



## ORIGINAL ARTICLE

# Clinical value and limitations of the preoperative C-reactive-protein-to-albumin ratio in predicting post-operative morbidity and mortality after deceased-donor liver transplantation: a retrospective single-centre study

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## SUMMARY

Liver transplantation is still associated with a high risk of severe complications and post-operative mortality. This study examines the predictive value of the preoperative C-reactive-protein-to-albumin ratio (CAR) regarding perioperative morbidity and mortality in deceased-donor liver transplantation (DDLT) recipients. In total, 390 DDLT recipients between 05/2010 and 03/2020 were eligible. Predictive abilities of CAR were examined through receiver operating characteristic curve (ROC) analyses. Groups were compared using parametric and non-parametric tests as appropriate. Independent risk factors for morbidity and mortality were identified using uni- and multivariable logistic regression analyses. A good predictive ability for CAR was shown regarding perioperative morbidity (comprehensive complication index  $\geq 75$ , Clavien–Dindo score  $\geq 4a$ ) and 12-month mortality, with an ideal cut-off of CAR = 26%. Patients with CAR > 26% had significantly higher median CCI scores (60 vs. 43,  $P < 0.001$ ), longer intensive care unit (ICU, 5 vs. 4 days,  $P < 0.001$ ) and hospital (28 vs. 21 days,  $P < 0.001$ ) stays and higher 12-month mortality rates (20% vs 6%,  $P < 0.001$ ). Multivariable analyses identified CAR > 26%, pre-OLT inpatient hospitalization (including ICU) and post-operative red blood cell transfusions as independent predictors of severe cumulative morbidity (CCI  $\geq 75$ ). Preoperative CAR might be a reliable additional tool to predict perioperative morbidity and mortality in DDLT recipients.

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## Key words

albumin, CRP, graft loss, morbidity, orthotopic liver transplantation, outcome

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## Introduction

Over the last 60 years, orthotopic liver transplantation (OLT) evolved from an experimental technique to the gold standard treatment for end-stage liver disease [1–3] with more than 30 000 liver transplantations carried out worldwide in 2018 [4]. A combination of factors enabled the successful clinical implementation of OLT, including a better understanding of hepatic pathophysiology and immunology, advances in surgical techniques and perioperative management, as well as refinement of patient selection criteria [2,5–7].

Nevertheless, OLT remains technically challenging and is still associated with an increased risk of severe complications, post-operative mortality and graft loss [2,7–10]. It stands to reason, therefore, that predictors of adverse outcomes are of great clinical and scientific interest, as they may allow for closer monitoring and earlier intervention in patients at risk. With this in mind, various prognostic scores have been evaluated and established in the OLT setting, such as the Model of End-stage Liver Disease (MELD) [9], Balance of Risk (BAR) [6] and Survival Outcomes Following liver Transplantation (SOFT) [7] scores, or the Donor Risk Index (DRI) [11,12]. Newer scores have also been developed, such as the Liver Graft Assessment Following Transplantation (L-GrAFT) [13] and Early Allograft Failure Simplified Estimation (EASE)[14] scores, which focus on early allograft dysfunction. Some workgroups have created simplified scores (such as Kong et al., who included recipient age, creatinine, bilirubin and albumin (Alb) [15]) or focused on individual parameters, such as post-operative platelet counts [5], body mass index (BMI) [16], recipient blood type [17] or recipient and donor gender as prognostic markers [18].

A composite parameter of interest is the ratio of C-reactive protein (CRP) to Alb in serum. Previous studies have demonstrated the predictive ability of the C-reactive-protein-to-albumin ratio (CAR) with regard to morbidity and mortality [19–21], early allograft dysfunction [22], and other outcomes in various populations, including critically ill [19,20], pre-transplantation or cirrhotic [23,24], post-operative [21,25–27], and oncological [28,29] patients.

Separately, CRP and Alb can predict poor outcomes, such as morbidity, mortality and prolonged hospital or intensive care unit (ICU) stay [19]. Increased CRP levels have been associated with malignancy, sepsis, and inflammatory diseases [19,27] and used as a prognostic marker in the critical care setting [19], as well as in post-operative [30], cirrhotic [31] and transplanted

patients [32,33]. Reduced Alb levels are common in critically ill patients and can be attributed to previous illness, liver failure, renal insufficiency, or malnutrition [19,22,27]. Whereas alterations of CRP and Alb levels alone can be unspecific, due to their association with multiple conditions, CAR is more consistent in relation to its prognostic ability [21,22,27], and more accurately reflects the severity of nutritional deficiency and inflammation [19,20,22,27,34].

To the best of our knowledge, despite its encouraging performance in other patient cohorts, CAR has not been previously investigated in the setting of deceased-donor liver transplantation (DDLT). Therefore, the aim of this study is to investigate the predictive value and limitations of preoperative CAR with regard to perioperative morbidity, mortality, and graft loss in adult DDLT recipients.

