

RESEARCH ARTICLE

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Multiple Myeloma in Iran: National Spatiotemporal Trends, Geographic Hotspots, and Projections to 2035

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Abstract

Background: Multiple myeloma (MM) is a malignant plasma cell disorder with a rising global burden; however, comprehensive national analyses in Iran remain limited. This study evaluated the national and provincial burden of MM in Iran, identified spatial and temporal patterns, and forecasted trends through 2035. **Methods:** Using data from the Global Burden of Disease Study 2021, we conducted an ecological analysis of MM incidence, prevalence, mortality, and disability-adjusted life years (DALYs) in Iran from 1990 to 2021, by sex and province. Spatial patterns were assessed using Moran's I and Getis-Ord Gi* statistics in ArcGIS. Future trends were forecast using autoregressive integrated moving average models with exogenous variables (ARIMAX). **Results:** In 2021, Iran recorded 767 new MM cases (ASIR: 0.98 per 100,000), 2,006 prevalent cases (ASPR: 2.41 per 100,000), and 593 deaths (ASMR: 0.79), accounting for 15,873 DALYs (ASDR: 19.38 per 100,000). Men consistently showed higher rates than women. Spatial analyses identified central-western provinces, including Isfahan, Lorestan, Tehran, Alborz, and Qazvin, as incidence and prevalence hotspots, while Zanzan and Markazi were identified as coldspots. Mortality and DALY hotspots were concentrated in Isfahan, Hamedan, Alborz, and Qom, whereas Mazandaran and Ilam showed lower burdens. Forecasts indicate continued increases by 2035, with incidence projected to reach 1.30 per 100,000 and prevalence projected to reach 3.15 per 100,000. Temporary declines during 2020–2021 likely reflected COVID-19–related disruptions in diagnosis and reporting. **Conclusions:** The burden of MM in Iran is increasing and geographically unequal. Strengthening early detection, diagnostic capacity, treatment access, and region-specific cancer control strategies is essential to reduce disparities and improve outcomes.

Keywords: multiple myeloma, epidemiology, spatiotemporal analysis, geographic hotspots, cancer burden, Iran

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Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation within the bone marrow, leading to end-organ damage including bone lesions, anemia, renal impairment, and hypercalcemia [1, 2]. Globally, MM accounts for approximately 1% of all cancers and around 10% of hematologic malignancies [3]. Over recent decades, its burden has risen steadily driven by population aging, advances in diagnostic capability, and changing environmental and lifestyle factors [1, 4, 5].

According to the Global Cancer Observatory (GLOBOCAN 2022), an International Agency for Research on Cancer (IARC) database, multiple myeloma

caused 188,000 new cases and 121,000 deaths worldwide in 2022, with projections suggesting that, if current trends persist, incidence and mortality could increase by more than 70% and 75%, respectively, by 2045 [6]. The highest rates are reported in high-income regions such as North America, Australia/New Zealand, and parts of Europe [7]. However, incidence is also increasing in low- and middle-income countries (LMICs), where late presentation, limited diagnostic infrastructure, and restricted access to effective therapies contribute to poorer outcomes [8].

In Iran, published data on multiple myeloma remain sparse and largely limited to single-province studies. For example, a population-based cancer registry analysis from Golestan Province (2004–2009) reported an age-

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standardized incidence rate (ASR) of 2.1 per 100,000 in men and 2.0 in women, with higher incidence in urban than rural settings [9, 10]. While informative, this study and others like it does not capture the nationwide epidemiology of MM, nor does it explore spatial clustering, temporal trends, or future burden projections.

Comprehensive national mapping of MM burden is essential for guiding resource allocation, optimizing diagnostic and treatment services, and identifying regions that may benefit from targeted screening or environmental investigation. Spatiotemporal analytical methods, including spatial autocorrelation, hotspot detection, and time-series forecasting models such as ARIMAX, have been applied successfully in other countries, including China [11] and Italy [12], to reveal geographic disparities and predict disease trends. To date, such methods have not been applied to MM in Iran.

This study aims to fill that gap by providing the first national-level spatiotemporal analysis of MM in Iran, using data from the Global Burden of Disease Study 2021. We assess provincial and national trends in incidence, prevalence, mortality, and disability-adjusted life years (DALYs) from 1990 to 2021, identify geographic hotspots, and project the disease burden to 2035. The findings are intended to inform national cancer control strategies and support equitable healthcare planning in the context of a resource-limited health system.

Materials and Methods

Study design and data sources

This ecological study used data from the Global Burden of Disease Study 2021 [13], obtained through the GBD Compare visualization tool [14]. Annual estimates for MM, including age-standardized incidence rates (ASIR), mortality rates (ASMR), and disability-adjusted life years (DALYs), were extracted for Iran at both national and provincial levels for the period from 1990 to 2021. These estimates were available in sex-disaggregated formats (male, female, and combined), allowing for gender-based comparisons via GBD Results Tool.

The GBD estimates are generated through a standardized methodology that incorporates multiple data sources, including cancer registries, vital registration systems, health surveys, and scientific literature. A combination of modeling approaches, such as the Cause of Death Ensemble model (CODEm) and DisMod-MR, is used to ensure consistency and comparability across locations and time periods.

Disease definition

Multiple myeloma was defined in accordance with the GBD classification system, based on the International Classification of Diseases, 10th Revision (ICD-10) codes C90.00 to C90.02. This definition allows for standardized case identification across different sources and regions [15].

Age standardization and data characteristics

All incidence, mortality, and DALY rates were age-standardized by the GBD research team using the GBD world standard population. Age standardization

is applied to adjust for differences in age distribution across populations and over time, enabling meaningful comparisons between provinces and at the national level. The rates are expressed per 100,000 population.

Spatial analysis

The geographical distribution of multiple myeloma (MM) incidence, mortality, and DALY rates (per 100,000 people) across Iranian provinces in 2021 was analyzed using rates for both sexes. Provincial-level rates were calculated and mapped using ArcGIS 10.8.2. The geographical distribution of MM in Iran were assessed using both global and local spatial autocorrelation analyses. First, global spatial autocorrelation indices, such as Moran's I and Getis-Ord's G, were calculated to evaluate the overall spatial dependence and patterns of MM across the country. These measures provided insights into the presence and strength of spatial autocorrelation, which is crucial for understanding the geographical distribution of MM. The Global Moran's I index was first applied. Using this statistic, it is possible to examine whether provinces with similar incidence, mortality, and DALY rates for MM are clustered or randomly distributed across the country. The formula for calculating this statistic is as follows:

$$I = \frac{N \sum_{i=1}^N \sum_{j=1}^N w_{ij} (x_i - \bar{x})(x_j - \bar{x})}{S_0 \sum_{i=1}^N (x_i - \bar{x})^2}$$

