ORIGINAL ARTICLE

Early CRP kinetics to predict long-term efficacy of first-line immune-checkpoint inhibition combination therapies in metastatic renal cell carcinoma: an updated multicentre real-world experience applying different CRP kinetics definitions

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Abstract

Objectives. Although biomarkers predicting therapy response in first-line metastatic renal carcinoma (mRCC) therapy remain to be defined, C-reactive protein (CRP) kinetics have recently been associated with immunotherapy (IO) response. Here, we aimed to assess the predictive and prognostic power of two contemporary CRP kinetics definitions in a large, real-world first-line mRCC cohort. **Methods.** Metastatic renal carcinoma patients treated with IO-based first-line therapy within 5 years were retrospectively included in this multicentre study. According to Fukuda *et al.*, patients were defined as 'CRP flare-responder', 'CRP responder' and 'non-CRP responder'; according to Ishihara *et al.*, patients were defined as 'normal', 'normalised' and 'non-normalised' based on their early CRP kinetics. Patient and tumor characteristics were compared, and treatment outcome was measured by overall (OS) and progression-free survival (PFS), including multivariable Cox regression analyses. **Results.** Out of 316 mRCC patients, 227 (72%) were assigned to CRP groups according to Fukuda. Both CRP flare- (HR [Hazard ratio]: 0.59) and CRP responders (HR: 0.52) had a longer PFS, but not OS, than non-CRP responders. According to Ishihara, 276 (87%) patients were assigned to the respective groups, and both normal and normalised patients had a significantly longer PFS and OS, compared with non-normalised group.

Conclusion. Different early CRP kinetics may predict therapy response in first-line mRCC therapy in a large real-world cohort. However, further research regarding the optimal timing and frequency of measurement is needed.

Keywords: biomarker, checkpoint inhibition, C-reactive protein, CRP flare-response, first-line therapy, metastatic renal cell carcinoma

INTRODUCTION

In recent years, the first-line treatment for metastatic renal cell carcinoma (mRCC) has undergone significant changes because of the introduction of immune checkpoint inhibition (IO)-based therapy regimens. Two different types of first-line combination therapies are currently applied for the treatment of mRCC, namely an intensified immune checkpoint inhibition (IO + IO) and a combination of immune checkpoint inhibition plus anti-angiogenic therapy (IO + TKI).[1–3] However, only a subset of patients responds to these first-line IO combination therapies.[1] Therefore, predictive biomarkers are needed to identify early therapy failure and avoid severe unnecessary side effects.

Several studies have linked the occurrence and kinetics of systemic inflammatory response reflected by serum C-reactive protein (CRP) with clinical outcome and treatment response in various cancers, including urothelial cancer, non-small-cell lung cancer and mRCC.[4–9] Previous research has explored CRP levels at the initial diagnosis or baseline before therapy initiation and associated increased systemic inflammation with a poor prognosis. As cancers can also trigger chronic inflammation, the kinetics of CRP levels during treatment may have predictive value for successful immunotherapy.[10] Here, a multitude of differing CRP kinetic models have been described for mRCC in various treatment lines including IO regimens. Klümper et al. and Fukuda et al., for example, investigated the predictive value of the CRP 'flare-response' phenomenon in mRCC cohorts receiving first-line standard of care therapy with either IO+IO or IO+TKI or second-line therapy with nivolumab.[11,12] Early CRP changes after IO treatment initiation were found to reliably predict therapy success and identify patients who are unlikely to benefit from IO combination therapy. However, both studies were limited by low patient numbers. Ishihara et al., on the contrary, examined the association between baseline and early on-treatment CRP levels and clinical outcomes in mRCC patients treated with nivolumab second line.[13] The study found that elevated baseline CRP levels were associated with poor overall survival (OS), progression-free survival (PFS) and objective response rate in mRCC patients. These and other studies highlight the potential predictive value of longitudinal CRP measurements and baseline CRP levels as a potential prognostic biomarker.[5,14,15] The aim of this study was to examine two CRP kinetic regimens in an updated, multicentre mRCC cohort of 316 patients receiving systemic first-line mRCC treatment.

RESULTS

Descriptive characteristics of the study population

The study cohort comprised 316 mRCC patients treated with first-line IO + IO/IO + TKI. Among those, 227 (72%) and 276 (87%) mRCC patients could be assigned to the respective CRP classifications by Fukuda et al. as well as Ishihara et al. (Supplementary figure 1). The patient and tumor characteristics did not significantly differ between patients that could be assigned to the respective groups compared with the remaining ones (Supplementary tables 1 and 2). The median follow-up in the whole cohort was 13 (Interquartile range (IQR): 6–23) months.

CRP dynamics according to Fukuda et al.

