Comparison of primary liver cancer mortality estimates from World Health Organization, global burden disease and global cancer observatory

Chenxi Li1 | Wen-Qiang He2,3

1Melbourne School of Population & Global Health, The University of Melbourne, Melbourne, Australia
2School of Population Health, UNSW Sydney, Sydney, Australia
3Childrens Hospital at Westmead Clinical School, The University of Sydney, Sydney, Australia

Correspondence
Wen-Qiang He, School of Population Health, UNSW Sydney, Samuels Building, F25, Samuel Terry Ave, Kensington NSW 2033, Australia.
Email: wen-qiang.he@unsw.edu.au

Handling Editor: Dr. Alejandro Forner

Abstract

Aims: This study aims to compare estimates of primary liver cancer mortality from World Health Organization (WHO), Global Burden Disease (GBD) and Global Cancer Observatory (GCO).

Methods: Liver cancer mortality was extracted from WHO, GBD and GCO for 92 countries for the most recent year. Age-standardized rate (ASR) was computed and used for current comparisons across the three data sources. Temporal trend for 75 countries was analysed and compared between WHO and GBD from 1990 to 2019 using joinpoint regression. Average annual percentage change for the most recent 10 years was used as indicator for change.

Results: The estimates of ASR were quite consistent across the three data sources, but most similar estimates were found between WHO and GCO in both region and country levels. The differences in ASR were negatively correlated with completeness of cause-of-death registration, human development index and proportion of liver cancer because of alcohol consumption. Consistent trends of ASR were found from 35 countries between WHO and GBD in the most recent 10 years. However, opposite trends were found from 10 countries with five from Southern America, four from Europe and one from Asia. Of the 18 countries for projection, opposite trends between WHO and GBD were found from seven countries.

Conclusion: While the ASR of primary liver cancer mortality was comparable across the three data sources, most similar estimates were found between WHO and GCO. The opposite trends found from 10 countries between WHO and GBD raised concerns of true patterns in these countries.

Keywords: age-standardized rate, average annual percentage change, completeness of cause-of-death registry, global burden disease, global cancer observatory, mortality, World Health Organization
1 | BACKGROUND

Primary liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020, accounting for approximately 906,000 new cases and 830,000 deaths. With the universal vaccination against hepatitis B virus (HBV) and administration of highly effective antiviral treatment for HBV and hepatitis C virus (HCV), significant decrease in liver cancer has been reported in some high-risk countries in Eastern and South-Eastern Asia. However, incident rates in formerly low-risk countries including Japan, Australia, Europe, Canada and the United States have been increasing in the last 20 years.1

To date, the global estimates of primary liver cancer mortality have been provided by three major international groups, the Mortality Database by the World Health Organization (WHO), the Global Burden Disease (GBD) by the Institute for Health Metrics and Evaluation (IHME), and the Global Cancer Observatory (GCO) by the International Agency for Research on Cancer (IARC). While the WHO Mortality Database was based on submitted data from each national/regional death registry,2,3 the mortality data from both GBD and GCO were estimated using some statistical modelling based on various data sources.4,5 Estimates for health data reflect massive initiatives by some of the world’s experts, yet the results for country-level estimates are dramatically different between different groups.6,7 Previous analyses have also shown that comparative studies of global health estimates are critical to prioritize health policy and to highlight less reliable estimates and data gaps in specific countries.8 To our knowledge, no study has compared the current estimates of primary liver cancer mortality across different data sources globally.

Previous studies have investigated the temporal trends of primary liver cancer mortality using estimates from WHO and GBD.9,10 Although the overall trends between them were similar for some countries with high risk of viral hepatitis in Eastern Asia (Japan and South Korea), variations were found across countries from other continents.9,10 Some of the trends were contradictory with large differences between these two sources. For instance, significant reduction was found from Norway, Finland and France from the study based on the WHO Mortality Database from 2000 to 20129 while increase was found from the other study based on GBD Study data in the same period.10 In addition, the study based on WHO Mortality Database only selected 28 countries to report the mortality rate with the majority of them from Europe and the study only selected 11 countries to show their trends over time.9 However, no study has compared the temporal trends of primary liver cancer mortality between them globally.

This study, therefore, aims to assess and compare the national and regional burden of liver cancer from 92 selected countries using most recent estimates of primary liver cancer deaths from WHO, GBD and GCO. We also made comparison of temporal trends from 1990 to 2019 for 75 countries and comparison of mortality projection up to 2030 for 18 countries between WHO and GBD.

2 | METHODS

2.1 | Data sources

Mortality of primary liver cancer was extracted from the WHO Mortality Database.5 The WHO Mortality Database comprises deaths registered in national/regional vital registration systems, with underlying cause of death as coded by the relevant national authority. Only medically certified deaths were published by WHO Mortality Database. The database contains number of deaths by country, year, sex, age group, cause of death and the total number of populations by age and sex. Data are included only for countries reporting data properly coded according to the International Classification of Diseases (ICD). A total of 92 countries from 9 regions were selected as they reported at least 10 cases from or after 2014 and 75 of them were included for trend analysis as they provided consistent data with at least 10 cases each year from 1990 to 2019. During the study period, two different revisions of the International Classification of Diseases (ICD) were used, including ICD-9 code 155.0–155.9 and ICD-10 C22.0–C22.9 for primary liver cancer from WHO Mortality Dataset. However, due to substantial variations of estimates from the transition year of ICD-9 to ICD-10 for some countries, we only considered the years since the adoption of ICD-10 for the following countries: France, Japan, South Korea, Dominican, El Salvador, Guatemala, Jamaica, Paraguay, Puerto Rico and Chile.

Primary liver cancer mortality data from the GBD 2019 Study was retrieved for the same 92 countries for the same year and 75 of them for the same calendar years through Global Health Data Exchange query tool.11 ICD-9 code 155.0–155.9 and ICD-10 codes C22.0–C22.9 were used for primary liver cancer over the period. The estimation process for primary liver cancer deaths has been described from the previous study.5 Data sources for the estimation include WHO vital registration (83% of data), cancer registry (14% of data), and verbal autopsy data and literature review (3% of data).12 If mortality data were not available, incidence data were transformed to mortality estimates using separately modelled incidence-to-mortality ratios. Data were adjusted for age groups, aggregated causes, uninformative causes of death and modelled by developing a large set of plausible models using different model types and combinations of covariates.13 Aggregated causes of liver cancer included alcohol consumption, HBV, HCV, mean body mass index, tobacco, diabetes and uninformative causes included education, health system access and socioeconomic index.13 GBD also generated its own population estimates for each country.5

Estimates of primary liver cancer mortality for the most recent year (i.e. 2020) was also obtained from GCO for the same 92 countries.14 ICD-10 code C22.0–C22.9 was used for primary liver cancer for year 2020. Estimates were either based on projections from WHO Mortality Database, extrapolates from neighbouring countries, or modes from incidence-to-mortality ratios as described previously.1 National population estimates for 2020 were extracted from the United Nations website.
To explore potential reasons for the difference in mortality estimates across WHO, GBD and GCO, the following variables were investigated: the completeness of cause-of-death registration from WHO, human development index (HDI) from United Nations, proportions of primary liver cancer attributable to HBV, HCV, alcohol consumption and NASH from GBD, and data sources used for estimation by GCO. We also collected Socio-Demographic Index (SDI) data at the national level from GBD.

