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FOXM1 and CHD4 expression is associated with chemoresistance in hepatoblastoma

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ABSTRACT

Hepatoblastoma (HB) is the most common malignant liver tumor in childhood. Although pre-operative cisplatin (CDDP)-based chemotherapy is often used in cases of HB, about 20% of HB patients exhibit resistance to CDDP. Forkhead box protein M1 (FOXM1) and chromo-domain-helicase-DNA-binding protein 4 (CHD4) have been associated with CDDP resistance in various tumors. We here analyzed the immunohistochemical expression of FOXM1 and CHD4 in HB specimens of 33 patients (mean age: 20 months) post-chemotherapy. The differentiation of specimens was assessed using the digital pathology software QuPath®, and then the relation between the FOXM1 or CHD4 expression and the differentiation and various other clinicopathological parameters was investigated. The histological type was epithelial in 19 cases (57.6%) and mixed epithelial and mesenchymal in 14 cases (42.4%). Nine cases had only a fetal component, 1 case had only an embryonal component, 22 cases had both fetal and embryonal components, and 1 case had no viable tumor. Both the FOXM1 and CHD4 immunoexpressions were found significantly more frequently in the embryonal than fetal components ($p<0.0001$ and $p<0.0001$, respectively). Regarding chemotherapy efficacy, the alpha-fetoprotein (AFP) level after chemotherapy was correlated with both the imaging shrinkage rate ($R=-0.52$) and histological residual rate (the percentage of the viable tumors of HB after chemotherapy)($R=0.62$). High FOXM1 score was correlated with a high-postoperative AFP value ($p<0.01$) and a low AFP attenuation rate ($p<0.05$), but the FOXM1 score was not correlated with the imaging shrinkage rate ($p=0.4418$) or histological residual rate ($p=0.4418$). High CHD4 score showed a nonsignificant trend toward correlation with high postoperative AFP value ($p=0.0849$) and was not significantly correlated with the other parameters. Collectively, our results showed that FOXM1 expression may be useful in evaluating the response to CDDP-based chemotherapeutic regimens. Accurate measurement of FOXM1 expression by our scoring system using QuPath® is important in cases with mixed HB components of various differentiation levels.

1. Introduction

Hepatoblastoma (HB) accounts for about 1% of pediatric solid tumors and is the most common malignant liver tumor in childhood, with a particularly high prevalence in children under 5 years old [1–3]. The incidence of HB is increasing due to improved survival of premature infants [2,3]. Among the current surgical therapeutic choices for HB, complete tumor resection remains the cornerstone of therapy for long-term disease-free survival. In addition, accurate risk stratification, effective chemotherapy, and liver transplantation have led to significant improvements in outcomes for patients with HB [1,4]. Many patients with HB have been treated with adjuvant or neoadjuvant chemotherapy using cisplatin (CDDP). Indeed, among patients with PRETEXT I/II tumors without distant metastasis or other annotation factors, CDDP has achieved 5-year survival rates greater than 90% in Japan (JPLT) [1], North America (COG) [4] and Europe (SIOPEL) [5]. However, about 20% of HB patients treated with CDDP-based neoadjuvant chemotherapy have a poor response to this treatment, and the prognosis in

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these patients is poor. There are various studies on CDDP-resistant cases of HB, but none of them are conclusive, so additional studies are needed to determine the causes of CDDP resistance and effective treatments for the CDDP-resistant patient.

The histological type of HB is divided into epithelial and mixed epithelial and mesenchymal [6]. About 90% cases of all HB contain both fetal and embryonal components in viable tumor, and they tend to be randomly distributed [7]. In histological grading, there is no difference in histology between fetal component and embryonal component [7], but some reports have suggested that there is a difference in prognosis depending on the histological grading [1,8,9].

