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Review Article

Clinical Study on Autosomal Dominant Polycystic Kidney Disease among North Tunisians

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Abstract

Background: Autosomal Dominant Polycystic kidney disease (ADPKD) is the most frequent renal hereditary disease, most commonly revealed in adulthood. It is characterized by the development of multiple cysts in the kidney and many other extra-renal manifestations. We aim to determine the epidemiological, clinical, therapeutic and prognostic factors of ADPKD progression to end stage renal disease (ESRD) among our patients.

Methods: In a retrospective multicentric study, we reviewed the records of 569 patients with ADPKD, hospitalized in a nephrology department or followed at the outpatient department of university and regional hospitals covering the north and the center of the country, during the period (1969-2016). Epidemio-clinical, paraclinical, therapeutic and evolutive data were collected based on medical observations. Prognostic factors of renal survival were analyzed by multivariate analysis using the comparison of the survival rates by the log rank test.

Results: The mean age of patients was 48,54 ± 13,68 years, 14% were young adults (<40 years). There were 272 female patients and 297 male patients (sex-ratio M/F = 1.09). Thirty eight percent of patients were from the northest. A family history of ADPKD was found in 43.7 % of cases. Renal symptoms were dominated by lombalgia, renal failure, hypertension and hematuria in respectively 51.9%, 48.2%, 29.1% and 24.6%. The median serum creatinine level was 459 µmol/l (range : 47-2454), hypertension had preceded the onset of ADPKD in 28.8% of cases. Extra-renal manifestations consisted in liver cysts (43.5%), cardiac involvement (31.9%), cerebral aneurysms (12.9%) and gastro-intestinal involvement (9.4%). Urologic complications were observed in 54.6% of cases. ESRD occured in 43.1% after a mean follow-up of 47 months (range : 0-384). Risk factors of poor renal prognosis were: age >40 years (P=0.009), hematuria (P= 0.034), hemoglobine >14 g/dl (p=0.0013), high uricemia level (P=0.001) and leucocyturia (P=0.02). Age >40 years and leucocyturia were independant factors associated with poor renal survival. Death occured in 59 cases (10.3%) mostly caused by infectious complications (44.1%).

Conclusion: In our study, ADPKD was tardily diagnosed for most cases. We emphasize the importance of the family screening which will enable early detection and management of the complications associated with the ADPKD.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disorder characterized by the development of multiple cysts in the kidney and associated with various extrarenal complications with cystic and non cystic manifestations. It accounts for 5% to 10% of patients with end-stage renal disease, making it the fourth leading global cause of kidney failure [1,2]. The incidence rates for ESRD due to ADPKD vary between countries, ranging from 3.9 to 5.3 (in Europe) and from 4.8 (in Japan) to 7.9 (in USA) cases per million population per year [3]. According to the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA) registry data, 21 000 patients with ADPKD in 2010, were receiving renal replacement therapy [4]. Diagnosing the disease include family history of ADPKD, age of patient, and number of kidney cysts. We aim to evaluate the demographics, outcomes, and complications of ADPKD and to determine prognostic factors of ADPKD progression to ESRD.

MATERIALS AND METHODS

We conducted a retrospective multicentric study including patients with ADPKD hospitalized in a nephrology department and / or followed at the outpatient department of university hospitals and regional hospitals covering the north and the center of the country, between 1969 and 2016. Epidemio-clinical, paraclinical, therapeutic and evolutive data for all cases were compiled electronically into Excel program and analyzed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).The following clinical variables were evaluated: age, sex, geographic origin, family history of ADPKD, clinical presentation at diagnosis, extrarenal complications, ultrasonographic and computed tomography findings, treatment modalities, evolution of hypertension, renal function decline, urologic complications, end-stage renal disease, causes of death. Follow-up time and disease-free survival time were calculated, as were Kaplan–Meier estimates of renal survival. The Cox proportional hazards model was adjusted for time intervals, gender, treatment modalities,

and age at ESRD, with time since onset of ESRD as the underlying time scale. These results are presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI). HR <1 denotes a better survival rate, and HR >1 denotes a poorer survival rate. To compare the rates, we used the Fisher exact test and to compare durations and delays, we used student test. Comparison of renal survival according to different parameters was made by Log Rank test. We have also calculated the mortality rate. Statistical significance was defined as $P < 0.05$.