2.2 Analysis

The current burden of primary liver cancer mortality was investigated and compared using number of deaths and age-standardized rates (ASR) of death in the most recent year. Depending on the availability of mortality data, most of the countries provided number of deaths in 2019 as the most recent year from WHO ($n = 57$), while some other countries had data from 2014 to 2018 as the most recent year ($n = 38$). Estimates in number of deaths for the most recent year were selected for the same year from WHO and GBD, but all the estimates from GCO were from year 2020. The number of deaths for each region was computed by summing the total number of deaths in each country within the region. ASR has been calculated for each country across the three data sources based on the same standard population. For this, direct method has been used based on the 2000 world population in 5-year age groups as the standard for each country and region as described previously. The pairwise difference in number of deaths and ASR in the most recent year for each country and region was computed as the pairwise absolute difference between two estimates divided by the mean of the two estimates from any two of the three data sources. To investigate the pairwise difference, countries were also grouped by their SDI into Low-SDI (0–0.45), Middle-Low SDI (0.45–0.61), Middle SDI (0.61–0.69), High-Middle SDI (0.69–0.81) and High SDI (0.81–1.00).

In addition, to assess the impact of including different years of estimates across the three data sources, a sensitivity analysis was conducted for the comparison of ASR from 21 selected countries where WHO Mortality data were available for the year 2020 with estimates from GBD in the year 2019 and GCO in the year 2020. Similarly, the estimates of ASR were calculated and pairwise difference was applied for comparisons.

Pearson correlation was used to investigate the correlation of ASR from each data source and the correlation of the differences in ASR across the three data sources with potentially explanatory variables mentioned above. Pearson correlation coefficients ($r$) were calculated to show the strength of the relationship and linear regression lines were plotted for each association. ANOVA was used for the comparisons of ASR and pairwise difference of ASR through the three data sources.

As the GCO used the same estimates of primary liver cancer deaths as those from WHO for the period of 1990 to 2019, the temporal trend analysis was only conducted based on estimates from WHO and GBD using joinpoint regression. Joinpoint regression analysis was used to identify years when a significant change of ASR in the linear slope of the temporal trend occurred over the period with a maximum of two joinpoints. The estimated annual percent change was then computed for each of the identified trends by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable. We calculated the average annual percent change (AAPC) over the last 10 years, based on an underlying joinpoint model, to show the most recent trend. The trend was considered as significant reduction if AAPC and its upper estimate of 95% were less than 0 and it was considered as significant increase if AAPC and its lower estimate of 95% were greater than 0. Otherwise, the trend was considered as no change or stable over the period. The results from the joinpoint analysis were then compared between WHO and GBD based on AAPC. Similar trend was defined as the same direction of change from the two comparisons. Opposite trend was defined as opposite direction of change from the two comparisons.

For the top 18 countries with the highest death number of primary liver cancer in the most recent year, estimates of mortality were projected to 2030. For this, we applied a logarithmic Poisson joinpoint regression model to each 5-year age-specific number of deaths, setting a maximum of two joinpoints, to identify the most recent trend segment. The detail of the projection was described as previously. In brief, we estimated age-specific numbers of deaths and the corresponding 95% prediction intervals (PIs) for 2030 by fitting a linear regression to the mortality data from each age-group over the most recent trend segment identified by the joinpoint model. We computed predicted age-specific and age-standardized death rates with 95% PIs using predicted age-specific numbers of deaths obtained from our model and predicted populations from United Nations.

3 RESULTS

Table 1 shows the key differences in estimates of primary liver cancer mortality by data sources and modelling methods from WHO, GBD and GCO. The WHO mortality data were based on submitted data by each member country to WHO by 5-year age groups and sex. No modelling methods have been used for WHO mortality data. In contrast, the estimates from the GBD study were based on various sources of data including WHO mortality data, cancer registry and verbal autopsy. After adjusting these data with some covariates using Cause of Death Ensemble model (CODEm), the GBD estimates were obtained by feeding these adjusted data to a Bayesian meta-regression modelling tool, DisMod-MR 2.1. However, the details of input data for each country were not publicly available although the output data were provided overall, by 5-year age groups, sex and aetiology for 204 countries. As for estimates from GCO, they were also based on a few different methods depending on the availability and quality of registration data, but no adjustments were made for the estimation. The details of input data were published for each
country and estimates were available overall, by age and sex for 185 countries.

Of the 92 countries included for current burden comparison, higher correlation of ASR was found between WHO and GCO \((r = 0.83, p < 0.001)\) than that between WHO and GBD \((r = 0.65)\) and between GBD and GCO \((r = 0.77)\) (Figure 1). Overall, ASR from GBD were slightly lower than those from WHO and estimates from GCO were slightly higher than those from WHO but without statistical significance. In country-specific estimate, the top three countries with the highest ASR of primary liver cancer deaths were Mongolia, Thailand and Egypt (Table 2).

**Figure 2** shows the comparisons of the differences in ASR across the three data sources. In region level, the mean difference was found lowest between WHO and GCO (21.0%) than that between WHO and GBD (29.7%) and GBD and GCO (31.7%). The difference between WHO and GCO was mainly driven by estimates from Africa (102.8%), while the differences between WHO and GBD and between GBD and GCO were mostly driven by estimates from Africa (65.9% and 44.4%) and Southern America (63.3% and 65.0%) (Figure 2A). In country level, the mean difference in ASR was found significantly lower between WHO and GCO (21.7%) than that between WHO and GBD (37.8%) and between GBD and GCO (40.7%) \((p < 0.001)\) (Figure 2B). The highest differences between WHO and GCO were found from 3 countries (all >100%): Libya, Egypt and Morocco (Table 2). As for the difference between the other two comparisons, 6 countries were found to have difference >100%: Kyrgyzstan, Libya, Qatar, Guatemala, Moldova and Morocco between WHO and GBD and Kyrgyzstan, El Salvador, Guatemala, Nicaragua, Romania and Moldova between GBD and GCO (Table 2). While similar findings were also found for the differences in number of deaths in both region and country levels (Figure 2C,D), the absolute differences in number of deaths between WHO and GBD were found highest from countries in Asia, including Japan, South Korea, Thailand (Table 2). The differences between the three pairwise comparisons were also performed by SDI groups. Across the three comparisons for the differences in number of deaths and ASR, highest differences were found from Low SDI countries (Figure 2E,F).

In the sensitivity analysis, the estimated ASR was found similar to that in the main analysis for the same country from the same data source across the three data sources (Table A1). The difference in ASR between WHO and GCO was smaller than that between WHO and GBD and between GBD and GCO in the sensitivity analysis.

In the analysis for the reasons of the differences across the three data sources (Figure 3), we found that completeness of cause-of-death registration showed a weak negative correlation with the difference in ASR between WHO and GBD \((r = -0.29, p = 0.02)\) and strong correlation with the difference in ASR between WHO and GCO \((r = -0.64, p = 0.02)\). Negative correlation was also found between human development index and the difference of ASR \((r = -0.56 \text{ between WHO and GBD and } r = -0.58 \text{ between WHO and GCO})\)
and GCO, \( p < 0.001 \). In contrast, positive correlation was found for the proportion of primary liver cancer attributable to HBV with the differences of ASR between WHO and GCO \( (r = 0.35, p < 0.001) \) but not between WHO and GBD \( (r = 0.14, p = 0.190) \). No correlation was found between the differences of estimates and proportion of liver cancer attributable to HCV. And the differences were negatively correlated with the proportion of liver cancer attributable to alcohol consumption. According to the data sources and methods used for the estimation by GCO, larger differences in ASR were found from countries without using registry data than those from countries based on complete or partial registry data (Figure 3).

