7DEOH *1) contd.....*

The Provinces	DALY per 100000										
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Esfahan	13.81	13.43	13.13	12.83	12.71	12.63	12.56	12.4	12.65	12.62	12.66
Fars	18.06	17.54	17.21	17.02	16.83	16.52	16.14	15.76	16.01	15.9	15.83
Gilan	8.297	8.011	7.963	7.792	7.568	7.487	7.482	7.505	7.703	7.751	7.798
Golestan	27.88	27.06	26.49	25.95	25.85	26.02	26.27	26.15	26.72	26.67	26.76
Hamadan	23.41	22.92	22.6	22.34	22.2	21.85	21.63	21.43	21.9	21.77	21.78
Hormozgan	13.74	13.2	13	12.68	12.35	11.98	11.63	11.22	11.27	11.15	11.1
Ilam	23.35	22.81	22.46	22.13	22.02	22.07	21.76	21.22	21.56	21.41	21.27
Kerman	22.12	21.48	20.83	20.16	19.5	19.08	18.64	18.17	18.44	18.34	18.39
Kermanshah	23.64	22.64	22.04	21.49	20.95	20.42	19.99	19.64	20.03	19.61	19.47
Khuzestan	26.52	25.66	24.99	24.11	23.61	22.91	22.18	21.65	21.96	21.72	21.62
Kohgiluyeh and Buyer Ahmad	21.32	20.91	20.58	20.23	19.89	19.42	18.83	18.25	18.2	17.64	17.32
Kurdistan	10.58	10.23	9.923	9.663	9.476	9.272	9.05	8.781	8.858	8.796	8.716
Lorestan	40.12	40.29	39.74	39.68	39.73	39.86	39.94	39.63	39.97	39.36	38.99
Markazi	21.75	20.54	19.56	18.84	18.36	17.98	17.85	17.56	17.82	17.64	17.61
Mazandaran	9.578	9.411	9.339	9.182	8.998	8.924	8.971	8.985	9.203	9.163	9.165
North Khorasan	25.69	25.07	24.77	24.53	24.42	23.98	23.48	22.77	22.87	22.32	22.08
Qazvin	17.36	16.99	16.76	16.56	16.47	16.41	16.39	16.06	16.25	16.09	16.05
Qom	30.2	28.15	26.29	24.67	23.63	22.49	21.83	21.45	21.72	21.56	21.49
Razavi Khorasan	20.37	19.51	18.98	18.56	18.09	17.41	16.69	15.95	15.99	15.59	15.39
Semnan	15.25	14.79	14.49	14.21	13.92	13.66	13.44	13.05	13.12	12.91	12.78
Sistan and Baluchestan	35.82	34.6	33.44	32.66	31.93	30.47	28.96	27.24	26.88	26.05	25.54
South Khorasan	25.06	24.22	23.34	22.64	21.99	21.2	20.6	19.95	19.93	19.32	18.99
Tehran	15.42	15	14.76	14.72	14.75	14.69	14.71	14.12	14.37	14.3	14.24
West Azarbaijan	16.69	16.04	15.64	15.32	15.13	14.86	14.59	14.26	14.47	14.31	14.24
Yazd	16.29	15.82	15.39	14.84	14.27	13.94	13.56	13.11	13.16	12.92	12.76
Zanjan	12.24	11.78	11.38	11.05	10.74	10.55	10.45	10.32	10.46	10.38	10.34

Table 2. Characteristics of high-risk and low-risk ALL clusters age-standardized rate of DALYs due to hepatitis B in Iran using the gini optimized cluster collection method.
(source: Global Burden of Disease).

