Original Research Article

Impact of Two-level Spatial Structure Model in Spatio-temporal Hospitalization of Female Breast Cancer Patients in Nigeria

ABSTRACT

This paper investigated the impact of two-level spatial structure model in spatio-temporal hospitalization of female breast cancer in Nigerian Health-care areas and States. The objective is to measure the relative contribution of each of the model parameters. The model has been fitted using full Laplace approximation strategy to an observational hospital-based female breast cancer mortality data from 2009 to 2016. The study explained risk variations across health-care areas and State-levels. The results showed that the State-level captured higher risk than the health-care area-level (24.18% against 17.60%). Furthermore, assessing each health-care area performance, six (6) health-care areas with large population States showed higher risk. The study recommended o further research on the risk factors responsible for the significant high risk in these health-care areas.

Keywords: Health care areas, female breast cancer mortality data and integrated nested Laplace approximations.

1.0 Introduction

Breast cancer is a major global public health problem accounting for massive morbidity and significant mortality worldwide. Factors contributing to breast cancer mortality have been a topic of intense research and discussion in the scientific world. There is, however, a dearth of information on the incidence of breast cancer mortality in most resource-poor countries including Nigeria. Available data from most African workers on breast cancer focused on incidence, risk factors, and complications rather than mortality, Amin *et al*. (2017).

Sequel to the activities of National System of Cancer Registries (NSCR) since inception in 2009, the number of cancer registries in Nigeria has increased from two Population Based Cancer

Registries (PBCRs) and eight Hospital Based Cancer Registries (HBCRs), to ten PBCRs and twenty HBCRs. In Nigeria, hospital-based cancer registries (HBCR) are fundamental sources of information on the frequent cancer sites in limited resource regions where population level data is often unavailable. In states where population-based cancer registries are not in existence, HBCRs are beneficial for policy making and planning Elima *et al*. (2015).

In Nigeria, there is growing need for the assessment of health systems performance as a means to improve their effectiveness, resilience and sustainability. Typically, the focus of performance analysis is put on country-average (at the most regional analysis) where measures talk about care provision, mainly, hospital care, the Organization for Economic Co-operation and Development (OECD, 2015). However, the study of variations in performance attributable to different decision levels has gained momentum (Bernal-Delgado *et al.* 2015 and Häkkinen *et al.* 2015) over the classical country-average oriented approach present in international reporting and turning the emphasis into the analysis of variations at sub-country (for example, regions) and sub-regional levels (for example, health care areas).

Few studies dealing with two-level spatial structure models have been proposed. Schrödle *et al*. (2011) used two-level structure spatial effects to analysed reported cases of bovine viral diarrhea in Switzerland because they suspected that the number of cases registered in each study area was highly influenced by the affiliation of those areas to a larger region structure. Recently, similar models have been used by Ugarte *et al*. (2015a) to described the temporal evolution of the geographical pattern of brain cancer incidence in Navarre. Ugarte *et al.* (2015b) analysed young people brain cancer mortality in Spanish provinces in the period 1986-2010. Ugarte *et al.* (2016) used two-level spatial structure and considered Health areas as the second level of spatial aggregation in order to identify potential difference in temporal evolutions for each health area.

Therefore, this paper is aimed to *i*nvestigate the impact of two-level spatial structure model in spatio-temporal hospitalization of female breast cancer in Nigeria and to measure the relative contribution of each of the model parameters.

2.0 Materials and Methods

2.1 Sources of data

The study used secondary data on female breast cancer which contains the number of cases and the number of deaths within 60 days of surgery in each hospital in 16 hospital-based cancer registries (HBCRs) in Nigeria. The data were extracted from the national system of cancer registries (NSCR) from 2009 to 2016.

The average bed capacity of the hospitals where these HBCRs are located is 469 beds per hospital and a total bed capacity is 6,513. All these registries used CanReg5 software for data entry and management and International Classification of Disease for Oncology, third edition (ICD-O-3) for coding the site. Data abstracted by the HBCRs included information on name, age, morphology and topography of tumor, tribe, address, treatment, education level, marital status, religion and cause of death.

2.2 Methods

A Poisson-log normal mixed model in the Bayesian hierarchical framework in three stages was implemented to fit the model using the integrated nested Laplace approximations (INLA) efficient estimation procedure. The first stage is the observational model: $y|x \sim \pi(y|x,\theta)$. The second stage is the latent Gaussian Markov random field (GMRF): $x|\theta \sim N(\mu(\theta), Q(\theta)^{-1})$ with precision matrix and third stage is the hyperparameters: $\theta \sim \pi(\theta)$ which are not necessarily Gaussian.

2.2.1 Study Design

This is an observational hospital-based female breast cancer mortality spatio-temporal study. The data was spatially structured in two-level; where the first-level areas (FLAs) composed of the 36 States and the federal capital and the second-level areas (SLAs) composed of the 16 Health-care Areas (HA).

