

# The Portal-Venous Enhancement Ratio of the Adrenal Glands and Spleen as a Short-Term Predictor of Mortality in Intensive Care Patients

## Das portalvenöse Anreicherungsverhältnis von Nebennieren und Milz als kurzfristiger Mortalitätsprädiktor bei Intensivpatienten

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### Key words

intensive care unit, mortality prediction, adrenal gland, spleen

received 30.11.2021

accepted 12.04.2022

published online 08.06.2022

### Bibliography

Fortschr Röntgenstr 2022; 194: 1250–1257

DOI 10.1055/a-1830-7412

ISSN 1438-9029

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Georg Thieme Verlag KG, Rüdigerstraße 14,  
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### ABSTRACT

**Background** In critically ill ICU patients, initial results showed that opposite enhancement of the adrenal glands (↑) and spleen (↓) on portal venous CT scans was associated with increased mortality over the next days to a month, with short-term mortality being best predicted. The study aimed to validate the adrenal-to-spleen ratio determined in a pilot study concerning mortality prediction.

**Method** 371 portal venous CT scans of 203 ICU patients (127 men, age:  $68.1 \pm 14.4$  years) were included in the retrospective analysis. Region-of-interest (ROI)-based Hounsfield units of the adrenal glands and the spleen and their density ratio were evaluated. The Matthews correlation coefficient (MCC) and ROC analysis were used to establish a threshold for the adrenal-to-spleen ratio regarding mortality within 72 hours of imaging. The quality of the classification of survivors and deceased patients in the current collective based on the threshold determined in a pilot study and on the current threshold was determined. The precision-recall curve (PRC) was used to test the influence of the addition of patients with low vital risk on the ROC.

**Results** The current threshold of 1.37 for the adrenal-to-spleen ratio provides good discriminatory power between those who died and those who survived (MCC: 0.87; sensitivity: 83.7%; specificity: 99.1%; PPV: 93.2%; NPV: 97.6%) and differs only slightly from the threshold of 1.41 determined in the pilot study, which consequently has comparable discriminatory power.

**Conclusion** As a reproducible image-based prognostic marker, the portal venous adrenal-to-spleen ratio has a high predictive power for short-term death in ICU patients. It is, therefore, suitable as an indicator of high risk of death within 72 hours after imaging.

### Key Points:

- In cases of shock, CT perfusion changes of the abdominal organs can be observed.
- These changes are summarized under the term CT hypoperfusion complex.
- Organ enhancement ratios allow conclusions about the patient's short-term survival.
- The portal venous adrenal-to-spleen ratio is a sufficient prognostic mortality parameter.

### Citation Format

- Winzer R, Hoffmann R, Fedders D. The Portal-Venous Enhancement Ratio of the Adrenal Glands and Spleen as a Short-Term Predictor of Mortality in Intensive Care Patients. Fortschr Röntgenstr 2022; 194: 1250–1257

## ZUSAMMENFASSUNG

**Hintergrund** Bei vital bedrohten Intensivpatienten zeigten erste Ergebnisse, dass ein konträres Kontrastmittelverhalten von Nebennieren ( $\uparrow$ ) und Milz ( $\downarrow$ ) in der portalvenösen CT mit einer erhöhten Mortalität in den folgenden Tagen bis zu einem Monat assoziiert ist, wobei die kurzfristige Mortalität am besten vorhergesagt wurde. Ziel der Studie ist die Validierung des in einer Pilotstudie bestimmten Nebennieren-Milz-Dichteverhältnisses bezüglich der Mortalitätsvorhersage.

**Methoden** 371 portalvenöse CT-Scans von 203 Intensivpatienten (127 Männer, Alter:  $68,1 \pm 14,4$  Jahre) wurden in die retrospektive Analyse eingeschlossen. Ausgewertet wurden die Region-of-interest (ROI)-basierten Hounsfield-Einheiten von Nebennieren, Milz sowie deren Verhältnis. Mit dem Matthews-Korrelationskoeffizienten (MCC) und der ROC-Analyse wurde ein Schwellenwert für das Nebennieren-Milz-Verhältnis bezüglich der 72-Stunden-Mortalität bestimmt. Die Klassifika-

tionsgüte bezüglich Überlebenden und Versterbenden wurde am aktuellen Kollektiv für den in einer Pilotstudie ermittelten sowie dem aktuellen Schwellenwert bestimmt. Mit der Precision-Recall-Curve (PRC) wurde der Einfluss von Patienten mit geringer vitaler Gefährdung auf die ROC überprüft.

