Modeling the Trend Changes of Liver Cancer Mortality in the 6 WHO Regions

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ABSTRACT

Background: *There is little information about comparison of the mortality patterns in different regions. The current study aimed to assess the trend changes of liver cancer mortality in 6 WHO regions.*

Methods: *The mortality rates of liver cancer in the 6 WHO regions during 1990 to 2017 were extracted from the Global Burden of Disease database. Growth mixture model was used to identify the latent patterns using a set of tools to handle both the within and between trajectory variations. All the modeling procedures were implemented in Mplus 7.4 software.*

Results: *The mortality rate in Africa showed a slow decreasing trend throughout the observation period, but a slow increase was observed in the Eastern Mediterranean region, European region, region of the Americas, and South-East Asia region. The slope of the rise in liver cancer mortality rate for Western Pacific region was 3-4 times higher than the other regions. 2-pattern growth mixture model was estimated as the best model. The Western Pacific region with annual increase of 0.20 in the liver cancer mortality rate was in the first pattern and the other 5 regions including Africa region, Eastern Mediterranean region, European region, region of the Americas, and South-East Asia region with annual increase of 0.05 in liver cancer mortality rate belonged to the second pattern.*

Conclusion: *Observed pattern in the Western Pacific region is not favorable. Taking into account a set of urgent prevention actions to control mortality rate of liver cancer in this region seems necessary.*

Keywords: *Liver cancer, mortality, trend, WHO regions*

INTRODUCTION

Liver cancer is predicted to be a major health problem. In 2018, liver cancer was among the 6 most common cancers and the fourth leading cause of cancer deaths in the world with 782 000 deaths. The incidence and mortality rate of this cancer in men is 2-3 times higher than women.[1] In 2015, liver cancer was the second leading cause of death with 887 000 deaths.[2]

Liver cancer deaths have been rising in the United States since the 1980s. The mortality rate in this region ranges from 2.3 to 6.8. The highest rates (5.5-6.8) were observed in the populations of Washington DC and the 3 islands of Louisiana, Mississippi, and Texas.[3] Since 1970, there have been many changes in the liver mortality in Europe. This rate has decreased quadruplet in southern European countries due to lower alcohol consumption but has increased in equal proportions in other European countries.[4]

In Asia, the 5 countries with the highest mortality rates from liver cancer are as follows: Mongolia (70.3 per 100 000 people), the Lao PDR (50.9 per 100 000 people), Vietnam (23.7 per 100 000 people), Cambodia (21.5 per 100 000 people), and Thailand (21.5 per 100 000 people). Also, 5 Asian countries with the lowest mortality rate due to liver cancer are Nepal (0.9 per 100 000 people), the Islamic Republic of Iran (2.3 per 100 000 people), Lebanon (2.4 per 100 000 people), Israel (2.5 per 100 000 people), and India (2.6 per 100 000 people).[5] The incidence and mortality of liver cancer in China is higher than other countries. China has about 19% of the world's population but accounts for more than 50% of all liver cancers and newly diagnosed deaths.[1]

Although information about liver cancer mortality in Africa is limited, previous studies in South Africa showed that the mortality rates increased between the ages of 50-59 and 60-69 in black African men in 2009-2010 and

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women in 2009-2015. Besides, the mean mortality rates were 4 and 3.3 for black African men and women and 2.2 and 1.8 for their white population, respectively.[6]

In Australia, the death rate from this cancer increased 184% between 1982 and 2015[7]; in Russia, liver cancer mortality rates was 39.4% in 2000-2004 and 39.1% in 2010-2014; the percentage of change in 2002-2012 was –1.0.[8]

Liver cancer has the third highest prevalence and the second highest mortality rate in Western Pacific region (WPR). Of the 37 countries in WPR, Mongolia and Leo PDR have the highest prevalence and mortality from liver cancer, and Samoa, New Zealand, and Australia have the lowest prevalence and mortality from this cancer.[9]

Although several studies have been conducted in different regions on the trend changes of liver cancer mortality, there is little information about comparison of the mortality patterns in different regions. Therefore, the current study aimed to assess the trend changes of liver cancer mortality in 6 WHO regions.

