Population-Based analysis for newly diagnosed hepatocellular carcinoma with brain metastases

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Research article

Keywords: Brain metastases, initial metastatic hepatocellular carcinoma, incidence, cancer-specific survival, overall survival

Posted Date: November 26th, 2019

DOI: https://doi.org/10.21203/rs.2.17900/v1

Abstract

Background: There is little population-based data on hepatocellular carcinoma (HCC) with brain metastases at initial diagnosis published. This study aimed to estimate incidence of brain metastases in initial metastatic HCC and its impact on prognosis. Methods: Newly diagnosed HCC cases from 2010 to 2015 in the Surveillance, Epidemiology, and End Results (SEER) database were screened for the presence of brain metastases. Data were stratified by age and ethnicity. Multivariable logistic and Cox regression were used to identify factors associated with brain metastases and factors associated with overall survival (OS) and cancer-specific survival (CSS), respectively. Kaplan-Meier method and log-rank test were used for survival analysis. Results : 141 cases presenting with brain metastases were identified, accounting for 0.35% of all HCC cases and 2.37% of cases with metastatic HCC disease. The incidence rate was highest among cases with age 50-59 (2.74%), respectively. Ethnicity was not associated with the presence of brain metastases at the time of HCC diagnosis. However, African American patients presented significantly lower disease-specific survival (median time: 1month; interquartile range (IQR):0-3.0 months). Initial lung or bone metastasis was independently associated with an increased risk of the presence of brain metastases (odds ratio (OR) 12.62, 95%CI 8.40-18.97), but not associated with worse OS and CSS among brain metastases cases. Conclusions: The study shows population-based incidence and survival of brain metastases at diagnosis of HCC. Brain metastases are most prevalent in initial metastatic HCC patients with lung or bone metastasis. The results may contribute to consider screening of the brain among HCC with initial lung or bone metastasis.

Background

Hepatocellular carcinoma is the most common form of primary liver cancer (80%), which is the sixth leading cause of cancer death worldwide and the second largest mortality contributor. [1,2] Incidence rates continue to increase rapidly for hepatocellular carcinoma, by about 3% per year in women and 4% per year in men.[3] The most common way for haematogenic metastases of primary liver tumors is via dissemination through the hepatic veins and thus to the lungs, bones and the brain[4,5]. Brain metastases from hepatocellular carcinoma (HCC) were thought to be very rare but data only based on estimates. Kim et al. reported in 1998 an incidence of 0.2% of HCC with brain metastases.[6] In recent years, it was expected that the incidence of brain metastases might increase over time, probably as a result of advances in early detection and treatment of hepatocellular carcinoma, which have led to a prolonged overall survival.[4,7,8] Two retrospective studies showed, that the incidence of brain metastases in hepatocellular carcinoma were 4.1% and 7.7%, respectively.[9,10] In addition, a meta-analysis including 2538 patients with brain metastases originated from gastrointestinal cancer found that 9.18% of patients had any type of liver cancer. [11] Few studies focused on population-based estimates of the incidence and prognosis of hepatocellular carcinoma with synchronous brain metastases at the time of diagnosis. Most studies based on findings in case reports and single institution experiences and showed heterogeneous results.[9,10,12-17]

To better define the incidence and survival of synchronous brain metastases in newly diagnosed HCC cases the SEER database was reviewed.

Methods

Data sources and Study population

The SEER database was used for analysis. SEER database included population-based cancer registries information on cancer incidence, treatment and survival, covering nearly 28% of the United States population.[18] Using the latest released data of the SEER database, 45597 cases (≥18 years old) who were diagnosed with hepatocellular carcinoma between January 1, 2010, and December 31, 2015 were identified. 5824 cases with unavailable information on brain metastases at time of diagnosis were excluded, leaving 39773 cases for analysis of the incidence. Of those, 141 (0.35%) had synchronous brain metastases upon primary diagnosis of HCC. Among the 39773 cases, 79 cases with undisclosed survival information were excluded, leaving 39694 cases for the Cox regression analysis. One case who had an unknown survival time was excluded, leaving 140 cases for the survival analysis (Figure 1).

Variables of interest were gender, age at diagnosis, ethnicity, year of diagnosis, AFP status, primary tumor stage, primary tumor size, tumor multiplicity (presence of multiple lesions), metastatic sites to lung, bone, and surgery of the primary site. Gender was classified as male versus female. Ethnicity was classified as Caucasian, African American, Other (American Indian/AK Native, Asian/Pacific Islander) and unknown. Data were stratified by age at diagnosis. All cases were divided into five categories: ages 30-49 years, ages 50-59 years, ages 60-69 years, ages 70-79 years, and ages 80+ years. Incidence rates were calculated after stratification by age at diagnosis. In SEER database, AFP status was divided into three categories: negative, positive, and other (test not done, borderline, and unknown). Further relevant biomarkers were not available in the database, SEER does not provide data on tumor recurrence or subsequent sites of disease involvement.

