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Hepatoma Research

Systematic Review

Global pattern and trend of liver cancer survival: a systematic review of population-based studies

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Abstract

Aim: To describe the global pattern and trend of liver cancer survival, using data from the population-based studies or cancer registration.

Methods: By searching CNKI, Wanfang Data, PubMed, Web of Science, EMBASE and SEER. All population-based survival studies of liver cancer from 1 January 2000 to 30 April 2020 were collected and evaluated by patient gender, time period, and country. The overall or age-standardized five-year relative survival rate was used to describe the pattern and changes in liver cancer survival over the past decades.

Results: Globally, the highest age-standardized five-year relative survival rate was observed in Italy (18.0%, 2005-2007) and the highest overall five-year relative survival rate was observed in Korea (34.6%, 2012-2016), when compared to other countries. The most remarkable increase in overall five-year relative survival rate can be seen in Korea (from 10.7% during 1993-1995 to 34.6% during 2012-2016). In general, worldwide, the five-year relative survival rate of younger patients with liver cancer was higher than old people. For most countries, the five-year relative survival rate of liver cancer was slightly higher in women than in men. In China, the overall five-year relative survival rate of liver cancer in Taiwan was higher than that in other areas, while Cixian of Hebei and Qidong of Jiangsu were lower.

Conclusion: Over the past decades, the survival rates of liver cancer have gradually improved, but great variations are also observed globally. Worldwide, younger patients with liver cancer have experienced a better prognosis. Gender disparity in liver cancer survival was not obvious.

Keywords: Primary liver cancer, relative survival rate, prognosis, population-based study, cancer registration

INTRODUCTION

Primary liver cancer (PLC) is the sixth most common cancer and the fourth most common cause of cancer death worldwide[1]. The top five countries with the highest incidence of liver cancer are Mongolia (71.8/100,000), Thailand (33.7/100,000), North Korea (32.3/100,000), Japan (27.9/100,000), and China (27.6/100,000)[2]. In the United States, the incidence has increased rapidly by 2% to 3% per year from 2007 to 2016, although the change was smaller than that in previous years[3]. According to Global cancer statistics 2018[1], an estimated 841,080 incident cases of liver cancer occurred worldwide, with 392,868 in China, accounting for 46.71%.

Certainly, incidence, mortality, and prevalence are commonly applied to describe the burden of disease. However, it is also crucial to comprehend and employ survival rate, which is another important descriptive indicator of disease burden and widely used in the evaluation of cancer prognosis. Survival data are available from three sources: clinical studies, hospital-based follow-up data, and population-based follow-up data[4]. Interpretations of the outcomes of each source are different. The population-based follow-up data include the survival information of all patients in the population, which can reflect the cancer survival status of the entire population. Population-based survival data usually exclude death certificate only (DCO) and autopsy cases during analysis because evidence of diagnosis is weak.

Cancer registries are the premise and foundation of cancer prevention and control. They help obtain comprehensive, accurate, and timely information on the incidence, mortality, survival, and other factors related to cancer in the population[4]. Survival analysis can be conducted with these data, and provide valuable indicators such as population-based relative survival rate (RSR) for the effectiveness of cancer control and reflect the prospects of cure in a country or region[5]. To describe the global pattern, chronological changes, and enable comparisons between different populations or regions, this review collected all available population-based survival rates of primary liver cancer in different populations.

METHODS

Data source

A literature search of related studies from 1 January 2000 to 30 April January 2020 was conducted using the databases of CNKI, Wanfang Data, PubMed, Web of Science, EMBASE and SEER, with the following keywords: “liver cancer”, “hepatocellular carcinoma”, “HCC”, “population-based survival studies”, “relative survival”, “observed survival” “cancer registry”. Two researchers collected the data independently according to the search criteria, and 129 articles were retrieved by titles and abstracts. After screening with the following criteria: (1) provided RSR or observed survival rate (OSR) of patients with primary liver cancer; and (2) data were population-based or from cancer registries, and excluding duplicate, incomplete or unavailable articles. The final analysis included 53 studies, 9 of which were in Chinese and the remaining 44 were in English [Figure 1].

