Iran Red Crescent Med J. 2017 August; 19(8):e15107. doi: 10.5812/ircmj.15107.

Published online 2017 July 24. **Research Article**

Clustering Asian Countries According to the Trend of liver cancer Mortality Rates: an Application of Growth Mixture Models

Maryam Salari,[1] Anoshirvan Kazemnejad,[2,*] and Farid Zayeri[3]

[1]Ph.D Student, Biostatistics, Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2]Professor, Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[3]Associate Professor, Department of Biostatistics, Member of Proteomics Research Center, School of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*]*Corresponding author*: Anoshirvan Kazemnejad, Professor, Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran. E-mail: kazem_an@modares.ac.ir

Received 2016 December 06; **Revised** 2017 February 28; **Accepted** 2017 March 28.

Abstract

Background: Liver cancer is considered as the 6[th] common cancer from which people are suffering all around the world. Poor prognosis is the main challenge regarding this disease.

Objectives: The aim of this study was to compare the changing trends in the liver cancer death rate in Asian countries from 1990 to 2015.

Methods: This ecological longitudinal study was performed to compare the death rate resulting from liver cancer. The data were gathered from all Asian countries provided by the global burden of disease's (GBD) online database in the global health research center at the University of Washington published in October 2016. The classification was done based on the death rate using the growth mixed model (GMM).

Results: The rate of liver cancer death in men was higher than women, there were 2 optimal classes. Both classes had an increasing trend. The first class had a steeper slope by a higher intercept. Taiwan, Thailand, Mongolia, North Korea, South Korea, China, and Japan were countries classified in this class. The mean of the intercept was estimated as 21.1 deaths per 100,000 people and the mean of the slope was 2.4. The other class had an increasing rate with a lower slope.

Conclusions: In general, our statistical analyses showed that most Asian countries had an increasing trend in the rate of their liver cancer mortality. Therefore, it is highly recommended that officials in the health policy-making identify the reasons for the increase in the mortality rate and take due actions such as interventional programs of countries which have succeeded in taking under control the ramifications of liver cancer.

Keywords: Liver Neoplasms, Growth Mixture Model, Trajectory, Asian Countries, Hepatitis, Mortality

1. Background

Genetic mutation, duplication, inversion, and chromosome deletion transform a normal cell into a cancerous cell (1). In 2013, almost 14.9 million cases of cancer and 8.2 million deaths from cancer were recorded (2). Cancer is considered an underlying health challenge worldwide (3). Today, it is the second most common cause of death in the global scale and is regarded as a major threat to the common health by many governments. In the United States alone, around 590,000 cases of cancer-related deaths and 1.7 million new incidences of cancer were recorded in 2016 (4). Primary liver cancer (PLC) is recognized as the second and the sixth leading cause of cancer deaths in males and females, respectively. Furthermore, it is one of the most lethal human malignancies worldwide and it is especially common in Asia (5). Its frequency rate is on the increase in many countries. Despite the advances in the treatment methods, the mortality rate of this cancer continues to remain high due to the late diagnosis of the disease in its advanced stages even among developed countries. Loss of certain tumor suppressors and the aberrant regulation of cellular growth signaling have been singled out as the cause of liver tumorigenesis (6). However, the exact reason for liver cancer has not yet been identified.

Primary liver cancer refers to a category of malignancies that originate from hepatocytes (hepatocellular carcinoma) (HCC), and intrahepatic cholangiocytes cholangiocarcinoma (ICC) (7). The most common type of primary liver cancer is hepatocellular carcinoma. HCC is ranked as the second leading cause of cancer-related deaths (8).

An annual number of 600,000 cases of Hepatocellular carcinoma deaths are recorded on the global scale (9). It is considered as one of the main causes of cancer-related deaths in the majority of Asian and African countries (9). Some of the prognostic factors of the disease include the size of the tumor, the number of the tumor nodules, portal vein tumor thrombus (PVTT), serum level of α-fetoprotein (AFP) and serum ferritin, and the existence or absence of metastasis (5). HCC is generally developed to a chronic liver disease; that is, 70% to 90% of patients have had chronic liver disease and cirrhosis (10). In addition to cirrhosis as its leading risk factor, HCC is associated with hepatitis virus B or C infection, exposure to aflatoxin B, alcohol abuse and obesity, eating habits and accumulation of ferritin (11, 12). Although the frequency of viral hepatitis HCC has decreased, its general prevalence is still on the rise due to non-alcoholic fatty liver or steatohepatitis (NAFLD/NASH) (13). Treatment options for HCC depend on the cancer stage and liver function; ranging from resecting part of the liver in localized cases to liver transplant in final stages of the cancer (14, 15).

Despite the surgical resection, the chance for 5-year survival plan is low which is due to the high relapse rate (16). In most Asian countries, non-communicable diseases are the main cause of adult deaths. However, disease mortality rate varies widely across, for example, India and China where there is remarkable heterogeneity in this regard (17). In the developed countries of Asia such as Singapore and Taiwan, there is a high rate of clinic referral for this disease (84% and 61.4%, respectively) whereas in Asian developing countries such as Vietnam and Thailand, there are more reports of self-remedy for the disease (57 to 69%, 48% respectively) (18).

