

A Spatiotemporal Analysis of Hemodialysis Incidence Rate and Impact of the COVID-19 Pandemic on the End-Stage Kidney Disease Trend

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Introduction. Limited research has been conducted on the spatial trend of end-stage kidney disease (ESKD), particularly hemodialysis (HD), in developing countries. This is problematic considering the growing demand for dialysis services in these regions. To bridge this research gap, this study evaluates the spatial trend of chronic dialysis incidence rates over a significant period (2007 to early 2021) in a large population, while also investigating the influence of the COVID-19 pandemic on this trend.

Methods. We used data from the Shiraz University of Medical Sciences Specific Diseases Affairs database (2007-2021) on 8,368 dialysis patients. A Bayesian spatiotemporal model analyzed the data to estimate ESKD trends and relative risks with hemodialysis in 29 counties.

Results. Among the patients receiving maintenance dialysis for end-stage kidney disease (ESKD), 3,348(40%) were female and 5,020(60%) were male. The average age was 57.58 ± 17 , with a median age of 56 (2-98) years. The standardized incidence rate in 2007 was 0.78, while in 2020-21, it increased to 0.86. The estimated mean relative risk was 1.20, ranging from 0.43 to 4.35. We observed a consistent fixed trend with a coefficient of 0.99. During the COVID-19 pandemic and outside of it, we noticed an increased spatiotemporal interaction in the central and northern regions of the province, despite the temporal trend remaining relatively stable.

Conclusion. Our study reveals previously unexplored geographic disparities in ESKD incidence within Fars province from 2007 to 2021. The notable increase in dialysis cases in the central and northern regions emphasizes the urgency of addressing this public health concern.

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INTRODUCTION

Chronic kidney disease (CKD) is a significant global public health issue, affecting over 850 million individuals worldwide.¹ By 2040, it is expected to rank as the fifth leading cause of death worldwide.²

For patients with CKD in irreversible stages, such as end-stage kidney disease (ESKD), either hemodialysis or kidney transplantation is necessary to manage renal dysfunction.³ The incidence rate of ESKD is increasing worldwide, with 2.6 million

ESKD patients receiving renal replacement therapy (dialysis and transplantation) in 2010, which will rise to 3.9 million in 2017.^{1,4}

While the overall incidence rate of ESKD has been on the rise, it is important to consider various geographic risk factors that may contribute to its occurrence. Factors such as age, sex, race, diabetes mellitus, socioeconomic status, level of deprivation, urban or rural residence, and proximity to healthcare facilities can influence ESKD risk.^{5,6} Several studies have investigated these risk factors of ESKD, taking into account spatial dependence. For instance, research conducted in France has identified significant geographic risk factors, including socioeconomic status and accessibility to healthcare, which impact ESKD incidence.⁶⁻⁸ Hemodialysis is a well-known procedure used to treat patients with ESKD by removing waste products and excess fluid from their blood.⁹ As part of their treatment, hemodialysis patients typically require dialysis sessions at least three times a week.¹⁰ Therefore, the accessibility to dialysis facilities plays a crucial role in the survival of these patients.¹¹ Moreover, the incidence and prevalence rates of ESKD are increasing in developing countries, necessitating the establishment of additional dialysis centers.¹²⁻¹⁴ This challenge is present in Iran, a developing country, and is notably significant in Fars Province, the largest and most populated province in the south. Despite the existence of documented evidence on regional variations in hemodialysis incidence, there is no study investigating the geographic pattern of hemodialysis incidence specifically in Fars province.

In this regard, this study aims to examine the geographical distribution of hemodialysis incidence rates in Fars province. It will analyze the trend and rate of incidence, using a Bayesian spatiotemporal model. Furthermore, approximately three years of data were gathered during the COVID-19 pandemic (2019-2021). Many articles have been published about the impact of severe COVID-19 on the increased incidence rate of acute kidney injury (AKI).¹⁵⁻¹⁷ This increase has coincided with an increase in the incidence of ESKD. As a further aim, the study will assess the influence of the COVID-19 pandemic on the spatial trend of ESKD incidence, specifically with hemodialysis (HD), across smaller areas. The focus of this research is on 29 counties within Fars province, covering the period from 2007 to 2021.