Statistical analysis

Estimates of one to five-year RSRs from the published studies were extracted. We used overall and age-standardized 5-year RSR mainly to describe and compare different countries or regions, age groups, and

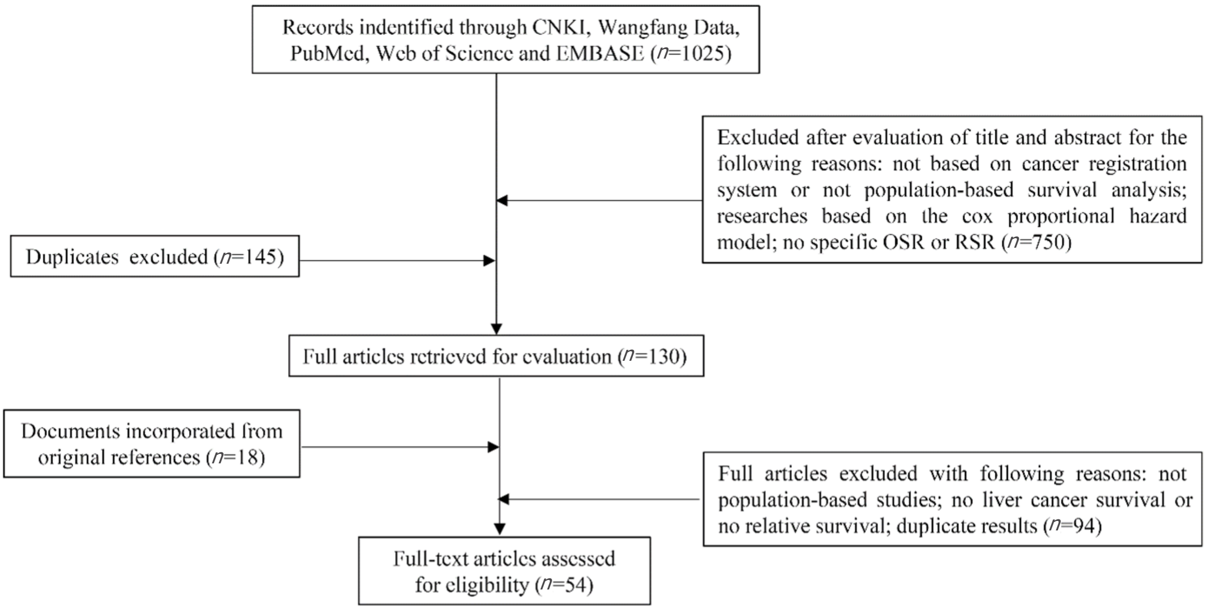

Figure 1. Study selection process. OSR: observed survival rate; RSR: relative survival rate

gender. Most of the included publications provided the age-standardized relative survival rates which were extracted. SPSS 22.0 and Excel 2016 were used for data management and analysis.

RESULTS

Global pattern and trend

Table 1 shows the sex-specific overall 5-year RSRs from Korea[6-11], Japan[12], Singapore[13], USA[14,15], and Europe[14,16-22]. Table 2 shows the sex-specific age-standardized 5-year RSRs mainly from Singapore[13] and Europe[16,19,23,24]. In addition, the overall 10-year RSRs in Japan during 2002-2006 were 9.6% for men and 9.1% for women. It can be inferred from Tables 1 and 2 that although the 5-year RSRs of PLC in women is higher than that in men in most countries or regions, the difference is not obvious. The greatest difference in overall 5-year RSRs between male and female was observed in Scotland during 2005-2007 (4.4% for male and 10.6% for female)[18], followed by the USA during 1986-1988 (3.5% for male and 8.5% for female)[14]. In age-standardized 5-year RSRs, the greatest difference was observed in Norway during 1990-1994 and 1994-1998 (both 5.0% for male and 11.0% for female)[24]. When comparing Tables 1 and 2 to determine whether age-standardization of 5-year RSRs has an effect on outcomes, the dissimilarity is not striking. In Europe (1990-1994)[16], after age standardization, the 5-year RSRs in both men and women decreased; in France (1989-1997)[19], the indicator in men increased, but remained the same in women. Besides, some studies have provided one to five-year RSRs or one and five-year age-standardized RSRs, as the details displayed in Supplementary Tables 1 and 2.

