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Baseline and Three-Month De Ritis Ratio and Gamma-Glutamyltransferase as Prognostic Biomarkers in Metastatic Renal Cell Carcinoma Treated with Targeted Therapy

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Abstract

Background: Liver function tests (LFTs)–derived parameters such as the De Ritis ratio (DRR) and **gamma**-glutamyltransferase (GGT) may reflect tumor biology and systemic inflammation. Thus, we evaluated both baseline and 3-month measurements of LFTs in patients with metastatic renal cell carcinoma (mRCC) receiving first-line targeted therapy (TT).

Methods: We retrospectively analyzed 264 patients with mRCC treated with first-line TT. Progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan–Meier and compared using the log-rank test. Associations of clinicopathological variables with PFS and OS were analyzed using univariate and multivariate Cox models.

Results: The median PFS and OS times for the cohort **were** 12.3 months (95% confidence interval [CI]: 10.7–13.8) and 45.6 months (95% CI: 38.4–52.9), respectively. At 3 months, patients with high DRR had inferior PFS (11.5 vs. 13.4 months, p=0.003) and OS (33.0 vs. 63.0 months, p<0.001) compared with those with low DRR. Similarly, patients with elevated GGT (>upper limit of normal) demonstrated shorter PFS (10.3 vs. 13.8 months, p<0.001) and OS (39.4 vs. 55.0 months, p<0.001). In multivariate analyses, high DRR was an independent predictor of shorter PFS (hazard ratio [HR]: 1.504, 95% CI: 1.126–2.009, p=0.006) and OS (HR: 2.108, 95% CI: 1.449–3.066, p<0.001). Elevated GGT was also independently associated with

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inferior PFS (HR: 1.624, 95% CI: 1.221–2.158, p<0.001) and OS (HR: 1.661, 95% CI: 1.198–2.303, p=0.002).

Conclusions: Elevated DRR and GGT values at 3 months were independent predictors of inferior survival in mRCC, underscoring their utility as practical biomarkers that may improve risk stratification in routine clinical care.

Keywords: De Ritis ratio; GGT, liver function tests; metastatic renal cell carcinoma; gamma-glutamyltransferase

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Introduction

Renal cancer constitutes a significant global health burden, ranking 14th among all malignancies, with more than 430,000 newly diagnosed cases in 2020 [1]. Renal cell carcinoma (RCC), which accounts for nearly 90% of kidney cancers, carries a favorable 5-year relative survival of 92% when localized, but this falls dramatically to 15% in metastatic RCC (mRCC), reflecting its poor prognosis [2,3]. Commonly used prognostic tools such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) **scoring** system classify patients with mRCC and assist in clinical decision-making processes. These algorithms are based on established clinical and laboratory variables. Despite their clinical utility, these systems do not adequately represent the complex biological variability of RCC, underscoring the necessity for practical and inexpensive biomarkers that may complement and strengthen established prognostic tools.

Among potential biomarkers, routine liver function tests (LFTs) are one of the promising candidates, including alanine aminotransferase (ALT),

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aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT), which are routinely assessed in all oncology patients, not only reflect hepatobiliary function but can also indicate systemic processes such as inflammation, oxidative stress, metabolic reprogramming, and occult liver involvement. Therefore, numerous studies have investigated the prognostic significance of individual enzymes and enzyme ratios in various malignancies, including oral and oropharyngeal cancer[4], bladder cancer[5], breast cancer[6], hepatocellular carcinoma[7], and pancreatic cancer [8]. However, there is scant data about the prognostic role of LFTs in RCC. For example, Canat et al. demonstrated that an increased preoperative De Ritis ratio (DRR, calculated as AST/ALT) associated with adverse histopathological characteristics—including renal vein invasion, capsule infiltration, and renal pelvis involvement—but did not independently predict survival outcomes in patients with localized RCC[9]. However, in the same population, Bezan et al. showed that a preoperative high DRR independently predicted worse survival outcomes and enhanced the prognostic accuracy of existing models[10]. Similar to DRR, the prognostic impact of ALP and GGT in RCC remains inconsistent across studies[11–14]. Altogether LFTs can be regarded as dual-purpose tools, reflecting both hepatic function and systemic tumor-related biology. Therefore, we aimed to evaluate the prognostic value of LFTs in predicting survival outcomes in patients with mRCC treated with first-line targeted therapy (TT).

