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Research Article

Mortality and Related Factors in Patients Admitted to Intensive Care Unit

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Abstract

Objectives: Intensive care units (ICUs) provide advanced monitoring and treatment for patients with life-threatening organ failure. This study aimed to evaluate the impact of vital signs and laboratory parameters on mortality in ICU patients.
Methods: A total of 498 patients were retrospectively analyzed. Patients aged ≥18 years who were hospitalized for at least 24 hours in the internal medicine ICU were included. Trauma patients, those admitted for surgical procedures, and postoperative patients were excluded. Demographic data, comorbidities, laboratory values, vital signs, nutritional status, respiratory support, and survival outcomes were obtained from electronic medical records.
Results: Of 498 patients, 266 (53.4%) died and 232 (46.6%) survived. Mortality was significantly associated with age, chronic renal disease, respiratory disease, impaired consciousness, APACHE score, and mechanical ventilation requirement. Deceased patients had higher levels of urea, creatinine, bilirubin, ALT, AST, CRP, MPV, lactate, and potassium, and lower levels of albumin, pH, HCO_3, sodium, and calcium ($p<0.05$).
Conclusion: Age, APACHE score, urea, albumin, eosinophil count, MPV, and lactate were identified as independent predictors of mortality in ICU patients.
Keywords: Intensive care unit, Mortality, Prognostic factors, Albumin

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Intensive care units (ICUs) provide advanced supportive therapies for patients with life-threatening acute or chronic organ failure and are associated with higher mortality rates compared with other hospital departments[1,2] Despite significant medical and technological advances, ICU mortality remains a major clinical challenge, particularly among elderly patients and those presenting with multiple comorbidities and severe physiological derangements.[3] Therefore, identifying reliable and easily applicable predictors of mortality at the time of ICU admission is of considerable clinical importance.[4]

Several scoring systems, including APACHE, SAPS, and MPM, have been developed to estimate mortality risk in ICU patients.[5] Although these models are useful for pop-

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ulation-level risk stratification and inter-institutional comparisons, their prognostic accuracy at the individual patient level is limited.[6] Moreover, many of these scoring systems were developed prior to current ICU patient profiles and treatment strategies and may not always be practical for routine clinical use.[7]

In recent years, increasing attention has been directed toward the potential prognostic value of simple clinical and laboratory parameters routinely obtained at ICU admission. Parameters such as serum albumin level, lactate, mean platelet volume (MPV), and eosinophil count reflect systemic inflammation, metabolic stress, and organ dysfunction and are readily available and cost-effective markers[8] Although these parameters have been reported to be associated with ICU mortality, their independent prognostic value in heterogeneous populations admitted to internal medicine ICUs has not been clearly established.

The aim of this study was to evaluate the relationship between admission clinical characteristics, routine laboratory parameters, and mortality in patients admitted to an internal medicine intensive care unit and to identify independent predictors of mortality using multivariate analyses.

Methods

Study Design and Population

This retrospective observational study included a total of 498 patients who were admitted to the internal medicine intensive care unit (ICU) of our institution between January 1, 2016, and December 31, 2019. Ethical approval for the study was obtained from the local Ethics Committee on August 28, 2019 (protocol number: 2019/144). The study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants or their legal representatives in accordance with institutional policy.

Patients aged 18 years and older who were hospitalized in the internal medicine ICU for at least 24 hours were eligible for inclusion. Patients admitted for trauma, those hospitalized for perioperative monitoring, patients prepared for elective surgical procedures, and individuals followed postoperatively were excluded from the study.

Data Collection

Demographic characteristics (age and sex), comorbid conditions, laboratory parameters, complete blood count results, arterial blood gas values, vital signs, nutritional status, respiratory support modalities, and survival outcomes were retrospectively retrieved from the hospital's electronic medical record system. All data were collected using a standardized data extraction approach to ensure consistency.

Statistical Analysis

Statistical analyses were performed using SPSS software for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as median and interquartile range (IQR), while categorical variables were expressed as frequencies and percentages.

The normality of continuous variables was assessed using both visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test). Comparisons between two independent groups were conducted using the Mann-Whitney U test for variables that were not normally distributed. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate.

Multivariate logistic regression analysis was performed to identify independent predictors of mortality. Variables that were clinically relevant or showed significance in univariate analyses were included in the regression model. Statistical significance was defined as a two-sided p-value <0.05.

Artificial intelligence-assisted technology (ChatGPT, OpenAI, GPT-5.3) was used only for language editing and formatting purposes. No AI tool contributed to study design, data analysis, or scientific conclusions.

Results

A total of 498 patients admitted to the internal medicine intensive care unit were included in the analysis. The overall mortality rate was 53.4% (n=266), while 46.6% of patients survived (n=232).

The most common reasons for ICU admission were pneumonia (18.1%), sepsis (14.7%), respiratory failure (14.1%), cardiac arrest (10.8%), cerebral infarction (7.0%), pulmonary edema (7.0%), gastrointestinal bleeding (5.4%), acute renal failure (3.6%), acute coronary syndrome (2.8%), and pulmonary embolism (2.4%), while intracranial hemorrhage accounted for 2.0% and other causes accounted for 12.0% of admissions.