Among 227 mRCC patients, 80 (35%) vs. 44 (19%) vs. 103 (45%) were non-CRP responder vs. CRP flare-responder vs. CRP responder. In general, patient and tumor characteristics did not significantly differ between the groups (Table 1). Only the proportion of patients receiving

Table 1. Patient and tumor characteristics of 227 metastatic renal cell carcinoma patients treated with first-line IO + IO/IO + TKI and C-reactive protein data available to be stratified according CRP kinetics defined by Fukuda *et al.*

	N	Overall, N = 227	Non-CRP responder, N = 80 (35%)	CRP flare-responder, N = 44 (19%)	CRP responder, N = 103 (45%)	*P*-value
Age at treatment initiation [years], Median (IQR)	227	66 (60, 73)	66 (58, 73)	67 (58, 72)	67 (60, 73)	0.7
Male gender, *n* (%)		157 (69%)	57 (71%)	31 (70%)	69 (67%)	
ECOG, *n* (%)	220					0.9
0		91 (41%)	31 (41%)	14 (33%)	46 (46%)	
1		107 (49%)	37 (49%)	25 (58%)	45 (45%)	
2		15 (6.8%)	5 (6.6%)	3 (7.0%)	7 (6.9%)	
3		6 (2.7%)	3 (3.9%)	1 (2.3%)	2 (2.0%)	
4		1 (0.5%)	0 (0%)	0 (0%)	1 (1.0%)	
IMDC, *n* (%)	226					0.2
Favorable		47 (21%)	20 (25%)	10 (23%)	17 (17%)	
Intermediate		128 (57%)	45 (57%)	27 (61%)	56 (54%)	
Poor		51 (23%)	14 (18%)	7 (16%)	30 (29%)	
Combined T-stage, *n* (%)	195					0.9
T1		49 (25%)	17 (23%)	8 (21%)	24 (29%)	
T2		18 (9.2%)	6 (8.2%)	4 (10%)	8 (9.6%)	
T3		90 (46%)	35 (48%)	21 (54%)	34 (41%)	
T4		19 (9.7%)	8 (11%)	4 (10%)	7 (8.4%)	
Tx		19 (9.7%)	7 (9.6%)	2 (5.1%)	10 (12%)	
Combined N-Stage, *n* (%)	185					0.7
N0		82 (44%)	29 (43%)	19 (50%)	34 (43%)	
N1		60 (32%)	20 (29%)	11 (29%)	29 (37%)	
Nx		43 (23%)	19 (28%)	8 (21%)	16 (20%)	
M-Stage, *n* (%)	223					0.068
M0		70 (31%)	31 (40%)	17 (40%)	22 (22%)	
M1		131 (59%)	40 (51%)	23 (53%)	68 (67%)	
Mx		22 (9.9%)	7 (9.0%)	3 (7.0%)	12 (12%)	
Nephrectomy, *n* (%)	217	135 (62%)	50 (68%)	30 (70%)	55 (55%)	0.12
Radiotherapy, *n* (%)	188	84 (45%)	22 (32%)	21 (57%)	41 (49%)	0.029
Clear-cell histology, *n* (%)		177 (82%)	66 (84%)	33 (79%)	78 (81%)	
Grade histology, *n* (%)	174					> 0.9
1		9 (5.2%)	3 (4.7%)	2 (5.6%)	4 (5.4%)	
2		69 (40%)	29 (45%)	12 (33%)	28 (38%)	
3		71 (41%)	24 (38%)	17 (47%)	30 (41%)	
4		25 (14%)	8 (12%)	5 (14%)	12 (16%)	
Systemic treatment combination, *n* (%)	224					0.4
IO-IO		86 (38%)	34 (43%)	18 (42%)	34 (33%)	
IO-TKI		138 (62%)	45 (57%)	25 (58%)	68 (67%)	
Baseline CRP [mg L^{-1}] Median (IQR)	227	9 (2, 38)	3 (1, 15)	7 (2, 17)	29 (6, 61)	< 0.001
Duration for 1 month CRP [days] Median (IQR)	227	21 (13, 22)	21 (12, 22)	21 (14, 22)	21 (14, 22)	0.8
Time to therapy [months] Median (IQR)	227	5 (1, 34)	12 (2, 56)	9 (1, 31)	3 (0, 24)	0.005
Maximum target lesion at 1st staging [%], Median (IQR)	99	−8 (−33, 27)	7 (−25, 50)	1 (−28, 27)	−20 (−41, −5)	0.002

All values are median (Interquartile range) or frequencies (%).
ECOG, Eastern Cooperative Oncology Group; IMDC, International metastatic RCC database consortium; IO, Immunotherapy; IQR, Interquartile range; TKI, Tyrosine kinase inhibitor.

