Adrenal gland volume measurement in septic shock and control patients: a pilot study

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Abstract
Objectives: To compare adrenal gland volume in septic shock patients and control patients by using semi-automated volumetry. *Methods:* Adrenal gland volume and its inter-observer variability were measured with tomodensitometry using semi-automated software in 104 septic shock patients and in 40 control patients. The volumes of control and septic shock patients were compared and the relationship between volume and outcome in intensive care was studied. *Results:* The mean total volume of both adrenal glands was 7.2± 2.0cm^3 in control subjects and 13.3± 4.7cm^3 for total adrenal gland volume in septic shock patients (p<0.0001). Measurement reproducibility was excellent with a concordance correlation coefficient value of 0.87. The increasing adrenal gland volume was associated with a higher rate of survival in intensive care. *Conclusion:* The present study reports that with semi-automated software, adrenal gland volume can be measured easily and reproducibly. Adrenal gland volume was found to be nearly double in sepsis compared with control patients. The absence of increased volume during sepsis would appear to be associated with a higher rate of mortality and may represent a prognosis factor which may help the clinician to guide their strategy.

Keywords CT · Adrenal gland · Volumetry · Septic shock · Intensive care

Introduction

Adrenal glands are often described on computed tomography (CT) as small, triangular glands located at the top of both kidneys. Their weights are considered to be about 4 g in non-stressed subjects (surgical specimen) and their volumes have never been properly evaluated by CT [1]. To date, only two studies have reported adrenal gland volumetry and this was performed manually by CT [2, 3], based on single thick slice acquisition of 3 mm. Automated and semi-automated volumetry are used successfully with other organs such as liver [4–9] or lungs [10–12] but no studies have been performed on adrenal gland. The volume of the adrenal glands can be modified by several pathological conditions (e.g. depression [2], Cushing's disease [13] and septic shock [14]). Septic shock is defined as the occurrence of a proven infection with cardiovascular failure needing vasopressor therapy [15, 16]. It is the most common life-threatening disease occurring in intensive care units (ICUs) leading to a mortality rate of 30–50% [17]. Relative adrenal insufficiency has been described to be very common during septic shock, and appears to be an independent prognostic factor, but its diagnosis and adequate treatment remain controversial in 2010 [16, 18]. The place of adrenal gland volume measurement in the early phase of management of septic shock has never been evaluated. Therefore, the purposes of our preliminary study were:

- To measure adrenal gland volumes by CT using a manufacturer's software (Myrian, Intrasense, Montpellier, France) in non-stressed control patients

– To evaluate the inter-observer reproducibility of this measurement
– To compare adrenal gland volume in control and septic shock patients and
– To evaluate its impact on mortality

Materials and methods

Study patients

The study design was approved by the local ethics committee of anaesthesia and intensive care. Two groups of patients were included between November 2007 and December 2008. Included in the control group were 40 consecutive patients with no current medical illness who had come in for virtual colonoscopy after medical investigation for abdominal pain or constipation. Included in the septic shock group were 104 consecutive patients in septic shock who had undergone an abdominal CT within the first 48 h of septic shock as defined by Bone et al. [15]. Briefly, patients in the septic shock group had a proven infection with hypotension, despite adequate fluid resuscitation and required vasopressors [15]. All CTs were collected in the picture and archiving communication system (PACS, GE Healthcare, UK) which is a high-security database with protection measures for patient confidentiality approved by the institutional review board for maintaining and renewing patient information. Women taking oral contraceptives, patients who had used any steroid preparation in the recent past and all patients with a history of endocrinopathy or chronic steroid use were not included to decrease the selection bias. Furthermore, we did not include patients with one unique adrenal gland.

CT of the adrenal glands

Examination of the adrenal glands was performed with 64-section spiral CT (Aquilon 64, Toshiba Medical Systems, Nasu, Japan). There was no standard protocol for the CT. In fact, the protocol was adapted according to renal function. CT examinations in the control group (n= 40) were performed without injection of contrast medium, as for virtual colonoscopy. In the septic shock group, 23 CTs were performed without intravenous contrast medium due to renal failure; 81 CTs were performed with intravenous contrast medium using a standardized protocol for critically ill patients (quadriphasic acquisition). Images were viewed on the PACS workstation for standard diagnostic interpretation. Subsequently, images were transferred to a workstation (Myrian, Intrasense, Montpellier, France) devoted entirely to adrenal volume measurements. A section thickness of 3 mm (without overlaps) was used for the volumetry. A magnification targeting factor of ×2 was used. The adrenal contour was semi-automatically traced by using the specially designed workstation (Myrian) by one radiologist (with 5 years' experience). Care was taken to try to exclude adjacent fat. Because the shape of the adrenals can be somewhat irregular, threshold values were established to exclude adjacent fat from the volume calculated. For example, only tissue with attenuation values of 25 to 200 Hounsfield units within the region of interest was included. The CT software (Myrian, Intrasense, Montpellier, France) automatically calculated the adrenal volume by totalling the area on each slice. Most subjects had clearly defined adrenal margins. The radiologist was unaware of the clinical status of the subjects. The measurement lasted 5 min per case. Patient and control adrenals were assessed in random order. To assess the facility and the reproducibility of the technique, each adrenal gland volume measurement for normal, non-stressed patients was performed by the radiologist and an intensivist. The measurement of the adrenal gland volume in 10 control subjects was considered a learning curve for the inter-observer agreement evaluation. Inter-observer variability was determined with the semi-automated measurement by comparing right and left adrenal gland volume values measured by each reader. To avoid bias, each observer was blinded to the results of the other observer. The same two observers each retrospectively performed two semi-automatic segmentations for each patient after a time interval of at least 2 weeks. The radiologist was blinded to the outcome of the septic patients.

