Background. Using time series and spatiotemporal analyses, this study aimed to establish an Early Warning System (EWS) for COVID-19 in Fars province Iran. Methods. A EWS was conducted on (i) daily basis city-level time series data including 53,554 cases recorded during 18 February–30 September 2020, which were applied to forecast COVID-19 cases during 1 October–14 November 2020, and (ii) the spatiotemporal analysis, which was conducted on the forecasted cases to predict spatiotemporal outbreaks of COVID-19. Results. A total of 55,369 cases were forecasted during 1 October–14 November 2020, most of which (26.9%) occurred in Shiraz. In addition, 65.80% and 34.20% of the cases occurred in October and November, respectively. Four significant spatiotemporal outbreaks were predicted, with the Most Likely Cluster (MLC) occurring in ten cities during 2–22 October ($P < 0.001$ for all). Moreover, subgroup analysis demonstrated that Zarrindasht was the canon of the epidemic on 6 October ($P < 0.04$). As a part of EWS, the epidemic was triggered from Jahrom, involving the MLC districts in the center, west, and south parts of the province. Then, it showed a tendency to move towards Zarrindasht in the south and progress to Lar in the southernmost part. Afterwards, it simultaneously progressed to Fasa and Sepidan in the central and northwestern parts of the province, respectively. Conclusion. EWS, which was established based on the current protocol, alarmed policymakers and health managers on the progression of the epidemic and on where and when to implement medical facilities. These findings can be used to tailor province-level policies to servile the ongoing epidemic in the area; however, governmental level effort is needed to control the epidemic at a larger scale in the future.
outbreaks, the surveillance system could act timely, prioritize times and locations for targeting interventions, allocate resources more efficiently, and improve decision-making in the area.

Time series data refer to a sequence of successive naturally temporal data, which are equally spaced in points of time. A time series analysis consists of methods for analyzing time series data and forecasting the future values based on the previously observed values [5]. Spatial and Temporal Scan (SaTScan) modeling discovers more about the space and time of an event occurrence. Space-time permutation scan statistic, which is derived from SaTScan, was first introduced by Martin Kulldorff in 2015 [6]. This model aims at determining whether the cases are distributed uniformly over time and space. The statistic utilizes scanning windows moving systematically across the study area to identify the clusters of cases. This modeling helps surveillance systems decide timely on more at risk areas [7]. Using one model output as another mode input, this study could develop a protocol of EWS in the area by (i) forecasting the COVID-19 cases, (ii) discovering the future space-time outbreaks of COVID-19, (iii) predicting the progression of epidemic, and (iv) having more control on the epidemic.

2. Methods

2.1. Study Design, Data Source, and Study Variable. Daily basis city-level time series data including 53 554 cases recorded in 26 cities of Fars province, Iran, during 18 February–30 September 2020 (225 days) were applied to forecast COVID-19 cases during 1 October–14 November 2020 (45 days). The cases were obtained from 44 COVID-19 sampling centers affiliated to Shiraz University of Medical Sciences (SUMS). All data were reported to SUMS either online, https://www.coronalab.sums.ac.ir, or by manual registration. There were no exclusion criteria, meaning that all cases were included in the study. The COVID-19 cases were the positive cases confirmed by real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR). Additionally, the geographical coordinates of the locations were obtained through Google-Earth (US Dept. of State Geographer 2021) based on the latitude-longitude coordinate system.

2.2. Case Study and Area. Fars province, the fourth most populated (4 852 274 dwellers) and widespread (122 608 km²) province amongst 31 provinces in Iran, is located at 27°3′ and 31°40′ northern latitude and 50°36′ and 55°35′ eastern longitude in south of Iran. It includes 26 cities, with Shiraz, the fifth most populated city in Iran, being the capital. Marvdasht, Jahrom, Fasa, Kazerun, Darab, Firoozabad, Lar, and Abade, also, are the most populated areas (more than 100 00 dwellers per capita). 67.6% of the province are urban dwellers (urban areas and suburbs), 31% are villagers (small towns and rural areas), and the rest are nomads (no fixed habitation who regularly move to and from the same areas breeding livestock) [8].

2.3. Statistical Analysis. Mean difference and Std. Error of difference were used to describe quantitative variables, and frequency (relative frequency) was used to describe qualitative variables.

The distribution of COVID-19 cases across cities and times are tested using independent-sample one way ANOVA and pair wise comparisons (LSD test). Additionally, time series analysis including (i) Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC), which are the estimators of the relative quality of time series models comparative to other models for a given set of data, (ii) Auto Correlation Function (ACF)/Partial Auto Correlation Function (PACF) sample/model, which assess the conformity of the observed and fitted pattern in the data, and (iii) residual analysis, which evaluates the presumptions of white noise parameter, was used to forecast the COVID-19 cases during 1 October–14 November 2020 (45 days). A set of time series models were applied, and the best ones were selected based on lower AIC/BIC scores, ACF/PACF conformity, and residual analysis.