Forkhead box protein M1 (FOXM1) is involved in DNA damage repair, cell proliferation, cell cycle progression, cell differentiation, and angiogenesis, and has been reported as a poor prognostic factor in various malignancies, and CDDP resistance has been reported in patients with high levels of FOXM1 [10–12]. Chromo-domain-helicase-DNA-binding protein 4 (CHD4) is a core member and the largest subunit of the nucleosome remodeling and deacetylase complex, which functions as a chromatin remodeler. CHD4 is involved in cell cycle regulation and DNA repair and has also been reported to be associated with CDDP resistance [13]. However, there have been no reports on the association between CDDP resistance and FOXM1 or CHD4 in HB.

In the present study, we analyzed the immunohistochemical expressions of FOXM1 and CHD4 in patients with HB, according to the histological differentiation. We also investigated the relationship between FOXM1 or CHD4 expression and clinicopathological parameters, and discussed the association of this relationship with CDDP resistance.

2. Materials and methods

2.1. Patients and tumor samples

Of the HB patients who underwent surgery at Kyushu University, Japan, between January 2001 and September 2022, 33 patients who received preoperative chemotherapy including CDDP were included. Six of 33 cases also included biopsy specimens prior to chemotherapy. We investigated the clinical data (serum alpha-fetoprotein (AFP) levels at the initial visit before neoadjuvant chemotherapy and again before surgery) by referring to the patients' medical records. The AFP attenuation rate was determined as the difference between the AFP level after chemotherapy and that at the initial visit divided by that at the initial visit. The tumor volume reduction by preoperative chemotherapy was evaluated by imaging using RECIST criteria [14] and also by histology. Tumor tissue from 33 post-chemotherapy resection specimens and 6 pre-chemotherapy biopsy specimens was fixed in formalin, embedded in paraffin, cut to a slice thickness of 3 μm, and stained with hematoxylin and eosin. All specimens of the maximally cut surface of the tumor were evaluated for viable cells and classified according to tumor differentiation (fetal or embryonal); the open-source, digital pathology software QuPath® was used to measure the percentages of fetal and embryonal differentiation (Supplementary figure 1). An average of 9 slide glasses (range 2–23), depending on tumor size, were reviewed for each case. We defined the histological residual rate as the percentage of the viable tumors of HB after chemotherapy. Because HB forms a fibrous capsule, we considered the area surrounded by the capsule as the original tumor, including any necrosis or fibrosis, and histological residual rate was calculated as the percentage of the area of viable tumor cells out of the area of the tumor surrounded by the capsule. The institutional review board at Kyushu University approved this study (No. 22293–01).

2.2. Immunohistochemistry

Surgically resected specimens were available in all 33 patients and pre-chemotherapy biopsy specimens were available in 6 patients. Immunohistochemical staining using the universal immunoperoxidase polymer method (Envision-kit; Dako-Japan, Tokyo) was performed for all available cases. Antigen retrieval was carried out by boiling slides with target retrieval solution (TRS; Dako, Carpinteria, CA). The primary antibody was rabbit monoclonal anti-FOXM1 (1:100 dilution in PBS; ab207298; Abcam, Cambridge, UK) or mouse monoclonal anti-CHD4 (1:500 dilution in PBS; ab70469; Abcam, Cambridge, UK).

The IHC specimens were independently evaluated by three pathologists (YH, KK, YO) who were blinded to the clinical data. The average score in each case was calculated. The FOXM1 positive rate was measured at 3 locations in each fetal or embryonal component of the representative sections, and the mean value was defined as the FOXM1 positive rate for each fetal or embryonal component. The CHD4 score was calculated by multiplying the intensity score (0,1,2,3) and proportion score (0: $\leq$10%; 1: 10–25%; 2: 25–50%; 3: $\geq$50%) in each fetal and embryonal component of the representative sections.

The FOXM1 score index and CHD4 score index were calculated for each case by multiplying the FOXM1 positive ratio and CHD4 score by the percentage of residual fetal or embryonal tumor, respectively (Supplementary figure 1).