As for temporal trends of ASR from 1990 to 2019 between WHO and GBD for the 75 selected countries, similar trends from these two datasets were found from 35 countries in the most recent 10 years (Figure 4 and Table 3), including 14 countries with significant reduction, 18 countries with increase and 3 countries with stable trend. In contrast, opposite trends were found from 10 countries between these two data sources in the most recent 10 years (Table 3) with one from Asia: Uzbekistan (AAPC, 1.2 from WHO vs. −0.6 from GBD), four of them from Europe: Latvia (3.2 vs. −0.9), Sweden (−0.4 vs. 2.3), Cyprus (3.3 vs. −0.4), Poland (−1.2 vs. 0.8) and five of them from Southern America: Colombia (−2.2 vs. 1.4), Cuba (−0.5 vs. 2.1), Dominican Republic (−4.2 vs. 4.2), Jamaica (−3.7 vs. 3.2), Mexico (−0.7 vs. 0.7). The remaining 30 countries showed stable trends over the last 10 years in one dataset, but a reduction or increase in the other (Figure 4 and Table 3).

Of the 18 countries with the highest average number of primary liver cancer deaths projected up to the year 2030, only South Korea showed a consistent reduction in liver cancer mortality from both WHO and GBD (Figure 5). Our projections from both data sources suggested that the ASR of liver cancer death would continue to increase or stabilize in another 10 countries. Interestingly, our projection from WHO indicated the ASR would decrease in Argentina, Italy, Japan, Mexico and Philippines, while projections from GBD suggested continuous increase up to 2030. In contrast, the ASR in Australia and United Kingdom would increase based on estimates from WHO, whereas it would decrease based on estimates from GBD.

### DISCUSSION

This study compared the ASR of primary liver cancer deaths in 92 countries from WHO, GBD and GCO in the most recent year. The
| Region/country | WHO | GBD | GCO | 
|----------------|-----|-----|-----| 
|                | No. of death | ASR | No. of death | ASR | No. of death | ASR |
| Asia           | 71890 | 7.8 | 93537 | 9.8 | 98118 | 10.3 |
| Armenia        | 462  | 11.6| 290  | 6.6 | 414   | 9.9 |
| Brunei Darussalam | 32  | 11.2| 35   | 11.0| 35    | 10.3 |
| Iran (Islamic Republic of) (2016) | 3142 | 4.7 | 2348 | 3.5 | 5324 | 7.4 |
| Armenia        | 462  | 11.6| 290  | 6.6 | 414   | 9.9 |
| Brunei Darussalam | 32  | 11.2| 35   | 11.0| 35    | 10.3 |
| Iran (Islamic Republic of) (2016) | 3142 | 4.7 | 2348 | 3.5 | 5324 | 7.4 |
| Iraq (2016)    | 557  | 3.3 | 1213 | 5.9 | 686   | 3.6 |
| Israel (2018)  | 333  | 2.8 | 315  | 2.6 | 360   | 3.1 |
| Japan          | 25264| 5.6 | 34514| 8.0 | 28155 | 6.6 |
| Jordan (2015)  | 117  | 2.7 | 103  | 2.2 | 197   | 3.4 |
| Kazakhstan     | 702  | 3.8 | 1116 | 6.3 | 988   | 5.1 |
| Kuwait         | 56   | 4.6 | 54   | 2.2 | 122   | 5.3 |
| Kyrgyzstan     | 347  | 7.8 | 118  | 2.6 | 465   | 10.0|
| Lebanon (2017) | 147  | 3.1 | 148  | 2.8 | 168   | 2.6 |
| Libya (2017)   | 43   | 1.3 | 234  | 4.9 | 213   | 4.9 |
| Malaysia (2014) | 909 | 4.5 | 1540 | 6.7 | 2050  | 6.7 |
| Maldives       | 11   | 4.6 | 17   | 5.3 | 28    | 9.4 |
| Mongolia (2016) | 1741 | 96.2| 2140 | 111.1| 2060 | 90.7 |
| Oman           | 35   | 2.1 | 83   | 4.5 | 121   | 4.4 |
| Philippines    | 6401 | 9.4 | 5276 | 6.4 | 9953  | 12.1 |
| Qatar          | 22   | 2.2 | 91   | 14.2| 54    | 5.4 |
| Singapore      | 531  | 7.6 | 658  | 8.0 | 1270  | 13.6 |
| South Korea    | 10586| 11.3| 14477| 15.5| 11158 | 11.7 |
| Tajikistan (2017) | 160 | 3.6 | 177  | 4.1 | 291   | 5.9 |
| Thailand       | 16288| 17.8| 24526| 23.3| 26704 | 25.0 |
| Turkey         | 2788 | 3.1 | 2536 | 2.8 | 5461  | 5.9 |
| Turkmenistan (2015) | 179 | 4.7 | 204  | 5.6 | 296   | 6.4 |
| Uzbekistan     | 1037 | 5.1 | 1324 | 6.4 | 1545  | 6.3 |
| Oceania        | 2468 | 4.6 | 1987 | 3.9 | 2503  | 4.8 |
| Australia      | 2204 | 4.9 | 1726 | 4.0 | 2142  | 4.9 |
| New Zealand (2016) | 264 | 3.4 | 261  | 3.6 | 361   | 4.3 |
| Region/country         | WHO/GBD | GBD | GCO | Pairwise difference in no. of death (%) | Pairwise difference in ASR (%) |
|------------------------|---------|-----|-----|----------------------------------------|-------------------------------|
|                        | No. of death | ASR | No. of death | ASR | No. of death | ASR | WHO/GBD | WHO/GCO | GBD/GCO | WHO/GBD | WHO/GCO | GBD/GCO |
| **Northern America**   |         |     |     |                                         |                               |
| Canada                 | 31,193  | 5.1 | 26,467 | 4.1 | 34,805  | 5.2 | 16.4 | 10.9 | 27.2 | 21.7 | 1.9 | 23.7 |
| United States          | 27,958  | 5.2 | 23,800 | 4.2 | 31,078  | 5.3 | 16.1 | 10.6 | 26.5 | 21.3 | 1.9 | 23.2 |
| **Southern America**   |         |     |     |                                         |                               |
| Argentina              | 1914 | 3.6 | 1172 | 2.0 | 2189 | 3.8 | 48.1 | 13.4 | 60.5 | 57.1 | 5.4 | 62.1 |
| Bahamas (2015)         | 10 | 3.0 | 11 | 3.0 | 16 | 3.9 | 9.5 | 46.2 | 37.0 | 0.0 | 26.1 | 26.1 |
| **Canada**             |         |     |     |                                         |                               |
| Brazil                 | 10,899 | 5.2 | 5,814 | 2.4 | 12,139 | 4.9 | 60.9 | 10.8 | 70.5 | 73.7 | 5.9 | 68.5 |
| **Chile (2018)**       | 1,348  | 5.7 | 712 | 2.9 | 1,473 | 5.3 | 61.7 | 8.9 | 69.7 | 65.1 | 7.3 | 58.5 |
| Colombia               | 1,955  | 4.2 | 1,394 | 2.5 | 2,220 | 4.0 | 33.5 | 12.7 | 45.7 | 50.7 | 4.9 | 46.2 |
| Costa Rica             | 393 | 7.5 | 269 | 5.0 | 438 | 6.9 | 37.5 | 10.8 | 47.8 | 40.0 | 8.3 | 31.9 |
| **Dominican Republic** |         |     |     |                                         |                               |
| **Dominican Republic** |         |     |     |                                         |                               |
| El Salvador (2018)     | 865 | 6.2 | 539 | 3.4 | 880 | 5.4 | 46.4 | 1.7 | 48.1 | 58.3 | 13.8 | 45.5 |
| Guatemala              | 1,526  | 16.2 | 521 | 4.5 | 1,889 | 16.9 | 98.2 | 21.3 | 113.5 | 113.0 | 4.2 | 115.9 |
| Jamaica (2014)         | 89 | 3.1 | 74 | 2.5 | 99 | 3.0 | 18.4 | 10.6 | 28.9 | 21.4 | 3.3 | 18.2 |
| Mexico                 | 6,727 | 6.4 | 4,176 | 3.5 | 7,175 | 5.9 | 46.8 | 6.4 | 52.8 | 58.6 | 8.1 | 51.1 |
| Nicaragua              | 320 | 7.7 | 172 | 3.9 | 577 | 12.0 | 60.2 | 57.3 | 108.1 | 65.5 | 43.7 | 101.9 |
| Panama                 | 170 | 4.5 | 126 | 2.9 | 215 | 4.8 | 29.7 | 23.4 | 52.2 | 43.2 | 6.5 | 49.4 |
| Paraguay               | 135 | 2.7 | 118 | 2.1 | 176 | 3.0 | 13.4 | 26.4 | 39.5 | 25.0 | 10.5 | 35.3 |
| Peru (2018)            | 1,392 | 4.9 | 847 | 2.6 | 2,093 | 6.0 | 48.7 | 40.2 | 84.8 | 61.3 | 20.2 | 79.1 |
| Puerto Rico (2017)     | 311 | 5.0 | 196 | 2.7 | 402 | 6.1 | 45.4 | 25.5 | 68.9 | 59.7 | 19.8 | 77.3 |
| Uruguay                | 155 | 2.9 | 129 | 2.2 | 159 | 2.8 | 18.3 | 2.5 | 20.8 | 27.5 | 3.5 | 24.0 |
| **Northern Europe**    |         |     |     |                                         |                               |
| Denmark (2018)         | 482 | 3.8 | 372 | 3.2 | 633 | 5.1 | 25.8 | 27.1 | 51.9 | 17.1 | 29.2 | 45.8 |
| Estonia                | 105 | 3.9 | 95 | 3.4 | 127 | 4.6 | 10.0 | 19.0 | 28.8 | 13.7 | 16.5 | 30.0 |
| Finland (2018)         | 533 | 4.1 | 505 | 3.8 | 600 | 4.3 | 5.4 | 11.8 | 17.2 | 7.6 | 4.8 | 12.3 |
| Iceland                | 23 | 4.0 | 16 | 2.7 | 22 | 3.5 | 35.9 | 4.4 | 31.6 | 38.8 | 13.3 | 25.8 |
| Latvia                 | 175 | 4.7 | 107 | 2.6 | 125 | 3.2 | 48.2 | 33.3 | 15.5 | 57.5 | 7.5 | 45.8 |

