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ORIGINAL ARTICLE

Revisiting Urinary Vanillylmandelic Acid in Pheochromocytoma: Insights from a 16-Year Tertiary Center Cohort

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Abstract

Background: This study aimed to evaluate the clinical, biochemical, and pathological characteristics of pheochromocytoma cases diagnosed at a tertiary center. Additionally, it investigated the diagnostic value of urinary catecholamines in predicting tumor size.

Methods: Sixty-six adult patients with histopathologically confirmed pheochromocytoma diagnosed between January 2008 and April 2024 were retrospectively analyzed. Demographic data, clinical symptoms, tumor size, and 24-hour urinary catecholamine levels were examined. Statistical analyses were performed using SPSS version 25.

Results: A total of 66 patients were included in the study; the mean age was 46.10 ± 15.84 years, and 62.1% were female. The most frequently reported symptoms were hypertension (71.4%), palpitations (46.0%), and headache (42.9%). Among patients with unifocal tumors, both VMA ($p=0.001$) and normetanephrine ($p=0.039$) levels were significantly higher in large tumors ≥4 cm compared to small tumors <4 cm. A VMA cutoff value of 6.61 mg/24h achieved 85.7% sensitivity and 70.6% specificity (AUC=0.807) in identifying large tumors.

Conclusions: Urinary VMA levels may serve as a useful biochemical marker for predicting tumor size in pheochromocytoma patients, particularly when plasma testing is not available. A structured diagnostic and follow-up process is necessary to achieve better outcomes in this rare but potentially life-threatening condition.

Keywords: Pheochromocytoma, catecholamines, vanillylmandelic acid, tumor size.

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INTRODUCTION

Pheochromocytoma is a rare neuroendocrine neoplasm arising from chromaffin cells of the adrenal medulla and classified as an intra-adrenal paraganglioma (1). These tumors predominantly affect adults between the third and fifth decades of life, with an annual incidence reported between 0.66-0.8 cases per 100,000 adults (2, 3).

Pheochromocytomas secrete excessive catecholamines, particularly norepinephrine and epinephrine, resulting in diverse clinical manifestations(4). The adrenergic effects commonly present as hypertension, tachycardia, headache, and diaphoresis, with secondary symptoms including nausea (5, 6). In severe cases, life-threatening multisystem complications may occur. The severity of paraganglioma-pheochromocytoma (PPGL) attacks has been demonstrated in large series, reporting cardiac involvement in up to 99% of patients during crisis episodes (7).

Biochemical confirmation remains the cornerstone of diagnosis. The 2014 Endocrine Society Clinical Practice Guideline recommends measurement of plasma free or urinary fractionated metanephrines as the initial biochemical testing for PPGLs (8). Plasma metanephrine and normetanephrine measurements offer particularly high sensitivity and specificity for diagnosis (9).

Imaging plays a pivotal role in localization and characterization. Computed tomography (CT) is suggested for initial imaging, while magnetic resonance imaging (MRI) provides superior soft tissue resolution, particularly valuable in patients with metastatic disease or when radiation exposure must be limited (8, 10).

The 2022 WHO classification acknowledges that all pheochromocytomas possess metastatic potential (1). Since histological features cannot reliably differentiate benign from malignant behavior, tumors are classified as metastatic only when distant spread is documented. Malignant pheochromocytoma risk is highest with SDHB mutations, large or extra-adrenal tumors, high catecholamine secretion, obesity, and older age. No single marker is definitive, so comprehensive evaluation and long-term follow-up are essential for all patients (11, 12).

Pheochromocytoma can mimic numerous medical conditions and may remain asymptomatic for extended periods, making diagnosis challenging. The condition is frequently underdiagnosed, with autopsy studies showing that up to 50% of pheochromocytomas are discovered only post-mortem (13-15) . This emphasizes the importance of clinical awareness regarding its diverse presentations.

Recent advances in genetic understanding have revealed that approximately 30-40% of pheochromocytomas are hereditary, making them among the most heritable tumors known (16, 17). The 2014 Endocrine Society guidelines recommend genetic testing for all patients with pheochromocytoma, particularly testing for SDHx mutations in patients with paragangliomas and SDHB mutations in those with metastatic disease (8).

Given the rarity of pheochromocytoma, every clinical dataset contributes valuable insights to our understanding of this complex tumor. This study aims to present recent clinical data from a tertiary care center, examining key patient characteristics including demographics, clinical presentation, biochemical markers—particularly vanillylmandelic acid (VMA)—and genetic factors to establish correlations with tumor features and inform diagnostic approaches.