Descriptions on time series models:

A simple additive decomposed time series model is

\[ x_t = m_t + s_t + e_t, \]

\( m_t \) is the trend, \( s_t \) is the seasonality, and \( e_t \) is the error or random white noise.

To be used to predict well founded values, a time series must be stationary, meaning that it should have a constant mean and variance across the time series. So, in order to allow forecasting, several time series models can be created including Autoregressive Model (AR), Moving Average Model (MA), and Autoregressive Moving Average (ARMA) model, which are used on stationary time series. Seasonal Autoregressive Moving Average (SARMA) model, however, is used for non-stationary time series.

Autoregressive Model: AR (p)

AR model uses observations from previous time steps as input to a regression equation to predict the value at the next step. It takes one argument, \( p \), which determines how many previous time steps will be input. The order, \( p \), can be determined by looking at the PACF. The PACF gives the partial correlation of a time series with its own lagged value, regressed of the time series at all shorter lags.

Moving Average Model: MA (q)

MA model is a time series model that accounts for very short-run autocorrelation. Basically, it states that the next observation is the mean of every past observation. The order of MA model, \( q \), can usually be estimated by looking at ACF plot.

Autoregressive Moving Average: ARMA (p, q)

ARMA and ARIMA models are simply a combination of an AR model and MA model.
The distribution of 53,554 COVID-19 cases by city and month is shown in Tables 1 and 2.

COVID-19 cases were not distributed uniformly across cities (test statistics $= 170.83$, df $= 25$, $P < 0.001$) and months (test statistics $= 21.3$, df $= 7$, $P < 0.001$) in Fars province during February 18–September 30, 2020. Pairwise comparisons of 53,554 COVID-19 cases by city and month have been shown in Tables 3 and 4.

COVID-19 cases were significantly higher in Shiraz than those in 25 other cities ($P < 0.05$ for all). Jahrom had more cases than Farashband, Khonj, Darab, Rostam, Kharame, Zarindasht, Sarvestan, Firoozabad, Ghirkarzin, Marvdasht, Lamerd, Mamasani, and Sepidan ($P < 0.05$ for all); however, fewer cases were seen in Jahrom compared with Lar ($P < 0.05$). In addition, Safashahr has lower cases compared with Fasa, Jahrom, Kazerun, Marvdasht, and Lar ($P < 0.05$ for all). Also, there were more cases in Fasa than those in Neiriz, Abade, Arsenjan, Stahban, Eghlid, Bavanat, Pasargad, Kharame, Farashband, khonj, Darab, Rostam, Zarindasht, Sarvestan, Firoozabad, Ghirkarzin, Marvdasht, Lamerd, Sepidan, and Mamasani ($P < 0.05$ for all); however, fewer cases were seen in Fasa compared with Lar ($P < 0.05$). Moreover, fewer cases were seen in Neiriz, Arsenjan, Stahban, Eghlid, Pasargad, and Bavanat than those in Jahrom, Kazerun, Marvdasht, and Lar ($P < 0.05$ for all, respectively). Furthermore, the cases were lower in Kharame, Khonj, Rostam, Ghirkarzin, Sarvestan, and Farashband than those in Kazerun, Marvdasht, and Lar ($P < 0.05$ for all, respectively). Additionally, the cases were lower in Abade than those in Jahrom, Kazerun, and Lar ($P < 0.05$ for all). Likewise, the cases were lower in Darab, Firoozabad, and Zarindasht than those in Kazerun, and Lar ($P < 0.05$ for all, respectively). Besides, the cases were more in Kazerun than those in Lamerd, Mamasani, and Sepidan ($P < 0.05$ for all); however, less cases were seen in Kazerun compared with Lar ($P < 0.05$). Also, the cases were higher in Marvdasht than those in Mamasani, and Sepidan ($P < 0.05$ for both); however, fewer cases were seen compared with Lar ($P < 0.05$). Moreover, there were fewer cases in Lamerd and Mamasani than those in Lar ($P < 0.05$ for both). The cases were higher in Lar than those in Sepidan ($P < 0.05$).

COVID-19 cases in February, March, April, and May were significantly lower than those in June, July, August, and

### Table 1: Distribution of 53,554 COVID-19 cases in 26 cities of Fars province, Iran, February 18–September 30, 2020.

| City               | Shiraz | Lar  | Jahrom | Fasa | Kazerun | Marvdasht | Darab | Abade |
|--------------------|--------|------|--------|------|---------|------------|-------|-------|
| COVID-19 (%)       | 53.49  | 8.64 | 6.25   | 5.95 | 5.24    | 3.32       | 2.07  | 1.63  |

### Table 2: Distribution of 53,554 COVID-19 cases in Fars province, Iran, February 18–September 30, 2020.

| Month   | February | March | April | May   | June  | July  | August | September |
|---------|----------|------|-------|-------|------|------|--------|-----------|
| COVID-19 (%) | 0.30    | 3.50 | 6.50  | 4.70  | 19.70| 22.60| 18.70  | 22.60     |

### 2.4. Validation Study.
A validation study using real data from 1 October–14 November 2020 was done to assess the accuracy of the results.

