Geospatial epidemiology of coronary artery disease treated with percutaneous coronary intervention in Crete, Greece

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Abstract

Coronary artery disease (CAD) constitutes a leading cause of morbidity and mortality worldwide. Percutaneous coronary intervention (PCI) is indicated in a significant proportion of CAD patients, either to improve prognosis or to relieve symptoms not responding to optimal medical therapy. Thus the annual number of patients undergoing PCI in a given geographical area could serve as a surrogate marker of the total CAD burden there. The aim of this study was to analyze the potential, spatial patterns of PCI-treated CAD patients in Crete. We evaluated data from all patients subjected to PCI at the island's sole reference centre for cardiac catheterization within a 4-year study period (2013-2016). The analysis focused on regional variations of yearly PCI rates, as well as on the effect of several clinical parameters on the severity of the coronary artery stenosis treated with PCI across Crete. A spatial database within the ArcGIS environment was created and an analysis carried out based on global and local regression using ordinary least squares (OLS) and geographically weighted regression (GWR), respectively. The results revealed significant inter-municipality variation in PCI rates and thus potentially CAD burden, while the degree and direction of correlation between key clinical factors to coronary stenosis severity demonstrated specific geographical patterns. These preliminary results could set the basis for future research, with the ultimate aim to facilitate efficient healthcare strategies planning.

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Introduction

Currently, cardiovascular disease (CVD) constitutes the leading cause of mortality, accounting for more than 27% of all deaths worldwide, with the corresponding percentage even higher in Europe and USA (WHO, 2020). In Europe, it has been estimated that more than 4 million people die from atherosclerotic disease annually corresponding to about roughly 45% of all deaths there. In addition, CVD is a major cause of morbidity and disability, while in parallel imposing significant economic burdens (Timmis *et al*., 2018; Movsisyan *et al*., 2020). It should however be emphasized that there is significant inter-country variation regarding age-adjusted cardiovascular risk within Europe, while heterogeneity in CVD- related morbidity and mortality has also been demonstrated at the level of country subdivisions or regions (Bhatnagar *et al.,* 2015).

The term CVD primarily encompasses peripheral arterial, cerebrovascular and coronary artery disease (CAD), with the latter demonstrating the highest relative contribution to CVD associated mortality (Timmis *et al.,* 2018). Individuals affected by CAD can present acutely with a clinical picture compatible with acute coronary syndrome (ACS), the spectrum of which includes ST-elevation on myocardial infarction (STEMI) (where ST is a segment on the electrocardiogram), non-ST- elevation myocardial infarction

(NSTEMI), unstable angina (UA) or stable angina, the latter a condition now termed chronic coronary syndrome (CCS). According to current guidelines, invasive coronary angiography is indicated in the vast majority of ACS patients, with percutaneous coronary intervention (PCI) as cornerstone approach. Indeed, primary PCI is the re-perfusion modality of choice in STEMI, while also constituting the preferred re-vascularisation strategy in most NSTEMI/UA patients (Ibanez *et al.,* 2017; Collet *et al.,* 2021). In CCS patients, on the other hand, coronary re-vascularisation is indicated, either for drug-resident angina symptoms or to prognostically treat significant coronary artery stenosis (Knuuti *et al.,* 2020). Although coronary artery bypass grafting (CABG) is the preferred re-vascularisation modality in the subset of patients with acceptable, operative risk; particularly with three-vessel left main CAD, impaired left ventricular function and/or diabetes mellitus, the percentage of patients re-vascularised with PCI is still considerably higher (Kataruka *et al.,*2020).

Taken together, these data suggest that the annual number of patients undergoing PCI in a given geographical area could serve as a satisfactory surrogate marker of the total CAD burden and its spatial distribution. Thus, assuming uniform access to a PCI capable cardiac catheterization laboratory and consistent management strategies across the area, regional differences in PCI rates could imply analogous variations in CAD prevalence. Identification of such variations can prove valuable in healthcare strategies planning, as they might imply heterogeneity with respect to cardiovascular risk, lifestyle-associated factors, socioeconomic status or access to healthcare facilities. The severity of coronary artery stenosis treated with PCI is a crucial clinical indicator as it directly affects patient outcomes and management decisions. Understanding the spatial patterns of severity provides valuable insights into the distribution of disease burden and the effectiveness of interventions. In this way, the analysis can provide more precise information on the impact of various clinical parameters (such as age, sex, clinical presentation and non-invasive evidence of ischemia) on disease severity at the local level.

Spatial analysis is a particularly important component of geographical information systems (GIS), because the method includes all transformations and manipulations that can be applied to geographical data to reveal spatial patterns and anomalies that are not readily apparent, thus rendering the dataset potentially more valuable in supporting decision-making. This approach includes, spatial autocorrelation analysis, spatial regression models, cluster detection techniques, spatial interpolation, spatial join and overlay analysis as mentioned by Tsatsaris *et al.* (2023).

The primary aim of the present study was to conduct a comprehensive spatial analysis of PCI-treated CAD in Crete, Greece focusing on potential geographical variations in CAD incidence and outcomes. The distribution of the severity of CAD aligns with the overall objective by providing detailed insights into its spatial pattern and the determinants involved.

Materials and Methods

Study design and sampling

This retrospective, cross-sectional study was conducted in Crete, Greece's largest island that has a permanent population of approximately 633,500 residents with an even gender distribution, 49.5% men and 50.5% women. The mean age is 40.3 years, while that of the country as a whole is 42.2 years. The island was selected as the core study area due to the fact that it is considered to have a relatively closed and genetically homogeneous population, with a well-defined demographic population pyramid, which is recommended for epidemiological studies.

The patient data were extracted from the records of the Cardiac Catheterization Laboratory of the University Hospital of Heraklion (UHH), which serves as the reference cardiac catheterization centre for about 90% of the Cretan population. Data from PCI-treated patients that underwent PCI during the 4-year period of 2013-2016 were analyzed. All patient data are routinely recorded in the electronic medical file of the Hospital Informatics System supported by the UHH. For this study, we used a dataset including patients subjected to either urgent PCI in the setting of an ACS (uPCI) or elective PCI (ePCI). The only exclusion criterion was lack of information regarding the patient's permanent residence.

