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Determinants of Intraocular Pressure and time to blindness for Glaucoma patients at Felege Hiwot Referral Hospital, Bahir Bar, Ethiopia; A Comparison of Separate and Joint Models

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Determinants of Intraocular Pressure and time to blindness for Glaucoma patients at Felege Hiwot Referral Hospital, Bahir Bar, Ethiopia; a comparison of Separate and Joint Models

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ABSTRACT

Background: Due to the substantial increase in the number of glaucoma cases within the next several decades, glaucoma is a significant public health issue. The main objective of this study was to investigate determinants for the variation of intraocular pressure and time to blindness of glaucoma patients under treatment at Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia.

Materials and Method: A retrospective cohort study design was conducted on 328 randomly selected glaucoma patients in ophthalmology clinic at the hospital under the follow-up period from January 2014 up to December 2018. A linear mixed effects model for intraocular data, a semi-parametric survival model for the time-to-blindness data and joint modeling of the two responses were used for data analysis.

Result: The comparison of joint and separate models revealed that joint model was more adequate and efficient inferences because of its smaller standard errors in parameter estimations. This was also approved using AIC, BIC and based on a significant likelihood ratio test as well. The estimated association parameter (α) in the joint model was 0.0160 and statistically significant (p - value = 0.0349). This indicated that there was strong evidence for positive association between the effects of intraocular pressure and the risk of blindness. The result indicated that the higher value of intraocular pressure was associated with the higher risk of blindness. As age increased by one year, the average IOP of the patients was also increased by 0.0726 mmHg (p-value < 0.0001) keeping all variables constant.

Conclusion: The predictors; age, blood pressure, type of medication and cup-disk ratio were significantly associated with the two responses of glaucoma patients. Health professionals should give more attention for patients who have blood pressure and cup-disk ratio greater than 0.7 during the follow-up time to reduce the risk of blindness of glaucoma patients.

Keywords: Intraocular pressure, time to blindness, linear mixed model, joint model, Cox proportional hazard model

BACKGROUND

Glaucoma is a leading cause of irreversible blindness worldwide and associated with characteristic damage to the optic nerve and patterns of visual field loss due to retinal ganglion cell degeneration [1]. Glaucoma encompasses a group of ophthalmic diseases that are believed to share the common pathophysiology of elevated intraocular pressure and causes irreversible visual loss [2].

IOP is the fluid pressure inside the eye and eye care professionals' uses tonometer to determine this. Most tonometer is calibrated to measure pressure in millimeters of mercury (mmHg) [3]. Ocular hypertension refers to a situation in which the pressure inside the eye is higher than 21 mmHg[4]. Normal eye pressure ranges from 10-21 mmHg.

Due to the substantial increase in the projected number of glaucoma cases within the next several decades, glaucoma is a significant public health issue. The visual outcome is the major concern of glaucoma patients [5]. At diagnosis, 34% of glaucoma patients are worried about the probability of becoming blind in the future; even if these percentage decreases to 11% at follow-up times.

Some studies have been conducted related to glaucoma to determine factors affecting the survival time and longitudinal outcomes separately[6]. A study conducted to determine factors that affect the longitudinal change of IOP using linear mixed model [7]. However, the linear mixed model of longitudinal data and the Cox proportional hazards model for time-to-event data, conducted separately do not consider dependencies or interrelationships between these two different data types of responses [8]. Hence, an alternative approach of joint modeling of these two types of responses was proposed by several researchers [8-12].

Joint models of longitudinal and survival data can incorporate all information simultaneously and provide valid and efficient inferences for the given data [13]. There is scarcity of researches conducted previously about joint models of longitudinal variation of IOP and time to blindness of glaucoma patients in the study area. Therefore, this study was aimed to investigate joint determinants of change of IOP and time to blindness of glaucoma patients under treatment at Felege Hiwot Referral Hospital, North-west Ethiopia. The result obtained in this investigation helps for glaucoma patients and health professionals as well to reduce the number of people being blind because of glaucoma and related diseases.