MATERIALS AND METHODS

Study area

In this retrospective study, we collected data on hemodialysis patients in Fars province from 2007 to 2021. Fars Province, situated in southern Iran, is the most densely populated region in the country. It consists of 29 counties and has a population of approximately 4.80 million people, with males comprising 51% of the population. According to the Census by the Statistical Centre of Iran, Fars Province's population remained relatively stable during the study period (SCI).¹⁸ Additionally, we acquired the annual population at risk from the SCI. Figure 1 illustrates that Shiraz, the capital city of Fars province, has the highest at-risk population.

Data

The electronic database for Specific Diseases Affairs at Shiraz University of Medical Sciences (SUMS) serves as a comprehensive registry for patients who have started treatment for ESKD in 29 metropolitan regions within Fars province. As the sole registry center in Fars province, this database contains information on all hemodialysis patients. All hemodialysis patients were included as participants throughout the study period, which extended from 2007 to 2021. Patients residing in neighboring provinces who registered in this longitudinal database were excluded from the study.

Statistical analysis

The observed number of new cases in a geographic unit (county) was assumed to follow a Poisson distribution. The Bayesian spatiotemporal models by extending the BYM (Besag-York-Mollies) model are the most popular full Bayesian models which have been explained in many studies in detail.¹⁹ In this study, we employed the direct method to calculate the standardized incidence ratio (SIR). SIR can be calculated as a ratio between the number of observed cases O_{ij} and the number of expected cases e_{ij} in the i th area ($i = 1, \dots, n$) and j th period ($j = 1, \dots, t$), where e_{ij} can be calculated by using census population counts p_{ij} as $\lambda_j = \sum_{i=1}^n O_{ij} / \sum_{i=1}^n p_{ij}$ and $e_{ij} = \sum_{j=1}^t p_{ij} \lambda_j$.

The spatiotemporal trend model can be written as

$$\eta_{ij} = \alpha + v_i + u_i + (\delta_i + \beta)t$$

In this model as suggested by Bernardinelli *et al.* the intercept (α) was assumed to follow an improper

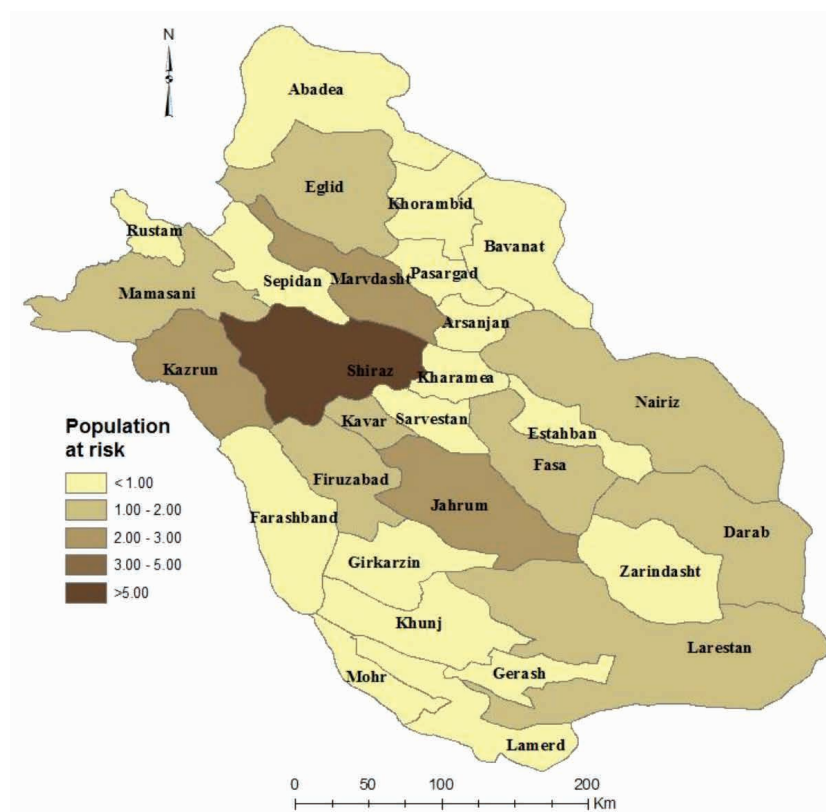


Figure 1. Map depicting general population density (scaled 1/100,000) for the 29 counties in Fars province.

uniform and normal distribution with a mean of zero and a small variance as prior, respectively. The structured spatial (u_i), the unstructured effects (v_i), and interaction between space and time (δ_i) are random effects and the precision parameters, controlling the amount of variability for the random effects, were assumed to follow a gamma distribution (0.50, 0.0005). Outcomes calculated as relative risk $RR = \exp(v_i + u_i)$ and temporal trend $TT = \exp(\delta_i + \beta)$.