The study parameters included day of hospital admission, gender, age, home address, and known risk factors for CVD (hypertension, diabetes mellitus, dyslipidemia, smoking status, family history of premature coronary artery disease, obesity or overweight, sedentary lifestyle and poor dietary habits). In addition we recorded admission diagnosis, type of admission (urgent or scheduled), degree of coronary artery stenosis (% diameter), coronary arteries affected as well as the outcome of hospitalization. For the scope of this study, the admission diagnosis was based on the International Classification Disease system (ICD-10) codes registered in the electronic medical records of the hospital.

Geospatial data

In order to create a geographical level of information that would include all the collected descriptive data for the entire number of patients, Google Earth platform was used in combination with the values of the field of the electronic medical record system entitled "Patient Address". The next step was geocoding each patient's residence and present it in shapefile format, *i.e.* points on a computer-generated map created by means of ArcGIS Pro ver. 3.2 software (ESRI, Redlands, CA, USA). The analysis included all 578 administrative units (LAUs) of Crete (data by the 2011 Population Census, provided by the Hellenic Statistical Authority). This aggregation was conducted using ArcGIS' 'spatial join' function summing up all patient data within the corresponding LAUs, which basically refers to the connection of the point-based patient file with the polygon-based space file.

Spatial analysis

After creation of the spatial database described above, autocorrelation was carried out followed by global and local regression applying ordinary least squares (OLS) and geographically weighted regression (GWR), respectively. We examined the potential presence of heterogeneity (clustering) of the PCI-treated CAD cases across all LAUs of Crete. All these investigations were applied within ArcGIS.

In the context of spatial analysis, the procedure examined locations, attributes and relationships through the generation of overlays and other analytical techniques, which can reveal patterns and underlying processes. More generally, the approach addresses the question "*what could have been the genesis of the observed spatial pattern*?" (Ripley, 1977). It is an exploratory process whereby we attempt to quantify the observed pattern and then explore the processes that may have generated the pattern observed (Gatrell *et al.,* 1996). Spatial analysis refers to quantitative geography and data analysis with quantitative methods and as a result it finds applications in most sciences in which statistical data are analyzed with geographical reference (Faka, 2020; Andreopoulos *et al.,* 2021; Faka *et al.,* 2021, 2022). It is inextricably linked to GIS and geoinformatics, a distinct field of basic and applied research considering spatial data and their impact. From the position of each observation, which can be defined by geographical coordinates in a cartographic projection system, additional information about an observation can be derived, such as its proximity and distance from other observations (Brunsdon *et al.,* 1998; Chalkias *et al.,* 2013).

Classical regression methods assume that the relationship between independent and dependent variables is constant in space. Thus, the spatial reference is often missing and the only way to test whether there is a lack of spatial stability in the relationships is to use local modelling. It is therefore necessary to switch from global to local analysis with the dynamic introduction of the spatial parameter. Global models represent processes that are spatially stable and therefore independent of location, while local models are spatial disaggregated global models, with results that vary by location (points in space). GWR is a commonly used regression method that allows the implementation of a local approach. It represents local statistics and can thus be used to model spatial changes regarding relationships and correlations. The difference between GWR and multiple linear regression lies in the fact that in the former the observations can be weighted by their geographical location in the model formulation. The first step in the spatial analysis involves OLS, which is used to generate predictions or to model a dependent variable in terms of its relationships to a set of explanatory variables (Donner, 1984; Dudley *et al.,* 1993; Goodman *et al.,* 2003; Berg & Mansley, 2004). This kind of analysis provides a unique regression formula for the whole area of interest (study area) and this is why this regression is called global (Fischer *et al.*, 2010).

Depending on the results of this analysis and especially on the clustering of the OLS residuals based on the corrected Akaike information criterion (AICc), GWR was applied (Hurvich *et al.,* 1998; Fotheringham *et al.,* 2002). GWR constructs a separate equation for every feature in the dataset incorporating the dependent and explanatory variables of features falling within the bandwidth of each target feature. Global regression models, such as OLS, are unreliable when two or more variables exhibit multicollinearity (when two or more variables are redundant or together tell the same "story"). GWR builds a local regression equation for each feature in the dataset. When the values for a particular explanatory variable cluster spatially, there is a high likelihood of local multicollinearity.

Results

The demographic characteristics of enrolled patients are presented in Table 1. The study population consisted of 2,494 patients, with a mean age of 62.9 years with a standard deviation (SD) of 11.7, grouped into 2,064 (82.8%) males and 430 (17.2%) females. There was no significant difference in the mean age between males and females. The majority of patients were Greeks (94.8%), with the remainder (5.2%) individuals of foreign nationalities residing permanently in Crete for at least 10 years. On average, 623 patients were re-vascularised with PCI per year, with a mean, annual increase of 18.3% during the 4-year study period.

Primary indications for PCI in the study population were ACS (57.0%) and stable angina pectoris (22.4%). Regarding the degree of coronary artery stenosis treated with PCI, 29.4% of patients had total occlusions (100% diameter), while in 54.7% of all PCIs were performed on lesions related to stenosis in the range of 71-90% diameter. The PCI success rate (as defined by the clinical proce-

Table 1. Clinical characteristics of patients with PCI-treated coronary artery disease (CAD) in Crete 2013-2016.

Parameter	Characteristic	N	%	95%CI
Gender	Male	2,064	82.8	81.3-84.3
	Female	430	17.2	15.7-18.7
Age (years)	Mean±SD (min max)	62.9±11.7 (20-99)		
	<45	188	7.5	6.6-8.6
	46-60	856	34.3	32.4-36.1
	61-75	1,059	42.5	40.7-44.6
	>76	391	15.7	14.2-17.0
Nationality	Greek	2364	94.8	93.9-95.6
	Foreign	130	5.2	4.4-6.1
Year of study	2013	474	19.0	17.5-20.5
	2014	613	24.6	22.8-26.3
	2015	633	25.4	23.7-27.2
	2016	774	31.0	29.2-32.9
PCI setting	Elective	1,385	56.1	54.3-58.1
	Urgent	1,084*	43.9	41.9-45.7
Hospitalization (days)	Mean ±SD (min max)	5.2±4.0 (0-87)		
	0 or 1	527	21.3	19.7-22.9
	2 to 7	1,436	58.2	56.2-60.1
	>8	506	20.5	19.0-22.1
Outcome	Alive at discharge	2,469	99.0	98.6-99.4
	Death	25	1.0	0.6-1.4

*PCI, percutaneous coronary intervention; CI, confidence interval; SD, standard deviation; CI, confidence interval; *25 missing values for this parameter (0.01%).*

dure report) was 98.5%. Interestingly, two-vessel PCIs were performed in 6.7% of the cases (Table 2).