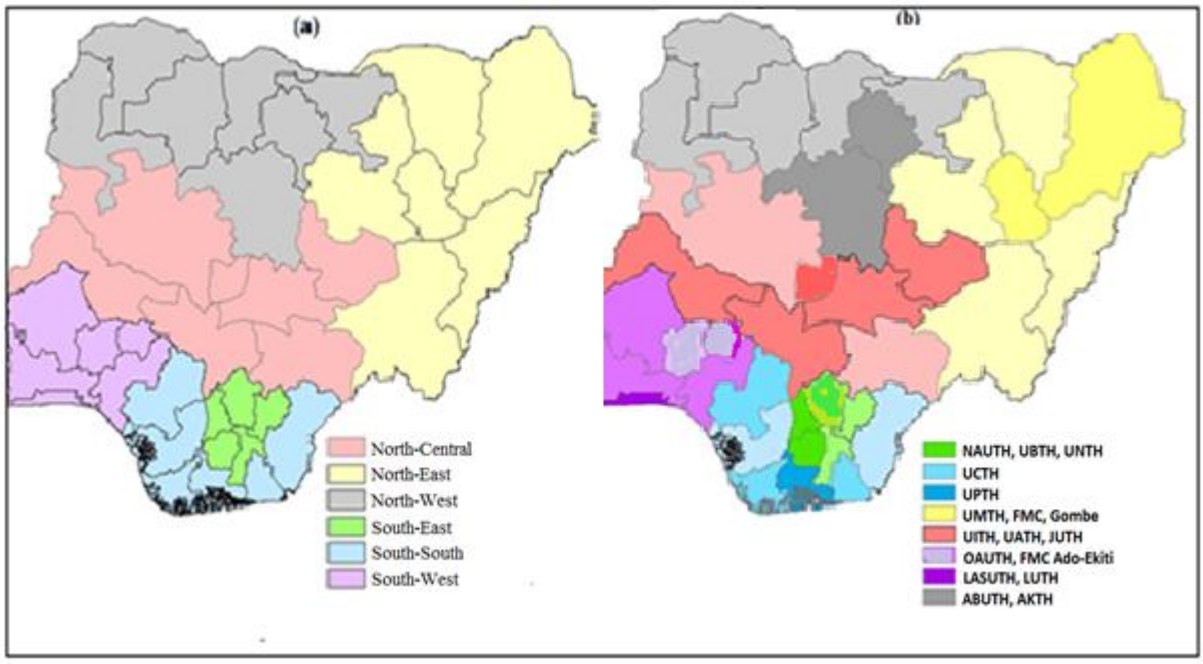


Figure 1: Map of the $n = 36$ states of Nigeria, (a) states are grouped in to geopolitical zones (b) states aggregated by SLAs.

2.2.2 Spatio-temporal model

Suppose we have a region with non-overlapping small areas divided into q first-level areas (FLAs) labeled as $i = 1, 2, \dots, q$ that can be aggregated into p second-level areas (SLAs) labeled as $j = 1, 2, \dots, p$, where $p < q$. For each area i, data are available for different time periods labeled by $t = 1, 2, \dots, T$. A spatio-temporal model that accounts for two-level spatial structure of dependence of the SLAs which are in FLAs and for the temporal dependence assumes that, conditional on the underlying relative risk r_{it}, the number of deaths counts in each area and time

period, y_{it}, follows a Poisson distribution with mean $\mu_{it} = r_{it} E_{it}$ for area i and time t written as:

$$y_{it}|r_{it} \sim \text{Poisson}(\mu_{it} = r_{it} E_{it}) \quad (1)$$

$$\log(\mu_{it}) = \log(r_{it}) + \log(E_{it}). \quad (2)$$

Here, $\log(E_{it})$ is an offset and depending on the specification of $\log(r_{it})$ different models are defined. To compute the number of expected deaths E_{it}, direct or indirect 'age' standardization procedures can be performed (other standardization variables could also be used in addition to for example, age). The direct and indirect standardization procedures are given in Equations (3) and (4) respectively:

$$E_{it} = \sum_{l=1}^{L} N_{igt} \frac{\sum_{i=1}^{q} y_{igt}}{\sum_{i=1}^{q} N_{igt}} \quad i = 1, 2, \dots, q \qquad t = 1, 2, \dots, T \quad (3)$$

where y_g and N_g are respectively the observed deaths and the population size in "age" groups $g \in \{1, \cdots, G\}$.

$$E_{it} = \sum_{g=1}^{G} \left(N_{igt} \frac{y_g}{N_g} \right) \quad i = 1, 2, \dots, q \qquad t = 1, 2, \dots, T \quad (4)$$

so that;

$$y_g = \sum_{i}^{q} \sum_{\mathrm{t}}^{T} y_{igt} \text{ and } N_g = \sum_{i}^{q} \sum_{\mathrm{t}}^{T} N_{igt} \quad (5)$$

The log-risk (r_{it}) is modeled taking into account the need of distinguishing between space organised in two-level structure (that is, FLAs and SLAs) and time components, and including interaction in space and time. It is assumed that:

$$\log(r_{it}) = b_0 + \alpha_i + \beta_{j(i)} + \eta_t + \gamma_{jt}. \quad (6)$$

where b_0 is an overall risk level, α_i represents the spatial level for the i^{th} State areas, $\beta_{j(i)}$ represents the spatial level for the j^{th}Health areas which are in State i^{th}areas, η_t represents temporal structured effect, and γ_{jt} are space-time interaction effects.

