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Serum Interleukin-6 Levels Correlate with the Efficacy of Antiangiogenic Therapy in Metastatic Colorectal Cancer

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Abstract: *This study aims to assess the correlation between IL-6 concentration in the blood and the efficacy of antiangiogenic therapy for liver metastases from colorectal cancer. In this retrospective study, we examined 53 patients with CRLM who received non-surgical treatment from June 2017 to June 2023. We collected serum IL-6 levels before starting treatment and evaluated their impact based on consensus guidelines. The ROC curve was used to determine the best cut-off point for IL-6. We compared treatment response rates using chi-square tests and estimated overall survival (OS) and progression-free survival (PFS) using Kaplan-Meier and multivariate Cox proportional hazard regression analyses. It was observed that patients who were treated with bevacizumab had a longer progression-free survival (PFS) compared to those who did not receive it (P=0.04). Out of the 24 patients who received chemotherapy alone, 12 had a shorter PFS compared to the remaining 12 who had lower IL-6 levels (P=0.03). Among the 29 patients who were treated with the bevacizumab combination therapy, no significant difference was observed in PFS between the 19 patients who had higher IL-6 levels and the other 10 patients who had lower IL-6 levels (P=0.76). We have concluded that patients with higher levels of IL-6 benefited from antiangiogenic therapy, whereas those with lower levels did not receive the same benefits from bevacizumab.*

Keywords: *colorectal cancer, bevacizumab, inflammation, interleukin-6 (IL-6)*

1. Introduction

Colorectal cancer has emerged as the third most prevalent malignant tumor worldwide and ranks as the second leading cause of cancer-related deaths[1]. The majority of deaths among patients with advanced tumors can be attributed to tumor metastasis and progression. Antiangiogenic therapy, a primary treatment modality for advanced tumor patients, has demonstrated unsatisfactory outcomes in numerous clinical studies, including breast cancer patients where its efficacy was found to be poor[2]. This ineffectiveness may be attributed to specific resistance mechanisms or tumor hypoxia during treatment, both of which promote tumor metastasis[3]. Several relevant studies have indicated that elevated levels of inflammation are typically associated with a worsened prognosis[4] IL-6, a multi-effector cytokine, not only regulates the cellular immune response but also facilitates tumor development by activating multiple oncogenic pathways and participating in angiogenesis[5][6] This may contribute to the resistance observed in anti-angiogenic therapy. Studies have demonstrated that IL-6 levels impact the prognosis of patients receiving bevacizumab as adjuvant therapy, whereas anti-inflammatory treatments like anti-IL-6 hinder tumor growth[7][8]. However, limited research has focused on exploring the relationship between antiangiogenic therapy and serum IL-6 levels.

Consequently, this study endeavors to further investigate the correlation between serum IL-6 concentration and antiangiogenic therapy in patients with liver metastatic colorectal cancer. It aims to accomplish this by examining the effects of varying serum IL-6 levels on the response to bevacizumab therapy.

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2. Patients and methods

This retrospective study included 131 patients diagnosed with colorectal cancer and liver metastases at the First Hospital of Chongqing Medical University from June 2017 to June 2023. These patients received appropriate and regular anticancer treatment. We collected various data including patients' serum levels of carcinoembryonic antigen (CEA), serum concentrations of IL-6, tumor diameters, treatment regimens, whether or not they underwent primary intestinal tumor resection, presence of underlying diseases, date of initial diagnosis, date of follow-up, date of first detection of disease progression, and date of death prior to the start of treatment. Tumor diameters were reevaluated within 2-3 months of treatment initiation. The dosage and regimen of treatment for all patients were determined according to the Chinese colorectal diagnosis and treatment guidelines[23].

The inclusion criteria for this study were as follows: primary colorectal cancer with liver metastasis, without extrahepatic metastasis, liver diseases cannot be removed, accurate pathological diagnosis, dMMR, IL-6 was tested before treatment began, expected survival time of more than three months, and received antineoplastic drugs. The exclusion criteria included irregular chemotherapy course (n=6), incomplete clinical data (n=33), invasive treatment for metastatic lesions (n=10), receipt of anti-EGFR therapy (n=25), and factors like tumor perforation, obstruction, and surgery can cause high inflammatory response were diagnosed before treatment (n=4). Finally, 53 patients were included in this study.

