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Spatial analysis of COVID-19 incidence and mortality rates in northwest iran for future epidemic preparedness

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The COVID-19 pandemic has underscored the critical need for effective public health strategies to combat infectious diseases. This study examines the epidemiological characteristics and spatial distribution of COVID-19 incidence and mortality in Zanjan Province, northwest Iran, to inform future epidemic preparedness. Using data from 39,739 hospitalized COVID-19 cases recorded between February 2020 and September 2021, sourced from the Medical Care Monitoring Center, we conducted descriptive and geospatial analyses. Demographic, clinical, and spatial variables were analyzed using logistic regression and advanced spatial techniques, including Kernel Density Estimation and Local Moran's I, to identify risk factors and disease hotspots. Results revealed that women accounted for 52% of cases, with higher incidence rates, while men exhibited higher mortality rates (7.86% vs. 7.80%). Urban areas, particularly the provincial capital, were identified as hotspots, with the highest patient density (20,384 cases per 10 km²). Comorbidities such as HIV/AIDS (OR: 4.85), chronic liver disease (OR: 3.6), chronic blood diseases (OR: 2.8), and cancer (OR: 2.5) significantly increased mortality risk, with ventilator use showing the highest odds ratio for death (OR = 91). Vaccination significantly reduced mortality, with fully vaccinated individuals experiencing a 6.3% mortality rate compared to 8.1% in unvaccinated individuals. Spatial analysis highlighted population density and mobility as key drivers of disease spread. These findings emphasize the importance of integrating spatial and epidemiological data to enhance pandemic preparedness. Targeted interventions in urban hotspots, early detection systems, and prioritizing vaccination for high-risk populations are critical for mitigating future outbreaks. This study provides a foundation for evidence-based public health strategies to strengthen global epidemic response and improve preparedness for future health crises.

Keywords COVID-19, Spatial analysis, Epidemiology, Incidence, Mortality, Vaccination, Comorbidities, Public health, Iran, Geospatial distribution, Epidemic preparedness

List of Abbreviations

WHO	World Health Organization
CVD	Cardiovascular Diseases
GIS	Geographical Information system
MCMC	Medical Care Monitoring Center
PCR	Polymerase Chain Reaction
LOS	Length of Stay
CT	Computed Tomography
SD	Standard Deviation
OR	Odds ratio
CI	Confident Interval
ASR	age-standardized rate
KDE	Kernel Density Estimation
LMI	Local Moran's I
N	Number

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ICU	Intensive Care Unit
EMS	Emergency Services
CKD	Chronic Kidney Diseases
CND	Chronic Neurological Diseases
CBD	Chronic Blood Diseases
CLD	Chronic Liver Diseases
IDD	Immunodeficiency Diseases
COPD	Chronic obstructive pulmonary disease
HH	High-High
HL	Low-High
HL	High-Low

The COVID-19 pandemic, declared a global health emergency by the World Health Organization (WHO) in March 2020, has profoundly impacted global health systems, economies, and societies. With rapid and extensive spread, COVID-19 has caused significant morbidity and mortality worldwide, challenging public health infrastructures and revealing vulnerabilities in disease response mechanisms[1,2]. The disease, characterized by symptoms ranging from mild to severe such as fever, cough, and dyspnea, highlighted the critical need for robust healthcare systems and effective public health strategies[3].

Populations with underlying health conditions, including the elderly and those with diseases like cancer, cardiovascular disease (CVD), or diabetes, experienced higher rates of severe outcomes and mortality[4].

The pandemic underscored the importance of protecting vulnerable populations and ensuring healthcare equity. Despite advancements in vaccines and treatments, the emergence of new variants, like Omicron, demonstrated the need for ongoing vigilance and adaptability in public health responses[5].

As COVID-19 transitions to an endemic phase, sensible preventive measures such as staying home when ill, remote working, and proper hygiene remain essential to mitigating the spread of not only COVID-19 but also other respiratory illnesses. This transition highlights the importance of sustainable health practices and the integration of public health recommendations into daily life[6]. Studies have shown a strong correlation between the use of personal protective equipment, like face masks, and the reduction of viral transmission, reinforcing the value of evidence-based interventions in managing infectious diseases[7].

Reliable data and comprehensive epidemiological studies are crucial for effective decision-making in public health[8]. Geographical Information Systems (GIS)-based studies, in particular, provide valuable insights into the spatial distribution of diseases, identifying high-risk areas and vulnerable populations[9]. These insights are essential for targeted public health interventions and resource allocation[10]. Since the onset of the pandemic, numerous studies in Iran have explored the epidemiological and spatial characteristics of COVID-19, contributing to a nuanced understanding of the disease's spread across different regions[11–13].

Spatial analysis of COVID-19 in Iran revealed varying patterns of incidence and mortality across the country's provinces. As of February 2024, Iran has reported 7,627,186 confirmed cases of COVID-19 and 146,811 deaths related to the virus. This places Iran among the countries with the highest burden of the pandemic in the region, with significant regional variations in incidence and mortality rates[14]. Initially, the central, north, and northwest regions were affected, followed by an increase in cases and deaths in the west and southwest regions[15]. The spread of COVID-19 in Iran was influenced by factors such as population density and proximity to high-risk clusters. For instance, the spread of COVID-19 in Tehran was exacerbated by high population density and the concentration of essential services in certain areas[16], while in Mashhad, higher rates were initially observed in suburban areas before spreading to the city center[11]. Mortality in Saveh was influenced by factors such as intubation, PO2 rate, diabetes, and dyspnea. Chronic diseases, such as cardiovascular disease, diabetes, and hypertension, were prevalent among patients who died, accounting for a significant proportion of cases[17]. These findings underscore the importance of considering geographical and socio-economic factors in pandemic response planning.

International studies have furthered our understanding of COVID-19 transmission dynamics and risk factors. Research from Detroit and the UK highlighted common comorbidities and demographic factors associated with severe outcomes, such as age, gender, and chronic conditions like obesity and kidney disease[18,19]. In Italy, spatial analysis revealed patterns of disease spread influenced by human mobility and demographic characteristics, emphasizing the need for tailored interventions based on local context[20–22]. Furthermore, Xiong's research showed that spatiotemporal and factor analysis can enhance decision-making for controlling the epidemic[23].

Urban epidemics like COVID-19 pose significant challenges due to factors such as high population density and the continuous emergence of new variants resulting from mutations[24–26]. In addition, there has been a observed decrease in antibody levels after vaccination, which further complicates disease control and prevention efforts[27]. Although vaccinations have been developed and widely distributed, the potential for future variants that could resist existing vaccines remains a significant concern. Additionally, the similarity of COVID-19 symptoms to other respiratory diseases, such as influenza, which can also spread rapidly through airborne transmission, underscores the ongoing risk of misdiagnosis and rapid disease spread[28]. The global increase in chronic diseases and the aging population, both of which have been shown to contribute to higher morbidity and mortality rates during epidemics, highlight the need for targeted health interventions and preventive measures. These populations are particularly vulnerable in the face of new and emerging infectious diseases, making it crucial to understand how epidemics like COVID-19 affect different demographic groups[29]. Furthermore, the evolving nature of respiratory viruses necessitates ongoing research into how such diseases spread within various environmental and socio-economic contexts. In many regions, especially those with dense populations and diverse health challenges, localized studies are essential for identifying unique risk factors and transmission dynamics. This is particularly important as health systems globally need to be prepared for future pandemics, which may arise from other pathogens with similar modes of transmission[30].

This study addresses the critical need for a detailed examination of COVID-19's behavior at a finer geographical scale to extract valuable lessons for future epidemic preparedness. By focusing on the epidemiological characteristics and spatial distribution of incidence and mortality rates in Zanjan province, northwest Iran, this research aims to provide a nuanced understanding of how COVID-19 spreads in rural and semi-urban areas. These insights are vital for developing effective public health strategies that can be tailored to specific local conditions, ensuring better readiness for future health crises. The findings will offer actionable recommendations for public health professionals and policymakers, contributing to more resilient health systems and informed epidemic response planning in similar future scenarios.

Materials and methods

Area and population studied

Zanjan province is situated in the northwest Iranian plateau, with geographical coordinates of 36.5018° N and 48.3988° E. It covers an area of 22,164 square kilometers, which accounts for 1.43% of the total area of the country. The province is further divided into eight counties and 48 rural districts, as per the latest political division of Iran (Fig. 1). According to the population data from 2016, Zanjan province was reported to have a population of 1,057,461 people.

Study design

This study employed a combined descriptive and geospatial analysis methodology, conducted in two sequential stages. The first stage utilized descriptive statistical techniques to examine the epidemiological characteristics of COVID-19 patients, providing insights into demographic, clinical, and temporal patterns. The second stage