2.3. Statistical analysis

All statistical analysis was performed using the JMP Pro software program (version 16.0; SAS Institute, Cary, NC). To evaluate correlations with the chemotherapy effect (serum AFP levels after chemotherapy, image shrinkage rate, and histological residual rate), Spearman's rank correlation coefficient and scatter plotting analyses were performed. A correlation coefficient of $|R|>0.4$ was considered significant. The Mann-Whitney U test was used to compare the fetal and embryonal component for the FOXM1 positive rate or CHD4 score, and between FOXM1 and CHD4 high/low index score groups and chemotherapy efficacy. Values of $p<0.05$ were considered significant.

3. Results

3.1. Patient characteristics

The clinical and pathological characteristics of the 33 (male, n=12 [36.4%]; female, n=21 [63.6%]) patients with HB are summarized in Table 1. Median age at diagnosis was 20 months (range: 3–183 months), PRETEXT stage at diagnosis was I in 2 cases (6.1%), II in 13 cases (39.4%), III in 7 cases (21.2%), and IV in 11 cases (33.3%). Six patients (18.2%) had distant metastases, including 5 patients with lung and 1 with bone metastasis. Only 1 case (3.0%) had rupture. The procedure performed in the first surgery was subsegmentectomy in 6 cases (18.2%), segmentectomy in 1 case (3.0%), right lobectomy in 7 cases (21.2%), left lobectomy in 1 case (3.0%), extended right hepatectomy in 5 cases (15.2%), extended left hepatectomy in 2 cases (6.0%), trisegmentectomy in 4 cases (12.1%), and explant in 7 cases (21.2%). The tumors in all but 1 case (97.0%) could be completely resected, including in 7 cases (21.2%) in which explantation was performed. Among the 33 patients, 26 survived and 5 died. The decedents included 3 patients who died of HB, 1 patient with acute myelocytic leukemia after chemotherapy, and 1 patient whose death had no known relationship to tumor or treatment. According to the WHO classification [6] for residual tumor after chemotherapy, the histological type was epithelial in 19 cases (57.6%) and mixed epithelial and mesenchymal in 14 cases (42.4%). Nine cases had only a fetal component, 1 case had only an embryonal component, 22 cases had both fetal and embryonal components, and 1 case had no viable tumor—i.e., no fetal component or embryonal component in the residual tumor.

3.2. Immunohistochemical findings

The expression of FOXM1 was significantly higher in the embryonal component (median 35.4% (14.7–70.7)) than in the fetal component

Table 1
Characteristics.

Age at diagnosis (months)	
Median (range)	20 (3–183)
Gender (%)	
Male	12 (36.4%)
Female	21 (63.6%)
PRETEXT (%)	
I	2 (6.1%)
II	13 (39.4%)
III	7 (21.2%)
IV	11 (33.3%)
Metastasis (%)	
No	27 (81.8%)
Yes	6 (18.2%)
Rupture (%)	
No	32 (97.0%)
Yes	1 (3.0%)
Outcome (%)	
Alive	26 (78.8%)
Dead	5 (15.2%)
Unknown	2 (6.0%)
Operation (%)	
Subsegmentectomy	6 (18.2%)
Segmentectomy	1 (3.0%)
Right lobectomy	7 (21.2%)
Left lobectomy	1 (3.0%)
Extended right hepatectomy	5 (15.2%)
Extended left hepatectomy	2 (6.0%)
Trisegmentectomy	4 (12.1%)
Explant	7 (21.2%)
Resection (%)	
Complete resection	32 (97.0%)
Incomplete resection	1 (3.0%)
Histological type (%)	
Epithelial	19 (57.6%)
Mixed epithelial and mesenchymal	14 (42.4%)

(median 3.7% (0.4–7.9)) ($p<0.0001$). The expression of CHD4 was significantly higher in the embryonal component (median 9 (3−9)) than in the fetal component (median 0 (0−6)) ($p<0.0001$) (Fig. 1).

There was generally no difference in FOXM1 expression among either the pre-chemotherapy biopsy or post-chemotherapy resection specimens with the same pathological differentiation (Supplementary table).

