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Association of Unobserved Heterogeneity & Observed Factors with Survival Time of Pediatric Cardiac Patients: A Frailty Model Analysis

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HIGHLIGHTS

- Gamma frailty model best-fit
- Heterogeneity affected survival
- Congenital disease increased mortality
- Pulmonary hypertension raised mortality
- Anemia increased mortality risk

Key Words:

Cardiac disease
Children
Frailty Model
Survival Analysis

ABSTRACT

Introduction: Cardiac disease is a major cause of mortality and disability worldwide and represents an important contributor to morbidity among children. Survival outcomes in pediatric cardiac disease may vary substantially between individuals because of differences in clinical characteristics, nutritional status, and other factors that may not be directly measurable. Accounting for such unobserved heterogeneity is therefore essential for accurately identifying determinants of survival. **Aim & Objective:** The present study aimed to assess the association of observed clinical and nutritional factors with survival among children with cardiac disease and to determine the contribution of unobserved heterogeneity to survival outcomes. **Material & Methods:** A retrospective cohort study was conducted among 323 children under follow-up at the Cardiac Center–Ethiopia. Clinical and demographic information was analyzed to identify factors associated with mortality. Shared frailty survival models were employed to account for unobserved individual-level heterogeneity. Model parameters were estimated using the Expectation-Maximization (EM) algorithm, and alternative frailty distributions were compared to determine the model providing the best fit. **Results:** The gamma frailty model demonstrated the best fit for the data. The estimated gamma frailty variance was 3.817 (95% CI: 1.024–6.620) and was significantly different from zero, indicating substantial unobserved heterogeneity in survival among children with cardiac disease. In the gamma frailty model, congenital cardiac disease was significantly associated with increased mortality risk (HR = 1.804, $p = 0.033$). Similarly, pulmonary hypertension (HR = 1.941, $p = 0.019$) and anemia (HR = 1.509, $p = 0.025$) were significant predictors of increased mortality risk. **Conclusions:** Survival among children with cardiac disease is influenced by important clinical and nutritional factors. The significant frailty variance further indicates substantial individual-level unobserved heterogeneity, highlighting the importance of incorporating frailty models into pediatric survival analyses.



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INTRODUCTION

Cardiac disease (CD) is leading cause of death and significant causes of disability and morbidity worldwide [1], contains congenital and acquired cardiac disease affecting infants, children, and adolescents [2]. About 17.3 million people have died of cardiac cases in 2016, 17.9 million deaths per year or 31% of all global deaths in 2020 [3], and this number will reach up to 23.3 million by 2030 [5]. The early diagnosis and effective management of cardiac are crucial for improving health outcomes and reducing the burden of morbidity and mortality [4].

Africa is believed to have one of the highest prevalence of cardiac diseases among children with an epidemiological pattern that is quite different from what is obtainable in the developed countries of the world [1],[5]. In addition, study conducted in Sub-Saharan Africa survey of cardiac disease identified a growing of cardiac disease from 13% to 17% [6] and it become one of the common causes of death for those who have a lower quality of life.

Despite significant advancements in medical care, the survival of children with cardiac disease is remains a concern. In Ethiopia, cardiac diseases have been recognized as a major contributor to childhood morbidity and mortality [7]. According to the world health organization [3], [8] report, 9% of all deaths in Ethiopia were due to cardiac disease, but the specific impact on children is not well studied. However, curbing morbidity and mortality in children have been a major focus of the Millennium Development Goals (MDG)[9].

The status of cardiac disease in children are not well studied in Ethiopia, few study on the patterns of cardiac disease are available [10], [11]. Most of the studies focused mainly on the pattern of congenital and acquired cardiac disease without highlighting any trends or associated factors [12], [13], [14].

Further studies are required. This study is exceptional in that it assesses the effect of observed covariates and unobserved heterogeneity on the survival of children with cardiac disease under follow-up. **Figure 1.** Conceptual framework illustrating the influence of socio-demographic and clinical factors, unobserved heterogeneity (frailty), and pathophysiological effects on cardiac function and survival outcomes.

When individuals are follow-up over time, individuals survival time are likely to be correlated. In this case the Cox proportional hazard (PH) model is not appropriate for modelling correlated survival data [15]. In survival analysis, the Cox proportional hazards model assumes independence between individuals. However, this assumption may be violated due to the presence of unobserved individual-level factors that influence survival outcomes. Such latent heterogeneity can lead to biased estimates if not properly accounted for. To address this issue, frailty models, an extension of the Cox proportional hazards model are employed. These models incorporate a subject-specific random effect that captures unobserved heterogeneity acting multiplicatively on the hazard function [16], [17]. Thus, in this study, we aimed to assess the association of observed factors and unobserved heterogeneity with the survival of children with cardiac disease having clinical follow-up at Cardiac Center-Ethiopia.