MATERIALS AND METHODS

Study area: This study was conducted at Felege Hiwot Referral Hospital, Bahir Dar, North West Ethiopia. The area is located 563 km far from Addis Ababa, capital city of the country. This hospital also serves as referral hospital for the people who referred from different district.

Study design: A retrospective cohort study design was carried out to retrieve relevant information from the medical records of glaucoma patients to address the objective of current investigation.

Source of population and data: The glaucoma patients were source of population for this study. The data was collected from the medical chart of glaucoma patients in ophthalmology clinic at the hospital whose follow-ups were January 2014 up to December 2018. Both the longitudinal and survival data were extracted from the patient's chart which contains socio-demographic and clinical information of all glaucoma patients under follow-ups. Hence, the data for current investigation was secondary.

Data collection procedures: Health staffs and clinical nurses were participated in collecting secondary data from cards of patients and a public health expert was assign as a supervisor and orientation was given for data collectors about the variables included in the investigation.

Quality of data: The data collection tool was pretested before the actual data collection to maintain data quality. The completeness and consistency of questions related to secondary data were checked and pre-tested on 45 sample data and proper amendments were included after getting feedbacks from pilot test. Data cleaning was conducted on daily basis and timely feedback was communicated to the data collectors.

Inclusion and exclusion criteria

Glaucoma patients with a minimum of two follow ups from January 2014 up to December 2018 were included in the study.

Sample size and sampling procedures

Thus, the sample size formula was determined using Cochran [14] and indicated as;

$$n = \frac{\frac{(Z_{\alpha/2})^2 P(1-P)}{d^2}}{1+\frac{1}{N}\{\frac{(Z_{\alpha/2})^2 P(1-P)}{d^2}-1\}} \quad \ldots\ldots (1)$$

where: n= the sample size needed, N = the size of study population, $Z_{\alpha/2}$ = the standard normal distribution at (1- α) % confidence level and α is the level of significance. P = the proportion or the probability of event occurred and d = the desired margin of error=5%.

Hence, the total population size of the glaucoma patients from January 2014 up to December 2018 was 2981 and by considering 95% confidence interval and 5% margin of error, the total sample size formula was 328.

Variables in the study

Response variables: The two response variables were measure of IOP in mmHg and the time to blindness of glaucoma patients. The IOP was measured in millimeters of mercury (mmHg) which was measured every 6 months irrespective of patient visits to ophthalmology clinic of the hospital and a patient with full follow ups had 11 visits including baseline. The censoring indicator was zero for patients not be blind and the event indicator was one for a patient be blind.

Independent variables

The independent variables for this study were gender (Female=0 and Male=1), Place of residence (Rural=0 and Urban=1), age in years, blood pressure (No=0 and Yes=1), diabetic disease (No=0 and Yes=1), type of medication (Timolol=0, Timolol with Pilocarpine=1 Timolol with Diamox=2, and Timolol with Diamox with Pilocarpine=3), duration of treatment (Short=0, Medium=1 and long=2), stage of glaucoma (Early=0, Moderate=1 and Advanced=2), cup-disc ratio ($\leq$ 0.7=0 and >= 0.7=1).

Data processing and analysis: In this study, R 3.5.3 version software was considered for data analysis. Statistical decision was made at 5% of level of significance.

Statistical Models

Linear mixed effect model

A linear mixed model is a parametric linear model for longitudinal or repeated measures data that quantifies the relationships between a continuous dependent variable and various predictor variables. It is extending from classical linear regression model that takes in to account both fixed effect and random effect. The random effect contains subject specific effect and the fixed effect contains the set of predictors that are fixed across the subjects or the same for all subjects. The fixed effect parameters describe the relationships of the predictors to the dependent variable for an entire population and random effects are specific to subjects within a population. Consequently, random effects are directly used in modeling the random variation in the dependent variable [15]. The random effects are not only determining the correlation structure between observations on the same subject but also take account of heterogeneity among subjects, due to unobserved characteristics.

