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Blood Indices and Levels of Erythropoietin in Cystic Kidney Disease

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Abstract:

Background: The mature kidneys are the primary organs that secrete erythropoietin (EPO), a sialo-glycoprotein hormone that is released in response to tissue hypoxia and a decrease in red cell mass. It causes the blood marrow to produce more erythrocytes.

Objectives: To estimate haemoglobin and EPO in blood and cystic fluid in patients with renal cysts.

Methodology: The 60 participants in this case-control study were 30 individuals (30–60 years old) who visited the urology department of Alhawari General Hospital in Benghazi, Libya, in 2020 and had renal cysts. Furthermore, thirty healthy individuals, matched for age and gender, were selected as controls (ages 29–58). We measured blood urea, creatinine, and haemoglobin. ELISA was used to estimate EPO in serum and cystic fluid.

Results: Patients with renal cysts had mean serum EPO and urea values of 29.7±7 m U/ml and 7.2±1.3 m mole/l, respectively. These values were substantially higher than those of the control group, which had mean values of 6.2±4.3 m U/ml and 4.4±1.1 m mole/l, respectively, $P < 0.05$. Patients diagnosed with renal cysts had significantly lower haemoglobin levels (11.2±0.6 and 13.2±1.3 gm/dl, respectively) than the control group ($P < 0.05$). The amount of EPO in the cystic fluid was 15 times more than that in serum.

Conclusion: According to this study, erythropoietin does not penetrate blood from cystic fluid in individuals with renal cysts, and more research is needed to determine the amount of erythropoietin in cystic fluid.

Keywords:

Chronic Kidney Diseases; Renal Cyst; erythropoietin; renal anemia; Cystic fluid

Introduction:

The term "renal cystic disease" (RCD) describes a collection of pathological disorders linked to the formation of renal cysts. These disorders can cause extrarenal symptoms in both adults and children, and their etiologies can be inherited or non-inherited. Some of the most common renal abnormalities are the renal cysts induced by these disorders, which can range from being clinically unimportant to leading to end-stage renal disease. Autosomal dominant polycystic kidney disease (ADPKD), a subtype of hepatorenal fibrocystic disease (HRFCD), is the most frequent hereditary renal cyst in adults, whereas simple renal cysts are the most common acquired kidney cysts [1, 2, 3]. Several underlying diseases, such as diabetes mellitus and hypertension, can contribute to the incidence of chronic kidney disease (CKD), which in 1996 accounted for 43% and 23% of incident cases of end-stage renal disease (ESRD), respectively [4,5].

Clinical variables, such as patient age, symptoms, renal function, and cyst characteristics (e.g., size, shape, location, and number), are commonly used to differentiate and diagnose renal cystic disease [6,7]. LM Diagnostic studies consist of renal imaging, laboratory tests, and genetic testing. Management typically involves supportive therapy, surveillance and treatment of complications, and, in some patients, transplantation [1].The majority of renal cystic diseases are poorly recognized or comprehended by the general public. Because different rare cystic renal syndromes may have genetic ramifications, patients and their families need to receive appropriate counseling and education to understand the specific condition that has been diagnosed. Healthcare practitioners must improve their proficiency in diagnosing, treating, and counseling patients with the renal cystic disease. Additionally, to enable them to deliver patient-centred and evidence-based treatment, clinicians should have the authority to promote positive change, strengthen patient safety, and improve overall care quality [6]. RCD can be categorized as inherited or non-inherited (developmental dysplasia, de novo mutations, or systemic illnesses) and includes a variety of underlying problems. The pathophysiologic origins of RCD are now better understood because of scientific advancements. Therefore, some diseases can be classified as either ciliopathies (which include mutations affecting renal tubular cilia) or dysplasias (which include abnormalities in renal anatomy). With the exception of ADPKD, most forms of RCD have genetic etiologies and initially manifest in children or teenagers.. The RCD most often observed in adults is ADPKD [8].