3.3. Clinical and histological findings

Clinical and histopathological findings related to chemotherapy efficacy are shown in Table 2. The median serum AFP level in the serum of patients before chemotherapy was 484,000 (3985–2622,926) ng/ml, and that after chemotherapy was 5573 (14.6–342,615) mg/ml. The median attenuation rate of AFP was 98.5 (-307.68–99.99)%. Median imaging tumor shrinkage rate was 43.2 (-21.8–62.5)%. The median histological residual rate was 28.4 (0–81.2)%, and the median

Table 2
Clinical and histologiacl findings of chemotherapy efficacy.

Serum AFP before chemotherapy (ng/ml)	
Median (range)	484,000 (3985 – 2622,926)
Serum AFP after chemotherapy (ng/ml)	
Median (range)	5573 (14.6 – 342,615)
Attenuation rate of AFP (%)	
Median (range)	98.5 (-307.68 – 99.99)
Imaging tumor shrinkage rate (%)	
Median (range)	43.2 (-21.8 – 62.5)
Histological viable tumor rate (%)	
Median (range)	28.4 (0 – 81.2)
-Fetal component	11.6 (0 – 74.2)
-Embryonal component	1.4 (0 – 81.2)

percentages of viable tumor cells in the fetal and embryonal components were 11.6 (0–74.2)% and 1.4 (0–81.2)%, respectively (Table 2). The AFP value after chemotherapy was correlated with both the imaging shrinkage rate ($R=-0.52$) and histological residual rate ($R=0.62$) (Fig. 2). When post-chemotherapy AFP values were divided by median values into high and low groups, the fetal component percentage of the viable tumor was significantly greater for the low-AFP group than the high-AFP group ($p<0.01$), and the embryonal component percentage of the viable tumor was significantly greater for the high-AFP group than the low-AFP group ($p<0.0001$) (Supplementary figure 2).

3.4. Comparison of FOXM1 expression with indices of chemotherapy efficacy

High FOXM1 score was correlated with high postoperative AFP value ($p<0.01$), or low AFP attenuation rate ($p<0.05$), but not with imaging shrinkage rate ($p=0.4418$) or histological residual rate ($p=0.4418$) by Mann-Whitney U test, when the FOXM1 score index was divided into high and low groups by a median value of 8.39 (Fig. 3).

3.5. Comparison of CHD4 expression with indices of chemotherapy efficacy

In analysis by Mann-Whitney U test using a median CHD4 score of 3.6 to divide samples into high and low CDH4 groups, there was a nonsignificant trend toward correlation of the CHD4 group with the postoperative AFP value ($p=0.0849$), and no significant correlation between the CHD4 group and the AFP attenuation rate ($p=0.2413$), imaging shrinkage rate ($p=0.9451$) or histological residual rate ($p=0.9817$) (Fig. 4).

4. Discussion

CDDP is the key drug in preoperative chemotherapy for HB and has been used consistently for over 30 years worldwide [1,15,16]. However, about 20% of HB patients have chemoresistance to CDDP, poor