Statistical analysis

Baseline characteristics for all HCC cases versus those who had synchronous brain metastases were compared with Pearson Chi-square test or Fisher exact test as appropriate. Factors of the presence of brain metastases and predictors associated with OS and CSS were identified. Multivariable logistic regression was used to identify whether demographics and tumor characteristics were associated with the presence of brain metastases among all HCC and initial metastasis cases. Gender, age at diagnosis, ethnicity, year of diagnosis, AFP status, primary tumor stage, primary tumor size, tumor multiplicity, and metastatic sites to lung, bone were included in the multivariable logistic regression analysis. Surgery of the primary site was not included in the multivariable logistic regression analysis as the surgery was

performed after the diagnosis of brain metastases. Survival analysis was assessed with the Kaplan–Meier method, and the results were compared with the log-rank test. A Cox proportional hazards model was applied for multivariate survival analysis. The forest plot was formulated by Microsoft Excel 2013 according to the results of multivariate analysis. The data were analyzed by SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). All P values were two-sided, and P-value <0.05 was considered as statistically significant.

Results

Clinical and demographic characteristics

Of the 39773 HCC cases 141 (0.35%) had synchronous brain metastases at time of primary HCC diagnosis. Median age of brain metastases cases was 61 years (range, 33-92 years; standard deviation (SD),11.3 years), and median age of all HCC cases was 63 years (range, 18-106 years; SD, 10.9 years). Cases with age 18-30 years had no brain metastases. Baseline clinical and demographic characteristics of all HCC and brain metastases cases were significantly different between groups except for gender, age at diagnosis, ethnicity, and year of diagnosis (Table 1). Most of cases were male (78.0%) and Caucasian (72.4%). Cases in the age 50-59 were the ones with the highest frequency of brain metastases (34.0%). 40.4% of cases were tumors >5 cm in size. 48.9% of cases were positive in preoperative AFP status, and 14.9% were negative. Initial lung or bone metastases were significantly associated with brain metastases (44.7%; all HCC: 8.3%). The same results were found in patients with synchronous metastases to both lung and bone (12.8%; all HCC: 1.0%).

Incidence

The incidence of HCC with synchronous brain metastases at time of diagnosis stratified by age is provided in Table 2. The 141 brain metastases cases accounted for 0.35% of all HCC cases and 2.37% of all initial metastatic cases. The incidence rate was highest in the age group 30-49 (0.47%), and lowest in group 60-69 and age 70-79 (both 0.30%). Rates of initially metastasized cases sorted according to age were: 2.66% for the age group 30-49, 2.74% for ages 50-59, 2.21% for ages 60-69, 1.97% for 70-79 and 2.42%, for age 80+,respectively.

On multivariable logistic regression analysis, initial metastasis to one site (vs no initial metastasis to lung or bone; OR 12.62, 95%CI 8.40-18.97), initial metastasis to two sites (vs no initial metastasis to lung or bone; OR 28.97, 95%CI 16.23-51.74) were independent predictors of the presence of brain metastases in all HCC cases (Figure 2). Initial metastasis to two sites (vs no initial metastasis to lung or bone; OR 1.88, 95%CI 1.08-3.30) was independently associated with an increased risk of the presence of brain metastases in all initially metastasized cases. No significant differences were observed for gender, ethnicity, age at diagnosis, year of diagnosis, AFP status, primary tumor stage, primary tumor size, and tumor multiplicity.

Survival

The 1-year OS was 8.4% and the 1-year CSS was 16.3% in cases with synchronous brain metastases, respectively (Figure 3A and 3B). Median survival of all HCC cases was 11.0 months (IQR: 2.0-39.0 months). For cases with synchronous brain metastases, the median survival was 2.0 months (IQR: 0-6.0 months; standard error (SE), 0.35 months). Cases with no synchronous brain metastases had a significantly better survival compared to cases with synchronous brain metastases (median survival: 12 vs 2 months, Figure 3C). Median survival of brain metastases and all initial metastatic cases stratified by age at diagnosis were presented in Table 2. Overall survival of synchronous brain metastases stratified by age at diagnosis was significant for the youngest patients (Figure 3D).

On multivariate survival analysis (Table 3), ethnicity (African American vs Caucasian; HR 1.68; 95%CI, 1.06-2.89) and the presence of multiple lesions (HR 3.52; 95% CI, 1.28-9.69;) were significantly associated with the worse OS for HCC cases with synchronous brain metastases. For the liver cancer specific survival, the results of multivariable cox regression indicated that ethnicity (African American vs Caucasian; HR 2.07; 95%CI, 1.16-3.70) was still significantly associated with the inferior CSS among synchronous brain metastases cases. Gender, age at diagnosis, year of diagnosis, AFP status, primary tumor stage, primary tumor size, and metastatic sites to lung, bone, as well as surgery of the primary site were not associated with the prognosis of OS and CSS.

