RESEARCH ARTICLE

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A Spatial Survival Model in Presence of Competing Risks for Iranian Gastrointestinal Cancer Patients

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Abstract

Background: Gastrointestinal cancer is one of the common causes of death from cancer in Iran. Survival analysis is usually used to detect prognostic factors of time to death from gastrointestinal cancers. The use of ordinary survival models, in the presence of competing risks and/or when data is collected within geographic areas, may lead to distorting the results. Therefore, the aim of this study is to use the spatial survival models in the presence of competing risks to assess the risk factors affecting the survival time of gastrointestinal cancer patients. **Methods:** The data in this study was collected from 602 patients who were diagnosed with gastrointestinal cancer in Golestan and Mazandaran provinces registered in Iran's National Institute of Health Research from 2002 through 2007 and were followed up to July 2017. The data was analyzed using the cause-specific hazard frailty model with multivariate conditional autoregressive distribution for frailties in the presence of competing risks (death from gastrointestinal cancer, heart disease, and other causes) via OpenBUGS software. **Results:** The hazard of death from gastrointestinal cancer in men patients, patients who lived in rural areas, patients whose relatives did not have a history of cancer, patients who did not undergo surgery, and patients with gastric cancer was significantly higher than others. Based on the deviance information criterion (DIC), frailty models and spatial frailty models seemed better than no-frailty model and non-spatial frailty model, respectively. **Conclusions:** This study showed that the use of the spatial frailty term in the model helps better fit the model. Also, the spatial pattern in the figures suggests the necessity of presence of some still missing, spatially varying covariates relevant for time to death from gastrointestinal cancer, heart disease, or other causes.

Keywords: Gastrointestinal cancer- survival analysis- competing risks- spatial survival model

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Introduction

After cardiovascular diseases and motor vehicle accidents, cancer is the third leading cause of death in Iran (Saadat et al., 2015). Esophageal, stomach and colorectal cancers are common between Iranian men and women and these are among the 10 most prevalent cancers in Iran (Darabi et al., 2016). About half of all cancer deaths in Iran are related to gastrointestinal cancers. Unfortunately, gastrointestinal cancers are often taken into consideration when people are at an advanced stage of the disease when ineffective or less effective treatments are available to them (Yazdanbod et al., 2004). Theoretically, these cancers can be cured in the early stages of the disease. So their early detection is desirable.

Survival models can be used for modeling the time until an event of interest occurs. When analyzing the survival data, more than one event can possibly be observed. These events are called competing risks. A competing risk is referred to as an event that changes the probability of the occurrence of the event of interest (Gooly et al., 1999). There are two major approaches to modeling survival data in the presence of competing risks: cause-specific hazard model (Prentice et al., 1978) and subhazard model (Fine and Gray, 1999). In the cause-specific hazard model, we investigate the causal relationship of a specific factor, while the purpose of the subhazard model is to compare the probability of the event of interest in the presence of competing risks (Pintilie, 2007).

Survival data are often collected within geographical areas. In this case, the cluster-specific frailties introduced in the hierarchical model could not be considered independent because the frailties corresponding to closer areas might also be similar in magnitude. In this case, spatial models - geostatistical or lattice approaches- can be used (Banerjee et al., 2003). In cluster data, underlying processes that affect competing risks could be different but correlated. For this reason, one random effect can be introduced for each of the events within clusters and the dependence between the random effects within the

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clusters can be taken into account (Christian et al., 2016). The multivariate conditional autoregressive (MCAR) distribution (Gelfand and Vounatsou, 2003; Jin and Carlin, 2005) can be used to consider simultaneously the correlation between random effects within clusters and the spatial correlation between random effects during clusters.

The purpose of this study is to evaluate the relationship between time to death from gastrointestinal cancer of Iranian patients and prognostic factors using the cause-specific hazard spatial frailty model in the presence of competing risks. The correlation between random effects in each cluster (clusters: wards of Mazandaran and Golestan provinces in Iran) as well as spatial correlation between random effects during clusters is considered using multivariate conditional autoregressive (MCAR) distribution.

Materials and Methods

The data in this research is from gastrointestinal cancer (gastric, esophageal and colorectal) patients who were registered between March 2002 and March 2007 in Mazandaran and Golestan provinces and were followed up until July 2017. The data was obtained from the Iran National Institute of Health Research. Ward of residence at the time of diagnosis was recorded for all patients. In 2002, Mazandaran and Golestan provinces had 15 and 11 wards, respectively.

Six hundred and two patients entered into the study. The variables in this study were age at diagnosis, gender, education, place of residence (rural or urban), the history of cancers in relatives, smoking, race (Turkmen or others), chemotherapy, radiotherapy, surgery, and cancer type (gastric, esophageal or colorectal).

Follow-up of patients was done by phone call. In the initial checklist, only the information about the variables of age at diagnosis, sex, place of residence and type of cancer was specified. Therefore, information about other variables was asked in the end of follow up period from patients or their families. The sampling method is that all patients who were diagnosed with gastrointestinal cancer during 2002 to 2007 and they were available at the end of follow-up period are considered as sample.