RESULTS

There were 569 patients with ADPKD representing residents of north and center of Tunisia in the 8 administrative counties shown in Figure (1). Sixty four percent of our patients were from northest Tunisia, 22.7% among them were from the capital, while 35.3 % were from the center of the country. The incidence of patients with ADPKD was estimated at 15.3 patients/ year. Age ranged from 8 to 85 (mean: 48,5) years. The distribution of patients by age at diagnosis showed that half were between 40 and 60 years of age. Fourteen percent of patients were young (<40 years). There were 297 male and 272 female patients, with a male-to-female ratio of 1.09. A family history for ADPKD was present in 249 of 569 cases (43.7%). Consanguinity of first, second and third degree was noted respectively in 26%,5%, and 5%, while 248 of 569 (64%) had no parental consanguinity. Kidney manifestations are presented in Table (1). They were dominated by palpable, bilateral flank masses in 66% of cases and hypertension in 58.8% of cases. The mean nage of onset of hypertension was 53±12.8 years. Two hundred and fourty-eight patients had extra-renal manifestations of ADPKD (Table 1), the most common of which was liver cysts in 213 patients (43.5%),

Table 1: Patients demographics and clinical characteristics.

Parameters	N	%
Age <30 years old	20	3.5
Age (40-60) years old	284	50
Female patients	271	47.6
Male patients	296	52
Family history of ADPKD	248	43.7
Familial survey of ADPKD	119	20.9
Clinical manifestations at diagnosis		
Lombalgia	296	51.9
Hematuria	140	24.6
Hypertension	321	58.8
Large kidneys at palpation	379	66
Urinary infection tract	27	4.7
Hepatomegaly	95	16.6
Gastro-intestinal involvement	47	9.5
Neurologic involvement	63	12.9
Cardiac murmur	35	7.9
Hernias	52	11.1
Laboratory findings		
Serum creatinine level (µmol/l)	459	-
Serum Urea level (mmol/l)	29.3	-
Proteinuria (g/24h)	0.32	-
Hemoglobine (g/dl)	10.26±2.98	-
Uricemia (mmol/l)	440 ± 153	-
Aseptic leucocyturia	82	46.3

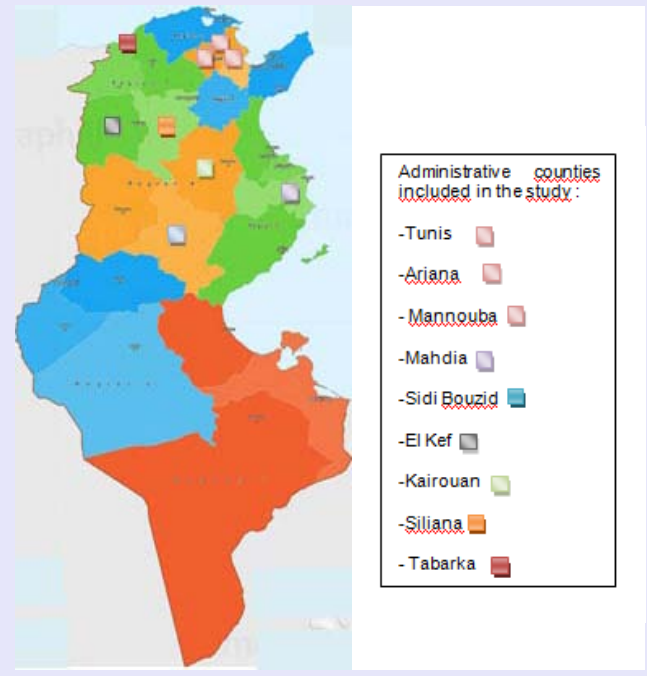

Figure 1 Contributing centres for nephrology and dialysis in northern and the center of Tunisia. To the left is the political algerian border, below is Lybia.