In formula, N is the total number of spatial units under study, which in this case is 31. x_i is the value of the variable (standardized incidence, mortality, or DALY rate of MM) at location (province) i . $\bar{x}$ is the observed mean value of the variable under investigation in the study. w_{ij} represents the spatial weight between provinces i and j , which quantifies the geographical proximity of these provinces. S_0 is the sum of all spatial weights, ensuring that the spatial relationships are properly normalized in the equation. To detect local spatial patterns, the Local Moran's I statistic is used. This index measures the spatial each province compared with its neighboring provinces and also assesses their significance. The Local Moran's I statistic is a decomposition of the global Moran's I and for province i can be calculated using the following formula:

$$I_i = \frac{(x_i - \bar{x})}{m_2} \sum_{j=1}^N w_{ij} (x_j - \bar{x})$$

The Getis-Ord's G statistic is used when the presence of a clustering pattern in the data collection points is confirmed; the purpose of using the Getis-Ord's G index is to detect the presence or absence of clustering of high or low values in spatial data. In other words, it aims to determine whether high values have created clusters or low values have formed clusters. This index can be calculated using the following formula:

$$G(d) = \frac{\sum_{i=1}^N \sum_{j=1}^N w_{ij}(d) x_i x_j}{\sum_{i=1}^N \sum_{j=1}^N x_i x_j}$$

In the next step, to precisely identify which provinces constitute hot spots and cold spots, the Local Getis statistic was used. These local indices allowed for the detection of localized patterns and anomalies that might not be apparent from the global analysis. Finally was determined through permutation tests to verify that these clusters were statistically significant and not just random variations. The Local Getis statistic for a province can be calculated using the following formula:

$$G_i = \frac{\sum_{j=1}^n w_{ij} x_j - \bar{X} \sum_{j=1}^n w_{ij}}{S \sqrt{\frac{N \sum_{j=1}^n w_{ij}^2 - \left(\sum_{j=1}^n w_{ij} \right)^2}{n-1}}}$$

In this formula, all the symbols and abbreviations are similar to the previous formulas. The only additional term in this formula is S, which represents the standard deviation of the variable under study [16-18]. Spatial boundary shapefiles were obtained from the Remote Sensing and GIS Training Academy of Iran and used as base maps. All spatial analyses, including mapping and geoprocessing, were performed using ArcMap (ArcGIS Desktop 10.8.2; ESRI, USA), and datasets were standardized to a common coordinate reference system.

Temporal trend analysis

To analyze patterns over time and estimate future values (2022–2035) of multiple myeloma incidence rates in Iran, we employed an Autoregressive Integrated Moving Average model with Exogenous Variables (ARIMAX). This modeling approach integrates three components(autoregression, differencing (integration), and moving average) while also incorporating external predictor variables. The general structure of the model can be expressed as:

$$y_t = \beta_0 + \sum_{i=1}^p \phi_i y_{t-i} + \sum_{j=1}^q \theta_j \varepsilon_{t-j} + \sum_{k=1}^K \gamma_k x_{k,t} + \varepsilon_t$$

In this equation, y_t denotes the multiple myeloma rate at time t ; ϕ_i and θ_j represent the autoregressive and moving average coefficients, respectively; $x_{k,t}$ refers to the k -th exogenous covariate at time t with associated coefficient γ_k and ε_t indicates the error term, assumed to follow a white-noise process. The above formulation reflects an ARIMAX(1,0,1) structure with exogenous terms measured at the same time point as the dependent variable. In cases where non-stationarity due to stochastic trends was detected, differencing ($d>0$) would be applied

prior to model estimation.

In our analysis, the exogenous predictors included two variables: (1) the calendar year, introduced as a continuous variable to model long-term deterministic trends, and (2) a binary indicator flagging the COVID-19 pandemic years (2020–2023) to capture potential disruptions in disease patterns. Model adequacy was evaluated through a set of diagnostic procedures, including visual inspection of residual autocorrelation, assessment of stationarity, and tests for heteroscedasticity. If diagnostics indicated model misspecification or non-stationary residuals, appropriate transformations or differencing were implemented before finalizing the forecasts. The forecast package in R was used for time series forecasting and ARIMAX modeling.

Results

Descriptive Epidemiology

In 2021, Iran's age-standardized incidence rate of multiple myeloma (MM) was 0.98 per 100,000 (95% UI: 0.63–1.21), with a prevalence of 2.41 per 100,000 (95% UI: 1.47–3.10), a mortality rate of 0.79 per 100,000 (95% UI: 0.51–0.96), and 19.38 DALYs per 100,000 (95% UI: 12.38–23.03). A total of 767 new cases, 2,006 prevalent cases, and 593 deaths were recorded nationwide (Table 1), with higher rates observed in males compared to females across all metrics. Male-specific rates were 1.15 incidence, 2.76 prevalence, 0.94 mortality, and 22.88 DALYs per 100,000 (Table S1); corresponding female rates were 0.81 incidence, 2.06 prevalence, 0.64 mortality, and 15.89 DALYs per 100,000 (Table S2).

Provincial variation was pronounced: Lorestan exhibited the highest incidence at 1.69 per 100 000, followed by Tehran at 1.67 and Yazd at 1.41. Tehran led in prevalence (4.41), with Lorestan (4.21) and Yazd (3.37) trailing. Mortality peaked in Lorestan (1.34) and Tehran (1.33), while DALYs rates reached 34.13 in Lorestan, 30.37 in Tehran, and 27.98 in Yazd (Figure 1).

Global Spatial Autocorrelation

Global Moran's I for prevalence was 0.08 ($Z = 1.78$; $p < 0.05$), indicating significant positive spatial autocorrelation (Figure S1). In contrast, incidence ($I \approx 0.01$), mortality ($I \approx 0.02$) and DALYs ($I \approx 0.01$) yielded Z-scores below critical thresholds, suggesting these metrics did not display strong clustering at the national level. The disparity between prevalence and the other measures justified a detailed local analysis (Figures S2-S4).

Local Cluster Analysis (Anselin Local Moran's I)

Local Moran's I identified high-high (HH) clusters of incidence and prevalence in central-western provinces. The provinces of Isfahan, Lorestan, Alborz and Qazvin formed significant HH clusters, indicating regions where high values were surrounded by similarly elevated neighbors. Zanjan and Markazi emerged as low-high (LH) outliers, suggesting anomalously low rates amidst high-burden surroundings. Mortality exhibited a parallel pattern: Isfahan, Hamedan, Alborz and Qom comprised HH clusters, whereas Mazandaran and Markazi were classified as LH outliers. Analysis of DALYs revealed HH

Table 1. National Burden of Multiple Myeloma in Iran in 2021, including age-standardized rates (per 100,000) and absolute case counts for incidence, prevalence, mortality, and disability-adjusted life years (DALYs), with 95% uncertainty intervals.