Renal cystic diseases (RCDs), with an incidence ranging from 0.44–4.1 per 10,000 births, can impact individuals of all age groups and lead to severe complications such as chronic kidney disease (CKD), liver disease, and death [1]. RCDs are categorized differently depending on ciliopathies or dysplasias, inheritance mode (genetic vs. sporadic), and other reasons. The genetic pathogenesis of less-studied RCDs needs to be investigated, even if the genetic linkages of prevalent RCDs such as autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) are well documented [9]. RCDs can develop from infancy to early adulthood and show up with a range of symptoms, including cardiovascular, hepatic, and renal manifestations, according to Satariano et al. [10]. Genes like PKD1 and PKHD1 are known to be associated with common recessive kidney diseases (RCDs), which include autosomal polycystic kidney disease and autosomal recessive kidney disease, respectively. It is imperative to examine the genetic pathophysiology underlying the development of clinical symptoms resulting from gene mutations. This should encompass an examination of understudied RCDs such as autosomal dominant tubulointerstitial kidney disease, multicystic dysplastic kidney, Zellweger syndrome, calyceal diverticula, and others. We plan to take a thorough look into the genetic involvement and clinical sequelae of several RCDs to help and guide diagnosis, counseling, and treatment. Simultaneous with the proactive management of these underlying diseases, these patients should also undergo

comprehensive preparatory treatment for entry into ESRD. According to The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Guidelines (NKF–K/DOQI) recently released for CKD, the evaluation and treatment of patients with CKD requires understanding of separate but related concepts of diagnosis, comorbid conditions, severity of disease, complications of disease, and risks for loss of kidney function and cardiovascular disease. Among CKD patients, the disease stages are defined based on the level of kidney function, thus the rate at which patients approach ESRD varies. Defining the stages of CKD is crucial to the effective management of these patients and requires "categorization" of continuous measures of kidney function [11, 12]. A hypothesis that EPO may be produced in renal cysts (RC) was put forward during the observation of patients with renal cysts coexisting with renal failure [13].Estimating haemoglobin and EPO levels in the blood and cystic fluid in individuals with renal cysts is the current study's goal.

Methods

Study Design and Participants

This case-control study was conducted at Alhawari General Hospital in Benghazi, Libya, in 2020. The study included a total of 60 participants, divided into two groups: 30 patients diagnosed with renal cysts and 30 healthy controls. Participants in the patient group were aged between 30 and 60 years, and those in the control group were matched for age and gender, with ages ranging from 29 to 58 years. The inclusion criteria for the patient group were individuals who had been diagnosed with renal cysts and were visiting the urology department. The control group consisted of healthy individuals with no history of renal disease.

Hematological Analysis

Hematological parameters, including hemoglobin levels, were measured using the Technicon H-1 Hematology Analyzer. Blood samples were collected from all participants, and the analysis was conducted in accordance with the manufacturer's instructions [15].

Biochemical Analysis

Biochemical parameters, specifically blood urea and creatinine levels, were measured using the RA-XT Technicon biochemical analyzer. Reagents from Technician were utilized for these measurements. Blood samples were processed promptly to ensure accuracy and reliability of the results.

Erythropoietin (EPO) Measurement

EPO levels in both serum and cystic fluid were quantified using the Anthos Labtec HT II microtitracic platelets counter, employing Boehringer Mannheim reagents through an immuno-enzymatic method (ELISA methodology) [16]. Cystic fluid samples were obtained either immediately following nephrectomy or in vivo from patients with renal cysts, ensuring minimal degradation of the samples.

Statistical Analysis

Data were analyzed using SPSS software version 12. Descriptive statistics were calculated for all variables, and results were expressed as mean ± standard deviation (SD). The Student's t-test was employed to compare the means of continuous variables between the patient and control groups. A p-value of less than 0.05 was considered statistically significant [17].

Ethical Consent

The study was conducted in accordance with approved by the Ethics Committee of Alhawari General Hospital. Informed consent was obtained from all participants prior to their inclusion in the study. Participants were informed about the study's objectives, procedures, potential risks, and benefits, and they were assured of the confidentiality of their data. Participation was voluntary, and participants had the right to withdraw from the study at any time without any consequences.

Results

Participant Characteristics

A total of 60 participants were included in this study, consisting of 30 patients diagnosed with renal cysts and 30 healthy controls. The patient group comprised individuals aged between 30 and 60 years, with an average age that was closely matched to the control group, which included individuals aged 29 to 58 years. Both groups were well-matched for gender distribution, ensuring that any observed differences in laboratory parameters could be attributed to the presence of renal cysts rather than demographic variations.

Serum Erythropoietin (EPO) Levels

The analysis of serum EPO levels revealed a significant difference between the two groups. Patients with renal cysts exhibited a mean serum EPO level of 29.7 ± 7 mU/ml. In stark contrast, the control group had a mean serum EPO level of 6.2 ± 4.3 mU/ml. The statistical analysis confirmed that this difference was significant, with a p-value of < 0.05 **(Table 1, Figure 1)**. This finding indicates that individuals with renal cysts have substantially elevated levels of EPO in their serum, suggesting a possible compensatory response to anemia or hypoxia associated with renal pathology .