Statistical analysis

Figure 1 shows the spatial variation of the total number of patients that underwent PCI per LAU, which roughly corresponds to the distribution pattern of the island's population. More importantly, however, the number of patients that underwent PCI per 1,000 population throughout the duration of the 4-year study period varied considerably across Crete and showed a range from 2.45 to 5.46 at p<0.001 (Table 3). Particularly striking is the difference in PCI rates between the two primary urban centres and most pop-

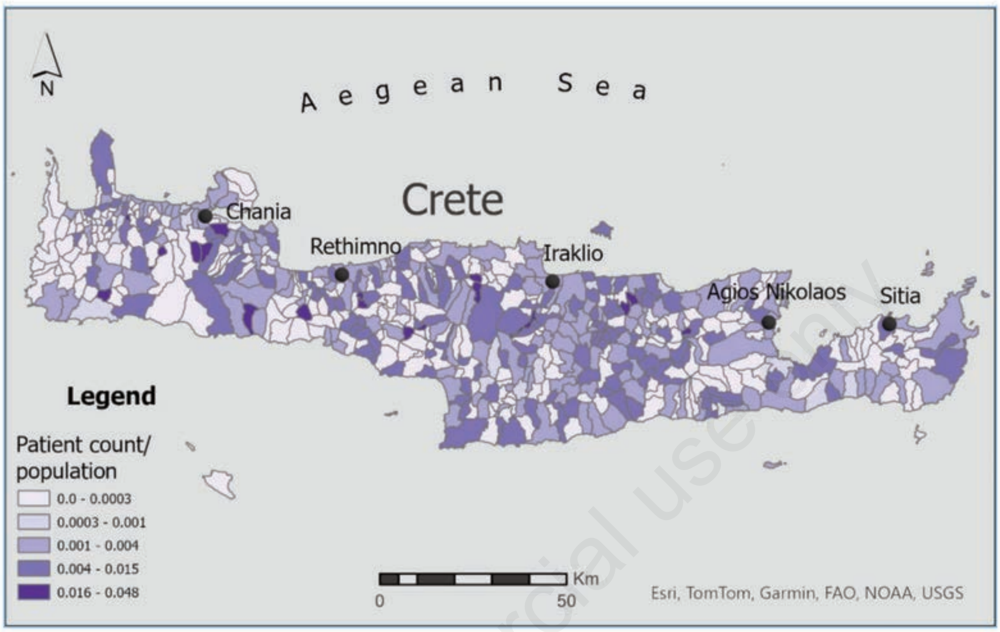

Figure 1. Patients subjected to percutaneous coronary intervention (PCI) per population in each local administrative unit (LAU) 2013-2016.

Table 2. Specific details of the percutaneous coronary interventions (PCIs).

Parameter	N	%	95%CI
Indication for PCI			
ACS	1,233	57.0	55.1-59.0
Unstable angina pectoris	485	22.4	20.7-24.2
Ischemia by non-invasive testing	397	18.4	16.8-20.0
Valve disease	16	0.7	0.4-1.1
Investigation of myocardial disease	29	1.3	0.9-1.9
Other	393	18.2	16.5-19.7
Arteries treated with PCI			
Left circumflex artery	403	16.2	14.6-17.5
Right coronary artery	692	27.7	26.0-29.5
Left anterior descending artery	1,102	44.2	42.1-46.2
First obtuse marginal branch	105	4.2	3.4-5.0
First diagonal branch	60	2.4	1.8-3.1
Ramus intermedius	20	0.8	0.4-1.2
Peripheral coronary vessels	112	4.5	3.7-5.3
Severity of stenosis (% diameter)			
<50	7	0.3	0.1-0.5
51-70	186	7.8	6.7-8.9
71-90	1,309	54.7	52.7-56.7
91-99	187	7.8	6.8-8.9
100	705	29.4	27.7-31.2
Intervention outcome (as stated in PCI report)			
Unsuccessful	38	1.5	1.0-2.0
Successful with 1-vessel PCI	2,456	98.5	98.0-99.0
Successful with 2-vessel PCI	168	6.7	5.8-7.7

ACS, acute coronary syndrome; CI, confidence interval.

ulous municipalities of the island, namely Heraklion and Chania (2.45 and 5.08, respectively) at $p<0.001$, whereas no significant difference was observed in the PCI rates between urban and rural areas (data not shown).

Ordinary Least Squares (OLS)

The dependent variable in the OLS analysis was the severity of coronary stenosis treated with PCI (% diameter), while the independent variables were the percentage of females, age, acute setting, presence of angina symptoms, ischemia detected by non-invasive testing, smoking and family history of early-onset CVD. The results are summarized in Table 4. Clinical presentation as ACS, presence of angina, smoking and positive results by non-invasive testing for ischemia showed a global relationship with stenosis severity, with ACS giving the strongest result (Table 4). The relationship between stenosis severity on the one hand, and female sex and family history of early-onset CVD on the other, was negative, although statistically weak in terms of significance. The AICc was 4230.46 and the overall as well as the adjusted R^2 was 0.96, showing that 96% of the variation of stenosis could be explained by the explanatory variables. The values of the variance inflation factor (VIF) indicated no bias due to multicollinearity.

Table 3. Percutaneous coronary interventions (PCI) by municipality 2013-2016.

Municipality	PCI procedures pereformed	Population 2011 Census	PCIs performed per 1,000 population
Minoa Pediados	86	1,7563	4.9
Chersonisos	132	26,717	4.94
Arhanes-Asterousia	90	16,692	5.39
Heraklion	884	173,993	5.08
AghiosVassilios	35	7,427	4.71
Sfakia	9	1,889	4.76
Anogia	13	2,379	5.46
LassithiPlateau	13	2,387	5.44
Malevizi	123	24,864	5.03
Festos	94	24,466	3.84
Viannos	23	5,563	4
Apokoronas	48	12,807	4.13
Rethimno	193	55,525	3.48
Gortys	52	15,632	3.33
Milopotamos	49	14,363	3.41
Mirabello	72	27,074	2.65
Ierapetra	80	27,602	2.9
Chania	266	108,642	2.45
Kantanos-Selino	16	5,583	2.87
Platanias	43	16,874	2.55
Sitia	45	18,318	2.46
Kissamos	24	10,790	2.22
Amari	14	5,915	2.37

Table 4. Global regression analysis by ordinary least squares (OLS).

