Epidemiology and outcomes of pediatric autosomal recessive polycystic kidney disease in the Middle East and North Africa

Mohamed A Salman[1*], Ahmed Elgebaly[2], Neveen A Soliman[3,4,5]

[1] CTI Clinical Trial and Consulting Services, Cairo, Egypt

[2] Smart Health Unit, University of East London, London, E16 2RD, UK

[3]Center of Pediatric Nephrology & Transplantation, Kasr Al Ainy Medical School, Cairo University, Cairo, Egypt

[4] Egypt Center for Research and Regenerative Medicine (ECRRM), Cairo, Egypt

[5] Egyptian Group for Orphan Renal Diseases (EGORD), Cairo, Egypt

*Corresponding Author

Name: Mohamed Ahmed Salman

Email: moh.salman.md@gmail.com

ABSTRACT

The incidence of rare diseases is expected to be comparatively higher in the Middle East and North Africa (MENA) region than in other parts of the world, attributed to the high prevalence of consanguinity. Most MENA countries share social and economic statuses, cultural relativism, religious beliefs, and healthcare policies. Polycystic kidney diseases (PKDs) are the most common genetic causes of kidney failure, accounting for nearly 8.0% of dialysis cases. The development of PKDs is linked to variants in several genes, including *PKD1, PKD2, PKHD1, DZIP1L,* and *CYS1*. Autosomal recessive PKD (ARPKD) is the less common yet aggressive form of PKD. ARPKD has an estimated incidence between 1:10,000 and 1:40,000. Most patients with ARPKD require kidney replacement therapy earlier than patients with autosomal dominant polycystic kidney disease (ADPKD), often in their early years of life. This review gathered data from published research studies and reviews of ARPKD, highlighting the epidemiology, phenotypic presentation, investigations, genetic analysis, outcomes, and management. Although limited data are available, the published literature suggests that the incidence of ARPKD may be higher in the MENA region due to consanguineous marriages. Patients with ARPKD from the MENA region usually present at a later disease stage and have a relatively short time to progress to kidney failure. Limited data are available regarding the management practice in the region, which warrants further investigations.

Keywords: Polycystic kidney diseases; Ciliopathies; Burden; Epidemiology; Middle East and North Africa

Introduction

'Ciliopathies' is a broad term that refers to several inherited disorders with a common feature of loss of motile or immotile ciliary function throughout body cells [1]. Polycystic kidney diseases (PKDs) are common forms of ciliopathies, accounting for nearly 8.0% of dialysis cases, with an incidence rate ranging from 1 in 543 to 1 in 4,000 newborns [2]. The development of PKDs is linked to variants in several genes, including *PKD1, PKD2, PKHD1, DZIP1L,* and *CYS1* [3]. These variants impact the corresponding proteins that have a vital role in ciliary function, including polyductin/fibrocystin, polycystin-1, and polycystin-2 [3]. Patients with autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) may develop isolated renal pathology or phenotypes with extrarenal manifestations [3]. The prevalence of ADPKD reached 42.6 and 39.6 per 100,000 people in the US and Europe, respectively [4, 5]. On the other hand, ARPKD has an estimated incidence between 1:10,000 and 1:40,000. Most patients with ARPKD require kidney replacement therapy (KRT) much earlier than ADPKD in their early years of life [2].

Although ARPKD is the less prevalent PKD, it is one of the most common causes of morbidity and mortality among children with cystic kidney diseases. Dilatation of the collecting ducts starts as early as fetal life and can present at any stage from prenatal phases till adulthood [6]. ARPKD mainly impacts the kidneys and liver; however, the factors influencing the presence of extrarenal features are still not fully comprehended [6]. *PKHD1* gene variants on chromosome 6 may have a role in the different ARPKD phenotypes currently identified; however, ARPKD genotypes alone are not the only influencing factor [2]. Almost 750 variants were detected on the 67-exons *PKHD1* gene coding for the protein fibrocystin/polyductin. Although not all the identified *PKHD1* variants are pathogenic, few are more frequently reported and can differ between global regions [7].

Without a doubt, the prevalence of ARPKD has a direct relation with parental consanguinity, which is evident in homozygous variants [8].