Significant differences were observed between deceased and surviving patients with respect to age, level of consciousness, APACHE score, need for mechanical ventilation, presence of chronic renal disease, and respiratory system disease ($p<0.05$). Patients who died were significantly older and had higher APACHE scores compared with survivors. Mortality was significantly higher in patients with chronic renal disease, whereas it was lower in patients with underlying respiratory diseases. In addition, mortality was significantly higher among patients presenting with impaired consciousness and those requiring mechanical ventilation (Table 1).

Table 1. Distribution of some descriptive and clinical features by mortality status

	(n=498)	Status		
		Survived (n=232)	Deceased (n=266)	p
Age (years)	75(64-84)	72(60-81)	77(67-85)	**<0.001[a]****
Gender				0.060[b]
Female	222(44.6)	93 (40.1)	129(48.5)	
Male	276(55.4)	139(59.9)	137(51.5)	
Presence of comorbidity	459(92.2)	212(91.4)	247(92.9)	0.540[b]
Comorbid disease				
Hypertension	193(38.8)	90 (38.8)	103(38.7)	0.987[b]
Cardiovascular disease	137(27.5)	55 (23.7)	82 (30.8)	0.076[b]
Neurological disease	118(23.7)	52 (22.4)	66 (24.8)	0.530[b]
Diabetes mellitus	112(22.5)	57 (24.6)	55 (20.7)	0.299[b]
Chronic renal disease	107(21.5)	39 (16.8)	68 (25.6)	0.018[b]*
Malignity	104(20.9)	41 (17.7)	63 (23.7)	0.100[b]
Respiratory disease	53 (10.6)	32 (13.8)	21 (7.9)	0.033[b]*
Hemodialysis	23 (4.6)	11 (4.7)	12 (4.5)	0.903[b]
Hepatobiliary tractus disease	13 (2.6)	9(3.9)	4(1.5)	0.157[c]
Presence of infection	312(62.7)	137(59.1)	175(65.8)	0.121[b]
Consciousness				
Coma	73 (14.7)	28 (12.1)	45 (16.9)	
Conscious	143(28.7)	94 (40.5)	49 (18.4)	
Confusion	193(38.8)	81 (34.9)	112(42.1)	<0.001[b]**
Lethargia	50 (10.0)	19 (8.2)	31 (11.7)	
Stupor	39 (7.8)	10 (4.3)	29 (10.9)	
APACHE score				
Mechanical ventilation				
NIMV	43 (8.6)	27 (11.6)	16 (6.0)	

#Continuous variables are presented as "median (interquartile range (IQR))" and categorical variables as "number (percent of column)"; a Mann-Whitney U test; b Pearson chi-square test; c Fisher's exact test; *p<0.05; ** p<0.01

No statistically significant association was found between mortality and sex, hypertension, cardiovascular disease, neurological disease, diabetes mellitus, hepatobiliary disease, hemodialysis, infection development, duration of ICU stay, or presence of malignancy (p>0.05) (Table 1).

Laboratory analyses demonstrated significant differences between survivors and non-survivors in terms of blood urea, creatinine, albumin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and C-reactive protein (CRP) levels (p<0.05). Deceased patients had significantly higher urea, creatinine, bilirubin, ALT, AST, and CRP levels, while albumin levels were significantly lower. No significant differences were observed for blood glucose or magnesium levels (Table 2).

Hematological parameters also differed significantly between groups. White blood cell count, neutrophil count, and mean platelet volume (MPV) were significantly higher in deceased patients, whereas eosinophil count and platelet count were significantly higher among survivors (p<0.05). No significant differences were found in lymphocyte, monocyte, basophil, red blood cell counts, hemoglobin, hematocrit, or mean corpuscular volume values (p>0.05) (Table 3).

Coagulation parameters, including activated partial thromboplastin time (APTT), prothrombin time (PT), and international normalized ratio (INR), were significantly higher in patients who died compared to survivors (p<0.05).

Arterial blood gas and electrolyte analyses revealed significant associations between mortality and pH, partial pres-

Table 2. Distribution of biochemical parameters by mortality status

	(n=498)	Status		p^a
		Survived (n=232)	Deceased (n=266)	
	Median (IQR)	Median (IQR)	Median (IQR)	
Glucose (g/dL)	142(112.0-204.2)	140(113.5-211.5)	146.5(109-202.2)	**0.269**
Urea (mg/dL)	85(47.0-136.5)	63(39-121)	98(63.8-156.5)	**<0.001****
Creatinine (mg/dL)	1.45(0.82-2.86)	1.12(0.75-2.20)	1.80(1.00-3.37)	**<0.001****
Albumin (g/dL)	2.9(2.5-3.5)	3.0(2.7-3.7)	2.8(2.4-3.3)	**<0.001****
Total bilirubin (mg/dL)	0.90(0.56-1.60)	0.80(0.50-1.34)	0.92(0.60-1.90)	**0.004****
Direct bilirubin (mg/dL)	0.40(0.20-0.74)	0.36(0.20-0.60)	0.48(0.28-1.00)	**0.001****
ALT (U/L)	22(13-45)	20.0(12.0-37.0)	24.0(14.0-54.2)	**0.008****
AST (U/L)	29(20-64)	26.0(17.0-52.0)	36.0(22.0-89.0)	**<0.001****
Magnesium (mEq/L)	1.91(1.70-2.20)	1.90(1.60-2.14)	1.98(1.70-2.21)	0.051
CRP (mg/L)	7.4(3.0-14.0)	5.4(2.0-12.2)	9.8(4.0-16.0)	**<0.001****

