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Review Article

Merged hepatopulmonary features in hepatoid adenocarcinoma of the lung: a systematic review

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Abstract: This study aimed to provide diagnostic clues for patients with elevated serum alpha-fetoprotein (AFP) in the absence of liver tumors and rectify some previously confused concepts about hepatoid carcinoma of the lung through a systematic review on hepatoid adenocarcinoma of the lung (HAL). A thorough search for original articles on HAL published prior to November 2020 was performed using the PubMed, EBSCOhost, Embase, WanFang Data, and China National Knowledge Infrastructure (CNKI) databases. Ninety-four patients from 88 studies met the eligibility criteria. HAL was rare and mainly occurred among male Asian smokers in their 60 s, presenting with cough, hemoptysis, chest pain, dyspnea and/or weight loss, as well as elevated serum AFP with a mass usually in the right upper lung lobe but no liver masses. Hepatoid differentiation regions, acinar or papillary structures in tumor tissues, and positive immunohistochemical expression of AFP, HepPar-1, and CK8/18 were crucial indicators for the diagnosis of HAL. Surgery-based strategies were recommended for stage I-III patients, while stage IV patients were mainly treated with chemotherapy-based strategy. The 1-, 3-, and 5-year overall survival rates were 40%, 35%, and 19%, respectively. The 1-year relapse-free survival rate was 58%. The postoperative monitoring of AFP contributed to the early detection of tumor recurrence, with a positive rate of 71.43%. In conclusion, patients with elevated serum AFP levels without any detectable hepatic lesions should be evaluated for the possibility of HAL.

Keywords: Pulmonary hepatoid adenocarcinoma, rare disease, alpha-fetoprotein

Introduction

Elevated serum alpha-fetoprotein (AFP) is usually associated with hepatocellular carcinoma (HCC) and some germ cell tumors. For patients with elevated AFP but no liver masses, what other diagnoses should be considered? Hepatoid adenocarcinoma (HAC) is a kind of extrahepatic malignant tumor similar to HCC, demonstrating both adenoid- and hepatocyte-like differentiation on immunohistochemical analysis. As a rare neoplasm, hepatoid adenocarcinoma of the lung (HAL) accounts for 2.3%-5% of all HACs [1, 2]. Ishikura H et al [3] first put forward the concept of HAL in 1990, using two essential criteria for the diagnosis of HAL: 1) a mixture of tubular or papillary adenocarcinoma with a sheet-like or trabecular proliferation of neoplastic cells; and 2) a cancerous component producing AFP, with morphological similarity to HCC. However, later reports described HAL with components of neuroendocrine carcinoma or signet-ring cells [4-6], and morphology and immunophenotyping could support the diagnosis of HAL in AFP-negative patients [7-10]. In 2014, Haninger DM et al [11] proposed modified diagnostic criteria for HAL as follows: 1) the tumor can be pure HAC or have a component of typical acinar or papillary adenocarcinoma, signet-ring cells or neuroendocrine carcinoma; and 2) AFP elevation is not mandatory as long as other markers of hepatic differentiation are expressed.

Heretofore, HAL was usually described in case reports, with summaries mainly focused on English literature, lacking a systematic review on multilingual literature. In some previous reports, HAL was conceptually confused with hepatoid carcinoma of the lung [12-15]. Therefore, we aimed in this review to include and analyze all eligible cases using Haninger's

diagnostic criteria to provide more information about the clinical manifestation, management and prognosis of this rare disease.

Patients and methods

Search strategy

Studies on HAL were identified by searching electronic databases and scanning the reference lists of relevant articles. No limits were applied for language, and foreign papers were translated. The MESH search terms "hepatoid or AFP", "adenocarcinoma" and "lung or pulmonary" were used. This search was applied in PubMed, EBSCOhost, Embase, WanFang Data, and China National Knowledge Infrastructure (CNKI). The last search was run on 5 November 2020.

Inclusion and exclusion criteria

The inclusion criteria consisted of the following: 1) HAL confirmed by pathology or clinical diagnosis based on the criteria proposed by Haninger DM et al in 2014 [11]; and 2) HAL mentioned in the title or full text. In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16], we did not impose language restrictions on the eligibility criteria.

The exclusion criteria were as follows: 1) duplicate data; 2) patients with simultaneous liver metastases; 3) other pathological subtypes such as fetal adenocarcinoma of the lung (FLAC), large cell lung carcinoma, pulmonary squamous cell carcinoma (SCC), small cell lung cancer (SCLC), and unclassified non-small cell lung cancer (NSCLC); and 4) patients with excessive missing data.

Data extraction

The data extracted from each study included the authors' names, case reporting country, publication year, characteristics of the patients (sex, age, smoking history, liver and other medical history), symptoms, tumor information (location, size, tumor markers, clinical and pathological stages, and immunohistochemical and genetic testing), treatment and prognosis (relapse and cause of death). The relevant data were extracted from all the papers by two review authors (Jia-Xi Mao and Yuan-Yu Zhao) and checked by the another two authors (Cong Liu and Ji-Qing Ma) after full-text assessment, with the aid of two professional translators, to achieve a complete understanding of each paper and reduce selective reporting bias.

Statistical analysis

The data were analyzed using SPSS 22 software (IBM, Armonk, NY, USA). Quantitative variables with a normal distribution are expressed as the mean ± standard deviation. Nonnormally distributed variables are represented as the median (minimum-maximum). Postoperative survival was calculated using the lifetable method. Univariate and multivariate analyses of overall survival (OS) and relapse-free survival (RFS) were assessed using Cox proportional hazards regression models. The differences in survival times were compared using the log-rank test. A p-value <0.05 was considered statistically significant.

Results

General information

Eighty-eight studies meeting the eligibility criteria were included in the systematic review, including 46 reports in English, 29 in Japanese, 12 in Chinese and one in Korean. The flow diagram of the study selection process is presented in **Figure 1**. A total of 94 patients were enrolled for analysis and their characteristics are summarized in **Table 1** [1, 2, 5-7, 10-15, 17-73].

The 94 included patients comprised 86 men and 8 women (male-to-female ratio of 10.75:1), with an average age of 61.98±9.97 years. The regional distribution of the patients is shown in **Figure 2**, with most patients in Asia. Of these 94 patients, 44 had a history of smoking (Brinkman index = 160-4000 number per day × years, with a median of 800 number per day × years), 6 had no history of smoking, and the smoking history of the other 44 patients was not mentioned in the original studies. Six patients had a history of alcohol consumption, 3 patients were diagnosed with diabetes, and 1 patient had a history of multiple drug abuse. Other past and family histories are shown in **Table 1**.

The patients were initially admitted because of cough (30/94), hemoptysis/bloody sputum (14/94), chest or intercostal pain (13/94), dys-

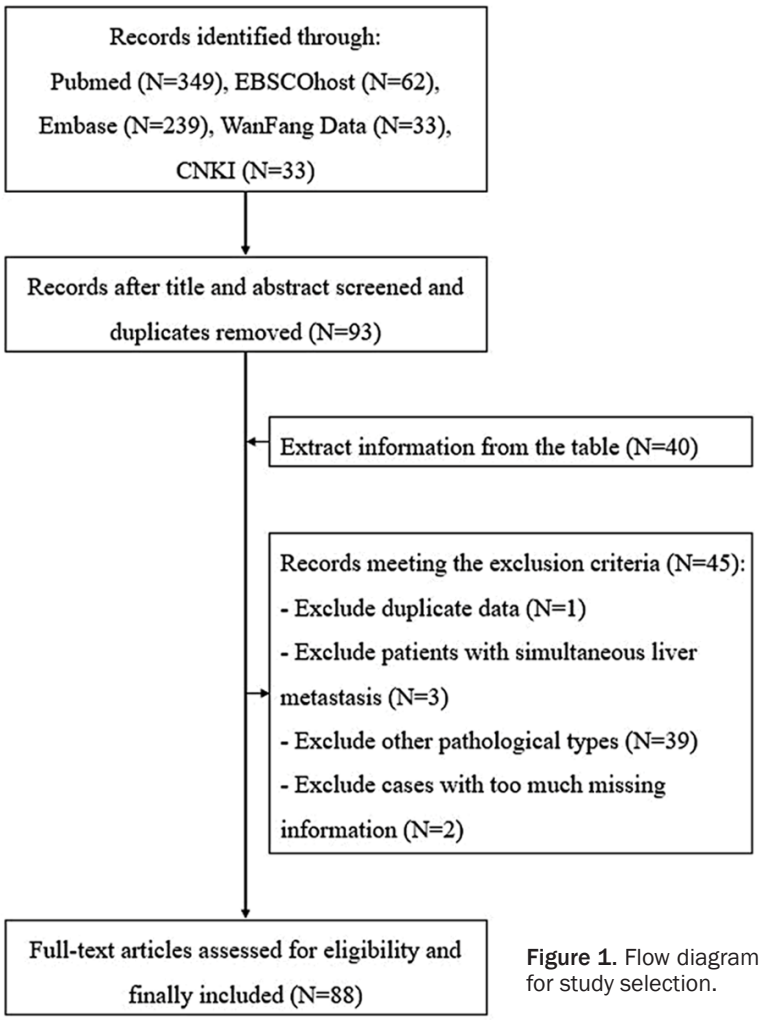

Figure 1. Flow diagram for study selection.

pnea (12/94), weight loss (10/94), sputum (9/94), shoulder or back pain (7/94), and/or asthenia (5/94), occasionally accompanied by numbness of the extremities (4/94), epigastric discomfort (3/94), fever (2/94), aphasia (2/94), headache (2/94), hearing loss (1/94), loss of balance (1/94), oedema (1/94), constipation (1/94), hoarseness (1/94), or dysphagia (1/94) (**Table 1**).

