SYSTEMATIC REVIEW

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Optimal treatment strategies for hepatoid adenocarcinoma of the lung: insights from a comprehensive analysis

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Abstract

Background   Hepatoid adenocarcinoma of the lung (HAL) is a distinctly uncommon subtype of lung adenocarcinoma (LAC), characterized by hepatoid features and an alarmingly low 5-year survival rate of approximately 8%. The scarcity of information on this condition has contributed to the absence of standardized treatment protocols, and the molecular underpinnings of its pathogenesis remain largely unexplored. To bridge these gaps, this study compiled data from 191 primary HAL patients to delineate treatment patterns, prognostic factors, and potential pathogenic mechanisms.

Methods   This study was divided into two cohorts: cohort 1, comprising 110 patients extracted from the Surveillance, Epidemiology, and End Results (SEER) database, and cohort 2, consisting of 70 patients identified through a comprehensive literature review via the PubMed, Web of Science, and Scopus databases, in addition to 11 patients from Tongji Hospital. The Cox proportional hazards regression model was employed to identify independent prognostic factors. Kaplan-Meier survival curves were generated to assess the impact of treatment modalities centered around surgery and chemotherapy. Moreover, this study evaluated the efficacy of first-line treatment regimens and conducted Gene Ontology function and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses on identified mutated genes.

Results   The demographic and clinical profile of HAL patients typically comprises older individuals who are smokers, with a predisposition for diagnosis at advanced disease stages, culminating in a high mortality rate. Key prognostic indicators identified included disease stage, chemotherapy and surgical interventions. The study suggests a treatment strategy that advocates chemotherapy for patients with stage IV HAL and surgery for those with non-stage IV disease. The combination of paclitaxel and platinum-based chemotherapy emerged as an efficacious first-line treatment, with the integration of immunotherapy and targeted therapies showing potential benefits. Genetic analysis underscored similarities between HAL and LAC, particularly highlighting aberrant kinase activity (serine, threonine, and tyrosine) and the activation of PI3K-Akt and MAPK signaling pathways as contributing factors to HAL pathogenesis.

Conclusion   Despite its relatively rare occurrence, this study underscores the significance of treatment strategies and concludes probable prognostic factors. Due to limited reports, a deeper understanding of the molecular mechanisms driving tumorigenesis and progression in HAL is needed.

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Introduction

Hepatoid adenocarcinoma of the lung (HAL) is a distinct form of lung adenocarcinoma (LAC) that histologically and morphologically resembles hepatocellular carcinoma (HCC), exhibiting hepatocellular features such as elevated production of alpha-fetoprotein (AFP) [1]. Since its formal description by Ishikura et al. in 1990 [2], increased attention has been given to this rare form of LAC. HAL exhibits a low prevalence, with a male predominance accounting for approximately 80% of cases [3]. HAL is associated with high mortality and an extremely poor prognosis, as reflected by a 5-year survival rate of only 8% [4]. Current treatment regimens are mainly based on LAC [5]. Unfortunately, the efficacy of these treatments is not satisfactory, and the optimal treatment modality and the specific regimen are still unclear.

Previous studies involving almost small sample retrospective analyses [4, 5] or case reports [6] lacked systematic integration and analysis of treatment options and patterns, and no articles were retrieved that summarized the treatment patterns and prognosis of patients with HAL using the Surveillance, Epidemiology, and End Results (SEER) database. Sun et al. [7] performed next generation sequencing (NGS) analysis in four cases of HAL to identify high-frequency mutations. However, the number of cases is limited and the relevant literature is sparse. Little attention has been given to differences in the oncogene spectrum between HAL, LAC and HCC. Therefore, we conducted a comprehensive analysis of 191 HAL patients by combining data from the SEER database since 1990 (n=110), Tongji Hospital since 2013 (n=11) and reported literature (n=70) to determine clinical features, identify independent prognostic factors and summarize the efficacy of specific first-line medical therapy regimens. To further discuss the possible molecular mechanisms involved, we analyzed 31 reported mutated oncogenes and compared them with those in LAC and HCC.

Materials and methods

Date sources and search strategy

The 191 patients were categorized into two cohorts according to the data source. The data for Cohort 1 were obtained from the SEER database (version 8.4.1.2). Within the data module, the "SEER Research Data, 17 Registries, Nov 2022 Sub (2000–2020)" was chosen. For the selection module, the criteria "Site recode ICD-O-3/ WHO 2008= "Lung and Bronchus" ICD-0-3 Hist/behav= "8576/3: hepatoid adenocarcinoma"" were applied. The Table module included research-relevant factors such as

"Patient ID, sex, age recode, stage-6/7/8th edition, therapy, survival months, year of death recode," with abbreviations in the collected information transcribed according to the "SEER Program Coding and Staging Manual 2023." The data for Cohort 2 were sourced from multiple databases, including PubMed, Web of Science, and Scopus. The keywords "primary hepatoid adenocarcinoma," "lung," and " hepatoid adenocarcinoma of the lung" were utilized for the literature search from January 1, 1990, to December 1, 2023, ensuring the inclusion of relevant and up-to-date information. Moreover, 11 HAL patients from Tongji Hospital were included in cohort 2, requiring components of a typical papillary/acinar adenocarcinoma of lung, expressed Immunohistochemical markers of hepatoid differentiation and eliminated primary HCC [8].