Primary Research Questions

1. Which socio-demographic and clinical factors significantly affect the survival time of children with cardiac disease?
2. Does unobserved heterogeneity (frailty) significantly influence survival outcomes among children with cardiac disease?
3. Which shared frailty distribution (gamma, inverse Gaussian, compound Poisson, or positive stable) best fits repeated survival data for pediatric cardiac patients?

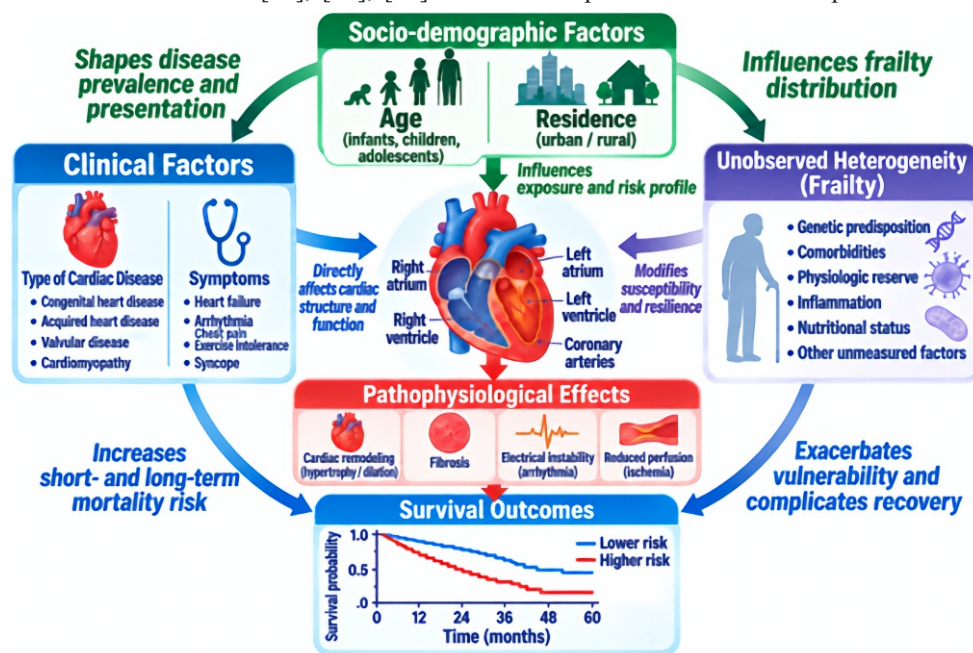


Figure 1. Conceptual framework linking socio-demographic, clinical, and frailty factors with cardiac pathophysiology and survival outcomes.

MATERIAL & METHODS

Study Setting

Observational study design is employed [18]. Researchers investigate the effects of certain factors or treatments without manipulating who is, or isn't, exposed to them. A retrospective cohort study design is used, where the cohorts are identified from past records, and outcomes are measured from that point forward.

Study Design

The study was conducted at the Cardiac Center-Ethiopia, located in Addis Ababa. The Center is a non-profit organization that provides specialized cardiac care for children and receives referrals from different regions of the country. It is currently one of the leading centers providing pediatric cardiac surgery services in Ethiopia. A retrospective cohort study design was employed using patient records from September 2021 to August 2022.

Study Population and Sampling

The study population consisted of pediatric cardiac patients (aged less than 18 years) who were under follow-up at the Cardiac Center-Ethiopia during the study period. The sampling frame included all eligible patients registered in the follow-up database. A simple random sampling technique was initially planned to select representative patient records from the registry. However, for the purpose of ensuring adequate follow-up information and reliable estimation of survival time, only patients who had at least three follow-up visits were included in the final analysis. Patients with fewer than three follow-up visits or with incomplete records were excluded. Therefore, the final analytic sample represents a subset of patients with sufficient follow-up information rather than a purely simple random sample of all registered patients.

Sample Size Determination

Before data is collected, emphasis is needed on determination of sample size. The sample size is determined based on financial affordability, time constraints, and data analysis method [19].

When we propose the sample size (n) data must at the very least meet criteria: small optimism in predictor effect, small absolute difference and precise estimation [20]. The values of n that meet all three criteria provide the optimum values required for study.

We designed a study to fit a model with time-to-event outcomes, we ensure the sample size is adequate in terms of the number of participants (n) and outcome of an events (E) relative to the number of predictor parameters (p). We assume there are p potential predictor for inclusion in the model, and for suitable choice of $R^2_{CS_{adj}}$ and $(\max R^2_{CS_{adj}})$ [20], [21], the required sample can be determined. We need to include $p = 10$ predictor used in the model with targeted expected shrinkage of 0.90, and the required sample size can be obtained by:

$$n = \frac{p}{(S_{VH}-1)\ln(1-\frac{R^2_{CS_{adj}}}{S_{VH}})} = \frac{10}{(0.90-1)\ln(1-\frac{0.24}{0.90})} = 323 \quad (1)$$

The optimum sample size required for the study was estimated to be 323 participants.

