

Research Article

Congestive Heart Failure Patients' Pulse Rate Progression and Time to Death at Debre Tabor Referral Hospital, Ethiopia

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Background. Heart failure is a progressive condition marked by worsening symptoms such as shortness of breath, coughing, exhaustion and lethargy, fluid retention with swelling of the legs and abdomen, and a reduced ability to exercise. As a result, this study aims to use a joint model application to determine the joint risk factors of longitudinal change in pulse rate and time to death of congestive heart failure patients and their association admitted to a hospital. **Methods.** A retrospective study was undertaken on congestive heart failure patients admitted to the Debre Tabor Referral Hospital from January 2016 to December 2019. A statistical joint modeling strategy was employed to match the repeated biomarker pulse rate and a survival outcome at the same time. A total of 271 patients with congestive heart failure were chosen. Data were analyzed with *R* statistical software via *joineRML*. **Results.** According to the findings, the association between longitudinal changes in pulse rate and time to death in heart failure patients is statistically significant. Sex, residence, left ventricular injection fraction, New York Heart Association class, and diabetes mellitus were all found to be significant risk factors for congestive heart failure patients' short survival time to death. Age, sex, residence, hypertension, left ventricular injection fraction, congestive heart failure, diabetes mellitus, tuberculosis, and etiology were all significant contributors in pulse rate progression. **Conclusion.** The computed association parameters revealed subject-specific values. The subject-specific linear time slope of PR measurement was positively related to the hazard rate of time to death of CHF patients in the study area. To reduce the risk level of CHF, health professionals, governmental organizations, and nongovernmental organizations must promote and allocate a suitable amount of budget for the treatment of CHF patients.

1. Introduction

Heart failure (HF) is a potentially fatal clinical consequence characterized by structural or functional dysfunction of the pericardium, myocardium, heart valves, and metabolic imbalances in the body [1, 2]. Shortness of breath, coughing, exhaustion and lethargy, fluid retention with swelling of the legs and abdomen, and diminished physical exercise ability are all symptoms of heart failure [3]. HF is a leading cause of premature morbidity and mortality, with a lifetime risk of 20–46% [4], and it continues to be a global epidemic affecting millions of people [5, 6]. It affects an estimated 33

million people around the world or 26.4% of the adult population, with 65.73% living in industrialized countries and 34.27% in developing nations [7].

According to a study conducted in 2014, the global prevalence of heart failure is estimated to be around 26 million patients [8]. Because this does not account for undetected cases of heart failure, a true estimate of the global burden of heart failure is unknown, although it is considered to be substantial [8]. Mortality rates for heart failure patients remain high, with 17 to 45% of deaths happening within one year of diagnosis and the majority of fatalities occurring within five years [3]. The prevalence of CHF in the adult

population in the developed world is approximately 1 to 2%, and it rises to more than 10% in those aged 70 years or older [9].

Heart failure is a well-recognized public health problem in industrialized countries such as the United States and Europe, reflecting a substantial burden of disease, and healthcare systems are the top causes of hospitalization and death in countries [10, 11]. Other studies revealed that more than 5.8 million people in the United States had CHF [10, 12]. Furthermore, heart failure afflicted over 6 million adults in the United States [13], and according to the 2013 death rate report, more than 2200 individuals died per day owing to cardiovascular illness, with heart failure being the underlying reason for the bulk of those deaths [14]. Heart failure is a particularly difficult ailment in Sub-Saharan Africa, and it occurs at a younger age than in other regions of the world. When access to echocardiography or serological markers is limited, misdiagnosis of HF is more likely [15]. Treatment trends indicate that evidence-based treatments are underutilized, compliance is low, and the hospital case fatality rate among people with HF in Sub-Saharan Africa ranges from 9 to 12.5% [15].