To assess spatial effects on relative risk, we coded in the Open BUGS version 3.2.3 and R 4.3.2. The model ran two chains with 1000 samples as burn-in and 10,000 samples as iteration. Convergence for the chains was confirmed by auto-correlations, trace, and densities plots.²⁰ Detailed explanations of these models can be found in various references, such as Lawson(2021)²¹ and Blangiardo, Cameletti (2015).¹⁹ The results were visualized on maps using ArcGIS 10.1.²²

RESULTS

During the period from 2007 to 2021, we identified a total of 8,368 new cases of hemodialysis in Fars

province. These cases represent individuals who commenced maintenance hemodialysis treatment. The mean age of the patients was similar among females and males, with an average of 57.53 ± 17.23 for females and 57.54 ± 17.86 for males. Among them, 3,348 (40%) were females and 5,020 (60%) were males. Furthermore, it was observed that 3,298 patients (39%) were from Shiraz, which is the capital of Fars province.

Table 1 provides an overview of new hemodialysis cases reported annually in Fars province over 15 years. The table includes information on the incidence rate per 100,000 population, age, as well as the number of females and males. The incidence rate of hemodialysis has been increasing steadily from 2007 to 2021. Age data analysis indicates that the average age of individuals increased from 2008 to 2018 and then remained constant until 2021. Analyzing the male-to-female ratios, the highest ratio of 2.35 was observed in 2007, indicating a higher proportion of males. In contrast, the lowest ratio of 1.01 was recorded in 2011, suggesting a more balanced distribution between males and females.

Table 2 provides information on the number of

Table 1. Incidence of hemodialysis per 100 000 persons between 2007 and 2021

year	No. of cases	Incidence rate (95% CI)	Age at onset (year)		No. of cases: M/F	M/F ratio	M to F P-value
			Mean $\pm$ SD	(Min-Max)			
2007	57	1.31 (0.97-1.65)	51.67 $\pm$ 17.33	(5-78)	40/17	2.35	.002*
2008	114	2.63 (2.15-3.11)	51.45 $\pm$ 17.41	(2-86)	76/38	2.00	< .001*
2009	136	3.14 (2.61-3.66)	54.20 $\pm$ 17.56	(8-87)	78/58	1.34	.086
2010	166	3.83 (3.24-4.41)	57.23 $\pm$ 15.85	(2-87)	102/64	1.59	.003*
2011	276	6.36 (5.61-7.11)	55.23 $\pm$ 16.66	(9-86)	139/137	1.01	.904
2012	422	9.18 (8.30-10.06)	55.57 $\pm$ 17.10	(5-90)	228/194	1.18	.098
2013	536	11.7 (10.67-12.65)	56.20 $\pm$ 17.86	(4-91)	332/204	1.63	< .001*
2014	637	13.86 (12.78-14.93)	55.86 $\pm$ 17.20	(5-92)	383/254	1.51	< .001*
2015	707	15.38 (14.25-16.51)	57.33 $\pm$ 17.19	(7-91)	426/281	1.52	< .001*
2016	813	17.69 (16.47-18.90)	58.64 $\pm$ 17.06	(8-94)	478/335	1.43	< .001*
2017	850	17.52 (16.34-18.7)	58.04 $\pm$ 17.38	(7-94)	507/343	1.48	< .001*
2018	863	17.79 (16.60-18.98)	58.87 $\pm$ 17.76	(3-96)	545/318	1.71	< .001*
2019	844	17.40 (16.22-18.57)	58.75 $\pm$ 17.86	(4-96)	495/349	1.42	< .001*
2020	856	17.64 (16.46-18.83)	58.23 $\pm$ 17.86	(6-93)	516/340	1.52	< .001*
2021	867	17.87 (16.68-19.06)	58.12 $\pm$ 18.17	(2-98)	544/323	1.68	< .001*

M: male, F: female

*indicates significant p-value.

