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Research Article

Global Outlook for Disability Adjusted Life Years: Brain and Central Nervous System Cancers

Yunus Emre Karatas, Songul Cinaroglu

Hacettepe University, Faculty of Economics and Administrative Sciences, Department of Health Care Management, Ankara, Türkiye

Abstract

Aim: In 2019, brain and central nervous system cancers were listed among the top 5 causes of death in men and women by absolute Disability Adjusted Life Years (DALY) burden globally. In this respect, it is important to define the current global status of deaths from neurological disorders and brain and central nervous system cancers. In this study, we aimed to examine the burden of disease metrics of deaths from neurological disorders and brain and central nervous system cancers in 204 different countries/regions by categorizing the countries.

Material and Method: Brain and central nervous system cancer DALYs, motor neuron disease deaths and multiple sclerosis deaths of 204 different countries were obtained from the "GBD Compare" tool of the Institute for Health Metrics and Evaluation. The k-means clustering algorithm, also known as unsupervised machine learning algorithm, was used to categorize the countries. The number of clusters was determined by the Silhouette score (s). The statistical difference between the medians of two independent groups was analyzed by Mann-Whitney U Test.

Results: According to the silhouette score obtained using the K-Means algorithm, the number of clusters was determined as 2 (s=0.684). Cluster I included 135 countries (African and Asian countries) and Cluster II included 65 countries (European and North American countries). The median (min; max) values of Cluster II countries for brain and central nervous system cancer DALYs, Multiple Sclerosis deaths and Motor Neuron Disease deaths variables were 201.77 (147.65;375.16), 0.62 (0.00;2.21), 1.13 (0.00;4.65), while the median (min; max) values of Cluster I countries are 64.50 (6.29;134.99), 0.04 (0.00;0.67), 0.00 (0.00;2.36), respectively ($p<0.001$).

Conclusion: The group of developed countries in Europe and North America has been found to have more deaths from neurological diseases and more DALYs from brain and central nervous system cancers. When the countries in the groups are evaluated, it is concluded that the geographical proximity and development level of the countries have a significant effect on the variables used in the grouping.

Keywords: Brain neoplasms, cluster analysis, disability adjusted life years, global burden of disease

INTRODUCTION

Brain tumors constitute an important disease group in neurosurgery. They cause many neurological, cognitive and psychosocial problems. The incidence of malignant and benign brain tumors is higher, especially in industrialized regions of Australia, Europe and North America (1). In the UK, the incidence of glioblastoma, one of the age-standardized tumor subtypes, increased from 3.27 and 2.00 per 100,000 population in 1995 in men and women, respectively, to 7.34 and 4.45 in 2013 (2). In the United States, the incidence of brain tumors, which are among the top four cancers in young adults, is 7.10 per 100,000 in the 20-24 age group and 15.5 in the 34-39 age group (3). In summary, brain and central nervous system cancer was listed among the top 5 causes in women and men according to absolute Disability Adjusted Life Years (DALY) burden globally in 2019 (4).

While many factors pose a risk for brain cancer, these factors can be classified as environmental, demographic, genetic and socioeconomic factors (5). These factors are also closely related to neurological disorders. In general, neurological disorders are defined as Alzheimer's and other dementias, Parkinson's, idiopathic epilepsy, multiple sclerosis, motor neuron disease, headache disorders (6). While epidemiologic studies have found a significant inverse association between Alzheimer's

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Corresponding Author: Yunus Emre Karatas, Hacettepe University, Faculty of Economics and Administrative Sciences, Department of Health Care Management, Ankara, Türkiye
E-mail: yekaratas@ankara.edu.tr

disease and cancer, increasing evidence has shown a higher risk of melanoma and brain cancer in Parkinson's patients (7,8). Research on the pathological relationship between epilepsy and brain tumors has reported epileptic symptoms attributed to intracranial tumors (9). Although the assessment of brain tumor formation in multiple sclerosis patients is complex, multiple sclerosis has been recognized as the primary pathology that often results in the development of brain gliomas (10). The best-known form of motor neuron disease is amyotrophic lateral sclerosis, and the level of evidence for carcinogenesis is low with few studies available (11). Although there are more than 600 diseases affecting the neurological system, the most well-known ones are the neurological disorders and brain tumors described above (12).

