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Original Article

Antibiotic susceptibility pattern of ESBLs-producing uropathogens in kidney transplant recipients in northern Iran

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Abstract

Background: Due to the increasing global prevalence of extended-spectrum beta-lactamase (ESBL)-producing uropathogenic strains, ongoing surveillance is required to monitor drug-resistant organisms causing urinary tract infections (UTIs) in kidney transplant recipients (KTRs). This study aimed to evaluate the antibiotic resistance profiles of uropathogenic isolates in KTRs with UTIs caused by ESBL-producing strains.

Methods: A total of 96 urine samples collected from KTRs were cultured on selective media and analyzed using phenotypic characterization and PCR methods. Antibiotic resistance patterns among uropathogenic isolates were evaluated using the disk diffusion and E-test methods. Data were analyzed using SPSS Version 21, and the level of significance was set at 0.05.

Results: Among the 26 uropathogenic isolates, uropathogenic *Escherichia coli* (UPEC) was the most prevalent (15, 57.7%), followed by *Klebsiella pneumoniae* (10, 38.5%) and *Enterococcus faecalis* (1, 3.8%). The rate of ESBL-producing isolates was 72% among UPEC and *K. pneumoniae* isolates. Antibiotic susceptibility testing revealed that ESBL-producing uropathogens exhibited significantly higher resistance rates ($p < 0.05$) than non-ESBL-producing strains to cefuroxime, cefepime, trimethoprim–sulfamethoxazole, ciprofloxacin, and levofloxacin. *E. faecalis* showed susceptibility to vancomycin, penicillin, and ampicillin and resistance to ciprofloxacin and levofloxacin.

Conclusion: The rate of ESBL-related UTIs among KTRs was notable in this study. Based on the in vitro results, fosfomycin appears to be a promising oral therapeutic option for UTIs caused by ESBL-producing uropathogens in KTRs in the study region. In addition, the high prevalence of ESBL-producing isolates underscores the potential value of targeted prophylactic strategies for high-risk patients.

Keywords: Urinary tract infections, Kidney transplant recipient, ESBLs, Uropathogen.

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Complications of bacterial urinary tract infections (UTIs) among kidney transplant recipients (KTRs) during the initial post-transplant year are associated with an increased risk of chronic functional impairment, graft lost, morbidity, and mortality (1). Infectious complications remain a major threat to successful outcomes after transplantation. Among post-kidney transplant infections, UTIs are the most common, occurring in 46.8% of KTRs (2). Nearly 70% of UTIs are caused by Gram-negative bacterial pathogens, with uropathogenic *Escherichia coli* (UPEC) being the predominant agent. Other frequent causative agents of UTIs are members of the family Enterobacteriaceae, *Enterococci spp*, *Pseudomonas* species, and *Staphylococcus saprophyticus* (3). The widespread use of antibiotics for the prophylaxis and management of UTIs has contributed to the emergence of multidrug-resistant (MDR) pathogens, including extended-spectrum beta-lactamases (ESBLs)-producing organisms, among KTRs, resulting in limited treatment options and a growing global health concern (4, 5).

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Previous studies have shown that, in kidney transplant recipients, repeated episodes of urinary tract infection represent a significant clinical challenge and are frequently linked to the emergence of antibiotic-resistant pathogens, subsequently leading to impaired renal function or even graft loss (4, 6). Rising resistance to commonly used antibiotics, particularly fluoroquinolones and trimethoprim–sulfamethoxazole, has significantly limited therapeutic options for UTIs in KTRs (7). As a result, there is a growing need to evaluate alternative antimicrobial agents for treating infections caused by ESBL-producing uropathogens in this vulnerable population. Given the clinical significance of UTIs in KTRs and the rising problem of antimicrobial resistance, continuous surveillance is essential to monitor resistant uropathogens across different geographic regions. Hence, the primary objective of this study was to assess the antibiotic resistance profiles of ESBL-producing uropathogenic strains isolated from KTRs with UTIs in northern Iran. The results are expected to provide essential epidemiological information on bacterial uropathogens and to aid in the planning and implementation of preventive, control, and treatment measures for UTIs among KTRs in the study region.