Study selection criteria

The following criteria were used to exclude studies from the literature: not pathologically diagnosed with primary HAL, duplicated recorded, not published in English, lacked available full text, insufficient patient survival data and lacked treatment information.

Data extraction

In Cohort 1, we collected 110 patients' IDs, age, gender, tumor classification (T), nodal classification (N), metastasis classification (M), clinicopathological stage, details of surgical, chemotherapy, and radiotherapy interventions, as well as survival time and status (Supplementary Table 1). For the 81 patients included in Cohort 2, demographic data such as the patient age, sex, and smoking history were extracted. Additionally, clinical and diagnostic information, including tumor size, location, serum AFP level, and TNM classification, was recorded. Specific gene mutations, treatment modalities and survival statuses were also documented, with overall survival time defined as the duration from pathological diagnosis to the last follow-up or death (Supplementary Table 2 [2–53]). Furthermore, if non-stage IV patients experienced postoperative recurrence within 3 months, they were reclassified as stage IV.

Statistical analysis

We evaluated the clinical features of 110 patients in cohort 1 and 81 patients in cohort 2. Then an analysis was conducted based on the fundamental patient survival data and clinicopathological characteristics using the Cox proportional hazards regression model to identify independent prognostic factors. Subsequently, the

patients were categorized into stage IV and non-stage IV groups based on clinicopathological staging. Survival curves were then generated using the Kaplan-Meier (K-M) method to explore the significance of survival in patients receiving treatment modalities based on surgery or chemotherapy. Statistical significance was set at $p < 0.05$. K-M curve analyses and Cox proportional hazards regression analyses were performed utilizing the R "survival" package (version 3.3.1) and "survminer" package. To evaluate the efficacy of specific chemotherapeutic regimens in cohort 2, we screened 21 patients with both detailed first-line medical treatment regimens and clear pre- and post-treatment outcomes and tumor statistics pre- and post-treatment as documented in the text were classified as stable disease (SD), progressive disease (PD), complete response (CR), or partial response (PR) in accordance with The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Subsequently, the objective response rate (ORR) was calculated to compare the efficacy of the regimens. Additionally, information regarding mutated genes from 32 patients was collected for Gene Ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The top 30 oncogenes associated with LAC and HCC were drawn from the cBioportal database (https://www.cbioportal.org/) for comparison with the oncogene spectrum. The GO-KEGG analysis was conducted using the R package "clusterProfiler" (v4.4.4). All analyses were performed using the R programming language (v4.2.1), and the results were visualized using the "ggplot2" package (v3.3.6). The specific procedure can be found in Fig. 1.

Results

Clinical features of HAL

Table 1 succinctly presents the essential clinical information for these patients. The demographic distribution revealed a male preponderance, constituting 57% (63 out of 110 patients) of cohort 1 and 91% (74 out of 81 patients) of cohort 2. Among the patients in cohort 2, 53 had a documented history of smoking. The median age at diagnosis with HAL was 66 years in cohort 1, ranging from 36 to 90 years, while it was 61 years in cohort 2, ranging from 33 to 82 years. The primary tumor was predominantly located in the upper lobe of the lung, accounting for 72% (67 out of 93 patients) of patients in cohort 1 and 68% (55 out of 81 patients) of patients in cohort 2. Serum alpha-fetoprotein (AFP) levels were available for 51 patients prior to treatment, of whom 39 patients (76%) displayed elevated levels. Notably, most patients presented with advanced-stage HAL at diagnosis, with 71 patients (68%) diagnosed with stage IV HAL in cohort 1 and 42 patients (53%) in cohort 2. Treatment modalities within cohort 1 included surgery in 10 patients, chemotherapy in 59 patients, and radiation therapy in 58 patients. In cohort 2, the treatment modalities included surgical resection (both complete and palliative) in 41 patients, chemotherapy in 49 patients, radiation therapy in 23 patients, immunotherapy in 14 patients, and targeted therapy in 14 patients. The mean survival time for patients was 13.64 months in cohort 1 and 17.70 months in cohort 2.

