


A High De Ritis Ratio is Associated with Mortality in Adult Trauma Patients

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Introduction: The De Ritis ratio, which is the ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT), has been suggested as a potential prognostic marker for various diseases. This study aimed to investigate the association between the De Ritis ratio and in-hospital mortality in adult trauma patients.

Methods: A total of 17,472 adult trauma patients hospitalized between January 1, 2009, and December 31, 2020, were allocated into groups according to the De Ritis ratio. The normal range of the De Ritis ratio was calculated from 3320 individuals in the National Taiwan Biobank. Statistical analyses were performed using SPSS software.

Results: Patients with a De Ritis ratio >1.6 had a significantly higher in-hospital mortality rate (7.3% vs 1.5%, odds ratio 5.29; Q1–Q3 2.72–10.30; $p < 0.001$) and a 2.71-fold higher in-hospital mortality rate (Q1–Q3 1.24–5.92; $p = 0.012$), after adjusting for sex, age, comorbidities, consciousness level, and injury severity, than those with a De Ritis ratio within the reference values.

Discussion: This study revealed that a De Ritis ratio >1.6 may serve as an early prognostic tool to identify adult trauma patients at high risk of in-hospital mortality.

Keywords: aspartate aminotransferase, AST, alanine aminotransferase, ALT, De Ritis ratio, in-hospital mortality, trauma

Introduction

The liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are commonly used to assess liver activity in individuals with different liver disorders.^{1–4} The majority of ALT is located in the cytoplasm of hepatocytes, and an elevated blood level of ALT suggests parenchymal liver disease with liver-specific malfunction. AST, on the other hand, is found in tissues other than the liver, including the brain, heart, kidneys, and skeletal muscle.⁵ Changes in AST levels are involved in systemic disorders other than parenchymal liver disease, such as ischemia-reperfusion injury, increased oxidative stress, and metabolic disorder.^{6–8}

Because ALT levels particularly suggest parenchymal liver disease, whereas AST levels are associated with various organs and thus impacted by numerous diseases, variations in these two enzymes may differ between diseases.⁵ Fernando De Ritis suggested the De Ritis ratio, a measure of blood AST and ALT values, for the detection of viral hepatitis in 1957.⁹ In addition, this ratio has been shown to be helpful in distinguishing between diverse sources of liver disease^{5,10,11} and is an important predictive factor in the management of a variety of cancer^{12–15} and non-malignant illnesses.^{6–8} The De Ritis ratio may be a proxy measure for ischemia end-organ damage¹⁶ and offers useful information for risk evaluations of patients with cardiovascular disease,^{16–18} cardiac failure,¹⁹ acute renal injury,^{20–22} sepsis,²³ and even COVID-19.^{24–27}

Although the ratio of ALT to other liver-related enzymes including alkaline phosphatase, gamma glutamyl transpeptidase, and glutamate dehydrogenase has been extensively studied, the De Ritis ratio is the only enzyme ratio that has withstood the test of time and is still widely used in clinical settings.⁵ However, the De Ritis ratio has not been studied in patients with trauma injuries, with the exception of two studies showing its utility in forecasting mortality in patients with major burn injuries²⁸ and after burn surgery²⁹. The objective of this observational research was to determine the

relationship between the De Ritis ratio at admission and the results of admitted trauma patients using a database from a trauma registry. A large-scale community-based sample from the Taiwan Biobank, the biggest national biobank in Taiwan³⁰ was used to determine the usual range of the De Ritis ratio. This research showed that a De Ritis ratio greater than or equal to 1.60 may be used as a predictive instrument to identify adult trauma patients with a high in-hospital mortality risk.

Materials and Methods

Population Research and Data Gathering

First, a study was conducted to establish the typical range of the De Ritis ratio using de-identified health data of adult patients from a large-scale community-based sample from Taiwan Biobank, the biggest national biobank in Taiwan. The Taiwan Biobank is managed by the Taiwanese government in order to attract Taiwanese participants and provide chances for joint study to primary scientists.^{30,31} Each Taiwan Biobank member completed an authorized informed consent document, and data was gathered in accordance with applicable government laws.³¹ From Oct 24, 2012 till June 30, 2022, 172,078 equally dispersed voluntary donors from northern, southern, and eastern Taiwan, correspondingly, were recruited. We requested the data of 3400 participants based on the criterion of randomly selected individuals having blood laboratory data, with a male-to-female ratio of 1:1 and the exclusion of malignant patients. The blood values of AST and ALT, as well as the calculated De Ritis ratio, were gathered from 3320 Taiwan Biobank participants. The 95% confidence interval (CI) of the De Ritis ratio of normal individuals from the biobank served as the standard for selecting the control group from the trauma patient cohort. Before the research was conducted, Chang Gung Memorial Hospital's Institutional Review Board (IRB) authorized the procedure (approval numbers 201800396B0 and 202100842B0). The necessity for specific patient permission was removed due to the retrospective nature of this research, in accordance with the IRB and Taiwan Biobank rule.