n: Number of patients; IQR: Interquartile range; a Mann-Whitney U test; *p<0.05; **p<0.01

sure of oxygen (pO_2), bicarbonate (HCO_3), base excess (BE), lactate, sodium, potassium, and calcium levels ($p<0.05$). Deceased patients exhibited higher pO_2, BE, lactate, and potassium levels, while pH, HCO_3, sodium, and calcium levels were significantly lower. No significant differences were observed for partial pressure of carbon dioxide (pCO_2), oxygen saturation (SO_2), or chloride levels.

Vital signs also differed significantly between groups. Body temperature and heart rate were significantly higher in deceased patients, whereas systolic and diastolic blood pressure values and oxygen saturation were significantly lower ($p<0.05$).

Regarding nutritional support, most deceased patients were fed via nasogastric tube (86.1%), followed by closed oral intake (8.3%), oral feeding (2.6%), PEG feeding (2.6%), and total parenteral nutrition (0.4%). Among survivors, 69.0% received nasogastric feeding, 10.8% had closed oral intake, 15.5% were orally fed, and 4.7% received PEG feeding. Nasogastric feeding was significantly more common among survivors ($p<0.05$).

In multivariate logistic regression analysis, age, APACHE score, blood urea, albumin, eosinophil count, MPV, and lactate levels were identified as independent predictors of

Table 3. Distribution of complete blood count parameters by mortality status

	(n=498)	Survived (n=232)	Deceased (n=266)	p^a
	Median (IQR)	Median (IQR)	Median (IQR)	
WBC (/mcL)	11.7(7.5-15.5)	10.9(7.0-15.4)	12.1(8.4-16.0)	**0.046***
Lymphocyte (/mcL)	1.00(0.60-1.60)	1.08(0.60-1.60)	0.90(0.57-1.60)	0.272
Monocyte (/mcL)	0.53(0.31-0.85)	0.54(0.33-0.80)	0.52(0.30-0.90)	0.858
Neutrophil (/mcL)	9.6(5.8-13.0)	8.6(5.0-13.0)	10.0(6.4-13.6)	**0.035***
Eozinophil (/mcL)	0.02(0-0.09)	0.03(0-0.11)	0.02(0-0.7)	**0.005****
Basophil (/mcL)	0.02(0-0.03)	0.01(0.01-0.03)	0.02(0-0.04)	0.831
Red blood cell (/mcL)	3.5(3.0-4.2)	3.6(3.1-4.3)	3.5(3.0-4.2)	0.223
Hemoglobin (g/dL)	10.0(8.8-12.0)	10.0(8.8-12.2)	10.0(8.7-12.0)	0.225
Hematocrit (%)	31.4(27.0-37.0)	31.8(27.4-38.0)	89.0(85.0-94.0)	0.381
MCV (fL)	89(85-93)	88.1(85-92)	89(85-94)	0.150
PLT (/mcL)	201.0(135.8-280.2)	216.5(155.2-295.0)	186.0(120.5-264.8)	**0.009****
MPV (fL)	9.4(8.6-10.4)	9.2(8.4-10.2)	9.6(8.7-10.7)	**<0.001****

n: Number of patients; IQR: Interquartile range; aMann-Whitney U test; *p<0.05; **p<0.01

Table 4. Independent effect of some possible predictors on mortality status *(Multivariate logistic regression analysis)*

	B	SE	Waldχ2	sd	OR (95 CI)	p
Age	0.020	0.008	7.2	1	1.020(1.005-1.036)	**0.007**
APACHE score	0.042	0.014	9.6	1	1.043(1.016-1.071)	**0.002**
Urea	0.004	0.002	6.0	1	1.004(1.001-1.007)	**0.014**
Albumin	-0.392	0.165	5.6	1	0.676(0.489-0.935)	**0.018**
CRP	0.025	0.013	3.8	1	1.026(1.000-1.052)	0.051
Eosinophil	-1.420	0.716	3.9	1	0.242(0.059-0.983)	**0.047**
MPV	0.122	0.065	3.5	1	1.130(0.995-1.284)	**<0.001**
Lactate	0.166	0.037	20.2	1	1.181(1.098-1.270)	**<0.001**
Fever	0.278	0.167	2.8	1	1.320(0.952-1.830)	0.095
Heart rate	0.004	0.004	0.9	1	1.004(0.995-1.013)	0.350

B: Regression coefficient; SH: Standard error; sd: degrees of freedom; OR: odds ratio; CI: Confidence interval Cox & Snell R: 0.22; Nagel kerke R: 0.29; Hosmer-Lemeshow χ2: 10.2, p=0.254

mortality ($p<0.05$). CRP, body temperature, and heart rate did not retain independent significance in the multivariate model (Table 4).

Discussion

Age has long been discussed as a prognostic factor in intensive care unit (ICU) patients, although its independent impact on mortality remains controversial. Kölgelier et al.[9] reported that advanced age was a significant factor affecting mortality, supporting our findings. Similarly, Nicolas et al.[10] demonstrated that mortality rates were more than twofold higher in patients over 65 years of age compared with those younger than 45 years, concluding that age is an important prognostic indicator, albeit less influential than disease severity.