2.2.3 Modelling the spatial dependency structure

In modeling the spatial random effects, the conditional autoregressive (CAR) prior by Leroux *et al.* (1999) (LCAR) was adopted for FLA spatial random effect given by:

$$\alpha = (\alpha_1, \dots, \alpha_{q=37})' \sim N\left(0, \left[\sigma_\alpha(\xi_\alpha S_\alpha + (1 - \xi_\alpha) I_{q=37}\right]^{-1}\right) \quad (7)$$

where ξ_α is a spatial smoothing parameter taking values between 0 and 1, $I_q$is an identity matrix of dimension 37×37, and S_α is the 37×37 spatial neighbourhood matrix with diagonal elements equal to the number of neighbours of each State and non-diagonal element:

$$(S_\alpha)_{ij} = \begin{cases} -1, & if\ States\ i\ and\ j\ are\ neighbours \\ 0, & if\ otherwise. \end{cases} \quad (8)$$

Here, two States are considered as neighbours if they share a common border.

The SLA spatial random effect is given by:

$$\beta = (\beta_1, \dots, \beta_{p=16})' \sim N\left(0, \left[\sigma_\beta(\xi_\beta S_\beta + (1 - \xi_\beta) I_{p=16}\right]^{-1}\right) \quad (9)$$

where S_β is the 16×16 spatial neighbourhood matrix of the SLAs and I_p is an identity matrix of dimension 16×16. This means that in space, each HA may have its own risk, but all HA within a State region share a common spatial effect.

For structured temporal effects $\eta = (\eta_1, \dots, \eta_T)'$ a random walk of first order (RW1) is considered and its distribution given by:

$$\eta = (\eta_1, \dots, \eta_T)' \sim N\left(0, [\sigma_\eta S_\eta]^-\right). \quad (10)$$

R_γ denotes the temporal structure matrix of a RW1 and the symbol "-"denotes the Moore-Penrose generalised inverse. That is, in time each year has two neighbors, the previous point and the following one, except for the first and last year, which only depends on one.

A completely structured interaction terms $\gamma = (\gamma_{11}, \ldots, \gamma_{\mathrm{nT}})'$ by Knorr-Hel, (2000) are adopted and assumed to be distributed normally for the FLA and SLA interactions in Equation (6) given by:

$$\gamma_{it} \sim N(0, \sigma_V (S_\alpha \otimes S_\eta)^-) \text{ and } \gamma_{jt} \sim N(0, \sigma_V (S_\beta \otimes S_\eta)^-).$$

The parameters of interest are thus $\theta = \{b_0, \alpha, \beta, \eta, \gamma\}$ with hyperparameters represented by:

$$\varphi = \{\sigma_\alpha, \xi_\alpha, \sigma_\beta, \xi_\beta, \sigma_\eta, \sigma_\gamma\}. \quad (11)$$

3.0 Results

3.1 Descriptive Statistics

The descriptions of facilities in each of the 16 HBCR is given in Table 1. Most of these 16 HBCRs in Nigeria started functioning about 10 years with five (5) of the 16 HBCRs described in this study established in 2009, when the Nigerian National Cancer Registry programme started.

Table 1: Descriptions of facilities in each of the 16 HBCR

Hospital Cancer Registry	Year of inception of cancer registry	Hospital Capacity (Number of Beds)	Number of Pathologists	Number of Surgeons	Radiotherapy/ unit	Chemotherapy/ Surgery Services
ABUTH Zaria	1970	593	6	18	No	Yes
AKTH Kano	1996	400	5	20	No	Yes
FMC Ado-Ekiti	2009	276	5	10	No	Yes
FMC Gombe	2009	200	4	9	No	Yes
JUTH Jos	1996	200	3	6	No	Yes
LASUTH Lagos	2009	481	6	33	No	Yes
LUTH Lagos	1998	300	2	15	No	Yes
NAUTH Nnewi	2009	350	5	29	No	Yes
OAUTH Ile-Ife	1989	617	6	25	No	Yes
UATH Abuja	1997	350	2	18	No	Yes
UBTH Benin	2008	250	2	22	No	Yes
UCTHCrossRiver	1983	451	5	29	No	Yes

UITH Kwara	1990	445	6	17	No	Yes
UMTH Borno	2003	400	4	20	No	Yes
UNTH Enugu	1988	500	5	29	Yes (Not in use)	Yes
UPTH Rivers	2009	700	7	40	No	Yes

Sources: Elima *e al*. 2012 and Nigerian National System of Cancer Registries (2017)

The average bed capacity of the hospitals where these HBCRs are located is 407 beds per hospital. There was an average of five (5) pathologists and twelve (21) surgeons per hospital. The majority 15 (90%) of hospitals lack radiotherapy services but all of them offer chemotherapy services.

Table 2. Number of cases, deaths and age standardized mortality rates per 100,000 person-years and variation statistics for the disease and year.