Cluster analysis has been widely used in the health literature for image segmentation, human genetic clustering, recommendation systems, data reduction, classification and prediction using stroke, diabetes, Alzheimer's data (13). For example, cluster analysis studies have been conducted using social, economic and health metrics together or alone to shed light on policies to be created to control a disease of specific interest (14). From identifying subgroups of brain tumors affecting the neurological system (15) to identifying distinct patterns in gene studies (16), cluster analyses have also found widespread use specifically in neurology. Cluster analysis is also widely used to group countries using various health outcome metrics. Many metrics such as COVID-19 case data, quality of life data, standardized mortality data have been used to classify countries through cluster analyses (17-19). In this context, our study aimed to group countries using multiple sclerosis disease, motor neuron disease mortality data and brain and central nervous system cancer DALY numbers, which are considered as neurological disorders, and clustering algorithm was used in grouping. Since our study aims to identify subgroups of countries that are different from each other among clusters, the study analyses were carried out with a country-centered approach. As a result of this study, it was aimed to show that the loss of healthy life years due to neurological disorders and brain cancer is not homogeneous in terms of the countries of the world.

MATERIAL AND METHOD

Data Set Selection and Definition of Parameters

Brain and central nervous system cancer DALYs (per 100,000 population), motor neuron disease deaths (per 100,000 population) and multiple sclerosis deaths (per 100,000 population) in 204 different countries, including Türkiye, constitute the variables for the statistical analysis of this study. Since disability-adjusted life-year data specific to motor neuron and multiple sclerosis disease are still insufficient, mortality data were used for these two variables. The data set for the variables was obtained from the "GBD Compare" tool of the Institute for Health Metrics and Evaluation (IHME), which allows comparison of diseases, deaths and risk factors at various levels (regional, gender, age, etc.) (IHME, 2024). As a result of the International Classification of Diseases 10th Revision (ICD-10) and the COVID-19 pandemic, diseases for the Global Burden of Disease are categorized into four main groups in the GBD Compare tool: Communicable Diseases (Group A), Non-Communicable Diseases (Group B), Injuries (Group C), Other Consequences of the COVID-19 Pandemic (Group D). Brain and central nervous system cancer DALYs for this study were compiled from the "Neoplasms" subgroup of the non-communicable diseases group. Data on variables related to the number of deaths were obtained from the "Neurological Disorders" subgroup of the noncommunicable diseases group (6).

DALY is a measure used especially in global burden of disease studies beyond crude mortality rates. In summary, a DALY represents the loss of one full healthy year. As given in Equation 1, DALY is the sum of years of life lost to premature death (YLLs) and years of life lost to disability due to illness or injury (YLDs) (20).

$$DALY = YLLs + YLDs \quad (1)$$

When calculating YLDs, health conditions are assigned a disability weight ranging between 0 and 1 (0: no disability; 1: loss equivalent to death). YLDs is obtained by multiplying the assigned disability weight by the time (years) spent in the disease. In the calculation of YLLs, the years of life lost due to premature death based on the reference life expectancy gives the value of YLLs (21).

All variables in the study dataset belong to 2021 and represent all age groups.

Methods for Study Analysis

The classification of countries according to the variables showing the number of deaths related to neurological disorders and the number of brain and central nervous system cancer DALYs was made with the k-means clustering method. Clustering analysis is based on the separation of data in a variable set into groups according to distance and proximity criteria or according to the differences or similarities between variables. The aim of clustering analysis is to achieve high similarity within clusters and low similarity between clusters (22). In this study, the variables Brain and central nervous system cancer DALY (Per 100,000 population), Multiple Sclerosis (Deaths per 100,000 population), and Motor Neuron Disease (Deaths per 100,000 population) were used together for similarity-based clustering. Clustering, also known as unsupervised machine learning algorithm, which is used in data mining, divides an unlabeled dataset of size N*D (N is the number of samples, D is the data size) into k groups with the same similarity (23).