The prevalence of risk factors linked with heart failure is increasing in low-income areas like Sub-Saharan Africa (SSA), and it has emerged as the most prevalent primary diagnosis for patients referred to hospitals in Africa with suspected cardiac disease [16]. According to a recent study, patients with heart failure in Africa were the youngest and most likely to be in New York Health Association functional class IV when compared to those in Asia, the Middle East, and South America [17]. The Sub-Saharan Africa Survey of Heart Failure [18] study identified a growing cause of heart failure from 23 to 43% in persons with heart failure. Diagnosis of heart failure might pose substantial issues in Africa due to a lack of access to proper diagnostics. With the rising trend in HF-related morbidity and death across Africa, especially Ethiopia [16, 19], there is a paucity of data on heart failure patients' self-care performance. According to the WHO [20], CHF was responsible for around 9% of all fatalities in Ethiopia in 2012. Depending on the diagnostic criteria employed and the population investigated, the global incidence of HF ranges from 100 to 900 cases per 100,000 person-years [21].

Monitoring the burden of congestive heart failure is required for patients to jointly assess the patient's health and survival time. To investigate the relationship between the two outcomes, the joint model was employed to assess the longitudinal biomarker and survival outcomes concurrently [22–24]. When observations over time are correlated, it enhances statistical inference efficiency and decreases bias [25]. Because of the time-to-event outcomes associated with longitudinal trajectories throughout time, separate analyses of longitudinal biomarkers and survival events may result in inefficient or biased conclusions. Joint models of longitudinal biomarkers and survival events incorporate all information at the same time, resulting in reliable and efficient inferences [26]. Joint model interest frequently rests in understanding the relationship between a process's longitudinal history and its effect on the risk of an event

[24, 27–31], and it enables more powerful, accurate, efficient, and robust estimations [26, 28, 32, 33]. Monitoring factors and the burden of congestive heart failure is essential to determine the patient's health and survival time.

As a result, the goals of this study are to determine the joint risk factors of longitudinal change in pulse rate and time to death in congestive heart failure patients admitted to Debre Tabor Referral Hospital in Ethiopia, as well as their association, using a joint model application.

2. Data and Methods

2.1. Study Area. This study was carried out at the Debre Tabor Referral Hospital (DTRH), which is located in North-West Ethiopia. This hospital serves as a referral hospital for the people in the surrounding area.

2.2. Study Design. To achieve the study's aims, a retrospective study was done to gather essential information from the medical files of patients with HF.

2.3. Data Source. The population for this trial was made up of DTRH patients with congestive heart failure. Data were acquired from the medical charts of DTRH congestive heart failure patients from January 1, 2016, to December 31, 2019. The timing of the death of congestive heart failure patients was the survival endpoint of interest.

2.4. Study Variable. The longitudinal changes in pulse rate and the survival time of CHF patients after initiating medication were the study's response variables.

Gender, residence, weight, type of CHF in patients, etiology of HF, NYHA classification, LVEF, observation time, presence of diabetes mellitus disease, presence of hypertension disease, presence of pneumonia disease, presence of tuberculosis disease, and presence of chronic kidney disease were all factors considered (see Table 1).

2.5. Statistical Analysis. The joint model of the longitudinal linear mixed-effect model and the event time model was investigated concurrently in this study. A statistical choice was taken at a 5% level of significance, and the analysis was carried out using R version 4.0.0. A linear mixed-effect (LME) model for longitudinal data and a Cox proportional hazard (PH) model for time-to-event data, with an association parameter, shows the effect of true longitudinal measurement on CHF time to death [26]. This is often referred to as the shared parameter α model approach.

3. Results

3.1. Data Exploratory. The number of patients reduced from 271 at the start to 11 at the end of the 16 consecutive visiting occasions. HF patients had mean and median survival periods of 18.83 and 18 months, respectively. From a total of 271 CHF patients, 56 (20.7%) died, while 216 (79.3%) were censored (Table 1).

TABLE 1: Baseline categorical variable characteristics for CHF patients with DTRH from January 1, 2016, to December 31, 2019.