Data Collection

The data used for this study were obtained from a retrospective cohort of children diagnosed with cardiac disease based on a review of patient cards and information sheets. Due to incomplete information in the computerized data management system, data were manually extracted from patient records. A structured data extraction checklist was prepared in English and pre-tested on randomly selected patient records to ensure data quality and consistency. Data collection was carried out by trained B.Sc. nurses. To ensure data accuracy and reliability, all extracted data were independently cross-checked by a second reviewer. Any discrepancies identified were resolved through discussion and verification against the original patient records. In addition, a random sample of 10% of the records was re-examined to further validate data quality prior to analysis. There were no missing data for the outcome (time to death or censoring) and key predictors, as records with incomplete information were excluded, resulting in a complete-case analysis.

Variables in the Study

The event of interest in this study is time to death due to cardiac disease. Patients were followed through multiple clinical visits during the study period; however, each individual contributes a single time-to-event outcome (death or censoring). The repeated visits represent follow-up observations rather than repeated survival events.

The outcome variable for this study is time to death due to cardiac disease. Time-to-death is measured for children followed-up from the time started diagnosis with cardiac case until death, lost to follow-up or was still on follow-up.

Outcome variable: Time-to-death due to cardiac disease.

Event indicator: The outcome variable for a cardiac patient's possible outcome (Death, Alive).

Predictor variables: The predictor variables are summarized in as the following (Figure 2).

Model Development

In this study, the frailty term represents unobserved individual-level heterogeneity rather than clustering due to repeated events. It captures the effect of unmeasured factors that may affect the hazard of death. The inclusion of a frailty term allows for more flexible modeling by accounting for latent differences in risk across individuals [22].

Suppose that X represents a covariate vector, T be a non-negative random variable representing an individual survival time, with t being a realization of random variable, then the Cox proportional hazard (Cox PH) model is [15]:

$$\lambda(t, X) = \lambda_0(t) \exp(X^T \beta) \quad (2)$$

Where $X = (X_1, \dots, X_n)$ and $\beta = (\beta_1, \dots, \beta_n)$ is a parameter vector.

Survival data analysis assumes that the time-to-event of the individuals considered in the study is independent. However, this may not always be the case, because there is a possibility that the survival times of individual or individual in the same group are correlated. According to [22], the data with correlated survival times are analyzed using frailty model [17], [22], [23].

Frailty Models

A frailty model is an extension of Cox PH model, where the frailty is assumed to be individual or group specific [17][22]. If observed vector of covariates X_{ij} ($1 \leq i \leq n$, $1 \leq j \leq n$) are available and associated with the survival time t_{ij} of i^{th} individual at j^{th} follow-up period, then the hazard model becomes:

$$\lambda_i(t|W_i, X_{ij}) = W_i \exp(\beta^T X_{ij}) \lambda_0(t) \quad (3)$$

where W_i is an unobserved subject specific random effect i (frailty), a β vector of regression coefficients and $\lambda_0(t)$ is baseline hazard function specified non-parametrically.

Frailty Distribution

Many distributions can be chosen for frailty. We assume the case where W are independently and identically distributed random variable follows a distribution $f_w(w; \alpha, \gamma)$, with realizations [22], [23];

$$f_w(w; \alpha, \gamma) = \exp(-\alpha \Psi(w; \gamma)) \quad (4)$$

with $\alpha > 0$ and $\gamma > 0$. This formulation is called power variance function (PVF) family of distributions. It includes several distributions, such as the gamma, positive stable, inverse Gaussian and compound Poisson distributions.

This is a popular extension of the Cox PH model where a random effect acts multiplicatively on the hazard rates of all individuals. Individuals with a large value of the (unobserved) frailty W_i will tend to experience the event at earlier times than individuals with a small value.

Estimation and Inference

For estimation of parameter of frailty models, the Expectation-Maximization (EM) algorithm has been used [24]. The EM algorithm alternates between two steps: the Expectation (E-step) and the Maximization (M-step).

Goodness of Fit

Given a choice of distributions for the frailty, the question comes in is selecting the most suitable one. A selection of frailty

