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CASE REPORTS

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Editorial

Prospect and Challenges of Artificial Intelligence Application in African Emergency Medicine

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Artificial intelligence (AI) is a computer system that can execute sophisticated tasks that simulate human cognition, such as thinking, decision-making, or problem-solving (1). In Africa, general healthcare and emergency medicine suffer resource and infrastructure-related challenges, such as qualified personnel (2), which are brought on by increased incidence of infectious diseases, trauma, and non-communicable illnesses (3). This discrepancy underlines the pressing need for innovative and practical approaches to improve the delivery of emergency care (1). Artificial Intelligence has emerged as a cutting-edge technology that can fill some gaps in African emergency medicine (1).

Implementing AI in African emergency medicine may encounter multiple challenges despite its potential. One of the significant issues is a palpable need for more trained healthcare workforce professionals in both emergency medicine and AI technologies. Financial limitations are another critical barrier that prevents many African countries from investing in innovative healthcare technologies. In low-resource contexts, funding AI initiatives in emergency medicine can take much work to secure. Furthermore, as AI systems highly rely on quality data, health data in many African nations tends to be insufficient or poorly organized, which is a significant obstacle to the efficient use of AI in emergency medicine. Lastly, the application of AI in healthcare involves questions about patient privacy, permission, and accountability, as are ethical and legal considerations. Also, access to stable internet and electrical infrastructure is necessary, making it difficult to realize the full potential of AI in improving emergency care across the continent (4, 5).

Artificial intelligence can significantly enhance emergency department operations, early condition and outcome identification, triage and disposition procedures, and therapeutic intervention. AI may also be utilized in intensive care units and emergency medical dispatch since it can analyze patterns and outcomes through predictive analysis. Artificial Intelligence can potentially enhance resource allocation and logistical management by predicting surges during epidemics or mass casualty events. Artificial Intelligence can improve telemedicine services by providing remote medical practitioners with quicker decision aid. Artificial Intelligence-driven training offers immersive experiences that emergency doctors can use. Finally, AI platforms can advance best practices in emergency care by fostering collaboration and knowledge sharing across African healthcare professionals (5).

In summary, the application of AI in emergency medicine in Africa has the potential to significantly improve the health of millions of people by addressing the majority of struggles facing the healthcare system. Even though there are many challenges to be solved, the integration of AI and its applicability depends on the fulfillment of infrastructure, data quality, training, and legal and ethical standards. High-quality empirical research with an African focus is suggested to advance the topic and improve its applicability to emergency care in Africa, as most of the literature reviewed is theoretical.

Authors Contribution
I contributed to the work's conception or design, and analysis, and critical revision for intellectual content.
I approved the version to be published and agreed to be accountable for all aspects of the work.

Conflict of interest
The author declares that there is no conflict of interest about this work.

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Original Article

Magnitude and Determinants of Biochemical Mineral Bone Disease Abnormalities among Predialysis Chronic Kidney Disease Patients in Tikur Anbessa Specialized Hospital

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Abstract

Introduction: *Mineral bone disease (MBD) abnormalities are common complications in patients with chronic kidney disease (CKD). The MBD abnormalities are known to be associated with increased morbidity and mortality. In spite of their importance, there are limited data on CKD-MBD abnormalities in Ethiopia. This study looked in to the magnitude and determinants of biochemical CKD-MBD abnormalities among predialysis CKD patients.*

Methods: *A cross-sectional study was conducted from July 1 to September 30, 2020 in Tikur Anbessa specialized hospital. One hundred patients who had had follow-up for at least 6 months with an estimated glomerular filtration rate (eGFR)<60ml/min/1.73m^2 using CKD-EPI equation without race factor were included. Serum calcium, albumin, phosphorus and PTH levels were determined. Demographic and clinical data were collected using a structured questionnaire. IBM SPSS software version 26 was used for analysis. Descriptive statistics was used to describe the demographic and clinical data. Chi-square was used to identify correlations between the grouped variables. The analysis for comparison among three or more categories was done using one-way ANOVA and Tukey post hoc test. Linear correlation and multiple regression analysis were used to identify associations between clinical and biochemical findings.*

Results: *Among the 100 patients included in this study; the median age was 58 years with IQR of 73. The male to female ratio was 2.7:1. Patients in stages 3a, 3b, 4 and 5 CKD accounted for 23%, 29%, 26% and 22%, respectively. The main causes of CKD were diabetes and hypertension. Among these patients, 31% had hyperphosphatemia, 36% had hypocalcemia, and 89% had hyperparathyroidism. The mean values of calcium in CKD stage 3a,3b,4 and 5 were 8.91, 8.81, 8.7 and 7.14mg/dl, respectively; where as those of serum phosphorus were 3.58, 3.83, 3.83 and 5.53mg/dl, respectively. The median values of PTH were 140.6, 137.2, 274.05 and 440.85Pg/ml, respectively. Estimated GFR correlated negatively with serum parathyroid hormone (PTH) level but correlated positively with serum calcium level. In addition, serum calcium level is inversely associated with diabetes and diastolic blood pressure whereas serum PTH is directly associated with diastolic blood pressure and female sex.*

Conclusion: *Hypocalcemia, hyperparathyroidism, and hyperphosphatemia are common biochemical CKD-MBD abnormalities among predialysis CKD patients in the renal clinic of Tikur Anbessa specialized hospital. Monitoring for CKD-MBD should begin earlier and treatment should be initiated accordingly to improve patient outcome.*

Keywords: *Chronic Kidney disease; Mineral bone disease; Hypocalcemia; hyperparathyroidism; hyperphosphatemia*

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Introduction

Chronic kidney disease (CKD) constitutes a public health problem estimated to affect more than 10% of the global population, and the prevalence of which has increased in recent years. (1) The pooled prevalence of CKD is 10.1% in the general population, 24.7% in hypertensive, and 16.6% among diabetes mellitus patients in Africa(2). The prevalence of CKD was 26% among hypertensive and diabetes mellitus patients in Ethiopia (3). According to the 2012 KDIGO guideline, CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health (4). It also classifies it according to severity from stages 1-5.

Bone mineral metabolism abnormalities that occur in

CKD patients are recently defined in KDIGO guidelines as CKD mineral and bone disorder (CKD-MBD)(5). CKD-MBD is a systemic disorder that is characterized by abnormal calcium, phosphorous, PTH, and Vitamin D metabolism, which, in addition to affecting the skeletal system, is related to the appearance of cardiovascular and soft tissue calcifications that in turn are associated with cardiovascular pathologies in patients with CKD (8,9). The biochemical abnormalities are common in CKD and are the primary indicators by which the diagnosis and management of CKD-MBD is made (4, 26).

Bone abnormalities are found almost universally in patients with CKD stage 5 and in majority of patients with stages 3-5 (4,23). The bone mineral metabolism abnormalities start during first stages of CKD as renal function decreases, long before the need for renal replacement therapy and can positively or negatively be influenced by the treatment strategy employed (4). Elevated PTH and hyperphosphatemia were recently identified as risk factors for mortality in dialysis patients(6,7).Elevated serum phosphate levels were independently associated with increased mortality risk among this population of patients with CKD(8). Patients with CKD-MBD are at an increased risk for bone fractures and increased CVD mortality (24, 25). As such, it is recommended that attending physicians monitor and control biochemical parameters early in the development of CKD, before the need for dialysis (5).

Because of the paucity of data in Ethiopia, an urgent need for a study in this area was felt to fill the knowledge gap. Therefore, the purpose of this study was to identify the prevalence, severity and determinants of MBD anomalies in predialysis chronic kidney disease patients.

Method

Study Setting and Design

This is a cross-sectional study which was conducted in the renal clinic of Tikur Anbessa specialized hospital located in Addis Ababa, Ethiopia. The hospital is one of the largest referral teaching hospitals in the country. The hospital provides both inpatient and outpatient services. The renal clinic gives service to wide variety of patients with renal problems; CKD comprising the majority of the cases. The study was conducted from July 1 to September 30, 2020.

Study population

The source population included consecutive patients who were ≥ 18yrs of age and have eGFR of < 60 ml/min/1.73m2 for at least 03 months with follow-up of at least 06 months. Those patients who had Stage 3-5 CKD by estimating GFR using CKD-EQI equation without race factor were included in the study. Patients on dialysis, patients who had primary hyperparathyroidism or undergone parathyroid surgery and patients who were taking Calcium supplements over the counter were excluded. One hundred consecutive patients who fulfilled the criteria were selected for the study after informed consent was obtained.

The sample size was calculated using 82 % as prevalence of MBD abnormalities among CKD patients from study done in India (27). A 95 % level of certainty and a margin of error of 5% were assumed. A single population proportion formula given below was used to calculate the sample size.

$$n = \frac{(Z\ \alpha/2)^2\ P(1-p)}{d^2} = 227$$

We deducted the sample size by finite population correction formula because our source population was less than 10,000 patients diagnosed with MBD, and the calculated sample size was larger than 5% of the source population.

n'=no/1+ no/N
Where -no- calculated sample =227
N-total population=150
n'-final population
n'=no/1+no/N=227/1+227/150=91
The corrected sample size was 91.

Sample size for secondary objective

The sample size for the second objective was calculated using Epi info version 7 with assumptions of 95% confidence level and power of 80%.

The calculated sample size for the first objective (91) was greater than sample size calculated for that of the second objective. Therefore adding 10 % non-response rate 100 was the minimum sample size required for this study. The sample size calculation is shown in the table below.

Table 1: sample size calculation

Variables	CI	Power	Unexposed: exposed	Control with exposure (%)	Cases with exposure (%)	COR	Sample size	Reference
Stage of CKD	95%	80	1	12.4	87.6	49.9	18	(27)

Data collection:
Data were collected using structured questionnaire through an interview, followed by chart review and blood sample collection. Five to ten ml of venous blood samples were taken using aseptic techniques and sent to Ethiopian public health institute laboratory for Serum Calcium, Phosphorus, albumin and PTH determination. Finally, to identify the management practice and CKD risk factors the patients' charts were revised.

Variables:
The dependent variables were Serum Calcium, Serum Phosphate and Serum PTH; whereas Age, sex, BMI, Blood pressure, place of residence, educational status, marital status, occupation, medical comorbidity, smoking history, eGFR, Cause of CKD and urine dipstick protein were the Independent Variables.

Operational definitions: In accordance with KDIGO guidelines:

CKD: serum creatinine level above laboratory baseline for sex for more than 03 months (4).

Stage 1 CKD: Estimated GFR above 90 ml/min/1.73m2
Stage 2 CKD: Estimated GFR b/n 90 and 60 ml/min/1.73m2
Stage 3A CKD: Estimated GFR b/n 59 and 45 ml/min/1.73m2
Stage 3B CKD: Estimated GFR b/n 44 and 30 ml/min/1.73m2
Stage 4 CKD: Estimated GFR b/n 29 and 15 ml/min/1.73m2
Stage 5 CKD: Estimated GFR less than 15 ml/min/1.73m2
Stage 5D CKD: Patients who have started dialysis

Mineral bone disease (MBD) abnormalities: Any patient who has either hypocalcemia, hyperphosphatemia or hyperparathyroidism (4).
Hypocalcemia: Corrected total calcium<8.5mg/dl (4)
Hypercalcemia: Corrected total calcium >10 mg/dl (4)
Hypophosphatemia: Phosphorus <2.5 mg/dl (4)
Hyperphosphatemia: Phosphorus >4.5mg/dl (4)
Hypoparathyroidism: Intact parathyroid hormone (iPTH)<15 pg/ml (4)
Hyperparathyroidism: Intact parathyroid hormone iPTH >65 pg/ml (4)

Smoking: Any patient who has smoked any number of cigarettes in the past or who, at the time of the survey, smoke either every day or some days.

BMI: was categorized as underweight (BMI<18.5); normal (BMI 18.0–24.9 kg/m2); overweight (BMI 25.0–29.9 kg/m2), or obese (BMI ≥30 kg/m2).

Data Analysis: The filled questionnaire was checked for incompleteness and Data were entered in SPSS version 26 for analysis. Descriptive statistics was used to describe the demographic and clinical data. Descriptive analysis of quantitative parameters was expressed as means, median and standard deviation. Chi-square was used to find the correlations between the stage of CKD and grouped biochemical results as significant if P- value is < 0.05. The analysis for comparison among three or more categories was done using one-way ANOVA and Tukey post hoc test. Linear correlations and Multiple linear regression analysis were used to identify relationships between clinical and biochemical findings.

Results
Patient's baseline characteristics
A total of 100 CKD patients were included in this study. The majority were males (73%), from Addis Ababa (86%) and in the age group of 50-64 (40%). Most of the patients had diabetes (40%) and Hypertension (25%). The median age was 58 years with IQR of 73 (Table 2). Among the 100 patient's that were included in this study during their follow-up of the previous 6 months, urine protein was determined in 97%, serum calcium in 61%, serum Phosphorus in 62% and serum PTH in 15%. Abdominal U/S was documented in only 55% and urine dipstick for protein in 97% of the patients since the start of their follow-up (Table 2). Even though treatment for CKD -MBD abnormalities was indicated for 58% of Hyperphosphatemia, 58.3% of Hypocalcemia and 12.3% of Hyperparathyroidism patients, only 19.3%,20% and 5.6%, respectively started the treatment (Table 3).

Table 2. Demographic and clinical characteristics of patients with CKD attending the adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

Characteristics	Category	Frequency (no = %)
Sex	Male	73
	Female	27
Age	18-34	14
	35-49	17
	50-64	40
	65-79	27
	≥ 80	2
Address	Addis Ababa	86
	Oromia	11
	Amhara	3
Marital Status	Single	16
	Married	74
	Divorced	6
	Widowed	4
Educational Status	Unable to read and write	11
	Able to read and write	13
	Primary education	23
	Secondary education	26
	College and above	27
Smoking	Never	94
	Former	5
	Current	1
Comorbidity	Family History of CKD	10
	Coronary Artery disease	8
	Heart failure	9
	Cerebrovascular disease	6
	PAD	3
Stage of CKD	3a	23
	3b	29
	4	26
	5	22
Cause of CKD	Hypertension	25
	Diabetes	40
	Chronic glomerulonephritis	6
	Polycystic Kidney disease	4
	Obstructive Uropathy	8
	Others[1]	17
BMI	Underweight	8
	Normal Weight	42
	Overweight	37
	Obese	13
Blood Pressure	Normal BP	34
	High Normal BP	11
	Grade 1 Hypertension	17
	Grade 2 Hypertension	8
	Grade 3 Hypertension	3
	Isolated systolic Hypertension	27

[1]Includes Unknown causes, TDF Nephropathy, Lupus Nephritis, Chronic Pyelonephritis 2o Reflux nephropathy and Tuberous Sclerosis

Table 3: Abdominal Ultrasound and urine dipstick finding among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

	Finding	Frequency
Abdominal Ultrasound (N=55)	Normal Kidney Size	21 (38.1%)
	Shrunken Kidney	21 (38.1%)
	Polycystic Kidney	4(0.7%)
	Hydronephrosis	6(0.12%)
	Others[1]	3(0.05%)
Urine Dipstick(N=97)	Negative	26 (26.8%)
	Trace to +1	12 (12.3%)
	+2 or more	59 (60.8%)
	Negative	26 (26.8%)

[1] Congenital renal anomaly

Table 4: Frequency of patients that need MBD treatment and are on treatment among those with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

MBD abnormality	Frequency	Needs Treatment	Frequency	On Treatment
Hyperphosphatemia	31	Phosphorus >5mg/dl	18 (58%)	6 (19.3%)
Hypocalcemia	36	Calcium <8mg/dl	21 (58.3%)	8 (20%)
Hyperparathyroidism	89	PTH ≥ 9x ULN	11 (12.3%)	5 (5.6%)

Laboratory results

Among the patients included in this study, 36% were Hypocalcemic, 31% were Hyperphosphatemic and 89% developed secondary Hyperparathyroidism. Hyperparathyroidism was the most common mineral bone abnormality observed in the present study. There was a gradual increase in the prevalence of Hypocalcemia, Hyperphosphatemia and Hyperparathyroidism as the severity of CKD increases. (Tables 5 and 6).

Table 5. Laboratory Results of patients with Stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

Parameter		Stage of CKD					P-alue
		3a (n=23)	3b (n=29)	4 (n=26)	5 (n=22)	Total	
Calcium	Mean ± SD (mg/dl)	8.91±0.48	8.81±0.92	8.7±0.49	7.14±1.62		
	Hypocalcemia	5 (21.7%)	6 (20.7%)	10 (38.5%)	15 (68.2%)	36(36.0%)	0.01
	Normal	17 (73.9%)	21 (72.4%)	16(61.5%)	7(31.8%)	61(61.0%)	
	Hypercalcemia	1 (4.3%)	2(6.9%)	0	0	3 (3.0%)	
Phosphorus	Mean ± SD (mg/dl)	3.58±0.51	3.83±1.25	3.83±1.03	5.53±2.0		
	Hypophosphatemia	0	1 (3.4%)	3 (11.5%)	0	4 (4.0%)	<0.001
	Normal	22 (95.7%)	21(72.4%)	15(57.7%)	7(31.8%)	65(65.0%)	
	Hyperphosphatemia	1(4.3%)	7 (24.1%)	8 (30.8%)	15(68.2%)	31(31.0%)	
PTH	Median (IQR) (pg/ml)	140.6(802.9)	137.2 (942.25)	274.05 (1064.06)	440.85 (1855.95)		
	Normal	2(8.7%)	8(27.6%)	1(3.8%)	0	11(11.0%)	0.006
	Hyperparathyroidism	21(91.3%)	21(72.4%)	25(96.2%)	22	89(89.0%)	
	PTH ≥2x of ULN	13 (61.9%)	15 (71.4%)	23 (92%)	19 (86.3%)	70 (78.6%)	0.003
	PTH ≥9x of ULN	1 (4.3%)	2 (6.9%)	1 (3.8%)	7 (31.8%)	11 (12.3%)	

There was a statistically significant difference in PTH, calcium and phosphorus levels (F (3,96) = 9.383, p = <0.0001) between the stages of CKD as determined by one-way ANOVA. A Tukey post hoc test revealed that hyperparathyroidism, hypocalcemia and hyperphosphatemia were significantly higher in stage 5 (p = <0.001) compared to those at stage 3. There was no statistically significant difference between stage 3a, 3b and stage 4 groups.