Variable	Coefficient	SEt-statistic	
Intercept	1.456165	0.578295	2.518031
Sex	-0.069531	1.881144	-0.036962
Age	1.097046	0.024640	44.522632
Presentation as ACS	16.137885	1.784221	9.044780
Presence of angina	11.151140	1.837115	6.069920
Ischemia by non-invasive testing	10.768360	1.987062	5.419236
Smoking	6.944992	1.456406	4.768584
Family history of early-onset CVD	-2.042527	4.987225	-0.409552

ACS, acute coronary syndrome; CVD, cardiovascular disease; SE, standard error.e.

The formula (1) of OLS in this circumstance could be expressed as:

$$\text{Stenosis severity (\% diameter)}=1.456-(0.07\times\text{Sex})+(1.097\times\text{age})+(16.138\times\text{presentation as ACS})+(11.151\times\text{presence of angina})+(10.768\times\text{evidence of ischemia by noninvasive testing})+(6.945\times\text{smoking})+(2.043\times\text{family history of early-onset CVD}) \quad \text{(Eq. 1)}$$

Figure 2 presents the residuals of the OLS analysis, i.e. the difference between the actual value and the value predicted by the model, while Moran's *I* for OLS residuals, which is a useful indicator of spatial auto-correlation shows that the residuals are random (Moran's I=0.004775, z-score=1.212442) (Komajda *et al.*, 2016). The OLS model captures the overall relationships between variables and stenosis severity across Crete adequately but fails to indicate the potential spatial autocorrelation of the residuals.

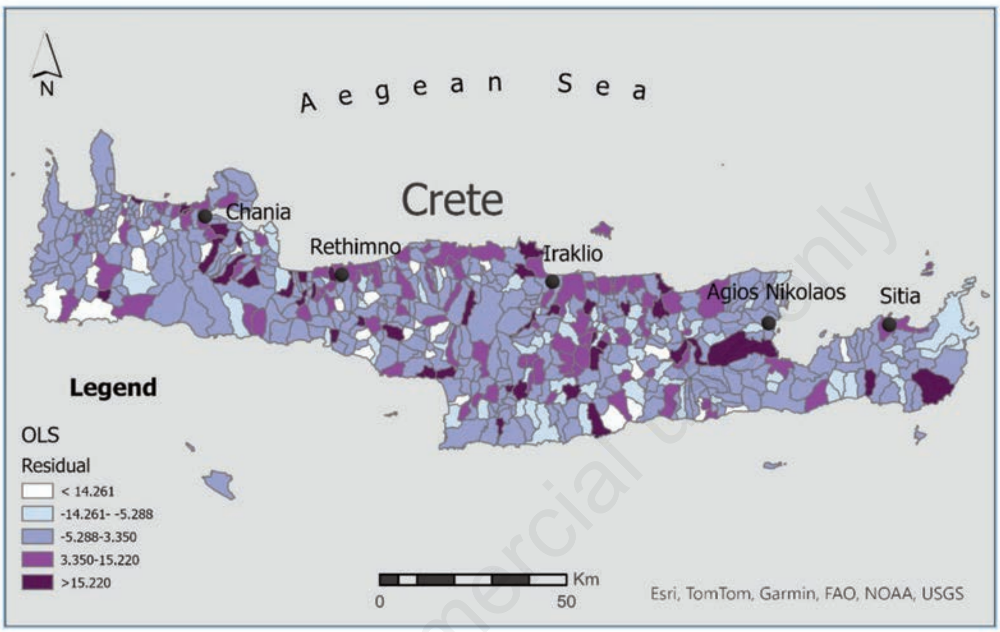

Figure 2. Map of the residuals of the OLS analysis.

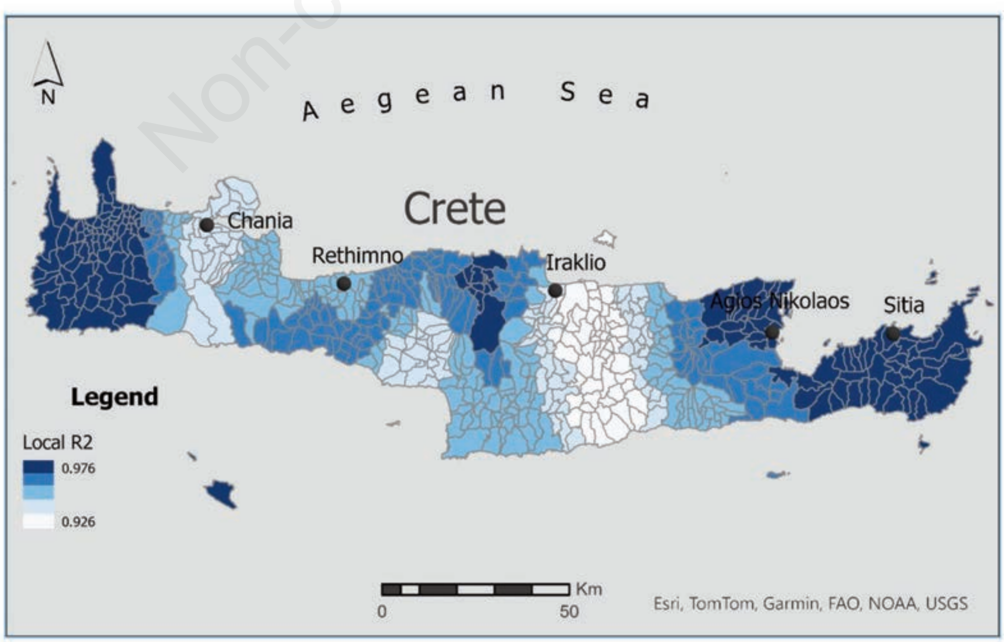

Figure 3. Local R^2 (use of Natural Breaks Jenks for the classification).