Table 2. Model estimates of Hemodialysis incidence in Fars, south of Iran, from 2007 to 2021.

County	dialyze cases (n)	Population (n)	Standard incidence rate (SIR)	Relative Risk	Temporal Trend	Spatiotemporal interaction (δ)
Abadeh	156	97067	0.90	0.43	1.08	0.09
Arsanjan	68	43321	0.88	1.10	0.98	-0.01
Estahban	128	70874	1.01	1.11	1.00	0.01
Eghlid	120	111377	0.60	0.52	1.02	0.03
Bavanat	53	48486	0.61	0.73	0.99	0.00
Jahrom	532	211391	1.41	4.35	0.89	-0.10
Khorambid	58	47386	0.69	0.73	1.00	0.01
Khunj	129	42077	1.72	1.96	0.99	0.00
Darab	280	185801	0.84	0.68	1.03	0.04
Rostam	77	47705	0.90	1.25	0.97	-0.01
Zarindasht	86	65593	0.73	1.18	0.96	-0.03
Sarvestan	65	26873	1.35	1.48	1.00	0.01
Sepidan	102	94331	0.61	0.70	0.99	0.00
Shiraz	3298	1749926	1.05	0.68	1.05	0.06
Farashband	63	47696	0.74	0.66	1.02	0.03
Fasa	495	201472	1.38	3.69	0.91	-0.09
Firozabad	223	121775	1.02	1.25	0.99	0.00
Ghirkarzin	98	68027	0.81	0.88	1.00	0.01
Kazeron	563	278343	1.13	1.15	1.00	0.01
Larestan	315	149097	1.18	1.65	0.97	-0.02
Lamerd	130	82169	0.89	1.01	0.99	0.00
Marvdasht	615	310540	1.11	1.28	0.99	0.00
Mamasani	192	125952	0.85	1.01	0.99	0.00
Mohr	72	56817	0.71	1.06	0.97	-0.02
Nairiz	156	112152	0.78	0.94	0.99	0.00
Pasargad	54	31986	0.94	1.06	0.99	0.01
Gerash	55	90280	0.34	0.50	0.97	-0.02
Khavar	89	104000	0.48	0.54	1.00	0.01
Kharameh	96	61000	0.88	1.35	0.96	-0.03
Total	8368	4683514	0.91	1.20	0.99	0.00

new hemodialysis cases, the standardized incidence rate (SIR), estimated relative risk, temporal trend, and Spatiotemporal interaction (speed). The mean values for SIRs and relative risks were 0.91 and 1.20, respectively.

Figure 2 shows maps illustrating the geographical distribution of hemodialysis incidence rates across the 29 counties of Fars province. The intensity of darker colors on the maps corresponds to regions with higher rates of hemodialysis incidence, indicating unfavorable conditions in terms of risk, trend, and speed of the disease.

Figure 2(A) presents the estimated relative risks using the BYM2 model. Notably, Fasa and Jahrom exhibited the highest relative risks for hemodialysis incidence, with values of 3.69 and 4.35 (standard deviation = 0.62, 0.71) respectively, indicating a significant level of risk in those areas. Furthermore, the spatiotemporal trend model estimated a time coefficient value of 0.99 (credible interval = 0.98, 0.99) for each subsequent year. This finding suggests a consistent and uniform trend of incidence across the Fars province. Furthermore, when examining the results of the Spatiotemporal trend model for each area in Figure 2(B), it becomes evident that Shiraz and Abadeh stand out with significantly higher coefficients representing the temporal trend. Specifically, Shiraz and Abadeh have values of 1.05 and 1.08 (standard deviation = 0.02, 0.01) respectively, indicating a notable and statistically significant temporal trend in those regions. Figure 2(C) displays the values of δ_i , representing the Spatiotemporal interaction or the speed of the

area-specific trend of incidence rate. When $\delta_i < 0$, it indicates that the trend in that area is less steep compared to the mean trend, whereas $\delta_i > 0$ suggests that the area-specific trend of incidence rate is steeper than the mean trend (global trend). Notably, Shiraz and Abadeh significantly stand out with values of 0.06 and 0.09 (standard deviation = 0.01, 0.02) respectively, indicating that their speed of trend is notably higher compared to the global trend.