The population of China is divided into two socio-economic groups of urban and rural populations. The urban population has more access to the educational and medical facilities and has a higher income level in comparison with the rural population (19). Ting-Ting Zuo et al. in their study showed the estimates of new liver cancer cases and deaths were 355,595 and 322,416, respectively, in China in 2011. The incidence and mortality were higher in rural areas than in urban areas and higher in males than in females. The age-specific incidence and mortality of liver cancer increased greatly with age, particularly after 30 years and peaked at 80 to 84 or 85+ years. Around 3.2 billion people live in the east, south and south eastern regions of Asia. The most common type of cancer in Thailand is liver and bile duct cancer and lung cancer ranks second (20). In general, in East Asian countries and China, liver cancer has a high prevalence whereas in India, it is recognized as a rare case of cancer (21). In Asia-Pacific region (South Korea, North Korea, Indonesia) and Middle East in particular, the most fundamental challenge in cancer treatment includes the suboptimal treatment of cancer symptoms, and the treatment toxicities (22). For instance, undertreated cancer pain in Asia has a prevalence of 59.1% which is higher than the values of 39.1 and 40.3% in North America and Europe, respectively (22). Certain essential opioid formulations, used to reduce the cancer-induced pain, were not available in Afghanistan, Cambodia, China (rural areas), Bangladesh, Bhutan, Cambodia, Kazakhstan, Laos, and Myanmar (22). Each year, an approximate number of 500,000 HCC cases are identified, half of which are located in Asia (23). In Asia-Pacific region, the prevalence of liver cancer among men is four times as much as its level among women and is more common in people aged 75 or higher (24). In the Southeast Asia region, hepatitis B virus is one of the main causes of liver cancer due to its high prevalence (25).

This study is conducted to investigate the recent trends in liver cancer mortality rate in Asian countries from 1990 to 2015. Due to huge differences in the Asian countries' situation, it is required to investigate them separately for spotting the regional differences, thus we can classify regions by their trend.

2. Methods

2.1. Data Source

The rates of death due to liver cancer were gathered from all Asian countries provided by the global burden of disease's (GBD) online database. The data contained the rate of death for both sexes in age-standardized groups for years 1990, 1995, 2000, 2005, 2010 and 2015. A recent study comprised of the proof for risk factor exposure and the attributable burden of disease has been issued by the global burden of diseases, injuries, and risk factors study 2015. On the condition that national and subnational evaluations (estimations) covering the last 20 years are provided, this research is able to inform debates emphasizing the significance of addressing risks in context (26). Data were collected and analyzed by a consortium of more than 1,800 researchers in more than 120 countries, the data contained premature death and disability from more than 300 diseases and injuries in 188 countries, based on age and sex, from 1990 to the present time, which provided a comparison over time, across age groups, and among populations. The GBD machinery's flexible structure provided the grounds for the regular updates through gaining access to new data and epidemiological studies. Thus, the tools are utilized at the global, national, and local levels to analyze the records pertaining to health trends over time, in the same way that gross domestic product data are used to monitor a country's economic activity. Policymakers in various countries ranging from Brazil, China, India, Indonesia, and Mexico, to Saudi Arabia, the United Kingdom, and other countries are collaborating with GBD researchers on the international scale to apply this approach for measuring the related population's health and to specify how it varies by different regions, socioeconomic status, or ethnic groups in their country. Asian Demographic and socioeconomic statistics is shown in Table 1.

2.2. Statistical Method

This study was an ecological longitudinal study. Stability and change procedures of both individuals and groups were examined by considering and applying longitudinal research studies with repeated measurements. Having panel data, the intra-individual development of substantive variables across time as well as inter-individual distinctions and resemblances regarding change patterns can be investigated. Although analyzing variance (ANOVA) and covariance (ANCOVA) traditionally assume the homogeneity of the underlying covariance matrix across the levels of the between-subjects factors and the same covariance patterns for the repeated measurements, the structural equation methodology offers an alternative plan: the latent growth curve models. These models both describe a single individual's developmental trajectory and capture individual differences in the intercept and slopes of those trajectories (27).

However, the assumption of a single population underlying the growth curves has to be relaxed in the case of unobserved heterogeneity. Instead of considering individual variation around a single growth curve, different classes of individuals should vary around different mean growth curves. A very suitable framework to handle the issue of unobserved heterogeneity is growth mixture modelling introduced by Muthen and Shedden (28).

These mixture models vary between successive and category-related variables which are unnoticed. The category-related latent variables represent mixtures of subpopulations where the product membership is deduced from the existing information. There is a similarity between the (normal, usual) increase curve models and intercept and slope variables which capture the continuous part of the model. Growth mixture models can also be seen as an extension of the structural modelling approach with techniques of latent class analysis (29).

In this study, the mortality rate was obtained using GMM method based on the Institute for health metrics and evaluation (IHME) classification. In this method, the intercept mean is estimated; furthermore, the change rate over time is shown as slope. Asian countries were analysed and classified based on the change rate using GMM method. Mplus version 6 was used for analysing data. Analysis type was mixture. This means that in each group of countries, the mortality rate caused by liver cancer begins with a specific mean and trajectory over time. There are many studies for categorizing countries with respect to the cause of death; however, the novelty of this study lies in its strong statistical methods that classified countries by their outcome trajectories. At the end of the analysis, GEE method of estimation was used for comparing the rate of liver cancer death in men and women without mentioning countries. Generalized estimating equation (GEE) is a marginal model popularly applied for longitudinal/clustered data analysis in clinical trials or biomedical studies.