Table 6: Frequency of various mineral metabolism disorders among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

Parameter	Mean±SD
Creatinine (mg/dl)	3±2.02
eGFR (ml/min/1.73m²)	29.6±14.70
Albumin (g/dl)	4±0.56
Corrected total Calcium (mg/dl)	8.4±1.18
Phosphorous (mg/dl)	4.1±1.47
Total PTH (pg/ml)	321.3 (4.9x)

.**Correlation of serum PTH, calcium and phosphorus with patient characteristics**

In the study using linear correlations, patients' serum total calcium was found to have direct correlation with eGFR (r= 0.476, P <0.001) and age (r=0.224, P=0.025) as well as inverse correlation with phosphorus (r= -0.5, P <0.001), PTH (r= -0.341, P = 0.001) and diastolic blood pressure (r= -0.246, P = 0.014). Additionally, serum Phosphorus was found to have direct correlation with PTH (r= 0.324, P=0.001), Urine dipstick (r= 0.161, P =0.044) and inverse correlation with GFR (r= -0.405, P<0.001), and Age (r= -0.229, P= 0.022) (Figure 1 and 4). Whereas serum PTH was found to have direct correlation with diastolic blood pressure (r= 0.25, P = 0.012), and inverse correlation with GFR (r= -0.441, P<0.001), and Age (r= -0.4, P<0.001) (Figure 2 and 3).

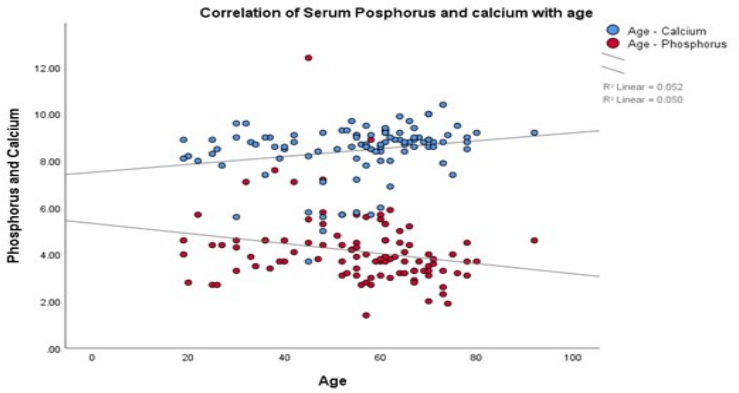

Figure 1. Correlation of Serum Phosphorus and calcium with age among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020

Figure 2. Correlation of Serum PTH with age among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

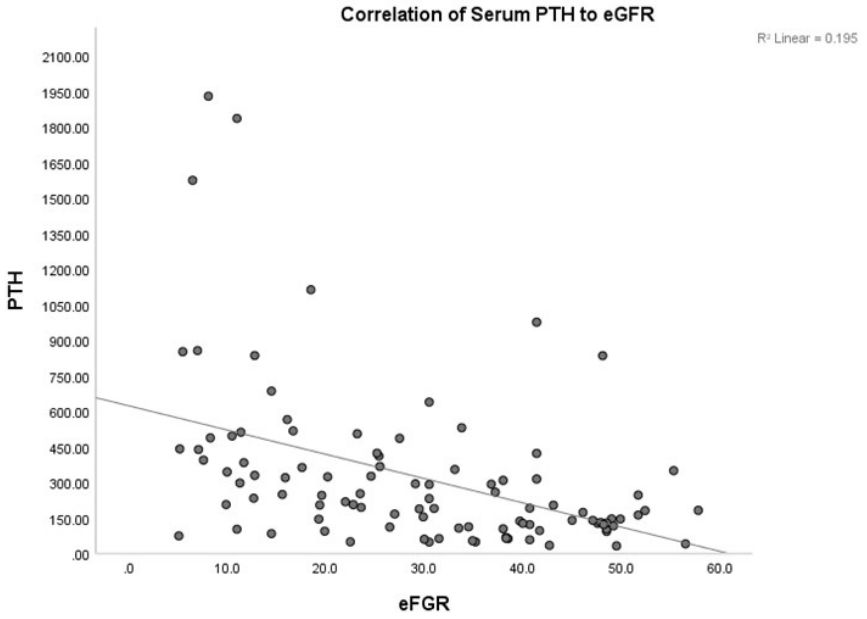

Figure 3: Correlation of Serum PTH with eGFR among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

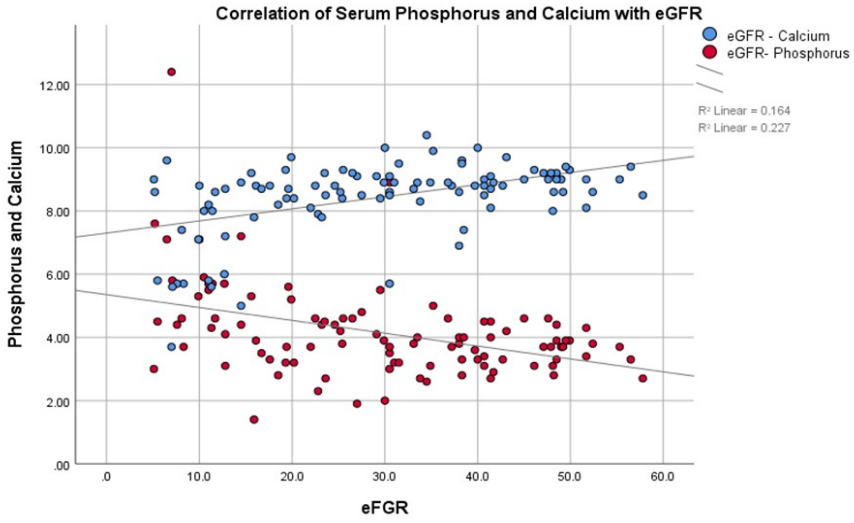

Figure 4: Correlation of Serum Phosphorus and calcium with eGFR among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

However, on Multiple linear regression analysis, which explained 43.3% of calcium variation, the only independent predictors for serum calcium level were eGFR, diabetes, diastolic blood pressure and serum phosphorus (Table 6). Similarly, taking PTH as dependent variable, which explained 37.3% of PTH variation, diastolic blood pressure, female sex and eGFR were the only independent predictors identified (Table 7). But none of the above variables identified on linear correlation were independent predictors of phosphorus level on multiple regression analysis.

Table 6. Predictors of serum calcium among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020**.**

Predictor	Beta	95%CI	P-value
Calcium	-	9.26 to 13.20	<0.0001
eGFR	0.349	0.01 to 0.04	0.001
Diabetes	-0.196	-0.87 to -0.07	0.022
DBP	-0.249	-0.04 to -0.01	0.004
Phosphorus	-0.275	-0.41 to -0.14	<0.0001

Table 7. Predictors of serum PTH among patients with stage 3-5 CKD attending adult renal Clinic of TASH, Addis Ababa, Ethiopia, 2020.

Predictor	Beta	95%CI	P-value
PTH	-	-932.24 to 829.21	0.908
eGFR	-0.249	0.01 to 0.04	0.025
Female sex	0.264	-0.87 to -0.07	0.006
DBP	0.191	-0.04 to -0.01	0.036

Discussion

The study revealed 31% of the CKD Stage 3–5 predialysis patients had hyperphosphatemia, 36% had hypocalcemia, and 89% had hyperparathyroidism. Estimated GFR correlated negatively with serum parathyroid hormone (PTH) level but correlated positively with serum calcium level. The mean values of calcium in CKD stage 3a,3b,4 and 5 were 8.91, 8.81, 8.7 and 7.14mg/dl, respectively where as those of serum phosphorus were 3.58, 3.83, 3.83 and 5.53mg/dl, respectively. The median values of PTH were 140.6, 137.2, 274.05 and 440.85Pg/ml, respectively.

Similar to our study, disordered mineral metabolism i.e., hypocalcemia, hyperphosphatemia and secondary hyperparathyroidism are common complications of CKD especially in those above stage 3(5,9). One study done on predialysis patients in south east Nigeria also found 70% hyperphosphatemia and 85% hyperparathyroidism which is similar with our finding of hyperparathyroidism.(10) Another study done in India in CKD patients stage 3-5D also showed hypocalcemia (23.8%), hyperphosphatemia (55.4%), secondary hyperparathyroidism (82.7%).(11) A similar high prevalence of disorders of mineral metabolism has been reported from the Western countries(9,12), India (11,13) and Nigeria(10,14).In addition, in our study the level of hypocalcemia, hyperphosphatemia and secondary hyperparathyroidism showed gradual increment with declining eGFR which was also demonstrated in other studies.(9,11).

Hyperparathyroidism was found in more than two thirds of the CKD patients, and its prevalence sharply increased with the decline in glomerular filtration, which is found in all of the patients with eGFR below 15 (stage 5). The possible mechanism for this is hypocalcemia and hyperphosphatemia which are the main physiological stimuli for increased PTH secretion (4,11). The results are similar to previous reports(15). For example, in the Study for the Evaluation of Early Kidney Disease (SEEK), 90% of the subjects with eGFR <20mL/min/1.73m2 had high levels of intact parathyroid hormone (iPTH) and the prevalence in early stages of CKD (i.e., at eGFR >80mL/min/1,73m2 and between 60-70mL/min/1.73m2) was around 12% and 21%, respectively.(9) In our study we also found that female sex and high Diastolic blood pressure were independent predictors of hyperparathyroidism. Similar positive correlation with DBP was also found in a study done in the south east Nigeria.(10) Furthermore, Blood Pressure Reduction After Parathyroidectomy and medical treatment with calcimmetics for Secondary Hyperparathyroidism was demonstrated in other studies.(16), (17)The mechanism for this correlation might be ascribed to alterations of calcium homeostasis and direct hypertensive activities induced by PTH.(18) In addition, in one study done on uremic patients also found that female patients have higher PTH level (approximately 69.6± 32.9 pg/ml) than males (13,19) The effect of gender on parathyroid activity may be regulated by sex steroids, since estrogen receptors are present in parathyroid cells and estrogens increase PTH mRNA levels,(15,20)

Hypocalcemia was found in almost one third of the CKD patients and its prevalence also increased with decline in eGFR. This relation was also demonstrated in other studies (11,12). Total serum calcium concentration decreases during the course of CKD due to phosphate retention, decreased calcitriol concentration, and resistance to the calcemic actions of PTH on bone (23). We found diabetes to be an independent predictor of lower levels of calcium, and this could be higher number of patients (40%) that were diabetic in our study. No significant correlation was identified in serum calcium when diabetics were compared to non-diabetic CKD patients in study done in India. (11) The correlation between hyperphosphatemia and hypocalcemia was also demonstrated in other studies. (14) The inverse correlation between calcium and DBP was demonstrated in some studies.(21,22), In one study done on patients with essential hypertension showed that Individuals with high diastolic blood pressure had significantly lower total serum

calcium (2.41 ± 0.10 vs. 2.47± 0.10 mmol/1, mean± SD; P<0.01)(22). The effect was attributed to widespread depression of Ca (2+)-ATPase activity with plasma Ca2+ depletion and cytosolic Ca2+ overload, which may reflect an underlying membrane abnormality in essential hypertension.

Hyperphosphatemia was also found in almost one third of the CKD patients and serum phosphate level also increased as the stage of CKD increased with 68% in stage 5. This was demonstrated in a Romanian study which showed that 93% of patients with high serum phosphate had a glomerular filtration rate below 30mL/min/1.73m2 (12). This is understandable given that the primary cause of hyperphosphatemia is a reduction in renal phosphate clearance, which frequently occurs as kidney excretion function declines (4,12). Even though the level of hyperphosphatemia increased with stage of CKD this wasn't demonstrated when multiple regression analysis was done.

Conclusion

This study found a spectrum of CKD-MBD in CKD Stage 3–5. It showed that secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, were quite common among Stage 3-5 CKD patients in TASH renal clinic. The most common type of MBD was hyperparathyroidism. The level of MBD abnormalities also increases with progressively worsening renal failure. In addition, serum calcium level is inversely associated with diabetes and diastolic blood pressure whereas serum PTH is directly associated with diastolic blood pressure and female sex.

Limitation of this study

Due to the cross-sectional nature of this study, patients were assessed only at presentation. Serum ALP, FGF-23 and 25(OH) D levels weren't determined. The number of patients included was small because the COVID pandemic limited CKD patient from visiting follow-up clinics, research time constraint and not enough funding to do the laboratory investigations.

Declarations

Acknowledgment

We would like to thank the Department of Internal Medicine, College of Health Sciences, Addis Ababa University, the renal clinic staff, Hana and EPHI chemistry laboratory staff who dedicated their time in the data collection process and all study participants.

Ethics consideration

The study was conducted after obtaining ethical clearance from Addis Ababa University, college of medicine, internal medicine department (Ref number???). Informed consent was taken from all patients after explaining the nature of the study using their own language. Medical record number was used for data collection. Access to the patient's data was limited to the research team and confidentiality was maintained throughout.

Authors contribution

SM conceived and designed the study. AM contributed to the conception, design of the study and interpretation of the findings. SM wrote the research proposal, conducted the research, performed statistical analysis and drafted the initial manuscript. All authors approved the final version of the manuscript.

Conflict of interest

The authors have declared that they have no known competing interests.

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Data availability

All relevant data are available upon reasonable request.

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Original Article

Clinical, Pathologic, and Endoscopic Characteristics of Esophageal Cancer Patients at St. Paul´s Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia: A Five-Year Retrospective Review

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Abstract

Background*: Esophageal cancer is the eighth leading cancer and the top sixth cause of cancer mortality worldwide. According to Globocan 2012 estimate, in Ethiopia, esophageal cancer ranks the seventh and eighth as the leading cause of cancer mortality and morbidity respectively.*

Methods: *A retrospective cross-sectional study using record review was employed at Gastroenterology and Hepatology Unit and Department of Pathology of SPHMMC with the aim to assess the clinical, pathological and endoscopic characteristics of esophageal cancer patient attending at St Paul Hospital Millennium Medical College (SPHMMC) from January, 2015 to December, 2019 in Addis Ababa, Ethiopia. . All newly confirmed esophageal cancer patients (n=255) who were registered at SPHMMC from January 2015 to December 2019 were included in this study. Patients chart, Endoscopy report and Histology data were reviewed . Finally, basic descriptive statistics (frequency, mean, median), bivariate and multivariable analysis were performed.*

Result: *A total of 255 esophageal cancer patients' charts were reviewed. and 222 patients have confirmed Histology report of esophageal cancer. There were 173 (77.9%) cases of squamous cell carcinoma. The mean age at diagnosis was 57 years with comparable male to female ratio. The Upper , middle . lower esophagus are involved in 10.4%,38.4%, and 48.6% of the patients respectively. Most patients 220(86.6%) seek esophagogastrduodenoscopy for dysphagia and only 15(6.8%) of patients have staging work up and majority presented at stage (80%).*

Conclusion*: Squamous cell carcinoma was the most predominant histologic type followed by adenocarcinoma affecting males and females equally. Most of the esophageal cancer patients were diagnosed in advanced stages affecting the treatment outcome of esophageal patients.*

Keywords: *Esophageal cancer; histology; endoscopic site; Ethiopia*
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Introduction

Esophageal carcinoma (EC) is the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality. Unfortunately, it is often associated with a poor prognosis, with a 5-year survival ranging from 4 to 40% depending on stage and an 18% overall 5-year survival(1; 2).

The epidemiology of EC presents many unusual features. Even over short distances, the incidence of EC varies considerably, usually more marked among females than males. The incidence is rising rapidly in some communities, often those that might be regarded as suffering from particularly modern forms of deprivation. Esophageal cancer has the fastest-growing incidence of any cancer in the United States, with an increase of 50% in the past two decades (1; 2; 3).

Histologically, EC can be squamous cell carcinoma (ESCC) or adenocarcinoma (EAC). Both types are more common in males than females. ESCC is more commonly encountered in individuals from low-resource regions like Africa and East Asia, while EAC is more prevalent in more developed countries

like the United States (4). Ethiopia is among the most pervasive countries in the East African region, “the so -called East African Esophageal Cancer Corridor,” which stretches from Sudan to South Africa. Multiple studies showed a tendency to increase EAC worldwide, including in Africa. In a recent Kenyan study, the prevalence of EAC among esophageal tumors was 18.9%, which is significantly higher than the 1978 study, which found the EAC to represent 1.1%, and a recent Ethiopian study showed EAC contributed to 13% of the total esophageal cancer patients (5; 6; 7; 8; 9).Risk factors, screening programs, and some management differ for the different types of histology of esophageal cancer and tumor sites. Hence, this study aims to analyze the prevalence and characteristics of esophageal cancer among SPHMMC patients sent for endoscopy examination in the last five years. This study will provide clinicians, policymakers, and society with valuable evidence to tackle this deadly cancer.

Methods

Study Area and Period

The study was conducted from May 15, 2020, to June 15, 2020at St. Paul Hospital Millennium Medical College (SPHMMC) in Addis Ababa, Ethiopia. SPHMMC is a teaching and tertiary referral hospital. It is the largest public hospital and was built in the early 1960s. SPHMMC is the only transplant center in Ethiopia and one of the two tertiary hospitals that provide sub-specialty training.

Study Design

A health facility-based, retrospective cross-sectional study using record review was conducted.

Study Population

The study included all endoscopically diagnosed esophageal cancer patients registeredatSPHMMC between January 2015 and December 2019 who fulfilled the eligibility criteria.

Inclusion and Exclusion Criteria

Patients diagnosed with esophageal cancer and registered with complete information, including age, sex, diagnosis, region of esophagus involved, and biopsy result, in the registration book or the chart were considered eligible for the study.All patients with incomplete Endoscopy reportswere excluded from the study.

Variables of Study

This study included variables such as the histology of esophageal cancer, the site of the cancer, the hemoglobin level, the MCV level, clinical symptoms, and background variables, including age, sex, and place of residence.

Operational Definition

Patient with esophageal cancer: Any patient diagnosed as having an esophageal mass lesion that was considered esophageal cancer by the gastroenterologist and confirmed to be cancer by the pathologist.

Upper Esophageal Cancer: Esophageal cancer that involves up to 19.9 cm from the mid-incisorand/or is reported by endoscopy-performing gastroenterologists as upper esophageal cancer.

Middle Esophageal Cancer: Esophageal cancer involving the distance between 20 cm and 34.9 cm from the mid-incisorand/or reported by endoscopy-performing gastroenterologists as middle esophageal cancer.

Lower Esophagus: Any esophagus cancer patient involving the esophagus starting from 35 cm from the mid incisor up to the cardia or reported by endoscopy -performing gastroenterologists as having lower esophagus cancer.