In contrast, Chelluri et al.[11] suggested that age alone is not a reliable independent predictor of long-term survival or quality of life in critically ill patients. In our study, age emerged as a strong predictor of mortality. The discrepancies between these findings may be attributed to differences in disease severity at ICU admission, variations in patient populations, and heterogeneity in admission criteria across ICUs.

Mechanical ventilation is a well-established marker of disease severity and poor prognosis in ICU settings. Ünal et al. reported that 44.1% of patients required mechanical ventilation for an average of 12.7±13.5 days, with a mortality rate of 85.7%.[2] Our findings regarding mechanically ventilated patients were consistent with previously published data. Moreover, our ICU frequently provided care to patients with poor prognostic profiles due to severe comorbidities or those receiving palliative support, which may have contributed to the higher mortality observed among mechanically ventilated patients.

The relatively low rate of non-invasive mechanical ventilation (NIMV) in our cohort also warrants consideration. Patients who tolerated NIMV were predominantly managed in hospital wards and were transferred to the ICU only in cases of clinical deterioration. This practice pattern likely resulted in a lower proportion of NIMV use within the ICU population.

Severity scoring systems such as APACHE II are commonly used to predict outcomes in critically ill patients. Uysal et al.[12] reported higher-than-expected mortality rates across all APACHE II subgroups, emphasizing that while these scoring systems are valuable for comparing study populations, their predictive accuracy decreases in ICUs with heterogeneous patient profiles. They recommended recalibration of scoring systems according to unit-specific characteristics. Delayed initiation of organ-supportive therapies prior to ICU admission and the time elapsed before ICU transfer, factors not fully captured by scoring systems, may partially explain these discrepancies.

Comorbidities have also been variably associated with ICU mortality. Ceylan et al. reported that although most patients had underlying diseases, no significant association was observed between mortality and comorbidity burden or length of ICU stay.[13] Conversely, the EPIC study identified organ failure, malignancy, and diabetes as mortality risk factors in univariate analysis, with cancer remaining significant in multivariate models.[14] In our cohort, mortality was significantly higher in patients with chronic renal disease, whereas patients with respiratory diseases demonstrated lower mortality. Subgroup analyses according to multiple comorbidities were not performed, and our cohort consisted exclusively of patients admitted to an internal medicine ICU, which may explain these findings.

Biochemical parameters provided important prognostic information in our study. Higher levels of blood urea, creatinine, total and direct bilirubin, ALT, AST, and CRP, along with lower serum albumin levels, were significantly associated with mortality. Serum bilirubin has been described as a stable and reliable marker of hepatic dysfunction and is incorporated into several prognostic scoring systems.[15,16] Kramer et al.[17] demonstrated that even mild elevations in bilirubin were associated with significantly reduced survival, findings that strongly support our results.

Hypoalbuminemia is frequently observed in the early stages of critical illness and has been linked to prolonged ICU stay, mechanical ventilation, infection development, and increased mortality.[18–20] Similarly, elevated serum creatinine has consistently been associated with adverse outcomes. Akkoç et al.[7] reported increased mortality with higher creatinine levels at admission, and multiple studies have shown that even small increases in creatinine are linked to increased mortality risk.[21] Acute renal failure remains a major contributor to ICU mortality, with reported mortality rates ranging from 40% to 60%.[22,23] In our study, elevated urea and creatinine were associated with mortality; however, the absence of baseline creatinine values and urine output data represents a limitation.

Inflammatory markers also played a significant role. CRP, a widely used acute-phase reactant, was significantly associated with mortality in our cohort. Lobo et al. demonstrated that elevated CRP levels at ICU admission were associated with increased risk of organ failure and death.[24] Although procalcitonin has been reported to outperform CRP in predicting outcomes in septic shock,[25] it was not routinely available during the study period. Nonetheless, CRP showed strong prognostic value in our population.

Hematological parameters further contributed to mortality prediction. Higher white blood cell count, neutrophil count, and mean platelet volume (MPV), together with lower eosinophil and platelet counts, were observed in deceased patients. Previous studies, including those by Zhang et al., have shown that elevated MPV and thrombocytopenia are associated with increased mortality, consistent with our findings.[26]

Finally, disturbances in acid-base balance, electrolytes, and lactate levels were significantly associated with mortality. Elevated lactate, reflecting tissue hypoxia and impaired microcirculation, has been repeatedly shown to be a strong predictor of mortality, particularly when present at ICU admission.[27,28] Base deficit, an indirect marker of lactic acidosis, has similarly been associated with poor outcomes in critically ill patients.[29]

Conclusion

Based on the findings of this study, age, APACHE score, blood urea, serum albumin, eosinophil count, mean platelet volume (MPV), and lactate levels were identified as independent predictors of mortality in patients admitted to the intensive care unit. These results highlight the prognostic value of routinely available clinical and laboratory parameters in critically ill patients. Incorporation of these variables into mortality risk assessment models may improve prognostic accuracy and assist clinicians in early risk stratification, clinical decision-making, and resource allocation in intensive care settings.