**Ergebnisse** Der aktuelle Schwellenwert von 1,37 für das Nebennieren-Milz-Verhältnis ergibt eine gute Trennschärfe zwischen Versterbenden und Überlebenden (MCC: 0,87; Sensitivität: 83,7 %; Spezifität: 99,1 %; PPV: 93,2 %; NPV: 97,6 %) und differiert nur gering vom in der Pilotstudie ermittelten Schwellenwert von 1,41.

**Schlussfolgerung** Das portalvenöse Nebennieren-Milz-Verhältnis hat als reproduzierbarer bildbasierter prognostischer Marker eine hohe Vorhersagekraft für das kurzfristige Versterben von Intensivpatienten. Er eignet sich daher als Indikator für ein hohes Risiko innerhalb von 72 h nach der Bildgebung zu versterben.

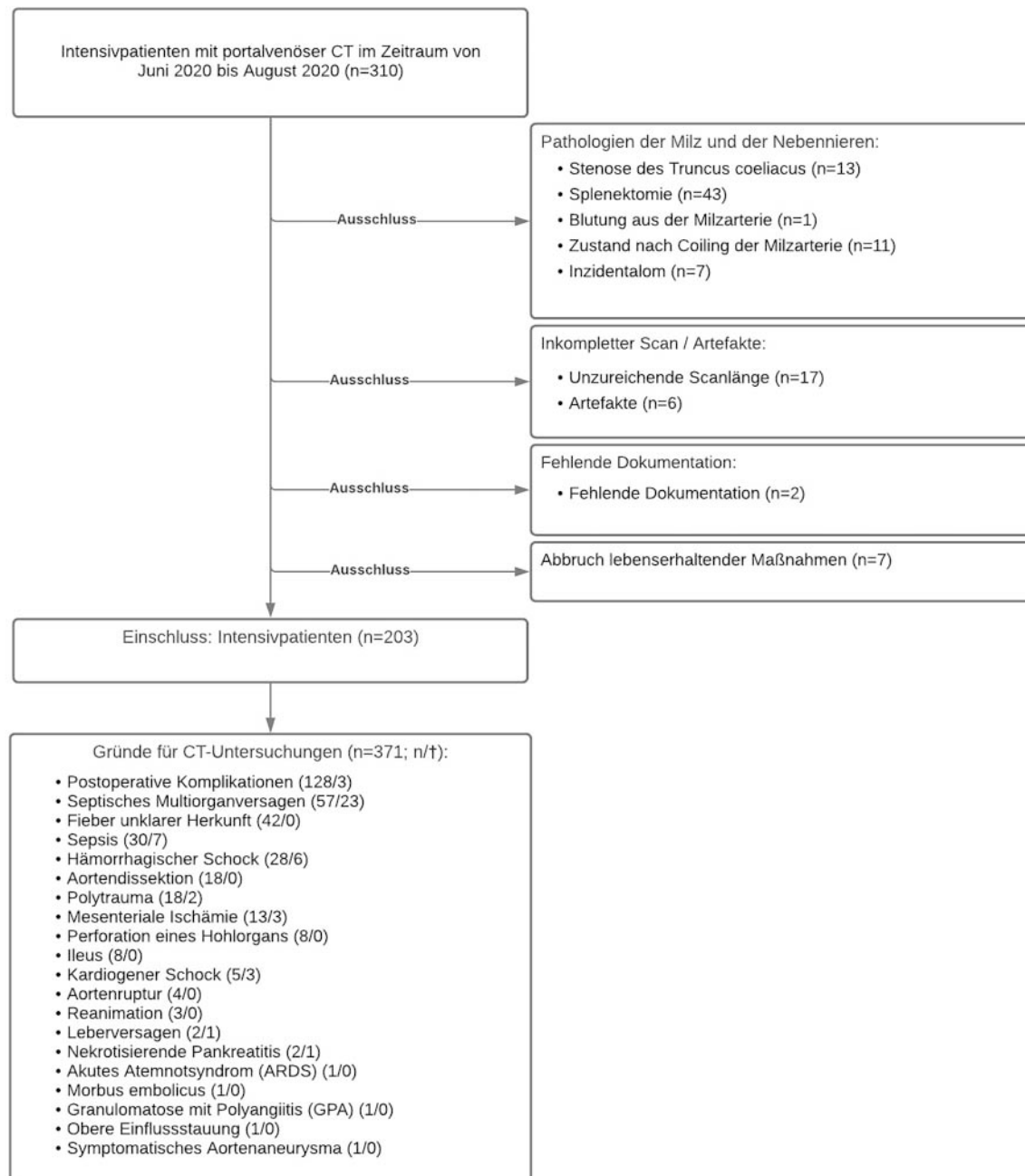
## Introduction

The CT hypoperfusion complex [1–5] includes a number of imaging features that can be seen when pronounced hypoperfusion is present in the case of organ conditions that are usually life-threatening. At the end of the 1980 s, the CT hypoperfusion complex was initially described in polytraumatized children. Perfusion changes in the gastrointestinal tract, pancreas, and spleen were seen in cases of hypovolemic shock [6]. The clinical signs of shock are often not reliable. Therefore, particularly in critical patients without shock symptoms, an image-based morphological indicator promised information about a decrease in a patient's overall hemodynamic condition and radiological identification of "patients at risk". Consequently, individual studies on ICU patients examining the classic "flat cava" sign of the vena cava [7] as well as additional organs were published. In 2020, Elst et al. stated that, even though it has been a long time since the sign was initially observed, there is still no consensus on the frequency or clinical relevance of this sign [8]. Reduced enhancement of the spleen [9], increased enhancement of the adrenal glands [10], and increased enhancement of the aorta [11, 12] are often seen in the CT hypoperfusion complex. Qualitative descriptions are based on ROI shy; (region of interest)-based analyses of the enhancement pattern of individual organs or measurements of organ and vascular diameters resulting in an elevated mortality risk in the group comparison. Arbitrary thresholds [13, 14] were used for classification purposes and allowed statements regarding individual risk to a limited degree [14].