However, diagnosing ARPKD remains challenging due to the complexity of polycystic kidney diseases. ADPKD can occasionally present a clinical phenotype closely resembling that of ARPKD [2]. Within the spectrum of ADPKD, the very early-onset ADPKD (VEO-ADPKD) phenotype can present at a significantly younger age compared to the classical disease and can, therefore, closely mimic ARPKD, both phenotypically and in terms of disease onset [9]. Therefore, genetic testing plays a crucial role in differentiating ARPKD and VEO-ADPKD, guiding the subsequent disease management strategies [10].

The incidence of rare diseases is expected to be comparatively higher in the Middle East and North Africa (MENA) region than in other parts of the world. The MENA region has one of the highest incidences of consanguineous marriages globally, estimated to be between 20.0 and 50.0% of their population. ARPKD is expected to have a higher prevalence in this part of the world [11]. Most MENA countries share social and economic statuses, cultural relativism, religious beliefs, and healthcare policies. This review gathered data from published research studies and reviews of ARPKD, highlighting the epidemiology, phenotypic presentation, investigations, genetic analysis, outcomes, and management. We covered the 20 MENA countries identified by the United Nations International Children's Emergency Fund (UNICEF) [12].

I. Review Development Methodology

We performed a bibliographic search on Medline via PubMed, Scopus, and Web of Science using a combination of specific keywords and MeSH terms, including "pediatrics", "child", "infant, newborn", "ARPKD", "autosomal recessive polycystic kidney disease", and "ARPKD

phenocopy". We did not restrict our search based on the country of origin, thereby ensuring diverse geographic representation in comparing the results from the MENA region to the rest of the world. The temporal scope was defined from inception to August 31, 2023. Our focus encompassed a range of study designs—original research, case reports, case series, and review articles—while editorial comments and opinion pieces were excluded to maintain empirical integrity.

II. Epidemiology:

a- Incidence of ARPKD

The incidence of ARPKD is estimated to be between 1 in 20,000 to 1 in 40,000 live births, which is relatively rare. However, some populations may have a higher incidence, particularly in countries with high rates of consanguineous marriages [13].

The incidence and prevalence of ARPKD have been seldom reported in the MENA region due to the lack of epidemiological studies and patient registries. However, some countries made attempts to estimate the prevalence of this disease in their population. Data regarding the epidemiology of ARPKD in Egypt were reported in two previous studies. In one study, ARPKD was the second most common inherited childhood cystic kidney disease in Egypt, following nephronophthisis (NPHP) [14]. Another study scanned 500 clinically healthy neonates to understand the prevalence of kidney anomalies in newborns. ARPKD represented 0.2% (20 per 10,000 neonates) of the total screened population in a single center [15].

A previous report screened the reason for oligohydramnios in 100 Egyptian pregnant women. Of them, 13.8% were found to have ARPKD [16]. In Oman, the estimated incidence of patients with ARPKD was 1 in 12,000 live births between 1993 and 2002 [17]. Screening of 1,171 newborns admitted to the neonatal intensive care unit in the Southwestern region of Saudi Arabia found that

0.7% of the total population was diagnosed with PKD; however, this study did not report the exact incidence of ARPKD patients [18]. An Iraqi study identified 4.3% of children with congenital kidney anomalies to have PKD. Again, it cannot reflect the disease prevalence or burden since it is a single-center study with no confirmation of the type of PKD identified [19].

Hence, while limited data are available, current figures suggest a comparatively higher incidence of ARPKD in the MENA region than in other parts of the world. While the exact causes of such higher incidence have not been comprehensively studied yet, a high rate of consanguinity can play a significant role in the comparatively high burden of ARPKD in the region. A study conducted in Turkey found that the incidence of ARPKD was higher in the southeastern region of the country, where consanguineous marriages are more common [20, 21]. The MENA region is well-known for the high rates of consanguineous marriages, reaching up to 50.0% of its population [22]. Several factors play a role in this high rate of consanguinity, including religious idols, geographic distribution, education levels, cultural beliefs, and many other key factors [23]. Given the autosomal recessive nature of this disease, consanguinity plays a major role in the prevalence and incidence of ARPKD in the MENA region. The rate of consanguinity among ARPKD studies from the MENA region ranged between 46.7–66.0% among the studied populations. Even on cystic kidney diseases, consanguinity reached 63.0% among 105 patients belonging to 100 unrelated families [14]. Comparatively, data from the European ARegPKD registry showed that consanguinity was documented in 16.0% of the families of patients with ARPKD [24].

