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Lactate Dehydrogenase Is a Useful Marker for Predicting the Efficacy of Bevacizumab-containing Chemotherapy in Patients With Metastatic Colorectal Cancer

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Abstract. *Background/Aim: No biomarkers that predict the benefit from anti-vascular endothelial growth factor (VEGF) antibodies have been identified. It is necessary to discover biomarkers that can identify patients who are more likely to benefit from bevacizumab-containing treatment, especially those who are more likely to benefit from treatment with bevacizumab beyond progression (BBP). Levels of serum lactate dehydrogenase (LDH), reported to be an indirect marker of hypoxia and angiogenesis, may be a useful marker for monitoring the efficacy of suppression of angiogenesis. Patients and Methods: The clinical data of 91 patients with unresectable metastatic colorectal cancer who were treated with bevacizumab-containing chemotherapy as first-line treatment were collected and studied. Results: In the second-line treatment, the bevacizumab plus chemotherapy group showed significantly better progression-free survival (PFS) in comparison to the chemotherapy-alone group in patients with low post-first-line-treatment serum LDH levels. On the other hand, no significant differences in the PFS rate were observed between the two groups in patients with high post-first-line-treatment serum LDH levels. Conclusion: The post-first-line-treatment serum LDH levels may, therefore, be useful marker for predicting the efficacy of treatment with BBP.*

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Key Words: Colorectal cancer, chemotherapy, lactate dehydrogenase, anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab beyond progression.

During the last two decades, due to development of new cytotoxic agents, such as oxaliplatin and irinotecan, and molecular targeted agents, such as anti-vascular endothelial growth factor (VEGF) antibody and anti-epidermal growth factor receptor (EGFR) antibody, the prognosis of metastatic colorectal cancer (CRC) has substantially improved and the median survival time has been increased by approximately 30 months (1, 2). In addition, in recent years, the prognosis of metastatic CRC patients has been further improved due to development of drugs used in later-line treatment, such as regolafenib and trifluridine/thymidine phosphorylase inhibitor (3, 4).

Biomarkers that predict the efficacy of anti-EGFR antibodies, such as the RAS status and the location of the primary tumor, have been reported (5, 6). However, no biomarkers that predict the benefit from anti-VEGF antibodies have been identified (7). Furthermore, in clinical practice, the selection of anti-VEGF antibodies after treatment failure of bevacizumab-containing chemotherapy in first-line treatment is often decided according to the physician's choice. Thus, it is necessary to discover biomarkers that can identify patients who are more likely to benefit from bevacizumab-containing treatment, especially those who are more likely to benefit from treatment with bevacizumab beyond progression (BBP).

Serum lactate dehydrogenase (LDH) levels have been reported to be a predictive marker of chemotherapeutic efficacy in patients with metastatic CRC (8). In addition, serum LDH levels have been reported to be an indirect marker of hypoxia and angiogenesis (8). Thus, the serum LDH levels may be a predictive marker of the efficacy of bevacizumab, which suppresses angiogenesis by inhibiting VEGF (9), and a marker for monitoring the efficacy of the suppression of angiogenesis.

The aim of this study was to assess the significance of the serum LDH levels as predictive marker of the efficacy of first-line bevacizumab-containing chemotherapy and of the efficacy of treatment with BBP.

Patients and Methods

Patients. Clinical data of 91 patients with unresectable metastatic CRC who were treated with bevacizumab in combination with fluorouracil + oxaliplatin/irinotecan as a first-line chemotherapy at the Osaka City University Hospital between April 2008 and November 2016 were collected. Regarding the primary lesion, symptomatic tumors were generally resected, however, huge tumors that invaded neighboring organs were not resected and instead only colostomy was performed. This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 2020-026) and was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Evaluation. Pretreatment blood samples were obtained within 1 week before the initiation of bevacizumab-containing first-line chemotherapy. Post-first-line-treatment blood samples were obtained within 2 weeks after treatment failure of the first-line treatment. An appropriate cut-off value of the serum LDH levels was determined based on a receiver operating characteristic (ROC) curve analysis. The patients were then classified into the low LDH group and the high LDH group. The response was evaluated by computed tomography every 8-10 weeks, according to the Response Evaluation Criteria in Solid Tumors (10). An objective response was defined as a complete or partial response. Disease control was defined as a complete or partial response or stable disease.

