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REVIEW ARTICLE

De Ritis Ratio: a Potent Marker in Cancer

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SUMMARY

Background: **The role of conventional liver function clinical laboratory marker De Ritis Ratio in evaluating the prognosis, assisting diagnosis, and monitoring therapeutic efficacy of cancer is gaining increasing attention, especially in the last decade. According to the most recent articles, the De Ritis Ratio functions have progressed, which indicates that the De Ritis Ratio appears to be a promising tumor marker. The aim of this review was to evaluate the clinical importance from studies made on this subject.**
Methods: **Using the search words "De Ritis Ratio", "aspartate transaminase/alanine transaminase", "aspartate transaminase", "alanine transaminase", "cancer", "prognostic significance", "diagnostic significance", and "predictive significance", a search was carried out on PubMed. Exclusion criteria were articles never published in English and articles evaluating tumor markers in cancer not involving the De Ritis Ratio.**
Results: **As a predictor of prognosis, the De Ritis Ratio is strongly associated with prognostic risk factors and can be used to assess therapeutic efficacy. As a predictor of incidence, the De Ritis Ratio could promote the prediction of the disease progression. As a biomarker, the De Ritis Ratio is more likely to improve diagnostics by being combined with other biomarkers. Therefore, since it is easily accessible, involves no additional laborious efforts, and is a relatively inexpensive marker, the De Ritis Ratio is emerging as an attractive and clinically valuable marker in cancer.**
Conclusions: **In the review, we explore the possible mechanisms of the De Ritis Ratio related to cancer and summarize the clinical importance of the De Ritis Ratio as a promising marker for cancer.**
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INTRODUCTION

The concept of the De Ritis Ratio (aspartate transaminase/alanine transaminase, AST/ALT) was given by De Ritis F for studying hepatitis etiology in 1957 [1]. It is commonly used to distinguish between liver diseases including fatty liver, alcoholic hepatitis, non-alcoholic fatty liver diseases [2]. With continued in-depth research, the De Ritis Ratio has assumed extensive clinical significance and is used as an effective marker for chronic diseases other than liver diseases, like cardiovascular disease [3] and metabolic syndrome [4]. In 2008,

Changchien and colleagues found that there was a close relationship between increased the De Ritis Ratio and adverse outcomes in hepatocellular carcinoma (HCC) [5]. In 2010, KimmH et al. reported that a high De Ritis ratio was an independent predictor for esophageal cancer [6]. Since then, more and more studies have proven that the De Ritis Ratio is strongly associated with cancers. The De Ritis Ratio has been widely used as a marker for prognosis, diagnosis, and efficacy prediction of cancers due to the test for AST and ALT is widely available, cheap, and quite reproducible, except in specific circumstances. In the review, we explore the possible mechanisms of the De Ritis Ratio related to cancer and summarize the De Ritis Ratio's clinical value as an easy-to-access, relatively inexpensive cancer marker.

Several mechanisms of the De Ritis Ratio are involved in cancer

A number of mechanisms underlie the association between cancer and the De Ritis Ratio remain unknown. AST and ALT are the major key enzymes in biological processes, and they play important roles in protein and carbohydrate metabolism [7]. Several metabolic abnormalities involved in cancer may be related to AST and ALT, and reflect the De Ritis Ratio (Figure 1).

Glycolysis

From a metabolic point of view, the most famous and common characteristic of cancer cells is increased glycolytic activity to produce adenosine triphosphate (ATP), regardless of oxygen availability. This phenomenon is known as the Warburg effect and was originally reported by Warburg in the 1920s [8]. Moreover, glycolysis is a major source of cytoplasmic nicotinamide adenine dinucleotide (NADH), which is critical to electron transport in mitochondria. A cancerous cell's metabolism switches from oxidative phosphorylation to aerobic glycolysis, resulting in a net increase in NADH [9]. AST is essential for aerobic glycolysis to allow NADH that has been produced in the cytoplasm to efficiently move within the mitochondria via malate-aspartate shuttle (MAS) pathway [2]. In brief, oxaloacetate (OAA) in the cytoplasm is converted into malate by malate dehydrogenase, and then malate is imported into mitochondria where it is converted to oxaloacetate, which reduces NAD+ to NADH in the mitochondria. OAA cannot cross the mitochondrial membrane but must pass through mitochondrial AST to become aspartate, which is transported into the cytoplasm by glutamate-aspartate exchange, and then is converted by cytoplasmic AST to OAA [10,11].The MAS is active in cancer cells [12,13] and in AST as an important MAS enzyme that might play a role in glucose metabolism in many malignancies that use glucose as a fuel.