Clustering algorithms are divided into two main groups: hierarchical clustering and partitioned clustering algorithms (24). While hierarchical clustering algorithms cluster data objects using either a bottom-up additive approach or a top-down divisive approach, partitioned clustering algorithms use combinatorial search of all possible values to obtain the optimum value, resulting in different k values (25). There are many clustering algorithms in the literature such as DBSCAN, CURE, Chameleon. However, the K-means clustering algorithm has been widely used in the literature as one of the most effective algorithms (26).

K-means, one of the unsupervised algorithms, calculates the distance between the center points and all data points in the space using randomly fixed starting/center (k) points and then assigns the data points to the nearest center point (27). Although this process can be done according to different distance measures, the Euclidean distance measure is used in this study. The Euclidean distance measure is calculated as in Equation 2.

$$d\left(x,c\right) = \sqrt{\sum_{i=1}^{D}\left(x_i - c_i\right)^2} \qquad (2)$$

In the equation, x represents the data point, c the center, D represents the total number of data points in space. The average distances of the center and data points are iterated until there is no change in the center and the calculated average, and the center is repositioned according to the average position. The formula used to assign the center after the repeated process is given in equation 3.

$$v_{ij} = \frac{1}{N_i}\sum_{k=0}^{N_i} X_{kj} \qquad (3)$$

Where v_{ij}: is the average centroid in cluster ith for the jth variable; N_i: is the number of members in cluster i; X_{kj}: is the k data values for variable j in the cluster.

Silhouette score was used to determine the most appropriate cluster number from the cluster numbers obtained. The Silhouette score, which provides insight into cluster quality by measuring the cohesion within clusters, represents how well each data point is classified, and indicates whether there is a reasonable level of separation between clusters, varies between -1 and +1 (28). A score of 0.6 and higher indicates an acceptable separation between clusters (29).

The difference between the averages of the sample group clustered as a result of the K-means algorithm for each variable was evaluated with an independent sample test to ensure the clustering analysis. Mann-Whitney U hypothesis test was used to compare continuous data groups. The relationship between the variables was analyzed with Spearman's rank correlation coefficient. Spearman's rank correlation coefficient ranging from $-1 \le r_s \le 1$ indicates that the strength of the relationship decreases as it approaches 0, while the strength of the relationship increases when it approaches 1 in absolute value in both directions.

For this study, clustering analysis was performed in Orange Data Mining (Version: 3.32.0) and independent sample test and correlation analysis were performed in IBM SPSS Statistic 22.0.

RESULTS

Descriptive Statistics

Within the scope of this research, descriptive statistics of the variables included in the clustering analysis before clustering analysis of 204 different countries/regions are presented in Table 1.

Table 1. Descriptive statistics of variables

Variables	Label	Median (Min-Max)
Brain and central nervous system cancer DALY *(Per 100,000 population)*	BCNSC_DALYs	91.54 (6.29-375.16)
Multiple sclerosis *(Deaths per 100,000 population)*	MS	0.09 (0-2.21)
Motor neuron disease *(Deaths per 100,000 population)*	MND	0.04 (0-4.65)

Since the data related to the variables do not show normal distribution, median, minimum and maximum values are presented as descriptive statistics. BCNSC_DALYs per 100,000 population ranged between 6.29 and 375.16, with a median of 91.54. The median of MS and MND deaths per 100,000 population classified as neurological disorders is 0.09 and 0.04, respectively. According to the results of the Spearman's rank correlation coefficient (rs) analysis, there is a significant and positive relationship between all variables (p<0.001). There was a moderate and positive relationship between BCNSC_DALYs and MS (rs=0.72), a moderate and positive relationship between BCNSC_DALYs and MND (rs=0.67), and finally a moderate and positive relationship between MS and MND (rs=0.72). Spearman's rank correlation coefficients, scatter plots and histogram plots of variables are given in the correlogram in Figure 1. When the histogram plots were analyzed, it was determined that especially MS and MND variables showed a right-skewed (positive) distribution (Figure 1).

