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Association of preoperative serum De Ritis ratio with oncological outcomes in patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma

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Abstract

Purpose: Identifying which patients are likely to benefit from cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma (mRCC) is important. We tested the association between preoperative serum De Ritis ratio (DRR, Aspartate Aminotransferase/Alanine Aminotransferase) and overall survival (OS) as well as cancer-specific survival (CSS) in mRCC patients treated with CN.

Material and methods: mRCC patients treated with CN at different institutions were included. After assessing for the optimal pretreatment DRR cut−off value, we found 1.2 to have the maximum Youden index value. The overall population was therefore divided into 2 DRR groups using this cut−off (low, <1.2 vs. high, ≥1.2). Univariable and multivariable Cox regression analyses tested the association between DRR and OS as well as CSS. The discrimination of the model was evaluated with the Harrel's concordance index (C-index). The clinical value of the DRR was evaluated with decision curve analysis.

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Results: Among 613 mRCC patients, 239 (39%) patients had a DRR ≥1.2. Median follow-up was 31 (IQR 16−58) months. On univariable analysis, high DRR was significantly associated with OS (hazard ratios [HR]: 1.22, 95% confidence interval [CI]: 1.01−1.46, $P = 0.04$) and CSS (HR: 1.23, 95% CI: 1.02−1.47, $P = 0.03$). On multivariable analysis, which adjusted for the effect of established clinicopathologic features, high DRR remained significantly associated with both OS (HR: 1.26, 95% CI: 1.04-1.52, $P = 0.02$) and CSS (HR: 1.26, 95% CI: 1.05−1.53, $P = 0.01$). The addition of DRR only minimally improved the discrimination of a base model that included established clinicopathologic features (C-index = 0.633 vs. C-index = 0.629). On decision curve analysis, the inclusion of DRR did not improve the net-benefit beyond that obtained by established subgroup analyses stratified by IMDC risk groups, type of systemic therapy, body mass index and sarcomatoid features, did not reveal any prognostic value to DRR.

Conclusion: Despite the statistically significant association between DRR and OS as well as CSS in mRCC patients treated with CN, DRR does not seem to add any further prognostic value beyond that obtained by currently available features.

Keywords: mRCC; Cytoreductive nephrectomy; OS; CSS; De Ritis ratio

1. Introduction

Renal cell carcinoma (RCC) represents 2% to 3% of all cancers with the highest incidence in developed countries [1]. Approximately 25% of patients with newly diagnosed RCC still present with metastatic disease (mRCC) [2]. Currently, cytoreductive nephrectomy (CN) before systemic treatment remains the standard therapy in selected mRCC patients [1]. To stratify patients and determine optimal therapeutic strategies, clinicians use the Memorial Sloan-Kettering Cancer Center (MSKCC, also known as Motzer score) [3] and the International metastatic RCC Database Consortium (IMDC, also known as Heng score) [4] prognostic models. However, significant intragroup heterogeneity exists among patients stratified according to MSKCC or IMDC categories. In consequence, an optimal patient selection for CN remains still challenging, and an accurate prognostic prediction is crucial when making decisions about treatment options.

The ratio of the serum activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), also known as the De Ritis ratio (DRR), was originally proposed as an indicator of liver function [5]. Nowadays, the serum levels of DRR have been shown to be associated with oncological outcomes in different urological malignancies such as bladder [6], upper tract urothelial [7,8], prostate [9], and testicular [10] cancers. It is hypothesized that tumor aggressiveness is correlated with an increase in DRR. Indeed, during active proliferation of cancer cells, an increased oxidative stress [11] and aerobic glycolysis occur which lead to an increase of this marker [12,13]. Previous studies have already suggested explanations for the DRR ability to predict oncological outcomes in patients with localized RCC [14−17]. Nevertheless, the DRR as a predictor of oncological outcomes in CN patients still remains unclear. Indeed, only one single center study with limited number of patients ($n = 118$) showed an association of the preoperative serum DRR with postoperative survival in mRCC patients after CN [18].

The aim of this study was to investigate the association between preoperative serum DRR and oncological outcomes in mRCC patients treated with CN. We also assessed the prognostic value of DRR in risk groups, according to the IMDC score.

2. Material and methods

2.1. Study design

We retrospectively reviewed our established international multicenter database to identify mRCC patients treated with CN at tertiary centers in the United States and Europe. We excluded patients with other malignant primaries tumors mRCC. However, concomitant hematological disorders and chronic liver diseases (hepatitis, liver cirrhosis, and severe fatty liver disease) within the last 12 months were not excluded.

