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Important prognostic factors for the long-term survival of subjects with primary liver cancer in Taiwan: A hyperendemic area

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ABSTRACT

This study used a large-scale cancer database in determining the survival prognostic factors among primary liver cancer (PLC) subjects. A total of 28,939 subjects diagnosed with PLC were analysed. Survival estimates were performed with Kaplan–Meier methods. Cox's proportional-hazards model estimated the death risk (hazard ratio (HR)) of prognostic factors. The prognostic indicators associated with higher risk of all-cause deaths are male gender (males versus females; HR = 1.16, 95% confidence intervals (CI), 1.13–1.20), diagnosis at later period (shown in 1990–1994 versus 1985–1989; HR = 1.04, 95% CI, 1.01–1.08), increasing age at diagnosis, subjects with adenocarcinoma/cholangiocarcinoma (CC) and with no therapy against those with chemotherapy. The overall 5-year survival rate for all causes of death was significantly poorer in males (13.7%) than females (17.2%). Subjects diagnosed with hepatoblastoma and treated by surgical resection alone had superior prognosis. Particularly, subjects with adenocarcinoma and CC were more likely to die in other metastatic cancer.

1. Introduction

Primary liver cancer (PLC) is among one of most common cancers in the world, especially in East and South-East Asia, where PLC incidence rate exceeds 30 per 100,000 persons.[1] The lowest incidence rates are observed in South and Central America and Oceania, where age-adjusted incidence rate of PLC is below 5 per 100,000 persons.[1] Due to the aggressive nature of the disease, the incidence and mortality rates are approximately equal. Because PLC comprises 85–90% hepatocellular carcinoma (HCC), the two terms are used interchangeably in most countries.[1] PLC is a highly malignant tumour with poor prognosis, diagnosed at a very advanced stage and poor prognostication imposes an important concern for clinicians. Many factors influence PLC survival including: gender, diagnostic age, anatomic site, morphologic type, and treatment modality.[2–13]

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Taiwan is a hyperendemic area for hepatitis B virus (HBV) infection, and chronic HBV infection is a known risk factor to PLC or HCC.[14–16] The prevalence of chronic HBV infection is approximately 60% of the general population.[17] In Taiwan, the age-adjusted incidence rate for PLC in 2001 was 52.62 per 100,000 for males and 21.16 per 100,000 for females (M:F = 2.49:1), making it the first most prevalent cancer among males and the fourth most prevalent cancer among females. The age-adjusted mortality rate of PLC in 2001 was 40.35 and 14.64 per 100,000 for males and females, respectively (M:F = 2.76:1).[18] Despite PLC incidence and mortality rates showing male predominance in Taiwan, gender has not yet been analysed as a predictor of survival rate of PLC. Prognostic factors to the survival of PLC subjects remain controversial. Presently, only few studies have compared the prognostic characteristics of PLC subjects in relation to gender. This study shall disclose the prognostic differences in survival between males and females with PLC.

2. Patients and methods

2.1. Study data

Two systems were enlisted. The Taiwan Cancer Registry (TCR), a large population-based database established by the National Department of Health of Taiwan, provided the information on PLC subjects (ICD-9 code 155). The other, the mortality database, submitted standardised certificates for each death, mandatory for physicians by the Department of Health. So the vital statistics published by the National Health Department of Taiwan are very complete, with a physician confirmation rate of 99%. Consequently, our study population (N = 28,939) comprised of all subjects diagnosed with PLC in 1985–1994, recruited via the TCR system then followed-up and matched accordingly to the mortality database. The subjects' survival days post-diagnosis were ascertained by active validation of their vital status until December 31, 2002.

