Improved Trends in the Mortality-To-Incidence Ratios for Liver Cancer in Countries With High Development Index and Health Expenditures

Chi-Chih Wang

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chung Shan Medical University Hospital

Hsin-Hung Chen

School of Medicine, Chung Shan Medical University

Wen-Wei Sung

School of Medicine, Chung Shan Medical University

Ming-Chang Tsai (✉ tmc1110@yahoo.com.tw)

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chung Shan Medical University Hospital

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Abstract

Primary liver cancer is one of leading causes of death globally. Liver cancer has the uniqueness of geographical distribution as it predisposes viral infection etiologies and aging effects. We speculate if the human development index (HDI), current health expenditure (CHE) per capita, and current health expenditure on gross domestic product (CHE/GDP) can affect the incidence numbers, mortality numbers, or mortality-to-incidence ratios (MIRs) of liver cancer worldwide. Data was obtained from GLOBOCAN health data and statistics from the World Health Organization. MIRs and the changes in MIR over time (δ MIR) were used to evaluate the correlation of expenditures on healthcare and the HDI disparities via Spearman's rank correlation coefficient. The incidence and mortality of crude rate have significant associations with HDI, CHE per capita, and CHE/GDP. Specifically, there were significant associations between δ MIR and HDI as well as between δ MIR and CHE per capita. However, there were no significant associations between δ MIR and CHE/GDP. We evidenced that favorable liver cancer δ MIR was not associated with CHE/GDP, although it had significant association with HDI and CHE per capita. This result is worthy of the attention of the public health system all over the world.

Introduction

Primary liver cancer is one of leading causes of death globally. In 2018, liver cancer was the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death in both sexes with about 841,000 new cases and 782,000 deaths annually¹. Liver cancer also has unique etiologies and a wide range of subtypes. In terms of etiology, primary liver cancer commonly results from hepatitis B virus, hepatitis C virus infection, alcohol use, and preexisting liver cirrhosis^{2,3}. According to the World Health Organization (WHO) classification, this type of cancer was classified into two categories: hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC)⁴. HCC is the fourth most common cause of cancer-related death worldwide, and its risk factors include chronic hepatitis B and hepatitis C, alcohol addiction, metabolic liver disease, and exposure to dietary toxins, such as aflatoxins and aristolochic acid⁵. As for ICC, it is known as the least common form of cholangiocarcinoma and it has increased in both sexes in Europe⁶, with both chronic liver disease and metabolic abnormalities now recognized as risk factors for ICC⁷.

The Human Development Index (HDI), which was created by the United Nations Development Programme, is a tangible indicator associated with clinical assessment. The HDI is a summary measure of a country's average level of achievement in the following major dimensions of human development: living a long and healthy life, being knowledgeable, and having a decent standard of living⁸. An investigation was conducted between HDI and mortality to incidence ratio for patients with existing liver cancer⁹. In addition to liver cancer, HDI was also utilized to examine other overall cancer condition and specific types of cancer outcomes, such as colorectal cancer, breast cancer, and prostate cancer, as well as disability and life expectancy¹⁰.

The mortality-to-incidence ratio (MIR) has been reported as a practical indicator for the evaluation of cancer care^{11,12}. Due to primary liver cancer's unique geographical distribution, predisposing viral infection etiologies, and aging effects, we speculated whether HDI, current health expenditure per capita, and current health expenditure on gross domestic product would affect the incidence numbers, mortality numbers, or the MIRs of liver cancer worldwide. Since this relationship has not been fully clarified yet, we carried out this study to enrich knowledge of the incidence numbers, mortality numbers, MIRs, and MIR differences between years of primary liver cancer.