Methods

Study population and bacterial identification: This one-year cross-sectional study was carried out between June 2019 to June 2020 in the Department of Microbiology, Virology and Microbial Toxins, Guilan University of Medical Sciences, Rasht, Iran, in collaboration with Razi Teaching Hospital. The study population consisted of adult KTRs aged >18 years who attended routine post-transplant follow-up visits during the study period. As part of standard clinical surveillance, midstream urine samples were collected from all KTRs, irrespective of urinary symptoms. A case of UTI was defined by the presence of at least one of the following: (i) clinical signs/symptoms (e.g., fever >37.5°C, dysuria, urgency, or frequency); or (ii) laboratory abnormalities including positive leukocyte esterase and/or nitrite, pyuria (≥10 WBC/mm³), or significant bacteriuria on urine culture. For patients not receiving antimicrobial therapy, significant bacteriuria was defined as $\geq 10^5$ CFU/mL; for those on antibiotics, the threshold was lowered to $\geq 10^4$ CFU/mL. Urine samples were collected from 96 KTRs meeting the inclusion criteria for suspected UTIs. Uropathogens were identified from positive urine cultures ($\geq 10^5$ CFU/mL in patients not on antibiotics; $\geq 10^4$ CFU/mL in those receiving antimicrobial therapy), using conventional bacteriological methods.

Uropathogen detection by PCR: Genomic DNA was isolated from each uropathogenic strain using the boiling technique. In this procedure, 500 µl of overnight Brain Heart Infusion (BHI) broth cultures (Merck, Germany) were centrifuged at 14,000 rpm for 10 minutes to obtain cell pellets. The pellets were then suspended in 400 µl of 1× Tris-EDTA buffer, heated at 95 °C for 10 minutes, and allowed to cool to room temperature for 5 minutes before further use. The suspension was then placed at −20°C for 10 minutes and after centrifugation at 14,000 rpm for 10 minutes at 4°C, were stored at −20°C until use. Conventional PCR was used to identification of different uropathogens. The primer sequences, expected amplicon sizes, and PCR amplification conditions are summarized in table 1. In each assay, the final volume of each reaction was 25 µL which contained 12.5-mL 2X master mix (Ampliqon, Odense, Denmark), 1 µL of each primer (10 pmol/µL), and 5 µL of each DNA sample. DNA was amplified in a Mastercycler Eppendorf (Eppendorf, Germany). Amplicons were separated by electrophoresis on a 1.5% agarose gel.

Table 1. Primers and PCR conditions used in this study

Bacteria	Genes	Primers	Initial denaturation	Denaturation	Annealing	Extension	Final extension	Size (bp)
E. coli	***malX***	5'-ATCGATCCCGGTAACTTTGC-3' 5'-TCAGATAAGCCTCATCAAGATCG-3'	95°C,5 m	40 cycles of 95°C,15 s	59°C,15 s	72°C,1 m	72°C,5 m	736
E. faecalis	***ddl***	5'-ATCAAGTACAGTTAGTCTTTATTAG-3' 5'-ACGATTCAAAGCTAACTGAATCAGT-3'	94°C,5 m	30 cycles of 94°C,1 m	55°C,45 s	72°C,1 m	72°C,10 m	941
K. pneumoniae	***khe***	5'-TGATTGCATTCGCCACTGG-3' 5'-GGTCAACCCAACGATCCTG-3'	94°C,3 m	30 cycles of 94°C,20 s	60°C,30 s	72°C,30 s	72°C,10 m	428

Antibiotic susceptibility: The antibiotic susceptibility of uropathogen isolates was assessed using disk diffusion for a range of antibiotics, including β-lactams, aminoglycosides, fluoroquinolones, sulfonamides, nitrofurans, fosfomycin, macrolides, and penicillin, while vancomycin susceptibility was determined by the E-test method, in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (8). ESBLs-producing isolates were phenotypically identified using the double-disk synergy test, following the CLSI 2021 guidelines. This involved testing ceftazidime (30 µg) and cefotaxime (30 µg) disks, both alone and in combination with clavulanic acid (10 µg). Strains were classified as ESBL producers if the inhibition zone diameter around the combination disk increased by ≥5 mm compared to the single antibiotic disk. For quality control, *E. coli* ATCC 25922 was used as a negative control, while *Klebsiella pneumoniae* ATCC 700603 served as a positive control.

