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Epidemiological profile and perception of patients on chronic hemodialysis through a Moroccan prospective cohort study

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ABSTRACT

Introduction: End-stage kidney disease (ESKD) is a major global public health problem. Knowledge of its epidemiology is crucial for its prevention and the optimal care.

Objectives: The objective was to study the epidemiological characteristics of patients on chronic hemodialysis, their outcomes and explore their perceptions of therapeutic modalities, through a prospective cohort.

Patients and Methods: A prospective study conducted between February 2019 and January 2020, at two public hemodialysis centers in Oujda, Morocco.

Results: Around 183 patients were enrolled. The mean age was 53±17 years. The initial nephropathy was undetermined in 37% of cases and dominated by diabetes in 25.7%. About 43% of patients had pre-dialytic nephrology follow-up. Only 32% patients initiated their hemodialysis by an arterial-venous fistula (AVF). The mean hemoglobin rate was 10.3±1.8 g/dL. Moreover, 74 % of patients were under erythropoietin. Serum calcium, phosphorus, vitamin D, and parathormone were within target ranges in 67%, 52%, 61%, and 51% of cases, respectively. Since, 80% of patients were not clearly informed about therapeutic modalities. The majority of patients opted for kidney transplantation (KT), with two major constraints preventing its realization, consisting the lack of related living donors and financial resources. Besides, 29% of patients were hospitalized for cardiovascular and infectious causes during the study year. The survival rate at 1 and 5 years after the start of dialysis was 97.2% and 95% respectively.

Conclusion: Early detection of chronic kidney diseases in high-risk people, their rigorous follow-up and early referral to the nephrologist would improve the quality of care. The promotion of KT and PD would better meet the hemodialysis patients' needs with better outcomes and lower costs.

Implication for health policy/practice/research/medical education:

This study will help to better understand the epidemiological profile of patients with end-stage kidney disease (ESKD) in our Moroccan region, and therefore to better meet their current and future needs and thus provide a more rational way, a sufficient and adequate supply of care in terms of infrastructure, human resources, and specific therapeutic methods.

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Introduction

Chronic kidney disease (CKD) and its corollary end-stage kidney disease (ESKD) are continually increasing around the world, and especially in developing countries (1-4). Thus, ESKD is a major global public health problem. It is associated with considerable morbidity

and mortality. Currently, it is estimated that about 850 million people worldwide present some type of kidney disorder; in 2030, approximately 5.4 million people could be under a form of renal replacement therapy (RRT) for the treatment of kidney failure (5). Because of the high cost of its management, it represents a heavy burden for

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patients, their families, and society (1–3). It is, therefore, a great challenge for the health systems of all countries, particularly in emerging countries characterized not only by the scarcity of resources but also paradoxically a growing demand for care along with limited and inequitable access to care (1,6–8). In Morocco, despite enormous investments and notable progress in the area of prevention and management of ESKD, its prevalence is increasingly rising. In 2004, the prevalence of treated ESKD was estimated at 162 mph according to the first data from the Magrédial register [Morocco Graft Dialysis], and rose from 197,8 mph in 2008, to between 433 to 759 mph in 2018 (4,6). To effectively manage this burdensome pathology, it is primordial to have access to current data on this patient population, allowing an accurate understanding of its epidemiological characteristics, a crucial step toward adequately responding to the existing demand for care and plan for future needs, through quality treatment and better cost-effectiveness. Hemodialysis remains the most used treatment method. It is nevertheless imperative to develop other treatment options such as kidney transplantation (KT) and peritoneal dialysis (PD), poorly developed in Morocco, in synergy with the preferences of patients suffering from ESKD and the medical indications of each method.

Objectives

The objective of our study was to determine the epidemiological profile of patients presenting ESKD on chronic hemodialysis (CHD), explore patients' perceptions of RRT, and determine patient outcomes during the study year through a prospective cohort.

Patients and Methods

Study design

This was a transversal, bicentric, prospective, descriptive, and analytic study conducted at two public hemodialysis centers established in the prefecture of Oujda (eastern region of Morocco): HASSAN II Center of Hemodialysis and Chronic Diseases, and the Al Farabi hemodialysis center. The study was conducted from February 2019 to January 2020.