Discussion

Metastases to the brain in HCC patients are rarely described in the literature[15]. The overall survival prognosis of two months is devastatingly low, as seen in our study .In non-symptomatic patients a brain scan is usually not part of the standard work up of newly diagnosed HCC cases. In the present study, the pattern of synchronous brain metastases in newly diagnosed initial metastatic hepatocellular carcinoma was shown to be extremely aggressive when other extrahepatic metastases exist. This finding re-enforces the hypothesis that metastasized tumors tend to further metastasize to other organs. The study revealed that 0.35% of all HCC cases and 2.37% of all initially metastatic HCC cases had brain metastases. The incidence proportion of brain metastases was highest among HCC cases with age 30-49. The median survival of cases with brain metastases was 2.0 months. According to the National Cancer Institute (NCI), the median age for the time of a cancer diagnosis is 66 years and advancing age is the most important risk factor for cancer overall.[19] However, concerning primary liver cancer, it cannot be stressed enough that HCC develops almost always in cirrhotic livers with Hepatitis being one of the main underlying reasons. Nowadays NASH is one of the main risk factors for HCC. Despite potent antiviral therapy there is a global increase in HCC. Therefore, a much younger group of patients is at risk to develop a metastatic disease.

Cagney et al [14] were the first group to perform population-based epidemiologic study on brain metastases in systemic malignancy at time of diagnosis in the United States including cases from 2010 to 2013. They reported that the incidence of brain metastases was 0.36% among all hepatobiliary cancer and 1.77% among all initially metastatic cases, respectively. However, this study did not specifically examine HCC cases. Han et al [20] retrospectively analyzed 5015 HCC patients who were diagnosed in South Korea between 2001 and 2012 and found that 0.65% of all HCC cases developed brain metastases . However, the incidence and survival were not stratified by age at diagnosis, and factors associated with the presence of brain metastases were unknown. In the current study, a trend toward higher proportion of younger cases (<50 years) with brain metastases was found. When analyzing factors associated with OS and CSS it was revealed that initial metastasis to one site (either lung or bone) as well as initial metastasis to both sites (lung and bone) were independently associated with a higher risk for the presence of brain metastases. Given the lack of routine brain screening in HCC patients with extrahepatic metastases, our finding that 2.37% of all initial metastatic cases had brain metastases at diagnosis likely underestimated the prevalence. Thus, brain involvement should be potentially investigated in all stage IVB patients during staging.

In this study, only ethnicity (African American vs Caucasian) was significantly associated with worse OS and CSS in cases with synchronous brain metastases. Compared with African-American patients, Caucasian patients had a significantly longer median survival time. This is in line with Jones et al[21] and who found that African American in the US presented at more advanced stages with larger tumors, and had shortest survival after HCC diagnosis. Patients of caucasian ethnicity had 36% reduced mortality rate compared to ones with African American. It is supported by data of population-based studies that found that African American had more advanced stage at diagnosis and lower rates of receiving treatment in the US.[22,23] The exact explanation for the disparity is not clear, but this may associate with underinsurance or lack of any insurance at all.[21]

The presence of multiple lesions was independently associated with OS, but was not associated with CSS on multivariate analysis.

There are limitations to our study. First, only cases with brain metastases of hepatocellular carcinoma at initial diagnosis were included since SEER does not provide data on tumor recurrence or subsequent sites of disease involvement. An analysis of HCC cases that developed brain metastases during the course of their disease is not possible.[14] In addition, National Comprehensive Cancer Network (NCCN) guidelines for hepatocellular carcinoma do not include the use of routine brain screening of brain metastases, most likely asymptomatic HCC cases with brain metastases will have been ignored. Therefore, the real incidence of brain metastases in HCC cases at time of diagnosis is potentially underestimated. One might assume that the existence of pulmonary and/or bone metastases would explain the rate of brain metastases, however this has not been proven yet for HCC as it has been for metastases of colorectal cancer.[24]

Second, since data on treatment of cases with brain metastases unavailable in the SEER database no further analysis is possible. The role of systemic treatment is not clear since only case reports on chemotherapy have been published to date[25]. Effects of sorafenib on brain metastases in HCC patients are not independently reported so far. However, results from retrospective studies suggest that surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) might prolong survival [17,26-28]. In fact, sorafenib as additive to the afore mentioned treatments has shown some promising primary results in brain metastases from renal cancer[29]. Third, data on tumor characteristics, such as tumor grade and AJCC stage are incomplete in the SEER database. Our major finding of AFP association can thus be critically seen when taking into account that 30% of cases didn't have a reported AFP status in our patient cohort. Tumor size was not a prognostic factor in this study although this has been described[30] . Another limitation is the marginal incidence variance among age groups which makes the biological relevance of this finding somewhat questionable. However, fact is that stakeholders are faced with a challenge when assessing the next screening guidelines for patients with HCC.