Squamous cell carcinoma: any esophageal biopsy sample reported as squamous cell carcinoma by a pathologist.

Adenocarcinoma: Any esophageal biopsy sample reported to be adenocarcinoma by a pathologist.

Undifferentiated: Any esophageal biopsy witha malignant character, but it is challenging to differentiate between adenocarcinoma and squamous cell carcinoma.

No Malignancy: Any esophageal biopsy sample considered by a gastroenterologist doing an endoscopy as an esophageal mass but whose histology result was benign.

Data Collection Tools and Procedures

Before the actual data collection started, the principal investigator assessed the patients' charts for relevant variables, and based on that, data extraction tools were prepared. Then, trained nurses working in endoscopy clinics extracted and collected the data.Before collecting the data, the patients' charts were identified by their medical record number, and the investigator extracted and reviewed them.

Data Analysis

Basic descriptive statistics (frequency, mean, and median) are used for data analysis.

Results

Sociodemographic characteristics

From January 2015 to December 2019, 4337 patients underwent EGD at SPHMMC. Among these, 255 patients were diagnosed with esophageal cancer by gastroenterologists working at SPHMMC. Of the patients diagnosed, males make up about 47.5%, and females make up 52.5%. The minimum and maximum age of patients at diagnosis were 22 and 92 years, respectively, with the mean age being 57 years old.

Most patients came from the Oromia region, 147 (57.6%), followed by the SNNP region, 44 (17.3%). Addis Ababa residents contributed about 34 (14.3%), and the Amhara region contributed 26 (10.3%). Other parts of the country contributed only 4 (1.5%) (see Table 1).

Table 1: Background characteristics and indications for EGD in esophageal cancer patients who underwent EGD at St. Paul Hospital Millennium Medical College (Ethiopia) from January 2015 up to December 2019

Gender	Frequency	Percent
Male	123	48.1
Female	132	51.9
Age (in years)		
20 -40	36	14.1
41-60	115	45.1
61-80	82	32.2
>80	22	8.6
Indications for EGD		
Dysphagia	220	86.3
Vomiting	27	10.6
weight loss	2	0.8
epigastric pain	3	1.1
Anaemia	3	1.1
Residence		
Oromia	147	57.6
Addis Ababa	34	13.3
Amhara	26	10.3
SNNP	44	17.3
Other Region	4	1.5

Histologic types, anatomic sites, and stage of esophageal cancer

Thirty-three of the 255 patients had no histologic report attached to their chart. Two hundred twenty-two patients had histological diagnosis results, of which 173 (77.9%) had squamous cell carcinoma, 45 (20.3%) had adenocarcinoma, 3 (1.2%) had undifferentiated malignancy, and one (0.4%) had a benign lesion. The distribution data for the number of patients and different types of esophageal cancer diagnosed is presented in Table 2 below.

Based on the site of esophageal involvement, 25 (10.1%) have upper esophageal involvement, 98 (39.7%) have middle esophageal involvement, and 124 (48.6%) have lower esophageal involvement. The distribution data for the number of esophageal cancer patients based on endoscopic site for mass is presented in Table 2 below

Thereare twenty-two cases of upper esophageal cancer, including one adenocarcinoma and twenty-one squamous cell carcinomas. However, eighty-four squamous cell carcinomas and three adenocarcinomas exist in the middle esophagus. The lower esophagus has sixty squamous cell carcinomas and forty-oneadenocarcinomas, as shown in Figure 1 below.

Table 2: Site, histology, hemoglobin, MCV, and stage of esophageal cancer patients who underwent EGD at St. Paul Hospital Millennium Medical College (Ethiopia) from January 2015 to December 2019.

Study Variables	Frequency	Percent
Site of esophageal cancer		
Upper	25	10.1
Middle	98	39.7
Lower	124	50.2
Histology		
Squamous	173	77.9
Adenocarcinoma	45	20.3
Undifferentiated	4	1.8
Haemoglobin		
Male		
>14	26	56.5
<13.9	20	43.5
Female		
>12	32	69.4
<11.9	14	30.6
MCV		
>100	4	4.8
80-1100	69	83.2
<80	10	12
Stage of Esophageal Cancer		
Stage I	0	0
Stage II	1	6.7
Stage III	2	13.3
Stage IV	12	80.0

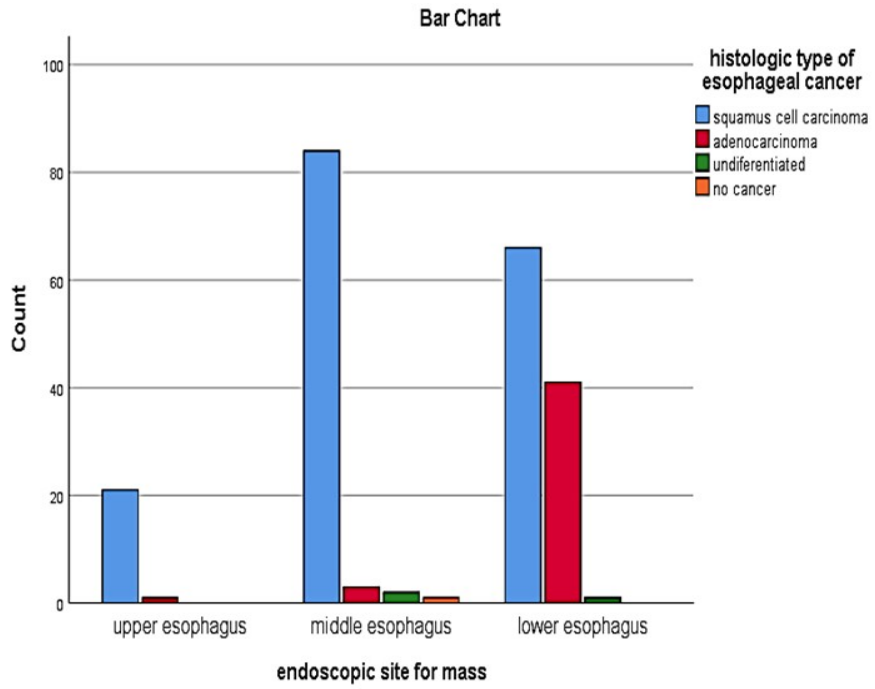

Figure 1: Comparison of different types of esophageal cancer histology with the endoscopic site of the esophageal cancer patients seen at SPHMMC from December 2015 to December 2019

Though only 15 (6.8%) patients have clinical staging workups, 93.3% of those who have workupsreached a very late stage.This small number with staging might be due to a lack of esophageal cancer treatment centers at SPHMMC, and patients are referred to other centers where treatment is available and staging is performed.

Indications for the EGD, hemoglobin, and MCV levels of the patients.

In terms of the presenting clinical symptoms, 220 (86.6%) have dysphagia, 27 (10.6%) have vomiting, 3 (1.2%) have epigastric pain, 2 (0.8%) have weight loss, and 2 (0.8%) have anemia as a primary symptom. Among the forty-six male patients with hemoglobin levels reported, 26 (56.5%) had hemoglobin levels less than 14 g/dl, which is in the anemic range for males. Among the forty-six female patients with hemoglobin determined, 14 (30.4%) had a hemoglobin below 12 g/dl, anemic for females.

Most patients (83.2%) have a normal MCV value between 80 and 100 fl, but 12% have a low MCV, and 4.8% are above one hundred fl (see Table 1).

Discussion

Among 4375 people who underwent esophagogastroduodenoscopy at the SPHMMC gastroenterology unit from January 1, 2015, to December 31, 2019, 255 werediagnosed with esophageal cancer by endoscopy, and 222 were confirmed with biopsy.

Female patients make up 51.9% of the total cases, and males make up 48.1%, which is different from other countries, where males are predominant in the studies from the USA, Europe, and South Africa.(1). A survey from neighboring Uganda showed that the male and female proportions were 74% and 26%, respectively. However, this is consistent with the previous Ethiopian studies, which showed females and males made 59%, 41%, 55%, and 45%, respectively, with a tendency for female predominance (10-12). Other data showed that the incidence rate of esophageal cancer is higher in females compared to males (3.3 vs. 2.2 cases per year per 100,000 people) (4), and in our cases, females made slightly higher. This might be due to less prevalent traditional risk factors, like cigarette smoking, among Ethiopian patients but more exposure of females to indoor pollution during cooking.

When we see the age distribution, there is a patient as young as 22 years and as old as 92 years, making the range 70 years. The mean age was 57, consistent with previous Ethiopian and other African studies.(7; 11; 13). This age is around ten years younger than the average in the Western world(14).

Most of our patients are from the Oromia region, 147 (57.6%). Previous studies done in other hospitals show the high prevalence of Oromia(10; 11; 15). This needs to be studied prospectively. Studies done in Iran, West Kenya, and Brazil showed that tea-drinking behavior (temperature, number of cups per day) and exposure to PAH are significantly associated with ESCC (16; 17; 18; 19).

Only fifteen (6.8%) patients have a CT scan for staging, which is very low to conclude. However, among these patients, twelve were in stage 4 disease, 80%, and 2 (13.3%) patients were in stage 3. This is consistent with another study done in Addis Ababa at another site, where stages 1, 2, 3, and 4 contributed 1.1%, 10%, 19%, and 69.9%, respectively (20).

Among all esophageal cancer diagnoses made by EGD in this period, 25 (10.1%) involved the upper esophagus, the middle esophagus was involved in 98 (39.7%), and 124 (48.6%) involved the lower esophagus. This is consistent with cases in the other hospitals based in Addis Ababa, which were 54.1%, 30.5%, and 15.4% in the lower, middle, and upper esophagus, respectively. However, another previous study from Addis Ababa and neighboring Uganda reported that the commonest site is the middle esophagus (10; 11). The discrepancy between middle and lower esophageal involvement might be due to interobserver differences (21).

The dominant type of histology was squamous cell carcinoma, which contributed 173 (77.9%), adenocarcinoma in 45 (20.3%), and undifferentiated carcinoma in 3 (1.4% of patients). The dominant type of histology was shown to be squamous cell carcinoma in Ethiopia. The results from previous publications reported squamous cells at 88% and adenocarcinoma at 12% (11). Another paper reported squamous cell carcinoma and adenocarcinoma as 90.3% and 9.4%, respectively, showing the majority being squamous cell carcinoma, which aligns with our study (10). Squamous cell carcinoma is the dominant histology type worldwide, making up 75% of the world's esophageal cancer histology (1). Studies in Kenya and Uganda also showed that squamous cell carcinoma is the dominant type, reporting 81.1% and 93% of squamous cell histology, which aligns with our study (7; 10). Adenocarcinoma is the dominant type of histology in North America (USA and Canada) (1). There is an increasing proportion of adenocarcinoma worldwide, including in this study, which is 20.3%, more significant than any previous reports from Ethiopia. This trend has been observed in Kenya, where the proportion of adenocarcinoma grew from 1.1% in 1978 to 18.9% in 2017, consistent with our observation and another Ethiopian study (7; 9).

When we compare esophageal region involvement and histology type by region involved, among the twenty-two cases in the upper esophagus, 21 (95.5%) were squamous cell carcinoma. In contrast, only 1 (4.5%) casewas adenocarcinoma. Among the eighty-nine cases with middle esophageal involvement and histology reports, 84 (94.4%) had squamous cell carcinoma, 3 (3.4%) had adenocarcinoma, and 2 (2.2%) had undifferentiated malignancy. One hundred seven patients have histology and EGD reports in the lower esophagus. Among these, 66 (61.7%) were squamous cell carcinomas, and 41 (38.3%) were adenocarcinoma. This is consistent with the Ugandan study, which showed the adenocarcinoma contribution of the upper, middle, and lower esophagus was 0%, 20%, and 80%, respectively (2).

The prevalence of anemia in our patients is higher than the national-level report. The prevalenceof anemia in males and females in our study is 56.5% and 30.4%, respectively, which is higher than the national prevalence for males, which is 18%, and females, which is 30.4% (22; 23; 24).

Since this is a retrospective study, there are many incomplete/partially filled data, which makes some conclusions difficult. Despite that, it has contributed significant information about the characteristics of esophageal cancer patients at SPHMMC and Ethiopia.

Conclusion

Esophageal cancer affects females in a slightly higher proportion than males, with the mean age being 57 years in Ethiopia, which is a productive age group affecting the economy. Though squamous cell carcinomas are the dominant histology, our data shows an increasing trend in adenocarcinoma. Most patients are from the Oromia region, which needs further prospective study to identify the cause and make public health interventions.

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Ethical Considerations: This research is approved by the SPHMMC Institutional Review Board.

Authors' contribution

Mifta Dellil Hamid is involved in literature preparation, manuscript writing, and editing.
All the authors are involved in manuscript writing and editing.
All the authors have read and approved the final manuscript.

Conflict of interest: **The authors declare no competing interests.**

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Original Article

Analysis of Bacteria-derived Extracellular Vesicles in the Urine of Patients with Sepsis

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Abstract
Background *: Extracellular vesicles (EVs) are secreted by all bacteria, including those that cause sepsis, and are distributed throughout the bloodstream before getting excreted in the urine. The study aimed to analyze bacterial-derived extracellular vesicles in the urine of patients with sepsis and compare them with those in healthy controls.*
Methods *: The study included a total of 25 patients, comprising 9 cases with positive bacterial cultures in clinically significant specimens and 11 healthy controls. Urine samples, either midstream or collected via Foley catheter, were obtained before the initiation of antibiotic treatment. Extracellular vesicles were isolated from these samples using centrifugation. Metagenomic analysis was conducted on the isolated EV samples, focusing on bacterial 16S rDNA to identify the bacterial genera present.*
Results *: In all febrile patients with culture-positive cases, genetic material from multiple bacterial genera was detected through metagenomic analysis, although the specific bacteria identified in clinical cultures were not found in most cases. The bacterial distributions observed in the normal control group were markedly different from those in the febrile patients.*
Conclusions *: The findings suggest that bacterial components are likely entering the bloodstream from multiple sites within the body in the form of extracellular vesicles, both in septic and normal states. The distinct bacterial distributions observed in the urine of sepsis patients compared to healthy individuals require further investigation to understand the underlying mechanisms.*

Keywords: *Extracellular vesicles, Sepsis, Bacteria-derive*
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Introduction

Sepsis and its extreme manifestation, septic shock, are major clinical problems that kill millions of people around the world each year with a mortality of 35~55% in the case of septic shock[1]. While sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, the treatment of sepsis usually demands fluid resuscitation, vasopressors, and other modalities beyond antibiotics.

The host response in sepsis is believed to be initiated and progressed by not only the microorganisms themselves but also their other cell components, including an endotoxin (lipopolysaccharide found in the bacterial outer cell membrane), peptidoglycan (a basic component of the bacterial cell wall) and their products including exotoxins. For this reason, the culprit organisms are not identified in up to 40-60% of patients with sepsis, even when the patients show full-blown septic manifestations[2].

On the other hand, the study of bacteria-derived extracellular vesicles (EVs) is a new research area that has recently been spotlighted in relation to the pathophysiology of infectious diseases and the pathogenesis of various noninfectious diseases. While EVs derived from Gram-negative bacteria were first discovered with the development of the electron microscope in the 1960s[3], recently, it was found that not only

Gram-negative bacteria but also Gram-positive bacteria such as *Staphylococcus aureus* secrete EVs[4].

EVs derived from bacteria are spherical vesicles with a size of 20-200 nm and have various biologically active substances such as proteins, lipids, and genetic material. As bacteria-derived EVs are released through the bacterial cell wall and the bacterial outer membrane, they contain components reflecting those structures, including lipopolysaccharides and peptidoglycans. Given that the properties of the bacteria-derived EVs overlap with several substances known to be involved in sepsis, it is likely that they are deeply involved in the pathogenesis of sepsis[5]. Moreover, bacteria-related substances, including endotoxins found in the body of sepsis patients, may actually exist in the form of EVs.

Bacteria-derived EVs are small-sized substances that are mostly excreted in the urine through the kidneys[6]. Therefore, it is expected that there will be a large amount of bacteria-derived EVs secreted from causative bacteria in the urine of patients with sepsis. Separation of these EVs from the urine of sepsis patients and analysis of the genetic material or proteins contained in the bacteria-derived EVs may reveal more precisely which bacteria and bacterial by-products are involved in sepsis.

This study was designed to analyze bacteria-derived EVs excreted in the urine of sepsis patients and evaluate if they are representative of the causative agents of sepsis.

Materials and methods

Participants

Patients with an acute fever over the age of 20 who visited the outpatient clinic or emergency room of Haeundae Paik Hospital of Inje University, were enrolled. People over the age of 20 who received a routine health check were selected as candidates for the healthy control group. We excluded patients with HIV infection or those who could not perform both methods to collect their urine: midstream urine or aseptic urine collection through a Foley catheter.

Sample collection

After explaining the study to the patients or their guardians and obtaining written consent, approximately 30-50 ml of midstream urine were collected in sterile containers. For the second method, the Foley catheter was inserted, and the urine was collected aseptically through the Foley catheter. Urine collection was performed before antibiotics were administered. The control group health checker collected urine at the time of the checkup. The collected urine was stored in a -70℃ freezer within 30 minutes of collection, and after being thawed, the EVs were isolated by centrifugation, and 16S metagenomics was performed at the time. This study was performed in accordance with the declaration of Helsinki. This study was approved by the Ethics Committee of Haeundae Paik Hospital of Inje University (No. 2013-051). Verbal informed consent was obtained from all the participants.

Extracellular vesicle (EV) isolation and DNA extraction from the urine samples

EVs in human urine were isolated using the differential centrifugation method, as described previously[7]. Briefly, urine samples were centrifuged at 10,000 x g for 10 min at 4˚C, and a 0.22 μg filter was used to eliminate bacteria and foreign particles from the supernatant. The DNA from the bacteria-derived EVs was extracted by boiling the filtrates for 40 min at 100˚C. DNA was then extracted using the DNeasy PowerSoil kit (QIAGEN, Germany).

