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The hollow adrenal gland sign: a newly described enhancing pattern of the adrenal gland on dual-phase contrast-enhanced CT for predicting the prognosis of patients with septic shock

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Abstract

Objective To investigate the incidence, CT appearance, and implication for prognosis of the hollow adrenal gland sign (HAGS).

Methods A total of 194 patients with septic shock and 24 patients with hemorrhagic shock (as control group) were retrospectively included in this study and the patients with septic shock were further divided into four subgroups (digestive tract diseases, DTD, $n = 49$; biliary and pancreatic diseases, BPD, $n = 41$; postsurgical infection, PI, $n = 64$; and other diseases, OD, $n = 40$). All patients underwent a dual-phase contrast-enhanced CT within 1 week after diagnosis. CT findings and clinical records were reviewed. If in the arterial phase the central zone of adrenal gland showed temporally much lower attenuation than the peripheral zone, it was defined as HAGS positive. The incidence of the HAGS in patients with septic shock and hemorrhagic shock, the demographic features, and mortality between HAGS-positive and HAGS-negative patients in each group were respectively compared.

Results The incidence of the HAGS in the septic shock group was nearly 30%, while it was 0 in the hemorrhagic shock group. There was no significant difference in age or gender between HAGS-positive and HAGS-negative patients in all groups, while the mortality of HAGS-positive patients was significantly higher than that of HAGS-negative patients in each group ($p < 0.05$). The concordance correlation coefficient value showed excellent reproducibility of the two observers ($\kappa = 0.977$).

Conclusion The HAGS is specific and common on dual-phase contrast-enhanced CT in patients with septic shock and predicts a poor prognosis.

Key Points

- *The hollow adrenal gland sign (HAGS) newly described in this study is a special enhancing pattern of adrenal gland on dual-phase contrast-enhanced CT in patients with septic shock.*
- *The HAGS is characterized by the much lower-attenuated central zone of the adrenal gland in arterial phase and it showed excellent reproducibility between different observers.*
- *The HAGS is specific and common on dual-phase contrast-enhanced CT in patients with septic shock and predicts a poor prognosis.*

Keywords Shock, septic · Shock, hemorrhagic · Prognosis · Tomography, X-ray computed · Retrospective studies

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Abbreviations

BPD	Biliary and pancreatic diseases
CT	Computed tomography
DTD	Digestive tract diseases
HAGS	Hollow adrenal gland sign
HU	Hounsfield unit
ICU	Intensive care unit
OD	Other diseases
OR	Odds ratio
PI	Postsurgical infection
RAI	Relative adrenal insufficiency

Introduction

The adrenal gland and glucocorticoids play an important role in the stress response, especially in serious medical conditions such as trauma, severe infection, shock, and surgery [1–3]. However, among the sickest patients, because of hypothalamic pituitary adrenal axis dysfunction [4, 5] and increased glucocorticoid resistance [6, 7], the serum glucocorticoid level may be insufficient to meet the body's requirement even when adrenal glands are at full capacity, which is called relative adrenal insufficiency (RAI) [8, 9]. The diagnosis of RAI mainly depends on clinical manifestations and hormonal examinations [8–10]. However, since the body's requirement for glucocorticoids can vary greatly according to different disease types and severity, diagnosing RAI solely based on hormonal examinations is very difficult [11]. In addition, early symptoms of RAI can be obscure and lack specificity [12]. Nougaret et al [13, 14] measured the adrenal gland volume in patients with septic shock on CT. The authors found that the adrenal glands in patients with septic shock were obviously enlarged, and the absence of adrenal gland enlargement during sepsis suggests a poor prognosis, which might be related to RAI. There were also studies that found the hyperattenuation of adrenal glands after contrast enhancement was associated with a higher mortality rate in the setting of ICU patients [15], especially for polytraumatized patients [16].

During clinical image review of a group of consecutive patients with septic shock in our institution, we recognized a special enhancing pattern on dual-phase contrast-enhanced CT in some critically ill patients. The adrenal glands of these patients underwent heterogeneous enhancement with the central zone showing a much lower attenuation than the peripheral zone in the arterial phase. We named this pattern the hollow adrenal gland sign (HAGS) owing to the "hollow" enhancement of the adrenal gland in the arterial phase. This study aims to introduce the CT appearance of the HAGS and investigate its incidence in patients with septic shock. Additionally, its implication for prognosis will be revealed by a comparison of the clinical outcomes between HAGS-positive and HAGS-negative patients.