The eligibility criteria for this study are that the gastrointestinal cancer has been diagnosed between 2002 and 2007 and the patient's place of residence at diagnosis has been in one of the wards of Mazandaran and Golestan.

For this study, three event types (death from gastrointestinal cancer, heart disease and other causes) were considered.

Statistical analysis

Five models were compared in this study. In the first model (no-frailty model), no frailty in the cause-specific hazard model was considered. In the second model (non-spatial frailty model), a random effect was considered in the cause-specific hazard model for each competing risk in each cluster. In this model, independent identically standard normal distribution is considered for frailties. The cause-specific hazard frailty model with a separate random effect for every type of event within each cluster (Christian et al., 2016) is:

$$h_{ijk}(t \mid w_i) = h_{0k}(t)\, exp\,(X_{ij}^T \beta_k + w_{ik})$$

Where X_{ij}^T and β_k are the $p\times1$ vector of covariates and p×1 vector of regression coefficients, respectively. Also, h_{0k} is the baseline hazard function for event type k that is considered to be a nonparametric form. In order to parametrize the baseline hazard function, the Gelfand (1995) approach (beta mixture approach) was used wherein the integrated baseline hazard is modeled as a mixture of monotone functions. In the third model (ICAR model), it is assumed that the random effects during clusters have a spatial correlation, but there is no correlation between the random effects within the clusters. The intrinsic conditional autoregressive distribution is used for the frailties during clusters for each of the competing risks. This is a multivariate normal distribution with mean 0 and precision matrix $\lambda\,(Diag\,(m_i) - C)$, where λ, m_i and C are the precision parameter associated with full conditional distributions, the number of neighbor regions of the ith region, and an adjacency matrix of the regions, respectively. The difference between the fourth model (proper CAR model) and the third model is the presence of property term α in the precision matrix of intrinsic conditionally autoregressive distribution- $\lambda\,(Diag\,(m_i) - \alpha C)$-, which eliminates the problem of the improperity of the intrinsic conditional autoregressive distribution (Banerjee et al., 2014). In the fifth model (MICAR model), in order to consider the correlation between random effects in each cluster and spatial correlation between random effects during clusters, the multivariate intrinsic conditionally autoregressive (MICAR) distribution was used for frailties. This is a multivariate normal distribution with mean 0 and precision matrix $\Lambda^{-1} \otimes (Diag\,(m_i) - C)$, where Λ is a $k\times k$ positive definite matrix regarding the random effects of within clusters. Also, ⊗ denotes the kronecker product (Gelfand and Vounatsou, 2003; Jin and Carlin, 2005). The bayesian approach - Gibbs sampler method (Gelfand and Smith, 1990) - was used to update the parameters in the model. For all regression coefficients, we assumed a vague normal prior. The Wishart prior is considered for precision matrix of random effects regarding the competing risks within clusters.

Two overdispersed parallel Markov Chain Monte Carlo (MCMC) chains with 100,000 iterations for each chain were run. Convergence was assessed with Brook-Gelman-Rubin diagnosis plot, trace plot and autocorrelation within the chains (Brooks and Gelman, 1998; Gelman and Rubin, 1992). After a burn-in period of 35,000 iterations for each chain, the retaining every 50th of the remaining 2×65,000=130,000 iterations yielded a final posterior sample of size of 2,600 for computing posterior summaries.

In order to choose the best-fitting model, the deviance information criterion (DIC) was used, defined as the expected deviance ($\bar{D}$) plus the effective number of parameters (p_D). The small values of the DIC indicate

performed models. All analysis was performed using OpenBUGS software (Spiegelhalter et al., 2014).

Results

In 602 patients of our study, the mean and standard deviation of age at diagnosis were 62.61 and 13.84, respectively. The number of patients with gastric, esophageal and colorectal cancer was 285 (47.34%), 175 (29.07%) and 142 (23.59%), respectively. In this study, the number of people who died from gastrointestinal cancer, heart disease and other causes was 441 (73.26%), 30 (4.98%) and 30 (4.98%). Table 1 lists a summary of the patient characteristics.

Table 1. Characteristics of Gastrointestinal Cancer Patients Diagnosed in Mazandaran and Golestan Provinces of Iran During 2002 to 2007

Covariates	Frequency (Percent)
Age at diagnosis (Mean ± SD)	62.61 ± 13.84
Sex	
Male	392 (65.12)
Female	210 (34.88)
Education	
Illiterate	386 (64.12)
Others	216 (35.88)
Place of residence	
Rural	319 (52.99)
Urban	283 (47.01)
History of cancer in relatives	
No	391 (64.95)
Yes	211 (35.05)
Smoking	
No	462 (77.08)
Yes	138 (22.92)
Race	
Turkmen	65 (10.80)
Others	537 (89.20)
Chemotherapy	
No	228 (37.87)
Yes	374 (62.13)
Radiotherapy	
No	399 (66.28)
Yes	203 (33.72)
Surgery	
No	238 (39.53)
Yes	364 (60.47)
Cancer type	
Gastric	285 (47.34)
Esophageal	175 (29.07)
Colorectal	142 (23.59)
Vital status in the end of study	
Alive	101 (16.78)
Death from gastrointestinal cancer	441 (73.26)
Death from heart disease	30 (4.98)
Death from other causes	30 (4.98)