Province	Mortality		DALY		Prevalence		Incidence	
	Count	ASMR	Count	ASDR	Count	ASPR	Count	ASIR
Iran	593.44 (384.85–717.27)	0.79 (0.51–0.96)	15873.24 (10103.34–18859.44)	19.38 (12.38–23.03)	2005.95 (1229.67–2606.16)	2.41 (1.47–3.1)	766.71 (489.75–954.74)	0.98 (0.63–1.21)
East Azarbaijan	29.07 (21.53–38.03)	0.75 (0.55–0.98)	782.35 (569.99–1023.13)	18.24 (13.29–23.58)	87.42 (60.6–122.33)	1.99 (1.38–2.71)	36.06 (25.81–48.72)	0.88 (0.64–1.17)
Isfahan	37.83 (24.16–52.25)	0.71 (0.45–0.98)	1018.97 (636.52–1368.87)	17.66 (11.1–24.04)	129.52 (77.37–180.43)	2.2 (1.34–3.07)	49.15 (31.16–67.02)	0.88 (0.56–1.21)
Semnan	5.23 (3.22–7.04)	0.75 (0.47–1.01)	139.42 (83.23–187.71)	18.53 (11.18–24.83)	16.73 (9.44–23.62)	2.19 (1.26–3.02)	6.65 (3.97–9.19)	0.92 (0.56–1.27)
Kerman	15.65 (11.11–22.14)	0.62 (0.44–0.89)	441.63 (304.17–600.87)	15.44 (10.82–21.37)	47.24 (32.09–66.47)	1.62 (1.12–2.3)	19.43 (13.61–27.36)	0.73 (0.51–1.06)
Gilan	15.13 (9.78–29.05)	0.48 (0.31–0.93)	400.05 (258.66–756.37)	12.01 (7.84–22.6)	51.63 (32.54–97.43)	1.51 (0.96–2.86)	19.73 (12.5–38.25)	0.61 (0.39–1.16)
Khorasan-e-Razavi	35.23 (25.71–50.03)	0.64 (0.46–0.92)	974.06 (710.65–1327.38)	16.14 (11.97–22.4)	103.53 (72.4–148.61)	1.69 (1.2–2.37)	43.34 (32.11–61.7)	0.76 (0.56–1.1)
West Azarbaijan	15.52 (11.94–22.96)	0.57 (0.44–0.85)	431.18 (326.01–628.2)	13.91 (10.62–20.33)	47.29 (33.8–70.55)	1.48 (1.07–2.22)	19.39 (14.61–29.2)	0.67 (0.5–1)
Lorestan	20.44 (6.75–30.44)	1.34 (0.45–2)	571.68 (182.28–846.73)	34.13 (11.05–50.46)	72.02 (23.45–114.29)	4.21 (1.4–6.51)	27.02 (8.89–40.79)	1.69 (0.56–2.53)
South Khorasan	4.5 (2.85–6.1)	0.6 (0.38–0.83)	118.55 (73.12–157.14)	15.21 (9.43–20.28)	13.08 (7.68–17.73)	1.67 (0.99–2.29)	5.48 (3.41–7.3)	0.72 (0.46–0.97)
Bushehr	3.98 (2.48–7.91)	0.45 (0.28–0.92)	112.26 (71.43–217.46)	11.23 (7.02–22.18)	13.79 (8.13–26.05)	1.34 (0.8–2.6)	5.21 (3.16–10.09)	0.56 (0.34–1.1)
Sistan and Baluchistan	7.94 (5.88–10.57)	0.52 (0.39–0.71)	245.26 (174.72–323.08)	14.01 (10.28–18.49)	19.96 (13.95–28.15)	1.15 (0.83–1.59)	9.25 (6.65–12.35)	0.58 (0.42–0.79)
Alborz	22.21 (14.26–29.47)	0.9 (0.58–1.19)	622.54 (391.7–824.45)	21.72 (13.79–28.7)	84.54 (52.55–117.48)	2.85 (1.79–3.88)	30.26 (19.32–40.69)	1.13 (0.74–1.53)
Khuzestan	27.66 (19.91–36.43)	0.75 (0.54–0.99)	792.86 (542.74–1035.18)	19.23 (13.59–24.98)	90 (61.49–122.28)	2.15 (1.5–2.88)	35.45 (24.94–46.76)	0.91 (0.66–1.21)
Ilam	2.83 (2.05–4.73)	0.56 (0.41–0.95)	79.59 (58.74–126.9)	14.17 (10.31–23.1)	9.49 (6.53–15.56)	1.66 (1.16–2.76)	3.67 (2.62–6.14)	0.69 (0.49–1.15)
Ardabil	6.15 (4.24–10.7)	0.52 (0.35–0.91)	168.02 (120.13–284.46)	13.1 (9.24–22.48)	19.39 (12.92–32.82)	1.48 (1–2.57)	7.79 (5.37–13.49)	0.63 (0.43–1.11)
Yazd	10.84 (4.22–15.93)	1.15 (0.46–1.7)	286.98 (107.36–424.39)	27.98 (10.63–41.22)	35.18 (12.66–54.28)	3.37 (1.24–5.07)	13.82 (5.32–20.42)	1.41 (0.55–2.1)
Kermanshah	13.21 (9.53–17.95)	0.66 (0.48–0.91)	364.69 (253.78–480.55)	17.01 (11.98–22.41)	40.16 (27.37–54.89)	1.85 (1.27–2.5)	16.47 (11.62–22.31)	0.8 (0.57–1.09)
Markazi	10.17 (6.41–13.74)	0.66 (0.42–0.89)	267.63 (164.31–349.08)	16.75 (10.31–21.95)	31.62 (18.17–43.05)	1.96 (1.13–2.63)	12.7 (7.87–17.22)	0.81 (0.51–1.1)
Golestan	8.82 (6.29–14.31)	0.55 (0.39–0.91)	256.36 (187.99–403.16)	14.38 (10.35–23.04)	25.86 (17.92–43.67)	1.42 (0.98–2.39)	10.91 (7.64–17.92)	0.65 (0.45–1.08)
Chahar Mahaal and Bakhtiari	3.92 (2.66–6.98)	0.46 (0.31–0.82)	108.27 (74.33–190.52)	11.56 (7.9–20.47)	15.13 (9.65–26.23)	1.59 (1.01–2.81)	5.36 (3.56–9.28)	0.6 (0.4–1.04)
Kohgiluyeh and Boyer-Ahmad	3.14 (2.27–4.29)	0.55 (0.4–0.78)	92.54 (65.99–122.94)	14.61 (10.6–19.7)	11.72 (7.69–16.51)	1.84 (1.22–2.64)	4.22 (3.02–5.93)	0.71 (0.51–1.03)
North Khorasan	3.51 (2.43–6.17)	0.48 (0.33–0.86)	97.8 (69.58–164.01)	12.42 (8.74–21.32)	10.03 (6.83–16.74)	1.26 (0.85–2.13)	4.28 (2.91–7.38)	0.57 (0.38–0.99)
Fars	27.76 (19.04–46.09)	0.59 (0.4–0.99)	778.44 (542–1251.78)	15.1 (10.42–24.61)	92.37 (61.63–148.74)	1.76 (1.17–2.86)	35.8 (24.06–59.14)	0.73 (0.49–1.23)
Hamadan	13.91 (8.77–18.59)	0.76 (0.48–1.01)	379.8 (231.07–499.17)	19.88 (12.15–26.06)	41.29 (25.44–57.47)	2.14 (1.34–2.96)	17.14 (10.75–22.86)	0.92 (0.58–1.23)
Mazandaran	20.37 (14.12–37.37)	0.53 (0.37–0.99)	550.88 (387.36–976.37)	13.49 (9.48–24.06)	74.26 (49.07–132.38)	1.78 (1.18–3.21)	27.2 (18.32–48.51)	0.69 (0.46–1.24)
Tehran	189.33 (71.22–266.85)	1.33 (0.49–1.82)	4709.37 (1744.16–6703.76)	30.37 (11.24–42.99)	695.58 (253.56–1063.99)	4.41 (1.62–6.67)	251.07 (93.59–366.23)	1.67 (0.63–2.41)
Zanjan	3.87 (2.27–8.14)	0.38 (0.22–0.81)	103.51 (62.04–212.87)	9.55 (5.71–19.86)	12.59 (7.19–25.06)	1.14 (0.65–2.32)	4.94 (2.87–10.35)	0.47 (0.27–0.99)
Kurdistan	11.93 (6.59–15.92)	0.77 (0.43–1.03)	326.29 (176.12–439.2)	19.59 (10.7–26.21)	37.12 (18.95–53.77)	2.2 (1.14–3.11)	14.97 (8.19–20.78)	0.94 (0.52–1.28)
Hormozgan	5.31 (3.28–10.04)	0.43 (0.26–0.84)	156.82 (100.02–282.77)	11.13 (6.92–20.86)	16.89 (10.06–29.95)	1.19 (0.71–2.15)	6.73 (4.08–12.34)	0.52 (0.31–0.99)
Qazvin	8.62 (6.24–11.23)	0.74 (0.54–0.99)	237.81 (169.95–304.44)	18.53 (13.29–23.66)	28.41 (19.84–39.6)	2.17 (1.53–2.99)	11.06 (7.8–14.86)	0.91 (0.65–1.21)
Qom	9.35 (5.29–12.28)	0.86 (0.5–1.13)	257.62 (140.84–343.24)	21.23 (11.82–27.98)	32.12 (17.5–44.96)	2.59 (1.45–3.57)	12.17 (6.85–16.4)	1.07 (0.61–1.42)

