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Research Article

The Longitudinal Mean Arterial Pressure Among Congestive Heart Failure Patients at Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia

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Background

Congestive heart failure could be defined as a condition where there is a performance or structural impairment of the heart. So, this study was targeted at the determinants of the longitudinal mean arterial pressure among heart failure patients treated from January 2016 to December 2019 at Felege Hiwot Referral Hospital in Bahir Dar, Ethiopia.

Methods

Hospital-based retrospective data were assembled from the medical charts of 218 randomly selected congestive heart failure patients. The linear mixed effects model corresponding to an unstructured covariance structure was employed to spot out the determinants of mean arterial pressure among inpatients with congestive heart failure.

Results

The individual profile plot of mean arterial pressure showed the existence of variability among and between those patients. Moreover, the mean profile plot demonstrated a linearly increasing pattern over the follow-up times. The random intercept and slope model corresponding to an unstructured covariance structure was the best fit (AIC: 6001.9(χ^2=80.83), P < 0.0001) as compared to the remaining models. The estimates for age, left ventricle ejection fraction, serum sodium concentration, visit times, serum hemoglobin concentration, residence (rural), and New York Heart Association Classes I, II, and III were given as 0.3758 (P-value: <0.0001), 0.2933 (P-value: <0.0001), 0.1941 (P-value: <0.0001), 0.4471 (P-value: 0.0059), 0.5501 (P-value: 0.0053), -9.9858 (P-value: <0.0001), 18.8943 (P-value: 0.0001), 10.8833 (P-value: <0.0001), and 2.7318 (P-value: 0.0001) respectively, and they are statistically associated with the longitudinal mean arterial pressure of congestive heart failure patients.

Conclusion

The linear mixed effects model corresponding to an unstructured covariance structure provides information on the existence of within- and between-subject variations and correlations in addition to identifying the significant factors associated with the longitudinal mean arterial pressure of congestive heart failure patients. So, an application of standard models may ignore such

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variation among successive measurements. Thus, a mixed effects model is recommended for such longitudinal data.

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Introduction

Heart failure is usually referred to as chronic heart failure (CHF) or congestive heart failure (CHF). Clinically, it's not possible to define heart failure (HF) by a single term; as a result, it is outlined as a fancy clinical syndrome where there's a functional or structural impairment within the heart. This results when one or both ventricles cannot pump enough blood to satisfy the metabolic needs of the body [1]. Nowadays, heart failure is a major clinical disorder reaching epidemic levels in the developed world with no illustrious cure. It is the fastest-growing vascular disorder; about 26 million people live with it, and nearly a million new cases are diagnosed annually worldwide. In economically developed countries, up to 1 person in 5 is anticipated to have a heart failure incidence at some point in their life [1], and it affects 1-3% of the general population [2][3]. In these countries, it is predominantly seen in the geriatric population, with nearly 80% of cases occurring in patients over the age of 65. Thus, its prevalence has been shown to follow associated exponential growth rising with age and affect 6-10% of people over the age of sixty-five [2]. Despite enhancements in care over the past twenty years, the outlook for patients with heart failure remains poor, and it has a higher mortality rate than several of the common malignancies [1][4]. One-year mortality in developed countries is about 20%, whereas five-year mortality is about 50-65% in population-based studies [4].

In Africa, the occurrence of CHF was more frequent in the younger age groups, with most cases recorded around the 5th and 6th decades, and it is not a disease of the elders in sub-Saharan Africa (SSA) as compared to the rest of the world [1]. This young age replicates the major contribution of rheumatic valvular disease to heart failure; however, infections could additionally be accounted for as they remain a typical cause of heart failure in several parts of the world and will strike at any age. Heart failure patients have a hospital case fatality rate that ranges from 9% to 12.5%. This consistent death rate ranked heart failure among the foremost causes of death of cardiovascular origin in Africa [5][6]. A study conducted in the Republic of Ghana revealed a high prevalence of heart failure of 76 percent, supporting the fact that CHF will be a major contributor to disorder in Sub-Saharan Africa. The studies from Cameroon demonstrated that heart failure is found to be the fifth to sixth explanation for hospital admissions. In the other components of sub-Saharan Africa, heart failure has been found to account for 5% to 10% of hospital admissions [2].