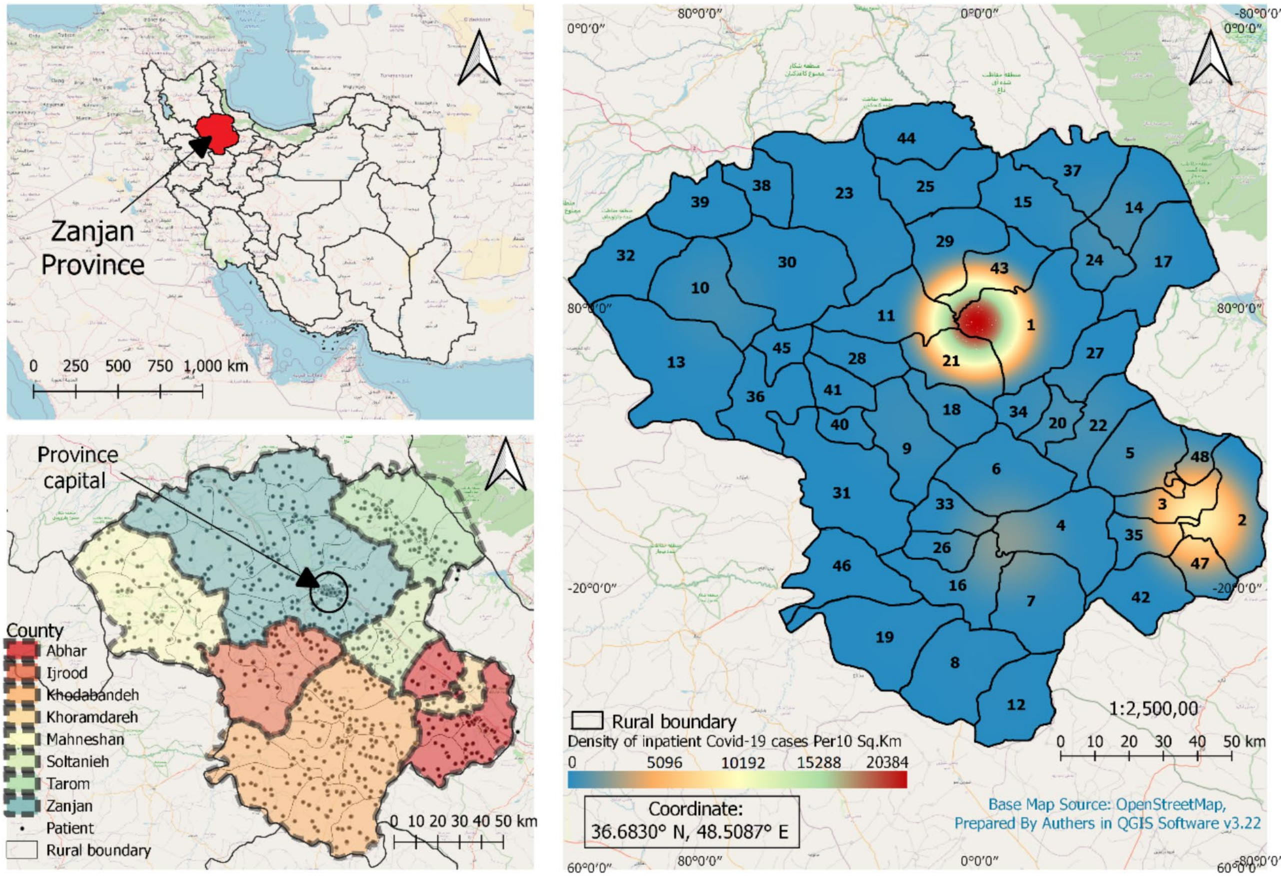

Fig. 1. COVID-19 case distribution in Zanjan province along with the geographical location of the study area. **Rural districts names:1**-Bonab, **2**- Howmeh (Abhar County), **3**- Khorramdarreh, **4**- Howmeh (Khodabandeh County), **5**- Sain Qaleh, **6**-Sojas, **7**- Khararud, **8**- Zarrineh Rud, **9**-Golabar, **10**- Mah Neshan, **11**- Zanjanrud-e Bala, **12**- Bizineh Rud, **13**-Anguran, **14**- Ab Bar, **15**- Chavarzaq, **16**-Karasf, **17**-Gilvan, **18**- Ijrud-e Bala,**19**-Shivanat, **20**- Soltaniyeh, **21**-Mojezat, **22**-Sonbolabad, **23**- Zanjanrud-e Pain, **24**- Dast Jerdeh, **25**- Qareh Poshtelu-e Bala, **26**-Sohrevard, **27**-Qareh Bolaq, **28**- Bughda Kandi, **29**-Sohrein, **30**- Qanibeyglu, **31**- Ijrud-e Pain, **32**-Oryad, **33**- Aq Bolagh, **34**- Guzal Darreh, **35**- Abharrud, **36**- Qaleh Juq, **37**-Darram, **38**-Chaypareh-ye Bala, **39**- Chaypareh-ye Pain, **40**- Saidabad, **41**-Qoltuq, **42**- Dowlatabad, **43**-Taham, **44**- Qareh Poshtelu-e Pain, **45**- Qezel Gechilu, **46**- Qeshlaqat-e Afshar, **47**- Darsajin, **48**-Alvand.

applied advanced spatial analysis indicators to identify hotspots, clusters, and high-risk areas for COVID-19 incidence and mortality at the rural district level within Zanjan Province. The analysis was based on the most recent and comprehensive dataset, encompassing five distinct epidemic peaks from the onset of the outbreak on February 23, 2020, to September 22, 2021, offering a robust framework for understanding the local dynamics of the pandemic.

Data collection

A total of 39,739 patient records were meticulously collected from the Medical Care Monitoring Center (MCMC) system over an 18-month period. The MCMC, established by the Iranian Ministry of Health and Medical Education, serves as a comprehensive database of hospitalized COVID-19 patients, recording detailed information such as demographics, comorbidities, symptoms, polymerase chain reaction (PCR) test results, and hospitalization details. For this study, all available COVID-19 patient data from the MCMC were included without exclusions, ensuring a comprehensive analysis of the epidemiological characteristics of COVID-19 in Zanjan Province.

The dataset encompassed a broad range of variables, including sex, age, residential address, date of symptom onset, healthcare worker status, type of hospital referral, method of COVID-19 confirmation, length of hospital stays (LOS), comorbidities, symptoms, history of exposure to infected individuals, vaccination status, inpatient department type (used to assess disease severity), and clinical outcomes. Additionally, the study included patients with negative PCR test results but clinical symptoms indicative of COVID-19, as confirmed by positive findings on chest computed tomography (CT) scans. This inclusive approach ensured a robust and comprehensive dataset for a detailed epidemiological analysis.

To ensure data integrity, MCMC employs standardized protocols for data entry and quality control across participating healthcare facilities. Despite these rigorous measures, certain limitations may persist, such as reporting errors or incomplete data entries, which are particularly prevalent in under-resourced healthcare settings. These issues can result in underreporting of cases or misclassification of outcomes, potentially introducing bias into the dataset. To address these challenges, initial checks for data consistency were conducted, and entries with substantial missing data were excluded. For variables with partial missing data, imputation methods were applied by grouping records and assigning the mean value. For instance, vaccination data were reported through variables such as vaccination status, vaccine name, vaccination date, and administration of the first and second doses. Significant missing data were observed in this category. To address this, we assumed that if any vaccination-related variable contained data, even if other variables were missing, the patient was considered to have received at least the first dose of a vaccine. Nonetheless, the use of secondary data inherently carries limitations that may impact the generalizability of the results. These constraints underscore the importance of cautious interpretation of the study's findings within the context of its methodological boundaries.

Statistical analysis

In this study, the Anderson-Darling test was utilized to assess the normality of the data distribution, an approach deemed appropriate given the substantial dataset size. Continuous variables were summarized as means with standard deviations (SD), and the T-test was employed to evaluate the null hypothesis under the assumption of normally distributed data. Categorical variables were presented as frequencies and percentages, with their distributions compared using the Chi-square test to analyze differences between genders and between survival and non-survival groups. Univariate logistic regression was conducted to explore associations between individual variables and the outcome of interest (non-survival), without accounting for potential confounding factors. To address these confounding effects and evaluate adjusted associations between independent variables and in-hospital mortality, multivariate logistic regression analyses were performed. Separate models were constructed for the complete dataset, comorbidities, and symptoms. Odds ratios (ORs) were calculated with corresponding 95% confidence intervals (CIs) to estimate the strength of associations, with coefficients expressed in odds ratio format. OR values exceeding 1.5 were specifically highlighted in the results. All statistical analyses were conducted using R software, version 4.0.5. A two-tailed significance level of $P < 0.05$ was considered statistically significant for all tests performed.

Spatial analysis

This study utilized the Asia-North-Lambert-Conformal-Conic projection system for GIS layer projection, adhering to professional geospatial standards. Patient residential addresses, sourced from MCMC, were geocoded with strict compliance to ethical guidelines and data confidentiality protocols. The MCMC collected patient addresses as a required field, recording latitude and longitude coordinates when complete addresses were available. In cases where complete addresses were unavailable, the nearest available address, within a 500-meter radius, was used to ensure data completeness while maintaining confidentiality. The geocoded data served as the foundational dataset for spatial analyses performed using QGIS and ArcGIS, both recognized for their precision and reliability in geospatial analysis. The crude incidence rate of COVID-19, expressed as cases per 100,000 population, was calculated by dividing the number of cases by the population and multiplying by 100,000. Age-Standardized Rates (ASR) for COVID-19 incidence were determined through direct standardization, using the 2016 Iranian population as the reference, categorized into the following age groups: 0–4, 5–14, 15–29, 30–44, 45–54, 55–64, and ≥65 years. Spatial analyses employing advanced methodologies, including Kernel Density Estimation (KDE), hotspot analysis, and Local Moran's I (LMI), provided detailed insights into the spatial distribution and intensity of COVID-19 cases across the study region. To ensure the accuracy of geocoding, quality control measures were implemented to reduce potential errors to the lowest level. Results were cross-validated by comparing the sum of district-level cases within the province to the total number of cases at the provincial level. Additionally, the latest and officially approved shapefile for the province, as endorsed by the

Zanjan Province governor's office, was used to ensure comprehensive geographic coverage of all data. These measures aimed to provide the most accurate and reliable geospatial analysis possible while maintaining ethical and confidentiality standards.

Kernel density Estimation
Density refers to the measure of mass per unit volume, representing the amount of space occupied by COVID-19 patients in a given area. Three common methods for estimating density are point density, linear density, and kernel density. KDE is a statistical technique that employs a non-parametric, distance-based method to construct a smooth, curved surface around each data point, with the density gradually diminishing as the distance from the point increases. This enables the identification of clusters and irregularities in the distribution of activity or exposures on a continuous surface. KDE also allows for the distribution of the risk of disease incidence, spreading the probability of incidence around the disease site within a certain radius, considering spatial relationships[31,32]. The constructed density levels are used to represent focal points, visually depicting the risk distribution. In this study, a 10 km^2 bandwidth was used to showcase the density of COVID-19 patients per 10 km^2 in Zanjan province, Iran.

Local indicators for spatial autocorrelation – hotspot (cluster) and outlier analysis
Hotspot analysis and LMI are widely recognized methods for identifying spatial autocorrelation and rigorously identifying high-risk areas (hotspots) and low-risk areas (coldspots) in relation to the incidence and mortality of COVID-19[11,12]. Hotspots are areas with significantly elevated or reduced rates surrounded by neighboring areas exhibiting similarly high or low rates. Spatial outliers are areas with significantly low or high rates surrounded by areas with significantly opposing rates[33]. LMI complements hotspot analysis by validating, augmenting, and revealing potential nuances, including the identification of outliers. In this study, spatial relationships were conceptualized using the "contiguity-edge-corner" option, where polygons touching each other were considered neighbors. Row standardization was used to create proportional weights for features with unequal number of neighbors, ensuring equitable analysis of spatial relationships. In an academic and professional context, hotspot analysis and LMI are indispensable tools for discerning spatial patterns and relationships in geospatial data. The hotspot analysis and LMI analysis have been chosen to analyze COVID-19 distribution patterns, as they are complementary but fundamentally different techniques. The hotspot analysis identifies hot and cold spots based on high or low values of a variable within a surrounding area, while the cluster and outlier analysis identify groupings or anomalous values according to proximity. Hotspot analysis provides critical information on the intensity and spatial distribution of statistically significant clusters, while LMI delves deeper into local clusters of similar or dissimilar values, detects outliers, and reveals intricate spatial dynamics[34]. By employing both techniques together, researchers can obtain a comprehensive and robust understanding of COVID-19 distribution and intensity across the study area, enabling a more informed and nuanced analysis of spatial patterns and trends associated with the disease.