clustering in Isfahan, Alborz and Qom and LH outliers in Mazandaran, Ilam and Markazi. No significant low-low (LL) clusters or high-low (HL) outliers were observed for any metric (Figure 2).

Generalized Getis–Ord G^* -Score

The Getis–Ord G^* hot spot analysis reinforced evidence of local spatial clustering. Incidence showed a Z-score of 2.12 ($p < 0.03$), and prevalence yielded a Z-score of 2.83 ($p < 0.01$), both indicating statistically significant clustering of high-value provinces. Mortality and DALYs also demonstrated significant clustering, with Z-scores of approximately 2.24 ($p < 0.05$) and 2.12 ($p < 0.05$), respectively, suggesting moderate but statistically significant aggregation of high-burden areas at the 95% confidence level. These findings highlight distinct geographic patterns in the distribution of multiple myeloma burden across Iran, particularly for prevalence and incidence, and support the need for localized public health investigation and resource allocation (Figures S5–S8).

Local Hotspot and Coldspot Detection (Getis–Ord G^*)

Local G^* statistics pinpointed Isfahan as a 99 percent confidence hotspot for all four indicators. Surrounding provinces including Lorestan, Qazvin, Tehran and Alborz consistently reached 95 percent hotspot status for incidence and prevalence. Peripheral areas such as Qom and Markazi occasionally crossed the 90 percent threshold, classifying them as lower-confidence hotspots. Notably, no province achieved significant coldspot status at the 95 percent level; however, Zanjan and Markazi appeared as 90 percent coldspots for prevalence, indicating localized pockets of unusually low disease burden (Figure 3).

The convergence of HH clusters and high-confidence hotspots in central-western Iran particularly around Isfahan, Lorestan, Alborz and Qazvin underscores a coherent spatial signature of MM burden. Conversely, identified LH outliers and low-confidence coldspots reveal potential areas of underdiagnosis or protective factors. These localized patterns highlight the importance of

targeted epidemiologic investigations into environmental exposures, healthcare access and genetic predispositions to explain regional heterogeneity.

Trend Analysis Using Arimax

The auto.arima function identified ARIMAX(2,0,0) as the optimal model structure for all outcomes. The autoregressive parameters were consistently large ($AR1 \approx 1.64$ – 1.84 ; $AR2 \approx -0.90$ to -0.75), indicating that each year's rates were strongly influenced by those from one and two years earlier. This second-order autoregressive structure effectively captured the pronounced serial dependence in the data. Intercepts (with standard errors) for each outcome and sex-stratified analysis are reported below, together with the estimated effects of the annual trend and the pandemic indicator on the age-standardized rate scale (Table S3).

Trends of Mortality Rates

The model intercept for overall mortality was 0.4926 (SE 0.0146), with intercepts of 0.3833 (SE 0.0128) for females and 0.5974 (SE 0.0188) for males. On the age-standardized scale the year term indicates a steady, gradual rise in mortality: the modelled overall mortality increased from 0.51 per 100 000 (95% CI 0.35 to 0.72) in 1990 to 0.79 (0.51 to 0.96) in 2021, and is projected to reach about 0.98 (0.94 to 1.03) in 2030 and 1.04 (0.99 to 1.09) in 2035 (Table 2). The model includes a pandemic indicator that produces a temporary downward shift in observed rates relative to the long term trend; on the modeled scale this short term change is of modest magnitude compared with the longer term increase (Figure 4).