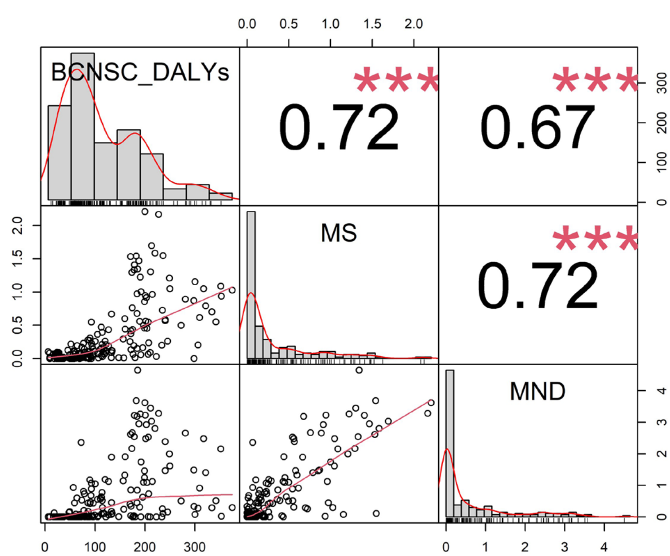

Figure 1. Correlogram graph for variables

Clustering Results

Using the k-means algorithm and Euclidean distance measure, the number of clusters was estimated by Silhouette coefficient for grouping countries in terms of brain and central nervous system cancer DALYs and two variables related to neurological disorders (MS, MND). When the Silhouette coefficients calculated up to 8 clusters were analyzed, it was determined that the best cluster number was k=2 (Figure 2). When the number of clusters was k=2, the Silhouette score was 0.684; when k=3, 0.663; when k=4, 0.559. The optimal number of clusters or Silhouette score, whose graphical analysis is presented in Figure 2, is the highest when the number of clusters is 2.

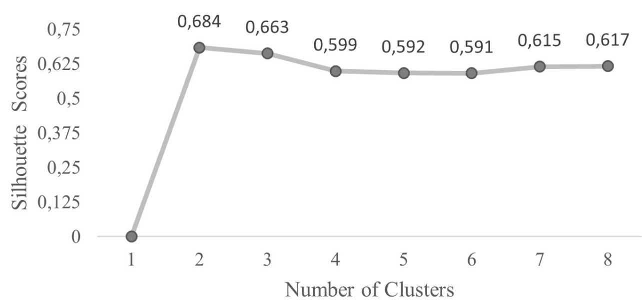

Figure 2. Silhouette scores for different cluster numbers

After the number of clusters determined as k=2 according to the Silhouette score, countries were grouped as shown in Table 2. According to the k-means algorithm, there were 135 countries/regions in Cluster 1 and 69 countries/regions in Cluster 2. The clusters of countries/regions are visualized and presented in Figure 3. The countries in Cluster I are colored in blue and Cluster II countries are colored in red. In Cluster I, countries in Africa and Asia are generally clustered, while in Cluster II, countries in Europe and North America are clustered.

Table 2. Country groups as a result of k-means algorithm

Cluster	Countries*
1 (n=135)	AFG, AGO, ARE, ARG, ASM, ATG, BDI, BEN, BFA, BGD, BHR, BHS, BLZ, BOL, BRB, BRN, BTN, BWA, CAF, CHL, CIV, CMR, COG, COK, COL, COM, CPV, CRI, DJI, DMA, DOM, DRC, DZA, ECU, ERI, ETH, FJI, FSM, GAB, GHA, GIN, GMB, GNB, GNQ, GRD, GTM, GUM, GUY, HND, HTI, IDN, IND, JAM, JOR, JPN, KAZ, KEN, KGZ, KHM, KIR, KNA, KOR, KWT, LAO, LBN, LBR, LCA, LKA, LSO, MAR, MDG, MDV, MEX, MHL, MLI, MMR, MNG, MNP, MOZ, MRT, MUS, MWI, MYS, NAM, NER, NGA, NIC, NIU, NPL, NRU, OMN, PAK, PAN, PER, PHL, PLW, PNG, PRI, PRK, PRY, QAT, RWA, SAU, SDN, SEN, SGP, SLB, SLE, SLV, SOM, SSD, STP, SWZ, TCD, TGO, THA, TKL, TLS, TON, TTO, TUN, TUV, TWN, TZA, UGA, VCT, VEN, VIR, VNM, VUT, WSM, YEM, ZAF, ZMB, ZWE
2 (n=69)	ALB, AND, ARM, AUS, AUT, AZE, BEL, BGR, BIH, BLR, BMU, BRA, CAN, CHE, CHN, CUB, CYP, CZE, DEU, DNK, EGY, ESP, EST, FIN, FRA, GBR, GEO, GRC, GRL, HRV, HUN, IRL, IRN, IRQ, ISL, ISR, ITA, LBY, LTU, LUX, LVA, MCO, MDA, MKD, MLT, MNE, NLD, NOR, NZL, POL, PRT, PSE, ROU, RUS, SMR, SRB, SUR, SVK, SVN, SWE, SYC, SYR, TJK, TJM, TUR, UKR, URY, USA, UZB