ALT participates in the ‘glucose-alanine cycle’ that connects carbohydrate metabolism with amino acid metabolism [14]. Glycolysis converts glucose into pyruvate, which is not only converted to lactic acid, but is also converted to alanine via ALT [15]. One study showed that glucose consumption switched to pyruvate in the more aggressive stages of bladder cancer progression, and ALT activity could be stimulated [16]. Therefore, cancer glycolysis can lead to a change of AST and ALT, and affect the De Ritis Ratio.

Glutaminolysis

Cancers do not only exhibit aerobic glycolysis but also display an increase in glutaminolysis, which provide their energy source [17]. Hans Krebs discovered the tricarboxylic acid cycle (TCA) in the 1930s, highlighting the importance of glutamine metabolism in animals [18]. In subsequent studies, glutamine has been found to play a key role in both normal and cancer cell growth. The majority of cancer cells rely on glutamine and cannot survive without glutamine, which is termed “glutamine addiction” [19,20]. Glutaminolysis is an energy-yielding pathway in which glutamine (Gln) converted into α-ketoglutarate (α-kG) to enter directly into the TCA cycle to support mitochondrial metabolism [21], which is considered an important hallmark for cancer-specific metabolism [22]. The metabolite a-KG is essential for the metabolism of Gln [23]. One important mechanism of Gln is being converted into α-KG to feed the TCA cycle. Gln in mitochondria is hydrolyzed into glutamate (Glu), followed by the conversion of Glu to α-KG by Glu dehydrogenase or ALT, AST [24]. Research has proven that ALT and AST regulate cellular glutaminolysis and is crucial for sustaining cancer progression [17,25-27]. Therefore, the De Ritis Ratio can be used as a marker in cancer.

Ferroptosis

Ferroptosis is a reactive oxygen species (ROS)-dependent and iron-reliant cell death, which is characterized primarily by changes in the cytology [28] and is associated with multiple pathological conditions, including cancer [29]. Ferroptosis plays a critical role in the depression of tumorigenesis, and inactivation of ferroptosis contributes to tumor development [30]. Recent reports have indicated AST has a significant role in the network of ferroptosis in cancer. Kremer DM and colleagues demonstrated that AST inhibition leads to pancreatic cancer cell death by ferroptosis, which was induced by inhibiting cystine import, glutathione (GSH) synthesis, or glutathione peroxidase-4 (GPX4) in synergy with AST [31]. Another study also indicated that miR-9 regulates ferroptosis in melanoma cells by targeting AST [32]. Therefore, AST and the De Ritis Ratio can reflect ferroptosis associated with cancer.

Oxidative stress

In general, AST is broadly expressed in a variety of tissues, while ALT is mainly present in the hepatocyte cytoplasm [33]. ALT level is progressively reduced with aging [34], because of exaggerated hepatic aging processes [35]. Hepatic aging is related to increased production of free radicals, resulting in significant oxida-

Table 1. Evaluation of the De Ritis Ratio as predictor of the incidence risk in cancers.

Author year	Study design	Pts. No.	Parameters evaluated	Types of cancer	Cutoff level	follow-up/ Incidence	HR or OR (95% CI)
Kimm et al. [6] 2010	P	782,632	De Ritis Ratio, smoking, alcohol intake	EC	2.0	14 - years/ 0.17%	3.2 (2.7 - 3.9)
Kobayashi et al. [38] 2022	R	85,658	De Ritis Ratio	EC, GC, PCa, UTC, BC, CC, LC, etc.	1.19	61.6 months/ 5.5%	NA
Chen et al. [64] 2022	P	9,946	De Ritis Ratio	LC, CC, TC, GC, BC, HCC, PCa, cCa, etc.	1	5 - years/ 5.63%	NA
Zhou et al. [65] 2020	case-control study: 194 PCa cases and 210 BPH controls	404	De Ritis Ratio	PCa	1.155	NA	2.313 (1.337 - 4.003)
Loosen et al. [66] 2022	R	248,224	FIB-4 index (age, De Ritis Ratio, PLT)	liver cancer	NA	NA	NA

P - prospective, R - retrospective, NA - not available for evaluation, EC - esophageal cancer, GC - gastric cancer, pCa - prostatic cancer, UTC - urinary tract cancer, BC - breast cancer, CC - colon cancer, LC - lung cancer, TC - thyroid cancer, HCC - hepatocellular carcinoma, cCa - cervical cancer, BPH - prostatic hyperplasia, PLT - platelet.