Measurements

For both groups, sex, age, weight, height, body surface area and underlying disease were recorded. In the septic shock group, the admission category (medicine or surgery), main diagnosis at admission and outcome at ICU discharge were recorded. The main endpoints were: first, the evaluation of adrenal gland volume in both groups; second, the evaluation of the inter-observer correlation; and, third, the comparison of adrenal gland volume in the control group and the septic shock group, and its association with mortality.

Statistics

Data are represented as means ± standard deviation (SD) or median and quartiles (25th–75th) as required. Data were analysed by using Student's t test, the Mann–Whitney test and the chi-squared or Fisher's exact test after a population normality assessment using the Kolmogorov–Smirnov test. Inter-observer measurements of adrenal gland volume were correlated with the inter-observer correlation coefficient for continuous variables. Relationships between adrenal volume, and subjects' weight, height, body mass index, age and mortality were examined by using the Pearson product-moment correlation coefficient for continuous variables. The within-subject variance was calculated by using a one-way variance analysis. The sensitivity and specificity of adrenal volume curves to predict mortality were assessed by a receiver operating characteristic (ROC) curve. $P<0.05$ was considered statistically significant. The statistical analysis was performed by using Medcalc Software 9.4.2.0 (Mariakerke, Belgium).

Results

Adrenal gland measurements in control subjects

The adrenal gland volume was measured in 40 control patients who were examined with virtual colonoscopy (control subjects). Demographic characteristics are reported in Table 1. The mean adrenal volume was 3.4±1.0 cm^3 for the right adrenal gland and 3.8±1.2 cm^3 for the left adrenal gland, with no significant difference. The mean total volume of both adrenal glands was 7.2±2.0 cm^3.

The total adrenal gland volume was larger in men (8.0±1.8 cm^3) than in women (6.2±1.7 cm^3) (p=0.003). There was no consistent correlation between adrenal volume and age (r^2=0.08) and height (r^2=0.53) but there were consistent positive correlations between adrenal volume and weight (r^2=0.73) (Fig. 1a, b) and body surface area (r^2=0.73) (Fig. 1c). After the first 10 measurements which were considered a trial period for the intensivist, the inter-observer reliability was evaluated (Table 2). The concordance correlation coefficient between the radiologist and the intensivist was 0.87 (0.76–0.93) for the total gland volume.

Adrenal gland volume in the control group versus the septic shock group

During the study period, we included 104 consecutive septic shock patients (septic shock group) who had undergone CT within the first 48 h of the septic shock. The characteristics of patients in septic shock are summarised in Table 1. There was no significant difference in weight (p=0.11), height (p=0.89) and body surface area (p=0.16) between the two groups, but subjects in the control group were significantly younger (p=0.0003) than patients in the septic shock group.

Whereas adrenal gland volume in the control group was correlated with weight and body surface area (Fig. 1a,c), adrenal gland volume in the septic shock group was not correlated with weight (r^2=0.04) or body surface area (r^2=0.09) (Fig. 2a, b). The mean total volume of both adrenal glands was 7.2±2.0 cm^3 in normal subjects and 13.3±4.7 cm^3 for total adrenal gland volume in septic shock patients (Fig. 3) (p<0.0001).

Among the 104 patients included in the septic shock group, 46 had undergone CT before the septic shock with a delay of 102 days (range 26–646). In this group of patients, 32 suffered from chronic illness (12 chronic pancreatitis, 8 cirrhosis, 10 cancers, and 2 liver transplantations). In this subgroup of 46 patients, the mean total volume of both adrenal glands was 9.5±3.6 cm^3 before the onset of septic shock and 13.4±4.8 cm^3 during septic shock (p<0.0001) (Fig. 4). In this subgroup of patients, the adrenal gland volume before septic shock (9.5±3.6 cm^3) was significantly larger than in the control group (7.2±2.0 cm^3) (p=0.005). Adrenal gland volume had increased between 10% and 50% in 9 patients (20%), between 50% and 100% in 7 patients (15%) and more than 100% in 10 patients (22%). There were no variations before or during septic shock in 20 patients (43%) and the adrenal gland volume had not decreased in any of the patients.