No.	Variable	Categories	Censored (%)	Observed event (%)	Total (%)
1	Sex	Male	66 (24.4)	34 (12.5)	100 (36.9)
		Female	149 (55.0)	22 (8.1)	171 (63.1)
2	Residence	Rural	64 (23.6)	21 (7.7)	85 (31.4)
		Urban	151 (55.7)	35 (12.9)	186 (68.6)
3	Type of CHF patients	Left ventricular	61 (22.5)	36 (13.3)	97 (35.8)
		Right ventricular	81 (29.9)	13 (4.8)	94 (34.7)
		Biventricular	73 (26.9)	7 (2.6)	80 (29.5)
4	New York Heart Association class of CHF patients	Class II	63 (23.2)	2 (0.7)	65 (24.0)
		Class III	78 (28.8)	20 (7.4)	98 (36.2)
		Class IV	74 (27.3)	34 (12.4)	108 (39.9)
5	Presence of hypertension	Yes	47 (17.3)	7 (2.6)	54 (19.9)
		No	168 (62.0)	49 (18.1)	217 (80.1)
6	Presence of pneumonia	Yes	32 (11.9)	8 (3.0)	40 (14.8)
		No	182 (67.4)	48 (17.8)	230 (85.2)
7	Presence of diabetes mellitus	Yes	40 (14.8)	29 (10.7)	69 (25.5)
		No	175 (64.6)	27 (10.0)	202 (74.5)
8	Presence of chronic kidney disease	Yes	22 (8.1)	6 (2.2)	28 (10.3)
		No	193 (71.2)	50 (18.5)	243 (89.7)
9	Presence of tuberculosis	Yes	42 (15.5)	41 (15.1)	83 (30.6)
		No	173 (63.8)	15 (5.5)	188 (69.4)
10	Etiology of heart failure	VHD	70 (25.8)	20 (7.4)	90 (33.2)
		HHD	44 (16.2)	9 (3.3)	53 (19.6)
		IHD	27 (10.0)	5 (1.8)	32 (11.8)
		Dilated cardiomyopathy	51 (18.8)	13 (4.8)	64 (23.6)
12	Status of survival time of the study	Other etiologies	23 (8.5)	9 (3.3)	32 (11.8)
		Censored	215 (79.3)	271 (100.0%)	
		Event (death)	56 (20.7)		

VHD = valvular heart disease, HHD = hypertensive heart disease, and IHD = ischemic heart disease.

The average age of CHF patients admitted to the hospital was 50 years, with a standard deviation of 18.53 years, while the patients' minimum and maximum ages were 18 and 86 years, respectively. The mean weight of CHF patients was 58.10 kg, with a standard deviation of 11.24 kg, and the lowest and highest weights were 35.0 and 93.0 kg, respectively. The mean LVEF of CHF patients was 51.29 with a standard deviation of 16.32, while the minimum and maximum LVEF were 13 and 84, respectively (Table 2).

3.2. Data Exploration. The longitudinal PR measure appears to satisfy the assumption of normality, and the box plot for the longitudinal PR shows that the PR's normality assumptions were approximately normally distributed, as indicated by the relative position of the median within the box that contained half of the data that satisfied the assumption of normality (Figures 1 and 2).

The profile plot of HF patients shows the diversity in PR over time within and across patients. Because the measurements were not evenly distributed amongst the subjects, the data were not balanced. The profile plot also shows that the horizontal loss smoothing approach indicates that the mean structure of PR is roughly linear over time (Figures 3 and 4).

3.3. Model Comparison. The AIC and BIC values in the first-order autoregressive (AR (1)) covariance structure are lower than those in the other covariance structures in PR. This

implies that the AR (1) covariance structure is the best fit for our data when compared to the other covariance structures for the longitudinal change in PR of CHF data (Table 3).

Based on its lower AIC (15528.45) and BIC values, the linear mixed-effect model with longitudinal changes in PR considered the model with random intercept and linear temporal slope to be the most parsimonious model for the linear mixed-effect model (15623.31) (Table 4).