In addition, we included admitted adult patients (equal or more than 20 years) with all types of trauma who were registered in the hospital's Trauma Registration System in a single trauma center^{32–34} between January 1, 2009 and December 31, 2020 (Figure 1). After excluding patients who lacked AST or ALT data ($n = 19,295$) and those with burns ($n = 981$), hanging injuries ($n = 17$), and who drowned ($n = 2$), there were 17,472 patients with traumatic injuries in the study population. Patients' medical information was obtained from the hospital's trauma registry, including sex, age, preexisting comorbidities (diabetes mellitus [DM], hypertension [HTN], coronary artery disease [CAD], cerebrovascular accident [CVA], congestive heart failure [CHF], and end-stage renal disease [ESRD]), serum AST and ALT levels (U/L)

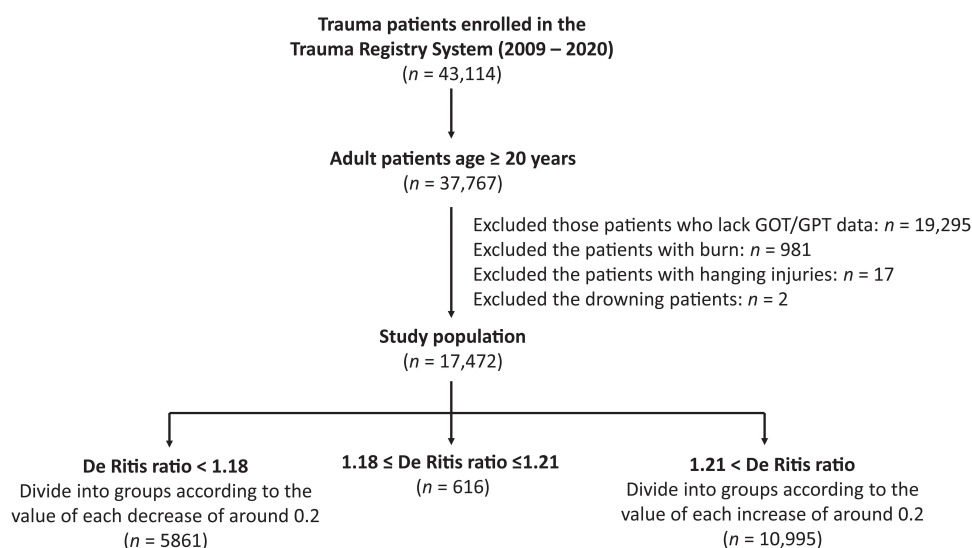


Figure 1 Diagram depicting the addition of admitted adult patients with all types of trauma from the Trauma Registration System and the distribution of these patients into three categories according to the De Ritis ratio.

upon arrival at the emergency room, derived De Ritis ratio, the conscious level of Glasgow Coma Scale (GCS) score, the injury severity by Injury Severity Score (ISS), and in-hospital mortality. The research population was divided into groups of patients with a De Ritis ratio between 1.18–1.21 ($n = 616$), < 1.18 ($n = 5861$), and > 1.21 ($n = 10,995$), following the selection of the control group (which had a mean De Ritis ratio of 1.20 and a 95% confidence interval of 1.18–1.21) as described earlier. The latter two divisions were split into categories based on the value of each decline or rise, using periods of about 0.2.