The study was approved by ethics institutional committees at all participating institutions and informed consent was obtained from eligible patients.

2.2. Management

Dedicated uropathologists assigned pathologic stage according to the 2010 American Joint Committee on Cancer (AJCC) tumor, node and metastasis (TNM) staging system. All pathology reports from prior to 2010 were reviewed according to 2010 criteria. According to the IMDC patients were stratified into favorable vs. intermediate vs. poor risk groups [4].

All laboratory tests were done within 1 month prior to the CN. The DRR was evaluated as the ratio of the serum activities of AST and ALT. *We performed a 2-step approach to identify the best cut-off value. First, the population was divided in quintiles based on the distribution of DRR and the overall survival (OS) was explored in each subgroup. Second,* we carried out a time−dependent receiver operating characteristic curve analysis for 3−year OS as the end−point, considering the median OS time (12 months), and determined a value of 1.2 as having the maximum Youden index value. *This second approach*

showed the best clinical applicability and ease of use. The study population was therefore dichotomized using the DRR at a cut−off of 1.2 (lower <1.2 vs. higher ≥1.2). OS time was calculated from the date of CN to death or last follow-up. Cancer-specific survival (CSS) time was calculated from the date of CN to death from disease or last follow-up.

2.3. Statistical analysis

Associations between DRR status and categorical variables were assessed using chi-square or Fisher's exact tests. Differences in continuous variables were analyzed with the Mann-Whitney *U* test. Univariable and multivariable Cox regression analyses tested the association of DRR with OS and CSS. The risk of survival was expressed as hazard ratios (HR) and 95% confidence intervals (95% CI). Kaplan-Meier survival curves were used to graphically depict the association between AGR and survival. The log-rank test was used to determinate the statistical difference between the DRR <1.2 and DRR ≥1.2 groups with respect to death. The discrimination of the model was evaluated using the Harrel's concordance index (C-index). The clinical value of the DRR was evaluated with decision curve analysis (DCA) [19,20]. Statistical significance was set at $P < 0.05$. All tests were 2-sided. Analyses were performed using R version 3.6.2. (2009-2020 RStudio, Inc.).

3. Results

Overall, 613 patients were included in the analyses. Among them, 239 (39%) patients had a DRR ≥1.2. Patient characteristics are shown in Table 1. The number of liver metastasis was significantly higher in the group of patients with high preoperative serum vs. low DRR level (3.7% vs. 11%, $P < 0.001$). The number of brain metastasis was significantly higher in the low DRR group (4.5% vs. 1.3%, $P = 0.03$).

At median follow-up of 31 (IQR 16−58) months, a total of 472 (77%) patients died and 99% of deaths, were due to mRCC. Kaplan-Meier analyses showed significantly lower OS (log-rank test $P = 0.04$) and CSS (log-rank test $P = 0.03$) rates in patients with high DRR compared to those with low DRR (Fig. 1). Median OS was 20 months (95% CI: 17−24 months) and 17 months (95% CI: 15−23 months) in patients with low and high DRR, respectively. On univariable Cox regression analyses, high preoperative serum DRR was associated with both OS (HR: 1.22, 95% CI: 1.01−1.46, $P = 0.04$) and CSS (HR: 1.23, 95% CI: 1.02−1.47, $P = 0.03$; Table 2).

On multivariable analysis which adjusted for the effect of established clinicopathologic features, high DRR remained significantly associated with worse OS (HR: 1.26, 95% CI: 1.04−1.52, P =0.02) and CSS (HR: 1.26, 95% CI: 1.05−1.53, $P = 0.01$). The addition of DRR only marginally improved the discrimination of a base model that included established clinicopathologic features (C-index = 0.633 vs. C-index = 0.629). On DCA, the model including IMDC risk groups, type of systemic therapy, body mass index (BMI), and sarcomatoid features led to superior outcomes for any decision associated with a threshold probability abode 25%. The inclusion of the DRR did not improve the net benefit of the model (Fig. 2).