Data analysis: Statistical analyses were conducted using SPSS™ software, Version 21.0 (IBM Corp., Armonk, NY, USA). The data were summarized as descriptive statistics based on percentage distributions. The Fisher's exact test was employed to assess relationships between variables, with a significance threshold set at $p < 0.050$.

Results

Of 96 KTRs, 5 (19.2%) males and 21 (80.8 %) females were diagnosed with UTIs. The majority of the patients had a mean age of 58.92±14.58 years (range: 29–79). Demographic and clinical characteristics in KTRs with urinary tract infections are shown in table 2. Considering table 2, it is notable that urine reflux, acute rejection, glomerulonephritis, and malignancy were not observed among KTRs with UTIs. A total of 26 bacterial uropathogens were isolated from KTRs with UTIs. Gram-negative bacteria were the most prevalent isolated uropathogens. UPEC was the most frequent isolates 15 (57.7%), followed by *Klebsiella pneumoniae* 10 (38.5%), and *Enterococcus faecalis* 1 (3.8%) was as the gram positive isolated uropathogen.

The antimicrobial resistance profiles of the uropathogenic isolates were assessed using different classes of antibiotics. Among the 25 *E. coli* and *K. pneumoniae* isolates, 18 (72%) were identified as ESBLs producers. The comparative resistance patterns of ESBLs-producing and non-ESBLs-producing *E. coli* and *K. pneumoniae* isolates are summarized in table 3. ESBL-producing uropathogens exhibited significantly higher resistance than non-ESBL-producing strains to cefuroxime, cefepime, trimethoprim-sulfamethoxazole, ciprofloxacin, and levofloxacin ($p < 0.05$). For the remaining antibiotics, resistance differences did not reach statistical significance; however, post-hoc power analysis revealed low statistical power (7-64%) for these comparisons, suggesting that some clinically relevant associations may have been missed due to limited sample size. Resistance to ampicillin, cefuroxime, cefepime (100%) were most prevalent among the ESBLs-producing isolates, followed by ciprofloxacin, levofloxacin (94.4%) and trimethoprim-sulfamethoxazole (88.9%). However, the highest susceptibility was toward amikacin, fosfomycin (a zone diameter of ≥16 mm against UPEC) (83.3%), cefoxitin, nitrofurantoin (72.2%), and meropenem (66.7%). *Enterococcus faecali* isolate showed most sensitivity to vancomycin, penicillin and ampicillin and most resistance to ciprofloxacin and levofloxacin.

Table 2. Demographic and clinical characteristics in KTRs with urinary tract infections

Variables	Number (%)
Male gender	5 (19.2)
Female gender	21 (80.8%)
Age ≤50 years	7 (26.9)
Age >50 years	19 (73.1)
Fever	
Yes	3 (11.5)
No	23 (88.5)
Recurrent UTI	
Yes	24 (92.3)
No	2 (7.7)
History of antibiotic use	
Yes	18 (69.2)
No	8 (30.8)

Variables	Number (%)
History of hospitalization	
Yes	18 (69.2)
No	8 (30.8)
Infectious diseases	
Yes	7 (26.9)
No	19 (73.1)
History of urinary catheterization	
Yes	6 (23.1)
No	20 (76.9)
Hypertension	
Yes	15 (57.7)
No	11 (42.3)
Urinary tract stone	
Yes	2 (7.7)
No	24 (92.3)
Diabetes mellitus	
Yes	8 (30.8)
No	18 (69.2)
Urine reflux	
Yes	0 (0)
No	26 (100)
Polycystic kidney	
Yes	4 (15.4)
No	22 (86.4)
Glomerulonephritis	
Yes	0 (0)
No	26 (100)
Use of ureteral stent	
Yes	14 (53.8)
No	12 (46.2)
History of immunosuppressive drugs use	
Yes	25 (96.2)
No	1 (3.8)
Malignancy	
Yes	0 (0)
No	26 (100)
Donor status	
Living donor	21 (80.8)
Deceased donor	5 (19.2)
Acute rejection	
Yes	0 (0)
No	26 (100)
***eGFR, mL/min/1.73 m^2**	57.19

*eGFR, estimated glomerular filtration rate; mL, milliliters; min, minutes; m^2, square meters.