Trends of Incidence Rates

The incidence intercept was 0.5091 (SE 0.0214) overall, 0.3993 (SE 0.0194) for females and 0.6126 (SE 0.0267) for males. The modeled overall incidence rose from 0.54 per 100 000 (0.36 to 0.75) in 1990 to 0.98 (0.63 to 1.21) in 2021; projections place incidence at 1.19 (1.13 to 1.25) in 2030 and 1.30 (1.24 to 1.36) in 2035. This pattern mirrors mortality in showing a persistent upward

Table 2. Age-Standardized Incidence, Prevalence, Mortality, and Disability-Adjusted Life Years (DALYs) for Multiple Myeloma in Iran Across Three Time Points: historical estimates for 1990, current estimates for 2021, and ARIMAX modeled projections for 2030 and 2035. Values are presented per 100,000 population with 95% uncertainty interval.

Gender	Year	DALY Rate	Mortality Rate	Incidence Rate	Prevalence Rate
Overall	1990	12.84 (8.5–17.52)	0.51 (0.35–0.72)	0.54 (0.36–0.75)	0.95 (0.62–1.35)
	2021	19.38 (12.38–23.03)	0.79 (0.51–0.96)	0.98 (0.63–1.21)	2.41 (1.47–3.1)
	2030	23.85 (22.8–24.9)	0.98 (0.94–1.03)	1.19 (1.13–1.25)	2.8 (2.6–2.99)
	2035	25.36 (24.28–26.44)	1.04 (0.99–1.09)	1.3 (1.24–1.36)	3.15 (2.94–3.35)
Female	1990	10.14 (6.51–15.77)	0.4 (0.25–0.61)	0.42 (0.27–0.65)	0.78 (0.49–1.21)
	2021	15.89 (8.65–20.8)	0.64 (0.36–0.84)	0.81 (0.45–1.07)	2.06 (1.06–2.85)
	2030	19.35 (18.47–20.23)	0.78 (0.74–0.82)	0.97 (0.92–1.02)	2.38 (2.21–2.55)
	2035	20.68 (19.78–21.57)	0.84 (0.8–0.87)	1.06 (1.01–1.12)	2.66 (2.49–2.84)
Male	1990	15.39 (8.64–23.57)	0.62 (0.35–0.99)	0.65 (0.36–1.01)	1.12 (0.64–1.65)
	2021	22.88 (13.7–28.57)	0.94 (0.56–1.21)	1.15 (0.67–1.48)	2.76 (1.51–3.65)
	2030	28.31 (26.96–29.65)	1.17 (1.11–1.23)	1.4 (1.33–1.48)	3.24 (3.01–3.48)
	2035	30.08 (28.69–31.47)	1.24 (1.18–1.3)	1.53 (1.45–1.6)	3.63 (3.39–3.87)

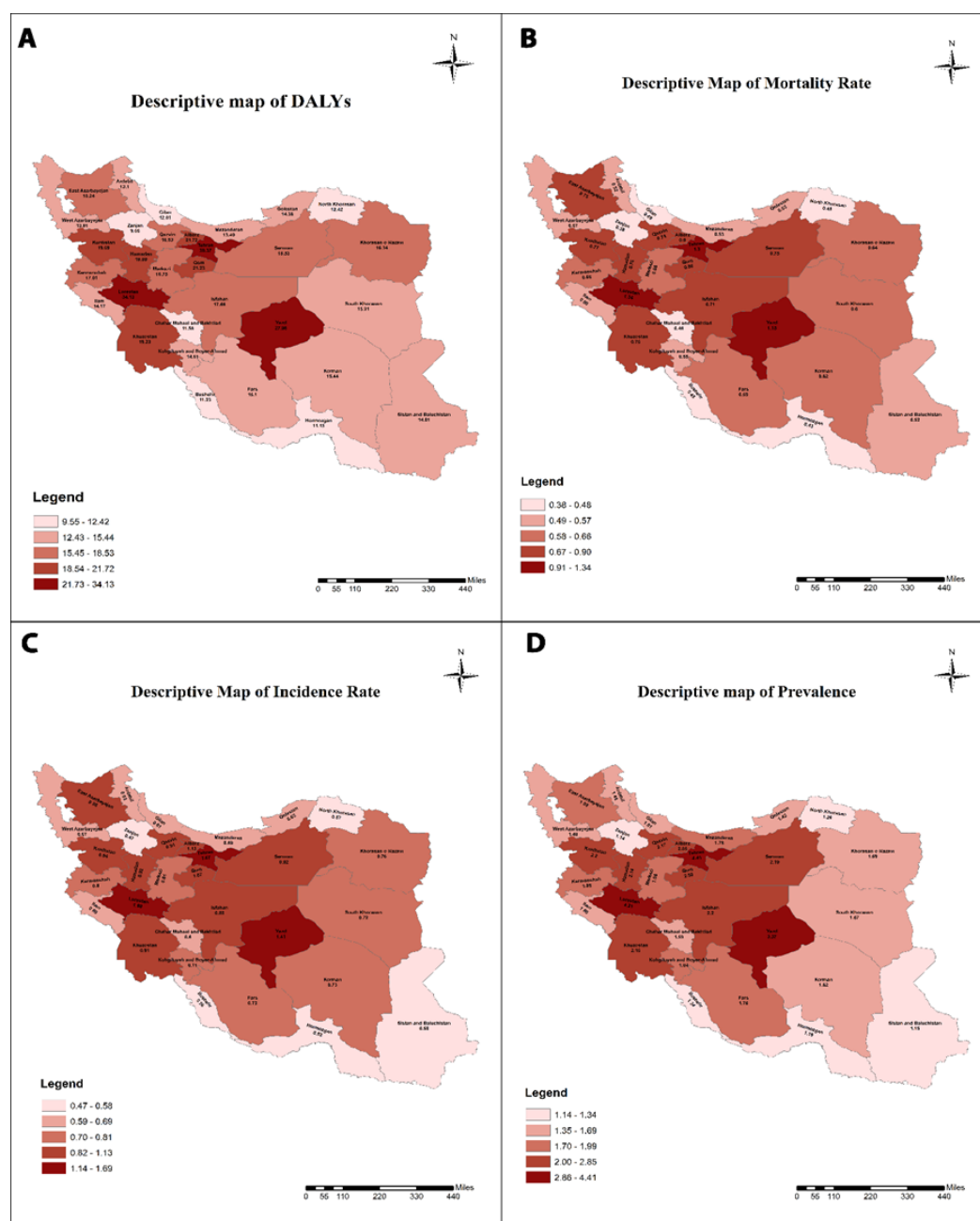


Figure 1. Provincial Variation in Age-Standardized Rates of Multiple Myeloma in Iran, 2021. Panel A: Disability-adjusted life years (DALYs); Panel B: Mortality; Panel C: Incidence; Panel D: Prevalence.

secular trend on the age-standardized scale, interrupted by a short run depression during the pandemic period captured by the indicator.