a nodular hepatomegaly was objectified only in 16.6% of cases. Cardiac involvement was revealed clinically by heart murmur in 7.9% of cases, but transthoracic echocardiography showed abnormalities in 105 cases (18.4%) consisting in hypertrophic cardiomyopathy (13.5%) and valvulopathies (28.2%) with respectively mitral , aortic and tricuspid insufficiency in 16.9%, 7.9% and 3.4%. Aneurysm of atrial septum was detected in two cases. Neurologic involvement (12.9%) consisted in headaches (30.1%), seizures (6.4%), strokes (49.2%), meningeal hemorrhage (3.2%) and coma (3.2%); cerebral aneurysms were found in 1.9% of cases. Gastro-intestinal involvement was observed in 9.5% of cases, commonly manifested by abdominal pain and diarrhea or/and constipation ; colic diverticulitis was found in 10 cases (1.75%), while hernias in 11% of cases. One hundred and ninety nine patients developed urologic complications (34.9%), the most frequent among them was urinary tract infection (24.4%) followed by nephrolithiasis (5%), intracystic hemorrhage (3.2%), and infected cysts (1.8%). The most common germs were *Escherichia Coli* (49.2%) and *Klebsiella Pneumonae* (16.4%). Laboratory findings are also summerized in Table (1). Renal failure was noted in 275 patients (48.2%), serum creatinine level ranged from 47 to 2454 µmol/l and serum nitrogen urea level ranged from 3.4 to 117 mmol/l. Normal renal function was noted in 142 patients (25%). Stage 1 to Stage 5 chronic kidney disease (CKD) was present respectively in 2, 5,11, 34 and 23%. Patients with initially stage 5 of CKD (n=131) were on dialysis (94.6%),

three patients underwent a preemptive kidney transplantation. Anemia was observed in 530 patients (93%) while polyglobulia was noted in 39 patients (8.8%), and hyperuricemia in 59% of cases (Figure 2). There was no proteinuria in 77% of cases. Nephrotic syndrome was found in 14 patients (2.4%), two among them were diabetic and one patient was diagnosed with amyloidosis. Angiotensin-converting enzyme inhibitors (ACEIs) were the most antihypertensive medications used in our patient (68%) followed by calcium channel blockers (CCB) in 42% of cases with a good control of blood pressure. The evolution of the renal function after a median follow-up of 47.1 months (range: 0-384), is illustrated in Table (2). A CKD was noted in patients with initially normal renal function in 36 cases (6.3%), after a median duration of one month (range :0-384). End stage renal disease (ESRD) was reached after a median duration of 25 months (range: 0-457) in 311 cases (54.6%). The mean age of hemodialysis onset was 54 ± 11,2 years old. Most of hemodialysis patients were men (62%). Death occured in 59 cases (10.9%) and was related to infectious, neurologic, metabolic, cardiovascular, and neoplasic in respectively 44.1, 10.2, 10.2, 6.7, 3.5% and it was not known in 25.3% of cases (Table 3). Many statistical correlations were found in our study. To begin, the incidence of hypertension in men was higher than in women (P=0.009), and the presence of a family history of hypertension is associated with a higher incidence of hypertension in our patients (P=0.02). Polykystic liver was more prevalent in young patients (age< 30 years) (P=0.002) and in women (P=0.006), and it is frequently associated with a bigger size of the kidneys (P=0.01).The mean renal survival was 152 ± 11months. In univariate analysis (Table 4), five risk factors of poor renal survival were determined: age >40 years (P=0.009), macroscopic hematuria (P=0.034), hyperuricemia (P<0.0016), leukocyturia (P=0.02) and hemoglobuline >14 g/dl (P=0.0013). In order to identify independent risk factors of progression of renal function, we conducted a multivariate analysis, that revealed 2 risk factors: Age> 40 years (HR: 3.4; P=0.009) and leukocyturia (HR:1.9 ; P=0.02) (Figure 3,4).

DISCUSSION

ADPKD is the most common hereditary kidney disease, with approximately half of patients experiencing ESRD by the age of 60 years [5]. It is caused by mutations in PKD1 in 85% of patients or in PKD2 in 15% of patients [6,7]. However, genetic study was not performed in our series. The prevalence of ADPKD in different countries was established. It is estimated at 1/2684 in England, 1/3058 in Germany, 1/1100 in France and 1/4033 in Japan [8-11]. There is a lack of statistical data on the prevalence of ADPKD in Tunisia and in Africa. In Tunisia, ADPKD is accounting for 6.9% patients who receive hemodialysis [12,13]. Unfortunately, a national register for ADPKD is not available in our country. In our sudy, the mean age at diagnosis of the disease was 48.5 years