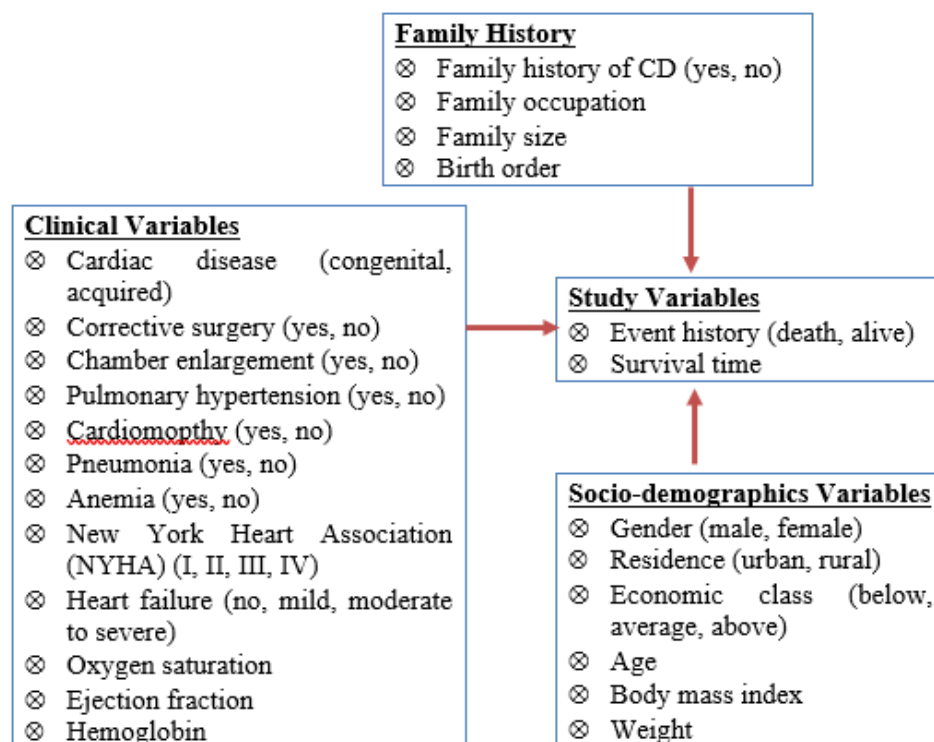


Figure 2: Variables considered in the study and their descriptions.

distributions is based on log-likelihood and Bayesian information criteria [25]. Model comparison was performed using the log-likelihood, Bayesian Information Criterion (BIC), and Akaike Information Criterion (AIC). The AIC was calculated as:

$$\text{AIC} = -2 \log L + 2k, \quad (5)$$

where L is the likelihood of the model and k is the number of estimated parameters. Models with lower AIC and BIC values were considered to provide a better fit to the data while accounting for model complexity. The selection of covariates was guided by clinical relevance and evidence from prior studies to avoid overfitting and ensure model interpretability, given the limited number of observed events.

Ethics Statement

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of the Cardiac Center–Ethiopia prior to data collection (ref. no: chfe/9815/17/2024). As this study was based on retrospective review of routinely collected clinical follow-up records, the requirement for informed consent was waived by the IRB. The waiver was granted because the study involved no direct contact with patients, posed minimal risk, and used de-identified secondary data. All data were anonymized before analysis to ensure confidentiality and privacy of patient information, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Descriptive Analysis

In this study, three hundred twenty three children with cardiac disease (CD) are included. Among them, 182 children (56.35%) are female, and 56.04% are under the age of 5 years. The mean age is 7.73 years, ranging from 1 day to 18 years (**Table 1**).

A majority of the children, 215 (66.56%) are resided in urban areas. Regarding the occupational status of the families, 43.65% of the fathers and 30.03% of the mothers are employed by the government. Additionally, 74.82% of the families have less than four family members (**Table 1**).

From total of 141 male and 182 female involved in the study, the death rate is higher in males (12.06%) compared to females (7.14%), and higher in urban residents (16.67%) compared to rural residents (5.58%). Looking into the family history, 27(8.36%) have history of cardiac disease and 129 (39.96%) of the study participants are aged between (24-59) months followed by 92(28.48%) between (60-144) months (**Table 1**). Congenital heart disease (CHD) is more prevalent than acquired heart disease, with 71.21% of children diagnosed with CHD and 29.79% with acquired heart disease. Among the study participants, 16.10% have pulmonary hypertension, and 35.29% have a

history of anemia. Under nutrition is identified in 59.29% of the children, with a higher prevalence in those with acquired heart disease (61.29%) compared to those with congenital heart disease (58.29%) as in **Table 2**.

Out of the study participants, only 30 children (9.28%) experienced the event of interest (death), while the remaining 293 children are censored. **Table 2** summarizes the descriptive statistics for the clinical covariates. There are 47 (14.55%) corrective surgeries done, and the remaining 276 (85.45%) are awaiting surgery during the study period. Moreover, 110 (34.05%) have no history of heart failure, 125 (38.69%) had mild heart failure, and the remains have moderate to severe heart failure (**Table 2**). Pneumonia is identified in 17.96% of children and anemia is also common in the study area, with prevalence rate of 35.29%.

The children are followed-up for a total of 24 months. The mean survival time of children with cardiac disease aged 18 years and younger based on a sample of 323 is 16.75 months with median and standard deviation of 17 and 5.95 month respectively. The graph of the Kaplan-Meier estimate of survival probability are shown in **Figure 2**, which indicates decreasing pattern of survivorship function as expected. The plots shown the pattern of one survivorship function lying above another, indicating the groups defined by the upper curve have a higher survival probability than the group defined by the lower curve (**Figure 3**). Looking into survival probability of children; non-anemic have higher experience of survival probability than anemic and children resident in urban have higher survival probability than those resident in rural. Comparing survival probability based on NYHA; the survival probability is lower for children in stage IV closely followed by stage III in concordance with several other literatures. Pulmonary hypertension is also lowers survival probability of cardiac patients (**Figure 3**).