Among the 53 patients, the median age was (64 ± 10.2) years, with a male-to-female ratio of 33:20. Twenty-six patients underwent resection of primary intestinal tumors and all received postoperative chemotherapy. Of these patients, 24 received oxaliplatin-based chemotherapy alone, while the remaining 29 received a regimen that included bevacizumab. Initial levels of serum CEA, serum IL-6, and plasma vascular endothelial growth factor were measured within one month before treatment initiation (*Table 1*). CT or MRI scans were performed three months after the start of the first treatment. The efficacy of the trial was evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST) (v1.1)[22], and efficacy was categorized as CR, PR, PD, and SD (PR and CR were considered adequate treatment, and PD and SD were considered ineffective treatment).

3. Statistical analysis

We conducted a retrospective analysis on the collected data, utilizing univariate analyses to examine the levels of IL-6. The purpose was to assess the impact of these factors on overall survival (OS) and progression-free survival (PFS). Our study involved 53 patients with liver metastases from primary colorectal cancer, who were enrolled at our institution between 2018 and 2023. It should be noted that we did not analyze survival for OS due to the limited duration of follow-up and the high margin of error in OS measurement. Moreover, none of the results obtained were statistically significant (P>0.05).

Regarding the determination of the optimal threshold for serum IL-6, we used the disease progression at the first review after treatment initiation as the endpoint. We found that a threshold of 4.83 ng/ml (AUC=0.644) provided the best discrimination (*Figure. 1*). Based on this threshold and the use of bevacizumab in the chemotherapy regimen, we categorized the cases into the low IL-6 group (22 cases) and the high IL-6 group (31 cases). Similarly, we categorized the cases into the chemotherapy-only group (24 cases) and the bevacizumab-chemotherapy group (29 cases). We then performed a survival analysis.

Table 1: Clinical characteristics of the patients

	(grand) total	percentage
Age (years)	64±10.2	
Sex		
Male	33	62.3
Females	20	37.7
Removal of the primary tumor		
YES	26	49.0
NO	27	51.0
Plasma CEA (pg/mL) [a]	24.1±122.7	
Serum IL-6 (pg/mL) [a]	5.3±33.8	

IL-6 Interleukin 6, CEA Carcinoembryonic Antigen
a Median ± standard deviation

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To further explore the impact of IL-6 and the use of bevacizumab on patients, we assessed the progression-free survival time (PFS) for all patients. As IL-6 was measured prior to treatment, we were unable to evaluate the relationship between the removal of the primary tumor and IL-6 levels.

The statistical analysis was conducted using SPSS 26.0 software. The $\chi 2$ test was employed to compare count data, while the Kaplan-Meier method was used to compare OS and PFS. The Log-Rank test was utilized to compare survival curves among different groups. Furthermore, multivariate analysis was performed using the Cox risk-proportional regression model to identify prognostic factors associated with the disease.

4. Results

In these 53 patients, the median serum IL-6, CEA, and age were 15.63 pg/ml, 148.02 pg/ml, and 62 years, respectively. There was no correlation between IL-6 and CEA levels ($r = -0.02$; $P = 0.86$), and there was no significant association between whether or not one received resection of the primary lesion and both PFS and OS ($P > 0.05$).