Year	Cases	Deaths	ASMR	SMR	CV
2009	947	396	9.24	2.60	1.38
2010	1,028	445	11.53	3.44	1.41
2011	1,053	473	12.47	3.73	1.47
2012	1,501	451	12.50	4.18	1.44
2013	1,624	511	12.59	4.61	1.53
2014	1,493	457	13.54	5.53	1.43
2015	1,379	387	14.09	5.87	1.40
2016	1,490	468	14.55	6.14	1.52

ASMR: Age Standardized Mortality Rates; **SMR:** Standardized Mortality Rates **CV:** Coefficient of Variation;

Table 2 shows the evolution of the population at risk of hospitalization for the disease. The age standardized mortality rates (ASMR) and standardized mortality ratios (SMR) per 100,000 person-years for each j^{th} HA and t^{th} year rose from 11.59 to 14.55 and from 3.44 to 6.14 respectively. Variation statistics show high and constant geographical variability in breast cancer along the study period

Table 3. Deviance information criterion (DIC) for two-level model using direct and indirect 'age' standardization procedures

Model	**Method**							
	Direct Method				**Indirect Method**			
	$\bar{D}$	pD	DIC	$\overline{LS}$	$\bar{D}$	pD	DIC	$\overline{LS}$
Two-								

level	1502.508	13.656	1516.640	0.1637	1506.646	9,8561	1516.507	0.1633

$\bar{D}$: mean deviance; $p_D pD$: effective number of parameters, DIC: deviance information criterion; and $\overline{LS}$: Mean Logarithmic Score.

Using the DIC presented in Table 3, as a tool for evaluating the fit of a model, suggests that the indirect standardization procedure is better suited for the data (with a DIC of 1516.507 against 1516.640). This means that, in all the analysis of spatio-temporal areal data, the indirect method for the calculation of expected cases is more appropriate. The indirect standardization procedure has been considered in this study.

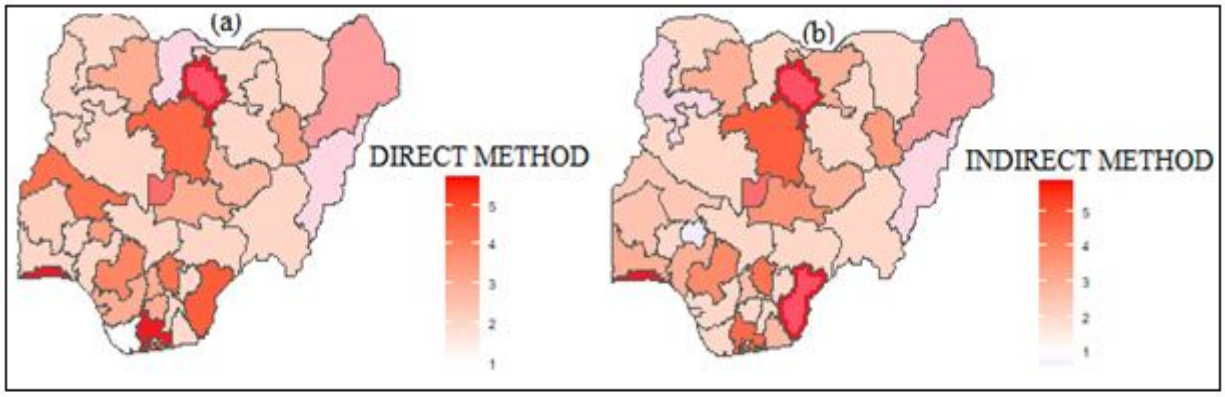


Figure 2. Map of the State level spatial patterns of mortality risk

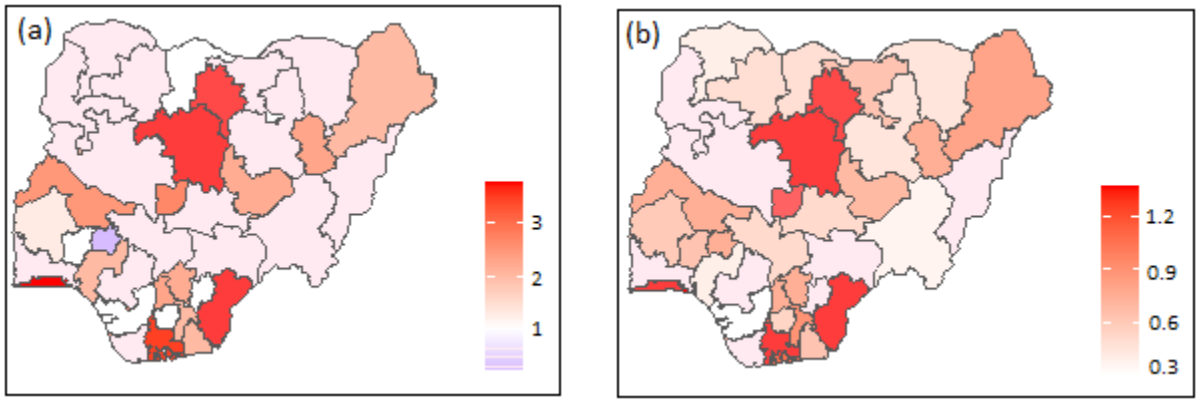
Figure 2 shows the maps of the State level spatial patterns of mortality risk using the two methods of expected case computation. The maps were generally similar in appearance; some differences can nevertheless be seen for both methods. In Figure 2 (a), the States with highest mortality risk were Kano, Lagos and Rivers. While in Figure 2 (b), the States were Kano, Lagos and Cross River. For the other category of relative risks; average and lowest mortality risks showed similar spatial patterns for both methods.