MATERIALS AND METHODS

The mortality rate of major diseases has been reported for 195 countries and made available through the Global Burden of Disease Collaborative Network website. In the current study, the mortality rates of liver cancer in the WHO regions between 1990 and 2017 were extracted from the Global Burden of Disease Study 2017 (GBD 2017) results.[10] WHO Member States are grouped into 6 regions including Africa region, Eastern Mediterranean region, European region, region of the Americas, South-East Asia region, and WPR.

Statistical Analyses

Growth mixture model (GMM) is a modern technique to identify the latent patterns using a set of tools to handle both the within and between trajectory variations. Each of the k latent patterns was estimated using the following equations:

$$y_{it}^{k} = \alpha_{i0}^{k} + \alpha_{i1}^{k}\lambda_{t}^{k} + \varepsilon_{it}^{k}$$

$$\alpha_{i0}^{k} = \alpha_{00}^{k} + \sum_{j}\beta_{01j}^{k}x_{j} + \varepsilon_{i0}^{k}$$

$$\alpha_{i1}^{k} = \alpha_{10}^{k} + \sum_{j}\beta_{11j}^{k}x_{j} + \varepsilon_{i1}^{k}$$

where α_{00}^{k} is the estimated overall mean for the mortality rates of liver cancer in *k*th pattern and α_{10}^{k} corresponds to the annual mean rate of trend changes in the liver cancer mortality for kth pattern. To estimate the number of patterns, *P*-value of likelihood ratio test was calculated for different number of patterns, and due to very small sample size, $P < .20$ was considered as statistically significant. All the modeling procedures were implemented in Mplus 7.4 software.

RESULTS

The trend changes of liver cancer mortality rate in the 6 WHO regions between 1990 and 2017 are shown in Figure 1. The mortality rate in Africa showed a slow decreasing trend throughout the observation period, but a slow increase was observed in the Eastern Mediterranean region, European region, region of the Americas, and South-East Asia region. As shown in Figure 1, the slope of the rise in liver cancer mortality rate for WPR was 3-4 times higher than the other regions (note that vertical scales are different in Figure 1). Looking at the graph for Western Pacific, there was a decline in the mortality after 2005 and then kind of plateau, subsequently rising steeply after 2013. Similarly, a continuous increase in mortality with time is obvious in the regions of the Americas which appears to be steeper than other regions.

To estimate the number of patterns, we summarized the *P*-value of likelihood ratio test and other fit indices in Table 1 for different patterns. Two-pattern GMM was estimated as the best model, and more characteristics of each pattern are reported in Table 2. The WPR with annual increase of 0.20 in the liver cancer mortality rate was in the first pattern. Also, the other 5 regions including Africa region, Eastern Mediterranean region, European region, region of the Americas, and South-East Asia

Main Points

- *The mortality rate in Africa showed a slow decreasing trend throughout the observation period, but a slow increase was observed in the Eastern Mediterranean region, European region, region of the Americas, and South-East Asia region.*
- *The slope of the rise in liver cancer mortality rate for Western Pacific region was 3-4 times higher than the other regions.*
- *The observed pattern in the Western Pacific region is not favorable.*