The study presented here focuses on intensive care patients. In the clinical routine in radiology, we noticed hyperdense adrenal glands on contrast-enhanced CT in many of these patients with some of these patients dying in the following days. As a result of the different approaches used in previous studies regarding the selection of contrast phases and organs, we decided to perform a

systematic comparison of enhancement patterns in the arterial and portal venous phases on the basis of ROI-based measurements [15, 16]. We focused on the adrenal glands, the spleen, and the large abdominal vessels. In ROC (receiver operating characteristics) analyses, the portal venous contrast phase showed the greatest relationship between organ density values and mortality. In this phase organ densities already have a substantial predictive value regarding the risk of death within the first three days after imaging [15]. However, the quality of the prediction increases significantly when the organ density values are viewed in relation to one another or to the large abdominal vessels [16]. In a pilot study including 133 patients, the most significant parameter for short-term mortality prediction in critically ill patients was the adrenal-to-spleen ratio. If the threshold of 1.41 was exceeded, the probability of death was high [16] with the best prediction results being achieved regarding mortality within 72 hours of imaging.

The organ parameters could be easily and quickly measured and could also be effectively reproduced. Therefore, the adrenal-to-spleen ratio seemed to be a suitable image-based screening instrument for the identification of short-term life-threatening conditions in critically ill patients. However, this predictor has not yet been examined with respect to stability in a large and different study cohort. That was the goal of the present study. In the new cohort, any reason for imaging was taken into consideration to thus recruit a representative group of intensive care patients needing radiological imaging. The goal was to examine whether the threshold calculated in the pilot study from the adrenal-to-spleen ratio also allows good discrimination between deceased patients and survivors in the new cohort. We also examined whether the new threshold calculated based on the new cohort differed significantly from the threshold calculated in the pilot study and if there was a relevant difference in the prediction quality of the two thresholds regarding short-term survival.



► **Fig. 1** Study flowchart with numbers/reasons of included/excluded patients. † = number of deceased patients.

