



Survival Analysis of Patients With High Blood Pressure Until Acute Renal Failure in the SPRINT Study

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Abstract

Background: High blood pressure (HBP) is one of the most prevalent diseases which has affected many people in different societies. It is also the cause of several other chronic and fatal diseases. Acute renal failure (ARF) represents an independent risk factor for morbidity, resulting in a prolonged period of hospitalization of the survived patients. Thus, survival analysis of the patients with HBP until ARF and determination of the associated factors are of utmost significance.

Materials and Methods: The current research examined the survival of patients with HBP until ARF using the Weibull model. We obtained the data from Systolic Blood Pressure Intervention Trial (SPRINT). The studied population included patients with systolic blood pressure (SBP of 130-180 mm Hg). The follow-up median was 3.26 years in our study.

Results: Out of a total of 842 patients, 590 subjects (70.1%) were male and 252 subjects (29.9%) were female. Moreover, from these 842 patients, 85 (4.5%) died of cardiovascular diseases, 298 (15.7%) were diagnosed with ARF, and 459 (54.5%) were censored. According to the outcomes of the Weibull model of competing risks, the indexes of gender, albumin/creatinine ratio in urine, glomerular filtration rate, and being in the category of patients with chronic kidney disease (CKD) were effective factors associated with the survival of patients.

Conclusion: According to the outcomes of this study, controlling blood pressure can greatly reduce the incidence of kidney failure.

Keywords: Survival analysis, Competing risks, Weibull model, Acute renal failure, High blood pressure

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Introduction

High blood pressure (HBP) is one of the most prevalent diseases which has affected many people in different societies. It is also the cause of several other chronic and fatal diseases such as heart attack, brain stroke, and renal and liver diseases (1). The disease is usually asymptomatic, however it can easily be controlled and treated by taking certain measures. The incidence of diseases, complications, and diseases related to HBP has been controlled over the past few decades via identifying the most important factors affecting it (2).

HBP is very prevalent among the adult population in the United States. It also affects about a billion adults around the world (3, 4). Among people aged 50 or over, systolic blood pressure (SBP) as the predictor of coronary events, heart failure, renal disease, and stroke, is more important than diastolic blood pressure (5-9). Clinical

trials have shown that treatment of HBP reduces the risk of cardiovascular diseases including stroke (35%-40%), heart attack (15%-35%), and heart failure (64%) (10, 11). Considering that cardiovascular diseases have been among the most serious health-related issues in the 20th century and the early years of the 21st century (12), and that cardiovascular diseases are one of the leading causes of morbidity in most countries of the world (13), and since one of the primary complications of HBP is acute renal failure (ARF) which is usually asymptomatic and is diagnosed by biochemical examination of patients admitted with recent increases in urea nitrogen and creatinine concentrations (14), the survival analysis of patients with HBP until ARF or death because of cardiovascular diseases (a competing risk) needs to be taken into account as a public health issue.

In medical sciences, survival studies constitute a major

part of researches. They include studies that examine the survival time of an individual. In this study, the response variable was time until the incidence of the event, and the intended event, like other medical studies, was death or recurrence of disease (15). In this field of study, if the event occurs to the individual, a failure has taken place, and if the person does not experience the event up to the end of the study or if he/she is excluded for a certain reason, then she/he is so-called censored (16). In the analysis of survival data, we may encounter cases who die before experiencing the event. This prevents accurate calculation of the survival time for the patients, using the conventional methods (17). It is worth noting that competing risks are not like censorship because when censored, there remains the probability of incidence of the intended event in the future while in the case of competing risks, incidence of an event prevents the incidence of the other events; thus, for each person, there is only failure time and once cause of failure (18).

The common methods of survival analysis are not appropriate for competing risks data because risks are considered as censors that usually result in overestimation. Some methods have been proposed to overcome this problem. According to these methods, two factors determine the survival time; the time of the first incidence and its type. The methods are called competing risks (19). Hence, in this study, ARF and cardiovascular morbidity were considered as two competing risks among people with HBP. The competing risks analysis was performed by assuming that time to the incidence of the events follows Weibull distribution, so a cumulative incidence function was modeled.

