



C-reactive protein-to-albumin ratio is a predictor of 1-year mortality following liver transplantation

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Background: Considering the importance of the inflammatory status of recipients on outcomes following liver transplantation (LT), we investigated the association between C-reactive protein-to-albumin ratio (CAR) and one-year mortality following LT and compared it with other parameters reflecting patients' underlying inflammatory status.

Methods: A total of 3,614 consecutive adult LT recipients were retrospectively evaluated. Prognostic parameters were analyzed using area under the receiver operating characteristic curve (AUROC) analysis, and subsequent cutoffs were derived. For survival analysis, Cox proportional hazards and Kaplan-Meier analyses were performed.

Results: The AUROC for CAR to predict one-year mortality after LT was 0.68 (0.65–0.72), which was the highest compared with other inflammatory parameters, with the best cutoff of 0.34. A CAR \geq 0.34 was associated with a significantly higher one-year mortality rate (13.3% vs. 5.8 %, log-rank $P < 0.001$) and overall mortality rate (24.5% vs. 12.9%, log-rank $P = 0.039$). A CAR \geq 0.34 was an independent predictor of one-year mortality (hazard ratio, 1.40 [1.03–1.90], $P = 0.031$) and overall mortality (hazard ratio 1.39 [1.13–1.71], $P = 0.002$) after multivariable adjustment.

Conclusions: Preoperative CAR (≥ 0.34) was independently associated with a higher risk of one-year and overall mortality after LT. This may suggest that CAR, a simple and readily available biomarker, maybe a practical index that may assist in the risk stratification of liver transplantation outcomes.

Keywords: C-reactive protein-to-albumin ratio; Inflammatory status; Liver transplantation; Mortality.

INTRODUCTION

In patients with end-stage liver disease, concomitant immune dysregulation is common and is a pathogenetic factor, even in the absence of overt infection [1,2]. Therefore, liver transplantation (LT) recipients' preoperative immune status may have an important role in determining post-LT survival [3–6]. The need for prognosticators of outcomes after LT are

of great clinical and scientific interest, as they may allow for closer observation and earlier intervention in those at risk.

The C-reactive protein (CRP)-to-albumin ratio (CAR) is a proxy of inflammation degree or nutritional deficiency and is considered as reliable predictor of morbidity and mortality among critically ill patients [7,8]. Elevated CRP, alone, is used as a prognostic marker in the critical care setting [9], as well as for patients in the postoperative state, for it reflects

patients' conditions in association with malignancy [10], sepsis, and inflammatory diseases [9]. Reduced albumin levels are common in critically ill patients and can reflect decompensated liver cirrhosis, renal insufficiency, or malnutrition [10,11]. The prognostic value of the CAR is reported to be higher and more consistent compared with CRP or albumin alone [12,13]. Previous studies have demonstrated the prognostic value of the CAR in the LT population: it may estimate the risk of early allograft failure after LT [14]. However, to our knowledge, the association between preoperative CAR and survival following LT has been studied only among living-donor LT or the sample sizes were rather small [15,16].

This study assessed the prognostic value of preoperative CAR on outcomes following LT in large numbers of cohort ($n = 3,614$). Specifically, we investigated whether the CAR could predict one-year mortality after LT and compared it with other inflammation-based indices, such as lymphocyte-to-monocyte ratio (LMR), modified Glasgow prognostic score (mGPS), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI). We further evaluated the association between the CAR and overall mortality following LT.

MATERIALS AND METHODS

Patients

The data of 4,655 recipients who underwent LT from January 2010 through December 2020 at Asan Medical center were collected using a computerized patient data recording system (Asan Biomedical Research Program [ABLE], Seoul, Korea). The inclusion criteria were the LT recipients at Asan Medical center during the observation time and the exclusion criteria were age < 18 years ($n = 215$); retransplantation ($n = 197$); and patients with chronic kidney disease ($n = 99$), toxic hepatitis ($n = 114$), and incomplete laboratory data ($n = 385$). Finally, 3,614 LT recipients were enrolled.