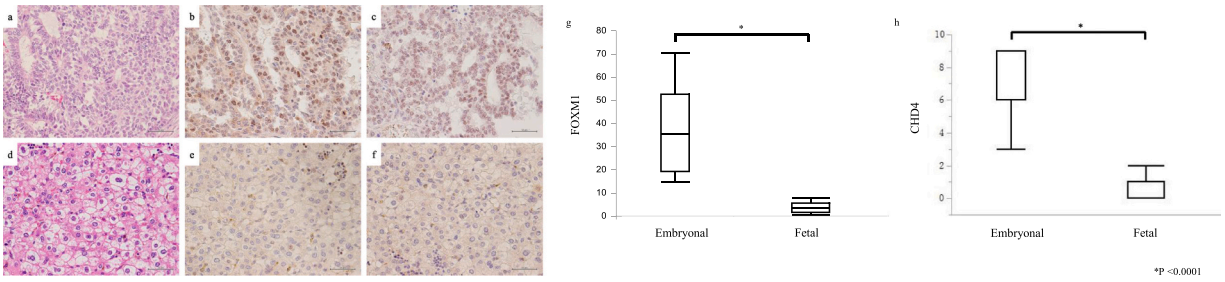

Fig. 1. Immunohistochemical findings. a-c: embryonal component; HE (a), FOXM1 positive rate 35.8% (b), CHD4 staining score of 9 (proportion score 3, intensity score 3) (c). d-f: fetal component; HE (d), FOXM1 positive rate 5.4% (e), CHD4 staining score of 0 (proportion score 0, intensity score 0) (f). g: FOXM1 positive rate in embryonal component 35.4% (14.7–70.7), FOXM1 positive rate in fetal component 3.7% (0.4–7.9) ($p<0.0001$). h: CHD4 staining score in embryonal component 9 (3−9), CHD4 staining score in fetal component 0 (0−6) ($p<0.0001$).

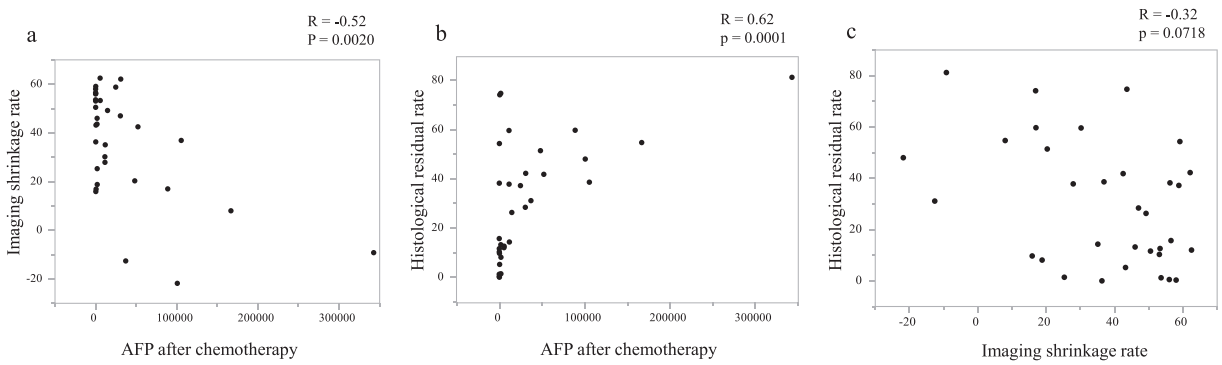

Fig. 2. Correlates of AFP value after chemotherapy, imaging shrinkage rate, and histological residual rate. Scatter plot of chemotherapy effects: AFP value after chemotherapy and imaging shrinkage rate (R=-0.52, a), and AFP value after chemotherapy and histological residual rate (R=0.62, b) were correlated between the two groups. Imaging shrinkage rate and histological residual rate (R=-0.32, c) were not correlated.