(Continues)
| Region/country                  | WHO  | GBD  | GCO  | WHO/GBD | WHO/GCO | GBD/GCO |
|--------------------------------|------|------|------|---------|---------|---------|
|                                 | No. of death | ASR | No. of death | ASR | No. of death | ASR | Pairwise difference in no. of death (%) | Pairwise difference in ASR (%) |
| Lithuania                       | 230  | 4.0  | 170  | 2.9     | 245     | 4.5     | 30.0 | 6.3     | 36.1     | 31.9 | 11.8 | 43.2 |
| Norway (2016)                   | 279  | 3.0  | 232  | 2.5     | 386     | 3.8     | 18.4 | 32.2    | 49.8     | 18.2 | 23.5 | 41.3 |
| Sweden (2018)                   | 737  | 3.4  | 618  | 2.9     | 861     | 3.8     | 17.6 | 15.5    | 32.9     | 15.9 | 11.1 | 26.9 |
| United Kingdom                  | 6001 | 4.2  | 5155 | 3.7     | 7061    | 4.9     | 15.2 | 16.2    | 31.2     | 12.7 | 15.4 | 27.9 |
| Western Europe                  | 20545| 4.6  | 18780| 4.3     | 23648   | 5.3     | 9.0  | 14.0    | 23.0     | 6.7  | 14.1 | 20.8 |
| Austria (2016)                  | 279  | 4.6  | 232  | 4.3     | 386     | 5.1     | 8.5  | 13.1    | 21.5     | 6.7  | 10.3 | 17.0 |
| Belgium (2018)                  | 938  | 3.9  | 861  | 3.6     | 1100    | 4.5     | 8.6  | 15.9    | 24.4     | 8.0  | 14.3 | 22.2 |
| France (2016)                   | 8639 | 6.4  | 7463 | 5.7     | 10274   | 7.1     | 12.2 | 17.3    | 29.4     | 11.6 | 10.4 | 21.9 |
| Germany                        | 8168 | 4.0  | 7743 | 3.8     | 8972    | 4.4     | 5.3  | 8.3     | 13.6     | 5.1  | 9.5  | 14.6 |
| Luxembourg                     | 53   | 4.8  | 37   | 3.4     | 50      | 4.6     | 35.6 | 5.8     | 29.9     | 34.1 | 4.3  | 30.0 |
| Netherlands                    | 1139 | 3.0  | 939  | 2.6     | 1446    | 3.8     | 19.2 | 23.8    | 42.5     | 14.3 | 23.5 | 37.5 |
| Switzerland (2018)             | 737  | 4.3  | 757  | 4.2     | 913     | 4.8     | 2.7  | 21.3    | 18.7     | 2.4  | 11.0 | 13.3 |
| Southern Europe                | 22974| 5.7  | 17530| 4.4     | 25033   | 6.3     | 26.9 | 8.6     | 35.3     | 25.7 | 10.0 | 35.5 |
| Bosnia and Herzegovina (2016)  | 423  | 7.1  | 483  | 7.8     | 517     | 7.9     | 13.2 | 20.0    | 6.8      | 9.4  | 10.7 | 1.3  |
| Bulgaria                       | 715  | 4.8  | 646  | 4.5     | 584     | 4.0     | 10.1 | 20.2    | 10.1     | 6.5  | 18.2 | 11.8 |
| Croatia                        | 497  | 5.5  | 311  | 3.4     | 529     | 5.6     | 46.0 | 6.2     | 51.9     | 47.2 | 1.8  | 48.9 |
| Cyprus (2018)                  | 58   | 3.7  | 63   | 3.1     | 99      | 5.0     | 8.3  | 52.2    | 44.4     | 17.6 | 29.9 | 46.9 |
| Greece                         | 1480 | 5.3  | 783  | 3.0     | 1522    | 6.0     | 61.6 | 2.8     | 64.1     | 55.4 | 12.4 | 66.7 |
| Italy (2017)                   | 9263 | 5.9  | 6647 | 4.5     | 9798    | 6.4     | 32.9 | 5.6     | 38.3     | 26.9 | 8.1  | 34.9 |
| Malta (2017)                   | 31   | 3.4  | 20   | 2.1     | 31      | 3.3     | 43.1 | 0.0     | 43.1     | 47.3 | 3.0  | 44.4 |
| Montenegro                     | 48   | 4.5  | 60   | 5.8     | 49      | 4.4     | 22.2 | 2.1     | 20.2     | 25.2 | 2.2  | 27.5 |
| North Macedonia                | 186  | 5.5  | 281  | 8.4     | 185     | 5.5     | 40.7 | 0.5     | 41.2     | 41.7 | 0.0  | 41.7 |
| Portugal (2018)                | 1240 | 5.4  | 1043 | 4.4     | 1518    | 6.6     | 17.3 | 20.2    | 37.1     | 20.4 | 20.0 | 40.0 |
| Romania                        | 2840 | 7.5  | 1113 | 3.0     | 3380    | 9.0     | 87.4 | 17.4    | 100.9    | 85.7 | 18.2 | 100.0 |
| Serbia                         | 731  | 4.9  | 885  | 5.2     | 956     | 5.5     | 19.1 | 26.7    | 7.7      | 5.9  | 11.5 | 5.6  |
| Slovenia                       | 275  | 5.7  | 222  | 4.9     | 310     | 6.5     | 21.3 | 12.0    | 33.1     | 15.1 | 13.1 | 28.1 |
| Spain                          | 5187 | 5.3  | 4973 | 4.9     | 5555    | 5.5     | 4.2  | 6.9     | 11.1     | 7.8  | 3.7  | 11.5 |
| Eastern Europe                 | 17921| 3.7  | 12423| 2.7     | 19435   | 4.1     | 36.3 | 8.1     | 44.1     | 31.2 | 10.3 | 41.2 |
| Belarus (2018)                 | 450  | 2.9  | 378  | 2.3     | 514     | 3.2     | 174  | 13.3    | 30.5     | 23.1 | 9.8  | 32.7 |
TABLE 2 (Continued)