Table 3. Antibiotic resistance pattern of *E. coli* and *K. pneumoniae* isolates according to producing of ESBLs

Antibiotics	ESBLs producers (18) Number (%)		Non-ESBLs producers (7) Number (%)		P-value	Post-hoc Power*
	Resistant	Susceptible	Resistant	Susceptible		
AM	18 (100.0)	0 (0.0)	6 (85.7)	1 (14.3)	0.30	0.58
SAM	11 (61.1)	7 (38.9)	1 (14.3)	6 (85.7)	0.06	0.64
AMC	11 (61.1)	7 (38.9)	2 (28.6)	5 (71.4)	0.20	0.30
PTZ	9 (50.0)	9 (50.0)	1 (14.3)	6 (85.7)	0.17	0.42
CZ	13 (72.2)	5 (27.8)	3 (42.9)	4 (57.1)	0.20	0.24
CXM	18 (100.0)	0 (0.0)	2 (28.6)	5 (71.4)	<0.001	0.99
CPM	18 (100.0)	0 (0.0)	2 (28.6)	5 (71.4)	<0.001	0.99
CRO	15 (83.3)	3 (16.7)	3 (42.9)	4 (57.1)	0.06	0.56
FOX	5 (27.8)	13 (72.2)	0 (0.0)	7 (100)	0.08	0.48
GM	7 (38.9)	11 (61.1)	1 (14.3)	6 (85.7)	0.36	0.26
AK	3 (16.7)	15 (83.3)	2 (28.6)	5 (71.4)	0.59	0.09
CIP	17 (94.4)	1 (5.6)	4 (57.1)	3 (42.9)	0.03	0.78
LEV	17 (94.4)	1 (5.6)	4 (57.1)	3 (42.9)	0.03	0.78
T/S	16 (88.9)	2 (11.1)	2 (28.6)	5 (71.4)	0.01	0.92
IMP	7 (38.9)	11 (61.1)	1 (14.3)	6 (85.7)	0.36	0.26
MEM	6 (33.3)	12 (66.7)	1 (14.3)	6 (85.7)	0.39	0.21
Fd	5 (27.8)	13 (72.2)	3 (42.9)	4 (57.1)	0.64	0.10
FOS	3 (16.7)	15 (83.3)	2 (28.6)	5 (71.4)	0.59	0.09
AZM	9 (50.0)	9 (50.0)	3 (42.9)	4 (57.1)	0.84	0.07

AM; Ampicillin, SAM; Ampicillin-sulbactam, AMC; Amoxicillin-clavulanate, PTZ; Piperacillin- tazobactam, CZ; Cefazolin, CXM; Cefuroxime, CPM; Cefepime, CRO; Ceftriaxone, FOX; Cefoxitin, IMP; Imipenem, MEM; Meropenem, GM; Gentamicin, AK; Amikacin, CIP; Ciprofloxacin, LEV; Levofloxacin, T/S; Trimethoprim-sulfamethoxazole, Fd; Nitrofurantoin, FOS; Fosfomycin, AZM; Azithromycin. *Post-hoc power was calculated for all antibiotic comparisons using Fisher's exact test (two-tailed, $\alpha = 0.05$), based on observed group sample sizes and odds ratios. Power ≥80% is generally considered adequate to detect a true association.

Discussion

Urinary tract infections represent a common infectious complication after renal transplantation and are considered a specific risk factor for graft loss, increased mortality in kidney transplant recipients, persistent infection, and the emergence of multidrug resistance (9). Improvement in patient survival is threatened by the spread of drug-resistant and ESBL-producing bacteria, particularly UPEC and *K. pneumoniae*. The limited therapeutic options in such settings often necessitate the use of second-line agents, which are frequently constrained by the need for intravenous administration or unacceptable toxicity (10). In this study, we evaluated the antimicrobial susceptibility patterns of ESBL-producing uropathogens isolated from KTRs with UTIs. The main finding of this study was the high prevalence of antimicrobial resistance among these isolates, particularly to commonly used antibiotics, highlighting the limited therapeutic options available for this high-risk patient population. In KTRs, optimal antimicrobial selection is essential to ensure the effectiveness of both empirical and prophylactic therapy for UTIs. The results of this study will provide essential information related to regional antibiotic resistance rates to improve antimicrobial stewardship programs and treatment

of UTIs among KTRs in our studied region. UPEC, *K. pneumoniae* and *E. faecalis* were the most prevalent UTI causative organisms in KDRs in this study. In agreement with other studies, in the literature review on etiology of UTIs in KDRs revealed the most prevalent organism in the present study was *E. coli* (11-13).