Geographically weighted regression (GWR)

The model used in this case was the Gaussian kernel function (Chalkias *et al.,* 2013), one of the most commonly used kernel types in GWR analyses. It assigns weights to neighbouring observations based on their distance from the target location, with closer observations receiving higher weights. The neighbourhood type, was a fixed-distance band approach, where the neighbourhood size (bandwidth) was set to a predetermined distance. Specifically, a fixed-distance bandwidth approach with a specified distance threshold to define the neighbourhood for each observation was used. The AICc was 4195.85. Although the AICc is not an absolute measure of goodness of fit, is useful for comparing models with different explanatory variables as long as they apply to the same dependent variable. If the AICc values for two models differ by more than 3, the model with the lower AICc value is held to be better. AICc value is one way to assess the benefits of moving from a global regression model (OLS) to a local one (GWR). Table 5 provides the GWR statistic results in this study. Although, the R^2 values are continuous and only vary slightly, the use of discrete classes allows for easier interpretation and comparison of regions with varying levels of model fit. For the local R^2 (Figure 3), the values range between 0.0 and 1.0 and indicate how well the local regression model fits observed y values (*i.e.* the depended variable). Very low values indicate that the local model is performing poorly. Mapping local R^2 values to notice where GWR predicts well and where it predicts poorly may provide clues about important variables that may be missing from the regression model.

In GWR, the negative and the positive values of the coefficients are crucial. As outlined in Figure 4, the coefficient of the percentage of females varies from negative to positive and again to negative within the west-east axis of Crete. This is means that in the western part of Crete (the Chania Region) female sex was found to correlate negatively to coronary stenosis severity (first class in the figure), while in central Crete (the Heraklion area) females appear to correlate positively to the this (fifth class in the

Table 5. Results of geographically weighted regression

Variable	Minimum	25% quartile	Median	75% quartile	Maximum	ST dev
Intercept	0,662195	1,4550415	1,4550415	1,78922025	1,990332	0,353766
Sex	-4,870044	1,45205	1,45205	2,73340525	5,751118	2,771207
Age	1,017134	1,085426	1,085426	1,12187225	1,287514	0,062138
Presentation as ACS	5,498967	14,7992455	14,7992455	18,9819675	23,31868	4,438639
Presence of angina	-4,848544	10,6004765	10,6004765	14,228133	22,07066	5,11491
Ischemia by non-invasive testing	-2,258985	9,2174995	9,2174995	14,9991955	20,06102	5,679353
Smoking	-2,176798	7,8721675	7,8721675	9,078355	11,30613	2,505885
Family history of early-onset CVD	-29,819254	1,379145	1,379145	3,19533425	9,481173	11,17707

ACS, acute coronary syndrome; CVD, cardiovascular disease; ST dev, standard deviation.

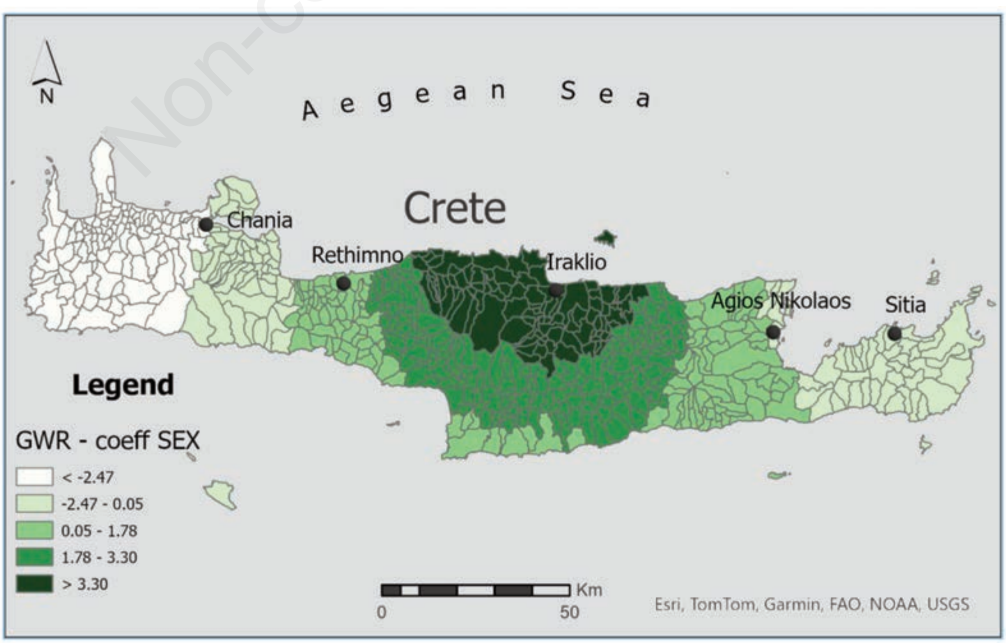

Figure 4. Variation of the coefficient of the percentage of females (SEX).

figure). These spatial variations in the relationship between the female sex and coronary stenosis severity may be influenced by several factors, including demographic differences, socioeconomic status, and access to healthcare services. Figure 5 presents the variation of the coefficient of age. All the coefficients are positive, meaning that age is positively correlated to stenosis in the entire study area. Figure 6 demonstrates the variation of the coefficient of the percentage of patients with ACS. All the coefficients are positive, and thus the presentation as ACS is positively correlated to stenosis severity.

Likewise, as shown in Figure 7, the coefficient of the percentage of patients with angina symptoms varies throughout the west-east axis of Crete. More precisely, in the western part of Crete, presence of angina is negatively correlated to stenosis severity (first class in the figure), while in Rethimnon and in the eastern part of Crete (Sitia Region) angina appears to correlate positively to stenosis severity (fifth class in the figure). Similarly, Figure 8 indicates that the coefficient of the percentage of patients with indications of ischemia on non-invasive testing for CAD varies throughout the west-east axis of Crete. In particular, in the western