Included were all patients with ESKD under CHD at the two centers. Thus, we included ongoing CHD patients from before the study year (ongoing cases), and new CHD patients of the study year (new cases). We excluded patients treated with hemodialysis for acute kidney failure and ESKD patients who had been under hemodialysis temporarily at the center during the study year.

The parameters studied were sociodemographic, clinical, biological, therapeutic, and evolutionary. The sociodemographic data were age, gender, place of residence and socioeconomic condition. Clinical data

were obtained as; initial nephropathy, antecedents and associated comorbidities, duration of dialysis, the vascular access route, and pre-dialysis nephrology follow-up. For this last parameter, we defined a patient with previous nephrology follow-up as having had a minimum of three months of follow-up before initiation of dialysis. The information received by patients about different RRT modalities before starting dialysis, as well as their choices between them (KT, hemodialysis, and PD), were also evaluated. The biological parameters studied were the levels of hemoglobin, ferritin, serum calcium, phosphorous, parathormone, and vitamin D. We also evaluated the evolution of the patients during the study year (mortality, hospitalization, transfer from one RRT modality to another). The laboratory report corresponds to the last one done for each patient and the treatment is the last medication prescribed during the study year.

As a data collection tool during our study, we used the files of the register MAGREDIAL [Morocco Graft Dialysis]. This is a register established by the ministry of health in partnership with the biomedicine agency and the Moroccan nephrology society in 2004, and which is not currently functional despite attempts to revive it. Our study made use of the initial statement, to which were added certain supplementary information (relating particularly to the pre-dialysis nephrology follow-up of the patient, his/her awareness of RRT methods and treatment preferences, the last lab work-up, and the last treatment prescribed).

All data collection was carried out through examination of the patients' medical files and interviews with the patients and their families, as well as with health professionals practicing at the hemodialysis centers, i.e., the treating physicians and the paramedical personnel.

Statistical analysis

All statistical analyses were conducted using the software SPSS version 25. Quantitative variables were described using means and standard deviation (SD), or medians as needed. Qualitative variables were described using proportions and percentages. For the comparison of groups, we used the Student's *t* test for the means, and the chi-square (χ^2) test or the Fisher's exact test when necessary, for frequencies. A *P* value < 0.05 was considered significant.

Results

During the study year, 183 patients were treated by CHD at two centers, of whom 34 patients were newly recruited and treated (18.58% of all cases treated). The mean age of the patients was 52.9±17 years with extremes of 11 and 85 years, and a slight male predominance (57.4%). The male/female sex ratio was 1.34. Physical autonomy was reduced

in 19% of cases. Most of our patients (93%) were of low socioeconomic level, and 91.3% came from an urban milieu. About 58% of patients had not been followed by a nephrologist before their initial dialysis and 80% of patients were not clearly informed about the different kidney replacement methods before initiation of RRT (PD, hemodialysis and KT). The initial nephropathy in our patients was diabetic in 25.7% of cases, hypertensive, and polycystic kidney disease (PKD) in 7.7% and 9.8% of cases, respectively. It remained undetermined in 37% of cases. The predominant comorbidities were hypertensive and diabetes in the respective proportions of 35% and 26% of cases. However, we noted the absence of associated comorbidities in nearly a quarter of patients (24.3%). Moreover, 9.3% of patients were tobacco users. Parathyroidectomy had been conducted in 4.4% of patients. About 20.8% had a history of red blood cell transfusion. Only 32% of our patients started their dialysis with access achieved via an arterial-venous fistula (AVF); in contrast, this vascular access modality is currently used in 86% of all cases, and in 93.5% of the ongoing cases. The duration of dialysis varied between the extremes of one month and 27 years, with a median of 54 [18-108] months. Concerning biological characteristics, our patients had a mean hemoglobin level of 10.3 ± 1.8 g/dL. Additionally, 53% of cases had a hemoglobin level of >10 g/dL and 31.7% had hemoglobin >11 g/dL. Around, 44.3% of cases had a ferritin level between 200 and 500 ng/mL with a median of 379 ng/mL [239-573]. The patients' mean calcium level was 89.8 ± 9.6 mg/L with normal calcium in 67% of cases. Phosphorous levels were within the normal range in 52% of cases with a mean of 44.6 ± 15 mg/L. Vitamin D levels were normal in 61% of cases, and parathormone (PTH) was normal in 51% of patients. Erythropoietin (EPO) was administered in 74% of cases and intravenous iron in 62% of cases. When interviewed during the study year about the information they had received on the different modalities of kidney replacement (PD, HD and KT) before initiation of dialysis, 80% of CHD patients were not clearly informed. As for their perception of these three methods, 151 patients (83%) had opted for KT. These patients had expressed two main concerns impeding the realization of KT: non-availability of a potential living related donor, and lack of financial resources. Accordingly, 27 patients chose to remain on CHD. Two patients wished to benefit from PD. Tables 1 and 2 reports all demographics, clinical and biological data of 183 patients.

