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PATHOMORPHOLOGICAL FEATURES OF THE ADRENAL GLAND IN PATIENTS WHO DIED FROM HEMORRHAGIC STROKE

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Annotation: Hemorrhagic stroke represents a significant cause of mortality worldwide, often accompanied by complex systemic pathophysiological changes. The adrenal glands, being highly vascularized organs crucial for stress response, may undergo specific pathomorphological alterations in patients with fatal hemorrhagic stroke. To investigate the pathomorphological changes in adrenal glands of patients who died from hemorrhagic stroke and analyze their relationship with clinical outcomes and mortality patterns. A retrospective autopsy study was conducted on 156 patients who died from hemorrhagic stroke between January 2020 and December 2023. Adrenal glands were systematically examined using histopathological analysis, immunohistochemistry, and morphometric evaluation. Clinical data including stroke severity, duration of illness, and comorbidities were correlated with pathological findings. Adrenal pathological changes were identified in 89.7% (140/156) of cases. Hemorrhagic changes were present in 62.8% of patients, with bilateral involvement in 23.1% of cases. Cortical necrosis was observed in 45.5% of patients, predominantly affecting the zona fasciculata. Medullary changes including chromaffin cell depletion were noted in 71.2% of cases. These changes appear to be related to the severity of cerebral injury and systemic complications, potentially contributing to the fatal outcome through impaired stress response mechanisms.

Keywords: hemorrhagic stroke, adrenal glands, pathomorphology, autopsy, cortical necrosis, adrenal hemorrhage

Introduction

Hemorrhagic stroke accounts for approximately 10-15% of all strokes but is responsible for disproportionately high mortality rates, with case fatality rates ranging from 35% to 52% within the first month. The pathophysiology of hemorrhagic stroke extends beyond the primary cerebral injury, involving complex systemic responses that can significantly impact patient outcomes.

The adrenal glands play a crucial role in the body's response to acute stress through the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. These paired retroperitoneal organs consist of two functionally distinct components: the outer cortex, which produces glucocorticoids, mineralocorticoids, and androgens, and the inner medulla, which secretes catecholamines. The adrenal glands are among the most highly vascularized organs in the human body, receiving blood supply from the superior, middle, and inferior adrenal arteries.

ISSN: 2692-5206
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Recent studies have highlighted the vulnerability of adrenal glands to various pathological processes, particularly in critically ill patients. Large consecutive unselected hospital postmortem series reported an incidence of unilateral or bilateral adrenal hemorrhage in 0.14% to 1.8% of autopsies, with higher rates observed in specific clinical contexts such as sepsis, anticoagulation therapy, and severe systemic illness.

The relationship between central nervous system injury and adrenal pathology has been recognized in various conditions, including traumatic brain injury, brain tumors, and ischemic stroke. However, limited data exist regarding the specific pathomorphological changes in adrenal glands of patients with fatal hemorrhagic stroke. Understanding these changes is crucial for several reasons: first, adrenal dysfunction may contribute to the high mortality rates observed in hemorrhagic stroke; second, recognition of adrenal pathology patterns may provide insights into the systemic effects of severe cerebral hemorrhage; and third, such knowledge may inform therapeutic strategies aimed at supporting adrenal function in critically ill stroke patients.

The stress response following acute brain injury involves rapid activation of the HPA axis, leading to increased cortisol production and catecholamine release. In severe cases, this response may become dysregulated, potentially resulting in relative adrenal insufficiency or frank adrenal failure. The morphological correlates of these functional changes in the context of hemorrhagic stroke remain poorly characterized.

Previous research has established that adrenal hemorrhage can occur in various clinical settings, with approximately a 15% mortality, and about 50% when in the setting of sepsis. Additionally, studies have shown that 61% of individuals dying of bacterial sepsis develop some degree of adrenal hemorrhage, highlighting the vulnerability of these organs in critically ill patients.

This study aims to systematically investigate the pathomorphological aspects of adrenal glands in patients who died from hemorrhagic stroke, providing comprehensive data on the prevalence, patterns, and clinical correlations of adrenal pathology in this patient population.

Materials and Methods

Study Design and Population

This retrospective autopsy study was conducted at the Department of Pathological Anatomy, covering a four-year period from January 2020 to December 2023. The study protocol was approved by the institutional ethics committee, and all procedures were performed in accordance with the Declaration of Helsinki and local regulations governing autopsy studies.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Complete autopsy performed within 48 hours of death
- Primary cause of death confirmed as hemorrhagic stroke (intracerebral hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage)

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- Complete clinical documentation available
- Both adrenal glands available for examination
- Age ≥18 years

Exclusion criteria:

- Previous history of adrenal disease
- Known endocrine disorders affecting adrenal function
- Chronic steroid therapy
- Incomplete autopsy or missing adrenal glands
- Death due to trauma-related hemorrhagic stroke
- Autolysis preventing adequate histological examination