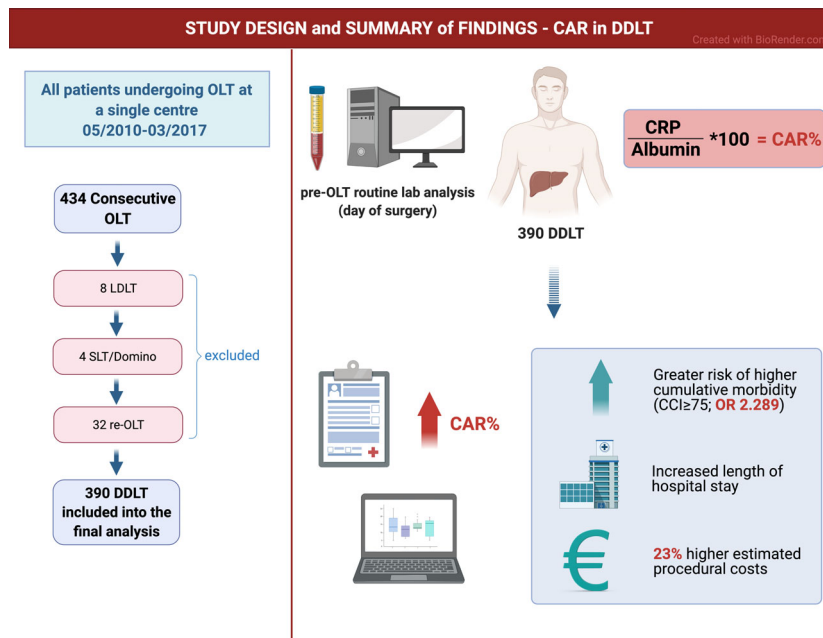
## Patients and methods

### Study design and endpoints

All adult patients who underwent DDLT at the University Hospital RWTH Aachen (UH-RWTH), Aachen, Germany, between May 2010 and March 2020 were considered for this retrospective study. Split and domino transplantations were excluded, as were re-transplantations within our cohort, which were analysed as part of post-operative graft loss (Figure 1). Three patients with re-cirrhosis and chronic graft failure decades following initial OLT in their childhood were still included in the study (classified under “other” together with other rare indications in the aetiology section of Table 1). The incidence of severe- and life-threatening perioperative complications within 90 days after liver transplantation, defined as Clavien-Dindo (CD)  $\geq 3b$  and CD  $\geq 4a$ , respectively [35], were selected as the main endpoints of the study. Further endpoints comprised the following perioperative outcomes: overall morbidity as defined by the Comprehensive Complication Index (CCI) [36]), mortality, length of ICU- and hospital stay, graft loss, and early allograft dysfunction (EAD) as defined by the Olthoff criteria and using the model of early allograft function score (MEAF) [37].

### Data collection and clinical considerations

Organ allocation conformed to national (Deutsche Stiftung Organtransplantation—DSO and Bundesärztekammer—BÄK) and international (Eurotransplant) regulations [38,39]. Surgical techniques were



**Figure 1** Study design and graphical summary of the main findings of the study. Abbreviations used: OLT, orthotopic liver transplantation; LDLT, living-donor liver transplantation; SLT, split liver transplantation; DDLT, deceased-donor liver transplantation; CRP, C-reactive protein; CAR, C-reactive-protein-to-albumin ratio; CCI, comprehensive complication index; OR, odds ratio.

standardized, as described previously [3,16]. Perioperative treatment and immunosuppression followed institutional protocols. Clinical data were recovered from a prospective institutional database and analysed in a retrospective fashion. Post-discharge follow-up was carried out at UH-RWTH and Maastricht University Medical Centre (MUMC) transplantation outpatient departments or community-based hepatology units. Complications were stratified according to CD and CCI. Definitions of EAD, MEAF, renal failure and other relevant variables have been previously described [10,37,40], as have calculations of the length of ICU and hospital stay and perioperative transfusions [5,8,41]. Risk-assessment scores used in this study (such as MELD, BAR and SOFT) have already been described and validated in various cohorts [2,6,7,9]. Finally, hospitalization costs were estimated using a validated cost-estimation tool, as previously reported [5,42].

Serum laboratory parameters were routinely measured perioperatively. Biochemical parameters, including CRP (mg/dL) and Alb (g/dL) levels, were measured by an automated chemistry analyser (Cobas® 8000 modular analyser series, Roche Diagnostics GmbH, Mannheim, Germany). A percentage value for CAR ( $\text{CRP}/\text{Alb} \times 100 = \text{CAR\%}$ ) was calculated using CRP and Alb values from the same blood sample, taken within 6 hours pre-OLT for all patients.

### Statistical analysis

Data were reported as means and standard deviations (SD) for normally distributed continuous variables, medians and interquartile range (IQR) for non-normally distributed continuous variables or absolute and relative frequencies for categorical and ordinal variables. Normality testing was performed using the Kolmogorov–Smirnov test. The predictive ability of preoperative CAR with respect to the defined endpoints was examined by calculating the area under the receiver operating characteristic curve (ROC) and the model goodness-of-fit was assessed using the Hosmer–Lemeshow Chi-square test. Group comparisons were carried out using the Mann–Whitney U test, the Chi-square test or Fisher’s exact test and Kruskal–Wallis H test as applicable. The Spearman correlation coefficient was used to further explore the association of various clinical outcomes with preoperative CAR values. Independent risk factors for morbidity and mortality were identified using uni- and multivariable binary logistic regression analyses. All  $p$  values  $<0.05$  were considered statistically significant. Statistical analysis was performed using SPSS Statistics v26 (IBM Corp., Armonk, NY, USA), and graphs were generated using Prism v8.0 (GraphPad Software, La Jolla, CA, USA).

**Table 1.** Donor and recipient characteristics for patients with a preoperative CAR below and above the cut-off value of 26%.