Results

Epidemiology of liver cancer according to the regions

The total number of new cases was 792,031 and number of deaths was 727,661 during this survey (Table 1). In both new cases and deaths, Asia had the highest cumulative risk of 12.8 new cases per 100,00 people and 11.8 deaths per 100,000

people. On the contrary, Africa had the lowest cumulative risk of 4.9 and 4.8 per 100,000 people for new cases and deaths, respectively. In terms of mortality-to-incidence ratio, Africa had the highest of 0.98 and North America has the lowest of 0.77.

Table 1
Summary of the number, crude rank, age-standardized rate and mortality-to-incidence ratio of liver cancer according to the regions.

Region	New cases			Deaths			MIR
	Number	CR	ASR	Number	CR	ASR	
Africa	63186	4.9	8.1	61962	4.8	8.0	0.98
Asia	578027	12.8	10.9	533364	11.8	10.0	0.92
Europe	73469	10.1	4.9	65993	9.1	4.1	0.90
Latin America and the Caribbean	34209	5.3	4.6	32376	5.0	4.4	0.94
North America	39416	11.1	6.5	30714	8.6	4.6	0.77
Oceania	3724	9.2	6.7	3252	8.0	5.5	0.87

Epidemiology and parameters of the development and health expenditure of liver cancer of the selected countries

The HDI ranged from 0.377 in Chad to 0.954 in Norway (Table 2). Per capita of current health expenditure ranged from 20 in Congo to 9818 in Switzerland. GDP percentage of current health expenditure ranged from 2.5% in South Sudan to 18.3% in Sierra Leone. In terms of the crude rates of incidence and mortality, Mongolia and Thailand had the first and second highest rates, respectively, and Nepal and Morocco had the first and second lowest rates, respectively. With regard to the ASR of incidence and mortality, Mongolia had the highest rates of 90.0 in incidence and 71.8 in mortality, while Morocco and Nepal both had the lowest incidence and mortality rates of 1.1 and 1.0, respectively. As for the δ MIR, Cuba had the highest at 0.22 and Portugal had the lowest at -0.09. We further analyzed the association between the crude rate of incidence/mortality and HDI, CHE per capita, USD, or CHE/GDP. The incidence/mortality of crude rate had significant associations with HDI, CHE per capita, and CHE/GDP (Fig. 1).

Table 2

Summary of human development index, current health expenditure, cancer incidence, cancer mortality, and mortality-to-incidence ratio in liver cancer of selected countries with incidence number > 923, the mean of all countries (n = 55).