In subgroup analyses, among 572 patients without liver metastases, on multivariate analysis DRR ≥1.2 was still associated with worse OS (HR: 1.27, 95% CI: 1.04−1.55, P = 0.02) and CSS (HR: 1.28, 95% CI: 1.05−1.56, P = 0.02) (Supplementary material 1). In subgroup analyses according to the IMDC prognostic model, on univariable and multivariable analyses preoperative serum DRR ≥1.2 was not associated with OS and CSS for favorable, intermediate or poor risk patients (all $P > 0.05$). In a subpopulation of patients treated with tyrosine kinase inhibitor (TKI) therapy, on univariable analyses, DRR was still not associated with OS or CSS (all $P > 0.05$). *In a subpopulation of patients not treated with targeted therapy, on multivariable analyses, DRR ≥1.2 was associated with worse OS (HR: 1.25, 95% CI: 1.02−1.52, P = 0.03) and CSS (HR: 1.26, 95% CI: 1.03−1.53, P = 0.02)* (Supplementary material 2).

On exploratory subgroup analyses based on the BMI, among 435 patients with BMI ≥25, DRR was still not associated with OS ($P = 0.08$) or CSS ($P = 0.07$). On univariable analyses in subpopulation of 111 patients with presence of sarcomatoid features, preoperative serum DRR was still not associated with OS ($P = 0.68$) or CSS ($P = 0.68$).

4. Discussion

In the present study, we found an association between preoperative serum DRR and OS or CSS rates in patients treated with CN for mRCC. Moreover, after adjusting for the effects of established clinicopathologic features in mRCC, DRR retained its statistical significance. These findings are in agreement with a previous retrospective analysis of 118 patients treated with CN for mRCC [18]. In that single center study, on multivariable analysis, a high DRR level (with cut-off at a 1.24) was independently associated with CSS (HR: 2.17, 95% CI: 1.01−4.98, $P = 0.04$) and OS (HR: 2.30, 95% CI: 1.10−5.08, $P = 0.03$) [18]. We expanded upon these previous findings by analyzing a large cohort of patients with mRCC originating from a multicenter cooperative database by investigating the clinical value of DRR. To evaluate the clinical improvement of DRR performance, we evaluated the C-index and the DCA. Methods that incorporate clinical consequences like DCA are crucial for the evaluation of biomarkers during late stages of research before clinical implementation of the biomarker [19]. We found that preoperative serum DRR did not show any net clinical benefit over the standard clinical factors. Moreover, its prognostic additive value as measured by the concordance index was only marginal (i.e., negligible). However, not all patients undergo CN today as only

Table 1
Clinicopathologic features of 613 patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma, stratified by De Ritis ratio (DRR)

Parameters	All ($n = 613$)	DRR <1.2 ($n = 374$)	DRR ≥1.2 ($n = 239$)	P value
Age, median (IQR)	57 (50−64)	57 (50−64)	57 (50−64.5)	0.63
BMI groups, *n* (%)				0.14
BMI ≥25	435 (71)	274 (73)	161 (67)	
BMI<25	178 (29)	100 (27)	78 (33)	
BMI, median (IQR)	27.5 (24.5−30.0)	28.0 (24.8−30.5)	27.0 (24.2−29.1)	**0.01**
Sex, *n* (%)				0.11
Male	428 (70)	270 (72)	158 (66)	
Female	185 (30)	104 (28)	81 (34)	
ECOG before nephrectomy, *n* (%)				0.91
0	410 (67)	248 (66)	162 (68)	
1	186 (30)	115 (31)	71 (30)	
2	17 (3)	11 (2.9)	6 (2.5)	
Prognostic groups according to IMDC criteria, *n* (%)				0.06
Favorable	186 (30)	109 (29)	77 (33)	
Intermediate	343 (56)	204 (55)	139 (58)	
Poor	84 (14)	61 (16)	23 (9)	
Karnofsky performance status				0.75
≥80%	596 (97)	363 (97)	233 (97)	
<80%	17 (3)	11 (3)	6 (3)	
Hemoglobin g/dl, median (IQR)	11.9 (10.5−13.5)	11.9 (10.7−13.6)	11.9 (10.3−13.4)	0.52
Abnormal hemoglobin, *n* (%)				0.94
≥LLN	299 (49)	182 (49)	117 (49)	
<LLN	314 (51)	192 (51)	122 (51)	
Calcium, mg/dl, median (IQR)	9.3 (8.9−9.7)	9.3 (8.9−9.7)	9.3 (8.9−9.7)	0.92
Abnormal calcium, n (%)				0.14
≤ULN	556 (91)	334 (89)	222 (93)	
>ULN	57 (9)	40 (11)	17 (7)	
Neutrophils, 10^9/l, median (IQR)	5.5 (4.2−7.0)	5.6 (4.4−7.1)	5.2 (4.1−6.6)	0.06
Abnormal neutrophils, *n* (%)				0.15
≤ULN	463 (76)	275 (74)	188 (79)	
>ULN	150 (24)	99 (26)	51 (21)	
Platelet, 10^9/l, median (IQR)	312 (240−410)	324 (239−410)	302 (243−414)	0.71
Abnormal platelet, *n* (%)				0.95
≤ULN	448 (73)	273 (73)	175 (73)	
>ULN	165 (27)	101 (27)	64 (27)	
Largest metastasis size, cm, median (IQR)	2.00 (2.00−3.00)	2.00 (2.00−3.00)	2.00 (2.00−3.00)	0.44
Number of metastasis sites, *n* (%)				0.53
Single	370 (60.4)	230 (61.5)	140 (58.6)	
Multiple	243 (39.6)	144 (38.5)	99 (41.4)	
Site of metastases, *n* (%)				
Adrenal glands	112 (18)	68 (18)	44 (18)	0.94
Bones	181 (30)	121 (32)	60 (25)	0.06
Brain	20 (3.3)	17 (4.5)	3 (1.3)	**0.03**
Liver	41 (6.7)	14 (3.7)	27 (11)	**<0.001**
Lung	415 (68)	255 (68)	160 (67)	0.75
Lymph nodes	138 (22.5)	86 (23)	52 (22)	0.72
Other	38 (6.2)	19 (5.1)	19 (7.9)	0.15
Time from diagnosis to nephrectomy				0.37
Less than 12 months	584 (95)	354 (95)	230 (96)	
More than 12 months	29 (5)	20 (5)	9 (4)	
Lymphadenectomy, *n* (%)				0.97
No	361 (59)	220 (59)	141 (59)	
Yes	252 (41)	154 (41)	98 (41)	
Histology, *n* (%)				0.37
Clear cell carcinoma	529 (86)	319 (85)	210 (88)	
Other	84 (14)	55 (15)	29 (12)	
Sarcomatoid features, *n* (%)				0.87
No	502 (81.9)	305 (81.6)	197 (82.4)	
Yes	111 (18.1)	69 (18.4)	42 (17.6)	