Table 2. Evaluation of the De Ritis Ratio as diagnostic marker in cancers.

Author year	Pts. No.	Parameters evaluated	Types of cancer	Cutoff level	AUC	Sensitivity	Specificity
Yang et al. [67] 2021	370	GGT, GGT/ALT, De Ritis Ratio, AFP	PHC	1	NA	NA	NA
Alsebaey et al. [68] 2016	87	talin-1, AFP, De Ritis Ratio, PLT	HCC	0.855	0.938	86%	86.4%

PHC - primary hepatic carcinoma, HCC - hepatocellular carcinoma, GGT - gamma-glutamyl transferase, AFP - α-fetoprotein, PLT - platelet.

tive stress [36]. Due to the liver's vital role in metabolic and immunological homeostasis and for protecting the body from exogenous and endogenous toxins, any alteration in its function may have potential effects on extrahepatic systems [37]. Cancer may occur in people who are exposed to more free radicals due to hepatic aging [38]. It is possible to be diagnosed with cancer during follow-up if someone has occult cancer at baseline, resulting in a decrease in ALT levels [38]. Therefore, the De Ritis Ratio can reflect cancer occurrences and developments.

The clinical value of the De Ritis Ratio as a cancer marker

In clinical practice, the De Ritis Ratio is typically an indicator of liver damage. However, in many studies, the De Ritis Ratio has also been identified as a valuable marker for different types of carcinomas.

De Ritis Ratio as prognostic marker

High preoperative De Ritis Ratio expression may be directly related to poor postoperative survival. The De Ritis Ratio was proposed as a useful prognosis indicator for nonmetastatic renal cell carcinoma (RCC) by Bezan

Table 3. Evaluation of the De Ritis Ratio as predictor of the therapeutic efficacy in cancers.

Author year	Study design	Pts. No.	Parameters evaluated	Types of cancer	Cutoff level	Follow-up/ progression rates	HR (95% CI)
Riedl et al. [69] 2020	p	202	De Ritis Ratio CA19-9	advanced PDAC	1.23	1-year/ low De Ritis Ratio: 81.3% high De Ritis Ratio: 94.9%	1.32 (1.00 - 1.75)
Sansa et al. [70] 2021	P	670	De Ritis Ratio HPV-DNA	HNSCC	1.37	5-years/ low De Ritis Ratio: 25.0% high De Ritis Ratio: 16.6%	1.97 (1.42 - 2.75)
Zhang et al. [71] 2021	R	160	De Ritis Ratio LDH	NPC	NA	1-year/ training cohorts: 13.21% validation cohorts: 16.67%	NA
Kang et al. [72] 2018	R	579	De Ritis Ratio	metastatic RCC	1.2	NA	1.69 (1.19 - 2.39

PDAC - pancreatic ductal adenocarcinoma, HPV - human papilloma virus, HNSCC - head and neck squamous cell carcinomas, NPC - naso-pharyngeal carcinoma, RM - recurrent or metastatic, LDH - lactate dehydrogenase, RCC - renal cell carcinoma.