Results
In Zanjan province, a total of 39,739 patients were hospitalized in medical centers due to COVID-19. During the 18-month study period, 3,113 patients (7.83%) succumbed to COVID-19, with women accounting for a slightly higher proportion of the deceased (52.6%). The mean LOS was marginally longer for men compared to women (5.36 ± 5.8 days vs. 5.35 ± 5.3 days, respectively). Furthermore, the majority of patients (87%) were from urban areas, as reflected in Table 1.

Age and gender
The analysis of gender differences in COVID-19 outcomes highlights significant disparities in incidence, severity, and mortality across various demographic and clinical factors. Females accounted for 52.4% of cases, while males represented 47.6%. Among pediatric cases (neonates and infants under one year), boys were more affected, comprising 55.7% of cases. Mortality rates were comparable between sexes, with 7.86% of females and 7.80% of males not surviving. However, among infant cases, boys exhibited a higher mortality rate compared to girls (51.4% vs. 48.6%). Disease severity also varied significantly by sex ($p < 0.001$), with males more likely to require ICU care (6.17% vs. 5.50%) but experiencing slightly lower ICU mortality compared to females (7.2% vs. 7.7%). Mortality rates in isolated wards were identical for both sexes (8.8%), while females in short-stay wards exhibited marginally higher mortality than males (6% vs. 6.3%). Vaccination status also played a critical role in outcomes, with vaccination rates of 85.9% in females and 86.1% in males. Mortality rates among vaccinated individuals were identical for both sexes (8%), but unvaccinated females had a significantly higher mortality rate than unvaccinated males (10.9% vs. 6.6%). The ASR of COVID-19 incidence was higher among women (3973 per 100,000) compared to men (3547 per 100,000). The mean age of all patients was 54.8 ± 20.8 years, with women being significantly older than men (55.17 ± 20 years vs. 54.28 ± 21.5 years, $p < 0.001$). The age group 45–59 had the highest frequency of cases (24.3%) and deaths (7.8%). Women had a higher frequency of cases in this age group (5104 vs. 4562), while men had a higher mortality rate (7.91% vs. 7.66%) (Fig. 2). A detailed analysis for gender-differences of COVID-19 incidence and mortality is provided in Supplementary File 1.

Clinical characteristics
COVID-19 patients were categorized into wards based on symptom severity and health status. Mild cases had a mean age of 46.8 ± 15.3 years, LOS of 5 ± 4.9 days, and 6% mortality. Severe cases had higher mortality (9%) and longer LOS (5.5 ± 5.7 days). Most were admitted to COVID-19 units (46%), while ICU patients had the highest mean age (61.2 ± 24 years), emphasizing the need for tailored triage and management (Table 1). Cough was the most common symptom (47%), while dermatitis was least frequent (0.1%). Mortality was highest (10%) in cases

Characteristic		Total *N* (%)	Sex *N* (%)			Age (Mean ± SD)	LOS (Mean ± SD)	End-point *N* (%)		
			Men	Women	*P*-Value			Survived	Not-Survived	*P*-Value
all patients		39,739 (100)	18,935 (48)	20,804 (52)	< 0.001	54.8 ± 20.8	5.2 ± 5.8	36,626 (92)	3113 (8)	< 0.001
place of residence	Urban areas	34,577 (87)	16,607 (48)	17,970 (52)	< 0.001	54.5 ± 20.3	6.1 ± 5.9	31,756 (92)	2821 (8)	< 0.001
	Rural areas	5162 (13)	2328 (45)	2834 (55)		56.7 ± 22.9	5.3 ± 4.9	4870 (94)	292 (6)	
COVID-19 confirmation type	PCR	20,136 (51)	9206 (46)	10,930 (54)	< 0.001	55.6 ± 18.8	5.3 ± 5.1	18,575 (92)	1561 (8)	0.82
	Clinical (CT-Scan)	31,038 (78)	14,773 (48)	16,265 (52)	0.70	54.6 ± 20.5	5.5 ± 5.3	28,370 (91)	2668 (9)	< 0.001
Being healthcare staff		233 (1)	111 (48)	122 (52)	1	44.3 ± 17.2	5.6 ± 7.5	211 (91)	22 (9)	0.42
Close contact with infected patients		23,414 (59)	10,954 (47)	12,460 (53)	< 0.001	54.7 ± 19.5	5.4 ± 5.6	21,565 (92)	1849 (8)	0.58
Vaccinated		5564 (14)	2632 (47.3)	2932 (52.7)	0.579	57.3 ± 18.4	4.7 ± 4.9	5211 (93.7)	353 (6.3)	< 0.001
Referred to hospital	With EMS	5559 (14)	2943 (53)	2616 (47)	< 0.001	61.1 ± 21.8	5.5 ± 6.2	5096 (92)	463 (8)	0.14
	Individual	34,180 (86)	15,992 (47)	18,188 (53)		53.7 ± 20.3	5.3 ± 5.5	31,530 (92)	2650 (8)	
Disease severity (Hospitalized in)	Special COVID-19 units	18,356 (46)	8810 (48)	9546 (52)	< 0.001	54.5 ± 20.7	5.4 ± 5.6	16,935 (92)	1421 (8)	< 0.001
	short-stay wards	4950 (12)	2325 (47)	2625 (53)		46.8 ± 15.3	5 ± 4.9	4645 (94)	305 (6)	
	Isolated wards	11,795 (30)	5348 (45)	6447 (55)		56 ± 20.1	5.5 ± 5.7	10,754 (91)	1041 (9)	
	ICU	4638 (12)	2452 (53)	2186 (47)		61.2 ± 24	5.4 ± 5.7	4292 (93)	346 (7)	
Treatment Plan	Connect to Ventilator	3285 (8)	1573 (48)	1712 (52)	0.79	55.5 ± 20.5	8.7 ± 9.8	1028 (31)	2257 (69)	< 0.001
	Oxygen therapy	15,020 (38)	7183 (48)	7837 (52)	0.59	54.3 ± 20.3	6.3 ± 5.5	12,870 (86)	2150 (14)	< 0.001

Table 1. Characteristics of hospitalized COVID-19 patients in Zanjan Province by gender, February 2020 to September 2021. N: Number, SD: standard deviation, LOS: Length of Stay, ICU: Intensive Care Unit, EMS: Emergency Services.

with dizziness and loss of consciousness (Table 2). Most patients exhibited combinations of symptoms. In 47% of patients, both cough and dyspnea were reported. Dyspnea (14.7%), cough (6.5%), and their combination (10.3%) were the most commonly reported symptoms, without the presence of other accompanying symptoms. The symptom dyspnea alone had the highest mortality rate at 15%, whereas dyspnea and cough were frequently accompanied by other symptoms, with 26 and 20 cases, respectively. The triple combination of cough, dyspnea, and myalgia (2.9%) and quadruple combination of cough, dyspnea, myalgia, and fever (1.1%) had the highest frequencies of occurrence (Fig. 3-a).

The most prevalent comorbidities were hypertension (19%), diabetes (12%), and CVD (10%) (Table 3). Hypertension had the highest mortality (14%). Hypertension, diabetes, and their combination were most frequent. The co-occurrence of hypertension and CVD was frequently observed in COVID-19-related fatalities, without the presence of any other comorbid conditions. Hypertension and diabetes had the highest frequency among all combinations. The co-occurrence of hypertension-diabetes, hypertension-diabetes-CVD, and hypertension-diabetes-CVD-chronic kidney diseases were found to be the most common (Fig. 3-b).

Time trend

Figure 4 depicts the temporal trend of COVID-19 hospitalization and mortality rates over 18 months in the study area. Zanjan province experienced five peaks, with escalating hospitalization and mortality rates in each peak. During the course of the COVID-19 pandemic in Zanjan province, Iran, the first peak which occurred from January 2020 to March 2020 had a hospitalization rate of 7.9% and a mortality rate of 7.8%. Conversely, the fifth peak which spanned from May 2021 to August 2021, had the highest hospitalization rate of 28.9% and a mortality rate of 6.5%. Hospitalization and mortality rates during the second to fourth peaks ranged from 12 to 29.7% and 7.4–8.6% respectively. The lowest hospitalization rate (2%) was observed in the fourth peak (Feb-2021), while the highest rate (13.9%) occurred in the fifth peak (Aug-2021).

Odds ratios for mortality rate

Figure 5 displays the odds ratios of the variables analyzed using univariate regression in the present study. Odds ratios exceeding 1.5 are reported to elucidate factors that exhibited substantial impact on in-hospital mortality