Emulsion-based PCR for metagenomic sequencing

Sequencing was performed by Macrogen (Seoul, South Korea) using a GS-FLX Titanium Sequencer System (Roche, Basel, Switzerland). Briefly, genomic DNA was amplified from urine by the polymerase chain reaction (PCR). The method used a 16S rDNA fusion primer (27F, 5′-GAGTTTGATCMTGGCTCAG-3′ and the primer 518R, 5′-WTTACCGCGGCTGCTGG-3′) to amplify the V1–V3 region. GS-FLX titanium libraries were prepared using PCR products following the instructions provided in the GS-FLX Titanium Library Preparation Guide. EmPCR corresponding to clonal amplification of the purified libraries was performed using a GS-FLX titanium emPCR kit (454 Life Sciences, USA). Each sample was loaded onto one region of a 70 mm-75 mm PicoTiter plate (454 Life Sciences, USA) equipped with an 8-lane gasket for sequencing on a GS-FLX Titanium (454 Life Sciences, USA).

Analysis of the bacterial composition of the microbiota

Sequencing reads with high quality were retained by the quality score threshold (mean Phred score > 20 and read length > 300 bp). Operational Taxonomy Unit (OTU) was obtained using UCLUST and the taxonomic assignment was performed using QIIME and GreenGenes 8.15.13 database. Based on the similarity, all sequences were classified as follows: species, > 97% similarity; genus, > 94% similarity; family, > 90% similarity; order, > 85% similarity; 5 class, > 80% similarity; phylum, > 75% similarity.

Results

A total of 25 febrile patients were recruited over the course of 4 months from September 2013 to January 2014. There were 9 cases with positive cultures of bacteria in meaningful clinical specimens and 16 cases of culture-negative patients (Table 1).Eleven healthy controls were also evaluated for comparison to the febrile patients.

Table 1. Clinical and microbiological diagnosis of febrile patients.

Case No.	Age	Gender	Clinical diagnosis	Cultured bacteria	Specimens of the positive cultures	Other evidence used for disease diagnosis
1	54	M	Acute pyelonephritis	Escherichia coli	Blood, Urine	
2	61	M	Spondylitis	Staphylococcus epidermidis	Blood	
3	31	F	Unknown	Streptococcus agalactiae	Urine	
4	62	M	Acute pyelonephritis	Escherichia coli	Urine	
5	62	F	Acute pyelonephritis	Escherichia coli	Blood	
6	66	M	Pneumonia	Klebsiella pneumoniae	Sputum	
7	57	M	Endocarditis	Staphylococcus aureus	Blood	
8	72	M	Pneumonia	Pseudomonas aeruginosa, Staphylococcus aureus	Sputum	
9	45	M	Pacemaker infection	Staphylococcus aureus	Blood, Generator	
10	33	F	Kikuchi's disease			Lymph node pathologic findings
11	38	M	Kikuchi's disease			Lymph node pathologic findings
12	23	M	Kikuchi's disease			Lymph node pathologic findings
13	39	F	Tsutsugamushi' s disease			
14	52	F	Tsutsugamushi' s disease			Serology (+)
15	59	F	Tsutsugamushi' s disease			
16	54	M	Tsutsugamushi' s disease			Serology (+)
17	71	M	Sepsis			
18	67	M	Antibiotic-associated colitis			
19	91	M	Antibiotic-associated colitis			Stool Clostridium difficile toxin (+)
20	18	M	FUO			
21	70	F	Toxic shock syndrome			
22	69	F	Spondylitis			
23	53	M	Pneumonia			
24	37	M	Spondylitis			
25	35	F	Pneumonia			

Table 2 shows the results of the metagenomic analysis of the 16S rDNA from the bacteria-derived EVs analyzed in the urine of the febrile patients. In all the patients, including those whose clinical cultures were positive, the distribution of the bacteria-derived EVs of their urine was much more diverse than the bacteria grown from the clinical samples. In fact, bacterial proportions analyzed from the bacteria-derived EVs of urine matched the cultured bacteria in just a few patients at negligible percentages. Many other bacterial genera that are not known to be common causative bacteria including Caulobacteraceae, Novosphingobium, Bacillus, Propionibacterium, Rhizophila, Brevibacterium, and Sphingobium were generally distributed at higher proportions.

Table 2. Relative genus level proportion of bacterial EVs isolated from febrile patient urine.

No	Clinical diagnosis	Cultured bacteria	> 10%	5~10%	Proportion of cultured bacteria
1	Acute pyelonephritis	Escherichia coli	Caulobacteraceae (45.6%), Pseudomonas (11.3%)		Escherichia coli (0%)
2	Spondylitis	Staphylococcus epidermidis	Novosphingobium (28.1%)	Pseudomonas (9.5%), Propinonibacterium (5.2%)	Staphylococcus epidermidis (0.02%)
3	Unknown	Streptococcus agalactiae	Bacillus (19.5%), Propionibacterium (10.8%)	Pseudomonas (9.2%)	Streptococcus agalactiae (0%)
4	Acute pyelonephritis	Escherichia coli	Pseudomonas (11%)	Propionibacterium (6.7%) Enterobacter (6.4%)	Escherichia coli (0.02%)
5	Acute pyelonephritis	Escherichia coli	Caulobacteraceae (40%)	Propionibacterium (5.4%)	Escherichia coli (0.04%)
6	Pneumonia	Klebsiella pneumoniae	Pseudomonas (13.4%)		Klebsiella pneumoniae (0%)
7	Endocarditis	Staphylococcus aureus	Staphylococcus (61.1%)		Staphylococcus aureus (2.8%)
8	Pneumonia	Pseudomonas aeruginosa, Staphylococcus aureus	Propionibacterium (18.5%), Pseudomonas (10.4%)		Pseudomonas aeruginosa (1.5%), Staphylococcus aureus (0.02%)
9	Pacemaker infection	Staphylococcus aureus		Pseudomonas (8.9%)	Staphylococcus aureus (0.02%)
10	Kikuchi's disease		Xanthomonas (72.9%)		
11	Kikuchi's disease		Pseudomonas (14.9%)		
12	Kikuchi's disease		Pseudomonas (12.2%)		
13	Tsutsugamushi' s disease		Sphingobium (15.5%), Pseudomonas (12.9%)	Propionibacterium (7.4%)	
14	Tsutsugamushi' s disease		Staphylococcus (70.5%)		
15	Tsutsugamushi' s disease		Pseudomonas (91%)		
16	Tsutsugamushi' s disease		Xanthomonas (53.9%)	Rhizophila (8.9%), Pseudomonas (5%)	
17	Sepsis		Pseudomonas (17.5%)	Propionibacterium (7%)	
18	Antibiotic-associated colitis		Rhizophila (30.5%), Brevibacterium (20.5%), Xanthomonas (10.7%)		
19	Antibiotic-associated colitis		Ureaplasma (51.1%), Propionibacterium (11.9%)		
20	FUO		Staphylococcus (88.6%)		
21	Toxic shock syndrome		Staphylococcus (19%)	Pseudomonas (8.4%), Propionibacterium (5.4%), Enterobacter (5.3%)	
22	Spondylitis		Staphylococcus (13.2%)	Pseudomonas (7.5%), Bacillus (5.2%)	
23	Pneumonia		Propionibacterum (17.2%), Pseudomonas (9.4%)		
24	Spondylitis		Staphylococcus (43%)	Propionibacterium (6.5%)	
25	Pneumonia		Propionibacterum (11.7%), Pseudomonas (11.2%)		

Staphylococcus was the most common bacterial genus identified from the bacteria-derived EVs in the urine from a case of toxic shock syndrome and 2 cases of spondylitis. In these cases, although the causative bacteria were unable to be cultured, S. aureus is known to be the most common causative agent of the diseases. However, the Staphylococcus EVs of those patients could have originated from species other than S. aureus. For example, in the case of the endocarditis enrolled in this study, the proportion of S. aureus was just 2.8%, even though the total Staphylococcus proportion was 61.1%. Analysis of the bacterial genera to the species level was not attempted for the culture from the non-febrile patients.

As a result of the 16S metagenomic analysis of the bacteria-derived EVs in the urine of the healthy control group, the pattern of the bacterial distribution was shown to be significantly different from that of the febrile patients (Fig. 1).

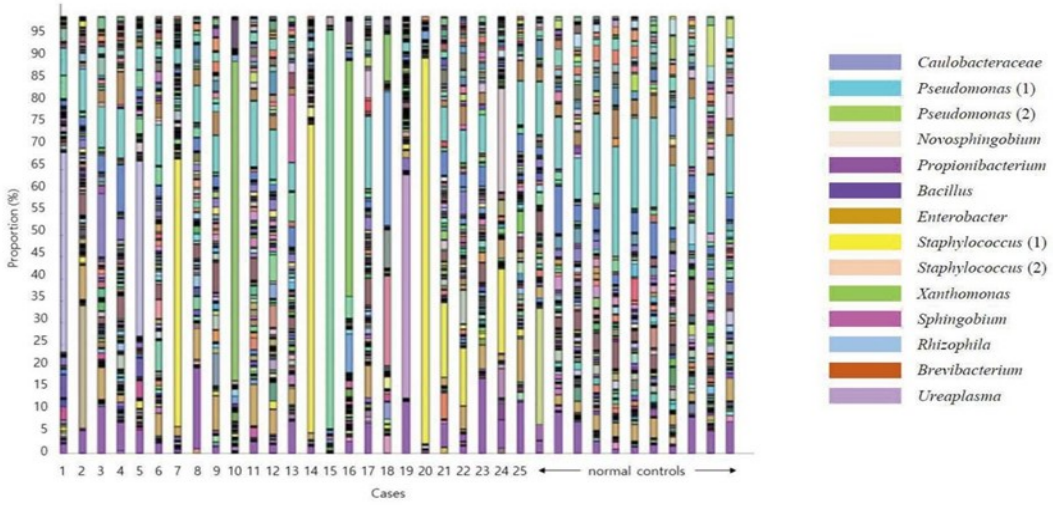

Figure 1.

Figure 1. Distribution of bacterial genera identified by 16S rDNA metagenomics of bacteria-derived extracellular vesicles in the urine of febrile patients and healthy people.

Discussion

The original purpose of this study was to develop a rapid and simple diagnostic method which helps identify the causative bacteria of sepsis by analyzing bacterial EVs in the urine of sepsis patients. However, the results of this study differed remarkably from our expectations. Evidence of the bacteria cultured in the clinical samples could not be found from the 16S metagenomic analysis of the bacteria-derived EVs in the urine of most cases. Even when they were detected in the bacterial EVs, the proportions were negligible. Instead, a variety of other bacteria prevailed as a repeated pattern in our analysis of the bacteria-derived EVs in the urine of sepsis patients, and most of the prevalent bacterial EVs were those not considered relevant causative agents in clinical practice. Rather unusual bacteria were also found in the urine of the healthy controls, although the distribution pattern differed from the febrile patients.

We initially were hesitant to publish these results as we could not explain the phenomena in a rational way. However, several articles with findings similar to ours have been released recently, leading us to decide to add our data to the discourse of this research area.

In a previous study, researchers conducted a 16s metagenomic analysis of blood from 75 febrile children in a West African country, Burkina Faso. They succeeded in matching blood cultured organisms in some cases; however, many unusual bacteria at the genus level were found in the 51 patients including Acinetobacter, Aerococcus, Shewanella, Rhodanobacter, Psillomonas, Flacklamia, Petrobacter, Geobacillus, Nocardioides, Filimonas, Propionispira, Lysobacter, Tissierella, eptotrichia, Paludimonas, Kineosphaera, Raoultella, Proteiniphilum, Amaricoccus, and Lutimonas[8]. The results were excluded from the analysis as irrelevant data, but they were too numerous to do so. A study analyzing 16S rDNA-based next-generation sequencing of blood and neutrophil-associated microbiomes in patients with severe acute pancreatitis found multi-

ple diverse bacterial genera in those patients regardless of their infection state[9]. In addition, bacterial genomes were found in healthy controls, whose distribution was different from those of severe acute pancreatitis patients. A similar study performed in patients with sepsis and healthy volunteers showed the presence of bacterial DNA both in septic and healthy participants with the bacterial diversity significantly higher in healthy volunteers[10]. Other numerous studies analyzing the bacterial genome in the blood of diverse participants have presented mixed results[11].

The most characteristic finding of this study is that diverse bacteria-derived EVs are present in the urine of both acute fever patients and healthy people. At the genus level, most of those bacteria are unusual microorganisms to be considered pathogens of sepsis. It is possible that contamination occurred during the testing process, especially in the case of those bacteria commonly found in the environment, such as dermatophytes, including *Propionibacterium* and *Bacillus,* or the so-called soil-bacteria like *Caulobacteraceae*, *Novosphingobium*, *Rhizophila*, *Brevibacterium*, and *Sphingobium*. However, considering the coincidence between the findings of this study and those of other previous publications demonstrating that the distribution pattern of the bacterial genome between sepsis patients and healthy people in blood and urine is different, we believe that the possibility of contamination is low. It would be more reasonable to assume that bacterial components come into our bodies and circulate throughout the body without our notice given the findings that the bacterial genomes are found even in the blood and urine of healthy people without evidence of infection.

In light of this evidence, we must carefully consider how bacterial components come into the bloodstream and are excreted in the urine. We have an abundant microbiota in our body that accounts for 10 times the number of cells as our own human cells and 150 times more bacterial genes than our own genome. This microbiota is particularly prevalent in the skin, oral cavity, gastrointestinal tract, and vagina[12]. Thus, the most likely origin of bacterial components, including EVs found in the blood and urine, is our normal flora. Because bacteria-derived EVs can be absorbed and bypass the GI tract mucosa[13], it would be reasonable to think that bacterial components often enter the bloodstream in the form of EVs rather than the bacteria themselves.

The reason why the genomes of bacteria-derived EVs in sepsis patients are different from the pattern of healthy people is not easy to postulate. Because polymicrobial infections are not common, it would be more reasonable to think that the bacterial components are also from sites inhabited by normal flora. Changes in the permeability of the mucosa induced by the septic process may permit the entrance of a variety of bacterial components, which would be blocked in normal conditions, causing the difference in the distribution of bacteria-derived EVs between sepsis patients and healthy people.

Our findings, together with previous studies demonstrating that abundant bacterial components from diverse bacterial genera circulate the body, suggest that the treatment paradigm for sepsis may need to be reconsidered. If cell-free bacterial components and EVs have a role in sepsis, antibiotics against cultured bacteria would be a little help as we have experienced in clinical settings. Anti-inflammatory medicine could help, but it would not significantly influence the circulating, abundant and diverse bacterial components. If we develop methods to filter out the bacterial components effectively from the bloodstream, it may offer an additional or possibly essential role in sepsis treatment.

A shortcoming of our study is that the analysis of the bacteria-derived EVs was not performed in blood samples simultaneously with the urine samples. Additional research needs to be done to see if the distribution of bacterial genomes in blood matches the pattern in the urine of sepsis patients. Another weak point of our study is that urine samples were collected just at one time before the start of antibiotics. Analysis of serial samples would give more information on the nature of the relationship between bacteria-derived EVs and sepsis. If experimental analysis with an animal sepsis model is performed, the data will also be much helpful to assess the influence of bacterial EVs in sepsis.

This work has special meaning in that the study performed 16S metagenomics for bacteria-derived EVs, not the bacteria themselves, in sepsis patients. Because the composition of the bacteria-derived EVs could be different from that of bacteria and the EVs are systemically distributed into many organs[13], the result of this study is expected to reflect the influence of the bacterial composition and its components on the pathologic process in sepsis more directly.

In conclusion, metagenomic analysis of 16S rDNA from bacteria-derived EVs in the urine of febrile patients showed the distribution of multiple bacterial genera that are generally uncommonly seen in relation to sepsis patients in clinical practice. Additional analysis of a healthy control group also produced a diverse bacterial distribution, the pattern of which was distinct from that of the febrile patients. Further studies, including simultaneous analysis of urine and blood samples, analysis at serial time points, and animal model studies, are needed to comprehensively explore

the nature of sepsis in relation to circulating bacterial EVs.

Data availability
All gene sequencing data analyzed during this study are available from the European Nucleotide Archive (ENA) database (https://www.ebi.ac.uk/ena/browser/home), accession number: PRJEB52409.

Competing Interests
The authors declare no competing interests.

Author Contributions
YKC contributed to the study concept, clinical data analysis, and manuscript writing. MR contributed to gene sequencing analysis. CK, JY, HS, TS, and YK contributed to EV isolation and gene sequencing. YJ and JK analyzed clinical data. SK contributed to study design, supervision, and manuscript review.

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Original Article

A Comparative Study of the Effects of Adding Intrathecal Morphine and Pethidine to Bupivacaine in Spinal Anesthesia During Cesarean Section: A Randomized Clinical Trial

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Abstract

Background: *Intrathecal opioids are routinely used during spinal anesthesia for post cesarean analgesia. In this research, the analgesic effects of adding pethidine or morphine to intrathecal bupivacaine have been compared.*
Methods: In a double-blinded, randomized trial, 110 parturients who were scheduled for elective cesarean section were randomized into two groups of 55 patients each. In one group, 12 mg of bupivacaine (0.5%) plus 200 mcg of intrathecal morphine and in the second group 12 mg of bupivacaine (0.5%) plus 20 mg of pethidine in a total volume of 3 cc was injected as an intrathecal injection. Data variables were recorded at 1st, 4th, and 24th hours postoperatively. The primary outcome was the pain intensity numerical rating scale (0-10). The secondary outcomes were nausea, vomiting, itching, sedation (Ramsey Sedation Scale), shivering, and demand for analgesic medication.
Results: *No statistically significant differences were found between the two groups in terms of shivering, sedation, pain and pain severity, duration of painlessness period, number of demanded analgesics and level of sensory block, at 1st, 4th, and 24th hours post-operatively. At 24 hours after surgery, the rate of nausea and vomiting was significantly lower in the pethidine group (3 vs. 11, p=0.02), but at the same time, itching complaints were higher in the morphine group (10 vs. 0, p=0.001).*
Conclusion: *Adding intrathecal morphine and pethidine to bupivacaine in spinal anesthesia for cesarean section both creates a long-term and acceptable analgesia. However, in controlling itching, nausea and vomiting, pethidine showed to be more effective than morphine. Thus, it is suggested that 12 mg of bupivacaine (0.5%) is applied in combination with 20 mg of pethidine in spinal anesthesia for this surgery.*

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Keywords: : *Intrathecal Injection, Morphine, Pethidine, Bupivacaine, Spinal anesthesia, Cesarean Section.*
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Introduction

Spinal anesthesia is the preferred method for cesarean surgery (1-5). And the most common drug used for this purpose is bupivacaine(3). This method is economical and can be easily performed(4). However, this method is accompanied by several adverse effects such as hypotension(6), shivering, itching, nausea and vomiting, limitation of block time and short-term analgesia after local anesthetic absorption (7, 8). Postoperative pain is one of the most important complaints of mothers after cesarean surgery, which can be moderate to severe pain (8, 9). If this pain is properly managed, the mother can recover faster and take better care of the baby. Also, due to the pain, the mother's activity can be limited and may increase the risk of thromboembolism (10, 11). In spinal anesthesia, to relieve abdominal and somatic pains during surgery and create a long-term period of analgesia after surgery, various adjuvant drugs can be used together with local anesthetics (9, 12, 13). Among these drugs, we can mention fentanyl, sufentanil, morphine, clonidine and pethidine (14, 15). Intrathecal morphine is both cost-effective and convenient due to its long-lasting analgesic effect(16). Intrathecal pethidine has also been considered due to fewer side effects, including respiratory depression(15). In various studies, these sup-

plements have been compared to investigate their effect on postoperative pain and their side effects but they got different results(9, 12, 14, 15). In current study, pethidine or morphine was added to intrathecal bupivacaine for spinal anesthesia during cesarean section. In patients with cesarean section, we didn't find any comparative study about pethidine and morphine as adjunctive in spinal anesthesia with these doses and similar consequences. Its main objective is to compare the adequacy of the analgesic effect of these additives on the intensity of postoperative pain and the secondary objectives were to compare their effect on postoperative nausea, vomiting shivering, and itch, sedation and the time of the first request for an analgesic.