2.2. Descriptive prognostic features

To evaluate the 5-year survival rates from PLC, time periods were categorised in terms of 1985–1989 and 1990–1994. Data included: gender, diagnostic period, diagnostic age, resident area, morphologic type diagnosis, and course of treatment. Subjects were categorised into three communities regarding their area of residence, defined when the population of each community exceeds 80% of the area's population: the Taiwanese Aborigines, Hakka and Hokkien. The morphologic types were defined under the histological categories in the ICD-O coding system. The PLC subjects were grouped as pathological or clinical and imaging diagnosis. The pathological diagnosis have several morphologic subtypes, such as adenocarcinoma (M8140), cholangiocarcinoma (M8160), hepatocellular carcinoma (HCC: M8170-8171), combined hepatocellular carcinoma and cholangiocarcinoma (M8180), hepatoblastoma (M8970), other carcinoma. Clinical and imaging diagnosis have subtype with no microscopic confirmation of carcinoma (M 9990), and they usually involve the diagnosis of signs, symptoms, serum alpha fetoprotein, hepatic sonography, biochemistry, technetium and gallium scan, or hepatic angiography. The treatment modalities examined were: surgical resection alone, radiation therapy (RT) alone, chemotherapy (CT) alone, surgery + RT/CT (including surgery + RT, surgery + CT or surgery + RT + CT), RT + CT, supportive-care therapy (ST) alone, other complex therapy (including immunotherapy, hormone therapy or traditional Chinese herbal medicine therapy), unknown therapy, and none therapy. The causes of death during the investigation period were broadly categorised by the ICD 9 coding system. These categories were liver cancer death, hepatic complication (including chronic liver disease and cirrhosis, other disorders of liver, liver abscess and sequelae of chronic liver disease, gastrointestinal haemorrhage, etc.), other cancer death (such as malignant neoplasm of gallbladder, extrahepatic bile ducts, trachea, bronchus, lung, stomach, and pancreas, etc.), and other causes.

2.3. Statistical analysis

PLC death and all-cause death were treated as two distinct outcomes for the purpose of this study. For PLC survival analysis, deaths fitting the ICD-155 criteria were classified as deaths from PLC, and those who died of other causes or were still alive were considered as censored observations. Likewise, deaths from any cause were classified as all-cause death, and subjects still alive were censored observations. For both PLC death and all-cause death, the gender curves differed significantly using log-rank test. So subjects with PLC were segregated into male and female groups.

Frequency distributions of demographic, clinical, and therapy characteristics in gender variations were compared by the chi-square test. Survival days of post-diagnosis were estimated by Kaplan–Meier methods and 5-year survival rates presented. Survival rates differed significantly for the outcome of each clinical factor by gender with the log-rank test. After log–log survival plots were used in verifying the proportion hazard assumptions for each predictor, the Cox proportional-hazards model was applied to estimate their contributions. Adjusted multiple variables of prognostic factors (diagnostic period, diagnostic age, resident area, morphologic type diagnosis, and therapeutic choice) were used to assess the hazard ratio (HR) of their relationship based on gender survival for PLC death and all-cause death. SAS version 8.2 statistical software was used for all analysis (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Distribution of prognostic characteristics by gender (Table 1)

A total of 28,939 subjects (81% males and 19% females) were analysed during the period 1985–1994. With the exception of resident area, each characteristic was associated with gender. Females diagnosed at a significantly older age (59.9 ± 13.5 years) than males (57.0 ± 13.0 years). Particularly in both genders, the proportion was significantly higher in 1990–1994 than 1985–1989. In terms of diagnostic age, the number of diagnosed males was predominantly higher than

Table 1 – Characteristics of primary liver cancer (PLC) subjects at time of diagnosis by gender in 1985–1994

Characteristics	Males (N=23,354) N (%)[a]	Females (N = 5585) N (%)[a]	P Value
Mean age (years) ± S.D.	57.0 ± 13.0	59.9 ± 13.5	< 0.0001
Period of diagnosis (years)			
1985–1989	9164 (39)	1674 (30)	<0.0001
1990–1994	14,190 (61)	3911 (70)	
Diagnostic age (years)			
⩽29	574 (3)	173 (3)	
30–39	1919 (8)	306 (6)	<0.0001
40–49	3578 (15)	597 (11)	
50–59	6343 (27)	1261 (23)	
60–69	6917 (30)	1798 (32)	
⩾70	4023 (17)	1450 (26)	
Resident area			
Aboriginal community	464 (2)	102 (2)	0.6082
Hakka community	1684 (7)	390 (7)	
Hokkien community	21,206 (91)	5093 (91)	
Morphologic type diagnosis			
Pathologic diagnosis	8935 (38)	2098 (38)	
Adenocarcinoma	263 (1)	142 (3)	<0.0001
CC	375 (2)	354 (6)	
HCC	7792 (33)	1408 (25)	
Combined HCC/CC	26 (<1)	7 (<1)	
HB	24 (<1)	9 (<1)	
Other carcinoma	455 (2)	178 (3)	
Clinical and imaging diagnosis	14,419 (62)	3487 (62)	
Treatment modality			
Surgical resection alone	1701 (7)	550 (10)	<0.0001
RT alone	323 (1)	73 (1)	
CT alone	2334 (10)	413 (7)	
Surgical resection + RT/CT	321 (1)	103 (2)	
RT + CT	123 (<1)	35 (<1)	
ST alone	8572 (37)	2311 (41)	
Other complex therapy	164 (<1)	34 (<1)	
Unknown therapy	5122 (22)	1065 (19)	
None[b]	4694 (20)	1001 (18)	