We employed the log-rank test to check out the significance of observed survival difference among categories of variables described in the Kaplan-Meier survival plot. The results are given in **Table 3**. Based on the result we found that there are significant differences in survival probability among children in different classes of NYHA clinical stage, chamber enlargement, pulmonary hypertension, corrective surgery, pneumonia, and anemia. However, there is no significant difference in survival probability between age, gender and residence of children.

Repeated Measured Survival Data

Repeated measured survival data involve measurements of survival time of subjects over multiple time points. Each subject is observed multiple times, leading to repeated measurements of survival data. Observations within the same subject are likely to be correlated. The follow-up and event history of an individual are visualized in **Figure 4**. Most of individuals have no events during their follow-up and different individual have different follow-up period. The length of the line indicates the length of follow-up time (in months X-axis) and the dots indicate an individual experience event.

Frailty Models for Repeated Measure Survival Data

Repeated measured survival data involve measurements of survival time of subjects over multiple time points. Each subject is observed multiple times, leading to repeated measurements of survival data. The Cox PH model is not good enough to analyze a correlated repeated measure survival data. But, shared frailty models can extend the Cox PH model and handle correlated repeated measured survival data by incorporating random effects for each subjects over follow-up periods. So, to see and quantify random effects over follow-up, we fit a shared frailty models.

Comparison of Frailty Models

Shared frailty models are used to account for unobserved heterogeneity in the data. They introduce a random effect (frailty) for each subject. Different frailty model are compared; gamma, inverse Gaussian, compound poisson, and positive stable distribution. Log-likelihood and Bayesian information criteria are used for models evaluation and selection[25]. **Table 6** show the result of log-likelihoods and Bayesian information criteria of fitted frailty models. The results indicate that the shared gamma frailty model has the highest log-likelihood (-420.704) & the lowest Bayesian information criteria (921.319),

making it the best fit for the data among the models compared (**Table 4**). The result from gamma frailty model indicates that corrective surgery, types of cardiac disease, pulmonary hypertension, anemia, body mass index, ejection fraction, and hemoglobin are statistically significant factors associated with survival of cardiac patients (**Table 5**). The gamma frailty variance estimate is 3.817, which is different from zero with 95% confidence interval (1.024, 6.620) and significant, which indicates the existence of substantial frailty or unobserved effects on survival of patients. This implies that unobserved heterogeneity is associated with individual survival over follow-up. A higher variance estimate suggests greater variability in the frailty effects, which means that the risk of the event (death in this case) differs more significantly for each individual at different follow-up period (**Table 5**).

The frailty variance from the gamma frailty model is different from zero and significant. This implies that the survival of the cardiac patients is not only associated with observed covariates, but also with unobserved effects or frailty. Subject with lower or higher frailty have lower or higher risk to death, respectively (**Figure 5**). Therefore, we can suggest that children at some follow-up period are associated with a higher risk of death.

Table 1. Socio-demographic characteristics of study participants under follow-up.

Covariates	Attributes	Total, n (%)	Death, n (%)	Censored, n (%)
Gender	Male	141 (43.65)	17 (12.06)	124 (87.94)
	Female	182 (56.35)	13 (7.14)	169 (92.86)
Age (months)	< 24	52 (16.10)	8 (15.38)	44 (84.62)
	24–59	129 (39.94)	10 (7.75)	119 (92.25)
	60–143	92 (28.48)	7 (7.61)	85 (92.39)
	≥ 144	50 (15.48)	5 (10.00)	45 (90.00)
Birth order	First	123 (38.08)	8 (6.50)	115 (93.50)
	Second and third	159 (49.23)	18 (11.32)	141 (88.68)
	Fourth or more	41 (12.69)	4 (9.76)	37 (90.24)
Residence	Urban	215 (66.56)	12 (5.58)	203 (94.42)
	Rural	108 (33.44)	18 (16.67)	90 (83.33)
Family history of cardiac disease	Yes	296 (91.64)	26 (8.78)	270 (91.22)
	No	27 (8.36)	4 (14.81)	23 (85.19)
Father's occupation	Employed	141 (43.65)	10 (7.09)	131 (92.91)
	Farmer	98 (30.34)	14 (14.29)	84 (85.71)
	Merchant	34 (10.53)	2 (5.88)	32 (94.12)
	Other	50 (15.48)	4 (8.00)	46 (92.00)
Mother's occupation	Housewife	182 (56.35)	21 (11.54)	161 (88.46)
	Employed	97 (30.03)	7 (7.22)	90 (92.78)
	Merchant	20 (6.19)	0 (0.00)	20 (100.00)
	Other	24 (7.43)	2 (8.33)	22 (91.67)
Economic status	Below average	160 (49.54)	17 (10.62)	143 (89.38)
	Average	122 (37.77)	8 (6.56)	114 (93.44)
	Above average	41 (12.69)	5 (12.20)	36 (87.80)
Family size	< 4	242 (74.92)	22 (9.09)	220 (90.91)
	≥ 4	81 (25.08)	8 (9.88)	73 (90.12)

Table 2. Some of clinical characteristics of study participants under follow-up.