In Sub-Saharan Africa, the prevalence of heart failure is higher among young people. Since it affects economically active people, it leads to a considerable decrease in economic production [7]. However, in this region, the incidence and prevalence of heart failure were not examined in detail in the population base [8]. Therefore, the source of data on the burden of heart failure was hospital-based studies. These studies revealed that among the total of 7-10% of all medical admissions due to cardiovascular diseases, 3-7% were due to congestive heart failure in African hospitals [9]. The quality of life among patients with heart failure is worse than that of most other diseases because it has a lot of complications [10].

In many clinical trials, longitudinal or repeated measures data are collected in order to monitor the patient's progress over time towards a clinical endpoint. One of the ways to account for the variability of longitudinal measurements on the same subject is through mixed-effect modeling. Since the repeated measurements of the same individual are most likely related to the event, they are endogenous. In Ethiopia, to the best of our knowledge, pieces of literature documented on the mixed-effect modeling of the longitudinal mean arterial pressure among CHF patients were scarce, except for the studies conducted to assess the common causes and patterns of heart failure using cross-sectional data. They used multiple linear regression and logistic regression to identify determinant factors without considering the correlations within the multiple outcomes or within and between subject variations due to these outcomes in congestive heart failure patients [11][12][13]. Although subject-specific random effects studies were previously done [14][15] regarding pulse rate, systolic blood pressure, diastolic blood pressure, and respiratory rate among CHF patients, mean arterial pressure (MAP) is

taken as a higher indicator of blood passage to very important organs than systolic blood pressure (SBP) [16]. Hence, in relevance to those pieces of literature and since very little is known despite a high prevalence of CHF, the aim of this study was to identify the determinants of longitudinal MAP among chronic heart failure patients treated at Felege Hiwot Referral Hospital from January 2016 to December 2019.

Materials and methods

Data source, study setting, and study design

A hospital-based retrospective follow-up study was conducted among congestive heart failure (CHF) patients under the outpatients' clinic from January 2016 to December 2019 at Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia. This hospital provides an organized CHF follow-up care program with mostly regional and national full-size laboratory equipment.

Operational definitions

New York Heart Association classes: a straightforward manner to categorize the severity of heart failure. It classifies patients into one of four stages based on how much physical activity restricts them; these restrictions and symptoms relate to everyday breathing and range from mild to severe angina and/or shortness of breath.

Study participants, sampling technique, and sample size

The study population was comprised of CHF patients receiving CHF treatment at Felege Hiwot referral hospital from January 2016 to December 2019. A simple random sampling technique was adopted for selecting a representative sample from the list of medical charts that contained the list of CHF patients' identification numbers, and patients were selected randomly using their unique identification numbers. The study excluded records of patients with fewer than two visits, records available outside of the study period, and records that were imprecise and incomplete. The sample size determination formula considered for this study was based on [17][18][19], which was given by

$$n = \frac{\left(Z_{\beta} + Z_{\frac{\alpha}{2}}\right)^2}{P_1 * P_0 * \gamma^2}$$

Where n = the sample size required, α = the level of significance, β = the power of the test, γ= the regression coefficient representing the effect of low blood sodium level, P_0 = the probability of death in normonatremia groups, and $P_1 = \text{the probability of death in hyponatremia groups}$. In this study, the power of 80% (Z_{β}= 0.84) and the power of the test and 5% ($Z_{\frac{\alpha}{2}}$ = 1.96) level of significance were used. The values of P_0, P_1, and γ were taken from the previous study done at the University of Gondar referral hospital [20], where patients were categorized as hyponatremia if their blood sodium level <135mmol/L and normonatremia if it was $\geq$ 135mmol/L at their first admission to the internal medicine department. Accordingly, the study found that 24.75 % (P_0) and 42.1% (P_1) of heart failure patients were dead within the study period (from December 2,2010 to November 30,2016) from normonatremia and hyponatremia groups, respectively. In addition, γ, is the regression coefficient representing the effect of low blood sodium level relative to normal blood sodium level on the survival of CHF patients, and it had the value extracted as the log of the hazard ratio of hyponatremia to normonatremia patients $(log 4.003 = 0.602)$. Using the above formula and adding a 5% non-response rate, the total sample size considered in this study was 218.