| Region/country       | WHO | GBD | GCO | Pairwise difference in no. of death (%) | Pairwise difference in ASR (%) |
|----------------------|-----|-----|-----|----------------------------------------|-------------------------------|
|                      | No. of death | ASR | No. of death | ASR | WHO/GBD | WHO/GCO | GBD/GCO | WHO/GBD | WHO/GCO | GBD/GCO |
| Czech Republic       | 908 | 4.0 | 633 | 2.8 | 35.7 | 3.9 | 31.9 | 35.3 | 5.1 | 30.3 |
| Georgia              | 365 | 6.1 | 211 | 3.5 | 397 | 6.2 | 35.3 | 54.2 | 1.6 | 55.7 |
| Hungary              | 859 | 4.2 | 512 | 2.5 | 937 | 4.7 | 35.3 | 50.7 | 11.2 | 61.1 |
| Moldova (2018)       | 430 | 8.4 | 137 | 2.3 | 555 | 9.4 | 35.3 | 114.0 | 11.2 | 121.4 |
| Poland               | 2060| 2.8 | 1455| 1.9 | 2455| 3.3 | 35.3 | 38.3 | 16.4 | 53.8 |
| Russia               | 10430| 2.8 | 6820| 2.9 | 11122| 4.5 | 35.3 | 36.6 | 6.9 | 43.2 |
| Slovakia             | 426 | 4.2 | 313 | 3.2 | 531 | 5.3 | 35.3 | 27.0 | 23.2 | 49.4 |
| Ukraine              | 1993| 2.8 | 1964| 2.5 | 2051| 2.8 | 35.3 | 11.3 | 0.0 | 11.3 |
| Africa               | 8705| 6.1 | 16801| 12.1 | 30122| 19.0 | 55.8 | 65.9 | 102.8 | 44.4 |
| Egypt                | 6606| 8.9 | 13542| 20.7 | 26253| 35.5 | 55.8 | 79.7 | 119.8 | 52.7 |
| Mauritius            | 54  | 3.4 | 34  | 1.9 | 63  | 3.4 | 35.8 | 56.6 | 0.0 | 56.6 |
| Morocco (2016)       | 211 | 0.7 | 586 | 2.1 | 1251| 3.5 | 35.8 | 100.0 | 133.3 | 50.0 |
| South Africa (2015)  | 1834| 4.7 | 2639| 6.3 | 2285| 5.0 | 35.8 | 29.1 | 6.2 | 23.0 |

Abbreviations: WHO, World Health Organization; GBD, Global Burden Disease; GCO, Global Cancer Observatory; ASR, age-standardized rate.
FIGURE 2. Comparisons of differences in age-standardized rates and number of deaths of primary liver cancer mortality between the pairs among WHO, GBD and GCO by region, country and socio-demographic index. WHO, World Health Organization; GBD, Global Burden Disease; GCO, Global Cancer Observatory; ASR, age-standardized rate; SDI, socio-demographic index.
Correlations of differences in age-standardized rates of primary liver cancer mortality from WHO, GBD and GCO with completeness of cause-of-death registration, human development index, proportion of liver cancer attributable to HBV, HCV and alcohol consumption, categories of data sources used by GCO. ASR, age-standardized rate; WHO, World Health Organization; GBD, Global Burden Disease; GCO, Global Cancer Observatory; r represents the correlation coefficient.

**FIGURE 3**

While the differences in ASR between GBD and WHO and between GBD and GCO were higher than that between WHO and GCO, it is the only data source to provide estimates by aetiology and year consistently. This would allow policy makers and clinicians to have a better understanding of the attributable risk of liver cancer mortality in each country and their temporal trends. The fact that these independent institutions make important effort to come up with global burden of primary liver cancer must be welcomed and appreciated. It is beneficial that not a single institution claims full authority on mortality estimates, which allows further discussion methods and provides improvement of estimates for relevant public health indicators.

Despite the variation of ASR in the most recent years, 35 out of 75 countries showed a similar trend of mortality rate in primary liver cancer in the most recent 10 years between WHO and GBD. Of the 35 countries, 18 of them showed increasing trends of primary liver cancer mortality over the period, highlighting the continuing increased burden of primary liver cancer from countries in Oceania, North America and Europe as reported previously. Multiple risk factors other than HBV and HCV are possibly the cause of the increasing trend from these countries, including nonalcoholic fatty liver diseases (NAFLD) associated with the global epidemic of liver disease.
FIGURE 4 Joinpoint regression analysis of age-standardized rates of primary liver cancer mortality for 75 countries from WHO and GBD, 1990–2019. WHO, World Health Organization; GBD, Global Burden Disease.
TABLE 3 Estimated Annual Average Percentage Change of primary liver cancer mortality in the last 10 years (2010–2019 or as indicated in the bracket) for 75 countries from WHO and GBD

