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Clinical Impact of Serum CRP Levels on Advanced HCC Treated With Durvalumab and Tremelimumab: A Multicentre Study

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ABSTRACT

Aim: This study aimed to evaluate the therapeutic efficacy and prognostic significance of C-reactive protein (CRP) in patients with advanced hepatocellular carcinoma (HCC) receiving durvalumab and tremelimumab (Dur/Tre).

Methods: A total of 167 patients treated with Dur/Tre between March 2023 and March 2024 in Japanese hospitals were included in this retrospective multicentre study. Patients were divided into two groups based on pre-treatment serum CRP levels: the low-CRP group (< 1 mg/dL, $n = 106$) and the high-CRP group (≥ 1 mg/dL, $n = 61$).

Results: The median age of the cohort was 74.0 years (interquartile range, 67.5–79.5), and 139 patients (83.2%) were male. The median progression-free survival (PFS) was 3.6 months (95% CI: 2.6–5.4) in the low-CRP group and 2.4 months (95% CI: 1.9–4.1) in the high-CRP group, with statistical significance ($p = 0.02$). The median overall survival (OS) was not reached in the low-CRP group, with a 1-year survival rate of 64.7% (95% CI: 49.0–76.7), while it was 7.9 months (95% CI: 5.8–11.8) in the high-CRP group. The low-CRP group demonstrated significantly better survival outcomes compared to the high-CRP group ($p < 0.001$). Multivariate analysis identified serum CRP level as an independent predictive factor for both PFS and OS ($p = 0.04$ and < 0.001, respectively). No significant differences in immune-related adverse events were observed between the two groups.

Conclusions: Serum CRP may serve as a prognostic biomarker in HCC patients receiving Dur/Tre, with a potential association with treatment efficacy.

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Summary

- Durvalumab and tremelimumab (Dur/Tre) are recommended as a first-line treatment for unresectable hepatocellular carcinoma (HCC).
- Serum C-reactive protein (CRP), a non-specific marker of inflammation, may serve as a prognostic biomarker in HCC patients receiving Dur/Tre, with a potential association with treatment efficacy.

1 | Introduction

Owing to remarkable advancements in systemic therapy for advanced hepatocellular carcinoma (HCC), effective systemic treatments are now widely available in clinical practice. IMbrave150 [1] demonstrated that the combination of atezolizumab and bevacizumab (Atez/Bev), combination therapy with a programmed death ligand 1 (PD-L1) inhibitor and an anti-vascular endothelial growth factor inhibitor, is superior to sorafenib in terms of progression-free survival (PFS) and overall survival (OS). HIMALAYA trial [2] reported that the combination of durvalumab and tremelimumab (Dur/Tre), PD-L1 inhibitor plus an anti-cytotoxic T lymphocyte–associated antigen 4 agent, showed better survival compared to sorafenib. BCLC and ASCO guidelines [3, 4] recommended both Dur/Tre and Atez/Bev as first-line treatments for advanced HCC.

C-reactive protein (CRP) is an acute-phase protein primarily produced in the liver [5]. It is stimulated by cytokines such as interleukin (IL)-1 and IL-6 and subsequently released into systemic circulation [5]. Previous studies reported CRP is an unfavourable prognostic factor in HCC patients undergoing systemic therapies, such as sorafenib [6], lenvatinib [7, 8] and Atez/Bev [9, 10]. However, the role of CRP in HCC patients treated with Dur/Tre remains unclear. Furthermore, only a few studies have investigated predictive factors for the efficacy of Dur/Tre treatment. This study aims to evaluate the therapeutic efficacy and prognostic significance of serum CRP levels in HCC patients receiving Dur/Tre.

2 | Methods

2.1 | Patients

In this retrospective study, 197 patients received Dur/Tre treatment from March 2023 to 2024 in our affiliated hospitals. Among these patients, we excluded the patients with BCLC stage 0, A and D ($n = 16$), those with Child–Pugh score ≥ 8 liver function ($n = 10$) and those without available serum CRP levels ($n = 4$). Accordingly, we included 167 patients in this study. The patient selection process is outlined in Figure S1. HCC was diagnosed based on pathological findings or typical clinical features according to the AASLD guidelines [11], characterised by enhancement during the arterial phase and washout during the portal venous or delayed phases on dynamic computed tomography (CT) or magnetic resonance imaging (MRI). We reviewed medical records and collected the clinical data including clinical course, underlying liver disease, laboratory data and radiological findings. We assessed tumour stage according to BCLC staging system [3], which incorporates performance status (PS), liver function and tumour spread. Liver function prior to Dur/Tre treatment was evaluated using the Child–Pugh classification. Additionally, ALBI scores were calculated according to a previous study [12] and liver function was further assessed using the mALBI grade [13].

2.2 | Dur/Tre Treatments

Before initiating Dur/Tre treatment, the presence of autoimmune diseases was evaluated to minimise the risk of immune-related adverse events (AEs). Patients were then intravenously administered a single dose of 300 mg of tremelimumab, followed by 1500 mg of durvalumab every 4 weeks until disease progression and/or the occurrence of unacceptable AEs. To facilitate early detection of AEs, patients visited the outpatient clinic every 1–4 weeks. CT and/or MRI were performed every 6–12 weeks to evaluate disease progression. Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST ver. 1.1) [14]. PFS was defined as the time from initiation of Dur/Tre treatment to disease progression or death, whichever occurred first. OS was defined as the time from the start of Dur/Tre treatment to death.