Figure 2A and B demonstrate age-standardized and overall 5-year RSRs since 1974 of PLC respectively, in selected countries and regions from Asia[6-12,25-28], North America[11,12,14,15,29-32], Europe[14,16,17,19,21,22,33-36], and Africa[37,38]. Figure 2A revealed that the highest age-standardized 5-year RSR was 18.0% and observed in Italy during 2005-2007[36], followed by Canada during 2004-2006[30], which was 17.0%. The lowest age-standardized 5-year RSR was 2.3% observed in Iceland during 1995-1999[17]. Figure 2B showed that in the 1980s and before, the overall 5-year RSRs in all regions was lower than 5%, with the lowest being the USA (1977-1981)[32] and Vaud of Switzerland (1984-1988)[22], both of which were 2.0%. However, after entering the 21st century, the 5-year RSRs in most regions have improved greatly. In general, the survival rates have

Table 1. Population-based sex-specific overall 5-year relative survival rates of primary liver cancer in selected countries

Region		Year	5-year RSR (%)	
			Male	Female
Korea[6-11]		1993-1995	9.9	13.6
		1996-2000	12.9	14.2
		2001-2005	20.1	20.3
		2007-2011	28.5	28.7
		2005-2009	25.1	25.1
		2008-2012	30.4	29.3
		2010-2014	33.1	31.9
		2012-2016	35.2	32.7
		2006-2010	26.6	26.7
Japan[12]		1993-1996	21.0	21.8
		1997-1999	23.7	21.8
USA[14,15]		1983-1985	2.7	6.2
		1986-1988	3.5	8.5
		1989-1991	3.4	7.0
		1992-1994	4.7	5.3
		1996-1998	8.3	9.1
		1999-2001	10.9	12.1
		2002-2004	14.9	14.7
		2005-2009	17.7	17.3
		2010-2016	20.8	20.9
Europe[14,16,17]		1983-1985	2.8	5.3
		1986-1988	3.7	5.2
		1989-1991	5.3	6.0
		1990-1994	7.0	7.0
		1992-1994	7.2	7.0
		1995-1999	8.9	8.4
Scotland[18]		1985-1989	0.4	0.5
		1990-1994	2.2	5.4
		1995-1999	5.5	7.1
		2000-2004	8.7	8.7
		2005-2007	4.4	10.6
France	Total[19]	1989-1997	7.0	9.0
	Côte-d'Or, Burgundy[20]	1976-1985	1.1	2.0
		1986-1995	4.6	2.6
		1996-2005	10.3	10.3
Spain[21]		2000-2007	13.8	10.6
Switzerland[22]	Vaud	1974-1978	-	22.0
		1984-1988	3.0	-
		1989-1993	8.0	7.0

-: No report or non-available in the original articles; RSR: relative survival rate

gradually increased in all regions with time. Korea's growth was the most obvious, rising from 10.7% in the early 1990s to 34.6% during 2012-2016[6-11].

Time changes in survival rates for liver cancer were also reviewed in our study. Figure 3 shows the age-standardized 5-year RSRs of PLC in specific regions in Europe[36] at a specific calendar period. It was confirmed again in Figure 3 that the RSRs of PLC have been increasing over time. During three identical periods, we found that the rates were almost higher in Southern Europe (12.0% during 1999-2001, 14.0% during 2002-2004, 17.0% during 2005-2007), but consistently poorest in Eastern Europe (6.0% during 1999-2001 and 2002-2004, 7.0% in 2005-2007).

Figure 4 shows a comparison of age-specific relative survival rates of PLC. Because some reports did not provide age-specific survival data, and some reports adopted different age groups, Figure 4 demonstrated

Table 2. Population-based sex-specific age-standardised 5-year relative survival rates of primary liver cancer in selected countries

Region	Year	Age-standardised 5-year RSR (%)	
		Male	Female
Singapore[13]	1968-1972	5.0	3.0
	1973-1977	1.0	6.0
	1978-1982	3.0	8.0
	1983-1987	2.0	3.0
	1988-1992	3.0	2.0
Europe[16]	1990-1994	6.2	6.7
Austria[16]	1990-1994	7.0	-
Czech Republic[16]	1990-1994	1.1	3.4
Denmark[16,23,24]	1989-1993	3.0	3.0
	1990-1994	-	2.3
	1994-1998	4.0	4.0
	1999-2003	3.0	5.0
England[16]	1990-1994	6.1	7.2
Estonia[16]	1990-1994	5.5	-
Finland[16,23,24]	1989-1993	4.0	5.0
	1990-1994	3.9	4.4
	1994-1998	7.0	7.0
	1999-2003	8.0	8.0
Iceland[23,24]	1989-1993	14.0	-
	1994-1998	7.0	-
	1999-2003	7.0	-
France[16,19]	1989-1997	8.0	9.0
	1990-1994	6.9	-
Germany[16]	1990-1994	-	3.8
Italy[16]	1990-1994	6.2	8.6
The Netherlands[16]	1990-1994	6.2	5.8
Norway[16,23,24]	1989-1993	6.0	8.0
	1990-1994	2.1	3.2
	1994-1998	5.0	11.0
	1999-2003	5.0	11.0
Poland[16]	1990-1994	-	1.3
Scotland[16]	1990-1994	-	4.8
Slovakia[16]	1990-1994	-	1.8
Slovenia[16]	1990-1994	-	4.9
Spain[16]	1990-1994	10.4	11.6
Sweden[16,23,24]	1989-1993	5.0	3.0
	1990-1994	2.9	3.1
	1994-1998	6.0	7.0
	1999-2003	7.0	8.0
Switzerland[16]	1990-1994	5.9	-
Wales[16]	1990-1994	5.1	6.3