Tumor information

Except for 19 patients without concrete location information, 46 patients developed tumors in the right lung (29 in the right upper lobe, 4 in the right middle lobe and 13 in the right lower lobe), 26 patients developed tumors in the left lung (18 in the left upper lobe and 8 in the left lower lobe), and 3 patients presented with bilateral lung tumors. The maximum tumor diameter ranged from 1 cm to 20 cm, with a median of 6 cm.

According to the American Joint Committee on Cancer (AJCC) 8th edition of cancer staging, 8 patients were classified as stage I, 8 as stage II, 28 as stage III, and 26 as stage IV, while 24 patients could not be staged due to incomplete information.

An analysis of tumor markers demonstrated that HAL could be positive for AFP (83.10%), CA724 (75.00%), CA19-9 (62.50%), CEA (44.12%), HCG (37.50%), CYFRA21-1 (25.00%) and NSE (11.76%) but negative for SCC, CA153, ferritin, Pro-GRP, PSA, CA125, SLX, TPA, HSP, and PIVKA-II (Supplementary Table 1).

Pathology

In gross appearance, the tumors were solid and grey-white/white (11/2 cases) at the section, soft/firm/brittle (6/5/1 cases) in texture, irregular in shape (1 case), with necrotic areas (8 cases), clear/unclear boundaries (2/1 cases), and no capsule (1 case).

Microscopically, the tumors could either be pure HACs or have a component of typical acinar or papillary adenocarcinoma, signet-ring cells or neuroendocrine carcinoma. In terms of pathomorphology, we divided HAL into two types: typical and atypical. In typical type, both adenocarcinoma and hepatocyte-like components were easy to be identified under microscopy. While in atypical type, the adenocarcinoma and/or hepatocyte-like components needed to be further confirmed by immunohistochemistry due to the unclear morphology. Except for 29 cases with unclear pathomorphological classification, 27 cases were typical HAL and 38 cases were atypical HAL. Among the 48 cases with descriptions of tumor differentiation, 5 were well-differentiated, 7 were

Table 1. Previously reported cases on hepatoid adenocarcinoma of the lung (HAL)

No	Author/ Year	Centre	Sex/ Age	Smoking history (pack-year)	Liver disease and other history	Symptom	Location/ Size (cm)	Tumor markers	AJCC 8th Edition Stage	Pathological type		Immunohistochemistry		Gene mutation	Treatment	Tumor relapse site	Prognosis/ Cause of death
										Morphology	Differentiation	Positive (+)	Negative (-)				
1	Tanabe H, 1979	Japan	M/67	N/A	N/A	N/A	LUL/N/A	AFP↑	N/A	N/A	P	AFP	N/A	N/A	O	N/A	18 mo alive
2	Kodama T, 1980	Japan	M/73	N/A	N/A	N/A	RML/5.5	AFP↑	N/A	N/A	P	AFP	N/A	N/A	O	N/A	16 mo dead/N/A
3	Morino H, 1980	Japan	M/68	N/A	N/A	N/A	LUL/N/A	AFP↑	N/A	N/A	M	AFP	N/A	N/A	R	N/A	16 mo dead/N/A
4	Yasunami R, 1981 [17]	Japan	M/67	N/A	N/A	Back pain	LUL/8	AFP↑, CEA↑	pT4N0M0 (IIIA)	Atypical	P	AFP, A1AT, A1ACT, CEA	HepPar-1	N/A	R, Immuno, C	Duodenojejunal flexure, bones (8 mo)	16 mo dead/ peritonitis
5	Nakano M, 1984	Japan	M/70	N/A	N/A	N/A	RLL	AFP↑	N/A	N/A	P	N/A	N/A	N/A	C, R	N/A	4 mo dead/N/A
6	Nishimura, 1985	Japan	F/47	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	O	N/A	16 mo alive
7	Miyake M, 1986 [18]	Japan	M/55	N/A	Pleurisy, subtotal gastrectomy, family history of malignant lymphoma	Cough, back pain	RUL/5	AFP↑, CEA→	pT4N2M1c (IVB)	Atypical	P	AFP	N/A	N/A	O	No	0.13 mo dead/respiratory failure
8	Satake, 1986	Japan	M/78	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
9	Tamura T, 1986 [19]	Japan	M/80	41.25	N/A	Bloody sputum, dyspnea, fever	LLL/4.1×3.5	AFP↑, CEA→	cT4N3M1a (IVA)	Atypical	P	AFP	N/A	N/A	C	No	36 mo alive
10	Yoshida, 1986	Japan	M/66	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	W	/	N/A	N/A	O	N/A	7 mo dead/N/A
11	Miyake M, 1987 [20]	Japan	M/73	N/A	N/A	Bloody sputum	LUL/5×6×5	AFP↑, β-hCG↑	pT3N2M0 (IIIB)	Atypical	P	AFP, A1AT, A1ACT, CEA, HCG	N/A	N/A	O, R	Brain (16 mo)	18 mo dead/ heart failure
12	Sugiyama, 1987	Japan	M/37	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	C	N/A	4 mo dead/N/A
13	Tsuji H, 1987 [21]	Japan	M/60	44	Family history of esophageal cancer, uterine cancer, lung cancer	Cough, chest pain	RML/13×11×8	AFP↑, CEA→	pT4N2M0 (IIIB)	Atypical	P	AFP	N/A	N/A	O, C, R	Brain (3 mo)	4 mo dead/ relapse

14	Tsuji H, 1987	Japan	M/57	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	M	N/A	N/A	N/A	O, C	N/A	60 mo dead/N/A
15	Yamanaka, 1987	Japan	M/73	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	W	N/A	N/A	N/A	O	N/A	0.067 mo dead/N/A
16	Kizuka, 1988	Japan	M/64	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	O, R	N/A	6 mo dead/N/A
17	Saka H, 1988 [22]	Japan	M/73	N/A	N/A	Cough, sputum	RUL/3.9×3×3	AFP↑, CA19-9→, CEA→	pT2aN0M0 (IB)	Atypical	W	AFP	HCG	N/A	O	No	28 mo alive
18	Kawashima, 1989	Japan	M/57	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	M	N/A	N/A	N/A	O	N/A	1 mo alive
19	Kawashima, 1989	Japan	M/62	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	O	N/A	1 mo alive
20	Kurimoto I, 1989 [23]	Japan	M/75	40	Acute myocardial infarction (AMI), DM	Cough, dyspnea	RUL/5	AFP↑, elastase-1↑, β-hCG↑, NSE→, SCC→	cT3N2M0 (IIIB)	Atypical	P	AFP	N/A	N/A	N/A	N/A	N/A
21	Yokoi, 1989	Japan	M/72	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	O,R	N/A	16 mo alive
22	Matsutani, 1990	Japan	M/63	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	N/A	N/A	N/A	N/A	O,C	N/A	54 mo alive
23	Ogawa, 1990	Japan	M/82	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	O,R	N/A	18 mo alive
24	Sakuma, 1990	Japan	M/69	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	N/A	N/A	N/A
25	Tachibana, 1990	Japan	F/70	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	P	N/A	N/A	N/A	C,R	N/A	6 mo dead
26	Fujita, 1991	Japan	M/64	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	N/A	N/A	N/A	N/A	C	N/A	Dead/N/A
27	Nakajima, 1991	Japan	M/79	N/A	N/A	N/A	N/A	N/A	N/A	N/A	P	N/A	N/A	N/A	R	N/A	Dead/N/A
28	Matsutani, 1992	Japan	M/62	N/A	N/A	N/A	N/A	AFP↑	N/A	N/A	W	N/A	N/A	N/A	O	N/A	alive
29	Kubota M, 1994 [24]	Japan	M/53	N/A	Pulmonary tuberculosis	Bloody sputum	RML/13×10	AFP↑	pT4N0M0 (IIIA)	Typical	P	AFP	N/A	N/A	O	No	22 mo alive
30	Okano R, 1994 [25]	Japan	M/71	100	Pleurisy, family history of lung and gastric cancer	Shortness of breath, cough, expectoration, weight loss	RLL/multiple, 0.3-1	AFP↑, CEA→, NSE→, β-hCG→, PIVKA-II→	cT4N2M1b (IVA)	Atypical	P	N/A	AFP	N/A	C	No	4 mo dead/respiratory failure, septic shock