Statistical analyses. All statistical analyses were performed using the SPSS software package for Windows (SPSS, Chicago, IL, USA). The significance of differences in the serum LDH level and the clinicopathological characteristics and response to chemotherapy were analyzed using a chi-squared test, Fisher's exact test, and Mann-Whitney's *U*-test. Survival curves were estimated using the Kaplan–Meier method, and the differences in the survival curves were assessed with the log-rank test. *p*-Values of <0.05 were considered to indicate statistical significance.

Results

The patient characteristics before initiation of first-line chemotherapy are shown in Table I.

Classification according to pretreatment serum LDH levels. The pretreatment serum LDH level, as a continuous variable, was used as the test variable and the 27-month survival (median survival time: 27 months) was used as the state variable. An ROC curve analysis revealed that the appropriate cut-off value of the pretreatment serum LDH levels was 296.5 (sensitivity=34.8%, specificity=100%) (Figure 1). The cut-off value was therefore set at 300.

Table I. *Patient characteristics before the initiation of first-line chemotherapy.*

Age (years)	
Median (range)	64 (18-89)
Gender, n	
Male	50
Female	41
Performance status, n	
0	83
1	8
Location of primary tumor, n	
Right side	24
Left side	67
Histological type, n	
Well, Moderately differentiated	80
Poorly differentiated	7
Mucinous	4
RAS status, n	
Wild-type	33
Mutant type	36
Unknown	22
Detection of unresectable tumor, n	
Synchronous	56
Metachronous	35
Number of metastatic organs, n	
1	63
≥2	28
First-line chemotherapy regimen, n	
FOLFOX+bevacizumab	39
CapeOX+bevacizumab	30
FOLFIRI+bevacizumab	15
SOX+bevacizumab	7
Pretreatment CEA level (ng/ml), n	
≤5	28
>5	63

RAS: Proto-oncogene; FOLFOX: 5-fluorouracil+leucovorin+oxaliplatin; CapeOX: capecitabine+oxaliplatin; FOLFIRI: 5-fluorouracil+leucovorin+irinotecan; SOX: S-1+oxaliplatin; CEA: carcinoembryonic antigen.

Correlations between the pretreatment serum LDH levels and clinicopathological factors. The correlations between the pretreatment serum LDH levels and the clinicopathological factors are shown in Table II. High LDH levels were significantly associated with a higher carcinoembryonic antigen (CEA) level, and tended to be associated with female sex, RAS mutation and synchronous metastases.

Treatment effects of first-line chemotherapy with reference to the pretreatment serum LDH levels. The low pretreatment LDH group had significantly better progression-free survival (PFS) and overall survival (OS) rates than the high pretreatment LDH group ($p=0.0315$, $p<0.0001$, respectively) (Figure 2); however, the objective response rates (ORRs) of the two groups did not differ to a statistically significant extent (Table III).

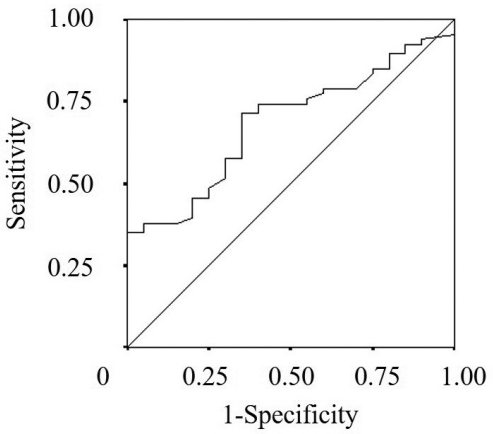

Figure 1. *The receiver operating characteristic curve of the pretreatment serum lactate dehydrogenase (LDH) levels for the overall survival status. Area under curve: 0.684; 95% Confidence Interval=0.565-0.802; p=0.013.*

Survival outcomes after treatment failure of first-line chemotherapy with reference to the post-first-line-treatment serum LDH levels. The OS rates after treatment failure of the first-line chemotherapy in the low post-first-line-treatment LDH group were significantly better than in the high post-first-line-treatment LDH group ($p<0.0001$) (Figure 3).

Treatment effects of second-line chemotherapy with reference to the post-first-line-treatment serum LDH levels in an analysis limited to patients treated with BBP. The low post-first-line-treatment LDH group had significantly better PFS and OS rates in comparison to the high post-first-line-treatment LDH group in second-line chemotherapy ($p=0.0333$, $p=0.0050$, respectively) (Figure 4); however, the ORRs of the two groups did not differ to a statistically significant extent (Table IV).