Abbreviations: S. D., standard deviation; CC, cholangiocarcinoma; HCC, hepatocellular carcinoma; HB, hepatoblastoma; RT, radiation therapy; CT, chemotherapy; ST, supportive-care therapy.
a May not total 100% due to rounding.
b Without therapy.

females in younger age groups (⩽59 years). In pathologic diagnosis, both genders were significantly more likely to present with HCC than other types, but males had a significantly higher percentage of HCC than females. Interestingly, females had more cholangiocarcinoma and adenocarcinoma than males. With the therapeutic choice, females were more likely to undergo surgical resection as opposed to a significantly higher proportion of males being treated with CT and no therapy.

3.2. *Survival for males and females associated with death from all-cause and death from primary liver cancer (PLC) (Table 2)*

During the follow-up study period, a total of 18,943 (66%) subjects died from PLC. The average rate for all-cause death in the studied period was 89% (18,943 + 6684 = 25,627 subjects died). The observational 5-year rate of survival for PLC death was 23.8% (22.2% for males, 31.1% for females). Overall, the 5-year survival rate for all-cause death was 14.4% (13.7% for males and 17.2% for females). Fig. 1 denotes males had a significantly lower survival curve ($p < 0.0001$) than females.

3.2.1. *All-cause death*

Five-year survival estimates were lower for subjects with older diagnostic age. In males, the 5-year survival rates were significantly higher in 1985–1989 than in 1990–1994 ($p < 0.0001$). Regarding pathological diagnosis, the results showed males diagnosed with combined HCC/CC, adenocarcinoma, and CC type were associated with lower survival estimates than males with HB. Females with CC, adenocarcinoma, and other carcinoma had poorer survival than females with HB. Of the cancer directed therapy, the best survival rate was surgical resection alone, followed by surgical resection + RT/CT, and CT alone.

Table 2 – Association between the prognostic characteristics and survival in primary liver cancer subjects

Characteristics	PLC death (%)[a]			All-cause death (%)[a]		
	Males (N = 15,733)	Females (N = 3210)	p Value[b]	Males (N = 20,797)	Females (N = 4830)	p Value[b]
All subjects	22.2	31.1	<0.0001	13.7	17.2	<0.0001
Period of diagnosis (years)						
1985–1989	23.5	32.0	<0.0001	13.9	16.6	0.0033
1990–1994	21.3	30.7	<0.0001	13.6	17.5	<0.0001
p Value[b]	<0.0001	0.0257		<0.0001	NS	
Diagnostic age (years)						
⩽29	27.7	31.8	NS	20.4	20.2	NS
30–39	22.8	38.8	<0.0001	15.7	26.1	<0.0001
40–49	21.5	34.1	<0.0001	13.6	20.3	<0.0001
50–59	21.0	33.7	<0.0001	13.2	18.6	<0.0001
60–69	22.3	28.9	<0.0001	13.6	16.3	0.0002
⩾70	23.4	28.1	0.0092	13.0	13.6	NS
p Value[b]	0.0035	0.0001		<0.0001	<0.0001	
Residence area						
Aboriginal community	29.9	39.2	NS	15.3	17.7	NS
Hakka community	24.3	35.1	0.0006	13.8	20.0	0.0058
Hokkien community	21.9	30.6	<0.0001	13.7	17.0	<0.0001
pValue[b]	0.0436	NS		NS	NS	
Morphologic type diagnosis						
Pathological diagnosis						
Adenocarcinoma	36.1	51.1	NS	11.4	12.0	NS
CC	70.4	62.1	NS	11.5	9.9	NS
HCC	23.5	29.2	<0.0001	17.1	21.5	<0.0001
Combined HCC/CC	26.7	85.7	NS	7.7	57.1	NS
HB	58.8	76.2	NS	45.8	66.7	NS
Other carcinoma	28.8	46.8	0.0008	14.1	20.8	NS
Clinical and imaging diagnosis	20.5	28.9	<0.0001	11.9	16.1	< 0.0001
p Value[b]	<0.0001	<0.0001		<0.0001	< 0.0001	
Treatment modality						
Surgical resection alone	39.7	45.4	0.0055	29.8	28.4	NS
RT alone	17.1	21.2	0.0285	9.3	9.6	NS
CT alone	21.7	31.7	<0.0001	14.6	20.6	0.0014
Surgical resection + RT/CT	27.7	53.1	<0.0001	20.3	27.2	NS
RT + CT	18.3	18.1	NS	11.4	8.6	NS
ST alone	18.9	28.7	<0.0001	10.8	15.6	<0.0001
Other complex therapy	18.8	37.6	NS	11.6	20.6	NS
Unknown therapy	22.6	29.8	<0.0001	13.9	15.9	NS
None[c]	21.2	27.5	<0.0001	12.6	14.6	0.0019
p Value[b]	<0.0001	<0.0001		<0.0001	<0.0001	

Abbreviations: NS, Not significant; CC, cholangiocarcinoma; HCC, hepatocellular carcinoma; HB, hepatoblastoma; RT, radiation therapy; CT, chemotherapy; ST, supportive-care therapy.
a 5-year survival rates (%) presented.
b Log-rank test.
c Without therapy.