31	Hirabayashi H, 1995 [26]	Japan	M/57	N/A	Pulmonary tuberculosis, right plantar fracture	Cough, sputum	LLL/7.5×5	AFP↑, CEA↑	pT4N0M0 (IIIA)	Atypical	W	AFP	N/A	N/A	O	No	30 mo alive
32	Yoshino I, 1996 [27]	Japan	M/54	N/A	adenosquamous cell carcinoma of the lung (pT3N0M0, 5 yrs ago)	None	RUL/2	AFP↑, CEA↑, β-hCG→, NSE→, SCC→	pT1bN0M0 (IA2)	Atypical	P	AFP	N/A	N/A	O	No	24 mo alive
33	Hirota F, 1999 [28]	Japan	M/80	45	Gastric ulcer, gallstone	Headache, aphasia	RLL/5×4	AFP↑, CEA↑	pT2bN2M1b (IVA)	Atypical	M	AFP	N/A	N/A	C	No	10 mo alive
34	Wang CS, 1999 [29]	China	M/65	N/A	N/A	None	RML/3.5×3.0×2.5	N/A	pT2aN0M0 (IB)	Atypical	N/A	CEA, AFP	N/A	N/A	O	N/A	N/A
35	Carlinfante G, 2000 [30]	Italy	M/65	Yes	N/A	Cough, dyspnea	LLL/3.5	CEA→	pT2aN0M0 (IB)	Atypical	N/A	AFP, CEA, A1AT, A1ACT, surfactant, ISH, albumin mRNA	CgA	N/A	O	No	84 mo alive
36	Genova S, 2001 [31]	Plovdiv	M/71	N/A	N/A	Dyspnea, weight loss, asthenia	LUL/7.7×6.4	N/A	pT4N0M0 (IIIA)	Typical	N/A	AFP	N/A	N/A	O	No	24 mo alive
37	Hayashi Y, 2002 [12]	Japan	M/55	87.5	N/A	None	RUL/5×4.8×6.5	CEA↑, SCC→, CYFPA21-1→, NSE→, ProGRP→	pT3N0M0 (IIB)	Typical	N/A	AFP, HNF-4a	N/A	N/A	O	No	32 mo alive
38	Lino K, 2003 [32]	Japan	M/63	200	AMI	None	RUL/2.8×2.6×2.4	CEA→, SCC→, CYFPA21-1→, NSE→, ProGRP→	cT1cN0M0 (IA3)	Typical	P	AFP, Hep-Par-1	N/A	N/A	O	No	5 mo alive
39	Terracciano LM, 2003 [33]	Switzerland	M/49	N/A	N/A	Cough, dyspnea, epigastric discomfort	LLL/5	AFP↑	pT2bN0M0 (IIA)	Typical	N/A	AFP, CEA, CK8, CK18, CK19	HepPar-1, CK7, CK20	N/A	O	Liver, adrenal, brain, hilar lymph nodes (1.2 mo)	2 mo dead/ relapse
40	Oshiro Y, 2004 [34]	Japan	M/76	N/A	N/A	N/A	RLL/18×17×12	N/A	pT4N0M0 (IIIA)	Typical	P	AFP, PIVKA-II	N/A	N/A	O	Liver (12 mo), bone (18 mo)	18 mo dead/ multiple liver and bone metastasis
41	Bai CG, 2006 [13]	China	M/48	N/A	N/A	Back pain	LUL/7×5×4	AFP→, CA19-9→, CEA→	pT3N0M1b (IVA)	Atypical	P	CKpan (AE1/AE3), Hep-Par-1, AAT, prealbumin, albumin, CEA, p53	AFP, SP-A, CA19-9, INV, P63, NSE	N/A	O, C	No	9 mo alive

42	No EJ, 2006 [35]	Korea	M/64	40 yr	Pulmonary tuberculosis	Chest pain, hemoptysis	RUL/9×8	AFP↑, CEA↑, α-hCG→, PSA→	cT4N1M0 (IIIA)	Atypical	P	AFP, CK, CEA	N/A	N/A	C	No	1 mo alive
43	Ivan M, 2007 [36]	Canada	M/54	40	N/A	Hemoptysis, chest pain	LUL (13×11) + RUL (3.3×2.6)	AFP↑	pT4N2bM1b (IVA)	Typical	N/A	CK20, CEA, AFP, CD10	CK7, TTF-1, PLAP, CD34, CD30	N/A	C, R	No	N/A
44	Kishimoto T, 2008 [5]	Japan	M/64	N/A	N/A	N/A	LLL/7.5×7×4	AFP↑	cT4N0M0 (IIIA)	Atypical	N/A	HepPar-1, AFP, Syn, HNF-4a	CgA, NSE	N/A	O	No	N/A
45	Li CJ, 2008 [37]	China	M/65	N/A	Fatty liver	None	RLL/6	AFP↑, CEA→	cT4N2M1 (IVA)	Atypical	P	N/A	N/A	N/A	TACE, TCM	Lung (13 mo), liver (14 mo)	16 mo dead/ lung infection & respiratory failure
46	Wang PC, 2008 [14]	China	M/44	40	N/A	Extremities numbness, aphasia, cough, hemoptysis	RUL/10	AFP↑	cT4N2bM0 (IIIB)	Typical	N/A	HepPar-1	N/A	N/A	C, R	Brain (3 mo)	14 mo dead/ disease progression
47	Kim L, 2009 [38]	N/A	M/49	N/A	N/A	N/A	LUL/6	AFP↑	pT3N1M0 (IIIA)	N/A	N/A	N/A	N/A	N/A	O	N/A	N/A
48	Fornasa F, 2010 [8]	Italy	F/68	No	N/A	Shoulder pain	LUL/4.5×4×4	AFP→	pT2bN0M1 (IVA)	Typical	N/A	N/A	N/A	N/A	C	No	15 mo alive
49	Kitada M, 2011 [39]	Japan	M/69	90	Alcoholic hepatitis	Epigastric pain	RLL/6.5	AFP↑, CA19-9↑, CEA↑, β-hCG→, CYFPA21-1→, NSE→, ProGRP→, SLX→	pT3N2M0 (IIIB)	Atypical	M	AFP, CK18, CK19, HepPar-1	P53	N/A	O, C	No	12 mo alive
50	Mokrim M, 2012 [40]	Morocco	M/52	20	N/A	Dyspnea, chest pain, weight loss	LUL/11.8×12×8	AFP↑, β-hCG→	cT4N1M0 (IIIA)	Typical	N/A	CK20, AFP, CD10, HepPar-1	CK7, TTF-1, PLAP, CK5, CK6, CD30	N/A	C	No	7 mo alive
51	Papatsimpas G, 2012 [41]	Greece	M/48	N/A	N/A	Shoulder pain	RUL/20×11×8	AFP↑	cT4N2bM0 (IIIB)	Atypical	P	CK8/CK18, AFP, HepPar-1	CK7/CK20, TTF-1	N/A	C, R	Mediastinum (2 mo)	6 mo dead/respiratory failure
52	Valentino F, 2012 [42]	Italy	M/71	No	N/A	Intercostal pain	RLL/2.8 & 1.9	AFP↑, CA19-9↑, CEA→, NSE→	pT3N3M1b (IVA)	Typical	N/A	AFP, HepPar-1, 2, CK7, CK19	TTF1, CK20	N/A	C, R, O, bevacizumab	Adrenal, thoracic vertebral (10 mo)	14 mo dead/ opportunistic infection

53	Cavalcante LB, 2013 [6]	Brazil	M/66	40 yrs	N/A	Cough, dyspnea, respiratory complaints, recurrent pneumonia, weight loss	RLL/5×3	CEA↑, AFP→, β-hCG→	pT2bN0M0 (IIA)	Atypical	P	CK7, CEA, AFP, HepPar-1, TTF-1, CK5/6	CK20, CgA, Syn, P63, β-hCG	N/A	Supportive treatment	No	0.4 mo dead/pulmonary thromboembolism
54	Feng GW, 2013 [43]	China	M/46	N/A	Calcification of the right lobe of the liver, cholecystolithiasis	None	LUL/2.0×2.4	AFP↑, CEA→	pT1cN0M0 (IA3)	Atypical	P	HepPar-1, AE1/AE3, AFP, CK7, CK19, CD56, TTF-1	EP-10	N/A	O, C	No	6 mo alive
55	Che YQ, 2014 [15]	China	M/66	70	Hepatic hemangioma (1.5×1.5 cm)	Back pain	LUL/5.3×4.6 & 7.9×10.0	AFP↑, CEA→, CYFPA21-1→, NSE→, SCC→	pT4N0M0 (IIIA)	Atypical	N/A	CK7, AFP, AE1/AE3, CK18, Vim, HepPar-1	CK20, RCC, TTF-1	N/A	C, R	Hilar LN (2 mo)	36 mo dead/ lung infection
56	Haninger DM, 2014 [11]	USA	M/51	45	HCV (+), tuberculosis	Cough, congestion	RUL/4.2×3.7	N/A	cT2bN3M0 (IIIB)	N/A	N/A	CK5/6 (1/5), CK7 (3/5), CK8 (5/5), CK14 (0/5), CK18 (5/5), CK19 (4/5), CK20 (1/5), AFP (3/5), HepPar-1 (5/5), TTF-1 (5/5), HEA125 (5/5), MOC31 (5/5), CEA (3/5) ERb (5/5) ALK 1 (0/5) Napsin-A (1/5)		N/A	C, R, O	No	14 mo dead/ disease progression
57	Haninger DM, 2014 [11]	USA	M/52	40	HCV (+), emphysema, alcoholism	Chest pain, headaches, hearing loss, paresthesias, loss of balance	RUL/2.5	N/A	pT1cN0M1c (IVB)	N/A	N/A			N/A	O, C, R	No	37 mo alive
58	Haninger DM, 2014 [11]	USA	M/64	75	Emphysema and degenerative disc disease, family history of lung cancer	None	LUL/3.2×2.2	N/A	pT2aN0M1b (IVA)	N/A	N/A			EGFR (-)	O, C, R	Liver (N/A)	10 mo dead/ disease progression
59	Haninger DM, 2014 [11]	USA	F/54	35	N/A	Sternal border pain	LUL/1	N/A	pT1aN0M1b (IVA)	N/A	N/A			N/A	C, R, O	Lung, skull bone, mediastinal LN, pericardium (48 mo)	108 mo alive
60	Haninger DM, 2014 [11]	USA	M/60	40	Emphysema	Emphysema, cough, weight loss, muscle spasms of right arm, hand and face	RUL/11.2×10.1×8.5	AFP↑	cT4N2M1b (IVA)	N/A	N/A			N/A	C, R	No	1 mo alive