Variables	All patients (n = 390)	CAR≤26% (n = 165)	CAR>26% (n = 225)	P-value
Donor age (years)	58 [19]	59 [20]	57 [19]	0.135
Donor BMI	28 [6]	28 [6]	28 [6]	0.284
Donor sex ratio (F/M)	186 (48%) / 204 (52%)	76(46%) / 89 (54%)	110 (49%) / 115 (51%)	0.581
Cause of donor death	CVA 226 (58%)	CVA 85 (52%)	CVA 141 (63%)	<b>0.028</b>
	Anoxia 93 (24%)	Anoxia 50 (30%)	Anoxia 43 (19%)	<b>0.010</b>
	Trauma 50 (13%)	Trauma 21 (13%)	Trauma 29 (13%)	0.962
	Other 21 (5%)	Other 9 (5%)	Other 12 (5%)	0.958
	Local 26 (7%)	Local 12 (7%)	Local 14 (6%)	0.681
Allocation type	Regional 193 (49%)	Regional 92 (56%)	Regional 101 (45%)	<b>0.034</b>
	National 171 (44%)	National 61 (37%)	National 110 (49%)	<b>0.019</b>
Recipient age (years)	57 [12]	57 [13]	56 [12]	0.754
Recipient BMI	27 [6]	27 [6]	27 [7]	0.711
Recipient sex ratio (F/M)	124 (32%) / 266 (68%)	54 (33%) / 111 (67%)	70 (31%) / 155 (69%)	0.735
Aetiology of liver disease	ALF 50 (13%)	ALF 9 (5%)	ALF 41 (18%)	<b>&lt;0.001</b>
	HCC 109 (28%)	HCC 62 (38%)	HCC 47 (21%)	<b>&lt;0.001</b>
	Alc. cirrhosis 83 (21%)	Alc. cirrhosis 29 (17%)	Alc. cirrhosis 54 (24%)	0.126
	Viral 26 (7%)	Viral 13 (8%)	Viral 13 (6%)	0.411
	PSC/PBC 40 (10%)	PSC/PBC 16 (10%)	PSC/PBC 24 (11%)	0.755
	AIH 8 (2%)	AIH 3 (2%)	AIH 5 (2%)	0.781
	Other 74 (19%)	Other 33 (20%)	Other 341 (18%)	0.658
	labMELD	17 [17]	11 [11]	23 [18]
BAR Score*	8 [10]	5 [5]	10 [10]	<b>&lt;0.001</b>
SOFT Score†	11 [10]	8 [7]	14 [14]	<b>&lt;0.001</b>
Recipient pre-OLT ventilated support‡	31 (8%)	3 (2%)	28 (12%)	<b>&lt;0.001</b>
Recipient pre-OLT ICU stay	86 (22%)	8 (5%)	78 (35%)	<b>&lt;0.001</b>
Recipient inpatient pre-OLT	130 (33%)	18 (11%)	112 (50%)	<b>&lt;0.001</b>
Recipient pre-OLT abdominal surgery	131 (34%)	57 (35%)	74 (33%)	0.700
Recipient pre-OLT encephalopathy	144 (37%)	43 (26%)	101 (45%)	<b>&lt;0.001</b>
Recipient pre-OLT ascites	224 (57%)	62 (38%)	162 (72%)	<b>&lt;0.001</b>
Pre-OLT renal failure	115 (30%)	26 (16%)	89 (40%)	<b>&lt;0.001</b>
Pre-OLT RRT	62 (16%)	13 (8%)	49 (22%)	<b>&lt;0.001</b>
Pre-OLT CRP (mg/dL)	1.1 [2.4]	0.3 [0.43]	2.4 [2.8]	<b>&lt;0.001</b>
Pre-OLT Alb (g/dL)	3.3 [1.2]	3.8 [1.0]	3.0 [1.0]	<b>&lt;0.001</b>
Pre-OLT CAR (%)	33 [84]	7 [12]	78 [111]	<b>&lt;0.001</b>

Values given as mean ± standard deviation (SD), median [interquartile range – IQR] or absolute and relative frequencies.

Bold values represent significant values.

AIH, autoimmune hepatitis; Alb, Albumin; Alc., alcoholic; ALF, acute liver failure; BAR, balance of risk; BMI, body mass index; CAR, C-reactive-protein-to-albumin ratio; CRP, C-reactive protein; CVA, cerebrovascular accident; HCC, hepatocellular carcinoma; ICU, intensive care unit; labMELD, laboratory model for end-stage liver disease; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RRT, renal replacement therapy; SOFT, survival outcomes following liver transplantation.

\*Refers to Schlegel et al.

†Refers to Rana et al.

‡Ventilated support was defined as mechanical ventilation or dialysis with cardiovascular support.

## Results

### Patient characteristics

A total of 434 consecutive OLT were carried out within the study period. After excluding living-donor ( $n = 8$ ),

split and domino ( $n = 4$ ) transplantations and re-transplantations within our institution ( $n = 32$ ), 390 patients remained in the final study cohort, of which 124 (32%) were female. The median donor and recipient ages were 58 [19] and 57 [12] years, respectively. The median pre-transplantation laboratory MELD score

(labMELD) was 17 [17] and 31 (8%) patients required ventilated support preoperatively. The most common transplantation indication was hepatocellular carcinoma (HCC, 28%), followed by alcoholic liver cirrhosis (21%) and acute liver failure (ALF, 12%). Cerebrovascular accident (CVA) was the leading cause of donor death (58%), followed by anoxia (24%) and trauma (13%). Detailed donor and recipient characteristics are outlined in Table 1.

Major complications ( $CD \geq 3b$ ) were recorded in 212 (54.4%) patients, of which 28 (7% of main cohort) died within 90 days of transplantation. The median CCI score was 52 [48], whereas early allograft dysfunction (EAD) and graft loss within 90 days were seen in 113 (29%) and 40 (10%) patients, respectively. Regarding post-operative length of stay, the median duration was 5 [6] days on ICU and 24 [21] days in total. A comprehensive breakdown of intra- and perioperative outcomes can be found in Table 2.