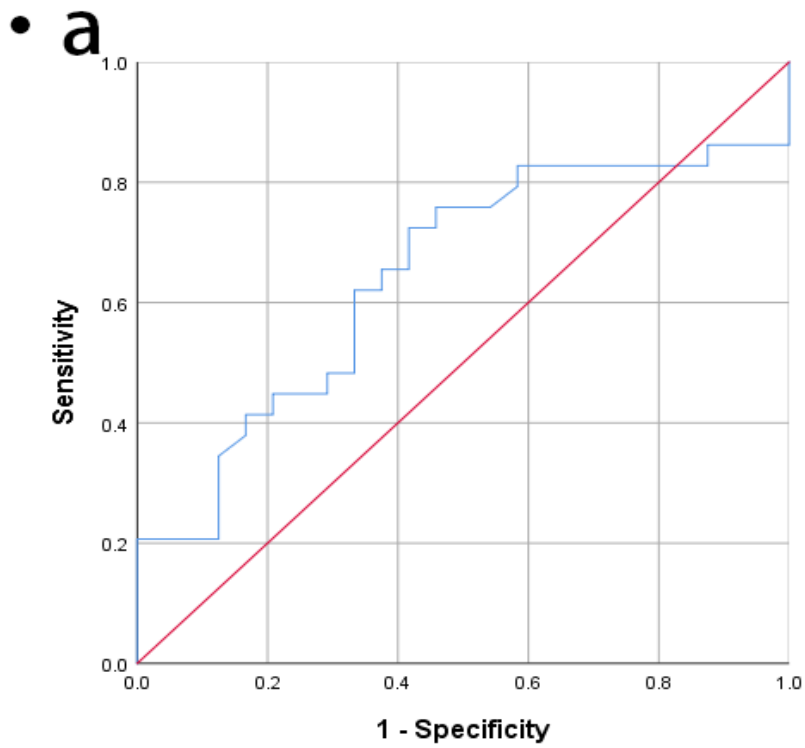

Figure 1: Working characterization curves for IL-6(a) subjects based on survival of 53 patients. The optimal threshold for IL-6 was 4.83 pg/mL, respectively.

4.1 Progression Free Survival

According to the results of this study, patients who underwent combination therapy with bevacizumab had a longer progression-free survival (PFS) compared to those who did not receive bevacizumab (P=0.04). This finding remained consistent regardless of their IL-6 levels (Figure 2a). Specifically, the median PFS for patients who did not receive bevacizumab as part of their chemotherapy regimen was 11 months, whereas for those who did receive bevacizumab, it was 17 months. However, when comparing subgroups based on their serum IL-6 levels, no statistically significant difference in PFS was observed (P=0.76).

Among the 22 patients with low serum IL-6 levels, there was no significant difference in PFS between the 10 patients who received combination chemotherapy and the 12 patients who received chemotherapy alone (P=0.71) (Figure 2b). The median PFS for the chemotherapy-alone group was 13 months, whereas for the combination therapy group, it was 15 months.

In contrast, among the 31 patients with high serum IL-6 levels, a significant difference in PFS was observed between the 19 patients in the bevacizumab combination therapy group and the 12 patients in

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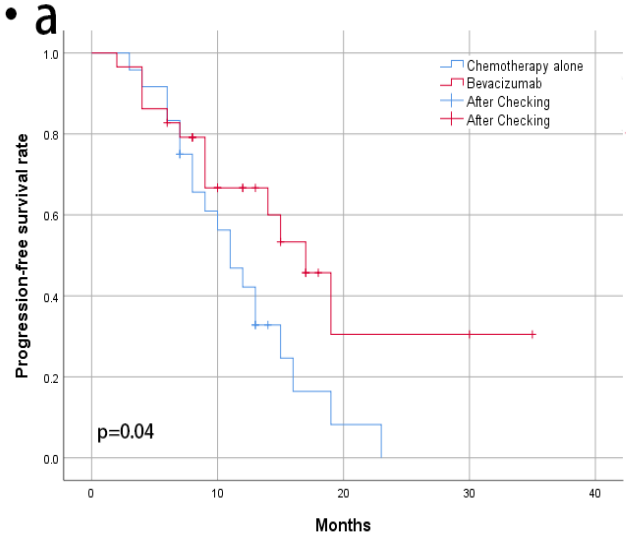
the chemotherapy-only group (P=0.02) (Figure 2c). The median PFS for the chemotherapy-only group was 7 months, while for the combination therapy group, it was 17 months.

Among the 24 patients who received chemotherapy alone, a significant difference in PFS was found between the 12 patients with higher IL-6 levels and the 12 patients with lower IL-6 levels (P=0.03) (Figure 2d). The median PFS for the lower IL-6 subgroup was 13 months, whereas for the higher IL-6 subgroup, it was 7 months.

Regarding the 29 patients treated with bevacizumab combination therapy, there was no significant difference in PFS between the 19 patients with higher IL-6 levels and the 10 patients with lower IL-6 levels (P=0.76) (Figure 2e). The median PFS for the subgroup with lower serum IL-6 was 15 months, whereas for the subgroup with higher IL-6, it was 17 months.