Table 4: Posterior estimates and DIC for the model parameters in Equation (6).

Parameters	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**
DIC= 1516.509					

b_0	0.0371	0.3597	0.0324	0. 0587	0.0734
σ_α	12.3924	4.4137	3.8460	1.2.3252	21.3264
ξ_α	0.9667	0.3641	0.2620	0.9610	1.7044
σ_β	69.3504	10.0996	49.8092	69.1880	89.8324
ξ_β	2.1298	0.3625	1.4285	2.1240	2.8647
σ_η	77.0241	20.1195	35.1063	73.7112	114.7685
σ_γ	106.4027	74.5801	38.1419	105.3460	257.0629

The estimated posterior means and quantiles intervals for the model parameters in Equation (11) and the DIC value are reported in Table 4. The DIC value obtained in Table 5 confirmed the DIC value in Table 3. The posterior mean of the intercept b_0 is 3.7% implies a morality rate across the States in Nigeria, with a 95% credibility interval ranging from 3.2% to 7.3%. The posterior means for the random effects of the FLAs σ_α and ξ_α have the lowest means of 12.3924 and 0.9667 as against the posterior means of the SLAs σ_β and ξ_β random effects of 69.3504 and 2.1298. This shows that the spatial smoothing at State level area is stronger than that at health area level. The posterior mean for temporal pattern σ_η common to all regions is 77.0241 The spatio-temporal interaction for FLAs and SLAs have the highest posterior mean of 106.4027.



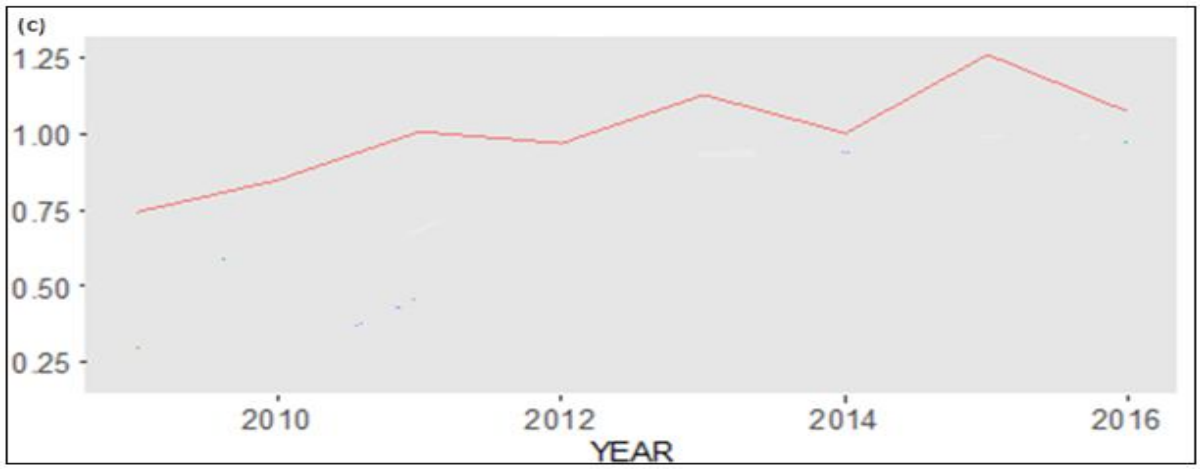


Figure 3. (a) Map of the spatial pattern of mortality risks; (b) Map of posterior probabilities of the spatial pattern of mortality risk; and (c) Graph of temporal trend of breast cancer mortality relative risk

The estimated spatial and temporal patterns are shown in Figure 3. The spatial mortality risk $\exp(\widehat{\alpha_\iota} + \widehat{\beta_{J(\iota)}})$ due to breast cancer at each health areas is shown in Figure 3(a) and the posterior probabilities that these risks are greater than one, $\left(P\left(\widehat{\alpha_\iota} + \widehat{\beta_{J(\iota)}}\right) > 1|y\right)$ is shown in Figure 3(b). Most literatures set posterior probability of spatial risk above 0.8 as a cutting point towards high-risk administrative regions and more detail about the thresholds and cut-off probabilities can be seen from Richardson *et al. (*2004) and Ugarte *et al. (*2009). From Figures 3 (a) and (b), it can be observed that, health areas in the north-west region, far south-west part and far south-south region are those with high risk or performed unusually well or poorly. The affected HAs include, ABUTH Zaria, AKTHH Kano, LASUTH Lagos, LUTH Lagos, UCTH Cross River and UPTH Rivers. The temporal pattern common to all States $(\widehat{\eta_t})$ is in Figure 3 (c) and shows a fairly uniform increase in the disease.