| Country                  | WHO AAPC in the most recent 10 years (95% CI) | WHO p value | GBD AAPC in the most recent 10 years (95% CI) | GBD p value |
|--------------------------|-----------------------------------------------|-------------|-----------------------------------------------|-------------|
| Armenia                  | 0.2 (−1.0 to 1.4)                              | 0.749       | −4.4 (−5.9 to −2.8)                            | <0.001      |
| Brunei Darussalam        | 0.3 (−1.2 to 1.8)                              | 0.686       | −0.8 (−0.9 to −0.7)                            | <0.001      |
| Israel (2018)            | 0.1 (−0.4 to 0.6)                              | 0.703       | 0.3 (0.2 to 0.4)                               | <0.001      |
| Japan                    | −5.5 (−5.9 to −5.1)                            | <0.001      | −2.6 (−3.2 to −2)                              | <0.001      |
| Kazakhstan               | −5.2 (−5.8 to −4.7)                            | <0.001      | −1.5 (−2 to −1.1)                              | <0.001      |
| Kuwait                   | −4.8 (−18.2 to 10.9)                           | 0.530       | −1.4 (−1.9 to −0.9)                            | <0.001      |
| Kyrgyzstan               | 1.3 (0.6 to 1.9)                               | 0.001       | 0.2 (−0.2 to 0.7)                              | 0.343       |
| Malaysia (2014)          | 0.8 (−0.2 to 1.9)                              | 0.101       | −0.5 (−0.9 to 0)                               | 0.031       |
| Philippines              | −1.7 (−2.2 to −1.2)                            | <0.001      | −0.2 (−0.3 to 0)                               | 0.051       |
| Singapore                | −1.9 (−2.2 to −1.6)                            | <0.001      | −1.6 (−1.8 to −1.3)                            | <0.001      |
| South Korea              | −4.5 (−5.0 to −4.0)                            | <0.001      | −2.8 (−3 to −2.6)                              | <0.001      |
| Thailand                 | −1.3 (−1.9 to −0.7)                            | <0.001      | −0.6 (−0.9 to −0.2)                            | 0.003       |
| Turkey (2016)            | 2.7 (1.4 to 4)                                 | 0.002       | 0.4 (0.1 to 0.7)                               | 0.018       |
| Turkmenistan (2015)      | 0.8 (−0.2 to 1.9)                              | 0.117       | 0.4 (0 to 0.8)                                 | 0.032       |
| Uzbekistan               | 1.2 (0.2 to 2.3)                               | 0.026       | −0.6 (−0.9 to −0.2)                            | 0.001       |
| Oceania                  |                                               |             |                                               |             |
| Australia                | 3.2 (3.1 to 3.3)                               | <0.001      | 0.8 (0.2 to 1.3)                               | 0.005       |
| New Zealand (2016)       | 2.2 (1.7 to 2.6)                               | <0.001      | 1.5 (1.2 to 1.8)                               | <0.001      |
| North America            |                                               |             |                                               |             |
| Canada                   | 2.4 (−0.6 to 5.5)                              | 0.118       | 1.5 (0.9 to 2)                                 | <0.001      |
| United States            | 1.4 (0.5 to 2.3)                               | 0.002       | 1.6 (1.5 to 1.7)                               | <0.001      |
| South America            |                                               |             |                                               |             |
| Argentina                | −0.5 (−1.4 to 0.4)                             | 0.301       | 1.1 (0.8 to 1.3)                               | <0.001      |
| Brazil                   | 0.8 (0.4 to 1.1)                               | <0.001      | 0.1 (−0.4 to 0.7)                              | 0.601       |
| Chile (2018)             | 0.2 (−0.4 to 0.8)                              | 0.401       | 1.7 (1.2 to 2.1)                               | <0.001      |
| Colombia                 | −2.1 (−2.6 to −1.6)                            | <0.001      | 1.2 (1 to 1.5)                                 | <0.001      |
| Costa Rica               | 3.2 (2.1 to 4.3)                               | <0.001      | 1.6 (0.9 to 2.3)                               | <0.001      |
| Cuba                     | −0.5 (−1 to −0.1)                              | 0.028       | 2.1 (1.8 to 2.3)                               | <0.001      |
| Dominican Republic (2018)| −4.2 (−5.6 to −2.7)                            | <0.001      | 4.2 (3.3 to 5.2)                               | <0.001      |
| Ecuador                  | 0.4 (−2.9 to 3.9)                              | 0.800       | 1.2 (0.9 to 1.4)                               | <0.001      |
| El Salvador (2018)       | −0.4 (−1.1 to 0.2)                             | 0.181       | 0.7 (0.6 to 0.9)                               | <0.001      |
| Guatemala                | 0.8 (0.1 to 1.4)                               | 0.024       | 2.3 (1.5 to 3)                                 | <0.001      |
| Jamaica (2014)           | −3.7 (−5.8 to −1.6)                            | 0.003       | 3.2 (2.3 to 4.1)                               | <0.001      |
| Mexico                   | −0.7 (−1.1 to −0.3)                            | 0.001       | 0.7 (0.4 to 1)                                 | <0.001      |
| Nicaragua                | 1.5 (0.9 to 2.1)                               | <0.001      | 1.6 (0.6 to 2.6)                               | 0.002       |
| Panama                   | 1.3 (0.3 to 2.3)                               | 0.015       | 0.2 (0 to 0.5)                                 | 0.054       |
| Paraguay                 | −0.4 (−1.1 to 0.4)                             | 0.335       | 1.3 (0.7 to 1.8)                               | <0.001      |
| Peru (2016)              | −4.1 (−6.8 to −1.4)                            | 0.006       | −0.7 (−1.1 to −0.4)                            | <0.001      |
| Puerto Rico (2017)       | 0.2 (−0.5 to 1.0)                              | 0.498       | −0.7 (−1.2 to −0.2)                            | 0.007       |
| Uruguay                  | 2.3 (1.6 to 3.0)                               | <0.001      | 1.0 (0.8 to 1.3)                               | <0.001      |

(Continues)
| Country               | AAPC in the most recent 10 years (95% CI) | p value | AAPC in the most recent 10 years (95% CI) | p value |
|-----------------------|------------------------------------------|---------|------------------------------------------|---------|
| **Northern Europe**   |                                          |         |                                          |         |
| Denmark (2018)        | 2.3 (1.3 to 3.4)                         | <0.001  | 0.9 (0 to 1.7)                           | 0.043   |
| Estonia               | 0.6 (−0.2 to 1.5)                        | 0.140   | 1.3 (0.6 to 2)                           | <0.001  |
| Finland (2018)        | 0.2 (−0.2 to 0.7)                        | 0.255   | 0.4 (0.2 to 0.6)                         | <0.001  |
| Iceland               | 1.7 (0.5 to 3)                           | 0.009   | 0.6 (−0.1 to 1.3)                        | 0.080   |
| Ireland (2015)        | 2.6 (2.1 to 3.2)                         | <0.001  | 3.6 (3.2 to 4.1)                         | <0.001  |
| Latvia                | 3.2 (0.3 to 6.1)                         | 0.030   | −0.9 (−1.6 to −0.1)                      | 0.026   |
| Lithuania             | 2.7 (2.1 to 3.4)                         | <0.001  | 0.7 (0.3 to 1.1)                         | 0.002   |
| Norway (2016)         | 5.1 (3.9 to 6.2)                         | <0.001  | 1.8 (1.6 to 2)                           | <0.001  |
| Sweden (2018)         | −0.4 (−0.7 to −0.1)                      | 0.006   | 2.3 (1.2 to 3.5)                         | <0.001  |
| United Kingdom        | 2.9 (2.3 to 3.5)                         | <0.001  | 1.6 (1.3 to 1.8)                         | <0.001  |
| **Western Europe**    |                                          |         |                                          |         |
| Austria               | −0.9 (−1.5 to −0.4)                      | 0.002   | −0.9 (−1.2 to −0.6)                      | <0.001  |
| Belgium (2018)        | 0.8 (0.6 to 1.1)                         | <0.001  | 2.4 (1.9 to 2.9)                         | <0.001  |
| France (2016)         | −0.6 (−0.9 to −0.4)                      | <0.001  | −0.3 (−0.4 to −0.1)                      | <0.001  |
| Germany               | −0.3 (−0.8 to 0.3)                       | 0.324   | 0.1 (−0.1 to 0.2)                        | 0.214   |
| Luxembourg            | −4.8 (−9.4 to 0)                         | 0.050   | −1.4 (−1.6 to −1.2)                      | <0.001  |
| Netherlands           | 2.6 (2.3 to 2.9)                         | <0.001  | 1.2 (0.8 to 1.7)                         | <0.001  |
| Switzerland (2018)    | −0.6 (−1.8 to 0.5)                       | 0.249   | −0.2 (−0.7 to 0.3)                       | 0.368   |
| **Southern Europe**   |                                          |         |                                          |         |
| Bulgaria              | −1.4 (−3.0 to 0.2)                       | 0.078   | −2.6 (−3.4 to −1.8)                      | <0.001  |
| Croatia               | −0.2 (−2.1 to 1.8)                       | 0.868   | −1.9 (−2.2 to −1.5)                      | <0.001  |
| Cyprus (2018)         | 3.3 (0.8 to 5.9)                         | 0.016   | −0.4 (−0.6 to −0.1)                      | 0.002   |
| Greece                | −0.8 (−1.8 to 0.3)                       | 0.153   | 1.1 (0.1 to 2.2)                         | 0.037   |
| Italy (2017)          | −1.5 (−2 to −1)                          | <0.001  | −0.2 (−0.7 to 0.4)                       | 0.533   |
| Malta (2017)          | 2.4 (1.3 to 3.6)                         | <0.001  | −0.3 (−0.7 to 0.1)                       | 0.161   |
| Portugal (2018)       | 3.1 (2.8 to 3.5)                         | <0.001  | 1.4 (1.2 to 1.6)                         | <0.001  |
| Romania               | 0 (−1.3 to 1.4)                          | 0.954   | 1.2 (0.5 to 1.9)                         | 0.002   |
| Serbia                | −1 (−1.3 to −0.7)                        | <0.001  | −1.6 (−1.9 to −1.3)                      | <0.001  |
| Slovenia              | 1.7 (1.4 to 2.1)                         | <0.001  | −0.1 (−0.6 to 0.5)                       | 0.844   |
| Spain                 | −0.4 (−0.9 to 0.1)                       | 0.095   | −0.3 (−0.4 to −0.2)                      | <0.001  |
| **Eastern Europe**    |                                          |         |                                          |         |
| Czech Republic        | −0.4 (−1.4 to 0.6)                       | 0.407   | −1.6 (−2.7 to −0.5)                      | 0.005   |
| Georgia               | 6.6 (2.9 to 10.4)                        | 0.002   | 3.4 (2.4 to 4.5)                         | <0.001  |
| Hungary               | 0.7 (−0.1 to 1.5)                        | 0.093   | −7 (−8.3 to −5.6)                        | <0.001  |
| Poland                | −1.2 (−1.6 to −0.7)                      | <0.001  | 0.8 (0.6 to 1)                           | <0.001  |
| Russia (2015)         | 0.6 (−0.2 to 1.5)                        | 0.156   | 3.2 (2.7 to 3.6)                         | <0.001  |
| Slovakia              | −0.9 (−1.3 to −0.6)                      | <0.001  | −2.5 (−3.3 to −1.6)                      | <0.001  |
| Ukraine               | 0.8 (−0.2 to 1.8)                        | 0.122   | −0.3 (−0.8 to 0.3)                       | 0.263   |
| **Africa**            |                                          |         |                                          |         |
| Egypt                 | 0.8 (−2.2 to 3.9)                        | 0.580   | −1.6 (−1.9 to −1.2)                      | <0.001  |
| Mauritius             | −3.2 (−4.7 to −1.8)                      | <0.001  | 0.2 (−0.6 to 0.9)                        | 0.637   |
| South Africa (2015)   | −2 (−2.3 to −1.6)                        | <0.001  | −2.1 (−2.5 to −1.7)                      | <0.001  |