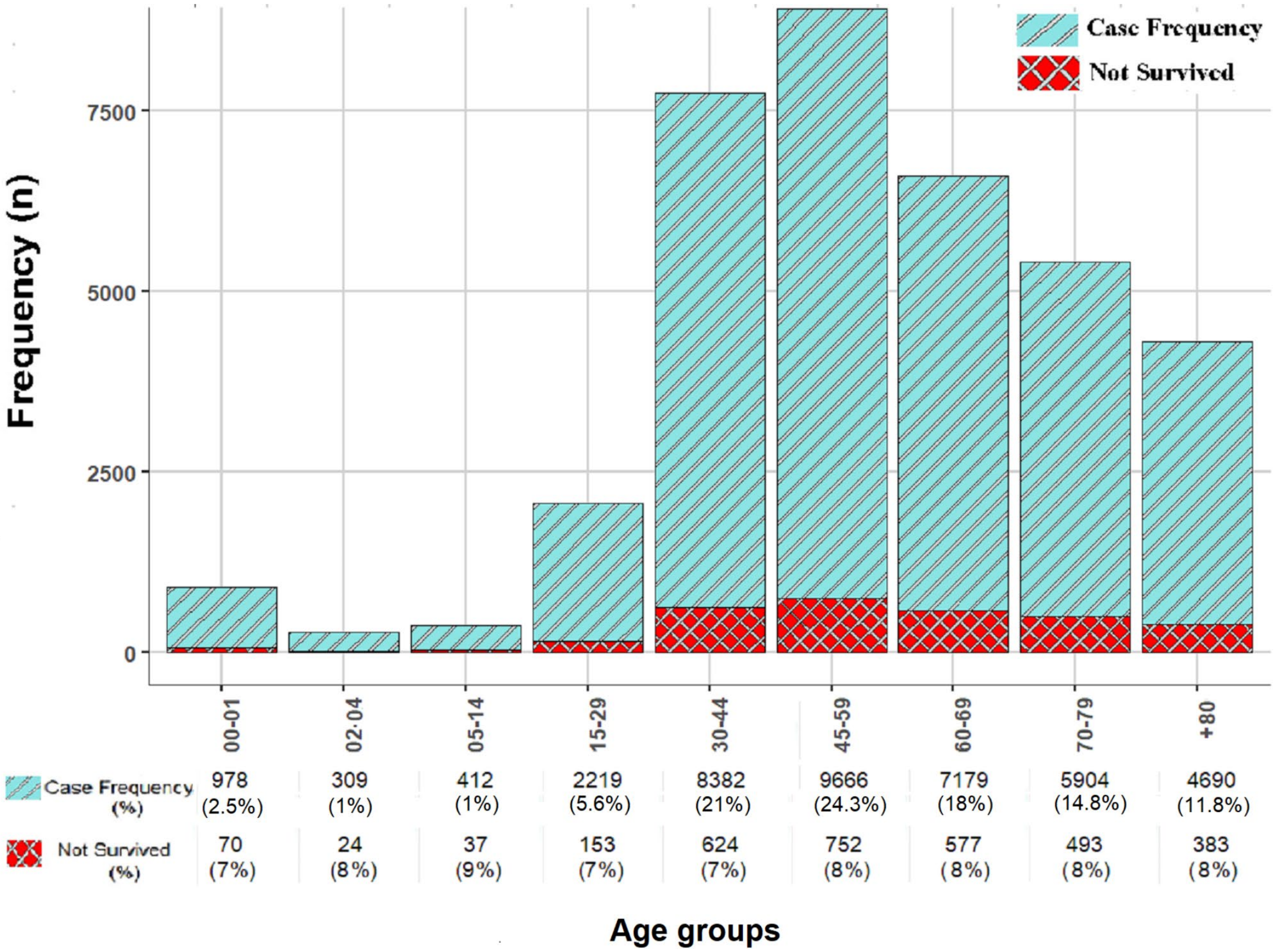

Fig. 2. Age-specific of COVID-19 incidence and mortality in Zanjan province, Iran.

associated with COVID-19. Patients who required ventilator support exhibited the highest odds ratio (OR = 91). Furthermore, patients with comorbidities of AIDS and cancer were five times more likely to experience mortality (OR = 5). Notably, patients with a positive CT scan for pulmonary disorder had nearly twice the odds of death (OR = 1.9) compared to those with a negative CT scan, indicating a significant association between pulmonary abnormalities and COVID-19 mortality.

The multivariate analysis identified key determinants of COVID-19 mortality, emphasizing the interplay of hospital factors, comorbidities, symptoms, physiological indicators, and vaccination status. Patients admitted to hospitals located in Zanjan County, such as Hospital Beheshti (OR: 0.57, 95% CI: 0.27–1.2, $p = 0.001$) and Hospital Nazaja (OR: 0.34, 95% CI: 0.19–0.82, $p = 0.01$), experienced significantly lower odds of mortality. Among comorbidities, HIV/AIDS (OR: 4.85, 95% CI: 0.85–2.7, $p < 0.001$), CLD (OR: 3.6, 95% CI: 1.8–7.4, $p < 0.001$), CBD (OR: 2.8, 95% CI: 1.4–5.8, $p = 0.001$), and Cancer (OR: 2.5, 95% CI: 1.7–3.6, $p < 0.001$) were strongly associated with increased mortality risk. Severe symptoms, including loss of consciousness (OR: 1.47, 95% CI: 1.11–1.94, $p = 0.007$) and Dizziness (OR: 1.39, 95% CI: 1.05–1.83, $p = 0.001$), emerged as significant predictors of poor outcomes. Breath counts outside normal ranges were similarly predictive of higher risk, with breath counts over 28 showing significantly lower odds of survival (OR: 0.25, 95% CI: 0.09–0.71, $p = 0.001$). Confirmation COVID-19 with CT-scans results was moderately associated with increased mortality risk (OR: 1.26, 95% CI: 1.08–1.47, $p = 0.003$). Full details of the analyses are provided in the Supplementary File 2.

Vaccination analysis

The vaccination analysis revealed that vaccinated individuals accounted for 14% of the study population and exhibited significantly better outcomes compared to their unvaccinated counterparts. Among vaccinated individuals, the overall mortality rate was 6.3% compared to 8.1% for unvaccinated individuals. Vaccinated patients were less likely to be admitted to the ICU (8.8% vs. 12.1%), and their survival rate across all hospital units was higher (93.7% vs. 91.9%). Further stratification by vaccination dose demonstrated that individuals receiving two doses had the lowest mortality rate (5.3%) compared to those with one dose (6.6%), highlighting the additional protective effect of completing the vaccination regimen. Analysis by vaccine type revealed variability in outcomes. Patients vaccinated with AstraZeneca had a mortality rate of 8.7%, while those vaccinated with Sinopharm experienced a slightly lower rate of 7.1%. Vaccines such as Iran-Barakat and other regional vaccines,

Symptoms	Total N (%)	Sex N (%)			Age (Mean ± SD)	LOS (Mean ± SD)	End-point N (%)		
		Men	Women	*P*-Value			Survived	Not Survived	*P*-Value
Caught	18,676 (47)	8878 (48)	9798 (52)	0.68	54.4 ± 20.6	5.2 ± 5.4	17,281 (93)	1395 (7)	0.01
Dyspnea	18,599 (47)	8916 (48)	9683 (52)	0.28	55 ± 20.8	5.4 ± 5.6	17,072 (92)	1527 (8)	0.009
Myalgia	12,989 (33)	6146 (47)	6843 (53)	0.36	54.4 ± 20.5	5.2 ± 5.5	11,977 (92)	1012 (8)	0.84
Fever	10,680 (27)	5077 (48)	5603 (52)	0.79	54.8 ± 20.5	5.3 ± 5.2	9848 (92)	832 (8)	0.86
Anorexia	3927 (10)	1870 (48)	2057 (52)	0.98	54.2 ± 20.6	5.1 ± 5.5	3615 (92)	312 (8)	0.80
Headache	3574 (9)	1650 (46)	1924 (54)	0.06	54.3 ± 20.1	5.2 ± 4.8	3288 (92)	286 (8)	0.71
Nausea	2812 (7)	1312 (47)	1500 (53)	0.28	54.4 ± 20.5	5.3 ± 5.3	2588 (92)	224 (8)	0.81
Vomiting	1976 (5)	987 (50)	989 (50)	0.03	54.6 ± 20.8	5.4 ± 5.2	1831 (93)	145 (7)	0.42
Dizziness	1502 (4)	679 (45)	823 (55)	0.06	55 ± 20.4	5.4 ± 5.5	1357 (90)	145 (10)	0.008
Thoracalgia	1409 (4)	684 (49)	725 (51)	0.51	54.3 ± 20.8	5.2 ± 4.8	1290 (92)	119 (8)	0.41
Loss of Consciousness	1321 (3)	652 (49)	669 (51)	0.21	55.9 ± 20.9	5.7 ± 6.7	1190 (90)	131 (10)	0.004
Stomachache	1153 (3)	584 (51)	569 (49)	0.04	55.5 ± 20.4	5.3 ± 4.8	1049 (91)	104 (9)	0.14
Anosmia	1110 (3)	492 (44)	618 (56)	0.02	55.1 ± 19.9	5.6 ± 5.7	1009 (91)	101 (9)	0.12
Diarrhea	1055 (3)	516 (49)	539 (51)	0.42	54.4 ± 20.7	5.3 ± 4.9	966 (92)	89 (8)	0.49
Ageusia	872 (2)	401 (46)	471 (54)	0.33	55.5 ± 20.7	5.7 ± 5.6	793 (91)	79 (9)	0.19
Paresis	293 (1)	150 (51)	143 (49)	0.24	54.1 ± 20.2	6.5 ± 7	266 (91)	27 (9)	0.43
Convulsion	220 (1)	94 (43)	126 (57)	0.16	57 ± 19.2	5.9 ± 7.2	205 (93)	15 (7)	0.66
Plegia	124 (0.1)	49 (40)	75 (60)	0.08	58 ± 21.4	5.4 ± 4.8	114 (92)	10 (8)	1
Cutitis	69 (0.1)	31 (45)	38 (55)	0.73	55.4 ± 18.5	4.5 ± 4.2	63 (91)	6 (9)	0.96

Table 2. Clinical symptoms of hospitalized COVID-19 patients in Zanjan Province by gender from February 2020 to September 2021. N: Number, SD: standard deviation, LOS: Length of Stay.

including Baharat, Fakhravac, Pastor, and Soberana, showed 0% mortality in their limited cohorts. Patients vaccinated with Sputnik demonstrated the highest mortality rate among the vaccinated group (16%), though this was based on a small sample size. Full details of these analyses are available in Supplementary File 3.

The analysis of vaccination by age group reveals significant differences in survival rates influenced by comorbidities and vaccination status (Table 4). Among individuals aged < 18, survival rates were same in those vaccinated (first or second doze) with unvaccinated individuals (92.1%). In the 18–39 age group, vaccinated individuals demonstrated superior survival, with achieving 94.1% survival compared to 92.7% among unvaccinated individuals. For the 40–59 age group, the trend persisted, with vaccinated patients showing a 93.8% survival rate compared to 91.9% for unvaccinated individuals. The impact of comorbidities was more pronounced in older age groups, particularly in those aged 60–79 and 80+, where survival rates for unvaccinated individuals dropped to 87.4% and 87%, respectively, compared to 93.14% and 95% for second-dose recipients in both age groups. Across all cohorts, individuals with no comorbidities consistently exhibited higher survival rates than those with comorbidities, regardless of vaccination status. These findings highlight the critical role of full vaccination, particularly for older individuals and those with comorbidities, in significantly improving COVID-19 survival rates.