Disclosures

Acknowledgement: This study was presented as an oral presentation at the 3rd International & 7th National Congress on Drug and Treatment (Iskele, Cyprus, TRNC; September 21–25, 2022).

Ethics Committee Approval: The ethics committee approval has been granted by Recep Tayyip Erdogan University on 28/08/2019 and protocol number: 2019/144. The study complied with the Declaration of Helsinki.

Informed Consent: Written consent was obtained from all participants.

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Research Article

Clinical and Demographic Characteristics of Patients with Non-Functional Pituitary Adenomas: A Retrospective Single-Center Study

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Abstract

Objectives: Non-functioning pituitary adenomas (NFPAs) are typically diagnosed due to tumor mass effects rather than hormone hypersecretion. However, variability in clinical presentation and outcomes remains incompletely defined.

Methods: This retrospective study included 200 patients diagnosed with NFPAs between 2013 and 2020. Clinical features, hormonal parameters, tumor size, and follow-up outcomes were analyzed.

Results: The mean age at diagnosis was 41.31 years. Macroadenomas were more frequent in males, whereas microadenomas predominated in females (p=0.002). Headache, hypogonadal symptoms, and fatigue were the most common presenting complaints. Mass effect–related symptoms were more prominent in males and larger tumors (p<0.05). The most frequent hormonal abnormalities were growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%), with a higher prevalence in larger tumors (p<0.05). Visual field defects were identified in 16% of patients and were strongly associated with larger tumors (p<0.001). Tumor size remained stable at one year, although new hormonal deficiencies developed during follow-up.

Conclusion: NFPAs demonstrate distinct sex- and size-related clinical patterns. Men tend to present later with larger tumors and a higher burden of mass effect–related symptoms. Progressive endocrine dysfunction may occur despite radiological stability, underscoring the need for long-term follow-up.

Keywords: Hypopituitarism, macroadenoma, non-functioning pituitary adenoma, pituitary incidentaloma, transsphenoidal surgery

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Pituitary adenomas are among the most common intracranial tumors, accounting for approximately 10–15% of all primary brain neoplasms. These tumors arise from adenohypophyseal cells and are broadly classified as functional or non-functional based on their hormonal activity. Pituitary adenomas are also classified by tumor size: lesions <10 mm are defined as microadenomas, ≥10 mm as macroadenomas, and ≥40 mm as giant adenomas.[1,2]

Most pituitary adenomas present with clinical findings related to hormone hypersecretion, such as hyperprolactinemia, acromegaly, and Cushing's disease. However, approximately 25–35% of pituitary adenomas are clinically silent and are classified as non-functioning pituitary adenomas (NFPAs).[3] NFPAs represent one of the most common subtypes of pituitary adenomas and are defined by the absence of clinically significant hormone hypersecretion.

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NFPAs are frequently detected incidentally on imaging performed for unrelated indications (pituitary incidentalomas) or become clinically evident due to local mass effects, most commonly hypopituitarism, headache, and visual field defects resulting from optic chiasm compression.[4-6] Consequently, the absence of clinically significant hormone hypersecretion often delays diagnosis until tumor enlargement produces compressive symptoms.

Although classified as non-functioning, NFPAs constitute a biologically heterogeneous group. Some tumors demonstrate no evidence of hormone production, whereas others show positive immunohistochemical staining for pituitary hormones without clinically evident hormone excess. These lesions are therefore referred to as clinically silent adenomas.[7,8]

Approximately 70–90% of clinically non-functioning pituitary adenomas are gonadotroph adenomas, arising from cells capable of producing follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[9] Owing to their limited hormonal activity, patients typically present with symptoms related to local tumor expansion, including visual disturbances, headache, and varying degrees of pituitary dysfunction.[10] In addition, clinically silent variants of somatotroph, corticotroph, thyrotroph, and lactotroph adenomas have also been described, demonstrating immunohistochemical hormone expression without corresponding clinical syndromes.[11-15]

After the detection of a pituitary adenoma, evaluation should focus on the presence of hormone hypersecretion and symptoms related to tumor mass effects. In patients with NFPA, the primary goals of treatment are relief of compressive symptoms, preservation or improvement of pituitary function, and prevention of tumor progression or recurrence. Transsphenoidal surgical resection is considered the standard first-line treatment modality, and surgery is generally recommended in the presence of compressive symptoms or documented tumor growth. Radiotherapy is infrequently used as primary treatment and is mainly reserved for patients unsuitable for surgery or as adjuvant therapy for residual disease. No medical therapy has demonstrated clear efficacy in NFPAs. Patients managed with observation are typically monitored every 3–6 months with clinical and radiological follow-up.[16]

The aim of this retrospective study was to evaluate the clinical, radiological, and pathological characteristics of patients diagnosed with non-functioning pituitary adenoma and to identify factors associated with tumor progression, recurrence, and treatment outcomes. In addition, we sought to assess the impact of tumor size, invasiveness, and treatment modalities on disease course and follow-up outcomes.