Material and Methods

Patient population and study design

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We retrospectively reviewed the medical records of patients diagnosed with metastatic renal cell carcinoma (mRCC) who received first-line targeted therapy at the Hacettepe University Cancer Institute and the Department of Medical Oncology, Dokuz Eylul University, between January 2015 and January 2025. Baseline demographic and clinicopathological variables were recorded, including age, sex, histological subtype, prior nephrectomy, sites of metastases, and type of TT received. LFTs, including ALT, AST, ALP, and GGT, were analyzed as a baseline value (within two weeks prior to TT initiation) and a follow-up value at three months (±2 weeks). **Serum AST, ALT, ALP, and GGT levels were measured using routine laboratory assays at both institutions, and the upper limits of normal (ULN) for these parameters were identical across centers, ensuring methodological consistency.** The DRR was calculated as AST/ALT. **The 3-month (±2 weeks) on-treatment timepoint was selected because it corresponds to the first routine response assessment window (approximately 8–12 weeks) used in pivotal mRCC trials and real-world practice during TT[15,16], providing a clinically meaningful early landmark for dynamic biomarker evaluation.** All patients had histopathological confirmation of RCC obtained from either nephrectomy or biopsy specimens. The IMDC score was calculated using performance status, hemoglobin, calcium, neutrophil and platelet counts, and time from diagnosis to treatment, stratifying patients into favorable, intermediate, and poor-risk groups[17]. Patients were excluded if they had: (i) a history of chronic liver disorders, including viral hepatitis, cirrhosis, autoimmune hepatitis, substantial alcohol consumption

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or hepatotoxic drug use; (ii) prior systemic therapy for metastatic disease; and (iii) incomplete clinical and laboratory documentation. Patients with incomplete clinical or laboratory documentation were excluded from the analysis. **A total of 22 patients were excluded, primarily due to missing baseline or 3-month LFT values.**

Statistical analyses

Continuous data are reported as medians with interquartile range (IQR) or mean with standard deviation (SD), and categorical data as counts and percentages. The primary endpoint was overall survival (OS), defined as the time from initiation of TT to death from any cause or last follow-up. The secondary endpoint was progression-free survival (PFS), defined as the time from treatment initiation to radiologic or clinical disease progression or death, whichever occurred first. Survival probabilities were estimated using the Kaplan–Meier method and compared with the log-rank test. The median follow-up time was estimated using the reverse Kaplan–Meier method. The prognostic value of the DRR, GGT, ALP, and other variables for PFS and OS **was** assessed using Cox proportional hazards regression in both univariate and multivariate models. **Prior to multivariate Cox regression analyses, multicollinearity among covariates, including the IMDC score and liver enzyme–derived parameters, was assessed using variance inflation factors. No evidence of significant multicollinearity was observed.** All variables with a p value of ≤0.2 in univariate analysis were evaluated in the multivariate analysis. All statistical analyses were performed using SPSS software version 27 (IBM

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Corp., Armonk, NY, USA), and a two-sided p value <0.05 was considered statistically significant.

Results

Clinicopathological Features and Treatment Distribution

A total of 264 patients with mRCC treated with first-line TT were included in the analysis. Baseline characteristics, including demographic, clinical, pathological, and treatment data, are presented in Table 1. The median age at diagnosis was 61 years (IQR, 53–68), and the majority were male (74.2%). Clear cell histology was the predominant subtype (78%), while 22% had non-clear cell variants. Most patients presented with high-grade tumors (70.5% grade III–IV), and lung metastases were the most common metastatic site (73.1%), followed by bone (26.5%), liver (21.2%), adrenal (13.3%), and brain (6.4%). According to the IMDC risk classification, 13.6% were favorable, 62.5% intermediate, and 23.9% poor risk. **The mean DRR was 1.13 (SD 0.06) at baseline and 1.18 (SD 0.15) at 3 months. Baseline mean ALP was 81.3 U/L (SD 28.4), with a median ALP of 92 U/L (IQR 73–120) at 3 months. Median GGT was 39 U/L (IQR 32–52) at baseline and 37 U/L (IQR 30–82) at 3 months.**