Abbreviations: WHO, World Health Organization; GBD, Global Burden Disease; AAPC, Average Annual Percentage Change is a summary measure of the trend over a pre-specified fixed interval. p less than 0.05 was considered as statistically significant.
FIGURE 5 The predicted age-standardized rates of primary liver cancer mortality up to 2030 in 18 selected countries from WHO and GBD. WHO, World Health Organization; GBD, Global Burden Disease.
Obesity and type 2 diabetes becoming the most rapidly growing contributor. Another 14 countries showed a consistent reduction of primary liver cancer mortality in the most recent 10 years from both WHO and GBD study, including Japan, Kazakhstan, Peru, Slovakia, South Africa. Most to these countries have high burden of HBV infections in the past, but because of the success of universal HBV vaccination programme as well as the introduction of HCV screening and administration of effective antiviral treatment for HBV and HCV. 

Our projections of a decrease and increase of primary liver cancer mortality up to 2030 for Japan and the United States, respectively, were consistent with previously reported projections until 2020 based on the WHO mortality data and the same method. Our trends were also generally consistent with those obtained in a different study using the age-period cohort model on GBD data for liver cancer incidence. Our projections suggested that mortality of primary liver cancer will continue or start to increase for another 10 countries based on both the WHO and GBD data, though these estimates were based on simplistic assumptions about the continuation of current trends and the model did not account for the recent introduction of HCV screening and the administration of effective treatment, which was already shown to impact cirrhosis and primary liver cancer incidence in studies from France, and the United States. More importantly, our results highlight how using the varying trends from WHO and GBD to predict the future burden of primary liver cancer mortality could result in opposite directions of change for these countries in the future, as seen in our projections for Argentina, Italy, Japan, Mexico, Philippines, Australia and United Kingdom. Therefore, caution should be taken for the choice of the source data for trend analysis and burden estimation.

The main strength of this study is the use of the most comprehensive mortality data from WHO, GBD and GCO to assess and compare the current burden of primary liver cancer mortality. Although the GBD and GCO provided mortality data for 195 and 185 countries or territories worldwide, only countries with available mortality registration data from the WHO were selected in this study. This brings to one of the limitations of this study is that countries without good quality registration data from vital registry were not included in this study. Therefore, this study did not analyse the burden and trend of primary liver cancer in some countries with high burden of liver cancer. This includes China and India, which in total accounts for about two thirds of primary liver cancer mortality worldwide. Another limitation is that while the correlation with potential factors leading to differences between the datasets were explored, specific reasons for the differences of ASR from GBD with that from the other two data sources could not be analysed because of lack of availability of detailed input data sources and modelling methods. However, the GCO has provided the detailed information of the data sources for each country, which allows us to identify the major differences of ASR between WHO and GCO were from countries with partial or no registry data. The other limitation of this study was that the estimates from GCO was only available for year 2020, while the estimates from WHO was from year 2019 or earlier. However, in the sensitivity by including countries from WHO with estimates in year 2020, the estimated ASR was found similar to that in the main analysis for the same country from the same data source. This suggests the inclusion of estimates from different year in this study did not result in the differences of ASR across the data sources. Finally, although our projections of primary liver cancer mortality were generally consistent with previous studies, our model was only based on simple assumptions about the continuation of current trends, and it did not consider the impact of the recent introduction of HCV screening or the administration of effective treatment. Therefore, more complex models are required for more accurate predictions. However, this would be enough for this study to show that the different choice of data sources for projections could result in opposite directions of change for some countries in the future.

In conclusion, while the estimates of primary liver cancer mortality were quite consistent across the three data sources for 92 countries overall, most similar estimates were found between WHO and GCO. Opposite trends of ASR between WHO and GBD were identified from one Asian country (Uzbekistan), four European countries (Latvia, Sweden, Cyprus and Poland) and five Southern American countries (Colombia, Cuba, Dominican Republic, Jamaica and Mexico). Caution should be taken for the choice of the source data for trend analysis and projection.
ACKNOWLEDGEMENT
We appreciate the data sources provided by World Health Organization, Global Burden Disease and Global Cancer Observatory. Open access publishing facilitated by University of New South Wales, as part of the Wiley - University of New South Wales agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