Survival Model

Non-parametric survival curve which was first proposed by Kaplan and Meier was applied in this invesitigation[16].

If n individuals are on test and ordered the observed lifetimes for these n individuals from $t_{(1)}$ to $t_{(n)}$ and r individaules are cured, then ordered cure times are t(1),…, t(r), where $r \leq n$. The probability that an individual cures during the small time interval is estimated by $\frac{c_j}{n_j}$, where c_j is censored time. The probability of surviving through the interval from $t_{(k)}$ to $t_{(k+1)}$, and all preceding intervals lead to the Kaplan-Meier estimate of the survival function, which is given by:

$$\hat{S}_{(t)} = \prod_{j=1}^{k} \frac{n_j - c_j}{n_j} \quad \text{.....(2)}$$

The log rank test was used to compare two or more independent survival curves and usefull for non-overlapping survival curves. The log rank test statistic for comparing two groups is given by:

$$X_{LR} = \frac{(\sum_{i=1}^{m} c_{1i} - \sum_{i=1}^{m} \hat{e}_{1i})^2}{\sum_{i=1}^{m} \hat{v}(\hat{e}_{1i})} \quad \text{.....(3)}$$

where m is the number of rank ordered cures times, c_{ji} is the number of people experiencing the event at time $t_{(i)}$ in group j, n_{ji} is the number of people at risk in group j at time $t_{(i)}$, c_i is the total number experiencing the event in both groups, $\hat{e}_{ji} = \frac{c_i n_{ji}}{n_i}$ is the estimated expected number

of individuals experiencing the event at $t_{(i)}$ in group j, $\hat{v}_{(\hat{e}_{ji})} = \frac{n_{1i}n_{2i}c_i(n_i-c_i)}{n_i{}^2(n_i-1)}$ is the estimated variance of $\hat{e}_{ji}$, n_i is the number of individuals at risk in both groups 1 and 2 just prior to event time $t_{(i)}$.

A Cox-proportional hazard model was also used for exploring the relationship between the survival time and several explanatory variables. The hazard function is proportional to the instantaneous risk at any time t, given that an individual has lived at least t_0 up to time t and denoted by h(t) and is defined by the following equation[16]:

$$h(t) = \lim_{\Delta t \to 0} \frac{P[t \le T \le t + \Delta t | T \ge t]}{\Delta t}$$

$$h(t) = P(t < T < (t + \Delta t) \mid T > t)$$

$$= \frac{f(t)}{1-F(t)} = \frac{f(t)}{s(t)} \quad \text{.....(4)}$$

Since h(t) is also equal to the negative of the derivative of $\ln(S(t))$, we have the useful identity:

$$S(t) = e^{-\int_0^t h(t)dt}$$

If we let H (t) = $\int_0^t h(t)dt$ be the cdf (cumulative hazard function), we have $S(t) = e^{-H(t)}$.

Two other useful identities that follow from these formulas are:

$$h(t) = -\frac{d}{dt} \ln s(t)$$

$$H(t) = -\ln S(t)$$

Joint modeling for longitudinal and survival data

In clinical trials, it is common to see repeated measures with time to event which generate both longitudinal data and survival data. One of the natural strategies considering in the joint analysis of longitudinal and survival data is to incorporate the longitudinal measures directly into the Cox PH model as time-varying covariates and then proceed with the Cox proportional hazard model analysis [16].

The intuitive idea behind these models is to couple the survival model, which is of primary interest, with a suitable model for the repeated measurements of the endogenous covariates that will account for its special features. In this situation, a linear mixed effect (LME) sub-model was used to model time-varying covariate to address measurement errors (to describe the evolution of

the marker in time for each patient) and a Cox proportional hazard sub model to model the survival data.