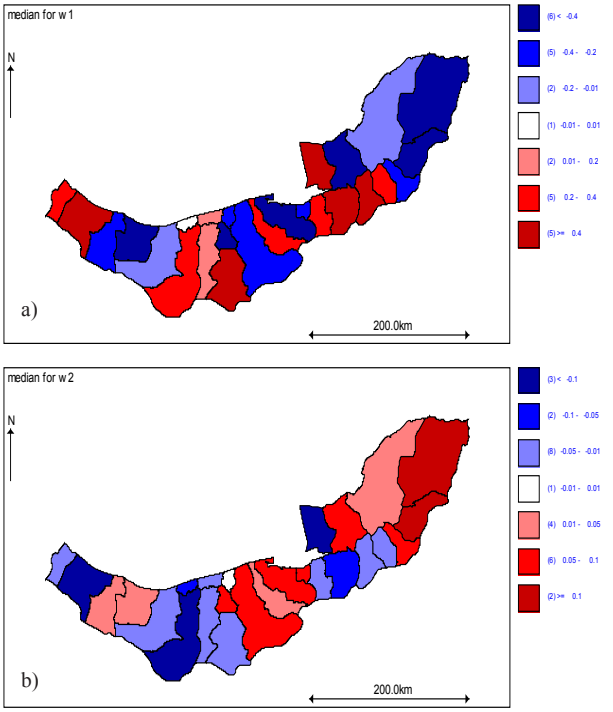

Figure 1. Posterior Median Frailties, Cause-specific Hazard Frailty Model with MICAR Distribution for Frailties in Presence of Two Competing Risks, (a) Death from Gastrointestinal Cancer; (b) Death from other Causes.

We first considered two competing risks (death from gastrointestinal cancer and death from other causes). Table 2 shows the posterior mean and 95 percent credible intervals (95% CI) for the model parameters and their hazard ratio for cause-specific hazard model (with two competing risks: death from gastrointestinal cancer and death from other cause) with MICAR distribution for frailties (Model 5). By controlling other variables, the males, the patients who lived in rural areas, and the patients who had not undergone surgery had a significantly higher hazard both for death from gastrointestinal cancer and death from other causes compared with the females, the patients who lived in urban areas, and the patients who had undergone surgery. Hazard of death from gastrointestinal cancer for patients whose relatives did not have a history of cancer and patients who had not received radiotherapy were higher compared to patients whose relatives had a history of cancer and patients who had received radiotherapy, respectively. Gastric cancer patients had a higher hazard of death from gastrointestinal cancer compared with esophageal cancer patients and colorectal cancer patients. Hazard of death from other causes for patients who had not received chemotherapy was higher compared to others.

In Table 4, we compared five varieties of the cause-specific hazard model (Model 1: no-frailty model, Model 2: non-spatial frailty model, Model 3: Intrinsic conditionally autoregressive (ICAR) model, Model 4: proper conditionally autoregressive (CAR)

Table 2. Results of Cause-specific Hazard Spatial Frailty Models with MICAR Distribution for Frailties in Presence of Two Competing Risks

Covariates	Posterior mean (% 95 CI[a])	HR[b] (% 95 CI)
Gastrointestinal cancer		
Intercept	0.955 (0.071, 1.935)	
Age at diagnosis	-0.003 (-0.015, 0.007)	0.997 (0.985, 1.007)
Sex (male to female)	0.548 (0.300, 0.809)	1.730 (1.350, 2.246)
Education (illiterate to others)	0.062 (-0.206, 0.322)	1.063 (0.814, 1.380)
Place of residence (rural to urban)	0.366 (0.119, 0.602)	1.443 (1.126, 1.826)
History of cancer in relatives (no to yes)	0.268 (0.047, 0.495)	1.308 (1.048, 1.640)
Smoking (no to yes)	0.006 (-0.258, 0.268)	1.006 (0.772, 1.307)
Race (turkmen to others)	-0.117 (-0.673, 0.446)	0.890 (0.510, 1.562)
Chemotherapy (no to yes)	0.060 (-0.203, 0.325)	1.061 (0.817, 1.384)
Radiotherapy (no to yes)	0.508 (0.233, 0.778)	1.661 (1.262, 2.176)
Surgery (no to yes)	2.522 (2.267, 2.791)	12.453 (9.650, 16.297)
Cancer type (gastric to esophageal)	0.587 (0.316, 0.858)	1.799 (1.372, 2.358)
Cancer type (gastric to colorectal)	1.554 (1.202, 1.913)	4.730 (3.327, 6.773)
Other causes		
Intercept	-3.362 (-5.240,-1.798)	
Age at diagnosis	0.017 (-0.003, 0.040)	1.017 (0.997, 1.041)
Sex (male to female)	0.986 (0.318, 1.669)	2.680 (1.374, 5.307)
Education (illiterate to others)	0.311 (-0.335, 0.971)	1.364 (0.715, 2.641)
Place of residence (rural to urban)	0.582 (0.039, 1.125)	1.790 (1.039, 3.080)
History of cancer in relatives (no to yes)	-0.158 (-0.724, 0.398)	0.854 (0.485, 1.489)
Smoking (no to yes)	0.049 (-0.630, 0.703)	1.050 (0.532, 2.021)
Race (turkmen to others)	-0.611 (-1.979, 0.583)	0.543 (0.138, 1.739)
Chemotherapy (no to yes)	0.819 (0.188, 1.451)	2.268 (1.207, 4.267)
Radiotherapy (no to yes)	0.293 (-0.391, 1.008)	1.341 (0.676, 2.740)
Surgery (no to yes)	1.500 (0.842, 2.151)	4.482 (2.321, 8.593)
Cancer type (gastric to esophageal)	0.588 (-0.157, 1.391)	1.800 (0.855, 4.019)
Cancer type (gastric to colorectal)	0.258 (-0.422, 0.960)	1.295 (0.656, 2.612)