3. Results

As mentioned earlier, in the first step, the data were collected from IHME website. Table 2 shows the liver cancer mortality rate per 100,000 people in Asian countries from 1990 to 2015. As presented in Table 2, the mean of liver cancer death rate per 100,000 people reached 9.8 in 2015 from 6.6 in 1990. However, the highest mortality rate per 100,000 people in 1990 and 2015 were 30 deaths and 55 deaths, respectively. Hence, these results point to a difference in mortality rate in various Asian countries which requires more detailed analysis. Furthermore, by fitting growth curve model, different trajectories for these countries were found. Figure 1 displays the growth trajectories for 52 countries (each line shows mortality rate trend over time for each country). Apparently, these trajectories demonstrate different trends for these countries; thus, the GMM was used to classify the countries according to their mortality trend over time.

First, the normality assumption was checked. For normality test, two-sided multivariate skew and kurtosis test of fit were used that imply Mplus. The results showed that data did not have normal distribution. P value = 0.021 for skew and kurtosis was 0.03. In the next step, MLR maximum likelihood parameter estimator was used. MLR is estimated with standard errors and a chi-square test statistic that are robust to non-normality. So for, more detailed analysis of all 52 countries were classified using GMM method. In GMM, individuals (or countries in this study) are classified based on the changing rate of the desired variable over time. Furthermore, the estimation in GMM is done via multivariate and structural equation methods. In this classification method, individuals are similar within classes in terms of variation trend but there are differences among classes. There are different criteria to determine the optimal number which forms the most distinctive classes. Criteria such as ABIC, AIC, and BIC are used to determine the optimal number. Lower values of these information criteria indicate the optimal number of classes.

In GMM, Lo-Mendel-Rubin adjusted LRT test (LRT) represents the optimal number of classes. The P value less than 0.05 (5%) shows the optimal number of classes (30). Due to the small sample size for classification, the 0.1 level of significance was determined to test the differences. Table 3 contains the indices values obtained for male and female groups, and also for both genders as one. The numbers of optimal classes with LRT test significant at 0.1 were 2

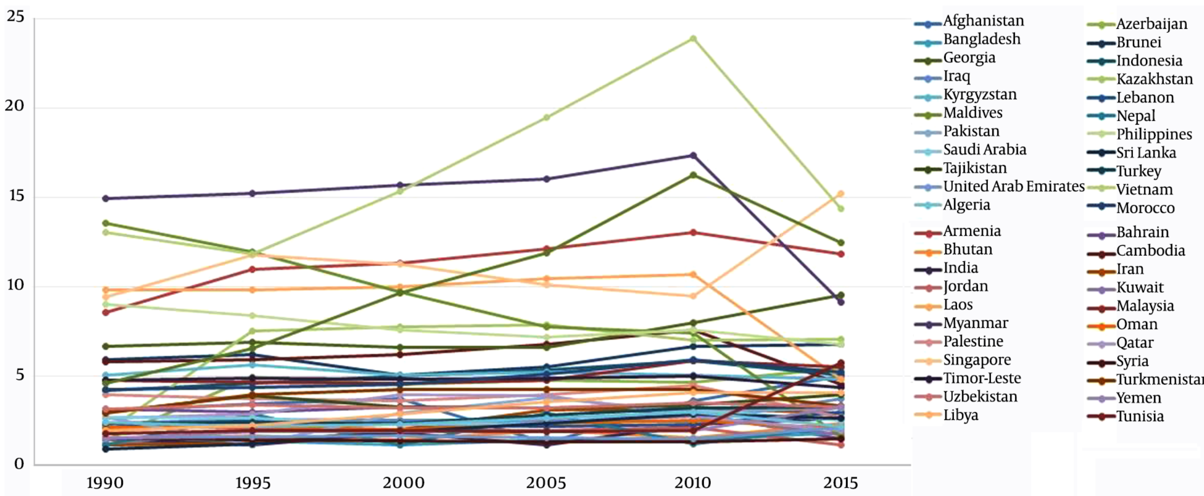

Figure 1. The Growth Fatality Rate of Liver Cancer Trajectories for Asian Countries

for both genders for all countries. Any change in the number of classes (increase in the number) converted significant values into insignificant values; therefore, it was not included in the In In 3 classes of men group, LRT statistics were close to the significance level. The intercept and slope of the classes are presented in Table 4.

In the females group, 2 optimal classes were analyzed. In the first class, the means of the intercept and slope were 15.04 and 3.1, respectively. This group had a higher starting point and steeper positive slope in the liver cancer fatality rate. North Korea, Taiwan, Thailand, Mongolia, and Japan were in this group. In the second class, the liver cancer death rate started with an estimated intercept mean of 3.5 but changed with a very lower positive slope of 0.09 over time. The other countries except the ones mentioned above are in this class. Figure 2 illustrates the changes of these classes over time.

Similarly, there were two optimal classes for males. In the first class, the mean of the intercept was estimated as 26.4 deaths per 100,000 people and the mean of the slope was 5.9. This means that the number of the liver cancer death rate was high and had a rising change pattern with a steep slope. Thailand and Taiwan were in this group. The mean of the intercept for the second class is 7.7 deaths per 100,000 people and changes with a very low increasing slope of 0.47. Most countries are placed in this group. Figure 3 illustrates the change pattern of these classes over time.

Due to the higher rate of death from liver cancer in men than in women, GEE method of estimation was used. The result showed that the rate of death from liver cancer in men is five 5 times as much as in women.