Materials and methods

Study patients

From May 2014 to May 2018, we retrospectively collected 233 consecutive patients with septic shock who were hospitalized in the ICU of our institution. We also collected 32 consecutive patients with hemorrhagic shock during the same period of time as the control group. All the patients underwent at least one dual-phase contrast-enhanced CT scan within 1 week after diagnosis of septic shock (diagnostic criteria as defined by Bone et al [17]). Briefly, a patient with septic shock should have hypotension secondary to a proven infection despite adequate fluid resuscitation, and vasopressors are required to maintain blood pressure [17] or hemorrhagic shock. Exclusion criteria included under 18 years old, with basic adrenal diseases (including adenoma or carcinoma, metastasis, infarction, tuberculosis, adrenal hemorrhage, history of adrenal surgery), with septic shock/sepsis and hemorrhagic shock at the same time.

Of the 233 patients with septic shock, 194 met the inclusion criteria, 39 were excluded because of age (29 patients), basic adrenal diseases (5 patients with adrenal adenoma, 1 patient with metastatic cancer, 2 patients with history of adrenal surgery), or the coexistence of hemorrhagic shock (2 patients). In the hemorrhagic shock group, 24 out of 32 patients met the inclusion criteria; the others were excluded because of age (3 patients), basic adrenal diseases (1 patient with adrenal adenoma), or the coexistence of septic shock/sepsis (4 patients). All patients' gender, age, and principal diagnosis were recorded. According to the principal diagnosis, patients in the septic shock group were further divided into the following subgroups: digestive tract diseases (DTD, including intestinal obstruction, digestive tract perforation, and intestinal necrosis, $n = 49$), biliary pancreatic disease (BPD, including biliary infection and pancreatitis, $n = 41$), postsurgical infection (PI, $n = 64$), and other diseases (OD, including pulmonary infection, urinary tract infection, complex abdominal infection, liver abscess, and graft versus host response, $n = 40$). The main study endpoint was the clinical outcome, either death or relief and discharge from the ICU (survival).

The study design was approved by the local ethics committee of anesthesia and intensive care. And all patients enrolled in this study provided written informed consent for participation. All procedures carried out in the study were in accordance with approved guidelines.

CT protocol

All patients were examined with a multislice spiral CT scanner (Aquilion 64, Canon Medical System) using the following scanning parameters: slice thickness, 0.5 mm; slice increments, 0.5 mm; pitch, 0.9; voltage, 120 kV; current, 180–250 mAs; and collimation, 64 × 0.5 mm. The contrast agent used in this study was iodinated contrast (Ultravist 300, Bayer-Schering), and the dosage was 70–90 ml based on the patient's body weight with an injection flow rate of 3.0 ml/s via an automatic injector, followed by a 40-ml bolus of saline solution. After contrast injection, images were acquired in a 35-s delay (the arterial phase) and a 65-s delay (venous phase).

The HAGS

The exact definition of the HAGS is as follows: in the arterial phase, the central zone of the adrenal gland shows less intense enhancement than does the peripheral zone; and in the venous phase, the whole adrenal gland is homogenously enhanced. Furthermore, there are two types: (a) the less intensely enhanced central zone is homogenous and forms a typical Y-shaped or I-shaped lower attenuated region (Figs. 1, 2); and (b) the central zone is heterogeneously enhanced and shows a mosaic appearance (Fig. 3). HAGS-positive patients were defined when the sign appeared on either side of adrenal gland; otherwise, they were defined as negative. If there were more than one examination in the duration of septic shock, once the sign was positive, the patient was defined as a HAGS-positive patient. The window level for image interpretation is 50–150 HU, and the window width is 120–300 HU. All images were independently qualitatively interpreted by two radiologists (with more than 10 years of experience), and discrepancies were resolved with consensus by a third radiologist (who also had more than 10 years of experience). All radiologists were blinded to the clinical outcome of the patients.