Methods

This retrospective cross-sectional study was conducted following approval from a Mersin University Ethics Committee (Decision no: 347, dated May 13, 2020). Patient records of individuals diagnosed with NFPA and managed between January 1, 2013, and March 31, 2020, at a tertiary referral center were systematically reviewed. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were age between 18 and 65 years and confirmed diagnosis based on clinical, hormonal, and radiological findings. Patients with incomplete hormonal evaluation or insufficient imaging data were excluded. A total of 200 patients (137 female, 63 male) were included. Demographic data, presenting symptoms, baseline hormonal parameters (PRL, FSH, LH, ACTH, TSH, cortisol, GH, IGF-1), tumor size, and imaging findings were recorded. Adenomas were classified as microadenomas (<10 mm) or macroadenomas (≥10 mm).

Patients were categorized according to treatment approach (surgical vs. non-surgical) and follow-up status. Follow-up duration, hormonal deficiencies, visual field defects, residual tumor, recurrence, and additional treatment requirements were evaluated.

Statistical Analysis

Statistical analyses were performed using STATISTICA version 13.5 (TIBCO Software Inc., Palo Alto, CA, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were expressed as mean ± standard deviation or as minimum–maximum values, depending on the distribution characteristics, while categorical variables were presented as frequencies (n) and percentages (%). Comparisons of continuous variables, including age at diagnosis, hormone levels, and tumor size, according to sex and tumor classification (microadenoma vs. macroadenoma), were performed using the independent samples t-test. Comparisons of categorical variables, such as presenting symptoms and hormonal abnormalities, were conducted using the chi-square test or Fisher's exact test when appropriate. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

A total of 200 patients were included in the study, of whom 137 (68.5%) were female and 63 (31.5%) were male. Microadenomas were detected in 106 patients, and macroadenomas were detected in 94 patients. Microadenomas were more commonly observed in females (60.6% vs.

36.5%), whereas macroadenomas were significantly more frequent in males (63.5% vs. 39.4%), and both of these differences were statistically significant (p=0.002). The mean age at diagnosis was 41.31±15.36 years. Male patients were diagnosed at a significantly older age than female patients (47.54±18.33 vs. 38.44±12.87 years). Similarly, patients with macroadenomas were older than those with microadenomas (49.09±15.98 vs. 34.41±10.88 years, p<0.001).

The most common presenting symptoms were headache, hypogonadal symptoms (menstrual irregularity, decreased libido, and impotence), and fatigue. In female patients, the most frequent symptoms were headache (59.9%), menstrual irregularity (44.5%), and fatigue (19%), whereas in male patients, headache (79.4%), fatigue (34.9%), and decreased libido (34.9%) were more prominent. Headache, visual disturbance, ophthalmoplegia, and fatigue were significantly more frequent in male patients (p<0.05). Table 1 shows the distribution of presenting symptoms according to sex.

When stratified by tumor size, patients with macroadenomas more commonly presented with headache, visual disturbance, and ophthalmoplegia, whereas hypogonadal symptoms and galactorrhea were more frequently observed in patients with microadenomas (p<0.001). Importantly, in all patients presenting with galactorrhea, the symptom was attributed to non-pituitary causes, and NFPA was identified incidentally during the diagnostic workup. Visual field defects were detected in 32 patients (16%), with a significantly higher prevalence in macroadenomas compared to microadenomas (32% vs. 0.9%, p<0.001) (Table 2).

The most common hormonal abnormalities were growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%). In male patients, growth hormone deficiency (34.9%), central hypogonadism (25.4%), and central hypothyroidism were the most frequent abnormalities, whereas in female patients, hyperprolactinemia (18.2%), growth hormone deficiency (16%), and central hypogonadism (13.9%) were more common. Growth hormone deficiency (p=0.005) and central hypothyroidism (p = 0.035) were significantly more frequent in male patients, while hyperprolactinemia was more common in female patients (p=0.016). Hormonal abnormalities were more prevalent in macroadenomas, particularly central hypogonadism (24%), central hypothyroidism (23.4%), and growth hormone deficiency (28.7%) (p<0.05). The distribution of hormonal abnormalities according to tumor size and sex is presented in Tables 3 and 4, respectively.

Regarding the initial point of contact, the majority of patients presented to the neurosurgery (n=79, 39.5%) and endocrinology (n=71, 35.5%) departments, while the remainder visited neurology (n=20, 10%), obstetrics and gynecology (n=11, 5.5%), and other clinics (n=19, 9.5%),

Table 1. Distribution of presenting symptoms according to sex

Symptom	Female (n=137), n (%)	Male (n=63), n (%)	p
Headache	82 (59.9)	50 (79.4)	0.007
Blurred vision	26 (19.0)	21 (33.3)	0.032
Ophthalmoplegia	4 (2.9)	7 (11.1)	0.038
Fatigue	26 (19.0)	22 (34.9)	0.020
Decreased libido	26 (19.0)	22 (34.9)	—
Menstrual irregularity	61 (44.5)	—	—
Galactorrhea	25 (18.2)	1 (1.6)	0.016
Short stature	0 (0.0)	1 (1.6)	—
Impotence	—	17 (27.0)	—
Weight change	5 (3.6)	2 (3.2)	—