3.4. Joint Modeling Approach. In the univariable analysis of pulse rate (PR), the main effects of sex, age, residence, observation period, LVEF, NYHA class of patients, type of CHF, DM, TB, etiology, and hypertension were significant at a level of significance of 0.25. Gender, residence, NYHA class, baseline weight, CHF type, LVEF, presence of HTN, CKD, TB, and DM were found as significant predictors by the log-rank and univariable Cox models at 25% for creating a multivariable Cox model. The statistical joint model analysis of pulse rate and survival time to death was performed using R software and the joinerML package, and the results are provided in Table 5.

The length of follow-up time for CHF patients had a statistically significant effect on the change in PR over time. When all other model parameters were kept constant, the average longitudinal change in PR in CHF patients was 0.677 bpm (p value = 0.002). A statistically significant longitudinal change in PR was connected with the age of CHF patients. The age of CHF patients was statistically significant in a

TABLE 2: Baseline characteristics of continuous variables of HF patients.

Variables	N	Minimum	Maximum	Mean	Stdev
Baseline age (year)	271	18	86	50.00	18.53
Baseline weight (kg)	271	35	93	58.10	11.24
Left ventricle ejection fraction (%)	271	13	84	51.29	16.32

Stdev: standard deviation.

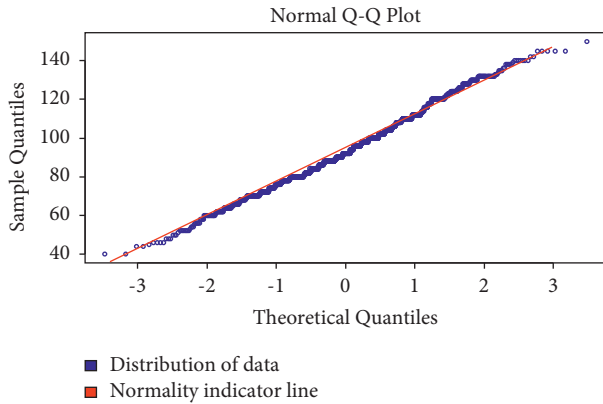


FIGURE 1: Normal Q-Q plot of the pulse rate for heart failure patients.

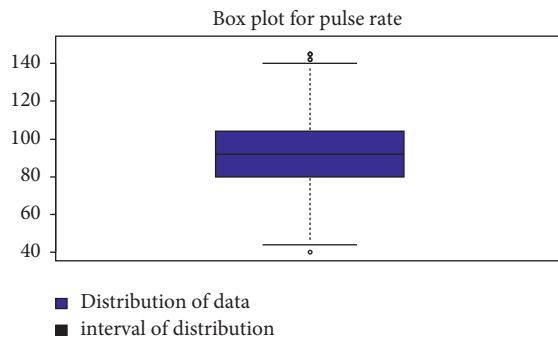


FIGURE 2: Box plot of the pulse rate for heart failure patients.

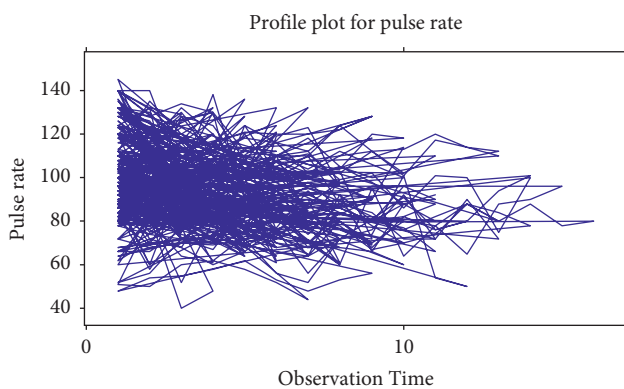


FIGURE 3: Profile plot of the pulse rate for heart failure patients.

mixed-effect model of the longitudinal pulse rate change. When all other risk factors were kept constant, the average longitudinal change in PR of CHF patients decreased by