Spatial analysis

The spatial distribution of COVID-19 patient density in Zanjan province, focusing on urban and rural areas, is presented in Figs. 1 and 6. Urban areas accounted for 87% of the total patient density, while rural areas comprised the remaining 13% ($P < 0.001$). KDE analysis revealed that the provincial capital had the highest patient density, with 20,384 cases per 10 km^2. Similarly, Abhar and Khorramdareh counties, the second and third largest urban areas in Zanjan province, exhibited high patient density, with 10,192 cases per 10 km^2. Notably, patient density

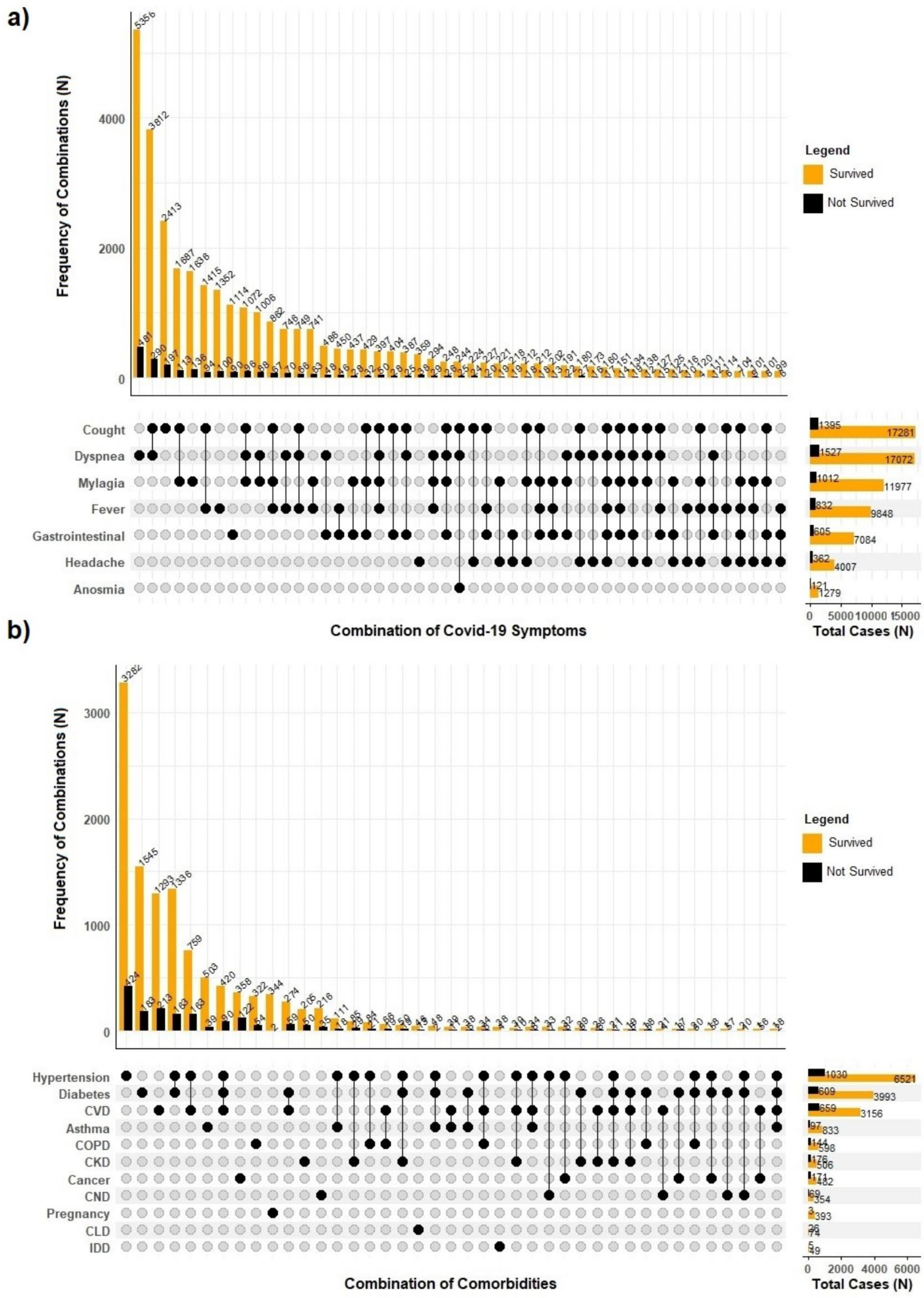

Fig. 3. Combinations of COVID-19 symptoms and co-morbidities in COVID-19 patients (non-survivors vs. survivors).

decreased with distance from county centers, as indicated by areas with blue color, suggesting lower COVID-19 incidence in those regions (Fig. 1).

The overall ASR of COVID-19 incidence in Zanjan province was estimated to be 3,694 cases per 100,000 population, with Abbar region having the highest incidence and mortality rates. Among men, Abbar region accounted for the highest incidence and mortality rates, while among women, Khorramdareh region had the highest incidence, with the highest mortality rate observed in Mahneshan region. Hotspot analysis revealed

Comorbidities	Total N (%)	Sex N (%) Men	Women	P-Value	Age (Mean ± SD)	LOS (Mean ± SD)	End-Point N (%) Survived	Not Survived	P-Value
Hypertension	7551 (19)	3617 (48)	3934 (52)	0.63	54.6 ± 20.5	6.4 ± 5.9	6521 (86)	1030 (14)	< 0.001
Diabetes	4602 (12)	2187 (48)	2415 (52)	0.86	54.4 ± 20.9	6.2 ± 5.6	3993 (87)	609 (13)	< 0.001
CVD	3815 (10)	1817 (48)	1998 (52)	0.99	55.1 ± 20.6	6.1 ± 5.7	3156 (83)	659 (17)	< 0.001
Asthma	930 (2)	409 (44)	521 (56)	0.02	54.1 ± 21.4	6.2 ± 5.4	833 (90)	97 (10)	0.003
Respiratory diseases except for asthma	742 (2)	338 (46)	404 (54)	0.26	57 ± 20.1	6.3 ± 6.3	598 (81)	144 (19)	< 0.001
CKD	682 (2)	300 (44)	382 (56)	0.058	55.1 ± 22	6.7 ± 8.9	506 (74)	176 (26)	< 0.001
Cancer	653 (2)	343 (53)	310 (47)	0.01	56 ± 20.6	6.1 ± 6.7	482 (74)	171 (26)	< 0.001
CND	423 (1)	195 (46)	228 (54)	0.55	54.2 ± 21.2	7.5 ± 8	354 (84)	69 (16)	< 0.001
Pregnancy	396 (1)	0 (0)	396 (100)	< 0.001	56.2 ± 21.6	4.1 ± 4.4	393 (99)	3 (1)	< 0.001
CBD	131 (0)	59 (45)	72 (55)	0.56	54.8 ± 21	5.1 ± 4.8	112 (85)	19 (15)	0.007
CLD	100 (0)	41 (41)	59 (59)	0.25	55.4 ± 19.9	5.4 ± 4.3	74 (74)	26 (26)	< 0.001
IDD	54 (0)	22 (41)	32 (59)	0.41	49.9 ± 20.9	5.2 ± 3.9	49 (91)	5 (9)	0.61
AIDS	19 (0)	7 (37)	12 (63)	0.50	56.6 ± 23.7	7.2 ± 9.2	14 (74)	5 (26)	0.01

Table 3. Prevalence of comorbidities among COVID-19 patients in Zanjan Province from February 23, 2020 to September 22, 2021. N: Number, SD: standard deviation, LOS: Length of Stay, CVD: Cardiovascular Diseases, CKD: Chronic Kidney Diseases, CND: Chronic Neurological Diseases, CBD: Chronic Blood Diseases CLD: Chronic Liver Diseases, IDD: Immunodeficiency Diseases.

significant hotspots for incidence and mortality rates in southeast areas, including Khorramdareh, AbharRud, and Alvand regions, with a 99% CI. Cluster and outlier analysis confirmed and complemented the results of hotspot analysis, identifying Khorramdareh as a High-High (HH) cluster for mortality rate, along with four Low-High (LH) outliers in the east and southeast regions. Bonab, where the capital of the province is located, was identified as a High-Low (HL) outlier for mortality rate (Fig. 6).

Discussion

This study highlights the epidemiological characteristics and spatial distribution of COVID-19 incidence and mortality in Zanjan province, Iran. Local variations in patient density, age-standardized rates, and hotspot areas underscore the need for region-specific prevention and control strategies. These findings emphasize the importance of tailoring interventions to local social, cultural, and geographical contexts to guide evidence-based decision-making and mitigate public health impacts.

The initial COVID-19 case in Zanjan was reported on March 3, 2020, approximately two weeks after the first documented case in Qom on February 19, 2020. This delay may be attributed to factors such as spatial distance and initial unfamiliarity with testing protocols among healthcare workers[13,35]. Similar delays have been observed in other regions; for instance, studies in the United States have noted that certain areas experienced later onset of cases due to geographic and infrastructural factors[36]. Understanding these temporal patterns is crucial for improving early detection and response strategies in future outbreaks.

In Zanjan province, the mean age of COVID-19 cases was 54.8 years, with a higher prevalence among women. Notably, infants under one year accounted for 2.5% of cases, experiencing a mortality rate of 7.2%. The 45–59 age group had the highest hospitalization rate, while the 5–14 age group recorded the highest number of deaths, aligning with previous studies[11,37,38]. A multinational cohort study involving 689,572 patients from 52 countries reported a median age of 58 years, with 49.4% male participants, and higher mortality in men (23.7%) compared to women (20%), consistent with our findings[8]. However, our study revealed a significant prevalence of COVID-19 in the younger age group (30–44 years), contrasting with earlier studies[11]. This discrepancy may be attributed to Iran's relatively younger population. It's important to recognize that age distribution of COVID-19 cases varies due to factors like population demographics, testing strategies, and preventive measures across regions. Therefore, local context and demographic characteristics are crucial when interpreting and applying findings related to COVID-19.