Table 2. Distribution of presenting symptoms according to tumor size

Symptoms	Microadenoma (n=106), n (%)	Macroadenoma (n=94), n (%)	p
Headache	48 (45.3)	84 (89.4)	<0.001
Blurred vision	12 (11.3)	35 (37.2)	<0.001
Ophthalmoplegia	0 (0.0)	11 (11.7)	<0.001
Fatigue	22 (20.8)	26 (27.7)	—
Hypogonadal symptoms (menstrual irregularity, decreased libido, impotence)	60 (56.6)	25 (26.6)	<0.001
Short stature	1 (0.9)	0 (0.0)	—
Weight change	4 (3.8)	3 (3.2)	—
Galactorrhea	24 (22.6)	2 (2.1)	<0.001

Table 3. Distribution of hormonal abnormalities according to tumor size

Hormonal abnormality	Macroadenoma (n=94), n (%)	Microadenoma (n=106), n (%)	p
Hyperprolactinemia	16 (17.0)	14 (13.2)	—
Hypoprolactinemia	8 (8.5)	3 (2.8)	—
Central hypogonadism	22 (23.4)	13 (12.3)	0.042
Central hypothyroidism	22 (23.4)	9 (8.5)	0.006
Cortisol deficiency	18 (19.1)	7 (6.6)	0.017
Growth hormone deficiency	27 (28.7)	17 (16.0)	0.040

Table 4. Distribution of hormonal abnormalities according to sex

Hormonal abnormality	Male (n=63), n (%)	Female (n=137), n (%)	p
Hyperprolactinemia	5 (7.9)	25 (18.2)	0.016
Hypoprolactinemia	7 (11.1)	4 (2.9)	—
Central hypogonadism	16 (25.4)	19 (13.9)	—
Central hypothyroidism	15 (23.8)	16 (11.7)	0.035
Cortisol deficiency	13 (20.6)	12 (8.8)	—
Growth hormone deficiency	22 (34.9)	22 (16.1)	0.005

including the emergency department, ophthalmology, general surgery, and urology.

Visual field examination was performed in all patients at initial presentation, revealing adenoma-related visual field defects in 32 patients (16%), including 1 patient (0.9%) with microadenoma and 31 patients (32%) with macroadenoma, with a significantly higher prevalence observed in macroadenomas ($p<0.001$). Notably, the microadenoma associated with visual field defect measured 9.5 mm and was located in close proximity to the optic chiasm.

Among the 112 patients who remained in follow-up, surgical intervention was performed in 41 cases, predominantly in those with macroadenomas ($p < 0.001$). Surgical indications mainly included optic chiasm compression, hormonal deficiencies, and persistent headache. Residual tumor was detected in 20 patients (48%), and recurrence occurred in 7 patients (17.1%). Postoperative hormonal evaluation showed that 12 patients (29.3%) had normal hormone profiles, 20 patients (48.8%) had panhypopituitarism, and the remaining 9 patients had one or more hormonal deficiencies. Postoperative radiotherapy was required in 8 patients (19.5%). Patients managed conservatively were followed at 3–6 month intervals, and a minority developed new hormonal deficiencies, including hypoprolactinemia, central hypogonadism, and growth hormone deficiency during follow-up.

Follow-up MRI at one year demonstrated no meaningful change in tumor size among 54 non-operated patients, with comparable mean diameters at baseline and at one year (8.74±6.34 mm vs. 8.69±6.09 mm).

Discussion

Non-functioning pituitary adenomas (NFPAs) demonstrate variability in demographic characteristics across different study populations. Previous studies have reported that NFPAs are more common in females before the fourth decade of life, whereas male predominance becomes more apparent in the later decades.[17-20] In addition, several reports have indicated that diagnosis typically occurs in the fifth decade in females and in the sixth decade in males, with an overall mean age ranging between 50 and 55 years.[18]

In line with previous studies, female patients constituted the majority in our cohort, and men were diagnosed at a significantly older age than women (47.54±18.33 vs. 38.44±12.87 years). Overall, the mean age at diagnosis in our cohort was lower than that reported in the literature. This difference may be attributed to earlier imaging, greater accessibility to healthcare, or differences in referral patterns. The statistically significant age difference between sexes and between tumor size groups suggests that tumor growth and delayed clinical presentation are closely related.

Consistent with previous studies, macroadenomas were more frequently observed in males, whereas microadenomas predominated in females. In addition, patients with macroadenomas were diagnosed at older ages compared to those with microadenomas, which is likely related to the absence of early endocrine symptoms and the delayed development of mass effect–related clinical findings. These findings are in line with prior reports demonstrating that tumor size is associated with both age at diagnosis and clinical presentation.

The initial point of healthcare contact for patients with NFPA remains an underexplored area in the literature. While some studies have suggested that patients commonly present to ophthalmology clinics,[21] our findings indicate that the majority of patients initially presented to neurosurgery outpatient clinics, likely due to the high prevalence of headache as the presenting symptom. Only a minority of patients presented initially to endocrinology clinics, highlighting the importance of multidisciplinary evaluation in these patients.