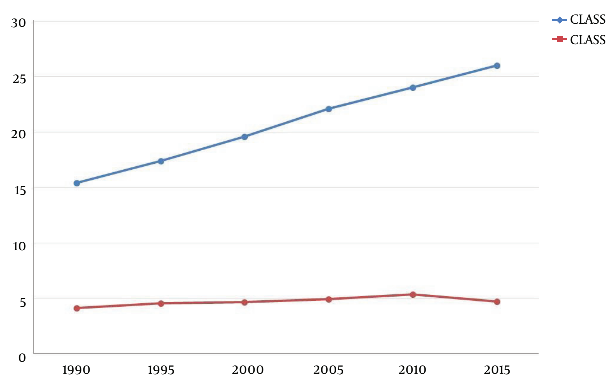

Figure 2. Estimated Trends Fatality Rate of Liver Cancer for Females in Different Classes from 1990 to 2015 Class 1 Includes North Korea, Taiwan, Thailand, Mongolia and Japan Class 2 Includes Other Countries

Regardless of gender, there were 2 optimal classes. As demonstrated in Table 3, the first class, presents the mean of the intercept estimated as 21.1 deaths per 100,000 people and the mean of the slope is 2.4. This means that the number of liver cancer deaths dropped by an average of 2.4 deaths per 100,000 people over each period of 5 years. North Korea, South Korea, Taiwan, Thailand, Mongolia, China, and Japan belong to this group. The mean of the intercept for the second class is 3.9 deaths per 100,000 people and changed with a very low increasing slope of 0.18. Most countries are in this group. Figure 4 shows changes in both classes over time. Geographic illustration of GMM classification is depicted in Figure 5.

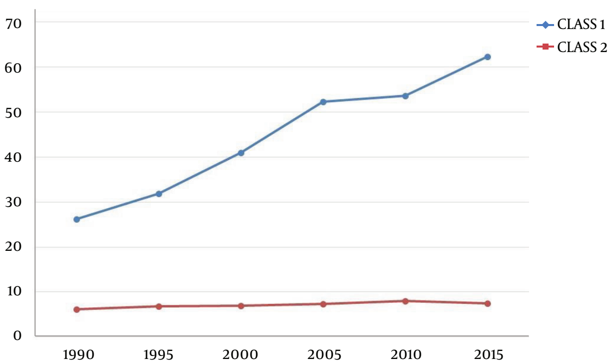

Figure 3. Estimated Trends Fatality Rate of Liver Cancer for Males in Different Classes from 1990 to 2015 Class 1 Includes Taiwan, Thailand Class 2 Includes Other Countries

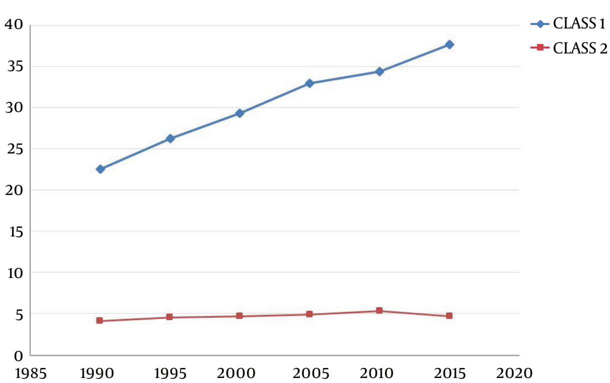

Figure 4. Estimated Trends Fatality Rate of Liver Cancer in Different Classes from 1990 to 2015 Class 1 Includes North Korea, South Korea, Taiwan, Thailand, Mongolia, China and Japan Class 2 Includes Other Countries

4. Discussion

HCC is regarded as the most common type of primary liver cancer. It is one of the most lethal cancers in Asia and Africa (31). The prevalence of HCC is higher in Asia and Africa in comparison with Western countries (32). Approximately, 85% of HCC cases are recorded in these two continents (33). HCC is associated with HBV or HCV infection, exposure to aflatoxin B, alcohol abuse and fatty liver.

Among Asia-Pacific countries, HBV is the leading cause of HCC in China and Hong Kong whereas in Japan, HCV ranks first. In China, HCC is the second leading cause of cancer mortality and around 80% of HCC patients are infected with HBV (34). China was one of the countries with a high rate of liver cancer death as a result shown by this study. The rate of the liver cancer deaths in this country was 20.88 in 1990 and it reached 28 in 2015.

In this study, the intercept of growth mixture model for the death rate of liver cancer for men was approximately twice the female death rate. Similarly, the slope of this model for men is two times as much as that of women.

In Korea, HCC is the second leading cause of cancer-related death which has more male than female patients. The cancer occurs mainly in their late fifties and more than half of the patients are diagnosed in tertiary hospitals. The main etiology of HCC was HBV infection (35).

Alcohol consumption is a major risk factor for liver cancer. As we found, South Korea was one of the countries with a high rate of liver cancer death. Eun-Young Lee et al, about trends of liver cancer and its major risk factors in Korea, showed that Korea had a very high rate of alcohol consumption, and as of 2010, approximately 10.3% of all men from Korea would use alcohol excessively and/or were alcohol addicts. Among Korean females, this percentage was 2.2%. The average estimate in the world health organization Western Pacific Region was 4.6% (36).

As stated earlier in this study, Thailand was another country with a high rate of liver cancer death. Cholangiocarcinomas that arise primarily from the epithelial lining of the bile duct (Intra- and extra-hepatic bile duct) are relatively rare, but high incidence rates are found in Thailand and other parts of Eastern Asia largely due to the elevated prevalence of liver fluke infection (37). Anti HBV vaccination can reduce the prevalence of HBV-induced HCC. In Thailand, for instance, the nationwide HBV vaccination reduced the HBsAg positive level from 4.5% to 0.6% (38).