Materials and Methods

In this study, the required data was extracted from the Systolic Blood Pressure Intervention Trial (SPRINT). SPRINT was a randomized trial including 9361 participants. The inclusion criteria were: a high risk of cardiovascular events, SBP of 130–180 mm Hg, and age of 50 years and over. The follow-up median was 3.26 years from the average 5-year plan in our study. Therefore, 298 subjects with ARF participated in the study and 85 participants who died of cardiovascular diseases (cerebral stroke, heart attack, heart failure, aortic rupture, and cardiac arrhythmias), all equal to 383 subjects with ARF or death owing to cardiovascular diseases. There were also 459 subjects in the control group (those who did not have ARF or cardiovascular morbidity). All in all, the total sample included 842 subjects.

The following demographic characteristics were considered for the patients in this study: gender (male, female), and clinical features such as total cholesterol, albumin/creatinine ratio in urine, the number of antihypertensive drugs used at the beginning of the study categorized as the subgroups of chronic kidney disease (CKD), and estimated glomerular filtration rate (eGFR)

and cardiovascular diseases. The time from entering the study until the incidence of renal failure or death from heart disease or censorship was considered as the dependent variable.

Statistical Analysis

In the competing risks data, there were at least two causes of failure that competed for the event. Therefore, the cumulative incidence function was used for analyzing the competing risks data. The cumulative incidence function is one of the important functions in the analysis of competing risks data. In this function, the type of event is considered as a variable and allows considering the possibility of simultaneous incidence of multiple events. Thus, when there is a competing risk, the normal distribution function which takes only time into account cannot be used; instead, the cumulative incidence function can be used (16, 20). So far, many methods have been proposed for modeling the cumulative incidence function such as Cox semi-parametric method and parametric methods. Because of simplicity and insufficient assumptions of the Cox proportional hazards semi-parametric model and not requiring a possible distribution for survival times, the researchers have used this model to analyze the survival data; however, the Cox proportional hazards model has some limitations, as well. For example, the validity of the Cox regression analysis largely depends on the establishment of a proportional hazards hypothesis; so in the absence of a proportional hazards hypothesis, it is not possible to model a cumulative incidence function. In analyzing competitive risks data, the most important disadvantage of the Cox model is censoring the competing risks (i.e. ignoring the risks), which result in their overestimation (21).

Nevertheless, in parametric models, analysis can be more robust than that in semi-parametric models, as assuming some hypotheses and choosing a probability distribution for survival times will yield more efficient estimates. Furthermore, parametric competing risks provide smooth graphs, so better graphs will be obtained. If a suitable pattern is fitted to the data, it is possible to predict the behavior of the data in the future (21, 22). Among the parametric models, the Weibull model is more popular than the other models since its risk function is not constant over time and has an additional parameter called the shape parameter that increases the flexibility of this model (23).

Accordingly, in this study, ARF and cardiovascular morbidity were considered as two competing risks; so competing risks analysis was performed on these patients by assuming that time to the incidence of the event has a Weibull distribution and the cumulative incidence function is modeled based on this hypothesis. The first step to fit a parametric model is to estimate its parameters. The Weibull distribution has a shape parameter (β) and a scale parameter (α) and its density function with (α, β)

parameters is as follows:

$$f_T(t) = \alpha\beta t^{\beta-1} \exp(-\alpha t^\beta) \quad \alpha > 0, \beta > 0, t > 0$$

Results

Out of the 842 examined patients, 590 (70.1%) were male and 252 (29.9%) were female. The survival time was calculated from the entering of patients with HBP to the study until the event of ARF. The average and median of survival time for these patients were 929.49 ± 14.88 and 1029 days. The competing risk was death due to cardiovascular diseases (heart attack, stroke, aortic rupture, heart failure, and cardiac arrhythmias). In addition, from 842 patients, 85 (4.5%) died of cardiovascular diseases, 298 (15.7%) were diagnosed with ARF, and 459 (54.5%) were censored. The mean (\pm standard deviation) levels of total cholesterol, albumin/creatinine ratio in urine, and EGFR were 185.82 ± 1.47 , 89.64 ± 10.45 , and 67.04 ± 0.77 , respectively. Other features of the categorical variables are shown in Table 1.

After fitting the Weibull Model to the data, the results showed that eGFR, CKD, albumin/creatinine ratio in urine, and gender affected the survival time of subjects with ARF ($P < 0.05$). However, the history of

Table 1. Frequency and Percentage of the Studied Patients, Based on Each Variable

Variables	No.	%	
	0	7.8	
	1	26	
The number of antihypertensive drugs used at the beginning of the study	2	33.3	
	3	26.2	
	4	6.3	
	5	4.0	
	Yes	321	38.1
CKD	No	521	61.9
History of cardiovascular diseases	Yes	206	24.5
	No	636	75.5

CKD, chronic kidney disease.

cardiovascular diseases, total cholesterol, and the number of antihypertensive drugs used at the beginning of the study did not affect the survival time of subjects with ARF (Table 2).