Regarding treatment choices, pazopanib was the most frequently used TT (56.1%), followed by sunitinib (37.5%) and cabozantinib (6.4%). **Among the 174 patients who received second-line systemic therapy, nivolumab was the most frequently used agent (82 patients, 47.1%), followed by everolimus (45 patients, 25.9%), axitinib (44 patients, 25.3%), and cabozantinib (3 patients, 1.7%). Among the 83 patients who received third-line systemic therapy, axitinib was the most**

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frequently administered agent (52 patients, 62.7%), followed by nivolumab (16 patients, 19.3%), everolimus (10 patients, 12.0%), and cabozantinib (5 patients, 6.0%).

Characteristics	All patients (n=264)
Age (years), IQR	61 (53-68)
Sex	
Female	68 (25.8%)
Male	196 (74.2%)
Baseline DRR, SD	1.13 (0.06)
DRR at 3 months, SD	1.18 (0.15)
Baseline ALP, SD	81.3 (28.4)
ALP at 3 months , IQR	92 (73-120)
Baseline GGT, IQR	39 (32-52)
GGT at 3 months, IQR	37 (30-82)
Histology	
Clear cell	206 (78%)
Non-clear cell	58 (22%)
Tumor grade	
I-II	78 (29.5%)
III-IV	186 (70.5%)
Metastatic sites	
Presence of lung metastasis	193 (73.1%)
Presence of bone metastasis	70 (26.5%)
Presence of liver metastasis	56 (21.2%)

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Presence of adrenal gland metastasis	35 (13.3%)
Presence of brain metastasis	17 (6.4%)
IMDC	
Favorable	36 (13.6%)
Intermediate	165 (62.5%)
Poor	63 (23.9%)
First-line treatment	
Pazopanib	148 (56.1%)
Sunitinib	99 (37.5%)
Cabozantinib	17 (6.4%)
Second-line treatment (n=174)	82 (47.1%)
Nivolumab	44 (25.3%)
Axitinib	45 (25.9%)
Everolimus	3 (1.7%)
Cabozantinib	
Third-line treatment (n=83)	
Nivolumab	16 (19.3%)
Axitinib	52 (62.7%)
Everolimus	10 (12.0%)
Cabozantinib	5 (6.0%)

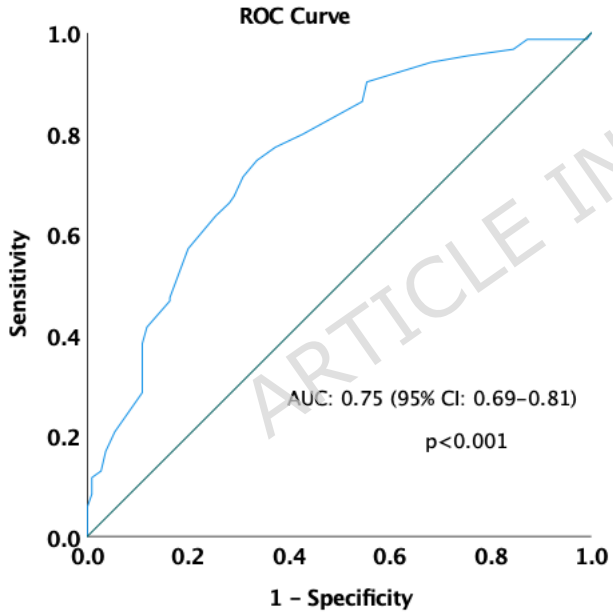
Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DRR: De Ritis ratio; GGT: Gamma-glutamyltransferase; IMDC: International Metastatic Renal

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Cell Carcinoma Database Consortium; IQR: Interquartile range; SD: Standard deviation

Survival outcomes

During a median follow-up of 56.5 months, 209 progression events and 154 deaths were observed. The median PFS for the cohort **was** 12.3 months (95% confidence interval [CI]: 10.7–13.8). ROC curve analysis identified 1.15 as the optimal threshold of the DRR at 3 months for predicting OS (AUC: 0.75, 95% CI: 0.69–0.81, p<0.001, Fig. 1). Based on this cut-off, patients were stratified into two prognostic groups: high-DRR (DRR ≥1.15) and low-DRR (DRR <1.15).