Adrenal gland enlargement and outcome

A small adrenal volume during septic shock was associated with higher mortality. Figure 5 shows the receiver operating characteristic (ROC) curve correlating adrenal volume and ICU mortality. An optimal cutoff value of

Table 1 Patient characteristics

	Control group (n=40)	Septic shock group (n=104)	p
Age (years, mean ± SD)	56±11	65±14	0.0003
Sex, n (%)			
Female	18 (45%)	30 (29%)	0.08
Male	22 (55%)	74 (71%)	
Body weight (kg, mean ± SD)	70±12	77±25	0.11
Body height (cm, mean ± SD)	169±7	169±8	0.89
Surface area (m^2, mean ± SD)	1.8±0.4	1.9±0.3	0.16
Number of deaths, n (%)	0	33 (32%)	
Type of patient, n (%)			
Medicine	40 (100%)	47 (45%)	NA
Surgery	0	57 (55%)	
Type of disease, n (%)			
Abdominal	0	38 (36%)	NA
Pulmonary	0	29 (28%)	NA
Both	0	37 (36%)	NA

Data are represented as means ± SD or n (%)

NA not available

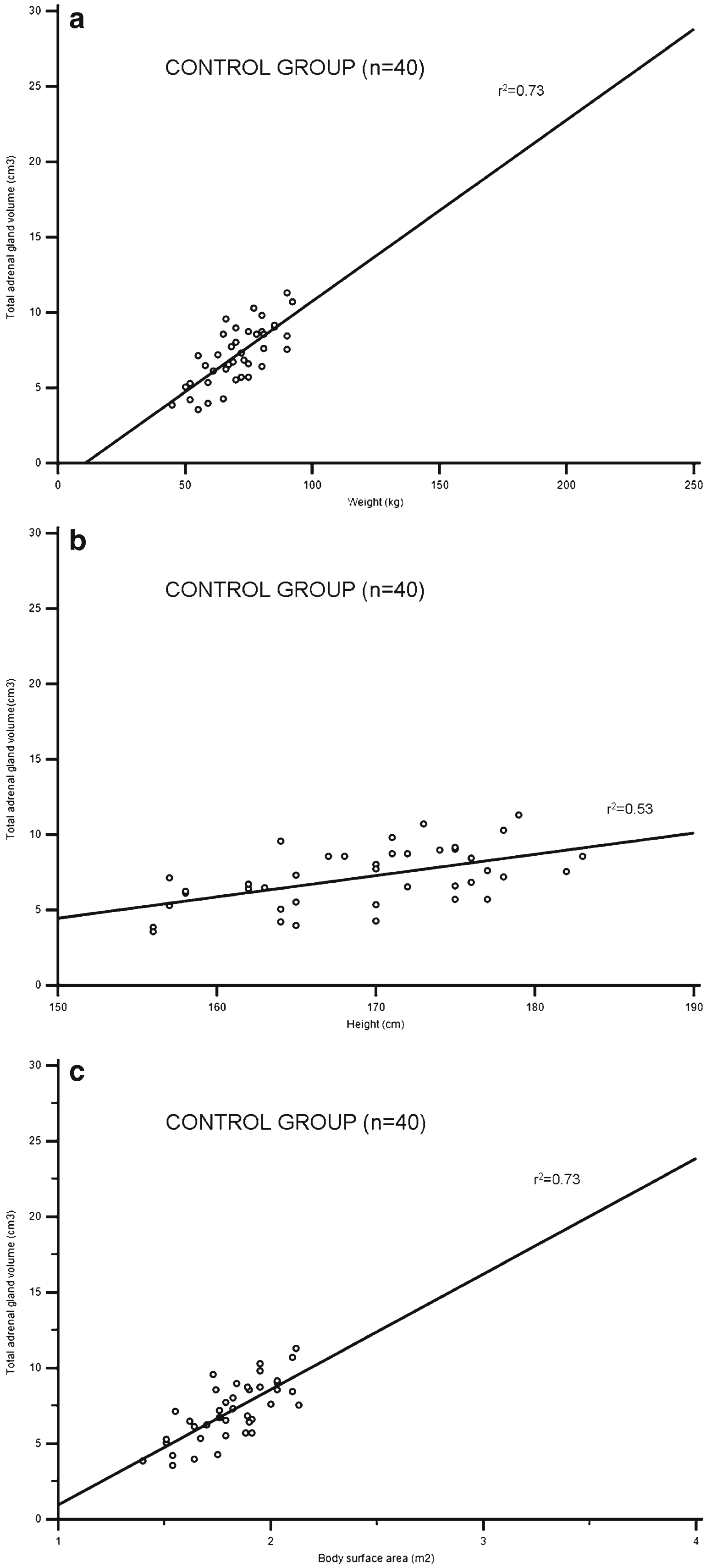


Fig. 1 **a** Scatterplot showing the results of regression analysis of adrenal gland volume and control patients' weight. A linear correlation between total adrenal gland volume and weight (r^2= 0.73) was found in the control group. **b** Scatterplot showing the results of regression analysis of adrenal gland volume and control patients' height. There was no linear correlation between total adrenal gland volume and height (r^2=0.53) in the control group. **c** Scatterplot showing the results of regression analysis of adrenal gland volume and control patients' body surface area. A linear correlation between total adrenal gland volume and body surface area (r^2=0.73) was found in the control group