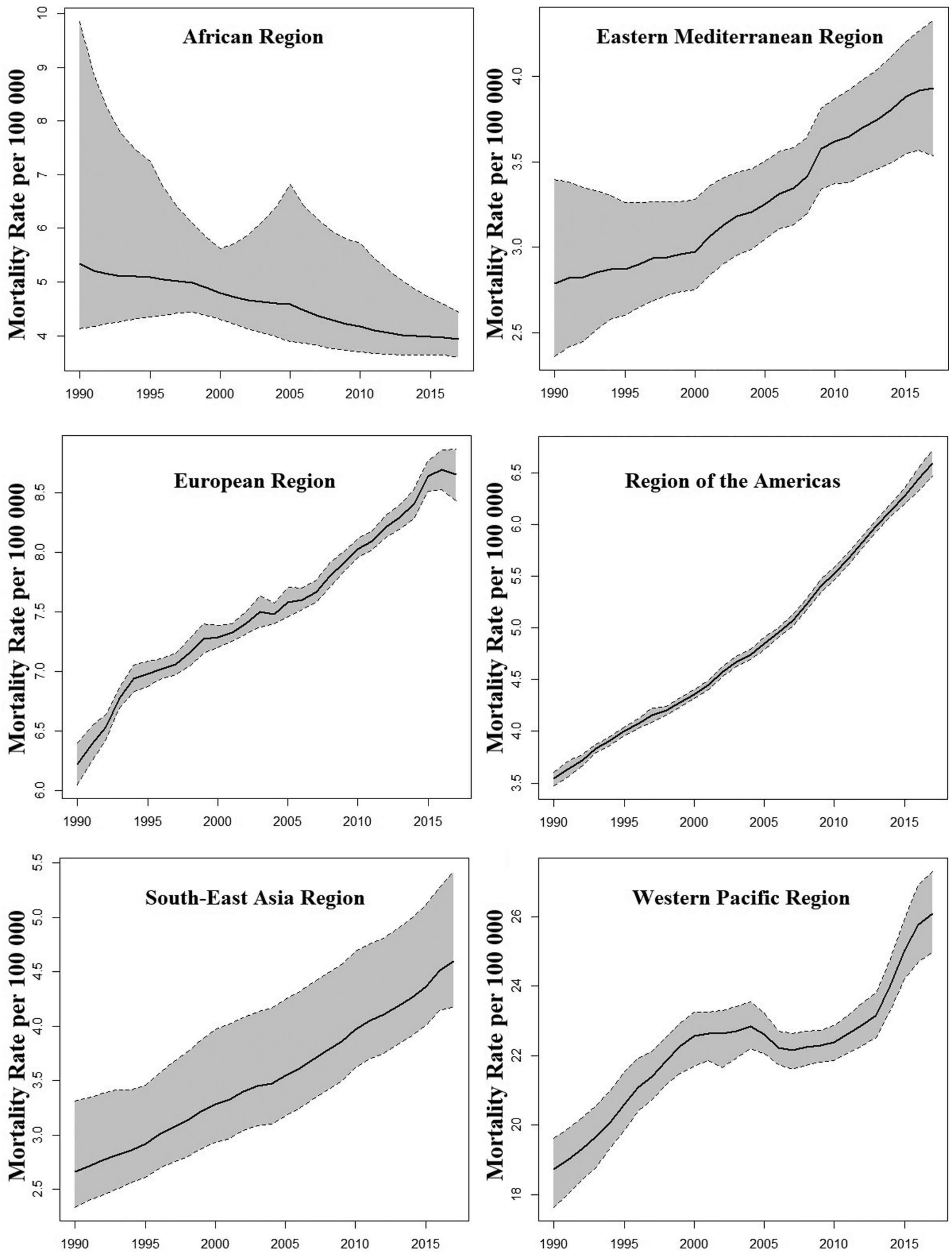

Figure 1. Trend changes of liver cancer mortality rate in the 6 WHO regions. WHO, World Health Organization.

Table 1. Fit Indices for Different Patterns

	Number of Pattern				
Fit Indices	1	2	3	4	5
AIC	1172	678	457	277	131
BIC	1166	671	449	269	123
SSBIC	1079	576	345	156	1.3
LRT *P*-value	-	0.18	0.36	0.61	0.56

AIC, Akaike information criterion; BIC, Bayesian information criterion; SSBIC, sample size adjusted Bayesian information criterion; LRT, likelihood ratio test.

region with annual increase of 0.05 in liver cancer mortality rate belonged to the second pattern. The behavior of trend changes in both patterns is displayed in Figure 2.

DISCUSSION

In this study, modeling trend changes of liver cancer mortality in the 6 WHO regions showed that there were 2 main patterns. The first pattern belonged to WPR with a slow rising trend, but the other regions were categorized in the second pattern, with almost constant mortality rate during the past decades.