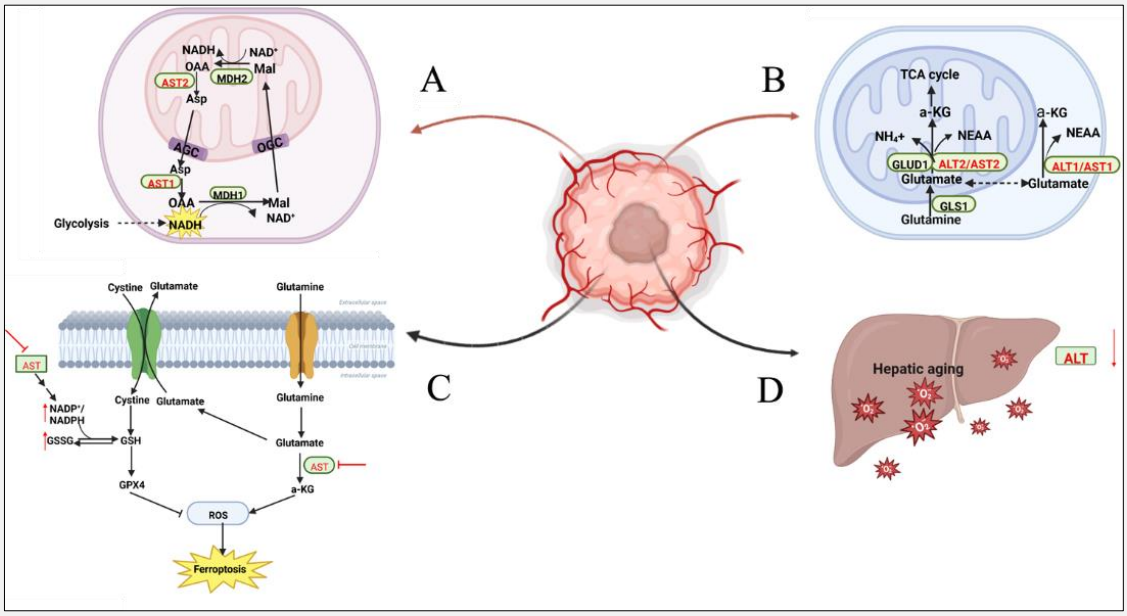

Figure 1. Pathogenesis of the De Ritis Ratio involved in cancer could be categorized into four mechanisms: A - Glycolysis: up-regulated aerobic glycolysis is a hallmark of cancers. The NADH produced by glycolysis transportation from the cytoplasm to mitochondria through the MAS, AST plays a role in MAS through converted OAA into aspartate. B - Glutaminolysis: Gln converted into Glu by GLS1, then converted to α-kG by ALT/AST, which replenish the TCA cycle. C - Ferroptosis: AST re-pression increases intracellular ROS accumulation via GSH-GPX4 pathway or Glu-α-kG pathway that leads to ferroptosis. D - Oxidative stress: ALT level is progressive reduction with hepatic aging, and hepatic aging may produce more free radicals and oxidative stress.

NADH - nicotinamide adenine dinucleotide, MAS - malate-aspartate shuttle, OAA - oxaloacetate, MDH1 - cytosolic malate dehydrogenase, MDH2 - mitochondrial malate dehydrogenase, Asp - aspartate, OGC - malate-2-oxoglutarate carrier, AGC - aspartate-glutamate carrier, GLn - glutamine, Glu - glutamate, GLS1 - glutaminase, GLUD1 - glutamate dehydrogenase, NEAA - nonessential amino acid, α-kG - α-ketoglutarate, TCA cycle - tricarboxylic cycle, GSH - glutathione, GSSG - oxidized glutathione, GPX4 - glutathione peroxidase-4, ROS - reactive oxygen species.
This image was created using BioRender (http://biorender.com/; accessed on December 14, 2022).

A in 2015, which represented the first evaluation of the De Ritis Ratio's prognostic potential. An increased preoperative De Ritis Ratio is closely related to unfavorable prognosis in nonmetastatic RCC [39]. This was confirmed subsequently in another propensity score-matched study by Lee et al. They found in the propensity score-matched cohort of 1,547 localized RCC patients, patients with increased De Ritis Ratio had poorer progression-free survival (PFS), over survival (OS), and cancer specific survival (CSS) outcomes (all $p < 0.001$) [40]. The predictive value of the De Ritis Ratio for cancer prognosis has been widely researched in multiple types of cancer [41-44]. Li et al. collected the preoperative De Ritis Ratio of 9,08l localized upper tract urothelial cancer (UTUC) patients and conducted postoperative follow-up, revealing that high expression of the De Ritis Ratio negatively affected survival outcomes, including PFS, CSS, and OS [45]. A multicenter study analyzed 1,940 patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) who were treated with hepatectomy from four hospitals in west China. Patients with HBV-related HCC following hepatectomy can be accurately predicted by baseline HBV-DNA and the De Ritis Ratio classifications. Regardless of HBV-DNA load, patients with a De Ritis Ratio > 1 had a poor prognosis [46]. Another study revealed that CSS and OS were significantly shorter for upper urinary tract urothelial carcinoma patients with De Ritis Ratio level exceeding the 1.6 threshold [47]. More studies indicated the cutoff of the De Ritis Ratio as a prognostic marker in different cancers is different, such as 1.44 fororal and oropharyngeal cancer [48], 1.35 for testicular cancer and non-muscle invasive bladder cancer [49,50], 1.1 for bladder urothelial carcinoma [51], and 1.5 for upper tract urothelial cancer [52]. Moreover, preoperative De Ritis Ratio was significantly related to recurrence-free survival after nephroureterectomy in patients with upper urinary tract urothelial carcinoma and in patients with nonmuscle invasive bladder cancer following transurethral resection [53,54].