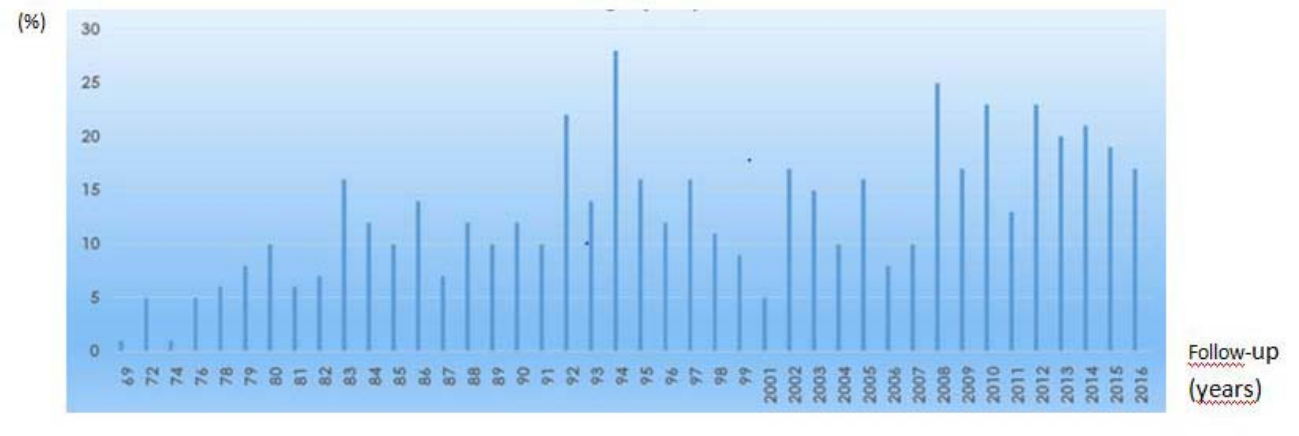

Figure 2 Incidence of ADPKD over the years.

Table 2: The evolution of renal function in ADPKD patients.

At initial presentation	N	%	At the end of the study	N	%
NRF	142	25	**NRF**	84	14.7
			CKD	22	3.8
			ESRD	36	6.3
Stage 1,2,3 CKD	100	17.5	**CKD**	66	11.5
			ESRD	44	7.3
Stage 4 CKD	194	34	**CKD**	94	16.5
			ESRD	100	17.5
Stage 5 CKD	131	23	**Total ESRD**	311	54.6

Abbreviations: N: Number; CKD: Chronic Kidney Disease; ESRD: End Stage of Renal Disease; NRF: Normal Renal Function

Table 3: Outcome of ADPKD patients.			
		N	%
ESRD		311	54.6
Dialysis	PD	28	5
	HD	270	47.4
RT		13	22.8
Complications			
Infectious C.		250	43
Metabolic C.		242	42.5
Cardio-vascular C.		140	24.6
Neurologic C.		18	3.1
Néoplasic C.		20	0.8
Out of sight		65	11.4
Death		59	10.3
Abbreviations: ESRD: End Stage Renal Disease; PD: Peritoneal Dialysis; HD: Hemodialysis; C.: Complications			

Table 4: Risk factors of progression to ESRD in ADPKD patients in univariate analysis.				
Parameters	N	% non ESRD	% ESRD	(P)
Age > 40 years	508	32.05	67.95	**0.009**
sex	508	32.05	67.95	0.43
Family history of ADPKD	481	33.06	66.94	0.19
Hypertension	506	31.42	68.58	0.5
Liver cysts	424	31.42	69.58	0.7
Neurologic symptoms	436	31.42	68.58	0.1
Macroscopic hematuria	428	34.35	65.65	**0.034**
Urinary lithiasis	411	31.9	69.10	0.056
Urinary tract infection	406	32.51	67.49	0.5
Hemoglobin >14 g/dl	486	31.89	68.11	**0.0013**
Hyperuricemia	430	33.28	64.72	**< 0.0016**
Proteinuria >0.5 g/24h	320	29.06	70.94	0.058
leukocyturia	354	32.2	67.8	**0.02**