Based on the Weibull distribution and estimates of variables with significant effects on survival time (eGFR, albumin/creatinine ratio in urine, CKD, and gender), the cumulative incidence function was drawn. The cumulative incidence function for subjects with ARF is shown in Figure 1. Regarding the effects of gender variable (Figure 2) and the subgroup of CKD (sub-CKD) on the survival time of subjects with ARF (Figure 3), the cumulative incidence functions are drawn separately.

Discussion

After fitting the Weibull model, the results showed that EGFR, CKD, albumin/creatinine ratio in urine, and gender affected the survival time of patients with ARF ($P < 0.05$). One of the objectives of competing risks analysis is to investigate the effect of secondary variables on survival time (24).

Fine and Gary used the Cox proportional hazards model for competing risks data and presented some inferences for studying the effect of treatment and other secondary variables. Many studies used the Fine and Gary model to examine the effect of independent variables on survival time (20, 25, 26).

Therefore, secondary variables are also included in the Weibull model and their effects on survival time are examined. Besides, the parameters of each of the causes of failure are estimated using the maximum exponential method.

Ameli et al reported the significance of the relationship between ARF and gender (27) which was in line with the current research, since the gender variable affected the survival time of the subjects until the event of ARF. Moreover, in a study encompassing several countries, the event of ARF in men was more than that in women (28).

In this study, being in the subgroup of cardiovascular diseases did not affect the survival time of the subjects with ARF, while, in several other studies, chronic heart failure, cardiovascular failure, and respiratory failure were identified as risk factors for ARF (29).

Table 2. The Outcomes of Fitting the Competing Risks Model to the Data of the Patients With HBP

Variables	Coefficient β	e^β	Coefficient (SE)	95% CI	P Value
The number of antihypertensive drugs	0.1077	1.11	0.0574	(0.995-1.24)	0.061
eGFR	-0.0005	0.999	0.0001	(0.999, 1.247)	< 0.001
CKD	0.9080	2.480	0.136	(1.899, 3.23)	< 0.001
Gender	-0.4209	0.656	0.138	(0.500, 0.861)	0.002
History of cardiovascular diseases	0.1910	1.21	0.132	(0.934, 1.568)	0.15
Total cholesterol	-0.0020	0.998	0.001	(0.994, 1.001)	0.25
Albumin/creatinine ratio in urine	-0.0007	0.999	0.0003	(0.999, 1.000)	0.022

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

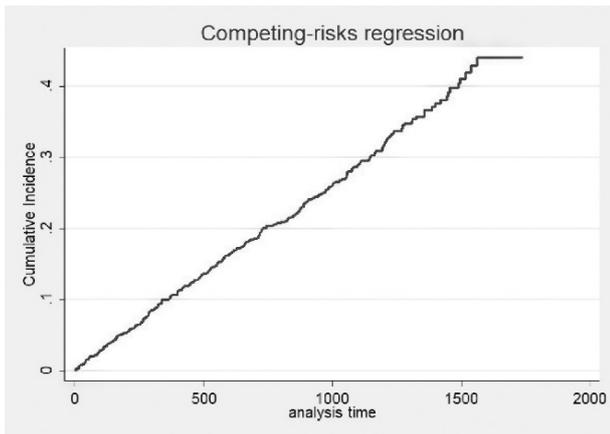


Figure 1. Cumulative Incidence Function Based on Weibull Model for Patients with Acute Renal Failure.

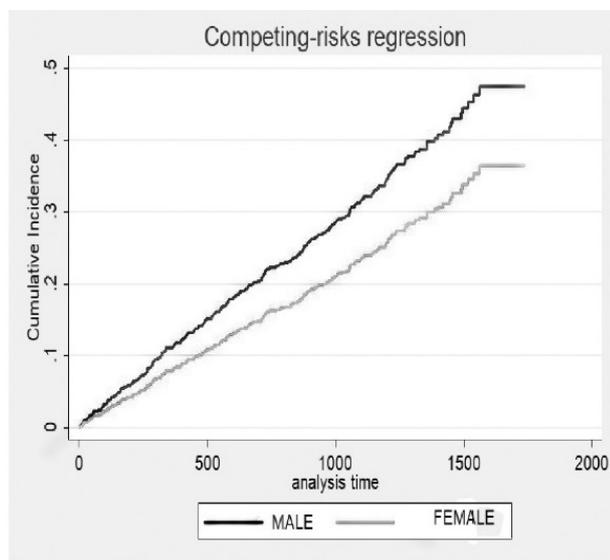


Figure 2. Cumulative Incidence Function Based on Gender Effect.