Masatoshi Kudo reported successful policy for decreasing the number of new cases of liver cancer. For instance, Japan Society of Hepatology (JSH) began the eliminate liver cancer program. Setting up educational conferences at least once a year, JSH has been able to instruct the general public and healthcare providers who were not specialized in liver cancer (39). However, Japan still remains among the countries with high rates of liver cancer death.

GMM is of interest to many researchers due to its flexibility in classifying individuals based on pattern changes and is usually preferred against clustering model through having different criteria for selecting the fitted classes (40). In the current study, the mortality rate of liver cancer was assessed in Asian countries in a period of 25 years from 1990 to 2015. There are few studies for clustering countries by mortality rates during the time. By using the result of this study, the intervention in the health policy or changing life style can show changes in mortality rate by different causes. The small sample size decreased the flexibility of GMM. Another limitation was the ecological fallacy such as ecological-level models which are not perfectly specified. Still another limitation was that ecological correlations are always substitutes for individual-level correlations.

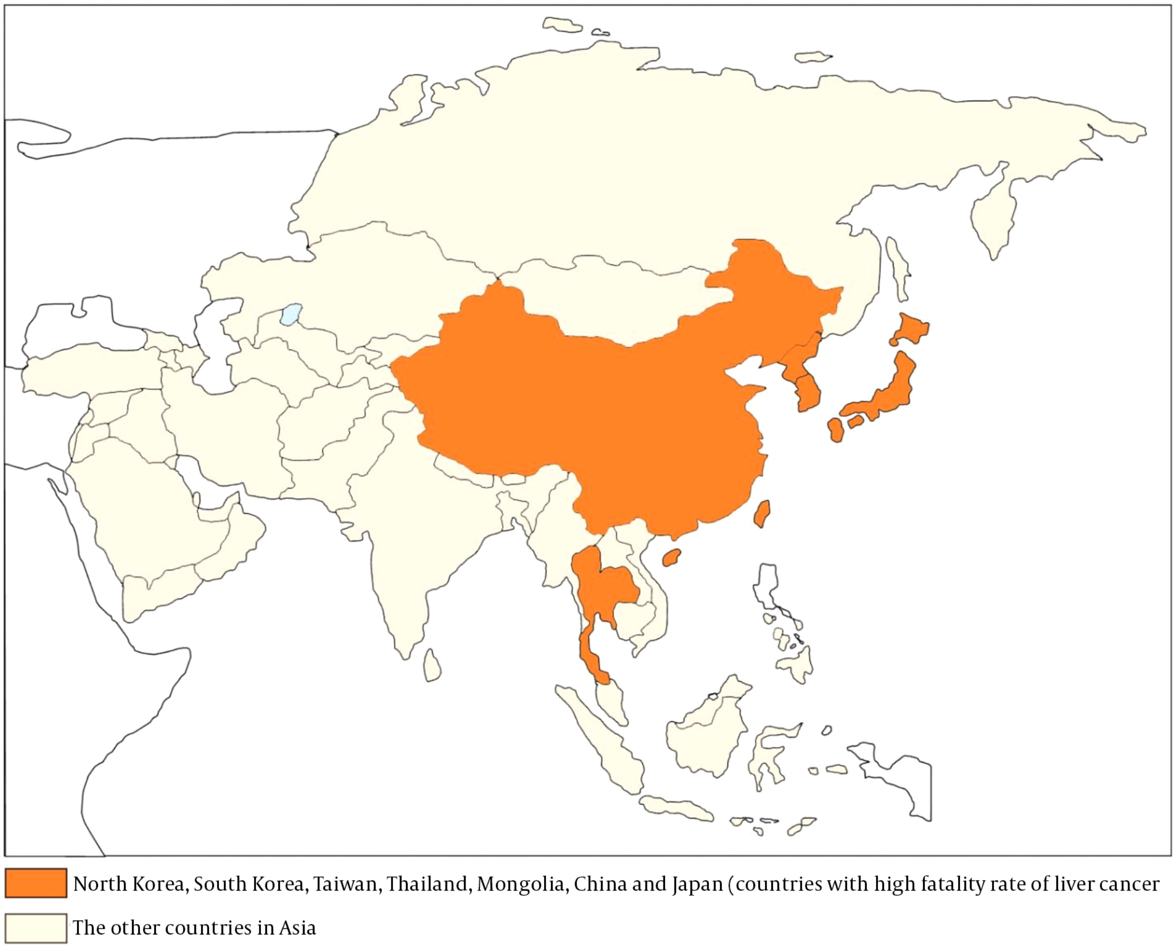

Figure 5. Geographic Illustration of GMM Classification for Trends Fatality Rate of Liver Cancer in Different Classes from 1990 to 2015

In a comparative study on the Asian and European HCC patients' quality of life, the Asian patients were proved to have a higher quality of life with respect to their emotional function, their sleeping pattern (insomnia), and their sexual activity level. Similarly, the married European patients had a lower quality of life in comparison with the single Asian participants (41). In future researches, the pattern could be compared with developed countries.

Therefore it is highly recommend that policymakers in the health field identify the reasons for the increase in the mortality rate and take due actions such as interventional programs of countries which have succeeded in taking under control the ramifications of liver cancer

The authors have declared that no conflict of interest exists.