## Materials and Methods

### Patients and study design

The ethics committee approved the retrospective study (EK 414 092 019). We searched the radiology information system (RIS) at our facility for intensive care patients who underwent contrast-enhanced CT of the abdomen in the portal venous phase between June and August 2020. Patients with pathologies of the spleen and adrenal glands, a lack of documentation, and death due to termination of life-sustaining measures were excluded.

290 intensive care patients underwent an abdominal CT scan. 371 CT scans of 203 intensive care patients (127 men, age:  $68.1 \pm 14.4$  years old) met the inclusion criteria (► **Fig. 1**).

### CT image acquisition and post-processing

The patients were examined with a 128- or 192-slice scanner (Somatom Definition AS or Edge and Force, Siemens, Forchheim, Germany). All examinations were performed with 110 kV and automatic tube current modulation (CAREDose 4D, Siemens). The contrast agent was administered by injecting 1 ml/kg body weight

► **Table 1** Two-sample t-test results (equal sample variance)/Welch's t-test (unequal sample variance) for 24-, 48- and 72-hour mortality.

Survivors vs. Deceased patients	Adrenal glands (HU)	Spleen (HU)	Adrenal-to-spleen ratio
<b>24-hour mortality</b>	84.95 ± 24.96 vs. 113.60 ± 34.42 (Welch's t-Test; p = 0.0016)	90.79 ± 29.42 vs. 54.61 ± 20.71 (t-Test; p < 0.0001)	1.00 ± 0.50 vs. 2.58 ± 1.47 (Welch's t-Test; p = 0.0001)
<b>48-hour mortality</b>	83.72 ± 22.88 vs. 109.70 ± 38.86 (Welch's t-Test; p = 0.0002)	93.07 ± 28.00 vs. 57.48 ± 26.70 (t-Test; p < 0.0001)	0.94 ± 0.36 vs. 2.34 ± 1.29 (Welch's t-Test; p < 0.0001)
<b>72-hour mortality</b>	82.92 ± 22.49 vs. 108.52 ± 35.95 (Welch's t-Test; p < 0.0001)	94.47 ± 27.23 vs. 57.03 ± 25.65 (t-Test; p < 0.0001)	0.89 ± 0.16 vs. 2.32 ± 1.24 (Welch's t-Test; p < 0.0001)

of a non-ionic iodized contrast agent (Ultravist 370 mg/kg, Bayer Schering Pharma, Berlin, Germany or Solutrast 370 mg/kg, Bracco Imaging Germany GmbH, Constance, Germany) with a flow rate of 3–4 ml/s, followed by 50 ml of a saline solution. The portal venous phase was documented 70 seconds after the start of contrast injection and stored in our image archiving and communication system (IMPAX Agfa HealthCare, Bonn, Germany).

### Image evaluation

A radiologist with 4.5 years of experience in abdominal CT evaluated the CT examinations. The image data was evaluated on a PACS workstation (IMPAX Agfa HealthCare, Bonn, Germany). The contrast enhancement of the adrenal glands and the spleen was analyzed on images in the portal venous phase in 3-mm slices. For the quantitative analysis, the Hounsfield units (HU) were determined and averaged preferably in the center of each adrenal gland based on ROI measurements in axial slices. All measurements were performed using highly magnified images to avoid adjacent fat. The HU of the spleen was determined by placing three circular ROIs (2.0 cm<sup>2</sup>) on three different axial planes through the cranial, middle, and caudal third of the spleen in the portal venous phase [9]. Hypodense triangular regions on the periphery of the spleen caused by small splenic infarctions were not included in the measurement. The averaged HU value was used for the data analysis. The dimensionless adrenal-to-spleen ratio was defined by the average HU of the adrenal glands divided by the average HU of the spleen.