-: No reports or non-available in the original articles; RSR: relative survival rate

the age-specific 5-year RSRs from Europe[16,17,36], USA[15], Japan[26], Canada[30,31], Korea[11], and China[39-41] in the period between 1990-2010. The 5-year RSRs decreased with age. The rates of patients aged 15-44, followed by those aged 45-54, were higher than other age groups, while the prognosis of patients aged 75 or older was poor. In the age groups of 35-44 and 45-54, the rate in Canada (2004-2006)[30] was markedly higher than that in other regions. In the age 65-74 group, the rate of Korea (2006-2010)[11] was markedly higher than that in other regions, and that in those age 75 or older, was highest in the Zhejiang Province (2005-2010)[41] of China compared to other regions or countries. Of note however, some reports estimate RSRs after excluding DCO and autopsy cases[11-14,18,21,22,24,26,28,30,31,35,36,39,40,42-45].

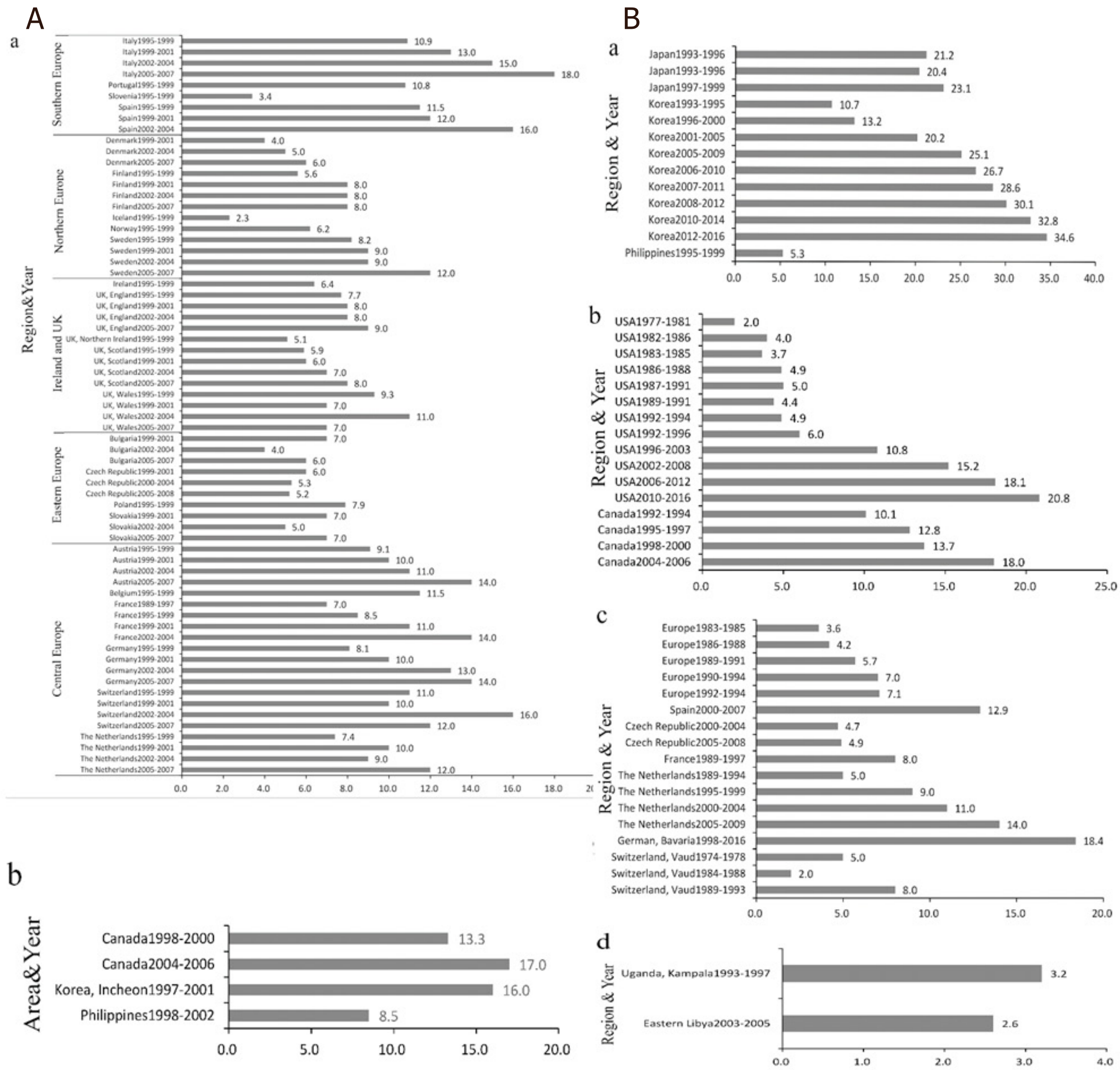

Figure 2. Age-standardised and overall 5-year relative survival rates of primary liver cancer in some selected countries during 1974-2016. A: Age-standardised 5-year relative survival rates (a: Europe*[17,19,35,36]; b: other regions[27,28,30,31]); B: overall 5-year relative survival rates (a: Europe[14,16,19,21,22,33-35]; b: Asia[6-12,25,26]; c: North America[11,12,14,15,29-32]; d: Africa[37,38]). *The divisions of Europe refer to the EUROCARE report

Liver cancer survival in China

Table 3 shows the details of the population-based overall and age-standardized 5-year RSRs of PLC in some areas in China. It mainly includes the survival of PLC in the nation[46], Beijing[45], Shanghai[39], Zhejiang Province[41], Liaoning Province[28], Taiwan[47], Hong Kong[28], Haining and Jiashan (Zhejiang Province)[48], Cixian (Hebei Province)[49,50], Huaian (Jiangsu Province)[51], Qidong (Jiangsu Province)[40,52], and Jintan district (Changzhou, Jiangsu Province)[53]. Among them, cases of DCO were explicitly excluded in the reports of Shanghai[39], Qidong of Jiangsu[40], Haining, and Jiashan of Zhejiang[48], and Liaoning[28].

As shown in Table 3, the 5-year RSRs of PLC improved gradually over time. The age-standardized 5-year RSRs of liver cancer patients in China (2003-2015) are lower than that of Korea and Japan for a similar time period. For the overall 5-year RSRs, gender difference was not found in our review as the survival rates of liver cancer in women were not consistently higher than that in men. The highest overall 5-year RSR of