Table 5. Relative contribution of each of the component in the model

Random effect	**Percentage of variability**
Spatial FLA (States) $\widehat{\boldsymbol{\alpha_\iota}}$	24.18%
Spatial SLA (Health Areas) $\widehat{\boldsymbol{\beta_{J(\iota)}}}$	17.60%

Temporal effect $\widehat{\boldsymbol{\eta_t}}$	46.88%
SLA spatio-temporal interaction $\widehat{\boldsymbol{\gamma_{Jt}}}$	11.34%

Table 5 shows the percentage of variability of the overall risk explained by the structured spatial and temporal effects and spatio-temporal interaction component. The spatial risk at FLAs (States) ($\widehat{\alpha_i}$) implied a fairly higher fraction of variation (24.18%) due to late presentation of the disease. While 17.60% variability is explained by the SLAs (health areas) ($\widehat{\beta_{J(i)}}$) due to health areas that may be attributed to factors associated to administrative health care service such as: health personnel and medical facilities for breast cancer treatment like oncologist, breast cancer surgeons and nurses trained to handle cancer cases. However, most of the risk variation is explained by the temporal effect ($\widehat{\eta_t}$) which is about 46.88% of the total variability. That is, the temporal risk for all heath areas that may be attributed to changes in distribution of the disease, and related policies affecting the States. While 11.34% of variability of the overall risk is explained by the health area-level with comparison to the whole region during the study period ($\widehat{\gamma_{Jt}}$). That is, the health area specific temporal risk trend that may reflect particular effect for the observed difference in each health area.

Table 6: Estimated posterior means for risk variations across heath care areas

ID	Mean	SD	2.5%	50%	97.5%
ABUTH Zaria	1.03316	4.479799	17.914371	25.55319	35.46033
AKTH Kano	1.00676	3.725149	12.674272	19.07398	27.27645
FMC Ado-Ekiti	0.35227	3.137354	7.777266	13.16035	20.03268
FMC Gombe	0.61451	4.217010	16.139026	23.33923	32.66079
JUTH Jos	0.61262	3.247440	8.825115	14.41722	21.52310
LASUTH Lagos	1.12507	3.575787	11.550232	17.70559	25.56152

LUTH Lagos	1.01358	4.047093	14.969414	21.89228	30.83059
NAUTH Nnewi	0.57438	3.436042	10.444382	16.36651	23.90158
OAUTH Ile-Ife	0.71700	3.882717	13.814468	20.47002	29.03415
UATH Abuja	0.84775	5.481106	24.640822	34.05316	46.07822
UBTH Benin	0.20845	3.802988	13.244421	19.76856	28.14619
UCTHCrossRiver	1.00427	5.755652	26.532123	36.45908	49.03855
UITH Kwara	0.19350	5.572778	25.268428	34.85142	47.06295
UMTH Borno	0.30845	3.802988	13.244421	19.76856	28.14619
UNTH Enugu	0.84775	3.575787	11.550232	17.70559	25.56152
UPTH Rivers	1.00507	4.479799	17.914371	25.55319	35.46033

Table 6 shows the predicted mortality rates across the 16 HBCRs. The column mean shows that six (6) hospitals namely: ABUTH Zaria, AKTHH Kano, LASUTH Lagos, LUTH Lagos, UCTH Cross River and UPTH Rivers have highest posterior means of the mortality rates above 100 %. This means that they perform poorly and contributed to increase the final risk. Columns 0.025quant and 0.0975quant contain the lower and upper limits of 95% credible intervals of the mortality rates. The posterior probabilities that these risks are greater than one is shown in Figure 4.