The additional effects of bevacizumab in second-line chemotherapy with reference to the post-first-line-treatment serum LDH levels. In the second-line treatment, the bevacizumab plus chemotherapy group showed significantly better PFS in comparison to the chemotherapy alone group in patients with low post-first-line-treatment serum LDH levels ($p=0.0264$) (Figure 5a). On the other hand, no significant differences in the PFS rate were observed between the bevacizumab plus chemotherapy group and the chemotherapy alone group in patients with high post-first-line-treatment serum LDH levels ($p=0.1737$) (Figure 5b).

Discussion

In this study, low pretreatment serum LDH levels were associated with better chemotherapeutic efficacy in patients treated with a bevacizumab-containing regimen as a first-line treatment. This is consistent with results from previous reports (8), that showed the significance of the serum LDH levels as a predictor of the efficacy of first-line bevacizumab-containing chemotherapy. Furthermore, low post-first-line-treatment serum LDH levels were associated with better overall survival after treatment failure of first-line chemotherapy.

Table II. *Correlations between serum lactate dehydrogenase (LDH) levels before initiation of first-line chemotherapy and clinicopathological factors.*

	Low LDH group (n=68)	High LDH group (n=23)	*p*-Value
Age (years)			
Median (range)	65 (18-89)	64 (43-77)	0.759
Gender, n			
Male	41	9	
Female	27	14	0.093
Performance status, n			
0	61	22	
1	7	1	0.674
Location of primary tumor, n			
Right side	18	6	
Left side	50	17	>0.999
Histological type, n			
Well, Moderately differentiated	58	22	
Poorly differentiated, Mucinous	10	1	0.279
RAS status, n			
Wild-type	29	4	
Mutant-type	25	11	0.083
Unknown	14	8	
Detection of unresectable tumor, n			
Synchronous	38	18	
Metachronous	30	5	0.082
Metastatic organ*, n			
Liver	27	18	
Lung	28	5	
Peritoneum	15	3	
Distant lymph node	18	4	
Other	7	3	
Number of metastatic organs, n			
1	46	17	
≥2	22	6	0.794
Primary tumor, n			
Resected	61	19	
Unresected	7	4	0.367
History of surgery for distant metastases before initiation of first-line chemotherapy, n			
Absence	62	21	
Presence	6	2	0.985
Pretreatment CEA level (ng/ml), n			
≤5	27	1	
>5	41	22	0.001

LDH: Lactate dehydrogenase; RAS: proto-oncogene; CEA: Carcinoembryonic antigen. *there was some overlapping.