• a



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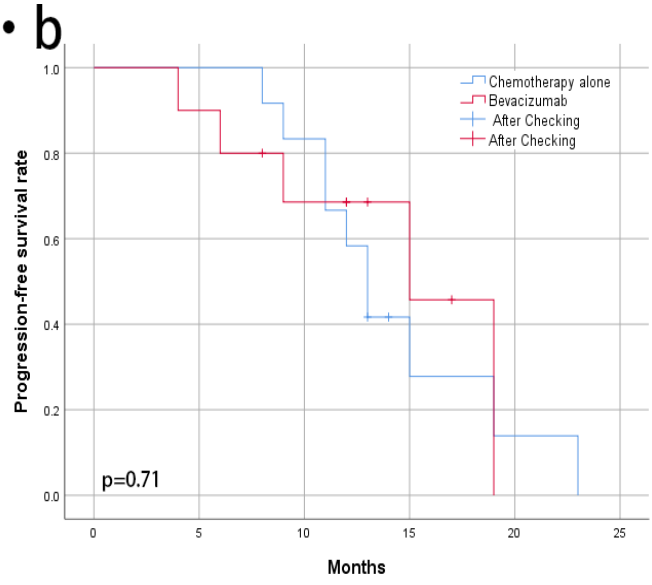

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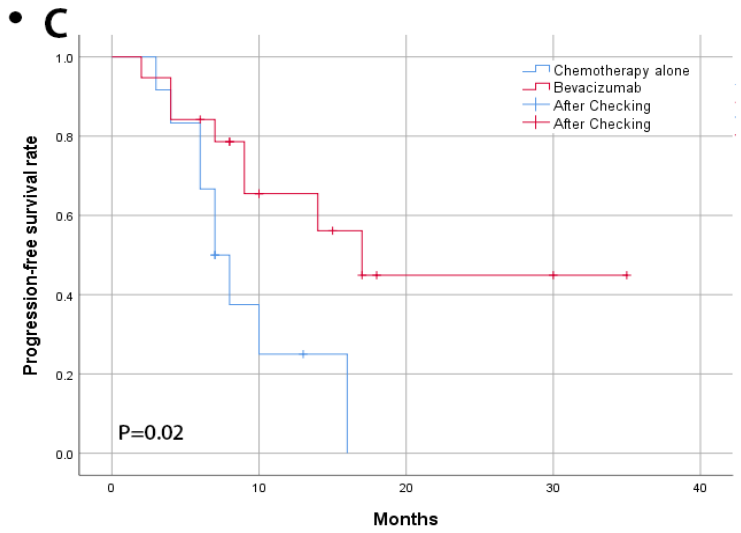

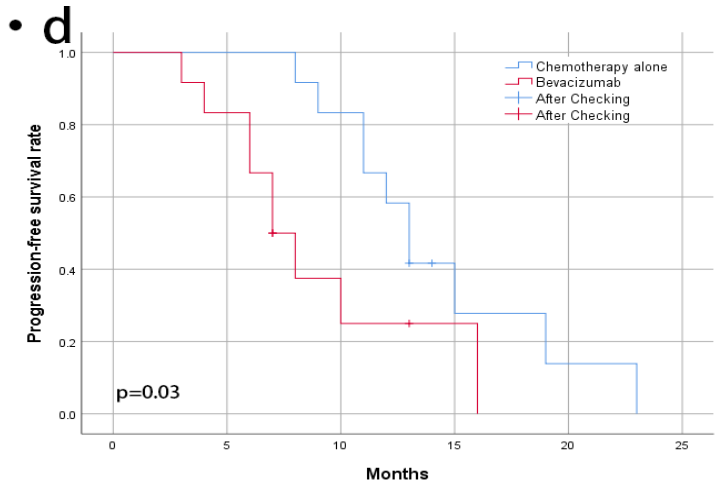

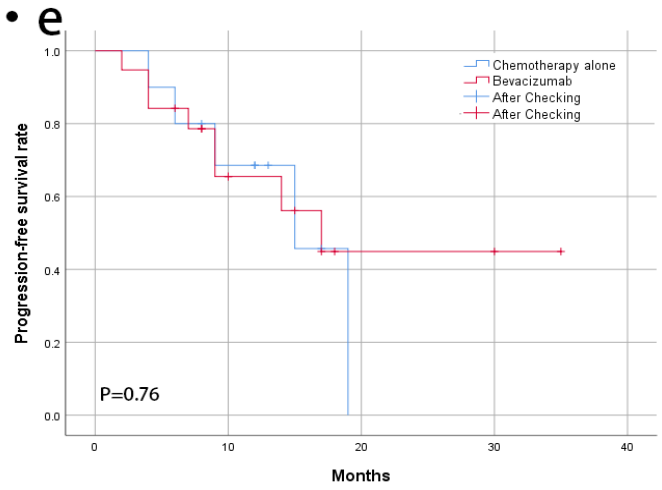

The utilization of bevacizumab demonstrated a significant extension in the progression-free survival of patients (a). No correlation between serum IL-6 levels and the clinical prognosis was observed among patients who received bevacizumab (e). Conversely, among patients who did not receive bevacizumab, higher serum IL-6 levels were associated with a poorer prognosis (e). Lastly, bevacizumab considerably enhanced the clinical prognosis of patients with higher serum IL-6 levels ©, while there was no significant improvement in the clinical prognosis of patients with lower serum IL-6 levels (b).