CRP, albumin, whole blood counts with differential counts, and platelet counts were routinely evaluated for all patients as part of preoperative laboratory evaluation. The CRP levels were divided by albumin levels, respectively, to calculate CARs. Lymphocyte counts were divided by monocyte counts, respectively, to calculate LMRs. The platelet count was divided by the lymphocyte count to calculate the PLR. The mGPS (0, 1, and 2) was defined as follows: 0, if CRP was within the normal range, regardless of albumin; 1, CRP > 1 mg/dl and albumin ≥ 3.5 g/dl; and 2, if both CRP > 1

mg/dl and albumin < 3.5 g/dl [17]. The SII was calculated as the preoperative absolute platelet count \times neutrophil count/lymphocyte count. The PNIs were calculated, respectively, as the sums of albumin levels and $0.005 \times$ absolute lymphocyte counts.

This study was approved by the Institutional Review Board of Asan Medical Center (no. 2022-0572), Seoul, Korea, which waived the requirement for written informed consent because of the study's retrospective design. This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975.

Outcome measures

Mortality data were collected from our institution's medical records database and LT registry, which is regularly updated by the Organ Transplantation Center. The primary aim was to investigate whether the CAR was associated with one-year and the secondary aim was overall mortality following LT.

Anesthetic technique and immunosuppressants

General anesthesia was performed according to our institutional protocol, as reported elsewhere [14]. Briefly, induction was conducted using propofol and rocuronium, with maintenance using 1% sevoflurane, a 50% O₂/air mixture, and continuous infusion with remifentanyl and rocuronium. Femoral and radial arterial blood pressure were monitored, and pulmonary artery catheters were inserted; deprived hemodynamic variables were monitored.

Statistical analysis

Continuous variables are described as mean \pm standard deviation or median and interquartile range (IQR) after testing distributional normality. Categorical variables are presented as frequencies (%). The Student *t*-test, the Mann-Whitney *U* test, and the chi-square test or the Fisher exact test were used for comparing between groups, as appropriate.

Area under the receiver operating characteristic curve (AUROC) values were computed to assess the discrimination ability of CAR, LMR, mGPS, SII, PLR, and PNI with one-year mortality. The variable with the highest AUROCs, CAR, was dichotomized using optimal cutoff points according to the maximum Youden index. To investigate the association with one-year and overall mortality, we conducted univari-

ate and multivariable Cox proportional hazards regression analysis using backward elimination with variables yielding $P < 0.1$ in the univariate analysis. The Kaplan–Meier analysis with log-rank testing was performed to compare cumulative one-year and overall mortality rates between high and low CARs.

All reported P values were two-sided and < 0.05 were considered significant. Data manipulation and analyses were performed using R, version 4.1.3 (The R Foundation for Statistical Computing, Austria). “plotROC” [18] and “survival” [19] packages were used.

RESULTS

Patient background

The demographics of the 3,614 patients are presented in [Table 1](#). Overall, there were 244 (6.8%) deaths within 1 year after LT.

Nonsurvivors had a higher mean Model for End-stage Liv-

er Disease-Sodium (MELD-Na) score (26 vs. 14, $P < 0.001$) and a higher prevalence of cardiovascular disease (31.6% vs. 19.2%, $P < 0.001$) compared with survivors. Nonsurvivors had higher inflammatory parameters. Specifically, higher CAR (median [IQR]: 0.33 [0.09, 0.83] vs. 0.10 [0.04, 0.31], $P < 0.001$) and SII (288 [134, 510] vs. 152 [87, 288], $P < 0.001$) and lower LMR (1.41 [0.85, 2.41] vs. 2.22 [1.36, 3.34], $P < 0.001$), indicating higher inflammatory status, were found in non-survivor compared to non-survivors.

Discrimination ability and best cutoff of one-year mortality

The AUROC was slightly higher for the CAR (AUROC = 0.68 [0.65–0.72]) compared with the LMR (AUROC = 0.65 [0.61–0.69]), although statistical significance was not reached (DeLong’s test $P = 0.248$). The CAR showed a statistically significant higher AUROC compared with the mGPS (AUROC = 0.64 [0.60–0.67], DeLong’s test $P < 0.001$), SII (AUROC = 0.64 [0.60–0.68], DeLong’s test $P = 0.080$), PLR

Table 1. Demographic and Perioperative Characteristics of Recipients for Liver Transplantation According to One-year Survival