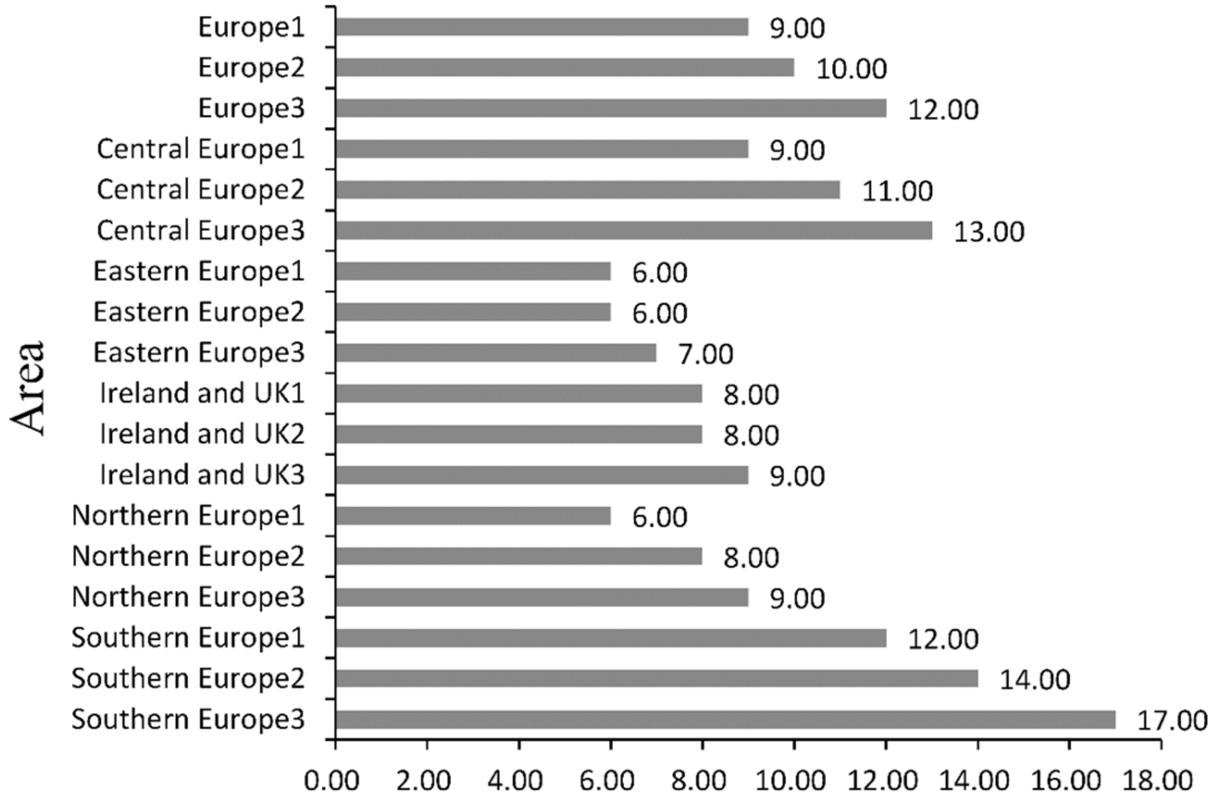

Figure 3. The age-standardised 5-year relative survival rates of primary liver cancer in different areas of Europe*, 1999-2007[36]. 1: 1999-2001; 2:2002-2004; 3: 2005-2007. *The divisions of Europe refer to the EUROCARE report

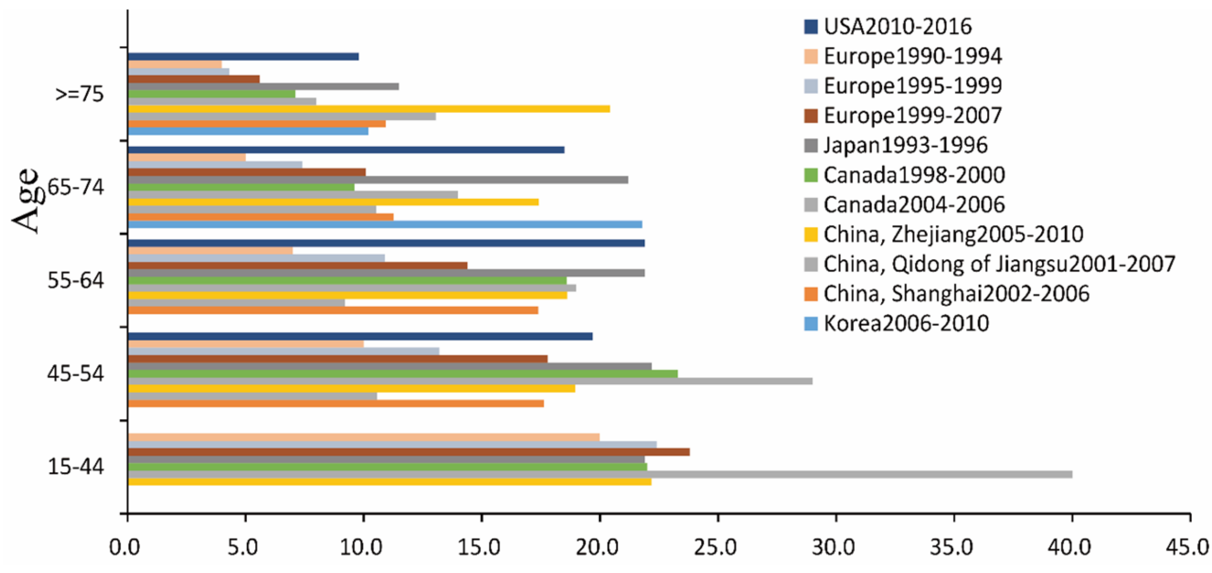

Figure 4. Age-specific 5-year relative survival rates of primary liver cancer in different years in some selected countries and regions[11,15-17,26,30,36,39-41]

28.9% was in Taiwan during 2004-2008, which was 28.1% and 31.7% in men and women respecitvely[47]. Since 2000, the overall 5-year RSR of Cixian (Hebei Province) was the lowest, at only 4.2% in 2000-2002[49].