2.3 | Statistical Analyses

Numerical variables were presented as medians with interquartile ranges (IQR), while categorical variables were reported as numbers with percentages. Comparisons were performed using the Mann–Whitney *U* test for continuous variables and either the chi-squared test or Fisher's exact test for categorical variables, as appropriate. The CRP cut-off value was determined based on previous studies [9, 10]. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were applied to identify predictive factors. The following factors were included in the multivariate analysis for PFS: age, gender, treatment setting (first- vs. later-line), BCLC stage (B vs. C), mALBI grade (1 or 2a vs. 2b), serum α-fetoprotein (AFP) level (≥ 100 vs. < 100 ng/mL), serum des-gamma-carboxy prothrombin (DCP) level (≥ 100 vs. < 100 mAU/mL) and CRP group (low vs. high CRP). For the multivariate analysis of OS, to avoid overfitting and ensure reproducibility and generalizability, the number of explanatory variables included in each model was limited to 5, given the 52 death events observed during the follow-up period in the present study. Two models were constructed: Model 1 included age, gender, treatment setting (first- vs. later-line), BCLC stage (B vs. C) and CRP group (low vs. high CRP); Model 2 included age, gender, treatment setting (first- vs. later-line), mALBI grade (1 or 2a vs. 2b) and CRP group (low vs. high CRP). All statistical analyses were conducted using EZR Ver. 1.67 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [15].

3 | Results

3.1 | Patient Characteristics

The median age of the entire cohort was 74.0 (IQR 67.5–79.5) years old and 139 patients (83.2%) were male. PS was 127 (76.0%),

32 (19.2%) and 8 patients (4.8%) in 0, 1 and 2, respectively. The underlying liver disease was chronic hepatitis C virus (HCV; $n=52$, 31.1%), hepatitis B virus (HBV; $n=31$, 18.6%), HBV and HCV ($n=3$, 1.8%), significant alcohol consumption ($n=35$, 21.0%) and other causes ($n=46$, 27.5%). Thus, liver disease due to viral infection accounted for 86 (51.5%) patients. According to the BCLC staging system, 52 (31.1%) and 115 patients (68.9%) were classified as BCLC intermediate and advanced stages,

TABLE 1 | Patient characteristics.

Factors		Overall ($n=167$)	The low-CRP group ($n=106$)	The high-CRP group ($n=61$)	p
Age (years)		74.0 [67.5, 79.5]	75.0 [69.0, 80.0]	72.0 [62.0, 79.0]	0.09
Gender, *n* (%)	Male	139 (83.2)	84 (79.2)	55 (90.2)	0.09
Performance status, *n* (%)	0	127 (76.0)	84 (79.2)	43 (70.5)	0.4
	1	32 (19.2)	18 (17.0)	14 (23.0)	
	2	8 (4.8)	4 (3.8)	4 (6.6)	
Underlying liver diseases, *n* (%)	HCV	52 (31.1)	41 (38.7)	11 (18.0)	0.02
	HBV	31 (18.6)	14 (13.2)	17 (27.9)	
	HCV plus HBV	3 (1.8)	1 (0.9)	2 (3.3)	
	Alcohol	35 (21.0)	23 (21.7)	12 (19.7)	
	Others	46 (27.5)	27 (25.5)	19 (31.1)	
Viral-related disease, *n* (%)		86 (51.5)	56 (52.8)	30 (49.2)	0.7
BCLC stage, *n* (%)	Intermediate	52 (31.1)	40 (37.7)	12 (19.7)	0.02
	Advanced	115 (68.9)	66 (62.3)	49 (80.3)	
Child–Pugh score, *n* (%)	5	78 (46.7)	59 (55.7)	19 (31.1)	<0.001
	6	68 (40.7)	41 (38.7)	27 (44.3)	
	7	21 (12.6)	6 (5.7)	15 (24.6)	
ALBI score		−2.25 [−2.56, −1.89]	−2.42 [−2.65, −2.10]	−2.01 [−2.29, −1.74]	<0.001
mALBI grade, *n* (%)	1	37 (22.2)	31 (29.2)	6 (9.8)	<0.001
	2a	45 (26.9)	33 (31.1)	12 (19.7)	
	2b	85 (50.9)	42 (39.6)	43 (70.5)	
Treatment settings, *n* (%)	First-line	58 (34.7)	39 (36.8)	19 (31.1)	0.5
	Later-line	109 (65.3)	67 (63.2)	42 (68.9)	
MVI, *n* (%)	Presence	38 (22.8)	17 (16.0)	21 (34.4)	0.01
EHS, *n* (%)	Presence	74 (44.3)	46 (43.4)	28 (45.9)	0.9
AFP, *n* (%)	≥100 ng/mL	70 (41.9)	43 (40.6)	27 (44.3)	0.7
DCP, *n* (%)[a]	≥100 mAU/mL	129 (77.7)	77 (73.3)	52 (85.2)	0.08
Serum level albumin	g/dL	3.5 [3.2, 3.8]	3.6 [3.3, 4.0]	3.2 [3.0, 3.5]	<0.001
Total bilirubin	mg/dL	0.7 [0.5, 1.0]	0.6 [0.5, 1.0]	0.8 [0.6, 1.2]	0.06
CRP	mg/dL	0.45 [0.17, 1.92]	0.25 [0.12, 0.42]	2.68 [1.60, 4.40]	<0.001
Platelet count	$\times 10^3/\mu L$	16.1 [11.3, 22.4]	15.4 [11.0, 20.0]	19.1 [12.5, 26.7]	0.002
FIB-4 index		3.28 [2.03, 5.67]	3.43 [2.39, 5.59]	3.17 [1.75, 5.76]	0.5
FIB-4 index, *n* (%)	≥2.67	102 (61.1)	67 (63.2)	35 (57.4)	0.5
Prothrombin time[b]	%	98 [84, 111]	100 [88, 113]	91 [80, 110]	0.07