	HDI	Current Health Expenditure		Incidence			Mortality			Mortality-to-incidence Ratio		
Country		Per Capita	% of GDP	Number	CR	ASR	Number	CR	ASR	MIR, 2012	MIR, 2018	dMIR
Argentina	0.830	998	6.8	2074	4.7	3.4	1850	4.2	3.0	1.07	0.89	0.18
Australia	0.938	4934	9.4	2231	9.2	5.5	2020	8.3	4.5	0.93	0.90	0.03
Austria	0.914	4536	10.3	994	11.7	5.2	821	9.6	4.1	0.94	0.82	0.12
Bangladesh	0.614	32	2.6	2940	1.8	2.1	2730	1.6	2.0	0.95	0.89	0.06
Brazil	0.761	780	8.9	11256	5.4	4.4	10673	5.1	4.1	1.04	0.94	0.10
Burkina Faso	0.434	33	5.4	1289	6.5	13.6	1262	6.4	13.3	0.97	0.98	-0.01
C?te d'Ivoire	0.516	75	5.4	1110	4.5	8.1	1119	4.5	8.2	0.95	1.00	-0.05
Cambodia	0.581	70	6.0	2474	15.3	20.8	2473	15.3	20.8	0.96	1.00	-0.04
Canada	0.922	4508	10.4	3534	9.8	5.1	3275	9.1	4.2	1.02	0.93	0.09
Chile	0.847	1102	8.1	1387	7.7	5.0	1261	7.0	4.5	1.11	0.91	0.20
China	0.758	426	5.3	378016	26.8	17.7	352962	25.0	16.4	0.97	0.93	0.04
Congo	0.459	20	4.3	3519	4.2	7.5	3530	4.2	7.7	0.92	1.00	-0.08
Czechia	0.891	1284	7.3	959	9.2	3.9	772	7.4	3.0	0.76	0.80	-0.04
Egypt	0.700	157	4.2	24724	25.0	31.2	24420	24.6	30.8	0.95	0.98	-0.03
Ethiopia	0.470	24	4.0	1574	1.5	2.6	1622	1.5	2.7	0.92	1.00	-0.08
France	0.891	4026	11.1	9525	15.1	7.6	8223	13.0	5.9	0.97	0.86	0.11
Germany	0.939	4592	11.2	7974	10.0	4.1	7467	9.3	3.5	0.84	0.93	-0.09
Ghana	0.596	80	5.9	2681	9.1	14.6	2665	9.1	14.6	0.97	1.00	-0.03
Guatemala	0.651	224	5.7	1627	9.5	13.9	1585	9.2	13.6	0.96	0.97	-0.01
Guinea	0.466	25	4.5	1573	12.1	21.5	1404	10.8	19.2	0.95	0.89	0.06
Hungary	0.845	894	7.2	1012	10.7	5.2	847	8.9	4.2	0.98	0.83	0.15
India	0.647	63	3.9	26651	2.0	2.1	24749	1.8	2.0	0.95	0.90	0.05
Indonesia	0.707	112	3.3	17890	6.7	7.2	17572	6.6	7.1	0.95	0.99	-0.04
Iran	0.797	366	7.6	3138	3.8	4.2	3085	3.8	4.1	0.95	1.00	-0.05
Italy	0.883	2700	9.0	10661	18.7	7.6	8490	14.9	5.3	0.86	0.80	0.06
Japan	0.915	3733	10.9	26641	21.9	6.9	20048	16.5	4.6	0.90	0.75	0.15
Kazakhstan	0.817	379	3.9	1091	6.0	5.5	974	5.3	4.9	0.95	0.88	0.07
Kenya	0.579	70	5.2	1325	2.6	5.2	1310	2.6	5.2	0.92	1.00	-0.08
Lao	0.604	53	2.8	1008	14.5	21.5	1005	14.5	21.5	0.95	1.00	-0.05