3.2.2. *Primary liver cancer (PLC) death*

A significant decreasing survival rate was observed for 1985–1989 versus 1990–1994. In males, the 5-year survival rates were significantly higher in the youngest age group (age <= 29 years) than other groups. In females, the highest 5-year survival rates were in the 30–39 age group. With pathologic diagnosis, subjects with HCC had the lowest survival rates (23.5% for males and 29.2% for females). Comparing treatment modalities, in males, the highest 5-year survival rates were 39.7% for surgical resection alone. In females, the highest survival rates were surgical resection + RT/CT (53.1%).

3.3. *Contribution of prognostic characteristics by each gender (Table 3)*

3.3.1. *All-cause death*

Males diagnosed in 1990–1994 had significantly poorer prognosis than in 1985–1989 (Table 3). The mortality trend correlated linearly with increasing diagnostic age. In terms of residence area, no disparity between genders was noted. In terms of morphologic type diagnosis, males with adenocarcinoma (HR = 1.27, 95% CI, 1.12–1.45), cholangiocarcinoma (HR = 1.16, 95% CI, 1.04–1.29), and other carcinoma

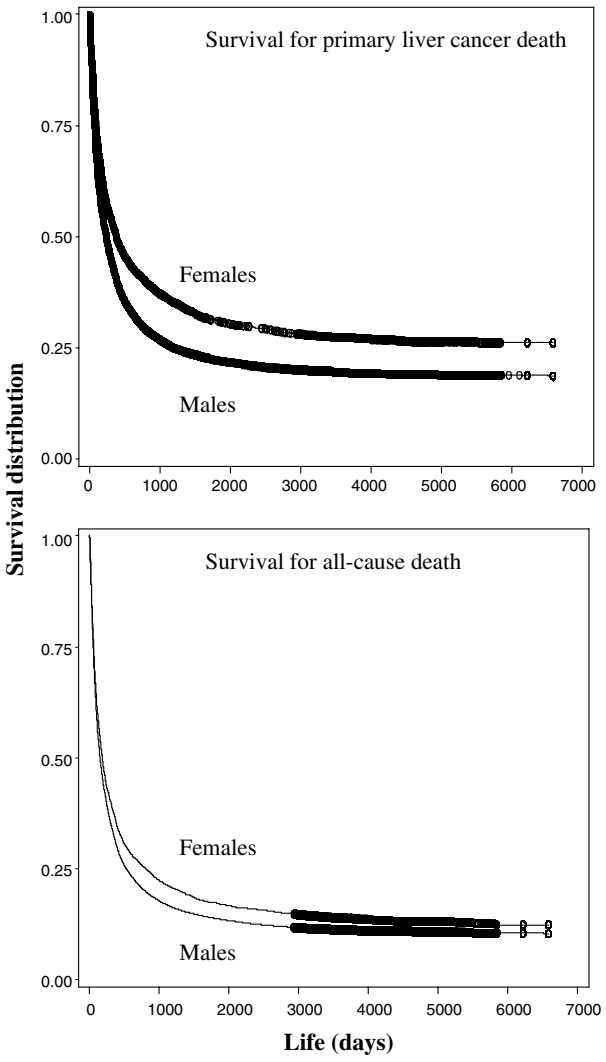

Fig. 1 – Survival days for gender according to liver cancer death (N = 18,943) and all-cause death (N = 25,627) as the endpoints ($p < 0.0001$).

(HR = 1.19, 95% CI, 1.15–1.22) had significantly poorer prognoses than HCC. Likewise, females with adenocarcinoma (HR = 1.43, 95% CI, 1.19–1.72), cholangiocarcinoma (HR = 1.47, 95% CI, 1.29–1.66), and other carcinoma (HR = 1.11, 95% CI, 1.04–1.20) had significantly poorer prognoses than HCC. In contrast, females diagnosed with hepatoblastoma showed reduced risk of death (HR = 0.26, 95% CI, 0.08–0.81) than those diagnosed with HCC. Compared with CT alone, subjects treated with surgical resection alone and surgery resection + RT/CT have reduced risk of death. Nonetheless, in subjects accepted, ST alone or no therapy had significant risk of death compared with CT alone.