### 2.5. Ethical Statement.
All ethical steps including data collection and analysis as well as reporting the results were in accordance with the standards approved by the Ethic Committee of the Ministry of Health, Treatment, and Medical Education (IR.SUMS.REC.1399.574). The work processes were anonymous, and the results were reported to the study participants.

### 3. Results

#### 3.1. Distributions of 53,554 COVID-19 Cases in Fars Province by City and Month, February 18–September 30, 2020.
From 53,554 COVID-19 cases, the maximum and minimum cases happened in Shiraz (53.49%) and Sarvestan (0.2%), respectively. In addition, the maximum and minimum cases happened in July (24%) and February (0.3%), respectively. The distribution of 53,554 COVID-19 cases by city and month is shown in Tables 1 and 2.

COVID-19 cases were not distributed uniformly across cities (test statistics $= 170.83$, df $= 25$, $P < 0.001$) and months (test statistics $= 21.3$, df $= 7$, $P < 0.001$) in Fars province during February 18–September 30, 2020. Pairwise comparisons of 53,554 COVID-19 cases by city and month have been shown in Tables 3 and 4.

COVID-19 cases were significantly higher in Shiraz than those in 25 other cities ($P < 0.05$ for all). Jahrom had more cases than Farashband, Khonj, Darab, Rostam, Kharame, Zarindasht, Sarvestan, Firoozabad, Ghirkarzin, Marvdasht, Lamerd, Mamasani, and Sepidan ($P < 0.05$ for all); however, fewer cases were seen in Jahrom compared with Lar ($P < 0.05$). In addition, Safashahr has lower cases compared with Fasa, Jahrom, Kazerun, Marvdasht, and Lar ($P < 0.05$ for all). Also, there were more cases in Fasa than those in Neiriz, Abade, Arsenjan, Stahban, Eghlid, Bavanat, Pasargad, Kharame, Farashband, khonj, Darab, Rostam, Zarindasht, Sarvestan, Firoozabad, Ghirkarzin, Marvdasht, Lamerd, Sepidan, and Mamasani ($P < 0.05$ for all); however, fewer cases were seen in Fasa compared with Lar ($P < 0.05$). Moreover, fewer cases were seen in Neiriz, Arsenjan, Stahban, Eghlid, Pasargad, and Bavanat than those in Jahrom, Kazerun, Marvdasht, and Lar ($P < 0.05$ for all, respectively). Furthermore, the cases were lower in Kharame, Khonj, Rostam, Ghirkarzin, Sarvestan, and Farashband than those in Kazerun, Marvdasht, and Lar ($P < 0.05$ for all, respectively). Additionally, the cases were lower in Abade than those in Jahrom, Kazerun, and Lar ($P < 0.05$ for all). Likewise, the cases were lower in Darab, Firoozabad, and Zarindasht than those in Kazerun, and Lar ($P < 0.05$ for all, respectively). Besides, the cases were more in Kazerun than those in Lamerd, Mamasani, and Sepidan ($P < 0.05$ for all); however, less cases were seen in Kazerun compared with Lar ($P < 0.05$). Also, the cases were higher in Marvdasht than those in Mamasani, and Sepidan ($P < 0.05$ for both); however, fewer cases were seen compared with Lar ($P < 0.05$). Moreover, there were fewer cases in Lamerd and Mamasani than those in Lar ($P < 0.05$ for both). The cases were higher in Lar than those in Sepidan ($P < 0.05$).

COVID-19 cases in February, March, April, and May were significantly lower than those in June, July, August, and
Table 3: Pairwise comparisons of 53 554 COVID-19 cases across 26 cities of Fars province, Iran, during February 18–September 30, 2020.