Therefore, to examine the impact of the longitudinal outcome to the hazard for an event, estimate of $m_i(t)$ was needed in order to reconstruct the complete true history $m_i(t)$ to each subject. The joint model of change of IOP and time to blindness was described by a linear mixed effects model as:

$y_{ij} = \{y_i(t_{ij}), j = 1, 2, \dots, n_i\}$ of i^{th} subject at time $t_{i1}, t_{i2}, \dots, t_{in_i}$ is modeled as [17].

$$y_i(t) = x_i'(t)\beta + z_i'(t)b_i + \varepsilon_i(t), \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (5)$$

$$= m_i(t) + \varepsilon_i(t), \quad m_i(t) = x_i'(t)\beta + z_i'(t)b_i$$

$$b_i \sim N(0, G), \qquad \varepsilon_i(t) \sim N(0, \sigma^2)$$

where $\boldsymbol{x_i(t)}$ and $\boldsymbol{z_i(t)}$ are the design vectors for fixed effects $\boldsymbol{\beta}$, and for the random effectes $\boldsymbol{b_i}$ respectively, $\boldsymbol{\varepsilon_i(t)}$ are the error terms.

RESULTS

The baseline characteristics of current investigation indicates that among the participants, 108(32.9%) were females , 146(45.5%) were from rural area , 98(29.9%) had plod pressure, and 48(14.6%) were diabetic patients, 65(19.8%), 82(25.0%), 111(33.8%) and 70(21.3%) patients were treated by Timolol, Timolol with Pilocarpine, Timolol with Diamox and Timolol with Pilocarpine with Diamox respectively. 135(41.2%), 106(32.3%) and 87(26.5%) patients had short treatment duration, medium treatment duration and long treatment duration respectively. 121(36.9%), 52(15.9%) and 155(47.3%) had early stage glaucoma, moderate stage glaucoma and advanced stage glaucoma respectively. Similarly, 173(52.7%) of the patients had a maximum of 0.7 cup-disk ratio and the rest 155(47.3%) of the patients had at least 0.7 cup-disk ratio.

Table1 displays that, among the total of 328 glaucoma patients, 106 (32.3%) were blind whereas 222 (67.7%) were censored. Among the blind patients, 28(8.5%) were females, 74(22.6%) were hypertensive, 33(10.1%) were diabetic patients. Similarly, 47(14.3%) had short term treatment, 45(13.7%) had medium term treatment and only 14(4.3%) were from long treatment duration. The mean IOP of females and males were 28.29 and 29.92 respectively (Refer to Table1).

Table1: Baseline characteristics of categorical variables of glaucoma patients

Variables	Categories	No. patient (%)	No. blind (%)	Mean IOP
Gender	Female	108(32.9)	28(8.5)	28.29
	Male	220(67.1)	78(23.8)	29.92
Place of residence	Rural	146(44.5)	61(18.6)	30.90
	Urban	182(55.5)	45(13.7)	28.05
Blood pressure	No	230 (70.1)	32(9.8)	27.09
	Yes	98(29.9)	74(22.6)	35.16
Diabetic disease	No	280(85.4)	73(22.3)	28.65
	Yes	48(14.6)	33(10.1)	33.71
Type of medication	Timolol	65(19.8)	23(7.0)	29.98
	Timolol & Pilocarpine	82(25.0)	22(6.7)	27.67
	Timolol & Diamox			
	Timolol , Pilocarpine & Diamox	111(33.8)	35(10.7)	29.66
Duration of treatment		70(21.3)	26(7.9)	30.60
	Short	135(41.2)	47(14.3)	30.08
	Medium	106(32.3)	45(13.7)	30.81
Stage of glaucoma	Long	87(26.3)	14(4.3)	27.51
	Early	121(36.9)	13(4.0)	26.95
Cup-disk ratio	Moderate	52(15.9)	11(3.4)	28.86
	Advanced	155(47.3)	82(25.0)	31.84
	≤ 0.7	173(52.7)	14(4.3)	26.84
	=> 0.7	153(47.3)	92(28.0)	32.59
	Minimum	maximum	mean	Std. deviation

Age in years	6	89	55.86	17.35

Table1 displays that the mean age of glaucoma patients at enrollment of ophthalmology clinic was 55.9 years with a standard deviation of 17.4, the youngest patient was 6 years old and the eldest was 89 years old.