Statistical Analyses

For all statistical studies, Windows SPSS statistical software (version 23.0; IBM Inc., Chicago, IL, USA) was utilized. Categorical data were analyzed using two-sided Fisher's exact test. Using the Kolmogorov–Smirnov test, the normalization of the continuously dispersed factors was assessed. Analysis of variance with Bonferroni post-hoc adjustment was used for normally distributed continuous data, while the Mann–Whitney *U*-test was used for non-normally distributed continuous data. Continuous and non-continuous data are presented as mean with standard deviation or median with interquartile range, respectively (IQR; Q1–Q3). Mortality within the hospital was the main result of this research. The odds ratio (ORs) of death was computed using a 95% confidence range. The primary outcome of this study is in-hospital mortality. Using logistic regression, the adjusted odds ratio (AOR) of death was determined, adjusting for factors with substantial variations in patient injury features. The log-rank (Mantel-Cox) test and Kaplan-Meier curves were used to evaluate the statistical significance of the time to mortality between patients with high De Ritis ratio vs those within the reference De Ritis ratio. In all studies, a two-tailed *p* value 0.05 was deemed significant.

Results

De Ritis Ratio of the Patients in the Taiwan Biobank

1330 (40.1%) of the 3320 sample Taiwan Biobank respondents were male, while 1990 (59.9%) were female. The average age of the patients was 57.6 ± 7.10 years (mean \pm SD). The mean serum AST and ALT values were 25.7 ± 12.8 U/L and 24.7 ± 18.9 U/L, respectively, and the mean De Ritis ratio was 1.20 ± 0.43 (mean \pm SD). These individuals' 95% confidence interval for the De Ritis ratio was 1.18–1.21, which was used to reflect the De Ritis ratio of the overall community.

Outcomes of the Trauma Patients According to Stratified De Ritis Ratio

As shown in Table 1, 1.5% (9/616) of individuals with a De Ritis ratio between 1.18 and 1.21 died. There was no statistically significant variation in the death rate between the groups of individuals with De Ritis ratios between 1.21 and 1.4 and between 1.4 and 1.6. Those with a De Ritis ratio > 1.6 had a substantially increased in-hospital mortality rate, and

Table 1 The Study Population Groups According to De Ritis Ratio and the Associated Odds of In-hospital Mortality Compared to Those Within the Reference De Ritis Ratio (1.18–1.21)

	n	Death, n (%)	OR (95% CI)	P
De Ritis ratio < 0.4	41	2(4.9)	3.50(0.72–16.56)	0.099
$0.4 \leq$ De Ritis ratio < 0.6	235	2(0.9)	0.58(0.12–2.70)	0.481
$0.6 \leq$ De Ritis ratio < 0.8	1023	11(1.1)	0.73(0.30–1.78)	0.491
$0.8 \leq$ De Ritis ratio < 1.0	1838	24(1.3)	0.89(0.41–1.93)	0.772
$1.0 \leq$ De Ritis ratio < 1.18	2724	39(1.4)	0.98(0.47–2.03)	0.956
$1.18 \leq$ De Ritis ratio ≤ 1.21	616	9(1.5)	–	–
$1.21 <$ De Ritis ratio ≤ 1.4	2964	72(2.4)	1.68(0.84–3.38)	0.142
$1.4 <$ De Ritis ratio ≤ 1.6	2629	74(2.8)	1.95(0.97–3.92)	0.055
$1.6 <$ De Ritis ratio ≤ 1.8	1854	95(5.1)	3.64(1.83–7.26)	< 0.001

(Continued)

Table 1 (Continued).

	n	Death, n (%)	OR (95% CI)	P
1.8 < De Ritis ratio ≤ 2.0	1342	80(6.0)	4.28(2.13–8.57)	<0.001
2.0 < De Ritis ratio ≤ 2.2	708	52(7.3)	5.35(2.61–10.94)	<0.001
2.2 < De Ritis ratio ≤ 2.4	473	36(7.6)	5.56(2.65–11.65)	<0.001
2.4 < De Ritis ratio ≤ 2.6	288	30(10.4)	7.84(3.67–16.75)	<0.001
2.6 < De Ritis ratio ≤ 2.8	185	18(9.7)	7.27(3.21–16.48)	<0.001
2.8 < De Ritis ratio ≤ 3.0	151	21(13.9)	10.90(4.88–24.33)	<0.001
3.0 < De Ritis ratio	401	61(15.2)	12.10(5.94–24.67)	<0.001

Note: The patients in the group with 1.18 a De Ritis ratio ≤ 1.21 were used as controls.