Clinical factors affecting HAL prognosis

To identify the key factors influencing the prognosis of HAL patients, we examined various parameters,
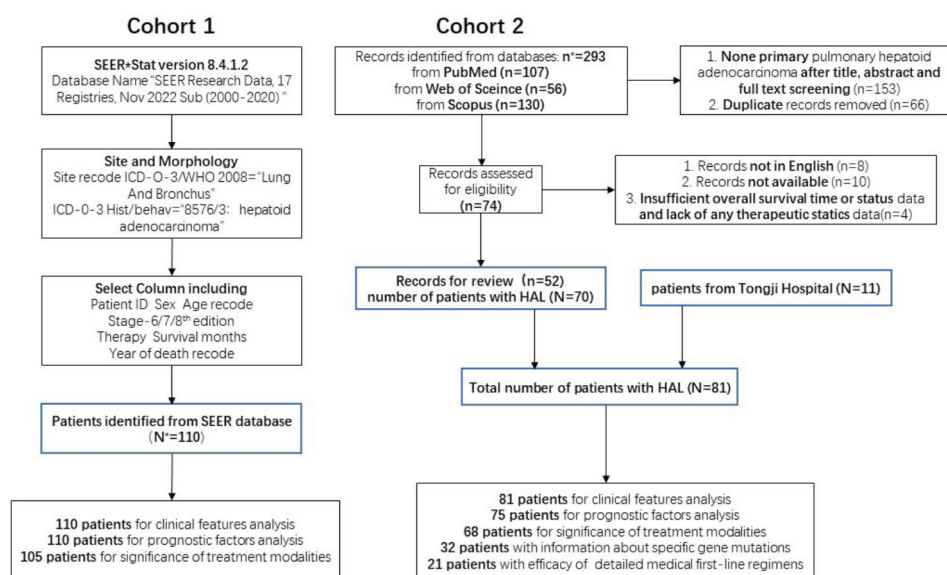

Fig. 1 The procedure of identification of studies via databases and registers. n*: the number of records; N*: the number of patients; HAL: hepatoid adenocarcinoma of the Lung

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Table 1 Clinical characteristics of 110 patients with HAL in Cohort 1 and 81 patients with HAL in Cohort2

Characteristics	Results	
	Cohort 1	Cohort 2
Median Age (years)	66(36–90)	61 (33–82)
Gender n (%)		
Male	63(57)	74(91)
Female	47(43)	7(9)
Tumor Location n (%)		
Upper Lobe	67(61)	55(68)
Non-Upper Lobe	26(24)	26(32)
Tumor Size (cm)	-	6.48±3.34(1–15)
AFP level n (%)		
Increase	-	39(76)
Normal	-	12(24)
Smoker n (%)		
Yes	-	53(82)
No	-	12(18)
Clinicopathological Stage n (%)		
I	11(10)	5(6)
II	9(9)	6(8)
III	14(13)	26(33)
IV	71(68)	42(53)
Treatment n (%)		
Surgery	10(9)	41(51)
Chemotherapy	59(54)	49(60)
Radiotherapy	58(53)	23(28)
Targeted therapy	-	14(17)
Immunotherapy	-	14(17)
Survival status n (%)		
Dead	99(90)	47(63)
Alive	11(10)	28(37)
Median overall survival (months)	13.64	17.70

including T, N, M, clinicopathological stage, administration of chemotherapy, radiotherapy, surgical interventions, and AFP levels, in relation to the patient survival status and overall survival time. The results were summarized in Table 2.

In the univariate analysis, we found that disease stage and surgical interventions had a significant impact on patient prognosis in both Cohort 1 and Cohort 2 (Stage: Cohort 1, $p<0.001$; Cohort 2, $p=0.005$; Surgery: Cohort 1, $p<0.001$; Cohort 2, $p=0.004$). Interestingly, data from the SEER database in Cohort 1 indicated that N classification ($p=0.029$), M classification ($p<0.001$), as well as the administration of chemotherapy ($p<0.001$) and radiotherapy ($p=0.047$) were significantly associated with the prognosis of HAL patients. Unfortunately, these factors affecting prognosis have not been confirmed in Cohort 2, which may be due to the insufficient sample size, with chemotherapy ($p=0.067$) and radiotherapy ($p=0.054$) demonstrating marginal significance. Our Cox analysis did not support AFP or gender related to prognosis [21, 54].

In the multivariate regression analysis of Cohort 1, stage ($p=0.008$), chemotherapy ($p=0.003$), and surgery ($p=0.005$) emerged as independent indicators. Additionally, in Cohort 2, stage ($p=0.029$) and surgery ($p=0.017$) were identified as key factors associated with survival, while chemotherapy ($p=0.064$) demonstrated approximate significance.

Exploring optimal treatment modalities for stage IV and non-stage IV patients

This study examines the viability of various treatment approaches tailored to disease staging for HAL patients. Access to treatment plays a crucial role in extending patients' lives, particularly for those in stage IV. The findings advocate for prioritizing chemotherapy for stage IV HAL patients, while also underscoring the potential effectiveness of surgery for non-stage IV patients.