Variables in the study

In this study, we have considered two types of variables, namely, response and explanatory variables.

Response variable

The response variable considered for this study is the longitudinal mean arterial pressure (MAP). The mean arterial pressure is the average pressure in a patient's arteries during one cardiac cycle (systole and diastole) with the normal range of {m/60-100/} mmHg. MAP functions to pass the blood to all the tissues of the body to keep them functional, then it is considered a better indicator of blood passage to vital organs than systolic blood pressure (SBP) [16].

MAP is generally given by;

$$MAP = \frac{1}{3}SBP + \frac{2}{3}DBP$$ [21][22]

Where the parameters SBP and DBP were collected at baseline (SBP0 and DBP0), and every 3 months thereafter.

Explanatory variables

The predictor variables included in this study were background characteristics of CHF patients and history

of epidemiological, clinical, and laboratory results as summarized in (Table 1).

Predictors	Category	Measurement
Sex	Female, Male	
Residence	Rural, Urban	
New York Heart Association	Class I, Class II, Class III, Class IV	
Sodium		mmol/L
Hemoglobin		g/dl
Left Ventricle Ejection Fraction		%
Albumin		g/dL
Thyroid Stimulating Hormone		mIU/L
platelets		mcL
Creatinine		mg/dl
Age		year
White Blood Cell		mcL
Potassium		mEq/L

Table 1. Description of Explanatory variables

Key: mmol/L (millimole per liter); g/dl (gram per deciliter); mIU/L (milli international unit per liter); mcL (micro liter); mEq/L (milli equivalent per liter); mg/dl (milli gram per deci liter).

Data processing and editing

Checking the consistency of the data, editing, labeling, treating missing values that exist in the data set, and conducting descriptive analysis were conducted through SPSS software Version 26. For further analysis of the data, we exported the data to the R statistical software. Variable selection was carried out using the purposeful variable selection method, where the univariable analysis was done at a 25% level and the multivariable analysis at a 5% level of significance.

Ethical considerations

Ethical clearance and approval to conduct the research were obtained from the research and ethical committee of the College of Science at Bihar Dar University, and permission for data collection was obtained from the Felege Hiwot Comprehensive Specialized Referral Hospital. The privacy of the patients was maintained, and cultural norms were respected properly. For their support, other responsible authorities were fully informed about the study objectives. Moreover, all the collection methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

Longitudinal data is defined as the data of repeated measurements at a limited number of time points with predetermined designs on the time scale, time interval, and other related conditions [23]. In fact, longitudinal data involves a minimum of two repeated measurements made over a relatively long period of time [24]. Measurements made on the same variable for the same subject are more likely to be correlated, and models fitted to longitudinal or repeated measures data involve the estimation of covariance parameters to capture this correlation [25]. In this case, standard statistical methods like simple linear regression that assume independent observations are not appropriate. Thus, the linear mixed-effects model was fitted for the analysis of longitudinal mean arterial pressure.

Linear mixed effects model (LMM)

The three most commonly used models for the analysis of longitudinal data are mixed effect models, marginal models (generalized estimating equations (GEE) models), and transition models. The mixed effects model provides flexible modeling of variances and covariances in addition to the mean of the longitudinal data. The Linear Mixed Effect Model allows for random effects to incorporate between-subject variation and within-subject correlation in the data and is represented in its most general fashion by [26]. Marginal models concern separate modeling of the mean structure and the covariance structure without distributional assumptions for the data, while transitional models involve modeling of the within-subject correlation through Markov structures.