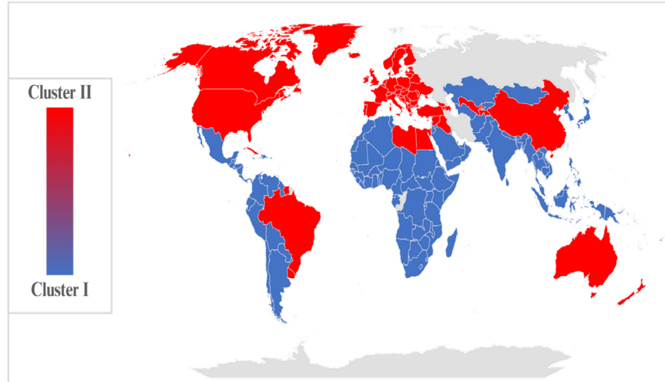

Figure 3. Clusters of countries in the k-means algorithm

The Silhouette score for each country included in the analysis is presented in Figure 4. The Silhouette scores of the countries in Cluster I range between 0.72 and 0.57, while the Silhouette scores of the countries in Cluster II range between 0.70 and 0.52.

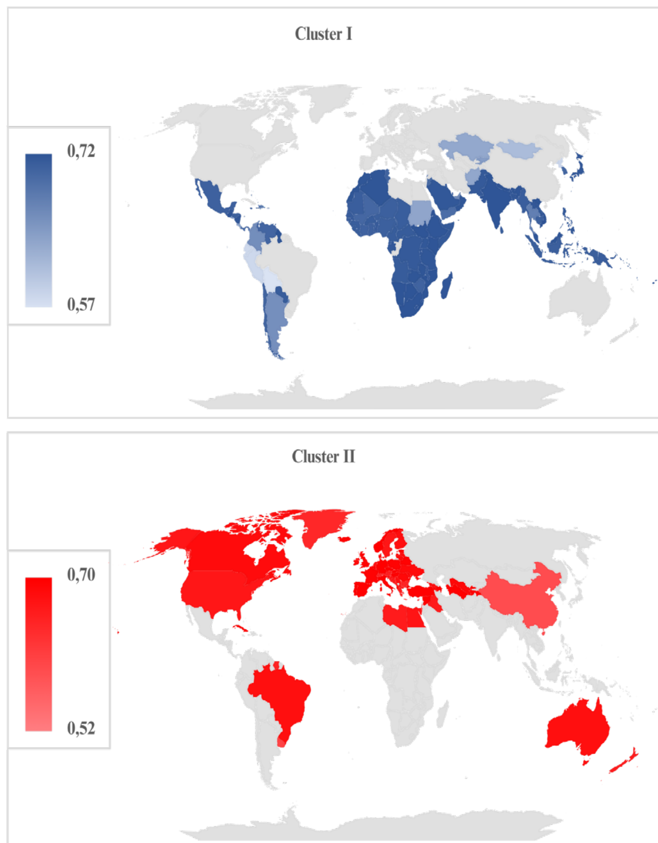

Figure 4. Silhouette scores of countries by cluster

Table 3 presents the test results of the differences between country groups in terms of health outcome variables. According to the Mann-Whitney U test results, there is a statistically significant difference between the rank means of the clusters in terms of all three variables (BCNSC_DALYs: U=0.00; MS: U=912; MND: U=1512; $p<0.001$). In terms of BCNSC_DALYs, MS and MND health outcome variables, Cluster II countries have higher rank means than Cluster I countries.