Methods:

Approval was obtained from the Research Ethics Committee of the Hormozgan University, School of Medicine (2017-11-26, HUMS.REC.1396.108). The trial was also registered in the Iranian Clinical Trials registry IRCT20140615018091N10. To calculate the sample size, refer to the study of Sawi et al(9), where the proportion of the patients with mild postoperative pain was 0.86 in the intrathecal morphine compared to 0.63 in the non-morphine group. In this study, α (type I error rate) = 0.05, 1- β (test power) = 0.9 was considered and the calculated minimum sample size was 55 for each group. The study was a double blinded, parallel group randomized clinical trial of 110 pregnant women with a gestational age of over 37 weeks. Inclusion criteria included the American Society of Anesthesiologists physical status I-II, term gestation (37-42 weeks), and desire for a spinal anesthesia.Exclusion criteria included contraindication to spinal anesthesia, cases with the emergency condition, a disease in heart valves, a history of allergy to the target drugs, the addicts or alcoholics, those afflicted with preeclampsia, diabetes and patients who declined consent. Moreover, patients whose spinal anesthesia was changed to general anesthesia for whatever reason were excluded. An extensive explanation of the study protocol was provided to all participating subjects including benefits and possible side effects of adjuvants added to local anesthesia in spinal anesthesia. They were asked to give full consent to take part in the research and they were ensured of the confidentiality of the data they provided and that was collected during the trial. Patients were randomly allocated to one of two study groups: 200 mcg intrathecal morphine or 20 mg intrathecal pethidine. Before study commencement, random allocation software was used to design a permuted block randomization table with a 1:1 allocation. The block sizes of 2, 4, and 6 were used. According to the size of each block concealed opaque sequentially numbered envelopes containing either assigned group A (receiving pethidine + bupivacaine) or B (receiving morphine + bupivacaine) was drawn. Allocation concealment and blinding to the block sizes will be applied to the primary anesthesiologist responsible for applying the study protocol. The patients and nurses were blinded to the group assignments. The research assistant responsible for recording the variable's data during the C/S surgery and postoperative recovery room and ward periods, was also blinded to the protocol groups and drugs applied. The 159 subjects were recruited. 16 were excluded who were not eligible. 17 patients needed drugs to complement of spinal anesthesia. In 10 patients, the anesthesia was changed to general anesthesia. The study was not completed by 6 patients.

The final analysis was applied on 110 patients (55 each group). All parturient went through standard monitoring. Before the study, all received 10 cc/kg of ringer and their initial hemodynamic parameters were recorded. Then, spinal anesthesia was induced in sitting position with a Quincke needle (n.25) [Dr.japan, disposable spinal needle] in the spinal interspaces of L3-L4 or L4-L5. After CSF free flow fluid was detected, The A group received 12 mg of bupivacaine (0.5%) plus 20 mg of preservative free pethidine (Pethidine 50 mg/mL, Exir Pharmaceuticals Co., Iran; www.exir.co.ir) previously prepared in insulin syringe in a total volume of 3 ccs. The B group received 12 mg of bupivacaine (0.5%) (5mg/ml, AstraZeneca, Sweden) plus 200 µg of morphine (Morphine sulfate, Faran Shimi Co. Lim. Iran) previously prepared in insulin syringe in a total volume of 3 ccs as an intrathecal injection. The quantity of morphine and pethidine was the mean recommended doses for intraspinal injection(15, 16).Then, all patients lay on their backs. Intraoperative vital signs and urine output were monitored throughout the surgery. It went on in the 1st, 4th, and 24th hours of the surgery. A systolic blood pressure < 90 mm Hg was defined as hypotension treated with 5 mg of ephedrine. A heart rate of <60 per minute was defined as bradycardia treated with 0.6 mg of atropine. The anesthesia level was checked. Once the block was stabilized at level T4 to T6, the surgery was authorized. All parameters were checked and recorded by the anesthesia assistant after the block.

Patients' severity of post-surgical pain was measured and recorded as patients self-reported NRS (Numeric Rating Scale)(17) in the 1st, 4th, and 24th hours after surgery. The most severe possible pain was scored 10 and total painlessness was scored 0. The other levels of pain ranged from 0 to 10 as self-rated by the patients.

The presence or absence of nausea and vomiting was recorded during surgery and in the 1st, 4th, and 24th hours after surgery. Nausea was treated with ondansetron (4 mg IV).

The presence or absence of itching was measured and recorded during surgery and in the 1st, 4th, and 24th

hour after the surgery. Ramsey Sedation Scale(18) was used during the surgery as well as in the 1st, 4th, and 24th hours as below: the patient is anxious and upset or restless or both (score 1); the patient is relaxed and cooperating (score 2); the patient only abides by the orders (score 3); the patient shows a rapid reaction to loud sound or a slow blow to the area between the eyebrows (score 4); the patient shows a slow reaction to loud sound or a slow blow to the area between the eyebrows (score 5); the patient would show no reaction at all (score 6). The time of the first request for an analgesic agent after the surgery was recorded in the minutes after the surgery. The dose of the analgesic was also recorded as in the number of Diclofenac suppositories (50 mg) applied. In case of repeated complaints of pain, Diclofenac suppositories were prescribed to the patient up to a maximum of 3 suppositories per day. The presence or absence of shivering was evaluated and recorded in all patients.

Statistical methods for the acquired data were applied by SPSS.19 for statistical analysis through descriptive statistics such as mean, standard deviation, percentage, etc. used along with the tests of normality, chi-squared test, Fisher's exact test, independent-sample T-test, and Mann-Whitney U-test. The level of significance was set at $P<0.05$.

Results:

The two research groups were compared in terms of demographic characteristics such as the mean age, weight, and height, and there was no significant difference (Table 1). The block-level was compared between the two groups and in both, it reached 58.2%, i.e., T4, (Table 2).

There was no significant difference between the pethidine and morphine groups regarding the severity of pain at different time points, the onset of pain after operation and the number of suppository analgesics required after the operation (Table 3).

The presence or absence of nausea and vomiting, itching, and shivering was also compared between the two groups at different times (Table 4). In the 24th hour after operation, post-operative nausea and vomiting was significantly higher in the morphine group ($P= 0.022$), additionally itching was also higher at this point in the morphine group ($P= 0.001$) (Table 4). The incidence of shivering was different among the two groups, but it was not statistically significant. The two groups were also compared in terms of the mean RSS (Ramsay Sedation scale), (Table 3) and no significant difference between the two groups was found during the surgery and in post-operative period.

Table 1: Two research groups compared in terms of age, weight and height

Variable	Research group				P-value
	Bupivacaine+pethidine		Bupivacaine+morphine		
	Mean	SD	Mean	SD	
Age (years)	28.23	7.51	30.48	9.66	.226
Weight (kg)	69.18	9.61	69.27	12.00	.844
Height (cm)	156.95	7.51	159.39	9.01	.173

Age and height between groups using independent test and weight between groups with Comparisons were made using the Mann Whitney U test. There was no significant difference ($P>0.05$).

Table 2: Cross-comparison of two research groups in terms of the level of sensory motor block

Sensory block level	Research group			
	bupivacaine plus +pethidine		Bupivacaine +morphine	
	No= total 55	%	No.= total 55	%
T4	32	58.2	32	58.2
T5	1	1.8	6	10.9
T6	22	40.0	17	30.9

Mann Whitney U test was used and there was no significant difference ($P>0.05$)

Table 3: Cross-comparison of two research groups in terms of mean RSS score, severity of pain, time interval between the outset of pain and number of suppositories taken by patients in pain

variable	time	Research group				p-value
		Bupivacaine+pethidine		Bupivacaine+morphine		
		mean	SD	mean	SD	
RSS	During surgery	1.98	0.23	1.95	0.23	0.416
	1st hour	1.98	0.13	1.96	0.19	0.560
	4th hour	2.04	0.19	1.98	0.23	0.182
	24th hour	2.00	0.19	1.98	0.13	0.567
Severity of pain (NRS)	1st hour	0.09	0.48	0.18	0.82	0.637
	4th hour	1.42	1.78	1.78	2.20	0.579
	24th hour	0.78	1.56	0.91	1.71	0.876
Time interval from the outset of pain (min.)		657.27	310.45	743.40	331.40	0.417
No. of suppositories		1.86	0.77	1.00	1.00	0.928

Mann Whitney U test is used. There was no significant difference (P>0.05)

Table 4: Distribution of patients with nausea and vomiting, itching and shivering in the research Groups

variable	time	Response	Research group				p-value
			Bupivacaine+pethidine		Bupivacaine+morphine		
			No.= total 55	%	No.= total 55	%	
Nausea & vomiting	During surgery	Yes	16	29.1	8	14.5	0.065
		no	39	70.9	47	85.5	
	1 hour later	Yes	2	3.6	4	7.3	0.679
		no	53	96.4	51	92.7	
	4 hours later	Yes	4	7.3	7	12.7	0.340
		no	51	92.7	48	87.3	
	24 hours later	Yes	3	5.5	11	20.0	0.022*
		no	52	94.5	44	80.0	
Itching	During surgery	Yes	3	5.5	0	0.0	0.243
		no	52	94.5	55	100.0	
	1 hour later	Yes	11	20.0	11	20.0	-
		no	44	80.0	44	80.0	
	4 hours later	Yes	2	3.6	7	12.7	0.161
		no	53	96.4	48	87.3	
	24 hours later	Yes	0	0.0	10	18.2	0.001*
		no	55	100.0	45	81.8	
shivering	During surgery	Yes	5	9.1	8	14.5	0.376
		no	50	90.9	47	85.5	
	1 hour later	Yes	10	18.2	16	29.1	0.178
		no	45	81.8	39	70.9	

Chi-squared test was used

Discussion:

The main finding of this randomized clinical trial was that the mean severity of pain in the 1st, 4th and 24th hours after surgery was lower in the pethidine group than in the morphine group but the difference was not statistically significant. The painless interval was slightly lower in the pethidine group than in the

morphine group, but this difference was not statistically significant..

Although during the surgery, the rate of nausea and vomiting was 29.1% and 14.5%, in the pethidine and morphine group respectively, this difference was not statistically significant. However, after the surgery, the rate of nausea and vomiting was lower in the former group than in the latter. Within 24 hours after surgery, nausea and vomiting reached 5.5% in the pethidine group while it was 20% in the morphine group. Thus, it can be concluded that nausea and vomiting were better controlled in the pethidine group in the post-operative period.

The rate of shivering during the surgery reached 14.5% in the morphine group and 9.1% in the pethidine group. One hour later, it reached 29.1% in the former and 18.2% in the latter. Therefore, it can be concluded that in one hour the trend of shivering was increased in both groups. Yet this increase was more in the morphine group.

In the present study, during surgery, 5.5% of patients in the pethidine group complained of itching. Yet no patient from the morphine group complained of any itching during surgery. However, in first hour after surgery, 20% of patients in both groups began to complain of itching. In the 4th hour after surgery, itching was reduced in both groups, but this reduction was more in the pethidine group. This decreasing trend continued in the same pethidine group until 24 hours after surgery when there was no complaint anymore. Later on, the rate of itching was slightly increased in the morphine group till it reached a significant level. Thus, it can be concluded that itching was attenuated in the pethidine compared to the morphine group. As far as we have searched this trend of itching issue has not been addressed in the other studies or related literature.

In this research, sedation scores (Ramsey Sedation Scale) did not differ between the two groups and there were no cases of respiratory depression in either group. No similar study was found on this topic.

Saracoglu et al(19). concluded that using morphine would lengthen the painless time after surgery and this painless interval showed to be longer in combination with hyperbaric bupivacaine. In the present study, in both groups 58.2% had a T4 block level. Nevertheless, in the study by Roy et al.(20), the median blocked segment in both groups was T2. The probable reason of such a difference can be due to the use of hyperbaric bupivacaine (0.75%) in the Roy's study instead of hyperbaric bupivacaine (0.5%) in the present research.

In the study conducted by Hong et al. (21), a similar rate of nausea and vomiting was reported in both groups which contrast with the present research. This contrast could possibly be due to different doses of bupivacaine, pethidine and morphine used.

In an investigation by Hong et al(21) the rate of shivering was found to be significantly lower in the pethidine group than the morphine (0.1 and 0.2 mg). They concluded that adding pethidine can better control the shivering in patients with spinal anesthesia for a C/S. In the present research, this difference was not statistically significant. This divergence can be explained by the difference in opioid doses that they used. In another research project by Roy et al. (20) the effect of adding meperidine to bupivacaine was investigated for controlling shivering in spinal anesthesia performed in C/S surgeries. Both groups received hyperbaric bupivacaine (0.75%, 10.5 mg) plus 0.15 mg of morphine. Besides this dose, the intervention group received 0.2 mg meperidine for each kg of body weight while the control group received an equal amount of normal saline. The results showed that the rate of shivering in the meperidine group (9 out of 20 patients, equal to 45%) was lower than the control (17 out of 20, equal to 85%). The rate of shivering in the present research was found to be much lower than that of Roy et al. (20) which can be due to the different doses of drugs (as in the present research 12 mg of bupivacaine (0.5%) was used plus 200 μg of morphine compared to hyperbaric bupivacaine (0.75% and 10.5 mg) plus 150 μg of morphine. Moreover, in the present study, 20 mg of pethidine was used in comparison to the 0.2 mg per kg of body weight). In other research, Nasseri et al. (22) reported the rate of shivering in their morphine group (0.5% hyperbaric bupivacaine plus 200 μg morphine) as 40% though, which was a much higher proportion compared to the present research shivering rate.

Among the limitations of the present study could be that we did not control central temperature and the peripheral body temperatures. Therefore, we suggest adding other options and trying different doses of adjunct opioids in future conducted studies would help to determine the exact effective safe dose of pethidine or morphine for spinal anesthesia in cesarean section surgery.

In Conclusion, we can conclude that adding intrathecal morphine and pethidine to bupivacaine in spinal anesthesia for a cesarean section helps to create a long-term and desirable painlessness. Despite the itching, nausea and vomiting following the addition of either morphine or pethidine to bupivacaine, pethidine showed to perform better considering side effect profile. Thus, it is suggested that a combination of 12 mg of hyperbaric bupivacaine (0.5%) and 20 mg of pethidine may be applied for a spinal anesthesia for the cesarean section surgery.

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Conflict of Interest:
There is no conflict of interest to be declared.

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Original Article

Acute Headaches: Patterns of MRI Findings

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Abstract
***Background**: There is a lack of research on imaging findings of acute headaches in Ethiopia. Most available studies for cross-reference are conducted in developed countries and do not consider clinical and epidemiologic factors unique to developing countries. This study aims to identify the most common radiologic findings in patients presenting with acute headaches and examine their relationship with sociodemographic and clinical variables in an Ethiopian context.*
***Methodology**: A cross-sectional study was adopted in this study. The brain MRI reports and files of 497 patients who were referred for the evaluation of acute headache (less than or equal to one-month duration) to Wudassie Diagnostic Center in Addis Ababa, Ethiopia, from January 2016 to September 2018 were analyzed. The demographic variables and the clinical data of the patients were correlated to the imaging findings. Data analysis was done using IBM SPSS Statistics for Windows Version 20.0.*
***Results**: 60.6% of the patients referred for the evaluation of acute headache had abnormal MRI findings. Nonspecific white matter lesions (which neither explain the reason for acute headache nor alter patient outcome and management) were the most frequently observed radiologic diagnosis (16%), followed by neoplasms (11.1%) and infections (7.7%). Tuberculoma was the most frequently diagnosed infectious cause. The majority of patients with comorbid illnesses (hypertension and HIV) had abnormal imaging findings. Age had a weak but significant positive correlation with abnormal imaging findings.*
***Conclusion**: The findings suggest that acute headaches are frequently associated with significant underlying pathologies, particularly in older patients and those with comorbidities such as HIV or hypertension. The prominence of tuberculoma among infectious causes reflects the influence of local epidemiological factors. These results highlight the importance of targeted imaging protocols to e*nhance diagnostic accuracy and optimize patient management in resource-limited healthcare settings.

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Introduction

Headache disorders are among the most prevalent and disabling conditions worldwide. According to the World Health Organization (WHO), approximately 40% of the global population, or 3.1 billion people, were affected by headache disorders in 2021, with a higher prevalence in females compared to males [1]. Acute headache is a prevalent reason for emergency department (ED) visits, accounting for approximately 2.2% of all ED visits in the United States, with an estimated 2.1 million visits annually [2].

It is often challenging for physicians to determine which patients presenting with acute headaches (lasting one month or less) are candidates for neuroimaging. Certain red flag signs and symptoms identified during the history and physical examination, as well as specific types of headaches, are associated with serious intracranial pathology and therefore indicate the need for emergency neuroimaging. These red flags include sudden severe headache described by the patient as the "worst headache of my life," headache triggered by cough, exertion, or sexu-

al intercourse, and headache accompanied by a change in mental status, loss of consciousness, or focal neurologic signs [2-4]. Additionally, new-onset headaches in patients diagnosed with cancer or HIV pose an increased risk of an intracranial lesion or infection [4,5].