radiotherapy was higher in CRP flare-responders *vs.* CRP responder and non-CRP responder (57% *vs.* 49%, *vs.* 32%, *P* = 0.02). The systemic treatment regimen did not differ between the groups. The median time from diagnosis to treatment initiation was significantly longer in the non-CRP
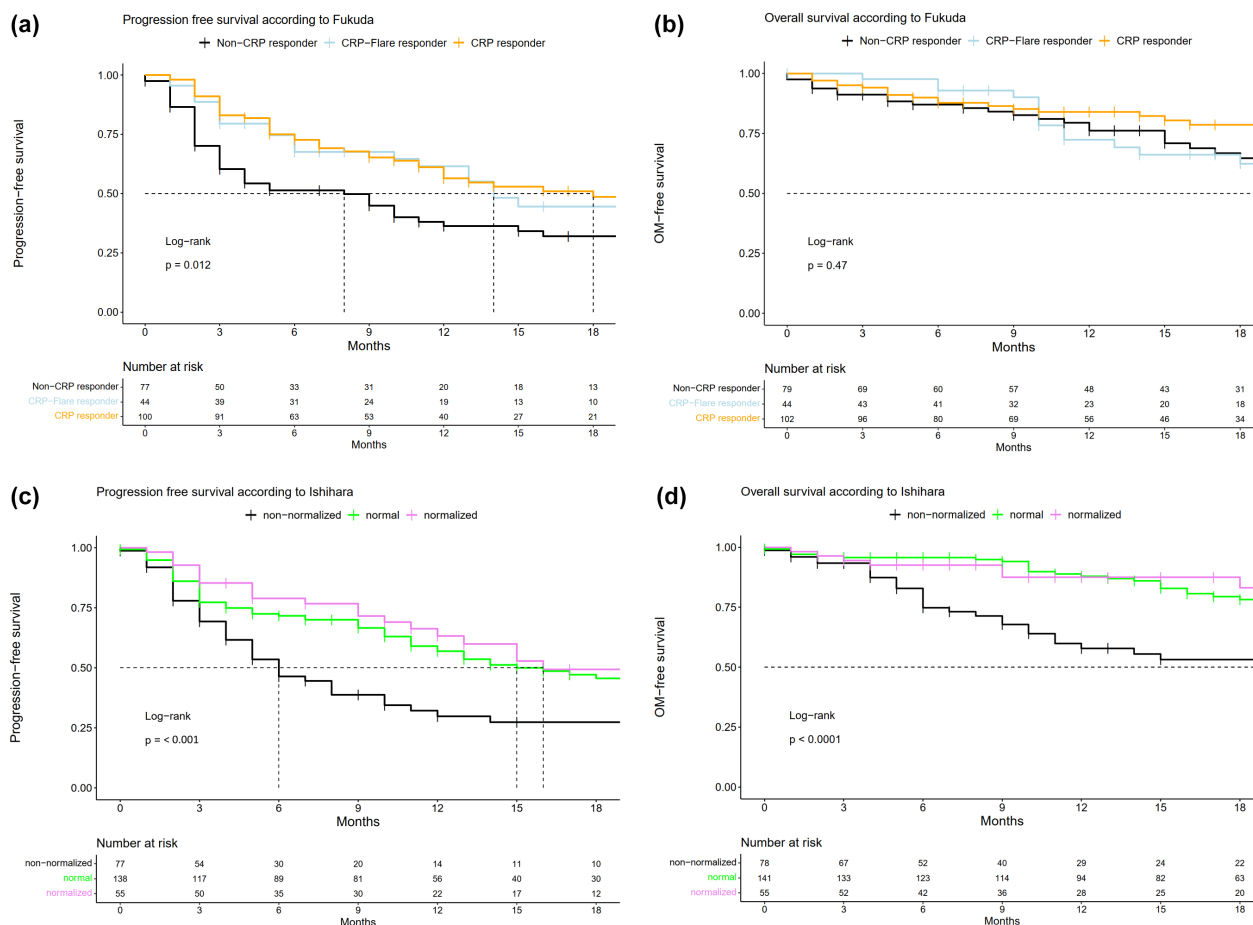
Figure 1. Kaplan–Meier plots depicting **(a, c)** progression-free survival and **(b, d)** overall survival for mRCC patients stratified according to C-reactive protein kinetics definition by Fukuda **(a, b)** or Ishihara *et al.* **(c, d)**.

responder group (12 months) than in the CRP flare-responder (9 months) and CRP responder group (3 months), respectively ($P = 0.005$). At first staging, median maximum target lesion change was 7 (IQR: −25; 50), 1 (IQR: −28; 27) and −20% (IQR: −41; −5) for non-CRP responder, CRP flare-responder and CRP responder ($P = 0.002$).

The median PFS was 8 (95% CI [95% confidence interval] 4; 15), 14 (95% CI 11; 30) and 18 months (95% CI 12; n.r. [not reached]) for non-CRP responder, CRP flare-responder and CRP responder (Figure 1a) and differed significantly ($P = 0.012$; Figure 2a). In univariate Cox regression analyses, CRP response (Hazard ratio [HR]: 0.55; 95% CI 0.37; 0.83), but not CRP flare-response, was associated with prolonged PFS. It is of note that following adjustment for covariables, both CRP responder (HR: 0.59; 95% CI 0.35; 0.99) and CRP flare-responder (HR: 0.52; 95% CI 0.33; 0.82) gained statistically significant predictors for PFS

(Supplementary table 3). The median OS was 32 (95% CI 23; n.r.), not reached (95% CI 18; n.r.) and 33 months (95% CI 31; n.r.) for non-CRP responder, CRP flare-responder and CRP responder and did not significantly differ. Moreover, CRP stratification was not predictive for OS in both univariable and multivariable Cox regression analyses (Figure 1b, Supplementary table 3).

CRP dynamics according to Ishihara *et al.*

Out of 276 mRCC patients, 79 (29%) *vs.* 141 (51%) *vs.* 56 (20%) were assigned to the non-normalised *vs.* normal *vs.* normalised groups according to Ishihara *et al*. In general, patient characteristics did not statistically significantly differ between the groups (Table 2). However, more patients in the normal CRP group were IMDC favorable risk and less poor risk than the other groups ($P < 0.001$). Moreover, the proportion of M1 patients was

Table 2. Patient and tumor characteristics of 276 metastatic renal cell carcinoma patients being treated with first-line IO + IO/IO + TKI and C-reactive protein data available to be stratified according to CRP kinetics defined by Ishihara *et al.*