| City               | Mean difference | P   | City               | Mean difference | P   | City               | Mean difference | P   | City               | Mean difference | P   |
|--------------------|-----------------|-----|--------------------|-----------------|-----|--------------------|-----------------|-----|--------------------|-----------------|-----|
| Shiraz-Safashahr   | 124.28          | <0.001 | Safashahr-Fasa     | −11.62          | <0.001 | Neireez-Jahrom     | −13.46          | <0.001 | Jahrom-Kharame     | 14.13           | <0.001 |
| Shiraz-Fasa        | 112.66          | <0.001 | Safashahr-Jahrom   | −12.33          | <0.001 | Neireez-Kazerun     | −11.07          | <0.001 | Jahrom-Farahband   | 13.10           | <0.001 |
| Shiraz-Neireez     | 125.41          | <0.001 | Safashahr-Kazerun  | −9.95           | <0.001 | Neireez-Marvdasht  | −6.52           | 0.01   | Jahrom-Kharame     | 14.11           | <0.001 |
| Shiraz-Abade       | 122.9           | <0.001 | Safashahr-Marvdasht| −5.39           | 0.04  | Neireez-Lar        | −19.13          | <0.001 | Jahrom-Darab       | 9.91            | <0.001 |
| Shiraz-Arsenjan    | 125.63          | <0.001 | Safashahr-Lar      | −18             | <0.001 | Abade-Jahrom       | −10.95          | <0.001 | Jahrom-Rostam      | 13.90           | <0.001 |
| Shiraz-Stahban     | 124.73          | <0.001 | Fasa-Neireez       | 12.7            | <0.001 | Abade-Kazerun      | −8.56           | 0.001  | Jahrom-Zarindasht  | 11.           | <0.001 |
| Shiraz-Eghlid      | 124.92          | <0.001 | Fasa-Abade         | 10.24           | <0.001 | Abade-Lar          | −16.62          | <0.001 | Jahrom-Sarvestan   | 14.32           | <0.001 |
| Shiraz-Bavanat     | 126.18          | <0.001 | Fasa-Arsenjan      | 12.98           | <0.001 | Arsenjan-Jahrom    | −13.69          | <0.001 | Jahrom-Firoozabad  | 12             | <0.001 |
| Shiraz-Pasargad    | 125.17          | <0.001 | Fasa-Stahban       | 12.08           | <0.001 | Arsenjan-Kazerun   | −11.3           | <0.001 | Jahrom-Ghirkarzin  | 12.26           | <0.001 |
| Shiraz-Jahrom      | 111.95          | <0.001 | Fasa-Eghlid        | 12.25           | <0.001 | Arsenjan-Marvdasht | −6.7            | 0.01   | Jahrom-Marvdasht   | 6.94            | 0.009  |
| Shiraz-Kharame     | 126.08          | <0.001 | Fasa-Bavanat       | 13.52           | <0.001 | Arsenjan-Lar       | −19.36          | <0.001 | Jahrom-Kharame     | 1.13            | <0.001 |
| Shiraz-Farashband  | 125.03          | <0.001 | Fasa-Pasargad      | 12.51           | 0.01  | Stahban-Jahrom     | −12.78          | <0.001 | Jahrom-Lamer       | 12.07           | <0.001 |
| Shiraz-khonj       | 126.3           | <0.001 | Fasa-Kharame       | 13.42           | <0.001 | Stahban-Kazerun    | −10.04          | <0.001 | Jahrom-Mamasani    | 12.04           | <0.001 |
| Shiraz-Darab       | 121.85          | <0.001 | Fasa-Farashband    | 12.37           | <0.001 | Stahban-Marvdasht  | −5.84           | 0.03   | Jahrom-lar         | −5.67           | 0.03   |
| Shiraz-Rostam      | 125.85          | <0.001 | Fasa-khonj         | 13.4            | 0.01  | Stahban-Lar        | −18.46          | <0.001 | Jahrom-Sepidan     | 12.46           | <0.001 |
| Shiraz-Zarindasht  | 123.46          | <0.001 | Fasa-Darab         | 9.19            | 0.001 | Eghlid-Jahrom      | −12.96          | <0.001 | Kharame-Kazerun    | −11.74          | <0.001 |
| Shiraz-Sarvestan   | 126.27          | <0.001 | Fasa-Rostam        | 13.19           | <0.001 | Eghlid-Kazerun     | −10.57          | <0.001 | Kharame-Marvdasht  | −7.19           | 0.007  |
| Shiraz-Firoozabad  | 123.96          | <0.001 | Fasa-Zarindasht    | 10.8            | <0.001 | Eghlid-Marvdasht   | −6.02           | 0.02   | Kharame-Lar        | −19.8           | <0.001 |
| Shiraz-Ghirkarzin  | 124.21          | <0.001 | Fasa-Sarvestan     | 13.61           | <0.001 | Eghlid-Lar         | −18.63          | <0.001 | Farashband-Kazerun | −10.69          | <0.001 |
| Shiraz-Kazerun     | 114.34          | <0.001 | Fasa-Firoozabad    | 11.30           | <0.001 | Bavanat-Jahrom     | −14.23          | <0.001 | Farashband-Marvdasht| −6.14           | 0.02   |
| Shiraz-Marvdasht   | 118.89          | <0.001 | Fasa-Ghirkarzin    | 11.55           | <0.001 | Bavanat-Kazerun    | −11.8           | <0.001 | Farashband-Lar     | −18.75          | <0.001 |
| Shiraz-Lamer       | 124.02          | <0.001 | Fasa-Marvdasht     | 6.23            | 0.01  | Bavanat-Marvdasht  | −7.29           | 0.006  | Kharone-Kazerun    | −11.3           | <0.001 |
| Shiraz-Mamasani    | 124.15          | <0.001 | Fasa-Lamer         | 11.36           | <0.001 | Bavanat-Lar        | −19.9           | <0.001 | Kharone-Marvdasht  | −7.17           | 0.007  |
| Shiraz-Lar         | 106.28          | <0.001 | Fasa-Mamasani      | 11.50           | <0.001 | Pasargad-Jahrom    | −13.22          | <0.001 | Kharone-Lar        | −19.78          | <0.001 |
| Shiraz-Sepidan     | 124.41          | <0.001 | Fasa-Lar           | −6.38           | 0.02  | Pasargad-Kazerun   | −10.84          | <0.001 | Marvdasht-Mamasani | 5.26            | 0.04   |
| Darab-Kazerun      | −7.52           | 0.005 | Fasa-Sepidan       | 11.75           | <0.001 | Pasargad-Marvdasht | −6.28           | 0.02   | Marvdasht-Lamar    | −12.61          | <0.001 |
| Darab-Lar          | −15.57          | <0.001 | Sarvestan-Kazerun  | −11.94          | <0.001 | Pasargad-Lar       | −19            | <0.001 | Marvdasht-Sepidan  | 5.52            | 0.03   |
| Rostam-Kazerun     | −11.52          | <0.001 | Sarvestan-Marvdasht| −7.38           | 0.005 | Ghirkarzin-Kazerun | −8.97           | <0.001 | Kazerun-Lamer      | 9.68            | <0.001 |
| Rostam-Marvdasht   | −6.95           | 0.009 | Sarvestan-Lar      | −19.99          | <0.001 | Ghirkarzin-Marvdasht| −5.32           | 0.04   | Kazerun-Mamasani   | 9.82            | <0.001 |