References

1. Lee B, Konen J, Wilkinson S, Marcus AI, Jiang Y. Local alignment vectors reveal cancer cell-induced ECM fiber remodeling dynamics. *Sci Rep.* 2017;**7**:39498. doi: 10.1038/srep39498. [PubMed: 28045069].
2. Arabsalmani M, Mohammadian-Hafshejani A, Ghoncheh M, Hadadian F, Towhidi F, Vafaee K, et al. Incidence and mortality of kidney cancers, and human development index in Asia; a matter of concern. *J Nephropathol.* 2017;**6**(1):30–42. doi: 10.15171/jnp.2017.06. [PubMed: 28042551].
3. Wang P, Wang M, Li S, Ma L, Xi S, He J. Association of the MDM2 SNP285 Polymorphism with Cancer Susceptibility: A Meta-Analysis. *Dis Markers.* 2016;**2016**:4585484. doi: 10.1155/2016/4585484. [PubMed: 27890964].
4. Costello LC, Franklin RB. Decreased zinc in the development and progression of malignancy: an important common relationship and potential for prevention and treatment of carcinomas. *Expert Opin Ther Targets.* 2017;**21**(1):51–66. doi: 10.1080/14728222.2017.1265506. [PubMed: 27885880].

5. Wen X, Lu F, Liu S. Prognostic value of p53 mutation for poor outcome of Asian primary liver cancer patients: evidence from a cohort study and meta-analysis of 988 patients. *Onco Targets Ther.* 2016;**9**:7425–33. doi: 10.2147/OTT.S121594. [PubMed: 27994473].
6. Tian C, Yao S, Liu L, Ding Y, Ye Q, Dong X, et al. Klf4 inhibits tumor growth and metastasis by targeting microRNA-31 in human hepatocellular carcinoma. *Int J Mol Med.* 2017;**39**(1):47–56. doi: 10.3892/ijmm.2016.2812. [PubMed: 27909734].
7. Cong WM, Bu H, Chen J, Dong H, Zhu YY, Feng LH, et al. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update. *World J Gastroenterol.* 2016;**22**(42):9279–87. doi: 10.3748/wjg.v22.i42.9279. [PubMed: 27895416].
8. Best J, Schotten C, Theysohn JM, Wetter A, Muller S, Radunz S, et al. Novel implications in the treatment of hepatocellular carcinoma. *Ann Gastroenterol.* 2017;**30**(1):23–32. doi: 10.20524/aog.2016.0092. [PubMed: 28042235].
9. Zhang H, Zhou D, Ying M, Chen M, Chen P, Chen Z, et al. Expression of Long Non-Coding RNA (lncRNA) Small Nucleolar RNA Host Gene 1 (SNHG1) Exacerbates Hepatocellular Carcinoma Through Suppressing miR-195. *Med Sci Monit.* 2016;**22**:4820–9. doi: 10.12659/MSM.898574. [PubMed: 27932778].
10. Alkhalili E, Greenbaum A, Luo L, Rodriguez R, Caldwell K, Estrada OM, et al. Viral hepatitis status does not affect survival in patients with hepatocellular carcinoma. *Ann Gastroenterol.* 2017;**30**(1):101–5. doi: 10.20524/aog.2016.0097. [PubMed: 28042245].
11. Jeric I, Maurer G, Cavallo AL, Raguz J, Desideri E, Tarkowski B, et al. A cell-autonomous tumour suppressor role of RAF1 in hepatocarcinogenesis. *Nat Commun.* 2016;**7**:13781. doi: 10.1038/ncomms13781. [PubMed: 28000790].
12. Zhang G, Fang X, Guo X, Li L, Luo R, Xu F, et al. The oyster genome reveals stress adaptation and complexity of shell formation. *Nature.* 2012;**490**(7418):49–54. doi: 10.1038/nature11413. [PubMed: 22992520].
13. Liang P, Huang C, Liang SX, Li YF, Huang SX, Lian ZP, et al. Effect of CyberKnife stereotactic body radiation therapy for hepatocellular carcinoma on hepatic toxicity. *Onco Targets Ther.* 2016;**9**:7169–75. doi: 10.2147/OTT.S112290. [PubMed: 27920555].
14. Lee K, Lee KB, Yi NJ, Suh KS, Jang JJ. Prognosis of Hepatocellular Carcinoma after Liver Transplantation: Comparative Analysis with Partial Hepatectomy. *J Pathol Transl Med.* 2017;**51**(1):79–86. doi: 10.4132/jptm.2016.10.13. [PubMed: 28013531].
15. Kawaguchi Y, Honda G, Endo I, Cherqui D, Kokudo N. Current Technical Issues for Surgery of Primary Liver Cancer. *Liver Cancer.* 2016;**6**(1):51–8. doi: 10.1159/000449345. [PubMed: 27995088].
16. Zhu W, Zhao Y, Zhou J, Wang X, Pan Q, Zhang N, et al. Monoacylglycerol lipase promotes progression of hepatocellular carcinoma via NF-kappaB-mediated epithelial-mesenchymal transition. *J Hematol Oncol.* 2016;**9**(1):127. doi: 10.1186/s13045-016-0361-3. [PubMed: 27884159].
17. Bawah A, Houle B, Alam N, Razzaque A, Streatfield PK, Debpuur C, et al. The Evolving Demographic and Health Transition in Four Low- and Middle-Income Countries: Evidence from Four Sites in the INDEPTH Network of Longitudinal Health and Demographic Surveillance Systems. *PLoS One.* 2016;**11**(6):e0157281. doi: 10.1371/journal.pone.0157281. [PubMed: 27304429].