3.3.2. *Primary liver cancer (PLC) death*

For PLC death, the diagnostic period was the significant predictor of PLC mortality in males, most evidently in the decreasing survival trend in the years 1990–1994. Males aged 30–39 years and 40–49 years were at higher risk of dying than those aged 29 years or younger. And with area of residence, the Taiwanese aboriginal community has significantly the lowest risk of mortality (HR, 0.86; 95% CI, 0.76–0.97) than the Hokkien community. In the morphologic types, males with cholangiocarcinoma (HR = 0.25) had significantly the lowest risk of death than HCC, followed by hepatoblastoma (HR = 0.46) and adenocarcinoma (HR = 0.78). For females, the risk of death was significantly lower for hepatoblastoma (HR = 0.21), cholangiocarcinoma (HR = 0.35) and adenocarcinoma (HR = 0.65) than for HCC.

Therapeutic modalities were also significant predictors of survival in both genders. There is a significant improvement of prognosis for males treated by surgical resection alone (HR = 0.68) than CT alone. Similarly, in males treated with surgery + RT/CT (HR = 0.82). Nonetheless, males accepted with ST, none, and RT treatment had a significant deleterious effect (HR = 1.30, 1.24 and 1.19, respectively). For females, the hazard ratio of surgical resection alone or surgery + RT/CT also showed significant improvement in prognoses compared to CT alone. Females with no therapy and ST alone also showed a significant risk of death compared to CT alone.

3.4. *Effects of the covariables on hazard ratio for gender (Table 4)*

For PLC death, the crude hazard ratio for males was 1.28 (95% CI, 1.23–1.33). After adjusting for all prognostic factors, males also had significantly higher risk of death than females (HR = 1.26; 95% CI, 1.21–1.31). In all-cause death, the crude hazard ratio also found males to have increased risk of death from PLC (HR = 1.12; 95% CI, 1.09–1.16). In adjusted analysis, the hazard ratios of males also had significantly poorer prognosis (HR = 1.16; 95% CI, 1.13–1.20) than females.

3.5. *A breakdown of death causes by morphological type for primary liver cancer subjects (Table 5)*

There were 49% males diagnosed with adenocarcinoma that died from PLC, and 51% males with adenocarcinoma that died from other causes of death. In addition, 36% females diagnosed with adenocarcinoma died from PLC death, and 64% females died from other death causes. In males diagnosed with CC, 18% died from PLC, and 82% died from other death causes. Likewise, 19% females with CC died from PLC, 81% females died from other causes of death.

In contrast, 82% males with HCC died from PLC and only 18% males died from other causes. In females with HCC, the death rates due to primary liver cancer and other causes were 80% and 20%, respectively.

4. Discussion

Past studies have focused on differences in incidence and prevalence of PLC with relation to gender,[1,18–20] but only modest information from PLC databases were available on survival and prognostic factors of PLC with relation to gender. In this study, we evaluated the survival differences in prognostic factors between genders at time of diagnosis of PLC from large databases. The two death outcomes, PLC death (eliminating competing causes of death) and all-cause death,

Table 3 – Multivariate proportional hazard ratio for primary liver cancer (PLC) death and all-cause death by each gender