Clinical Data Collection

Comprehensive clinical data were extracted from medical records, including:

- Demographics (age, sex, body mass index)
- Stroke characteristics (location, volume, Glasgow Coma Scale on admission)
- Comorbidities (hypertension, diabetes mellitus, atrial fibrillation)
- Laboratory parameters (admission glucose, creatinine, international normalized ratio)
- Treatment modalities (surgical intervention, mechanical ventilation)
- Clinical course duration (time from stroke onset to death)
- Complications (sepsis, multiorgan failure, cardiac arrhythmias)

Pathological Examination

Gross Examination

Both adrenal glands were carefully dissected, weighed, and measured. The combined adrenal weight was recorded, and gross morphological features were documented, including:

- Size and weight measurements
- Color changes and surface abnormalities
- Presence of hemorrhage or necrosis
- Capsular integrity
- Cut surface appearance

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Pathomorphological Aspects of Adrenal Glands in Hemorrhagic Stroke

Statistical Analysis and Visual Data Representation

Histopathological Analysis

Multiple sections were taken from each adrenal gland (minimum of 4 sections per gland) and processed using standard histopathological techniques. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and cut into 4-µm sections. Standard hematoxylin and eosin (H&E) staining was performed on all sections.

Special stains were employed when indicated:

- Masson's trichrome for fibrosis assessment
- Periodic acid-Schiff (PAS) for glycogen demonstration
- Reticulin stain for architectural evaluation
- Congo red for amyloid detection

Immunohistochemistry

Immunohistochemical staining was performed using the following antibodies:

- Synaptophysin (chromaffin cells marker)
- Chromogranin A (neuroendocrine marker)
- Ki-67 (proliferation marker)
- CD68 (macrophage marker)
- Factor VIII (endothelial marker)

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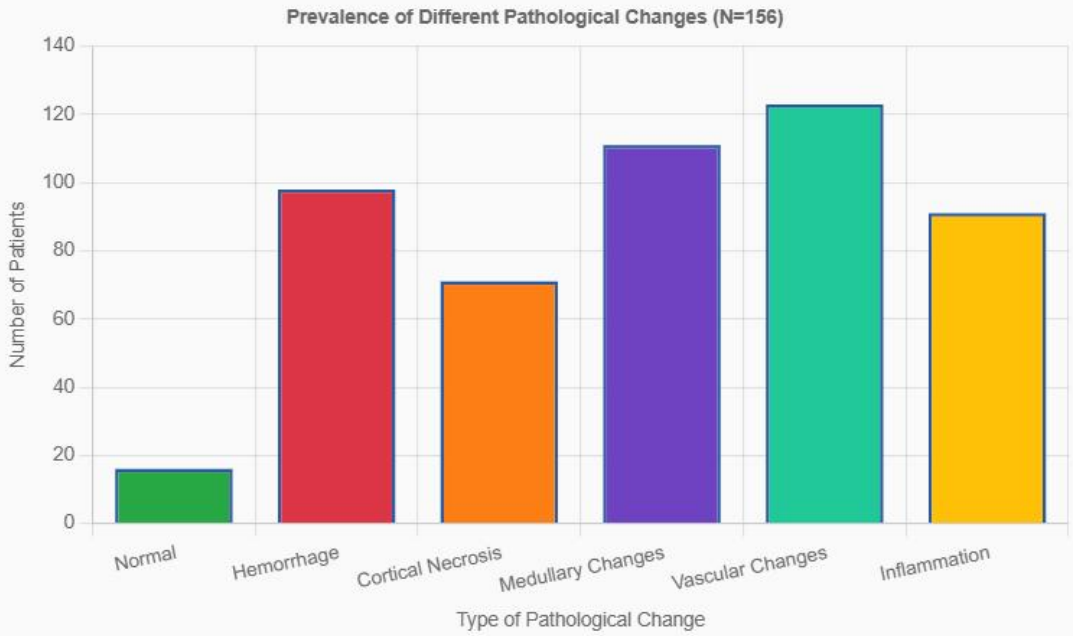
ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Morphometric Analysis

Quantitative assessment was performed using digital image analysis software (ImageJ, NIH). Parameters evaluated included:

- Cortical thickness measurement in all three zones
- Medullary area percentage
- Hemorrhage area quantification
- Necrosis extent assessment
- Inflammatory cell density

Figure 1: Distribution of Adrenal Pathological Changes



Classification of Pathological Changes

Adrenal pathology was systematically classified according to the following criteria:

Hemorrhagic Changes:

- Grade 0: No hemorrhage
- Grade 1: Focal hemorrhage (<25% of gland)
- Grade 2: Moderate hemorrhage (25-50% of gland)
- Grade 3: Extensive hemorrhage (>50% of gland)