	N	Overall, N = 276	Non-normalised, N = 79 (29%)	Normal, N = 141 (51%)	Normalised, N = 56 (20%)	P-value
Age at treatment initiation [years], Median (IQR)	276	67 (60, 73)	66 (60, 72)	67 (60, 73)	66 (58, 74)	> 0.9
Male gender, n (%)		192 (70%)	54 (68%)	100 (71%)	38 (68%)	
ECOG, n (%)	266					0.3
0		111 (42%)	34 (45%)	56 (41%)	21 (39%)	
1		130 (49%)	35 (46%)	70 (51%)	25 (46%)	
2		18 (6.8%)	4 (5.3%)	7 (5.1%)	7 (13%)	
3		6 (2.3%)	3 (3.9%)	3 (2.2%)	0 (0%)	
4		1 (0.4%)	0 (0%)	0 (0%)	1 (1.9%)	
IMDC, n (%)	275					< 0.001
Favorable		54 (20%)	8 (10%)	42 (30%)	4 (7.1%)	
Intermediate		160 (58%)	45 (57%)	83 (59%)	32 (57%)	
Poor		61 (22%)	26 (33%)	15 (11%)	20 (36%)	
Combined* T-stage, n (%)	240					0.14
T1		60 (25%)	10 (15%)	38 (30%)	12 (26%)	
T2		26 (11%)	7 (10%)	17 (13%)	2 (4.3%)	
T3		108 (45%)	28 (42%)	57 (45%)	23 (49%)	
T4		26 (11%)	14 (21%)	7 (5.6%)	5 (11%)	
Tx		20 (8.3%)	8 (12%)	7 (5.6%)	5 (11%)	
Combined* N-Stage, n (%)	230					0.8
N0		105 (46%)	28 (45%)	59 (47%)	18 (42%)	
N1		69 (30%)	19 (31%)	34 (27%)	16 (37%)	
Nx		56 (24%)	15 (24%)	32 (26%)	9 (21%)	
M-Stage, n (%)	271					0.002
M0		85 (31%)	16 (21%)	51 (36%)	18 (33%)	
M1		164 (61%)	58 (76%)	71 (51%)	35 (64%)	
Mx		22 (8.1%)	2 (2.6%)	18 (13%)	2 (3.6%)	
Nephrectomy, n (%)	254	152 (60%)	33 (50%)	91 (68%)	28 (51%)	0.013
Radiotherapy, n (%)	236	104 (44%)	31 (46%)	52 (41%)	21 (50%)	0.6
Clear-cell histology, n (%)		220 (83%)	58 (76%)	124 (91%)	38 (72%)	0.03
Grade histology, n (%)	210					0.063
1		14 (6.7%)	4 (8.7%)	9 (7.3%)	1 (2.5%)	
2		89 (42%)	17 (37%)	58 (47%)	14 (35%)	
3		79 (38%)	16 (35%)	48 (39%)	15 (38%)	
4		28 (13%)	9 (20%)	9 (7.3%)	10 (25%)	
Systemic treatment combination, n (%)	272					0.13
IO-IO		108 (40%)	37 (48%)	54 (39%)	17 (31%)	
IO-TKI		164 (60%)	40 (52%)	86 (61%)	38 (69%)	
Baseline CRP [mg L^{-1}], Median (IQR)	276	9 (2, 41)	55 (26, 101)	2 (1, 5)	33 (20, 56)	< 0.001
Duration for 1 month CRP [days], Median (IQR)	238	21 (14, 23)	20 (7, 25)	21 (17, 22)	21 (14, 24)	0.3
Time to therapy [months], Median (IQR)	276	5 (1, 33)	2 (0, 10)	11 (2, 53)	3 (0, 17)	< 0.001
Maximum target lesion at 1st staging [%], Median (IQR)	123	−16 (−38, 15)	−19 (−34, 11)	−11 (−36, 20)	−32 (−48, −8)	0.2

All values are median (Interquartile range) or frequencies (%).

ECOG, Eastern Cooperative Oncology Group; IMDC, International metastatic RCC database consortium; IO, Immunotherapy; IQR, Interquartile range; TKI, Tyrosine kinase inhibitor.

higher in CRP non-normalised patients ($P = 0.002$). Median baseline CRP values differed between the groups with 55 (IQR: 26;101) *vs.* 2 (IQR: 1; 5) *vs.* 33 (IQR: 20; 56) mg L^{-1} for the non-normalised *vs.* normal *vs.* normalised groups, respectively (Table 2). At first staging, median maximum target lesion change was −19 (IQR: −34; 11), −11 (IQR: −36; 20) and −32% (IQR: −48; −8) for the non-normalised *vs.* normal *vs.* normalised groups, and did not significantly differ.

The median PFS was 6 (95% CI 5; 10), 15 (95% CI 12; 23) and 16 months (95% CI 13; n.r.) for the non-normalised *vs.* normal *vs.* normalised groups (Figure 1c) and differed significantly (*P* < 0.001). In univariable Cox regression analyses for PFS, both the normal (HR: 0.54, 95% CI 0.37; 0.83) and the normalised groups (HR: 0.40, 95% CI 0.24; 0.66) were associated with prolonged PFS (Supplementary table 4). It is of note that following adjustment for other covariables, both normal and normalised CRP dynamics remained statistically significant predictors for PFS in multivariable Cox regression analyses (Supplementary table 4).