The findings, depicted in Fig. 2A and B for stage IV patients in both Cohorts 1 and 2, demonstrate a significantly improved survival rate among those who received chemotherapy compared to those who did not, with $p<0.001$ respectively. In contrast, for non-stage IV patients (Fig. 2C, D), individuals who underwent surgery had a better prognosis than those who did not undergo surgery. However, a subgroup analysis was performed among non-stage IV surgical patients, some of whom received either preoperative or postoperative adjuvant chemotherapy. Unfortunately, this analysis did not reveal a statistically significant difference in survival outcomes (Fig. 2E).

Efficacy of first-line medical treatment regimens

In Cohort 2, only 21 patients were available for assessing the efficacy of specific first-line medical treatment regimens before and after their application. The results are summarized in Table 3.

Among the individual first-line chemotherapy regimens, the combination of paclitaxel and platinum was the most commonly used (5 out of 12 patients), one of which achieved a partial response [20]. Other first-line chemotherapy regimens, such as pemetrexed or gemcitabine, had an effective relief rate of 0%. When immunotherapy or targeted vascular endothelial growth factor (VEGF) drugs were added to paclitaxel or etoposide combined with platinum-based regimens, the effective relief rate reached 43%(3 out of 7 patients). The combination of etoposide and platinum agents with immunotherapy achieved a partial response in one patient. Among the targeted drugs used individually for specific mutations, crizotinib showed a partial response when applied to a patient with anaplastic lymphoma kinase (ALK) gene rearrangement [14]. However, targeted drugs used for patients without specific mutation sites, such as erlotinib

Table 2 The univariate and multivariate analysis result of cohort 1 and cohort 2 through COX proportional hazards regression model. Stage, chemotherapy, surgery and radiation were included in the construction of the multivariate COX model

Characteristics	Total(N)	Cohort1		Total(N)	Cohort2	
		Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis
		P value Hazard ratio (95% CI)	P value Hazard ratio (95% CI)		P value Hazard ratio (95% CI)	P value Hazard ratio (95% CI)
Gender	110			75		
Female	47	Reference		7	Reference	
Male	63	0.449 0.856 (0.573–1.280)		68	0.147 0.419 (0.129–1.360)	
Age	110			75		
>65	57	Reference		26	Reference	
≤65	53	0.116 0.728 (0.489–1.082)		49	0.662 0.877 (0.486–1.582)	
T classification	92			58		
T3+T4	56	Reference		35	Reference	
T1+T2	36	0.080 0.665 (0.422–1.049)		23	0.657 1.168 (0.589–2.315)	
N classification	86			49		
N2+N3	48	Reference		22	Reference	
N0+N1	38	**0.029** 0.597 (0.375–0.949)		27	0.071 0.470 (0.270–1.068)	
M classification	107			56		
M0	36	Reference		31	Reference	
M1	71	**<0.001** 3.269 (2.026–5.276)		25	0.118 1.764 (0.866–3.589)	
Stage	105			73		
IV	71	Reference	Reference	38	Reference	Reference
Non-IV	34	**<0.001** 0.285 (0.174–0.468)	**0.008** 0.485 (0.284–0.827)	35	**0.005** 0.410 (0.222–0.759)	**0.029** 0.346 (0.133–0.899)
Chemotherapy	110			70		
No/Unknown	59	Reference	Reference	34	Reference	Reference
Yes	51	**<0.001** 0.489 (0.328–0.731)	**<0.001** 0.442 (0.286–0.682)	36	0.067 0.552 (0.292–1.042)	0.064 2.810 (0.940–8.400)
Radiation	109			70		
None/Unknown	51	Reference	Reference	47	Reference	Reference
Yes	58	**0.047** 0.666 (0.446–0.994)	0.094 0.681 (0.434–1.068)	23	0.054 0.545 (0.294–1.011)	0.148 0.593 (0.292–1.203)
Surgery	110			70		
None/Unknown	100	Reference	Reference	31	Reference	Reference
Yes	10	**<0.001** 0.148 (0.053–0.409)	**0.001** 0.120 (0.033–0.439)	39	**0.004** 0.405 (0.219–0.752)	**0.017** 0.394 (0.183–0.848)
AFP level	-	-	-	49		
Increase	-	-	-	38	Reference	
Normal	-	-	-	11	0.110 1.956 (0.859–4.457)	

in a patient without epidermal growth factor receptor (EGFR) mutations, resulted in tumor progression [37].