### Statistical analysis

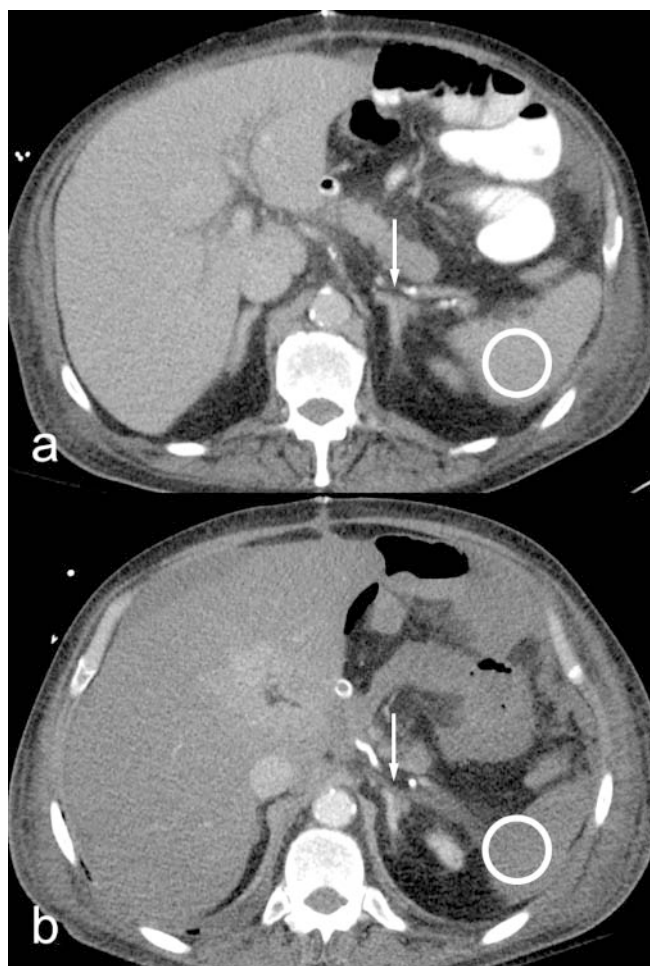
The data analysis was performed using MedCalc 19.6.1 (MedCalc Software bvba, Ostende, Belgium). Characteristics of the study population were given as means and standard deviations for continuous variables. After calculation of the adrenal-to-spleen ratio from the organ density values, the patients were classified based on the threshold defined in pilot studies for 72-hour (short-term) mortality. In addition, the corresponding Matthews correlation coefficients (MCCs) were calculated based on the data points and the assigned binary confusion matrices of the current ROC curve

for the 72-hour mortality, and the current threshold for the adrenal-to-spleen ratio, the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), as well as the positive and negative likelihood ratios were calculated for the maximum MCC [17]. The MCC was used as the maximization criterion in both the pilot study and the current study since a predictor reaches a high MCC in both balanced and unbalanced datasets when it correctly classifies most cases under consideration of all categories of the confusion matrix [18, 19]. The area under the precision-recall curve (PRC) was additionally calculated. The PRC as a performance metric should take into account the influence of the inclusion of survivors with an adrenal-to-spleen ratio below the threshold in the new cohort and the resulting potentially relevant increase in the imbalance between deceased patients and survivors. As a result of the increase in specificity, this can result in an ROC curve with an increased area under the ROC curve and thus a presumably better test result. The positive predictive value (= precision) addressed solely in the PRC is important for evaluating whether patients with an adrenal-to-spleen ratio above the threshold actually died. Only an improvement in the PRC indicated an actual improvement in test performance. The ROC, PRC, relative chance, and relative risk are shown for the best mortality prediction [20, 21]. Statistical significance was defined as p < 0.05.

## Results

### Patient outcome

20 intensive care patients (9.9 %) died within the first 24 hours, 38 patients (18.7 %) within 48 hours, and 49 patients (24.1 %) within 72 hours of imaging. For all time intervals, there was a significant difference in the group comparison between patients who died and patients who survived for the density of the spleen and adrenal glands as well as the adrenal-to-spleen ratio, with the group of survivors on average having an adrenal-to-spleen ratio of less than or equal to 1 while those who died had a value of approx. 2.4–2.6 (► **Table 1**, ► **Fig. 2**).



► **Fig. 2** **a** Initial abdominal portal venous CT scan of a 53-year-old patient after gastrectomy. The white arrow points to the adrenal gland (averaged adrenal density values:  $\approx 72$ ); the white circle lies in the spleen (averaged spleen density values:  $\approx 72$ ; adrenal-to-spleen ratio:  $\approx 1$ ). The patient survived the 72 hours following imaging. **b** Repeated abdominal portal venous CT scan of the same patient at a later time point due to vital endangerment. The white arrow points to the adrenal gland (averaged adrenal density values:  $\approx 107$ ); the white circle lies in the spleen (averaged spleen density values:  $\approx 24$ ; adrenal-to-spleen ratio:  $\approx 4.46$ ). The patient died of septic multiorgan failure within the next 72 hours.