Conclusions

The presented data provide updated estimates on the incidence and survival of patients with brain metastases in hepatocellular carcinoma in the United States. Due to advances in HCC treatment and increased patients survival the risk for development of brain metastases may be increasing. The current study aims to contribute to the consideration of routine screening of the brain among initially metastasized HCC patients with lung or bone metastasis.

Abbreviations

HCC: hepatocellular carcinoma

OS: overall survival

CSS: cancer-specific survival

AFP: Alpha fetoprotein

SEER: Surveillance, Epidemiology, and End Results

Declarations

Ethics approval and consent to participate

N/A (The SEER Database did not prerequisite any ethics approval since patient data are pseudonymised)

Consent for publication

The authors have consented to publication after having read the final manuscript.

Availability of data and material

SEER Data are available after registration. The authors will provide any additional data if needed.

Competing interests

The authors have declared no conflicts of interest.

Funding

This work was supported by China Scholarship Council [File No.201708080137]. We acknowledge financial support by Deutsche Forschungsgemeinschaft within the funding program Open Access Publishing, by the Baden-Württemberg Ministry of Science, Research and the Arts and by Ruprecht-Karls-Universität Heidelberg.

Authors' contributions

JF: Funding acquisition, study concept and design, writing–original draft, data collection, data analyses, and interpretation of data. GP: Funding for publication, writing–review and editing, data collection, data analyses, and interpretation of data. UH: data collection, data analyses, and interpretation of data. AM: data analyses, and interpretation of data. KH: Study supervision, study concept and design, draft and editing of manuscript and project administration.

Acknowledgements

N/A

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2):87-108.

2. Parkin DM, Ferlay J, Curado MP, et al. Fifty years of cancer incidence: CI5 I-IX. *Int J Cancer.* 2010;127(12):2918-2927.
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.
4. Wang S, Wang A, Lin J, et al. Brain metastases from hepatocellular carcinoma: recent advances and future avenues. *Oncotarget.* 2017;8(15):25814-25829.
5. Wu W, He X, Andayani D, et al. Pattern of distant extrahepatic metastases in primary liver cancer: a SEER based study. *J Cancer.* 2017;8(12):2312-2318.
6. Kim M, Na DL, Park SH, Jeon BS, Roh JK. Nervous system involvement by metastatic hepatocellular carcinoma. *Journal of neuro-oncology.* 1998;36(1):85-90.
7. Soffietti R, Ruda R, Mutani R. Management of brain metastases. *J Neurol.* 2002;249(10):1357-1369.
8. Shao YY, Lu LC, Cheng AL, Hsu CH. Increasing incidence of brain metastasis in patients with advanced hepatocellular carcinoma in the era of antiangiogenic targeted therapy. *The oncologist.* 2011;16(1):82-86.
9. Natsuizaka M, Omura T, Akaike T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. *Journal of gastroenterology and hepatology.* 2005;20(11):1781-1787.
10. Jiang W, Zeng ZC. Is it time to adopt external beam radiotherapy in the NCCN guidelines as a therapeutic strategy for intermediate/advanced hepatocellular carcinoma? *Oncology.* 2013;84 Suppl 1:69-74.
11. Esmaeilzadeh M, Majlesara A, Faridar A, et al. Brain metastasis from gastrointestinal cancers: a systematic review. *Int J Clin Pract.* 2014;68(7):890-899.
12. De Salvo L, Arezzo A, Razzetta F, Tassone U, Mattioli FP. Drainage and sepsis in thyroid surgery. *Annali Italiani di Chirurgia.* 1998;69(2):165-167.
13. Chen SF, Tsai NW, Lui CC, et al. Hepatocellular carcinoma presenting as nervous system involvement. *European journal of neurology.* 2007;14(4):408-412.
14. Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol.* 2017;19(11):1511-1521.
15. Choi HJ, Cho BC, Sohn JH, et al. Brain metastases from hepatocellular carcinoma: prognostic factors and outcome: brain metastasis from HCC. *J Neurooncol.* 2009;91(3):307-313.
16. Uchino K, Tateishi R, Shiina S, et al. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. *Cancer.* 2011;117(19):4475-4483.
17. Jiang XB, Ke C, Zhang GH, et al. Brain metastases from hepatocellular carcinoma: clinical features and prognostic factors. *BMC cancer.* 2012;12:49.
18. Surveillance E, and End Results (SEER) Program Research Data (1975–2015), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2018, based on the November 2017 submission. http://www.seer.cancer.gov. Accessed.