Pre-to-postoperative dynamic detection of the De Ritis Ratio has a stronger prognostic value. In one study, 670 patients undergoing radical nephrectomy for nonmetastatic RCC were investigated, revealing that the pre-to-postoperative dynamics of the De Ritis Ratio showed a significant prognostic value for CSS and OS, while preoperative De Ritis Ratio alone was not sufficient for predicting prognosis [55].

Elevated De Ritis Ratio is more likely to be found in cancer patients with unfavorable clinicopathologic features such as high tumor grade, large tumor size. The De Ritis Ratio is related to significantly worse pathologic outcomes when it comes to higher pathologic stages of cancer. The serum De Ritis Ratio has been found to be valid indicator of disease-free survival in stage II and stage III colorectal cancer patients (HR = 1.53, $p = 0.026$ in multivariate analysis; HR = 1.63, $p = 0.052$ in univariate analysis), but no statistically significant association between the De Ritis Ratio and OS [56]. The De Ritis Ratio was significantly correlated with age, tumor volume, tumor size, tumor volume percent, TNM stage, liver cirrhosis and can predict OS rate of primary hepatic carcinoma patients [57]. A study on localized cancer demonstrated that higher De Ritis Ratio was associated with older age, Gleason Score, higher tumor stages, positive surgical margin, and lymph node metastasis, presence of seminal invasion [58]. Canat et al. reported that a significant association was found between a high preoperative De Ritis Ratio with renal vein invasion, renal pelvis involvement, and renal capsule infiltration in non-metastatic RCC patients. However, there was no influence of De Ritis Ratio on OS or CSS risks [59].

Metastasis is the leading cause of poor outcomes in patients with cancer. De Ritis Ratio could help predict metastasis under the assumption of non-invasive, non-destructive early detection. A retrospective study found testicular cancer patients with increased De Ritis Ratio (≥ 1.3) were more likely to develop organ metastasis and retroperitoneal lymph node involvement [60]. Ha YS and colleagues analyzed clinicopathological data of patients with nonmetastatic rothelial bladder cancer who had undergone radical cystectomy. They signed that the De Ritis Ratio was independently linked to metastasis (HR, 2.389, $p = 0.018$) [61].

Prognostic models based on the De Ritis Ratio combined with other parameters provide clinically valuable information on patient outcome of cancer. Li L and colleagues established a nomogram model containing age, clinical stage, and De Ritis Ratio to predict overall survival of gastric cancer patients. The nomogram model provided greater overall benefits than TNM staging across a broad range of threshold probabilities [62]. Another nomogram model included the De Ritis Ratio, histological subtype, metastasis at surgery, collecting system invasion, and serum albumin could well predict OS in patients with renal cell carcinoma and venous tumor thrombus after operation [63] (Supplemental Table 1).

The De Ritis Ratio as a predictor of the incidence risk

The De Ritis Ratio is closely related to the incidence of various types of cancers and can serve as a predictor of incidence risk. The results of a large 14-year prospective cohort study of Korean men published in 2010 showed for the first time that smoking, alcohol consumption, and the De Ritis Ratio are independent risk factors for esophageal cancer in men. Among these three risk factors, there was an additive, not multiplicative interaction [6]. Another large retrospective cohort study involving 85,658 participants confirmed that men with higher De Ritis Ratios (> 1.19) tended to be more likely to develop cancer in the future, especially among regular drinkers. In women, irrespective of alcohol consumption, the De Ritis Ratio had no association with cancer development [38]. A study enrolling 494 patients with newly diagnosed cancer indicated that the population with increased De Ritis Ratio had a higher cumula-

tive cancer incidence rate during follow-up period [64]. In patients with a De Ritis Ratio > 1.155, the incidence risk of prostate cancer (PCa) was higher. The De Ritis Ratio played an important role in predicting the PCa incidence risk and could be used to predict PCa incidence [65]. The latest study indicated that the FIB-4 index which is calculated based on patients' age, De Ritis Ratio, and platelet was related to an increased risk of liver cancer and could estimate liver cancer risk even among unselected patients who did not have pre-existing liver disease [66] (Table 1).