Statistical analysis

Data are presented as the means ± standard deviation or median and quartiles (25th–75th) as required. Data were analyzed by using independent-samples *t* test, the Mann–Whitney test, and the chi-squared or Fisher exact test after a population normality assessment using the Kolmogorov–Smirnov test. McNemar test and Cohen's kappa were used to rate interobserver agreement. Statistical analysis was performed by using the Statistical Package for Social Sciences for Windows Package 19.0. $p < 0.05$ was considered statistically significant.

Results

The demographic characteristics and incidence of the HAGS in both septic shock group and hemorrhagic shock group are reported in Table 1. There was no significant difference in age ($p = 0.557$) or gender composition ($p = 0.282$) between the septic shock group and the hemorrhagic shock group. And the incidence of the HAGS in septic shock group is significantly higher than that in the hemorrhagic shock group ($p = 0.001$): the former was nearly 30% while the latter was 0.

The demographic characteristics of each subgroup of patients with septic shock are reported in Table 2. The incidence of the HAGS in each subgroup was also around 30%. There was no significant difference in age ($p_t = 0.119$, $p_1 = 0.108$, $p_2 = 0.891$, $p_3 = 0.620$, $p_4 = 0.194$) or gender composition ($p_t = 0.463$, $p_1 = 0.584$, $p_2 = 0.524$, $p_3 = 0.961$, $p_4 = 0.816$)