Neuroimaging plays a pivotal role in evaluating acute headache. Common radiologic findings include subarachnoid hemorrhage, identifiable on non-contrast CT as hyperdense areas in the basal cisterns or sulci [6,7]. Intracranial masses, such as metastatic lesions, are frequently detected in cancer patients and visualized on contrast-enhanced MRI as enhancing lesions with surrounding edema [8,9]. Sinusitis with intracranial complications, such as abscess or thrombosis, is seen as sinus opacification on CT or diffusion restriction and contrast enhancement on MRI [10,11]. Cerebral venous sinus thrombosis, a cause of acute headache commonly found in young females or postpartum patients, appears on MRI with MR venography as an absence of normal venous flow [11]. Other findings include white matter changes associated with demyelinating diseases, such as multiple sclerosis, which manifest as hyperintense lesions on T2-weighted MRI [11,12]. These findings emphasize the importance of correlating clinical presentations with imaging results to improve diagnostic accuracy and patient outcomes.

The choice of imaging modality depends on clinical suspicion. The first-line imaging modality usually ordered for patients presenting with acute headaches is non-contrast CT, which can detect hemorrhage, ischemic changes, or edema [13]. However, post-contrast or non-contrast MRI is appropriate as first-line imaging in many conditions, such as new-onset headache with papilledema, cancer, or in immunocompromised patients presenting with new headache suspected of encephalitis, and sinonasal infection with feared intracranial complications [3,14]. Thunderclap headache, characterized by severe pain peaking within 60 seconds of onset, is particularly concerning for neurovascular disorders such as subarachnoid hemorrhage, ruptured aneurysm, or reversible cerebral vasoconstriction syndrome [5]. Up to 8% of patients reporting thunderclap headaches are found to have subarachnoid hemorrhage [14,15].

This study was undertaken to identify the most common radiologic findings in patients presenting with acute headaches and examine their relationship with sociodemographic and clinical variables. Given that most studies on this topic are conducted in developed countries, this research offers a critical perspective on the unique epidemiological and clinical factors influencing imaging outcomes in a developing country setting. Moreover, there is a significant gap in MRI-based studies focusing on acute headaches, highlighting the importance of this study in evaluating the utility, specificity, and sensitivity of MRI in diagnosing the causes of acute headaches. By addressing these gaps, this study aims to enhance our understanding of the diagnostic challenges and improve patient management in similar healthcare contexts.

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted at Wudassie Diagnostic Center in Addis Ababa, Ethiopia. The study analyzed head MRI records collected from September 2016 to January 2018, using one MRI and two CT machines available for imaging services.

Sample Size

The sample size was estimated using Daniel's formula:

$$n = \frac{Z^2 p(1-p)}{d^2}$$

where:

- **n** = required sample size
- **Z** = 1.96 (standard score corresponding to a 95% confidence interval)
- **P** = 0.50 (assumed prevalence)
- **d** = 0.05 (margin of error)

Substituting these values: n = 384

The calculated sample size was 384. However, to enhance the study's precision, all 497 eligible patients who met the inclusion criteria during the study period were included in the analysis.

Sampling Procedure

Data collection was conducted using a consecutive sampling method. A structured questionnaire was used to record demographic information, headache duration, and additional neurologic symptoms. The MRI reports were retrospectively reviewed. These reports were prepared by two licensed radiologists, each with over 10 years of professional experience. A nurse trained specifically for this study collected the data. All patients who met the inclusion criteria were included consecutively until the end of the study period.

Equipment (MRI machine)

MRI scanning was performed with a Siemens Magnetom C 0.35T machine, with and without contrast based on clinical indications. Imaging techniques included Axial TSE T2, Axial SE T1, Sag SE T1, Cor FLAIR, and Axial epi DWI with ADC-map. Contrast-enhanced images were acquired using gadodiamide when necessary, and interpreted by the two experienced radiologists. MRI findings were categorized as normal, minor abnormalities, or clinically significant abnormalities, to identify those im-

pacting headache etiologies or requiring further clinical action.

Operational Definitions

- **Acute headache**: Defined as a headache lasting less than or equal to one month.
- **Minor abnormalities**: These refer to nonspecific findings on imaging that do not explain the cause of the headache and do not influence the clinical or therapeutic approach. Examples include nonspecific white matter changes like chronic ischemia, small arachnoid cysts, and prominent perivascular CSF spaces.
- **Clinically significant abnormalities**: These are imaging findings that directly influence the etiology of the headache or require further clinical action or intervention. Examples include neoplastic lesions, infections, and other conditions directly associated with the cause of the headache.
- **Normal findings**: Imaging results that show no abnormalities and do not contribute to explaining the headache or influence clinical or therapeutic approaches. These findings are categorized as neither minor nor clinically significant.

Variables

- **Dependent variable**: MRI findings (categorized as normal, minor abnormalities, or clinically significant abnormalities).
- **Independent variables**: Patient demographics, headache duration, associated symptoms, and comorbid illnesses.

Data Management

All collected data were reviewed for completeness before analysis. To ensure accuracy and reliability, data were securely stored and regularly checked for inconsistencies by the research team.

Data Analysis

Data were analyzed using SPSS Version 20.0. Quantitative and qualitative comparisons were conducted using Pearson correlation and Phi correlation analyses, respectively. Statistical significance was set at $p < 0.05$. Results were presented in tables and charts as appropriate.

Ethical consideration

Ethical clearance was obtained from the Ethics and Research Committee of the Department of Radiology (with reference number DRC/001/2021), and permission to use the imaging records was granted by the Wudassie Diagnostic Center. Informed consent was not applicable as the study was retrospective with no direct patient interaction; however, the ethical committee confirmed that the data usage was ethically sound and compliant with local regulations.

Results

This study analyzed MRI data from 497 patients at Wudassie Diagnostic Center in Addis Ababa, Ethiopia (Sep 2016 - Jan 2018), focusing on acute headache evaluation. Findings highlight a patient age range of 3 to 89, with a slight female majority (56%). The average age was approximately 41 years. Most patients fell into the 18-49 age bracket. Neurological symptoms were diverse, including seizures (5.4%), vertigo (13%), and vision loss (8.7%), with nearly 39% presenting a neurological deficit like hemiplegia (13.9%), monoplegia (1%), or paraplegia (4%) (Table 1).

Table 1: Neurological signs and symptoms of patients presenting with acute headache at Wudassie Diagnostic Center, Addis Ababa, Ethiopia, September 2016 to January 2018.

Neurological signs and symptoms	Present	Absent
Seizure	27 (5.4%)	470 (94.6%)
Neurological deficit	193 (38.8%)	304 (61.2%)
Hemiplegia	69 (13.9%)	428 (86.1%)
Monoplegia	5 (1%)	492 (99%)
Paraplegia	19 (4%)	478 (96%)
Vertigo	65 (13%)	432 (87%)
Numbness and tingling	8 (1.6%)	489 (98.4%)
Decreased and/or loss of vision	43 (8.7%)	454 (91.3%)
Fever	14 (2.8%)	483 (97.2%)
Neck stiffness	6 (1.2%)	491 (98.8%)

Regarding comorbid illnesses, as shown in Table 2, most cases had no documented comorbid conditions. The most commonly documented comorbid illness was a history of hypertension, which was present in 17.1% of cases and explicitly noted as absent in 0.4% of records.

Table 2: Incidence of comorbid illnesses among patients presenting with acute headache at Wudassie Diagnostic Center, Addis Ababa, Ethiopia, September 2016 to January 2018.

Comorbid Illness	Present	Absent	Unknown
Hypertension	85 (17.1%)	2 (0.4%)	410 (82.5%)
Diabetes	37 (7.4%)	3 (0.6%)	457 (92%)
HIV	29 (5.8%)	3 (0.6%)	465 (93.6%)

Imaging Findings in Patients with Acute Headache

The imaging results indicate that 39.4% of patients had normal findings, while the remaining 60.6% had abnormal findings. Among those with abnormal imaging findings, non-specific white matter lesions were the most frequently observed diagnosis (16%), followed by neoplasms (11.1%) and infections (7.7%).

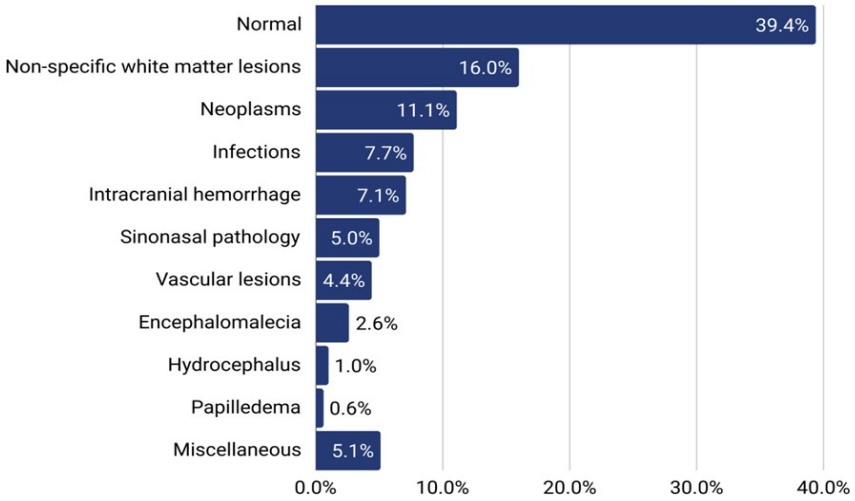

Figure 1: Radiological diagnoses of patients presenting with acute headache at Wudassie Diagnostic Center, Addis Ababa, Ethiopia, September 2016 to January 2018.

53 patients had imaging findings suggestive of tumors, including 23 with extra-axial tumors, 17 with intra-axial tumors, and 13 with pituitary adenomas. 39 patients had imaging findings indicative of infection, with 20 showing tuberculomas.

Imaging Findings in Patients with Comorbidities

Out of the 85 patients who had hypertension, 76.7% had abnormal imaging findings. Similarly, abnormal imaging results were found in 73% and 72.6% of patients with diabetes and HIV, respectively (Table 3).

Table 3: Percentage of patients with comorbid illnesses and abnormal imaging findings among those presenting with acute headache at Wudassie Diagnostic Center, Addis Ababa, Ethiopia, September 2016 to January 2018.

Comorbidities	Normal	Abnormal	Total
Hypertension	20 (23.3%)	66 (76.7%)	86
Diabetes mellitus	10 (27%)	27 (73%)	37
HIV	8 (27.6%)	21 (72.6%)	29

The most frequently found significant radiologic diagnosis for patients with hypertension, diabetes, and those with a history of trauma is intracranial hemorrhage. For patients with HIV, however, the most frequently found radiologic diagnosis is infections (Table 4).

Table 4: Radiologic diagnoses observed in patients with hypertension, diabetes, HIV, and those with a history of trauma.

	Hypertension [%]	**Diabetes [%]**	**HIV [%]**	**Trauma [%]**
Neoplasms	16	4	5	5
Infection	0	4	33	3
Sinonasal pathology	3	7	5	9
Intracranial hemorrhage	19	11	5	26
Vascular lesions	8	4	19	14
Nonspecific white matter lesions	46	63	10	17
Encephalomalacia	2	4	5	17
Hydrocephalus	0	0	10	0
Papilledema	0	0	5	0
Miscellaneous	6	11	5	9

It can be seen from Table 5 below that the majority of the imaging findings (68%) were normal for patients who are less than 18 years of age. For patients who are 18-49 years of age, the majority of the findings (60%) were abnormal. For patients above 50 years, the majority (67%) had abnormal imaging findings. The correlation analysis showed a weak (Pearson correlation coefficient = 0.152) but significant ($p<0.001$) positive correlation between age and abnormal imaging findings in general, indicating that as the age of patients increases, the likelihood of an abnormal imaging result will increase. There is no significant correlation between gender and history of trauma with imaging findings.

Table 5. Correlation between age and abnormal imaging findings in patients presenting with acute headache at Wudassie Diagnostic Center, Addis Ababa, Ethiopia, September 2016 to January 2018.

Age	**Normal**	**Abnormal**
<18	27 (68%)	13 (33%)
18-49	121 (40%)	184 (60%)
≥50	50 (33%)	101 (67%)
Pearson correlation coefficient	0.152	
P-value	<0.001	

When the presence of neurological symptoms is assessed in relation to imaging findings, there was no strong association identified except for fever, which showed a significant correlation with abnormal imaging findings. The results of the Phi correlation analysis are presented in Table 6.

Table 6. Relationship between neurological symptoms and imaging findings among patients presenting with acute headache at Wudassie Diagnostic Center, Addis Ababa, Ethiopia, September 2016 to January 2018

	Imaging findings				
Symptoms	Normal	Abnormal	Total	Phi correlation coefficient	P-value
Seizure	12	15	27	-0.023	0.615
Neurological deficit	68	25	193	0.075	0.095
Numbness and tingling	2	6	8	0.039	0.387
Decrease or loss of vision	24	19	43	-0.100	0.025
Vertigo	31	34	65	-0.062	0.165
Neck stiffness	2	4	6	0.015	0.743
Fever	2	12	14	0.089	0.048

Discussion

This analysis indicates that while age and the presence of fever are significantly correlated with abnormal imaging findings in patients presenting with acute headache, other demographic variables and clinical signs, including neurologic deficits and comorbid diseases like HIV, show varied associations. The most common abnormal imaging findings are nonspecific white matter lesions, neoplasms, and infections [13,16].

Correlation analysis for comorbid illnesses like hypertension, diabetes, and HIV was limited due to the majority of patient statuses being unknown. However, it is inferred that a significant portion of patients with these conditions—73% of those with hypertension and 62% of HIV-positive patients—had abnormal brain scans. Studies consistently indicate that HIV patients with new-onset headaches are more likely to have serious brain issues. Although it is unclear whether hypertension was diagnosed at emergency departments (ED) or had a longer history, its presence at the time of the ED visit has been previously linked to brain problems. Analysis specific to HIV patients revealed infections as the most common brain scan finding, aligning with prior research highlighting infectious causes like cryptococcal meningitis and CNS toxoplasmosis, especially prevalent in patients with low CD4 counts in developing countries.

While 40% had normal brain MRIs, the remaining 60% showed abnormalities, with non-specific white matter lesions being the most common but not altering clinical outcomes. Clinically significant findings included neoplasms (11%), infections (8%), and intracerebral hemorrhage (7%), indicating a possibly more effective imaging selection or MRI's higher sensitivity over CT. This study's higher abnormal finding rates contrast with lower yields in previous U.S. studies, attributing differences to imaging criteria or MRI's enhanced sensitivity for certain conditions. Notably, extra-axial tumors were the most frequent neoplastic findings, diverging from other studies that identified bacterial meningitis and viral encephalitis as top infectious causes, possibly reflecting epidemiologic variations in tuberculosis prevalence affecting the higher incidence of tuberculoma observed here [17].

The majority of patients had normal or minor brain MRI findings, indicating inappropriate selection criteria for imaging in patients presenting with acute headaches. The most frequently clinically important brain MRI findings in patients presenting with acute headaches are neoplasms, which is a distinct finding compared to previous studies. Older age is associated with an increased rate of abnormal imaging findings. The most common infectious cause of acute headaches was found to be tuberculoma, which shows variation from findings in previous studies, most likely due to epidemiologic differences. In HIV seropositive patients, the most common causes of acute headaches were found to be intracranial infections, which is in agreement with findings from previous studies.

Conclusion

This study demonstrates a notable correlation between age and MRI abnormalities in patients with acute headaches, suggesting increased risks of abnormalities with aging. Neurologic symptoms and comorbidities, particularly hypertension and HIV, significantly influence the incidence of abnormal imaging, with infections prevalently detected in HIV -positive patients. The high occurrence of nonspecific white matter lesions and the frequent identification of neoplasms highlight MRI's vital role in acute headache assessment. Despite some inconsistencies with previous research, this study's findings advocate for improved imaging criteria tailored to patient demographics and health conditions, emphasizing a detailed approach in neuroimaging to improve diagnostic precision and patient outcomes.

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Author Contributions
Dr. A.M W: Conceptualization, Resources, Writing – Original Draft.
Dr. T.K L: Writing – Original Draft.
Dr. N S: Writing – Original Draft.
Dr. M.A N: Writing – Review & Editing.

Conflict of Interest
The authors declare no conflicts of interest.

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Case Report

Neonatal Thyrotoxicosis Presenting with Heart Failure

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Abstract
Thyrotoxicosis in the newborn is usually the result of the passage of thyroid stimulating antibodies from the mother to the fetus. This is a case report of a ten-day-old male neonate who presented with signs of neonatal thyrotoxicosis and heart failure. He had a high T3 (>7.7nmol/l), high T4 (> 300nmol/l), and low TSH (0.14 uIU/ml). He was hospitalized at the neonatal intensive care unit of Myungsung Comprehensive Specialized Hospital and was successfully treated with propylthiouracil, propanolol, furosemide, lugols iodine, hydrocortisone, and supportive care. Clinical features and management of neonatal thyrotoxicosis are discussed with a literature review.

Keywords: *Thyrotoxicosis, newborn, heart failure*
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Case report
This is a ten-day-old male neonate delivered at Myungsung Comprehensive Specialized Hospital to a 28-year-old primi para mother at a gestational age of 39 weeks and 2 days. The mother is known to have Graves' disease and has been on propylthiouracil (PTU) for the last two years.

It was a normal vaginal delivery with a birth weight of 3685 grams. Neonatal examination was normal except for the presence of anterior neck mass. A thyroid function test done at birth from venous blood revealed a normal T3 (1.68nmol/l), low T4 (24.2nmol/l), low free T4 (4.37 pmol/l), and high TSH (> 60uIU/ml). He was appointed for follow-up in the outpatient clinic. On the tenth day of life, he presented with irritability and excessive crying. He had frequent watery stool. On examination, he was tachycardic (210 beats/min), tachypneic (100 breaths/min), Spo2 was low (71%) and restless. He had lost 550g from his birth weight, Laboratory tests showed; high T3 (>7.7nmol/l), high T4 (> 300nmol/l), high free T4 (>100pmol/l), and low TSH (0.14 uIU/ml). CBC and CRP were in the normal range. Ultrasonography of the neck showed a diffusely enlarged thyroid gland with markedly increased flow on doppler study. Chest x-ray showed cardiomegaly with normal pulmonary vasculature (figure 1). He was provided intranasal oxygen and managed with propylthiouracil, propanolol, furosemide, lugols iodine, and hydrocortisone. On the 2nd day, his oxygen demand progressively increased and could not maintain his saturation with a high liter of oxygen using face a mask. He was intubated and was on mechanical ventilation. He showed gradual improvement with normalization of heart rate and reduced oxygen demand and was successfully extubated after 48 hours. On the sixth day of hospitalization, the serum level of T3 and T4 had normalized but TSH was low. Patient was discharged after seven days of hospitalization in a stable condition with a follow-up arrangement at an outpatient clinic.

