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Modelling Time-to-First Recurrence of Gastric Cancer Patients: A Case Study at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia

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Abstract:

Background:

Gastric cancer is a malignant tumor of the stomach and it is one of the leading causes of death in the world. The study aimed to model time to first recurrence of gastric cancer patients in Tikur Anbesa specialized hospital.

Methods:

The data for this study was Gastric cancer patients under follow- up at Tikur Anbesa Specialized Hospital, Oncology center, Addis Ababa, from 1 January 2015 through 31 December 2019. We used Weibull, log-logistic and lognormal as baseline hazard functions with the gamma and the inverse Gaussian frailty distributions. Data analysis done using R statistical software.

Results:

The median recurring time of the patients was about 24.7 months with maximum recurring time of 50.83 months of which about 69.04% were experienced first recurrences of gastric cancer. The clustering effect is significant on modeling time to first recurrence of gastric cancer. According to the result from the log-logistic inverse Gaussian frailty model the Gender of the patients, tumor size, treatment taken, vascular invasion, stage of disease, helicobacter pylori infection and histology type were the significant prognostic factors at 5% level of significance.

Conclusion and Recommendation:

The log-logistic-inverse Gaussian frailty model is the model that best described time to recurrence of the gastric cancer dataset. Gender of the patients, tumor size, treatment taken, vascular invasion, stage of disease, helicobacter pylori infection and histology type were the determinant prognostic factors. This calls for actions on improvement of patient's health status and prevent recurrence based on significant risk factors and special attention should be given for patients with such factors.

Key words: survival data analysis; parametric shared frailty model; acceleration factor; heterogeneity.

Background:

Gastric cancer is a malignant tumor of the stomach and it can develop in any part of the stomach. It is also called stomach cancer [22]. Gastric cancer is one of the leading causes of death in the world and represents a tremendous burden on patients, families, and societies [25]. Based on Global burden of cancer 2018 data, GC is the 5th most common neoplasm and the 3rd most deadly cancer, with an estimated 783,000 deaths in 2018. Over a million new cases of GC are diagnosed, worldwide, each year [2]. Despite the universal decline in GC incidence and mortality, it is still the second most common cancer worldwide [14].

In this study, the event of interest was the time to first recurrence of GC after treatment. PH model popularized by Cox is the classical model for this kind of data. However, the correct inference based on Cox's models needs identically and independently distributed samples. Often, subjects may be exposed to different risk levels, even after controlling for known risk factors. This is because the covariates that are relevant to the researcher are often unavailable or even unknown. In current study, shared frailty models explored assuming that patients within the same cluster (region) shares similar risk factors, which would take care of the frailty term at region level. The study aimed to model time to first recurrence of gastric cancer patients in TASH.

This thesis considered parametric frailty models to investigate the relationship between different potential covariates (demographic, clinical and environmental factors) and time to recurrence of GC for clustered survival data with random right censoring. The choice of distribution for the hazard is very important than the choice of frailty distribution [6]. The advantage of parametric method over the semiparametric method shows that having distribution may calculate the quantiles, simplicity and completeness are reasons for the popularity of parametric distributions [13]. Hence, in this study Weibull, log-logistic and lognormal baseline hazard functions used. On the other hand, among frailty distribution we have assumed gamma and inverse Gaussian distributions to fit GC data set. Gamma and inverse Gaussian are the two most common choices of frailty distributions due to their mathematical tractability. For comparison of different models, the AIC criteria used

Methods:

Study setting and design:

A retrospective study was conducted on GC patients under follow- up at Tikur Anbesa Specialized Hospital, Oncology center, Addis Ababa, from 1 January 2015 through 31 December 2019. The total number of patients considered in the study was 409 who were patient from all nine regions and two city administrations of Ethiopia. Regions that contribute single patients were omitted. Therefore, a total of 407 GC patients were considered in this study. For analysis of the data, R statistical software has been used.