Table 2 Inter-observer correlation coefficient (ICC) for right, left and both adrenal glands

	Radiologist	Intensivist	ICC
Right adrenal gland volume, cm^3 (mean ± SD)	3.3±1.0	3.4±1.0	0.87 [0.76–0.93]
Left adrenal gland volume, cm^3 (mean ± SD)	3.7±1.1	3.9±1.3	0.83 [0.72–0.93]
Total adrenal gland volume, cm^3 (mean ± SD)	7.1±1.9	7.3±2.0	0.87 [0.76–0.93]

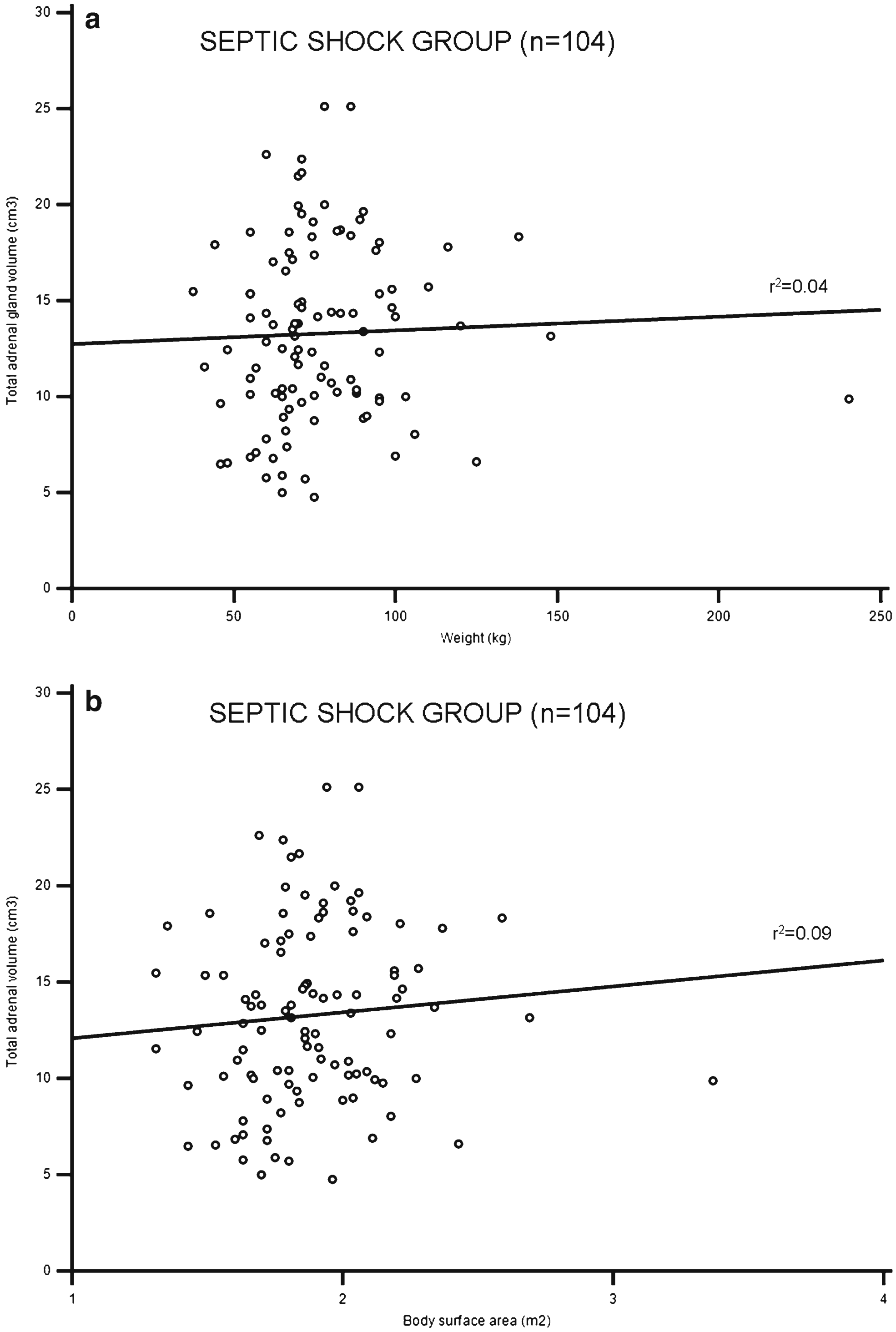


Fig. 2 **a** Scatterplot showing the results of regression analysis of adrenal gland volume and septic shock patients' weight. There was no linear correlation between total adrenal gland volume and weight (r^2=0.11) in the septic shock group. **b** Scatterplot showing the result of regression analysis of adrenal gland volume and septic shock patients' body surface area. There was no linear correlation between total adrenal gland volume and body surface area (r^2=0.16) in the septic shock group