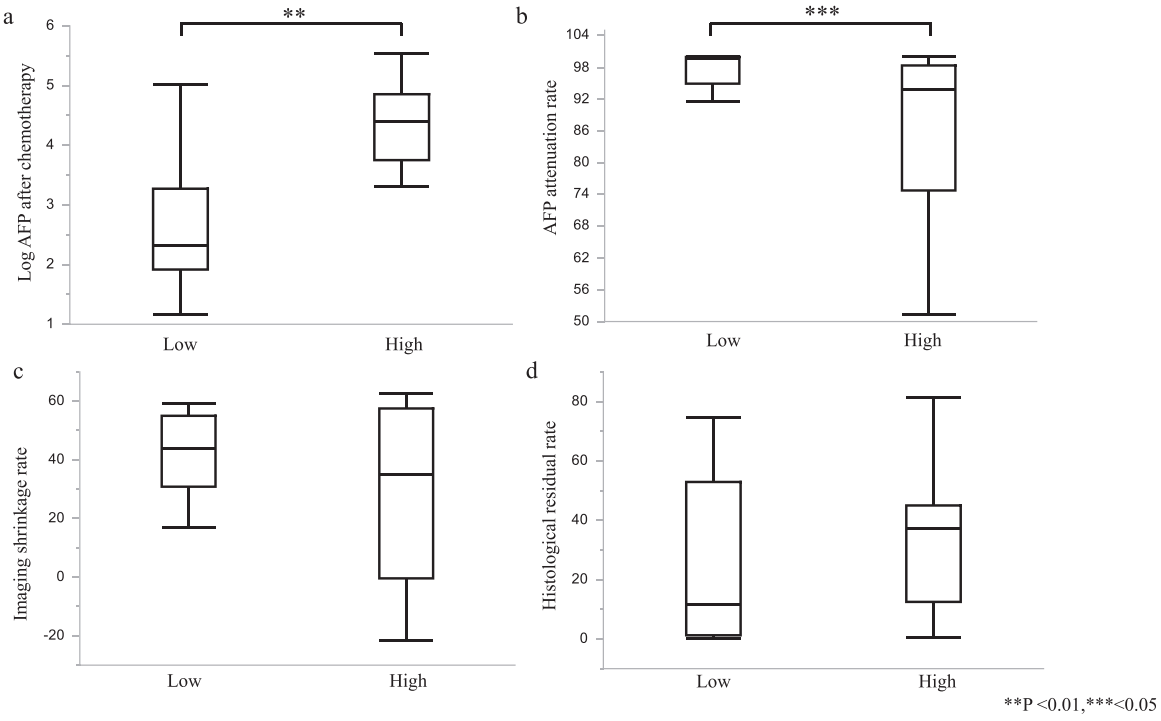

Fig. 3. Comparison of FOXM1 expression with indices of chemotherapy efficacy. The median FOXM1 score of 8.39 was used to divide patients into high and low FOXM1 groups, and high FOXM1 score was correlated with high postoperative AFP value ($p<0.01$, a) or low AFP attenuation rate ($p<0.05$, b), but not with imaging shrinkage rate ($p=0.4418$, c) or histological residual rate ($p=0.4418$, d) by Mann-Whitney U test.

prognosis, and high recurrence rate [17,18]. Therefore, new markers are needed to predict the response to CDDP-based chemotherapy for HB. In our present study, we focused on the association of FOXM1 and CHD4 immunoexpression with the response to CDDP-based chemotherapy. Our results indicated that FOXM1 expression after chemotherapy is associated with the chemotherapy response, suggesting that FOXM1 may be useful in determining the response to CDDP-based chemotherapy for HB.

Predictions of chemotherapy response are usually made using biopsy specimens collected at the time of initial diagnosis. However, HB is often diagnosed based on clinical findings and AFP levels and treated without biopsy. In such cases, a prechemotherapy specimen to evaluate FOXM1 is not obtained, but confirmation of chemotherapy susceptibility may be a factor in estimating prognosis if chemotherapy is continued after surgery. Since there was generally no difference in FOXM1 expression among either the pre-chemotherapy biopsy or post-chemotherapy resection specimens with the same pathological differentiation in our 6 cases, we believe that the post-chemotherapy resection specimen can be substituted if a pre-chemotherapy biopsy specimen cannot be obtained. FOXM1 expression has been implicated in chemoresistance [19]. It has been reported that CDDP administration increases FOXM1 expression in CDDP-resistant breast cancer [10] and nasopharyngeal carcinoma [20] cell lines, but this is the first time that FOXM1 has been evaluated by the differentiation level in HB. Although further accumulation of cases will be needed, our present results suggest that a higher dose or duration of CDDP than is used in current regimens may be required to increase FOXM1 expression in HB.