However, it should be noted that most studies from the MENA region are single-center, and several countries have scarce data. Further research is needed to better understand the incidence and prevalence of ARPKD in the MENA and improve the diagnosis and treatment for affected individuals.

b- Age at presentation of ARPKD and role of antenatal screening

Patients with ARPKD are diagnosed in the prenatal, neonatal, infancy, early and late childhood, and even adulthood stages of life, mostly in infancy or childhood. The disease can have a wide range of severity, and some individuals may have mild or atypical symptoms that are not recognized as ARPKD until adulthood [2]. The age at which ARPKD presents can also vary depending on whether the affected individual has other associated conditions. For example, individuals with ARPKD have congenital hepatic fibrosis; however, the age of presentation and severity affect the clinical course and the development of portal hypertension and variceal bleeding. The onset and severity of hepatic symptoms can affect the age at which ARPKD is diagnosed [25].

This was evident in the MENA region, where ARPKD was clinically or radiologically detected in different age groups. In the MENA region, the age at presentation of ARPKD patients widely varied among the region countries. Two studies found that the median age of PKD patients was approximately 2.5 years; however, these studies were limited by the small sample size and the fact that, in one of these two studies, it is unknown if PKD was of autosomal dominant or recessive inheritance [14, 26]. Nonetheless, a considerable number of cases were diagnosed after the first year of life up to adulthood in Middle Eastern countries (Table 1). Comparatively, in Europe, data from the ARegPKD registry showed that the median age at diagnosis was younger than MENA patients (0.7 [range 0.1–6.0]) [24].

The variance in the age of presentation for ARPKD patients between the MENA region and Europe might be underpinned by multiple factors. The rates of prenatal ultrasonography are comparatively higher in Europe than in the MENA region, potentially contributing to earlier detection. It is worth noting that prenatal ultrasonography screening for ARPKD is not done routinely in MENA

countries but only when there is a specific indication or family history of the disease. Genetic backgrounds between the regions could also introduce variations in disease onset, with certain mutations resulting in earlier or later symptoms [27]. European countries, having more consolidated healthcare infrastructure and robust prenatal screening programs, could detect ARPKD earlier than some MENA nations. Heightened awareness and education about ARPKD in Europe might contribute to earlier consultations and diagnoses. Cultural nuances in the MENA region could potentially delay medical consultations until symptoms intensify. Additionally, disparities in registry criteria and reporting methodologies, such as those seen between the European ARegPKD registry and MENA studies, could influence the comparative age data. Moreover, the small sample sizes in the MENA studies might not be entirely representative, potentially skewing comparative insights.

The findings of older age at presentation in the MENA region underscore the importance of antenatal screening using ultrasonography. The most common method of antenatal screening for ARPKD is through fetal ultrasound. Enlarged echogenic kidneys, oligohydramnios, and a small or absent bladder on ultrasound typically characterize ARPKD. These ultrasound findings may be detected as early as 18 weeks gestation [28]. The antenatal detection rate of ARPKD was variable in the MENA region, ranging between 6.3 – 21.0% of all diagnosed cases. In the study by Soliman et al., only 21.0% of patients with cystic kidney diseases were detected antenatally. The same was found in an Omani study, where 20.0% of ARPKD patients recorded between 2015 and 2018 were diagnosed antenatally [29]. Another study identified ARPKD antenatally in 17.1% of congenital kidney and urinary tract anomalies after screening 640 pregnant women [30]. A Tunisian study prenatally detected ARPKD in 16.0% of 43 cases of lethal urinary tract congenital anomalies [31].

Another multicenter study in three Iraqi ultrasound centers detected ARPKD antenatally in 6.9% of detected congenital anomalies after screening 5,142 pregnant women [32].