(*continued*)

Table 1 (***Continued***)

Parameters	All ($n = 613$)	DRR <1.2 ($n = 374$)	DRR ≥1.2 ($n = 239$)	P value
Grade, *n* (%)				0.17
G1/G2	65 (10.6)	34 (9.1)	31 (13.0)	
G3/G4	548 (89.4)	340 (90.9)	208 (87.0)	
Neoadjuvant therapy, *n* (%)				0.82
No	500 (82)	304 (81)	196 (82)	
Yes	113 (18)	70 (19)	43 (18)	
Adjuvant therapy, *n* (%)				**<0.001**
No	132 (22)	61 (16)	71 (30)	
Yes	481 (78)	313 (84)	168 (70)	

Bold P values are considered statistically significant (P value < 0.05).

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group performance status; IMDC = International Metastatic RCC Database Consortium Risk Model; IQR = interquartile range; LLN = lower limit of normal; ULN = upper limit of normal.

favorable risk and some intermediate risk patients may benefit from a surgery first strategy [21,22].

In subgroup analyses according to the IMDC prognostic model, a high preoperative serum DRR was neither associated with OS nor CSS. The same results were found in subgroup analyses of patients treated with TKI therapy. *Notably, in subgroup analyses of patients not treated with targeted therapy, high DRR was associated with both OS and CSS.* This is in contrast to data obtained in a retrospective study comprising 360 patients treated with first-line TKI therapy for mRCC [23]. On multivariable analysis, the authors found that patients with a pretreatment serum DRR ≥1.2 had worse OS (HR: 1.69, 95% CI: 1.19−2.39, $P = 0.003$) and CSS (HR: 1.61, 95% CI: 1.13−2.30, $P = 0.008$). Moreover, the prognostic impact of the DRR was more prominent among mRCC patients with an intermediate MSKCC risk classification (log-rank test = 0.04 for OS and log-rank test = 0.02 for CSS), but did not affect the favorable and poor risk groups. These results may be explainable by the predominant number of patients ($n = 248$) they had intermediate risk. Furthermore, these results could be associated with the use of the previous common risk classification (MSKCC) and obviously the TKI first strategy.