Table 3. Comparison of country clusters in terms of variables

	BCNSC_DALYs	MS	MND
	Median (Min;Max)	Median (Min;Max)	Median (Min;Max)
Cluster I	64.50 (6.29;134.99)	0.04 (0.00;0.67)	0.00 (0.00;2.36)
Cluster II	201.77(147.65;375.16)	0.62 (0.00;2.21)	1.13 (0.00;4.65)
Cluster I vs Cluster II	U=0.00; p<0.001	U=912; p<0.001	U=1512; p<0.001

*U =Mann-Whitney U Test U score

DISCUSSION

As a result of the clustering analysis, 204 countries/regions were grouped into two different clusters according to MS, MND mortality and brain and central nervous system cancer DALY data. Cluster I included 135 countries, while Cluster II included 69 countries. In Cluster I, African and Asian countries are grouped in general. Cluster II includes countries from Europe and North America. When the countries in the clusters are analyzed, it is seen that countries with geographical proximity are mostly grouped in the same cluster. Cluster I countries are better in terms of mortality data and brain tumor DALYs. However, this is thought to be related to the fact that tumor registry coverage is lowest in Southeast Asia and Africa (30). The level of data evidence is also known to be low in Africa, Central and South America and most countries in Asia (31). Again, in terms of protocols for determining death according to brain death/neurological criteria, it is thought that some African, South American and South Asian countries do not have national protocols and therefore cannot provide reliable information (32). In this respect, the fact that the health outcome variables of the countries in Cluster I seem to be in better condition compared to the other cluster may be associated with the low level of data reliability reported.

In terms of the health system, countries that provide adequate preventive and curative health services and are in better condition in terms of human resources and physical health infrastructure were included in Cluster II. For example, while the number of doctors (per 1000 people) in the European region in Cluster II is 4.3, this number is 0.2 in Sub-Saharan Africa countries in Cluster I. It is thought that this situation may be related to the fact that the countries in Cluster II have more diagnostic equipment such as Computed Tomography and Magnetic Resonance and a relatively higher number of neurologists, as well as accurate and timely diagnosis (33). When health human resources are evaluated in terms of minimum labor intensity, researchers have reported that physician intensity is the lowest in Sub-Saharan Africa, South Asia and North Africa (34).

Access to care and availability of health services have been reported in previous studies to be important factors influencing the burden of disease and mortality used in the study for countries in both clusters. (35). As a matter of fact, easy access to health institutions enables the recording of diseases and causes of death in the right number and in the right category.

According to the findings of our study, countries that exhibit a similar outlook according to their income levels are grouped in the same cluster. The fact that especially low-income countries are in Cluster I is related to data quality and more importantly data availability (35). As a result of our study, it is known that life expectancy at birth and urbanization are high in countries in cluster II (36). In this respect, it is thought that the high life expectancy at birth causes the disease burden of brain and central nervous system cancer to be higher in direct proportion. In a study investigating the incidence of brain tumors in high-income and middle-income countries, it was found that the incidence rates of tumors were significantly higher in high-income countries (37). The incidence of brain and other central nervous system tumors in childhood and adolescence is also reported to be highest in high-income countries (38). In addition, increased risk for brain and central nervous system tumors is associated with increasing socioeconomic status (39). In summary, the grouping of developed countries in the same group is closely related to the use of advanced diagnostic techniques, the higher proportion of the elderly population and the high prevalence of health screenings. The fact that dietary type, alcohol/tobacco use, and occupational exposures differ according to the development and geographical proximity of the countries is thought to affect the health outcome variables used in the grouping. In this respect, as a result of the clustering analysis used in our study, the grouping of high- and middle-income countries in one cluster and low-income countries in the other cluster is consistent with other studies in the literature.

CONCLUSION

As a result of our study, countries with geographical proximity and approximately similar levels of development as known from previous studies are grouped in the same clusters. European and North American countries were found to have higher mortality rates from MS and MND affecting the individual's neurological system and higher loss of healthy life years due to brain tumor cancer compared to the rest of the globe. In addition, countries with high life expectancy at birth have the highest mortality rates from central nervous system diseases.

For future studies, it is recommended that the regional differences in neurological disorders reported in our study should be evaluated from different perspectives such as the level of neurologists/neurosurgeons, the income level of countries and socioeconomic level.

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