FUNDING STATEMENT
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

ORCID
Wen-Qiang He https://orcid.org/0000-0002-7475-8485

REFERENCES
1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.
2. Hung KY, Horng JL, Yen HJ, Lee CY, Lin LY. Changing incidence patterns of hepatocellular carcinoma among age groups in Taiwan. J Hepatol. 2015;63(6):1390-1396.
3. Li C, He WQ. The impact of universal hepatitis B vaccine on the trend of liver cancer from the global burden of disease study 2017. Liver Int. 2021;41:1762-1774.
4. World Health Organization, WHO Mortality Database. [Internet]. 2020 [cited January 3, 2021]. https://www.who.int/data/data-collec tion-tools/who-mortality-database
5. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet. 2020;396(10258):1204-1222.
6. García-Basteiro AL, Brew J, Williams B, Borgdorff M, Cobelens F. What is the true tuberculosis mortality burden? Differences in estimates by the World Health Organization and the global burden of disease study. Int J Epidemiol. 2018;47(5):1549-1560.
7. Bhalla K, Harrison JE. GBD-2010 overestimates deaths from road injuries in OECD countries: new methods perform poorly. Int J Epidemiol. 2015;44(5):1648-1656.
8. Alkema L, You D. Child mortality estimation: a comparison of UN IGME and IHME estimates of levels and trends in under-five mortality rates and deaths. PLoS Med. 2012;9(8):e1001288.
9. Bertuccio P, Turati F, Carlioli G, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol. 2017;67(2):302-309.
10. Lin L, Yan L, Liu Y, Qu C, Ni J, Li H. The burden and trends of primary liver cancer caused by specific etiologies from 1990 to 2017 at the global, regional, national, age, and sex level results from the global burden of disease study 2017. Liver Cancer. 2020;9(5):563-582.
11. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. : Institute for Health Metrics and Evaluation (IHME): 2019. [Internet]. 2019 [cited March 28, 2021]. https://ghdx.healthdata.org/gbd-results-tool
12. Collaboration GbDc. Global, regional, and National Cancer Incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. JAMA Oncol. 2018;4(11):1553-1568.
13. Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and National Level: results from the global burden of disease study 2015. JAMA Oncol. 2017;3(12):1683-1691.
14. International Agency for Research on Cancer. Global Cancer Observatory. Cancer Today [Internet]. 2020 [cited January 15, 2022]. https://gco.iarc.fr/today/home
15. United Nations. Department of Economic and Social Affairs Population Dynamics. World Population Prospects 2019. [Internet]. 2019 [cited March 1, 2021]. https://population.un.org/wpp/DefinitionOfProjectionVariants/
16. World Health Organization. The Global Health Observatory. Completeness of Cause-Of-Death Registration (%) [Internet]. 2021 [cited June 1, 2021]. https://www.who.int/data/gho/indicator- metadata-registries/whodcd/indicators/odr/4741
17. United Nations Development Programme. Human Development Reports. Human Development Index (HDI) [Internet]. 2020 [cited June 6, 2021]. https://hdr.undp.org/en/content/human-development-index-hdi
18. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Socio-Demographic Index (SDI) 1950–2019. : Institute for Health Metrics and Evaluation (IHME), 2020. [Internet]. 2020 [cited June 17, 2022]. https://ghdx.health data.org/record/ihme-data/gbd-2019-socio-demographic-index -sdi-1950-2019
19. He WQ, Li C. Recent global burden of cervical cancer incidence and mortality, predictors, and temporal trends. Gynecol Oncol. 2021;163(3):583-592.
20. Suthar AB, Khalifa A, Yin S, et al. Evaluation of approaches to strengthen civil registration and vital statistics systems: a systematic review and synthesis of policies in 25 countries. PLoS Med. 2019;16(9):e1002929.
21. Mathers CD. History of global burden of disease assessment at the World Health Organization. Arch Public Health. 2020;78:77.
22. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol. 2019;71(4):793-801.
23. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology. 2020;72(5):1605-1616.
24. He WQ, Guo GN, Li C. The impact of hepatitis B vaccination in the United States, 1999-2018. Hepatology. 2021;75:1566-1578.
25. Fanning GC, Zoulim F, Hou J, Bertoletti A. Therapeutic strategies for hepatitis B virus infection: towards a cure. Nat Rev Drug Discov. 2019;18(11):827-844.
26. He WQ, Gao X, Gao L, Ma Y, Sun D, Sun J. Contrasting trends of primary liver cancer mortality in Chinese Mongol and non-Mongol. Asian Pac J Cancer Prev. 2021;22(9):2757-2763.
27. Wong MC, Jiang JY, Goggins WB, et al. International incidence and mortality trends of liver cancer: a global profile. Sci Rep. 2017;7:45846.
28. Carrillo FJ, Paranañgu-Vezozzo DC, Chagas AL, Alencar R, da Fonseca LG. Epidemiology of liver cancer in Latin America: current and future trends. Semin Liver Dis. 2020;40(2):101-110.
29. Menyhárt O, Fekete JT, Györrfy B. Demographic shift disproportionately increases cancer burden in an aging nation: current and expected incidence and mortality in Hungary up to 2030. Clin Epidemiol. 2018;10:1093-1108.
30. Farkas K, Szűcs M, Nyári TA. Trends in gastrointestinal cancer mortality rate in Hungary. Pathol Oncol Res. 2016;22(4):681-688.
31. Liu Z, Xu K, Jiang Y, et al. Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: a modelling study. Int J Epidemiol. 2021;50(1):128-142.
APPENDIX A

TABLE A1  The comparison of primary liver cancer death in number of deaths and ASR across the three data sources. Only countries with deaths reported in year 2020 from WHO dataset were included

| Region/country | WHO | GBD | GCO | % difference in ASR |
|----------------|-----|-----|-----|---------------------|
|                | No. of death | ASR | No. of death | ASR | No. of death | ASR | WHO/GBD | WHO/GCO | GBD/GCO |
| Asia           |     |     |     |             |     |     |     |     |     |
| Kazakhstan     | 659 | 3.5 | 1116 | 6.3 | 988 | 5.1 | 58.7 | 38.4 | 21.6 |
| Qatar          | 31  | 3.0 | 91   | 14.2| 54  | 5.4 | 131.0 | 58.4 | 89.8 |
| Singapore      | 563 | 7.7 | 658  | 8.0 | 1270| 13.6| 4.3  | 55.5 | 51.4 |
| Oceania        |     |     |     |             |     |     |     |     |     |
| Australia      | 2192| 4.7 | 1726 | 4.0 | 2142| 4.9 | 16.6 | 3.7  | 20.3 |
| Southern America|    |     |     |             |     |     |     |     |     |
| Costa Rica     | 371 | 5.8 | 269  | 5.0 | 438 | 6.9 | 13.9 | 18.1 | 31.9 |
| Ecuador        | 744 | 4.4 | 539  | 3.4 | 880 | 5.4 | 25.9 | 19.7 | 45.0 |
| Guatemala      | 1632| 14.5| 521  | 4.5 | 1889| 16.9| 105.1| 15.1 | 115.6|
| Mexico         | 6771| 5.5 | 4176 | 3.5 | 7175| 5.9 | 45.3 | 7.1  | 52.0 |
| Northern Europe|    |     |     |             |     |     |     |     |     |
| Estonia        | 132 | 4.7 | 95   | 3.4 | 127 | 4.6 | 30.5 | 1.6  | 28.9 |
| Iceland        | 16  | 2.5 | 16   | 2.7 | 22  | 3.5 | 8.1  | 34.5 | 26.6 |
| Latvia         | 184 | 4.6 | 107  | 2.6 | 125 | 3.2 | 55.4 | 35.4 | 21.1 |
| Lithuania      | 235 | 4.1 | 170  | 2.9 | 245 | 4.5 | 32.7 | 10.2 | 42.5 |
| Western Europe |    |     |     |             |     |     |     |     |     |
| Austria        | 847 | 4.3 | 800  | 4.3 | 993 | 5.1 | 1.0  | 16.6 | 17.6 |
| Germany        | 8457| 4.1 | 7743 | 3.8 | 8872| 4.4 | 6.8  | 8.2  | 15.0 |
| Netherlands    | 1268| 3.2 | 939  | 2.6 | 1446| 3.8 | 23.5 | 15.8 | 38.9 |
| Southern Europe|    |     |     |             |     |     |     |     |     |
| Serbia         | 646 | 4.3 | 885  | 5.2 | 956 | 5.5 | 18.9 | 24.3 | 5.5  |
| Slovenia       | 301 | 6.2 | 222  | 4.9 | 310 | 6.5 | 24.1 | 4.0  | 28.0 |
| Spain          | 5021| 4.7 | 4973 | 4.9 | 5555| 5.5 | 3.7  | 15.6 | 11.9 |
| Eastern Europe |    |     |     |             |     |     |     |     |     |
| Czech Republic | 872 | 3.7 | 633  | 2.8 | 873 | 3.8 | 27.4 | 1.6  | 28.9 |
| Georgia        | 457 | 7.6 | 211  | 3.5 | 397 | 6.2 | 73.4 | 20.9 | 54.6 |
| Africa         |    |     |     |             |     |     |     |     |     |
| Mauritius      | 55  | 3.0 | 34   | 1.9 | 63  | 3.4 | 45.8 | 12.2 | 57.2 |