61	Liu HY, 2014 [44]	China	M/64	20 yrs	N/A	Cough, hemoptysis	RLL/8×5.5×5.0	AFP↑, CA153→, CEA→, NSE→	pT4N0M0 (IIIA)	Typical	N/A	HepPar-1, AFP, CK8/18, CK19, CKpan, P53, CDX2, CK20	CD56,Syn, CgA, NSE, S-100, CK7, CK14, CK5/6, CK10/13, 34βE12, P63, PLAP, CD117, CD30, CD10, ALK, TTF-1, CEA, Napsin-A, Vim	N/A	O	No	6 mo alive
62	Shaib W, 2014 [45]	USA	F/53	40	Alcohol abuse, COPD, rheumatoid arthritis, pleuritis	N/A	RUL/9.5×9.0×8.0	AFP↑	pT4N0M0 (IIIA)	Typical	N/A	CK, CAM 5.2, HepPar-1, CD34, PTF-1	CK7, CK20	N/A	O, C	No	48 mo alive
63	Al-Najjar H, 2015 [46]	UK	M/71	30 yr, cease 28 yr	knee replacement due to osteoarthritis, T_2DM, cholecystectomy due to gallstones	Fatigue, weight loss, cough	RLL/multiple	AFP↑	cT4N3M1a (IVA)	Typical	N/A	MNF116, HepPar-1, Ber-EP4, CK7, TTF1	N/A	N/A	C	Spine (4 mo)	12 mo dead/relapse
64	Gavrancic T, 2015 [47]	USA	M/64	N/A	N/A	Hemoptysis	RUL/3.8×2.9	AFP↑	cT2aN2M1 (IVA)	Typical	N/A	AFP, HepPar-1, CK7, Napsin-A, TTF-1	CK5, CK6, CK20, histochemical mucicarmine	EGFR (-)	C, Sorafenib, R	Lung (3 mo); mediastinal/hilar/subcarinal LN, liver (after 3 cycles of vinorelbine and sorafenib)	11 mo dead/disease progression
65	Udovicic-Gagula D, 2015 [48]	Bosnia and Herzegovina	M/68	N/A	N/A	Chest pain, blood sputum	RUL/multiple (max = 8.5)	AFP↑	N/A	Atypical	N/A	CKpan, AFP, HepPar-1, hCG	N/A	no overrepresentation of 12p	C	N/A	N/A
66	Zhong MY, 2015 [49]	China	M/61	N/A	N/A	Cough, sputum, hemoptysis	LUL/5.7×4.3	AFP↑, CEA→	cT3NxM1c (IVB)	Atypical	N/A	AFP, AAT, CK7, TTF-1	P63, Syn, Vim, HepPar-1, CEA, CK20	N/A	C, R	No	alive without following time

67	Grossman Kate, 2016 [10]	USA	M/54	Yes	Polysubstance abuse	Cough, shortness of breath, hemoptysis, weight loss	RUL/5.1×4.1	AFP→,	cT3N0M1b (IVA)	Typical	N/A	HepPar-1, CK7, CAM 5.2 (CK8/18), CEA	AFP, CK20, P63, CDX-2, PSA, S-100, CgA, TTF-1	ALK (-), EGFR (-), K-ras (-)	C, R	Brain (2 mo)	3 mo dead/ brain metastasis & disease progression
68	Liu ZJ, 2016 [50]	China	M/59	N/A	N/A	Cough, sputum	RUL/4.5×3.5×3.5	CEA→, CYFPA21-1→, HSP→, NSE→	pT2bN0M0 (IIA)	Atypical	M	HepPar-1, CD3, CD10	AFP, CK8/18, TTF1, CD56, CgA, Syn, NapsinA	N/A	O	N/A	N/A
69	Qian GQ, 2016 [51]	China	M/79	50	N/A	Cough, sputum	RUL/2.7×2.6	AFP↑, CEA↑, CA153→, CA19-9→, CYFPA21-1→, NSE→	cT1cN0M0 (IA3)	Atypical	N/A	N/A	N/A	N/A	Erlotinib	No	0.83 mo dead/ lung infection
70	Sun JN, 2016 [52]	China	M/59	Yes (ceased 9 yrs)	Mild alcohol consumption; T_2DM for 8 years	Cough	RUL/4.5×3.5×3.5	CEA→, CYFPA21-1→, NSE→	pT2bN0M0 (IIA)	Atypical	P	HepPar-1, CD10, CD34	AFP, TTF-1, CK8/18, CD56, CgA, Syn, Napsin-A	N/A	O	No	23 mo alive
71	Wang S, 2016 [53]	China	M/56	N/A	N/A	None	RUL/4.0×4.1×4.8	N/A	cT4N1M0 (IIIA)	Atypical	N/A	AFP	/	N/A	N/A	N/A	N/A
72	Hou Q, 2017 [54]	China	M/59	Yes	N/A	Cough, bloody sputum	RUL/4.5×3.5×3.5	AFP→, CA153→, CEA→, NSE→	pT2bN0M0 (IIA)	Atypical	N/A	HepPar-1, CD10, CD34	GPC-3, CEA, AFP, CK8/18, TTF-1, CD56, CgA, Syn, Napsin-A	N/A	O	No	24 mo alive
73	Long ZH, 2017 [55]	China	M/50	40	N/A	Cough, hoarseness, chest pain, dysphagia, weight loss	LUL/N/A	AFP→, CEA→, NSE→, CA125→, CYFRA21-1→, Serum ferritin→	cTxN3M1c (IVB)	Typical	P	HepPar-1, CK7, CK8/18, CEA, Syn	Gly-3, TTF-1, Naspin-A, CK20, villin, AFP, S100, CgA, CD56	N/A	Supportive treatment	No	4 mo dead/ disease progression
74	Long ZH, 2017 [55]	China	M/58	30	N/A	Cough, sputum, fever, chest pain, weight loss	LLL/3.8×4.2×5.2	AFP→, CEA→, NSE→, CA125→, CYFRA21-1→, Serum ferritin→	cT3N3M1c (IVB)	Typical	N/A	Gly-3, AFP, CK, CD34	HepPar-1, CK7, TTF-1, P63, Syn, CgA	N/A	Anti-infection	N/A	18 mo alive

75	Basse V, 2018 [56]	France	M/43	8	Lynch syndrome and lieberkuhnian adenocarcinoma (treated at 31 years with no relapse)	N/A	N/A	N/A	cTxN3M1c (IVB)	Atypical	N/A	CK7, 19, 20, HepPar-1, CEA, TTF-1	caudal type homeobox 2 protein, Programmed death ligand 1 (PD-L1)	EGFR (-), KRAS (-), ALK (-), ROS1 (-), a loss of expression of mutL homolog 1 and PMS1 homolog 2	C, durvalumab anti-PD-L1 therapy	No	dead without following time/ infectious complications
76	Esa NYM, 2018 [57]	Malaysia	M/50	40	Family history of breast malignancy	Shoulder pain, numbness and weakness of arm	LUL/6×5×6	AFP↑	IIIB	Typical	P	CK, AE1/3, HepPar-1, TTF-1, CK7	CK20, AFP, Napsin-A, S-100, PLAP, P63	N/A	R, C	No	7 mo dead/ disease progression, sepsis, shock
77	Li Q, 2018 [58]	China	M/52	60	N/A	Cough, bloody sputum	RUL/N/A	CA19-9↑, CA724↑, CEA↑, AFP→	cT2N2M0 (IIIA)	Atypical	N/A	HepPar-1, CK, CK19	TTF-1, Napsin-A, P63, P40, CK5/6, GATA-3, Gly-3, Arg, Vim	N/A	C, R	Brain (1 mo)	2 mo dead/pulmonary thromboembolism
78	Nakashima K, 2018 [59]	Japan	M/60	40	Emphysema, sinusitis	None	RUL/6.3×4.8	AFP↑, CEA↑	pT3N0M0 (IIB)	Atypical	N/A	HepPar-1, TTF-1	/	N/A	O	No	8 mo alive
79	Ruiz CD, 2018 [60]	N/A	F/69	70	N/A	Cough, dyspnea, weight loss	LUL/8×8×5	AFP→	cT4N1M0 (IIIA)	Atypical	N/A	CK7, HepPar-1	CK20, CK5/6, P63, TTF-1	N/A	R	Adrenal (1 mo)	1 mo dead
80	Ayub A, 2019 [61]	USA	M/61	40	COPD	N/A	RUL/2.3	N/A	pT1cN0M0 (IA3)	Typical	M	TTF-1, HepPar-1, CK7, CK8, CEA, CK19	AFP, P40, Napsin-A, CD10	N/A	O, R	Spine and sacrum (3 mo)	6 mo dead/ disease progression
81	Barbara CD, 2019 [62]	N/A	M/63	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	EGFR (-), ALK(-)	C, R, nivolumab	Skin (N/A)	7 mo dead/ disease progression
82	Chen HF, 2019 [1]	China	M/53	no	N/A	Cough, phlegm, fever	RUL/5.3×3.5	AFP↑	pT3N0M0 (IIB)	Atypical	N/A	TTF-1, HepPar-1, AFP, CK	Napsin-A, CK5/6, P63, CD56, Syn	EGFR p.L747_P753delinsS; EGFR exon 20 T790M mutation	O, C, icotinib, R, osimertinib, anlotinib	Pleural effusion, bone (9 mo), brain (21 mo)	36 mo alive

83	Chen Y, 2019 [63]	China	M/47	45	N/A	Chest pain, cough, dyspnea, fatigue	RLL/9.7×6.1×6.9	AFP→	cT4N3M1c (IVB)	Atypical	N/A	CK7, Hep-Par-1, AFP	PAX8, CK5/6, TTF-1	/	C	No	2 mo dead/ disease progression
84	El Khoury A, 2019 [64]	UK	M/59	>30	Family history of colon cancer	Chest pain	RUL/9.3×7.2×6.8	CEA↑, AFP→	cT4N2M1b (IVA)	Typical	P	CK7, Hep-Par-1	TTF1, CK5/6	EGFR (-), ALK (-), BRAF w/t. ROS-1 (-), PDL1≥50%	C	No	14 mo alive
85	Fan XL, 2019 [65]	China	M/70	120	Fatty liver, alcohol abuse	Cough, bloody sputum	LLL/6.0×6.0×1.5	CEA↑, CYFPA21-1↑, NSE↑	pT3N1M0 (IIIA)	Atypical	N/A	HepPar-1, CKpan, AFP, CEA, CD34, Syn	Agr-1, SALL-4, CK7, TTF-1, Napsin-A, P40, P63, P53, EGFR, ALK, CD56, CD31, D2-40	N/A	O	No	23 mo dead/ lung infection & respiratory failure
86	Kuan K, 2019 [66]	USA	M/47	Yes	N/A	Chest pain, fatigue, edema	RUL/14	N/A	cT4N0M0 (IIIA)	Typical	N/A	CK7, EMA, CEA, Hep-Par-1	TTF-1, Napsin-A, CK20, AFP	EGFR (-), ALK (-),PD-L1 (high)	O	Malignant pleural effusion (1 mo)	4 mo dead/ relapse
87	Li J, 2019 [67]	China	M/71	No	N/A	Stomachache, fatigue, constipation	RLL/7×4.5	AFP↑	cT3N3M1b (IVA)	Typical	P	CK, SALL-4, CK18, CK8, CK7, AFP, HepPar-1, STAT-6, CD117	CK20, P63, P40, CK5/6, Syn, CD56, CgA, Vim, Calretinin, TTF-1, Napsin-A, CD34, D2-40, ALK, PD-L1	EGFR, ALK, ROS1, PD-L1, BRAF, HER2, KRAS, MET, RET-Wild type; FAT1-Mutated, Copy number loss; MSI-Stable; TMB-1.69 mutations/Mb	R	No	5.5 mo dead/respiratory failure
88	Malik SA, 2019 [68]	N/A	F/56	Yes	N/A	Shortness of breath	RLL/2×2	AFP→	N/A	N/A	N/A	CK7, HepPar-1, MOC31, Napsin-A	TTF1, CK20, CDX2, GATA3, S-100	N/A	N/A	No	2 mo dead/ multi-organ failure, septic shock