Cluster Number in Fig. (6)	Risk	Number of Provincial Involved	Coordinate of Center	Radius(km)	Relative Risk	P-value	LLR	Cluster Type
1	High	6	33.5 N & 48.8 E	192.03	2.31	<0.001	238.59	Most likely
2	High	2	37.4 N & 57. 2 E	203.8	1.97	<0.001	167.63	Secondary
3	Low	3	36.5 N & 48.4 E	157.8	0.23	<0.001	218.03	Most likely
4	Low	4	31.1 N & 53.2 E	378.4	0.31	<0.001	153.69	Secondary
5	Low	3	38.9 N & 51. 3 E	181.31	0.45	<0.001	131.72	Secondary

The full epidemiological, statistical, demographic, and geographic characteristics of the clusters discovered by Gini Optimized are shown in Table **2**. According to the results of this table, it can be said that the most likely high-risk cluster with LLR=238.59 is located in the west of Iran (centered at 33.5 N & 48.8 E), which has a radius of 192.03 km and includes the provinces of Lorestan, Kermanshah, Hamadan, Markazi, Khuzestan. It was Ilam (cluster 1 in Fig. **3**). In this cluster, the relative risk of incidence is estimated to be 2.31, which means that the amount of DALYs inside this cluster is 2.31 times that of the areas outside the cluster. Also, a secondary high-risk cluster with LLR=167.63 was identified in northeastern Iran, which included North Khorasan and Golestan provinces. On the other, the most probable low-risk cluster with LLR=218.03 was discovered in the northwestern part of Iran (centered at 36.5 N & 48.4 E), which had a radius of 157.8 km and included the provinces of Zanjan, Gilan, and Kurdistan (cluster 3 in Fig. **3**). The relative risk in this cluster was estimated to be 0.23, which means that the amount of DALYs inside the cluster is lower than outside the cluster and 0.23 times. Two secondary low-risk clusters were identified in the central and northern regions of Iran (clusters 4 and 5 in Fig. **3**), in which the relative risk was estimated at 0.31 and 0.45, respectively.