Antenatal detection of ARPKD was mainly triggered in the MENA region by either (i) early suspicion or identification by ultrasound in pregnancy, (ii) family history of kidney disorders, or (iii) parental consanguinity [33]. However, most cases in the MENA region are diagnosed after birth. A study from Palestine detected ARPKD in 9.1% of 55 patients diagnosed with major birth defects at birth [34]. Missed antenatal diagnosis could result from atypical or asymptomatic presentation of ARPKD. The absence of oligo- or anhydramnios in the third trimester, missed detection of enlarged hyperechogenic kidneys, and the absence of extrarenal ultrasound findings may aid in undiagnosed ARPKD during routine prenatal ultrasound.

c- Gender distribution

Globally, the gender ratio among ARPKD patients varied between the studies. This variation was also observed in the MENA region. A female predominance reached 2:1 in some studies from the MENA region [26, 29, 35, 36]. While the exact reasons for the female predominance among ARPKD patients from the MENA region are unclear, this observation may result from genetic predispositions, environmental factors, and even the role of sociocultural influences in the MENA region that might affect the recognition and reporting of symptoms in different genders.

III. Clinical Presentation:

Clinical heterogeneity in ARPKD warrants a high index of clinical suspicion. Intrafamilial variability was also reported, where the phenotypic presentation varies widely within the same family. The clinical manifestations of ARPKD depend largely on the severity of the disease and the age of onset. Abdominal distension due to enlarged kidneys and systemic hypertension are

common presentations of ARPKD. Over time, the kidney functions deteriorate and progress to kidney failure, with symptoms such as fatigue, anemia, and fluid retention. Hepatomegaly and portal hypertension due to hepatic fibrosis can also be detected in ARPKD. Infants with severe ARPKD may have pulmonary hypoplasia, which can lead to respiratory distress and require respiratory support [37].

Abdominal distension with or without palpable masses is a common feature at presentation in children with ARPKD in the MENA region [14, 35, 38]. Enlarged abdominal masses and hypertension were the main presenting signs among patients from the MENA region [35]. Organomegaly was not exclusive to the kidneys since hepatomegaly, with or without splenomegaly, was detected among ARPKD patients at presentation, even in the neonatal period [35]. A Saudi study detected hepatomegaly in 88.0% of ARPKD patients and only one patient with splenomegaly [35]. An Egyptian study on 32 ARPKD patients showed that abdominal distension was the most common presenting manifestation in almost 53.0% of patients. However, splenomegaly was also present in only one patient (3.0%), and no cases with hepatomegaly were recorded at presentation [39].

Children with ARPKD in the MENA region presented to healthcare professionals with kidney manifestations other than abdominal distension, including polyuria, enuresis, edema, urolithiasis, and symptoms of kidney failure [39, 40]. Extrarenal symptoms were recorded in ARPKD patients. For instance, in Soliman et al., 43% of the studied children had extrarenal manifestations. The most common extrarenal manifestations were neurological (18.1%; mainly seizures, psychomotor retardation, and microcephaly), dysmorphic features (15.2%), hepatic (14.3%; mainly hepatomegaly, hepatic cysts, and congenital hepatic fibrosis), ophthalmological (9.5%; mainly retinal dystrophy, microphthalmia, choroidal coloboma), and cardiac (8.9%; mainly mitral valve

prolapse with regurge and hypertrophic cardiomyopathy with arrhythmia) [14]. Another report from Egypt demonstrated that extrarenal manifestations were evident in ARPKD patients, including hepatic (44%), neurological (6%), and cardiac (6%). Respiratory distress in the neonatal period was also reported in 6.3% of the neonates with ARPKD [39].

Accidentally discovering ARPKD in the MENA region was relatively uncommon, accounting for not more than 6.0% of diagnosed patients [39].

The incidence of comorbidities associated with ARPKD can vary widely depending on the severity and progression of the disease. The risk of developmental delays in individuals with ARPKD was noted to be high (prevalence is approximately 25%), and patients may experience cognitive or motor delays [41]. Individuals with ARPKD may be more susceptible to urinary tract infections (UTIs) [42]. UTIs were common, reaching up to 44.0%. Other individually reported comorbidities included intracranial aneurysms and autoimmune hemolytic anemia, which were reported in a few case reports [43, 44].