Note: There were missing data for [a]1 and, [b]1 patients, respectively.
Abbreviations: AFP, α-fetoprotein; ALBI score, albumin-bilirubin score; BCLC stage, Barcelona Clinic Liver Cancer stage; CRP, C-reactive protein; DCP, des-gamma-carboxy prothrombin; EHS, extrahepatic spread; FIB-4, fibrosis-4 index; HBV, hepatitis B virus; HCV, hepatitis C virus; mALBI grade, modified albumin-bilirubin grade; MVI, macroscopic vascular invasion.

respectively. The median ALBI score was −2.25 (IQR −2.56 to −1.89) and 37 (22.2%), 45 (26.9%) and 85 patients (50.9%) were stratified into mALBI grades 1, 2a and 2b, respectively. Among the cohort, 58 patients (34.7%) received Dur/Tre treatment as first-line treatment, while 109 patients (65.3%) received it as later-line treatment. The median CRP value was 0.45 mg/dL (IQR 0.17–1.92). A Fibrosis-4 index ≥ 2.67 was observed in 102 patients (61.1%).

Patients were divided into two groups based on serum CRP levels: the low-CRP group (< 1 mg/dL, $n = 106$) and high-CRP group (≥ 1 mg/dL, $n = 61$). The proportion of HCV-related HCC was significantly higher in the low-CRP group than in the high-CRP group ($p = 0.02$). The percentage of BCLC stage B HCC patients was significantly higher in the low-CRP group compared to the high-CRP group (37.7% vs. 19.7%, $p = 0.02$). Regarding the ALBI score and the mALBI grade, the low-CRP group had significantly better liver function than the high-CRP group (both $p < 0.001$). Additionally, the frequency of macroscopic vascular invasion was significantly lower in the low-CRP group than that in the high-CRP group ($p = 0.01$). The details of patient characteristics were shown in Table 1.

3.2 | Treatment Outcomes

In the entire cohort, overall tumour response was assessed as partial response (PR) in 26 patients (15.6%), stable disease (SD) in 48 patients (28.7%), progressive disease (PD) in 80 patients (47.9%) and not evaluated (NE) in 13 patients (7.8%). No patients achieved complete response during the observation period. Accordingly, the overall response rate (ORR) and disease control rate (DCR) were 15.6% and 44.3%, respectively. The ORR and DCR in the low-CRP group were 13.2% and 48.1%, while the ORR and DCR in the high-CRP group were 19.7% and 37.7%, respectively. No significant differences were observed between the two groups ($p = 0.3$ and $p = 0.2$, respectively). The results of overall tumour response were described in Table 2.

The median PFS for the entire cohort was 3.2 months (95% confidence interval [CI] 2.5–4.2). During the observation period, 125 PFS events were detected. The median OS was 11.9 months (95% CI 10.5–not applicable). A total of 52 patients died, and the median observation period was 6.7 months (IQR 3.4–9.8). Kaplan–Meier curves for PFS and OS are shown in Figure 1a,b.

The median PFS was 3.6 months (95% CI 2.6–5.4) in the low-CRP group and 2.4 months (95% CI 1.9–4.1) in the high-CRP group. The low-CRP group showed significantly better PFS than the high-CRP group ($p = 0.02$; Figure 2a). Multivariate analysis showed that the high-CRP group (hazard ratio [HR] 1.50, 95% CI 1.02–2.21, $p = 0.04$) and later-line treatment (HR 1.75, 95% CI 1.18–2.62, $p = 0.006$) were significant unfavourable factors for PFS (Table 3). Adjusted PFS curves are presented in Figure S2a.

The median OS was not reached in the low-CRP group, with a 1-year survival rate of 64.7% (95% CI 49.0–76.7). In contrast, the median OS in the high-CRP group was 7.9 months (95% CI 5.8–11.8). The low-CRP group showed significantly better survival compared to the high-CRP group ($p < 0.001$; Figure 2b). Based on 52 OS events, two prognostic models were constructed, each involving 5 explanatory variables. The CRP group was identified as a prognostic factor in multivariate analyses (HR 3.62, 95% CI 2.00–6.54, $p < 0.001$ in model 1, HR 2.87, 95% CI 1.58–5.22, $p < 0.001$ in model 2; Table 4). Adjusted OS curves are provided in Figure S2b.