Table2: Results of the log-rank test for each categorical variable of glaucoma patients

Covariates	DF	chisq	p-value
Gender	1	1.8	0.2000
Residence area	1	3.5	0.0600
Blood pressure	1	110	<0.0001
Diabetic disease	1	24.4	<0.0001
Type of medication	3	117.5	<0.0001
Duration of treatment	2	155	<0.0001
Stage of glaucoma	2	45.4	<0.0001
Cup-disk ratio	1	101	<0.0001

Table2 indicates that all categorical variables under the log-rank test were statistically significant at 25% level of significance.

To identify the appropriate covariance structure, the three commonly used covariance structures (compound symmetry (CS), first order autoregressive (AR (1)) and unstructured (UN)) were considered as shown in Table3.

Table3: Comparison of covariance structure for linear mixed-effects model

Covariance structure	AIC	BIC	Log Likelihood
CS	15528.87	15620.52	-7748.434
AR (1)	**15526.72**	**15618.37**	**-7757.362**

UN	15526.87	15619.79	-7748.434

Table3 indicates that first order autoregressive (AR (1)) covariance structure was selected due to the smallest AIC and BIC compared to the remaining covariance structures.

Based on first order autoregressive (AR (1)) covariance structure, different models under the random component were employed to include the subject-specific random effects. The information criterion were used for the selection of models under random components as indicated in Table4. **Table4:** Selection of random effects to be included in the LMM

Models for random effect	AIC	BIC	Log Likelihood
Random intercept	15531.24	15621.43	-7751.621
Random slope	15657.57	15737.76	-7814.782
Random intercept and slope	**15526.72**	**15618.37**	**-7947.362**

Table4 indicates that, among the random effects, random intercept and slope model allow the intercept and coefficient to vary randomly among individuals. That means, individual IOP of glaucoma patients vary from visit to visit randomly. Therefore, the random intercept and slope was better to the data for the linear mixed effects model because of its lower values of AIC and BIC.

The two models namely null and saturated/full model were compared using information criterion (AIC, BIC and log likelihood) and saturated model was selected because of its smaller information criterion.

Multivariable analysis of linear mixed model was done by considering all significant covariates at univariable analysis (Table2). Table5 displays the result of final linear mixed model, the result showed that the predictors, age, place of residence blood pressure, type of medication, cup-disk ratio and visits were significantly associated with the average IOP at 5% of level of significance. Under the random effects result, the estimated subject-specific variability was statistically significant at 5% level of significance.

Table5: Result of the final linear mixed model for glaucoma patients

Covariates	Estimate	Std. error	95% CI		p-value
			Lower	Upper	
Intercept	25.1829	1.3011	22.6374	27.7286	<0.0001
Age	0.0662	0.0216	0.0260	0.1064	0.0013
Residence(ref=rural)					
Urban	-1.5994	0.6317	-2.8353	-0.3634	0.0114
Blood pressure(ref=no)					
Yes	4.9043	0.7799	3.3785	6.4301	<0.0001
Type of medication (ref=Timolol)					
Timolol & Pilocarpine	-2.0206	1.0164	-4.0127	-0.0285	0.0468
Timolol & Diamox	-0.0253	1.0976	-2.1766	2.1259	0.9816
Timolol, Pilocarpine &Diamox	0.8961	1.2050	-1.4656	3.2579	0.1085
Cup-disk ratio(ref=≤0.7)					
Greater than 0.7	2.6025	0.6924	1.2437	3.9614	0.0002
Visits	-0.3377	0.0659	-0.4666	-0.2088	<0.0001
Random effect	Std. dev	95% CI			
		Lower	Upper		
Intercept(b_{0i})	5.5785	4.7898	6.4970		

Visits(b_{1i})	0.4951	0.3234	0.7580
Corr(b_{0i}, b_{1i})	-0.5709	-0.7496	-0.3148
Residual (ε_i)	6.5360	6.2929	6.7884

Univariable and multivariable analysis for Cox proportional hazard model

The variables which were significant at the p-values less than 0.25 at univariable analysis were included in the multivariable analysis. The result of the univariable analysis indicated that all predictors were statistically significant at 25% level of significance for Cox proportional hazard model and taken as candidate variables for multivariable analysis.