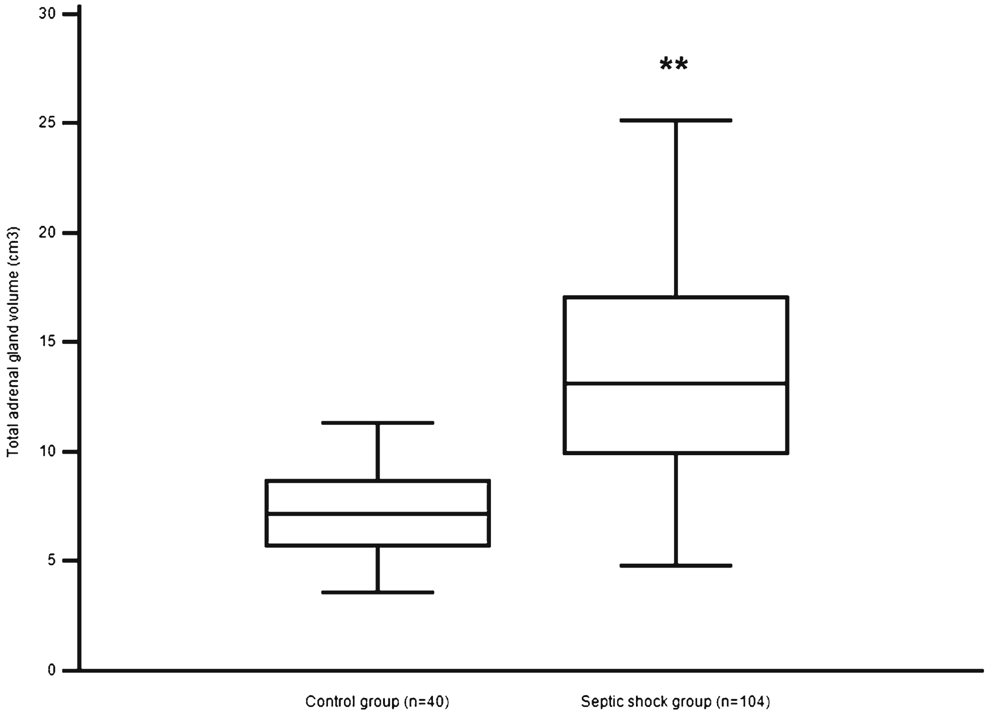


Fig. 3 Box and whisker plot showing the results of total adrenal gland volume in the control group and in the septic shock group. Each box ranges from the 25th percentile at the *lower edge* to the 75th percentile at the *upper edge*. The median is shown as a *line across the box*. There are two adjacent values *below* and *above* the box: the largest value is below the upper inner limit and the smallest value is above the lower inner limit. There was an increase in total adrenal gland volume in the 104 patients who underwent CT during septic shock in comparison to the adrenal volume of the 40 control subjects (**p<0.0001)

10 cm^3 provided a sensitivity of 69% and a specificity of 94% for the risk of mortality in the ICU. The likelihood ratio for dying with an adrenal gland volume of less than 10 cm^3 was evaluated to be 3.1.

In Figs. 6 and 7, we present two case reports of septic shock patients. A 62-year-old woman was examined by CT for back pain that revealed no disease except for osteoporosis. Her total adrenal gland volume was 8.5 cm^3 (Fig. 6a). Two months later she developed community-acquired pneumonia with septic shock and CT performed 6 h after the onset of shock showed that her total adrenal gland volume was 9.0 cm^3 (Fig. 6b). She died 6 days after admission to the ICU. A 68-year-old woman was referred for CT for a colon cancer evaluation. Her total adrenal gland volume was 10.2 cm^3 (Fig. 7a). She was admitted to the ICU 15 days later for nosocomial peritonitis with septic shock after colectomy. The total adrenal gland volume had increased and measured 19.6 cm^3 (Fig. 7b).