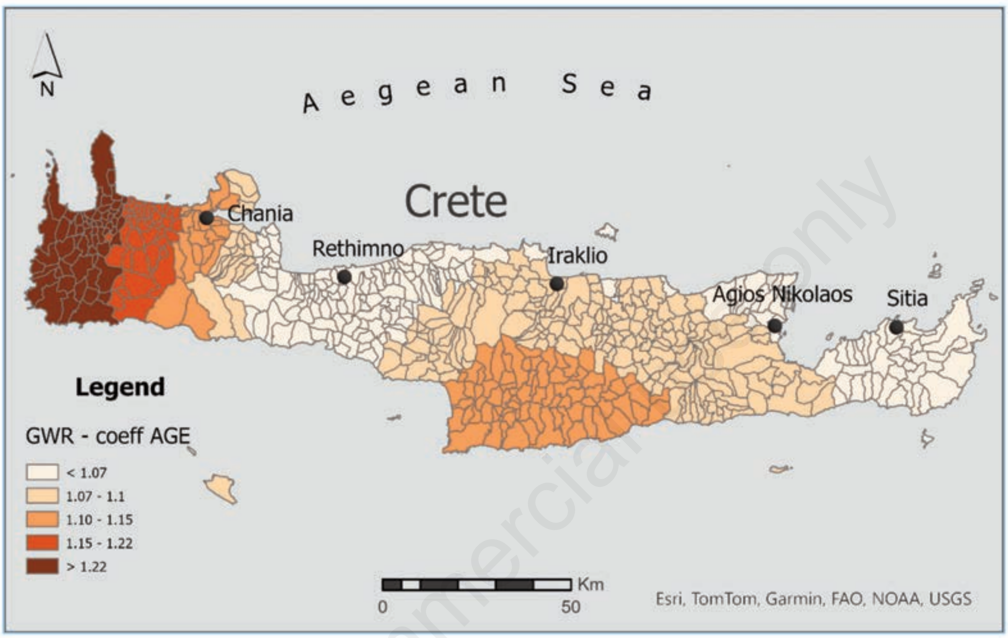

Figure 5. Variation of the coefficient of age.

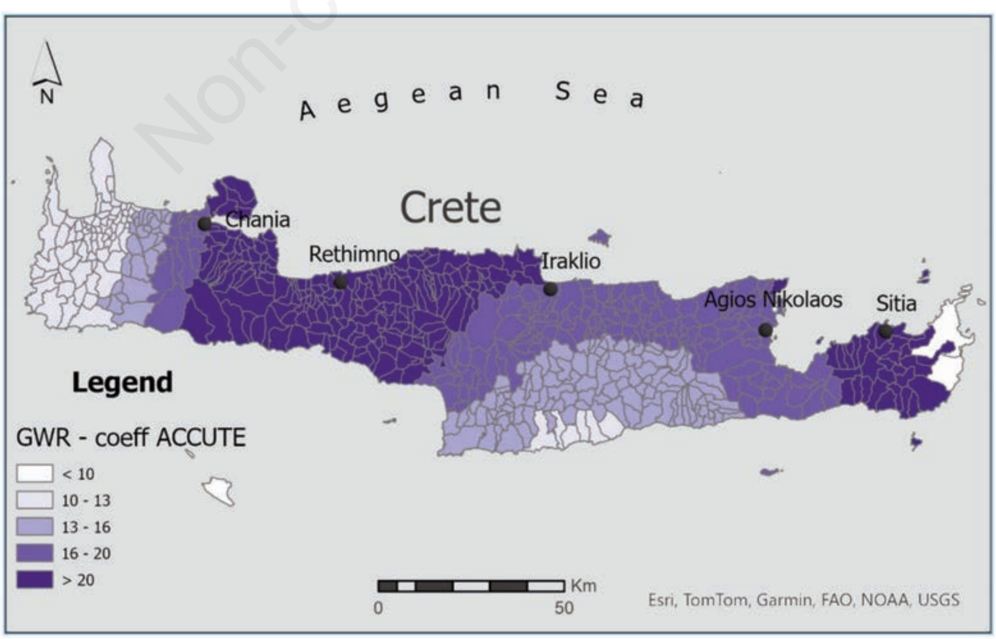

Figure 6. Variation of the coefficient of the percentage of presentation as ACS.

part of the island evidence of ischemia is negatively correlated to stenosis severity (first class in the figure), with the association becoming positive (fifth class in the figure) in eastern Crete. With respect to smoking (Figure 9), patients who were habitual smokers showed a negative correlation to stenosis severity in the eastern part of Crete and near Rethimnon (first class in the figure), while the opposite was true for the north-western part of the island (fifth class in the figure). Finally, the coefficient of the percentage of patients with family history of early-onset CVD varied throughout Crete (Figure 10), with a negative correlation to stenosis severity being apparent in the western part of Crete (first class) and a positive correlation in central Crete (Rethimnon and Heraklion regions - fifth class in the figure). The variable that demonstrated the strongest correlation to stenosis severity in the present analysis was presentation as ACS, as highlighted by both the OLS and GWR models. The GWR model, in particular, revealed that this relationship was not uniform across the study area as the residuals of GWR (for residuals: Moran's *I*=-0.001077, z-score=0.122157).

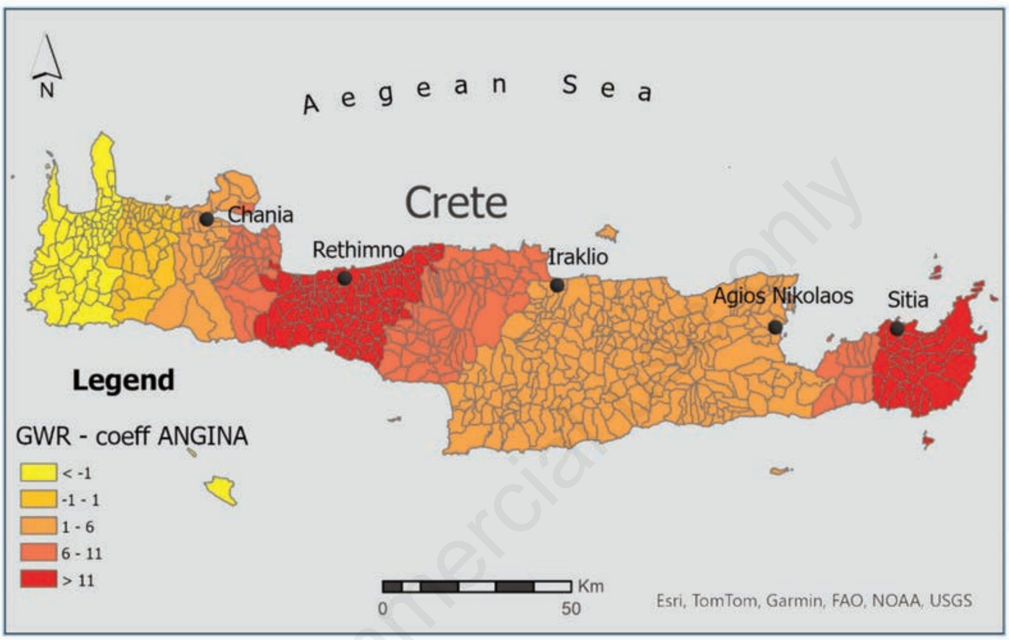

Figure 7. Variation of the coefficient of the percentage of presence of angina symptoms.