Variables in the Study:

The response variable is time to first recurrence of GC from registry time to study ends. The explanatory variables considered in this study were: Age (in years), Gender of patients, Residence, Marital status, Smoking history, Helicobacter pylori infection, Family history, Obesity status, Tumor location, Stage of GC, Initial Treatment, Vascular invasion, Tumor size and Histology type. These were categorized as follows:

Age were categorized as (≤49, 50-69 and ≥70), Gender(Male and Female), Residence(Urban, married, divorced and widowed), Smoking history(No, yes), Vascular invasion(Absent, Present), Obesity (Normal, Underweight, Overweight), Family history(Negative, Positive), Tumor location(Non-gastro intestinal and Gastro intestinal), Stage(I, II, III and IV), Treatment taken (Surgery alone, Chemotherapy, Radiotherapy and Combination of ≥2), Helicobacter pylori infection(Absent and Present), Tumor size(<5cm and ≥5cm) and Histology type(Well-differentiated tumors, Poorly differentiated tumors and Signet ring cell cancer).

Shared frailty models:

A shared frailty model is a random effects model where the frailties are common (or shared) among groups of individuals or spells and are randomly distributed across groups. They are conditional independence model in which frailty is common to all subjects in a cluster. It is also known as a mixture model because the frailties in each cluster are assumed to be random [8].

Conditional on the random term, called the frailty denoted by w_i, the survival times in cluster i $(1 \leq i \leq n)$ are assumed to be independent and an accelerated failure time frailty model which assumes:

$$h_{ij}(t/X_{ij}, w_i) = ho(\phi t)exp(\beta' X_{ij} + w_i)$$

Where $\phi = exp(\beta' X_{ij} + w_i)$, called acceleration factor, i indicates the i^{th} cluster and j indicates the j^{th} individual for the i^{th} cluster, $h_0(.)$ is the baseline hazard, wi the random term of all the subjects in cluster i, X_{ij} the vector of covariates for subject j in cluster i, and β the vector of regression coefficients.

The main assumption of a shared frailty model is that all individuals in cluster i share the same value of frailty Z_i $(i = 1, \ldots, n)$, and this is why the model is called the shared frailty model.

Gamma shared frailty distribution:

Gamma frailty model belongs to the power variance function family [9] and can be expressed in terms of its Laplace transform from which properties such as mean and variance are easily derived [7]. From a computational and analytical point of view, it fits very well to failure data. It is widely used due to mathematical tractability [24]. Assuming that the frailty term z_i is a gamma with $E(Z) = 1$ and $Var(Z) = \theta$, then $\gamma = \frac{1}{\theta}$.

The density of a gamma-distributed random variable frailty term zi with parameter θ is:

$$f_z(z) = \frac{Z_i^{\frac{1}{\theta}-1} \exp\left(\frac{Z_i}{\theta}\right)}{\theta^{\frac{1}{\theta}}\, \Gamma\left(\frac{1}{\theta}\right)}, \theta > 0$$

Where: Γ (.) is the gamma function; it corresponds to a Gamma distribution Gam (μ, θ) with μ fixed to 1 for identifiability and its variance is θ.

Inverse-Gaussian frailty distribution:

The inverse Gaussian (inverse normal) distribution was introduced as a frailty distribution alternative to the gamma distribution by [10]. The probability density function of an inverse Gaussian distributed random variable Z with parameter θ > 0 is given by:

$$f_Z(Z) = \frac{1}{\sqrt{2\pi\theta z^3}} exp\left(-\frac{(z-1)^2}{2\theta z}\right)$$

It has a mean 1 and variance θ

Descriptive Summary of Gastric cancer patients:

Of all 407 GC patients 281(69.04%) were experienced the event (first recurrence of GC) and 126(30.96%) were censored (Table 1). The estimated median recurrence time for GC patients was found to be 24.70 months. The minimum and the maximum recurrence time observed in the data were 0.93 and 50.83 months respectively.