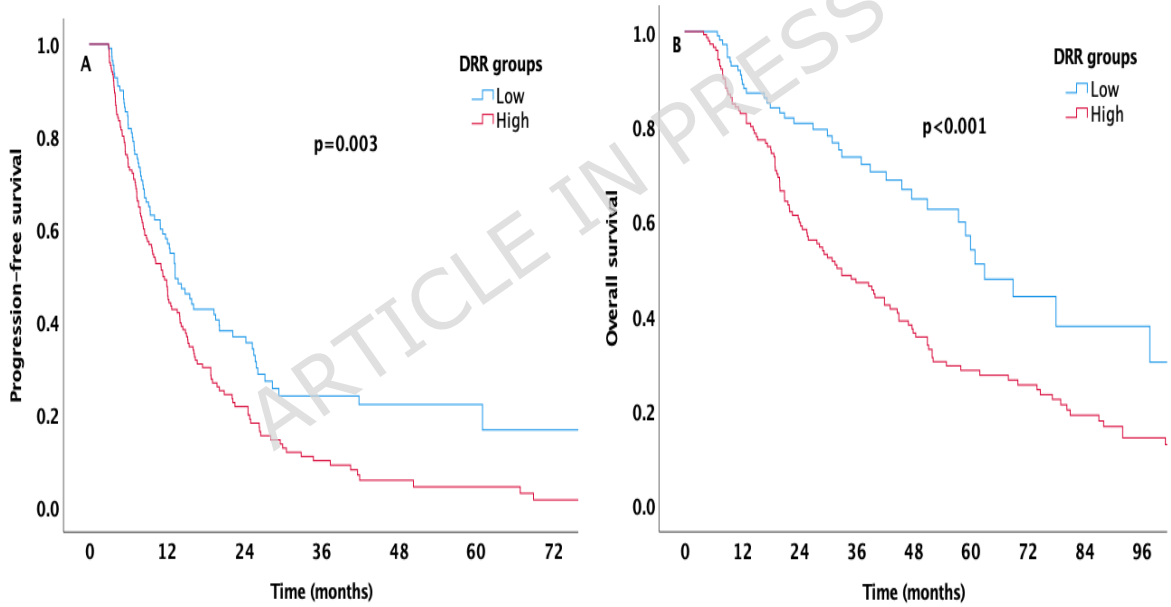
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Fig 1. ROC curve analysis of the DRR for predicting OS.

At the 3-month evaluation, patients with a high DRR had inferior PFS, with a median of 11.5 months (95% CI: 9.6–13.3), compared with 13.4 months (95% CI: 10.5–16.2) in those with a low DRR (p=0.003, Fig. 2A). Similarly, patients with elevated GGT levels had a shorter median PFS than those with below the ULN (10.3 months, 95% CI: 7.1–13.5 vs 13.8 months 95%

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CI: 11.2–16.4, p<0.001, respectively, Fig. 2C). The median OS for the cohort was 45.6 months (95% CI: 38.4–52.9). At 3 months, patients with a high DRR showed a markedly shorter median survival than those with a low DRR (33.0 months, 95% CI: 23.6–42.4 vs 63.0 months 95% CI: 51.9–74.1, p<0.001, respectively, Fig. 2B). Similarly, patients with GGT values above the ULN had inferior OS than those with below the ULN (39.4 months 95% CI: 26.2–52.5 vs 55.0 months 95% CI: 36.9–73.1, p<0.001, respectively, Fig. 2D).