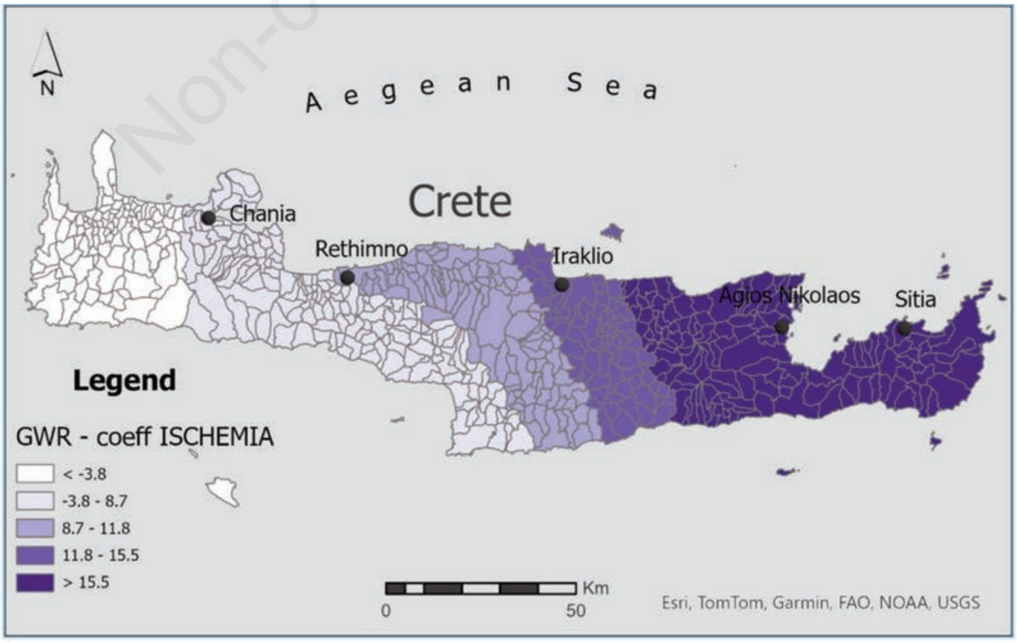

Figure 8. Variation of the coefficient of the percentage of evidence of ischemia on non-invasive testing.

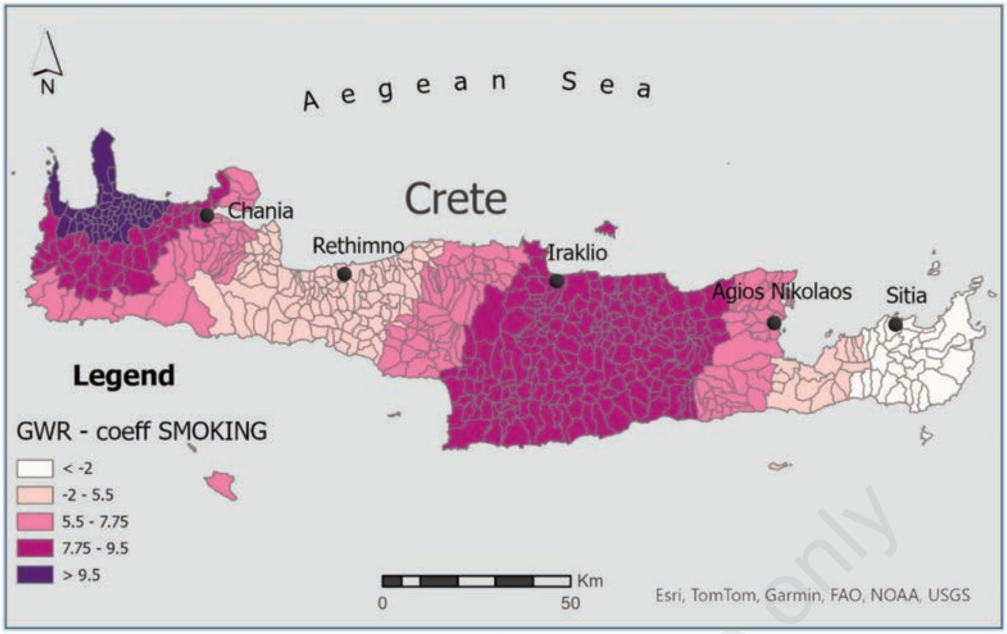

Figure 9. Variation of the coefficient of the percentage of smoking.

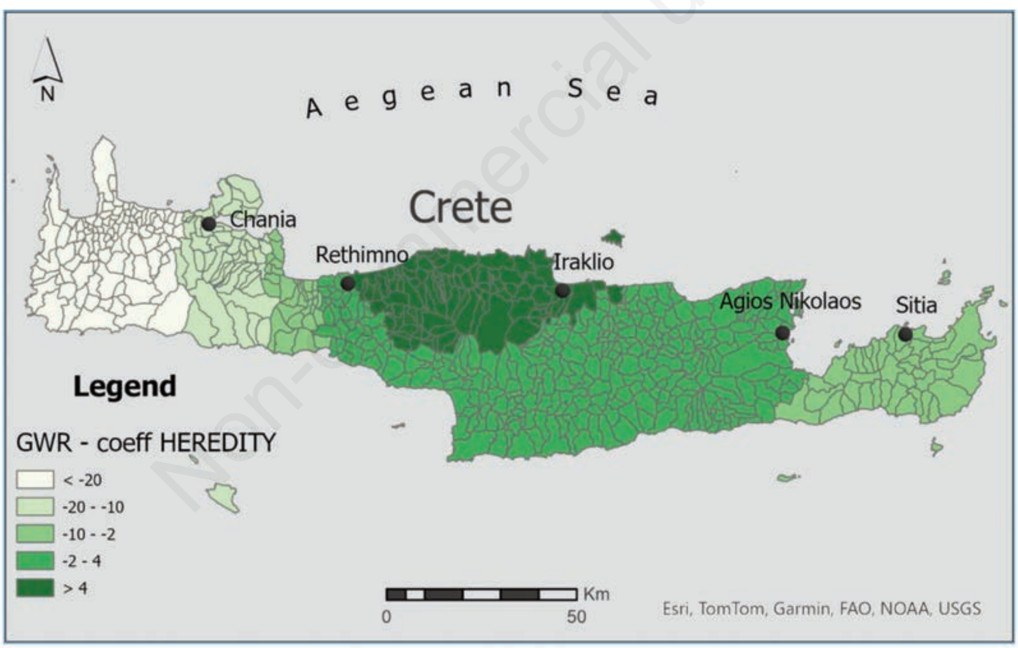

Figure 10. Variation of the coefficient of the percentage of family history of early-onset CVD.