### Validation of the prediction quality of the ROC-based adrenal-to-spleen ratio threshold determined in the pilot study regarding the 72-hour mortality prediction

Using the threshold for the adrenal-to-spleen ratio determined in the pilot study (1.41) to classify the data resulted in 96 % of intensive care patients (= accuracy) being classified correctly in the confusion matrix with regard to adrenal-to-spleen ratio over or under the threshold as well survival or death within 72 hours of imaging (sensitivity = 81.63 %, specificity = 99.07 %, PPV = 93.00 %, NPV = 97.30 %,  $+L = 87.62$ ,  $-L = 0.19$ ). As in the pilot study, the adrenal-to-spleen ratio provided good discriminatory power for mortality prediction (AUC = 0.97) with a high sensitivity and specificity. At a threshold of 1.41, 13 of 371 datasets were classified incorrectly (false positive: 3, false negative: 10).

### Accuracy of current ROC-based organ thresholds for the adrenal gland and spleen regarding 72-hour mortality prediction

With a low MCC and a very low sensitivity, the adrenal gland threshold on its own is not suitable as a prognostic factor (► **Table 2**). In general, the spleen has significantly better values for the individual predictive parameters but has insufficient sensitivity.

### Accuracy of the current ROC-based adrenal-to-spleen ratio threshold regarding 72-hour mortality prediction

The adrenal-to-spleen ratio threshold determined based on the current cohort (1.37) deviates only minimally from the threshold determined in the pilot study and has a slightly higher sensitivity of 83.67 % (95 % CI: 70.3–92.7) and an identical specificity of 99.07 % (95 % CI: 97.3–99.8) for the risk of death within the first 3 days after imaging (AUC = 0.97,  $p < 0.0001$ , MCC = 0.87) (► **Fig. 3**, ► **Table 2**).

The positive likelihood quotient was 89.55 (95 % CI: 28.9–278.9), the negative likelihood quotient was 0.16 (95 % CI: 0.09–0.3) with a resulting post-test probability of approximately 93 % with a pretest probability of 24.1 % (72-hour mortality). The relative chance was 544.95 (95 % CI: 139.01–2136.45); the relative risk was 38.09 (95 % CI: 19.12–75.87).

At a threshold of 1.37, 11 of 371 datasets were classified incorrectly (false positive: 3, false negative: 8).

### PRC analysis for 72-hour mortality

Using an adrenal-to-spleen ratio threshold of 1.37, the PRC showed (► **Fig. 4**) a high sensitivity and a high PPV (PRAUC = 0.922) with a correct prediction rate of 93.2 %.

## Discussion

The goal of the study was to evaluate the suitability of the adrenal-to-spleen ratio as an image-based screening parameter for predicting short-term mortality. The prediction quality of the adrenal-to-spleen ratio threshold determined in the pilot study and the newly determined adrenal-to-spleen ratio threshold was determined and compared based on a new cohort of intensive care patients. In contrast to the cohort in the pilot study with vital indication and triphasic emergency CT, intensive care patients without vital endangerment were also included in our study since an image-based prognostic parameter should be applicable for every intensive care patient.

Our results show that the thresholds of different cohorts deviate only slightly from one another, and the adrenal-to-spleen ratio can effectively predict short-term mortality even when including patients without vital endangerment.

The discrimination between survivors and deceased patients using the thresholds is highly accurate regardless of whether the threshold is from our own cohort or a different cohort. Therefore, the adrenal-to-spleen ratio threshold determined in the study collective (1.37) can identify critically ill patients with a high risk of death within 3 days of CT examination with high sensitivity



► **Table 2** Results of the ROC analysis of the studied mortality predictors. Cut-off values/ratios for 72-hour mortality prediction in the portal venous phase. AUC = area under the curve. SENS = sensitivity. SPEC = specificity. PPV = positive predictive value. NPV = negative predictive value. +LR = positive likelihood ratio. -LR = negative likelihood ratio. MCC = Matthews correlation coefficient. PRAUC = area under the precision-recall curve.