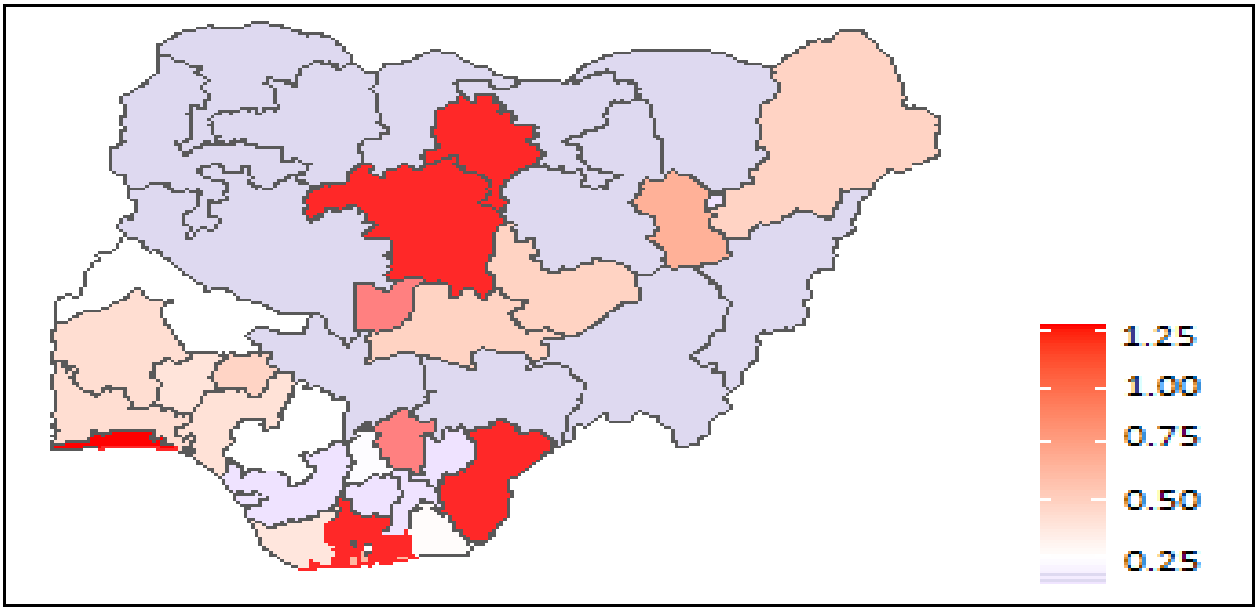
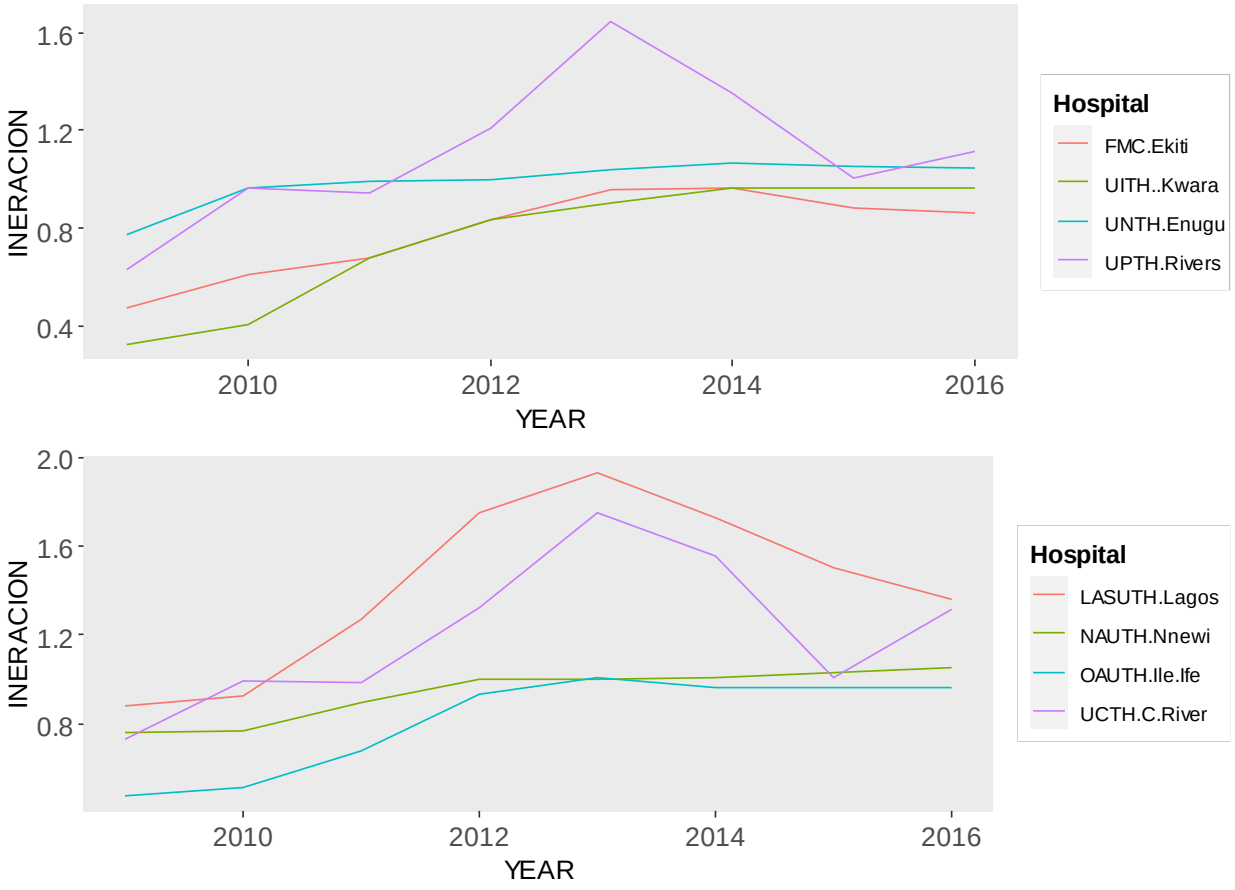