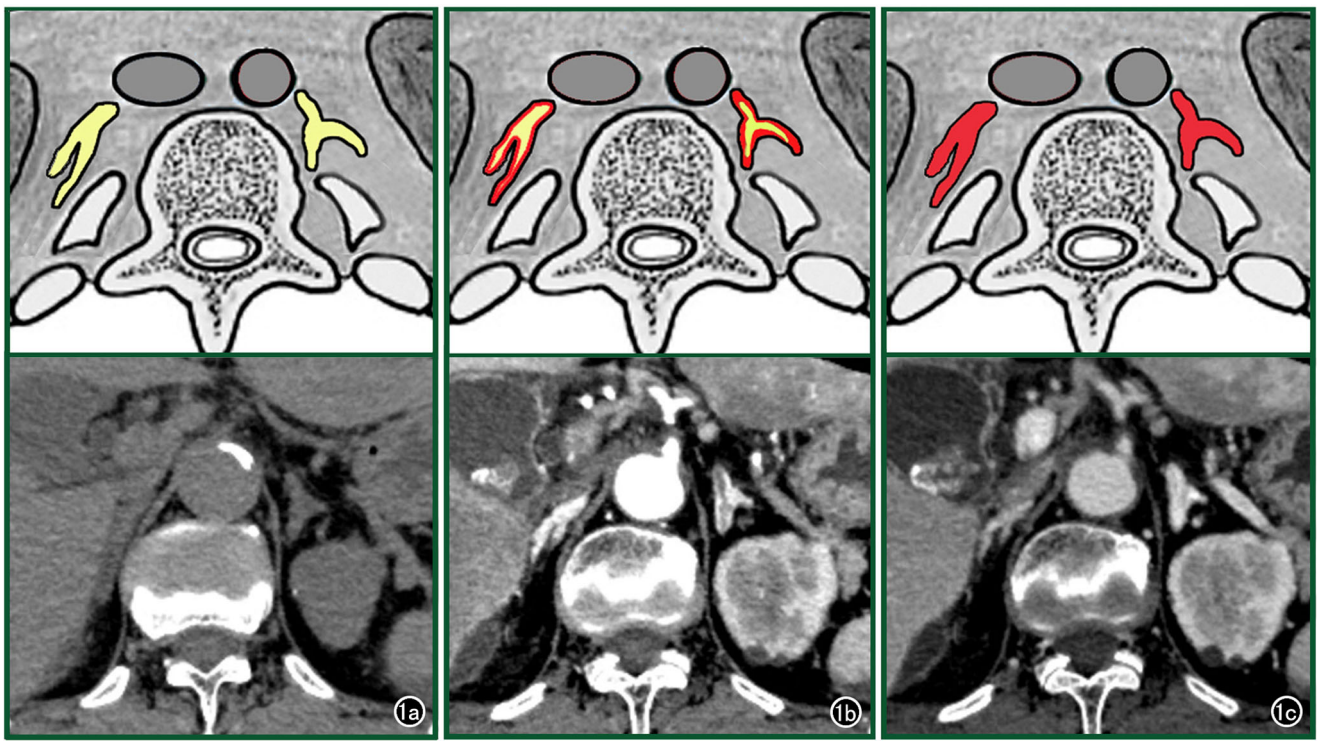

Fig. 1 The typical HAGS: bilateral adrenal glands were swelling (1a). In the arterial phase, the peripheral zone of the left adrenal gland was avidly enhanced as normal, while the central zone became "hollowed out," showing a typical Y-shaped or I-shaped lower-enhancing zone (1b). In the venous phase, the left adrenal gland became more uniformly enhanced (1c)

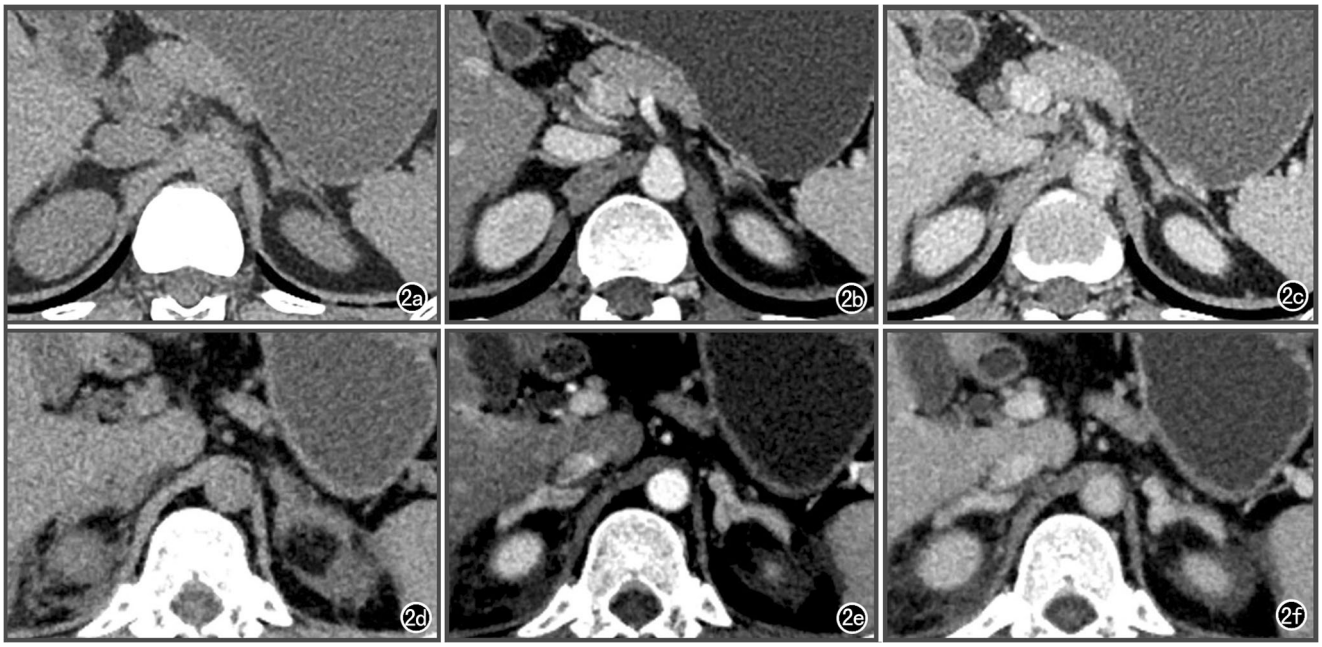

Fig. 2 Another case of the typical HAGS, which showed a 38-year-old male with septic shock secondary to postsurgical infection after radical resection of rectal carcinoma. One month before the operation, a dual-phase contrast-enhanced CT showed normal appearance (2a) and homogenous enhancement of bilateral adrenal glands in both arterial phase (2b) and venous phase (2c), while postsurgical CT showed changes in both volume (2d) and enhancement of adrenal glands. There was I-shaped "hollowed out" zone in bilateral adrenal glands in arterial phase (2e), and they became homogenously enhanced in venous phase (2f)

between HAGS-positive and HAGS-negative patients in the overall septic shock group and in each subgroup.