Variables	Categories	Recurrence status		Total (%)	Median (months)
		Censored (%)	Event (%)		
Gender of patients	Male	80(32.8)	164(67.2)	244(59.9)	19.55
	Female	46(28.2)	117(71.8)	163(40.1)	23.93
Age of patients (in years)	≤49	32(33.7)	63(66.3)	95(23.3)	20.53
	50-69	65(29.7)	154(70.3)	219(53.8)	28.90
	≥70	29(31.2)	64(68.8)	93(22.9)	19.13
Residence	Urban	72(28.7)	179(71.3)	251(61.7)	22.68
	Rural	54(34.6)	102(65.4)	156(38.3)	20.77
Smoking history	No	12(7.8)	140(92.1)	152(37.3)	23.63
	Yes	100(39.2)	155(60.8)	255(62.7)	19.57
Marital status	Single	12(25.5)	35(74.5)	47(11.5)	21.80
	Married	97(32.9)	198(67.1)	295(72.5)	19.63
	Widowed	7(17.5)	33(82.5)	40(9.8)	18.93
	Divorced	10(40.0)	15(60.0)	25(6.1)	18.80
Tumor size(cm)	<5.0cm	46(58.2)	23(41.8)	79(19.4)	24.53
	≥5.0cm	51(15.5)	277(84.5)	328(80.6)	19.57
Treatment taken	Surgery	5(33.3)	10(66.7)	15(3.6)	18.23
	Chemotherapy	42(28.0)	108(72.0)	150(36.9)	20.32
	Radiotherapy	32(35.2)	59(64.8)	91(22.4)	19.63
	Combination of two or more	47(31.1)	104(68.9)	151(37.1)	25.80
Stage of Gastric cancer	I	11(28.9)	27(71.1)	38(9.4)	26.85
	II	47(45.4)	59(55.6)	106(26.0)	22.81
	III	41(29.3)	99(70.7)	140(34.4)	19.53
	IV	27(23.9)	96(76.1)	123(30.2)	18.93
Tumor location	Non-gastro intestinal	73(32.0)	155(68.0)	228(56.1)	19.57
	Gastro intestinal	53(29.6)	126(70.4)	179(43.9)	19.57
Vascular invasion	Absent	40(28.4)	101(71.6)	141(34.6)	25.69
	Present	86(32.3)	180(67.7)	266(65.4)	19.56
Helicobacter infection	No	47(38.5) 79(27.7)	75(61.5)	122(30)	21.69
	Yes		206(72.6)	285(70)	18.14
Obesity	Normal	31(25.5)	111(74.5)	142(34.9)	22.92
	Underweight	62(30.4)	126(69.6)	188(46.2)	19.16
	Overweight	33(42.9)	44(57.1)	77(18.9)	18.36
Histologic type	Well-differentiated tumors	33(40.2)	49(59.8)	82(20.2)	18.93
	Poorly-differentiated tumors	42(27.6)	110(72.4)	152(37.3)	18.76
	Signet ring cell cancer	51(29.5)	122(70.5)	173(42.5)	22.80
Family history of GC	No	72(35.1)	133(64.9)	205(50.4)	19.51
	Yes	54(26.7)	148(73.3)	202(49.6)	19.47
Total		126(39. 96)	281(60.04)	407(100)	24.70

Table 1: Descriptive summaries of patient's diagnosed for GC

Multivariable analysis and comparison of models:

For time-to-recurrence of GC disease, the multivariable survival models of the Weibull, log logistic and lognormal for the baseline hazard function; and the gamma and the inverse Gaussian frailty distributions were fitted again by assuming all the significant covariates in the Univariable analysis at 25% level of significance. The output of the log-logistic- inverse Gaussian multivariable frailty model is as shown in Table 3.

Using the entire multivariable shared frailty models, the covariate gender, tumor size, treatment taken, stage of disease, vascular invasion, helicobacter pylori infection and histology type were significant at 5% level of significance indicating that, it is the significant prognostic factor for the time to recurrence of GC disease. Whereas age of patients and tumor location were not a significant factor for recurrence of GC using the entire multivariable shared frailty models.

The variance of the random effect or frailty distribution (θ) is significant for all baseline frailty models at 5% level of significance. From this we observed that variance of random effect is larger when we assume the inverse-Gaussian frailty distribution (θ= 0.23) than for gamma frailty distribution (θ=0.21) for log-logistic baseline hazard function. The Kendall's tau (τ) is used to measure the dependence within the clusters (regions) and it is higher for the higher variance of random effect (θ) values. Accordingly, the dependence within the clusters for the log-logistic-inverse Gaussian frailty model (τ=0.103) is the maximum followed by the log-logistic-gamma frailty model (τ= 0.095). This indicates that within group correlation were largest when we consider log-logistic-inverse Gaussian frailty distribution than others.

