yes	67 (14.8)
Antibiotics received		Dysuria	
No	103 (22.7)	No	432 (95.4)
Yes	350 (77.3)	Yes	21 (4.6)
Diabetes mellitus		Headache	
No	130 (28.7)	No	436 (96.2)
Yes	323 (71.3)	Yes	17 (3.8)
Chronic renal failure		Others	
No	392 (86.5)	No	96 (21.2)
Yes	61 (13.5)	Yes	357 (78.8)

▽Mean±SD, *Median (IQR), AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase.

Table 2. Prognostic factors of mortality from melioidosis in multivariate analysis using Cox PH, Cox PH-TVC and AFT models (n=453).

Variable	AFT			Cox PH			Cox PH-TVC		
	β	Adjusted *TR* (95% *CI*)	*P*	β	Adjusted *HR* (95% *CI*)	*P*	β	Adjusted *HR* (95% *CI*)	*P*
Age	-	-	-	0.001	1.011 (1.001, 1.022)	0.049	0.012	1.012 (1.001, 1.023)	0.04
Systolic blood pressure	-	-	-	-0.003	0.989 (0.984, 0.996)	0.002	-0.013	0.987 (0.981, 0.994)	<0.001
Diastolic blood pressure	0.052	1.053 (1.023, 1.085)	0.001	-	-	-	-	-	-
Urea	-0.047	0.954 (0.924, 0.985)	0.004	0.020	1.020 (1.008, 1.032)	0.001	0.001	1.001 (1.001, 1.002)	0.007
Platelet	-	-	-	-0.001	0.998 (0.997, 0.999)	0.020	-0.002	0.998 (0.996, 0.999)	0.002
Albumin	0.092	1.096 (1.041, 1.154)	<0.001	-0.010	0.967 (0.948, 0.987)	0.001	-0.001	0.999 (0.999, 0.999)	0.013
AST	-0.004	0.996 (0.994, 0.998)	<0.001	-	-	-	-	-	-
Chronic lung disease				-	-	-	-	-	-
No	0	1							
Yes	-4.591	0.010 (0.001, 0.315)	0.009	-	-	-	-	-	-
Pneumonia									
No	0	1							
Yes	-0.883	0.414 (0.188, 0.909)	0.028	-	-	-	-	-	-
Type of melioidosis distribution									
Non-bacteremic	0	1		0	1		0	1	
Bacteremic	-4.323	0.013 (0.001, 0.171)	0.001	1.779	7.482 (1.816, 30.833)	0.005	2.910	18.360 (2.538, 132.83)	0.004

AFT: accelerated failure time model, Cox-PH: Cox proportional hazards model, Cox PH-TVC: Cox proportional hazards with time-varying coefficient model.

on multivariate analysis. The Cox PH-TVC model obtained after the time-varying coefficients was applied to fit the violation of PH assumption in Cox PH model. In all three models, prognostic factors of mortality from melioidosis were urea, albumin, and type of melioidosis distribution. However, the study revealed that age, systolic blood pressure, and platelet predictors were only significant in the Cox PH and Cox PH-TVC model but did not significantly affect mortality from melioidosis in the AFT model. Meanwhile, the prognostic factors of mortality from melioidosis that were only found in the AFT model but not in other models were diastolic blood pressure, AST level, chronic lung disease, and pneumonia.

In the Cox PH-TVC model, melioidosis patients with an increase of one unit of urea had higher risk towards mortality (adjusted *HR*: 1.001; 95% *CI* 1.001-1.002; *P*=0.007). The finding in the AFT model found a similar interpretation indicating that increase of one unit of urea will shorter the time to experience the mortality with 4.6% (adjusted *TR*=0.954; 95% *CI* 0.924-0.985; *P*=0.004). The direct and estimation of variable albumin in all three models showed similar findings in predicting the prognostic factors of mortality from melioidosis. The Cox PH and Cox PH-TVC model showed a positive direction of bacteremic melioidosis towards mortality in terms of direction and estimation of the variable type of melioidosis distribution. On the other hand, the AFT model showed a negative direction of bacteremic melioidosis towards the time to experience the mortality, indicating that all models proved that bacteremic melioidosis showed a risk factor of mortality from melioidosis.