TABLE 2 | Overall tumour response.

Factors	Overall ($n = 167$)	The low-CRP group ($n = 106$)	The high-CRP group ($n = 61$)	p
Best response, *n* (%)				
CR	0 (0.0)	0 (0.0)	0 (0.0)	0.1
PR	26 (15.6)	14 (13.2)	12 (19.7)	
SD	48 (28.7)	37 (34.9)	11 (18.0)	
PD	80 (47.9)	48 (45.3)	32 (52.5)	
NE	13 (7.8)	7 (6.6)	6 (9.8)	
ORR (%)	15.6	13.2	19.7	0.3
DCR (%)	44.3	48.1	37.7	0.2

Abbreviations: CR, complete response; CRP, C-reactive protein; DCR, disease control rate; NE, not evaluated; ORR, overall response rate; PD, progressive disease; PR, partial response.

3.3 | Adverse Events

The most frequent immune-related AE was rash or pruritus ($n = 25$, 15.0%), followed by colitis or diarrhoea ($n = 20$, 12.0%) and liver injury ($n = 12$, 7.2%). There were no statistically significant differences in the frequency of any grade and grade ≥ 3 immune-related AEs, including liver injury, interstitial pneumonia, thyroid dysfunction, colitis or diarrhoea, rash or pruritus and other imAEs between the two groups. Details of the AE profiles are described in Table 5.

4 | Discussion

The main findings of the present study were that the low-CRP group showed significantly better PFS and OS than the high-CRP group ($p = 0.02$ and < 0.001, respectively). Multivariate analysis identified the low-CRP group as a favourable predictive factor for PFS and OS in advanced HCC patients receiving Dur/Tre treatment (both $p < 0.001$, respectively). No significant differences in immune-related AEs were observed between the two groups. Based on these present findings, serum CRP levels appear to be a promising predictor of the efficacy of Dur/Tre treatment in HCC patients.

Systemic inflammation within the tumour microenvironment is recognised as a critical prognostic indicator in various cancers [16]. Previous studies reported that CRP could predict clinical outcomes in HCC patients undergoing various treatments such

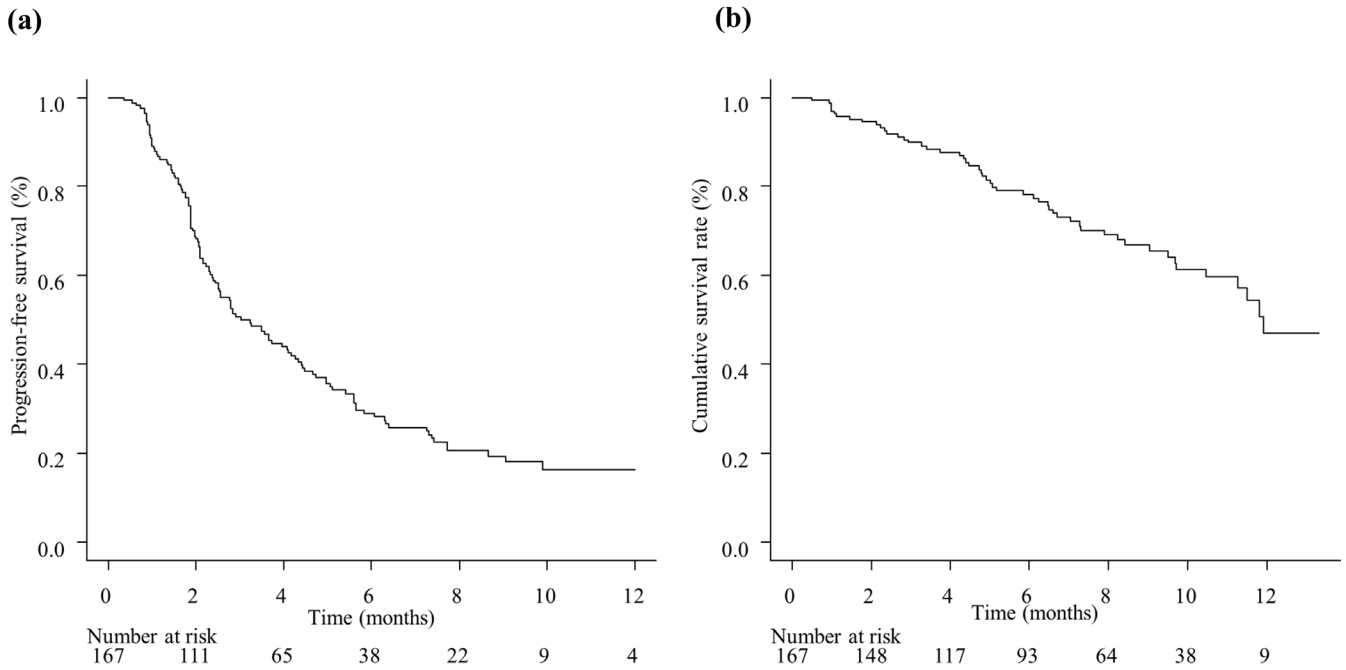

FIGURE 1 | Progression-free survival (a) and overall survival (b) in the entire cohort.