Based on AIC, a model having the minimum AIC value was preferred. Accordingly, the AIC value of the log-logistic- inverse Gaussian model that is (AIC=1148.1444) was the minimum from all the other AIC values of the alternative models which indicates that it is the most efficient model to describe the GC dataset among the different parametric shared frailty models (Table 2).

Model		AIC
Baseline hazard function	Frailty distribution	
Weibull	Gamma	1152.3721
	Inverse-Gaussian	1152.3260
Log logistic	Gamma	1152.3253
	Inverse-Gaussian	1148.1444
Lognormal	Gamma	1174.9902
	Inverse-Gaussian	1175.0488

Table 2: AIC values of the models used in the study.

Analysis based on log-logistic-inverse Gaussian frailty model shows that the gender of patients, tumor size, treatment taken, stage of GC disease, vascular invasion, Helicobacter pylori infection and histology type were significant at 5% level of significance (Table 3). This indicates that they are the contributing factor for the recurrence of GC patients.

The result of this study suggested that Gender of patient has significantly different time to recurrence of GC. Females have significantly different recurring time than the reference group males with acceleration factor (ϕ = 1.305). Therefore, females had prolonged time to recurrence of GC disease by a factor of ϕ=1.305 than male patients (reference).

When the effect of other factor keeps fixed, the estimated acceleration factor for patients with tumor size greater than 5cm estimated to be 0.087 with confidence interval [95%CI, 0.022-0.348] and P-value is small (p=0.001). This indicates that patients Tumor size of greater than 5cm have significantly different recurring time than the reference groups (sized < 5cm). An acceleration factor of less than 1 indicates decreasing survival time to event. Therefore, holding other covariates constant and accounting for frailty, patient's tumor sized greater than or equal to 5cm (≤5cm) has shorten recurrence time by a factor of ϕ=0.087 than the reference group.

Covariates		Coef	S.E	ϕ	95% CI	p-value
Gender						
Male		Ref		1		
Female		0.266	0.131	1.305	[1.009, 1.687]	0.046*
Age						
	≤49	Ref		1		
	50-69	-0.139	0.161	0.874	[0.637, 1.198]	0.388
	≥70	-0.132	0.185	0.939	[0.649, 1.361]	0.474
T.size(cm)						
	<5.0cm	Ref		1		
	≥5.0cm	-2.435	0.704	0.087	[0.022, 0.348]	0.001***
Treatment						
surgery alone		Ref		1		
chemotherapy		-0.310	0.176	0.724	[0.513, 1.022]	0.078.
radiotherapy		-0.359	0.204	0.766	[0.514, 1.142]	0.077.
combination of two or more		0.405	0.206	1.499	[1.001, 2.245]	0.047*
Stage						
	I	Ref		1		
	II	-0.020	0.167	0.935	[0.675,1.297]	0.69
III		-0.130	0.059	0.0878	[0.782, 0.985]	0.041*
IV		-0.142	0.058	0.867	[0.774, 0.972]	0.012*
T.location						
Non-gastro intestinal		Ref		1		
Gastrointestinal		0.004	0.125	1.004	[0.784, 1.286]	0.977
Helicobacter pylori Infection		Ref				
		-0.373	0.146	0.689	[0.517, 0.917]	0.01*
Vasc.inv						
Absent		Ref		1		
present		-5.250	1.007	0.005	[0.001,0.038]	<.001***
Hist. type						
Well-differentiated tumors		Ref		1		
Poorly differentiated tumors		-0.366	0.151	0.708	[0.529,0.951]	0.015*
Signet ring cell cancer		-0.040	0.198	0.961	[0.652,1.416]	0.838

θ=0.23(SE=0.029) *	$\lambda = 1.653(SE = 0.705)$	$\rho = 2.590(SE = 0.154)$
τ=0.103 AIC=1148.1444		