In mixed effect models, the random effects not only determine the correlation structure between observations on the same subject; they also take into account the heterogeneity among subjects due to unobserved characteristics. In a linear mixed effects model, the sequence of the longitudinal measurements Y_{i1} , Y_{i2},....., Y_{ini} for the i^{th} subject at times t_{i1} , t_{i2},....., t_{ini} is modeled as:

$$Y_i(t) = X_i(t)\beta + Z_i(t)\gamma_i + \varepsilon_i(t)$$

Where:

$Y_i(t) = n \times 1$ Vector of observed responses in i^{th} patient at a time t,

$X_i(t) = n \times p$ known design matrix of fixed covariate for i^{th} subject at a time t,

$\beta = p \times 1$ Vector of unknown constants, the fixed effects of the model,

$\gamma_i - = q \times 1$ Vector of unknown random effects from MVN (0,G),

$Z_i(t) = n \times q$ known design matrix of random effects for i^{th} subject at time

$\varepsilon_i(t) = n \times 1$ vector of error terms from MVN (0,R) [27]

Hence, β and γ_i represent the fixed and random effects respectively, and the variance components are represented by G and R.

Generally, $\mathrm{E}\begin{bmatrix}\gamma_i \\ \varepsilon_i\end{bmatrix} = \begin{bmatrix}0 \\ 0\end{bmatrix}$, $\mathrm{var}\begin{bmatrix}\gamma_i \\ \varepsilon_i\end{bmatrix} = \begin{bmatrix}G & 0 \\ 0 & R\end{bmatrix}$ and $\mathrm{Y} \sim \mathrm{N}(\mathrm{X}\beta, \mathrm{V})$ where, $\mathrm{V} = Z_i G_i Z_i' + \mathrm{R}$

Results and discussion

Results

The sample was composed of 218 patients who were treated at the outpatient clinic of Felege Hiwot Referral Hospital to recover from heart failure or to check for the incidence of complications continuously. The average mean arterial pressure among the sampled patients increased from baseline to every 3 months, then after up to the last 48 months of follow-up time. The baseline mean arterial pressure among CHF patients was 84.7767 mmHg (SD = 11.76193) and increased to 92.4322 mmHg (SD = 11.43457). Whereas, the mean arterial pressure for the first and the last two visits of CHF patients was 84.7767, 86.3805, 103.5368, and 105.1850 mmHg, respectively. The majority (56.4%) of participants were female. The majority, 151 (69.4%) of congestive heart failure patients, resided in urban areas. On the other hand, a large proportion (44%) of patients were identified as NYHA class IV (Table 2).

Variables	Categories	Count	Percent
Sex	Male	95	43.6
	Female	123	56.4
Residence	Rural	67	30.7
	Urban	151	69.3
NYHA	Class I	38	17.4
	Class II	36	16.5
	Class III	48	22
	Class IV	96	44

Table 2. Descriptive statistics for categorical variables

The average, minimum, and maximum ages (in years) of CHF patients treated at Felege Hiwot Referral Hospital were 50.58, 16, and 82, respectively. The result also shows the average serum hemoglobin concentration (g/dl), serum sodium concentration (mmol/L), and left ventricular ejection fraction (%) were 13.19, 122.03, and 48.47, respectively (Table 3).

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Variable	Mean	Median	Standard deviation	Minimum	Maximum
Age(Year)	50.58	52.5	20.274	16	82
Creatinine(mg/dl)	0.9448	0.8200	1.40245	0.1	20
Sodium(mmol/L)	122.0297	135.90	44.554	40.32	194.45
Hemoglobin(g/dl)	13.1929	13.400	5.422	4.73	21.5
Albumin(g/dL)	2.842	2.300	4.1923	0.25	6.19
Platelets(mcL)	167469.4929	147747.9956	122896.3592	99295.4123	729000
White blood cell(mcL)	14994.6387	10250.001	2526.0142	3482.86	22220.07
TSH(mIU/L)	6.7323	3.860	76.8514	0.0029	12.4786
LVEF (%)	48.47	55	24.974	11	88
Potassium(mEq/L)	5.1483	4.2800	5.76365	1.002	6.07
Time(Month)	23.4	22.00	14.037	0	48

Table 3. Descriptive statistics for continuous variables

The overall and individual profile plots depicted the patterns of the overall individual plots of the longitudinal measurements among CHF patients over time and showed the existence of within-subject correlation and between-subject variations by their mean arterial pressure (Fig 1).