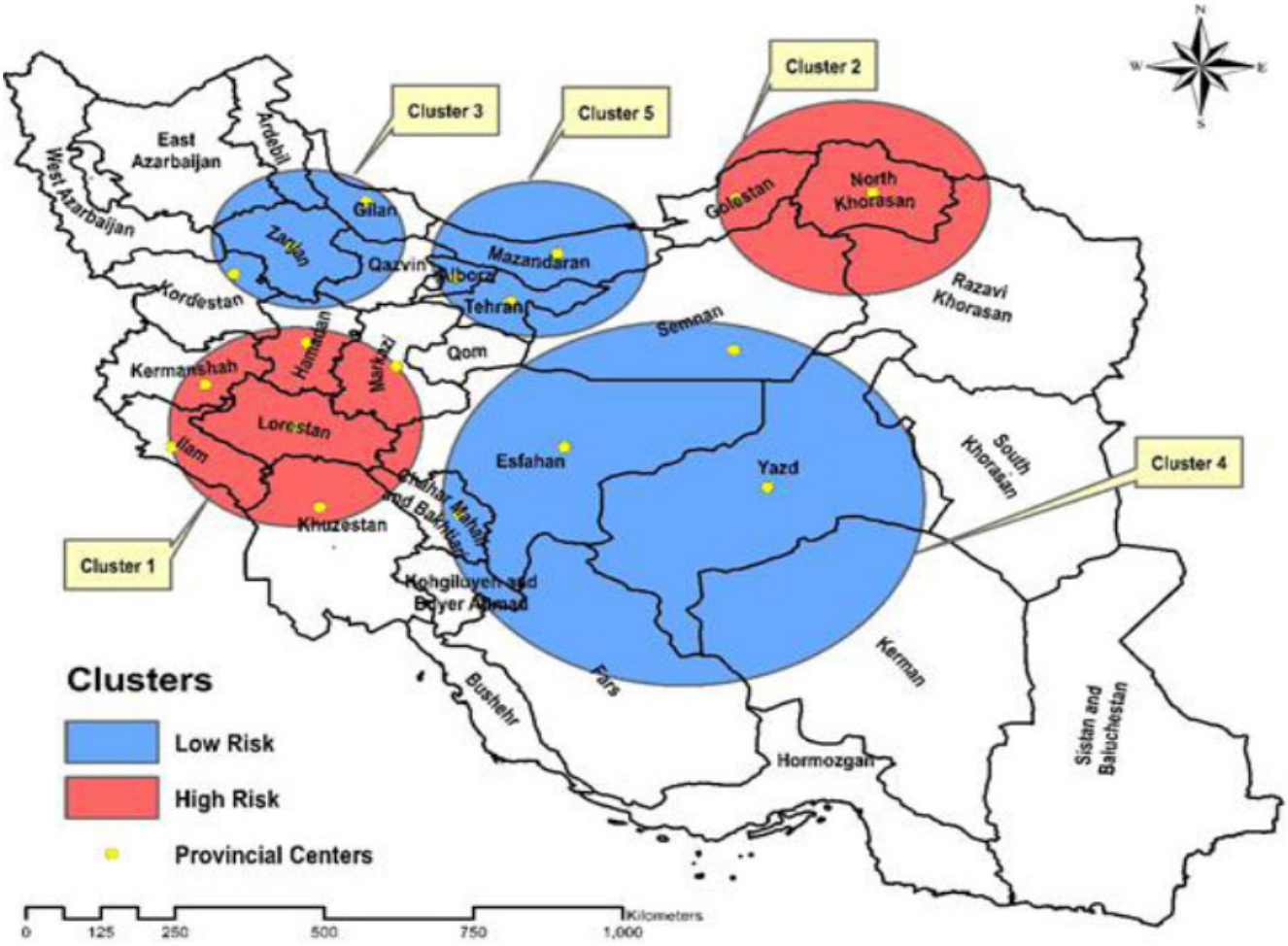

Fig. (3). High-risk and low-risk clusters of Age-standardized rate of DALYs hepatitis B in Iran using the Gini Optimized Cluster Collection method.
(source: Global Burden of Disease).

The relative risk of DALYs in all provinces was estimated using Kuldorff's spatial scan statistic, and finally, to illustrate the estimated RR values, a dotted map according to the estimated RR at the level of different provinces was produced in GIS (Fig. **4**). As can be seen, these results were completely consistent with the results of the spatial distribution of DALYs in the provinces of Iran, such that high RR was observed in provinces with high DALYs, and low RR was observed in provinces with low DALYs. The three provinces with the highest relative risk include the provinces of Lorestan (RR=2.22), Sistan and Baluchistan (RR=1.73), Golestan (RR=1.46), and the three provinces with the lowest relative risk include the provinces of Gilan (RR=0.41), Mazandaran (CIR= 0.48) and Kurdistan (CIR=0.51).

3.2. Time Trend Results

The results related to the evaluation of the time trend of total and average DALYs during the years 2009 to 2019 by Joinpoint regression are shown in Figs. (**5** and **6**). Fig. (**5**) shows the time trend of total DALYs by year. According to the obtained results, the time trend of total DALYs has decreased significantly between 2009 and 2015 and decreased by 2.08% annually ($p<0.05$). But in the continuation of this time trend, a join point was observed in 2015, and the total DALYs at this time point have undergone a noticeable change. So, the total number of DALYs decreased between 2015 and 2019 with a lower slope and intensity (APC=-0.61%). In general, during the years 2009 to 2019, the total DALYs decreased by 1.5% annually ($p<0.05$). More information about this time trend is shown in Table **3**.