4. Discussion

The present study's findings showed the comparison of three statistical models in determining the prognostic factors of mortality among melioidosis patients in Northern Malaysia. Estimating risk for the predictor variables and comparing the model used in this study was similarly reported with the previous study[16,21]. In addition, many studies reported the comparison of parameters produced by using different statistical models[16,19,22,23], but there was still no published study reported the comparison of statistical modeling using the melioidosis data.

The finding of the study showed an example of the condition when the assumption of the PH was violated in the Cox PH regression. The Cox model was commonly used in clinical research compared to the AFT survival analysis used in industrial design research to analyze survival data[25]. Nowadays, the use of AFT

survival analysis is increasingly reported in clinical research papers but is still considered a new and unfamiliar model[25]. The problem with analyzing the time to event data using the Cox model is that the assumption of the PH models needs to be fulfilled. The skip of testing the PH assumption in the Cox model can lead to the wrong interpretation of the results among the published papers.

This research showed that the results of the Cox model were inaccurate in interpreting the parameter estimates in the prognostic factors of mortality from melioidosis due to the violation of the PH assumption. Therefore, the time-varying coefficients was applied to the Cox model to fix the problem with the violated PH assumption. Furthermore, when comparing the three statistical models, the AFT model showed the lowest value of AIC. Other than that, based on the cumulative hazard plot of the Cox-Snell residuals in the AFT model, it provides more evidence that the AFT model is more appropriate compared to the other Cox models.

Our findings were similar to the study reported using the TB/HIV dataset that reported the AFT model showed a better estimation when PH assumption was not met[19]. In addition, another study in Iran reported using the data based on leukemia patients comparing three survival analyses: AFT model, Cox PH, and Cox time-varying coefficient model. The study proposed that the AFT model was superior to the Cox model and the Cox time-varying coefficients model[16].

A recent study conducted in Lubumbashi, Congo, South Africa, based on the re-infection of Malaria, reported that AFT models were more fit compared to the Cox model[23]. The Cox-Snell residuals plot and AIC assessed the fit of the model. In the study, the Gamma distribution model, one of the AFT survival analyses, showed the lowest AIC and the most fitted Cox-Snell residuals plot[23]. The same research in Nigeria among neonatal jaundice also reported the AFT model performed better than the Cox model[24].

Applying appropriate statistical analysis in determining the prognostic factors of mortality in a disease is not easy. The need to check the model assumption and the goodness of fit is compulsory to promote an appropriate interpretation of the results and the data analysis involving survival data is not always satisfied with the PH model assumption. When the assumption is not met, there will be various methods to apply. Different results and interpretations will be obtained when used the technique in fitting the violated PH assumption. The best way to avoid the wrong interpretation of the results from the model, the AFT model, is an alternative to analyze the survival data without considering the PH assumption. The parameter estimates in AFT model was reported to be more efficient than Cox model under specific condition[14,15].

The current study showed that data with violated PH assumption and compared the goodness of fit results between the AFT model and adjusting the Cox model with time-varying coeffcients. It can be concluded that the AFT model was the best model for the data and suggest that using the Cox PH model is not always the optimum approach in analyzing the time to event data. The study wants to highlight the alternative method of analyzing the survival data using the AFT survival analysis. In addition, reporting the time ratio as the risk estimator in the AFT model makes it easier to interpret by the researchers.

It is also essential to compare the goodness of fit between the models to select the best model in determining the more consistent and reliable prognostic factors. Comparing the statistical model by using the research data will help the researcher interpret the finding in the best and most appropriate ways.

The increase of fatality among melioidosis patients was due to lack of clinical suspicion and delay in diagnosis or treatment. The predictors of mortality from melioidosis in the study can help the clinicians estimate the risk of mortality of the patient, which can be crucial in the prioritization to manage a melioidosis patient.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

N.W and N.N.N were involved in planning and supervised the work, K.M processed the data, performed the analysis, drafted the manuscript and designed the figures. M.R.A.H and H.C Chan involved with the project administration and resources. All authors discussed the results and commented on the manuscript.

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