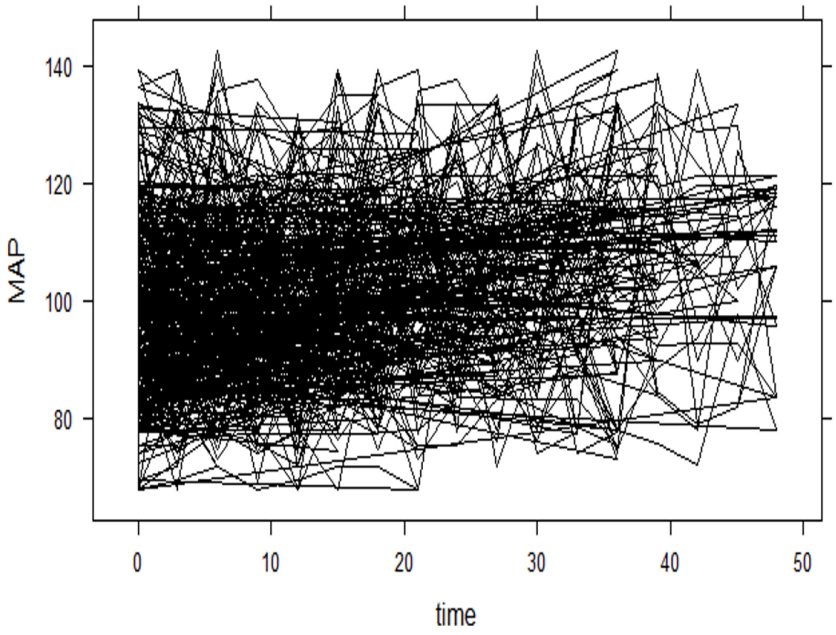

Fig 1. Individual profile plot

The line of loess smoothing technique suggested that the mean structure of the variable was linear (i.e., the relationship between MAP and follow-up times was linear). The plotted profiles tend to come up with a linearly increasing pattern, which rationalizes the appropriateness of a linear mixed-effects model for the progress of mean arterial pressure (Fig 2).

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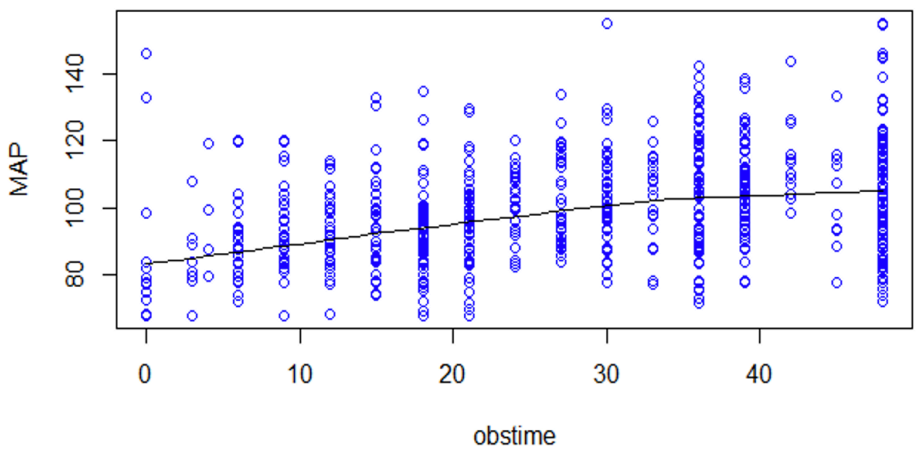

Fig 2. Mean profile plot

Covariance structure

In many clinical trials, repeated measurements made on the same subject were correlated; in this case, this correlation and covariance among the repeated measurements should be modeled accurately. The simplest way to select an appropriate covariance matrix structure is to fit a mixed-effects model with each covariance matrix, and then the one corresponding to the mixed-effects model with the smallest information criteria is the best fit to the data.

Results from the following table revealed that the linear mixed-effects model corresponding to the unstructured covariance structure was the best fit due to its smallest value for the fit statistics. Accordingly, the remaining analytical procedures were performed with this structure (Table 4).