Characteristics	PLC death (N = 18,943)		All-cause death (N = 25,627)	
	Males HR (95% CI)	Females HR (95% CI)	Males HR (95% CI)	Females HR (95% CI)
Period of diagnosis (years)				
1985–1989	1.00 –	1.00 –	1.00 –	1.00 –
1990–1994	1.11 (1.07–1.15)*	1.05 (0.97–1.14)	1.04 (1.01–1.08)*	0.99 (0.93–1.06)
Diagnostic age (years)				
⩽29	1.00 –	1.00 –	1.00 –	1.00 –
30–39	1.13 (1.00–1.26)*	0.82 (0.64–1.04)	1.15 (1.04–1.28)*	0.81 (0.66–1.00)
40–49	1.12 (1.01–1.25)*	0.83 (0.67–1.04)	1.18 (1.07–1.30)*	0.89 (0.74–1.08)
50–59	1.10 (0.99–1.23)	0.85 (0.69–1.04)	1.17 (1.06–1.29)*	0.94 (0.79–1.12)
60–69	1.05 (0.95–1.17)	0.91 (0.74–1.11)	1.15 (1.04–1.26)*	1.00 (0.84–1.19)
⩾70	1.03 (0.92–1.15)	0.98 (0.80–1.20)	1.19 (1.08–1.31)*	1.16 (0.97–1.38)
Resident area				
Hokkien community	1.00 –	1.00 –	1.00 –	1.00–
Aboriginal community	0.86 (0.76–0.97)*	0.88 (0.66–1.16)	0.99 (0.90–1.09)	1.05 (0.85–1.30)
Hakka community	0.98 (0.92–1.04)	0.97 (0.84–1.11)	1.04 (0.98–1.09)	0.95 (0.85–1.07)
Morphologic type diagnosis				
Pathological diagnosis				
HCC	1.00 –	1.00 –	1.00 –	1.00 –
Adenocarcinoma	0.78 (0.65–0.93)*	0.65 (0.48–0.88)*	1.27 (1.12–1.45)*	1.43 (1.19–1.72)*
CC	0.25 (0.19–0.32)*	0.35 (0.27–0.45)*	1.16 (1.04–1.29)*	1.47 (1.29–1.66)*
Combined HCC/CC	0.75 (0.42–1.31)	0.42 (0.11–1.68)	1.24 (0.83–1.85)	0.66 (0.25–1.77)
HB	0.46 (0.24–0.89)*	0.21 (0.05–0.83)*	0.64 (0.37–1.09)	0.26 (0.08–0.81)*
Other carcinoma	1.09 (1.05–1.13)*	0.97 (0.89–1.06)	1.19 (1.15–1.22)*	1.11 (1.04–1.20)*
Clinical and imaging diagnosis	0.91 (0.81–1.03)	0.71 (0.56–0.89)*	1.14 (1.03–1.26)*	1.15 (0.97–1.36)
Treatment modality				
CT alone	1.00 –	1.00 –	1.00 –	1.00 –
Surgical resection alone	0.68 (0.63–0.74)*	0.74 (0.62–0.88)*	0.71 (0.66–0.76)*	0.80 (0.69–0.92)*
RT alone	1.19 (1.03–1.36)*	1.10 (0.79–1.54)	1.19 (1.05–1.34)*	1.19 (0.92–1.55)
Surgical resection + RT/CT	0.82 (0.71–0.94)*	0.65 (0.46–0.91)*	0.80 (0.71–0.91)*	0.78 (0.62–1.00)*
RT + CT	0.90 (0.72–1.13)	1.42 (0.91–2.21)	0.98 (0.81–1.18)	1.21 (0.84–1.73)
ST alone	1.30 (1.23–1.37)*	1.22 (1.07–1.40)*	1.33 (1.27–1.40)*	1.30 (1.16–1.46)*
Other complex therapy	1.15 (0.95–1.38)	0.93 (0.57–1.50)	1.16 (0.98–1.37)	0.98 (0.66–1.45)
Unknown therapy	0.92 (0.87–0.98)*	0.97 (0.84–1.13)	0.93 (0.88–0.98)*	1.06 (0.93–1.20)
None[a]	1.24 (1.17–1.32)*	1.20 (1.03–1.39)*	1.27 (1.20–1.33)*	1.31 (1.15–1.48)*

Abbreviations: HR, hazard ratio; CI, confidence interval; CC, cholangiocarcinoma; HCC, hepatocellular carcinoma; HB, hepatoblastoma; RT, radiation therapy; CT, chemotherapy; ST, supportive-care therapy.

a Without therapy.

* Statistical significance ($p < 0.05$).

Table 4 – Crude and adjusted hazard ratio for males versus females according to primary liver cancer death (PLC) and all-cause death

	PLC death (N = 18,943) M:F[a] HR (95% CI)	All-cause death (N = 25,627) M:F[a] HR (95% CI)
Crude hazard ratios	1.28 (1.23–1.33)*	1.12 (1.09–1.16)*
Adjusted hazard ratios		
Adjusted for the period of diagnosis (years)	1.29 (1.25–1.34)*	1.13 (1.10–1.17)*
Above plus diagnostic age, resident area,	1.29 (1.24–1.34)*	1.14 (1.10–1.17)*
Above plus morphological type diagnosis, Treatment modality	1.26 (1.21–1.31)*	1.16 (1.13–1.20)*

Abbreviations: HR, hazard ratio; CI, confidence interval.

a M:F: Male-to-female ratio.

* Statistical significance ($p < 0.0001$).