Figure 4: Map of Health areas with posterior means greater than one



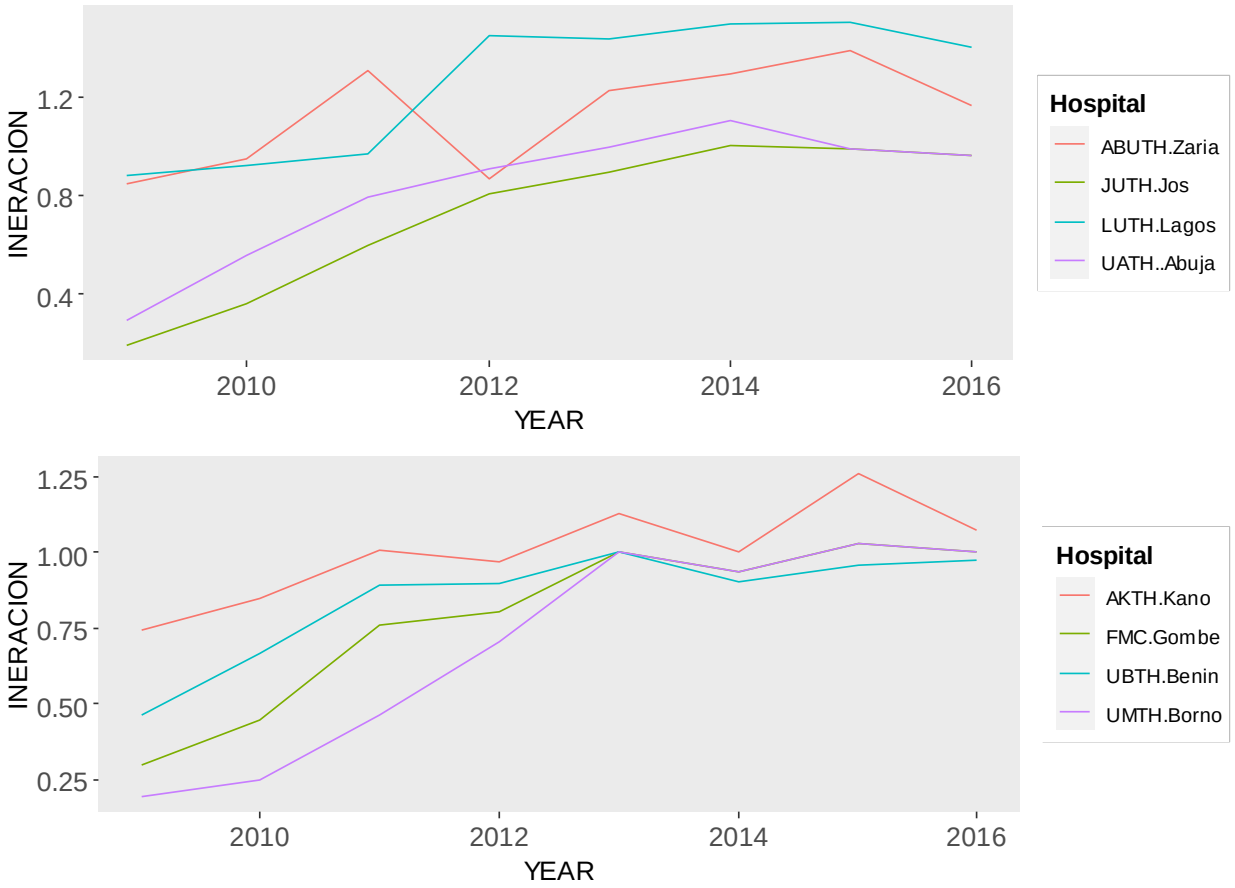


Figure 5: Space-time interaction term $\widehat{\gamma_{jt}}$ for each health area.

Figure 5 shows space-time interactions for SLAs. These showed how each health area temporal trends differ in the contribution to increase in the final risk, these include: ABUTH Zaria, AKTH Kano, LASUTH Lagos, LUTH Lagos, UCTH Cross River and UPTH Rivers, while those that performed fairly well are FMC Ado-Ekiti, FMC Gombe, JUTH Jos, NAUTH Nnewi, OAUTH Ile-Ife, UATH Abuja, UBTH Benin, UITH Kwara, UMTH Borno and UNTH Enugu.

4.0 Discussion

This paper demonstrated the effect of two-level spatial structure model in spatio-temporal Bayesian approach. The $\overline{D}$, pD, DIC, and $\overline{LS}$ suggested two-level model that used indirect standardization procedure for the calculation of expected cases turned out to be the best fit for the data.

Recall that, this model included two-level spatial random effects, that is, a State-level spatial effect and a health area-level spatial effect, both of them with a Leroux CAR prior distribution, a structured temporal random effect with a RW1 prior and a completely structured interaction effect. The estimated log-relative risk was decomposed into its separate components.

In this study, the State-level captured higher risk variation than at health area-level (24.18% against 17.60%). This means that, in a population of over 1.2 million people in a State, 24.18% of breast cancer patients are at risk due to hesitation in seeking healthcare facilities on time and 17.60% of risks are as a result of poor medical service delivery or less effective treatment. In addition, most of the risk variation was captured by temporal effect. This means that during the period 2009-2016, the incidence of female breast cancer mortality rate inclined by approximately 47% in many States and 12% in health areas. These results are consistent with studies by Melkamu *et al.* (2018), Librero *et al.* (2017) and Ugarte *et al.* (2016). Furthermore, the 12% estimated female breast cancer mortality rate across the health areas, the study found that six (6) hospitals namely: ABUTH Zaria, AKTH Kano, LASUTH Lagos, LUTH Lagos, UCTH Cross River and UPTH Rivers were the most responsible. This result is similar to the result by (Murthy *et al*. 2016; Boyle & Levin, 2008 and IAEF 2003).

5.0 Conclusion

The model has yielded a classical methodology for assessing the spatial variations in first-level areas and their influence in second-level areas on disease outcome. There is high mortality rate associated with female breast cancer in Kaduna, Kano, Lagos, Cross River and Rivers health areas. To identify the risk factors responsible for the significant high risk in these health areas, a further study is recommended. In addition, a well-coordinated government at State-level sponsored intensive awareness about the disease for women in both rural and urban areas and

proper structures for breast cancer screening programmes, with every State having a structured and affordable mammography screening programme for the early detection.

While, a functional radiotherapy services, medical oncology services or specialized chemotherapy units are put in place especially, at the poorly performed health-care areas. These would contribute to early detection and effective control of breast cancer in Nigeria.

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