### ROC and group analysis

An ROC analysis was carried out to determine the predictive power of CAR with respect to various endpoints (Supplement I, Figure S1, Table S1). In the case of morbidity, the two upper quartiles of the CCI scale ( $CCI \geq 50$  and  $CCI \geq 75$ ) were used to define severe cumulative morbidity. These aligned closely to the 50<sup>th</sup> and 75<sup>th</sup> percentiles of the CCI distribution in our cohort. The results showed a good predictive ability (area under the curve -  $AUC > 0.65$ ) for preoperative CAR with respect to multiple endpoints. Only three of these were found to have a good model fit in the Hosmer–Lemeshow analysis, namely severe cumulative morbidity ( $CCI \geq 75$ ), life-threatening complications ( $CD \geq 4a$ ) and 12-month mortality (Table 3). As a result, further analysis focused on these three endpoints. The Youden Index analysis identified an ideal cut-off value for CAR of 26% ( $J = 0.313$ ), which was used to divide the study population into two groups, with median CAR values of 7 [12] and 78 [111], respectively.

The group with preoperative CAR above 26% ( $n = 225$ ) had a significantly higher proportion of patients with ALF (17% vs 5%,  $P < 0.001$ ), while the opposite was true for HCC patients (21% vs 38%,  $P < 0.001$ ). The median labMELD (23 [18] vs. 11 [11],  $P < 0.001$ ), BAR (10 [10] vs. 5 [5],  $P < 0.001$ ), and SOFT (14 [14] vs. 8 [7],  $P < 0.001$ ) score values were significantly higher in the  $CAR > 26\%$  group, as were the need for pre-operative ventilated support (12% vs 2%,  $P < 0.001$ ) and renal replacement therapy (RRT, 22%

vs 8%,  $P < 0.001$ ) before transplantation. An overview of the two groups can be found in Table 1, while relevant odds ratios are summarized in Table 4.

### Association of preoperative CAR with perioperative outcomes

As detailed in Table 2, patients with  $CAR > 26\%$  required more intra- and post-operative transfusions and suffered higher rates of life-threatening complications ( $CD \geq 4a$ , 48% vs 22%,  $P < 0.001$ ), which was reflected in the median CCI (60 [60] vs 43 [35],  $P < 0.001$ ). The incidence of graft loss was also significantly higher in this group (15% vs 4%,  $P < 0.001$ ). Although the median MEAF score was higher in the  $CAR > 26\%$  group (4.21 [2.74] vs 3.76 [2.91],  $P = 0.014$ ), EAD rates were the same across all groups (29%). Furthermore, median ICU (5 [8] vs. 4 [4] days,  $P < 0.001$ ) and hospital stay (28 [27] vs. 21 [12] days,  $P < 0.001$ ) were significantly longer and perioperative mortality rates were significantly worse in the  $CAR > 26\%$  group (11% vs 2%,  $P < 0.001$ ). The inferior perioperative outcomes were reflected in 23% higher estimated procedural costs in the  $CAR > 26\%$  group (57600 [50700] vs. 46700 [23300] EUR,  $P < 0.001$ ).

This association between worse outcomes and higher CAR values was confirmed in the Spearman correlation analysis, which demonstrated weak but significant correlations for CCI ( $r = 0.278$ ,  $P < 0.001$ ), post-OLT ICU stay ( $r = 0.235$ ,  $P < 0.001$ ) and total hospital stay ( $r = 0.256$ ,  $P < 0.001$ ).

When further dividing the study population into groups, according to the quartiles of the preoperative CAR distribution, significant differences in CCI score ( $P < 0.001$ ), post-operative red blood cell transfusions ( $P < 0.001$ ), total hospital stay ( $P < 0.001$ ), and estimated cost ( $P < 0.001$ ) were seen between the fourth and all lower quartiles (Figure 2 and Supplement I, Table S2).

As seen in Table 5, the uni- and multivariable logistic regression analyses identified  $CAR > 26\%$  (OR 2.289, 95%CI 1.025–5.110,  $P = 0.043$ ), inpatient hospitalization including ICU pre-OLT (OR 2.744, 95%CI 1.172–6.423,  $P = 0.020$ ) and the number of post-operative red blood cell (OR 1.161, 95%CI 1.057–1.274,  $P = 0.002$ ) transfusions as independent predictors for the development of severe cumulative morbidity ( $CCI \geq 75$ ). For complications  $CD \geq 4a$  and 12-month mortality,  $CAR > 26\%$  was found to be a significant predictor only in the univariable analyses, details of which can be found in Supplement I (Table S3 and Table S4). Nevertheless, 12-month mortality rates for patients with

**Table 2.** Perioperative outcomes for patients with a preoperative CAR below and above the cut-off value of 26%.

Variables	All patients (n = 390)	CAR≤26% (n = 165)	CAR>26% (n = 225)	P-value
Cold ischaemia time (minutes)	494 [152]	481 [141]	508 [167]	0.077
Warm ischaemia time (minutes)	45 [10]	46 [12]	45 [10]	0.197
Intraoperative RBC units	8 [8]	6 [7]	9 [9]	<b>&lt;0.001</b>
Intraoperative FFP units	16 [10]	16 [10]	16 [10]	0.126
Post-operative RBC units*	2 [5]	1 [4]	2 [6]	<b>&lt;0.001</b>
Post-operative FFP units*	2 [7]	0 [4]	2 [9]	<b>0.021</b>
90-day morbidity / mortality <sup>†</sup>	CD0 28 (7%)	CD0 17 (10%)	CD0 11 (5%)	<b>0.041</b>
	CD1 13 (3%)	CD1 6 (4%)	CD1 7 (3%)	0.775
	CD2 70 (18%)	CD2 38 (23%)	CD2 32 (14%)	<b>0.025</b>
	CD3 134 (35%)	CD3 68 (41%)	CD3 66 (30%)	<b>0.015</b>
	CD4 116 (30%)	CD4 33 (20%)	CD4 83 (37%)	<b>&lt;0.001</b>
	CD5 28 (7%)	CD5 3 (2%)	CD5 25 (11%)	<b>&lt;0.001</b>
90-day CCI <sup>‡</sup>	52 [48]	43 [35]	60 [60]	<b>&lt;0.001</b>
90-day CCI≥75	107 (27%)	21 (13%)	86 (38%)	<b>&lt;0.001</b>
90-day CD≥4a	144 (37%)	36 (22%)	108 (48%)	<b>&lt;0.001</b>
90-day graft loss	40(10%)	7 (4%)	33 (15%)	<b>0.001</b>
12-month mortality	53 (14%)	9 (6%)	44 (20%)	<b>&lt;0.001</b>
EAD <sup>§</sup>	113 (29%)	48 (29%)	65 (29%)	0.998
MEAF <sup>¶</sup>	3.95 [2.88]	3.76 [2.91]	4.21 [2.74]	<b>0.014</b>
Post-OLT ICU stay (days)**	5 [6]	4 [4]	5 [8]	<b>&lt;0.001</b>
Post-OLT Hospital stay (days) <sup>††</sup>	24 [21]	21 [12]	28 [27]	<b>&lt;0.001</b>
Estimated Cost (€) <sup>‡‡</sup>	52600 [38000]	46700 [23300]	57600 [50700]	<b>&lt;0.001</b>