Table 5 – Causes of death categorised according to morphologic type diagnosis during the investigation period

Characteristics	Males (N = 20,797)				Females (N = 4830)			
	Primary liver cancer death (%)[a]	Hepatic complication (%)[a]	Other cancer death (%)[a]	Other causes (%)[a]	Primary liver cancer death (%)[a]	Hepatic complication (%)[a]	Other cancer death (%)[a]	Other causes (%)[a]
Morphologic type diagnosis								
Pathologic diagnosis								
Adenocarcinoma	117 (49)	9 (4)	103 (43)	10 (4)	46 (36)	6 (5)	66 (52)	10 (8)
CC	59 (18)	11 (3)	247 (74)	19 (6)	63 (19)	13 (4)	237 (72)	15 (5)
HCC	5576 (82)	471 (7)	471 (7)	302 (4)	954 (80)	85 (7)	99 (8)	62 (5)
Combined HCC/CC	12 (50)	2 (8)	8 (33)	2 (8)	2 (50)	2 (50)	0 (0)	0 (0)
HB	9 (64)	0 (0)	1 (7)	4 (29)	2 (67)	0 (0)	1 (33)	0 (0)
Other carcinoma	268 (65)	24 (6)	93 (23)	25 (6)	75 (49)	10 (7)	56 (37)	12 (8)
Clinical and imaging diagnosis	9692 (75)	1344 (10)	1318 (10)	600 (5)	2068 (69)	352 (12)	390 (13)	204 (7)

a May not total 100% due to rounding.

were used in our studies to clear arbitrary effect of death from other causes.

4.1. *Gender differences in survival of subjects diagnosed with PLC*

Our findings show the long-term survival rate is significantly superior in females, despite the average diagnostic age being significantly higher in females (59.9 ±13.5 years) than males (57.0 ± 13.0 years) ($p < 0.0001$). This result is consistent with other publications that males with PLC or HCC score significantly worse survival rates.[3–6,15,21–23] On the other hand, few studies have extracted no significant differences in survival between genders.[7–10,24,25] Our large PLC database confirmed gender to be an independent predictor of PLC prognosis by the multivariate Cox analysis, regardless of PLC death and all-cause death; males diagnosed with PLC had a risk 1.26 and 1.16 times higher than females, respectively. Comparably with other studies, gender has not being a predictive factor associated with survival from PLC.[25,26]

4.2. *Presentation of prognostic factors in survival of subjects diagnosed with PLC*

In this study, a proportion of PLC males in 1990–1994 (61%) was significantly higher than in 1985–1989 (39%). During the time, PLC still posed diagnostic and therapeutic challenges, with prognosis extremely poor. Our study found a significant rise in mortality trend for PLC males between 1985–1989 and 1990–1994. Explanation for this deterioration is not straightforward. Conceivably, the decline in survival rates may be due to there being no improvement in earlier detection or treatment effectiveness. On the contrary, there have been small improvements in survival rates of subjects with HCC recorded in 1977–1996 in the United States.[7] Likewise, a European Union study showed minimal improvement in 5-year survival rates over the 1978–1989 period.[10] Our striking finding in an overall declining trend of PLC males from 1985–1989 to 1990–1994 warrants further attention.

When reviewing the effects of diagnostic age on all-cause death, subjects with increasing age, especially those older than 70 years, presented as a significant risk factor in males. The results reflect other reports that advanced age has an adverse effect on survival for HCC or PLC patients.[6–8,25] The majority of past PLC studies focused on clinical factors and emphasised less on morphologic type. A Japanese study showed no substantial differences between genders with respect to histopathology of HCC.[23] In this study, males were more likely to have HCC (33%) than females (25%), and frequently a carcinoma of an invasive type. Presumably, the higher degree of alcohol abuse in males accelerates cirrhosis to HCC.[20] The impact of morphologic diagnosis on PLC death (eliminating competing cause of death) was noted in subjects with CC, HB and adenocarcinoma and resulted in significant improvement in prognosis, compared with HCC type. Due to the affected cell having different histological types, the prognosis for HCC is worse than hepatoblastoma.[27]

Surprisingly, hazard ratios for all-cause death as outcome with adenocarcinoma and CC have a significantly poorer prognosis than those with HCC. This is comparable to a Japa-

nese study acknowledging that those with HB have the best 5-year survival rates (44.5%), followed by others (34.0%), mixed HCC/CC (9.3%), HCC (2.4%), and the poorest in CC (1.1%).[11] Purportedly, subjects with adenocarcinoma and cholangiocarcinoma may have more comorbid conditions (for instance, they died with metastatic cancer) than those with purely HCC (Table 5). The 5-year survival rates of subjects with adenocarcinoma and cholangiocarcinoma in all-cause death were lower than those having HCC. These results partly explain subjects with adenocarcinoma and cholangiocarcinoma having adverse prognosis in all-cause death than those with HCC.