[a]Credible Interval; [b]Hazard Ratio

model, and Model 5: multivariate intrinsic conditionally autoregressive (MICAR) model). The DIC value in Model 1 (no-frailty model) is larger than Models 2-5 (frailty models), indicating the need for frailty term in the model. The DIC value in Model 2 (non-spatial frailty model) is larger than Model 3 (ICAR model) and Model 4 (proper CAR model), which is an indication of the need for spatial frailty term rather than ordinary frailty term in the model. The DIC value in Model 4 (proper CAR model) is smaller than Model 3 (ICAR model), which shows the ability of property term (α) to improve the model. The DIC value in Model 5 (MICAR model) is smaller than Model 3 (ICAR model). This indicates the need to take into account the correlation between the random effects (correlation between competing risks) within the clusters.

Figure 1 maps the posterior median of the spatial frailties or spatial residuals in cause-specific hazard frailty model with MICAR distribution for frailties in presence of two competing risks which capture the spatial variations already unexplained by the main effect. When there is no spatial pattern in these maps, it indicates the absence of an additional spatial story in the data beyond what is described by the main effect. In Figure 1 Panel (a), two clusters of wards with higher median frailties or higher hazard (wards with red colors) and one cluster with lower hazard (wards with blue colors) relevant for death from gastrointestinal cancer can be detected. In Figure 1 Panel (b), two clusters of wards in the central and east part of map with a higher hazard (wards with red colors) and one cluster with lower hazard (wards with blue colors) related to death from other causes can be identified. According to the observed trend in Figures 1 and 2, it can be realized that the model needs variables with spatial effects.

For a more precise examination of the prognostic factors of the event of interest (gastrointestinal cancer) as well as obtaining prognostic factors of death from heart disease in patients with gastrointestinal cancers, the cause-specific hazard model in presence of three competing risks (death from gastrointestinal cancer, death from heart disease and death from other causes) had fitted our data. By controlling other variables, higher age at diagnosis increased the hazard of death from heart disease but not the death from gastrointestinal cancer and the death

Table 3. Results of Cause-specific Hazard Spatial Frailty Models with MICAR Distribution for Frailties in Presence of Three Competing Risks