Note: P values less than 0.05 are considered statistically significant.
can predict COVID-19 cases in Jahrom during October 1st–November 14th 2020. In July were significantly higher than those in August (P < 0.05 for all, respectively); COVID-19 cases in August were significantly lower than those in September (P < 0.05 for all).

### 3.2. Forecasting COVID-19 Cases in Fars Province during 1 October–14 November 2020

From the 53 554 observed cases during 18 February–30 September 2020, 55 369 cases were forecasted during 1 October–14 November 2020 using a variety of time series models. The frequency of 55 369 forecasted cases alongside the results of time series analysis for the 26 cities has been presented in Table 5.

From the 55 369 forecasted cases during 1 October–14 November 2020, the highest proportion was related to Shiraz (26.9%). Additionally, 65.80% and 34.20% of the cases were forecasted to occur in October and November, respectively. The time series results for Jahrom and Shiraz have been presented in Figures 1 and 2, respectively. The interpretation of the results was similar for the 24 other cities.

#### 3.2.1. COVID-19 Time Series Analysis in Jahrom during 1 October–14 November 2020

To reach the stability of variance, Box-Cox transformation was set zero. Besides, SARMA$_{12}$ (3, 4) was fitted with the observed quadratic trend and seasonality of 12. The estimated COVID-19 cases during 18 February–30 September 2020, the predicted COVID-19 cases during 1 October–14 November 2020 (45 days), and ACF/PACF sample/model for Jahrom have been presented in Figure 1.

SARMA$_{12}$ (3, 4) model was shown to be a good fit that can predict COVID-19 cases in Jahrom during October 1st–November 14th 2020. The results of the spatiotemporal analysis including 55 369 COVID-19 forecasted cases at the city level on a daily basis together with the results of subgroup analysis have been presented in Table 6.

Overall, four outbreaks occurred in Fars province during 1 October–14 November 2020, the largest and longest of which occurred in ten cities during 2–22 October, with Jahrom being the canon (MLC). Outbreaks 2 and 3 occurred in Sepidan and Fasa, respectively, and lasted from 3 to 13 November. Besides, outbreak 4 occurred in Lar and Zarrindasht on 21 October. The results of subgroup analysis demonstrated that Zarrindasht was the canon of the epidemic on 6 October.

As a part of EWS, the progression of COVID-19 epidemic resulting from spatiotemporal outbreaks of the 55 369 COVID-19 cases in Fars province, Iran, during 1 October–14 November 2020 has been shown in Figure 3.

COVID-19 epidemic inclined to trigger from Jahrom on 2 October, involving the MLC districts in the center, west, and south parts of the province; then, it showed a tendency to move towards the south in Zarrindasht on 6 October. Afterwards, it progressed to the southernmost part in Lar on 21 October. Afterwards, it simultaneously progressed to Fasa and Sepidan in the central and northwestern parts of the

### 3.3. Spatiotemporal Analysis

The results of the spatiotemporal analysis have been presented in Figure 2.