MATERIALS AND METHODS

Study Design and Setting

This descriptive study was conducted using a retrospective design at Ankara University Faculty of Medicine Hospitals, a tertiary care institution. The study utilized data from the hospital research data system for patients admitted between January 2008 and April 2024. Ethical consent was obtained with decision number İ04-333-24 from The Human Research Ethics Committee of Ankara University Faculty of Medicine (dated 13.05.2024).

Study Population

All pheochromocytoma patients admitted to Ankara University Faculty of Medicine between 2008 and 2024 were retrospectively enrolled. Inclusion criteria consisted of confirmed histopathological diagnosis of pheochromocytoma, age ≥18 years at diagnosis, and availability of complete clinical and biochemical data. Therefore, 66 patients were included in the final analysis.

Patient data were extracted from electronic medical records and included clinical features (presenting symptoms, hypertension status, and familial history), biochemical markers (24-hour urinary levels of catecholamines and their metabolites including VMA, HVA, metanephrine, normetanephrine, epinephrine, and dopamine), pathological findings (tumor size, laterality, and PASS score), genetic alterations (RET and SDH mutations), and associated conditions such as medullary thyroid carcinoma or other endocrine neoplasms.

Biochemical Analysis

All patients received standardized 3-day dietary instructions including avoidance of vanilla-containing foods, bananas, chocolate, coffee, tea, and excessive caffeine intake. Medication adjustments were made when clinically appropriate. On the third day following dietary preparation, patients began 24-hour urine collection using standard protocols with hydrochloric acid preservative. Collection adequacy was verified through creatinine excretion assessment when available. Patients received detailed instructions on proper collection techniques including the importance of complete urine collection and maintaining the cold chain.

Elevated biomarkers were defined as values exceeding the upper limit of normal (ULN) reference ranges and significant elevation was defined as values >2x ULN. Reference ranges were established based on institutional normal values:

- Metanephrine: 52-341 μg/24h
- Normetanephrine: 88-444 μg/24h
- Vanillylmandelic acid (VMA): 1.8-6.7 mg/24h
- Epinephrine: 2-22 μg/24h
- Norepinephrine: 20-81 μg/24h
- Dopamine: 40-400 μg/24h
- Homovanillic acid (HVA): 0.5-6.2 mg/24h

Tumor Size Classification

Patients were stratified based on maximum tumor diameter:

- Small tumors: <4 cm diameter
- Large tumors: ≥4 cm diameter

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25. Descriptive statistics were used to summarize patient demographics and clinical characteristics. Categorical variables were expressed as frequencies and percentages. Normally distributed continuous variables were presented as means and standard deviations, while non-normally distributed variables were reported as medians with interquartile ranges or as medians with minimum and maximum values.

The Mann-Whitney U test was used to compare continuous variables between tumor size groups. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of urinary VMA and normetanephrine levels in predicting tumor size. A p-value of <0.05 was considered statistically significant.

RESULTS

Patient Demographics and Clinical Characteristics

The final study population consisted of 66 adult patients with histologically confirmed pheochromocytoma. The cohort comprised 41 females (62.1%) and 25 males (37.9%), with a mean age of 46.10 ±15.84 years. Age distribution analysis revealed that 43.9% of patients were diagnosed between 18-39 years (Table 1). Among the 55 patients who presented for at least one postoperative follow-up visit, the mean follow-up duration was 59.6 ± 54.7 months (median: 43 months).

Clinical Presentation

Among 66 patients, 35 (53.0%) were evaluated due to clinical suspicion of pheochromocytoma, whereas 31 (47.0%) were diagnosed incidentally following imaging for unrelated reasons. There was no significant difference in age between the two groups: the mean age was 47.5 ± 17.6 years in the incidental group and 44.9 ± 14.3 years in the suspicion-based group (p = 0.501). The frequency of clinical symptoms at the time of diagnosis, based on the number of patients evaluated for each feature, is presented in Table 2.

At the time of presentation, hypertensive status was evaluable in 56 patients; of these, 40 (71.4%) had documented hypertension, while 16 (28.6%) were normotensive. In 10 patients, hypertensive status could not be determined due to missing clinical data.

Table 1. Demographics of Patients with Pheochromocytoma	
Variable	**Patients Number (%) N=66**
Gender	
Female	41 (62.1)
Male	25 (37.9)
Age Groups	
18-29 years	13 (19.7)
30-39 years	16 (24.2)
40-49 years	10 (15.2)
50-59 years	11 (16.7)
60-69 years	9 (13.6)
70-79 years	7 (10.6)

Table 2. Clinical Features in the Study Population (N = 66)

Clinical Feature	Evaluated Patients (n)	Positive Cases n (%)
Hypertension	56	40 (71.4%)
Palpitations	50	23 (46.0%)
Headache	42	18 (42.9%)
Diaphoresis	46	14 (30.4%)
Weight loss	44	7 (15.9%)
Nausea	44	6 (13.6%)
Tremor	41	3 (7.3%)
Pallor	59	2 (3.4%)

Biochemical Profile

Preoperative biochemical evaluation revealed elevated urinary catecholamines and metabolites in a considerable number of patients. Detailed results are presented in Table 3.