Covariates	Death from gastrointestinal cancer Posterior mean (% 95 CI) HR (95% CI)	Death from heart disease Posterior mean (% 95 CI) HR (95% CI)	Death from other causes Posterior mean (% 95 CI) HR (95% CI)
Intercept (posterior mean)	0.900 (0.020,1.686)	-8.233 (-11.939,-4.890)	-1.513 (-4.197,1.183)
Age at diagnosis	-0.003 (-0.012,0.008) 0.997 (0.988,1.008)	0.060 (0.021,0.103) 1.062 (1.022,1.108)	-0.013 (-0.047,0.020) 0.987 (0.954,1.020)
Sex (male to female)	0.559 (0.317,0.795) 1.748 (1.372,2.213)	1.297 (0.317,2.370) 3.658 (1.373,10.697)	0.771 (-0.134,1.722) 2.162 (0.875,5.596)
Education (illiterate to others)	0.067 (-0.184,0.325) 1.069 (0.832,1.383)	0.162 (-0.801,1.134) 1.176 (0.449,3.108)	0.231 (-0.709,1.192) 1.260 (0.492,3.294)
Place of residence (rural to urban)	0.365 (0.142,0.597) 1.440 (1.153,1.816)	0.260 (-0.552,1.058) 1.297 (0.576,2.881)	0.905 (0.120,1.751) 2.472 (1.127,5.760)
History of cancer (no to yes)	0.266 (0.040,0.499) 1.304 (1.041,1.647)	-0.517 (-1.294,0.278) 0.596 (0.274,1.320)	0.318 (-0.473,1.146) 1.375 (0.623,3.146)
Smoking (no to yes)	0.014 (-0.252,0.274) 1.014 (0.777,1.315)	-0.648 (-1.915,0.397) 0.523(0.147,1.487)	0.468 (-0.362,1.313) 1.596 (0.696,3.717)
Race (turkmen to others)	-0.094 (-0.648,0.478) 0.911 (0.523,1.612)	-1.940 (-5.222,0.254) 0.144 (0.005,1.290)	0.004 (-1.814,1.709) 1.004 (0.163,5.523)
Chemotherapy (no to yes)	0.058 (-0.191,0.305) 1.059 (0.826,1.357)	0.514 (-0.440,1.488) 1.672 (0.644,4.428)	0.902 (0.035,1.797) 2.464 (1.036,6.032)
Radiotherapy (no to yes)	0.502 (0.247,0.756) 1.652 (1.280,2.130)	-0.305 (-1.202,0.623) 0.737 (0.301,1.865)	1.271 (0.114,2.626) 3.564 (1.121,13.818)
Surgery (no to yes)	2.516 (2.263,2.771) 12.379 (9.612,15.975)	1.439 (0.448,2.380) 4.216 (1.565,10.805)	1.553 (0.527,2.526) 4.726 (1.694,12.503)
Cancer type			
gastric to esophageal	0.588 (0.317,0.857) 1.800 (1.373,2.356)	0.080 (-1.023,1.253) 1.083 (0.360,3.501)	1.089 (-0.025,2.334) 2.971 (0.975,10.319)
gastric to colorectal	1.541 (1.207,1.874) 4.669 (3.343,6.514)	-0.487 (-1.510,0.539) 0.615 (0.221,1.714)	0.980 (-0.111,2.177) 2.663 (0.895,8.820)

from other causes. A ten-year increase in age at diagnosis will multiply the hazard of death from heart disease by 1.82. Males had a significantly higher hazard of death from gastrointestinal cancer and heart disease compared to females. Patients who lived in rural areas had a significantly higher hazard of death from gastrointestinal cancer and other causes compared to patients who lived in urban areas. Patients whose relatives did not have a history of cancer had a higher hazard of death from gastrointestinal cancer compared to patients with a history of cancer in their relatives. Hazard of death from other causes for patients who had not received chemotherapy was higher compared to others. Patients who had not received radiotherapy had a higher hazard of death from gastrointestinal cancer and other causes compared to others. Patients who had not undergone surgery had a significantly higher hazard of death from gastrointestinal cancer, heart disease and other causes compared to patients who had undergone surgery. Gastric cancer patients had a higher hazard of death from gastrointestinal cancer but not from death from heart disease and other causes, compared to esophageal cancer patients and colorectal cancer patients. The posterior mean and 95 percent credible interval for the model parameters and their hazard ratio are given in Table 3.

In Figure 2 Panel (a), we can identify two clusters of wards with higher median frailties or a higher hazard (wards with red colors), and one cluster with lower median frailties or lower hazard in the east of the map (wards with blue colors) related to death from gastrointestinal cancer. In Figure 2 Panel (b), we can identify one cluster of wards with a higher hazard in the east of the map (cluster of wards with red colors) and two clusters with a lower hazard (cluster of wards with blue colors) related to death from heart disease. In Figure 2 Panel (c), we can identify one cluster of wards with a higher hazard in the central part of the map (cluster of wards with red colors), and one cluster of wards with a lower hazard in the east of the map (cluster of wards with blue colors) related to death from other causes. These trends strongly suggest the need for fitting spatial covariates in our model related to death from gastrointestinal cancer, heart disease and other causes.

Table 5 compares the five varieties of cause-specific hazard model in presence of 3 competing risks (Model 1: no-frailty model, Model 2: non-spatial frailty model,

Table 4. Posterior Mean Deviance ($\bar{D}$), Effective Number of Parameters (p_D) and Model Comparison Criterion (DIC) for Various Cause-specific Hazard Frailty Models in Presence of Two Competing Risks

Models	$\bar{D}$	(p_D)	DIC
Cause-specific hazard model (no-frailty model)	7738	25.16	7763.16
Cause-specific hazard frailty model (no-spatial frailty model)	7617	76.51	7693.51
Cause-specific hazard frailty model with ICAR distribution for frailties (ICAR model)	7627	64.18	7691.18
Cause-specific hazard frailty model with CAR distribution for frailties (proper CAR model)	7622	57.89	7679.89
Cause-specific hazard frailty model with MICAR distribution for frailties (MICAR model)	7625	61.61	7686.61

Table 5. Posterior Mean Deviance ($\bar{D}$), Effective Number of Parameters (p_D) and Model Comparison Criterion (DIC) for Various Cause-specific Hazard Frailty Models in Presence of Three Competing Risks