Table 3: Log-logistic-inverse Gaussian multivariable analysis
Source: *Tikur Anbesa specialized hospital, A.A, Ethiopia; from January 1, 2015 to December 30, 2019*

After controlling for other prognostic factors, patients who took combination of two or more treatment had extended time of recurrence than others by acceleration factor of ϕ=1.499. The confidence interval of the acceleration factor for combination of two or more treatments was [95%CI, 1.001-2.245] and p-value=0.047, indicating that using 'Combination of two or more treatment' is also significant prognostic factor for the time to recurrence for GC patients. Therefore, patients who took combination of two or more treatment has prolonged time to recurrence than surgery alone group (ϕ=1.499) at 5% level of significance.

Patients with advanced stages GC disease (III and IV) have significantly different recurring time than the reference groups (stage I) with acceleration factor of (ϕ=0.0878) and (ϕ= 0.867) respectively and their respective confidence interval [95%CI, 0.782- 0.985] and [95%CI, 0.774-0.972]. Therefore, patients with stage III and IV GC disease had decelerated/shorter time to recurrence by a factor of 0.0878 and 0.867 respectively than the reference group (stage I).

Patients who were infected by helicobacter pylori infection have significantly different recurring time than the reference group with acceleration factor (ϕ=0.689) and confidence interval [95%CI, 0.517-0.917]. This result suggested that an infected patient has shorter survival time to recurrence as compared to not infected. In other words, Helicobacter pylori infection had decelerated survival time to recurrence of GC disease by a factor of ϕ=0.689 than reference group.

Vascular invasion of patient has significantly different time of recurrent event. Patients with vascular invasion have significantly different recurring time than the reference group with acceleration factor (ϕ= 0.005) and confidence interval [95%CI, 0.001-0.038]. Therefore, existence of vascular invasion had shortened recurrence time of GC disease by a factor of ϕ=0.005 than those without vascular invasion.

The histology type of patients was also known to be significant covariate. Patients with histology type of poorly differentiated have significantly different recurrence time than well differentiated tumor with acceleration factor (ϕ=0.708) and confidence interval [95%CI, 0.529-0.951 and p-value=0.015]. This result suggested that histology type was prognostic factor for recurrence of GC and patients with poorly differentiated tumor have shorter survival time to recurrence of GC disease than well differentiated tumor.

The estimated value of the shape parameter in the log-logistic-inverse Gaussian frailty model is (ρ=2.590) shown in (Table 4.3). This value is greater than unity that indicates shape of hazard function is unimodal, which means, it increases up to some time and then decreases. The variability (heterogeneity) in the population of clusters (region) estimated by our best model log-logistic-inverse Gaussian frailty model is θ=0.23, and the dependence within clusters is about τ=0.103(10.3%).

Survival by treatment taken:

The survival time to recurrence of the treatment group who took combination of two or more (bold line) is larger than the other treatment groups particularly at the mid times but almost similar at the beginning and a little bit close at the ending times (Figure 1). This indicates that the probability of prolonging recurrence time at a given specific time is greater for patients who took combination of two or more treatments.

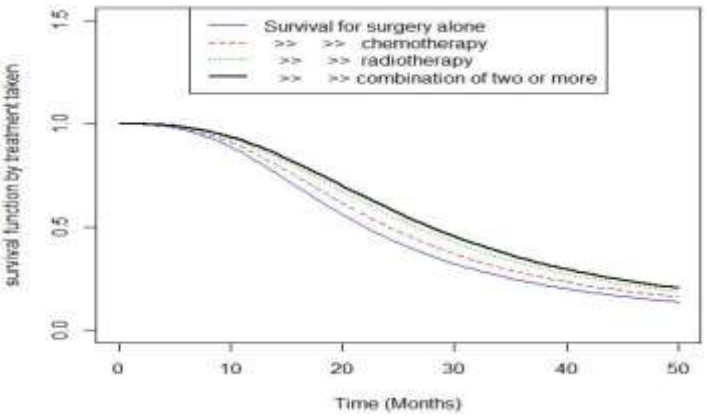

Figure 1: The survival functions of different treatment group of GC patients using the log logistic- inverse Gaussian frailty model.