Regarding the impact of the COVID-19 pandemic on the trend of hemodialysis incidence rate, there were no significant changes observed in the relative risk among consecutive years. Specifically, when examining specific areas, Shiraz and Abadeh exhibited a consistent and gradual increase in relative risk, both before and during the COVID-19 pandemic. Conversely, Jahrom and Fasa displayed a steady and gradual decrease in relative risk during the same period. These findings are illustrated in Figure 3(A), highlighting the stable and smooth nature of the relative risk trends in these areas, unaffected by the pandemic. In contrast, Figure 3(B) depicts the average value of the Spatiotemporal interaction, which exhibits a gentle slope both before and during the COVID-19 pandemic. In particular, when examining specific areas, we noticed that Shiraz and Abadeh displayed gradual and consistent increases in incidence speed, while Jahrom and Fasa highlighted a mild and declining trend in incidence speed throughout the same period. These observations highlight the smooth and mild stable nature of the incidence speed

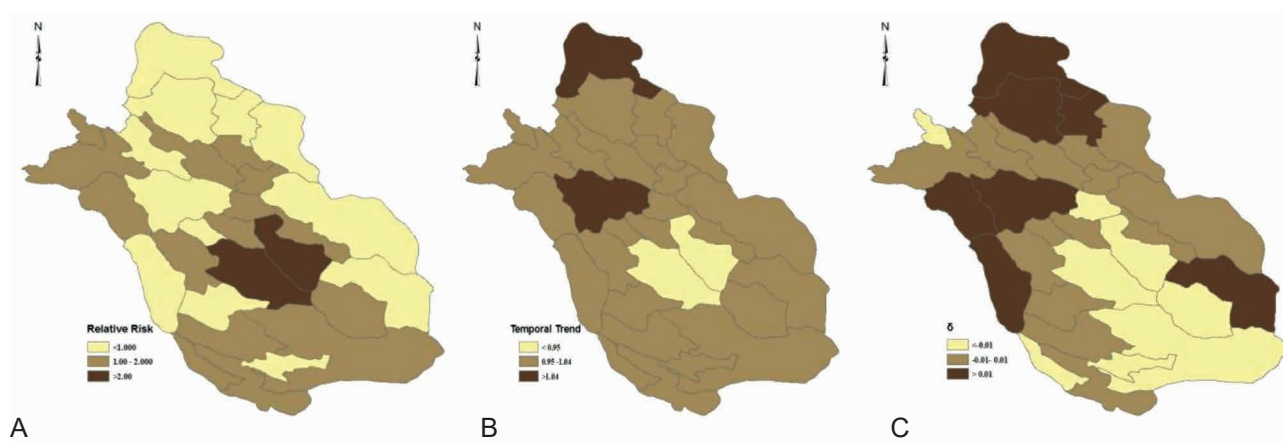


Figure 2. A general map of relative risks for hemodialysis incidence in Fars province between 2007-2021, estimated by the BYM2 model (A), A map of a temporal trend for hemodialysis incidence rate (B), A map of Spatiotemporal interaction (speed) for hemodialysis incidence rate (C).