Consistent with prior reports from Iran and other regions, our findings also demonstrated a high prevalence of ESBL-producing UPEC and *K. pneumoniae* isolates among KTRs with UTIs (12, 14, 15). In line with findings from various regions, the majority of UPEC and *K. pneumoniae* isolates in our study were resistant to ampicillin, ciprofloxacin, levofloxacin, and sulfamethoxazole-trimethoprim. This resistance precludes the use of these antibiotics as first-line empirical treatments for UTIs (16, 17). The non-significant resistance differences observed for certain antibiotics (e.g., ampicillin-sulbactam, ceftriaxone) should be interpreted cautiously, as post-hoc power was low (30-64%) despite clinically notable effect sizes, likely due to small sample size. The rise in antibiotic resistance in various regions of Iran over the years has posed significant challenges to the empirical treatment of UTIs. This increase can be attributed to variations in infection control policies, as well as the inappropriate and excessive use of antibiotics (4).

On the other hand, our findings are consistent with several previous reports from Iran and other countries, which have shown that most ESBL-producing isolates remain susceptible to amikacin, fosfomycin, cefoxitin, and nitrofurantoin (17, 18). Although the high resistance to carbapenems (meropenem and imipenem at 33.3% and 38.9%, respectively) among ESBL-producing strains is a concerning finding in our region, the recent emergence of carbapenemase-producing Enterobacteriaceae has led to substantial changes in antimicrobial susceptibility patterns. These resistance mechanisms fuel the rise of difficult to treat clinical strains, and in KTRs with UTIs, carbapenem-resistant strains have been associated with a higher risk of microbiological failure compared to infections caused by ESBL-producing or fully susceptible isolates (19). These findings highlight the importance of ongoing monitoring of local antimicrobial resistance trends to guide evidence-based empirical treatment of UTIs following kidney transplantation. Due to the high antibacterial efficacy of carbapenems as β-lactam antibiotics, which are frequently employed as primary therapeutic options for managing infections caused by ESBLs-producing pathogens, it is crucial to consider alternative drugs to prevent the rise of carbapenem-resistant strains (20). Effective oral treatment options for resistant organisms are limited, making fosfomycin and nitrofurantoin promising alternatives. Nitrofurantoin is a broad-spectrum agent indicated primarily for uncomplicated cystitis. Therefore, if trimethoprim-sulfamethoxazole cannot be used for primary prophylaxis of UTIs following kidney transplantation, alternative agents include nitrofurantoin, but only in patients with an eGFR >60 mL/min. Although fosfomycin is not routinely recommended for cystitis in KTRs to preserve its activity against highly resistant pathogens, it may be cautiously considered for the treatment of multidrug-resistant UTIs, particularly when the infection is confined to the bladder (i.e., cystitis) (21).

Our results showed that the frequency of *E. faecalis* was 3.8%, similar to other published report (12). Some previous studies have shown that *E. coli* and *Enterococcus spp.* are mostly responsible for post-renal transplantation UTIs (22, 23). Consistent with previous studies, in our results *E. faecalis* isolate showed sensitivity to vancomycin, penicillin and ampicillin and resistance to ciprofloxacin and levofloxacin (23, 24). Kidney transplant recipients constitute a vulnerable population with numerous risk factors for UTIs. Consistent with previous studies, females accounted for the majority of KTRs who developed post-transplant UTIs compared to males (80.8% vs. 19.2%, respectively), a disparity attributed to anatomical, hormonal, immunological, and behavioral factors. Significant risk factors for UTIs in KTRs include a history of pretransplant UTIs, prolonged hemodialysis prior to transplantation, polycystic kidney disease, diabetes mellitus, postoperative bladder catheterization, immunosuppression, allograft trauma, deceased donor status, a history of vesicoureteral reflux, and complications related to ureteral anastomosis (11, 12, 25).