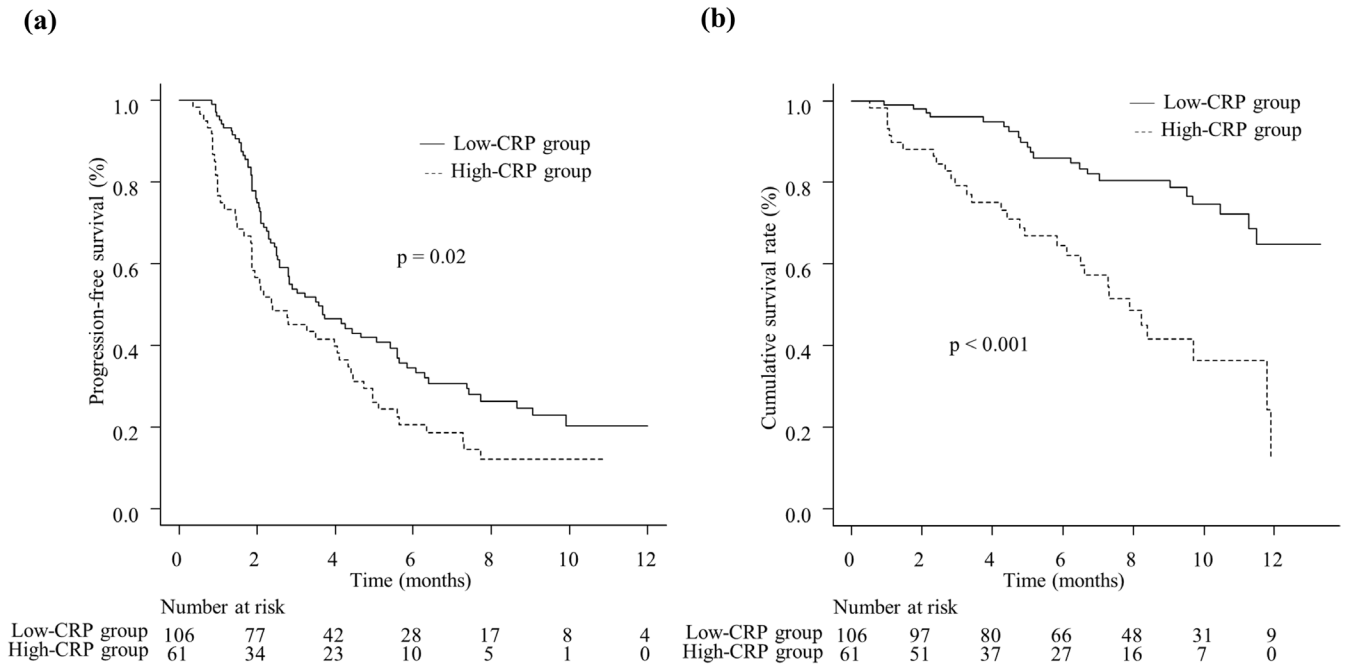

FIGURE 2 | Progression-free survival (a) and overall survival (b) according to the low- and high-CRP groups. CRP, C-reactive protein.

as hepatic resection [17, 18], liver transplantation [19, 20] and transarterial chemoembolization [21]. Regarding systemic therapies, CRP alone or models incorporating CRP with other factors have been shown to predict therapeutic efficacy and prognosis in advanced HCC patients [6–8, 22, 23]. However, predictive biomarkers for assessing the efficacy of Dur/Tre treatments remain unclear. To our knowledge, this is the first study to demonstrate that serum CRP levels may be a potential biomarker associated with the efficacy of Dur/Tre treatment in patients with HCC.

Several mechanisms could potentially explain why the therapeutic efficacy of Dur/Tre is reduced in cases with elevated CRP levels. A previous study reported that high IL-6 levels, which primarily regulate CRP production, had reduced activation of peripheral CD8+ T cells compared with patients with low IL-6 levels [24]. Moreover, excess IL-6 impaired cytokine production and proliferation of CD8+ T cells [24], suggesting that high baseline IL-6 levels may attenuate T-cell immunity. Another study demonstrated that CRP itself suppresses the activation, proliferation and effector function of CD4+ and CD8+ T cells, disrupts immune synapse formation and inhibits T-cell receptor signalling [25]. Additionally, CRP promotes the expansion of myeloid-derived suppressor cells and enhances their immunosuppressive functions, including the suppression of T cell proliferation via

TABLE 3 | Multivariate analyses associated with progression-free survival.