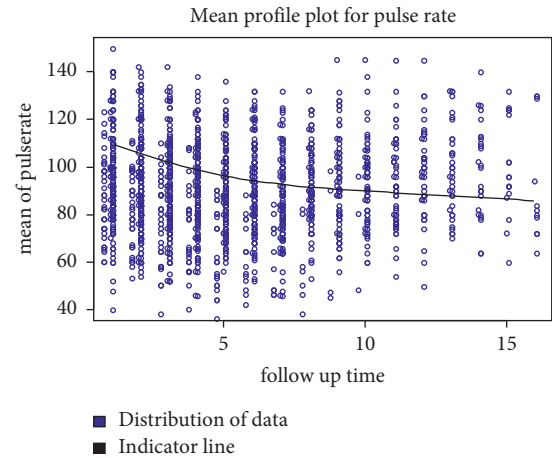


FIGURE 4: Mean profile plot of the pulse rate for heart failure patients.

TABLE 3: Comparison of the covariance structure of a linear mixed-effect model.

Covariance structure	Pulse rate		
	AIC	BIC	LogLik
CS	15627.27	15722.14	-7796.64
AR (1)	15528.45	15623.31	-7747.22
UN	15625.27	15714.56	-7796.64
TOEP	15591.75	15681.13	-7779.87

0.097 bpm (p value = 0.021) as their baseline age increased by a year (Table 5).

Gender has a significant relationship with the average longitudinal change of pulse rate, and male patients increased the average longitudinal change of PR by 5.91 bpm (p value = 0.003) when all other parameters in the model were kept constant.

The average longitudinal change of PR is very different depending on where you live. When all other parameters were kept equal, urban patients had a 3.59 bpm lower average longitudinal change in PR (p value = 0.006) than rural patients.

The baseline LVEF of CHF patients increased by 1%, but the average longitudinal change in PR dropped by 16.1% bpm (p value < 0.001), while all other variables remained constant. The left ventricular type of the congestive heart failure patient significantly reduced the average longitudinal change in PR by 3.871 bpm (p value = 0.012) compared to biventricular type in CHF patients, while all other parameters were similar. Being a NYHA class IV CHF patient increased the average longitudinal change in PR by 8.314

TABLE 4: Selection of random effects to be included in the LMM for PR and RR CHF patients' data.

Model for random effect	AIC	BIC	LogLik
Random intercept only model	15627.27	15722.14	-7796.64
Random slope only model	15528.45	15623.31	-7747.22
Random intercept and random slope model	15625.27	15714.56	-7796.64

TABLE 5: Joint model analysis of PR and the time to death of CHF patient's data at DTRH.

Parameter	Longitudinal process			Parameter	Survival process			
	$\hat{\beta}$	Se ($\hat{\beta}$)	<i>p</i> value		$\hat{\beta}$	Se ($\hat{\beta}$)	HR	<i>p</i> value
Intercept	103.15	4.71	<0.001	Sex (male)	1.393	0.761	4.027	0.028
Age	-0.097	0.042	0.021	Residence (urban)	0.090	0.842	1.094	0.020
Residence (urban)	-3.590	1.870	0.006	LVEF	-0.026	0.011	0.974	0.027
Sex (male)	5.910	1.960	0.003	Weight	-0.017	0.017	0.983	0.326
HTN (yes)	1.517	1.760	0.039	HTN (yes)	0.737	0.920	2.090	0.423
CHF type (ref = biventricular)								
Right ventricular	-2.679	2.130	0.209	Right ventricular	-0.573	0.823	0.564	0.485
Left ventricular	-3.871	2.057	0.012	Left ventricular	0.614	0.573	1.848	0.284
LVEF	-0.161	0.047	<0.001	NYHA class				
NYHA (ref = class II)				Class III	3.010	2.957	20.290	<0.001
Class III	3.632	2.239	0.105	Class IV	3.570	2.773	35.520	<0.001
Class IV	8.314	2.159	<0.001	CKD (yes)	-0.600	0.946	0.549	0.526
DM (yes)	5.314	2.011	0.008	DM (yes)	0.313	0.439	1.368	0.005
TB (yes)	7.017	2.503	0.005	TB (yes)	1.141	0.631	3.130	0.071
Etiology (ref = VHD)				Gamma_1 (α)	0.018	0.009	1.018	0.045
HHD	-6.399	2.424	0.008					
IHD	0.991	2.845	0.728					
Cor pulmonale	-2.061	3.058	0.500					
Dilated cardiomyopathy	-2.439	2.561	0.341					
Other etiologies	-1.928	2.751	0.484					
Observation time	-0.677	0.216	0.002					
Random effect	Std. dev							
Intercept(b_{0i})	202.930							
Obstime(b_{1i})	5.795							
Cov(b_{0i}, b_{1i})	-26.890							
Residual (ϵ_i)	9.914							

CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, HHD = hypertensive heart disease, HTN = hypertension, IHD = ischemic heart disease, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, PR = pulse rate, Ref = reference category, Se = standard error, TB = tuberculosis, and VHD = valvular heart disease.

bpm (*p* value < 0.001) compared to being a NYHA class II patient when other factors kept constant.

When all other parameters were maintained constant, patients with congestive heart failure who had DM illness showed increase in their average longitudinal change in PR by 5.314 bpm (*p* value = 0.008) compared to patients who did not have DM illness. When all other parameters were maintained constant, patients with congestive heart failure who had TB disease showed increase in their average longitudinal change in PR by 7.017 bpm (*p*-value = 0.005) compared to patients who did not have TB disease. When all other parameters were maintained constant, patients with congestive heart failure who had HTN disease showed increase in their average longitudinal change in PR by 1.517 bpm (*p* value = 0.039) compared to patients who did not have HTN illness. When all other parameters were kept constant, HHD as the etiology of CHF patients lowered the average longitudinal change in PR by 6.399 bpm (*p* value = 0.008) compared to VHD as the etiology of CHF patients.

The variation of the random intercepts in PR for the random portion of the linear mixed-effect model was 202.93, with a random slope of 5.795. This indicates that there is a greater baseline difference in PR at the start of their treatment. With the random intercept covariance, the random slope of the biomarker PR was -26.89 and the variance of the joint model was 9.914 (Table 5).

In the combined model, the estimated value of the association parameter alpha was 0.018 (HR = 1.018, *p* = 0.045), indicating that the average longitudinal change in PR had a positive relationship with the time to death of CHF patients across time.

Being male was statistically related to an increased risk of death in CHF patients (HR = 4.027, *p* value = 0.0277), implying that male patients had 4.027 times higher risk of death than female patients when all other factors in the model were kept constant. Being an urban patient was statistically related to an increased risk of mortality in CHF patients (HR = 1.094, *p* value = 0.020), which means that urban

patients had 1.094 times higher risk of death than rural patients when all other factors in the model were kept constant.

4. Discussion

The average longitudinal change in PR demonstrated a negative relationship with the length of follow-up for CHF patients. This conclusion is also consistent with the earlier finding obtained by [34]. The average longitudinal change in PR had a statistically significant detrimental influence on the age of CHF patients. This study's findings contrast those of a previous study conducted in [34]. Age shows a substantial positive correlation with the prevalence of HF [35]. According to another study [36], younger people may have less HF understanding and become at risk.

The left ventricular ejection fraction had a negative significant influence on the average longitudinal change in PR and was linked to a higher risk of death in CHF patients. This finding was consistent with previous research [34]. However, a study conducted in [36] found no indication of a link between LVEF and quality of life in HF patients. Another study [37] revealed that LVEF illness did not affect HF mortality.

The rise in the New York Heart Association class of CHF patients had a positive significant influence on the average PR evaluation of CHF patients admitted to the hospital and was related to an increased risk of death in CHF patients. This outcome was consistent with the findings of [34]; other studies [36] found that greater NYHA class worsened the quality of life of HF patients. Another study [38] showed that NYHA has no significant effect on the mortality of HF.