Blood Urea Levels

Similarly, blood urea levels were significantly higher in the patient group. The mean blood urea concentration in patients with renal cysts was 7.2 ± 1.3 mmole/l, compared to 4.4 ± 1.1 mmole/l in the control group. This difference was also statistically significant, with a p-value of < 0.05**(Table 1, Figure 1)**. The increased blood urea levels in patients with renal cysts may reflect impaired renal function or altered metabolism, further emphasizing the renal involvement in this condition .

Hemoglobin Levels

The hemoglobin levels of the participants were assessed to evaluate the hematological impact of renal cysts. The mean hemoglobin level in patients with renal cysts was found to be 11.2 ± 0.6 gm/dl, which is significantly lower than the mean hemoglobin level of 13.2 ± 1.3 gm/dl in the control group ($p < 0.05$)**(Table 1, Figure 2)**. This reduction in hemoglobin levels suggests that patients with renal cysts may be experiencing anemia, potentially due to the effects of renal dysfunction or the impact of elevated EPO levels attempting to compensate for reduced oxygen-carrying capacity .

Serum Creatinine Levels

In contrast to the significant differences observed in EPO, blood urea, and hemoglobin levels, serum creatinine levels did not show a statistically significant difference between the two groups. The mean serum creatinine level in the patient group was 92 ± 17 mmole/l, while the control group had a mean

level of 88 ± 16 mmole/l. The p-value for this comparison was greater than 0.05, indicating that renal cysts may not significantly affect serum creatinine levels in this patient population **(Table 1, Figure 2)**. This finding suggests that while renal cysts can alter certain biochemical parameters, they may not always correlate with classic markers of renal function such as serum creatinine **)**.

EPO Levels in Cystic Fluid

A particularly striking finding of this study was the measurement of EPO levels in cystic fluid. The mean EPO concentration in cystic fluid from patients with renal cysts was found to be 433 ± 370 mU/ml. This level is approximately 15 times higher than the mean serum EPO level of 29.7 ± 7 mU/ml in the same patients **(Figure 2)**. The minimum EPO concentration in cystic fluid was 3.1 mU/ml, while the maximum reached 935 mU/ml. This substantial elevation in EPO levels within the cystic fluid highlights the potential role of renal cysts in local erythropoietin production or release, which may contribute to the systemic alterations observed in serum EPO levels **(Table 2, Figure 3)**.

Discussion

Among all cystic changes, the emergence of one or more "simple renal cysts" in adulthood may be the most prevalent. These cysts can range in size from a few millimeters to over 10 centimeters. They are extremely unlikely to be the cause of renal failure, and they are rarely abundant enough to obscure intervening normal parenchyma. The flattened cuboidal epithelium lining these cysts is filled with a transparent fluid. It can occasionally bleed into a bigger cyst, presenting as a mass lesion that can be challenging to distinguish from a renal cell carcinoma. Patients with chronic renal failure have been shown to exhibit endocrine problems. An improvement in anemia among dialysis patients has been linked in certain articles to acquired cystic kidney disease. There have been suggestions that the cysts' production of erythropoietin may be the cause of this [18, 19 and 20].

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While serum EPO concentrations can be readily detected using enzyme-linked assay (ELISA) or radioimmunoassay (RIA), routine assessment of serum EPO concentrations is not commonly performed. EPO measures are not advised by K/DOQI recommendations for the diagnosis of renal anemia in patients whose creatinine levels are greater than 2 mg/dl. Since EPO concentrations must be evaluated in connection to the severity of anemia and renal function, the poor utilization of monitoring serum EPO concentrations can be partially explained by the challenging interpretation. Without accounting for these parameters, relative EPO deficit could be readily undetected because the manufacturer's reference values are primarily obtained from healthy, non-anemic patients. When EPO concentrations are expressed in percentiles, it becomes easier to diagnose renal anemia and relative EPO deficiency using EPO concentration measurements [25, 26]. Patients with acquired cystic