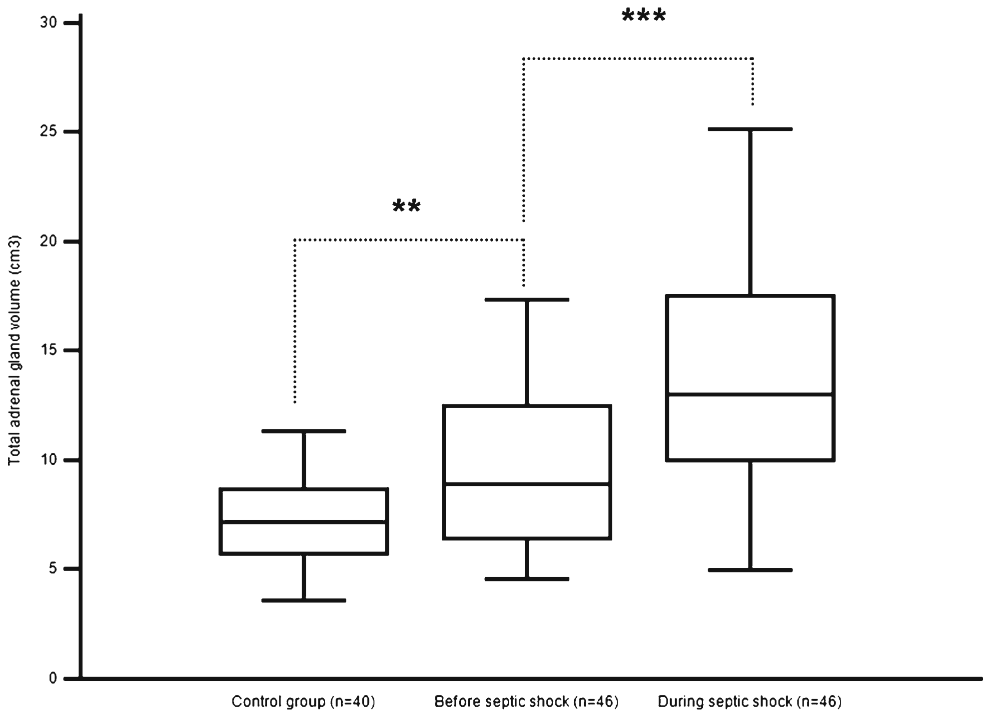
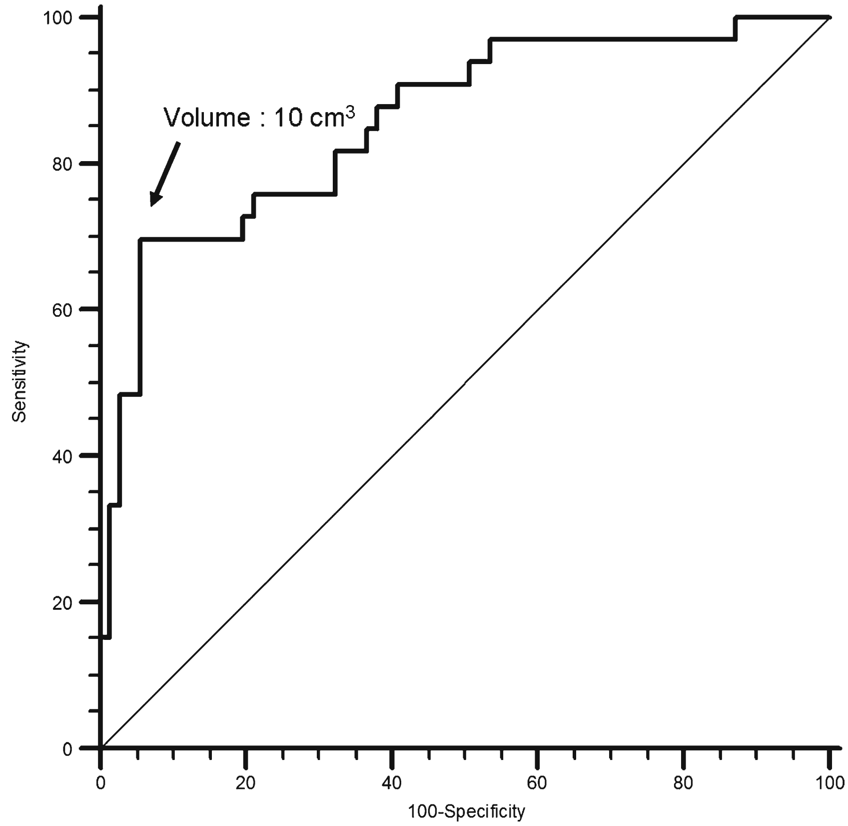


Fig. 4 Box and whisker plot showing the results of total adrenal gland volume for the 46 septic shock patients who underwent CT before and during septic shock and for the control group (n=40). The description of each box is the same as for Fig. 3. Total adrenal gland volume was greater during sepsis compared with CT performed before the septic shock (***p<0.0001) for the same group of patients. The adrenal gland volume was larger in those patients who were explored by CT before the septic shock than in control patients (***during vs before septic shock, p=0.005; **before septic shock vs control group, p=0.005)

Fig. 5 Receiver operating characteristic curve, between total adrenal gland volumetry and mortality, showing a sensitivity of 69% and a specificity of 94% with an AUC=0.86 for a cutoff at 10 cm^3