Model	$\bar{D}$	(p_D)	DIC
Cause-specific hazard model (no-frailty model)	7813	40.06	7853.06
Cause-specific hazard frailty model (non-spatial frailty model)	7686	95.63	7781.63
Cause-specific hazard frailty model with ICAR distribution for frailties (ICAR model)	7701	75.89	7776.89
Cause-specific hazard frailty model with CAR distribution for frailties (proper CAR model)	7697	73.45	7770.45
Cause-specific hazard frailty model with MICAR distribution for frailties (MICAR model)	7695	82.95	7777.95

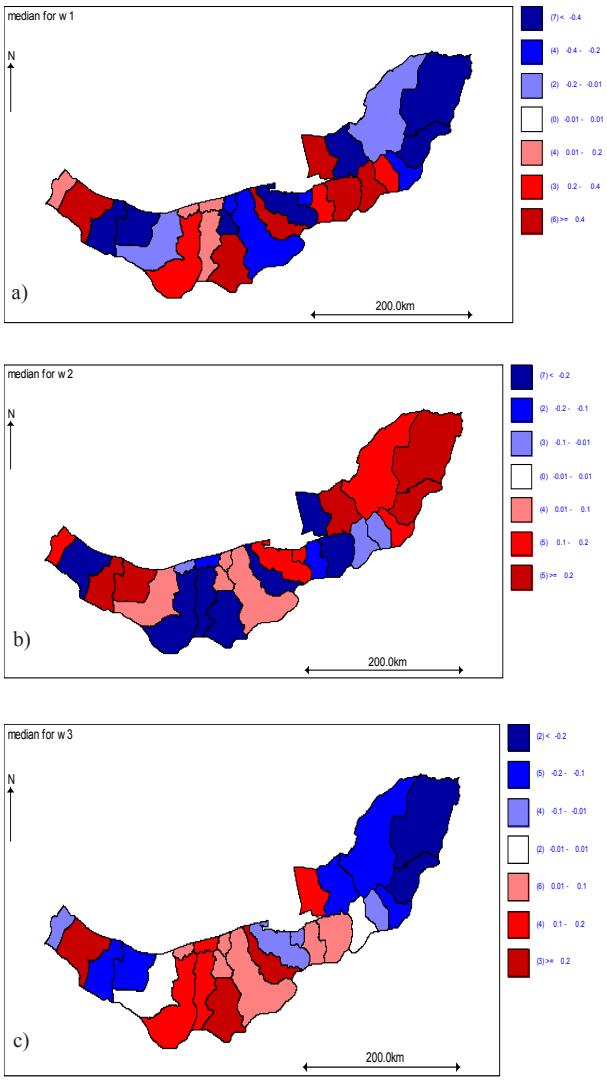

Figure 2. Posterior Median Frailties, Cause-specific Hazard Frailty Model with MICAR Distribution for Frailties in Presence of Three Competing Risks, (a) Death from Gastrointestinal Cancer; (b) Death from Heart Disease; (c) Death from other Causes.

Model 3: Intrinsic conditionally autoregressive (ICAR) model, Model 4: proper conditionally autoregressive (CAR) model, and Model 5: multivariate intrinsic conditionally autoregressive (MICAR) model). Although the deviance mean ($\bar{D}$) in Model 5 is lower than that of Model 3, there is no significant difference between the DIC values of two models due to higher effective number of parameters (p_D) in Model 5 as compared to Model 3. The rest of the results in this table are similar to Table 4.

Discussion

In this study, the cause-specific hazard model with multivariate spatial frailties was used to determine the prognostic factors of gastrointestinal cancers, heart disease, and other causes. This study was performed on data from gastrointestinal cancer patients in Mazandaran and Golestan provinces in the north of Iran. Various models (no-frailty model, non-spatial frailty model, ICAR model, proper CAR model, and MICAR model) were fitted on the gastrointestinal cancer data in presence of two or three competing risks and were compared with deviance information criterion (DIC).

In addition to the variables in the study, there may be some still-missing spatially varying covariates relevant for gastrointestinal cancer or competing risks. These unknown or unobserved variables could be controlled by adding the terms of random effects to the model and by considering the spatial correlation between random effects during regions. Therefore, the contribution of this study is to analyze the time to death from gastrointestinal cancer in the presence of competing risks using spatial survival models.