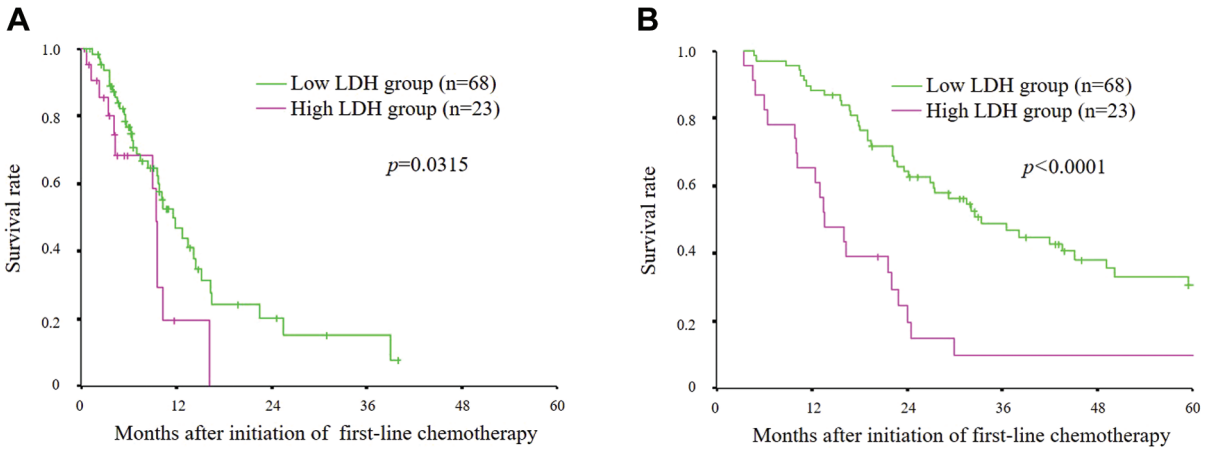

Figure 2. *Treatment effects of first-line chemotherapy with reference to the pretreatment serum lactate dehydrogenase (LDH) levels. (A) The low pretreatment LDH group showed a significantly better progression-free survival rate than the high pretreatment LDH group in first-line chemotherapy (p=0.0315). (B) The low pretreatment LDH group had a significantly better overall survival rate after the initiation of first-line chemotherapy in comparison to the high pretreatment LDH group (p<0.0001).*

Table III. *Treatment response to first-line chemotherapy according to pretreatment serum lactate dehydrogenase (LDH) levels.*

Response	Low LDH group (n=68)	High LDH group (n=23)	*p*-Value
Complete response	5	0	
Partial response	22	7	
Stable disease	27	9	
Progressive disease	11	4	
Not evaluable	3	3	
Objective response rate	41.5%	35.0%	0.795
Disease control rate	83.1%	80.0%	0.745

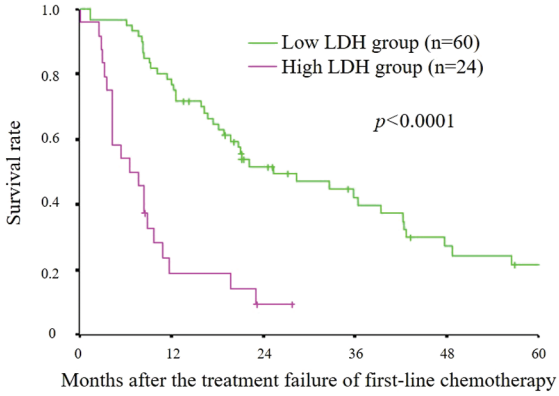

Figure 3. *Overall survival after treatment failure of first-line chemotherapy with reference to post-first-line-treatment serum lactate dehydrogenase (LDH) levels. The overall survival rate after treatment failure of the first-line chemotherapy in the low post-first-line-treatment LDH group was significantly better than that in the high post-first-line-treatment LDH group (p<0.0001).*

Table IV. *Treatment response to second-line chemotherapy according to the post-first-line-treatment serum lactate dehydrogenase (LDH) levels in an analysis limited to patients treated with bevacizumab beyond progression.*

Response	Low LDH group (n=27)	High LDH group (n=11)	*p*-Value
Complete response	1	0	
Partial response	4	3	
Stable disease	12	1	
Progressive disease	9	5	
Not evaluable	1	2	
Objective response rate	19.2%	33.3%	0.396
Disease control rate	65.4%	44.4%	0.432

Cancer cells, unlike normal cells, have been reported to prefer anaerobic glycolysis (11, 12). In the anaerobic metabolism pathway, LDH plays an important role as an enzyme responsible for the conversion of pyruvate to lactate (13). Thus, LDH is up-regulated when the angiogenetic pathway is activated by the hypoxic environment associated with rapid tumor growth (14-16). In previous reports, high serum LDH levels were revealed to be associated with the high expression of VEGF-A and a high density of microvessels (17,