During this study year, 29% of patients were hospitalized for reasons that were essentially cardiovascular, infectious, or digestive. Transfer to KT was recorded concerning four patients (2.2%); PD was not performed on any patient. Furthermore, 13 patients died during the year (7.1% of

cases). The causes of death were markedly cardiovascular and tumor-related conditions. The time from the start date of dialysis to the date of death varied between one and 268 months with a median of 21 [5.5-130.5] months. Table 3 reports all evolution data of 183 patients.

Discussion

In our study, the mean age was relatively young, in contrast with the more advanced ages observed in North America, Japan, and Europe (9). The most affected age group was between 45 and 64 years and the same result had been reported earlier in Oman (10). Male subjects were more frequently affected, in agreement with previous work (11,12). However, a female predominance was reported in some studies conducted in Cayman Islands (13). In our cohort, diabetic nephropathy was the direct cause of ESKD in 26% of patients. It was reported in the same proportions in Saudi Arabia but at higher proportions in earlier studies conducted in the countries of the gulf cooperation council (GCC) (60% in Kuwait, 50% in Qatar), in North America and Japan (9,14). In our study, AHT was an underlying cause of ESKD in lesser proportions (7.7%), while it accounted for 21% in Jordan and 31% of cases in the GCC countries (48% in Bahrain) (9). PKD was causal in 9.8% of our patients, as it was for 6% and 8% of cases in Algeria and Tunisia (6). In Dubai, PKD was only 2.43% among all causes (15).

In addition to their considerable contribution to ESKD, diabetes and hypertension are the main associated comorbidities in our patients. This observation is not specific to our country; indeed, hypertensive comorbidity is very frequent in other countries, but in much higher proportions, especially in Peru (95%) and the GCC countries (92%) (16,17). The same is true for the preponderance of diabetes in other countries such as the GCC countries, with (71%) of cases in Bahrain, (69%) in Kuwait and (66%) in Qatar (17). In Morocco, the prevalence of these two burdensome pathologies is disturbing. According to the results of the national survey "Stepwise 2017-2018", the prevalence of diabetes and hypertension in adults aged 18 and over is respectively 10.6% and 29.3% compared with 6.6% and 33.6% in adults aged 20 and over in 2000 (18,19). These alarming results underline the urgency of the need to multiply efforts to prevent the avoidable risk factors of kidney diseases, in this case, diabetes and hypertension, to avoid or at least slow down the progression of CKD toward onerous and costly complications, particularly ESKD. The underlying etiologies remained undetermined in 37% of cases. Prognosis and treatment of CKD are highly dependent on their identification (2). In emerging countries, where access to diagnostic methods, including biopsy, is limited or unavailable, the underlying pathologies of