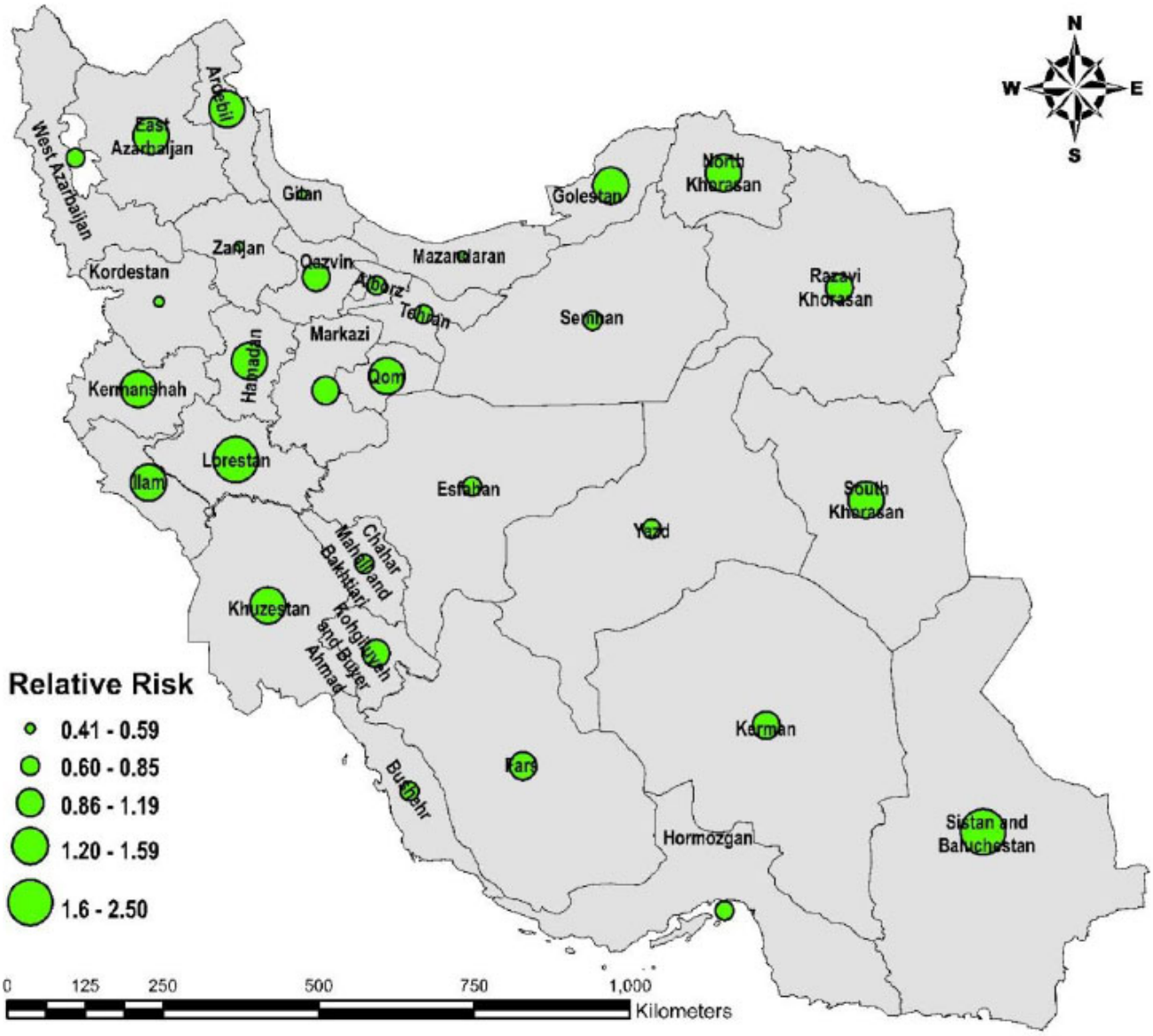

Fig. (4). Dotted map of estimated RR **of DALYs due to hepatitis B** at the level of Iranian provinces during 10 years. (source: Global Burden of Disease).

Table 3. More details of temporal analysis with join point regression models fitted to sum and mean of DALYs. (source: Global Burden of Disease).

The Number of Figure-related	The Time Frame of the Trend	APC		-	AAPC	-	-
		Point Estimate	95%CI	-	Point Estimate	95% CI	
5	2009-2015	-2.08	-2.4, -1.7	<0/001	-1.5	-1.8, -1.2	<0/001
	2015-2019	-0.61	-1.3, 0.1	0.1			
6	2009-2015	-2.08	-2.4, -1.7	<0/001	-1.4	-1.7, -1.1	<0/001
	2015-2019	-0.6	-1.4, 0.2	0.2			

Abbreviations: APC: Annual Percent Change, AAPC: Annual Average Percent Change.