#### 3.2.2. COVID-19 Time Series Analysis in Shiraz during 1 October–14 November 2020

To reach the stability of variance, Box-Cox transformation was set zero. Besides, SARMA$_{8}$ (1, 0) was fitted with the observed quadratic trend. The estimated COVID-19 cases during 18 February–30 September 2020, the predicted COVID-19 cases during 1 October–14 November 2020 (45 days), and ACF/PACF sample/model for Shiraz have been presented in Figure 2.

### Table 3: Continued.

| City          | Mean difference | P     | City          | Mean difference | P     | City          | Mean difference | P     | City          | Mean difference | P     |
|---------------|-----------------|-------|---------------|-----------------|-------|---------------|-----------------|-------|---------------|-----------------|-------|
| Rostam-Lar    | 19.57 < 0.001   |       | Firoozabad-Kazerun | 9.62 < 0.001   |       | Ghirkharzin-Lar  | 18 < 0.001    |       | Kazerun-Lar  | 8.06 < 0.002  |       |
| Zarindasht-Kazerun | -9.13 0.001 |       | Firoozabad-Lar   | 17.68 0.001    |       | Lamerd-Lar      | -17.74 < 0.001 |       | Kazerun-Sepidan | 10.08 < 0.001 |       |
| Zarindasht-Lar | -17.19 < 0.001 |       | Lar-Sepidan     | 18.13 < 0.001  |       | Mamasani-Lar    | -17.88 < 0.001 |       |                |                 |       |

Note: std. error for all difference $s$ is 2.66; just statistically significant differences were reported.

#### Table 4: Pairwise comparisons of 53 554 COVID-19 cases by month in Fars province, Iran, during 18 February–30 September 2020.

| Sammonth | Mean difference | Std. error | Adj. P | Sample median | Mean difference | Std. error | Adj. P |
|----------|-----------------|------------|--------|---------------|-----------------|------------|--------|
| February-June | -13.02 2.45 | < 0.001    |        | April-June | -9.05 1.85 | < 0.001 |
| February-July  | -16 2.45 | < 0.001    |        | April-July | -12.04 1.85 | < 0.001 |
| February-August | -12 2.42 | < 0.001    |        | April-August | -7.23 1.81 | < 0.001 |
| February-September | -15.08 2.45 | < 0.001    |        | April-September | -11.2 1.85 | < 0.001 |
| March-June | -11.15 1.84 | < 0.001    |        | May-June | -10.3 1.85 | < 0.001 |
| March-July | -1.14 1.84 | < 0.001    |        | May-July | -13.3 1.85 | < 0.001 |
| March-August | -9.33 1.80 | < 0.001    |        | May-August | -8.48 1.81 | < 0.001 |
| March-September | -13.21 1.84 | < 0.001    |        | May-September | -12.36 1.85 | < 0.001 |
| July-August | 4.81 1.81 | 0.008      |        | August-September | -3.88 1.81 | 0.03    |

Note: just statistically significant differences were reported.

September (P < 0.05 for all, respectively); COVID-19 cases in July were significantly higher than those in August (P < 0.05 for all); COVID-19 cases in August were significantly lower than those in September (P < 0.05 for all).
3.4. Validation Study. 59 980 cases were recorded during 1 October to 14 November 2020, from which 64.2%, 57.0%, 5.5%, 2.2%, 2.2%, 2.1%, 2%, 1.8%, 1.4%, 1.2%, 1.2%, 1.1%, 1%, 0.9%, 0.8%, 0.7%, 0.7%, 0.4%, 0.4%, 0.4%, 0.4%, 0.3%, 0.3%, and 0.2% occurred in Shiraz, Jahrom, Fasa, Kazerun, Lar, Abade, Firoozabad, Neireez, Sarvestan, Mamasani, Darab, Kharame, Pasargad, Safashahr, Bavanat, Arsenjan, Rostam, Sarvestan, Zarindasht, Farashband, Marvdasht, Ghirkazin, Lamerd, and Khonj, respectively. In addition, 51.2% and 48.8% of the cases occurred in October and September, respectively. The space-time outbreaks of the 59 980 COVID-19 incidence cases accompanied by subcluster analysis in Fars province, Iran, during 1 October to 14 November 2020 are shown in Table 7.

province, respectively on 3 November. This progression alarmed the policy makers and health managers on the potential starting point of ongoing epidemic (Jahrom city on 2 October, 2020) and, also, on when and where to prioritize the medical facilities and staffs; moreover it could intervene with the transmission chain of COVID-19 in the area.

TABLE 5: The frequency 55 369 forecasted cases during 1 October–14 November 2020 accompanied by the results of time series analysis in the 26 cities of Fars province, Iran.
to get involved in an outbreak during 2020/10/2–2020/10/22.