19. National Cancer Institute at the National Institutes of Health. Accessed April 30. https://www.cancer.gov/about-cancer/causes-prevention/risk/age. Accessed.
20. Han MS MK, Lee KH, et al. Brain metastasis from hepatocellular carcinoma: the role of surgery as a prognostic factor. BMC Cancer. 2013, 13:567.
21. Jones PD, Diaz C, Wang D, Gonzalez-Diaz J, Martin P, Kobetz E. The Impact of Race on Survival After Hepatocellular Carcinoma in a Diverse American Population. *Dig Dis Sci.* 2018;63(2):515-528.
22. Sloane D CH, Howell C. Racial disparity in primary hepatocellular carcinoma: tumor stage at presentation, surgical treatment and survival. J Natl Med Assoc. 2006;98(12):1934-9.
23. Ha J YM, Aguilar M, et al. Race/Ethnicity-specific Disparities in Hepatocellular Carcinoma Stage at Diagnosis and its Impact on Receipt of Curative Therapies. J Clin Gastroenterol. 2016;50(5):423-30.
24. Duan H, He ZQ, Guo CC, et al. Bone metastasis predicts poor prognosis of patients with brain metastases from colorectal carcinoma post aggressive treatment. *Cancer Manag Res.* 2018;10:2467-2474.
25. Tamura T, Kawamura Y, Ikeda K, et al. Hepatocellular carcinoma metastasis to the brain mimicking primary pituitary tumor around the sella turcica. *Clin J Gastroenterol.* 2013;6(4):319-325.
26. Yamakawa Y, Moriguchi M, Aramaki T, et al. Brain metastasis from hepatocellular carcinoma: The impact of radiotherapy on control of intracranial hemorrhage. *Hepatol Res.* 2015;45(11):1071-1075.
27. Han JH, Kim DG, Chung HT, et al. Stereotactic radiosurgery for brain metastases from hepatocellular carcinoma. *Journal of neuro-oncology.* 2013;115(1):45-51.
28. Park Y, Kim KS, Kim K, et al. Nomogram prediction of survival in patients with brain metastases from hepatocellular carcinoma treated with whole-brain radiotherapy: a multicenter retrospective study. *Journal of neuro-oncology.* 2015;125(2):377-383.
29. Arneson K, Mondschein J, Stavas M, et al. A phase I trial of concurrent sorafenib and stereotactic radiosurgery for patients with brain metastases. *J Neurooncol.* 2017;133(2):435-442.
30. Kim S, Choi Y, Kwak DW, et al. Prognostic factors in hepatocellular carcinoma patients with bone metastases. *Radiat Oncol J.* 2019;37(3):207-214.

Tables

Table 1. Characteristics of 39773 HCC and 141 brain metastases cases in SEER database 2010-2015

	All HCC cases		Brain metastases cases		*P*
Variable	No.	%	No.	%	
Gender					0.458
Male	29958	75.3	110	78.0	
Female	9815	24.7	31	22.0	
Age at diagnosis					0.428
18-49	2316	5.8	11	7.8	
50-59	11567	29.1	48	34.0	
60-69	14132	35.5	43	30.5	
70-79	7598	19.1	23	16.3	
80+	4160	10.5	16	11.4	
Ethnicity					0.335
Caucasian	27761	69.8	102	72.4	
African-American	5471	13.8	23	16.3	
Other	6335	15.9	15	10.6	
Unknown	206	0.5	1	0.7	
Year of diagnosis					0.885
2010-2012	18576	46.7	65	46.1	
2013-2015	21197	53.3	76	53.9	
AFP status					<0.001
Negative	8717	21.9	21	14.9	
Positive	22040	55.4	69	48.9	
Other[a]	9016	22.7	51	36.2	
Primary tumor stage					<0.001
T1	16676	41.9	38	27.0	
T2	8060	20.3	18	12.8	
T3	9111	22.9	34	24.1	
T4	1470	3.7	8	5.7	
TX	4456	11.2	43	30.5	
Primary tumor size					<0.001
≤2cm	4754	12.0	8	5.7	
2-5cm	14566	36.6	28	19.9	
>5cm	14533	36.5	57	40.4	
Unknown	5920	14.9	48	34.0	
Tumor multiplicity					<0.001
Single lesion	20380	51.2	47	33.3	
Multiple lesions	14301	36.0	54	38.3	
NOS	5092	12.8	40	28.4	
Metastatic sites to lung, bone					<0.001
None	35773	89.9	48	34.0	
Lung or bone	3297	8.3	63	44.7	
Lung and bone	397	1.0	18	12.8	
Unknown	306	0.8	12	8.5	
Surgery of the primary site					<0.001
No	30352	76.3	136	96.5	
Yes	9300	23.4	5	3.5	
Unknown	121	0.3	0	0.0	

[a]Not done or bordeline or unknown.
AFP, alpha fetoprotein; NOS, not otherwise specified.