Figure 2: All patients were categorized into low and high serum IL-6 groups, as well as chemotherapy alone and bevacizumab combination chemotherapy groups, based on their serum IL-6 levels. Survival analysis was conducted separately for each group, considering the inclusion or exclusion of bevacizumab in the chemotherapy regimen.

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4.2 Response to treatment

We reviewed liver CT or MRI 2-3 months after the initiation of the first chemotherapy and evaluated the efficacy using the Response Evaluation Criteria In Solid Tumors (RECIST) (v1.1), CR and PR were defined as therapeutically effective, and PD and SD were defined as therapeutically ineffective; grouped according to whether or not the chemotherapeutic regimen included bevacizumab, we produced four-compartmental tables of information separately and performed chi-square tests to compare the efficacy of chemotherapy alone and in combination with chemotherapy, and compared the effect of serum IL-6 on the efficacy of early antitumor therapy.

The chi-square test confirmed that the effective rate at the beginning of treatment was significantly and statistically higher in patients with lower serum IL-6 levels (63.6%) than in patients with higher serum IL-6 levels (32.3%) (P=0.02).

When only observing the patients with chemotherapy alone, there was a significant difference between the initial treatment efficiency of patients with lower serum IL-6 levels (75%) and that of patients with higher levels (25%) (P=0.01); when we set the observation to patients with bevacizumab, there was no significant difference between the pre-treatment efficiency of patients with lower serum IL-6 levels (50%) and that of the patients in the higher group (36.8%) were not significantly different (P=0.49).

Using the COX proportional risk model to analyze PFS in the chemotherapy-only and combination chemotherapy groups, respectively, in the chemotherapy-only group, serum IL-6 level was a predictor of PFS (P=0.03) (Table 2), whereas age, gender, CEA, whether the primary lesion was resected or not, and whether the initial treatment was effective or not, were not predictive factors of PFS. In the BEV chemotherapy group, none of the factors were predictors of PFS except whether the initial treatment was effective (P=0.03) (Table 3).

Table 2: Multifactorial analysis of 24 patients receiving chemotherapy alone (Cox proportional risk model)

	risk ratio	95% CI	P-value
Age (over 65)	0.3	0.6-1.2	0.09
male	0.9	0.3-2.7	0.79
High serum IL-6 (>4.83 pg/ml)	5.0	1.2-21.6	0.03
High plasma CEA (>4.85 pg/ml)	0.5	0.1-2.1	0.33
futile treatment	2.4	0.8-7.1	0.10
Removal of colorectal tumors	1.2	0.4-3.8	0.71

CI Confidence Interval, IL-6 Interleukin 6, CEA Carcinoembryonic Antigen

Table 3: Multifactorial analysis of 29 patients receiving bevacizumab chemotherapy (Cox proportional risk model)

	risk ratio	95% CI	P-value
Age (over 65)	0.8	0.2-3.1	0.70
male	0.5	0.1-2.5	0.39
High serum IL-6 (>4.83 pg/ml)	0.6	0.2-2.2	0.47
High plasma CEA (>4.85 pg/ml)	0.6	0.2-2.4	0.46
futile treatment	7.2	1.2-42.6	0.03
Removal of colorectal tumors	2.1	0.5-8.3	0.28

CI Confidence Interval, IL-6 Interleukin 6, CEA Carcinoembryonic Antigen

5. Discussion

It has been over fifty years since Folkman initially proposed anti-tumor angiogenic therapy.[9] Anti-tumor angiogenesis therapy has become a significant approach in tumor treatment. Bevacizumab, a humanized monoclonal IgG antibody, has demonstrated effectiveness in treating advanced colorectal cancer when combined with adjuvant chemotherapy[10]. However, numerous studies have indicated that the improvements in overall patient survival associated with bevacizumab are not significant, and its efficacy is generally limited until the development of drug resistance[2]. Additionally, it has been observed that a considerable number of patients do not experience benefits from the combination therapy involving bevacizumab, possibly due to pre-existing mechanisms like vascular co-selection that counteract the "tumor starvation" effect of bevacizumab[11]. The increased incidence of recurrence and death among

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patients treated with bevacizumab in the AVANT et al. trial indicates a rise in tumor aggressiveness following antiangiogenic therapy[12] Therefore, further investigation is necessary to determine whether specific resistance mechanisms that develop during treatment are accountable for the current inadequate efficacy.