Abbreviations: CI, confidence interval; OR, odds ratio.

those with a larger De Ritis ratio had a higher risk of in-hospital mortality (Figure 2). Those with a De Ritis ratio between 2.0 and 2.2 had a 5.35-fold (95% CI 2.61 to 10.94) greater risk of in-hospital mortality compared to those within the standard De Ritis ratio, whereas those with a De Ritis ratio >3 had a 12.10-fold (95% CI 5.94 to 24.67) higher risk of in-hospital mortality.

Outcomes of Patients with a De Ritis Ratio >1.6

To minimize the impact of initial patient traits on the outcome assessment, we computed the adjusted in-hospital mortality rate of patients with a De Ritis ratio >1.6 versus those with a De Ritis ratio between 1.18 and 1.21. Patients with a De Ritis ratio greater than 1.6 were more likely to be female, were older, and had higher AST levels but lower ALT levels than those within the reference De Ritis ratio (Table 2). The rates of pre-existing conditions did not vary significantly, with the exception of CAD, which was greater in patients with a De Ritis ratio >1.6 than in patients within the standard De Ritis ratio. Patients with a De Ritis ratio >1.6 had a significantly lower GCS (median [IQR, Q3-Q3]: 15 [14–15] vs 15 [15–15], respectively; $p < 0.001$) but a higher ISS (9 [8–17] vs 9 [4–13]; $p < 0.001$) than those within the reference De Ritis ratio. Compared to individuals with a De Ritis ratio within the reference range, those with a ratio larger than 1.6 had a much higher death rate (7.3% vs 1.5%, OR: 5.29, Q1-Q3: 2.72–10.30; $p < 0.001$) and an adjusted in-hospital mortality rate (AOR: 2.71, Q1-Q3: 1.24–5.92; $p = 0.012$). This difference in the time to mortality was statistically significant between the groups of patients with a ratio larger than 1.6 and those with a ratio within the reference range ($p < 0.001$) on applying Log Rank (Mantel-Cox) analysis (Figure 3).

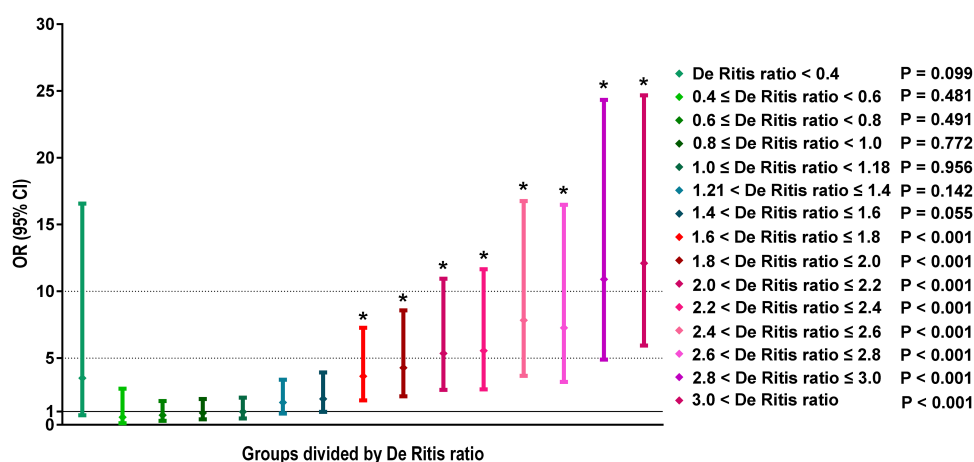


Figure 2 The associated odds of in-hospital mortality of patients who had been stratified by each decrease or increase of approximately 0.2 in the De Ritis ratio compared to those within the reference De Ritis ratio (1.18–1.21). *Indicate $P < 0.05$ when compared to those within the reference De Ritis ratio.

Table 2 The Injury and Patient Characteristics of Patients with a De Ritis Ratio >1.6 vs Those Within the Reference De Ritis Ratio (1.18–1.21)