Table 1. Sociodemographic and clinical data of patients on chronic hemodialysis

Parameters	Ongoing patients (n= 149) No. (%)	New patients (n= 34) No. (%)	All patients (N= 183) No. (%)	P value
Median age (y)*	52.3±17	55.8±13	52.9±17	0.556
Male gender	83 (56)	22 (65)	105 (57.4)	0.223
Physical autonomy (yes)	123 (84)	26 (79)	149 (81.4)	0.328
Pre-dialysis nephrology follow-up	61 (41.4)	15 (45.5)	76 (42.7)	
Initial nephropathy				
Undetermined	60 (40.3)	7 (20.5)	67 (36.6)	0.023
Diabetic	34 (23)	13(38.5)	47 (25.7)	0.054
AHT	12 (8.1)	2 (5.9)	14 (7.7)	0.498
PKD	13(8.8)	5 (14.7)	18 (9.8)	0.223
Other	30 (20.2)	7 (20.6)	37 (20.2)	0.558
Comorbidities				
Diabetes	34 (22.8)	15 (44.2)	49 (26)	0.013
AHT	58 (38.9)	14 (41.2)	72 (35)	0.489
Cardiovascular pathologies	40 (26.9)	9 (26.5)	49 (26)	0.567
Tobacco use	15 (10.1)	2 (5.9)	17 (9.3)	0.362
Parathyroidectomy	8 (5.4)	0 (00)	8 (4.4)	0.186
Red blood cell transfusion	27 (18.1)	11 (32.4)	38 (20.8)	0.021
1 st vascular access (AVF)	49 (34)	9 (26.5)	58 (32)	0.673
Current vascular access (AVF)	139 (93.5)	18 (53)	157 (86)	<0.001
Duration of dialysis (months)**	72 (40-139.5)	8 (4.9-12)	54 (18-108)	
Previous information on RRT (No)	120 (82)	24 (73)	144 (78.7)	0.179
Choice of modalities of RRT				
Kidney transplantation	128 (84.8)	23 (15.2)	151 (82.5)	0.020
Hemodialysis	19 (70.4)	8 (29.6)	27 (14.8)	
Peritoneal dialysis	0 (00)	1 (100)	1 (0.5)	
Number of sessions/week				
Duration of sessions (h)*	4.09±0.25	3.96±0.58	4.06±0.34	0.004
Frequency of 3 sessions/week	116 (78)	11 (33)	127 (70)	0.000
Weekly duration ≥12 h	114 (76.5)	9 (27.3)	124 (68)	0.181
4 hours or more per session	147 (98.6)	28 (84.8)	175 (95.6)	0.001
Body mass index (kg/m ²)*	23.47±4.94	24.30±3.88	23.6±4.8	0.608
Dry weight (kg)*	62.3±14.7	65.6±13.2	63.0±14.5	0.242

AHT: Arterial hypertension, AVF: Arteriovenous fistula, PKD: Polycystic disease, KRT: Renal replacement therapy

* Variables expressed as mean ± standard deviation

** Variables expressed as median (quartiles).

CKD generally remain unknown (2). This may be due to delayed referral to the nephrologist. Patients presenting CKD usually do not go to the hospital until after the onset of severe symptoms of uremia. At that point, it is difficult to determine the primary cause of ESKD due to the risks of kidney biopsy, difficult to perform at an advanced stage of CKD (20). This situation calls for deciders to increase their efforts to sensitize people at risk and to set up diagnostic and screening facilities appropriate to kidney disease. This problem of delayed referral to nephrologists is recurrent and has already been described elsewhere (21).

In our study, only 43% of our patients were followed by a nephrologist at the pre-terminal stage, which explains the presence of comorbidities and low level of AVF confection at the initiation of HD (only 32% of patients initiated HD with an AVF, same result was described in the United States (22)). This underlines the crucial role of early and opportune referral of kidney disease patients to nephrologists for optimal comprehensive care. Early nephrology referral was significantly associated with reduced mortality, hospitalization, anemia and better dialysis preparation including early placement of dialysis

Table 2. Biological data of patients on chronic hemodialysis

Parameters	Ongoing patients (n= 149)	New patients (n= 34)	All patients (N= 183)	P value
	No. (%)	No. (%)	No. (%)	
Hemoglobin (g/dL)*	10.3±1.7	10±1.9	10.3±1.8	0.173
>10	79 (55)	14 (44)	93 (52.8)	
Ferritin (ng/mL)**	411 (248-596,5)	263 (136-401)	379 (239-573)	0.069
<200	24 (16.9)	9 (31)	33 (18)	
200-500	66 (46.5)	15 (51.7)	81 (44.3)	
>500	52 (36.6)	5 (17.3)	57 (31.1)	
Parathormone (pg/mL)**	307 (143-500)	198.5 (122-257)	266 (139-460)	0.062
< 83.5 (<2 time the normal value)	19 (13.5)	4 (13.8)	23 (13.5)	
83.5-376 (2 to 9 the normal value)	67 (47)	20 (69)	87 (50.9)	
>376 (>9 time the normal value)	56 (39.5)	5 (17.2)	61 (35.7)	
Calcium (mg/L)*	90.8±9.5	84.9±8.4	89.8±9.6	0.043
<84	30 (21.5)	13 (42)	43 (25)	
84-102	98 (69.5)	17 (55)	115 (66.9)	
>102	13 (9.2)	1 (3.2)	14 (8.1)	
Phosphorous (mg/L) *	44±15.6	47.6±11.6	44.6±15	0.118
<23	13 (9.2)	0 (0)	13 (7.7)	
23-47	75 (53.2)	13 (46.5)	88 (52.1)	
>47	53 (37.6)	15 (53.6)	68 (40.2)	
Vitamin D (ng/mL)*	36.1±13.5	25.2±15.0	34.4±14	0.002
<10	3 (2.1)	4 (14.3)	7 (4.1)	
10-30	44 (31)	14 (50)	58 (34.1)	
30-70	93 (65.5)	10 (35.7)	103 (60.6)	
>70	2 (1.4)	0 (0)	2 (1.2)	