Trends of Daly Rates

Because of the outcome scale, DALY intercepts are larger: 12.3939 (SE 0.3580) overall, 9.7793 (SE 0.3073) for females and 14.8096 (SE 0.4678) for males. The overall age-standardized DALY rate is estimated at 12.84 (8.50 to 17.52) in 1990 and 19.38 (12.38 to 23.03) in 2021, with projections of 23.85 (22.80 to 24.90) in 2030 and 25.36 (24.28 to 26.44) in 2035. On the modeled scale the annual increment in DALYs is larger than for the other measures, and the pandemic indicator corresponds to a more noticeable short term drop in standardized DALY rates, though the projected long term increase remains

evident.

Trends of Prevalence Rates

Prevalence intercepts were 0.8425 (SE 0.0672) overall, 0.6771 (SE 0.0591) for females and 0.9941 (SE 0.0831) for males. The modeled overall prevalence increased from 0.95 per 100 000 (0.62 to 1.35) in 1990 to 2.41 (1.47 to 3.10) in 2021, and is projected to 2.80 (2.60 to 2.99) in 2030 and 3.15 (2.94 to 3.35) in 2035. Like incidence and mortality, prevalence shows a steady upward trajectory on the age-standardized scale with a pandemic period deviation captured by the indicator.

Discussion

This study provides the first national-level assessment

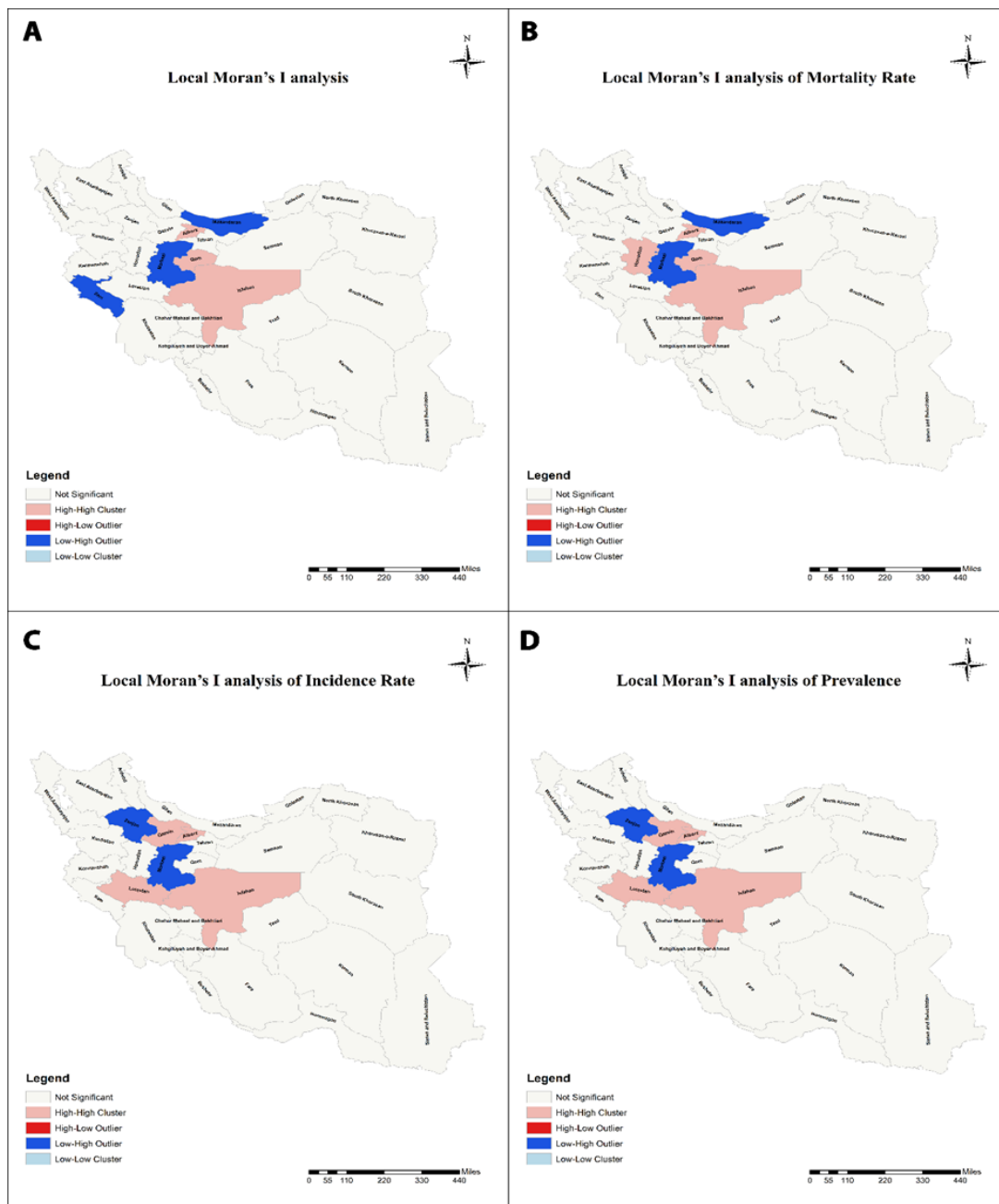


Figure 2. Local Moran's I Cluster Maps of Multiple Myeloma in Iran, 2021, showing significant high-high (HH) and low-high (LH) clusters. Panel A: DALYs; Panel B: Mortality; Panel C: Incidence; Panel D: Prevalence.

of multiple myeloma in Iran, examining its burden and distribution over more than three decades. The findings are clear: incidence, prevalence, mortality, and DALYs have all increased steadily since 1990, and forecasts suggest this rise will continue through at least 2035. Across all metrics, the burden is higher in men, and certain provinces most notably Isfahan, Lorestan, Alborz, and Qazvin emerge as persistent high-burden clusters.

Geographic patterns and possible explanations

The spatial clustering observed in central and western provinces likely reflects a combination of healthcare system factors and underlying risk exposures. Regions with stronger oncology infrastructure, more comprehensive cancer registries, and greater access to diagnostic technologies inevitably detect more cases. At

the same time, industrial activity, agricultural pesticide use, and urban environmental pollutants factors previously linked to MM risk [7, 8] are more common in some of these provinces. Higher socioeconomic status in some of these areas may also contribute by increasing healthcare utilization and diagnostic uptake. In contrast, provinces appearing as low-burden outliers, such as Markazi and Mazandaran, may not have genuinely lower incidence; incomplete registry coverage and underdiagnosis remain plausible explanations.