The median OS was 23 (95% CI 11; n.r.), 39 months (95% CI 32; n.r.) and not reached (95% CI 33; n.r.) for the non-normalised *vs.* normal *vs.* normalised group (Figure 2b) and differed significantly (*P* < 0.001, Figure 1d). Moreover, normal (HR: 0.36, 95% CI 0.22; 0.59) and normalised (HR: 0.32, 95% CI 0.16; 0.65) CRP dynamics were associated with prolonged OS in univariable Cox regression analyses (both *P* < 0.01). Its predictor status remained unchanged following the adjustment for other variables in multivariable Cox regression analyses (Supplementary table 4).

## Comparison of both CRP kinetics definitions

When stratifying the CRP kinetics groups by clinical response at first staging, the proportion of clinical responders (complete response [CR] + partial response [PR] + stable disease [SD]) was higher in CRP flare-responders than in CRP nonresponders (83.2% *vs.* 55.6%) and normalised patients according to Ishihara than non-normalised patients (89.7% *vs.* 67.7%; Figure 3a and b). In direct comparison, the proportion of patients with progressive disease was slightly higher in CRP flare-responders than in normalised patients (16.7% *vs.* 10.3%). When comparing both CRP kinetics definitions, the overlap of patients belonging to the corresponding groups was low (Figure 4).

DISCUSSION

Against the background of increasing treatment options in first-line mRCC therapy, offering clinical benefit to a significant number of patients on the one hand, but on the other hand subjecting nonresponders to considerable side effects, reliable predictive biomarkers represent an unmet need.[16] Although the PD-L1 expression on tumor cells has

been linked with a negative prognostic role in mRCC,[17] its predictive value could ultimately not be confirmed.[18,19] Moreover, it remains questionable from a biological point of view, whether the primarily metastasis-directed systemic therapy should be guided by the analysis of the primary tumor.[20] Hence, the ideal biomarker should rather provide a snapshot of all tumor cells, and potentially its dynamic changes during therapy. Liquid biomarkers may combine all these requirements, and especially the inflammatory marker CRP is not only easy to measure and cost-effective, but also nearly ubiquitously available.[6,12]

The concept of quantifying the immunological activation status of the patient by measuring CRP values before treatment initiation is not new, and its prognostic power in RCC had already been hypothesized by Iimura *et al.* in 2009.[21] However, in order to predict therapy response, the dynamic measurement of biomarkers might exert a significantly higher predictive power.[22] Ishihara *et al.* recently proposed their definition of CRP kinetics, differentiating three patient groups: those whose pretreatment levels were < 10 mg L^{-1} before therapy ('normal'), those with decreasing CRP levels from ≥ 10 mg L^{-1} before treatment initiation to nadir levels below < 10 mg L^{-1} within 3 months ('normalised') and 'non-normalised' patients with CRP levels ≥ 10 mg L^{-1} before and under therapy. 'Normal' and 'normalised' patients had a significantly longer OS and PFS under second-line nivolumab therapy in mRCC.[23] On the contrary, Fukuda *et al.* proposed to differentiate 'CRP flare-responders' (at least doubling of CRP levels within 1 month after initiation and the decrease to lower baseline within 3 months), 'CRP responders' (decrease ≥ 30% from baseline within 3 months w/o flare) and 'non-CRP-responders' (all other remaining CRP dynamics).[11] The predictive power of the CRP flare-up phenomenon as an on-treatment biomarker has been confirmed by different groups in different tumor entities, such as urothelial or lung carcinoma.[12,24,25] Recently, Guer *et al.* investigated CRP kinetics – combined with early-on treatment related adverse events – as a predictor for treatment success in mRCC.[9] Even though that the authors reported noteworthy findings, the results need to be interpreted under the light of a small, single-centre study cohort (*n* = 57) and limited follow-up. As a consequence, above-mentioned diverging definitions of the CRP kinetics have not been compared in a large, contemporary real-world first-line mRCC cohort, hence, we performed the

(a)