In our study, we investigated only the DRR, however, its combination with other preoperative markers such as systemic inflammation may be helpful in the prediction of oncologic outcomes in patients with RCC [24]. To improve survival stratification offered by the current IMDC and MSKCC risk models, one recent study evaluated the prognostic value of DRR as well as systemic inflammatory markers in 158 patients treated with first-line targeted therapy for mRCC [25]. A new model that incorporated DRR and neutrophil-to-lymphocyte ratio had significantly better predictability (C-index = 0.727) than the IMDC and MSKCC risk model (C-index = 0.661 and 0.612, respectively) for OS. Combination of complementary and independent biomarkers is likely to capture the biologic potential of a tumor than any single biomarker [19,26].

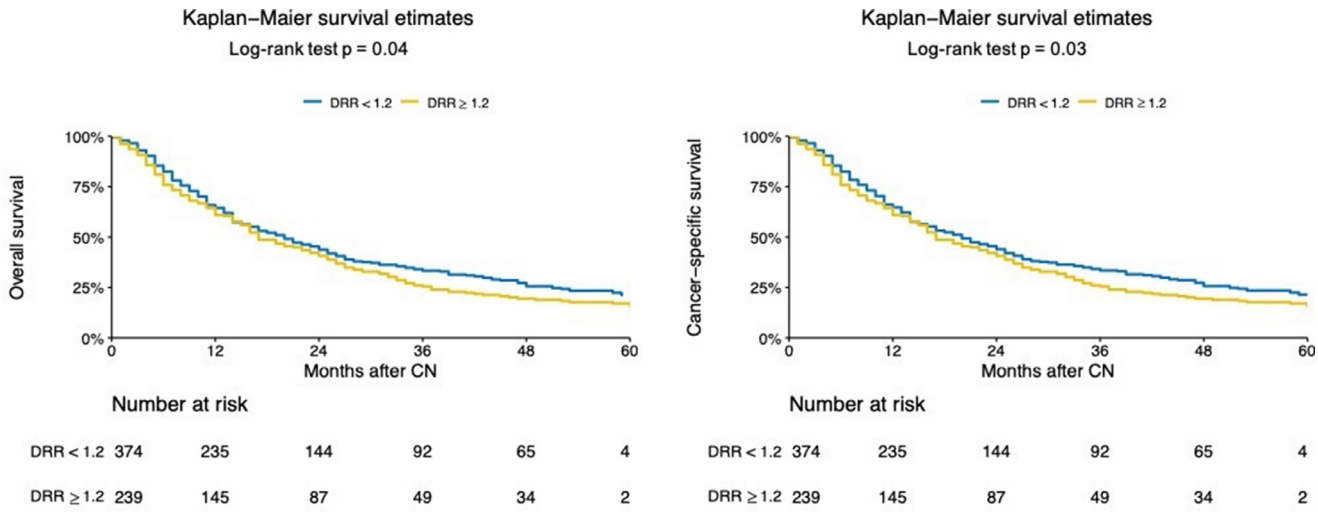

Fig. 1. Kaplan-Meier analysis for overall and cancer-specific survival in 613 patients treated with cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma, stratified according to the De Ritis ratio (DRR) at a cut-off of 1.2.

Table 2
Univariable and multivariable Cox regression analyses predicting overall survival (OS) and cancer-specific survival (CSS) in patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma

Variables	OS				CSS			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.00	0.33	1.01	**0.002**	1.00	0.38	1.01	**0.003**
Sex (female)	1.05	0.61	0.91	0.37	1.04	0.71	0.90	0.30
BMI ≥25	0.91	0.37	0.89	0.27	0.91	0.34	0.88	0.24
ECOG ≥1	1.05	0.65	1.06	0.58	1.04	0.68	1.05	0.61
IMDC criteria								
Favorable	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Intermediate	1.19	0.09	1.08	0.45	1.20	0.08	1.09	0.41
Poor	1.52	**0.01**	1.62	**0.002**	1.51	**0.01**	1.61	**0.003**
DRR ≥1.2	1.22	**0.04**	1.26	**0.02**	1.23	**0.03**	1.26	**0.01**
Multiple metastatic sites	1.43	**<0.001**	1.53	**<0.001**	1.44	**<0.001**	1.53	**<0.001**
Clear cell carcinoma histology	0.55	**<0.001**	0.54	**<0.001**	0.55	**<0.001**	0.53	**<0.001**
Sarcomatoid features	1.94	**<0.001**	1.84	**<0.001**	1.95	**<0.001**	1.85	**<0.001**
C-index with DRR	0.633				0.635			
C-index without DRR	0.629				0.630			

Bold *P* values are considered statistically significant (*P* value < 0.05).
BMI = body mass index; CSS = cancer-specific survival; DRR = De Ritis ratio; ECOG = Eastern Cooperative Oncology Group performance status; IMDC = International Metastatic RCC Database Consortium Risk Model; OS = overall survival.