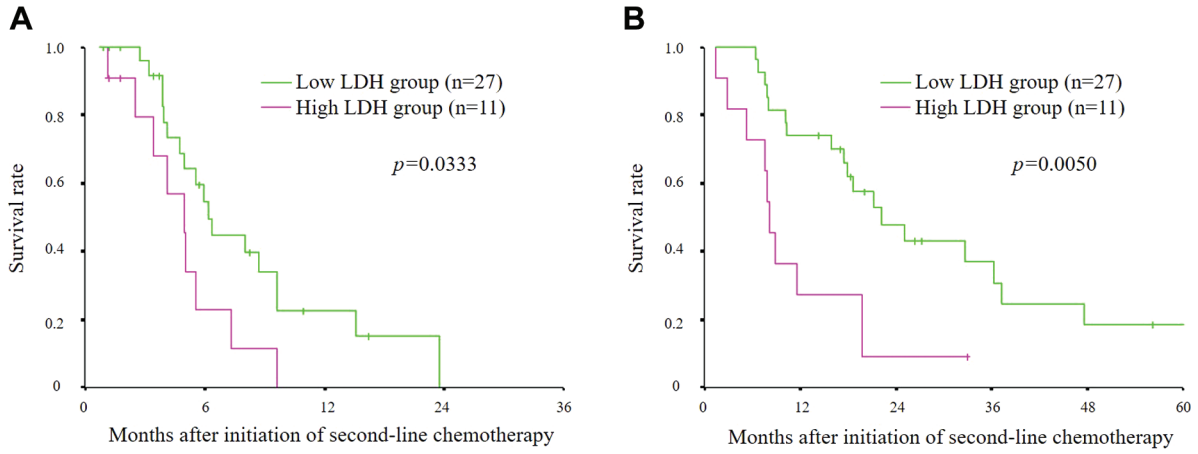

Figure 4. *The treatment effects of second-line chemotherapy with reference to the post-first-line-treatment serum lactate dehydrogenase (LDH) levels in an analysis limited to patients treated with bevacizumab beyond progression. (A) The low post-first-line-treatment LDH group had a significantly better progression-free survival rate than the high post-first-line-treatment LDH group in second-line chemotherapy (p=0.0333). (B) The low post-first-line-treatment LDH group had a significantly better overall survival rate after the initiation of second-line chemotherapy in comparison to the high post-first-line-treatment LDH group (p=0.0050).*

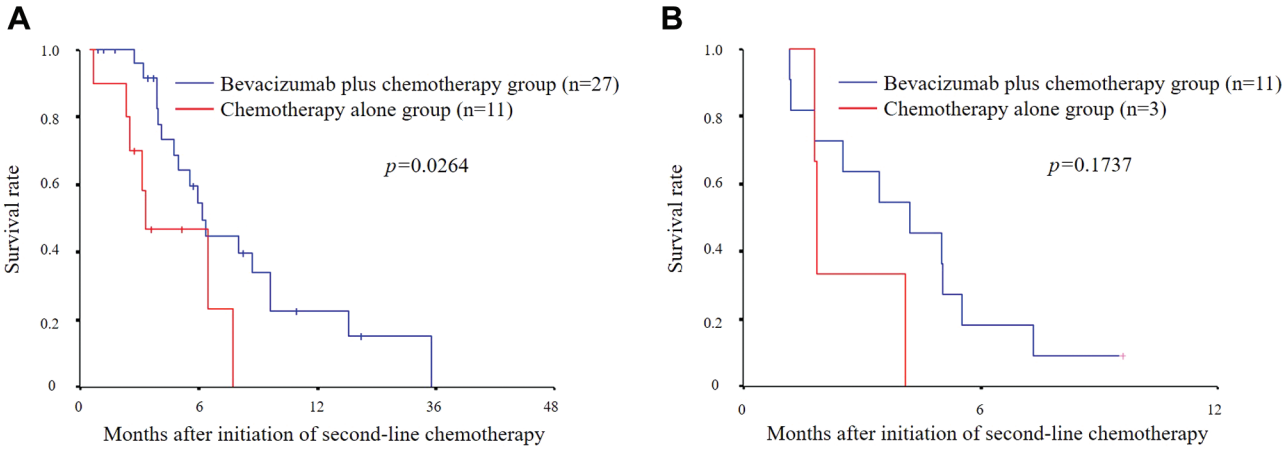

Figure 5. *The additional effects of bevacizumab in second-line chemotherapy with reference to the post-first-line-treatment serum lactate dehydrogenase (LDH) levels. (A) The bevacizumab plus chemotherapy group had a significantly better progression-free survival rate than the chemotherapy alone group in patients with low post-first-line-treatment serum LDH levels (p=0.0264). (B) There was no significant difference in the progression-free survival rates of the bevacizumab plus chemotherapy group and the chemotherapy alone group in patients with high post-first-line-treatment serum LDH levels (p=0.1737).*

18). As serum LDH levels are considered to be an indirect marker of activated tumor angiogenesis in association with hypoxia in the cancer microenvironment, high serum LDH levels are associated with a high tumor burden, rapid proliferation, enhanced tumor aggressiveness, and thus a worse prognosis (19, 20). Recently, Ahmed *et al*. reported that LDH reflects tumor growth and the dynamics of LDH are linked to the clinical course (21). The efficacy of a treatment, including chemotherapy, is therefore likely to deteriorate in patients with high serum LDH levels. In addition, serum LDH levels after treatment reflect the therapeutic efficacy and is associated with the survival time after treatment failure, as the biological phenomenon underlying the serum LDH levels is dynamic and is affected by the therapeutic effect (19).