Table 2. Number and incidence of brain metastases at time of HCC diagnosis stratified by age at diagnosis

Age at diagnosis	All HCC cases, N	Cases with metastatic disease, N	Brain metastases cases, N	Incidence of PM,%		Median survival,95%CI,Mo	
				Among all HCC cases	Among Cases with metastatic disease	brain metastases cases	Cases with metastatic disease
18-49	2316	414	11	0.47	2.66	3.0(0-8.4)	2.0(1.4-2.6)
50-59	11567	1754	48	0.41	2.74	1.0(0-2.2)	2.0(1.8-2.2)
60-69	14132	1945	43	0.30	2.21	3.0(0.7-5.3)	2.0(1.8-2.2)
70-79	7598	1168	23	0.30	1.97	1.0(0.1-1.9)	2.0(1.8-2.2)
80+	4160	660	16	0.38	2.42	2.0(0-5.2)	2.0(1.7-2.3)
All	39773	5941	141	0.35	2.37	2.0(1.3-2.7)	2.0(1.9-2.1)

Figures

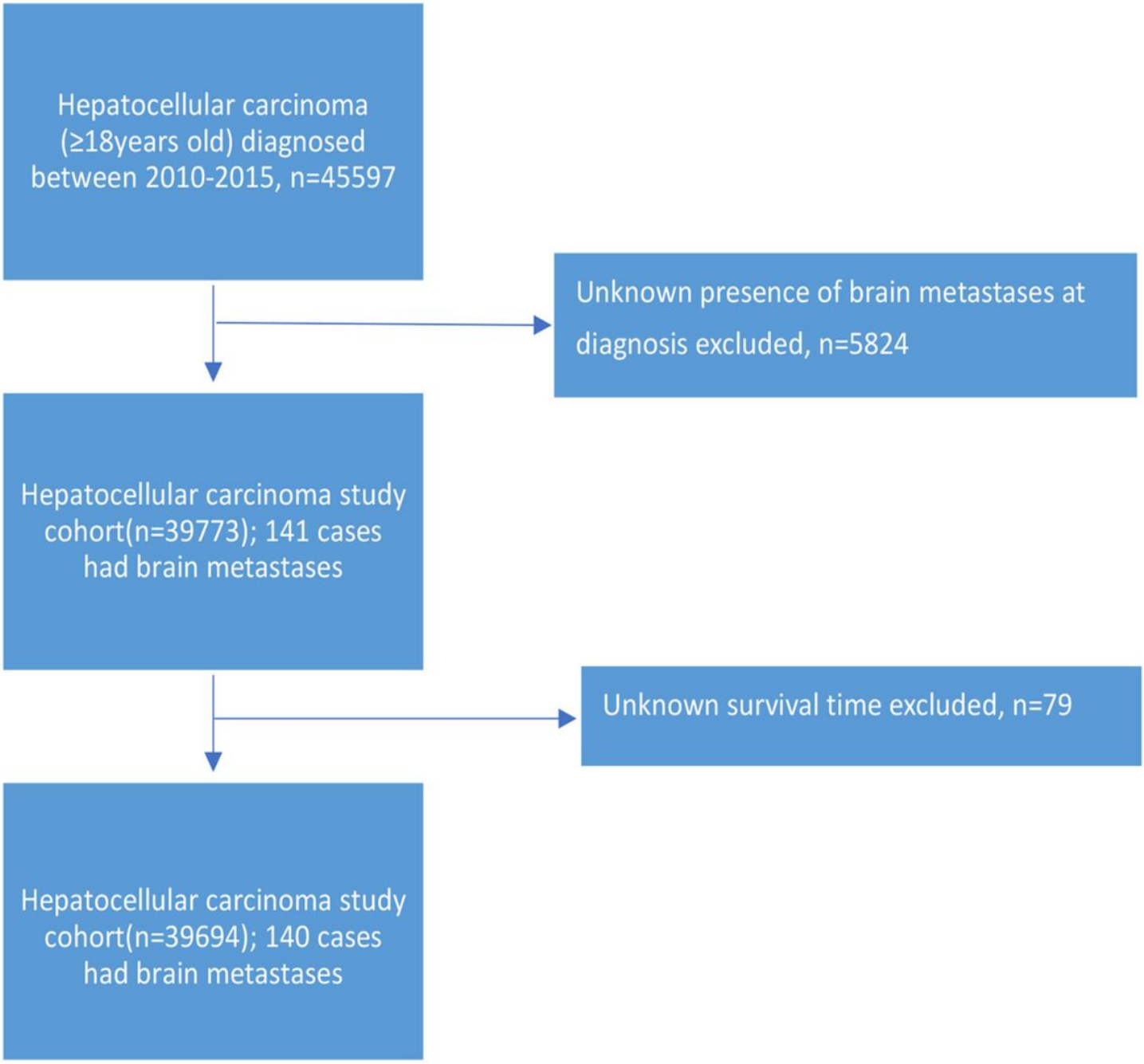
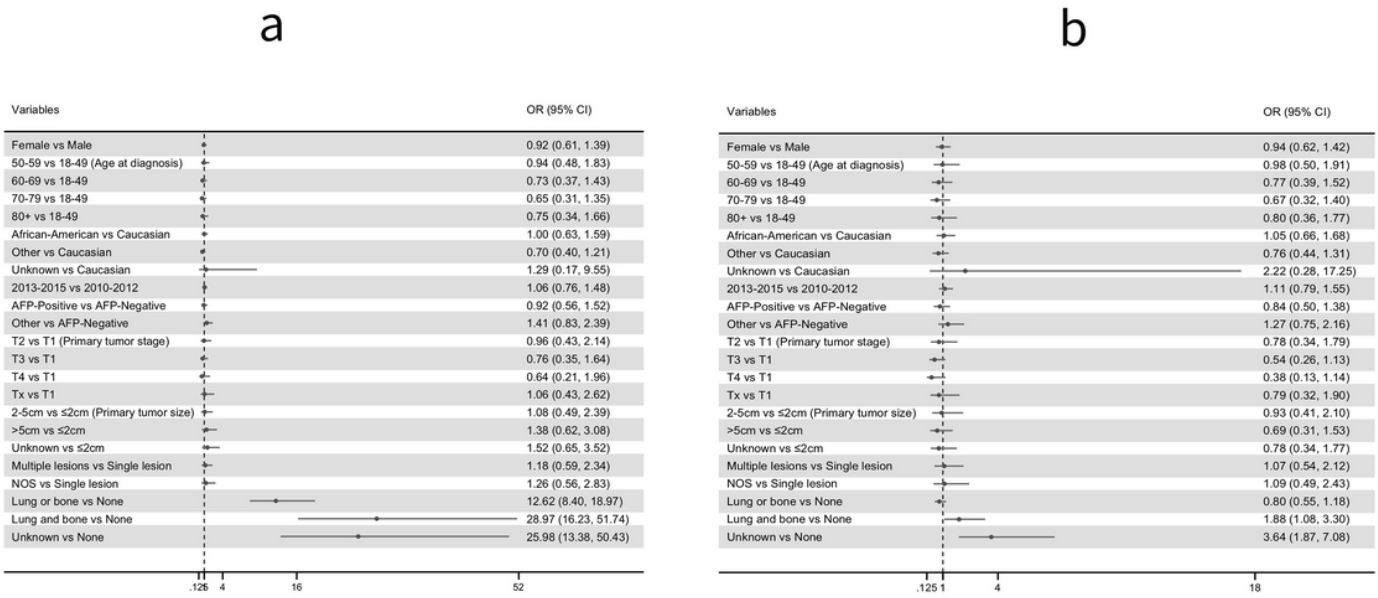