Variables	De Ritis Ratio		OR (95% CI)	P
	>1.6 n = 5402	1.18–1.21 n = 616		
Gender				0.004
Male, n (%)	2881(53.3)	366(59.4)	0.78(0.66–0.93)	
Female, n (%)	2521(46.7)	250(40.6)	1.28(1.08–1.52)	
Age (years)	56.9±20.7	54.1±18.3	–	<0.001
AST (U/L)	75.0±179.2	55.1±93.5	–	<0.001
ALT (U/L)	33.6±55.8	44.4±63.5	–	<0.001
Comorbidities				
DM, n (%)	853(15.8)	114(18.5)	0.83(0.67–1.03)	0.082
HTN, n (%)	1745(32.3)	207(33.6)	0.94(0.79–1.13)	0.513
CAD, n (%)	277(5.1)	19(3.1)	1.70(1.06–2.72)	0.026
CVA, n (%)	262(4.9)	24(3.9)	1.26(0.82–1.93)	0.292
CHF, n (%)	54(1.0)	2(0.3)	3.10(0.75–12.75)	0.098
ESRD, n (%)	153(2.8)	14(2.3)	1.25(0.72–2.18)	0.423
GCS, median (IQR)	15(14–15)	15(15–15)	–	<0.001
≤8	663(12.3)	26(4.2)	3.18(2.13–4.74)	<0.001
9–12	401(7.4)	27(4.4)	1.75(1.17–2.61)	0.005
13–15	4338(80.3)	563(91.4)	0.38(0.29–0.51)	<0.001
ISS, median (IQR)	9(8–17)	9(4–13)	–	<0.001
1–15, n (%)	3381(62.6)	478(77.6)	0.48(0.40–0.59)	<0.001
16–24, n (%)	1259(23.3)	106(17.2)	1.46(1.18–1.82)	0.001
≥ 25, n (%)	762(14.1)	32(5.2)	3.00(2.08–4.31)	<0.001
Mortality, n (%)	393(7.3)	9(1.5)	5.29(2.72–10.30)	<0.001
AOR of mortality	–	–	2.71(1.24–5.92)	0.012

Note: AOR of mortality, mortality adjusted by gender, age, existence of CAD, GCS, and ISS.

Abbreviations: ALT, alanine aminotransferase; AOR, adjusted odds ratio; AST, aspartate aminotransferase; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CVA, cerebral vascular accident; DM, diabetes mellitus; ESRD, end-stage renal disease; GCS, Glasgow Coma Scale; HTN, hypertension; IQR, interquartile range; ISS, injury severity score; OR, odds ratio.

Discussion

This research showed that among adult trauma patients, those with a De Ritis ratio >1.6 had a substantially increased in-hospital mortality rate, and a greater De Ritis ratio was associated with an increased likelihood of death. Even after accounting for the variance in initial features of the research group, the adjusted death rate of patients with a De Ritis ratio >1.6 was 2.71 times that of those with a De Ritis ratio within the standard values. Hence, the De Ritis ratio is applicable not just to patients with liver injuries, but also to patients with other forms of trauma injuries. If the De Ritis ratio is more than 1.6 in adult trauma patients who have been injured by any type of trauma, this should serve as a warning indication that the patient is at an increased risk for in-hospital mortality.

For patients with liver damage, hepatocyte loss is raised above typical baseline values, with AST elevated at a rate greater than twofold that of ALT.³⁵ However, our Trauma Registration System had 1.54% of trauma victims with liver injury.³⁶ Notably, AST and ALT play important roles in carbohydrate and protein metabolism, which is a component of the malate-aspartate shuttle pathway that allows NADH/NAD⁺ conversion² and is involved in aerobic glycolysis, whereas ALT plays a crucial role in the glucose-alanine cycle to produce glucose to meet glucose requirements.⁵ Due to the fact that AST and ALT activate nucleotides and non-essential amino acids engaged in aerobic glycolysis and boost glutamine metabolism in growing cancer cells,^{37–40} the De Ritis ratio is associated with tumor metabolism in numerous tumors that utilize glucose.⁴¹ Therefore, we propose that an increased De Ritis ratio represents the need for glucose intake in trauma patients experiencing stress. Given that a multifactorial mechanism is more likely to account for the