Table 3. Population-based overall and age-standardised 5-year relative survival rates of PLC in some areas of China

Area			Year	5-year RSR (%)			Age-standardised 5-year RSR (%)		
				Total	Male	Female	Total	Male	Female
China[46]			2003-2005	-	-	-	10.1	10.2	10.3
			2006-2008	-	-	-	10.1	10.0	11.0
			2009-2011	-	-	-	9.8	9.8	10.7
			2012-2015	-	-	-	12.1	12.2	13.1
East China	Shanghai[39]		2002-2006	15.5	16.0	14.8	-	-	-
	Zhejiang	Total[41]	2005-2010	19.1	19.5	18.0	-	-	-
		Haining and Jiashan[48]	2003-2006	10.3	9.8	11.4	10.2	-	-
			2007-2010	8.9	9.5	7.9	9.0	-	-
			2011-2014	10.6	11.3	8.9	10.2	-	-
	Jiangsu	Huaian[51]	2010	8.4	8.9	6.9	-	-	-
		Jintan District of Changzhou[53]	2012-2013	11.6	-	-	-	-	-
		Qidong[40,52]	1972-2011	4.7	4.5	5.4	-	-	-
			1973-1977	2.8	-	-	-	-	-
			1978-1982	1.4	-	-	-	-	-
			1983-1987	2.6	-	-	-	-	-
			1988-1992	4.7	-	-	-	-	-
			1993-1997	4.7	-	-	-	-	-
			1998-2002	5.1	-	-	-	-	-
			2001-2007	10.0	9.8	10.6	-	-	-
			2003-2007	7.1	-	-	-	-	-
	Taiwan[47]		2004-2008	28.9	28.1	31.7	27.6	27.0	31.5
North China	Beijing[45]		1982-1983	-	2.2	2.4	-	-	-
			1987-1988	-	3.4	5.3	-	-	-
	Hebei[49,50]	Cixian	2000-2002	4.2	-	-	-	-	-
			2003-2013	7.6	7.1	8.7	-	-	-
South China	Hong Kong[28]		1996-2001	-	-	-	22.4	-	-
Northeast China	Liaoning[28]		2000-2002	-	-	-	10.7	8.8	15.2

-: No reports or non-available in the original articles; RSR: relative survival rate

DISCUSSION

Survival data based on clinical trials, hospital-based follow-up studies, and population-based cancer registration are disparate in their aims, methods of survival estimation, and application. This study collected overall or age-standardized RSRs of liver cancer worldwide so that we can describe the prognosis of liver cancer in the general population, and make comparisons between different countries and regions. All publications in the study were from the cancer registries or population-based survival analysis, which aimed to provide valuable information for epidemiologists, basic scientists, oncologists, and clinical physicians in liver cancer research.

The aim of clinical trials and hospital-based follow-up studies are quite different from that of population-based survival studies. The survival obtained from clinical trials or studies comes from the evaluation of certain therapeutics, and generally adopts overall survival (defined as the date from randomization to death from any cause) and progression-free survival (defined as the date from randomization until progression or death from any cause) as endpoints. For instance, a randomized, phase 3 clinical trial published in the New England Journal of Medicine evaluated cabozantinib as compared with placebo in previously treated patients with advanced hepatocellular carcinoma, and demonstrated that cabozantinib treatment significantly prolonged survival in patients with longer overall survival and progression-free survival (median overall survival and median progression-free survival were 10.2 months and 5.2 months, respectively) compared to placebo (8.0 months and 1.9 months, respectively)[54]. Hospital-based survival or follow-up studies rely on hospital-based cancer follow-up or registries that collect survival information of patients who have been hospitalized, which reflects the service's capacity and treatment effects in a particular department. For example, using follow-up data in a hospital's registry, a study in Qidong of Jiangsu Province from China[55] calculated the 5-year observed survival rate of patients with liver cancer from 2002 to 2016 to be 14.6% [Supplementary Table 3], which was higher than the population-based OSR of 8.9% reported in the general population of Qidong during 2001-2007. For hospital-based survival, the follow-up time starts from the first hospitalization date, while the population-based cancer registry starts from the date of diagnosis of cancer. However, according to the data in China, the survival rates of PLC in the more developed areas such as Shanghai and Zhejiang were higher than that of other areas and the national average during the similar period, and studies have additionally supported the observation that the survival rates of PLC in urban areas were higher than that in the rural areas for the same period.