Treatment with BBP is performed based on the theory that resistance to first-line treatment is caused by cancer cells

becoming refractory to cytotoxic anticancer agents but not to bevacizumab (22). However, in some basic research, it was reported that continuous use of bevacizumab may cause resistance to bevacizumab by activating pathways other than VEGF, such as fibroblast growth factor (23). Therefore, among patients treated with BBP, some patients may develop resistance to bevacizumab and there is a need to identify biomarkers that can be used to select patients who are likely to benefit from treatment with BBP. In this study, high post-first-line-treatment serum LDH levels were associated with worse chemotherapeutic efficacy in treatment with BBP. Although high serum LDH levels before second-line chemotherapy may simply predict a poor chemotherapeutic effect in second-line chemotherapy, similar to the mechanism seen in first-line chemotherapy, elevated post-first-line-treatment serum LDH levels, an indirect marker of activated angiogenesis, is also considered to be associated with poor inhibition of angiogenesis by bevacizumab. In this study, no additional effect of bevacizumab was observed in second-line treatment in patients with high post-first-line-treatment serum LDH levels, while an additional effect of bevacizumab was observed in second-line treatment in patients with low post-first-line-treatment serum LDH levels. Thus, as low post-first-line-treatment serum LDH levels are associated successful inhibition of angiogenesis, it is considered that bevacizumab will have effects in patients with low post-first-line-treatment serum LDH levels, and these patients are considered to be likely to benefit from the continuous use of bevacizumab. Taken together, serum LDH levels may be a useful marker for monitoring the efficacy of the suppression of angiogenesis and for predicting the efficacy of treatment with BBP.

In this study, serum LDH levels correlated with survival time, but not with objective response rate. The reason for this finding is due to the fact that among the responders to bevacizumab, there are some patients with no tumor shrinkage, however, they do demonstrate morphological changes. In such cases, a pathological response is often observed (24, 25). That is, morphological changes represent the death of cancer cells by chemotherapy. Therefore, a prolonged survival time may be obtained, even if imaging examinations do not show a reduction in the tumor diameter. These results showed the same tendency as the results from past clinical trials "NO16966" which investigated the additional effect of bevacizumab (26).

The present study was associated with several limitations. First, the current study was a retrospective study with a small cohort and was performed in a single center. Second, although we set 300 IU/l as the cut-off value of the serum LDH levels, other studies have used various cut-off values (27-29). Therefore, large prospective studies should be performed to identify the appropriate cut-off value for serum LDH. Third, there are several isozymes in LDH and not all are associated with cancer. Furthermore, although LDH is an indirect marker of angiogenesis, it is unclear how accurately the serum LDH levels reflect the degree of angiogenesis. As describe above, LDH is a comprehensive index and not a specialized index for cancer or angiogenesis. Therefore, LDH may be imperfect as a marker for predicting the effect of bevacizumab. However, considering that there are no markers that can effectively predict the effect of bevacizumab, this study is significant in that LDH has the potential to be useful for predicting and monitoring the effect of bevacizumab. Fourth, the serum VEGF level and the lactate level should also be assessed, but we were not able to obtain such data. If the relationships between the serum LDH levels and these values could be verified, it would further support that the serum LDH levels reflect the degree of angiogenesis. Finally, it is unclear whether other angiogenic inhibitors, with a different functional mechanism from bevacizumab, such as ramucirumab or aflibercept, would be effective for patients with high post-first-line-treatment serum LDH levels who are unlikely to benefit from treatment with BBP, as this study only targeted patients treated with bevacizumab.

In conclusion, serum LDH levels have the potential to be a useful marker for predicting the efficacy of bevacizumab-containing chemotherapy in patients with metastatic CRC, especially those treated with BBP.

Conflicts of Interest

The Authors declare that they have no competing interests in regard to this study.

Authors' Contributions

MS designed the study, performed the statistical analysis and drafted the manuscript. HN, TF, YI, EW and YO collected the clinical data and revised the manuscript critically. KM, SK, KH and MO designed the study and critically reviewed the manuscript. All Authors read and approved the final manuscript.

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