Table 6 conglomerates studies of PLC survival based on morphologic type. According to our present study, subjects with HB had the highest 5-year survival rates (51.5%) of all-cause death, subsequently combined HCC/CC (18.2%), HCC (17.8%), other carcinoma (16.0%), clinical and imaging diagnosis (12.7%), and adenocarcinoma (11.6%). The lowest survival rates were 10.7% scored in subjects with CC. In other studies, the 5-year survival rates of subjects with HB varied between 35.0% and 47.0%,[11,27,28] and subjects with HCC ranged between 2.0% and 37.0%;[2,4,5,7,9,11,12,27,28] the 5-year survival rate of subjects with combined HCC/CC ranged between 9.3% and 24.0%.[11,12]

Until now, complete surgical resection or liver transplantation offer potentially effective therapies for HCC patients.[29] Surgical resection and/or support therapy, radiotherapy and chemotherapy have been mainstay treatments for PLC in this study. A previous study showed no statistical significance in types of treatment of HCC.[5] Most middle-aged and elderly females stay at home as housewives, and, correspondingly, spend more time in accessing the health care system. In this study, 10% of females accepted surgical resection alone, while 7% of males were treated with such therapy. The proportion of no therapy in males (20%) was significantly higher than females (18%). Previous studies also noted females to have better postoperative survival, translating into better prognosis for them.[2,22,23] Differences in aspects of medical intervention contribute to gender disparity in survival rates.

In both PLC related death and all-cause death, we uncovered a protective effect in surgical resection. This finding is consistent with another study where subjects treated with

Table 6 – Studies of 5-year survival rates in subjects with primary liver cancer (PLC)

First author (Reference)	Year	Morphological type	Number	(%)	5-year survival rates (%)	Follow-up (years)
Population-based						
Present	1985–1994	All primary liver cancer	28939		14.4	9–18
		HB	33	(<1)	51.5	
		Combined HCC/CC	33	(<1)	18.2	
		HCC	9200	(32)	17.8	
		Other carcinoma	633	(2)	16.0	
		Clinical and imaging diagnosis	17906	(62)	12.7	
		Adenocarcinoma	405	(1)	11.6	
		CC	729	(3)	10.7	
Kunio[11]	1968–1977	HB	52	(3)	44.5	10
		Other carcinoma	11	(1)	34.0	
		Combined HCC/CC	39	(2)	9.3	
		HCC	1424	(84)	2.4	
		CC	175	(10)	1.1	
Lee[27]	1988–1992	All primary liver cancer	109		19.0	3–8
		HB	17	(16)	47.0	
		HCC	28	(26)	17.0	
		Other carcinoma	4	(4)	–	
		Clinical and imaging diagnosis	60	(55)	11.0	
Exelby[28]	1965–1974	HB	129	(57)	35.0	2–10
		HCC	98	(43)	13.0	
Cance[9]	1985–1996	HCC	2401		M:5.6 F:9.5	12
El-Serag[7]	1977–1981	HCC	1193	(16)	2.0	20
	1982–1986		1560	(21)	3.0	
	1987–1991		2063	(28)	4.0	
	1992–1996		2573	(35)	5.0	
Hospital-based						
Jarnagin[12]	1985–1999	HCC	27	(35)	37.0	15
		CC	23	(30)	33.0	
		Combined HCC/CC	27	(35)	24.0	
Cong[2]	1982–1991	HCC	316		27.5	10
Dohmen[5]	1989–2000	HCC	704		24.6	12
Ng[4]	1984–1994	HCC	278		28.0	11

Abbreviations: M, males; F, females CC: cholangiocarcinoma; HCC: hepatocellular carcinoma; HB: hepatoblastoma.
a May not total 100% due to rounding.

surgical resection had a greater survival, in contrast to those who accepted CT alone.[9] Previous reports indicated unfavourable prognosis in subjects who did not receive any specific treatment for PLC.[9,13,26] We found subjects treated with surgery + RT/CT to have significant improvement in survival rates than with CT alone. However, those treated with ST alone or without therapy suffered a higher risk of death from PLC death and all-cause death.

The survival of PLC is strongly dependent upon staging the carcinoma. Information pertaining to staging is unavailable to TCR in Taiwan, but the subjects' therapeutic choices can be treated as a clinical reference. Data suggested an earlier clinical staging of cancer was eligible for surgical resection alone or surgical reception + RT/CT. Without therapy or treated with CT alone, RT, ST alone may indicate they were diagnosed in advanced stages of the disease. Nonetheless, improvements may owe themselves to differences in carcinoma staging, rather than effectiveness of therapeutic methods.

Conflict of interest statement

None declared.

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