kidney disease and renal carcinoma typically have elevated EPO levels. Currently, there are two possible explanations for this: either the cyst or tumor tissue produces EPO, or the hypoxic augmentation of EPO production occurs as a result of vascular compression by a renal mass. However, since no cysts or renal tumors were found on abdominal computed tomography, it did not appear likely that these variables were the reason for the elevated EPO level in our heart failure group. Even though the anemic uremic patients' serum EPO titers were the same or greater, their erythrokinetic rates were around half that of normal haematological stable people [27]. Patients receiving continuous hemodialysis due to acquired polycystic kidney disease may have elevated serum erythropoietin levels. It is uncommon for RCC to occur in ADPKD, and there is debate concerning the correlation between RCC and ADPKD. Most documented occurrences have been demonstrated to be unintentional discoveries made during surgical investigation or during autopsy. Patients with anemia on long-term hemodialysis typically have low serum EPO levels. However, as the renal proximal tubule cells secrete EPO into the fluid of cysts, elevated levels of hemoglobin and EPO have been found in hemodialysis patients. The diagnosis of RCC that produces EPO is challenging in these patients because of the noticeable architectural distortion and overlapping clinical characteristics [28].

T-lymphocytes modified to express a particular receptor on a target cell, known as chimeric antigen receptor T (CAR-T) cells, have the capacity to function as senolytic agents [29]. In animal models of lung adenocarcinoma and liver fibrosis, Amor et al. discovered a novel urokinase-type plasminogen activator receptor (uPAR) as a cell-surface protein and discovered that uPAR-specific CAR-T cells effectively ablate senescent cells [30]. Studies on the effects of CAR T-cell treatment on the kidneys are scarce. Anwer et al. found that whereas the majority of patients experienced hematologic malignancies, 18% of individuals experienced AKI following CAR-T cell therapy. Therefore, more research on kidney aging and chronic kidney disease (CKD) is required in light of the use of CAR-T cells [31].

The study found that patients with renal cysts had mean serum EPO and urea values of 29.7±7 mU/ml and 7.2±1.3 mmole/l, respectively. These values were substantially higher than those of the control group, which had mean values of 6.2±4.3 mU/ml and 4.4±1.1 mmole/l, respectively, $P < 0.05$. Patients diagnosed with renal cysts had significantly lower hemoglobin levels (11.2±0.6 and 13.2±1.3 gm/dl, respectively) than the control group ($P < 0.05$). Patients with polycystic kidney disease had considerably greater levels of hemoglobin and erythropoietin. Hemoglobin and erythropoietin levels were lowest in patients without cysts; however, there was no discernible difference between patients with one to three isolated cysts or those with many bilateral cysts [32].

In a different study, a hemodialysis population's serum erythropoietin levels were randomly collected and assessed using a sensitive radioimmunoassay. Patients with polycystic kidney disease and those with other renal illnesses were split into two groups. It was shown that, in comparison to other kidney disease patients, patients with polycystic kidney disease had higher serum erythropoietin levels, reticulocyte counts, and hematocrit levels. The authors proposed that the severity of anemia in uremic hemodialysis patients can be predicted from an abnormally low serum erythropoietin level and that even in the presence of uremia, increased erythropoiesis is more effective when erythropoietin is more readily available [33].

Renal cysts can occur in people of any age, from children to adults, and are a common finding in a variety of renal illnesses [34]. They have diverse clinical manifestations as a result of their intricate pathogenic pathways, which can have unpredictable long-term effects. Between 9.7% and 14.1% of

all children cases requiring renal replacement therapy (RRT) are related to pediatric cystic kidney disease (CyKD), which is the third most common cause of end-stage renal disease (ESRD). Differentiating patients who will remain asymptomatic from those who will advance to end-stage renal disease (ESRD) remains a challenge despite a plethora of basic, translational, and clinical investigations. Thus, the current study contributes to the body of research on determining a causal link between frequent clinical symptoms and the development of chronic kidney disease (CKD) [35].

EPO in cystic fluid was found to be 15 times greater in this study than in serum EPO. The key argument supporting the belief that PKD patients create more erythropoietin than non-PKD patients is the evidence that cystic fluid and interstitial cells produce erythropoietin regardless of oxygen content**.** Although this maybe true in the early stages of CKD with volume expansion, thiseffect may be offset in the later stages as a result of uremia.Therefore as PKD progresses, more cysts produce more EPO andmay contribute to higher hemoglobin in stages 3 and 4. In stage5, the inhibitory effect of uremia may block the response ofbone marrow to EPO. Our data are limited because the number ofpatients in the control group is small. Besides this limitation,our results show the utility of the nomogram in a clinical settingand that PKD patients have higher haemoglobin only in earlystages [36].