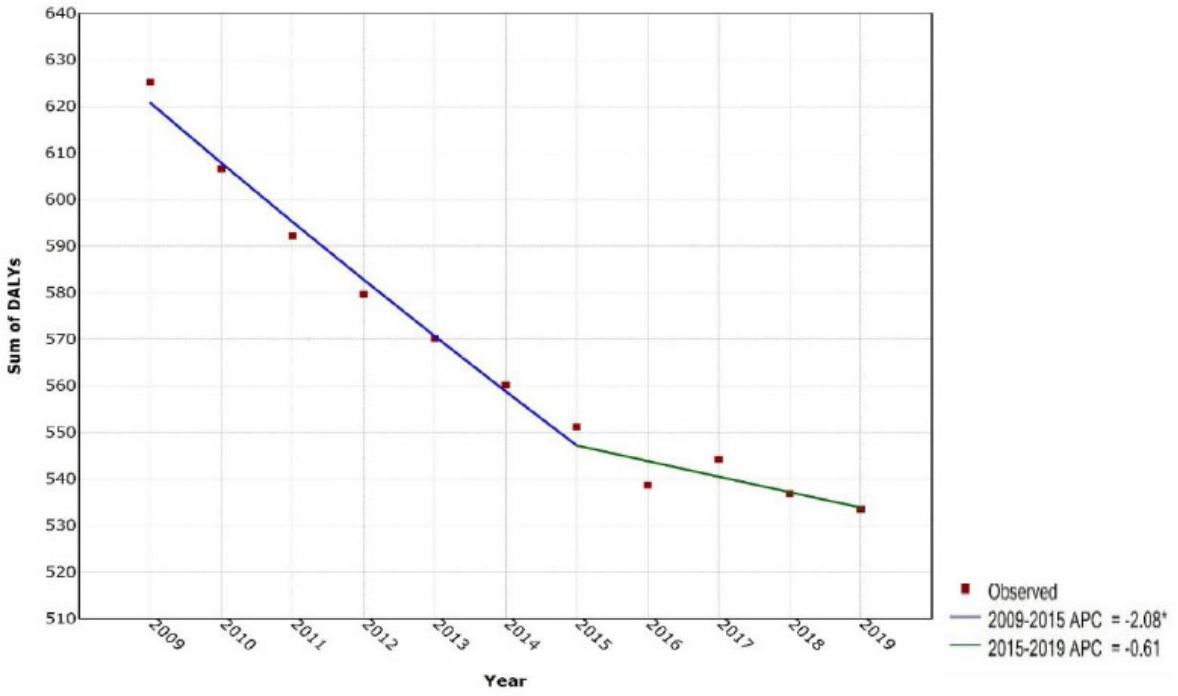

Fig. (5). Temporal analysis with join point regression model fitted on the sum of **DALYs due to hepatitis B** during 2009-2019 indicates that Annual percent change (APC) is significantly difference from zero at the alpha =0.05 level. Final Selected Model: 1 joint-point.