Importantly, differences between incidence and mortality patterns across provinces should also be considered. For example, Lorestan shows both relatively high incidence (1.69) and high mortality (1.34), which may suggest not only higher disease occurrence but also delayed diagnosis and/or limited access to modern

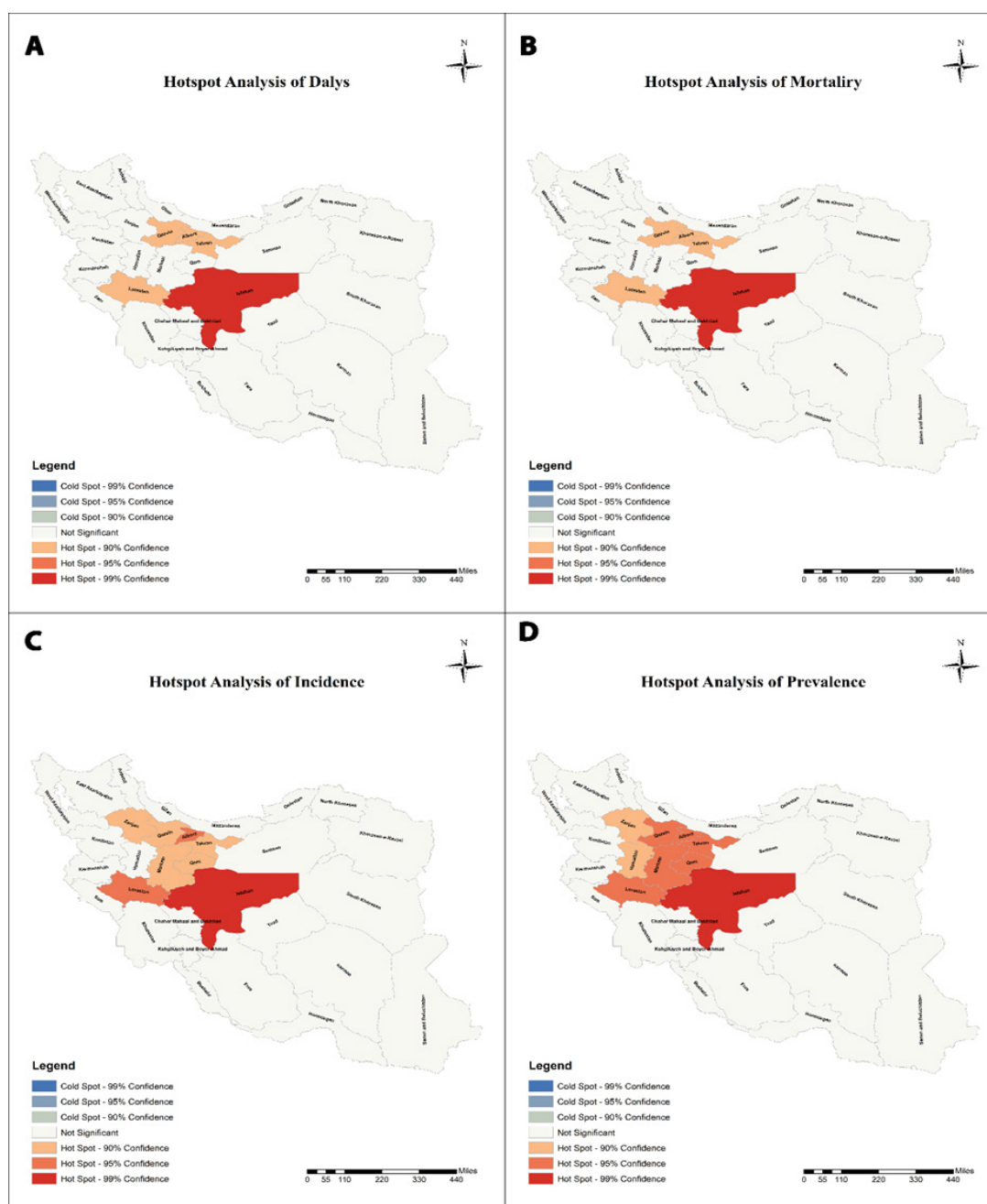


Figure 3. Local Getis–Ord G_i^* Hotspot Maps of Multiple Myeloma in Iran, 2021, identifying statistically significant high-burden and low-burden provinces. Panel A: DALYs; Panel B: Mortality; Panel C: Incidence; Panel D: Prevalence.

treatment options, including novel therapeutic agents and hematology-oncology services. In contrast, Tehran presents a similar incidence (1.67) but a slightly lower mortality (1.33), which may reflect better access to specialized care, earlier diagnosis, and more effective treatment infrastructure.

In addition, interpretation of low-burden “coldspot” provinces requires caution. For instance, Zanzan shows a markedly lower incidence (0.47), which may represent either a truly lower underlying risk or, more plausibly, underdiagnosis and incomplete case ascertainment. Similar uncertainty applies to provinces such as Markazi and Mazandaran, where lower observed burden may be influenced by variability in diagnostic capacity, registry completeness, and healthcare-seeking behavior.

These regions may also have distinct demographic or environmental profiles that require further investigation to determine whether they confer true protective effects or reflect data limitations.

Temporal trends in a global context

The rising trajectory we document is consistent with reports from other regions, including North America, Europe, and Asia [5, 7, 11]. Part of this trend likely reflects a true increase in disease incidence, but improved diagnostic capabilities such as routine bone marrow biopsy, flow cytometry, and advanced imaging have undoubtedly played a role. Equally important is the impact of novel therapeutics, including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies,