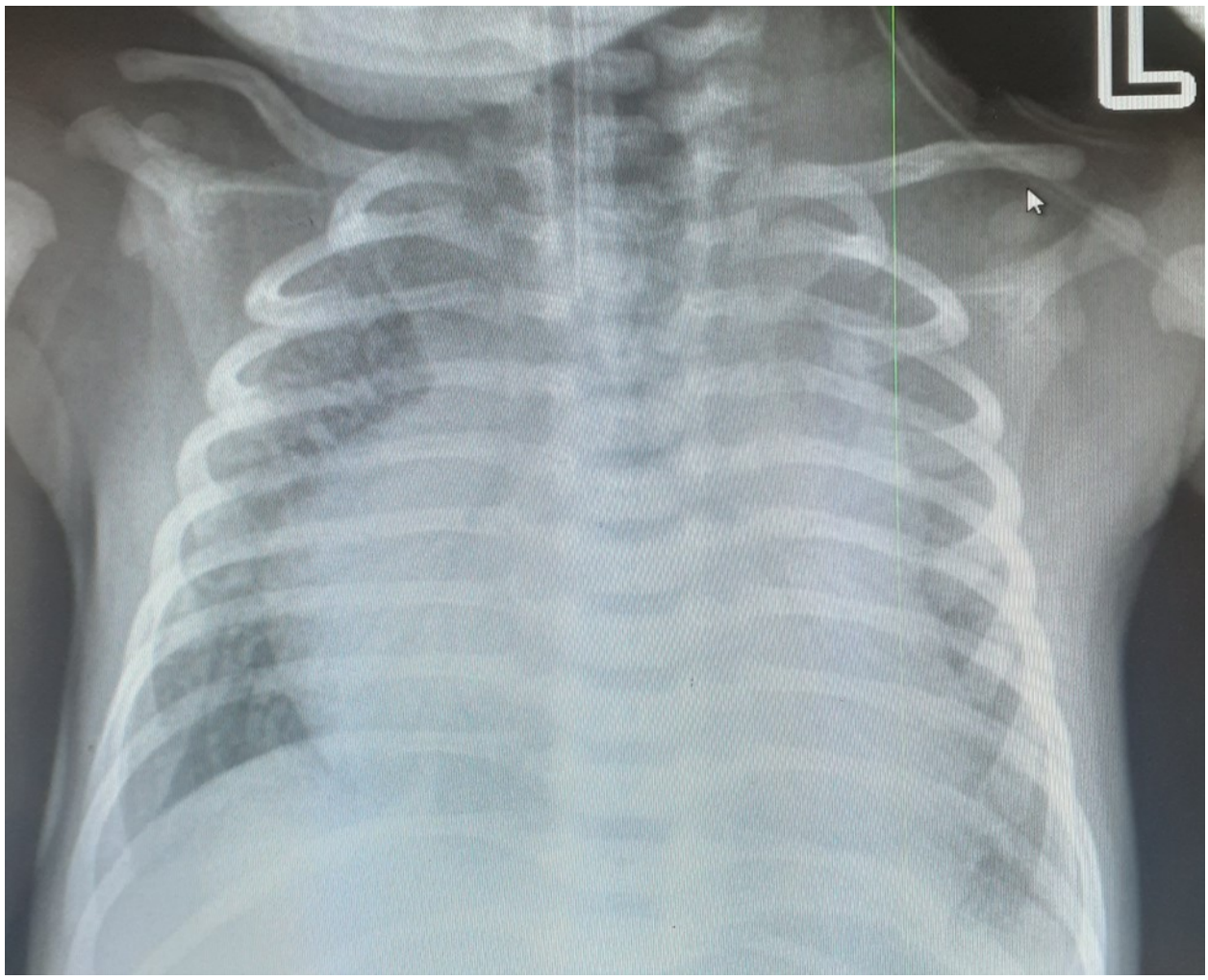

Figure 1 Chest x-ray of the infant taken on the 11th day of life showing cardiomegaly

Discussion

Thyrotoxicosis in the newborn is usually the result of the passage of thyroid-stimulating antibodies from the mother to the fetus towards the end of pregnancy. Women with Graves' disease have Thyroid Receptor Antibodies (TRSAbs) which are usually the cause of this disease. Approximately 0.2% of pregnant women have Graves' disease, and between 1% and 12.5% of their offspring are expected to have overt thyrotoxicosis. Because the mother's TRSAbs readily crosses the placenta, TRSAb transfer to the fetus may result in hyperthyroidism in utero and/or after birth (1). Manifestations of neonatal thyrotoxicosis persist in the newborn until the maternal antibodies disappear from its circulation (2, 3, 4).

The presence of thyrotropin receptor–blocking antibodies and the transplacental passage of antithyroid drugs taken by the mother may modify the onset, severity and course of the disease. Manifestation of neonatal hyperthyroidism is delayed by 3-4 days if the infant has been exposed to antithyroid drugs, as the maternally derived antithyroid drug is metabolized (5). Manifestation in newborns typically begins during the first one to two weeks (6).

This newborn didn't have clinical manifestations and laboratory findings suggestive of thyrotoxicosis for the first 9 days which could be due to the effect of propythiouracil which was taken by the mother. However, as the effect of PTU disappeared the newborn started to manifest signs of hyperthyroidism.

The main characteristic signs and symptoms of neonatal thyrotoxicosis include tachycardia, irritability, prominent eyes, and poor weight gain. If there is goiter it may be related to maternal antithyroid drug treatment as well as to the neonatal Graves' disease itself. If treatment is delayed or inadequate it may result in ar-

rhythmias and cardiac failure which may cause death. Without treatment it is associated with deleterious long-term consequences, including cranial synostosis, developmental delay and failure to thrive (6).

This newborn had typical manifestations including tachycardia, tachypnea, irritability, weight loss, diarrhea, goiter and heart failure with an enlarged heart and requiring management of heart failure.

The treatment of neonatal thyrotoxicosis is mainly by providing antithyroid medications like propylthiouracil or methimazole which inhibits the synthesis of thyroid hormone. The addition of Lugol or potassium iodide solution is recommended for severe cases as it avoids the entry of thyroid hormones into the circulation (7). Steroids, which prevent the production of thyroid hormone and peripheral transformation of T4 to T3, are reserved for severe cases (8). Propranolol effectively restores a normal heart rate (9).

This newborn was treated with antithyroid drugs, propylthiouracil, propanolol, and steroids in addition to the supportive care given for heart failure.

At presentation the patient's condition was grave; however urgent administration of medications, supportive care, and meticulous follow-up saved his life.

Conclusion

Early identification of infants at risk of neonatal thyrotoxicosis and prompt initiation of treatment is life-saving.

Consent

Patient's parents gave verbal consent for the case study.

Competing interests

There was no funding for the study and no conflicts of interest to disclose.

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The authors would like all health professional involved in the management of the patient. Our especial thanks go to the MCM NICU nurses who were at the bedside of the patient providing intensive monitoring and care throughout his hospitalization.

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Case Report

A Rare Case of Appendiceal Polyp From Screening Colonoscopy – A Case Report

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Abstract

***Background**: Appendiceal adenomatous polyps are rare and present diagnostic challenges. The reported incidence of these polyps during autopsy ranges from 0.004% to 0.08%. The identification of appendiceal polyps during colonoscopy is uncommon, and there is limited literature on this subject. This case highlights the importance of thorough assessment of the appendix during colonoscopy.*

***Case Presentation**: A patient with a history of chronic constipation presented with complaints of per rectal bleeding and rectal pain. The patient had previously undergone a surveillance colonoscopy several years ago, which showed normal findings. During the current colonoscopy, a 0.5 cm x 0.5 cm polyp was identified at the appendiceal orifice.*

***Discussion**: Appendiceal polyps are rare findings during colonoscopy, and their detection can be difficult due to the anatomical location of the appendix. The significance of these polyps lies in their potential to cause complications such as malignancy, intussusception, or chronic appendicitis. While guidelines for the follow-up of patients with appendiceal orifice polyps are limited, this case emphasizes the need for careful examination of the appendix during colonoscopy.*

***Conclusion**: A thorough assessment of the appendix during colonoscopy is essential for detecting appendiceal polyps and preventing potential complications. Further research and clearer follow-up guidelines are needed for patients with appendiceal opening polyps.*

***Keywords:** Appendiceal Polyp, colonoscopy, Screening colorectal, colonic polyp*
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Introduction

A polyp is a term used to describe a mucosal protrusion that may originate from any mucosal layer in the body. Colonic polyps arise from the mucosal layers of the colon and can be further classified into inflammatory, hamartomatous, serrated (hyperplastic), or adenomatous polyps based on their histopathology [1].

It is well-established that the most common type of colorectal cancer originates from adenomatous polyps [2].

Adenomatous polyps can be classified into three histopathological types: tubular, tubulovillous, and villous adenomas. Another classification method for adenomas is based on their gross appearance during endoscopy, where they may be pedunculated, sessile, flat, depressed, or excavated. Most patients with adenomatous polyps exhibit no symptoms, and the polyps are often incidentally discovered during screening procedures such as colonoscopy [2].

The occurrence of benign appendiceal polyps is rare, typically being found incidentally during autopsy or surgery [3]. The reported incidence of these polyps during autopsy ranges from 0.004% to 0.08% [4].

The identification of appendiceal polyps during colonoscopy is uncommon, and there is limited literature on this subject. Nonetheless, to accurately recognize appendiceal pathologies, the endoscopist should be attentive to abnormal features in the appendiceal orifice [5].

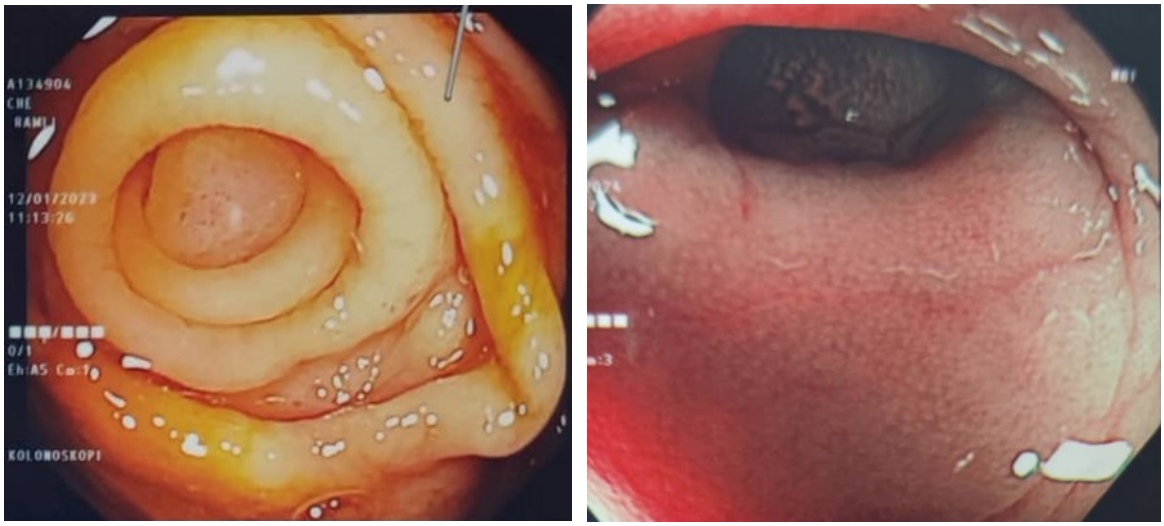
Case Report

We present a case report detailing the discovery of an appendiceal orifice polyp during a colonoscopy at Hospital Universiti Sains Malaysia (USM), Malaysia. The subject of this report is a 60-year-old gentleman with a history of underlying prostate cancer , he was diag-

nosed 2 years ago on 2022 , who had previously undergone radiotherapy for prostate cancer after he was diagnosed. The indication for the colonoscopy was post-radiotherapy proctitis, as the patient presented with symptoms of rectal pain and per rectal bleeding following radiotherapy.

The patient had previously undergone surveillance colonoscopy several years ago due to chronic constipation. However, during that initial colonoscopy, no abnormalities were found. It remains uncertain whether the findings were overlooked or if the polyp had not yet developed at that time.

Before the colonoscopy procedure, the patient underwent preparation involving the ingestion of oral laxatives to thoroughly cleanse the contents of the bowel. Subsequently, the colonoscopy was conducted with the patient under sedation. The scope was advanced throughout the large bowel, reaching as far as the cecum. During this examination, a polyp measuring 0.5 cm x 0.5 cm was identified within the appendiceal lumen, as shown in Picture 1.It is a pedunculated polyp with a broad base. No additional abnormalities were observed throughout the entirety of the large bowel. No biopsy was obtained from the identified polyp, as it appeared benign and its broad base made it very difficult for polypectomy. The patient was not keen on surgical removal, so surveillance colonoscopy was recommended.



Picture 1. Picture of Appendiceal Orifices Polyp from our colonoscopy findings.

Discussion

The appendix originates embryologically from the cecum and exhibits histological similarities to colorectal tissues [6]. The similarity in embryological origin between the appendix and the cecum may account for the 4.1% incidence of synchronous appendiceal neoplasia observed in patients with colorectal cancer [7].

Regardless of their location in the gastrointestinal tract, both tubulovillous adenomas and serrated adenomas are considered precancerous polyps and require removal. Given the analogous mucosal pattern between the appendix and the colon, it is hypothesized that appendiceal adenocarcinoma may contribute to 1% of all colorectal malignancies [3].

Serrated adenomas located in the appendix are generally considered more aggressive than those found in the colon and rectum. Histologically, serrated polyps are categorized into three subgroups: hyperplastic polyps, sessile serrated adenomas, and traditional serrated adenomas. Hyperplastic polyps in the appendix are rare and exhibit morphological similarities to those found in the colon [8].

Retrospective histopathological analyses of appendectomy specimens have revealed that the predominant malignant neoplasms in the appendix are carcinoid tumors, with adenocarcinomas being the second most common type. Additionally, adenomatous polyps of the appendix are frequently documented in case reports. Generally, benign tumors of the appendix tend to be asymptomatic, affecting approximately 10% of patients [3].

Hence, the early identification of precancerous appendiceal polyps is crucial. However, these polyps are often discovered incidentally during surgical procedures, particularly in cases involving complications like appendicitis or intussusception. Approximately 10% of these polyps are fortuitously identified through laparotomy during unrelated appendiceal procedures [9].

The absence of polyp detection in poorly visualized areas can compromise the quality of screening colonoscopy. Detecting polyps in regions like the appendiceal lumen can pose challenges due to the limited accessibility with a standard endoscope. Endoscopic identification of appendiceal lesions is infrequent and typically confined to the base of the cecum and the appendiceal orifice. Nonetheless, accurate recognition of appendiceal pathologies requires the endoscopist to be vigilant for abnormal features associated with the appendiceal orifice [3].

Identifying these polyps can serve as a preventive measure against complications such as appendicitis and intussusception. Moreover, it might influence the timing of subsequent surveillance colonoscopy. Furthermore, detecting and removing such polyps can mitigate the risk of potential future occurrences of appendiceal or colorectal cancer [10].

In a case review presented by Afshin Amini in *Gastroenterology Case Reports*, three occurrences of appendiceal orifice polyps were recorded, initially escaping notice during the initial visualization of the cecum. These polyps were later identified through a careful and thorough evaluation, which included deflation of the cecum in a subsequent colonoscopy procedure [10].

As per A. Al Toma et al., their findings revealed that in three out of four patients with pre-malignant polyps, histopathological examination of the appendiceal wall after surgical resection indicated inflammatory changes. It is suggested that polyps in the appendiceal region may contribute to luminal obstruction. The persistent secretion of mucus could lead to increased intraluminal pressure and luminal distension. This sequence of events might eventually culminate in the development of chronic appendicitis, potentially serving as the origin of abdominal complaints in these patients [3].

The endoscopist should consistently consider the potential presence of an appendiceal neoplasm. Hence, it is crucial to thoroughly inspect the appendiceal region during colonoscopy. Based on our experience, the optimal inspection of the appendiceal orifice occurs when it is visualized continuously for a few seconds, allowing any concealed polyps—colloquially referred to as "vanishing polyps"—to become apparent. The decision to perform polypectomy during endoscopy or to refer all such cases for resection depends on the discretion of the endoscopist [3].

Complete removal of this type of polyp presents challenges and is associated with a heightened risk of recurrence or perforation. As a result, surgery is generally the preferred approach [11].

Conclusion

Appendiceal polyps present a rare occurrence that is often overlooked during colonoscopy, particularly when performed by less experienced operators. Studies indicate instances where appendiceal polyps were initially missed during the first colonoscopy but later detected in subsequent examinations. Similar to other colorectal polyps, appendiceal polyps carry the risk of malignancy.

Therefore, a thorough assessment of the appendix area during colonoscopy is imperative to prevent complications such as malignancy, intussusception, or chronic appendicitis. The decision to remove appendiceal polyps during the colonoscopy itself depends on the surgeon's preferences and comfort level. However, removing a polyp from the appendiceal opening area is challenging and carries the risk of ceacum or appendix base perforation. Consequently, surgical resection at a later stage is often preferred to reduce morbidity, and it allows for adequate resection margins if malignancy is suspected.

Lastly, the current follow-up guidelines for patients with appendiceal opening polyps lack clear recommendations or guidelines. Advocacy for incorporating specific protocols for such cases into existing guidelines is encouraged.