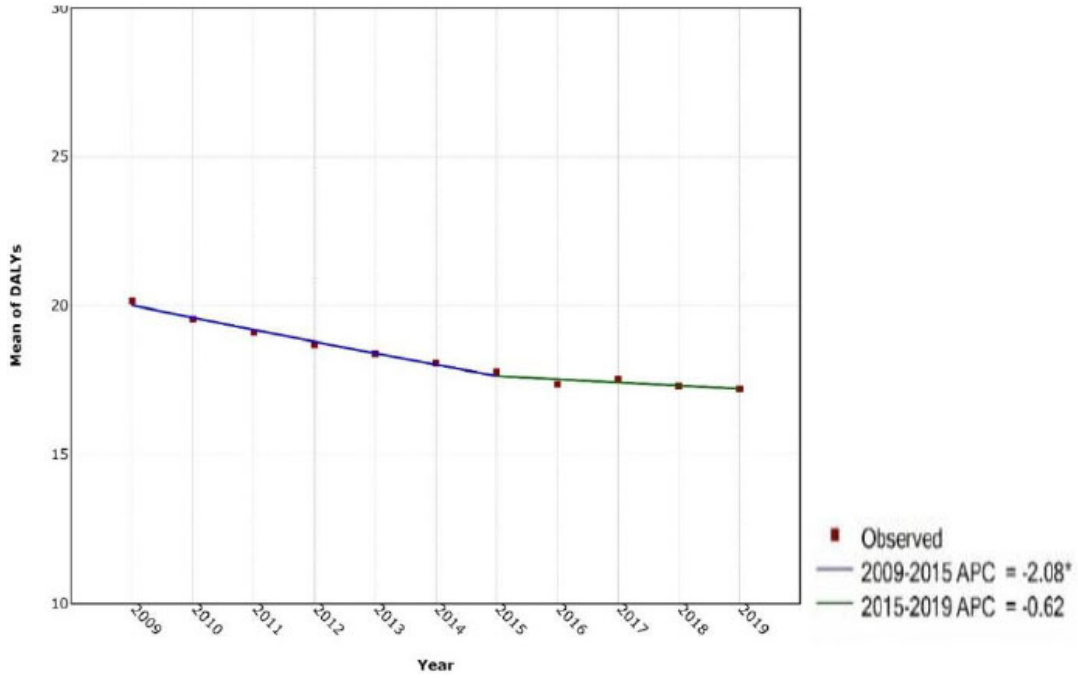

Fig. (6). Temporal analysis with join point regression model fitted on the mean of **DALYs due to hepatitis B** during 2009-2019. indicates that Annual percent change (APC) is significantly difference from zero at the alpha =0.05 level. Final Selected Model: 1 joint-point.

Fig. (**6**) also shows the time trend of average DALYs by year. As can be seen, the time trend of the average DALYs has decreased significantly between 2009 and 2015 and decreased by 2.08% per year ($p<0.05$). But in the continuation of this time trend, a join point was observed in 2015, and the average DALYs between 2015 and 2019 decreased with a lower slope and intensity. (APC = -0.62%) In general, during the years 2009 to 2019, the average DALYs Annual average (AAPC) had a significant decrease of 1.4% ($p<0.05$). More information about this time trend is shown in Table **2**.

4. DISCUSSION

The burden caused by hepatitis B was not evenly distributed around the world, which was attributed to the different seroprevalence of HBV from country to country. HBV is endemic in developing countries in Asia and Africa. Although a series of preventive measures, such as extensive coverage of HBV vaccination, have been implemented for years, the burden of hepatitis B disease in these countries is still at a high level [23]. The results of this study provide the national estimate of DALY for hepatitis B in the provinces of Iran. The use of a single measure such as DALY, which allows the integration of the effects of mortality and disease-related morbidity into a single measure, especially for diseases where death is not the primary outcome and can cause major disability, is a distinct point of view in It presents their impact on population health. The most likely high-risk cluster of hepatitis B disease in the west of Iran includes Lorestan, Kermanshah, Hamedan, Markazi, Khuzestan, and Ilam provinces. In this cluster, the relative risk incidence was estimated to be 2.31. A secondary high-risk cluster was identified in the northeast of Iran, which includes North Khorasan provinces, And it was Golestan. The most likely low-risk cluster in the northwestern part of Iran included the provinces of Zanjan, Gilan, and Kurdistan. The relative risk in this cluster was estimated at 0.23. The three provinces with the highest relative risk include Lorestan, Sistan Baluchistan, and Golestan and the three provinces with the lowest relative risk include Gilan, Mazandaran, and Kurdistan provinces. The burden attributable to HBV varies worldwide. For example, it was 10.34 in Germany [24], 20.4 in Spain [25], 17 in the state of Santa Catarina in Brazil [26], 63.4 in Guangdong [27], and 230 in Shandong in China [28] which is consistent with the results of studies in Iran.

The results of our study showed a significant decrease in the total changes of DALYs between 2009 and 2015, which decreased by 2.08% annually. The time trend of average DALYs changes during the years 2009 to 2015 also showed a significant decrease and decreased by 2.08% annually. In Moradi *et al.*'s study, the HBV load has decreased significantly in all age groups, and the adjusted HBV load decreased from 1.9 in 2008 to 0.99 in 2015 per 1000 population, which is consistent with the results of the present study [29].