18. Tran BX, Nguyen LH, Nong VM, Nguyen CT. Health status and health service utilization in remote and mountainous areas in Vietnam. *Health Qual Life Outcomes.* 2016;**14**:85. doi: 10.1186/s12955-016-0485-8. [PubMed: 27267367].
19. Jiang B, Li B, Wang Y, Han B, Wang N, Li Q, et al. The nine-year changes of the incidence and characteristics of metabolic syndrome in China: longitudinal comparisons of the two cross-sectional surveys in a newly formed urban community. *Cardiovasc Diabetol.* 2016;**15**:84. doi: 10.1186/s12933-016-0402-9. [PubMed: 27255215].
20. Pittayapan P. Health Insurance for Cancer Care in Asia: Thailand. *Asia Pac J Oncol Nurs.* 2016;**3**(1):54–7. doi: 10.4103/2347-5625.178173. [PubMed: 27981139].
21. Chandra S, Kusum A, Chandra H, Yadav K, Verma SK. Familial Hepatocellular Carcinoma- First Reported Case from India. *J Clin Diagn Res.* 2016;**10**(3):ED11–2. doi: 10.7860/JCDR/2016/17746.7427. [PubMed: 27134884].
22. Keefe D, Al Garni A, Villalon A, Hassan A, Kwong D, Li P, et al. Challenges in supportive cancer care: perspectives from the Asia Pacific and Middle East. *Support Care Cancer.* 2016;**24**(11):4479–81. doi: 10.1007/s00520-016-3381-1. [PubMed: 27543163].
23. Si T, Chen Y, Ma D, Gong X, Yang K, Guan R, et al. Preoperative transarterial chemoembolization for resectable hepatocellular carcinoma in Asia area: a meta-analysis of random controlled trials. *Scand J Gastroenterol.* 2016;**51**(12):1512–9. doi: 10.1080/00365521.2016.1216588. [PubMed: 27598831].
24. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. *Gut Liver.* 2016;**10**(3):332–9. doi: 10.5009/gnl15257. [PubMed: 27114433].
25. Chassagne F, Rojas Rojas T, Bertani S, Bourdy G, Eav S, Ruiz E, et al. A 13-Year Retrospective Study on Primary Liver Cancer in Cambodia: A Strikingly High Hepatitis C Occurrence among Hepatocellular Carcinoma Cases. *Oncology.* 2016;**91**(2):106–16. doi: 10.1159/000446398. [PubMed: 27250992].
26. Available from: http://www.healthdata.org/.
27. Salzborn S, Davidov E, Reinecke J. Methods, theories, and empirical applications in the social sciences. Springer; 2012.
28. Muthen B, Shedden K. Finite mixture modeling with mixture outcomes using the EM algorithm. *Biometrics.* 1999;**55**(2):463–9. [PubMed: 11318201].
29. Muthén B. A general structural equation model with dichotomous, ordered categorical, and continuous latent variable indicators. *Psychometrika.* 1984;**49**(1):115–32. doi: 10.1007/bf02294210.
30. Wang J, Wang X. Structural equation modeling: Applications using Mplus. John Wiley & Sons; 2012.
31. Wang H, Liu J, Hu X, Liu S, He B. Prognostic and Therapeutic Values of Tumor Necrosis Factor-Alpha in Hepatocellular Carcinoma. *Med Sci Monit.* 2016;**22**:3694–704. doi: 10.12659/MSM.899773. [PubMed: 27739418].
32. Lamarca A, Mendiola M, Barriuso J. Hepatocellular carcinoma: Exploring the impact of ethnicity on molecular biology. *Crit Rev Oncol Hematol.* 2016;**105**:65–72. doi: 10.1016/j.critrevonc.2016.06.007. [PubMed: 27372199].
33. Hafeez Bhatti AB, Dar FS, Waheed A, Shafique K, Sultan F, Shah NH. Hepatocellular Carcinoma in Pakistan: National Trends and Global Perspective. *Gastroenterol Res Pract.* 2016;**2016**:5942306. doi: 10.1155/2016/5942306. [PubMed: 26955390].
34. Xu Y, Chen J, Wang H, Zheng H, Feng D, Zhang A, et al. Perioperative and long-term outcomes of liver resection for hepatitis B virus-related hepatocellular carcinoma without versus with hepatic inflow occlusion: study protocol for a prospective randomized controlled trial. *Trials.* 2016;**17**(1):492. doi: 10.1186/s13063-016-1621-9. [PubMed: 27724929].
35. Hong YM, Yoon KT, Cho M, Kang DH, Kim HW, Choi CW, et al. Trends and Patterns of Hepatocellular Carcinoma Treatment in Korea. *J Korean Med Sci.* 2016;**31**(3):403–9. doi: 10.3346/jkms.2016.31.3.403. [PubMed: 26955241].
36. Lee EY, Xuan Mai TT, Chang Y, Ki M. Trends of liver cancer and its major risk factors in Korea. *Epidemiol Health.* 2015;**37**:e2015016. doi: 10.4178/epih/e2015016. [PubMed: 25773443].
37. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev.* 2010;**19**(8):1893–907. doi: 10.1158/1055-9965.EPI-10-0437. [PubMed: 20647400].
38. Posuwan N, Wanlapakorn N, Sa-Nguanmoo P, Wasitthankasem R, Vichaiwattana P, Klinfueng S, et al. The Success of a Universal Hepatitis B Immunization Program as Part of Thailand's EPI after 22 Years' Implementation. *PLoS One.* 2016;**11**(3):e0150499. doi: 10.1371/journal.pone.0150499. [PubMed: 26938736].

39. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. *Liver Cancer.* 2014;**3**(3-4):458–68. doi: 10.1159/000343875. [PubMed: 26280007].
40. Muthen BO. Analysis of longitudinal data using latent variable models with varying parameters. UCLA; 2011.
41. Chie WC, Blazeby JM, Hsiao CF, Chiu HC, Poon RT, Mikoshiba N, et al. Differences in health-related quality of life between European and Asian patients with hepatocellular carcinoma. *Asia Pac J Clin Oncol.* 2016 doi: 10.1111/ajco.12464. [PubMed: 27038366].

Table 1. Asian Demographic and Socioeconomic Statistics (WHO REPORT AT 2015)

Country	Population (000S) (2013)	Sex Ratio (2013)	Aged > 60 Years a (2013), %	Aged < 15 Years a (2013), %	Gross National Income Per Capita (2013), g (pp int.$
Afghanistan	30522	1.05	4	47	2000
Algeria	39208	NA	7	28	12990
Armenia	2977	1.12	14	20	8140
Azerbaijan	9413	1.13	9	22	16180
Bahrain	1332	1.02	3	21	NA
Bangladesh	156595	1.04	7	30	2810
Bhutan	754	1.05	7	28	7210
Brunei	418	1.047	25	31	NA
Cambodia	15135	1.045	30	24	2890
China	1393337	1.12	18	37	NA
Egypt	82056	1.05	31	25	10850
Georgia	4341	NA	18	38	7040
India	1252140	1.12	29	26	5350
Indonesia	249866	1.05	29	28	9260
Iran	77447	1.05	24	29	156000
Iraq	33765	1.05	40	10	15220
Japan	127144	1.06	13	49	37630
Jordan	7274	1.08	34	23	11660
Kazakhstan	16441	1.06	26	29	20570
Kuwait	3369	1.04	25	29	NA
Kyrgyzstan	5548	1.05	30	25	3070
Laos	6770	1.04	35	21	4570
Lebanon	4822	1.05	21	30	17390
Libya	6202	1.05	30	27	NA
Malaysia	29717	1.07	26	27	22460
Maldives	3345	1.05	29	25	9890
Mongolia	2839	NA	27	27	8810
Morocco	33008	NA	28	27	7000
Myanmar	53259	NA	25	29	NA
Nepal	27797	1.04	35	22	2260
North Korea	NA	NA	NA	NA	NA
Oman	3632	1.05	23	26	NA
Pakistan	182143	1.05	34	23	4920
Palestine	NA	NA	NA	NA	NA
Philippines	98394	1.05	34	23	7820
Qatar	2169	1.06	13	23	123860
Saudi Arabia	28829	1.05	29	28	53780
Singapore	5412	1.08	16	38	76850
South Korea	NA	1.07	NA	NA	NA
Sri Lanka	21273	1.04	25	31	9470
Syria	21898	1.06	35	22	NA
Taiwan	NA	NA	NA	NA	NA
Tajikistan	8208	1.05	39	22	2500
Thailand	67010	1.05	18	37	13510
Timor-Leste	1133	1.05	46	17	6410

Table 2. The Maximum, Minimum, Std. and Mean of the Rates of Liver Cancer Deaths Per 100,000 People in Asian Countries from 1990 to 2015

Year	Min	Max	Mean	IQR	Median	Std.
y1990	0.94	30.88	6.6	6.02	2.71	7.28
y1995	1.16	34.69	7.47	6.95	3.25	8.35
y2000	1.15	35.41	7.99	7.05	3.18	9.29
y2005	1.14	39.07	8.69	7	3.1	10.49
y2010	1.20	41.34	9.25	6.07	3.37	11.04
y2015	1.17	55.34	9.8	6	3.21	13.35

Table 3. Fit indices for Latent Growth Mixture Models with Different Numbers of Classes for Liver Cancer Fatality Rates Per 100,000 in Both Genders

Sex	Fit Indices	Number of Classes		
		2	**3**	**4**
Female	AIC	1325	1321	1337
	BIC	1352	1254	1376
	SSBIC	1308	1300	1313
	ENTROPY	0.95	0.93	0.88
	LRT p value	0.114	0.871	0.715
Male	AIC	1600	1554	1560
	BIC	1627	1578	1599
	SSBIC	1583	1534	1536
	ENTROPY	0.91	0.87	0.85
	LRT p value	0.08	0.521	0.741
Both	AIC	11407	1398	1405
	BIC	1434	1431	1444
	SSBIC	1390	1377	1382
	ENTROPY	0.99	0.96	0.94
	LRT p value	0.093	0.612	0764

Table 4. Estimates of Latent Growth Mixture Model Parameters for Liver Cancer Fatality Rates Per 100,000 People in Both Genders

Sex	Class	Intercept		Slope	
		Estimate	**SE**	**Estimate**	**SE**
Male	1	26.4	1.79	5.9	0.3
	2	7.7	1.3	0.47	0.11
Female	1	15.04	3.1	2.06	0.32
	2	3.5	0.45	0.09	0.04
Both	1	21.1	1.8	2.4	0.42
	2	3.9	0.49	0.18	0.07