Variable	Preoperative NLR			P value
	One-year survivor (n = 3,370, 93.2%)	One-year non-survivor (n = 244, 6.8%)	Total (n = 3,614)	
Patients’ demographics				
Age (yr)	54 (49 ± 59)	57 (49 ± 63)	54 (49 ± 59)	< 0.001
Male sex	2,502 (74.2)	180 (73.8)	2,682 (74.2)	0.930
Body mass index (kg/m ²)	24.2 (22.0 ± 26.5)	23.7 (21.4 ± 26.4)	24.2 (22.0 ± 26.5)	0.058
MELD-Na score	14 (9 ± 24)	26 (14 ± 38)	14 (9 ± 25)	< 0.001
Cardiovascular disease	646 (19.2)	77 (31.6)	723 (20.0)	< 0.001
Diabetes	800 (23.7)	74 (30.3)	874 (24.2)	0.025
Hypertension	593 (17.6)	36 (14.8)	629 (17.4)	0.297
Etiology of cirrhosis				
Viral	2,177 (64.6)	131 (53.7)	2,308 (63.9)	0.001
Alcoholic	792 (23.5)	63 (25.8)	855 (23.7)	0.456
Biliary	117 (3.5)	12 (4.9)	129 (3.6)	0.319
Other disease	51 (1.5)	4 (1.6)	55 (1.5)	1.000
Deceased-donor	408 (12.1)	88 (36.1)	496 (13.7)	< 0.001
Inflammatory parameters				
C-reactive protein-albumin ratio	0.10 (0.04, 0.31)	0.33 (0.09, 0.83)	0.10 (0.04, 0.34)	< 0.001
LMR	2.22 (1.36, 3.34)	1.41 (0.85, 2.41)	2.17 (1.32, 3.29)	< 0.001
mGPS (0/1/2)	2,572 (76.3)/180 (5.3)/618 (18.3)	120 (49.2)/30 (12.3)/94 (38.5)	2,692 (74.5)/210 (5.8)/712 (19.7)	< 0.001
SII	152 (87, 288)	288 (134, 510)	158 (89, 301)	< 0.001
PLR	79 (56, 116)	82 (54, 129)	79 (56, 116)	0.440
PNI	36 (31, 40)	36 (31, 39)	36 (31, 40)	0.141

Values are expressed as the mean ± SD, number (%), or median (1Q, 3Q) for continuous variables. NLR: neutrophil to lymphocyte ratio, MELD-Na score: Sodium-adjusted Model for End-Stage Liver Disease score, LMR: lymphocyte-to-monocyte ratio, mGPS: modified Glasgow prognostic score, SII: systemic immune-inflammation index, PLR: platelet-to lymphocyte ratio, PNI: prognostic nutrition index.

(AUROC = 0.52 [0.47–0.56], DeLong’s test $P < 0.001$), and PNI (AUROC = 0.53 [0.49–0.57], DeLong’s test $P < 0.001$) (Fig. 1). The optimal CAR cutoff value for detecting one-year mortality was 0.34, with a sensitivity of 50% and a specificity of 76.8%. CAR was dichotomized at a cutoff 0.34 for further analysis.

One-year and overall mortality after LT

Overall, 244 patients (6.8%) died within 1 year of LT, and 572 (15.8%) died by the end of follow-up (Table 2). Significantly higher one-year mortality (120 of 901 [13.3%] vs. 124 of 2,713 [4.6%], log-rank $P < 0.001$, Fig. 2) and overall mortality rates (221 of 901 [24.5%] vs. 351 of 2,713 [12.9%], log-rank $P = 0.039$) were observed among patients with high CARs (≥ 0.34) relative to those with lower CARs (< 0.34).

To evaluate the risk factors associated with one-year mortality, univariate and multivariate Cox-proportional hazards analysis revealed that high CAR (≥ 0.34) was significantly associated with a higher risk of one-year mortality, before (hazard ratio, HR [95% confidence interval, 95% CI] = 3.09 [2.40–3.97], $P < 0.001$) and after multivariate adjustment (HR [95% CI] = 1.40 [1.03–1.90], $P = 0.031$). Other clinical variables associated with one-year mortality were age, MELD-Na score, diabetes, cardiovascular disease, and de-

ceased-donor LT (Fig. 3).