Top oncogene mutations in HAL and comparison with HCC and LAC

In Cohort2, 32 cases provided detailed information on specific gene mutations in HAL. The study identified a total of 31 genes with significant frequency of occurrence, and GO-KEGG analysis was performed to understand their functional implications. The top three

messages from the GO-KEGG analysis (Fig. 3A) revealed that these mutated genes were primarily involved in molecular functions (MF) associated with protein serine, threonine, and tyrosine kinases activity (10 genes). KEGG analysis indicated that these mutated oncogenes were primarily enriched in typical pathways of hepatocellular adenocarcinoma (11 genes), non-small cell lung cancer (8 genes). Among all the mutated genes, TP53 (25%), STK11 (15.63%), SMARCA4 (12.50%), CDKN2A (12.50%), KRAS (9.38%), CDK8 (6.25%), and EPHA5
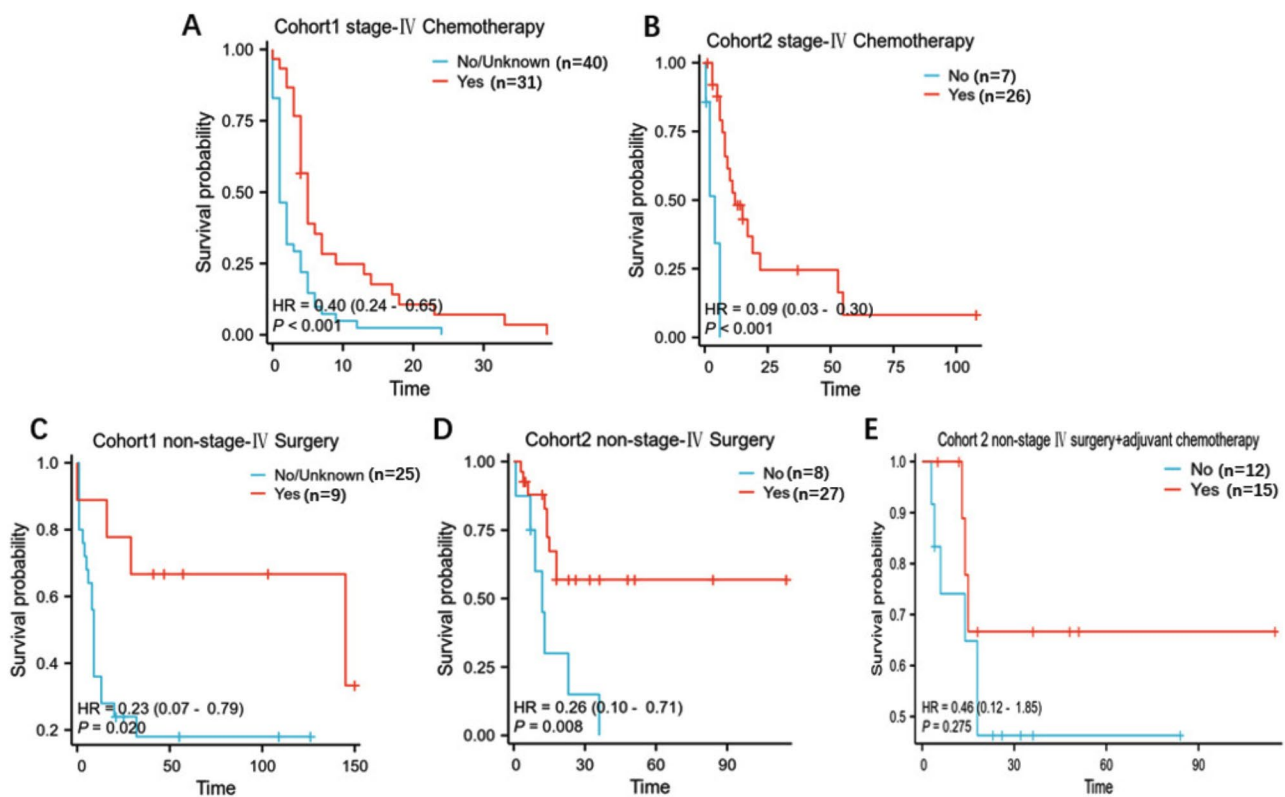
Fig. 2 The Kaplan-Meier (K-M) analysis results of stage IV and non- stage IV patients in Cohort 1 and Cohort2. **A**: Comparison between stage IV patients receiving chemotherapy ($n=31$) and those not receiving chemotherapy or unknown ($n=40$) in Cohort1. **B**: Comparison between stage IV patients receiving chemotherapy ($n=26$) and those not ($n=7$) in Cohort2. **C**: Comparison between non- stage IV patients receiving surgery ($n=9$) and those not or unknown ($n=25$) in Cohort1. **D**: Comparison between non- stage IV patients receiving surgery ($n=27$) and those not ($n=8$) in Cohort2. **E**: Comparison between non-stage IV patients receiving surgery and adjuvant chemotherapy ($n=15$) and those only surgery ($n=12$) in Cohort2

(6.25%) were found to be more commonly mutated in HAL cases. Additionally, seven patients exhibited mutations in two or more genes. Notably, TP53, SMARCA4, CDKN2A, and STK11 showed a tendency towards co-mutation (Fig. 3B).