A common reason to study population-based cancer survival is to estimate the net survival, a measure of patient survival following primary cancer in the absence of other causes of death[56], which can be obtained by calculating disease-specific survival. Since the estimation of net survival must rely on complete and accurate information on the cause of death, which is often difficult to obtain, an alternative indicator - RSR[5] - can be used. RSR is defined as the ratio of the observed survival rate (where all causes of deaths are considered as events) to the expected survival rate (which is estimated from national population life tables stratified by sex, age, and calendar period) in the general population with the same distribution of key demographic factors (sex, age, calendar, period, and country). It provides a measure of the excess mortality hazard experienced by cancer patients, irrespective of whether the excess mortality is directly or indirectly attributable to the cancer[56] and enables direct comparison of survival rates between different populations or regions by eliminating the effects of age, gender, ethnicity, and calendar period on cancer survival to some extent. In addition, to further eliminate the effect of age structure, international comparisons of RSRs ought to use age-standardized relative survival[57].

It is apparent from our review then that the prognosis of PLC has shown continuous improvement overtime, whether in China or around the world. Over the past decades, numerous changes in clinical practice, public health, and social economy may affect the survival of PLC. For instance, advances in imaging diagnosis, clinical treatment such as chemoembolization, ablation, and surgical resection techniques, increased surveillance and screening for early-stage disease and anti-cancer health education, the improvement of socio-economic status (SES) and the transformation of peoples' health consciousness and lifestyles[39,58,59]. However, it is these factors that can improve survival rates that may lead to regional disparity in survival rates of PLC as well, because of their varying degrees of development between different regions. Globally, the 5-year RSRs in Africa such as Eastern Libya and Uganda Kampala are much poorer than in the countries of Europe and North America during the same time period, and 5-year RSRs of PLC were also varied across regions in Europe. Studies have shown that people from the highest SES have better survival outcomes compared to those in the lowest SES[60-62]. The low SES and the attendant delayed diagnosis and treatment, unfair distribution of medical resources, incomplete medical insurance systems, lack of health education, and other factors will all affect cancer survival.

The data we have summarized from the literature implied that there are gender and age disparities in liver cancer survival. For example, in the majority of countries and regions, the prognosis of liver cancer in women was better than men, although the situation was not systematic. Therefore, it is inappropriate to draw the conclusion that the prognosis of women with PLC is better than men. Gender-specific distinctions in the survival rate of PLC require more population-based follow-up studies. In terms of the age at diagnosis, survival was highest among patients in the 35-44 age group, followed by the 45-54 age group, and lowest for the 75 or older age group. This might have been due to the presence of comorbidities and various chronic diseases in the aged patients that reduced their tolerance of cancer treatments or affected physicians' decisions for treatment options, as compared to younger patients[63-65]. In addition, studies have suggested that the proportion of late-diagnosis of PLC in the older age group was higher, resulting in poor long-term survival[39].

When comparing survival rates in different countries, times, or populations, *etc*., the following points need to be considered. Firstly, the relative survival rate was the only indicator analyzed in this review. However, descriptive indicators of cancer survival also include observed survival rate (all the OSRs collected were showed in Supplementary Table 3), cause-specific survival, *etc*. The estimation methods and their interpretations are completely different and cannot be substituted for each other. Next, close attention to additional comorbidities or variables (such as age, gender, ethnicity, *etc*.) used in survival rate estimation in the study is required. As in this review, some studies excluded patients aged under 15 or 20 during analysis[11,18,21,30,34,35,44,47]. Thirdly, it should be noted whether DCO cases or autopsy cases were excluded from the analysis, which would affect outcomes.

In conclusion, we summarized one to five-years RSRs of liver cancer, which were markedly distinct between different regions or periods in the same region. This implied that the region, period, and age might affect the survival rate of PLC; however, whether gender is a relevant factor remains to be studied. Therefore, more attention should be drawn to PLC prevention and screening, in particular, must be developed and implemented. Epidemiological, basic, and clinical studies of PLC have a long way to go still.

DECLARATIONS

Authors' contributions

Conducted the study and collected publications and abstract data and wrote the first draft: Jiang YF
Double check the collected publications and abstract data: Li ZY
Reviewed and approved the final version of the paper: Jiang YF, Li ZY, Ji XW, Shen QM, Tuo JY, Yuan HY, Xiang YB
Primary responsibility for final content, designed the research study and obtained funding: Xiang YB

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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