Values given as mean±SD, median [IQR] or absolute and relative frequencies.

Bold values represent significant values.

Alb, Albumin; CAR, C-reactive-protein-to-albumin ratio; CCI, comprehensive complication index; CD, Clavien–Dindo score; CRP, C-reactive protein; EAD, early allograft dysfunction; FFP, fresh frozen plasma; MEAF, model for early allograft function; RBC, red blood cell.

\*Refers to blood products given during the first 7 days following OLT.

<sup>†</sup>Refers to Dindo et al.

<sup>‡</sup>Refers to Slankamenac et al.

<sup>§</sup>Refers to Olthoff et al.

<sup>¶</sup>Refers to Pareja et al.

\*\*Refers to the days spent in ICU from OLT until first transfer to a standard care unit.

<sup>††</sup>Refers to the days spent in hospital from OLT till discharge to outpatient care or rehabilitation.

<sup>‡‡</sup>Refers to Staiger et al. and <https://www.assessurgery.com/cost-prediction/>

CAR>26% were significantly higher in the group analysis, (20% vs 6%,  $P < 0.001$ ), as seen in Table 2.

### Subgroup analysis with the exclusion of recipients with ALF

To further explore the predictive capabilities of CAR, we partially repeated the analysis after excluding patients with ALF, as they represent a generally critically ill subpopulation, with a different pathophysiology compared to cirrhosis and chronic liver disease. This was reflected in the higher median labMELD, BAR and SOFT scores and the higher proportion of patients requiring pre-OLT ICU and

ventilated life support in the ALF group, as seen in Table S5. The median pre-OLT CAR was also significantly higher in patients with ALF (66 [98] vs. 29 [80],  $P = 0.001$ ). Patients with ALF displayed higher 12-month mortality rates (24% vs 12%,  $P = 0.021$ ) and a higher median MEAF score (4.89 [1.86] vs 3.79 [2.87],  $P < 0.001$ ).

In the population without ALF, ROC and Youden Index analysis determined CAR = 26% to still be the best cut-off for predicting severe cumulative morbidity (CCI≥75), life-threatening complications (CD≥4a) and 12-month mortality (data not shown). As in the main analysis, the median labMELD (20 [15] vs. 10 [9],  $P < 0.001$ ), BAR (9 [8] vs. 5 [5],  $P < 0.001$ ), and SOFT (13 [12] vs. 8

**Table 3.** Summary of ROC analyses and goodness-of-fit testing for preoperative CAR as a predictor for morbidity, mortality, EAD and graft loss.

Binary Endpoint	AUC	SE	95% CI	P-value*	HL	P-value†
CD≥3b	0.64	0.03	0.583–0.692	<0.001	7.81	0.452
CD≥4a	<b>0.66</b>	0.03	0.604–0.716	<0.001	15.32	0.053
CCI≥50	0.65	0.03	0.592–0.700	<0.001	7.945	0.439
CCI≥75	<b>0.70</b>	0.03	0.636–0.756	<0.001	10.22	0.250
90-day mortality	<b>0.68</b>	0.06	0.571–0.788	<0.001	<b>25.70</b>	<b>0.001</b>
12-month mortality	<b>0.66</b>	0.04	0.576–0.740	<0.001	13.18	0.106
EAD	0.50	0.03	0.433–0.561	0.918	n.a.	n.a.
90-day graft loss	0.60	0.05	0.505–0.697	<b>0.036</b>	<b>24.44</b>	<b>0.002</b>
12-month graft loss	0.62	0.04	0.542–0.697	<b>0.002</b>	<b>15.67</b>	<b>0.047</b>

Bold values represent significant values.

Alb, Albumin; AUC, area under the curve; CAR, C-reactive-protein-to-albumin ratio; CCI, comprehensive complication index; CD, Clavien–Dindo score; CI, confidence interval; CRP, C-reactive protein; EAD, early allograft dysfunction; HL, Hosmer–Lemeshow  $\chi^2$  test; ROC, receiver operating characteristic; SE, standard error.

\* $P < 0.05$  rejects the null hypothesis of AUC = 0.5.

† $P < 0.05$  rejects the null hypothesis of an adequate fit.

**Table 4.** Odds ratios for post-operative outcomes according to the cut-off CAR>26%.

Endpoint	CAR≤26% (n = 165)	CAR>26% (n = 225)	OR (95% CI)	P-value
CD≥4a	33 (20%)	84 (42%)	2.831 (1.761–4.549)	<0.001
CCI≥75	18 (11%)	61 (31%)	3.511 (1.975–6.240)	<0.001
12-month mortality	9 (6%)	44 (20%)	4.214 (1.994–8.905)	<0.001

Results given as odds ratios (OR) with 95% confidence intervals (95% CI) and absolute and relative frequencies.