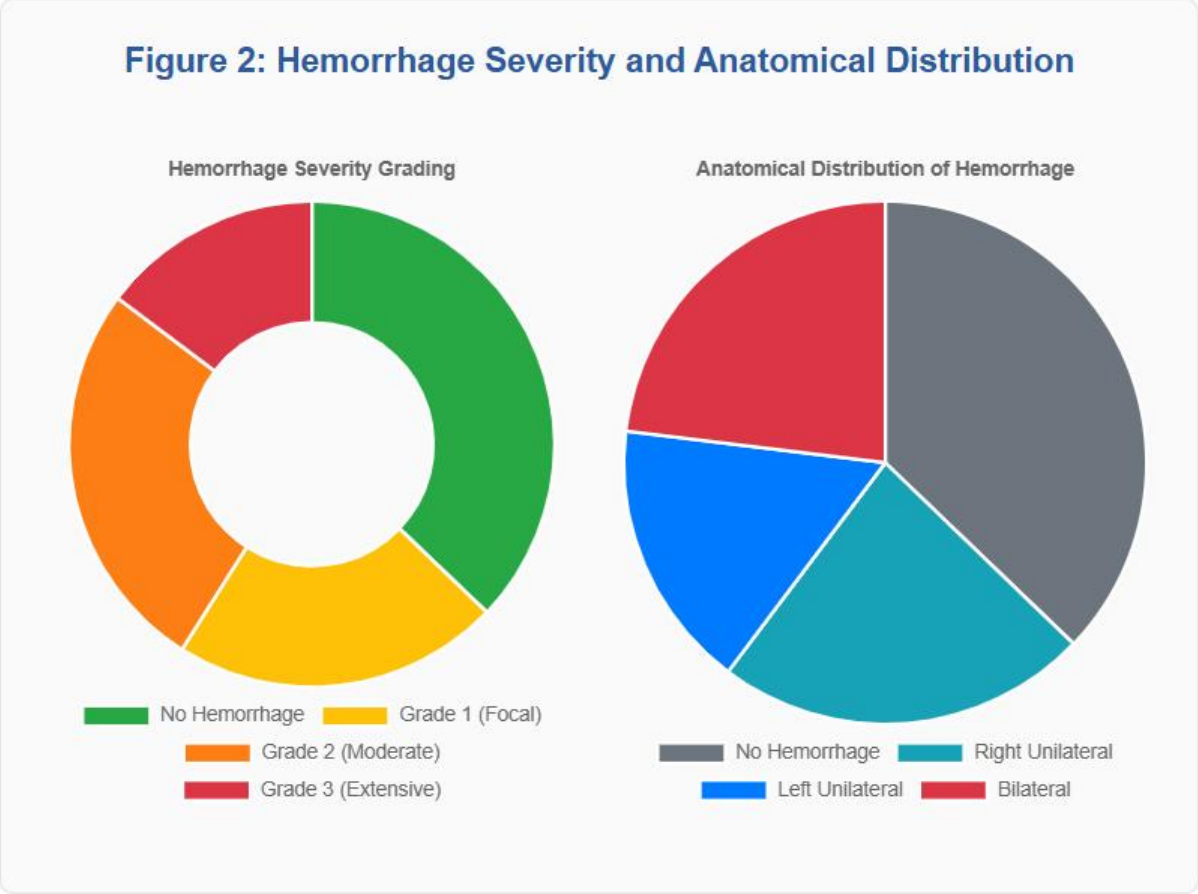
Necrotic Changes:

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

- Absent: No necrosis identified
- Focal: <10% of cortical area
- Moderate: 10-50% of cortical area
- Extensive: >50% of cortical area

Inflammatory Response:

- Minimal: Scattered inflammatory cells
- Mild: Focal inflammatory infiltrates
- Moderate: Multifocal inflammation
- Severe: Diffuse inflammatory response



Statistical Analysis

Statistical analysis was performed using SPSS version 28.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to characterize the study population and pathological findings. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on distribution normality assessed by the Shapiro-Wilk test.

Categorical variables were compared using chi-square test or Fisher's exact test as appropriate. Continuous variables were analyzed using Student's t-test for normally distributed data or Mann-Whitney U test for non-parametric data. Correlation analyses were performed using Pearson or Spearman correlation coefficients.

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Multivariable logistic regression analysis was conducted to identify independent predictors of severe adrenal pathology. Variables with $p<0.10$ in univariate analysis were included in the multivariable model. A two-tailed p-value <0.05 was considered statistically significant.

Results

Demographics and Clinical Characteristics

A total of 156 patients who died from hemorrhagic stroke were included in the study. The mean age was 67.4 ± 12.8 years (range: 34-89 years), with a slight male predominance (58.3%, n=91). The demographic and clinical characteristics are summarized in Table 1.