Covariates	Attributes	Total, n (%)	Death, n (%)	Censored, n (%)
Cardiac disease	Congenital	230 (71.21)	24 (10.43)	206 (89.57)
	Acquired	93 (28.79)	6 (6.45)	87 (93.55)
Chamber enlargement	Yes	167 (51.70)	22 (13.17)	145 (86.83)
	No	156 (48.30)	8 (5.13)	148 (94.87)
Pulmonary hypertension	Yes	52 (16.10)	14 (26.92)	38 (73.08)
	No	271 (83.90)	16 (5.90)	255 (94.10)
Corrective surgery	Yes	47 (14.55)	3 (6.38)	44 (93.62)
	No	276 (85.45)	27 (9.78)	249 (90.22)
Nutritional status	Underweight	192 (59.44)	27 (14.06)	165 (85.94)
	Healthy weight	131 (40.56)	3 (2.29)	128 (97.71)
NYHA functional class	I	110 (34.05)	2 (1.82)	108 (98.18)
	II	125 (38.70)	5 (4.00)	120 (96.00)
	III	62 (19.19)	9 (14.52)	53 (85.48)
	IV	26 (8.05)	14 (53.85)	12 (46.15)
Heart failure	No	110 (34.05)	2 (1.82)	108 (98.18)
	Mild	125 (38.70)	5 (4.00)	120 (96.00)
	Moderate to severe	88 (27.25)	23 (26.14)	65 (73.86)
Anemia	Yes	114 (35.29)	14 (12.28)	100 (87.72)
	No	209 (64.71)	16 (7.66)	193 (92.34)
Pneumonia	Yes	58 (17.96)	9 (15.52)	49 (84.48)
	No	265 (82.04)	21 (7.92)	244 (92.08)
Cardiomyopathy	Yes	78 (24.15)	12 (15.38)	66 (84.62)
	No	245 (75.85)	18 (7.35)	227 (92.65)

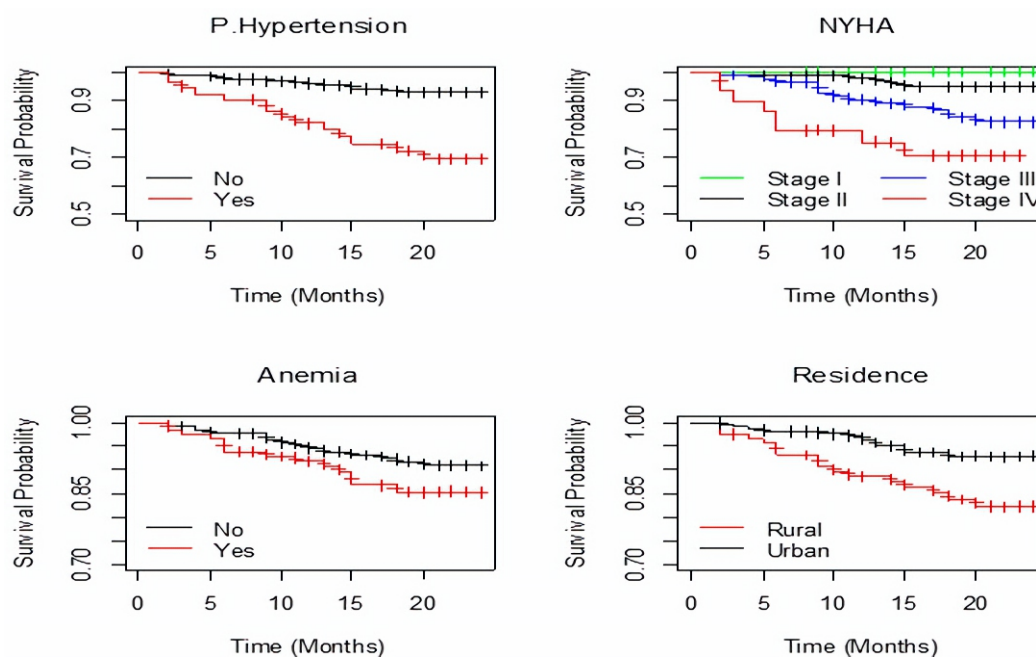
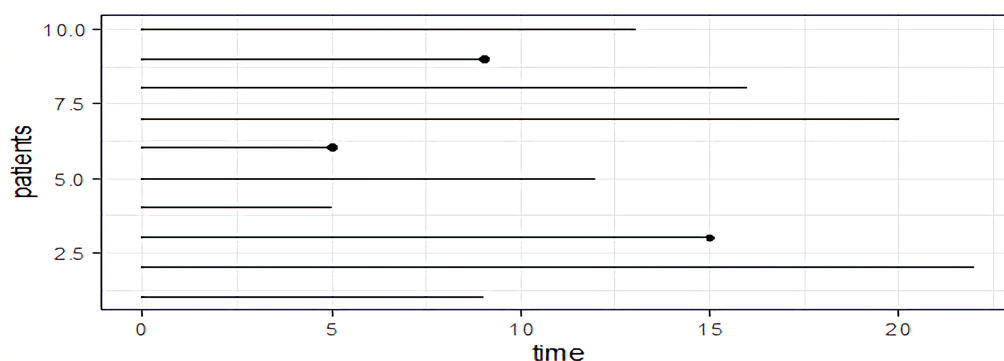
**Figure 3. Kaplan-Meier survival plots of children with cardiac disease under follow-up.****Figure 4. Plot of follow-up and event history of randomly selected individual's over follow-up.**