Factors		Hazard ratio (95% CI)	*p*
Age	Per year	1.00 (0.98–1.02)	0.8
Gender	Male	1.00 (0.62–1.60)	1.0
Treatment settings	Later-line	1.75 (1.18–2.62)	0.006
BCLC stage	Intermediate	0.81 (0.55–1.19)	0.3
mALBI grade	2b	1.13 (0.77–1.66)	0.5
AFP	≥100 ng/mL	1.15 (0.79–1.69)	0.5
DCP	≥100 mAU/mL	0.77 (0.48–1.22)	0.3
CRP	≥1 mg/dL	1.50 (1.02–2.21)	0.04

Abbreviations: AFP, α-fetoprotein; BCLC stage, Barcelona Clinic Liver Cancer stage; CI, confidence interval; CRP, C-reactive protein; DCP, des-gamma-carboxy prothrombin; mALBI grade, modified albumin-bilirubin grade.

increased production of intracellular reactive oxygen species [26]. Moreover, IL-6 induced compensatory proliferation of hepatocytes in a diethylnitrosamine (DEN)-induced hepatocarcinogenesis model [27]. IL-6 also promoted tumour progression via STAT3 signalling in an obesity-induced liver tumour mouse model [28]. These findings indicate that serum CRP plays a crucial role in modulating the therapeutic efficacy of immunotherapy in advanced HCC patients.

In real-world settings, Shimose et al. reported that DCR in patients receiving Dur/Tre as first-line treatment was significantly higher than in those receiving it as later-line treatment [29]. Similarly, Mori et al. found that patients who had received prior Atez/Bev treatment had significantly lower ORR and DCR, as well as shorter PFS, compared to those without prior exposure [30]. The findings of these studies align with the present study, which also identified treatment setting (first- vs. later-line) as an unfavourable factor in multivariate analysis.

The ORR was numerically higher in the high-CRP group (19.7%) than in the low-CRP group (13.2%) in the present study, although the difference was not statistically significant ($p = 0.3$).

TABLE 4 | Multivariate analyses associated with overall survival.

		Model 1		Model 2	
Factors		**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age	Per year	1.01 (0.98–1.03)	0.6	1.01 (0.98–1.03)	0.6
Gender	Male	1.18 (0.57–2.44)	0.7	1.08 (0.52–2.23)	0.8
Treatment settings	Later-line	1.63 (0.82–3.22)	0.2	1.66 (0.84–3.29)	0.2
BCLC stage	Intermediate	0.87 (0.47–1.62)	0.7		
mALBI grade	2b			2.15 (1.17–3.94)	0.01
CRP	≥1 mg/dL	3.62 (2.00–6.54)	<0.001	2.87 (1.58–5.22)	<0.001

Abbreviations: BCLC stage, Barcelona Clinic Liver Cancer stage; CI, confidence interval; CRP, C-reactive protein; mALBI grade, modified albumin-bilirubin grade.

TABLE 5 | Immune-related adverse events.

Factors		Overall ($n = 167$)	The low-CRP group ($n = 106$)	The high-CRP group ($n = 61$)	*p*
Liver injury	Any grade	12 (7.2)	9 (8.5)	3 (4.9)	0.5
	Grade ≥3	9 (5.4)	7 (6.6)	2 (3.3)	0.5
Interstitial pneumonia	Any grade	6 (3.6)	6 (5.7)	0 (0.0)	0.09
	Grade ≥3	2 (1.2)	2 (1.9)	0 (0.0)	0.5
Thyroid dysfunction	Any grade	3 (1.8)	3 (2.8)	0 (0.0)	0.3
	Grade ≥3	0 (0.0)	0 (0.0)	0 (0.0)	NA
Colitis or diarrhoea	Any grade	20 (12.0)	12 (11.3)	8 (13.1)	0.8
	Grade ≥3	17 (10.2)	12 (11.3)	5 (8.2)	0.6
Rash or pruritus	Any grade	25 (15.0)	18 (17.0)	7 (11.5)	0.4
	Grade ≥3	7 (4.2)	5 (4.7)	2 (3.3)	1.0
Others	Any grade	14 (8.4)	11 (10.4)	3 (4.9)	0.3
	Grade ≥3	6 (3.6)	3 (2.8)	3 (4.9)	0.7

Abbreviations: CRP, C-reactive protein; NA, not applicable.

In contrast, PFS was better in the low-CRP group. One possible explanation for this discrepancy is that patients in the high-CRP group may have had more aggressive tumours, resulting in a shorter duration of response. Another possibility is that the ORR was observed in only 26 patients (15.6%), which may have limited the statistical power. With a larger sample size and more responders, the results might have been different.

There were some limitations associated with the present study. First, the number of patients was relatively small, and the observation period was short. A longer observation period and a larger patient cohort may yield results that differ from the present findings. Second, two-thirds of the patients in the present cohort received Dur/Tre as a later-line treatment. Although no significant differences in treatment settings were observed between the low- and high-CRP groups, treatment settings may still have influenced the results. Third, we were unable to evaluate the role of CRP levels during treatment in the present study. Further analysis is warranted to investigate whether changes in CRP levels influence treatment efficacy. Fourth, differences in patient characteristics, such as liver function and tumour burden, existed between the low- and high-CRP groups. Although we performed multivariate analysis to account for these imbalances, propensity score matching or inverse probability of treatment weighting could further reduce confounding in future studies with larger sample sizes and longer observation periods.