89	Shi YF, 2019 [69]	China	M/60	No	HBcAb (+), HBeAb (+), HbsAb (+), esophageal polypectomy, gastric ulcers	Cough, sputum	RUL/7× 7×5	AFP↑, CA153→, CA724→, CEA→	pT3N2M0 (IIIB)	Atypical	N/A	EGFR, CK-pan, CK18, Napsin-A, CK8, CD117, HepPar-1	TTF-1, Syn, CgA, PD-1, PAS, Villin, Vim, CK7	N/A	O, C	No	15 mo dead/ disease progression
90	Wang C, 2019 [70]	China	M/70	50	N/A	None	RUL/6.0× 4.6	N/A	cT3N2M0 (IIIB)	Typical	N/A	HepPar-1, CK, EA, CDX-2	AFP, TTF-1, Napsin-A, P63, P40, CD56, Syn	TP53 mutation	C, R, bevacizumab	Gingiva, submandibular LN (3 mo)	9 mo dead/ disease progression
91	Wang XP, 2019 [71]	China	M/48	Yes	N/A	Cough, shortness of breath	LUL/multiple	AFP↑, CA19-9↑, CA724↑, NSE↑	cT4N3M1a (IVA)	Typical	N/A	AFP, HepPar-1, Arg-1	P40, CK5/6, P63, TTF-1, ALK, CgA, Syn, CD56, PGP9.5, Napsin-A	EGFR (-), ALK (-), ROS1 (-), KRAS (-), BRAF (-)	C	Bone (N/A)	12 mo alive
92	Yang K, 2019 [2]	China	M/70	120	Alcoholic intake over 30 years	Cough, bloody sputum	LLL/6× 6×5.5	CEA↑, CYFPA21-1↑	pT3N1M0 (IIIA)	Typical	P	HepPar-1, CKpan, CK8/18, CK19, MOC31, AFP, CEA, CD34	Arg-1, SALL-4, CK5/6, CK7, CK14, CK20, Syn, CD56, TTF-1, Napsin-A, P40, P63, P53, EGFR, ALK	N/A	O	Multiple organ distant metastases (18 mo)	18 mo dead/ multiple organ failure caused by distant metastases
93	Chen JX, 2020 [72]	China	M/63	N/A	N/A	Lumbar soreness, skin tear sensation	LLL+RUL/ N/A	CEA↑, CA19-9↑, CA724↑, CYFPA21-1↑	pT4N3M1c (IVB)	Atypical	P	N/A	N/A	N/A	N/A	No	4 mo dead/ multiple organ failure caused by distant metastases
94	Chen LL, 2020 [73]	China	F/65	No	N/A	N/A	Left lobe (7×5.1) + Right lobe (9.2×4.6)	AFP↑	pT4NxM1b (IVA)	Typical	N/A	SALL4, AFP, GPC3, CK7, Villin	TTF, Napsin-A, HepPar-1	ALK (-), EGFR (-), KRAS hotspot G12V (c. 35G>T) mutation	C, bevacizumab, anlotinib, Sintilimab	No	52 mo dead/ interstitial pneumonia

A1AT, α1-antiitrypsin; A1ACT, α1-antichymotrypsin; AFP, α-fetoprotein; ALK, anaplastic lymphoma kinase; AMI, acute myocardial infarction; Arg, arginase; β-hCG, beta-human chorionic gonadotropin; BRAF, b-rafproto-oncogene; C, chemotherapy; CD, cluster of differentiation; CEA, carcinoembryonic antigen; CgA, chromogranin A; CK, cytokeratin; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen; FAT, FAT atypical cadherin1; Gly-3, glypican-3; HepPar-1, hepatocyte paraffin 1; HER2, human epidermal growth factor receptor 2; LLL, left lower lobe; LN, lymph node; LUL, left upper lobe; MSI, microsatellite instability; mo, month; N/A, not mentioned; NCAM, neural cell adhesion molecule; NSE, neuron-specific enolase; O, operation; P53, protein 53; PD-L1, programmed death ligand 1; R, radiotherapy; RCC, renal cell carcinoma; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SALL-4, spalt like transcription factor 4; STAT-6, signal transducer and activator of transcription 6; Syn, synaptophysin; T_2DM, type-2 diabetes mellitus; TACE, transarterial chemoembolization; TCM, traditional Chinese medicine; TMB, tumor mutation burden; TTF-1, thyroid transcription factor-1; VEGF, vascular endothelial growth factor; Vim, vimentin.

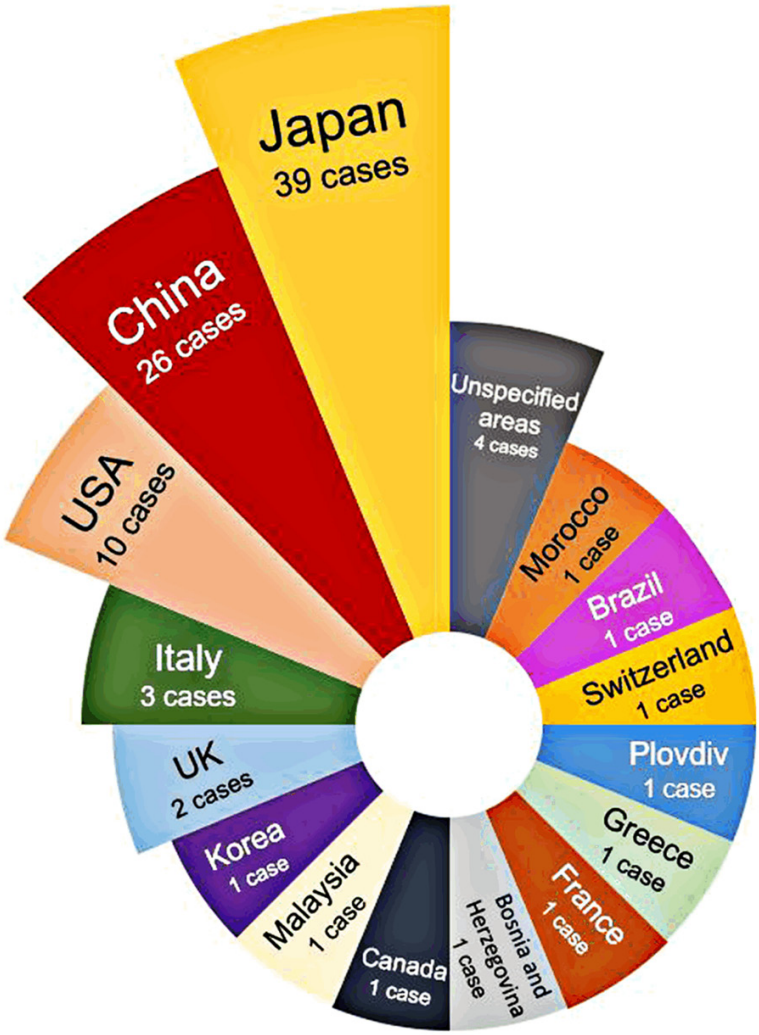

Figure 2. The geographical distribution of 94 patients with hepatoid adenocarcinoma of the lung.

moderately-differentiated, and 36 were poorly-differentiated.

Immunohistochemistry showed that HAL was positive for CKpan (AE1/AE3), MOC31, A1AT, Erb, and HEA125; mostly positive for CK19, HepPar-1, CK7, CK18, CK8, CEA, AFP, CD10, and CD34; partly positive for P53, TTF-1, CK20, Syn, Napsin-A, Vim, CK5, CK6, and CD56; and negative for P63, CgA, ALK, CK14, P40, and S-100 (**Table 2**). Additionally, the Ki67 index was reported at 20-80% in 12 cases, and the MIB-1 index was reported at 40% in 1 case.

Thirteen patients underwent genetic testing, which showed a highly enhanced expression of PD-L1 (2 cases) [64, 66], KRAS mutation (1 case of KRAS hotspot G12V c. 35G>T mutation) [73], EGFR mutation (1 case of EGFR p.L747_P753delinsS; EGFR exon 20 T790M mutation) [1], TP53 mutation (1 case) [70], and FAT1 and TMB mutation (1 case) [67], as well as wild type or negative status for EGFR (10 cases), ALK (8 cases), KRAS (4 cases), ROS1 (4 cases), BRAF (3 cases), PD-L1 (2 cases), HER2, MET and RET (1 case).