However, Bavanat (2020/11/1–2020/11/14), Rostam (2020/11/1–2020/11/14), and Darab (2020/11/14), which were detected in validation study, were not predicted in EWS outbreaks.

The prediction of the epidemic consideration: real data showed that the epidemic was started from Jahrom on 2020/10/27 and progressed to Sarvestan, Rostam, Fasa, Zarindasht, Ghirkarzin, Farashband, Bavanat, Sepidan, Firoozabad and Darab; moreover, in EWS, the epidemic was triggered from Jahrom on 2020/10/2 and progressed to MLC districts, Zarindasht, Lar, Fasa, and Sepidan.

A total of 12 cities got involved in the outbreaks during 1 October–14 November 2020 using real data, nine of which were predicted in the EWS. The EWS predicted time periods were either the same as the observed periods or occurred earlier. Based on the validation study findings, the results of EWS were shown to be valid enough for our purpose.

4. Discussion

Covid-19 cases did not distributed uniformly across cities and times during 18 February–30 September 2020 in Fars province, Iran. In this protocol presented as EWS, 55 369 COVID-19 cases were forecasted from the 53 554 daily basis city-level time series data recorded during 18 February–30 September 2020. The forecasted cases resulted in the prediction of four significant spatiotemporal outbreaks of COVID-19 in the area including the MLC and three other clusters. The MLC, which was also the largest and the longest cluster, included ten cities during 2–22 October, with Jahrom being the canon. This finding, schematically presented as the progression of the epidemic during 1 October–14 November 2020, revealed that the epidemic inclined to trigger from Jahrom on 2 October, involving the MLC districts in the center, west, and south parts of the province; then, it showed a tendency to move towards the south in Zarindasht on 6 October. Afterwards, it progressed to the southernmost part in Lar on 21 October. Later, it simultaneously progressed to Fasa and Sepidan in the central and northwestern parts of the province, respectively on 3 November. To the best of our knowledge, this protocol alarmed the surveillance system to focus on the progression of the epidemic and especially on the starting point, Jahrom, so that proper interventions could be done on the transmission chain of SARS-CoV-2 resulting in lower prevalence of the disease in the area. Moreover, the surveillance system can
dedicate more test sites, medical resources, community quarantine, vaccination coverage, and travel bans on more at risk locations at specified detected times. Despite being the most important transmission line of the disease, it should be explained why the most populated city, Shiraz, with the maximum number of COVID-19 cases
was not included in the predicted outbreaks. Shiraz was ignored in permutation scan statistics analysis, in which clusters are ranked by their likelihood ratio scores rather than by the population density or the area size. This can be attributed to the fact that, with the capital city of Fars province being with advanced medical services, many patients from nearby cities travel to Shiraz to receive health services, thereby transmitting the infection to other cities of the province.

Time series models based on statistical methods were revealed to fit well for forecasting time dependent data. They presented well-fit results in case of the COVID-19 epidemic as well. For instance, the AR model could forecast the confirmed COVID-19 cases in Iran [10]. Additionally,
ARIMA-based time series analysis forecasting near future could assist the government to be prepared for the upcoming emergencies of the current epidemic in India [11–14]. In another study, ARIMA models were fitted to forecast short-term COVID-19 cases in the five most affected countries of the world including Italy, Spain, France, the United Kingdom, and the United States of America [15].

Space-time permutation scan statistics could well manage space-time dependent variables through informing the policymakers on the progression of the epidemic in China [16–18]. In the United States, the space-time outbreaks of COVID-19 were detected during two periods of time (22 January to 9 March 2020 and 18 January to 27 March 2020) using space-time statistics [19]. Space-time scan statistics also resulted in the detection of space-time outbreaks in Hong Kong during 23 January–14 April 2020 [20]. Furthermore, space-time permutation scan statistics worked better for predicting highly frequent infectious diseases with high transmission rates [8, 21, 22]. Another study employed almost the same protocol as the one used to establish the EWS in the current study in order to detect the vulnerable districts for COVID-19 in India. Using ARIMA time series model for forecasting short-term COVID-19 cases and performing spatial analysis, they indicated that the western and southern parts of the country were highly vulnerable for COVID-19 infection [23, 24].

EWS establishment could effectively warn the surveillance system about the progression of the epidemic in Fars province, Iran. However, it had several limitations, which might have affected the results. Firstly, the surveillance system of infectious diseases in Iran is a passive system, and many SARS-CoV-2 infected people with mild to moderate symptoms did not refer to health centers and were not diagnosed. Therefore, the forecasted cases of COVID-19 might have been underestimated. This could affect estimating the required health services and medical facilities. Secondly, permutation scan statistics discover more than one cluster in a given area and time. Hence, interpretation of the results could be somewhat difficult, especially when incorporating main-cluster and sub-cluster results. Regarding clinical and statistical significance, prioritizing the clusters can also be difficult. Another limitation of scan statistics is that it uses a circular scan window. Thus, the precise limits of the detected clusters remain uncertain. In other words, either the site within the detected clusters may not have a high risk, or a high risk site may be out of the cluster. Yet, using subgroup analysis for detecting significant clusters within large clusters could solve the problem. Further investigations are suggested to assess the genetic variation and meteorological risk factors of COVID-19 in the long run.