High CARs (≥ 0.34) were independently associated with higher overall mortality, before (HR [95% CI] = 2.08 [1.76–

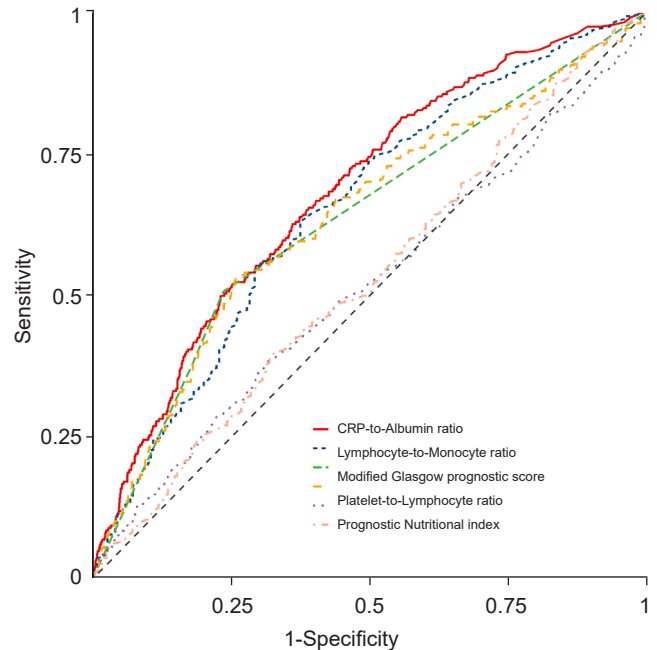


Fig. 1. Receiver operating characteristic curve between inflammation-based variables for predicting one-year mortality after liver transplantation. CRP: C-reactive protein.

Table 2. Demographic and Perioperative Characteristics of Recipients for Liver Transplantation According to C-reactive Protein-to-albumin Ratio (CAR < 0.34 , ≥ 0.34)

Variable	Preoperative C-reactive protein-to-albumin ratio		P value
	CAR < 0.34 (n = 2,713, 75.1%)	CAR ≥ 0.34 (n = 901, 24.9%)	
Patients’ demographics			
Age (yr)	54 (49 ± 59)	54 (47 ± 60)	0.241
Male sex	2,005 (73.9)	677 (75.1)	0.490
Body mass index (kg/m ²)	24.3 (22.3 ± 26.6)	23.8 (21.3 ± 26.4)	< 0.001
MELD-Na score	12 (9 ± 18)	28 (20 ± 37)	< 0.001
Cardiovascular disease	480 (17.7)	243 (27.0)	< 0.001
Diabetes	630 (23.2)	244 (27.1)	0.021
Hypertension	497 (18.3)	132 (14.7)	0.014
Etiology of cirrhosis			
Viral	1,878 (69.2)	430 (47.7)	< 0.001
Alcoholic	553 (20.4)	302 (33.5)	< 0.001
Biliary	66 (2.4)	63 (7.0)	< 0.001
Other disease	35 (1.3)	20 (2.2)	0.069
Deceased-donor	186 (6.9)	310 (34.4)	< 0.001
Outcome			
One-year mortality	124 (4.6)	120 (13.3)	< 0.001
Overall mortality	351 (12.9)	221 (24.5)	< 0.001

Values are expressed as the mean ± SD or number (%). CAR: C-reactive protein-to-albumin ratio, MELD-Na score: Sodium-adjusted Model for End-Stage Liver Disease score.