Treatment

The therapeutic methods for HAL varied among individual cases with different tumor stages and general conditions. These methods were categorized into three strategies. The first one was surgery-based strategy, which included surgery combined with or without chemotherapy, radiotherapy, targeted drugs or immunotherapy. The second one was chemotherapy-based strategy, which included chemotherapy combined with or without radiotherapy, targeted drugs or immunotherapy. Other therapeutic methods, including radiotherapy alone, targeted drug alone, TACE, traditional Chinese medicine and supportive treatment, were categorized as other strategies.

Surgery-based strategies were recommended for stage I-III patients, while stage IV patients were principally managed with chemotherapy-based strategy (Supplementary Table 2). Chemotherapy played an important role in the treatment of HAL and was also adopted in a surgery-based comprehensive therapy, especially in patients with high risk of relapse. The recommended chemotherapy regimen was platinum-based double or triple combination with gemcitabine, taxol or both.

Follow-ups

Among the 59 patients with elevated AFP, 3 patients had further increases in their AFP levels after treatment and were confirmed to have tumor relapse. Twenty patients experienced AFP reduction (including 12 patients with AFP

Table 2. Immunohistochemistry markers of hepatoid adenocarcinoma of the lung (HAL) (N≥5) compared with hepatocellular carcinoma (HCC)

Markers	HAL		HCC positive rate
	Positive/negative/N/A	Positive rate	
CKpan (AE1/AE3)	15/0/79	100.00%	75%-95%
MOC31	7/0/87	100.00%	Not typically performed
A1AT	5/0/89	100.00%	35%-55%
Erb	5/0/89	100.00%	Not typically performed
HEA125	5/0/89	100.00%	Not typically performed
CK19	13/1/80	92.86%	5%-15%
HepPar-1	42/4/48	91.30%	75%-95%
CK7	15/3/76	83.33%	15%-35%
CK18	15/3/76	83.33%	75%-95%
CK8	14/3/77	82.35%	75%-95%
CEA	19/5/70	79.17%	55%-75%
AFP	47/13/34	78.33%	35%-55%
CD10	5/2/87	71.43%	55%-75%
CD34	5/2/87	71.43%	75%-95%
P53	2/3/89	40.00%	15%-35%
TTF-1	15/24/55	38.46%	<5%
CK20	5/20/69	20.00%	5%-15%
Syn	3/12/79	20.00%	5%-15%
Napsin-A	4/19/71	17.39%	5%-15%
Vim	1/5/88	16.67%	5%-15%
CK5	2/15/77	11.76%	<5%
CK6	2/15/77	11.76%	5%-15%
CD56	1/11/82	8.33%	5%-15%
P63	0/14/80	0.00%	<5%
CgA	0/12/82	0.00%	Not typically performed
ALK	0/10/84	0.00%	<5%
CK14	0/7/87	0.00%	Not typically performed
P40	0/7/87	0.00%	<5%
S-100	0/5/89	0.00%	5%-15%

levels decreased to the normal range 0.33-6 months after treatment, with a median time of 1.5 months), while AFP levels were not reported for 36 patients after treatment.

The survival status of 12 patients was not described in the original reports, while 37 patients were alive and 45 died in 2 days-108 months of follow-up after treatment. The 1-, 3-, and 5-year OS rates were 40%, 35%, and 19%, respectively, with a median of 19.08 months (**Table 3**). The cause of death was not mentioned for 13 patients, and the remaining 32 patients died of disease progression or relapse (16 cases), infection (7 cases), respiratory failure (4 cases), respiratory failure combined with pulmonary infection (2 cases), pulmonary embolism (2 cases) or heart failure (1 case). Multivariate analysis showed that therapeutic method and tumor relapse correlated with OS (HR = 2.539, P<0.001; HR = 2.172, P = 0.034, respectively, **Table 4**).

During the follow-up period, 24 patients presented with tumor relapse, which was defined as recurrence after surgery or newly-occurred lesions after non-surgical treatments, 42 patients did not experience relapse, and 28 patients did not have relapse information, displaying 1-year RFS rate of 58% (**Table 3**). The tumor relapse sites consisted of bone (8 cases), brain (7 cases), liver (5 cases), lung (3 cases),

Table 3. Overall survival (OS) and relapse-free survival (RFS) rates of HAL patients

	Overall survival rate					Relapse-free survival rate				
	1-year	3-year	5-year	Median (year)	χ^2, P	1-year	3-year	5-year	Median (year)	χ^2, P
Sex					$\chi^2 = 1.190$, P = 0.275					$\chi^2 = 1.301$, P = 0.254
Male (N = 86)	37%	30%	15%	1.53		54%	54%	54%	7.00	
Female(N = 8)	63%	63%	38%	4.50		85%	85%	/	4.82	
AJCC 8th Edition stages*					$\chi^2 = 3.640$, P = 0.056					$\chi^2 = 1.526$, P = 0.217
Early (N = 16)	70%	70%	70%	7.00		76%	76%	76%	7.00	
Advanced (N = 54)	32%	26%	15%	1.45		47%	47%	/	1.86	
Pathomorphological classification**					$\chi^2 = 0.010$, P = 0.920					$\chi^2 = 1.141$, P = 0.286
Typical (N = 27)	36%	36%	/	1.50		35%	35%	/	1.62	
Atypical (N = 38)	42%	28%	28%	1.67		60%	60%	60%	7.00	
Pathological differentiation***					$\chi^2 = 1.353$, P = 0.508					$\chi^2 = 2.236$, P = 0.327
Well-differentiated (N = 5)	56%	/	/	2.00		100%	/	/	2.00	
Moderately-differentiated (N = 7)	49%	49%	0%	1.97		78%	/	/	1.00	
Poorly-differentiated (N = 36)	28%	28%	/	1.30		41%	41%	/	1.80	
Therapeutic methods****					$\chi^2 = 35.027$, P<0.001					$\chi^2 = 5.613$, P = 0.060
Surg (N = 49)	53%	53%	36%	5.18		66%	66%	40%	4.61	
Chemo (N = 30)	30%	18%	/	1.00		51%	51%	/	4.00	
Others (N = 8)	0%	/	/	0.75		0%	/	/	1.38	
Total (N = 94)	40%	35%	19%	1.59		58%	58%	39%	4.41	

Notes: *26 patients with unclear AJCC 8th Edition stage; **29 cases with unclear pathomorphological classification; ***45 cases with unclear pathological differentiation; ****7 patients with unclear therapeutic method. Chemo, chemotherapy-based strategy; Surg, surgery-based strategy.

Table 4. Uni- and multivariate analysis of risk factors affecting the overall survival (OS) of HAL patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (year)	0.990	0.961, 1.020	0.505			
Sex (M/F)	0.666	0.235, 1.888	0.445			
Smoking (Y/N)	1.286	0.441, 3.748	0.645			
Brinkman index (number per day × years)	1.000	1.000, 1.001	0.453			
Elevated AFP (Y/N)	0.564	0.242, 1.317	0.186			
Maximum diameter (cm)	1.043	0.956, 1.138	0.338			
AJCC 8th Edition stage (early/advanced tumor)	2.471	0.866, 7.052	0.091			
Pathomorphological classification (typical/atypical)	0.986	0.490, 1.983	0.968			
Pathological differentiation (well-/moderately-/poorly-differentiated)	1.252	0.619, 2.533	0.532			
Therapeutic method (Surg/Chemo/Others)	2.535	1.661, 3.867	<0.001	2.539	1.520, 4.240	<0.001
Tumor relapse (Y/N)	2.350	1.207, 4.576	0.012	2.172	1.060, 4.452	0.034

Notes: The variables with *P* value <0.1 in univariate analysis were included in multivariate analysis. AFP, alpha-fetoprotein; Chemo, chemotherapy-based strategy; F, female; HAL, hepatoid adenocarcinoma of the lung; M, male; N, no; Surg, surgery-based strategy; Y, yes.

Table 5. Uni- and multivariate analysis of risk factors affecting the relapse-free survival (RFS) of HAL patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (year)	0.987	0.944, 1.032	0.568			
Sex (M/F)	0.543	0.110, 2.671	0.452			
Smoking (Y/N)	1.337	0.297, 6.022	0.705			
Brinkman index (number per day × years)	1.000	0.999, 1.001	0.905			
Elevated AFP (Y/N)	0.994	0.279, 3.540	0.992			
Maximum diameter (cm)	1.110	1.002, 1.229	0.045	1.109	1.000, 1.228	0.049
AJCC 8th Edition stage (early/advanced tumor)	2.015	0.591, 6.866	0.263			
Pathomorphological classification (typical/atypical)	0.683	0.282, 1.653	0.398			
Pathological differentiation (well-/moderately-/poorly-differentiated)	2.145	0.445, 10.352	0.342			
Therapeutic method (Surg/Chemo/Others)	1.868	0.990, 3.525	0.054			

Notes: The variables with *P* value <0.1 in univariate analysis were included in multivariate analysis. AFP, alpha-fetoprotein; Chemo, chemotherapy-based strategy; F, female; HAL, hepatoid adenocarcinoma of the lung; M, male; N, no; Surg, surgery-based strategy; Y, yes.

adrenal gland (3 cases), hilar lymph node (3 cases), mediastinal lymph node (2 cases), malignant pleural effusion (2 cases), peritoneum (1 case), duodenojejunal flexure (1 case), mediastinum (1 case), gingiva (1 case), submandibular lymph node (1 case) and cutaneous metastases (1 case). The time to relapse ranged from 1 to 48 months (with a median of 3 months). Multivariate analysis showed that maximum tumor diameter was the only independent risk factor for tumor relapse (HR = 1.109, P = 0.049, **Table 5**). Among the 24 patients with tumor relapse, 5 presented with elevated AFP and 2 with AFP in normal range, while the AFP levels of 17 were not mentioned when relapse was confirmed, which resulted a positive predictive rate of AFP of 71.43% for the relapse of HAL after treatment.