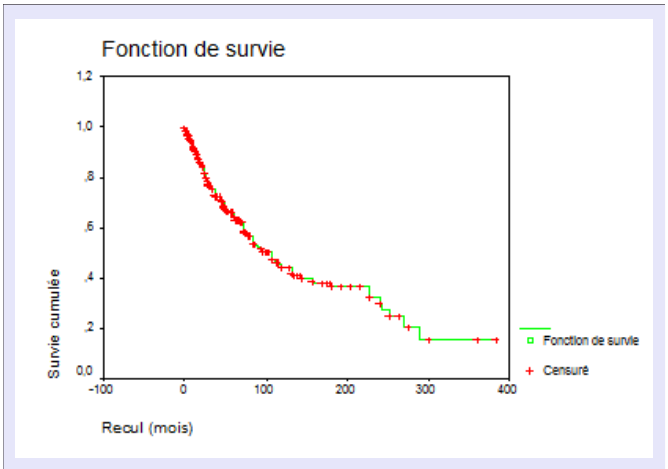

Figure 3 Kaplan-Meier renal survival curve.

while in other series, varied between 21 and 46 years old [14,15]. This could be attributed to the delay of diagnosis of ADPKD in our country. However, we should mention that, although an increasing number of patients with ADPKD reached ESRD in Tunisia, their age at onset of ESRD also increased significantly throughout the period. Family history of ADPKD was found only in 43.7 of our population which was less than in other series [14,15]. It was reported that, ADPKD is slightly more severe in males than in females, but the difference is not statistically significant and that symptoms generally increase with age [16,17]. Hypertension occurs in more than 60% of patients with ADPKD before even a significative loss in renal function, with an average age of onset of 30 years [3]. In our series, it accounted for 58.8% of patients with a mean nage of onset at 53 years. There are multifactorial reasons, but the most essential cause is the activation of renin-angiotensin aldosterone system [18]. The enlargements of renal

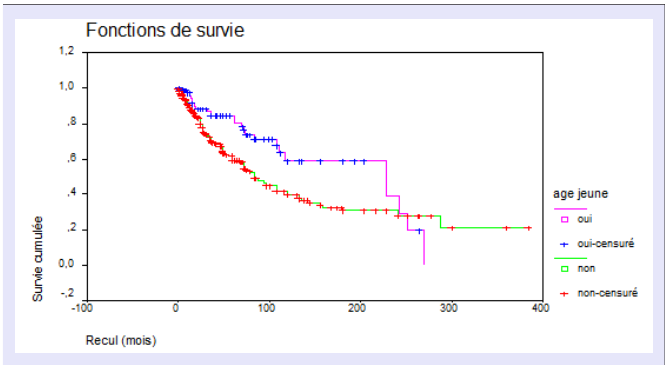

Figure 4 Young age (<40 years) as an idependant risk factor of ESRD (P=0.009).