The multivariable analysis of Cox proportional hazard model in Table6 indicates that, the predictors; age, blood pressure, diabetic disease, duration of treatment and cup-disk ratio were significantly associated with time to blindness of glaucoma patients at 5% of level of significance.

Table6: Result of the final Cox proportional hazards model for glaucoma patients

Covariates	Estimate	St. Error	HR(95% CI)	p-value
Age	0.0177	0.0084	1.0179(1.0013, 1.0347)	0.0344
Blood pressure(Ref=no)				
Yes	1.0341	0.2666	2.8127(1.6681, 4.7426)	<0.0001
Diabetic disease(Ref=no)				
Yes	0.4672	0.2322	1.5954(1.0121, 2.5149)	0.0442
Type of medication				
(Ref.=Timolol)				
Timolol & Pilocarpine	-0.5902	0.2988	0.5542(0.3086, 0.9955)	0.0483
Timolol & Diamox	-0.3549	0.2698	0.7012(0.4133, 1.1898)	0.1883
Timolol, Pilocarpine				

&Diamox	-0.0805	0.2865	0.9227(0.5262, 1.6179)	0.2241
Duration of treatment(Ref.=short)				
Medium	-3.7940	0.5370	0.0225(0.0079, 0.0645)	<0.0001
Long	-7.7605	1.1528	0.0004(0.00004, 0.0041)	<0.0001
Cup-disk ratio(Ref. ≤ 0.7)				
Greater than 0.7	1.3079	0.3208	3.6985(1.9724, 6.9354)	<0.0001

To fit joint model for variation of IOP and time to blindness, potential covariates were incorporated to investigate their significance on the two responses as indicated in Table7.

Table7: Result of joint model of longitudinal IOP and time to blindness of glaucoma patients

Parameter	**Longitudinal process**			**Survival process**		
	$\hat{\beta}$	Se($\hat{\beta}$)	p-value	$\hat{\beta}$	Se($\hat{\beta}$)	p-value
Intercept	25.1515	1.0830	<0.001	23.34	0.98	<0.001
Age	0.0726	0.0171	<0.001*	0.0197	0.0064	0.002*
Residence(rural)						
Urban	-1.8443	0.5297	0.065	-0.3521	0.89	0.002
BP(Ref.= No)						
Yes	4.5076	0.6420	<0.001*	0.7556	0.2640	0.0042*
Diabetic(Ref.=No)						
Yes	0.2321	0.7521	0.0653	0.4474	0.2261	0.0478
Treatment medication(ref.=Timolol)						

Timolol & Pilocarpine	1.8900	0.6260	0.0025*	0.5603	0.2578	0.0298*
Timolol & Diamox	0.0247	0.8697	0.0873	0.3438	0.2174	0.0938
Timolol, Pilocarpine &Diamox	0.7991	0.9724	0.1119	0.0647	0.2638	0.0962
Cup-disk ratio(ref≤ 0.7)						
Greater than 0.7	2.9238	0.5744	<0.0001*	1.3170	0.3331	<0.0001*
Visits	-0.3489	0.0549	<0.0001*	-0.2351	0.6754	<0.0001*
Associated(α)				0.8160	0.0076	0.0349*
Random effect	value					
Intercept(b_{0i})	5.4965					
Visits (b_{1i})	0.2049					
Corr(b_{0i}, b_{1i})	-0.7788					
Residual (ε_i)	6.5024					

Table7 indicates that age, blood pressure, type of medication, cup-disk ratio and visits were jointly and significantly associated with both average IOP and time to blindness of glaucoma patients. The estimate of the association parameter (α) in the survival sub model under joint analysis was significantly different from zero, providing that there is strong evidence of association between the two outcomes.