Being male had a substantial favorable effect on the average longitudinal change of PR and was a risk factor for death in CHF patients. This finding is consistent with the prior finding in [36], which found that males had a positive correlation with lower quality of life. However this result contradicts a previous study [34] and other research [35] that found a favorable correlation between females and the prevalence of HF. Another study conducted in [39] discovered that gender has no significant effect on HF mortality.

When compared to rural settings, patients who lived in an urban area had a negative significant influence on the average longitudinal change in PR and risk factors for death. This study supported [36], which found that the quality of life in rural heart failure patients was lower than in urban patients due to poorer perceived control and symptoms of the disease. Patients with congestive heart failure who had DM disease had a beneficial influence on the average longitudinal change of PR and were at a higher risk of death. This result supports prior research [40] that has shown that the presence of DM has a positive and significant effect on the quality of HF. However, other studies [38] found that DM has no significant effect on HF.

Patients with congestive heart failure who had HTN disease showed a positive significant influence on the average longitudinal change in PR. This result supports prior research [35, 39, 41, 42] that found HTN to be highly

linked with heart failure and to have a favorable significant influence on heart failure. Having an etiology of HHD was connected with a lower PR of congestive heart failure. This is inconsistent with a prior study [41] that found no significant relationship between HF and any of the etiologies of HF (ischemic heart disease, dilated cardiomyopathy, hypertensive heart disease, valvular heart disease, and other etiologies) except cor pulmonale.

5. Conclusion

The linear mixed-effect model with the subject value of PR measurement (in bpm) was a good fit for the longitudinal change PR evaluation in this investigation. At a 5% level of significance, the cofactors including baseline age, gender, residency, CHF type, NYHA class, DM, HTN, and TB illness, LVEF, etiology, and observation period were statistically significant factors that affect the mean longitudinal change of PR measures of the patients. The Cox PH model showed a good fit for the time to death of patients.

The fitted Cox model results revealed that sex, residency, LVEF, NYHA class, and DM disease were the factors that influenced the hazard rate of time to death of CHF patients in the study area at a 5% level of significance. However, the independent variables such as weight, TB, CKD, and CHF type have no association with the hazard rate of time to death of CHF patients.

For the joint modeling of the data, the joint model with random intercepts and time of slope from the longitudinal model and the survival model was appropriate. The computed association parameters revealed subject-specific values, and the subject-specific linear time slope of PR measurement was found to be positively related to the hazard rate of time to death of CHF patients in the study area. To reduce the risk level of CHF, health professionals, governmental organizations, and nongovernmental organizations must promote and allocate a suitable amount of budget for the treatment of CHF patients.

Abbreviations

AIC:	Akaike information criterion
AR:	Autoregressive order
BIC:	Bayesian information criteria
CHF:	Congestive heart failure
CKD:	Chronic kidney disease
CS:	Compound symmetry
DM:	Diabetes mellitus
DTRH:	Debre Tabor Referral Hospital
HHD:	Hypertensive heart disease
HTN:	Hypertension
IHD:	Ischemic heart disease
LME:	Linear mixed effect
LVEF:	Left ventricular ejection fraction
NYHA:	New York Heart Association
PR:	Pulse rate
REML:	Restricted maximum likelihood
TB:	Tuberculosis
SD:	Standard deviation

UN: Unstructured
 VHD: Valvular heart disease
 WHO: World Health Organization.

Data Availability

The data, which are now in the hands of the original author, will be made available to public upon request.

Ethical Approval

Ethical approval was acquired from the ethical review board of Bahir Dar University's College of Sciences, and authorization for data collection was acquired from the Debre Tabor Referral Hospital Patient's Ethical Committee.

Consent

Each patient additionally provided informed consent before data collection.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

AT was involved in the study design, performed the data extraction, analyzed the data, and produced the manuscript; DB was involved in the study design, counseled at each stage, and read the paper. AT, DB, and SG contributed to the manuscript's development. The final paper was critically evaluated and approved by all authors.

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