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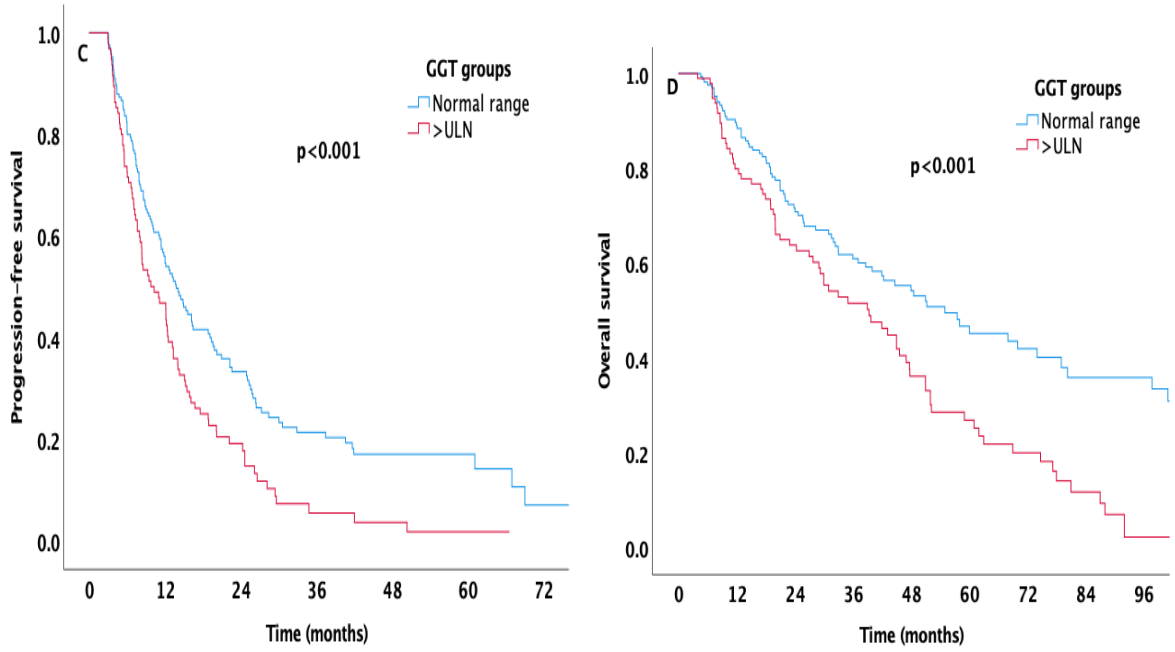


Fig 2. Kaplan–Meier curves estimating PFS (A) and OS (B) in patients grouped by DRR **categories**, and PFS (C) and OS (D) in patients grouped by GGT categories at 3 months following initiation of TT.

As presented in Table 2, the significant clinicopathological variables associated with poorer PFS were IMDC classification system (p<0.001), elevated DRR (hazard ratio [HR]: 1.543, 95% CI: 1.161–2.050, p=0.003) and high GGT levels (HR: 1.606, 95% CI: 1.214–2.125, p<0.001). Liver (p=0.066), bone (p=0.100), and lung metastases (p=0.159) were determined as potential variables in predicting PFS. In the multivariate analyses, the independent predictors of inferior PFS were the IMDC classification (intermediate vs. favorable: HR: 1.643, 95% CI: 1.066–2.531, p=0.024; poor vs. favorable: HR: 3.316, 95% CI: 2.021–5.439, p<0.001), an elevated DRR (HR: 1.504, 95% CI: 1.126–2.009, p=0.006), and high GGT levels (HR: 1.624, 95% CI: 1.221–2.158, p<0.001).

As shown in Table 3, the presence of liver metastasis was associated with worse OS (HR: 1.475, 95% CI: 1.020–2.133, p=0.039), as were bone (HR:

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1.816, 95% CI: 1.296–2.546, p<0.001) and brain metastases (HR: 1.885, 95% CI: 1.065–3.334, p=0.029). Across IMDC risk groups, patients in the intermediate-risk category had a modestly elevated risk of death (HR: 1.735, 95% CI: 1.005–2.996, p=0.048), whereas poor-risk patients exhibited nearly a fourfold higher mortality compared with the favorable group (HR: 3.898, 95% CI: 2.133–7.122, p<0.001). Among the LFTs, an elevated DRR (HR: 2.123, 95% CI: 1.474–3.057, p<0.001) and higher GGT levels (HR: 1.833, 95% CI: 1.329–2.527, p<0.001) were both significantly associated with inferior survival. In contrast, increased ALP was associated with a trend toward poorer survival but did not reach statistical significance (HR: 1.272, 95% CI: 0.881–1.837, p=0.199). In the multivariate analysis, independent factors associated with poorer OS were bone metastasis (HR: 1.976, 95% CI: 1.340–2.912, p<0.001), brain metastasis (HR: 1.947, 95% CI: 1.075–3.524, p=0.028), and liver metastasis (HR: 1.643, 95% CI: 1.116–2.420, p=0.012). The IMDC poor-risk score was also determined as a strong independent prognostic factor (HR: 4.067, 95% CI: 2.195–7.534, p<0.001), whereas the intermediate-risk group demonstrated only a nonsignificant tendency toward inferior survival (HR: 1.629, 95% CI: 0.926–2.868, p=0.091). Among the LFTs, high values of DRR and GGT were independent predictors of worse survival (HR: 2.108, 95% CI: 1.449–3.066, p<0.001; HR: 1.661, 95% CI: 1.198–2.303, p=0.002), whereas ALP showed no independent prognostic relevance in the adjusted model (HR: 1.026, 95% CI: 0.673–1.564, p=0.903). **Bootstrap validation (1,000 resamples) confirmed the robustness of the**

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selected DRR cut-off, with consistent effect estimates across resampled datasets.

Table 2: Univariate and multivariate Cox regression analyses of clinicopathological variables and LFTs for PFS.

	Univariate		**Multivariate**	
Variable	**HR (95 CI%)**	**P value**	**HR (95 CI%)**	**P value**
Age, years	0.997 (0.984-1.010)	0.648	-	-
Gender (male vs female)	0.889 (0.653-1.249)	0.453	-	-
Histology (clear vs non-clear)	1.028 (0.738-1.433)	0.869	-	-
Tumor grade (III-IV vs I-II)	1.209 (0.803-1.821)	0.362	-	-
Lung metastasis (present vs absent)	0.802 (0.591-1.090)	0.159	0.770 (0.561-1.056)	0.104
Liver metastasis (present vs absent)	1.368 (0.979-1.910)	0.066	1.283 (0.917-1.795)	0.145
Bone metastasis (present vs absent)	1.286 (0.953-1.736)	0.100	1.145 (0.841-1.560)	0.390
Brain metastasis (present vs absent)	1.263 (0.741-2.154)	0.392	-	-
IMDC risk scoring system Favorable	1 (reference)	<0.001 0.037	1 (reference)	<0.001 0.024

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Intermediate Poor	1.580 (1.029-2.426) 3.077 (1.890-5.009)	<0.001	1.643 (1.066-2.531) 3.316 (2.021-5.439)	<0.001
DRR (high or low)	1.543 (1.161-2.050)	0.003	1.504 (1.126-2.009)	0.006
ALP (high or low)	0.995 (0.721-1.375)	0.978	1.026 (0.673-1.564)	0.903
GGT (high or low)	1.606 (1.214-2.125)	<0.001	1.624 (1.221-2.158)	<0.001

Abbreviations: CI: Confidence interval; DRR: De Ritis ratio; GGT: Gamma-glutamyltransferase; HR: Hazard ratio; IMDC : International Metastatic Renal Cell Carcinoma Database Consortium; LFTs : Liver function tests; OS : Overall survival; PFS : Progression-free survival; ULN : Upper limit of normal

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Table 3: Univariate and multivariate Cox regression analyses of clinicopathological variables and LFTs for OS.

	Univariate		**Multivariate**	
Variable	**HR (95 CI%)**	**P value**	**HR (95 CI%)**	**P value**
Age, years	0.992 (0.978-1.007)	0.296	-	-
Gender (male vs female)	1.075 (0.749-1.541)	0.696	-	-