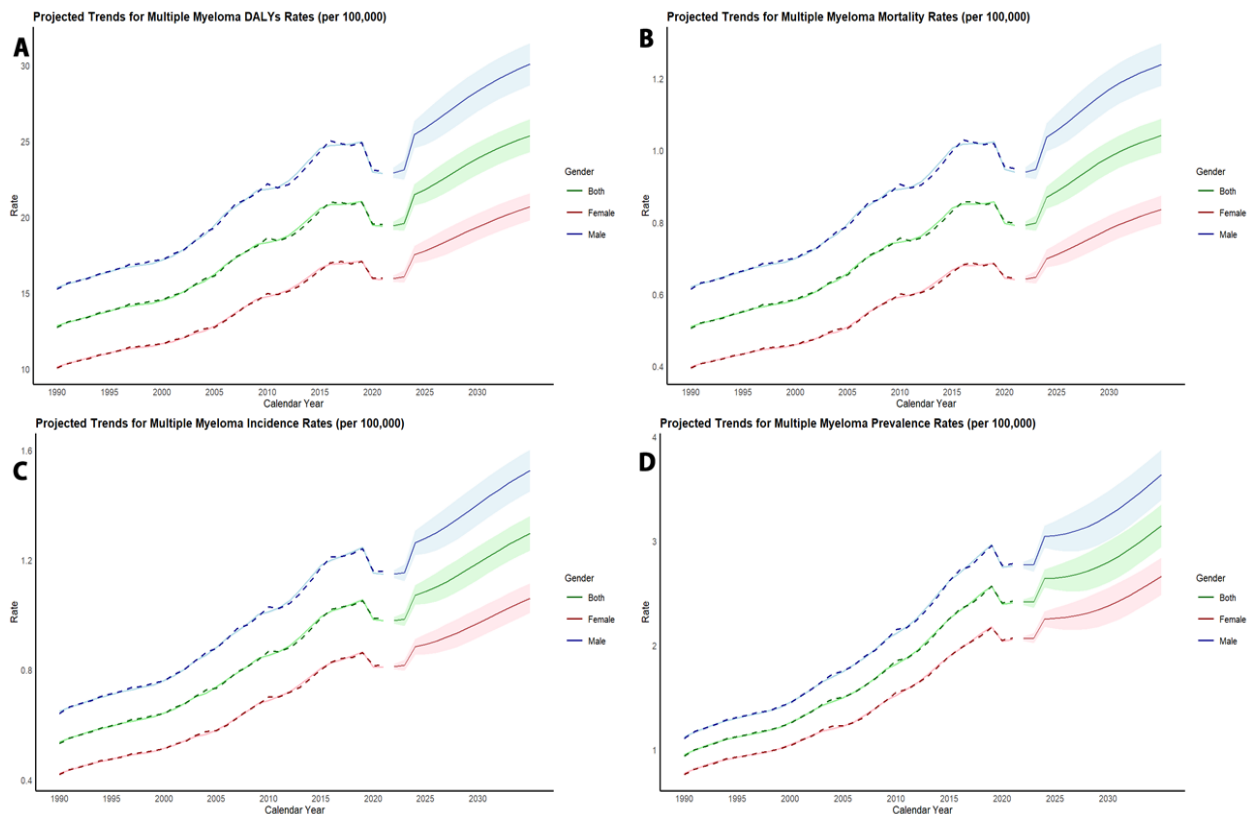


Figure 4. Temporal Trends in Age-Standardized Rates of Multiple Myeloma in Iran from 1990 to 2021, with ARIMAX-modeled projections to 2035. Panel A: DALYs; Panel B: Mortality; Panel C: Incidence; Panel D: Prevalence. Shaded areas represent 95% confidence intervals.

which have significantly extended survival [1, 3, 4], expanding the pool of prevalent cases.

The temporary decline in rates during 2020–2021 is almost certainly an artifact of the COVID-19 pandemic, which disrupted cancer diagnostic pathways, delayed elective procedures, and affected registry operations worldwide [13]. Similar pandemic-related drops in recorded incidence have been documented in other cancers, with subsequent rebounds once healthcare access normalised. Our ARIMAX projections assume a return to baseline registry functioning, but the long-term effects of the pandemic on diagnostic timeliness and treatment initiation in Iran remain to be fully understood.

Policy and practice implications

Translating these findings into action requires targeted strategies that acknowledge Iran's complex healthcare landscape. The persistent hotspots identified particularly Isfahan, Lorestan, Alborz, and Qazvin demand locally tailored interventions. In Isfahan and Tehran, where industrial activity coincides with high MM burden, environmental audits of manufacturing zones should be prioritized to evaluate potential carcinogen exposure. For rural high-burden regions like Lorestan, integrating monoclonal protein screening into existing mobile NCD programs could circumvent barriers to specialized diagnostics. Meanwhile, provinces with proximity to tertiary centers (e.g., Alborz, Qazvin) are prime candidates for scaling up novel therapy access through hub-and-spoke distribution models potentially leveraging Tehran's

referral infrastructure for cost-efficient drug delivery.

Critically, implementation must contend with Iran's resource realities. Drug import constraints, uneven distribution of hematology specialists, and fragmented registry systems necessitate pragmatic approaches:

- Mobile screening could capitalize on Iran's extensive rural health house network (~18,000 nationally) for initial blood collection, with samples referred to regional labs.
- Environmental investigations might focus on high-risk industries (petrochemicals, agriculture) using existing regulatory mechanisms to avoid new fiscal burdens.
- Therapy access expansions should be phased initially anchoring to high-volume centers like Shariati Hospital before gradual provincial rollout.

For provinces with anomalously low burden (e.g., Markazi, Mazandaran), enhancing passive surveillance through primary care physician training in MM diagnostic coding offers a low-cost alternative to registry overhauls. Simultaneously, sentinel surveillance in districts with migration ties to hotspots could clarify whether observed "cold spots" reflect true epidemiology or systemic under-ascertainment.

These proposals align pragmatically with Iran's National Cancer Control Plan. Success will depend on cross-sector coordination—for instance, engaging environmental agencies in hotspot analyses—to maximize limited resources while confronting this geographically unequal and rising malignancy.

Strengths and limitations

While our study benefits from standardized GBD data spanning decades and robust analytical methods, several caveats warrant consideration. First, the GBD's model-dependent estimates while invaluable for cross-national comparisons may not fully capture subprovincial heterogeneity in Iran's diverse districts. For instance, industrial exposures in Isfahan's urban centers versus its rural peripheries likely drive varying MM risk, yet our province-level aggregation obscures such micro-geographic patterns.

Second, despite GBD's adjustments for under-ascertainment, residual gaps in registry completeness (particularly in resource-limited provinces like Sistan-Baluchestan) could attenuate true burden estimates. Finally, our projections assume stable diagnostic practices and healthcare access a tenuous assumption given Iran's evolving sanctions landscape and potential advances in screening technologies (e.g., widespread serum-free light chain assay adoption).

Future directions

Future studies should move beyond mapping to investigate the drivers of geographic variation. Linking registry data with environmental exposure records, occupational histories, and genetic information would allow a more detailed exploration of causation. Analytical methods such as geographically weighted regression could help disentangle the effects of socioeconomic status, healthcare access, and environmental hazards. Additionally, integrating registry data with clinical datasets could shed light on regional differences in treatment patterns and survival outcomes.

In conclusion, multiple myeloma in Iran is becoming more common and remains unevenly distributed, with identifiable geographic hotspots that have persisted over time. Without targeted, region-specific interventions, the upward trajectory projected to 2035 is unlikely to change. These findings provide a strong evidence base for focused cancer control policies that combine early detection, equitable treatment access, and enhanced surveillance, tailored to the needs of high-burden regions

Author Contribution Statement

MRT and GJ designed the study. GK, ST, HR, BS, HM, SG, and MV contributed to data collection, analysis, and interpretation. MRT drafted the manuscript. MB supervised the project and is the corresponding author. All authors critically revised the manuscript and approved the final version.

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Ethics approval and consent to participate

This study is a secondary analysis of publicly available data from the Global Burden of Disease (GBD) Study. As

no individual-level or identifiable human data were used, ethical approval and informed consent were not required.

Consent for publication Not applicable

Availability of data and materials The datasets analyzed during the current study are publicly available from the Global Burden of Disease (GBD) repository at <http://ghdx.healthdata.org/gbd-results-tool>.

Competing interests

The authors declare that they have no competing interests.

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