Gender also plays a significant role in COVID-19 vulnerability. In our study, women comprised 52% of hospitalized patients, differing from some studies[11,39]. but aligning with others[8]. Male gender was associated

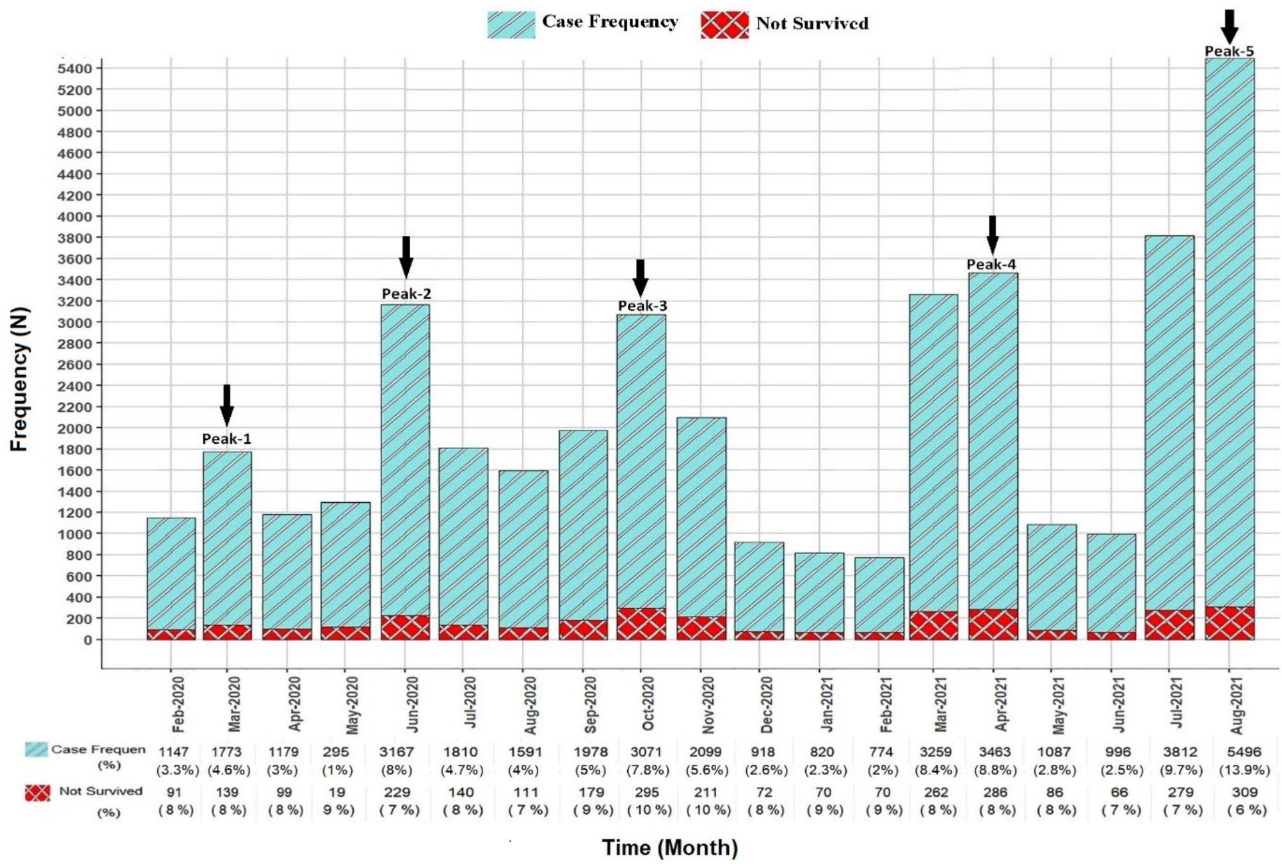

Fig. 4. Temporal trend of hospitalization, mortality rates, and peaks of COVID-19 in Zanjan province from Feb 2020 to Sep 2021.

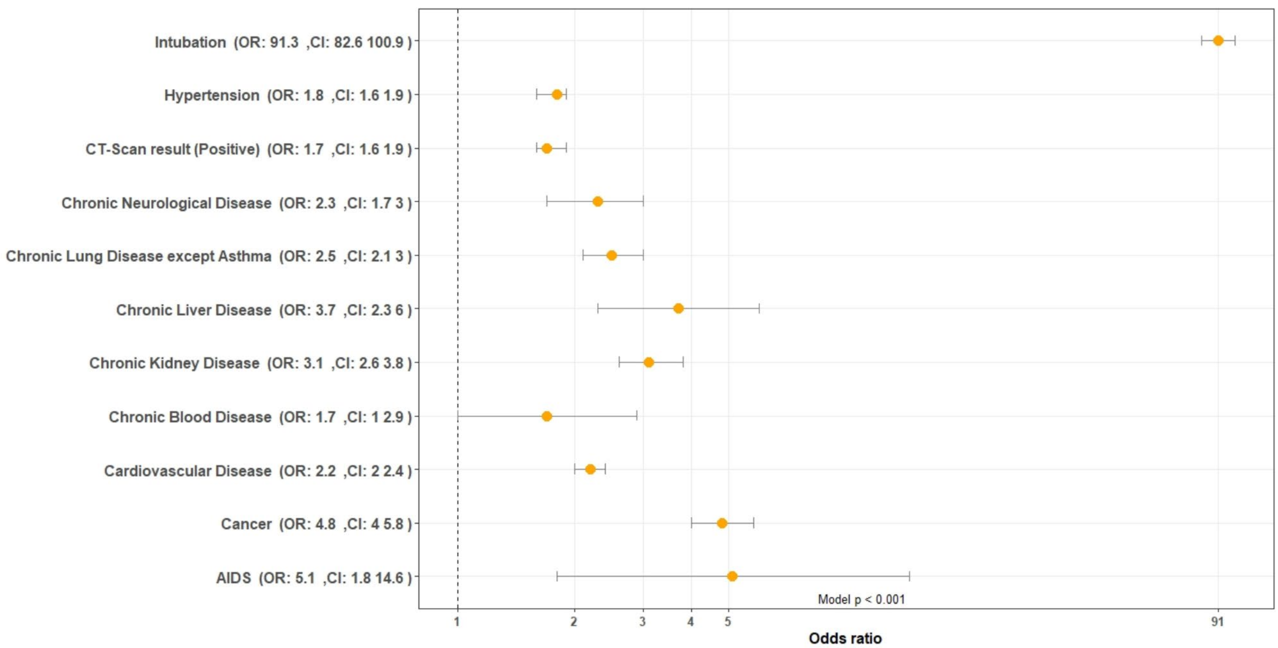

Fig. 5. Odds Ratio of death in COVID-19 patients with a certified outcome based on Univariate Regression Analysis.

					Vaccinated								
		Cases N (%)			First-Doze N (%)			Second-Doze N (%)			Unvaccinated N (%)		
Age Group	Has Comorbidity	Cases N (%)	Survived N (%)	Not-Survived N (%)	Cases N (%)	Survived N (%)	Not-Survived N (%)	Cases N (%)	Survived N (%)	Not-Survived N (%)	Cases N (%)	Survived N (%)	Not-Survived N (%)
< 18	No	717 (42.8)	706 (98.5)	11 (1.5)	39 (5.4)	39 (100)	0 (0)	24 (3.3)	23 (95.83)	1 (4.2)	654 (91.2)	644 (98.5)	10 (1.5)
	Yes	959 (57.2)	838 (87.4)	121 (12.6)	42 (4.4)	37 (88.1)	5 (11.9)	35 (3.6)	30 (85.71)	5 (14.3)	882 (92)	771 (87.4)	111 (12.6)
	Total	**1676 (4.2)**	**1544 (92.1)**	**132 (7.9)**	**81 (4.8)**	**76 (93.8)**	**5 (6.2)**	**59 (3.5)**	**53 (89.8)**	**6 (10.2)**	**1536 (91.6)**	**1415 (92.1)**	**121 (7.9)**
18–39	No	3058 (41.5)	2991 (97.8)	67 (2.2)	199 (6.5)	195 (97.99)	4 (2)	84 (2.7)	83 (98.81)	1 (1.2)	2775 (90.7)	2713 (97.8)	62 (2.2)
	Yes	4304 (58.5)	3843 (89.3)	461 (10.7)	271 (6.3)	248 (91.51)	23 (8.5)	119 (2.8)	107 (89.92)	12 (10.1)	3914 (90.9)	3488 (89.1)	426 (10.9)
	Total	**7362 (18.6)**	**6834 (92.8)**	**528 (7.2)**	**470 (6.4)**	**443 (94.3)**	**27 (5.7)**	**203 (2.8)**	**190 (93.6)**	**13 (6.4)**	**6689 (90.9)**	**6201 (92.7)**	**488 (7.3)**
40–59	No	5073 (39.9)	4935 (97.3)	138 (2.7)	682 (10.6)	669 (98.09)	13 (1.9)	154 (15.1)	151 (98.05)	3 (1.9)	4237 (83.5)	4115 (97.1)	122 (2.9)
	Yes	7646 (61.1)	6795 (88.9)	851 (11.1)	1020 (13.3)	925 (90.69)	95 (9.3)	203 (2.7)	186 (91.63)	17 (8.4)	6423 (84)	5684 (88.5)	739 (11.5)
	Total	**12,719 (32.2)**	**11,730 (92.2)**	**989 (7.8)**	**1702 (13.4)**	**1594 (93.7)**	**108 (6.3)**	**357 (2.8)**	**337 (94.4)**	**20 (5.6)**	**10,660 (83.8)**	**9799 (91.9)**	**861 (8.1)**
60–79	No	5552 (42.4)	5407 (97.4)	145 (2.6)	706 (12.7)	690 (97.73)	16 (2.3)	169 (3)	167 (98.82)	2 (1.2)	4678 (84.3)	4550 (97.3)	128 (2.7)
	Yes	7530 (57.6)	6606 (87.7)	924 (12.3)	991 (13.2)	884 (89.2)	107 (10.8)	175 (2.3)	163 (93.14)	12 (6.9)	6364 (84.5)	5559 (87.4)	805 (12.6)
	Total	**13,082 (33.1)**	**12,013 (91.8)**	**1069 (8.2)**	**1697 (13)**	**1574 (92.8)**	**123 (7.2)**	**344 (2.6)**	**330 (95.9)**	**14 (4.1)**	**11,042 (84.4)**	**10,109 (91.6)**	**933 (8.4)**
80+	No	1983 (42.1)	1936 (97.6)	47 (2.4)	234 (11.8)	226 (96.58)	8 (3.4)	45 (2.3)	45 (100)	0 (0)	1704 (85.9)	1665 (97.7)	39 (2.3)
	Yes	2722 (57.9)	2386 (87.7)	336 (12.3)	289 (10.6)	264 (91.35)	25 (8.7)	60 (2.2)	57 (95)	3 (5)	2373 (87.2)	2065 (87)	308 (13)
	Total	**4705 (11.9)**	**4322 (91.9)**	**383 (8.1)**	**523 (11.1)**	**490 (93.7)**	**33 (6.3)**	**105 (2.2)**	**102 (97.1)**	**3 (2.9)**	**4077 (86.7)**	**3730 (91.5)**	**347 (8.5)**

Table 4. Age group and Comorbidity-Specific survival analysis of COVID-19 patients stratified by vaccination status and dose in Zanjan Province, Iran. N: Number.

with higher mortality, consistent with previous research[8,11,40]. Biological factors, such as differences in immune response influenced by sex hormones and genetic factors, may contribute to this disparity[41]. Social factors, including higher occupational exposure among men and differences in health-seeking behaviors, may also contribute to increased mortality in men[40,42]. These findings underscore the necessity of integrating both biological and social considerations in public health strategies to effectively address gender disparities in COVID-19 outcomes.