The OS and RFS rates were analyzed separately in terms of sex, tumor staging, pathomorphology and pathological differentiation. The 1-, 3-, and 5-year OS rates of male patients were 37%, 30%, and 15%, respectively, with a median OS of 18.36 months and a 1-year RFS rate of 54%, while the 1-, 3-, and 5-year OS rates of female patients were 63%, 63%, and 38%, respectively, with a median OS of 54.00 months and a 1-year RFS rate of 85%. The 1-year OS rate of patients with early tumors (stage I-II) was 70%, with a median OS time of 84 months and a 1-year RFS rate of 76%. The 1-, 3-, and 5-year OS rates of patients with advanced tumors (stage III-IV) were 32%, 26% and 15%, respectively, with a median OS time of 17.40 months and a 1-year RFS rate of 47%. The 1-year OS rates for typical and atypical

tumors were 36% and 42%, with median survival times of 18.00 and 20.04 months and 1-year RFS rates of 35% and 60%, respectively. The 1-year OS rates for well-, moderately- and poorly-differentiated tumors were 56%, 49%, and 28%, with median OS times of 48.00, 23.64, and 15.60 months and 1-year RFS rates of 100%, 78% and 41%, respectively. The 1-year OS rate of patients using surgery-based strategy, chemotherapy-based strategy and other strategies were 53%, 30% and 0%, respectively and 1-year RFS rates of 66%, 51% and 0%, respectively (**Table 3**).

Among the patients using surgery-based strategy, the 1-year OS rates of typical and atypical HAL patients were 39% and 61%, respectively, while among those using chemotherapy-based strategy, the 1-year survival rates of typical and atypical HAL patients were 35% and 33%, respectively (Supplementary Table 3).

Hepatoid large cell carcinoma of the lung (HLCCL)

In previous studies, the pooled analyses of the pathological types of HAL were somewhat vague, and some other pathological types, especially large cell carcinoma, were mistakenly included as HAL. We established a preliminary definition of HLCCL as follows: 1) typical large cell carcinoma without glandular or squamous differentiation by morphology or immunohistochemistry; and 2) AFP expression is not mandatory to confirm the diagnosis as long as other markers of hepatic differentiation are expressed. The main difference between HAC and HLCCL is the morphological and immunohistochemical type.

We summarized data on previously reported HLCCL cases (**Table 6**) [4, 7, 9, 18, 26, 74-82], including 17 men and 2 women (male-to-female ratio of 8.5:1), with a mean age of 61.58±10.02 years. Aside from 5 patients without reporting concrete tumor location, the tumors in 10 patients were in the right lung (5 in the right upper lobe, 1 in the right middle lobe and 4 in the right lower lobe), and those in 4 patients were in the left lung (2 in the left upper lobe and 2 in the left lower lobe). The maximum tumor diameter ranged from 3.5 cm to 12 cm, with a median of 7.4 cm. Nine patients had a history of smoking (Brinkman index: 460-3000 number per day × years, with a median of 850 number per day × years), and the histories of the other 10 patients were not disclosed. Tumor markers were positive for AFP (89.47%), HCG (16.67%), and CEA (11.11%). Among the 17 patients with elevated AFP at admission to hospital, 2 had AFP increased after treatment and were confirmed as tumor relapse, 8 had AFP reduced, while 7 patients had AFP levels unreported after treatment. According to the AJCC 8th Edition, 1 patient was classified as stage I, 2 patients as stage II, 8 patients as stage III, and 2 patients as stage IV, while the other 6 patients could not be staged due to incomplete information. Surgery-based therapies were recommended for stage I-III patients, while stage IV patients were essentially managed with chemotherapy. One HLCCL patient with ALK gene rearrangement was treated by crizotinib (250 mg orally every 12 hours), which improved his symptoms of chest pain, cough, intermittent night sweats and anemia after 2 weeks of therapy. However, this regimen was discontinued due to tumor progression after 6 months of therapy [9]. The immunohistochemical markers of HLCCL were positive for AFP (100%) and CEA (60%). Five patients relapsed 6-8 months after treatment (median = 7 months), with AFP elevated again in 3 of them and unmentioned in 2 at the time of relapse. The 1- and 2-year OS rates were 37% and 28%, respectively. The cause of death of four patients was unmentioned, while six patients died of tumor relapse (3 cases) or infection (3 cases).

Discussion

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death worldwide [83]. The lung is also the third most common site for extrahepatic HACs, following the stomach (63%) and ovary (10%) [2]. The clinical manifestations, treatments and prognosis of HAC largely depend on the primary site. There are four major histological types and more specific subtypes of lung cancer, among which the responses to treatments, as well as prognosis, are varied [83]. The clinical manifestations of HAL are similar to those of common lung cancers, and most HAL patients have a history of smoking, with a Brinkman index >400 number per day × years. Unlike other lung adenocarcinomas, which are more common in women, the incidence of hepatoid

Table 6. Previously reported cases of hepatoid large cell carcinoma of the lung (HLCCL)

No	Author/ Year	Centre	Sex/ Age	Smoking history (pack-year)	Liver disease and other history	Symptom	Location/Size (cm)	Tumor markers	AJCC 8th Edition Stage	Treatment	Immunohistochemistry		Tumor relapse site	Prognosis/ Cause of death
											Positive (+)	Negative (-)		
1	Koizumi, 1979	Japan	M/63	N/A	N/A	N/A	N/A	AFP↑	N/A	C,R	N/A	N/A	N/A	5 mo dead/N/A
2	Yokoyama K, 1981 [74]	Japan	M/69	N/A	N/A	Bloody sputum, fever, cough	RLL/11×11×7	AFP↑	pT4N0M1b (IVA)	C, Immuno	AFP, A1AT, A1ACT, CEA	N/A	Kidney, brain (N/A)	2 mo dead/N/A
3	Saga, 1983	Japan	M/64	N/A	N/A	N/A	N/A	AFP↑	N/A	C, R	N/A	N/A	N/A	30 mo dead
4	Miyake M, 1986 [18]	Japan	M/40	23	History of appendectomy and gastric ulcer, family history of gastric cancer and tuberculosis	Bloody sputum, cough	RUL/8×9×7	AFP↑, CEA→	pT4N2M0 (IIIB)	O	AFP	N/A	Peritoneum (8 mo)	14 mo dead/ intraperitoneal metastasis
5	Sakamoto O, 1987 [75]	Japan	M/72	50	None	Dry cough, weight loss	RLL/8×12	AFP↑	cT4N1M0 (IIIA)	C,R	AFP	N/A	No	4.5 mo dead/ cancerous pleurisy and empyema
6	Yoshimoto T, 1987 [76]	Japan	F/61	N/A	N/A	Bloody sputum	LUL/N/A	AFP↑, CEA↑, β-hCG↑	N/A	C	N/A	N/A	brain (6 mo)	7 mo dead/ relapse
7	Kamishiro, 1987	Japan	M/73	N/A	N/A	N/A	N/A	AFP↑	N/A	C	N/A	N/A	N/A	19 mo dead/N/A
8	Taguchi, 1989	Japan	M/58	N/A	N/A	/	N/A	AFP↑	N/A	O, C	N/A	N/A	N/A	9 mo alive
9	Okunaka T, 1992 [77]	Japan	M/49	N/A	N/A	Cough, bloody sputum	RUL/6×5×5	AFP↑, CA19-9→, CEA→	pT3N0M0 (IIB)	O	AFP	N/A	No	11 mo alive
10	Ohshima, 1992	Japan	M/55	N/A	N/A	/	N/A	AFP↑	N/A	O	N/A	N/A	N/A	N/A
11	Hayashi A, 1995 [78]	Japan	M/54	35	Family history of gastric cancer, alcohol abuse	Cough, sputum	LML/3.5×2.5	AFP↑, CEA→, SCC→, CA19-9→, β-hCG→	pT2aN0M0 (IB)	O	AFP	CEA	N/A	18 mo alive
12	Hirabayashi H, 1995 [26]	Japan	M/55	N/A	Pulmonary tuberculosis, diabetes, chronic hepatitis	None	RLL/5×5	AFP↑	pT2bN0M0 (IIA)	O	AFP	N/A	N/A	132 mo alive
13	Bessho T, 1996 [79]	Japan	M/81	150	Gastric ulcer surgery	Fatigue	LLL/10×8×5	AFP↑, TPA↑, IAP↑, NSE↑	pT4N0M0 (IIIA)*	O	N/A	N/A	No	10 mo alive
14	Nasu M, 1997 [80]	Japan	M/63	N/A	Pleuritis	Bloody sputum, fever	RUL/8	AFP↑, β-hCG→, CA19-9→, CEA→, PIVKA-II ↑	cT4N1M1c (IVB)	C	AFP, PIVKA-II, A1AT, A1ACT	CgA	Lung, right adrenal, brain (N/A)	11 mo dead/ bronchopneumonia
15	Hiroshima K, 2002 [4]	Japan	M/71	45	N/A	Common cold	RLL/10.5×8.5×7	AFP↑, CA19-9↑, CEA→	pT4N1M0 (IIIA)**	O, R	AFP, CgA, NCAM, VEGF	Syn, CEA	Brain (5 mo), left lung (6 mo)	12 mo dead/ brain metastasis

16	Wu ZY, 2007 [7]	China	M/50	40	N/A	Weight loss	RUL/6×5×5	AFP→, CEA→, NSE→	cT4N1M0 (IIIA)	O	AFP	HepPar-1, CA199	No	45 mo alive
17	Khozin S, 2012 [9]	USA	F/56	Yes	N/A	Chest pain, cough, intermittent night sweats, weight loss	RML/5.5&1.8	AFP→, β-hCG→	cT4N0M0 (IIIA)	Crizotinib***	AE1/AE3, CAM5.2, CK7, CK5/6, HepPar-1, Claudin 4, EMA, OCT4, CEA, CD10	TTF-1, BHCG, CK20, Vim, GCDFP-15, P63, CHG, thyroglobulin, RCC	No	6 mo alive
18	Yu JH, 2012 [81]	Korea	M/70	50	N/A	None	LLL/6×5.2	AFP↑, PIVKA-II↑, CEA→, α-hCG→	cT3N3M0 (IIIC)	C	N/A	N/A	No	12 mo dead/lung infection, respiratory failure
19	Lin SF, 2013 [82]	China	M/66	40	Hepatitis B virus carrier for 30 years, gallbladder polyps, rheumatoid arthritis	Cough	RUL/7.4×6×4.8	AFP↑, β-hCG→, CEA→, SCC→	pT4N2M0 (IIIB)	O, C	AE1/AE3, AFP, Gly-3, CEA	CK7, CK20, TTF-1, HepPar-1, CgA, Syn, CD56	No	48 mo alive