Bold values represent significant values.

Alb, Albumin; CAR, C-reactive-protein-to-albumin ratio; CCI, comprehensive complication index; CD, Clavien–Dindo score; CI, confidence interval; CRP, C-reactive protein.

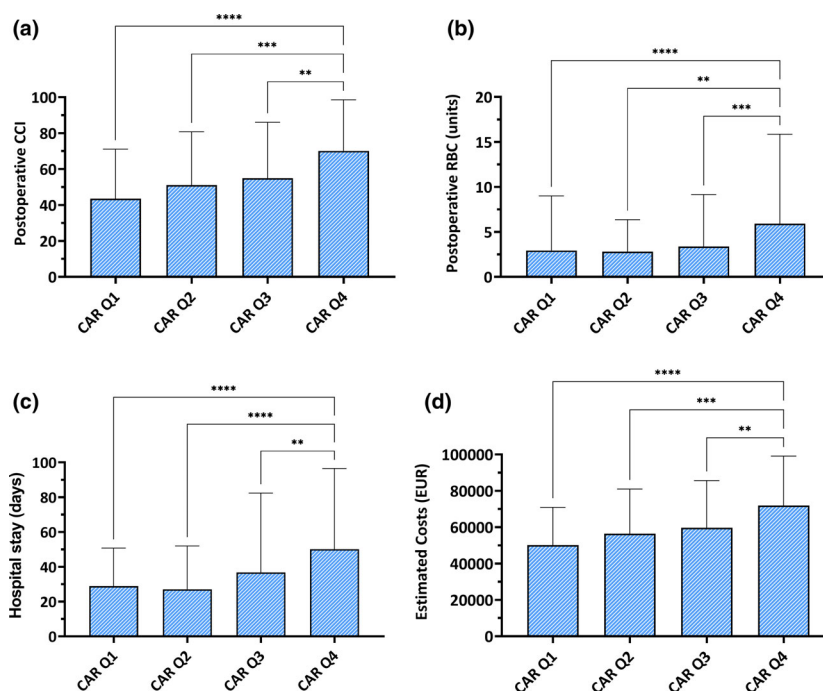
[6],  $P < 0.001$ ) score values remained significantly higher in the CAR>26% group, as was the need for pre-operative ventilated support (10% vs 1%,  $P < 0.001$ ).

Moreover, patients with CAR>26% required more intra- and post-operative transfusions and suffered higher rates of CD≥4a complications and 90-day graft loss (37% vs. 21%,  $P = 0.001$  and 14% vs. 4%,  $P < 0.001$ , respectively). Median CCI was still higher in the CAR>26% group (60 [59] vs. 44 [35],  $P < 0.001$ ), as were perioperative and 12-month mortality rates (10% vs. 1%,  $P = 0.001$  and 18% vs. 5%,  $P < 0.001$ , respectively). Other relevant outcomes also remained significantly worse in the CAR>26% group after exclusion of patients with ALF, as detailed in Table S8. Again, CAR>26% was found to be an independent predictor (OR 2.125, 95%CI 1.052–4.293,  $P = 0.036$ ) for the development of severe cumulative morbidity (CCI≥75) in the uni- and multivariable logistic regression analyses, but only in the univariable analysis for the other two endpoints (Tables S9–S11).

## Discussion

Since Fairclough et al. [43] first proposed CAR as a prognostic marker to identify acutely sick patients, multiple studies have demonstrated its predictive value regarding morbidity and mortality in critically ill patients [19,20,22,29], in cirrhotic patients awaiting liver transplantation [23,24], as well as in patients undergoing colorectal [21,30], pancreatic [25], gastro-oesophageal [44,45] and liver [26,46] surgery. In oncological patients, an association has been shown between high CAR and lower overall- [44,47,48] and disease-free survival rates [26,29], as well as advanced tumour stage [25,26,47,48]. In all of these scenarios, alterations in serum levels of CRP and Alb are attributed to inflammation and malnutrition [47,48], in some cases combined with liver dysfunction [20,28] and/or post-operative stress [21,22,25].

In liver transplantation, serum CRP levels [32,33,49] and the albumin-to-bilirubin ratio (ALBI) [50] have



**Figure 2** Quartile-based analysis of (a) CCI, (b) post-operative red blood cell transfusions, (c) length of hospital stay, (d) predicted hospitalization costs according to CAR. Abbreviations used: CAR, C-reactive-protein-to-albumin ratio; Q1-4, quartiles 1-4; CCI, comprehensive complication index; RBC, red blood cell; \* $P < 0.05$ ; \*\* $P \leq 0.01$ ; \*\*\* $P \leq 0.001$ .

been associated with overall and recurrence-free survival for patients with HCC. However, despite the multitude of studies on CAR in other areas, we could not identify any previous report focusing on CAR in DDLT. Park et al. studied living-donor liver transplantation (LDLT) recipients, showing higher rates of EAD, poor kidney function, infection, graft loss and mortality in patients with an increased CAR [22]. Contrary to that study, no association between CAR and EAD was shown in our cohort using the same traditional binary definition of EAD as described by Olthoff et al. [10]. Nevertheless, a significantly higher MEAF score has been recorded in the high CAR group. MEAF was previously shown to be a superior predictor of clinically relevant EAD compared to the Olthoff criteria [51].