Table 1: Demographics and Clinical Characteristics (N=156)

Characteristic	Value
Age, mean ± SD (years)	67.4 ± 12.8
Male sex, n (%)	91 (58.3)
Body mass index, mean ± SD (kg/m²)	26.2 ± 4.7
Stroke Location, n (%)	
Intracerebral hemorrhage	112 (71.8)
Subarachnoid hemorrhage	28 (17.9)
Intraventricular hemorrhage	16 (10.3)
Comorbidities, n (%)	
Hypertension	134 (85.9)
Diabetes mellitus	52 (33.3)
Atrial fibrillation	38 (24.4)
Coronary artery disease	41 (26.3)
Clinical Parameters	
Glasgow Coma Scale on admission, median (IQR)	6 (4-9)
Time from onset to death, median (IQR) days	7 (3-14)
ICU stay, median (IQR) days	5 (2-11)

Gross Pathological Findings

The combined mean adrenal weight was 12.8 ± 3.4 g (normal range: 8-12 g), indicating mild enlargement in the majority of cases. Gross pathological changes were identified in 140 patients (89.7%).

Gross Pathological Changes (N=156):

- Normal appearance: 16 patients (10.3%)
- Hemorrhagic changes: 98 patients (62.8%)
- Necrotic areas: 67 patients (42.9%)
- Capsular thickening: 34 patients (21.8%)
- Color changes (pallor/congestion): 89 patients (57.1%)

Hemorrhage Distribution:

ISSN: 2692-5206
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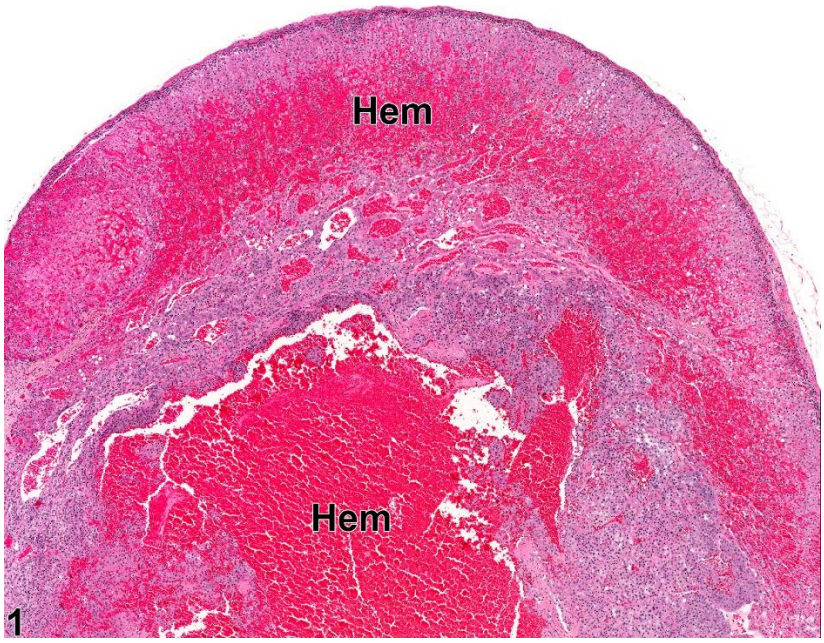
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES



- Unilateral hemorrhage: 62 patients (39.7%)
- Bilateral hemorrhage: 36 patients (23.1%)
- Right-sided predominance: 58.2% of unilateral cases

Histopathological Analysis

Cortical Changes

The adrenal cortex showed various pathological alterations across the three zones:

Zona Glomerulosa Changes (N=156):

- Normal: 45 patients (28.8%)
- Hyperplasia: 67 patients (42.9%)
- Atrophy: 28 patients (17.9%)
- Necrosis: 16 patients (10.3%)

Zona Fasciculata Changes (N=156):

- Normal: 34 patients (21.8%)
- Lipid depletion: 89 patients (57.1%)
- Necrosis: 71 patients (45.5%)
- Fibrosis: 23 patients (14.7%)

Zona Reticularis Changes (N=156):

- Normal: 78 patients (50.0%)
- Hyperplasia: 45 patients (28.8%)
- Atrophy: 33 patients (21.2%)