* Variables expressed as mean ± standard deviation

** Variables expressed as median (quartiles).

Table 3. Evolution of patients including transfer, hospitalization, and death

Parameters	Ongoing patients (n= 149)	New patients (n= 34)	All patients (N= 183)	P value
	No. (%)	No. (%)	No. (%)	
Hospitalization during the study year	42 (23.1)	11 (32.4)	53 (29.1)	0.802
Causes of hospitalization				
Infectious	6 (14.3)	5 (45.5)	11 (20.7)	0.034
Cardiovascular	11 (26.2)	5 (45.5)	16 (30.2)	0.154
Hematologic	4 (9.6)	1 (9.1)	5 (2.8)	0.649
Digestive	7 (16.7)	1 (9.1)	8 (9.5)	0.540
Other	13 (31)	1 (9.1)	14 (26.5)	0.222
Transfer between KR modalities				0.436
HD to KT	4 (2.7)	0	4 (2.2)	
HD to PD	0	0	0	
Mortality	10 (6.7)	3 (8.8)	13 (7.1)	0.448
In hospital	8 (5.4)	3 (5.8)	11 (84.6)	
At home	2 (1.3)	0 (0)	2 (15.4)	
Median time between death-start of dialysis			21 (5.5-130.5)	
Causes of death				
Cardiovascular	5 (50)	0	5 (38.5)	
Neoplastic disease	3 (30)	1 (33.4)	4 (30.8)	
Hyperkalemia	1 (10)	0	1 (7.7)	
Other	1 (10)	2 (66.6)	3 (23.1)	

HD, Hemodialysis; KT, kidney transplantation; PD, Peritoneal dialysis.

access (23). Such timely care is enhanced by allowing for the patient to be well prepared through being actively involved in decision making and clearly informed about his/her kidney disease and the choice of RRT. Concerning these last two parameters, we noticed that unfortunately, About 80% of our patients were not well-informed about the different therapeutic options before initiation of HD. This may be explained by the fact that most patients are started on dialysis in emergency circumstances and HD is the only method used in an emergency for the adult in our context; this creates a link between the patient and HD. Nevertheless, about 83% of patients had opted for KT and had expressed two main concerns that hindered its realization: the unavailability of a family donor and financial constraints. Only two patients wanted to use PD. Thus, KT remains the preferred option for most CHD patients. It offers better results in terms of improved duration and quality of life and is less costly (24). This means positive financial repercussions not only for the patient but also for the durability of the health system, given its cost-effectiveness benefit. Despite these advantages, not many KT are performed in Morocco, and most of those use living donors. In 2019, only 558 cases received transplants. In our cohort, only 4 patients benefited from a KT. Thus, the establishment of a solid organ harvesting program in case of donor brain death, waiver of fees as well as the costs of immunosuppressive drugs for disadvantaged patients could all help to better meet the real needs of patients in ESKD. This is all the more achievable, given the ongoing generalization of universal medical insurance coverage in our country. As for PD, it is rarely used in Morocco, contrary to some countries that show high percentages of patients on PD, thanks to motivating health policies (Hong Kong, where PD is the most used in the world, and China (25). Similarly, autodialysis is not practiced these days despite its many advantages (26). Thus, for appropriate patients, these two options could provide other alternatives to CHD with greater autonomy, flexibility, and lower cost. Our patients underwent dialysis sessions with a mean duration of 243.6 ± 20.4 minutes at a rhythm of 3 sessions per week in 70% of cases, with a weekly duration of 12 hours or more in 68%. It is slightly longer than that recorded in the USA and Middle East (25,27). The longest weekly durations of dialysis were recorded in Australia, New Zealand (27). Data published these past years have shown that the survival of dialyzed patients is strongly associated with the dose duration of dialysis delivered (28). There is an association between a longer dialysis session length and better survival and fewer hospitalizations among hemodialysis patient (27). Currently, a rhythm of three dialysis sessions of 4-5 hours per week is considered the world standard (25).