Based on the interaction between the gene mutation spectrum of LAC, HAL, and HCC, there were 5 genes (TP53, ATM, NF1, ARID1A, PIK3CA) shared between the three types of cancers. In contrast, HAL and LAC shared 6 identical mutated genes (EGFR, KRAS, STK11, FAT1, SMARCA4, EPHA5), while no specific overlap was observed between HAL and HCC (Fig. 3C). This suggests that HAL shares a closer similarity to LAC in terms of the mutational landscape. Through further GO-KEGG analysis of the remaining 20 non-intersected mutated genes in HAL (Fig. 3D), the MF category showed significant enrichment in protein serine, threonine, and tyrosine kinases activity. KEGG pathway analysis indicated enrichment in the PI3K-Akt signaling pathway and MAPK signaling pathway. These results align with the findings of the 11-gene analysis unique to LAC (Fig. 3E). However, the MF result of non-intersected 17 genes in HCC were related to beta-catenin, enriching in typical pathways of hepatocellular adenocarcinoma and gastric cancer (Fig. 3F).

Discussion

Hepatoid adenocarcinoma (HAC) is a distinct form of adenocarcinoma that histologically and morphologically resembles hepatocellular carcinoma, although it occurs outside of hepatic organs or tissues. Since its initial report in 1970 [55], HAC has been observed in various organs including the stomach, ovary, lung, and gallbladder [56]. Comprising approximately 5% of all HAC cases [56]. HAL is a rare subtype of lung adenocarcinoma characterized by hepatocyte differentiation. Clinical symptoms typically include cough, chest pain, and weight loss, mirroring those of common types of lung cancer [4]. HAL has a higher incidence in men, with the majority of patients being smokers, suggesting a potential association between smoking and the prevalence of HAL in men [41]. HAL predominantly localizes to the upper lobes of the lungs and is frequently diagnosed at advanced pathological stages, often presenting unspecific findings on physical examination and imaging. Therefore, it is challenging to make the accurate diagnosis of HAL due to the

Table 3 The first-line regimens of HAL and summaries of therapeutic efficacy

First-line Regimens	Total (N)	Therapeutic Efficacy		
		ORR n/N (%)	SD n/N (%)	PD n/N (%)
Individual chemotherapy regimens	12	1 (8%)	6 (50%)	5 (42%)
Paclitaxel + Platinum	5	1 (20%)	3 (60%)	1 (20%)
Pemetrexed + Platinum	3	0 (0%)	1 (33%)	2 (67%)
Gemcitabine + Platinum	2	0 (0%)	0 (0%)	2 (100%)
Vinorelbine + Platinum	1	0 (0%)	1 (100%)	0 (0%)
S-1 chemotherapy	1	0 (0%)	1 (100%)	0 (0%)
Chemotherapy combined with anti-VEGF therapy or immunotherapy	7	3 (43%)	3 (43%)	1 (14%)
Paclitaxel + Platinum + Anti-VEGF therapy	4	1 (25%)	2 (50%)	1 (25%)
Paclitaxel + Platinum + immunotherapy	2	1 (50%)	1 (50%)	0 (0%)
Etoposide + platinum + immunotherapy	1	1 (100%)	0 (0%)	0 (0%)
Individual target therapy	2	1 (50%)	0 (0%)	1 (50%)
Erlotinib	1	0 (0%)	0(0%)	1 (100%)
Crizotinib	1	1 (100%)	0 (0%)	0 (0%)

ORR: Objective Response Rate; SD: Stable Disease; PD: Progressive Disease. VEGF: Vascular Endothelial Growth Factor

lack of specific clinical manifestations, often depending on histopathological examination. Two proposed criteria for HAL diagnosis [21] include tumors that are purely hepatoid adenocarcinomas or present classical acinar or papillary adenocarcinomas, signet ring cells, or neuroendocrine carcinomas as components. Furthermore, the presence of AFP is not mandatory for diagnosis as long as other markers of hepatic differentiation are expressed. Immunohistochemical (IHC) features is widely used for the differential diagnosis with metastatic HCC, while IHC results may vary among individuals with HAL. Specific markers such as Glypican-3, CK18, CK19, AFP, CEA, and HepPar-1 are commonly positive in HAL [57]. CK7, CEA, and EMA are often positive in HAL but negative in HCC, whereas TTF-1 and HepPar-1 are consistently positive in both HAL and HCC [8, 21].

HAL is characterized by rapid progression and a poor prognosis, with reported cases of metastasis to the brain [44], liver [40] and even tonsil [20]. Previous research has suggested a lower incidence of HAL in females, who also exhibited longer survival compared to males [21]. However, our COX analysis did not support this observation. Although AFP could be used as an independent prognostic indicator in HAC [58] and it was demonstrated in the hepatoid adenocarcinoma of the stomach (HAS) that AFP levels before treatment were strongly associated with prognosis [59], AFP levels did not show indications to be used as an independent prognostic indicator in HAL. Previous research [4] suggested that surgical

resection may improve survival outcomes, although factors such as gender, age, tumor location, size, and T classification were not found to significantly influence prognosis, which was consistent with our findings. Furthermore, our study identified surgery, stage and chemotherapy as independent prognostic factors, while N, M classification, and radiotherapy were also associated with survival duration. Without treatment, the prognosis for HAL is notably bleak, but certain therapeutic interventions such as chemotherapy, radiotherapy, or surgery may offer some benefit in extending survival. Surgery-based treatments have been highlighted as potentially beneficial for HAL patients, particularly those not in stage IV, while chemotherapy-based regimens may offer survival advantages for stage IV patients.