Such a decrease in HBV burden was due to a significant decrease in new HBV cases, which in turn caused a decrease in mortality after the implementation of the HBV vaccination program for infants and family members of people with HBV since 1994 [30]. Therefore, the best approach to control and reduce the burden of hepatitis is to prevent the occurrence of the disease, especially in high-risk groups, to diagnose and treat the disease faster, which can reduce the mortality rate and ultimately control the burden of hepatitis.

In the study of Moradi *et al.*, in the study of the adjusted HBV burden distribution map based on the population, the results showed that the eastern and northeastern provinces, including Razavi Khorasan, Golestan, and Sistan and Baluchestan, are the main focus of this disease [30]. The results of the present study also showed that the most likely high-risk cluster in the west of Iran includes the provinces of Lorestan, Kermanshah, Hamedan, Markazi, Khuzestan, and Ilam. In this cluster, the relative risk of incidence was estimated to be 2.31. A secondary high-risk cluster was identified in the northeast of Iran, which includes The provinces were North Khorasan and Golestan.

The results showed that in 2019, the highest burden of hepatitis disease in Iran is related to the provinces of Lorestan, Golestan, Sistan and Baluchistan, Ardabil, and North Khorasan respectively. To control and change the trend of HBV load, attention to the following is highly recommended; The first and most important way to reduce the incidence of hepatitis B and DALYs caused by this disease is vaccination and primary prevention. Reducing unnecessary injections in health centers, training health workers to ensure safe injections, educating and informing drug addicts about the transmission of the disease through injections, better management of dialysis patients and HIV/AIDS patients, and increasing the coverage age for HBV diagnostic tests.

Especially for vulnerable groups, it is obvious that the most efficient way to reduce the burden of disease is prevention and reduction of disease incidence. An important measure to prevent HBV is to reduce its reservoirs in the community. The results of this study show the success of the vaccination program in controlling HBV. Therefore, it is necessary to continue the current policies. In addition, to increase effectiveness, health authorities should expand the coverage of programs across as well as other age groups in the country.

4.1. Limitations

This study suffers from the general limitations of GBD studies. The availability and quality of primary data, which are the foundation of the GBD analysis, is the main limitations of GBD estimates, particularly in regions with countries that have poor completeness. Ecological studies have substantial limitations and, although valid for hypothesis generation, are not considered useful for hypothesis testing because of unmeasured and uncontrolled confounding.

4.2. Future Direction

Quantifying indicators related to the health of society

requires indicators that are the losses caused by premature deaths. For any reason, put together the burden caused by the disabilities that arise during the course of the disease and its various consequences. Data and express them based on a common unit, and on the other hand, the level of health and its distribution in the society in the form of an index. Therefore, studies of the burden of diseases are one of the most important needs to determine the current situation. The effectiveness of policies and health programs and the prioritization of interventions are considered.

CONCLUSION

The incidence of hepatitis B disease has significantly decreased during the last 20 years with the implementation of the general vaccination program in vaccination program for children at birth, but the burden caused by this disease is still high due to the cases of the disease from the years before vaccination. Therefore, redistribution of health resources to identify patients, control transmission, and treat infected patients is highly recommended.

AUTHORS' CONTRIBUTIONS

E.G and Z.K. contributed to design, E.G., Z.K, and MTS contributed to Data Collection and/or Processing, E.G and SRP contributed to Analysis or Interpretation, E.G, S KH and Z.K helped in the writing of the manuscript.

LIST OF ABBREVIATIONS

DALY	=	Disability-Adjusted Life Years
GBD	=	Global Burden of Disease
APC	=	Annual Percent Change
AAPC	=	Average Annual Percentage Change

ETHICAL STATEMENT

The study was approved by the ethics committee of Lorestan University of Medical Science, Iran, with ID number IR.LUMS.REC.1401.215. This article has used the burden of disease data and the data were at the province level and did not require the informed consent of the individual.

CONSENT FOR PUBLICATION

This article has used the burden of disease data and the data were at the province level and did not require the informed consent of the individual.

AVAILABILITY OF DATA AND MATERIALS

All the data used in this research were made available to the public at http://ghdx.healthdata.org/gbd-results-tool

FUNDING

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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