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Fit statistics	Covariance structure			
	CS	AR(1)	Toep	UN
-2 Log Likelihood	6172.1	6172.1	6172.1	6172.1
AIC	6178.1	6178.1	6178.1	6176.1
AICC	6178.1	6178.1	6178.1	6176.1
BIC	6188.2	6188.2	6188.2	6182.9

Table 4. Selection of Covariance Structure

Model selection

The presence of subject-specific random effects in longitudinal studies makes model selection different from standard methods. Accordingly, different linear mixed-effects models were considered to analyze the longitudinal mean arterial pressure among CHF patients by unstructured covariance structure, and the one with the smallest value of the fit statistics was the best model. The following table indicated the appropriateness of the random intercept and slopes model due to its smallest value for (-2 log likelihood) statistics and statistically significant likelihood ratio test to fit the longitudinal mean arterial pressure among CHF patients with the possible clinical and demographical predictors. In the random intercept and slope model, both the intercept and the regression coefficients are allowed to vary across each subject (Table 5).

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Fit statistics	Random-intercept		Random slope	
	Null Model	Using predictors	Random slope model	Random intercept and slope model
-2Log Likelihood	6172.1	6024.9	6003.5	6001.9
LRT	Chi-Square	80.83		
	P- value	<0.0001		

Table 5. Model selection

Linear mixed effects model

Multi-variable analysis of a linear mixed effects model was fitted through all the significant predictors in the uni-variable analysis. Accordingly, Table 6 displays the results of the linear mixed effects model with fixed and random effect estimates, their standard error, Z value, and p-value. Among the predictors in the final linear mixed effects model, age, residence, NYHA classes, LVEF, blood sodium concentration, visit time, and serum hemoglobin concentration were significant predictors for the longitudinal MAP of CHF patients. Moreover, the estimates from the random effect results revealed that the estimated subject-specific variability with the longitudinal MAP was statistically significant at the five percent level of significance over the follow-up times (Table 6).

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Estimates for fixed effects					
variable	**categories**	**Estimate**	**S E**	**Z- value**	**P-value**
Intercept		87.6829	1.7033	51.48	<.0001
Age		0.3758	0.03863	9.73	<.0001
Residence(ref= urban)	rural	-9.9858	1.5794	-6.32	<.0001
Sodium		0.1941	0.01820	10.66	<.0001
Time		0.4471	0.06371	7.02	0.0059
Hemoglobin		0.5501	0.1963	2.80	0.0053
NYHA(ref= class IV)	Class I	18.8943	4.8987	3.86	0.0001
	Class II	10.8833	2.1517	5.06	<.0001
	Class III	2.7318	0.5877	3.94	0.0001
LVEF		0.2933	0.04556	6.44	<.0001
Estimates for random effects					
Cov Parm	estimate	S E	Z	pr>|Z|	
UN(1,1)	190.21	63.1196	3.01	0.0013	
UN(2.1)	-6.6120	2.4601	-2.69	0.0072	
UN(2,2)	0.2767	0.09103	3.04	0.0012	
Residual	133.20	8.1419	16.36	<.0001	

Table 6. Parameter estimates for the linear mixed effects model

Discussion

In this study, secondary data from 218 randomly selected congestive heart failure patients were analyzed using the linear mixed effects model, and significant factors associated with the longitudinal mean arterial pressure were identified.

The estimated coefficient of the fixed effect intercept was 87.6829, which indicated that the average MAP of CHF patients was 87.6829 mmHg at the first visit by excluding all the variables in the model (p-value < 0.0001). As the age of patients increased by a year, the average MAP of CHF patients significantly increased by 0.3758 mmHg (p-value < 0.0001), and one more CHF follow-up resulted in a 0.4471 mmHg (p-value =0.0059) increment in the average mean arterial pressure. The result is conformable to the study done by Avolio, A., et al. in urban and rural communities in China [28], where an age increment among patients significantly increased the mean arterial pressure. For a one mmol/L increment in blood sodium concentration, the average MAP of CHF patients significantly increased by 0.1941 mmHg (p-value <.0001). This result is conformable to a study done by Inrig, J.K., et al. in 2015 [29], where the average arterial pressure throughout all treatments was lower with low sodium concentrations compared with treatments with high sodium concentrations. For a one percent increment in the left ventricular ejection fraction, the average MAP of CHF patients significantly increased by 0.2933 mmHg (p-value <.0001). The result was consistent with the study conducted by Gottesman, R.F., et al. at the Johns Hopkins University School of Medicine [30], where a low ejection fraction was associated with low MAP and a high ejection fraction was associated with high MAP among cardiac patients. Additionally, for a one g/dl increase in serum hemoglobin concentration, the average MAP of CHF patients significantly increased by 0.5501 mmHg (p-value<0.0001). This result is conformable to the study