Currently, there is no standardized chemotherapy regimen for HAL, and its low survival rate emphasizes the importance of employing specific first-line chemotherapy regimens with superior efficacy. The most frequently utilized regimen is paclitaxel plus platinum, which has demonstrated enhanced efficacy compared to other conventional chemotherapy regimens such as pemetrexed plus platinum and gemcitabine plus platinum. However, HAL generally exhibits limited sensitivity to conventional chemotherapy regimens. Combining drugs targeting specific molecules or integrating immunotherapy appears to significantly enhance patient outcomes. A patient reported EGFR mutation achieved partial response with icotinib and remained progression-free for 8 months after switching to another targeted agent, despite the subsequent development of an EGFR T790M resistance mutation [33]. Additionally, a case report documented ALK gene rearrangement, which was effectively controlled by crizotinib, resulting in a substantial reduction in the baseline lesions and disease progression-free status without signs of relapse after 6 months [14]. While immunotherapy is typically administered following the failure of front-line therapy, combining it in the first-line treatment may also yield favorable efficacy. Both paclitaxel- or etoposide-based regimens in combination with pembrolizumab achieved partial responses in the initial efficacy assessment [25, 26]. Notably, a patient maintained on pembrolizumab alone experienced stable disease for 4 months, despite a PD-L1 status of less than 5% in the original report [46]. Furthermore, a case was documented where a mismatch repair-deficient (dMMR) patient achieved partial response after receiving durvalumab, despite a negative PD-L1 status [32], possibly indicating that dMMR patients may benefit from immunotherapy [60]. In conclusion, paclitaxel in combination with platinum may be the more recommended traditional chemotherapy regimen for HAL. Additionally, combining targeted drugs or immunotherapy to enhance efficacy in first-line chemotherapy is also worthy of consideration.
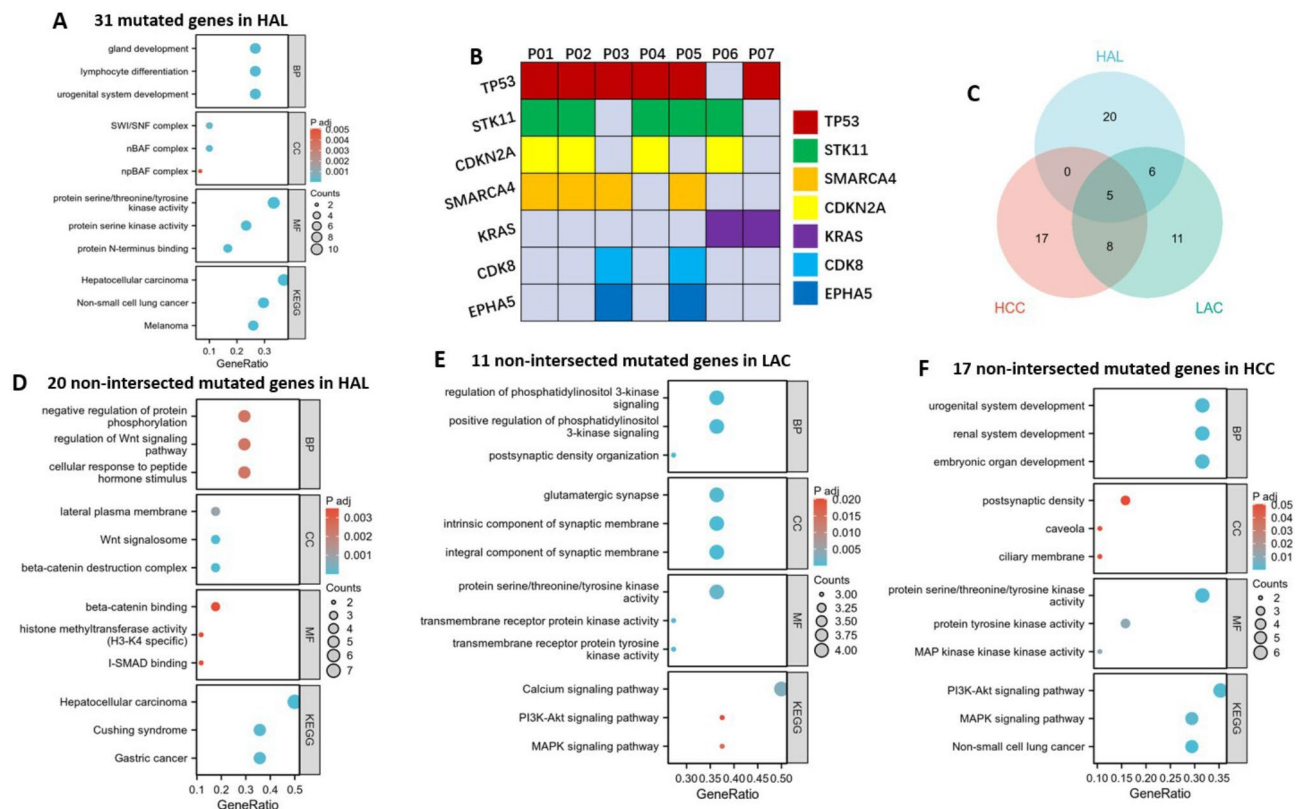
Fig. 3 The analysis of top oncogene mutations in HAL and comparison with HCC and LAC. **A**: The GO-KEGG analysis result of 31 reported mutated genes in HAL. **B**: The heatmap of co-mutated genes in different patients. **C**: the Venn diagram illustrated the overlap among the top 30 genes of LAC, HCC and all reported 31 genes of HAL. **D**: The GO-KEGG analysis result of 20 non-intersected mutated genes in HAL. **E**: The GO-KEGG analysis result of 11 non-intersected mutated genes in LAC. **F**: The GO-KEGG analysis result of 17 non-intersected mutated genes in HCC