In our present study, when examined by degree of differentiation, FOXM1 was significantly more highly expressed in the embryonal than the fetal component. It has been reported that the presence of a fetal component of HB is a favorable prognostic factor compared with other histologic types [1,8], especially the embryonal component [9]. FOXM1 has been reported as a proliferative and poor prognostic factor in a variety of tumors [11,12,21,22]. These results may indicate differences in

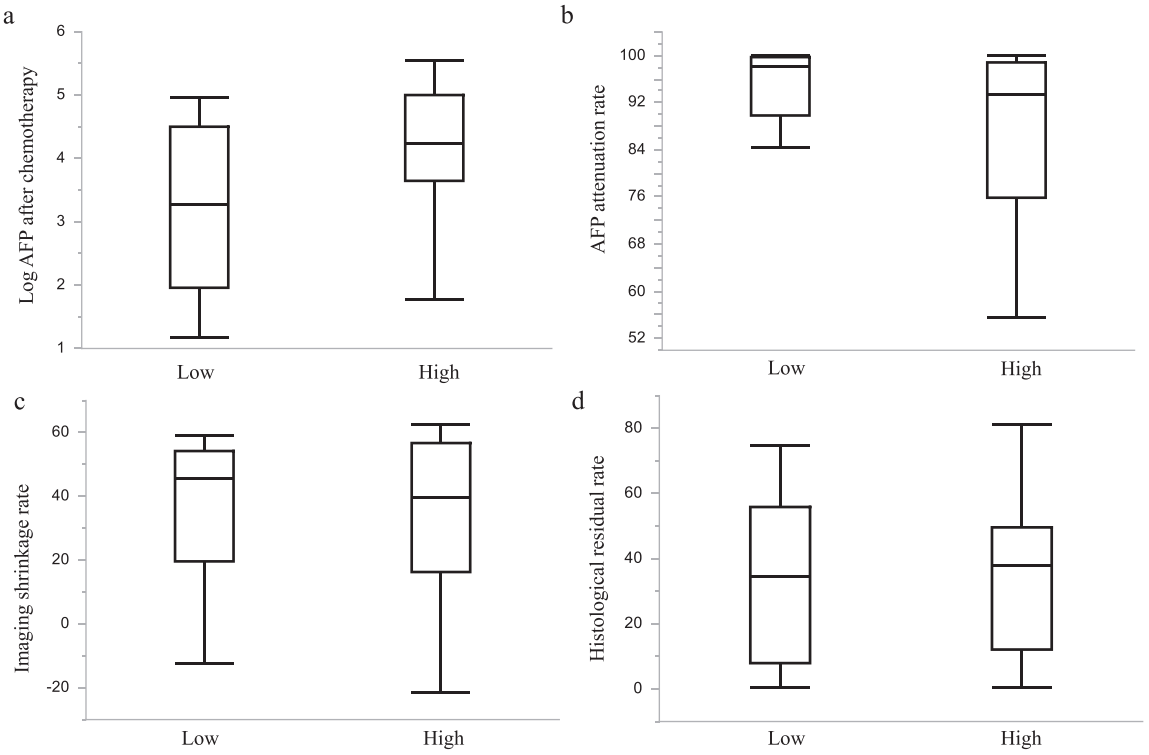

Fig. 4. Comparison of CHD4 expression with various indices of chemotherapy efficacy. In analysis by Mann-Whitney U test using a median CHD4 score of 3.6 to divide samples into high and low CDH4 groups, there was a nonsignificant trend toward correlation of the CHD4 group with the postoperative AFP value (p=0.0849, a), and no significant correlation between the CHD4 group and the AFP attenuation rate (p=0.2413, b), imaging shrinkage rate (p=0.9451, c) or histological residual rate (p=0.9817, d).

histological proliferative activity. Therefore, accurate assessment of FOXM1 expression in case with mixed components of various differentiation should be evaluated with our scoring system using QuPath®.