(b)
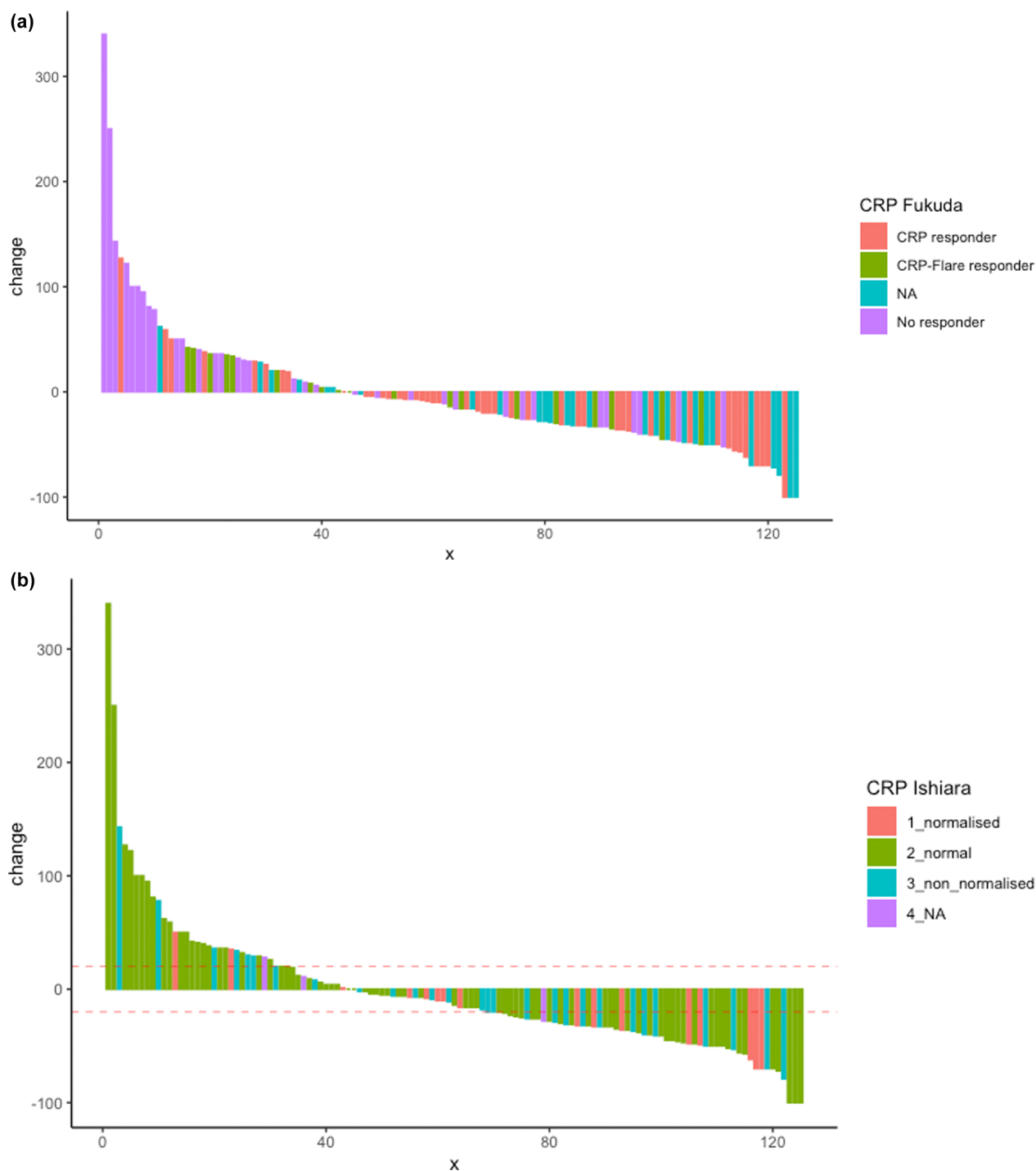
Figure 2. Waterfall plots depicting target lesion change at first line, stratified by the C-reactive protein kinetics definition according to Fukuda *et al.* **(a)** and Ishihara *et al.* **(b)**.

present analysis comprising more than 300 mRCC patients. Ultimately, the application of both definitions enabled to correctly identify many therapy (non)responders, as CRP (flare) response and normal/normalised CRP values were significant independent predictors of OS and PFS.

However, in our German real-world clinical experience, early CRP measurements within the

(a)
Fukuda

(b)
Ishihara
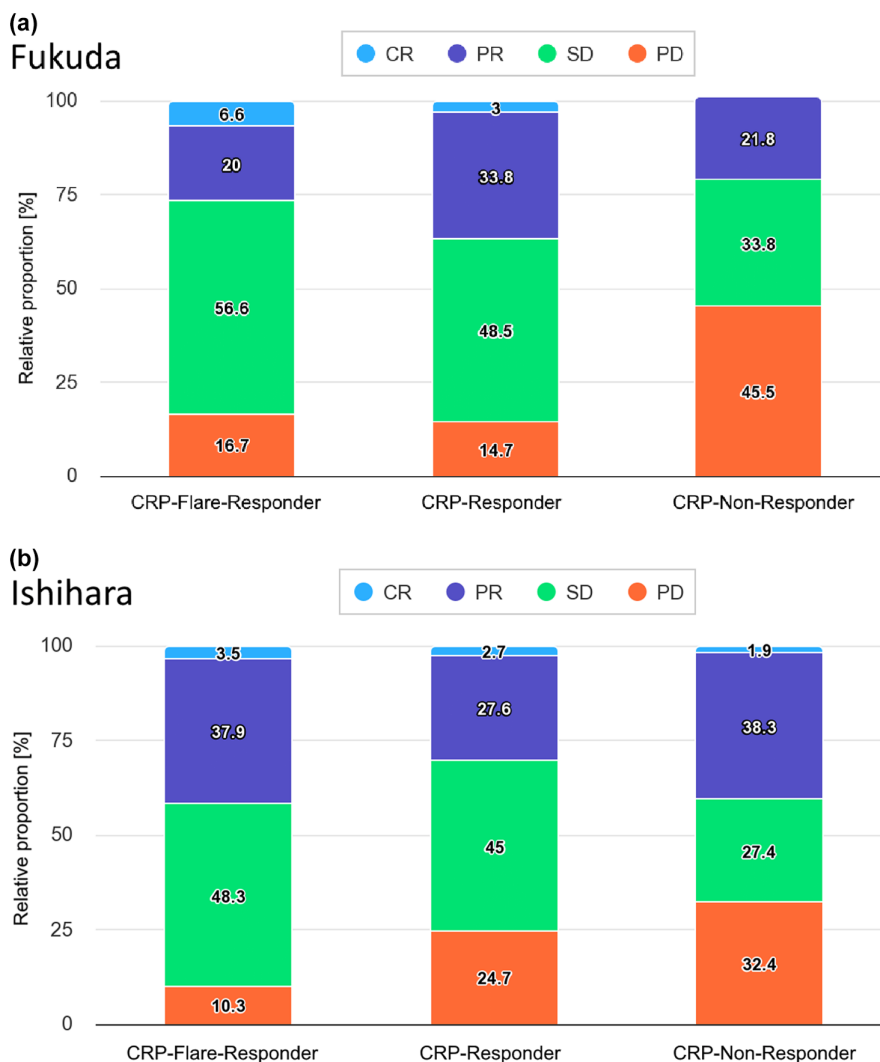
Figure 3. Stacked bar plots stratifying patients by C-reactive protein kinetic group according to Fukuda **(a)** or Ishihara *et al*. **(b)** by the respective target lesion change at first staging 3 months after therapy initiation. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