Diagnostic plots of parametric baselines:

To check the adequacy of our baseline hazard the Weibull is plotted by $log\ (-log\ (\hat{s}(t)))$ vs. $log\ (t)$; the log-logistic is plotted by log odds of failure or $\log\left(\frac{(1-\hat{s}(t))}{\hat{s}(t)}\right)$ vs. $\log(t)$ and the log-normal is plotted by the $\Phi^{-1}\{1-\hat{s}(t)\}$ vs. $\log(t)$ (Figure 2). Plot of log-logistic is more linear than the other plots; hence it is appropriate in the model.

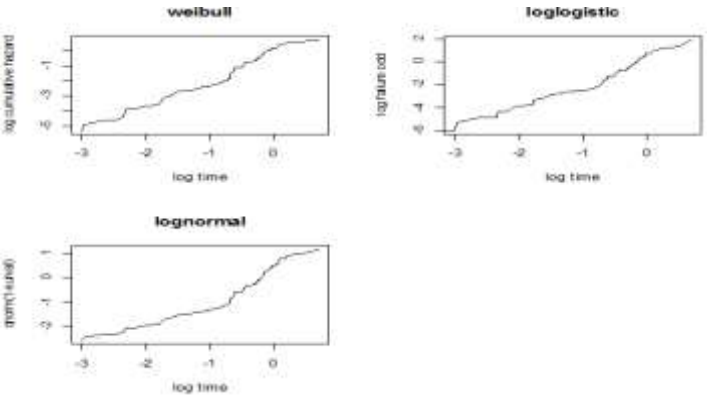

Figure 2: Graphical evaluation of the Weibull, log-logistic and log-normal assumptions

Cox-Snell residuals:

Cox-Snell residuals are one way to investigate how well the model fits the data. The Cox- Snell residuals obtained from fitting the log-logistic model to our data via maximum likelihood estimation (Figure 3). By comparing with Weibull and log normal, this plot

shows that the line related to the Cox-Snell residuals of the log-logistic models were nearest to the line through the origin, again indicating that this model describes the GC dataset well.

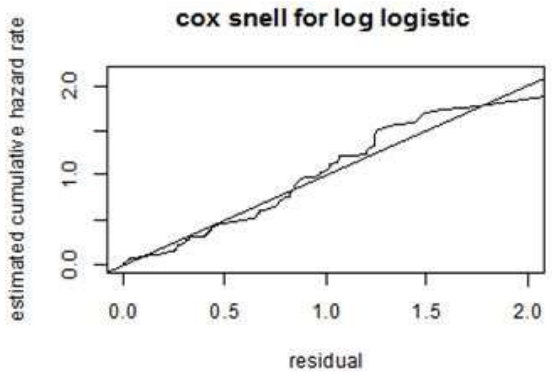

Figure 3: Cox-Snell residuals obtained by fitting log-logistic to the GC dataset

Adequacy of accelerated failure time:

A quantile-quantile or q-q plot is made to check if the accelerated failure time provided an adequate fit to the data using two different groups of population. We shall graphically check the adequacy of the accelerated failure-time model by comparing some significantly different stage groups (patients with GC stage III and IV), patients with vascular invasion, treatment taken (combination of two or more treatment) (Figure 4). The figures appear to be approximately linear for all covariates. Therefore, accelerated failure time model using the log logistic as baseline was best to describe GC data set.