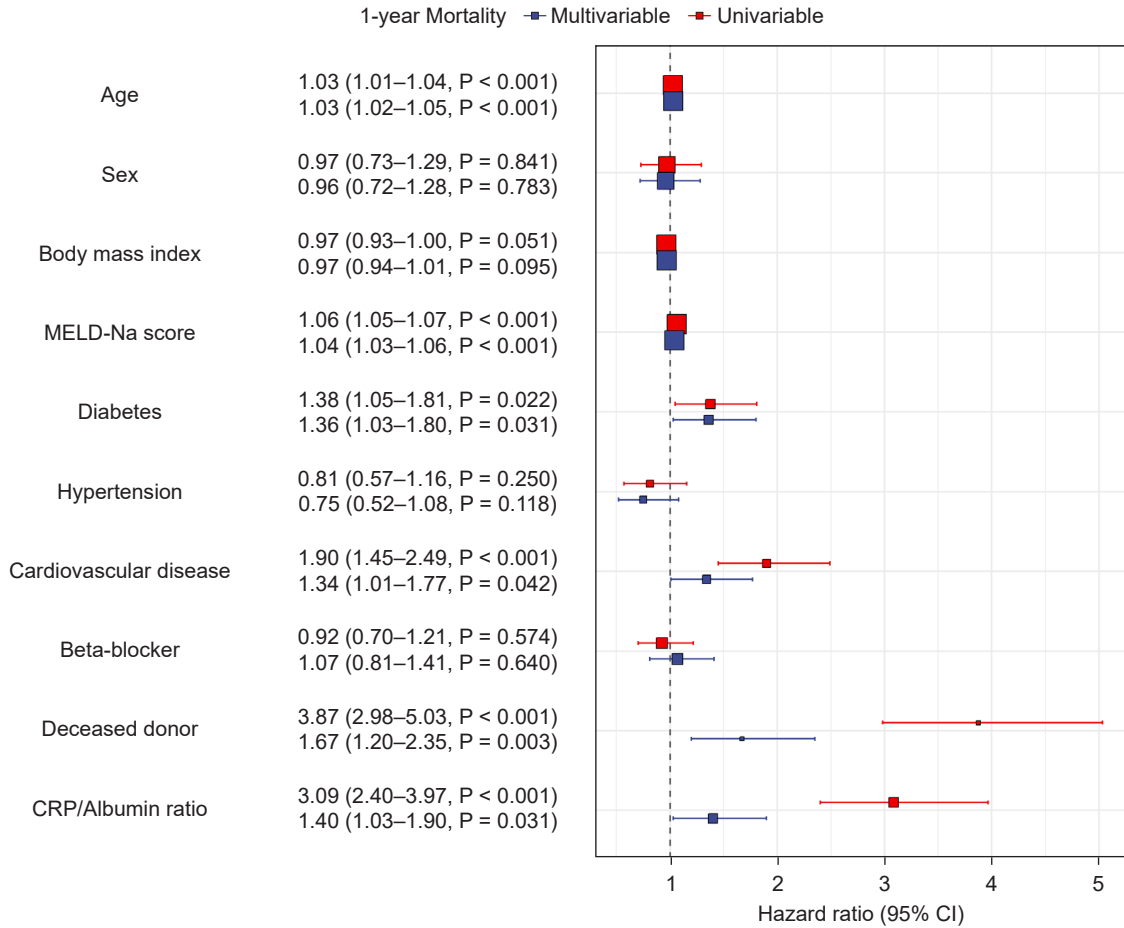


Fig. 2. Univariable and multivariable analysis of risk factors with one-year mortality after liver transplantation as the outcome. MELD-Na score: Sodium-adjusted Model for End-Stage Liver Disease score, CRP: C-reactive protein, CI, confidence interval.

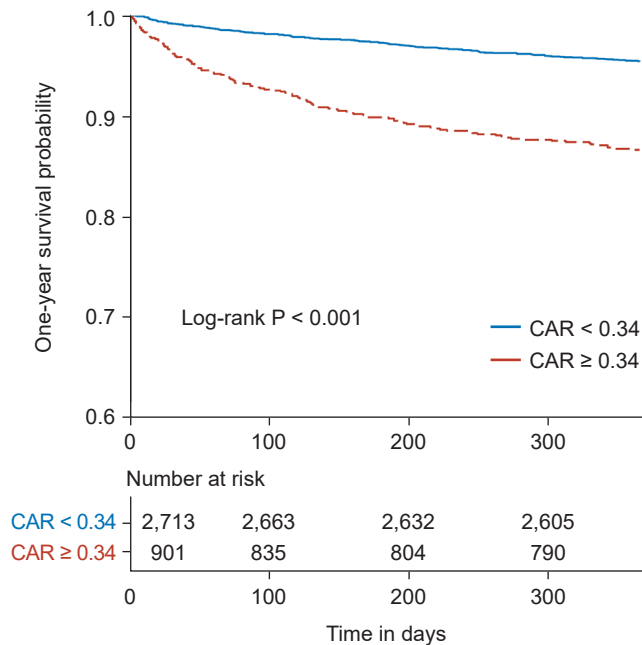


Fig. 3. Cumulative one-year mortality risk according to Kaplan-Meier analysis. CAR: C-reactive protein-to-albumin ratio.

2.46], P < 0.001) and after multivariate adjustment (HR [95% CI] = 1.39 [1.13–1.71], P = 0.002) (Fig. 4).