Table 3. The result of log-rank test for categorical covariates.

Covariates	Chi-square (χ^2)	p-value
Gender	1.802	0.182
Age	4.332	0.213
Residence	8.341	0.004*
Anemia	2.208	0.001*
Pulmonary hypertension	4.632	0.022*
NYHA functional class	1.429	0.013*
Cardiac disease	1.248	0.026*
Corrective surgery	0.782	0.038*
Chamber enlargement	6.724	0.011*
Pneumonia	4.172	0.042*
Cardiomyopathy	2.673	0.011*

Table 4. Comparison of shared frailty models.

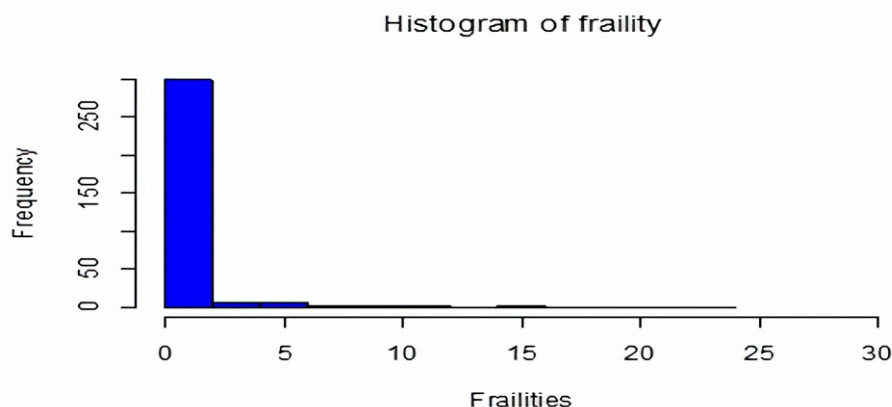
Criteria	Gamma	Inverse Gaussian	Positive Stable	Compound Poisson
Log-likelihood	-420.704	-425.484	-428.729	-429.836
BIC	921.319	930.879	937.369	938.584

Table 5. Parameters estimate of gamma and Inverse Gaussian shared frailty model.

Covariates	Gamma				IG (Inverse Gaussian)			
	exp()	se()	p-value		exp()	se()	p-value	
Residence: Urban	-0.367	0.692	0.411	0.150	-0.371	0.689	0.630	0.160
Corrective: Yes	-0.059	0.942	0.343	0.039	0.053	1.055	0.564	0.092
CD: Congenital	0.590	1.804	0.502	0.033	0.607	1.835	0.649	0.035
Economic: Average	-0.663	0.515	0.262	0.318	-1.357	0.257	0.744	0.028
: Above	-1.495	0.224	0.326	0.047	-2.322	0.098	0.792	0.041
Pulmonary: Yes	0.663	1.941	0.181	0.019	0.665	1.945	0.400	0.108
Anemia: Yes	0.411	1.509	0.155	0.025	0.397	1.487	0.378	0.030
BMI	-0.313	0.730	0.092	0.001	-0.379	0.684	0.103	0.001
Ejection	-0.062	0.939	0.012	0.001	-0.076	0.926	0.023	0.001
Hemoglobin	-0.650	0.521	0.108	0.001	-0.762	0.466	0.184	0.001
Frailty Measures	coef.	95% CI			coef.	95% CI		
	3.817	(1.024, 6.620)			4.625	(2.108, 7.142)		
	0.085	(0.050, 0.158)			0.036	(0.050, 0.105)		

Table 6. Parameter estimate of compound Poisson and positive stable shared frailty model.