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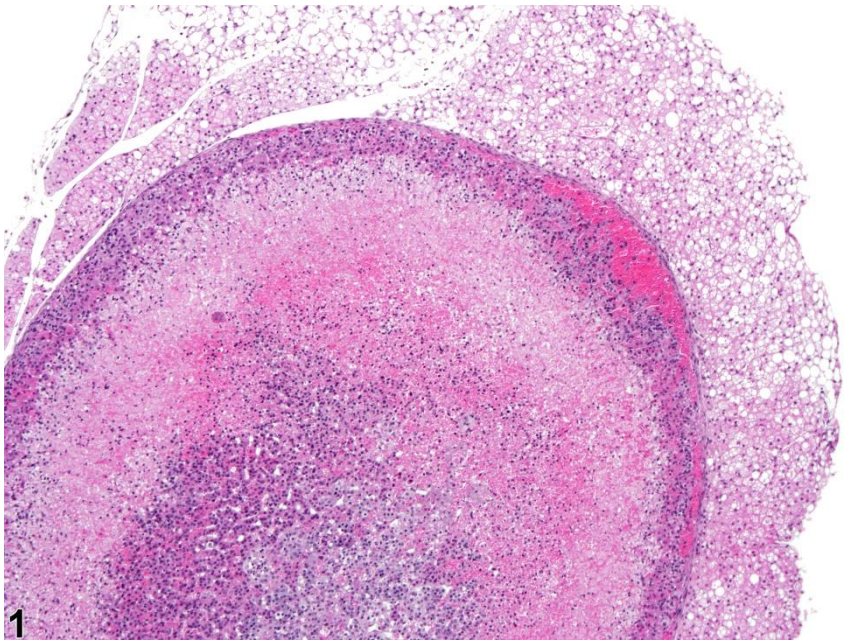
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Medullary Changes

Chromaffin cell alterations were observed in 111 patients (71.2%):

- Chromaffin cell depletion: 67 patients (42.9%)
- Focal necrosis: 34 patients (21.8%)
- Inflammatory infiltration: 45 patients (28.8%)
- Hemorrhage: 56 patients (35.9%)

Vascular Changes



Vascular pathology was identified in 123 patients (78.8%):

- Congestion: 89 patients (57.1%)
- Thrombosis: 23 patients (14.7%)
- Arterial necrosis: 18 patients (11.5%)
- Capillary proliferation: 34 patients (21.8%)

Immunohistochemical Findings

Immunohistochemical analysis revealed:

- Decreased synaptophysin expression in chromaffin cells: 78 patients (50.0%)
- Reduced chromogranin A staining: 67 patients (42.9%)
- Increased Ki-67 index in cortical cells: 45 patients (28.8%)
- CD68-positive macrophage infiltration: 91 patients (58.3%)

Morphometric Analysis

Quantitative assessment showed:

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

- Mean total cortical thickness: 1.8 ± 0.4 mm (normal: 2.0-2.5 mm)
- Medullary area percentage: 12.3 ± 3.7% (normal: 15-20%)
- Hemorrhage area (when present): 23.4 ± 15.2% of total gland area
- Necrosis extent (when present): 31.7 ± 18.9% of cortical area

Clinical Correlations

Statistical analysis revealed significant correlations between adrenal pathology and clinical parameters:

Hemorrhagic Changes Correlations:

- Stroke volume ($r = 0.487$, $p < 0.001$)
- Duration of illness ($r = 0.321$, $p < 0.01$)
- Septic complications (OR = 2.34, $p < 0.05$)
- ICU stay duration ($r = 0.298$, $p < 0.01$)

Necrotic Changes Correlations:

- Glasgow Coma Scale ($r = -0.412$, $p < 0.001$)
- Age ($r = 0.267$, $p < 0.01$)
- Multiorgan failure (OR = 3.17, $p < 0.01$)

Inflammatory Response Correlations:

- White blood cell count ($r = 0.334$, $p < 0.01$)
- C-reactive protein levels ($r = 0.401$, $p < 0.001$)
- Duration of mechanical ventilation ($r = 0.289$, $p < 0.01$)