We found that the number of the liver metastasis was significantly higher in group of patients with high-preoperative serum DRR. This finding is not surprising as AST and ALT levels are predictive markers to identify hepatic disease [27]. The elevation of AST has been already suggested as valuable prognostic factors in patients with liver metastasis [28]. *It should be stressed that worse survival outcomes in the high DRR group (higher number of liver metastases) could be associated with the fact that the liver metastases sites cause a dramatic drop in the survival rate. However, in subgroup analyses, among patients without liver metastases, high DRR level was still associated with worse OS and CSS. Moreover, the multiplicity of metastases plays a more critical role in survival outcomes than localization [29]. In our study, patients in high- and low-DRR level groups did not differ according to a number of metastases sites. For this reason, we supposed that our findings should not be biased by this issue.* Our study showed that the number of brain metastasis was higher in the low DRR group. In nonaffected organs, AST is commonly produced in the liver, heart, skeletal muscle, kidney and brain; ALT is specifically found in the liver [30]. Moreover, AST has a vital role in anaerobic glycolysis, allowing cancer cells to generate the energy required for their survival and growth

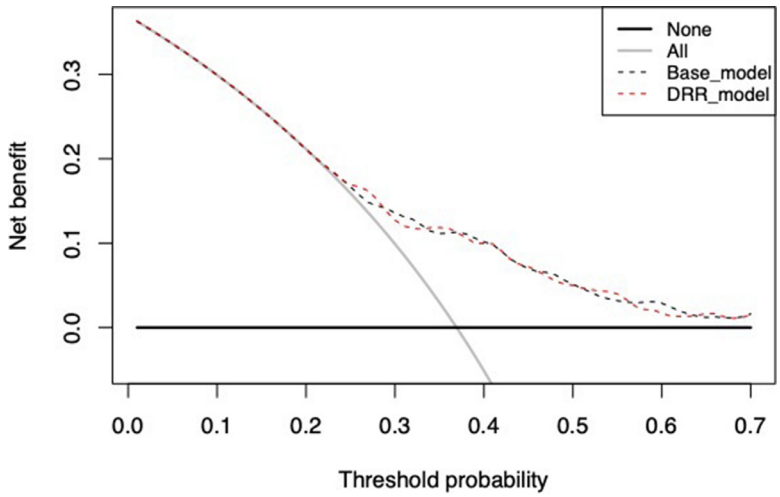

Fig. 2. Decision curve analysis assessing the clinical impact of current prognostic models (Base model) with the integration of the De Reitis ratio (DRR model) estimating overall mortality at 1 year, in 613 patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma. The 2 models are compared with the strategies of treating all or none of the patients with cytoreductive nephrectomy.

[31,32]. Therefore, the AST could be actively involved in the development of brain metastasis thereby affecting the level of DRR.

Our study is not devoid of limitations. The main limitation of the study was its retrospective and multicenter design, which may result in a lack of standardized laboratory, pathological, surgical, and treatment approaches that could confound the results. Another limitation of our study is that the DRR might have been biased by the presence of an undetected liver disease or drug interaction which may have affected the liver function. Despite all these limitations, currently, there is a lack of evidence of the association of DRR with oncologic outcomes in mRCC. To cover this field, we studied the largest series investigating the DRR in mRCC cohort originating from an established multicenter database. Further intensive studies to identify optimal predictive and prognostic biomarkers or its combination in mRCC patients are needed.

5. Conclusion

Despite the statistically significant association of the DRR with OS and CSS in patients treated with CN for mRCC, it does not seem to add any prognostic or clinical benefit beyond that obtained by currently available characteristics. High DRR level can be an indicator of liver metastases.

Ethical standards

This study has been approved by the appropriate ethics committee (UT SW IRB File 0698 26900).

Author‘s contribution

Ekaterina Laukhtina – Data analysis, Manuscript writing; Benjamin Pradere – Data analysis, Manuscript writing; David D‘Andrea – Data analysis, Manuscript editing; Giuseppe Rosiello – Manuscript editing; Stefano Luzzago – Manuscript editing; Angela Pecoraro – Manuscript editing; Carlotta Palumbo – Manuscript editing; Sophie Knipper - Manuscript editing; Pierre I. Karakiewicz - Manuscript editing, Project development; Vitaly Margulis – Project development; Fahad Quhal – Manuscript editing; Reza Sari Motlagh – Manuscript editing; Hadi Mostafaei – Manuscript editing; Keiichiro Mori – Data analysis; Shoji Kimura – Manuscript editing; Dmitry Enikeev – Manuscript editing, Project development; Shahrokh F. Shariat - Manuscript editing, Project development.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.08.013.