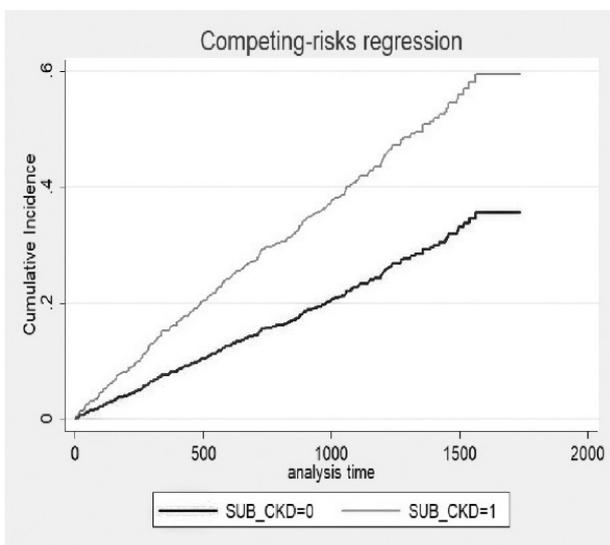


Figure 3. Cumulative Incidence Function Based on CKD.

In the present study, the number of antihypertensive drugs used at the beginning of the study did not affect the survival time of subjects with ARF. While in another study, the use of nephrotoxin had a significant effect on the event of ARF, and reducing the dose of this drug significantly reduced the event of ARF (27).

In a study by Akbari et al, the most common disease among subjects with ARF was hypertension which was consistent with the present study in that all the subjects with ARF had HBP (30).

Although the effect of gender on patients' survival is a controversial issue, Brian Lau reported the male gender and old age as prognostic factors for ARF (25). Yet, Shahbazian et al observed no significant relationship between gender and ARF (21). In this study, the survival time of subjects with ARF was affected by the gender variable, and all the subjects in the study were over 50 years of age.

Rasmussen et al reported chronic hypertension and CKD as risk factors for ARF (31), and Attar et al reported that in the presence of CKD, with a reduced intensive blood pressure, the chance of ARF is dramatically increased (32). In the same vein, patients in the subgroup of CKD in this study affected the survival of subjects with ARF and all the patients had HBP.

Although in the competing risks model, risks are not censored, the type of incident is included in the analysis. Huang and Zhang (33) and Chen (34) pointed out that censoring the risks can lead to biased results.

One of the strengths of our study was that it did not consider subjects who had died of cardiovascular diseases as censorship and considered them as competitive risk. In this way, it provided more accurate estimates of the patients' conditions.

Therefore, the use of competing risks method instead of conventional methods of survival analysis is recommended because of its ability in including several competing events in the analyses since the usual survival analyses are based on just one event and consider the other events among the censored subjects. The competing risks method uses more information of individuals and censors only those that are not available after a certain period of time. The limitation of using a competitive risks model is that competitive risks data is usually limited.

Conclusion

In this study, using the Weibel model, albumin/creatinine ratio in urine, eGFR, the number of used drugs, and gender were recognized as variables with significant effects on the survival time of subjects with ARF, but total cholesterol and subgroup of cardiovascular diseases did not affect the survival of subjects with ARF. According to the outcomes of this study, controlling blood pressure can greatly reduce the incidence of kidney failure. It is also possible to decrease the incidence of ARF by reducing the dose of antihypertensive drugs. The people with CKD need more

control to reduce the event of ARF. Thus, survival analysis with competing risks method is suggested for this type of studies because knowing the survival time of subjects with ARF and its associated factors can contribute to providing them with better services, as well as special care to control and reduce the incidence rate of renal failure and to increase the patients' survival time.

Conflict of Interests Disclosure

None.

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Ethical Statement

The Ethics Committee of Kermanshah University of Medical Sciences approved the study (Ethical code: IR.KUMS.REC.1396.448).

Authors' Contribution

AH supervised and managed the study. LS was statistical analyzer and Article writer. MR was the statistical consultant for the project, and AA was the clinical consultant of the project.

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Informed Consent

Informed consent was obtained from all the participants.

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