first weeks after initiation of first-line therapy in mRCC are no standard, as portrayed by 89 (28.2%) missing early measurements to successfully classify our cohort according to CRP kinetics defined by Fukuda. Of note, especially the CRP flare-response phenomenon appears to occur within the first 2 weeks after therapy initiation.[24] Widespread indication of such measurements obviously could have the power to identify patients undergoing progression *before* first staging with the potential not to delay further interventions or therapy lines. On the contrary, easy-to-apply CRP algorithms pre-/post-therapy initiation as introduced by Ishihara *et al.* are also available and applicable in the majority of treating centres – although 40

(12.7%) patients could neither be classified according to the definition by Ishihara. It is of note that this definition also possesses a significant predictive power as illustrated in our analysis and can potentially lead to better patient care in the sense of treatment oversight and planning.

Interestingly, both examined CRP kinetic definitions in the cohort presented here vastly differ: CRP kinetics defined by Fukuda rely on relative changes in CRP values independently from the magnitude of initial CRP values, whereas Ishihara's definition is based on absolute CRP thresholds. Moreover, the overlap of patients belonging to comparable CRP kinetics group was
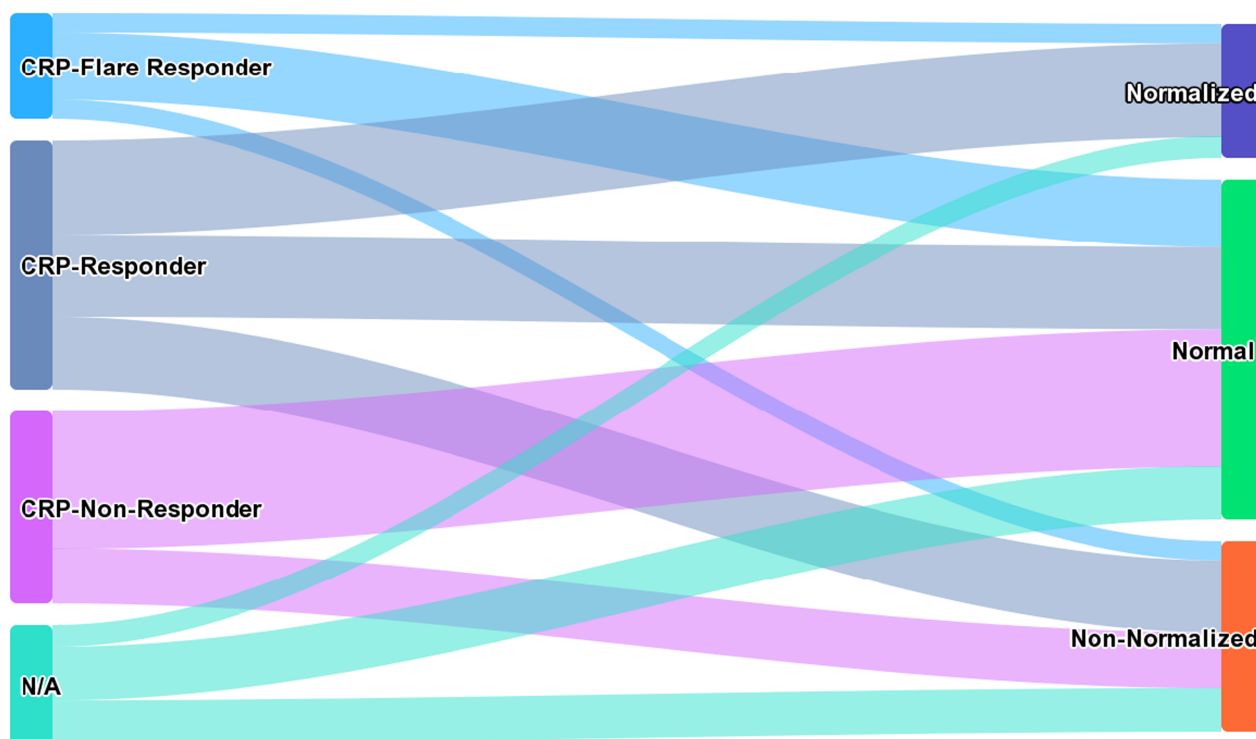
Figure 4. Sankey diagram illustrating the patient distribution compared between the two diverging C-reactive protein kinetics definitions by Fukuda *et al.* and Ishihara *et al.*

low; however, this did not affect the predictive power of both definitions. In our opinion, further investigation is warranted to potentially identify patients profiting exceptionally from therapy (or not). Ideal questions to be asked here would aim at the significance of initial CRP values and their subsequent kinetic, be it relative proportions or absolute drop. For instance, Klümper *et al.* recently further distinguished CRP flare-responders into short- and long-flare-responders,[24] or integrated also albumin levels within the 'modified Glasgow prognostic score' (mGPS).[26] However, these approaches were beyond our study objective.