cysts have been associated as well, with renin-angiotensin system stimulation. A prospective study found a significant reduction in left ventricular mass index in hypertensive ADPKD patients after blood pressure control <120/80 mmHg [19]. Another study, showed that proteinuria decreased significantly only on treatment with ACEIs, when compared with treatment with CCB [20]. Thus, it seems that with ACEIs, more patients reached BP control [21], which may influence the age of onset of ESRD [22]. This finding was concordant with our results. Given that ADPKD is a systemic disease, hepatic cysts, cerebral aneurysms, and cardiac valvular abnormalities were well described in literature [23,24]. In our, series ADPKD was associated with liver cysts in 43.5%, while valvular abnormalities and cerebran aneurysms were observed only in respectively 28.2 and 1.9%. Biological signs of ADPKD were dominated by the prevalence renal failure and hyperuricemia. The most frequent sign that revealed the disease in our study was renal failure (48.2%), which was a higher rate comparing with other studies [14,15,25]. This may be due to the delay of diagnosis and mostly to a selection bias, giving that all patients were admitted in a nephrology departement or seen by a nephrologue. The prevalence of hyperuricemia increases with the decline of renal function [26]. Our study confirmed that high levels of uricemia, were associated with an increased risk of progression to the ESRD (P<0.0001). However polygolubulia was noted only in 8.8% of cases in our study. This may be explained by the hight prevalence of the later stages of CKD, as a result of uraemia. The diagnostic of ADPKD relies essentially on imaging (Figure 5). Ultrasonography is the gold standard imaging modality, given its availability, safety, and low cost. Typical imaging findings reveal large kidneys with multiple bilateral cysts [27]. In our series, abdominal echography and computed tomography allowed sceening for the disease in respectively 64 and 21%. In patients with ADPKD, pharmacologic therapy include controlling of blood pressure, abnormalities related to renal failure, urologic comlications and braking kidney cysts enlargement. But one of the limitations of treating early stages of ADPKD in our country was the unavailability of tolvaptan. Tolvaptan demonstrated its effectiveness in slowing disease predression to ESRD [28]. However, it is indicated only in patients with age <50 years old, stage 1 to 3A of CKD and with a rapid progression of renal failure [29]. Cardiovascular pathology and infectious complications account for approximately 90% of deaths of ADPKD patients [30,31]. Another cause of mortality in ADPKD is subarachnoid hemorrhage from intracranial aneurysms [32], which were rare and severe. Our results were concordant with those reports. These reports agree well with our results. In literature, the major factors predicting CKD progression in ADPKD were genotype, younger age, male sex, black race, initial renal function, and total kidney volume [27,33-35]. Several cohort studies demonstrated that genotype can predict the age of onset of ESRD [36,37], which was not studied in this analysis. Strinkingly, older age was identified as a predictive factor of renal failure progression. This finding can be explained by the fact that, the majority of our patients were diagnosed tardily, at an advanced age. Not all studies could show that male gender was in fact a risk factor of progression [38,39] and neither in our series. In another hand, the lower incidence rate of female patients with onset of ESRD could reflect better predialysis survival. However, one of the limitations of this study was the lack of survival data on all patients with ADPKD before onset of ESRD. Therefore, the association between predialysis mortality rate in female patients and lower ESRD remains unclear. Risk factors of severe renal disease included as well, hypertension, proteinuria >1 g/d, hematuria [34], and left ventricular hypertrophy. In our study, hypertension did not seemed to be correlated to a poorer renal survival. However, treatment with either an ACEI or angiotensin receptor blocker seemed to be more effective in the control of blood pressure in our population ; although this finding has not been clearly demonstrated [40,41]. Since echocardiography was not performed in all of our patients, left vantricular hypertrophy was not studied in this context. Proteinuria was not significantly associated with poor renal survival in our series, while hematuria, lecocyturia and hyperuricemia have been indeed, predictive factors of progression of CKD.

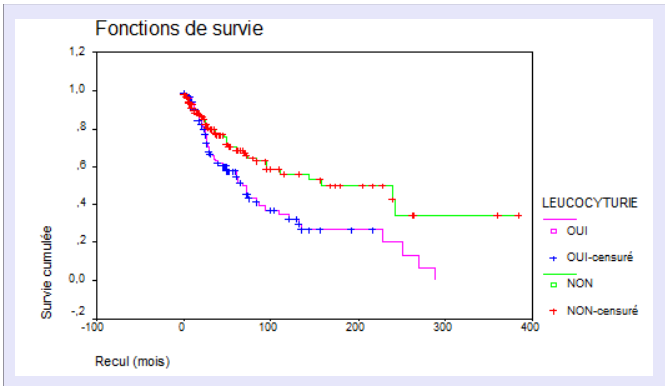

Figure 5 Leukocyturia as an independant risk factor of ESRD (P=0.02).

CONCLUSION

In our study, ADPKD was diagnosed in most of cases at the stage of renal failure. Therefore, we emphasize the importance of the family screening, for early detection and treatment of complications associated with ADPKD and for assessment of antihypertensive medications and renal replacement therapy needed in our country. Tolvaptan has been approved to slow the progression of ADPKD ; we hope that our patients will benefit from its prescription in the years to come. A national multicentric study is necessay for determination of the current prevalence of ADPKD in Tunisia, the geographic distribution and possible areas of predilection for ADPKD.

DECLARATIONS

-Competing interests: The authors declare that they have no competing interests.

-Funding: This study was not funded.

-Authors' contributions: SB and MH analyzed and interpreted the patient data. BZ performed the statistical analysis, and provided the survival curves. MH have written the manuscript. All authors contributed to the medical care of the patients. All authors contributed to the fulfillment of this work. All authors read and approved the final manuscript.

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Collaborating authors names (appendix).

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