Overall, the clinical presentations of ARPKD in the MENA appear to be comparable to patients from the United States (US) and Europe [24, 45].

a- Systemic Hypertension in ARPKD

Systemic hypertension is a relatively common complication among children with ARPKD, especially in neonatal survivors. Previous literature suggested that hypertension affects up to 55.0–75.0% of ARPKD patients [24, 46]. Systemic hypertension was evident in up to 74.0% of children with ARPKD in the MENA region [26, 39]. A Saudi study found that children with PKD had the highest prevalence of hypertension (88.2%) among patients with polycystic kidney diseases,

followed by multicystic dysplasia (6.3%) and nephronophthisis (66.0%); however, separate data on ARPKD patients were not reported [26].

The majority of patients with hypertension were treated with anti-hypertensives; however, uncontrolled and intractable hypertension was reported. One study found that almost 36.0% of patients with initial systemic hypertension remained hypertensive despite a combination of anti-hypertensives. One patient was recorded to receive five classes of anti-hypertensive drugs to manage resistant hypertension. Cases of hypertensive encephalopathy were also recorded in the region, with one study from Egypt showing a rate of 3% [39]. Children with ARPKD received various classes of anti-hypertensives, including angiotensin-converting-enzyme inhibitors (ACE inhibitors), alpha-1 adrenergic receptor antagonists, calcium-channel blockers, direct vasodilators, and beta-adrenergic receptor antagonists.

b- Hepatic Manifestations of ARPKD

Hepatic involvement in patients with ARPKD is common, affecting up to 45% of the patients. In the MENA region, the reported prevalence of hepatic involvement was up to 37.0% [14]. Comparatively, European cohorts show a higher incidence of portal hypertension, affecting 68.6% of ARPKD patients [24]. This variation highlights regional differences in disease presentation.

Congenital hepatic fibrosis (CHF) and its complications, cholangitis and portal hypertension, are the main hepatic involvement in ARPKD. Data from the MENA region show that CHF is prevalent in ARPKD children, with occurrences between 32.0 and 77.5% [14, 29, 39]. The incidence of portal hypertension varied in the region between 5.9 – 17.0%. In two Saudi studies on 15 and 17 children with ARPKD, only one patient in each study had portal hypertension [35, 38]. In other Egyptian studies, 14.8 – 17.0% of patients developed portal hypertension [14, 39]. Cholangitis was

also recorded, reaching up to 6.0% of patients in the MENA region [39]. In Europe, portal hypertension was observed in 56.0% of the ARPKD patients [24].

In the MENA region, CHF is more frequently observed during childhood or juvenile stages rather than in perinatal or neonatal stages [29, 39]. However, the age of onset for these manifestations varies across the region [39]. A study from Oman showed that most ARPKD patients who developed CHF were diagnosed clinically and by ultrasonography [29]. This indicates the need for timely diagnosis and regular follow-up evaluation, laboratory investigations, and radiological assessment regarding the expected hepatic complications that might develop, including portal hypertension.

The incidence of splenomegaly was recorded between 26.7 – 47.5% of patients with ARPKD in the MENA region [29, 38]. This prevalence warrants a deeper exploration, especially considering the pathophysiological implications of splenomegaly in ARPKD. In an Omani study, the majority of splenomegaly cases developed simultaneously with hepatic fibrosis detection. This correlation suggests that splenomegaly in ARPKD patients is likely a consequence of portal hypertension rather than a direct result of the CHF itself. However, in some cases, splenomegaly was reported even before hepatic fibrosis or hepatomegaly [39]. This atypical presentation raises important questions about the underlying mechanisms. It suggests the possibility of additional factors contributing to splenomegaly in ARPKD patients independent of hepatic fibrosis. These factors could include pre-sinusoidal portal hypertension or vascular anomalies, which might manifest earlier than hepatic fibrosis [35, 47].

Although considered rare, ARPKD children with Caroli syndrome were reported in several studies from Egypt, Oman, and Morocco [14, 48, 49]. Cholestasis was reported as the presenting

manifestation in one child with ARPKD in an Egyptian study [14, 39]. Other general hepatic manifestations were also recorded throughout the region, including hepatomegaly [14].