Inflammation has garnered significant attention in the field of tumor therapy, with numerous studies indicating a correlation between higher levels of inflammation in the body and poorer prognosis for tumor patients. This mechanism is evident in the direct promotion of tumor development through NF-κB by inflammation[13]. Additionally, inflammation stimulates tumor angiogenesis[14]. Masayasu Hara et al. discovered that serum IL-6 levels influence the effectiveness of antiangiogenic therapy for tumors[15]. In response to systemic inflammation, IL-6 levels were examined to determine their impact on the effectiveness of antiangiogenic therapy in patients with hepatic metastatic intestinal cancer. The study revealed that serum IL-6 levels did not exhibit a strong association with patients' overall survival (OS) and progression-free survival (PFS), but were linked to the tumor response at the initiation of treatment (this distinction was not observed among patients receiving bevacizumab). This discrepancy may be attributed to the prolonged survival period of patients, and the measured serum IL-6 concentration in this trial solely represents the inflammation level at the time of diagnosis, rather than the average level during treatment, which may differ from other studies.

Among patients with elevated serum IL-6 concentrations, the combination of bevacizumab and chemotherapy displayed a significantly extended progression-free survival (PFS), while no notable difference was noted in patients with lower serum IL-6 concentrations. Patients who did not receive bevacizumab exhibited shorter PFS with higher IL-6 concentrations. Conversely, higher serum IL-6 concentrations did not seem to exert a significant impact on PFS in patients undergoing bevacizumab treatment. This could be attributed to the mitigating effect of bevacizumab on the pro-tumor angiogenic properties of IL-6, indicating a potential association between the pro-angiogenic effects of IL-6 and vascular endothelial growth factor.

Studies have demonstrated that IL-6 induces the upregulation of vascular endothelial growth factor production in cancer-associated fibroblasts (CAF) through the activation of the Stat3 mutant (Stat3C)[20][16]. Numerous prior articles have sought to establish a connection between serum VEGF levels and the effectiveness and prognosis of antiangiogenic therapies. However, multiple studies have reported a lack of substantial correlation between serum VEGF levels and the efficacy and prognosis of antiangiogenic therapies[17] Wei LH et al. demonstrated that IL-6 can facilitate cervical tumorigenesis by activating vascular endothelial growth factor-mediated angiogenesis through the STAT3 pathway[18,19]. Nevertheless, a phase III randomized trial evaluating napabucacin (BBI608) targeting the STAT3 pathway was prematurely halted due to its ineffectiveness in an interim analysis[21]; Hence, we posit that there are intricate mechanisms beyond STAT3 involved in the process of inflammation-induced colorectal cancer development. IL-6 is merely a systemic response to inflammation and is not specific to tumors. Heightened inflammation levels can induce the production of VEGF and VEGM, leading to VEGF-dependent pro-tumor angiogenic effects, thereby amplifying the impact of lower VEGF concentrations, akin to a magnifying glass. This notion is supported by the fact that tocilizumab, an antibody targeting the IL-6 receptor, hinders tumor progression and angiogenesis. This study still has certain limitations, such as a small study population and potential selection bias. Nonetheless, we assert that this study yields significant findings. However, further investigations involving larger patient cohorts and additional basic research are necessary to validate these conclusions and establish a potential association between IL-6 and tumor angiogenesis.

6. Conclusions

Patients with advanced colorectal cancer who have higher levels of serum IL-6 tend to have shorter progression-free survival (PFS). For those patients with elevated IL-6 levels, antiangiogenic therapy may be beneficial and should be prioritized. However, those with lower serum IL-6 concentrations may not see significant benefits from antiangiogenic therapy.

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Author Contributions

All authors were involved in the conceptualization, design, and preparation of materials for the study;

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data collection and analysis were done by Yu Chen. The first draft of the manuscript was written by Yu Chen, and all authors commented on a previous version of the manuscript. All authors read and agreed to the final manuscript.

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