DISCUSSION

Accumulating evidence from previous studies suggests that the CAR is a reliable prognosticator of outcome and indicator of patient status [7,8,12–16]. Specifically, among patients undergoing LT with prevalent concomitant immune dysregulation [20], a higher CAR is reported to be associated with poorer liver cirrhosis prognosis and higher early allograft dysfunction following LT [14].

The results from our large, single-center cohort expand the prognostic value of the CAR to predict survival following LT. A high CAR was associated with an increased risk of mortality, shown by the independent association of CAR ≥ 0.34 with a 1.4-fold higher risk of one-year survival compared with CAR < 0.34. This association was independent of the

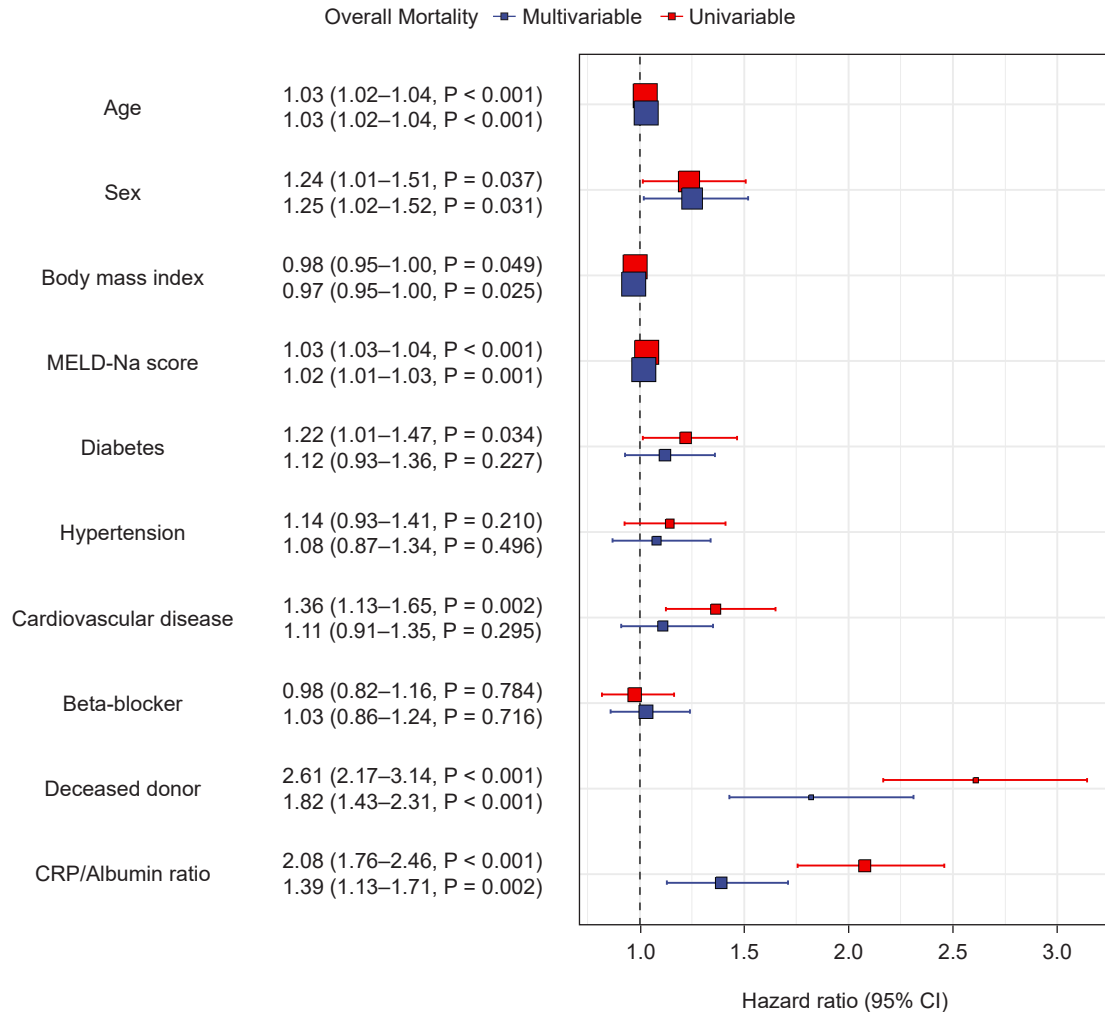


Fig. 4. Univariable and multivariable analysis of risk factors with overall mortality after liver transplantation as the outcome. MELD-Na score: Sodium-adjusted Model for End-Stage Liver Disease score, CRP: C-reactive protein, CI, confidence interval.

recipient's general condition, as shown by the MELD-Na score or donor status (deceased or living). The CAR was also predictive of long-term prognosis, as indicated by an independent association of long-term mortality after LT. Of note, the CAR was a superior prognostic index compared with other inflammation-based parameters.