done by Göbel, B.O., et al. in 2016 [31], where there is a positive and significant correlation between the mean arterial pressure and blood hemoglobin concentration among patients. The average MAP of rural CHF patients was significantly lower by 9.9858 mmHg (p-value < 0.0001) compared to the average MAP of urban CHF patients. This result is conformable to a study done by Avolio, A., et al. in urban and rural communities in China [28], where the arterial pressure among rural patients was lower than that of urban patients. Moreover, the average MAP of CHF patients with NYHA class I, NYHA class II, and NYHA class III symptoms was significantly higher by 18.8943 mmHg (p-value=0.0001), 10.8833 mmHg (p-value <0.0001), and 2.7318 mmHg (p-value =0.0001) as compared to the average MAP among CHF patients with NYHA class IV symptoms groups, respectively. This result is consistent with the study done by Domanski, M.J., et al. in Bethesda, Maryland; Boston, Massachusetts; and Ann Arbor, Michigan [32], where higher mean arterial pressure was associated with a lower New York Heart Association functional class.

Conclusions

This study aimed to investigate the determinants of the longitudinal mean arterial pressure among CHF patients at Felege Hiwot Referral Hospital, Amhara Region, Ethiopia. This was a four-year (from January 2016 to December 2019) hospital-based retrospective study based on 218 random samples of CHF patients attending their follow-up under an outpatient clinic at Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia. The individual profile plot of longitudinal MAP revealed within- and between-subject variability among CHF patients based on their MAP over the follow-up times. Moreover, the mean profile plot tends to generate a linearly increasing pattern, which rationalizes the use of a linear Mixed Effects model to analyze the trajectory of MAP. The random intercept and slopes model corresponding to the unstructured covariance matrix was the best fit among the set of models to fit the data due to its smallest values for the information criterion as well as the significance of the likelihood ratio test, which is an implication of a good fit. It can be generalized that, if we have longitudinal outcomes with within-subject correlations and between-subject variations, the application of mean models by eliminating this variability may give spurious results, but linear variation through random effects. Among the predictors in the linear mixed effects model, age, residence, NYHA classes, blood hemoglobin concentration, blood sodium concentration, observation time, and left ventricular ejection fraction were significantly associated with the mean arterial pressure of congestive heart failure patients. Since the linear mixed effects model depicts within-subject correlations and between-subject variations with better accuracy, fitting a linear mixed effects model is advisable for such variables.

Limitation of the study

In the final linear mixed effect model, the authors did not see the interaction effect of the predictors over time. Therefore, researchers should consider the contribution of the interaction effect of the predictors on the respective outcome variable via a mixed effect model.

Abbreviations

CHF: Congestive Heart Failure, CVD: Cardiovascular Diseases, WHO: World Health Organization, MAP: Mean Arterial Pressure, MmHg: Millimeter Mercury, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, NYHA: New York Heart Association, LVEF: Left Ventricular Ejection Fraction, TSH: Thyroid Stimulating Hormone, WBC: White Blood Cell, LMM: Linear Mixed Model, AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria, CI: Confidence Interval

Declarations

The authors affirm that this study was a result of their own real work. All documents used for writing it were appropriately acknowledged.

Availability of data and materials

If someone wants to request the data from this study, the data supporting the findings are fully available, and the recognized data concerning this study can be accessed by the authors.

Competing interests

The authors declare that they have no form of competing interests.

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The authors do not have support or funding to report.

Authors' contributions

NM wrote the proposal, analyzed the data, and wrote the manuscript. DL reviewed the proposal with

revisions, analyzed the data, and contributed to manuscript writing. Both NM and DL browsed and approved the most recent manuscript.

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