ROC analysis for 72-hour mortality predictors												
Predictor	Cut-off	AUC	SENS (%)	SPEC (%)	PPV (%)	NPV (%)	+LR	-LR	p-value	MCC	Accuracy	PRAUC
Adrenal glands	> 142 HU	0.730	16.33	98.76	66.70	88.60	13.14	0.85	<0.0001	0.29	87.88 %	0.262
Spleen	≤ 43 HU	0.870	44.9	99.69	95.70	92.20	144.57	0.55	<0.0001	0.63	92.45 %	0.704
Adrenal-to-spleen ratio	> 1.37	0.974	83.67	99.07	93.20	97.60	89.81	0.16	<0.0001	0.86	97.03 %	0.922

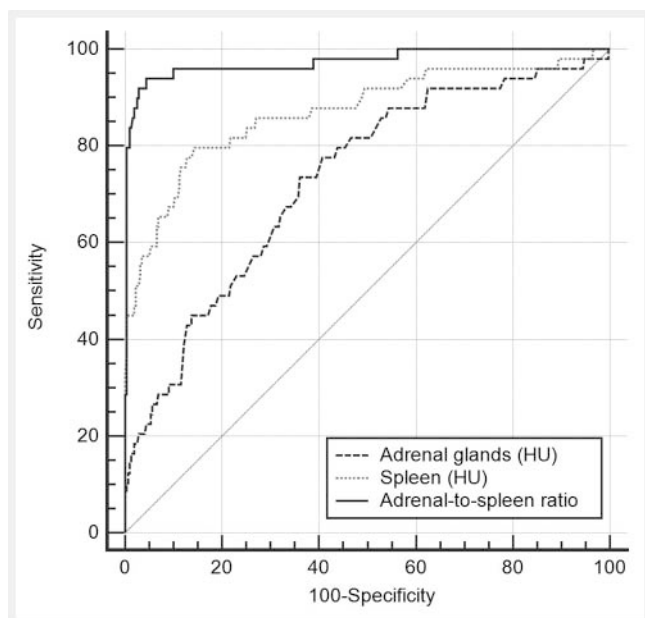
(83 %) and accuracy (93 %). The threshold determined in the pilot study (1.41) yields almost identical values with a sensitivity of 82 % and an accuracy of 93 %.

The spleen is a highly perfused organ that serves as a reservoir for thrombocytes and red blood cells [15]. In life-threatening conditions, activation of the sympathetic nervous system and humoral effects on the supply vessels and the spleen's own connective tissue seem to reduce arterial inflow and to increase venous outflow [6]. These drainage effects can be reflected in a decrease in density values after contrast administration as shown by our results from the comparison of means and the ROC analysis.

Patients with sepsis or septic organ failure make up the largest percentage (23 %) and one in three of these patients died. Di Serafini et al. emphasize that, even with comparable CT findings, the pathogenic mechanisms of hypotensive shock and septic shock are very different [22]. In general, elevated adrenal density values are associated with activation of the hypothalamic-pituitary-adrenal axis. However, it should be assumed that the hypothesis regarding greater enhancement of the adrenal glands due to increased secretion of catecholamines [10] in stressful situations is not sufficient. Therefore, Peng et al. observed a specific enhancement pattern of the adrenal glands on contrast-enhanced two-phase CT in a collective of 194 critically ill patients with septic shock [23]. Significantly less washout was seen in the central zone of the adrenal gland than in the peripheral zone in the arterial phase. Given the high mortality in both groups, the incidence of this sign was significantly higher in the septic shock group (almost 30 %) than in the hemorrhagic shock group (0 %). The authors postulated that specific pathophysiological changes occur during septic shock, with disrupted microcirculation of the adrenal gland in the arterial phase having a greater effect on the central zone of the adrenal gland with less enhancement than in the peripheral zone. Moreover, swelling of the adrenal gland is a sign of functional and structural damage. It is unclear whether the adrenal gland changes are an epiphenomenon of critical circulatory situations or have a direct connection to these.

A mortality factor that must be considered is the administration of exogenous catecholamines in intensive care patients since the vasoconstrictive effect can result in nonocclusive mesenteric ischemia in a relevant portion of intensive care patients, which is associated with a high mortality rate.