Tumor Characteristics and Location

Tumor localization analysis revealed right adrenal involvement in 28 cases (42.4%), left adrenal in 24 cases (36.4%), and bilateral disease in 14 cases (21.2%). Using a 4 cm cutoff, tumors were classified as small (<4 cm; n=28, 42.4%) or large (≥4 cm; n=38, 57.6%).

Tumor laterality and focality revealed bilateral/multifocal disease in 14 patients (21.2%) and unilateral/unifocal disease in 52 patients (78.8%).

Pathological and Genetic Features

Chromogranin immunohistochemical staining was positive in 51 of 53 evaluated tumor specimens (96.2%). PASS scoring was available for 40 patients, revealing scores <4 in 15 patients (37.5%), intermediate scores (4-6) in 20 patients (50.0%), and high-risk scores >6 in 5 patients (12.5%).

Among patients evaluated for specific mutations at our center, RET mutations were detected in 5 of 10 tested patients (50%), while SDH complex mutations were identified in 2 of 13 patients (15.4%). Medullary thyroid carcinoma was diagnosed in 18 (27.3%). Genetic testing for the remaining MTC patients may have been performed at external centers, but these data were not available in our institutional records. Twelve patients (18.2%) developed metastatic pheochromocytoma during follow-up.

Tumor Size and Biochemical Correlations

In patients with unifocal tumors, both VMA (p=0.001) and normetanephrine (p=0.039) levels were significantly higher in large tumors compared to small tumors. No significant differences were found for other catecholamines and metabolites between tumor size groups (all p>0.05) (Table 4).

Diagnostic Performance of VMA for Tumor Size Prediction

ROC curve analysis was performed to evaluate the diagnostic accuracy of VMA and normetanephrine in predicting tumor size in unifocal cases. VMA demonstrat-

Table 3. Preoperative Biochemical Profile (n=66)

Biomarker	Evaluated Patients (n)	Elevated Cases n (%) >Upper limit of normal	Significant Elevated Cases n (%) > 2x Upper limit of normal
Normetanephrine	59	33 (55.9)	24 (40.7)
Metanephrine	58	31 (53.4)	18 (31.0)
VMA	51	28 (54.9)	12 (23.5)
Norepinephrine	47	24 (51.1)	17 (36.2)
Epinephrine	46	26 (56.5)	15 (32.6)
HVA	45	16 (35.6)	7 (15.6)
Dopamine	43	12 (27.9)	4 (9.3)

Note. VMA, vanillylmandelic acid; HVA, homovanillic acid.

Table 4. Urinary Catecholamine Levels of Patients with Unifocal Tumors Comparing Small vs Large Tumor Groups (n=52)

Variable	Small Tumors N=21 Median (IQR)	Large Tumors N=31 Median (IQR)	p-value
VMA, mg/24h	5.30 (4.05-6.98)	11.00 (7.00-21.85)	0.001*
Normetanephrine, μg/24h	648.51 (273.40-1105.70)	1233.33 (477.40-4269.98)	0.039*
Metanephrine, μg/24h	346.90 (186.58-714.00)	535.90 (106.37-1576.75)	0.696
Norepinephrine, μg/24h	59.95 (27.87-146.61)	273.40 (52.30-818.67)	0.077
Epinephrine, μg/24h	13.22 (10.89-35.90)	28.37 (10.82-75.45)	0.251
Dopamine, μg/24h	205.37 (136.40-292.46)	284.24 (140.34-564.17)	0.334
HVA, mg/24h	4.55 (3.37-6.11)	4.70 (3.00-7.98)	0.899

*Note. VMA, vanillylmandelic acid; HVA, homovanillic acid *Statistically significant (p<0.05)*
Mann-Whitney-U test

ed good diagnostic performance with an AUC of 0.807 (p=0.001); optimal cutoff of 6.61 mg/24h yielded 85.7% sensitivity and 70.6% specificity with Youden Index of 0.563. Normetanephrine showed fair discrimination with an AUC of 0.682 (p=0.039); optimal cutoff of 799.6 μg/24h yielded 69.2% sensitivity and 68.4% specificity with Youden Index of 0.376.

DISCUSSION

This 16-year single-center study provides comprehensive clinical and biochemical insights into pheochromocytoma, emphasizing the potential utility of urinary VMA levels in estimating tumor size. Among patients with unifocal tumors, VMA levels were significantly higher in those with large tumors (≥4 cm), suggesting a correlation between tumor volume and catecholamine metabolism. This finding, while exploratory, highlights a possible role for VMA in supporting tumor characterization in specific clinical contexts.