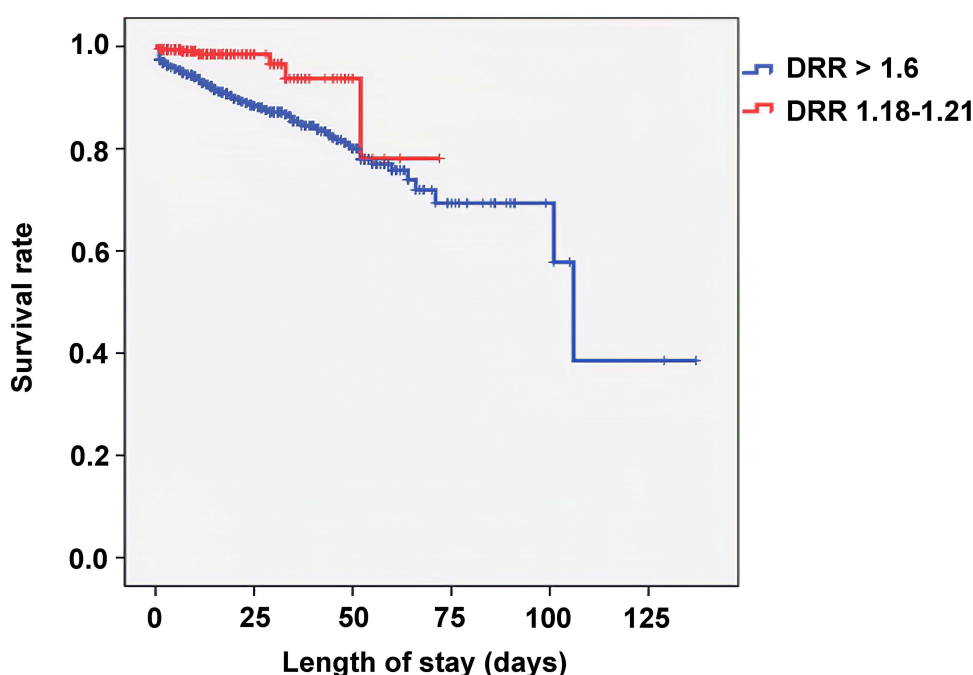


Figure 3 The log-rank (Mantel-Cox) test and Kaplan-Meier curves in the comparison of the time to mortality between patients with a ratio larger than 1.6 and those with a ratio within the reference range ($p < 0.001$).

higher De Ritis ratio, the idea of increased glucose uptake constitutes one of the potential mechanisms that will require more investigation in future studies.

There is currently no consensus on the reference ranges for the De Ritis ratio. In this research, the normal range of the De Ritis ratio was computed based on the normal population in a national biobank, and a De Ritis ratio of 1.6 was identified as the benchmark for identifying trauma patients with a greater chance of death. Clearly, the threshold number of the De Ritis ratio can differ significantly based on disease. For instance, among heart valve replacement surgery patients, a De Ritis ratio ≥ 1.19 on entry was substantially associated with bleeding propensity under warfarin treatment.⁴² A De Ritis ratio ≥ 1.2 suggested an increased risk for patients with acute myocardial infarction¹⁶ and forecasted both cancer-specific survival and total survival outcomes in patients treated for advanced renal cell carcinoma.⁴³ A De Ritis ratio ≥ 1.35 was a meaningful predictive indicator for chemotherapy-treated individuals with advanced prostate cancer.⁴⁴ A De Ritis ratio ≥ 1.5 is a major predictive factor for renal cell cancer patients undergoing surgery.⁴⁵ Following surgery, a threshold De Ritis ratio of 1.6 was found for overall and cancer-specific mortality in individuals with urothelial carcinoma of the upper urinary system.⁴⁶ Patients with peripheral vascular occlusive disease who had a De Ritis ratio greater than 1.67 had a twofold increased risk of developing critical limb ischemia.⁴⁷ As a predictive indicator for individuals with alcoholic hepatitis^{48,49} and distal cholangiocarcinoma,⁵⁰ a De Ritis ratio > 2.0 was utilized.

This research has several limitations. To begin, the way the retrospective study was set up could have introduced selection bias. Furthermore, a possible selection bias in the outcome assessment was introduced by measuring in-hospital mortality but not long-term mortality, since the latter is not present in the coded trauma database. In addition, the removal of individuals without entry AST and ALT values may have led to selection bias. Another disadvantage is the lack of time between the injury and the initial AST/ALT measurements in the hospital, given that De Ritis ratio temporal variations among individual individuals might vary greatly. In addition, a patient's De Ritis ratio may also change due to the existence of an undetected liver disease, the use of drugs that affect AST or ALT values, or even life-saving interventions like cardiopulmonary resuscitation (CPR). Since this study only included patients at one urban trauma center, its results may have limited relevance outside of that institution.

Conclusions

This research showed that a De Ritis ratio > 1.6 may be used as a predictive indicator to identify adult trauma patients at high risk for in-hospital mortality.

Data Sharing Statement

Data available on request.

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Disclosure

The authors declare that they have no competing interests.

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