IV. Diagnosis

Historically, the diagnosis was predominantly based on clinical features, with presentations ranging from renal symptoms in utero or early childhood to hepatic complications manifesting later in life. Radiological findings, such as enlarged, echogenic kidneys with poor corticomedullary differentiation, further support clinical diagnosis. However, with advancements in genetic technology, molecular diagnostic methods, specifically genetic testing, have become more accessible and are now considered the gold standard for confirming ARPKD [27]. ARPKD, known as polycystic kidney and hepatic disease-1, is considered to have an autosomal recessive mode of inheritance due to variants in the *PKHD1* gene (OMIM 606702). The cytogenetic location of the *PKHD1* gene is mapped to chromosome 6p12.3-p12.2 [50]. Although it impacts both kidneys and the liver, the *PKHD1* gene was found to be highly expressed in kidney tissue since fetal life; however, gene expression in the liver and other tissues was minimal [51].

In the present literature review, we found that only three studies from the MENA region utilized genetic analysis to detect ARPKD (Table 1). Given the high rates of consanguinity observed in certain regions, there is an increased likelihood of encountering other genetic diseases that might "phenocopy" ARPKD, including conditions like ADPKD and HNF1beta [52]. In cases like ADPKD, the inheritance of two mutant alleles can lead to a severe early-onset disease that can closely mimic ARPKD [53]. Therefore, while clinical presentations provide invaluable preliminary insights, they may not be distinct enough to differentiate ARPKD from its phenocopy conditions without the aid of genetic testing. It is essential to recognize the limitations of a purely

clinical diagnosis and the potential ambiguities it might introduce when distinguishing ARPKD from similar genetic disorders in the current published studies from the MENA region.

Pathogenic variants in the *PKHD1* gene (Table 2) were identified among 67.0% of 18 Saudi patients with ARPKD. However, one variant was common among eight patients. Also, genetic analysis confirmed the diagnosis of ADPKD in some patients who were clinically phenotyped as ARPKD by identifying the disease-causing gene variants in *PKD1* and *PKD2*; thus, proper differentiation between ADPKD and ARPKD is critical as it impacts the disease course and management plans [54]. A case report from Egypt revealed a rare homozygous missense variant in *PKHD1* [55]. It is worth noting that there is a distinct genetic pattern in the MENA region's ARPKD population, characterized by a higher prevalence of homozygous mutations, contrasting with the compound heterozygous mutations commonly found in European cohorts [24]. This notable difference is likely influenced by factors such as higher rates of consanguineous marriages in the MENA region, unique population-specific mutations, and possible historical founder effects.

DZIP1L variants (OMIM 671570) were also reported in children with ARPKD. Homozygous variants were identified in seven cases of Turkish and Arab origins, including Egyptians and Palestinians [56]. Pathogenic variants in *DZIP1L* gene included c.269C>T, p.(Ala90Val); c.273G>C, p.(Gln91His); c.463C>T, p.(Gln155*); and c.1061_1062del, p.(Glu354Alafs*39). DZIP1L plays a crucial role in the formation and function of primary cilia, cellular structures essential for various signaling pathways and proper kidney and liver development. Mutations in this gene can disrupt ciliary function, leading to the cystic changes seen in ARPKD [56]. Patients with *DZIP1L* variants typically present with features of CKD, hypertension, polyuria, and polydipsia. Additionally, the patients might exhibit extrarenal manifestations, such as liver fibrosis [56].

In the MENA region, genetic analysis is crucial due to the high rate of consanguinity. Despite the availability of genetic testing in many tertiary centers in the region, genetic analysis is not a routine diagnostic tool in the practice of pediatric nephrologists in the region. As a result, physicians in the region depend on their clinical experience, suspicion index, and radiological skills [14]. There is a strong demand to implement routine genetic testing for suspected cases in the region to improve the clinical management of the patients.