In conclusion, serum CRP may serve as a prognostic biomarker in HCC patients receiving Dur/Tre, with a potential association with treatment efficacy.

Author Contributions

T.H. and Y.Y. contributed to the concept, design and execution of the study. T.H., Y.Y., A.H., T.Tad., M.H., K.Kar., J.T., M.A., K.Tak., E.I., S.K., S.F., K.Ts., T.I., K.Taj., H.To., Y.K., C.O., H.N., T.Ni., K.Kaw., H.Ko., K.M., A.N., H.Ta., H.Oh., H.K., T.M., T.Ao., H.Oc., M.I., S.N., Y.Ka., K.Tan., F.T., O.Y., K.N., A.M., A.T., T.Na., N.I., T.O., T.Ar., H.E., M.Ka., Y.H. and M.Ku. contributed to data curation. T.H. conducted statistical analyses and interpreted the data. T.H. wrote the first draft of the manuscript. Y.Y., A.H., T.Tad., S.K., A.N. and T.K. reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

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Ethics Statement

This retrospective study was approved by the Institutional Ethics Committee of NHO Takasaki General Medical Center (IRB No. 2024-03) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before treatment, and this study received ethical approval for the use of an opt-out methodology.

Conflicts of Interest

Takeshi Hatanaka received lecture fees from Eisai. Atsushi Hiraoka received lecture fees from Eli Lilly, AstraZeneca and Chugai. Toshifumi Tada received lecture fees from AbbVie, Eisai and Chugai. Satoru Kakizaki received lecture frees from AbbVie. Hidenori Toyoda received lecture fees from Eisai, Chugai, Takeda, Terumo, AbbVie, Gilead, Fujifilm WAKO, Abott, Kowa, AstraZeneca and Bayer. Hidekatsu Kuroda received lecture fee from Eisai. Kazuhiro Nouso received lecture fees from AbbVie, Aska Pharmaceutical, AstraZeneca, Bayer, Century Medical, Chugai, Covidien, Eisai, Gilead, Kowa, Lilly and Otsuka; and received research funding from CureApp, Denka, Fuji film and Medtronic. Masatoshi Kudo received honoraria from Bayer, Chugai, Eisai, Eli Lilly, MSD and Takeda; and received research funding from AbbVie, EA Pharma, Eisai, GE Healthcare, Gilead Sciences, Otsuka, Sumitomo Dainippon Pharma, Taiho and Takeda. The other authors declare no conflicts of interest associated with this study.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. R. S. Finn, S. Qin, M. Ikeda, et al., "Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma," *New England Journal of Medicine* 382, no. 20 (2020): 1894–1905.

2. G. K. Abou-Alfa, G. Lau, M. Kudo, et al., "Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma," *NEJM Evidence* 1, no. 8 (2022): EVIDoa2100070.

3. M. Reig, A. Forner, J. Rimola, et al., "BCLC Strategy for Prognosis Prediction and Treatment Recommendation: The 2022 Update," *Journal of Hepatology* 76, no. 3 (2022): 681–693.

4. J. D. Gordan, E. B. Kennedy, G. K. Abou-Alfa, et al., "Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update," *Journal of Clinical Oncology* 42, no. 15 (2024): 1830–1850.

5. A. Peisajovich, L. Marnell, C. Mold, and T. W. Du Clos, "C-Reactive Protein at the Interface Between Innate Immunity and Inflammation," *Expert Review of Clinical Immunology* 4, no. 3 (2008): 379–390.

6. H. Nakanishi, M. Kurosaki, K. Tsuchiya, et al., "Novel Pretreatment Scoring Incorporating C-Reactive Protein to Predict Overall Survival in Advanced Hepatocellular Carcinoma With Sorafenib Treatment," *Liver Cancer* 5, no. 4 (2016): 257–268.

7. T. Hayashi, M. Shibata, S. Oe, K. Miyagawa, Y. Honma, and M. Harada, "C-Reactive Protein Can Predict Dose Intensity, Time to Treatment Failure and Overall Survival in HCC Treated With Lenvatinib," *PLoS One* 15, no. 12 (2020): e0244370.

8. T. Okumura, T. Kimura, T. Iwadare, et al., "Prognostic Significance of C-Reactive Protein in Lenvatinib-Treated Unresectable Hepatocellular Carcinoma: A Multi-Institutional Study," *Cancers (Basel)* 15, no. 22 (2023): 5343.

9. S. Kaneko, Y. Asahina, M. Murakawa, et al., "Prognostic Significance of C-Reactive Protein in Unresectable Hepatocellular Carcinoma Treated With Atezolizumab and Bevacizumab," *Hepatology Research* 54, no. 6 (2024): 562–574.

10. T. Hatanaka, S. Kakizaki, A. Hiraoka, et al., "Prognostic Impact of C-Reactive Protein and Alpha-Fetoprotein in Immunotherapy Score in Hepatocellular Carcinoma Patients Treated With Atezolizumab Plus Bevacizumab: A Multicenter Retrospective Study," *Hepatology International* 16, no. 5 (2022): 1150–1160.