A limitation of the study is its retrospective design. A prospective study with additional inclusion of laboratory parameters, intensive care medication, and organ function scores would therefore be desirable. A further limitation is the measurement accuracy. The relatively small adrenal glands were digitally magnified in an attempt to minimize inaccuracies. Nonetheless, adjacent fat tissue and partial volume effects could have affected the measurements. Using a combination of spleen and adrenal measurements to determine the organ ratio can also result in error propagation. We tried to limit this by averaging spleen measurements and excluding triangular, wedge-shaped, and inhomogeneous regions. The measurements in this study were performed by a single radiologist since the intraclass correlation coefficient of previous studies (0.90) [15, 16] showed very high agreement among evaluators.

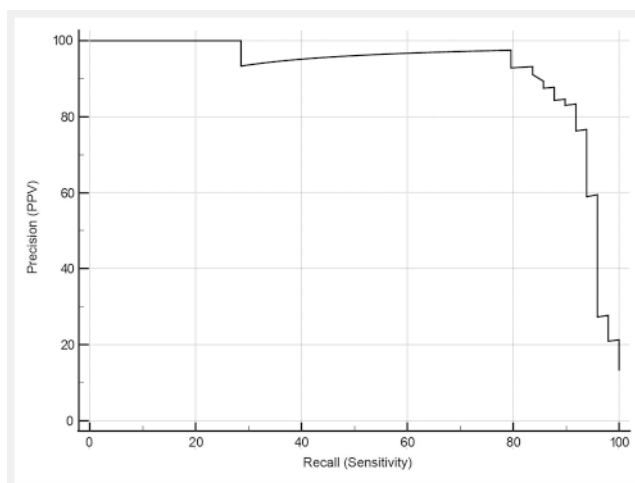


► **Fig. 3** Comparison of ROC curves regarding short-term mortality prediction: the adrenal-to-spleen ratio is best suited for short-term mortality prediction (AUC = 0.974). The area under the curve as a measure of diagnostic accuracy is significantly larger for the adrenal-to-spleen ratio than for the organ density values of the adrenals ( $\Delta$ AUC = 0.244;  $p < 0.0001$ ) and spleen ( $\Delta$ AUC = 0.104;  $p = 0.0013$ ).

The adrenal-to-spleen ratio takes into consideration the opposite enhancement patterns with decreasing density of the spleen and increasing density of the adrenal glands. The organ enhancement ratio has excellent discriminatory power for differentiating between deceased patients and survivors (AUC: 0.97) regarding the 3-day mortality rate. It can be assumed that a presumable cause, i. e., the condition of the intensive care patient, and effect, i. e., the death of the patient, are much more closely related in this short interval after imaging than at later points in time. The MCC was selected as a classifier because it is an adequate statistic in unbalanced datasets with a significantly higher number of patients who survived than died. The inclusion of patients requiring intensive care but without a vital indication and with low test results, i. e., in our case a low adrenal-to-spleen ratio, can generally significantly improve an ROC curve without increasing the sensitivity or the positive predictive value of the evaluated parameter. However, the use of the PRC as a further performance metric resulted in the adrenal-to-spleen ratio in the current cohort also being characterized by a good positive predictive value.

#### CLINICAL RELEVANCE

- In a substantial percentage of intensive care patients, opposite enhancement patterns of the adrenal glands and the spleen can be observed in the portal venous CT phase and are associated with an increased short-term mortality rate.
- Quantitative analysis of the adrenal-to-spleen ratio in critically ill patients provides retrospective information about



► **Fig. 4** Precision-recall curves (PRC) for the adrenal-to-spleen ratio (PRAUC = 0.922). For a threshold of  $> 1.37$ , the best ratio of precision (93.2 %) to sensitivity (83.67 %) is obtained.

the mortality and survival risk in the follow-up period since there is an extremely high risk of death within the next 72 hours if a threshold of approximately 1.4 is exceeded.

- The adrenal-to-spleen ratio can be easily and quickly determined and can be reliably reproduced.
- This radiological parameter can be used with reliable reproducibility in prospective studies to identify patients with an elevated risk of short-term death and can be included in therapeutic considerations of intensive care physicians.

#### Conflict of Interest

The authors declare that they have no conflict of interest.

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