V. Outcome

a- CKD

Data from Europe showed that the rate of KRT among ARPKD patients was 11.9% [24]. On the other hand, limited studies are available regarding the proportion of ARKDP who develop CKD in the MENA region. Current published reports mainly investigate the underlying causes of CKD in pediatric patients. For instance, a Saudi study on cystic kidney diseases observed that PKD was the most common cause of CKD progression among all patients, with a mean GFR of 35.1 mL/min/m^2 among all PKD patients, and one of the follow-up three patients progressed to kidney failure. On the other hand, 4.8% of patients with other kidney cystic disorders developed kidney failure in this study; however, separate data on ARPKD patients were not reported [26]. In an Egyptian study, 14.0% of patients reached kidney failure between the ages of 3.4 and 10.1 years [39]. While investigating the reason for kidney failure in children from the MENA region, between 1.0 and 8.0% of kidney failure patients were diagnosed with ARPKD. Out of 48 kidney failure Kuwaiti children on hemodialysis, ARPKD was the etiology in almost 8.0% of them [57]. A similar prevalence was found in Jordan, where ARPKD represented almost 7.1% of children with kidney failure [58]. However, two other studies from Jordan observed a lower percentage of ARPKD in children with kidney failure, accounting for almost 1.0 – 3.2% of kidney failure

etiologies [36, 59]. Another Omani study on children and adults with kidney failure found that ARPKD was the etiology of kidney failure in 7.2% of patients on regular hemodialysis [60].

b- Mortality

The mortality rate dropped from 10.0% in neonates (< 28 days) to 5.0% in infants less than one year of age [29]. A Saudi study recorded four deaths (26.7%) among 15 ARPKD patients during a 2.7-year follow-up period. However, no deaths were recorded in ARPKD patients who survived the first six months of life [38]. These figures show a slightly lower mortality rate in the MENA region than in other parts of the world; such difference can be attributed to the geographical variation and differences in population samples examined in various studies. It is also worth noting that there is a lack of comprehensive studies from the MENA region. The reported mortality rates from the region are founded on a limited number of recent studies.

This finding could indicate the prognosis of ARPKD patients who survived the first 1 or 6 months of life. A study from Jordan identified ARPKD as the highest cause of death (46.2%) in autopsied infants with kidney cystic diseases in ten years. Almost all patients died before the age of three months. Liver abnormalities were evident in deceased ARPKD patients, especially bile duct proliferation [61]. The reasons for death in ARPKD patients varied in the MENA region. Most deaths were related to kidney complications of kidney failure. However, early deaths were partly related to respiratory complications. Other non-kidney causes of death were related to uncommon reasons, including multiple cerebral aneurysms with uncontrolled hypertension, arrhythmia, and neonatal sepsis with cholestasis [14]. However, the cost-effectiveness of early neurologic screening in ARPKD patients is yet to be confirmed.

Conclusion and Future Directions:

Although limited data are available, the published literature suggests that the incidence of ARPKD may be higher among the MENA highly inbreeding population. Patients with ARPKD from the MENA region usually present at a later disease stage and have a relatively short time to progress to kidney failure. Accordingly, the high index of clinical suspicion, screening, and antenatal diagnosis are exceptionally heightened in the MENA region due to the high rate of consanguineous marriages. Regular antenatal ultrasonography should be performed after the 18th week of pregnancy in women with a family history of ARPKD. On the other hand, limited data are available regarding the management practice in the region, which warrants further investigations.

However, we acknowledge that the current review poses several limitations, which call for further research. The current literature does not encompass all countries within the MENA region. Our review, therefore, could only incorporate data from certain parts of this region, specifically Egypt, Oman, Lebanon, Turkey, Saudi Arabia, Jordan, Iraq, Libya, and Kuwait. It should be noted that this concentration might induce some under-representation or bias, given the variations in sample sizes, inclusion criteria, and data sources across different studies. The challenges associated with conducting comprehensive research across the entire MENA region, such as data accessibility and availability, coupled with socio-cultural and political factors, cannot be overlooked. Future regional studies are needed to comprehensively reflect the landscape of ARPKD in the region.

It is worth acknowledging the limitations in our review concerning the comprehensive understanding of genetic analyses in ARPKD in the MENA region. Existing literature, upon which our review is based, does not provide a detailed account of the percentage of patients undergoing genetic workup, the components of these workups, their subsequent results, or the prevalence of non-ARPKD cases that initially present with an ARPKD phenotype. This shortfall in the available data imposes a limitation on our review's scope, restraining our ability to highlight the complexities

of ARPKD genetics and its phenotypic presentation. This significant gap in the literature underscores the need for future research in the MENA region to improve our understanding of the genetic aspects associated with ARPKD.