The high-FOXM1 score index group showed significantly higher AFP values and lower AFP attenuation rates after chemotherapy, compared with the low-FOXM1 score index group. Therefore, it was suggested that a high-FOXM1 score index was associated with a poor chemotherapy response including chemoresistance. AFP is known to represent disease activity in HB, and AFP is an indicator of risk classification [23]. The post-chemotherapy AFP value and the AFP attenuation rate (AFP decline) have been used to evaluate chemotherapy efficacy [17,24–26] and as indicators of tumor recurrence [24,27]. It has also been reported that AFP at the time of surgery in liver transplant cases affects event-free survival [28]. On the other hand, FOXM1 has also been reported to be associated with resistance to CDDP-based and other chemotherapeutic regiments in various tumors such as breast cancer [10], metastatic nasopharyngeal carcinoma [20], non-small cell lung cancer [29], and osteosarcoma [30]. CDDP administration increased FOXM1 expression and downregulation of FOXM1 expression enhanced the sensitivity to CDDP in cell lines of CDDP-resistant breast cancer [10] and of CDDP-resistant nasopharyngeal carcinoma [20]. Therefore, FOXM1 expression in HB may also be involved in the tumor's inherent CDDP resistance because we have now reported a correlation between FOXM1 immunoexpression and CDDP chemotherapy response in HB.

Imaging evaluation of chemotherapy response in HB has also been reported, but RECIST criteria has shown to be difficult to predict prognosis [26,31], because of heterogeneous shrinkage due to central necrosis [32], hemorrhage, and fibrosis associated with postchemotherapy changes [26]. Histological evaluation has been reported to correlate with prognosis in terms of the percentage of viable tumor [33] and percentage of tumor necrosis [32], and multifocal tumor [33,34], vascular invasion, and metastasis [34] are poor prognostic factors. However, the post-chemotherapy surgical specimen usually demonstrates regressive and necrotic changes, and changes in the nuclei, sometimes making it difficult to evaluate the characteristics of persistent viable tumor [8]. Although previous reports indicate that AFP, imaging, and histological evaluation can be indicators of chemotherapy efficacy, our present results newly show that the post-chemotherapy AFP value is correlated with both the imaging shrinkage rate and histological residual rate.

On the other hand, CHD4 expression levels have also been reported to be associated with CDDP resistance in ovarian cancer [13,35,36] and colorectal cancer [37]. In our present study, the CHD4 score in the embryonal component was significantly higher than that in the fetal component. These results, like those of FOXM1, may indicate differences in histological proliferative activity. While high CHD4 score group tended to have higher AFP values after chemotherapy and was not significantly correlated with the other parameters. These results showed that CHD4 expression had weaker relation with CDDP chemotherapy response comparing to the FOXM1 expression.

The present study had some limitations. First, the study was conducted at a single institution; a study with a larger number of cases is needed, including data from patients with relapsed disease. Second, the direct anti-tumor effects of the cell-line experiments have not been verified; this task remains for a future study. Third, only 6 prechemotherapy biopsy specimens could be evaluated of the 33 cases for which resection specimens were available in this study. Although the present report was based on postchemotherapy resection specimens, it may be possible to predict the chemotherapy efficacy in the future with the accumulation of cases of prechemotherapy biopsy specimens.

In conclusion, our study suggested that FOXM1 expression is associated with CDDP chemotherapy response in patients with HB. Therefore, FOXM1 expression may be useful in evaluating the response to CDDP-based chemotherapeutic regimens. FOXM1 expression could be

treated as a biomarker that predict CDDP chemotherapy response in HB treatment, that would help HB treatment in a different way from AFP in the future.

Compliance with ethical standards

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki. The study was approved by the Ethics Committee of Kyushu University (No. 22293–01). Informed consent was obtained from the subjects or guardians.

Author contributions

Y. Hino performed the research and wrote the paper. K. Kohashi, A. Tamaki, N. Kawakubo, H. Hamada, M. Fukuhara, and Y. Shibui contributed to the research design and slide review. T. Tajiri and Y. Oda designed the research and gave final approval of the manuscript. All authors critically reviewed and approved the manuscript.

CRediT authorship contribution statement

Masahiro Fukuhara: Investigation. **Hiroshi Hamada:** Investigation. **Naonori Kawakubo:** Investigation. **Yuko Hino:** Writing – original draft. **Yoshinao Oda:** Supervision. **Akihiko Tamaki:** Investigation. **Kenichi Kohashi:** Writing – review & editing. **Tatsuro Tajiri:** Supervision. **Yuichi Shibui:** Investigation.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prp.2024.155348.

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