Therefore, pre-treatment genetic testing is recommended to facilitate the identification of suitable sensitive targeted or immunotherapy drugs.

In terms of pathogenesis, it is suggested that the adenocarcinoma and hepatocyte-like lesions of HAC may stem from the same clone, likely originating from pluripotent precursor stem cells [56]. The loss of p53 family function has been observed to result in defective endodermal differentiation in embryonic stem cells (ESCs), thereby preventing ESCs from transitioning out of pluripotency [61]. TP53 is the most frequently mutated gene in HAL according to collected mutation information, it is hypothesized that functional abnormalities in the p53 family may serve as the initiator of bilinear differentiation in HAL. Furthermore, analysis of gene co-mutation information suggests that TP53, STK11, and CDKN2A demonstrate frequent co-mutation, indicating that disruptions in the cell cycle and the abnormal p53 signaling pathway may represent significant mechanisms in HAL pathogenesis [62, 63]. In the systematic comparison of the mutation spectrum of HAL, HCC and LAC, HAL may more closely resembled LAC than HCC at the genomic level. The majority of reported mutated genes in HAL were enriched in protein serine, threonine, and

tyrosine kinases activity, triggering downstream signaling pathways like the PI3K/AKT/mTOR pathway and the MAPK pathway to promote tumor growth, inhibit apoptosis, and stimulate proliferation. We hypothesize that, the pluripotent precursor cells are seemingly subjected to malignant transformation at an early stage by these tumorigenic factors; at the same time, they maintain the ability to differentiate into the mucosal epithelium. Advanced technologies, such as single-cell sequencing, is necessary to enhance our understanding of HAL heterogeneity and pathogenesis.

Conclusion
HAL remains an unclear malignancy with a poor prognosis. Treatment regimens based on surgery or chemotherapy was necessary to prolong the survival time. Clinical treatment of HAL should not be based only on the common treatments of LAC; combing immunotherapy or target specific mutated gene drugs in first-line treatment should be implemented. All reported mutated oncogenes were collected, but due to limitations in available reports, thoroughly exploring the pathogenic driving mechanisms of HAL is challenging. Additional research is required to identify the primary abnormalities in disease progression

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or metastasis and to determine the most recommended treatment regimens and targets for this rare disease.

Abbreviations

HAL   Hepatoid adenocarcinoma of the lung
LAC   Lung adenocarcinoma
HCC   Hepatocellular carcinoma
HAC   Hepatoid adenocarcinoma
AFP   Alpha-fetoprotein
SEER   Surveillance, Epidemiology, and end results

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12885-024-12682-z.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Deng: Resources, Conceptualization, Investigation, Methodology, Formal analysis, Visualization, Writing - review & editing Wang: Data curation, Investigation, Methodology, Formal analysis.Li: Resources, Conceptualization, Investigation.Zhan: Resources, Conceptualization, Investigation.Huang: Conceptualization, Methodology, Writing – review & editing.

Data availability

The data generated in the present study are included in the figures and/or tables of this article.

Declarations

Ethics approval and consent to participate

The ethical approval is not applicable by the Ethics Committee of Tongji Hospital. All of our new patients provided their written informed consent to participate in this study.

Consent for publication

Written informed consent was obtained from the patients for the publication of any potentially identifiable images or data included in this article.

Statement

During the preparation of this work the authors used ChatGPT-3.5 in order to improve the readability of some sentences. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Competing interests

The authors declare no competing interests.

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