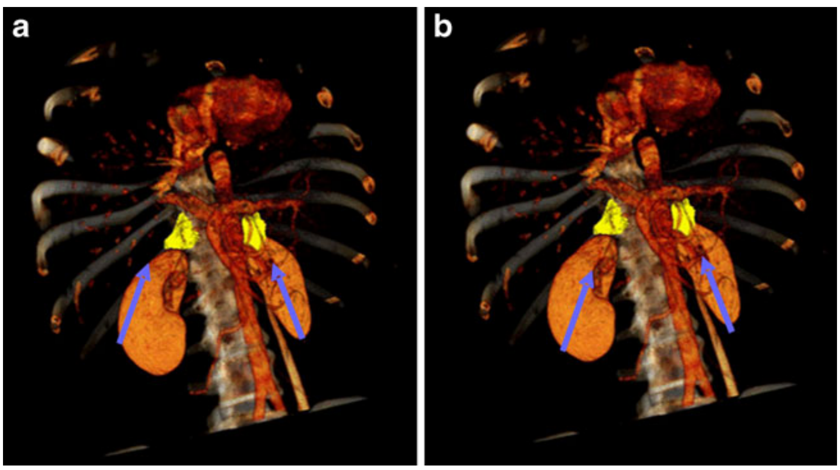
The patient recovered from sepsis and was discharged from the ICU.

Discussion

The main results of our study are, first, that the adrenal gland volume in control patients is 7.2±2.0 cm^3 and is positively correlated with weight and body surface area; second, the measurement is reproducible between specialists and intensivists with a concordance correlation coefficient of 0.87; and finally, for the first time, we report that the adrenal gland volume in septic shock patients is nearly twice that of control patients and the total adrenal gland volume enlargement seems to be positively associated with a better outcome and quicker discharge from the ICU.

There are numerous clinical applications for solid abdominal organ volumetry [19–26] but organ volume assessments are not routinely performed, partly because of the extensive user input and time required with the current

Fig. 6 **a** Three-dimensional volume-rendered abdominal CT of a 62-year-old woman who underwent a CT 2 months before the onset of septic shock, showing a normal adrenal gland volume (8.5 cm^3). During the septic shock (**b**) total adrenal gland volume did not increase (9.0 cm^3). Death occurred in the ICU



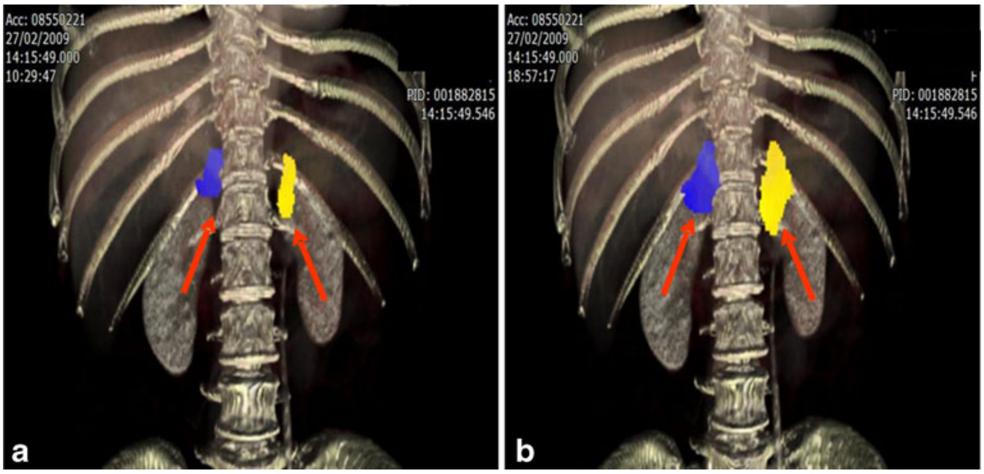


Fig. 7 **a** Three-dimensional volume-rendered abdominal CT of a 68-year-old woman who underwent CT 2 weeks before she presented septic shock and showing a normal adrenal gland volume (10.2 cm^3). During septic shock (**b**) the total adrenal gland volume increased (19.6 cm^3). She was discharged from the ICU

manual techniques. Use of semi-automated and automated organ segmentation would resolve the issues related to the user input and time required for volumetric analysis and enable imaging-based organ segmentation to become a routine process. This potential has prompted diverse and rapidly evolving innovations in the field of imaging-based segmentation. Indeed, CT evaluations of liver volume do have an impact on mortality before major liver resection [6, 26, 27]. Furthermore, several studies have reported that lung volume assessments with CT may reduce the deleterious consequences of mechanical ventilation and could improve oxygenation in those critically ill patients [11, 28]. Several volumetry classification techniques have been used. These schemes include classifications of automation (manual, semi-automatic and automatic), technique (MR imaging, CT), the number of datasets (single, multiple and multispectral), and also the type of volume algorithm calculation. These methods of measuring liver volume, described in the literature, are reproducible and accurate [4–8, 28–31].

Since 1978, several groups described the radiographic appearance of normal [32–34] and enlarged [35] adrenal glands by CT. Two studies reported a manual estimation of adrenal volume by CT [2, 3]. These two studies were both carried out with sequential acquisition and volumetry was calculated manually.

In our study, semi-automated software (Intrasense, Montpellier, France) appeared to be adequate for measuring adrenal gland volume. Furthermore, after a short training period, any physician who was not a radiologist could measure the adrenal gland volume with excellent inter-observer reliability.