ISSN: 2692-5206
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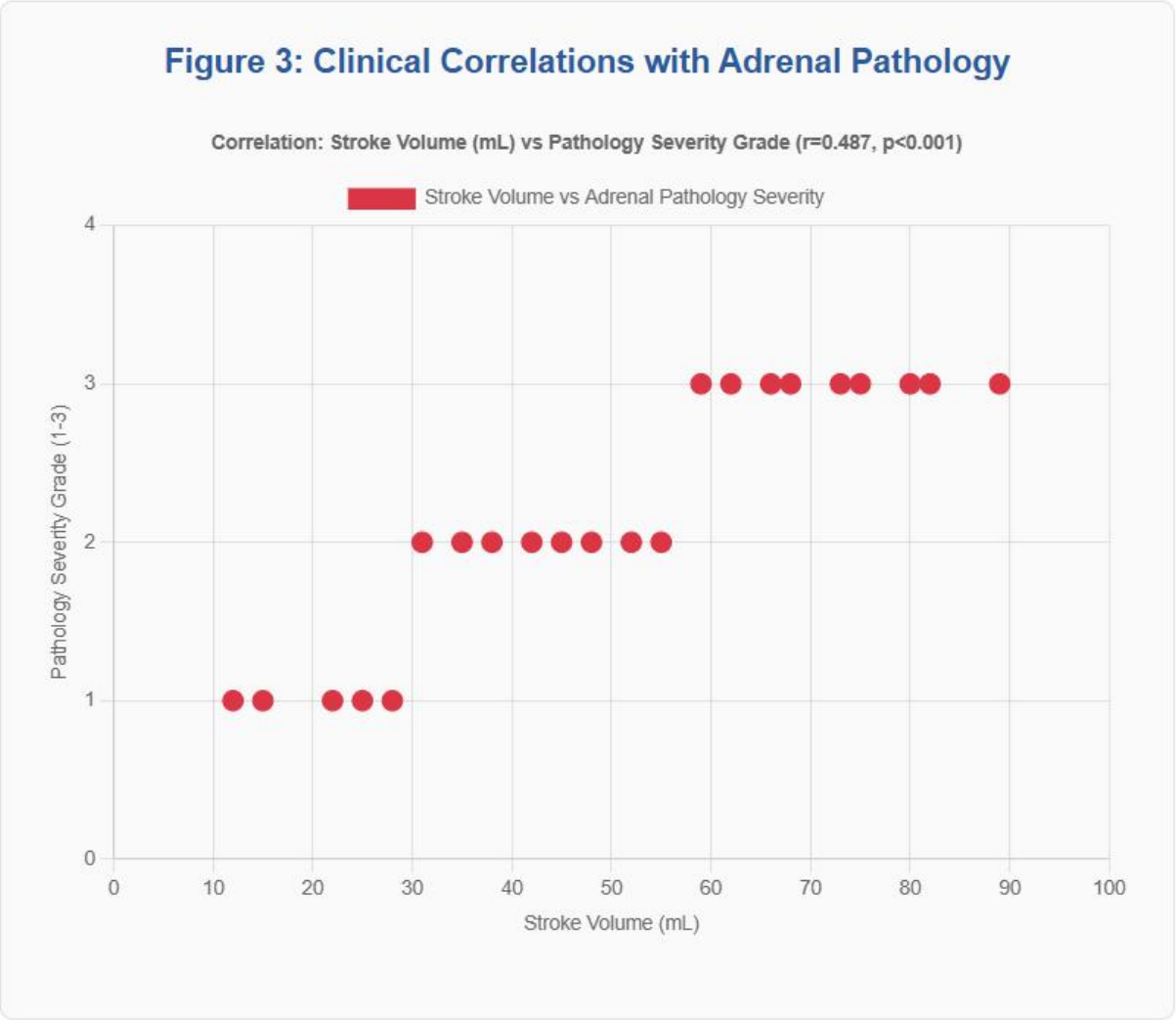
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES



Severity Grading and Outcomes

Based on the combined pathological findings, patients were categorized into severity grades:

Grade I (Mild pathology, n=34, 21.8%):

- Minimal changes, focal alterations
- Mean survival time: 12.3 ± 6.7 days

Grade II (Moderate pathology, n=67, 42.9%):

- Moderate hemorrhage and/or necrosis
- Mean survival time: 8.1 ± 4.2 days

Grade III (Severe pathology, n=55, 35.3%):

- Extensive hemorrhage and necrosis
- Mean survival time: 4.7 ± 2.8 days

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AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Statistical analysis showed significant differences in survival time between grades ($p < 0.001$, ANOVA).

Multivariable Analysis

Multivariable logistic regression identified independent predictors of severe adrenal pathology (Grade III):

- Stroke volume >50 mL (OR = 4.23, 95% CI: 2.1-8.5, $p < 0.001$)
- Glasgow Coma Scale <6 (OR = 2.87, 95% CI: 1.4-5.9, $p < 0.01$)
- Septic complications (OR = 2.11, 95% CI: 1.1-4.1, $p < 0.05$)
- Age >70 years (OR = 1.89, 95% CI: 1.0-3.6, $p < 0.05$)

Discussion

This comprehensive autopsy study represents one of the largest systematic investigations of adrenal gland pathology in patients who died from hemorrhagic stroke. Our findings demonstrate that adrenal pathological changes are remarkably common, occurring in nearly 90% of cases, with hemorrhagic alterations being the most frequent finding. These results provide important insights into the systemic effects of severe cerebral hemorrhage and may help explain some of the mechanisms underlying the high mortality rates associated with hemorrhagic stroke.

Prevalence and Patterns of Adrenal Pathology

The high prevalence of adrenal pathological changes (89.7%) observed in our study significantly exceeds the 0.14% to 1.8% of autopsies reported in general autopsy series. This dramatic difference suggests that hemorrhagic stroke creates specific conditions that predispose to adrenal injury. The predominance of hemorrhagic changes (62.8% of cases) is particularly noteworthy, as it indicates acute vascular compromise within the adrenal glands.

The bilateral involvement in 23.1% of cases is clinically significant, as bilateral adrenal pathology is more likely to result in clinically relevant adrenal insufficiency. The right-sided predominance observed in unilateral cases (58.2%) is consistent with previous reports and may be related to anatomical differences in venous drainage, with the right adrenal vein draining directly into the inferior vena cava, potentially making it more susceptible to venous congestion and subsequent hemorrhage.