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Tables

Table 1: Clinical presentation and outcomes of ARPKD patients in the MENA region

Country	Study (Reference)	Design	No. of ARPKD	Age at Presentation (range)	Clinical Presentation	Comorbidities	Mode of diagnosis	Antenatal Diagnosis n (%)	ESKD	Mortality
Egypt	Nabhan et al. [40]	Retrospective	25	(8 days – 17 years)	- Hepatic (41.0%) - Neurological (5.6%), - Cardiac (5.6%).	- UTIs (44.0%) - Systemic hypertension (42.0%) - Portal hypertension (17.0%)	Ultrasound and kidney biopsy	2 (6.3%)	- Incidence (6.3%) - Median age = 72.7 months	NR
Iran	Yousefichaijan et al. [63]	Retrospective	60	11 months**: <2 months (15.0%) 3-7 months (36.6%) 7-12 months (23.3%) >12 months (25.0%)	NR	NR	Ultrasound and kidney biopsy	NR	NR	NR
Oman	Al Alawi et al. [30]	Retrospective	40	Birth-1 month (15.0%) 2-12 months (37.5%) 1-8 years (22.5%) 9-13 years (5.0%)	- Congenital hepatic fibrosis (77.5%) - Splenomegaly (47.5%) - Pulmonary hypoplasia (17.5%)	- Systemic hypertension (72.5%)	Mutational analysis	8 (20.0%)	- Incidence (30.0%)	- Perinatal (10.0%) - Postneonatal (5.0%)

Saudi	Al-Hamed et al. [64]	Retrospective		Antenatal	NR	NR	Mutational analysis	4 (9.1% of all screened families)	NR	NR
Saudi	Mattoo et al. [39]	Retrospective	15	9 months* (2 days – 7 years)	NR	- Systemic hypertension (73.7%)	Ultrasound and kidney biopsy	Unknown	- Incidence (6.7%)	- 26.7%
Saudi	Edrees et al. [60]	Retrospective	12	(2 months – 13 years)	NR	NR	Mutational analysis	NR	NR	NR
Saudi	Patel et al. [36]	Cross-sectional	17	8.9 months** (1 day – 6 years)	- Bilateral abdominal mass (100.0%) - Hypertension (35.3%) - Hepatomegaly (70.6%) - Splenomegaly (5.9%) - Respiratory distress syndrome (23.5%)	- Liver cysts (5.9%) - Renal stone (5.9%) - Bilateral vesicoureteric reflux (5.9%) - Renal calcification (5.9%)	Not reported	3 (17.6%)	NR	NR

* Median age

** Mean age

Table 2: Genetic Analysis Findings of ARPKD Cases from MENA

Country	Chr	No. of patients	No of families	Zygosity	Gene	Coding mRNA variation	Amino acid variation	Coding	Type
Saudi	6	8	NR	Homozygous	*PKHD1*	c.4870C>T	p.(Arg1624Trp)	Ex32	Missense
	6	1	NR	Heterozygous	*PKHD1*	c.5725C>T	p.(Arg1909Trp)	Ex35	Missense
	6	1	NR	Heterozygous	*PKHD1*	c.2027C>G	p.(Pro676Arg)	Ex21	Missense
	6	1	NR	Heterozygous	*PKHD1*	c.1736C>T	p.(Thr579Met)	Ex19	Missense
	6	1	NR	Homozygous	*PKHD1*	c.10628T>G	p.(Leu3543Trp)	Ex61	Missense
Egypt	6	1	NR	Homozygous	*PKHD1*	c.3367G>A	p.(Gly1123Ser)	Ex30	Missense
Oman	6	NR	16	Homozygous	*PKHD1*	c.107C > T	p.(Thr36Met)	Ex3	Missense
	6	NR	5	Heterozygous	*PKHD1*	c.406A > G	p.(Thr136Ala)	Ex6	Missense
	6	NR	3	Heterozygous	*PKHD1*	c.4870C > T	p.(Arg1624Trp)	Ex32	Missense
	6	NR	1	Homozygous	*PKHD1*	c.4870C > T	p.(Arg1624Trp)	Ex32	Missense
	6	NR	1	Heterozygous	*PKHD1*	c.9370C > T	p.(His3124Tyr)	Ex58	Missense