References

[1] Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. Renal Cell carcinoma EAU guidelines on renal cell carcinoma: 2019. Eur Urol 2019. https://doi.org/10.1016/j.eururo.2015.01.005.

[2] Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008. https://doi.org/10.1016/j.ctrv.2007.12.001.

[3] Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999. https://doi.org/10.1200/jco.1999.17.8.2530.

[4] Heng DYC, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009. https://doi.org/10.1200/JCO.2008.21.4809.

[5] Wu J, Chen L, Wang Y, Tan W, Huang Z. Prognostic value of aspartate transaminase to alanine transaminase (De Ritis) ratio in solid tumors: a pooled analysis of 9,400 patients. Onco Targets Ther 2019. https://doi.org/10.2147/OTT.S204403.

[6] Ha YS, Kim SW, Chun SY, Chung JW, Choi SH, Lee JN, et al. Association between de Ritis ratio (aspartate aminotransferase/alanine aminotransferase) and oncological outcomes in bladder cancer patients after radical cystectomy. BMC Urol 2019. https://doi.org/10.1186/s12894-019-0439-7.

[7] Mori K, Janisch F, Mostafaei H, Lysenko I, Kimura S, Egawa S, et al. Prognostic value of preoperative blood-based biomarkers in upper tract urothelial carcinoma treated with nephroureterectomy: a systematic review and meta-analysis. Urol Oncol: Semin Orig Investig 2020. https://doi.org/10.1016/j.urolonc.2020.01.015.

[8] Mori K, Janisch F, Mostafaei H, Kimura S, Lysenko I, Karakiewicz PI, et al. Prognostic role of preoperative De Ritis ratio in upper tract urothelial carcinoma treated with nephroureterectomy. Urol Oncol Semin Orig Investig 2020. https://doi.org/10.1016/j.urolonc.2020.02.008.

[9] Wang H, Fang K, Zhang J, Jiang Y, Wang G, Zhang H, et al. The significance of De Ritis (aspartate transaminase/alanine transaminase) ratio in predicting pathological outcomes and prognosis in localized prostate cancer patients. Int Urol Nephrol 2017. https://doi.org/10.1007/s11255-017-1618-7.

[10] Gorgel SN, Akin Y, Koc EM, Kose O, Ozcan S, Yilmaz Y. Impact of increased aspartate aminotransferase to alanine aminotransferase (De Ritis) ratio in prognosis of testicular cancer. Investig Clin Urol 2019. https://doi.org/10.4111/icu.2019.60.3.169.

[11] Sookoian S, Pirola CJ. Liver enzymes, metabolomics and genome-wide association studies: from systems biology to the personalized medicine. World J Gastroenterol 2015. https://doi.org/10.3748/wjg.v21.i3.711.

[12] Hsu PP, Sabatini DM. Cancer cell metabolism: warburg and beyond. Cell 2008. https://doi.org/10.1016/j.cell.2008.08.021.

[13] Heiden MGV, Cantley LC, Thompson CB. Understanding the warburg effect: the metabolic requirements of cell proliferation. Science 2009. https://doi.org/10.1126/science.1160809.

[14] Lee H, Lee SE, Byun SS, Kim HH, Kwak C, Hong SK. De Ritis ratio (aspartate transaminase/alanine transaminase ratio) as a significant prognostic factor after surgical treatment in patients with clear-cell localized renal cell carcinoma: a propensity score-matched study. BJU Int 2017. https://doi.org/10.1111/bju.13545.

[15] Canat L, Ataly HA, Agalarov S, Alkan I, Alturende F. The effect of AST/ALT (De Ritis) ratio on survival and its relation to tumor histopathological variables in patients with localized renal cell carcinoma. Int Braz J Urol 2018. https://doi.org/10.1590/s1677-5538.ibju.2017.0173.

[16] Ikeda T, Ishihara H, Takagi T, Fukuda H, Yoshida K, Iizuka J, et al. The De Ritis (Aspartate Transaminase/Alanine Transaminase) Ratio

as a Prognosticator in Patients With End-stage Renal Disease–associated Renal Cell Carcinoma. Clin Genitourin Cancer 2020. https://doi.org/10.1016/j.clgc.2019.12.012.