5. Conclusion

The EWS presented here would alarm the policy makers and health managers on the potential starting point of ongoing epidemic and, also, on when and where to prioritize the medical facilities and staffs. The MLC, which was also the largest and the longest cluster, included ten cities during 2–22 October, with Jahrom being the canon. This finding revealed that the epidemic inclined to trigger from Jahrom on 2 October, involving the MLC districts in the center, west, and south parts of the province; then, it showed a tendency to move towards the south in Zarrindasht on 6 October. Afterwards, it progressed to the southernmost part in Lar on 21 October. Afterwards, it simultaneously progressed to Fasa and Sepidan in the central and northwestern parts of the province, respectively, on 3 November. To the best of our knowledge, this protocol alarmed the surveillance system to focus on the starting point and progression of the epidemic as well as to dedicate more test sites, medical resources, stricter quarantine, vaccination coverage, and travel bans on more at risk locations at specified times. These findings can

Table 7: The space-time outbreaks of the 59 980 COVID-19 incidence cases accompanied by subcluster analysis in Fars province, Iran, during 1 October–14 November 2020.

| Cluster | Location | Radius (km) | Canon | Start date | End date | Test statistic | Critical value* | P value<sup>*</sup> |
|---------|----------|-------------|-------|------------|----------|----------------|-----------------|-----------------|
| Cluster1 | Zarindasht, Darab, Lar | 76.03 | Zarindasht | 2020/11/8 | 2020/11/14 | 189.3 | 5.6 | <0.001 |
| Cluster2 | Fasa | 0 | Fasa | 2020/11/4 | 2020/11/14 | 138.18 | 5.6 | <0.001 |
| Cluster3 | Sepidan | 0 | Sepidan | 2020/11/13 | 2020/11/14 | 55.54 | 5.6 | <0.001 |
| Cluster4 | Firoozabad, Farashband, Ghirkarzin, Sarvestan | 79.70 | Firoozabad | 2020/11/8 | 2020/11/14 | 36.89 | 5.6 | <0.001 |
| Cluster5 | Bavanat | 0 | Bavanat | 2020/11/11 | 2020/11/14 | 21.47 | 5.6 | <0.001 |
| Cluster6 | Rostam | 0 | Rostam | 2020/11/1 | 2020/11/14 | 17.86 | 5.6 | <0.001 |
| Cluster7 | Jahrom | 0 | Jahrom | 2020/10/27 | 2020/11/14 | 6.72 | 5.6 | 0.02 |

Sub-cluster results

| Cluster1 | Darab, Zarindasht | 46.57 | Darab | 2020/11/14 | 2020/11/14 | 6.08 | 2.4 | <0.001 |
| Cluster2 | Darab | 0 | Darab | 2020/11/5 | 2020/11/14 | 2.1 | 1.53 | 0.01 |
| Cluster3 | Ghirkarzin | 0 | Ghirkarzin | 2020/11/7 | 2020/11/14 | 18.23 | 2.71 | <0.001 |
| Cluster4 | Sarvestan | 0 | Sarvestan | 2020/10/31 | 2020/11/14 | 14.58 | 2.71 | <0.001 |
| Cluster5 | Farashband | 0 | Farashband | 2020/11/8 | 2020/11/14 | 14.25 | 2.71 | <0.001 |
| Cluster6 | Firoozabad | 0 | Firoozabad | 2020/11/14 | 2020/11/14 | 7.61 | 2.71 | <0.001 |

* Statistical significance was evaluated using Monte Carlo hypothesis testing at 0.05 significance level. † Standard Monte Carlo critical value. MLC, most likely cluster.

(continued)
be used to tailor province-level policies to servile the ongoing epidemic in the area; however, governmental level effort is needed to control the epidemic at a larger scale in the future.

Data Availability

The health service data used to support the findings of this study are restricted by the Ethics Committee of the Ministry of Health, Treatment, and Medical Education affiliated to Shiraz University of Medical Sciences. In order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran, in order to protect patient privacy. Data are available from Marjan Zare, Central Building of Shiraz University of Medical Sciences, Vice Chancellor for Health, fourth floor, Zand St, Shiraz, Iran.

Ethical Approval

All ethical steps including data collection and analysis as well as reporting the results were in accordance with the standards approved by the Ethic Committee of the Ministry of Health, Treatment, and Medical Education (IR.SUMS.REC.1399.574). The work processes were anonymous, and the results were reported to the study participants.

Conflicts of Interest

No conflicts of interest were declared by the authors.

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