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Histology (clear vs non-clear)	1.270 (0.873-1.848)	0.211	-	-
Tumor grade (III-IV vs I-II)	1.381 (0.833-2.289)	0.211	-	-
Lung metastasis (present vs absent)	1.122 (0.782-1.611)	0.531	-	-
Liver metastasis (present vs absent)	1.475 (1.020-2.133)	0.039	1.643 (1.116-2.420)	0.012
Bone metastasis (present vs absent)	1.816 (1.296-2.546)	<0.001	1.976 (1.340-2.912)	<0.001
Brain metastasis (present vs absent)	1.885 (1.065-3.334)	0.029	1.947 (1.075-3.524)	0.028
IMDC risk scoring system Favorable Intermediate Poor	 1 (reference) 1.735 (1.005-2.996) 3.898 (2.133-7.122)	<0.001 0.048 <0.001	 1 (reference) 1.629 (0.926-2.868) 4.067 (2.195-7.534)	<0.001 0.091 <0.001
DRR (high or low)	2.123 (1.474-3.057)	<0.001	2.108 (1.449-3.066)	<0.001
ALP (high or low)	1.272 (0.881-1.837)	0.199	1.026 (0.673-1.564)	0.903
GGT (high or low)	1.833 (1.329-2.527)	<0.001	1.661 (1.198-2.303)	0.002

Abbreviations: CI: Confidence interval; DRR: De Ritis ratio; GGT: Gamma-glutamyltransferase; HR: Hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; LFTs: Liver function tests;

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OS: Overall survival; PFS: Progression-free survival; ULN: Upper limit of normal

Discussion

The present study aimed to evaluate the prognostic value of routinely measured liver function–derived parameters, particularly the DRR and GGT, in patients with mRCC treated with TT. Our analysis revealed that elevated DRR and GGT values at three months were independently associated with both shorter PFS and OS. To the best of our knowledge, this represents one of the first studies to systematically assess dynamic changes in DRR and GGT as prognostic biomarkers in this clinical setting. These findings suggest that simple and inexpensive biochemical parameters, which are already part of routine oncologic practice, may provide additional prognostic information beyond established risk models. Regarding **the** mechanistic role LFTs in cancer, AST plays an essential role **in** aerobic glycolysis, as it facilitates the transfer of nicotinamide adenine dinucleotide hydrogen to the mitochondria via the malate-aspartate shuttle[18]. In contrast, ALT **is involved in** glutaminolysis and pyruvate production, both of which are accentuated in tumor metabolism[19]. Thus, the DRR can be used as an indicator of the metabolic state of cancer cells and may be linked to tumor progression. Elevated ALP, although commonly linked to liver or bone pathology, also reflects osteotropic metastasis and changes in the bone microenvironment that may drive tumor progression and independently predict poorer survival outcomes[11]. GGT is an important mechanistic regulator of cellular redox balance and glutathione homeostasis[20]. It enhances the production of reactive oxygen species

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(ROS) by promoting glutathione catabolism[21]. Excessive ROS accumulation promotes oxidative DNA damage and genomic instability, which are well-recognized drivers of malignant transformation[22]. Beyond DNA-damaging effects, increased ROS levels also stimulate central oncogenic signaling cascades, including the nuclear factor kappa B and mitogen-activated protein kinase pathways. Activation of these signaling cascades drives tumor progression by fostering a chronic inflammatory microenvironment, promoting tumor cell proliferation, and inducing angiogenesis[23].

Kang et al. showed that a pretreatment DRR≥ 1.2 independently predicted worse cancer-specific survival (CSS) and OS in mRCC patients undergoing first-line TT[24]. Consistent with this study, Ishihara et al. reported that preoperative DRR ≥ 1.24 independently predicted poorer CSS and OS in patients with mRCC undergoing cytoreductive nephrectomy[25], highlighting its potential value in risk stratification. However, Janisch et al. demonstrated that although the DRR did not independently predict survival outcomes across all mRCC patients receiving TT, it was associated with inferior OS in selected subgroups such as intermediate-risk patients and clear-cell RCC , suggesting context-specific prognostic utility[26]. Regarding the prognostic role of ALP, Koseci et al. demonstrated that integrating albumin-to-ALP ratio (AAPR) and HALP (Hemoglobin, Albumin, Lymphocyte, Platelet score) into a combined score provided strong prognostic discrimination in mRCC receiving TT[12], suggesting it may complement established prognostic models. Simic et al. investigated the clinical significance of GGT levels in patients with mRCC, with a focus on