Notes: *Pathology showed HLCCL complicated with squamous cell carcinoma; **Pathology showed large cell neuroendocrine carcinoma; ***Gene mutation examination showed EGFR (exons 18-21), KRAS (exons 2, 3), BRAF (exon 15), AKT (exon 1), PIK3CA (exons 9, 20), NRAS (exons 2, 3): Wild type; HER2 rearrangement (46%); ALK (72.8%). A1AT, α1-antiitrypsin; A1ACT, α1-antichymotrypsin; AFP, α-fetoprotein; ALK, anaplastic lymphoma kinase; β-hCG, beta-human chorionic gonadotropin; BRAF, b-rafproto-oncogene; C, chemotherapy; CD, cluster of differentiation; CEA, carcinoembryonic antigen; CgA, chromogranin A; CK, cytokeratin; EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen; Gly-3, glypican-3; HepPar-1, hepatocyte paraffin 1; HER2, human epidermal growth factor receptor 2; LLL, left lower lobe; LN, lymph node; LUL, left upper lobe; N/A, not mentioned; NCAM, neural cell adhesion molecule; NSE, neuron-specific enolase; O, operation; P53, protein 53; PD-L1, programmed death ligand 1; R, radiotherapy; RCC, renal cell carcinoma; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; Syn, synaptophysin; TTF-1, thyroid transcription factor-1; VEGF, vascular endothelial growth factor; Vim, vimentin.

adenocarcinoma is higher in men in their 60 s. Despite the finding that the majority of female patients were diagnosed at an advanced stage (stage III or IV), their prognosis seemed better, and one female patient even survived for 9 years. Estrogen protection may contribute to the better prognosis in women, but the exact mechanism is still unknown.

HAL needs to be distinguished from pulmonary metastasis secondary to HCC, which is morphologically similar to HAL but histologically different, usually without an acinar or papillary structure. In terms of immunohistochemistry, pulmonary metastatic HCC can express AFP, HepPar-1, and CK8/18, rather than CK7, CK19, CK5/6 and CK20. We outlined the immunohistochemical results of HAL compared with those of typical HCC in **Table 2**.

Approximately 50% of lung adenocarcinomas harbor somatic mutations in genes that encode proteins in the EGFR signaling pathway, such as K-RAS, EGFR, HER2, HER4, BRAF and PIK3CA [11]. Gene detection and targeted drugs are increasingly being utilized in the diagnosis and management of advanced lung cancers, combined with chemotherapy and radiotherapy. One unresectable HAL patient with the KRAS-G12V mutation received multiline chemotherapy with the PD-1 inhibitor sintilimab and achieved an OS of 52 months [73]. Chen et al [1] reported EGFR mutations of p.L747_P753delinsS and exon 20 T790Min a HAL patient with multiple bone and brain metastases after surgery. The patient was treated with icotinib, osimertinib and anlotinib, and stable during a follow-up of 36 months. A stage IV HAL patient with wild-type EGFR was treated with chemotherapy (switching from carboplatin/paclitaxel to vinorelbine and then gemcitabine), sorafenib and radiotherapy. He achieved partial response during the course and survived for 11 months after diagnosis [47]. Another HAL patient with TP53 mutations was given erlotinib followed by chemotherapy (docetaxel and nedaplatin), radiotherapy and bevacizumab, and survived for 9 months after admission [70]. Basse V et al observed a partial response to anti-PD-L1 durvalumab after chemotherapy (carboplatin, gemcitabine and docetaxel) in a HAL patient with PD-L1 negative but mismatch repair deficiency status [56].

Our systematic review has several advantages. First, we did not impose language restriction on the eligibility criteria, and all eligible cases were included according to the unified definition for HAL to reduce publication bias. Second, HLCCL cases, which were previously considered to be HAL cases, were summarized separately for the first time. Third, the survival rates were analyzed separately in terms of sex, tumor staging and pathological types, and the risk factors affecting the OS and RFS of HAL patients were investigated, providing more comprehensive information about this rare disease. There are also some limitations in our study. First and foremost, the sample size was still relatively small due to the rarity of this disease and limited access to some databases such as Ichushi. On the other hand, HAL cases were reviewed only from a clinical perspective, but its pathogenesis is still unclear and necessitates more investigations.

In conclusion, HAL is a rare but highly aggressive malignant disease with a median OS of 19.08 months and a 1-year RFS rate of 58%. HAL should be considered in elderly male smokers presenting with large lung masses and elevated serum AFP level. Moreover, hepatoid differentiation regions and/or acinar or papillary structures in lung tumor tissues, as well as positive immunohistochemical expression of AFP, HepPar-1, and CK8/18, can assist in the diagnosis of HAL. Surgery-based strategy is recommended for stage I-III patients, while chemotherapy-based strategymay provide a survival benefit for stage IV patients. The postoperative screening of serum AFP levels is important for evaluating tumor relapse. The control of disease progression and prevention of infections contribute to a better prognosis.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. The tumor markers of the 94 HAL patients

Tumor markers	Full name	Elevated	Normal	N/A	Positive rate
AFP	alpha fetoprotein	59	12	23	83.10%
CA724	carbohydrate antigen 724	3	1	90	75.00%
CA19-9	carbohydrate antigen 19-9	5	3	86	62.50%
CEA	carcinoembryonic antigen	15	19	60	44.12%
HCG	human chorionic gonadotropin	3	5	86	37.50%
CYFRA21-1	cytokeratin 19 fragment 21-1	3	9	82	25.00%
NSE	neuron specific enolase	2	15	77	11.76%
SCC	squamous cell carcinoma antigen	0	5	89	0.00%
CA153	carbohydrate antigen 153	0	4	90	0.00%
Ferritin	ferritin	0	3	91	0.00%
Pro-GRP	progastrin releasing peptide	0	3	91	0.00%
PSA	prostate-specific antigen	0	3	91	0.00%
CA125	carbohydrate antigen 125	0	2	92	0.00%
SLX	sialyllewis X	0	2	92	0.00%
TPA	tissue polypeptide antigen	0	2	92	0.00%
HSP	heat shock protein	0	1	93	0.00%
PIVKA-II	protein induced by vitamin K absence or antagonist-II	0	1	93	0.00%

Supplementary Table 2. Tumor stages, pathological types and relapse among different strategy groups

Treatment (N = 94)	Surg group (N = 49)	Chemo group (N = 30)	Others (N = 8)	Not mentioned (N = 7)
AJCC 8th Edition Stage				
Stage I (N = 8)	7 (1)	0 (0)	1 (0)	0 (0)
Stage II (N = 8)	7 (2)	0 (0)	1 (0)	0 (0)
Stage III (N = 28)	16 (5)	9 (6)	1 (1)	2 (0)
Stage IV (N = 26)	6 (3)	15 (4)	3 (1)	2 (0)
N/A (N = 24)	13 (0)	6 (1)	2 (0)	3 (0)
Pathomorphological classification				
Typical (N = 27)	12 (6)	12 (6)	2 (0)	1 (0)
Atypical (N = 38)	19 (3)	12 (4)	4 (2)	3 (0)
N/A (N = 29)	18 (2)	6 (1)	2 (0)	3 (0)
Pathological differentiation				
Well-differentiated (N = 5)	5 (0)	0 (0)	0 (0)	0 (0)
Moderately-differentiated (N = 7)	5 (1)	1 (0)	1 (0)	0 (0)
Poorly-differentiated (N = 36)	18 (4)	10 (2)	5 (1)	3 (0)
N/A (N = 46)	21 (6)	19 (9)	2 (1)	4 (0)
Tumor relapse (Y/N/N/A)	11/22/16	11/14/5	2/4/2	0/2/5

Notes: The number in parentheses is the number of relapse cases. Chemo, chemotherapy-based strategy; N, no; N/A, not mentioned; Surg, surgery-based strategy; Y, yes.

Supplementary Table 3. Overall survival of HAL patients with different pathological types receiving surgery- or chemotherapy-based strategy

	Overall survival rate				
	1-year	3-year	5-year	Median (year)	χ^2, P
Surg group (N = 49)					
Pathomorphological classification*					χ^2 = 1.567, P = 0.211
Typical (N = 12)	39%	39%	/	1.68	
Atypical (N = 19)	61%	61%	61%	7.00	
Pathological differentiation**					χ^2 = 0.219, P = 0.896
Well-differentiated (N = 5)	23%	/	/	2.00	
Moderately-differentiated (N = 5)	22%	22%	0%	5.33	
Poorly-differentiated (N = 18)	41%	/	/	1.77	
Chemo group (N = 30)					
Pathomorphological classification***					χ^2 = 0.842, P = 0.359
Typical (N = 12)	35%	35%	/	1.48	
Atypical (N = 12)	33%	11%	/	1.00	
Pathological differentiation****					χ^2 = 2.425, P = 0.119
Moderately-differentiated (N = 1)	/	/	/	/	
Poorly-differentiated (N = 10)	22%	22%	/	0.79	

Notes: *18 cases with unclear pathomorphological classification; **21 cases with unclear pathological differentiation; ***6 cases with unclear pathomorphological classification; ****19 cases with unclear pathological differentiation. Chemo, chemotherapy-based strategy; Surg, surgery-based strategy.