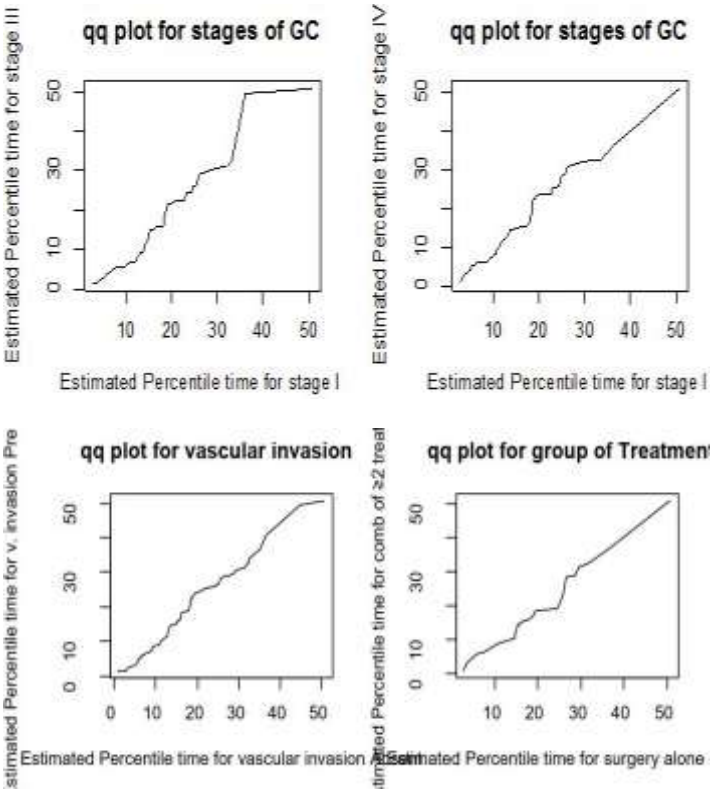

Figure 4: Q-Q plots to check the adequacy of the accelerated failure time model

Discussion:

The findings of this study revealed that increasing tumor size and stage of disease, poorly differentiated histology type, history of helicobacter pylori infection and presence of vascular invasion significantly shorten/decelerate the time-to-recurrence of GC, while using combination of two or more treatment and Gender of patients(female) accelerates time-to-recurrence among GC patients in Tikur Anbesa specialized hospital. The estimated median recurring time was 24.7 months (approximately 2.06 years). Which is almost similar with the [12] reported that about 66.5% of GC patients experienced recurrence within 2 years. This also agrees with gastric cancer recurrence usually occur within first two years [16].

Our findings showed that gender of patients significantly influenced time to recurrence of GC disease. Acceleration factor of $\phi = 1.305$ indicates that, female patients have prolonged time to recurrence of GC as compared to males. Similar Study by [16] reported that GC recurrence more often happen in men than women. From result of this study coefficient of contracting this type of cancer is 1.8–2 times higher for men in comparison to women. This study is also consistent with [2], they revealed that GC is more likely to be diagnosed in males than females and men are at higher risk than women for GC. The reason for such difference is thought that female reproductive hormones such as estrogen and progesterone help protect against GC development in female [27].

The results of this study suggested that tumor size at diagnosis was significantly affected the recurrence of GC. The acceleration factor was less than 1 for patients with tumor size ≥5cm ($\phi = 0.087$). This shows patient's tumor sized ≤5cm took shorter time to experience recurrence of GC as compared to the reference group of patients. In a study conducted in China, it was observed that tumor size was significant factor for recurrence of GC and the relative risk of those patients with advanced tumor size were higher than those with early tumor size [4]. Also, this finding is consistent with study done by [11]. They reported from their finding that, the tumor size has a significant effect on increasing the risk of GC recurrence. Furthermore, another study done by [3] reported that Patients with larger tumor sizes was known to be highly prevalent to GC recurrence.

The result of this study also revealed that the type of treatment the patient took is another risk factor for the recurrence of GC disease. Literatures like ([21] and [19]) also identified treatment as a prognostic factor of GC recurrence. Study conducted by [26], reported that patients treated with surgery alone were significantly experience recurrence of GC at shorter period of time. This is consistent with present studies finding, since group of patients who took 'combination of two or more treatment' were found to have prolonged time or greater survival time than surgery alone group, meaning that surgery alone group has decelerated time to recurrence of GC. Furthermore, this result was in agreement with findings of [17], reported that combination of different treatments contribute better improvement on recurrence of GC.