With regard to morbidity and mortality, however, our study did show a significant correlation with CAR, in agreement with the aforementioned study of Park et al. [22]. Specifically, the ROC analysis showed a moderate predictive ability for CAR regarding our endpoint of severe complications ( $CD \geq 3b$ ,  $AUC = 0.64$ ) and a slightly better predictive ability ( $AUC = 0.66$ ) for life-threatening complications ( $CD \geq 4a$ ). Although  $CAR > 26\%$  was not an independent predictor of  $CD \geq 4a$  complications in the multivariable analysis, significantly more patients in the  $CAR > 26\%$  group suffered from

$CD \geq 4a$  complications. A stronger predictive effect was seen in the case of CCI, where the  $AUC$  for  $CCI \geq 75$  was higher than all other endpoints and  $CAR > 26\%$  was an independent predictor of  $CCI \geq 75$  in the multivariable logistic regression analysis. In addition, the CAR-quartile analysis showed significantly higher CCI scores for the upper two quartiles of CAR. Our results suggest that a higher preoperative CAR may not directly predict the severity of complications (in terms of CD), but can identify patients at risk of multiple complications, who in turn suffer from a higher cumulative complication burden (which is better reflected by the CCI) and spend more time on the ICU and in hospital. This was reflected in the significantly increased length of ICU and hospital stay seen in patients with increased CAR, as well as the increased estimated patient costs (23% higher in the  $CAR > 26\%$  group). In terms of mortality, the predictive ability of CAR was poor for the first 90 days post-OLT, even though significantly more patients died within that time period in the  $CAR > 26\%$  group. However, a good predictive ability regarding 12-month mortality was demonstrated ( $AUC 0.66$ ), although  $CAR > 26\%$  was shown to be a significant predictor only in the univariable logistical regression analysis. Similar to morbidity, it seems a raised CAR can indicate which patients are at higher risk of mortality



**Table 5.** Association of perioperative factors with severe cumulative post-operative morbidity (CCI $\geq$ 75).

Perioperative factor	Univariable logistic regression analysis		Multivariable logistic regression analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
CAR>26%	3.511 (1.975–6.240)	<0.001	<b>2.289 (1.025–5.110)</b>	<b>0.043</b>
Donor age (years)	0.995 (0.979–1.011)	0.526		
Donor BMI	0.981 (0.945–1.018)	0.315		
Donor sex (male)	1.074 (0.651–1.772)	0.779		
Cause of donor death	0.974 (0.735–1.291)	0.855		
Allocation type	0.325 (1.237–0.810)	1.891		
Recipient age	1.012 (0.988–1.036)	0.320		
Recipient BMI	1.034 (0.984–1.087)	0.183		
Recipient sex (male)	1.017 (0.592–1.749)	0.951		
Aetiology of liver disease	1.025 (0.924–1.137)	0.642		
labMELD	1.073 (1.046–1.100)	<0.001	1.009 (0.964–1.056)	0.708
BAR Score*	1.157 (1.101–1.216)	<0.001		
SOFT Score <sup>†</sup>	1.098 (1.065–1.132)	<0.001		
Recipient pre-OLT ventilated support (yes) <sup>‡</sup>	8.492 (3.295–21.886)	<0.001		
Recipient pre-OLT ICU (yes)	6.567 (3.693–11.678)	<0.001		
Recipient pre-OLT abdominal surgery (yes)	0.841 (0.487–1.451)	0.534		
Recipient inpatient pre-OLT (yes)	4.053 (2.405–6.829)	<0.001	<b>2.744 (1.172–6.423)</b>	<b>0.020</b>
Recipient pre-OLT encephalopathy (yes)	2.185 (1.314–3.635)	<b>0.003</b>	1.138 (0.568–2.279)	0.715
Recipient pre-OLT ascites (yes)	2.061 (1.209–3.513)	<b>0.008</b>	0.574 (0.264–1.246)	0.160
Pre-OLT renal failure (yes)	4.310 (2.545–7.299)	<0.001	1.450 (0.594–3.543)	0.414
Pre-OLT RRT (yes)	4.778 (2.552–8.945)	<0.001	1.990 (0.690–5.734)	0.203
Cold ischaemia time (minutes)	1.002 (1.000–1.004)	0.093		
Warm ischaemia time (minutes)	0.992 (0.961–1.024)	0.617		
Intraoperative RBC units	1.087 (1.048–1.127)	<0.001	1.004 (0.949–1.062)	0.888
Intraoperative FFP units	1.025 (1.000–1.050)	0.051		
Post-operative RBC units <sup>§</sup>	1.259 (1.175–1.348)	<0.001	<b>1.161 (1.057–1.274)</b>	<b>0.002</b>
Post-operative FFP units <sup>§</sup>	1.135 (1.087–1.184)	<0.001	1.042 (0.990–1.097)	0.119

Results given as odds ratios (OR) with 95% confidence intervals (95% CI). Factors showing significant results in the univariable analysis were included in the multivariable logistic regression model. To avoid a multicollinearity effect, certain variables found to be significantly different in the subgroup analysis were not included in the multivariable logistic regression analysis (e.g. BAR and SOFT scores).

Bold values represent significant values.

Alb, Albumin; BAR, balance of risk; BMI, body mass index; CAR, C-reactive-protein-to-albumin ratio; CCI, comprehensive complication index; CRP, C-reactive protein; FFP, fresh frozen plasma; ICU, intensive care unit; labMELD, laboratory model of end-stage liver disease score; OLT, orthotopic liver transplantation; RBC, red blood cell; RRT, renal replacement therapy; SOFT, survival outcomes following liver transplantation.

\*Refers to Schlegel et al.

<sup>†</sup>Refers to Rana et al.

<sup>‡</sup>Ventilated support was defined as mechanical ventilation or dialysis with cardiovascular support.

<sup>§</sup>Refers to blood products given during the first 7 days following OLT.

following DDLT, but lacks precision in distinguishing those in danger of early post-operative death.