Our cohort's demographic characteristics align with prior population-based studies, with a slight female predominance and peak incidence between the third and fifth decades of life (2, 3). The classical symptom triad—headache, palpitations, and diaphoresis—remained common, although approximately half of the patients were diagnosed incidentally. These results underscore the heterogeneity of pheochromocytoma presentations and the importance of maintaining diagnostic vigilance(4, 5).

Biochemical evaluation plays a central role in diagnosing pheochromocytoma. Current guidelines recommend plasma-free or urinary fractionated metanephrines due to their superior diagnostic performance (8, 9). However, access to these tests may be limited in certain healthcare settings. In our study, urinary VMA showed good discrimination for identifying larger tumors (AUC: 0.807), with a sensitivity of 85.7% and specificity of 70.6% at a cutoff of 6.61 mg/24h. While metanephrines remain the gold standard for biochemical diagnosis, our findings suggest that VMA may still provide clinically relevant information in select situations.

Larger pheochromocytomas generally exhibit greater biosynthetic and secretory capacity, resulting in increased levels of catecholamines and their metabolites. This increase, particularly in norepinephrine and epinephrine turnover, may lead to elevated urinary VMA levels that indirectly reflect tumor burden and catecholamine output (18, 19). The observed association between urinary VMA levels and tumor size may be explained by the underlying catecholamine metabolism. Larger pheochromocytomas generally contain greater cellular mass and exhibit increased activity of enzymes such as catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), which sequentially degrade norepinephrine and epinephrine into VMA. This enhanced enzymatic turnover may lead to proportional accumulation of urinary VMA, reflecting the overall tumor burden(20, 21). While VMA is not considered a first-line diagnostic marker, its measurement remains practical and cost-effective, particularly in settings where plasma metanephrine assays are unavailable. In such contexts, VMA may help inform clinical decisions regarding further imaging or expedite radiological evaluation when access to CT or MRI is limited. However, further studies are needed to confirm its reliability and assess its potential cost-effectiveness as a complementary tool in clinical practice.

Despite these findings, the interpretation of VMA as a surrogate marker for tumor size should be approached with caution. Several factors may confound urinary VMA measurements, including renal function, completeness of urine collection, dietary intake, and interfering medications(19, 22). Moreover, direct tumor measurement via imaging modalities (CT or MRI) remains the standard for assessing tumor size, with high spatial resolution and anatomical precision (10). Therefore, we do not propose that VMA replace imaging, but rather that it may complement biochemical and radiological evaluation in select cases, particularly in settings where advanced diagnostic tools are limited.

Another relevant observation in our study is the absence of a similar correlation between tumor size and metanephrine or norepinephrine levels, which contrasts with some earlier reports(19). This discrepancy could reflect tumor heterogeneity, differences in catecholamine metabolism, or methodological variations in urine collection and assay techniques.

The strengths of this study include its relatively large sample size for a rare disease, standardized biochemical protocols, and long follow-up duration. However, the retrospective design introduces inherent limitations, including possible selection bias and missing data. Most notably, plasma metanephrines were not available for the majority of patients, and urine collection adequacy could not be verified in all cases. Genetic testing was also incomplete, especially among patients referred from external centers, limiting genotype-phenotype correlations.

Prospective studies incorporating standardized biochemical sampling, imaging, and genetic analysis are warranted to further explore the relationship between tumor size, secretory profile, and biochemical markers. Additionally, integrating VMA data with clinical and radiologic risk stratification models may enhance prediction of tumor behavior in resource-limited settings.

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Abbreviations List

AUC: Area Under the Curve
CT: Computed Tomography
HVA: Homovanillic Acid
IBM: International Business Machines
IQR: Interquartile Range
MEN2: Multiple Endocrine Neoplasia Type 2
MRI: Magnetic Resonance Imaging
PASS: Pheochromocytoma of the Adrenal Gland Scaled Score
PPGL: Paraganglioma-Pheochromocytoma
RET: Rearranged during Transfection (gene)
ROC: Receiver Operating Characteristic
SDH: Succinate Dehydrogenase
SDHB: Succinate Dehydrogenase Complex Iron Sulfur Subunit B
SDHx: Succinate Dehydrogenase complex genes
SPSS: Statistical Package for the Social Sciences
VMA: Vanillylmandelic Acid
WHO: World Health Organization

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Human Research Ethics Committee of Ankara University Faculty of Medicine (Decision No: i04-333-24, dated 13.05.2024).

Consent for Publication

This manuscript does not contain any individual personal data that requires consent for publication.

Availability of Data and Materials

The datasets used and analyzed during the current study are not publicly available due to privacy and institutional policies but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests or commercial associations that might pose a conflict of interest.

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