In our cohort, the most common presenting symptoms were headache, hypogonadal symptoms, and fatigue, which are consistent with the known effects of tumor mass and pituitary dysfunction. Although symptom distribution varies across populations, our findings were largely in agreement with previous studies.[16,18,19,22-26] Evidence regarding sex-related differences in the presenting symptoms of non-functioning pituitary adenomas remains limited and, at times, inconsistent across studies. Di Somma et al.[25] reported a higher prevalence of headache and visual disturbances in male patients, whereas other analyses did not demonstrate a clear association between headache and sex.[27] Similarly, Ferrante et al.[19] observed comparable rates of hypogonadal symptoms between females and males (42.5% vs. 37.9%)[19], while Cury et al.[28] reported a markedly higher prevalence in females (78% vs. 35%)[28]. In contrast to these heterogeneous findings, our results suggest a more distinct sex-related pattern of clinical presentation. Specifically, male patients in our cohort more frequently exhibited symptoms related to tumor mass effect, including headache, visual disturbance, ophthalmoplegia, and fatigue. Our findings indicate a distinct sex-related pattern in clinical presentation, likely reflecting differences in tumor burden as well as variations in symptom perception and referral pathways.

Tumor size also played a significant role in symptom presentation. Patients with macroadenomas more frequently presented with symptoms related to local mass effect, including headache, visual disturbance, and ophthalmoplegia, whereas hypogonadal symptoms and galactorrhea were more commonly observed in microadenomas. These findings are consistent with prior reports showing that mass effect–related symptoms are more prominent in larger tumors.[29]

Previous studies have reported a wide range in the prevalence of hormonal abnormalities in non-functioning pituitary adenomas, varying between 30% and 85%, while panhypopituitarism has been reported in approximately 10% of cases. The most frequently described deficiencies include growth hormone deficiency (61–100%), gonadotropin deficiency (36–96%), and adrenal insufficiency (17–62%), although these rates differ substantially depending on the studied population and diagnostic criteria.[16,19,30,31] In comparison, our cohort demonstrated a lower overall frequency of hormonal abnormalities, with growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%) being the most common findings. This discrepancy may be attributed to differences in patient selection, earlier-stage disease at diagnosis, or the retrospective nature of our study. Notably, new hormonal abnormalities developed during follow-up in a subset of patients, suggesting a dynamic and potentially progressive course of pituitary dysfunction.

Sex-based differences in hormonal abnormalities were also evident. Growth hormone deficiency and central hypothyroidism were significantly more frequent in males, whereas hyperprolactinemia was more commonly observed in females. Although partially consistent with previous studies, these findings also highlight variability across different cohorts, which may reflect differences in tumor characteristics, hormonal evaluation methods, and population-specific factors.

Hormonal dysfunction was more pronounced in patients with macroadenomas. Central hypogonadism, central hypothyroidism, cortisol deficiency, and growth hormone deficiency were all significantly more frequent in macroadenomas, supporting the concept that larger tumors exert a greater mass effect on normal pituitary tissue. These findings are consistent with previous studies demonstrating a strong association between tumor size and hypopituitarism.

Visual impairment is a well-recognized complication of NFPAs, primarily resulting from compression of the optic chiasm. Previous studies have reported visual field defects in approximately one-third of patients. In our cohort, visual field defects were identified in 16% of patients at initial endocrinology outpatient evaluation and were significantly more frequent in macroadenomas. Notably, the only microadenoma associated with a visual field defect measured 9.5 mm and was located in close proximity to the optic chiasm, emphasizing the importance of tumor location in addition to size.

Surgical management remains the mainstay of treatment in symptomatic patients. In our study, all operated patients underwent transsphenoidal surgery. Postoperatively, a substantial proportion of patients had persistent hormonal deficiencies, and nearly half had residual tumor tissue. Recurrence and the need for adjuvant radiotherapy were observed in 17.1% (n=7) and 19.5% (n=8) of patients, respectively. These findings are consistent with previous reports indicating that complete resection is often challenging due to tumor size and invasiveness.[5,19,32-34]

Long-term follow-up is essential in patients with NFPAs. In our study, newly developed hormonal abnormalities were observed during follow-up, despite overall stability in tumor size. Among non-operated patients with available imaging at one year, no significant change in tumor size was detected, in line with previous studies suggesting that a considerable proportion of NFPAs remain stable over time. However, the emergence of new hormonal abnormalities underscores the need for regular endocrine evaluation, even in patients managed conservatively.

Several limitations of this study should be acknowledged. The retrospective design and single-center setting may have influenced the interpretation of the findings; however, the comprehensive clinical characterization and real-world data provide meaningful insight into the clinical behavior of NFPAs.

Conclusion

In conclusion, this study provides a comprehensive characterization of patients with non-functioning pituitary adenomas, demonstrating that delayed diagnosis—particularly in male patients—is associated with a higher prevalence of macroadenomas and a predominance of mass effect–driven presentation. Additionally, the observed sex-specific differences in clinical features suggest that both biological and diagnostic factors may influence disease recognition and should be considered in clinical evaluation.

Importantly, our findings highlight the dynamic nature of pituitary dysfunction in NFPAs, as hormonal axes that are initially preserved may deteriorate over time, even in the absence of overt radiological tumor progression. Furthermore, the high frequency of residual disease and recurrence following surgical intervention underscores the need for long-term, multidisciplinary follow-up. Taken together, these findings support a more individualized and longitudinal approach to NFPA management. Future prospective, multicenter studies incorporating standardized follow-up strategies are warranted to further refine surveillance and improve patient outcomes.

Disclosures

Ethics Committee Approval: This retrospective cross-sectional study was conducted following approval from a Mersin University Ethics Committee (decision no: 347, dated May 13, 2020).

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

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