Hepatocellular carcinoma (≥18years old) diagnosed between 2010-2015, n=45597
Unknown presence of brain metastases at diagnosis excluded, n=5824
Hepatocellular carcinoma study cohort(n=39773); 141 cases had brain metastases
Unknown survival time excluded, n=79
Hepatocellular carcinoma study cohort(n=39694); 140 cases had brain metastases

Figure 1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Variables
OR (95% CI)
Female vs Male
0.92 (0.61, 1.39)
50-59 vs 18-49 (Age at diagnosis)
0.94 (0.48, 1.83)
60-69 vs 18-49
0.73 (0.37, 1.43)
70-79 vs 18-49
0.65 (0.31, 1.35)
80+ vs 18-49
0.75 (0.34, 1.66)
African-American vs Caucasian
1.00 (0.63, 1.59)
Other vs Caucasian
0.70 (0.40, 1.21)
Unknown vs Caucasian
1.29 (0.17, 9.55)
2013-2015 vs 2010-2012
1.06 (0.76, 1.48)
AFP-Positive vs AFP-Negative
0.92 (0.56, 1.52)
Other vs AFP-Negative
1.41 (0.83, 2.39)
T2 vs T1 (Primary tumor stage)
0.96 (0.43, 2.14)
T3 vs T1
0.76 (0.35, 1.64)
T4 vs T1
0.64 (0.21, 1.96)
Tx vs T1
1.06 (0.43, 2.62)
2-5cm vs ≤2cm (Primary tumor size)
1.08 (0.49, 2.39)
>5cm vs ≤2cm
1.38 (0.62, 3.08)
Unknown vs ≤2cm
1.52 (0.65, 3.52)
Multiple lesions vs Single lesion
1.18 (0.59, 2.34)
NOS vs Single lesion
1.26 (0.56, 2.83)
Lung or bone vs None
12.62 (8.40, 18.97)
Lung and bone vs None
28.97 (16.23, 51.74)
Unknown vs None
25.98 (13.38, 50.43)
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16
52
b
Variables
OR (95% CI)
Female vs Male
0.94 (0.62, 1.42)
50-59 vs 18-49 (Age at diagnosis)
0.98 (0.50, 1.91)
60-69 vs 18-49
0.77 (0.39, 1.52)
70-79 vs 18-49
0.67 (0.32, 1.40)
80+ vs 18-49
0.80 (0.36, 1.77)
African-American vs Caucasian
1.05 (0.66, 1.68)
Other vs Caucasian
0.76 (0.44, 1.31)
Unknown vs Caucasian
2.22 (0.28, 17.25)
2013-2015 vs 2010-2012
1.11 (0.79, 1.55)
AFP-Positive vs AFP-Negative
0.84 (0.50, 1.38)
Other vs AFP-Negative
1.27 (0.75, 2.16)
T2 vs T1 (Primary tumor stage)
0.78 (0.34, 1.79)
T3 vs T1
0.54 (0.26, 1.13)
T4 vs T1
0.38 (0.13, 1.14)
Tx vs T1
0.79 (0.32, 1.90)
2-5cm vs ≤2cm (Primary tumor size)
0.93 (0.41, 2.10)
>5cm vs ≤2cm
0.69 (0.31, 1.53)
Unknown vs ≤2cm
0.78 (0.34, 1.77)
Multiple lesions vs Single lesion
1.07 (0.54, 2.12)
NOS vs Single lesion
1.09 (0.49, 2.43)
Lung or bone vs None
0.80 (0.55, 1.18)
Lung and bone vs None
1.88 (1.08, 3.30)
Unknown vs None
3.64 (1.87, 7.08)
.125
1
4
18