Our data suggest specific strengths and limitations of CAR in predicting post-transplant outcomes. However, the exact mechanistic explanation for this clinical observation is not clear. As mentioned above, a plethora of studies have demonstrated the changes in CRP and Alb levels after major surgery, such as liver transplantation

[21,22,25]. We avoided this post-operative effect by calculating CAR preoperatively. Nevertheless, a large part of our study population was critically ill (22% on ICU and 8% on ventilated support pre-OLT), more than half had ascites and almost a third suffered from renal failure, all conditions associated with increased CAR. Clearly, CAR is not directly causative of perioperative morbidity and mortality, although hypoalbuminemia

has proved to be an independent factor for post-operative morbidity [52]. Rather, it serves as an indicator of sicker patients, which can be seen in the large difference between CAR levels in our study and that of Park et al., as well as the broad range of CAR values within our cohort. All in all, however, our results show that CAR can be a useful predictor of perioperative morbidity and mortality.

Interestingly, the predictive effect of CAR remained strong when removing patients with ALF and the pattern of predictive strength remained the same as for the main population: namely, the predictive capability was stronger for severe cumulative morbidity ( $CCI \geq 75$ ) than for life-threatening complications or 12-month mortality. Further studies in larger, homogeneous cohorts are needed in order to elucidate the association between CAR and underlying liver disease leading to transplantation.

Certain limitations to this study must be acknowledged, starting from its retrospective, single-centre nature, which warrants validation in prospective, multi-centre studies. A larger sample-size would have strengthened our results and conclusions, particularly in the case of life-threatening complications, which are relatively rare. Furthermore, CAR was measured at just one timepoint, giving us only a snapshot of each patient's condition and ignoring longitudinal improvements or deteriorations. In relation to that, CAR is only suitable for depicting the pathophysiological status of the recipient pre-transplant and does not reflect the quality of the graft or surgical-technical aspects of the liver transplantation procedure [3,53]. It may be interesting to investigate the dynamic changes in CAR post-operatively in future studies and elucidate the predictive abilities of CAR kinetics in respect to post-operative outcomes.

Moreover, an intrinsic limitation of CAR is its lack of specificity, as CRP and Alb levels are affected by a multitude of factors, as previously mentioned. Both CRP and Alb are synthesized in the liver [26,28,46,48], which explains their inclusion in clinical scores such as SOFT [7] and Child-Pugh [54], which are used to stratify risk of adverse outcomes in patients with liver disease. Although the exact relationship between serum levels of CRP / Alb and liver dysfunction is a matter of dispute [20,28], it stands to reason, that patients with liver dysfunction may exhibit more distorted preoperative CAR, making comparisons with other patient cohorts undergoing surgery difficult.

Finally, a known problem with CAR is the large variation in cut-off values that have been reported in the literature, making it difficult to standardize it as a

predictive test. This stems from differences in study populations, treatment regimens, timing of CAR measurement, laboratory measurement units and methods used to calculate the CAR. Furthermore, where some studies carry out an ROC analysis to determine the optimal cut-off, others use arbitrary cut-offs or different statistical methods to define cohort-specific cut-off values. Nevertheless, multiple studies (including this one - see Supplement I) have shown that CAR is more accurate in predicting morbidity and mortality in multiple scenarios, compared to CRP or Alb alone [20,21,25,26,28,44–46] or other inflammation scores [28,29,47]. Although this may justify the utilization of CAR, validation and standardization would go a long way to increase its usefulness and clinical applicability.

In any case, despite the multitude of scoring systems designed to predict outcomes in OLT recipients, the value of CAR lies in its simplicity. The exact mechanism of its predictive ability, as well as potential associations with long-term survival and graft loss, should be addressed in future studies. Although CAR may never replace the subjective assessment of “fitness for transplant” by an experienced transplant physician, it could serve as a useful additional clinical tool, with some caveats.

## Conclusion

The preoperative CAR is a reliable predictor of perioperative severe morbidity and mortality in DDLT recipients.

## Authorship

The study was designed by the initiating study team (IA, DE, SL, UN, ZC). Data collection and analysis were carried out by IA, JB, FM, DE, AM, WL, DJ, JoB ZC. The manuscript was drafted by IA, DE, ZC. All additional authors (PS, FU, JoB, PB) contributed substantially to the final version of the manuscript. All authors have read and approved the final version of the manuscript.

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data collection, data analysis, manuscript preparation or the decision to publish.

### Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

### Ethical approval

The study was conducted under the ethical approval of the Institutional Review Board of the RWTH Aachen University (EK-047/18) and in accordance with the current version of the Declaration of Helsinki, the Declaration of Istanbul, and good clinical practice guidelines (ICHGCP). Informed consent was waived due to the retrospective study design and collection of readily available clinical data.

### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** ROC analysis of CAR as a predictor of perioperative complications CCI $\geq$ 75, perioperative complications CD $\geq$ 4a, and 12-month mortality.

**Table S1.** Summarised results of the ROC analysis for CAR vs. CRP or Alb alone.

**Table S2.** Kruskal-Wallis quartile analysis for CAR.

**Table S3.** Association of perioperative factors with postoperative morbidity (CD $\geq$ 4a).

**Table S4.** Association of perioperative factors with 12-month mortality.

**Table S5.** Donor and recipient characteristics for patients with and without acute liver failure.

**Table S6.** Perioperative outcomes for patients with and without acute liver failure.

**Table S7.** Donor and recipient characteristics for patients excluding acute liver failure, with a preoperative CAR below and above the cut-off value of 26%.

**Table S8.** Perioperative outcomes for patients excluding acute liver failure, with a preoperative CAR below and above the cut-off value of 26%.

**Table S9.** Association of perioperative factors with postoperative morbidity (CCI $\geq$ 75) in patients excluding acute liver failure.

**Table S10.** Association of perioperative factors with postoperative morbidity (CD $\geq$ 4a in patients excluding acute liver failure.

**Table S11.** Association of perioperative factors with 12-month mortality in patients excluding acute liver failure.

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