The clinical outcomes of patients with septic shock were listed in Table 3, and the predictive value of the HAGS for

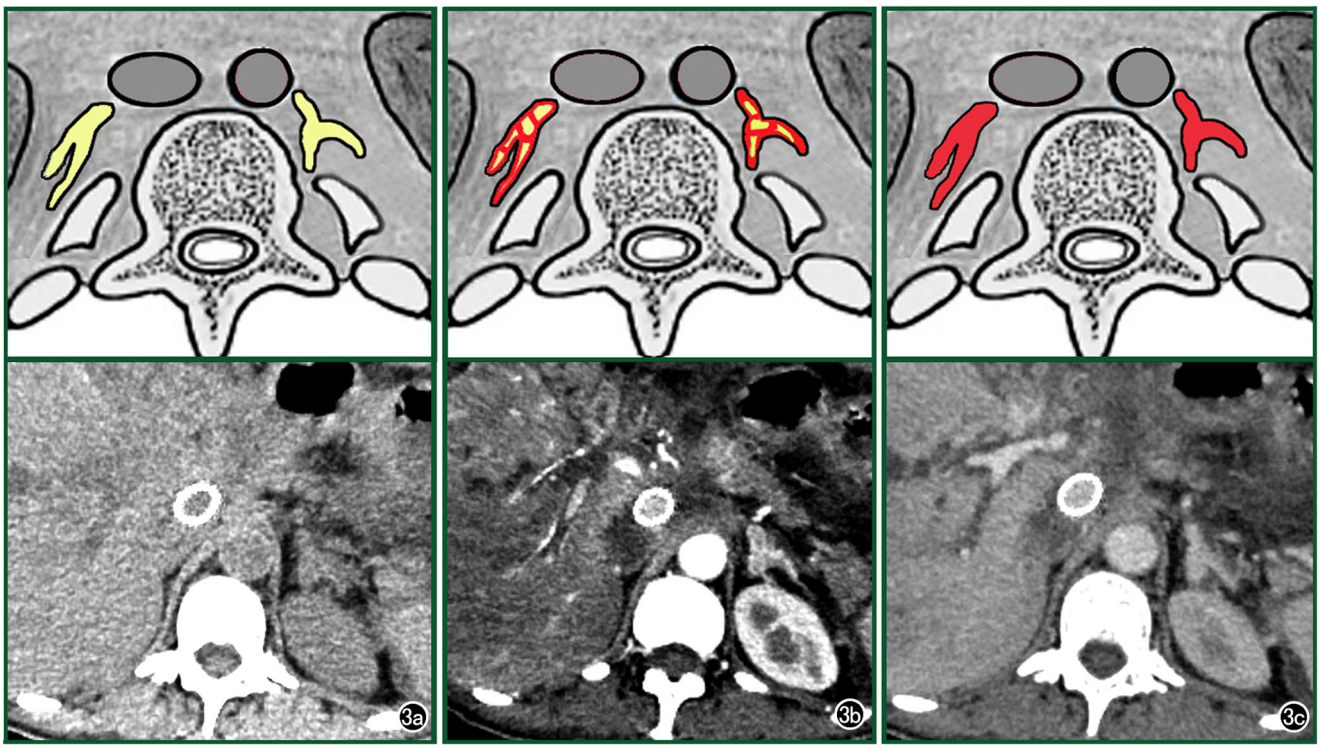

Fig. 3 The atypical HAGS: swelling of adrenal glands were also shown (3a). In the arterial phase, rim enhancement was shown at the edge of the bilateral adrenal glands, while the inner part showed heterogeneously weaker enhancement (3b). In the venous phase, the central zone of the bilateral adrenal glands exhibited more uniform enhancement (3c)

Table 1 Demographic characteristics and incidence of the HAGS in septic shock patients and hemorrhagic shock patients

		Septic shock	Hemorrhagic shock	*p*
Number of cases		194	24	
Age (years, mean ± SD)		60 ± 17	63 ± 21	0.557
Gender, *n* (%)	Male	124	18	0.282
	Female	70	6	
Mortality, *n* (%)		119 (61%)	12 (50%)	NA
The HAGS	+	63 (32%)	0 (0%)	0.001
	–	131 (68%)	24 (100%)	

death was also evaluated. The specificities of the HAGS for predicting death were good, from 0.78 to 0.93. And in the overall septic shock group, it could also be up to 0.86. However, the sensitivities were rather low, only 0.50 or less.