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Case Report

A Disseminated Peritoneal Melanosis in a 71-year-old Ethiopian Woman Diagnosed with Ovarian Mucinous Adenocarcinoma: Case Report

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Abstract
Background:*Peritoneal melanosis is a benign disease that can be encountered during laparotomy. We are reporting this extremely rare condition with less than 20 cases reported in the world literature and also in Ethiopia. This condition is usually incidental finding during laparotomy and is mainly associated with ovarian lesions.*
Case: *A 71-year-old woman presented to gynecology out-patient department with abdominal swelling of 1-year duration. Abdominopelvic mass with gross ascites detected, likely arising from the ovary. She then underwent a unilateral salpingo-oophorectomy followed by total abdominal hysterectomy and unilateral salpingo-oophorectomy with a high index of an advanced ovarian cancer. The intraoperative findings showed a diffuse dark pigmentation involving the greater omentum, the visceral peritoneum, and serosa of the large and small bowel segments. The histopathology revealed a moderately differentiated mucinous adenocarcinoma with benign peritoneal melanosis. With this diagnosis she completed adjuvant chemotherapy.*
Conclusion:*Though occurrence of peritoneal melanosis with ovarian adenocarcinoma doesn't suggest different treatment or prognosis. We recommend surgeons during laparotomy to be aware of this benign condition during laparotomy. Little is known about this rare condition therefore, women with peritoneal melanosis should be followed closely for the long-term outcome*

Keywords: *Peritoneal melanosis, Mucinous adenocarcinoma, Ovarian tumor*
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Introduction

Peritoneal melanosis is a rare condition characterized by dark brown pigment deposition in the peritoneum. Benign peritoneal melanosis may occur in association with other congenital cystic conditions such as ovarian dermoid, peritoneal, enteric duplication cysts, or even gastric triplication (1).

There are few cases of peritoneal melanosis associated with mucinous cystadenoma of the ovary and peritoneal melanosis associated with serous carcinoma of the ovary (2,3,4). This condition is usually incidental finding during laparotomy and is mainly associated with ovarian lesions (2).

Different literatures mention rupture of ovarian dermoid cyst or melanogenic tumors, ill-migrated neural crest remnants or pinched-off multipotent mesothelial cells of the peritoneum during developmental period and differentiation of coelomic epithelium as possible causes for the development of peritoneal melanosis (2,6,7,8,9).

We report a case of peritoneal melanosis associated with a mucinous cystadenocarcinoma of the ovary. This case has been reported following the SCARE criteria 2020 (5).

Case report

A 71-year-old para 12 Abortion 0 woman presented with progressive abdominal swelling of 1year duration. She has associated early satiety, loss of appetite, un-

quantified but significant weight loss and bilateral lower leg swelling.

On physical examination, she was generally sick looking, cachectic, and in pain with an Eastern Cooperative Oncology Group (ECOG) performance status of 3. The vital signs were unremarkable.

On abdominal examination, a grossly distended abdomen with positive fluid thrill and shifting dullness suggestive of gross ascites. There was a 24 weeks' size and ballotable abdominopelvic mass. Except for the cul-de-sac bulge on digital vaginal exam the rest of the pelvic and rectal examinations were unremarkable. The tumor markers had moderate increase in CA125 (86.4 U/mL) level; AFP, CEA, CA19.9, CA15.3 were all with in normal ranges. Abdominopelvic ultrasound and CT scan showed a 24.3 cm *13.5 cm*18.5 cm abdominal pelvic mass with solid and cystic lesions with calcification likely arising from the right adnexa and with metastatic deposits on the omentum. Otherwise, the uterus, the left adnexa, the liver, large and small bowel were unremarkable (Figure 1).

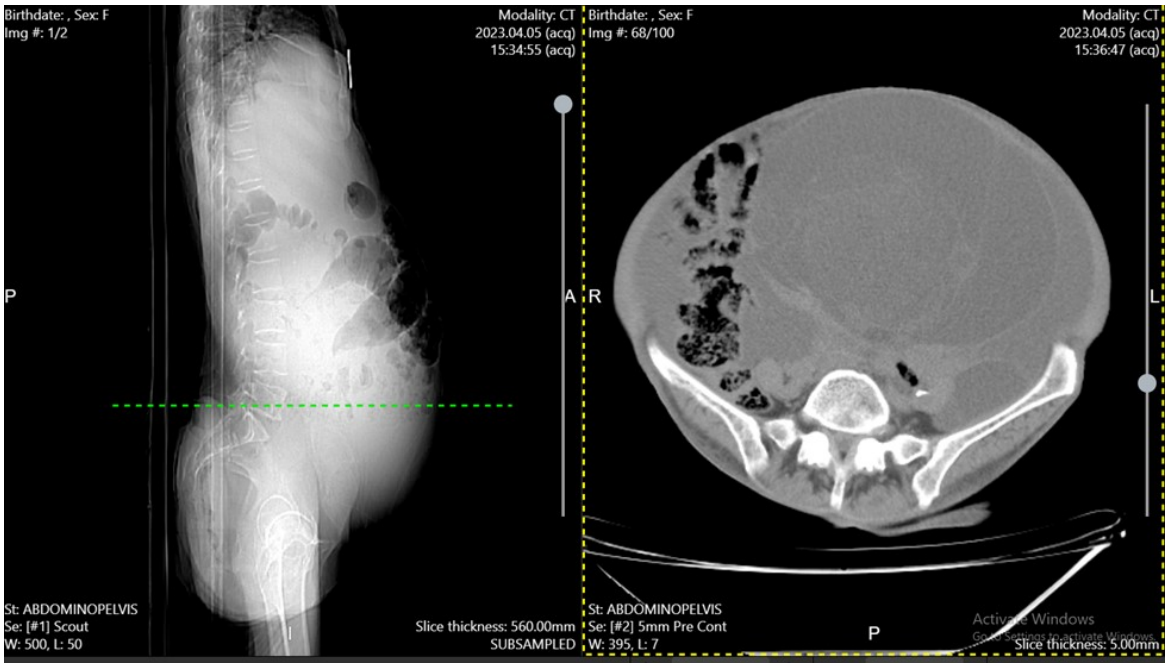

Figure 1: Abdominopelvic CT scan shows abdominal pelvic mass with solid and cystic mass with calcification likely from right adnexa,

As the patients had poor functional status with ECOG performance status of 3, predominantly cystic ovarian mass inaccessible for core needle biopsy and absence of frozen section, laparotomy with short operative time was decided for tissue diagnosis.

After necessary preoperative preparation and preanesthetic evaluation done and the abdominal cavity entered through the midline abdominal incision extending from suprapubic area to the level of 4cm above the umbilicus. The Intra operative finding showed, about 10 liters' dark mucoid peritoneal fluid which was sucked out. There was dark pigmentation of the omentum, mesentery, the visceral and parietal peritoneum. There were multiple peritoneal nodules of size less than 1cm in diameter on the anterior abdominal wall on the left lower quadrant. There was about 25cm by 20cm left complex ovarian mass (with continuous leakage of mucinous content to the peritoneal cavity) with filmy adhesion to the anterior abdominal wall and bladder (Figure 2). Due to her poor performance status, the surgery was limited to unilateral salpingo-oophorectomy and the tissue sent for histopathological examination.

The histopathology reported revealed a moderately differentiated mucinous adenocarcinoma. Following surgery, she was on high protein diet and an additional nutritional support for two months.
After her performance status has shown an improvement with ECGO performance status of 1, a complete cytoreductive surgery was made.

The intraoperative finding showed, around 300ml ascitic fluid, the same dark hyperpigmentation of both the visceral and parietal peritoneum including the omentum and mesentery. Atrophied right ovary with unremarkable uterus. There was a diffuse deposit on the parietal peritoneum of right anterolateral abdominal wall and multiple small nodules of size about 1cm on the omentum (Figure 2). The cytoreductive surgery performed carefully by the team of gynecologic surgeons lead by the same senior gynecologic oncologist and there were no intra- or postoperative complications.

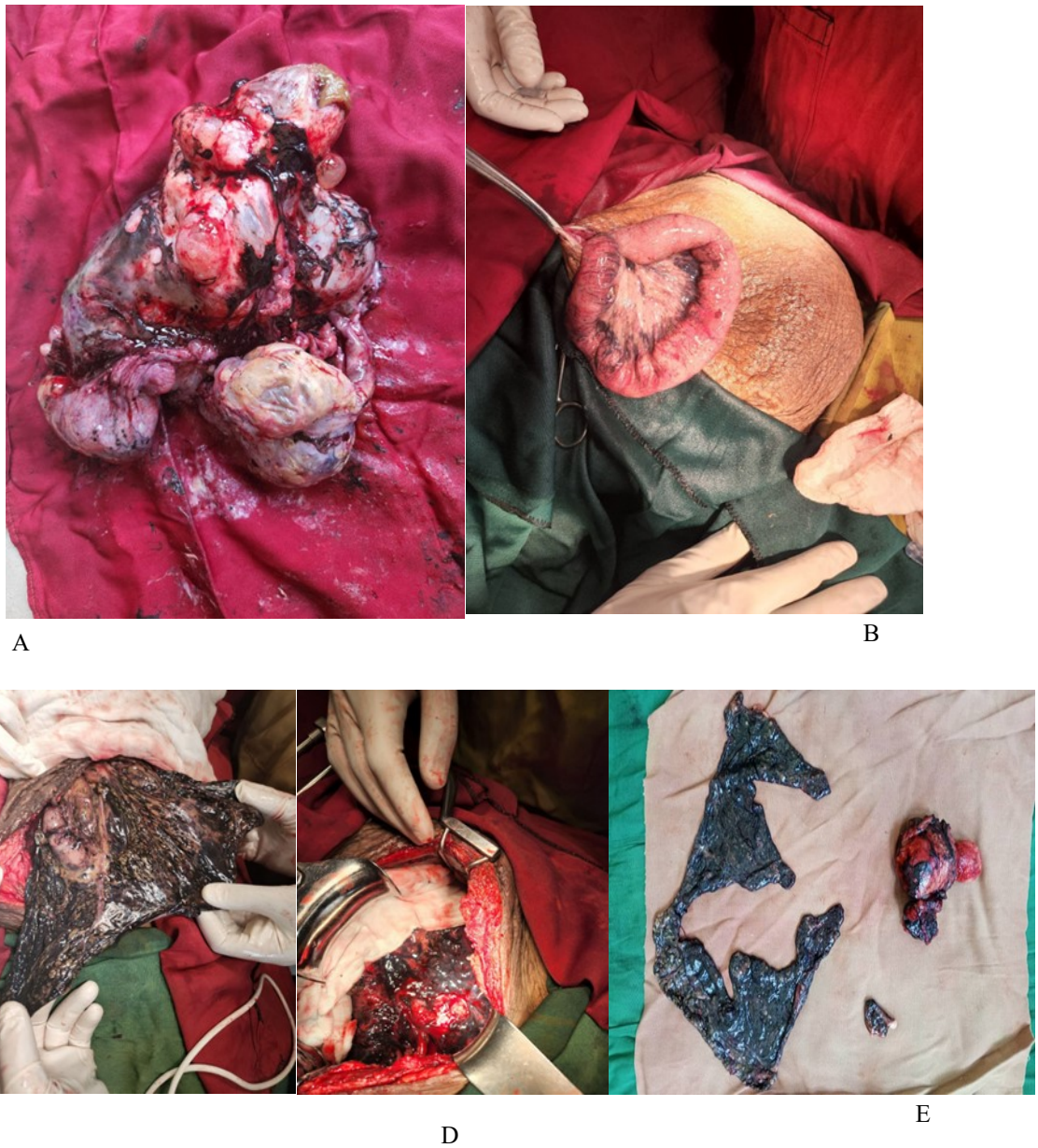

Figure 2. A) multi lobulated ovarian mass with ruptured capsule, there are black colored staining of the surface. B) there is black staining of the mesentery and bowel surface C), D) and E) Dark brown pigmentation of omentum pelvic peritoneum uterus, ovarian surface and Appendix

The histopathology reported by the same pathologist showed the uterus being unremarkable, sections from the left ovary, tube, appendix, omentum, and the anterior abdominal wall lesions showed surface histocytes with dark brown pigment deposition. No features of malignant cell seen (Figure 3).

Currently, the patient is on her 8th month after the second surgery and she had smooth postoperative course with no major complaints and having good performance status. she was given carboplatin and paclitaxel adjuvant chemotherapy as per the local guideline.

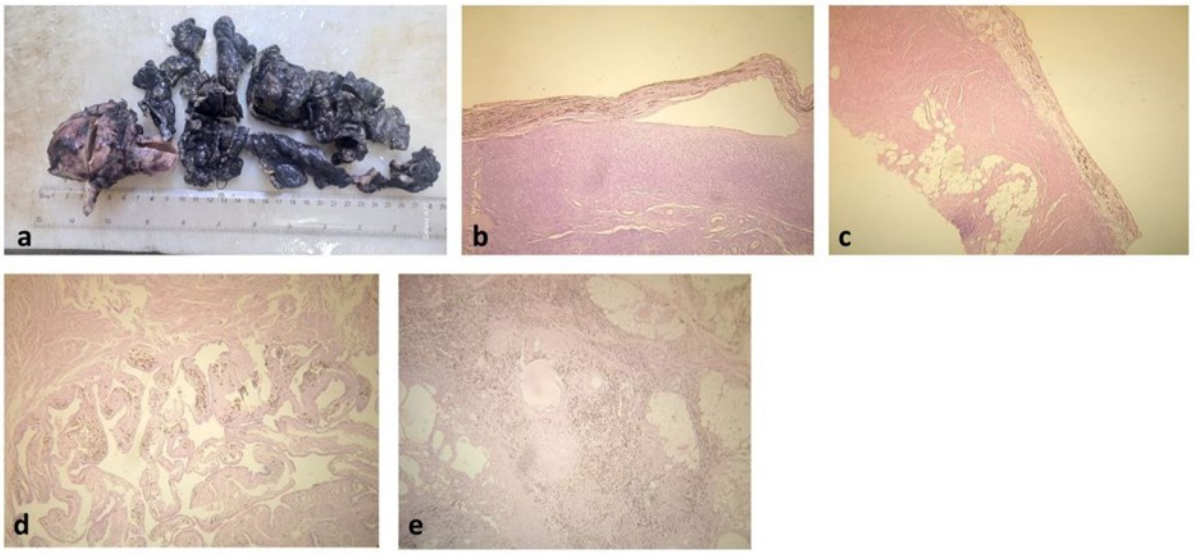

Figure 3: (a) gross picture of the uterus, cervix, unilateral ovary and fallopian tube, along with appendix and omentum showing extensive darkening of external surfaces. (b) and (c) (H&E) brownish coarse pigment deposition on the surfaces of ovary and appendix respectively. (d) (H&E) pigment is seen in the plicae of the fallopian tube, and (e) (H&E) abundant pigment laden macrophages also present in the omentum.

Discussion-

A case of peritoneal melanosis secondary to the rupture of a bilateral ovarian cystic teratoma was reported by Afonso in 1962 (1). Melanosis peritonei is an extremely rare condition with around 20 reported cases in the English literature. In most cases the clinical presentation and intraoperative finding was similar to our case (3,4,7).

Although peritoneal melanosis is considered a benign condition, it is usually associated with other disorders like desmoid ovarian cyst, enteric duplication cyst, gastric triplication, and ovarian cystadenomas. More than half of the peritoneal melanosis is associated with ovarian lesions. There was a case where peritoneal melanosis was associated with malignant ovarian cancer. Peritoneal melanosis mostly affects females, age 6 month to 28 years, women age 42-79 and male patients were rare in cases reported (3,7).

Pigmentation of peritoneal melanosis may result from the rupture of ovarian dermoid cysts or of melanogenic tumors into the abdominopelvic cavity or hemorrhage in the teratoma containing the gastric mucosa and gastric ulceration (6,7). However, those theories are only validated for cases associated with a ruptured ovarian teratoma. Another theory hypothesized that peritoneal melanosis might appear as a final result of multifactorial etiologies such as ill-migrated neural crest remnants (8) or pinched-off multipotent mesothelial cells of the peritoneum during the developmental period (9). It was also suggested that both the serous lining and pigmented peritoneal mesothelial cells originate from the coelomic epithelium, and that differentiation occurs under local or unknown factors (2).

Endometriosis, peritoneal lipofuscinosis, and malignant conditions, including metastatic malignant melanoma, should be excluded during diagnosis. Endometriosis can be easily distinguished from peritoneal melanosis by the presence of glands surrounded by endometrial stroma and hemosiderin deposits. Peritoneal lipofuscinosis differs from peritoneal melanosis in that histochemically demonstrated pigment is not melanin but lipofuscin (9).

The main differential diagnosis of peritoneal melanosis is metastatic melanoma. Metastatic melanoma

has a poor prognosis in comparison with benign peritoneal melanosis.Metastatic melanoma is differentiated by identifying the primary lesion, and clear examination of the skin, the anorectal canal and the ocular epithelium. Microscopically, both peritoneal melanosis and metastatic melanoma share similar presentation but in case of metastatic melanoma cells hematoxylin and eosin-stained sections is used and diagnosis can be confirmed using Immunohistochemistry (IHC) with S-100 and HMB-45 (1,10,11).
Despite the presence of peritoneal melanosis, management of the primary cases in the literature wasn't changed. In the majority of this cases, they were followed for 6 months up to 5 years with no change in the course of the disease (2,3,4,7).

Conclusion
This is a case report depicting peritoneal melanosis with moderately differentiated mucinous adenocarcinoma. We urge surgeons to be aware of this benign condition during laparotomy as it could be an incidental finding. Though little is known about the clinical implication of peritoneal melanosis in association with ovarian tumor, patients with this diagnosis should be followed for long term outcome..

Consent to publish
Consent for publication was taken from the patient.

Authors' Contribution
Dr Binyam Esayas: Assistant professor in Obstetrics and Gynecology, Addis Ababa University, department of Obstetrics and Gynecology: He has written the article, and participated in the surgery.
Dr Shiferaw Negash: Associate professor in Obstetrics and Gynecology, Addis Ababa University, department of Obstetrics and Gynecology: He has participated in the surgery, and supervised the writing of manuscript.
Dr Husnia Lobi : Assistant professor in Obstetrics and Gynecology, Addis Ababa University, department of Obstetrics and Gynecology: She has participated in the surgery, and supervised the writing of manuscript.
Dr Motuma Gutu: Assistant professor in Obstetrics and Gynecology, Addis Ababa University, department of Obstetrics and Gynecology: He has helped writing the article.
Dr Tesfaye Adem: Assistant professor in Obstetrics and Gynecology, Addis Ababa University, department of Obstetrics and Gynecology: He has helped writing the article.
Dr Selam Gebrechristos: Assistant professor in Addis Ababa University, department of Pathology: Interpretation of histological data, preparation of pathology slides and confirm the histological diagnosis.
Dr Isa Salo Abdo: MD, Pathology Resident, Addis Ababa University, department of Pathology: Interpretation of histological data and preparation of pathology slides

conflict of interest
The authors declare that they have no competing interests.

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Data Availability
Data sharing does not apply to this article as no new data were created or analyzed in this study.

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