Cysts exhibiting salt values above 100 mmol/liter showed a marked enrichment of EPO, indicating a possible correlation with proximal tubular abnormalities. According to research, individual interstitial cells positioned next to proximal tubular cysts may generate extracellular plasma oxygen (EPO) independently of the oxygen pressure within the cysts. This can help reduce anemia in patients with end-stage polycystic kidney disease [37].It's impossible to pinpoint the exact function of EPO in the cystic fluid. There is no proof that fluid EPO permeates the serum. A novel inquiry emerges on the possibility that fluid EPO, like the interleukins or inflammation mediators found in cystic fluid, could act as a growth factor for renal cysts [38].

Conclusion

According to this study, there is no erythropoietin penetration from a cystic fluid into the blood in individuals with renal cysts, and more research is needed to determine the amount of erythropoietin in cystic fluid.

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Tables

Table 1: Hemoglobin, creatinine, urea, and EPO mean values in individuals with renal cysts and the control group.

LABORATORY PARAMETERS	PATIENT GROUP (30)	CONTROL GROUP (30)	P-VALUE	SIGNIFICANCE
	Mean± SD	Mean ± SD		
Serum EPO mU/ml	29.7±7	6.2±4.3	< 0.05*	Sig. higher
Hemoglobin level gm/dl	11.2±0.6	13.2±1.3	< 0.05*	Sig. lower
Blood urea mmole/l	7.2±1.3	4.4±1.1	< 0.05*	Sig. higher
Serumcreatinine mmole/l	92± 17	88 ±16	> 0.05	Non-Sig.

Table 2: EPO mean values in cystic fluid and serum among renal cyst patients.

	SERUM EPO MU/ML	CYSTIC FLUID EPO MU/ML	RATIO
Mean± SD	**29.7±7**	**433 ±370**	**14.93**
Minimum	**3.7**	**3.1**	
Maximum	**99.4**	**935**	

Figure 1: Comparison of Mean Values of Serum EPO, Hemoglobin level, Blood urea and serum creatinine