The WPR, as one of the WHO regions, comprises about a quarter of the world's population. The WPR is a highly heterogeneous region and includes densely populated countries such as China to small islands in the Pacific.[9] Overall, approximately 30% of all cancers in the world are in the WPR with liver, stomach, and nasopharyngeal cancers having the highest prevalence of 63%, 60%, and 53%, respectively, among other cancers.[11] In 2012, hepatitis B vaccination in 5-year-old population reduced the incidence of chronic hepatitis B infection (of the most common causes of liver cancer) to less than 2% in 30 out of the 37 countries of the WPR, with efforts to reduce it in the future. Hepatitis B-related disease leads to higher mortality among adults who have not been vaccinated. In China and many other countries in the region, the prevalence of chronic HBV infection leading to liver cancer is more than 6%.[11]

Table 2. Intercept and Slope of the Estimated Linear Trend for Each Pattern

	Intercept		Slope	
Region	Estimate	SE	Estimate	SE
Western Pacific region	19.49	0.08	0.20	0.01
Other regions	4.08	0.69	0.05	0.02

SE, standard error.

According to our findings, from 1990 to 2017, the mortality rate from liver cancer had a steady trend with a slight increase in South East Asia. Consistent with the findings presented in the study of Kim et al[12] based on the mortality data from the Korean Statistical Information Service, it was shown that mortality rates have remained stable over the past decades. Also Wu et al[13] in a study conducted in East and Southeast Asia, showed that the incidence of liver cancer in Thailand was constant from 1983 to 1999 and after 1999, it started to increase rapidly. Despite the successful control of HBV and aflatoxins in this region, other risk factors such as obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) due to changes in lifestyle and dietary habits have continued to increase liver cancer and mortality.[14]

The results of the study carried out by Mohammadian et al[5] showed that the standard mortality rate for liver cancer in Asia ranged from 0.9 per 100 000 people in Nepal to 70.3 per 100 000 in Mongolia. Hu et al[15] stated in their research that the ratio of mortality and incidence of gastrointestinal cancer, including the liver, had an inverse relationship with human development index (HDI) at the national and regional levels.

Wong et al[16] have shown that in the Asia-Pacific region, hepatitis B virus (HBV), Hepatitis C virus (HCV), alcohol overdose, metabolic syndrome, and concomitant liver disease are major contributors to chronic liver damage and end-stage liver pathology. Moreover, in countries such as China, widespread implementation of hepatitis B vaccination has reduced the incidence of liver cancer. The prevalence of NAFLD is increasing due to lifestyle changes and diets. As a result, the uptrend in NAFLD is comparable to Western countries.[16]

According to our findings from 1990 to 2017, the mortality rate of liver cancer was approximately constant in European region. Pimpin et al[4] note that the liver disease is a complex, diverse, and important disease in Europe. Various risk factors in Europe such as consumption of alcoholic beverages[17], liver diseases related to liver viruses including HBV and HCV,[18] and NAFLD including obesity[19] and type 2 diabetes[20] have led to the incidence and mortality of liver cancer. Besides, the main reasons for the increase in liver cancer in Australia are aging population, increased prevalence of metabolic syndrome, NAFLDs and type 2 diabetes, and increased migration from HBV endemic countries. Hepatitis C virus infections have also been a key risk factor for hepatocellular carcinoma (HCC); however, the use of direct antiviral drugs in Australia is