	HDI	Current Health Expenditure		Incidence			Mortality			Mortality-to-incidence Ratio		
Country		Per Capita	% of GDP	Number	CR	ASR	Number	CR	ASR	MIR, 2012	MIR, 2018	dMIR
Malaysia	0.804	386	4.0	1869	5.9	6.0	1851	5.8	5.9	1.15	0.98	0.17
Mexico	0.767	535	5.9	6412	4.9	5.0	6044	4.7	4.7	0.95	0.96	-0.01
Mongolia	0.735	152	3.9	2182	70.1	90.0	1716	55.1	71.8	0.89	0.79	0.10
Mozambique	0.446	28	5.4	1165	3.8	6.3	1138	3.7	6.4	0.93	0.97	-0.04
Myanmar	0.584	59	4.9	5214	9.7	9.8	5270	9.8	9.9	0.94	1.01	-0.07
Nigeria	0.534	97	3.6	5053	2.6	4.7	5078	2.6	4.8	0.97	1.00	-0.03
Pakistan	0.560	38	2.7	4280	2.1	3.0	4159	2.1	2.9	0.96	1.00	-0.04
Peru	0.759	323	5.3	2032	6.3	6.0	1967	6.1	5.8	0.98	0.97	0.01
Philippines	0.712	127	4.4	9234	8.7	10.8	9096	8.6	10.6	0.96	0.99	-0.03
Poland	0.872	797	6.3	2252	6.0	3.1	1935	5.2	2.5	1.04	0.87	0.17
Portugal	0.850	1722	9.0	1191	11.9	5.1	1178	11.8	4.9	0.90	0.99	-0.09
Russian Federation	0.824	524	5.6	9513	6.7	3.7	10282	7.2	3.9	1.25	1.07	0.18
Senegal	0.514	36	4.0	1060	6.5	12.2	1068	6.6	12.3	0.95	1.02	-0.07
Singapore	0.935	2280	4.3	1206	21.1	11.1	1128	19.7	10.2	0.98	0.93	0.05
South Korea	0.906	2013	7.4	15687	31.1	16.8	10978	21.7	11.0	0.73	0.70	0.03
Spain	0.893	2354	9.2	5822	13.0	6.2	4518	10.1	4.4	0.82	0.78	0.04
Tanzania	0.528	32	6.1	1483	2.5	4.7	1462	2.5	4.7	1.00	1.00	0.00
Thailand	0.765	217	3.8	22051	32.2	20.3	21900	32.0	20.2	0.95	0.99	-0.04
Turkey	0.807	455	4.1	4044	5.0	4.2	3989	4.9	4.1	0.93	0.98	-0.05
Uganda	0.528	46	7.3	1793	4.1	7.4	1534	3.5	6.6	0.95	0.85	0.10
Ukraine	0.750	125	6.1	1714	4.0	2.2	2106	4.9	2.6	1.06	1.23	-0.17
United Kingdom	0.920	4356	9.9	6458	10.0	4.7	5415	8.4	3.6	0.97	0.84	0.13
United States of America	0.920	9536	16.8	35868	11.2	6.7	27430	8.6	4.7	0.80	0.77	0.03
Uzbekistan	0.710	134	6.2	1352	4.2	5.2	1195	3.7	4.6	0.97	0.88	0.09
Venezuela	0.726	973	3.2	1077	3.3	3.3	1039	3.2	3.2	0.94	0.97	-0.03
Viet Nam	0.693	117	5.7	24493	25.7	22.9	24571	25.7	22.9	0.95	1.00	-0.05

The association between MIR and δ MIR and parameters of the development and health expenditure of the selected countries

We analyzed the associations between MIR or δ MIR and HDI, CHE per capita, or CHE/GDP (Fig. 2, 3). MIR had significant associations with HDI (p : -0.523, $p < 0.001$), CHE per capita (p : -0.534, $p < 0.001$), and CHE/GDP (p : -0.284, $p = 0.003$). Moreover, there are significant associations between δ MIR and HDI (p : 0.452, $p < 0.001$) or CHE per capita (p : 0.450, $p < 0.001$), except the δ MIR to CHE/GDP (p : 0.177, $p = 0.063$).

Discussion

Primary liver cancer has unique geographical distribution and predisposing viral infection etiologies, which comprises HCC and ICC. HCC is the most common type, with hepatitis B, hepatitis C, alcohol use, and preexisting liver cirrhosis being the most important risk factors¹. Furthermore, the incidence of HCC generally follows the geographical distribution of hepatitis B, hepatitis C virus, liver cirrhosis, and increasing prevalence among patients with nonalcoholic fatty liver disease². This indicates that a region with risk factors for HCC would be the region with a high incidence of primary liver cancer. Although HCC typically occurs in adults, 0.5%-1% of cases are reported to occur in patients less than 20 years old³. It is the second most common (20%) primary liver malignancy in adolescents and most commonly affects children between 10 to 19 years old⁴. Specifically, children in Asian countries are 10 times more likely than children¹ in North America to perinatally acquire hepatitis B infection⁵. Although treatments for liver cancer have improved gradually, primary liver cancer is still one of the leading causes of cancer death annually⁶.

In order to elucidate the associations between incidence/mortality of liver cancer and development within countries, we considered whether HDI, CHE per capita, and CHE/GDP influence the incidence numbers, mortality numbers, MIRs, and δ MIR of liver cancer worldwide.