The McNemar test showed no significant difference ($p = 0.500$) in image interpretation between the two radiologists (Table 4). The kappa coefficient was 0.977, which indicated excellent image interpretation consistency between the two observers.

Discussion

In our study, we explored the enhancement features of adrenal glands in patients with septic shock by using dual-phase contrast-enhanced CT, and we found a special enhancing pattern of adrenal glands (i.e., the HAGS) in some of the sickest patients (63 out of 194) for whom follow-up showed a poorer prognosis. The HAGS may be specific for patients with septic shock. So far, we did not find that it appeared in other patients such as hemorrhagic shock patients (0 out of 24), although they both lead to circulatory dysfunction.

Considering that different primary diseases could have a large impact on the prognosis of patients with septic shock, we further divided all septic shock cases into four subgroups. The positive rates of the HAGS in the overall septic shock group and in each subgroup were all as high as approximately 30%, indicating that the HAGS is not uncommon in patients with septic shock. Additionally, the HAGS was obviously associated with a higher mortality risk, especially in the PI ($OR_3 = 9.7$) and OD ($OR_4 = 9.3$) subgroups. In general, the HAGS had a very good specificity for prediction of poor prognosis, up to 93% in the PI and OD subgroups. However, its sensitivity was rather low. This low sensitivity may be because the images in the dual-phase contrast-enhanced CT scan were actually acquired at certain time points. If the sign appeared later than the scanning time point for the arterial phase or ended earlier than the time point, it would be incorrectly interpreted as HAGS negative. Therefore, the

Table 2 Demographic characteristics of each subgroup of patients with septic shock

		DTD (*n* = 49)			BPD (*n* = 41)			PI (*n* = 64)			OD (*n* = 40)			Total (*n* = 194)		
The HAGS		+	–	p_1	+	–	p_2	+	–	p_3	+	–	p_4	+	–	p_t
Number of cases		18 (37%)	31 (63%)	NA	13 (32%)	28 (68%)	NA	21 (33%)	43 (67%)	NA	11 (28%)	29 (72%)	NA	63 (32%)	131 (68%)	NA
Age (years, mean ± SD)		68 ± 22	62 ± 14	0.108	57 ± 19	58 ± 16	0.891	61 ± 16	59 ± 16	0.620	63 ± 12	56 ± 20	0.194	62 ± 18	59 ± 16	0.119
Gender, *n* (%)	Male	9 (50%)	18 (58%)	0.584	7 (54%)	18 (64%)	0.524	16 (76%)	33 (77%)	0.961	6 (55%)	17 (59%)	0.816	38 (60%)	86 (66%)	0.463
	Female	9 (50%)	13 (42%)		6 (46%)	10 (36%)		5 (24%)	10 (23%)		5 (45%)	12 (41%)		25 (40%)	45 (34%)	

DTD, digestive tract diseases; *BPD*, biliary pancreatic diseases; *PI*, postsurgical infection; *OD*, other diseases

Table 3 Clinical outcomes of patients with septic shock and the predictive value of the HAGS for death

	The HAGS	Number of cases	Mortality, *n* (%)	*p*	Odds ratio (95% CI)	Sensitivity	Specificity
DTD	+	18	13 (72%)	0.041	3.6 (1.0–12.6)	0.50	0.78
	–	31	13 (42%)				
BPD	+	13	9 (69%)	0.026	4.8 (1.1–19.6)	0.50	0.83
	–	28	9 (32%)				
PI	+	21	20 (95%)	0.014	9.7 (1.2–79.4)	0.41	0.93
	–	43	29 (67%)				
OD	+	11	10 (91%)	0.022	9.3 (1.1–82.6)	0.40	0.93
	–	29	15 (52%)				
Total	+	63	52 (83%)	< 0.001	4.7 (2.2–9.7)	0.44	0.86
	–	131	66 (50%)				

DTD, digestive tract diseases; *BPD*, biliary pancreatic diseases; *PI*, postsurgical infection; *OD*, other diseases

scanning time point for the arterial phase may need to be further optimized to observe the HAGS. The utilization of a bolus-tracking technique or multiphase contrast-enhanced CT scans (especially around the arterial phase) may probably solve the problem in the future. The second reason for the low sensitivity may be that in some of the sickest patients, the overall enhancement degree of the adrenal gland is evidently decreased probably because they were in the late stage of circulation failure; thus, the sign may not be very obvious and difficult to accurately recognize.