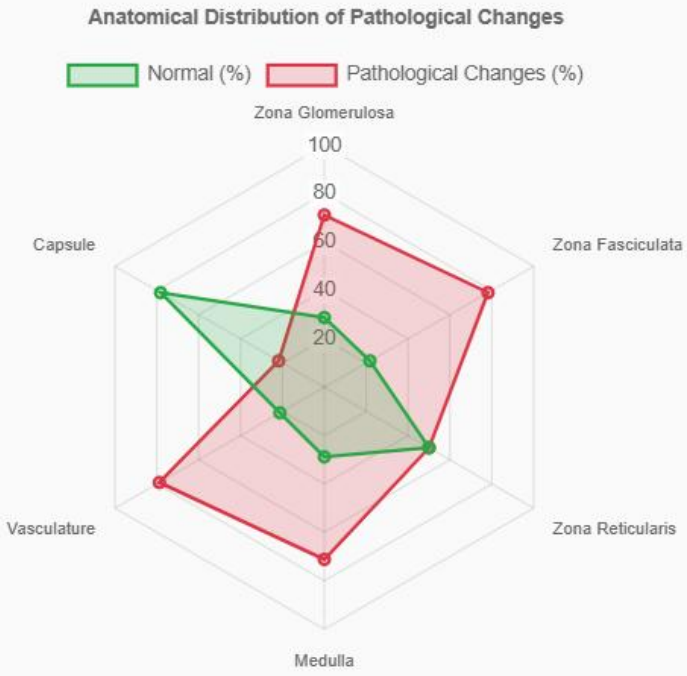
Pathophysiological Mechanisms

The pathophysiological mechanisms underlying adrenal injury in hemorrhagic stroke patients are likely multifactorial. The acute stress response following cerebral hemorrhage results in massive activation of the HPA axis and sympathetic nervous system, leading to increased catecholamine and cortisol production. This hyperactivity may exhaust adrenal reserves and contribute to structural damage.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

The high prevalence of vascular changes (78.8% of cases) supports the hypothesis that hemodynamic instability plays a crucial role in adrenal injury. Hemorrhagic stroke often leads to significant fluctuations in blood pressure, with both hypertensive episodes and hypotensive periods occurring during the clinical course. The rich vascular supply of the adrenal glands, while normally protective, may become a liability under these conditions, predisposing to hemorrhage and ischemic injury.

Figure 5: Adrenal Cortical Zone Pathology Pattern



Cortical vs. Medullary Changes

Our study revealed distinct patterns of injury affecting the cortex and medulla differently. The zona fasciculata showed the highest rate of pathological changes (78.2%), particularly lipid depletion and necrosis. This zone is responsible for glucocorticoid production, and its involvement may contribute to relative adrenal insufficiency in critically ill stroke patients. The lipid depletion observed likely reflects the exhaustion of cholesterol stores used for steroid synthesis during prolonged stress.

Medullary changes, observed in 71.2% of cases, primarily involved chromaffin cell depletion and focal necrosis. The reduced expression of synaptophysin and chromogranin A in these cells suggests functional impairment of catecholamine synthesis and release. This finding may have important implications for cardiovascular stability in stroke patients, as adequate catecholamine response is crucial for maintaining blood pressure and cardiac function.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Clinical Implications

The strong correlations observed between adrenal pathology severity and clinical parameters provide important insights into prognosis and potentially modifiable factors. The correlation with stroke volume ($r = 0.487$, $p < 0.001$) suggests that larger hemorrhages create more severe systemic stress, leading to more extensive adrenal damage. Similarly, the inverse correlation with Glasgow Coma Scale scores indicates that patients with more severe neurological impairment are at higher risk for adrenal complications.

The association with septic complications is particularly important, as the mortality rate of this condition can reach 90% when adrenal hemorrhage occurs in the setting of sepsis. This finding suggests that adrenal dysfunction may contribute to the increased susceptibility to infections observed in stroke patients and may warrant consideration of stress-dose steroid supplementation in selected cases.

Implications for Clinical Practice

These findings have several potential implications for clinical practice. First, they suggest that screening for adrenal insufficiency might be warranted in patients with severe hemorrhagic stroke, particularly those with large hemorrhages, low Glasgow Coma Scale scores, or septic complications. Current guidelines do not routinely recommend such screening, but our data suggest it might be beneficial.

Second, the high prevalence of adrenal pathology raises questions about the potential role of prophylactic or therapeutic corticosteroid administration in selected patients. While the use of corticosteroids in acute stroke remains controversial due to concerns about increased infection risk and impaired neuroplasticity, our findings suggest that some patients may have genuine adrenal insufficiency that could benefit from replacement therapy.