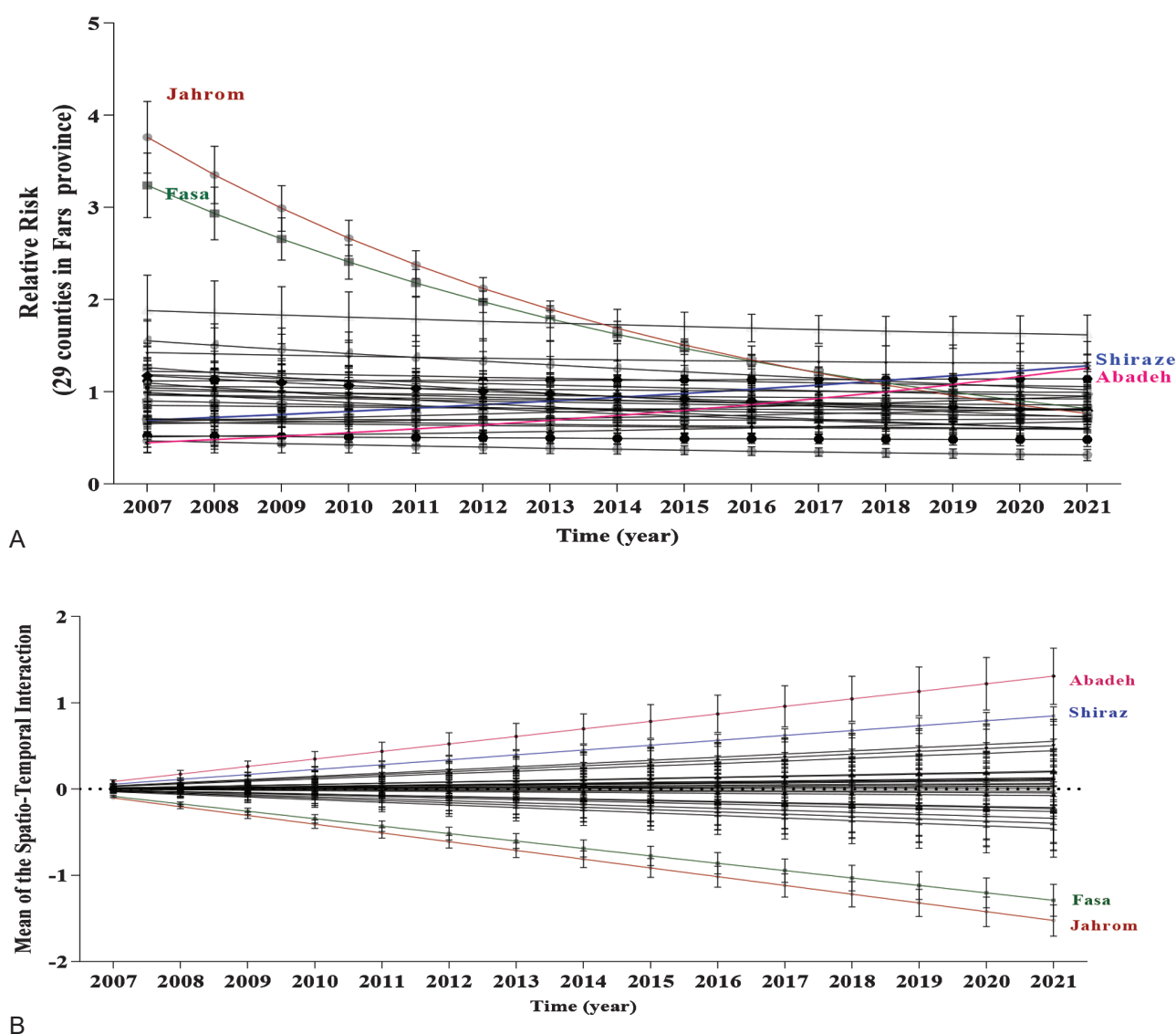


Figure 3. (A) Shows Relative Risk (29 counties in Fars province) between 2007 and 2021. (B) Shows the mean of the Spatiotemporal interaction between 2007 and 2021.

trends in these areas, unaffected by the presence of the COVID-19 pandemic.

DISCUSSION

To the best of our knowledge, this study represents the first attempt to assess the spatial distribution of hemodialysis incidence in Fars province. The researchers employed a Bayesian spatial model to generate maps depicting the hemodialysis incidence rate. The findings revealed that two regions, Jahrom and Fasa, situated between the central and southern parts of the province, characterized by hot and dry climates, exhibited the highest posterior means of relative risk during

the period from 2007 to 2021. However, it is worth noting that these two regions displayed a declining trend, albeit at a slower pace than the global incidence rate. In contrast, two zones, Darab and Shiraz, located in the northern and central parts of the province with cool and temperate climates, demonstrated the lowest posterior means of relative risk during the same period. Interestingly, these regions exhibited an increasing trend in incidence, surpassing the global incidence rate in terms of speed. Despite encountering the COVID-19 pandemic during the study period, the researchers observed no significant impact on the trend of chronic hemodialysis incidence.