Countries with higher development and health expenditures have higher incidence rates, and this statistic is possibly due to the wide implementation of early cancer screening systems⁷. The higher the HDI, current health expenditure, and CHE/GDP are, the higher the incidence of crude rate will be ($p < 0.001$, $p < 0.001$, $p = 0.002$ Fig. 1A, 1C, 1E respectively).

On the contrary, countries with higher HDI, CHE per capita and CHE/GDP have lower mortality rates ($p < 0.001$, $p < 0.001$, $p = 0.004$ Fig. 1B, 1D, 1F respectively). This suggests that a country may have a better health care system, which results in an increased elderly population and increased incidence and mortality rates in cancer patients⁸. Therefore, MIR—which is a practical indicator for the evaluation of cancer care—is inversely proportional to HDI, CHE per capita, and CHE/GDP based on our analysis (Fig. 2).

Additionally, there are significant associations between δ MIR and HDI as well as CHE per capita (Fig. 3A and 3B). However, the δ MIR had no significant correlation with CHE/GDP (Fig. 3C). This indicates that a country with higher CHE/GDP does not affect the outcomes of δ MIR for liver cancer in years. It is worth to note that valuables of δ MIR result from the difference between valuables in 2012 and those in 2018 in each country.

There are some limitations in our study. For example, our results were calculated from the WHO database and any errors in the primary data would have influenced our secondary database study. Secondly, the use of the HDI, CHE per capita, and CHE/GDP to represent the healthcare disparities would be a major limitation itself. In future studies, other additional factors should be investigated.

We evidenced that favorable liver cancer δ MIRs are not associated with CHE/GDP, although it has a significant relationship with HDI and CHE per capita. This result is worth the attention of the public health system all over the world.

Methods

Liver cancer, ICD-10 C22, and epidemiological data were obtained from the online Global Cancer Observatory (GLOBOCAN) 2012 and 2018 database. HDI data were obtained from the online United Nations Development Programme, Human Development Report Office. Data on health expenditures, including the CHE per capita and CHE/GDP, were obtained from the WHO Statistics online database.

The MIR was defined as the ratio of the crude rate (CR) of mortality to the CR of incidence^{13–16}. The exclusion criteria for country selection were based on the missing data in the WHO statistics (N = 12), on the missing HDI data (N = 2), on the unavailability of calculable MIR (N = 3), on the MIR outliers (N = 19), and incidence less than 200 per 100,000. A total of 111 countries were included in the final analysis. The δ MIR was defined as the difference between the MIR in 2012 and in 2018 (δ MIR = MIR [in 2012] – MIR [in 2018])¹⁷. Associations among the MIR, δ MIR, and other factors in various countries were estimated using Spearman's rank correlation coefficient by using the SPSS statistical software version 15.0 (SPSS, Inc., Chicago, IL). *P* values of < 0.05 were considered statistically significant. Scatterplots were generated with Microsoft Excel.

Declarations

Author contributions

Chi-Chih Wang and Ming-Chang Tsai conceived and supervised the study. Chi-Chih Wang and Hsin-Hung Chen collected data. Wen-Wei Sung performed statistical analyses and prepared figures. Hsin-Hung Chen and Wen-Wei Sung wrote the first draft manuscript. Ming-Chang Tsai reviewed and edited the manuscript.

Additional Information

The authors declare that they have no competing interests.

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Figures

Figure 1

The association between human development index, current health expenditure and the crude rates of (A, C, and E) incidence, and (B, D, and F) mortality in liver cancer.

Figure 2

The (A) human development index, (B) current health expenditure per capita, and (C) current health expenditure as percentage of gross domestic product are significantly associated with mortality-to-incidence ratio in liver cancer.

Figure 3

The (A) human development index, and (B) current health expenditure per capita are statistically associated with delta mortality-to-incidence ratio in liver cancer. The current health expenditure as percentage of gross domestic product (C) is not significantly associated with delta mortality-to-incidence ratio in liver cancer.

Supplementary Files

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