11. A. G. Singal, J. M. Llovet, M. Yarchoan, et al., "AASLD Practice Guidance on Prevention, Diagnosis, and Treatment of Hepatocellular Carcinoma," *Hepatology* 78, no. 6 (2023): 1922–1965.

12. P. J. Johnson, S. Berhane, C. Kagebayashi, et al., "Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach-The ALBI Grade," *Journal of Clinical Oncology* 33, no. 6 (2015): 550–558.

13. A. Hiraoka, K. Michitaka, T. Kumada, et al., "Validation and Potential of Albumin-Bilirubin Grade and Prognostication in a Nationwide Survey of 46,681 Hepatocellular Carcinoma Patients in Japan: The Need for a More Detailed Evaluation of Hepatic Function," *Liver Cancer* 6, no. 4 (2017): 325–336.

14. E. A. Eisenhauer, P. Therasse, J. Bogaerts, et al., "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)," *European Journal of Cancer* 45, no. 2 (2009): 228–247.

15. Y. Kanda, "Investigation of the Freely Available Easy-to-Use Software 'EZR' for Medical Statistics," *Bone Marrow Transplantation* 48, no. 3 (2013): 452–458.

16. J. H. Jang, D. H. Kim, and Y. J. Surh, "Dynamic Roles of Inflammasomes in Inflammatory Tumor Microenvironment," *npj Precision Oncology* 5, no. 1 (2021): 18.

17. K. Hashimoto, Y. Ikeda, D. Korenaga, et al., "The Impact of Preoperative Serum C-Reactive Protein on the Prognosis of Patients With Hepatocellular Carcinoma," *Cancer* 103, no. 9 (2005): 1856–1864.

18. J. M. Chun, H. J. Kwon, J. Sohn, et al., "Prognostic Factors After Early Recurrence in Patients Who Underwent Curative Resection for Hepatocellular Carcinoma," *Journal of Surgical Oncology* 103, no. 2 (2011): 148–151.

19. T. Meischl, S. Rasoul-Rockenschaub, G. Györi, et al., "C-Reactive Protein Is an Independent Predictor for Hepatocellular Carcinoma Recurrence After Liver Transplantation," *PLoS One* 14, no. 5 (2019): e0216677.

20. H. J. An, J. W. Jang, S. H. Bae, et al., "Serum C-Reactive Protein Is a Useful Biomarker for Predicting Outcomes After Liver Transplantation in Patients With Hepatocellular Carcinoma," *Liver Transplantation* 18, no. 12 (2012): 1406–1414.

21. W. Sieghart, M. Pinter, F. Hucke, et al., "Single Determination of C-Reactive Protein at the Time of Diagnosis Predicts Long-Term Outcome of Patients With Hepatocellular Carcinoma," *Hepatology* 57, no. 6 (2013): 2224–2234.

22. T. Tada, T. Kumada, A. Hiraoka, et al., "New Prognostic System Based on Inflammation and Liver Function Predicts Prognosis in Patients With Advanced Unresectable Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab: A Validation Study," *Cancer Medicine* 12, no. 6 (2023): 6980–6993.

23. B. Scheiner, K. Pomej, M. M. Kirstein, et al., "Prognosis of Patients With Hepatocellular Carcinoma Treated With Immunotherapy - Development and Validation of the CRAFITY Score," *Journal of Hepatology* 76 (2021): 353–363.

24. H. Yang, B. Kang, Y. Ha, et al., "High Serum IL-6 Correlates With Reduced Clinical Benefit of Atezolizumab and Bevacizumab in Unresectable Hepatocellular Carcinoma," *JHEP Reports* 5, no. 4 (2023): 100672.

25. T. Yoshida, J. Ichikawa, I. Giuroiu, et al., "C Reactive Protein Impairs Adaptive Immunity in Immune Cells of Patients With Melanoma," *Journal for Immunotherapy of Cancer* 8, no. 1 (2020): e000234.

26. R. V. Jimenez, V. Kuznetsova, A. N. Connelly, Z. Hel, and A. J. Szalai, "C-Reactive Protein Promotes the Expansion of Myeloid Derived Cells With Suppressor Functions," *Frontiers in Immunology* 10 (2019): 2183.

27. D. Schmidt-Arras and S. Rose-John, "IL-6 Pathway in the Liver: From Physiopathology to Therapy," *Journal of Hepatology* 64, no. 6 (2016): 1403–1415.

28. E. J. Park, J. H. Lee, G. Y. Yu, et al., "Dietary and Genetic Obesity Promote Liver Inflammation and Tumorigenesis by Enhancing IL-6 and TNF Expression," *Cell* 140, no. 2 (2010): 197–208.

29. S. Shimose, I. Saeki, T. Tomonari, et al., "Initial Clinical Experience With Durvalumab Plus Tremelimumab in Patients With Unresectable Hepatocellular Carcinoma in Real-World Practice," *Oncology Letters* 28, no. 2 (2024): 397.

30. N. Mori, N. Tamaki, S. Takaki, et al., "Treatment Response to Durvalumab Plus Tremelimumab After Progression With Previous Immune Checkpoint Inhibitor in Unresectable Hepatocellular Carcinoma," *Investigational New Drugs* 42 (2024): 559–565.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.