The variable of age at diagnosis was not significantly associated with time to death from gastrointestinal cancer. This result is similar to the results of O'Gorman et al., (2000), Hiripi et al., (2012) and Hamashima et al., (2015) but is not comparable with the results of the studies by Wei et al., (2017) and Guller et al., (2015). In our study, the hazard of death from gastrointestinal cancer in men

was higher than that of women, consistent with the studies of Wang et al., (2011) and Bohanes et al., (2012). In our study, the variable of education was not significantly associated with time to death from gastrointestinal cancer. In the study of Ghadimi et al., (2011) and Rasouli et al., (2017), an increase in the level of education led to a decrease of the hazard of death from gastrointestinal cancer. This relationship was not significant in the first article but it was in the second study. In our study, along with the studies of Aghcheli et al., (2011) and Dixon et al., (2016), the hazard of death from gastrointestinal cancer in people living in rural areas was significantly higher than those living in urban areas. However, in the study of Ghadimi et al., (2011), the place of residence was not significantly associated with the time to death from gastrointestinal cancer. In our study, the hazard of death from gastrointestinal cancer in patients who did not have a history of cancer in their relatives was higher than the others. This result was similar to the study of Yuequan et al., (2010). Similar to our study, in the studies of Tustumi et al., (2016) and Hassan et al., (2016), the survival of patients whose relatives had a history of cancer was higher than others. Unlike our study, however, the history of cancer in the relatives was not associated with time to death from gastrointestinal cancer in theirs studies. Also, contrary to our study, the history of cancer in relatives was not associated with time to death from gastrointestinal cancer in the studies of Ghadimi et al.,(2011), Baghestani et al., (2017) and Rasouli et al., (2017). In our study, similar to the studies of Aghcheli (2011), Ghadimi et al., (2011), Zhang et al., (2013) and Okada et al., (2017), and also in contrast with the studies of Rasouli et al., (2017) and Lin et al., (2012), smoking variable was not associated with time to death from gastrointestinal cancer. Contrary to the study of Aghcheli et al., (2011) and in line with the study of Ghadimi et al., (2011), the hazard of death from gastrointestinal cancer in Turkmen patients was not significantly different from the others. The hazard of death from gastrointestinal cancer in patients who had received radiotherapy was lower than those who did not receive radiotherapy. This result is consistent with the studies of Aghcheli et al., (2011), Dixon et al., (2016), and Lin (2012). Also, similar to findings of Aghcheli et al., (2011) and Guller (2015), the hazard of death from gastrointestinal cancer in patients who had undergone surgery was lower than those who did not undergo surgery. In the study of Moghimbeigi et al., (2014), contrary to our study, radiotherapy and surgery was not associated with time to death from gastrointestinal cancer. In our study, the hazard of death in colorectal cancer patients was lower than gastric cancer patients. This is consistent with the findings of Moghimi et al., (2009) and Kuchler et al., (2007). Moreover, in our study, like the study of Kuchler et al., (2007), the hazard of death from esophageal cancer was smaller than that of gastric cancer. However, in the study of Ghadimi et al., (2011) and Chau et al., (2004), the type of cancer did not have a significant relationship with the survival time.

One of the limitations of this study is the low sample size, which reduces the number of failures from competing events and distorts the estimation of parameters. Some of the variables in this study have been retrieved at the end of the follow-up period from the patients or their families. Due to this long interval time, the information bias may occur.

In the two-competing-risk model and the three-competing-risk model, based on the deviance information criterion (DIC), the frailty models seemed better than the no-frailty model. Also, the spatial frailty models seemed better than the non-spatial frailty models. This indicates that the effects of unobserved factors in the model at closer areas to one another may be more similar to each other. The MICAR model is better fitted compared to the ICAR model in presence of two competing risks. In the presence of three competing risks, the DIC values of these two models are not significantly different, although the deviance mean of Model 5 is lower than Model 3. In addition, the spatial pattern in the figures suggests the necessity of the presence of some still missing, spatially varying covariates related to time to death from gastrointestinal cancer, heart disease or other causes.

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References

Aghcheli K, Marjani H-A, Nasrollahzadeh D, et al (2011). Prognostic factors for esophageal squamous cell carcinoma-a population-based study in Golestan Province, Iran, a high incidence area. *PLoS One*, **6**, e22152.

Baghestani AR, Moamer S, Pourhoseingholi MA, et al (2017). Demographic and pathological predictors of colorectal cancer survival in competing risk model, using generalized weibull distribution. *Int J Cancer Manag*, **10**, e7352.

Banerjee S, Carlin BP, Gelfand AE (2014). Hierarchical modeling and analysis for spatial data, Crc Press, pp 306-8.

Banerjee S, Wall MM, Carlin BP (2003). Frailty modeling for spatially correlated survival data, with application to infant mortality in Minnesota. *Biostatistics*, **4**, 123-42.

Bohanes P, Yang D, Chhibar RS, et al (2012). Influence of sex on the survival of patients with esophageal cancer. *J Clin Oncol*, **30**, 2265.

Brooks SP, Gelman A (1998). General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat*, **7**, 434-55.

Chau I, Norman AR, Cunningham D, et al (2004). Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer-pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol*, **22**, 2395-403.

Christian NJ, Ha ID, Jeong JH (2016). Hierarchical likelihood inference on clustered competing risks data. *Stat Med*, **35**, 251-67.

Darabi M, Lari MA, Motevalian SA, et al (2016). Trends in gastrointestinal cancer incidence in Iran, 2001-2010: a joinpoint analysis. *Epidemiol Health*, **38**, e5941.