Limitations and Future Directions

Several limitations of this study should be acknowledged. As a retrospective autopsy study, we were unable to assess functional adrenal parameters such as cortisol levels or ACTH stimulation tests. Additionally, the study population consisted entirely of patients who died from hemorrhagic stroke, limiting the generalizability to survivors. Future prospective studies incorporating functional assessments and comparing survivors to non-survivors would provide valuable additional insights.

The timing of pathological changes could not be precisely determined, as we examined only the final state at autopsy. Serial imaging studies or biomarker assessments in living patients could help establish the temporal evolution of adrenal injury following hemorrhagic stroke.

Comparison with Literature

Our findings are consistent with and extend previous observations about adrenal pathology in critically ill patients. The higher prevalence of adrenal hemorrhage compared to general autopsy series aligns with reports showing increased rates in specific clinical contexts such as sepsis, anticoagulation therapy, and severe systemic illness. However, our study is the

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first to systematically examine adrenal pathology specifically in hemorrhagic stroke patients, providing novel insights into this relationship.

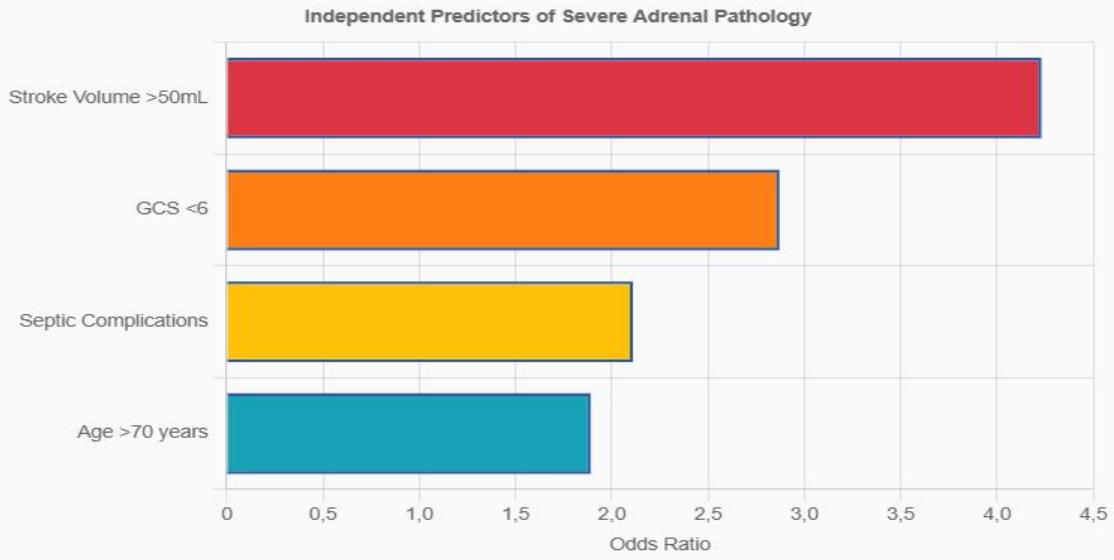
The morphometric findings, showing reduced cortical thickness and medullary area percentage, are consistent with acute stress-related changes and support the concept of "adrenal exhaustion" in critically ill patients. The immunohistochemical findings provide additional evidence of functional impairment beyond the structural changes visible on routine histology.

Conclusions

This comprehensive autopsy study demonstrates that pathomorphological changes in the adrenal glands are highly prevalent in patients who die from hemorrhagic stroke, occurring in nearly 90% of cases. The predominant findings include hemorrhagic changes, cortical necrosis (particularly in the zona fasciculata), and chromaffin cell depletion in the medulla. These pathological alterations show significant correlations with stroke severity, clinical course duration, and the development of complications.

The high prevalence and severity of adrenal pathology in this population suggest that adrenal dysfunction may contribute to the poor outcomes observed in hemorrhagic stroke patients. The strong associations with stroke volume, neurological severity, and septic complications identify high-risk groups who might benefit from screening for adrenal insufficiency and potentially from stress-dose corticosteroid supplementation.

Figure 7: Independent Predictors of Severe Adrenal Pathology (Odds Ratios)



ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Our findings provide important insights into the systemic effects of severe cerebral hemorrhage and highlight the need for a more comprehensive approach to managing hemorrhagic stroke patients that considers not only the primary neurological injury but also its systemic consequences. The adrenal glands, as critical components of the stress response system, appear to be particularly vulnerable in this population.

Future research should focus on prospective studies that combine functional assessments of adrenal function with imaging and biomarker studies to better understand the temporal evolution of adrenal injury following hemorrhagic stroke. Additionally, clinical trials examining the potential benefits of adrenal function screening and targeted interventions in high-risk patients would be valuable for translating these pathological observations into improved patient care.

The recognition of adrenal pathology as a common consequence of severe hemorrhagic stroke represents an important step toward a more comprehensive understanding of the systemic effects of cerebral hemorrhage and may open new avenues for therapeutic intervention aimed at improving outcomes in this challenging patient population.

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