Clinical manifestations of COVID-19 range from asymptomatic to severe presentations, evolving over time[43]. Early symptoms, such as loss of smell, taste, shortness of breath, and cough, have been replaced by fever, cough, tiredness, and loss of taste or smell as common symptoms according to WHO[44]. In this study, cough and respiratory symptoms were frequently reported, with cough-dyspnea emerging as the dominant pattern. This contrasts with other studies where fever[18,45,46]and dyspnea-cough-fever[8,11,47,48]were more prevalent. These variations underscore the heterogeneity of COVID-19 symptomatology across populations and timeframes, highlighting the need for healthcare providers to remain vigilant in recognizing diverse symptom patterns to ensure timely diagnosis and effective management. The epidemiological profile of COVID-19 in children differs significantly from adults. Globally, children constitute less than 15% of reported cases and are more likely to experience asymptomatic or mild infections[49]. In this study, a substantial proportion of hospitalized children had underlying health conditions, consistent with observations from Wuhan, China[50]. These findings align with reports that children with pre-existing conditions are at a heightened risk of severe illness[49,51,52]. Such evidence emphasizes the importance of implementing tailored precautions and interventions to safeguard this vulnerable group.

Most patients in this study presented with mild symptoms and recovered within a week of hospitalization. Those admitted to general wards exhibited less severe symptoms, lower mortality rates, and longer hospital stays than patients in isolated wards or ICUs. International data from 52 countries reported 15.9% ICU admissions among hospitalized COVID-19 patients, with one-third admitted on the first day[8]. This percentage aligns with other studies showing ICU admission rates between 17.1% and 35%[19,52]. Severe cases often involve complications such as thromboembolic events, acute cerebrovascular illness, and multiorgan failure, further underscoring the need for robust healthcare infrastructure to manage critical cases[53,54]. Similar findings from studies conducted in Detroit, the United Kingdom, and China highlighted the role of age, obesity, chronic kidney disease, and male gender in increasing mortality and ICU admission rates[18,19,55]. These results underscore the necessity of

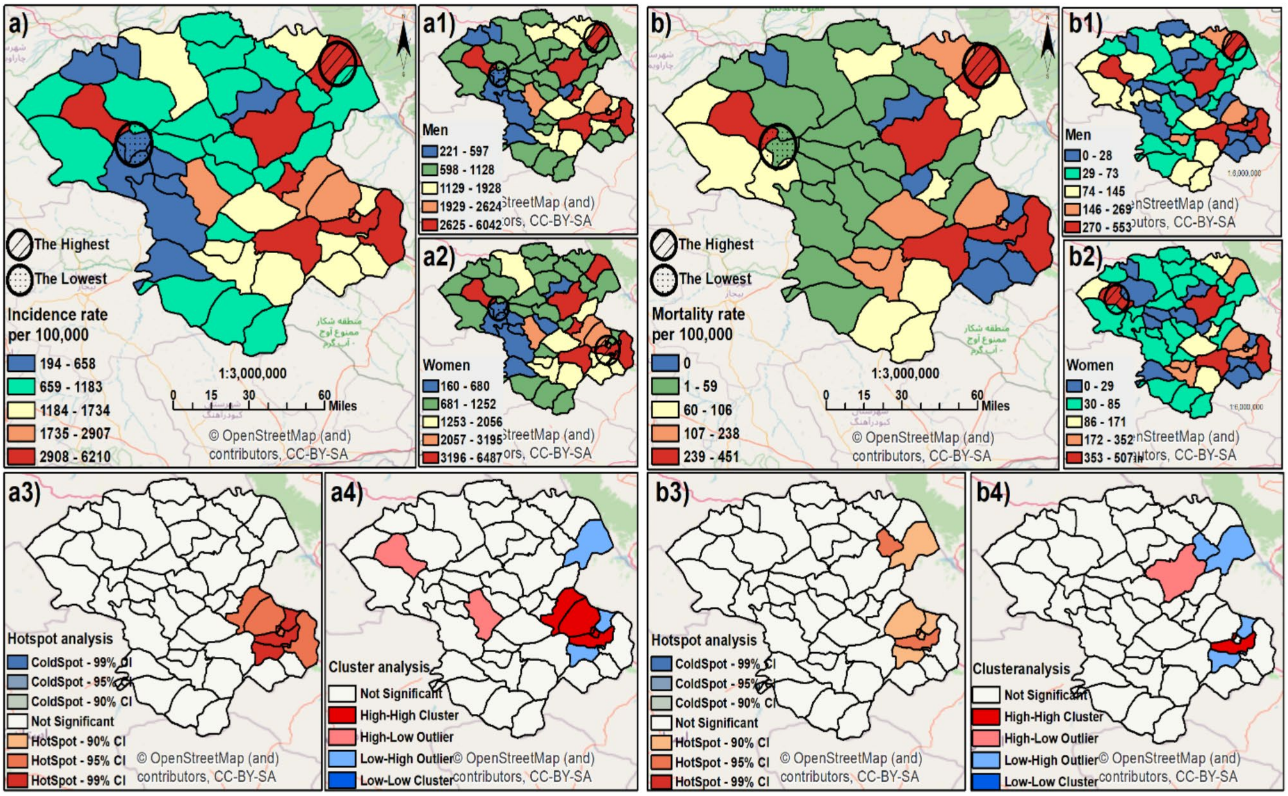

Fig. 6. Spatial distribution of age-standardized rate, hotspots, and clusters for COVID-19. **(a)** Incidence rate of COVID-19 in Total, **a1)** Incidence rate of COVID-19 in Men, **a2)** Incidence rate of COVID-19 in Women, **a3)** Hotspot analysis of Incidence rate, **a4)** Cluster analysis of Incidence rate, **(b)** Mortality rate of COVID-19 in Total, **b1)** Mortality rate of COVID-19 in Men, **b2)** Mortality rate of COVID-19 in Women, **b3)** Hotspot analysis of Mortality rate, **b4)** Cluster analysis of Mortality rate.

prioritizing high-risk populations in disease management strategies, particularly during resource allocation for critical care.

Comorbidities such as HIV/AIDS, CLD, CBD, and cancer were strongly associated with severe COVID-19 outcomes in this study, consistent with findings from international research. Studies have highlighted the increased susceptibility of individuals with cancer due to immunosuppression, either from the disease itself or from treatments such as chemotherapy and radiotherapy, which compromise the immune response to viral infections[56,57]. Similarly, patients with CLD are predisposed to severe outcomes, as liver dysfunction can impair systemic immunity and increase susceptibility to complications such as cytokine storms[58]. Research has also shown that individuals with HIV/AIDS have elevated risks of severe disease and mortality, likely due to immune dysregulation and higher rates of coexisting conditions[59]. Chronic blood diseases, such as sickle cell anemia and hemophilia, can also exacerbate COVID-19 severity by impairing oxygen transport, increasing infection risks, and complicating treatment due to coagulopathy and immune dysfunction[60]. These findings emphasize the necessity of tailored healthcare strategies for managing patients with these specific comorbidities, ensuring early intervention and optimized care to reduce mortality. The integration of comorbidity-specific protocols into pandemic preparedness plans can significantly improve outcomes for vulnerable populations.

This study found that healthcare workers accounted for only 1% of COVID-19 cases in Zanjan province, a rate significantly lower than the global estimate of 14% reported by the WHO[61,62]. This discrepancy may reflect the impact of prioritizing healthcare workers for vaccination in Iran, potentially reducing hospitalization rates among this group. International studies have shown variable seroprevalence rates among healthcare workers, with a meta-analysis reporting an average of 8.7% seroprevalence. Key risk factors for healthcare worker infections included male sex, frontline roles, and patient-facing duties, with nurses being the most affected subgroup[62]. These findings emphasize the importance of rigorous infection control measures and vaccination campaigns to protect this high-risk population.

This study demonstrated that stringent lockdown measures during the first and second epidemic peaks significantly reduced COVID-19 transmission rates, leading to a flattening of the epidemic curve. Regions with early, comprehensive lockdowns experienced a faster decline in case numbers, aligning with international studies highlighting the efficacy of such measures in controlling outbreaks[63,64]. Additionally, the initiation of mass vaccination campaigns before the fourth and fifth peaks was associated with substantial reductions in incidence and mortality, reinforcing findings from Saudi Arabia and China where coordinated interventions effectively curbed COVID-19 spread[26]. By mid-2021, a vaccination campaign known as the "I Vaccinate" initiative was launched to administer booster doses, aiming to enhance immunity among the general population. This campaign was actively promoted by the Zanjan University of Medical Sciences and contributed to a notable decline in both incidence and mortality rates during the later peaks (May 2021 to August 2021). The synergistic impact of combining lockdowns with vaccination underscores the importance of timely, integrated public health strategies. In Zanjan province, preventive measures such as mask usage, physical distancing, and hand hygiene played pivotal roles, particularly as 59% of patients reported contact with confirmed cases. Similar strategies in China and Saudi Arabia, including quarantine, public awareness campaigns, and restrictions on movement, proved effective in reducing transmission[26,64]. However, the economic, cultural, and social consequences of lockdowns, such as impacts on individual freedoms and increases in domestic violence, necessitate cautious implementation[63].

The Iranian Ministry of Health's color-coded system for identifying high-risk areas and enforcing strict protocols echoes global efforts to tailor interventions to local epidemiological conditions. Screening, diagnostic testing, and personal protective equipment have been shown to be cost-effective strategies when combined with measures like mask-wearing and travel restrictions, though lockdowns are generally less cost-efficient and more disruptive[63]. Accelerating vaccination efforts, bolstering healthcare infrastructure, and implementing targeted, long-term preventive measures are essential for effective pandemic control. Promoting public awareness and behavior change remains critical for sustained adherence to preventive practices and mitigating future outbreaks.