Covariates	CP (Compound Poisson)				PS (Positive Stable)			
	exp()	se()	p-value		exp()	se()	p-value	
Residence: Urban	-0.306	0.736	0.573	0.290	-0.424	0.653	0.799	0.260
Corrective: Yes	-0.141	0.868	0.523	0.079	0.055	1.057	0.612	0.193
CD: Congenital	0.654	1.924	0.551	0.224	0.852	2.344	0.862	0.233
Economic: Average	-0.226	0.797	0.641	0.573	-1.650	0.192	0.829	0.065
: Above	-1.012	0.363	0.731	0.118	-3.098	0.045	0.961	0.001
Pulmonary: Yes	0.656	1.928	0.359	0.047	0.506	1.659	0.442	0.066
Anemia: Yes	0.398	1.490	0.335	0.025	0.327	1.387	0.413	0.043
BMI	-0.277	0.757	0.084	0.001	-0.422	0.655	0.116	0.001
Ejection	-0.051	0.950	0.022	0.03	-0.075	0.927	0.025	0.001
Hemoglobin	-0.607	0.545	0.172	0.001	-0.749	0.472	0.197	0.001
Frailty Measures	coef.	95% CI			coef.	95% CI		
	2.642	(1.501, 4.209)			0.475	(0.336, 0.500)		
	0.104	(0.058, 0.182)			0.476	(0.334, 0.501)		

**Figure 5. Histogram of estimated frailty of shared gamma frailty model.**

DISCUSSION

The main objective of this paper is to assess the effect of observed factors and unobserved heterogeneity on the survival of children with cardiac disease. We fit semi-parametric frailty models. The parameters are estimated using the EM (Expectation-Maximization) algorithm. The results suggest the existence of unobserved heterogeneity that can affect survival of cardiac patients.

The results in this paper do not deviate much from the findings obtained by [26], frailty is a significant predictor of survival of children with cardiac disease, and similar with the study [26]. In some cases, adding a frailty term can change a result significance in the frailty model [27] but, not concordance with this study. The study indicates that frailty is a factor associated to mortality of cardiac patients.

Our study also reveals, survival probability of children varies with the severity of disease, and survival probability is higher for children with no history of pulmonary hypertension concordance with result in [27,28]. The risk of death of children with pulmonary hypertension is 41.94% higher compared to no history of pulmonary hypertension. This rate is lower in other studies, which range from 16 to 25% [28,29]. In this study, the death rate is 9.28%, and it is lower than reports from Nigeria [30], but higher in the study from Kenya [29]. A lower death identified in Kenya could be attributed to the availability of better care and surgical intervention for children with cardiac disease [29]. The high occurrence of malnutrition in a study conducted in Ethiopia could also explain the noted mortality [31].

Anemia is common attributes for death in our study, and agreed with findings from Kenya [28,29]. This goes in line with the high prevalence of childhood anemia and nutritional status in Ethiopia, and reported anemia occurrence among children with cardiac disease [31].

CONCLUSION

The main objective of this paper is to assess the effect of observed factors and unobserved heterogeneity on the survival of children with cardiac disease. To achieve this, we employed semi-parametric frailty models, with parameters estimated using the EM (Expectation-Maximization) algorithm. We evaluated four frailty models: gamma, inverse Gaussian, compound Poisson, and positive stable. Among these, the gamma frailty model provided the best fit for the data. The results suggest the existence of unobserved heterogeneity that can affect survival of cardiac patients. The estimate of the frailty variance is 3.817 and significant, indicating the existence of unobserved heterogeneity (frailty). This implies that the survivals of cardiac patients are influenced not only by observed covariates but also by unobserved effects. Subjects with lower or higher frailty have a correspondingly higher or lower survival probability. Consequently, children at some follow-up period are associated with the risk of death. Furthermore, the model confirms that nutritional status, anemia, hemoglobin levels, uncorrected.

surgery, ejection fraction, and pulmonary hypertension are predictors of the risk of death in children with cardiac disease. Therefore, continuous follow-up is crucial for improving cardiac conditions, which can lead to significant reductions in morbidity and mortality. The authors conclude that accounting for frailty in a survival model is essential and useful in situations where individual variation over follow-up periods needs to be considered.

LIMITATIONS & FUTURE PERSPECTIVES

This study has several limitations. First, the relatively small number of observed events (30 deaths) compared to the number of covariates included in the model may increase the risk of overfitting and reduce the precision and stability of the estimated hazard ratios. Although efforts were made to include clinically relevant predictors and to use appropriate model selection criteria, the findings should be interpreted with caution. Future studies with larger sample sizes and more events are recommended to validate these results.

Future research could focus on multi-center studies with larger cohorts to validate findings, evaluate long-term outcomes, and explore innovative diagnostic & management strategies for appendicular perforation, improving patient prognosis and reducing complications

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient care, diagnosis, and treatment outcomes. By highlighting real world relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

HR: Hazard Ratio

CI: Confidence Interval

EM: Expectation-Maximization

PH: Pulmonary Hypertension

CHD: Congenital Heart Disease

GC: Gamma Frailty Model

CV: Cardiovascular

WHO: World Health Organization

BMI: Body Mass Index

CD: Cardiac Disease

NYHA: New York Heart Association

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines

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Patient & public involvement statement: Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this protocol. Because of this scoping review's broad inclusion criteria, I anticipate that the study populations will be too heterogeneous to involve representative patient input. Rather, the final results may be used to inform narrative intervention development by refining the information that is still needed from patients for whom future interventions are intended to benefit.

CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research directions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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