Discussion

We aimed to examine how various demographic and clinical factors influence the severity of coronary artery stenosis among patients undergoing PCI. By investigating these inter-regional differences in treatment outcomes, we sought to provide insights into the effectiveness of PCI interventions and potential disparities in patient care across different geographical areas within Crete. The annual increase (>15% per year) in PCIs performed on an urgent basis observed during the study period reflects the considerable improvement that has been achieved in healthcare infrastructure allowing timely referral of an increasing proportion of ACS patients to the local cardiac catheterization reference centre.

In our study population, a strikingly high male-to-female ratio (4.8:1) was observed, which is much higher than the 2.3:1 recent epidemiological data suggest (Komajda *et al.,* 2016). It is unclear whether this truly reflects an analogous difference in the prevalence of obstructive CAD between males and females in the Cretan population, or merely a lower referral rate of females with possible

CAD for cardiac catheterization and potentially for PCI, and further research is required to elucidate the aetiology underlying this observation. The vessel most frequently treated with PCI was the left anterior descending artery (44.2%), followed by the right coronary (27.7%) and circumflex coronary arteries (16.2%), with the respective percentages being grossly consistent with international literature (Chhabra *et al.,* 2018).

Similarly, the fact that uPCI was accompanied with higher in-hospital mortality than ePCI is in agreement with what has been reported in other studies, as is the case for the association between length of stay and mortality (Bauer *et al.,* 2011). In addition, both procedural failure and in-hospital mortality –the primary outcome indices of our study- were shown to positively correlate to stenosis severity, which is also in accordance with other reports (Hannan *et al.,* 2018). With respect to variables positively associated to coronary stenosis severity, as expected, presentation with a clinical picture compatible with ACS demonstrated the strongest correlation in our study population.

Local-based models, such as GWR, are valuable exploratory methods for investigating local variations in the relationship between stenosis severity and clinical parameters (explanatory variables). The spatial analysis yielded some notable findings: A remarkable inter-municipality variation in PCI rates was observed, with the number of PCI procedures performed during the 4-year study period per 1,000 of population ranging from minimum 2.45 to maximum 5.46 across the island's municipalities (Table 3). Importantly, the striking difference that was observed in PCI rates between the two primary urban centres of Crete Heraklion (5.08/1,000) vs Chania (2.45/1,000), which do not differ significantly in terms of demographics was unexpected and warrants further investigation. It should be emphasized that the patient transfer time to UHH (the sole cardiac catheterization centre) from Chania General Hospital to UHH is normally less than 2 hours, which permits the preference of primary PCI over intravenous thrombolysis as a re-perfusion modality in STEMI cases. Moreover, CAD management strategies are consistent throughout all Cardiology Departments of Cretan hospitals, while the cardiac catheterization referral system is well-defined and accessible to all cardiologists. This suggests that the aforementioned difference in PCI rates between the island's most populous municipalities cannot be adequately explained by the absence of a primary PCI-capable laboratory in Chania during the study period, but could instead reflect a true difference in the prevalence of obstructive CAD. Future research aiming to elucidate this paradox should primarily focus on potential differences in the prevalence and perhaps most importantly the degree of control of well-established cardiovascular risk factors, as well as in the efficiency of primary healthcare between the populations of the two largest cities of Crete. In addition, no distinct urban versus rural area predominance pattern was identified by the spatial analysis with respect to 4-year PCI rates, suggesting that the negative effect inherently linked to the urban environment, such as pollution, psychological and occupational stress might not have been significant in Crete (Panagiotakos *et al.,* 2005; Patel *et al.,* 2010; Namayande *et al.,* 2016; Alston *et al.,* 2017; Mena *et al.,* 2018; Tong *et al.,* 2019).

Further, the degree and direction (positive versus negative) of correlation between age, sex, presence of angina symptoms, presence of evidence of inducible myocardial ischemia on non-invasive testing and smoking status on the severity of the coronary stenosis lesion that was treated with PCI (% diameter) varied significantly across the island, with specific geographical patterns observed in each case. It is uncertain whether these variations could be of clinical significance, because the severity of CAD in a given patient is not adequately described solely by the % luminal stenosis of the single lesion that was judged to be amendable to treatment with PCI. Nonetheless, the geospatial patterns outlined above are remarkable and require further investigation.

The fact that females in the western part of Crete (the Chania Region) were found to correlate negatively to coronary stenosis severity, while they correlated positively in central Crete (the Heraklion area) is probably multifactorial requiring further research to reveal the underlying mechanisms driving this particular spatial pattern.

Our study has several limitations, the most important being its retrospective nature and reliance on information available either through the electronic patient records of the UHH, where admission diagnosis is not always entered directly by medical personnel and some ICD-10 codes might be inaccurate, or through the PCI-procedure reports database, in which key clinical parameters such as symptoms and results of non-invasive ischemia testing are mentioned with a varying degree of completeness. However, to the best of our knowledge, the hereby presented work constitutes the first effort to provide comprehensive geospatial epidemiological data of CAD and, in particular, at a LAU level in a major administrative subdivision of Greece.

Conclusions

The findings of our study reflect the potential of geospatial epidemiology in identifying significant inter-regional differences in the incidence or prevalence of CAD, even within the margins of a relatively closed and genetically homogenous population, such as the one of Crete. Despite the fact that, at present, we do not have sufficient evidence to adequately support possible etiological explanations of the variations observed between LAUs in PCI rates and the impact of several clinical parameters on the severity of coronary stenotic lesions, our work can set the basis for the conduct of future research to elucidate the clinical significance of our observations, with the ultimate aim to facilitate efficient healthcare strategies planning.

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