The De Ritis Ratio as diagnostic marker

The diagnosis performance of De Ritis Ratio is limited, which needs to be combined with other indicators for cancer diagnosis. A study showed that when the De Ritis Ratio is combined with gamma-glutamyl transferase (GGT) activity and GGT/ALT was to help in the early diagnosis of primary hepatic carcinoma (PHC). In patients with chronic hepatitis B and cirrhosis after hepatitis B, when GGT was increased, GGT/ALT and De Ritis Ratio were both greater than 1, even if AFP was negative, PHC should also be considered [67]. Another study showed HCC had higher values of serum AFP, serum talin-1, De Ritis Ratio, FIB4 score, and fibro-α score than those with cirrhosis. The De Ritis Ratio had 86% sensitivity and 86.4% specificity with a 0.855 cutoff for detection of HCC [68] (Table2).

The De Ritis Ratio as predictor of the therapeutic efficacy

Chemotherapy and radiotherapy are the primary clinical treatments in addition to surgery for cancer. The De Ritis Ratio cannot only forecast the prognosis following chemotherapy and radiotherapy, but can also be used to evaluate whether there is chemotherapy or radiotherapy resistance. A post hoc analysis of a multicenter, prospective, noninterventional study showed that patients with advanced pancreatic ductal adenocarcinoma treated with ingemcitabine/nab-paclitaxel, the pretreatment De Ritis Ratio predicts poor outcome and response rates [69]. Sansa et al. found that head and neck squamous cell carcinomas with a high De Ritis Ratio had almost twice the risk of local recurrence following radiotherapy, suggesting that these cancers with high De Ritis Ratio were less sensitive to radiotherapy [70]. A score prediction model combined with the dynamic change of lactate dehydrogenase and De Ritis Ratio showed predictive and prognostic value for nasopharyngeal carcinoma patients who were treated with programmed cell death protein 1 inhibitors [71].

De Ritis Ratio levels also have the potential to reflect the therapy efficacy of immunotherapy. In patients treated with first-line systemic tyrosine kinase inhibitors for metastatic renal cell carcinoma, the De Ritis Ratio was higher (≥ 1.2), the CSS and OS outcomes were poorer [72] (Table 3).

De Ritis Ratio may predict postoperative complications

Patients with postoperative acute kidney injury (AKI) had higher mean preoperative serum De Ritis Ratios than patients without post-operative AKI. The De Ritis Ratio of 1.29 was the most suitable cutoff point to predict postoperative AKI. Pre-operative De Ritis Ratio could be used as a noninvasive predictor of postoperative AKI risk [73].

CONCLUSION

The De Ritis Ratio plays a significant role in prognosing, diagnosing, and predicting of cancers, especially solid cancers. Its relevance today may be strengthened because serum transaminase estimations are now one of the least expensive and available laboratory tests and all laboratory information systems can easily do the calculations. However, the clinical significance of the De Ritis Ratio should be comprehensively considered through clinical information analysis because liver diseases, cardiovascular disease, and metabolic syndrome, as well as serum hemolysis and alcohol use, may influence the level of the De Ritis Ratio. As a predictor, the De Ritis Ratio has been extensively studied in the last decade. The increased De Ritis Ratio level indicates cancer stage progression and signifies a poor prognosis. Other clinicopathological features of cancers are also significantly associated with serum De Ritis Ratio, and preoperative or postoperative De Ritis Ratio levels could predict postoperative survival. The efficacy of chemotherapy and radiotherapy in cancer could all be well assessed by serum De Ritis Ratio levels. In addition, the De Ritis Ratio is one of the most crucial variables in predicting cancer risk. However, the value of the De Ritis Ratio in cancer diagnosis is limited and needs to be combined with other indicators to improve performance.

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This is a Review Article. The Institutional Review Board of Gansu Provincial Hospital has confirmed that no ethical approval is required.

Declaration of Interest:

The authors have no relevant financial or non-financial interests to disclose.

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