The temporal trends in End-stage kidney disease (ESKD) incidence have been extensively studied, particularly about the incidence of renal replacement therapy (RRT). In the years leading up to 2000, there was a notable rise in the number of patients starting RRT in Western industrialized countries.²³ Several factors likely contributed to this trend, including an aging population, a higher prevalence of risk factors such as obesity and diabetes mellitus, and improved accessibility to dialysis treatment.^{24,25} Following the year 2000 and into the early 21st century, there have been indications of a shift towards stabilization and, in some cases, a reduction in the incidence of ESKD.²³ Regrettably, there is a lack of available data on temporal trends and geographical variations in RRT incidence in developing countries like Iran. However, our study aligns with previous research that has observed a stabilization in the incidence of RRT.²⁶⁻²⁹ This stabilization could potentially be attributed to improvements in the overall health status of the population as well as demographic characteristics specific to the counties under investigation. Nevertheless, it is worth noting that two counties, Darab and Shiraz, displayed an upward trend in RRT incidence with one of them being the capital of the province. This increase could potentially be attributed to factors such as improved accessibility to hemodialysis (HD) centers and the relocation of patients seeking access to one of Iran's prominent transplant centers. Additionally, the risks associated with residing in a large city, such as a sedentary lifestyle and exposure to air pollution, may contribute to the higher incidence rates. Furthermore, it is noteworthy that Shiraz, as the capital of Fars province, is also known as one of the major cities with a significant immigrant population. It is important to highlight that regional variations in RRT incidence have been the focus of several studies predominantly conducted in developed countries. However, limited research has been conducted on this topic in developing countries such as Iran.³⁰⁻³⁴ Multiple studies conducted in various countries, including Japan and Austria, have consistently identified significant regional disparities in the incidence of ESKD. These studies have highlighted that the incidence of diabetes mellitus and CKD may serve as potential underlying factors contributing to these regional variations.^{30,34} In a study

conducted in England, Dhoul *et al.* discovered that a combination of socio-deprivation factors and biomedical markers accounted for up to 40% of the incidence of RRT.³¹ Another study conducted in the UK highlighted the significant impact of access to health services on the variation of RRT incidence.³³ In a study conducted in the United States, researchers investigated the hypothesis that the prevalence of albuminuria (excess protein in the urine) and decreased estimated glomerular filtration rate (eGFR) is associated with region-specific incidence rates of ESKD. However, the study findings revealed only a modest correlation between these parameters and ESKD incidence. As a result, the researchers suggested that the burden of CKD may not fully explain the variations observed in ESKD incidence across different geographical areas.³² Thus, it can be concluded that regional variations in the incidence of ESKD are influenced by multiple factors and cannot be solely attributed to the prevalence of CKD or risk factors like diabetes mellitus (DM).

In Iran, there have been rapid changes in climate conditions and lifestyle.³⁵ However, we encountered limitations in our study as we did not have access to environmental covariates such as climate data, dietary patterns, sunlight exposure, industrial air pollution levels, and other factors specific to each region over the period from 2007 to 2021. This limited our ability to identify spatially-related risk factors accurately. It is important to note that Iran is a developing country, and its information registration system is continuously improving and evolving.

To address this issue, we recommend employing spatial models that incorporate areal covariates to identify environmental risk factors within the province. By utilizing such models, public health investigators and researchers can effectively prevent the incidence of chronic kidney disease and strategically establish hemodialysis centers in areas identified as high-risk based on our study results.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Code of Ethics: IR.SUMS.MED.REC.1400.227). All data were collected and analyzed in accordance Declaration of Helsinki to ensure the confidentiality and anonymity of participants.

INFORMED CONSENT

For this retrospective analysis of de-identified data, additional consent was waived by the ethics committee.

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AUTHOR CONTRIBUTION

N.S contributed to study conception, proposal writing, data analysis, and draft writing. SH.E. helped in cleaning data and discussion writing. M.B. was responsible for draft editing, draft revising, and manuscript preparation. F.N and M.T. and M.K. performed data collection. Z.SH. Contributed to study conception, and article revision. All authors reviewed the manuscript.

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DATA AVAILABILITY

Datasets are available from the corresponding author upon reasonable request.

CONSENT TO PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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