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its potential role as a biomarker and found that serum GGT levels are significantly elevated in patients with mRCC, highlighting its high sensitivity as a biomarker[27]. Hofbauer et al. reported that higher pretherapeutic serum GGT levels correlated with unfavorable tumor characteristics—such as increased size, advanced stage, and higher grade—and independently predicted worse CSS and OS in RCC[14]. More recently, in the TT era, elevated serum GGT was confirmed as an independent prognostic factor for OS in patients with mRCC treated with vascular endothelial growth factor– and mammalian target of rapamycin –targeted agents. Ishiyama et al. showed that high baseline serum GGT and its early rise during nivolumab therapy were associated with significantly worse PFS and OS in mRCC, suggesting that GGT may serve as a simple predictive biomarker in the immune checkpoint inhibitor (ICI) setting. **Taken together, these findings support the concept that DRR and GGT primarily reflect tumor-related metabolic and inflammatory biology rather than isolated treatment-related hepatotoxicity. Nevertheless, because TTs and ICIs may alter liver enzymes, distinguishing tumor-driven biomarker changes from treatment-related liver injury requires confirmation in prospective studies with detailed toxicity data.**

The major strength of the present study is the inclusion of a relatively large cohort derived from two high-volume oncology centers, providing robust real-world evidence. To our knowledge, it represents one of the few investigations assessing both baseline and dynamic three-month changes in the DRR and GGT, thereby offering novel insights into their prognostic

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role. Another notable strength is the focus on biochemical tests that are already part of standard practice, which improves the practicality of applying these findings in clinical practice. Furthermore, multivariate analyses demonstrated that DRR and GGT at three months are independent predictors of survival outcomes after adjusting for established prognostic factors such as the IMDC risk score, highlighting their clinical utility as simple and cost-effective biomarkers.

Nevertheless, the present study has several limitations that should be acknowledged. First, the retrospective design of this study limits the ability to establish causal relationships and may have introduced selection or information bias. Second, although patients with known liver disease were excluded, subclinical liver impairment or drug-related effects could not be fully ruled out. Third, while we demonstrated prognostic significance for OS, the biological mechanisms underlying these associations warrant further translational investigation. Prospective studies integrating dynamic changes in liver enzymes with molecular and immunologic profiling could clarify the pathways linking hepatic function, systemic inflammation, and tumor progression. **Fourth, the study was conducted in patients treated with first-line TT alone. Therefore, the generalizability of the prognostic value of DRR and GGT to contemporary ICI-based or combination regimens requires further validation.**

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Conclusion

Elevated DRR **and** GGT at 3 months were independent predictors of OS after adjustment for established prognostic factors, underscoring the

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potential role of dynamic monitoring of DRR and GGT in refining prognostic assessment, rather than relying solely on baseline measurements. Future translational studies integrating serial biochemical data with molecular and immune-based analyses are needed to explore the underlying biology and to assess the predictive value of DRR and GGT in guiding the therapeutic decision-making in mRCC.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author (Oktay Halit Aktepe, oktayhalit.aktepe@deu.edu.tr) on reasonable request.

Abbreviations

AAPR: Albumin-to-ALP ratio

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

CI: Confidence interval

CSS: Cancer-specific survival

DRR: De Ritis ratio (AST/ALT)

GGT: Gamma-glutamyltransferase

HR: Hazard ratio

ICI: Immune-checkpoint inhibitor

IQR: Interquartile range

IMDC: International Metastatic Renal Cell Carcinoma Database

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Consortium

LFTs: Liver function tests

mRCC: Metastatic renal cell carcinoma

OS: Overall survival

PFS: Progression-free survival

RCC: Renal cell carcinoma

ROS: Reactive oxygen species

SD: Standard deviation

TT: Targeted therapy

ULN: Upper limit of normaL

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Declarations

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Ethics declarations

Ethics approval and consent to participate

This retrospective study involving human participants was reviewed and approved, and the need for informed consent was waived by the Ethic Commission of Dokuz Eylul University. All procedures in the present study were performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Authors' contributions

OHA, ME, and SY designed the study. OHA, HSS, TU, EA, HSS, and SY collected and analyzed the data. HSS, AK, and ME provided guidance on data analysis. OHA, TU, EA, ITU, and AK searched relevant literature, generated partial figures and drafted the initial manuscript. HSS, ME and SY reviewed and edited the manuscript. All authors reviewed the manuscript and approved the submitted version.