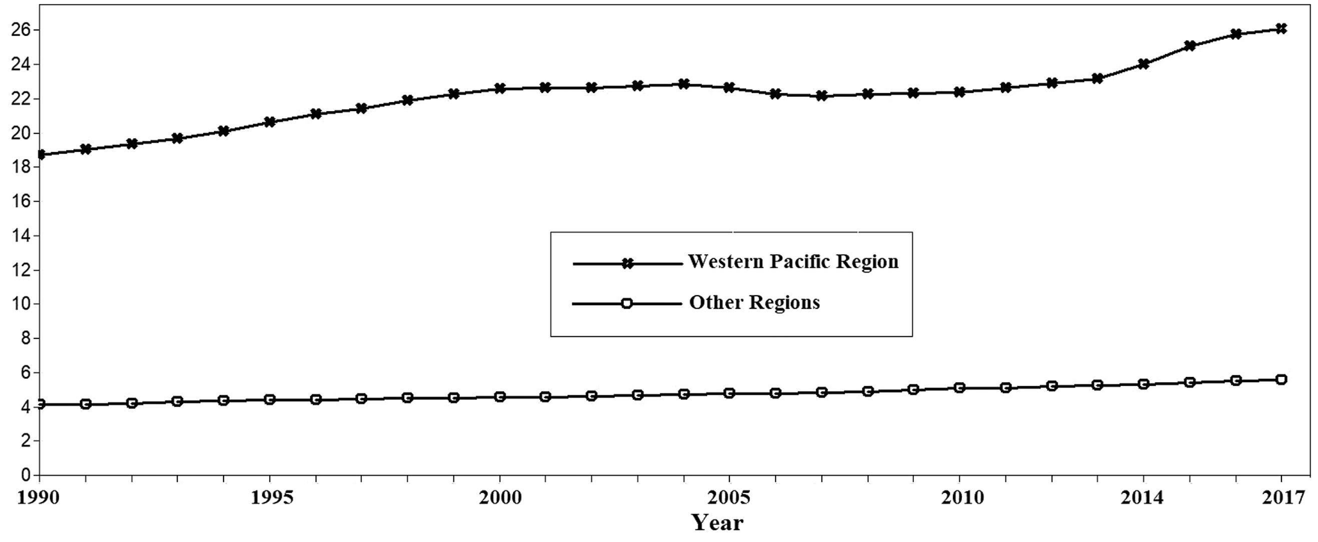

Figure 2. Behavior of trend changes in the identified patterns via growth mixture model.

expected to make HCV a less commonly observed risk factor.[21-23]

For the trend observed in the African countries, we can point to the high prevalence of HBV,[24] HCV,[25] and human immunodeficiency virus (HIV) infections[26] According to the studies conducted by Yang et al[27] in Egypt, HCV was the leading cause of HCC, and in other African countries, HBV was the main cause of HCC. Yang et al[27] in their studies in Africa state that for the initial prevention of chronic hepatitis, measures such as general hepatitis B vaccination, identification of high-risk populations (patients with HCV or HBV) by general population screening, prevention of liver disease progression and disorder in liver function through antiviral therapy, reduction of aflatoxin exposure through postoperative interventions, monitoring of hepatocellular carcinoma among individuals at risk, and establishment of hepatocellular carcinoma treatment centers are the key components of efforts to prevent death from liver cell carcinoma in Africa.

In line with our studies, a study of cirrhosis and liver cancer mortality in the United States from 1999 to 2016 found that cirrhosis mortality rate was lower in non-Hispanic Americans than in Hispanic Americans. During this period, the Northeastern United States has seen the lowest increase (1.6%, 1.1-2.1%), while the South has the fastest growth (3.5%, 2.8-4.2%). The fastest increase in liver cell cirrhosis and related mortality occurred in the Western and Southern United State. These variations may dovetail with economic recession in the United States and unemployment which is related to trends in alcohol misuse in young mean.[28] The findings show that in the United States, the prevalence and mortality rate of liver cancer varies by geography, ethnicity, race, age, and gender.[3] In the United States, HCV is the main reason leading to liver cancer and mortality.[29] Other risk factors for HCC include alcohol overuse,[30] chronic HBV infection,[31] diabetes,[32] obesity,[33] and NAFLD.[34]

Recently, Wong et al[35] in a study of the global trend of liver cancer mortality in 2018 found that the highest rates were in East Asia, North Africa, and Southeast Asia, respectively. They cited the main causes of the rising trend in liver cancer mortality, apart from racial and ethnic differences, socioeconomic, and poverty factors, such as diabetes, metabolic syndrome, obesity, alcohol, HBV, and HCV.

To the best of our knowledge, this study is the first assessment of the trend changes of mortality rate due to liver cancer in the 6 regions of the world. This study uses a highly advanced statistical model along with the most up-to-date epidemiological data about this cancer. Lack of statistical studies in some parts of the world and accurate statistics on mortality rates from liver cancer in some less developed countries due to the shortage of facilities caused limitations in conducting this study. For future investigation in this line, using advanced models to forecast the incidence and mortality of this cancer is highly suggested. In conclusion, observed pattern in the WPR is not favorable. Taking into account a set of urgent prevention actions to control mortality rate of liver cancer in this region seems necessary.

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Informed Consent: N/A.

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