Biologically, the mean level of hemoglobin was 10.3 ± 1.8 , a level of >10 g/dL in 53% of cases and >11 g/dL in 31% despite EPO and injectable iron was administered respectively to 74% and 62.5% of cases. In the GCC countries, the mean hemoglobin exceeded 10 g/dL but more than 90% of patients were treated with EPO in the GCC, in Malaysia, in Canada, and the UK (25). Following KDIGO guidelines, conformity with recommended ranges was 52.1%, 67%, and 51% for phosphorous, calcium, and PTH levels, respectively. Hyperparathyroidism was found in 36% of cases and hypoparathyroidism in 13.5%. The mean vitamin D level was 34.4 ± 14 ng/mL with recommended levels in 61% of patients. The survival rate at 1 and 5 years after the start of dialysis was 97.2%, and 95% respectively. Thirteen patients died during the study year. Cardiovascular and neoplastic pathologies were the main causes of death. In Oman, the average mortality rate among the hemodialysis patients is 10% annually (29). the highest mortality rate among prevalent HD patients, was reported in Belgium, Sweden, and the US (approximately 20 deaths per 100 patient-years) (30). The contribution of cardiovascular disease to deaths in HD patients has already been reported (12,14,29). In CCG, the most common cause of death was cardiovascular disease (37%) and sepsis (19%) (12). In Latin America, infections and neoplastic diseases represent respectively, 13 and 6% of the causes of deaths (31). Thus, the diagnosis and treatment of comorbidities and regular monitoring of the different parameters in the CHD patient would make it possible to reduce both morbidity and mortality in the short and long term. In our study, 29% of patients were hospitalized for reasons that were essentially cardiovascular, infectious, or digestive. In a GCC study, it was reported that the main cause of hospitalization was cardiovascular disorders, followed by problems related to vascular access, while ischemic cardiac disorders led to 19% of total hospitalizations (14).

Conclusion

Our study showed that ESKD is common in young adults, its etiology is dominated by diabetic nephropathy; but remains undetermined in more than a third of cases. The most common comorbidities are diabetes and hypertension. Pre-dialytic follow-up, initiation of HD by AVF and informed patient information on RRT; remain insufficient. Despite the constraints, KT remains the preferred method in hemodialysis patients. These findings highlight the importance of strengthening the early detection of kidney disease in high-risk groups, rigorous monitoring of CKD with patient involvement in his own management and therapeutic choice, in order to delay progression to ESKD. Our study is certainly a contribution to the epidemiology of ESKD at the local

and regional levels. It has presented a more or less precise epidemiological profile of ESKD at the local level (study sites), CHD patients' perceptions of the different RRT, patient outcomes, as well as their transfers between the different RRT, but other wider studies are needed. Thus, the revival of the MAGREDIAL register at the national level involving all the sectors (public, private, and non-profit) has become an absolute necessity. This would make it possible to better understand the current status of ESKD in Morocco and its risk factors, which would facilitate the implementation of appropriate preventive actions and the development of other alternatives to CHD (KT and PD) that offer better results to eligible patients.

Limitations of the study

Our study had some limitations, notably: the small sample size, incompleteness of some data (biological), and the advent of the COVID-19 pandemic which hampered access to and examination of some files.

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Authors' contribution

Conceptualization: MR and YB.

Methodology: MR and YB.

Resources: MR and YB.

Data curation: MR and YB.

Validation: MR, YB, SB, FZB, HB and NA.

Formal analysis: MR, YB and NA.

Investigation: MR.

Visualization: MR.

Writing-original draft: MR.

Writing-review and editing: MR, YB, SB, FZB, HB and NA.

Supervision: YB.

Project administration: YB.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Our study was approved by the Ethics Committee under N°08/2018. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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