This study identified urban areas in Zanjan province, particularly central and southern regions, as hotspots for COVID-19 transmission, primarily due to high population density and close contact in crowded environments. These findings align with similar patterns observed in Tehran, Qom, and Mashhad, where high infection rates were linked to densely populated residential areas, metro stations, shopping malls, and public transportation hubs[11,16,65,66]. International studies from China and India further corroborate the association between population density and COVID-19 spread, emphasizing the global relevance of these findings[22,67]. Additionally, socioeconomic factors such as aging populations, urbanization, literacy rates, and healthcare accessibility significantly influence transmission dynamics in both Iranian and global contexts[12]. These insights highlight the critical need for targeted public health interventions in urban settings to mitigate transmission risks effectively.

The vulnerability of densely populated areas is further exacerbated by the challenges of maintaining social distancing and the higher susceptibility of older populations with weakened immune systems[66]. While Bonab had the highest number of cases, Abbar exhibited the highest ASR and mortality rates, likely driven by factors such as extensive social interactions, travel connections with northern cities, delays in seeking medical care, and limitations in healthcare infrastructure. These findings highlight the multifactorial nature of COVID-19 transmission and emphasize the need for region-specific strategies, including improving healthcare accessibility, promoting compliance with public health measures, and reducing travel-related risks in high-incidence areas.

Mortality rates are a critical measure of the severity and impact of COVID-19, and understanding their determinants is essential for effective pandemic management. In this study, the overall mortality rate was 7.85%. This aligns with findings from a systematic review and meta-analysis reporting rates ranging from 2.3 to 49%, depending on disease severity and population characteristics[68]. Regionally, the mortality rate in Mashhad, Iran, was reported as 17.7%[11], while studies in China documented rates between 11.5% and 15%[69]. Variations in mortality rates across studies can be attributed to differences in geographic location, study design, population demographics, and healthcare systems. Additional factors such as genetic predispositions, comorbidities, aging populations, and regional healthcare capacities further contribute to these disparities. Similar patterns have been observed in international research, emphasizing the role of demographic and healthcare inequalities in shaping COVID-19 outcomes. Recognizing and addressing these variables is crucial for interpreting mortality data and developing targeted strategies to reduce the disease burden.

The vaccination analysis underscores the critical role of immunization in mitigating COVID-19 mortality and severity, particularly for high-risk populations. Vaccinated individuals demonstrated significantly lower mortality (6.3%) compared to unvaccinated individuals (8.1%), with full vaccination offering the greatest benefit. Stratified analysis by age and comorbidities revealed the amplified protective effect of two vaccine doses, especially in older populations (60+), where mortality rates dropped to 5.3% compared to 87–87.4% among unvaccinated individuals. These findings align with international studies, including large-scale analyses in Canada and Israel, which demonstrated substantial reductions in severe outcomes and mortality among fully vaccinated populations[70,71]. The variability in outcomes by vaccine type reflects broader trends reported in real-world effectiveness studies. For example, Sinopharm and AstraZeneca vaccines, both widely used globally, have been shown to significantly reduce severe outcomes, consistent with the study findings[72,73]. Conversely, the higher mortality observed among Sputnik recipients, though limited by sample size, warrants further evaluation, mirroring concerns raised in smaller regional studies[74]. International experiences underscore the importance of rapid deployment strategies to maximize vaccine impact[71,75]. Future efforts should also focus on booster programs to counteract waning immunity and emerging variants. These findings emphasize the critical role of vaccination in pandemic control, offering valuable insights for tailoring global and local public health strategies.

This study provides valuable insights into the epidemiology of COVID-19 in Iran, offering a comprehensive analysis of the disease's patterns, localized transmission dynamics, and public health implications. The study's strengths include its large sample size, extended duration, and fine-grained geographical analysis, which facilitate a nuanced understanding of COVID-19 trends over time and across different regions. The integration of clinical, demographic, and spatial data further enhances the robustness of the findings, highlighting the multifaceted nature of the disease and its varying impact in different settings.

The geographical variability in disease spread, particularly the delayed detection of cases in Zanjan province, highlights the urgent need to strengthen early warning systems and rapid response capabilities, particularly in regions with limited healthcare infrastructure. Tailoring public health interventions to local contexts is critical, considering factors such as population density, urbanization, and regional healthcare resources. This study also underscores the essential role of healthcare workers in mitigating disease transmission. The lower proportion of healthcare workers among COVID-19 patients in Zanjan, compared to global averages, reflects the effectiveness of prioritizing protective measures and vaccinations for medical staff, emphasizing the need for comprehensive strategies to safeguard healthcare personnel and maintain healthcare system resilience.

The emergence of new variants, such as Omicron, underscores the limitations of current vaccines and the necessity of adaptable vaccination strategies and ongoing surveillance. Equitable vaccine distribution and international collaboration are imperative to address global health disparities, particularly in low- and middle-income countries. Furthermore, enhancing diagnostic capabilities and real-time data tracking is essential for resource allocation and effective pandemic response.

The COVID-19 pandemic has exposed critical gaps in global and local health systems, including delays in case detection, insufficient resource allocation, and challenges in public health communication. In Zanjan, the surge in cases during the fifth peak demonstrated the importance of geospatial analysis and real-time data tracking in identifying hotspots and optimizing resource deployment. Globally, misinformation and vaccine hesitancy continue to hinder public health responses, necessitating culturally tailored communication strategies. The success of vaccination campaigns in reducing hospitalization rates among healthcare workers in Zanjan highlights the importance of building community trust and engagement in public health initiatives. By integrating these lessons, public health systems can enhance their resilience, equity, and preparedness for future pandemics while addressing the needs of diverse populations.

Limitations

This study provides valuable insights into the COVID-19 dynamics in Zanjan province, but several limitations should be considered when interpreting the findings and assessing their generalizability. First, the retrospective design and reliance on secondary data may introduce biases and affect the reliability of the results. The study was conducted solely within Iran, which limits the applicability of the findings to populations with differing healthcare infrastructures, socio-economic conditions, and demographic profiles. For instance, variations in hospital bed availability, intensive care unit capacity, and healthcare resources between Zanjan and other regions may influence patient outcomes and the relevance of the findings elsewhere. Additionally, the study did not account for important socioeconomic factors, such as income, education, and healthcare access, which are known to significantly affect health outcomes and the severity of COVID-19. The primary data source, the Medical Care Monitoring Center (MCMC), includes only clinical and demographic information, excluding key socioeconomic variables. This limitation restricts the comprehensiveness of the study and its ability to assess the impact of socio-economic disparities on the incidence and mortality of COVID-19. Furthermore, the study did not consider individual behaviors, which can influence disease transmission and outcomes. The geographical analysis, while valuable, was also limited by the absence of socioeconomic data, which likely contributes to the spatial distribution of COVID-19 incidence and mortality. Despite the use of rigorous geocoding procedures, residual errors in address standardization could slightly affect the spatial results. Finally, the study's findings are specific to the healthcare policies, demographics, and public health interventions of Zanjan province. These measures, including lockdowns and vaccination strategies, may differ significantly in other regions and countries, affecting the generalizability of the results. The rapidly evolving nature of the pandemic, along with ongoing policy changes, further limits the long-term relevance of these findings.

Future research should seek to address these limitations by incorporating a broader range of socioeconomic variables, improving the scope of geospatial analyses, and considering diverse regional and national contexts. By integrating these factors, future studies can provide more holistic insights into the dynamics of COVID-19 and contribute to the development of effective, equitable public health strategies.

Conclusions

This study provides critical insights into the epidemiology, transmission dynamics, and determinants of COVID-19 outcomes in Zanjan province, Iran. The findings emphasize significant demographic, geographic, and clinical factors influencing disease spread and patient outcomes. Women exhibited a higher prevalence of COVID-19, while men demonstrated higher mortality rates, aligning with global patterns of gender-based differences. Advanced age and comorbidities, including HIV/AIDS, CLD, CBD, and cancer emerged as key predictors of mortality, underscoring the vulnerability of elderly and chronically ill populations. Urban areas were identified as transmission hotspots, highlighting the role of population density and mobility in accelerating spread. Vaccination, particularly with two doses, significantly reduced mortality and disease severity, affirming its central role in pandemic control. Delayed case detection and healthcare disparities in Zanjan underscore the need for robust early warning systems and equitable resource distribution. Spatial and demographic variations in outcomes stress the importance of localized, data-driven public health strategies. Key recommendations include enhancing early detection systems through advanced diagnostics and real-time surveillance, expanding vaccine coverage for high-risk groups, and addressing vaccine hesitancy through targeted campaigns. Urban hotspots require stricter enforcement of preventive measures, while vulnerable populations need personalized care and improved access to healthcare services. Global cooperation remains essential for equitable vaccine distribution, research on emerging variants, and the sharing of best practices to bolster pandemic preparedness. Strengthening healthcare infrastructure, workforce training, and emergency response capacities will ensure resilience against future health crises. These findings provide a foundation for evidence-based public health interventions, optimizing resource allocation, and enhancing pandemic response strategies to safeguard health outcomes globally.

Data availability

The datasets are available from the corresponding author upon reasonable request.

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Author contributions
The study design was developed by the lead author, M.S, in collaboration with co-author A.J, with M.S serving as supervisor for manuscript drafting, revising, and statistical analysis. Data acquisition was conducted by M.S and A.J manuscript revision was carried out by M.S. All authors provided their full agreement on all aspects of the work and approved the final version for publication in a professional and scholarly manner, reflecting the rigor and ethical standards of the academic community.

Declarations

Ethics approval and consent to participate
This study did not involve human participants or animals. The research was based solely on retrospective data collected from existing records within the Medical Care Monitoring Center (MCMC) system. As such, no direct interaction with human subjects or animals was required. The study was conducted in adherence with the ethical guidelines stipulated by the Ethics Committee of Zanjan University of Medical Sciences, and received approval under Protocol Number: IR.ZUMS.REC.1400.102. The data used in the study was obtained from the Medical Care Monitoring Center, which was also approved by the Health Systems Research (HSR) committee of Zanjan University of Medical Sciences under project Number: A-12-1073-8.

Consent for publication
Due to the retrospective nature of this study, which utilized de-identified data stored in the MCMC system, obtaining individual consent for publication was not applicable. The study did not use any identifiable or demographic information of patients, ensuring their anonymity and privacy in accordance with ethical guidelines. As a result, specific consent for publication was deemed unnecessary.

Competing interests
The authors declare no competing interests.

Additional information
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