Table7 indicates that without considering covariates in the analysis, the average IOP of glaucoma patients was 25.15 mmHg. As age increased by one year, the average IOP of patients was increased by 0.0726 mmHg (p-value < 0.0001) keeping all variables constant. The hazard of being blindness for such increased age patients was also increased by 2% (exp (0.0197) = 1.02), p-value < 0.002) keeping the other covariates constant.

The average IOP of a glaucoma patient who was had blood pressure was increased by 4.51 mmHg (p-value < 0.0001) compared to glaucoma patient but free from blood pressure keeping all other variables constant. The hazard ratio of being blindness for glaucoma patients who had also blood pressure was 2.13 times (exp (0.7556)), p-value = 0.0042) the hazard of being

blindness for glaucoma patients but free from blood pressure, Keeping the other covariates constant.

The average IOP of glaucoma patient who took Timolol and Pilocarpine medication were increased by 1.89 mmHg (p-value=0.0025) compared to the patient who took Timolol medication keeping all other variables constant. The hazard ratio of being blind for patients who took Timolol and Pilocarpine medication was increased by 75 % (exp (0.5603) =1.7512), p-value = 0.0298) keeping the other variables constant.

The average IOP of a glaucoma patient with cup-disc ratio > 0.7 was increased by 2.9 mmHg (p-value < 0.0001) compared to a patient who had less than or equal to 0.7 cup-disk ratio keeping all other variables constant. The estimated hazard ratio of being blindness for glaucoma patients with cup-disk ratio > 0.7 was 3.732 (exp (1.3170) = 3.732), p-value<0.001), times that of glaucoma patients with cup-disk ratio < 0.7 keeping all other variables constant

For a unit increased in the follow up visits, the average IOP of glaucoma patients was significantly decreased by 0.3489 mmHg (p-value < 0.0001) and the hazard of being blindness was decreased by 0.2351 mm Hg(p-value <0.0001) keeping all other variables constant.

The estimated association parameter, α was 0.0160 (p-value=0.0349), which indicates that there was a positive association between IOP and time to blindness of glaucoma patients. The result indicates that the higher the value of IOP was associated with the higher risk of blindness.

Comparison of separate and joint model

The estimates of the parameters of the separate and joint models are quite similar to each other but not identical. To compare separate and joint models based on standard error computed in the two models for significant predictors. The model with smaller standard error is the better fits for the data. When evaluating the overall performance of both the separate and joint models in terms of model parsimony and goodness of fit, the joint model was performed better based on its lower AIC, BIC and based on a significant likelihood ratio test as well. The association parameter being significance was also an evidence that the joint model was better fit than the separate models in this study. The residual variability was smaller in joint model analysis as compared to separate model analysis which indicates that the standard errors were adjusted for the correlation between the two responses in joint model.

DISCUSSION

In this study, three different models were explored, the linear mixed effects model for longitudinal IOP, Cox proportional hazards model for time to blindness of glaucoma patients independently, and jointly modeling of the two outcomes together.

The mean of the longitudinal IOP as well as being blindness were linearly decreasing over time.

In this study, the association parameter was statistically significant in the joint model, indicates that the two responses were correlated and shows that the joint model is better fit to the data than the separate models. This finding was consistent with another study [18].

Age is an important socio-demographic predictor of IOP and time to blindness implies that the average IOP and risk of blindness increases with increase in age. This result in lined with another study [19], the result shows that higher age was a significant risk factor for blindness of glaucoma patients [19]. The result is also consistent with another study conducted previously[20].

The average IOP was found evolving differently between patients with blood pressure and patients without blood pressure based on the result of separate and joint models. The average IOP is higher for patients with blood pressure compared to patients without blood pressure. This result was consistent with another studies [21] and [7].