The mean total volume measured by CT in normal subjects was 7.2 ± 2.0 cm^3 which was larger (5.3 ± 0.5 cm^3) than the volume reported by Rubin and Phillips [3] or that reported by Amsterdam et al. (3.5 ± 0.5 cm^3) [2]. The difference in adrenal size among previous studies is mainly explained by the technological advances in CT imaging. The thin slice imaging we use nowadays provides greater accuracy. Also, to a lesser degree, differences in CT calibration or in tracing the borders of the adrenals may have caused these discrepancies. Our results in normal subjects found a correlation between total adrenal gland volume and weight and body surface area (Fig. 1) similar to that discovered by Rubin and Phillips [3].

In patients with proven severe sepsis, early CT of the abdomen showed an enlargement of the adrenal glands compared with control patients. This result has only been reported in case reports [14]. Moreover, for the first time, we found that in septic shock and contrary to control patients, there was no correlation between patient weight or body surface area and adrenal gland volume (Fig. 2).

Few studies have reported morphological changes in adrenal volume apart from in endocrinopathy (e.g. Cushing's syndrome); only two studies have shown increased adrenal gland volume in depressed patients [2, 36].

The abnormalities of adrenal gland volume occurring in sepsis may be explained by the pathophysiology of the adrenal glands during sepsis. Indeed, several lines of evidence support the fact that adrenal gland response is altered during sepsis, mainly due to hypothalamic-pituitary adrenocortical dysfunction, decreased production of steroids by the adrenal gland and also due to peripheral resistance to steroids [37].

In the 46 patients who underwent CT before and during septic shock, the total adrenal gland volume had increased significantly between the two CTs. This morphological change may be related to sepsis in the same patient (Fig. 4). Indeed, like others, we found no correlation between adrenal gland volume and age [3]. We therefore speculate that sepsis may influence the adrenal gland size all by itself. Moreover, regarding the difference between control group and the septic group before the onset of sepsis, adrenal glands were significantly larger in 44% of the case group before onset of sepsis in comparison to control group. We speculated that this enlargement was due to chronic disease. In fact, 32 suffered from chronic illness (12 chronic pancreatitis, 8 cirrhosis, 10 cancers, 2 liver transplantation).

Finally, we reported that adrenal gland volume seems to be associated with the mortality rate of patients in the ICU. Indeed, the absence of adrenal gland enlargement (less than 10 cm^3) was associated with a higher mortality in the ICU. Because of its positive impact on outcome, it seems reasonable to hypothesise that the increased adrenal gland volume found during sepsis may be interpreted as an adaptation rather than oedema or necrosis of the gland.

Nevertheless we should bear in mind the limitations of this study because of the retrospective design; this meant that we did not perform a sample size calculation, which represents a limitation of our study. However, the homogeneity of the control group volume distribution and the statistical significance of the volume between control and septic patients are probably not related to a type I error. Moreover, we cannot exclude the possibility of a discrepancy between CT-estimated adrenal volume and the actual gland volume. Indeed, certain errors may be attributable to a partial volume effect at the adrenal edge, or adhesion to the adjacent tissues with attenuation similar to that of the adrenal parenchyma. Although a discrepancy cannot be excluded, the inter-observer correlation was 0.87 and adrenal gland volume in control patients was similar to that in the literature [33, 36]. Furthermore, with this technology, the adrenal cortex and medulla cannot be visually separated, and it is possible that some of the variations in adrenal volume estimates may be accounted for by the adrenal medulla. Moreover, the study of adrenal CT density was not practicable because of the lack of a standardised protocol for contrast medium injection. Finally, we did not perform a millimetric analysis of the CT slices; but because this was performed in both the control and the septic shock groups, we speculated that the potential measurement error was observed in both groups. Ideally an analysis of the adrenal density without injection and/or after standard weight-related and timed enhancement should be performed.

Initial evaluation of the critically ill patients admitted to the ICU with a septic shock often includes CT for diagnosis and complication evaluation (such as acute bowel ischaemia). The technique of adrenal gland volume measurement is easy to use, reproducible, may be associated with outcome and has never been evaluated before in this indication. Furthermore, in opposition to ICU specialised scores which often need clinical and complex biological parameters (e.g. bilirubin, arterial blood gases, platelets count, plasma creatinine etc.) [38] for several days to describe a kinetic evolution, we reported that a single adrenal gland volume measurement seems to be strongly associated with outcome. Because of our results and the necessity for the intensivist to have a prognostic factor, we believe that radiologists should be aware of these findings.

Conclusion

For the first time, this study demonstrates that adrenal gland volume can be measured easily with semi-automated software and that its measurement is reproducible. Also, for the first time, we observed that the total adrenal gland volume was nearly twice as high in septic shock patients as in control patients. Absence of an increased adrenal gland volume was associated with a higher mortality rate in the ICU and deserves further investigation by clinical studies.

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