[17] Bezan A, Mrsic E, Krieger D, Stojakovic T, Pummer K, Zigeuner R, et al. The preoperative AST/ALT (De Ritis) ratio represents a poor prognostic factor in a cohort of patients with nonmetastatic renal cell carcinoma. J Urol 2015. https://doi.org/10.1016/j.juro.2015.01.083.

[18] Ishihara H, Kondo T, Yoshida K, Omae K, Takagi T, Iizuka J, et al. Evaluation of Preoperative Aspartate Transaminase/Alanine Transaminase Ratio as an Independent Predictive Biomarker in Patients With Metastatic Renal Cell Carcinoma Undergoing Cytoreductive Nephrectomy: a Propensity Score Matching Study. Clin Genitourin Cancer 2017. https://doi.org/10.1016/j.clgc.2017.04.011.

[19] Shariat SF, Lotan Y, Vickers A, Karakiewicz PI, Schmitz-Dräger BJ, Goebell PJ, et al. Statistical consideration for clinical biomarker research in bladder cancer. Urol Oncol Semin Orig Investig 2010. https://doi.org/10.1016/j.urolonc.2010.02.011.

[20] D'Andrea D, Soria F, Zehetmayer S, Gust KM, Korn S, Witjes JA, et al. Diagnostic accuracy, clinical utility and influence on decision-making of a methylation urine biomarker test in the surveillance of non-muscle-invasive bladder cancer. BJU Int 2019. https://doi.org/10.1111/bju.14673.

[21] Marchioni M, Bandini M, Preisser F, Tian Z, Kapoor A, Cindolo L, et al. Survival after Cytoreductive Nephrectomy in Metastatic Non-clear Cell Renal Cell Carcinoma Patients: a Population-based Study. Eur Urol Focus 2019. https://doi.org/10.1016/j.euf.2017.11.012.

[22] Bex A, Albiges L, Ljungberg B, Bensalah K, Dabestani S, Giles RH, et al. Updated European Association of Urology Guidelines for Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Clear-cell Renal Cell Carcinoma. Eur Urol 2018. https://doi.org/10.1016/j.eururo.2018.08.008.

[23] Kang M, Yu J, Sung HH, Jeon HG, Jeong BC, Park SH, et al. Prognostic impact of the pretreatment aspartate transaminase/alanine transaminase ratio in patients treated with first-line systemic tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma. Int J Urol 2018. https://doi.org/10.1111/iju.13574.

[24] De Martino M, Pantuck AJ, Hofbauer S, Waldert M, Shariat SF, Belldegrun AS, et al. Prognostic impact of preoperative neutrophil-to-lymphocyte ratio in localized nonclear cell renal cell carcinoma. J Urol 2013. https://doi.org/10.1016/j.juro.2013.06.082.

[25] Kim SH, Park EY, Joo J, Chung J. The De Ritis and Neutrophil-to-Lymphocyte Ratios May Aid in the Risk Assessment of Patients with Metastatic Renal Cell Carcinoma. J Oncol 2018:1–8.

[26] Soria F, Krabbe LM, Todenhöfer T, Dobruch J, Mitra AP, Inman BA, et al. Molecular markers in bladder cancer. World J Urol 2019. https://doi.org/10.1007/s00345-018-2503-4.

[27] Botros M, Sikaris KA. The de ritis ratio: the test of time. Clin Biochem Rev 2013.

[28] O'Reilly SM, Richards MA, Rubens RD. Liver metastases from breast cancer: the relationship between clinical, biochemical and pathological features and survival. Eur J Cancer Clin Oncol 1990. https://doi.org/10.1016/0277-5379(90)90080-D.

[29] McKay RR, Kroeger N, Xie W, Lee JL, Knox JJ, Bjarnason GA, et al. Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. Eur Urol 2014. https://doi.org/10.1016/j.eururo.2013.08.012.

[30] Shibata N, Higuchi I, Sugiyama M, Nakamura T. High concentration of serum aspartate aminotransferase in older underweight people: results of the Kanagawa Investigation of the Total Check-Up Data from the National Database-2 (KITCHEN-2). J Clin Med 2019. https://doi.org/10.3390/jcm8091282.

[31] Greenhouse WV, Lehninger AL. Occurrence of the malate-aspartate shuttle in various tumor types. Cancer Res 1976;36:1392–6.

[32] Warburg O. On the origin of cancer cells. Science (80-) 1956. https://doi.org/10.1126/science.123.3191.309.