Figure 2

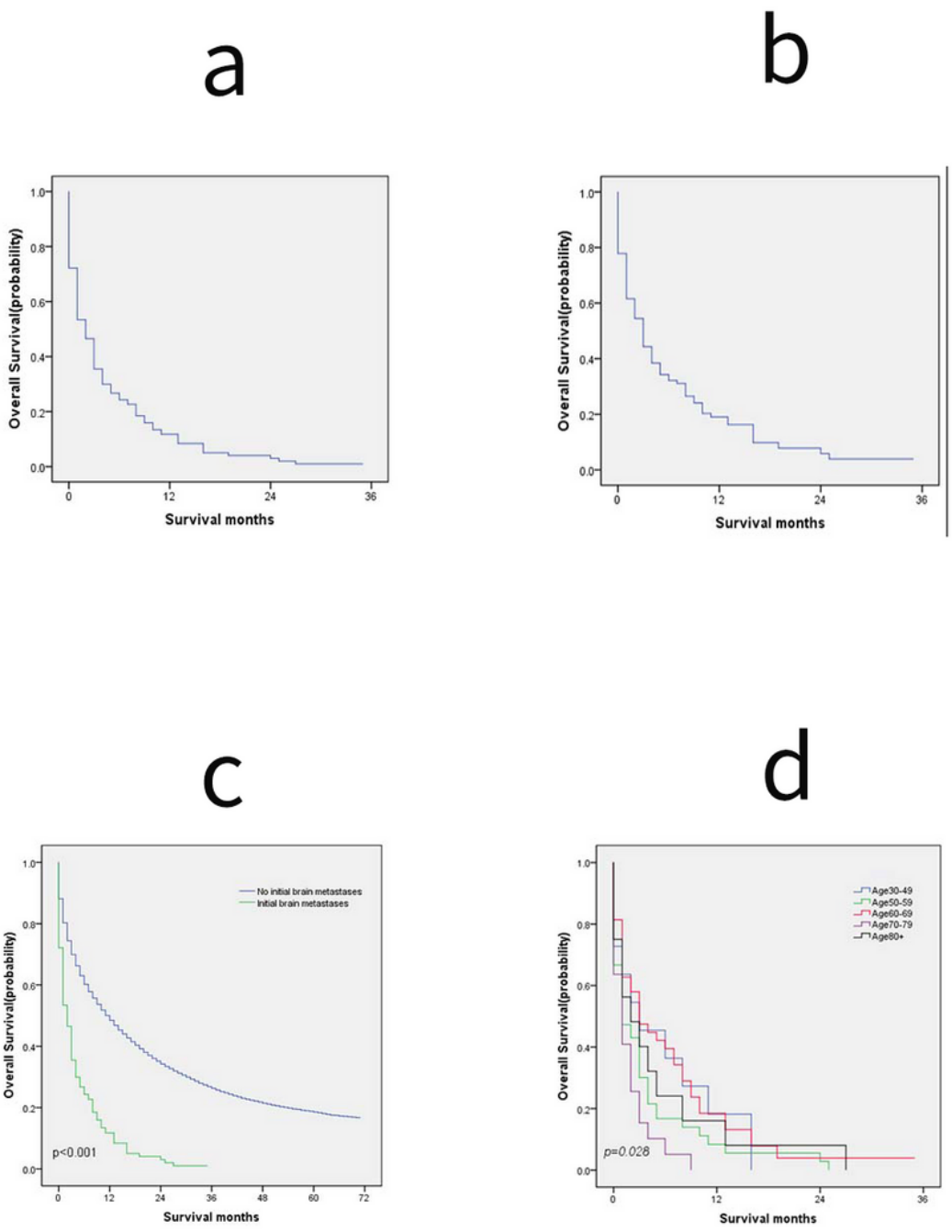

Figure 3

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable.docx