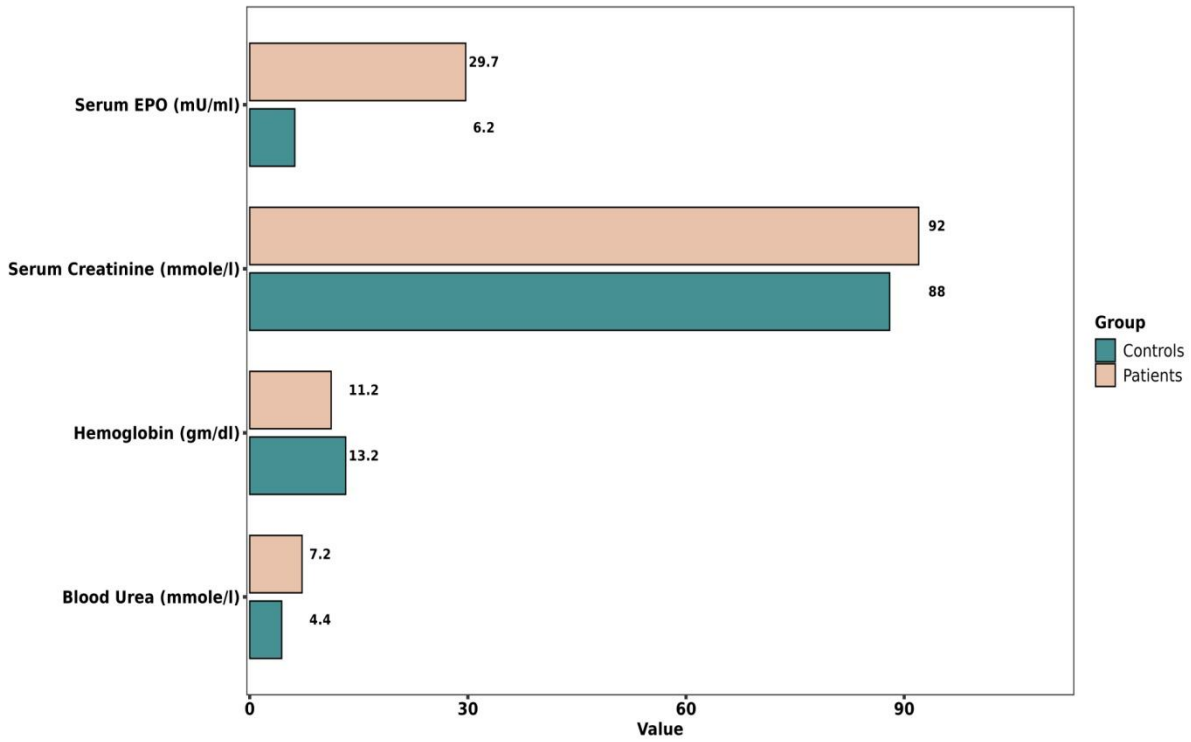

Figure 2: Comparison of EPO Levels in Serum and Cystic Fluid

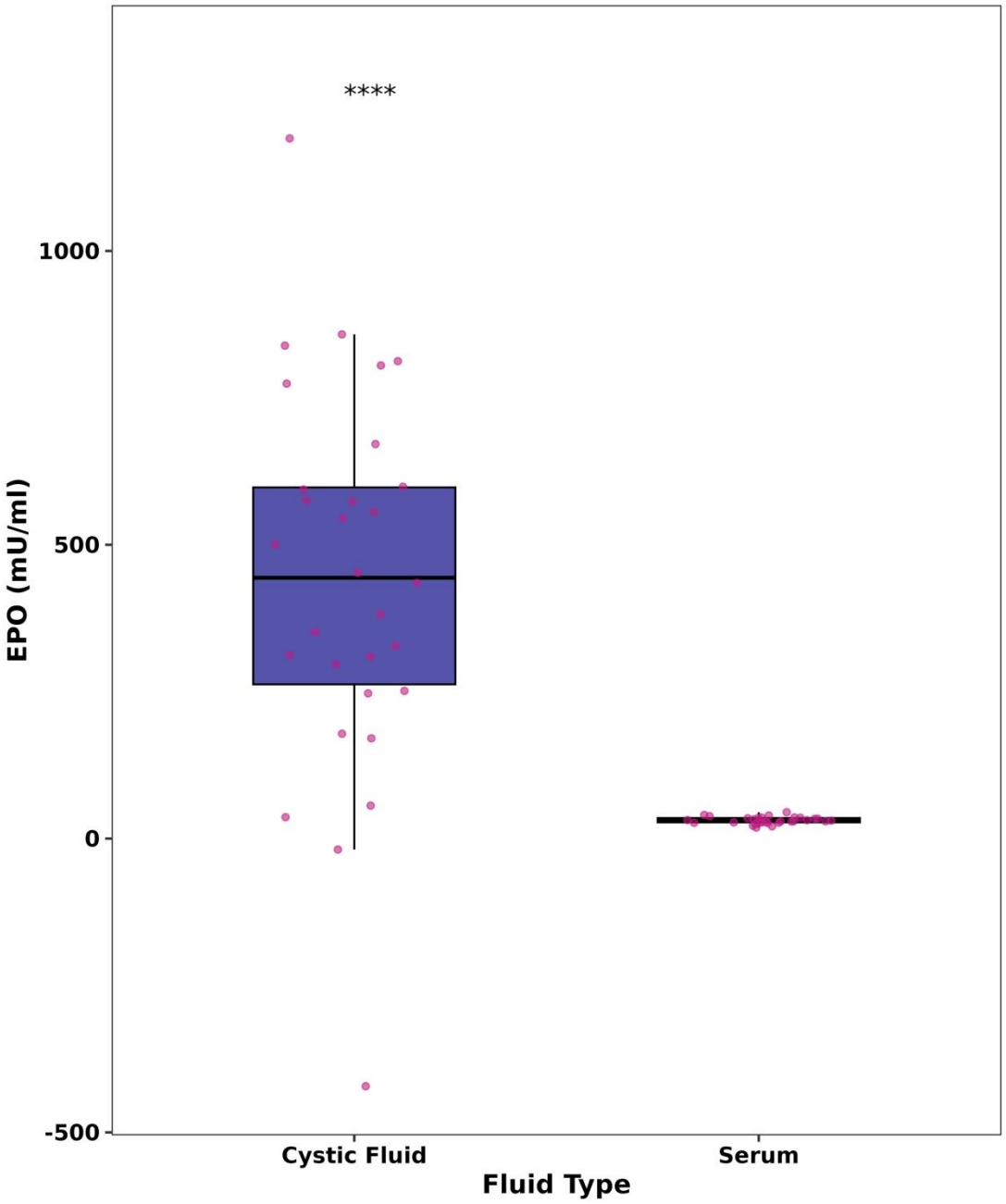

Figure 3: EPO levels in the Serum and Cystic Fluid