Nougaret et al [13] proved that the adrenal gland volume could be significantly increased in patients with septic shock, otherwise they may have poor prognoses. Although the adrenal gland volume was not assessed in this study, according to our experience, many of the patients with septic shock appeared swelling of adrenal glands in different extents (Fig. 2). However, considering that adrenal gland volume can be affected by various factors, such as height, weight, race, and even geographical regions, its normal reference range for different populations may vary [13, 18–20]. As the HAGS can easily be recognized on the original CT images if patients had ever received a dual-phase contrast-enhanced CT scan, it could be a good complement to the previous study. The combination of the HAGS and changes in adrenal gland volume may provide better sensitivity and specificity in predicting the prognosis, which merits further study. Other studies [15, 16] reported that hyperattenuation of adrenal glands after contrast enhancement in the setting of ICU patients (especially for polytraumatized patients) was associated with a high mortality. But since the pathogeneses between hypovolemic shock and septic shock are quite different, the mechanisms of hyperattenuation of adrenal glands may probably differ from the HAGS.

The mechanism of the HAGS may be related to the specific pathophysiological changes during septic shock. Previous studies revealed hypothalamic pituitary adrenal axis dysfunction [4, 5], increased glucocorticoid resistance [6, 7], and inflammatory mediator-induced adrenal gland injury during septic shock [21], which may lead to overcompensation, ischemia, edema, and even microbleeds and necrosis of adrenal glands. On CT, these changes may present as swelling of the overall adrenal gland. In the arterial phase, the impaired microcirculation of the adrenal gland resulted from both local pathophysiological changes and systemic circulatory failure may have a greater influence on the inner part, which lead to lower enhancement than the peripheral zone. In the venous phase, the central zone undergoes delayed progressive enhancement and the whole adrenal gland finally gets homogenously enhanced, which suggests the blood supply of the inner zone could still be compensated even if the HAGS is presented. When this condition finally converts to adrenal insufficiency, mortality will be increased [22].

When identifying the HAGS in patients with septic shock, some other adrenal gland diseases must be differentiated, for example, venous infarction of the adrenal glands [23, 24], adrenal tuberculosis [25], and adrenal hyperplasia [26]. These diseases may also lead to clinical symptoms of adrenal insufficiency and enlargement of the adrenal gland on CT. However, as long as the dual-phase enhancing pattern of the HAGS is kept in mind, differential diagnosis is not difficult.

Our study also has some limitations. First, the retrospective design of this study meant that we did not perform a sample size calculation. However, the statistical significance of the

Table 4 Interobserver reliability for the HAGS

		Radiologist A	Radiologist B	*p* (McNemar test)	κ
The HAGS	+	65	63	0.500	0.977
	–	129	131		

Cases agreed on, 192; cases with different interpretations, 2

mortality between HAGS-positive and HAGS-negative patients in all groups are probably not related to a type I error. Second, no hormonal examination or autopsy was performed in this study, and there was no evidence indicating the mechanism of the HAGS, which must be further elucidated in prospective studies and animal experiments. Third, for most patients with non-abdominal diseases, a dual-phase contrast-enhanced CT scan is not routinely performed, and only a small portion of these patients were included in this study. Therefore, the results of this study may mainly apply to patients with septic shock secondary to abdominal diseases and abdominal surgeries. Whether septic shock secondary to other diseases could act in the same way may need further confirmation.

For the first time, this study defines and describes the HAGS, which is a special enhancing pattern of adrenal glands on dual-phase contrast-enhanced CT. The HAGS can be specifically observed in patients with septic shock and suggests a poor prognosis. The sign can be easily recognized with excellent reproducibility and is very convenient for clinical use since it is only based on the original CT images. Therefore, familiarity with the HAGS is necessary for both radiologists and ICU physicians. However, the mechanism of the HAGS remains unknown, and further research will be needed.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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