A history of pre-transplant urinary tract infections (UTIs) may serve as a risk factor for post-transplant UTIs and poses a threat to long-term graft survival by potentially contributing to chronic rejection (11). In contrast to our findings, several studies have reported a higher incidence of UTIs among KTR of deceased donors compared to those receiving grafts from living donors (25, 26). Consistent with previous reports, no cases of acute rejection were observed among KTRs with UTIs. Although acute rejection does not occur after every UTI, some prior studies have suggested an association between UTIs and the onset of acute rejection, potentially due to intense immunosuppression (23, 25).

The impact of ureteral stenting on the risk of UTIs remains controversial. However, the use of ureteral stents was not shown to be a risk factor for UTIs (27). In our study, vesicoureteral reflux was not observed among KTRs with UTIs. Vesicoureteral reflux or stenosis at the ureterovesical anastomosis, both major lower urinary tract dysfunctions,

can predispose patients to recurrent UTIs (12). Our results revealed a high prevalence of recurrent UTIs among KTRs (92.3%). In contrast, other studies have reported a recurrence rate of 54% for UTIs caused by ESBLs-producing bacteria. Notably, the risk of ESBL-related UTIs appears to increase with the number of prior UTI episodes, likely due to repeated antibiotic exposure driving selective pressure for resistant strains (12, 14). Previous studies have shown that delayed graft function, often resulting from acute kidney injury, can lead to a significant reduction in estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m^2) during UTIs caused by ESBL-producing bacteria in KTRs (14). Previous studies have reported that older age (>50 years) is associated with a higher risk of UTIs following kidney transplantation (25).

Urinary tract infections in KTRs represent a critical clinical challenge, not only due to their high incidence but also because of the complex interplay between host-related factors (e.g., immunosuppression, older age), uropathogen characteristics (notably the rising prevalence of multidrug-resistant Enterobacterales), and anatomical or surgical complications (such as vesicoureteral reflux or ureteral stenosis). This multifactorial etiology underscores the need for a comprehensive, approach to both prevention and management.

Given the limited therapeutic choices, particularly the alarming emergence of carbapenem resistance, and the heightened risk of graft dysfunction associated with recurrent or inadequately treated UTIs, ongoing local surveillance is essential. Future prospective studies integrating microbiological, clinical, and pharmacokinetic data will be instrumental in guiding empirical and targeted antimicrobial therapy, optimizing prophylactic strategies, and ultimately curbing the spread of resistant uropathogens in this vulnerable population.

This study has several limitations. First, the one-year study period may not adequately reflect fluctuations in uropathogen prevalence or longer-term trends in antimicrobial resistance among KTRs. Given the evolving nature of resistance patterns, a more extended surveillance period would provide a more comprehensive picture. Second, the relatively small sample size may limit statistical power, reduce the ability to detect significant associations, and constrain the generalizability of the findings to broader transplant populations. To address these constraints, future studies should employ a multicenter design with prolonged surveillance (e.g., 2–3 years) to increase sample size, enhance statistical power, and capture temporal variations in resistance patterns among KTRs. Additionally, phenotypic and molecular assays for the detection of carbapenemase-producing strains were not conducted, which limits our ability to fully characterize the spectrum of resistance mechanisms in the isolated uropathogens.

ESBL-producing bacteria, such as *E. coli* and *K. pneumoniae*, are difficult to eradicate and often require prolonged courses of broad-spectrum antibiotic therapy. In our study, we observed a high incidence of ESBL-related UTIs among KTRs. Recurrent UTIs place KTRs at particularly high risk for infection with ESBL-producing pathogens. Although prevention of the initial UTI episode is critically important in this population, prophylactic antibiotics should be used only for the shortest duration necessary. Based on in vitro susceptibility results, fosfomycin appears to be a promising oral therapeutic option for UTIs caused by ESBL-producing uropathogens among KTRs in our study region. Moreover, the high prevalence of ESBL-producing isolates highlights the potential value of targeted prophylactic strategies in high-risk patients.

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Authors' contribution: Raheleh Sheikhi: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing. Mojgan Sigarchi: Methodology. Ali Monfared: Methodology. Masoud Khosravi: Methodology. Sara Darvishvand: Methodology. Afagh Hassanzadeh Rad: data analysis. Elham Ramezanzade: Methodology. Mohammad-kazem Lebadi: Methodology. Yalda Haghdar-Saheli: Methodology. Pegah Aghajanzadeh: Methodology. Ali Movassaghi: Methodology. All authors read and approved the final manuscript.

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