Dixon M, Mahar AL, Helyer LK, et al (2016). Prognostic factors in metastatic gastric cancer: results of a population-based,

retrospective cohort study in Ontario. *Gastric Cancer*, **19**, 150-9.
Fine JP, Gray RJ (1999). A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*, **94**, 496-509.
Gelfand AE, Mallick BK (1995). Bayesian analysis of proportional hazards models built from monotone functions. *Biometrics*, **51**, 843-52.
Gelfand AE, Vounatsou P (2003). Proper multivariate conditional autoregressive models for spatial data analysis. *Biostatistics*, **4**, 11-5.
Gelman A, Rubin DB (1992). Inference from iterative simulation using multiple sequences. *Stat Sci*, **7**, 457-72.
Ghadimi M, Mahmoodi M, Mohammad K, et al (2011). Family history of the cancer on the survival of the patients with gastrointestinal cancer in northern Iran, using frailty models. *BMC Gastroenterol*, **11**, 104.
Gooley TA, Leisenring W, Crowley J, et al (1999). Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*, **18**, 695-706.
Güller U, Tarantino I, Cerny T, et al (2015). Population-based SEER trend analysis of overall and cancer-specific survival in 5138 patients with gastrointestinal stromal tumor. *BMC Cancer*, **15**, 557.
Hamashima C, Shabana M, Okamoto M, et al (2015). Survival analysis of patients with interval cancer undergoing gastric cancer screening by endoscopy. *PLoS One*, **10**, e0126796.
Hassan M, Suan M, Soelar SA, et al (2016). Survival analysis and Prognostic Factors for colorectal cancer patients in Malaysia. *Asian Pac J Cancer Prev*, **17**, 3575-81.
Hiripi E, Jansen L, Gondos A, et al (2012). Survival of stomach and esophagus cancer patients in Germany in the early 21st century. *Acta Oncol*, **51**, 906-14.
Jin X, Carlin BP (2005). Multivariate parametric spatiotemporal models for county level breast cancer survival data. *Lifetime Data Anal*, **11**, 5-27.
Küchler T, Bestmann B, Rappat S, et al (2007). Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial. *J Clin Oncol*, **25**, 2702-8.
Lin Y, Su X, Su H, et al (2012). Prediagnostic smoking and postoperative survival in lymph node-negative esophagus squamous cell carcinoma patients. *Cancer Sci*, **103**, 1985-8.
Moghimbeigi A, Tapak L, Roshanaei G, et al (2014). Survival analysis of gastric cancer patients with incomplete data. *J Gastric Cancer*, **14**, 259-65.
Moghimi-Dehkordi B, Safaee A, Zali MR (2009). Comparison of colorectal and gastric cancer: survival and prognostic factors. *Saudi J Gastroenterol*, **15**, 18.
O'Gorman P, McMillan DC, McArdle CS (2000). Prognostic factors in advanced gastrointestinal cancer patients with weight loss. *Nutr Cancer*, **37**, 36-40.
Okada E, Ukawa S, Nakamura K, et al (2017). Demographic and lifestyle factors and survival among patients with esophageal and gastric cancer: The Biobank Japan Project. *J Epidemiol*, **27**, 29-35.
Pintilie M (2007). Analysing and interpreting competing risk data. *Stat Med*, **26**, 1360-7.
Prentice RL, Kalbfleisch JD, Peterson Jr AV, et al (1978). The analysis of failure times in the presence of competing risks. *Biometrics*, **34**, 541-54.
Rasouli MA, Moradi G, Roshani D, et al (2017). Prognostic factors and survival of colorectal cancer in Kurdistan province, Iran: A population-based study (2009–2014). *Medicine*, **96**, e5941.
Saadat S, Yousefifard M, Asady H, et al (2015). The most important causes of death in Iranian population; a Retrospective Cohort Study. *Emergency*, **3**, 16.
Tustumi F, Kimura CMS, Takeda FR, et al (2016). Prognostic factors and survival analysis in esophageal carcinoma. *Arq Bras De Cir Dig*, **29**, 138-41.
Wang B-Y, Goan Y-G, Hsu P-K, et al (2011). Tumor length as a prognostic factor in esophageal squamous cell carcinoma. *Ann Thorac Surg*, **91**, 887-93.
Wei EK, Colditz GA, Giovannucci EL, et al (2017). A comprehensive model of colorectal cancer by risk factor status and subsite using data from the Nurses' Health study. *Am J Epidemiol*, **185**, 224-37.
Yazdanbod A, Naseri MS, Malekzadeh R (2004). Upper gastrointestinal cancer in Ardabil, North-West of Iran: A review. *Arch Iranian Med*, **7**, 173-7.
Yuequan J, Shifeng C, Bing Z (2010). Prognostic factors and family history for survival of esophageal squamous cell carcinoma patients after surgery. *Ann Thorac Surg*, **90**, 908-13.
Zhang F, Han H, Wang C, et al (2013). A retrospective study: the prognostic value of anemia, smoking and drinking in esophageal squamous cell carcinoma with primary radiotherapy. *World J Surg Oncol*, **11**, 249.