Limitations

Even though the majority of patient and tumor characteristics did not differ between patients with sufficient CRP information to be classified according to Fukuda or Ishihara compared to those without sufficient CRP information, same characteristics differed statistically significantly in sensitivity analyses. As a consequence, a potential selection bias could not be formally ruled out; yet, its magnitude and clinical relevance for interpreting the current results is of limited nature.

CONCLUSIONS

In summary, both examined CRP kinetics presented here reliably predicted mRCC patient outcomes in first-line mRCC therapy, highlighting further potential improvements of patient care. Interestingly, there was no significant group overlap of both examined models suggesting that further improvement through CRP kinetic model modification might be possible.

METHODS

Study population

This multi-institutional retrospective study included mRCC patients treated with either IO+IO or IO+TKI 1st line between 11/2017 and 12/2022 in eight tertiary referral centres. Patients with sufficient CRP data to be stratified according to the CRP kinetics classifications previously introduced by Fukuda *et al.* ('Fukuda') and Ishihara *et al.* ('Ishihara') were identified and further analysed (Supplementary figure 2a, b). Regarding 'Fukuda', minimum CRP data consisted of (a) CRP prior (< 6 weeks) to treatment initiation, (b) CRP within 1 month of treatment initiation and (c) at least one further CRP prior to first staging. Regarding 'Ishihara', minimum CRP data consisted of (a) CRP prior to treatment initiation (< 30 days) and at least one further CRP prior to first staging. Relying on the 'Fukuda'

definition, mRCC patients were classified as 'CRP flare-responder', 'CRP responder' and 'non-CRP responder' following CRP dynamics, whereas following the 'Ishihara' definition, mRCC patients were classified as 'normal', 'normalised' and 'non-normalised', respectively.[11,13] Patient demographics and baseline parameters, including IMDC (International Metastatic RCC Database Consortium) risk criteria, were obtained. Tumor response was graded according to response evaluation criteria in solid tumors (RECIST v1.1).[27] Serum CRP concentration was measured in accredited routine laboratories in each participating centre and is given in mg L^{-1} (clinical reference < 5 mg L^{-1}). For each patient, a recent follow-up was conducted. This study was conducted according to the Declaration of Helsinki and approved by the local responsible ethical review boards (reference #20201211-01).

Statistical analyses

Metastatic renal carcinoma patients with sufficient CRP data to be classifiable according to 'Fukuda' definition, patient and tumor characteristics were tabulated according to CRP dynamics. Descriptive statistics included frequencies and proportions for categorical variables. Medians and IQRs were reported for continuously coded variables. Maximum target lesion change for the three different CRP dynamic groups at first staging was depicted relying on waterfall plot illustration. Subsequently, separate Kaplan–Meier plots and Cox regression analyses were used to test for (a) PFS and (b) OS differences according to CRP dynamics. Progression was defined according to the RECIST v1.1 criteria including death from any cause. In Cox regression analyses, IMDC criteria (favorable *vs* intermediate *vs* poor), age at treatment initiation (per year), ECOG (Eastern Cooperative Oncology Group) performance status (continuously) and combined tumor stage (T1/2 *vs* T3/4 *vs* Tx) were defined as adjustment variables. In order to test for a potential underlying selection bias, sensitivity analyses were conducted to compare the tumor and patient characteristics between 'Fukuda'-eligible mRCC patients and patients for whom CRP data were missing. The statistical approach was repeated for mRCC patients who had enough CRP data to be classified according to the 'Ishihara' definition ('normal', 'normalised', 'non-normalised'). All tests were two-sided with a level of significance set at $P < 0.05$ and R software environment for statistical computing and graphics (version 4.1.1) was used for all analyses.[28]

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AUTHOR CONTRIBUTIONS

Benedikt Hoeh: Conceptualization; data curation; formal analysis; writing – original draft. **Cristina Cano Garcia:** Data curation; software. **Severine Banek:** Data curation; supervision. **Niklas Klümper:** Data curation; investigation; writing – review and editing. **Alexander Cox:** Data curation; writing – review and editing. **Jörg Ellinger:** Supervision; writing – review and editing. **Philipp Schmucker:** Data curation; writing – review and editing. **Oliver Hahn:** Conceptualization; data curation; writing – review and editing. **Angelika Mattigk:** Data curation; investigation; visualization; writing – review and editing. **Friedemann Zengerling:** Resources; writing – review and editing. **Philippe Becker:** Conceptualization; data curation; writing – review and editing. **Kati Erdmann:** Data curation; methodology; writing – review and editing. **Bjoern Thorben Buerk:** Data curation; supervision; writing – review and editing. **Luka Flegar:** Data curation; writing – review and editing. **Johannes Huber:** Supervision; writing – review and editing. **Charis Kalogirou:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Philip Zeuschner:** Conceptualization; data curation; formal analysis; methodology; project administration; software; visualization; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

DATA AVAILABILITY

All data sets generated for this study are included in the manuscript.

ETHICS CONSENT STATEMENT

The study was conducted according to the Declaration of Helsinki and approved by the responsible ethical review board (reference #20201211–01).

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Supporting Information

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