It is reported that patients with cirrhosis have a high probability of bacterial infections and systemic inflammation and endotoxemia derived from gut microbiota [21], which is associated with a worse prognosis. Therefore, early detection and adequate management may be essential to improving the prognosis in this population [22]. Previous studies have shown that parameters reflecting systemic inflammatory status, such as CRP levels [23] or serum gamma globulin [21], are associated with increased risk of mortality. Therefore, inflammation-based prognostic scores, possibly easily

calculated with high predictability, may be practical in risk stratification in LC populations.

Use of the CAR as prognostic marker was first proposed by Fairclough et al. [24] for identifying acutely sick patients. Since then, the usefulness of the CAR as predictor of outcomes has been reported in studies investigating diverse cohorts, such as critically ill patients [7,8,25], in cirrhotic populations awaiting LT [14], as well as in patients undergoing colorectal [26], pancreatic [27] and gastro-esophageal [10] surgery.

Previous studies on the use of the CAR in LT recipients have used relatively small sample sizes. Park et al. [16] showed the association between early allograft dysfunction and graft survival with the CAR in 588 patients undergoing living-donor LT. A study by Amygdalos et al. [15] demonstrated higher post-LT morbidity and mortality among pa-

tients with high CARs undergoing deceased-donor LT (n = 390). Our study finding is in line with previous studies and expand the implications of the CAR to predicting mortality after LT regardless of donor status. Interestingly, the predictive ability of the CAR remained strong in predicting overall survival, which was in line with previous studies of deceased-donor LT; however, further studies are needed to confirm this association.

The high predictive value of CAR may lie in that it is composite of two renowned predictive factors. Separately, CRP is a well-known, indicator of systemic inflammation, and the predictive value is documented in the critical care setting [9] and post-operative stage. Albumin reflects patients' nutrition status, therefore reduced albumin levels are commonly found in critically ill patients [10,11] and is proven to be associated with post-operative morbidity after major surgery [28-30]. The possible explanation for the strong relationship between the CAR and mortality is that it is a single variable reflecting both systemic inflammation and nutritional status. In other words, it may accurately indicate "sicker" patients by including more information about patients' underlying status, compared with other inflammation-based variables, such as the LMR. However, the exact mechanistic explanation for this clinical observation should be elucidated in future research.

One other interesting finding of current study is that deceased-donor was significantly associated with one-year and overall mortality. Although the underlying mechanism is not clear in both studies, it may be due to the difference of intraoperative process (such as less transfusion in living donor LT) and shorter waiting time.

Our study has some limitations. First, as this was a retrospective study, we cannot be certain that all probable confounding factors were considered. Although we attempted to adjust for diverse factors associated with LT outcomes using multivariable analysis, unanticipated confounding variables contributing to mortality may exist. Second, we were unable to explain the underlying mechanisms causing our findings. Future prospective research is needed to explain the mechanisms underlying the association between the CAR and mortality after LT, which may lead to the development of beneficial therapeutic interventions.

In summary, our study proposes the CAR as an additional prognostic tool based on its prognostic for LT recipients. Notably, the CAR could discriminate the risk of one-year and overall mortality independent of patients' liver function, as shown by MELD-Na scores and the type of donor (deceased

or living). The CAR, an easily calculated variable from laboratory findings, provides additional information that may improve risk stratification and assist the overall assessment of persons awaiting LT.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Data curation: Kyoung-Sun Kim, Jae Hwan Kim, Ji-Woong Yang. Formal analysis: Hye-Mee Kwon. Methodology: Kyoung-Sun Kim, Gyu-Sam Hwang. Project administration: Gyu-Sam Hwang. Visualization: Jae Hwan Kim, In-Gu Jun, Gyu-Sam Hwang. Writing - original draft: Kyoung-Sun Kim. Writing - review & editing: Hye-Mee Kwon, Jun-Gol Song, Gyu-Sam Hwang. Resources: Jun-Gol Song. Supervision: Hye-Mee Kwon, In-Gu Jun, Jun-Gol Song.

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