The stage of GC found to be significant factor for time to recurrence of GC patients. The findings of this study showed that patients with advanced stages of disease (Stage III and Stage IV)

experience recurrence of GC at shorter period of time than patients with stage I GC disease. This result is consistent with [23] also reported that the stages of GC at diagnosis have been significantly affected the recurrence of GC patients. From the results of this study the hazard rate for recurrent events of GC was greatest as the stage increases likewise, in present study acceleration factor of GC patients with advanced stage of disease (Stage III and Stage IV) were small, indicating that it takes shorter time to recurrence for advanced stages of GC disease. This is due to early-stage GC can simply be cured by available cancer treatments but not advanced stages. This result is also in agreement with study by [18].

Acceleration factor of less than 1 indicates decelerated time to event; hence from the result of this study the GC patents with positive vascular invasion had the smaller acceleration factor for recurrence of GC, meaning that presence of vascular invasion decelerates/shorten time to recurrence of GC disease. This result argued by the findings of study by [3]. Furthermore, study by [4] has also reported the same result from their findings.

According to different literatures like [5][2]. Helicobacter pylori have been identified as prognostic factor for development as well as recurrence of gastric cancer disease. Prospective studies from western countries suggest that GC is 2–3 times more common in individuals with chronic Helicobacter pylori infection [20]. Also, as a report of American institute of cancer research, in fact, helicobacter pylori have been found to increase the odds ratio of GC by 5.9 times within ten years of infection. In line with previous findings, in current study, infection with helicobacter pylori was found to be significant factor for recurrence of GC disease.

Lastly the histology type at diagnosis was significantly affected the recurrence of GC and the acceleration factor for patients with (poorly differentiated tumor) were smaller as compared to patients with histology type of well differentiated(reference). Similar report has been indicated in the study done by [3].

This study also showed that there was a clustering (frailty) effect on modeling time to recurrence of GC which might be due to the heterogeneity within regions from which the patients came from. Assuming patients coming from the same region share similar risk factors related to GC, indicating that it was important considering the clustering effect in modeling the hazard function. The heterogeneity in the regions was significant and estimated to be $\phi = 0.230$, and the dependence within clusters is about τ =0.103(10.3%). These values were the maximum among the variance of the random effects and the Kendall's tau of all the models. This result consolidates the idea that larger values of θ indicates that there is a higher degree of heterogeneity among groups and strong association within groups [1]. Clusters with minimum median time have smaller frailties, so that such clusters are predicted to have a high hazard [7], more probable to recur in this case.

Nonetheless, the most acknowledged parametric model is the Weibull, as it allows the PH and AFT model [10]; the GC data set was best described by the log-logistic baseline as compared to the Weibull and lognormal hazard functions.

Conclusion:

The log-logistic inverse Gaussian frailty model is a model that best described the time to recurrence of GC patients' data set. Since log-logistic baseline distribution has different shapes of hazard function, that means it can fit non-monotonic hazards, and generally fits best when the underlying hazard rises to a peak and then falls, which may be plausible for this kind of disease. Our study revealed that, Gender of patients, stage of disease, Tumor size, vascular invasion, Helicobacter pylori infection and Histology type were found to be statistically significant risk factors for recurrence of Gastric cancer patients. According to the study, the median recurring time of the Gastric cancer patients was high, since median recurrence time for patients in this study was greater than two years. There is a frailty (clustering) effect on the time-to-recurrence of Gastric cancer that arises due to heterogeneity between the regions of the patients.

Recommendation:

Actions on improvement of patient's health status should be taken based on significant risk factors and concerned bodies should work to protect against recurrence of GC. The ministry of health of the country, policy makers and Tikur Anbesa Specialized Hospital should work on awareness of the disease so that the patients have protect themselves from the complication of diseases by being treated early stage of the disease because of the disease is curable if diagnosed early. Further studies should be done to identify other factors that are not identified in this study and studies considering other successive recurrences are recommended.

Abbreviations:

TASH: Tikur Anbesa Specialized Hospital; AIC: Akanke's Information Criteria; CI: confidence interval for acceleration factor; HR: hazard ratio; GC: Gastric cancer; SE: standard error; ϕ: acceleration factor; θ: Variance of the random effect; τ: Kendall's tau; ρ: shape; λ: scale

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Competing interests:

The authors declare that they have no competing interests.

Author's contributions:

MEL: conceptualized the study, data collection, analysis, interpretation and drafting the manuscript and finalizing manuscript.

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