The glaucoma patients treated with a combination of different medication are exposed to increase of IOP and this further leads to blindness as compared to patients treated with only one type of medication. The potential reason for this might be interaction effect of different medication and management problem of such combined treatment by patients. This finding was consistent with another study [22], the result showed that the use of a single class of glaucoma medication as simple to manage to reduced hazard of blindness and this is due to lack of knowledge by patients about glaucoma disease to take the medication and patients might be careless for managing combine medication due to the disease nature (the disease most of the time is painless). However, the result obtained in current investigation is contradict with another study [22].This needs further investigation.

The risk of being blindness of patients who had cup-disk ratio greater than 0.7 is higher compared to patients who had cup-disk ratio less than or equal to 0.7. This finding was consistent

with another study Gardiner, Johnson [23], the result showed that increased the incidence of blindness in a larger cup–disc ratio > 0.7. The result associated with cup disc-ratio with size of IOP and hardness of being blindness is consistent with previous studies [24] and [8].

The result shows that the significance of the shared parameter that links the two processes together in joint model while also taking into account the association between them and the reduction in the standard error of the parameter estimates and more efficient inferences when compared to separate model estimates. Therefore, the joint model analysis fit the data better compared to the separate models in current investigation. However, the betterment of joint model in current investigation may not be true in any other studies because of the nature of data collected from the field.

Conclusions

A joint model and the corresponding separate sub models were built using a retrospective cohort data obtained from ophthalmology clinic of glaucoma patients under the follow-up 2014-2018 at Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia. This study addressed the relationship between the repeated measures IOP and time to blindness of glaucoma patients using joint modeling with a linear mixed effects sub model and a Cox proportional hazards survival sub model.

In conclusion, the results of both separate and joint analyses were quite similar but not identical. However, the use of a joint model analysis compared to separate model analysis adjusted for the correlation between the two responses which indicates that reduce the standard error and efficient inferences can be made using joint model estimates. In current investigation the predictors; age, blood pressure, type of medication, cup-disk ratio and visits were jointly and significantly associated with the two response variables namely the change of IOP and time to blindness.

The way forward: The health staff should conduct health related education for individuals to examine or a continuous check-up of their eye based on their age. Health professionals, government and non-governmental organizations give more attentions to minimize the risk of blindness of glaucoma patients by reducing patient intraocular pressure during the follow-up time and create awareness for patients about irreversible blindness caused by glaucoma disease. Health professionals give more attention for type of medication to reduce progression of glaucoma when the patients come back again in the hospital. Health professionals give more

attention for patients who have blood pressure and patients who have cup-disk ratio greater than 0.7 during the follow-up time to reduce intraocular pressure and to minimize the risk of blindness of glaucoma patients.

List of abbreviations: IOP = Intraocular pressure, LMM = Linear mixed model, AIC=Akaike Information Criterion, BIC= Bayesian information Criterion,

DECLARATIONS

Ethics approval and consent to participate: The authors got ethical approval certificate from

Bahir Dar University Ethical approval committee, Bahir Dar, Ethiopia with Ref≠ Stat-S/55/2018 to use the secondary data related to patients. The Ethical approval certificate obtained in this committee can be attached up on request. Since the data used in current investigation was secondary, there was no verbal or written consent from the participants.

Consent to publication: This manuscript has not been published elsewhere and is not under consideration by any other journal. Both authors approved the final manuscript and agreed with its submission to this journal. We agreed about authorship and order of authors for this manuscript.

Availability of data: The data used for current investigation is available with hands of corresponding author.

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Authors' contributions: The first author wrote the proposal, developed data collection format, supervised the data collection process, analyzed and interpreted the data. The second author participated in the design and data analysis, and critically read the manuscript and gave constructive comments for the betterment of the manuscript applying their rich experience. Finally, all authors approved the manuscript to be submitted to this journal.

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