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Infection Epidemiology and Microbiology. 2018;4(1):35-40. DOI: 10.29252/modares.iem.4.1.35

Risk Factors Associated with ESBL and CPE Acquisition among Pediatrics: A Systematic Review

ARTICLE INFO

Article Type
Systematic Review

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How to cite this article
Ghasemian A.M, Norouzi F, Shokouhi Mostafavi S Kh, Hasanvand F, Nojoomi F. Risk Factors Associated with ESBL and CPE Acquisition among Pediatrics: A Systematic Review. Infection Epidemiology and Microbiology. 2018 ;4(1):35-40.

ABSTRACT

Aims Infections by extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing Enterobacteriaceae (CPE) are increasing problems in pediatrics and are usually associated with higher hospital costs and mortality rates. The aims of this study were the statistical investigation of the worldwide prevalence and risk factors of ESBL and CPE family members among pediatric population.

Instruments & Methods From October 1, 1995 to July 27, 2017, some keywords including "ESBLs", "carbapenemase", "pediatrics", "children", and "risk factor" were searched in the searching databases such as Google Scholar, Embase, Scopus, PubMed, and Web of Science among original research articles. The univariate and multivariate analysis of the collected data was performed by Graph Pad Prism 6.1 software.

Findings The mean percentage of ESBL production was 20.23±22.31 and the mean percentage of CPE was 1.81±2.77. *E. coli* (n=991) and *K. pneumonia* (n=627) were the predominant ESBL-producers. Nephrology (n=5005) and NICU (n=1805) were predominant hospital wards. ESBL-PE had significantly higher prevalence in the infants unit (OR=0.9832, 95% CI=12.271-19.519; p<0.001). Moreover, ICU ward was a significant and independent risk factor for CPE acquisition (OR=0.849, 95% CI=2.211-5.415; p=0.0035). ESBL-PE and CPE were significantly isolated from blood samples (OR=0.9276, 95% CI=1.508-2.433, p<0.0001) and fecal specimens (OR=0.968, 95% CI=2.829-5.133, p<0.0001), respectively.

Conclusion Most of risk factors between ESBL-PE and CPE are similar including previous hospitalization and prolonged use of antibiotics, cephalosporins, and previous colonization. Other possible potential risk factors that should be considered include presence of catheters and travel history. Detection of risk factors provides useful information for formulation of infection control policy.

Keywords Enterobacteriaceae; Extended-spectrum beta-lactamase; Carbapenemases; Risk Factors; Pediatrics

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Article History
Received: December 5, 2017
Accepted: February 3, 2018
ePublished: March 20, 2018

CITATION LINKS

[1] Nosocomial outbreak of Klebsiella infection ... [2] The epidemiology of candida ... [3] β-Lactams: Chemical structure, mode of ... [4] An overview of carbapenem ... [5] Prevalence of clinically isolated ... [6] Federal funding for the study of ... [7] NHSN annual update: Antimicrobial-resistant ... [8] Ecology drives a global network ... [9] Effect of overgrowth or decrease ... [10] Antibiotic resistance patterns and ... [11] Carbapenemases: The versatile ... [12] Carbapenemase genes and ... [13] Biochemical sequence analyses ... [14] Co-resistance to different ... [15] Outbreak of multiply ... [16] Detection of gastrointestinal pathogens ... [17] Influx of extended-spectrum ... [18] Faecal carriage of extended-spectrum ... [19] Prevalence and spread of ... [20] Epidemiology and risk ... [21] Risk factors for acquisition ... [22] Fecal colonization with ... [23] Colonisation with ... [24] Molecular epidemiology ... [25] Diagnosis and management ... [26] The mother as most ... [27] Prevalence of ESBL-producing ... [28] Risk factors for ... [29] Extended-spectrum ... [30] Risk factors for the ... [31] Risk factors in community ... [32] Risk factors for community ... [33] Fecal carriage of ... [34] The prevalence of plasmid ... [35] Antimicrobials increase ... [36] International travel is a risk factor ... [37] Risk factors associated with ... [38] Multidrug-resistant ESBL ... [39] Extended-spectrum beta-lactamase-producing ... [40] Bloodstream infections by ... [41] Risk factors for extended ... [42] Molecular epidemiology of an SHV-5 extended-spectrum ... [43] Infection due to extended-spectrum ... [44] Multi-drug-resistant Enterobacteriaceae in a Portuguese ... [45] ESBL-producing Escherichia ... [46] Fecal carriage of ESBL-producing ... [47] High rate of fecal carriage of ... [48] Risk factors for carbapenem-resistant ... [49] Molecular characterization and risk factors for carbapenem-resistant ... [50] High gastrointestinal colonization rate with ...

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Introduction

Infections due to the multidrug-resistant Gram-negative bacteria are rising in the pediatric population and they pose serious problems in the limited therapeutic options and long-time hospitalization.

Showing resistance to penicillin and cephalosporins as well as to non-beta-lactam antibiotics, Extended-spectrum beta-lactamase-producing Enterobacteriaceaee (ESBL-PE) have been described since the 1990s as nosocomial pathogens[1-3]. Furthermore, the recent emergence and spread of carbapenemase-bearing strains (CPE) among children have limited the therapeutic choices as the carbapenems are the last resorts of eradication of infections due to ESBL[4, 5]. These types of infections are associated with the high rate of mortality as the pediatrics is a vulnerable population.

Two members of the Enterobacteriaceaee family, *Klebsiella pneumonia* and Enterobacter spp., are placed in the ESKAPE pathogens, standing for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter species group[6] and this family members are among the most common causes of device-related infections[7].

Because of plasmid-borne or extrachromosomal expression of ESBLs and carbapenemases, the transmission of encoding genes between human micobiota as well as from livestock bacteria occurs rapidly and easily[8, 9]. It has been reported that gastrointestinal infections are the primary causes of death in children; thus, the detection of drug-resistant Enterobacteriaceae and uncovering most significant risk factors is critical in order to foster the proper treatment regimens[10].

The ESBLs are encoded by CTX-M, TEM and SHV genes, which have been reported worldwide in both healthcare and community settings and are associated with the high rate of mortality among pediatrics. Furthermore, carbapenemases are encoded by various classes including OXA-48, KPC and GES, and metallo-β-lactamases such as IMP, VIM, and NDM1 genes[11, 12]. The spread of these genes will make the treatment options very limited, especially for vulnerable population of pediatrics, because both ESBL and carbapenemase-producing strains carry resistance elements to other classes of antibiotics[13, 14].

Risk factors of fecal colonization and infection with ESBL-PE in adults include hospital stay more than 5 days, chronic care facilities, catheterization, antibiotic exposure, comorbid conditions, sputum suction, meat use associated with the agricultural antibiotic apply, underlying diseases, and international travel, especially for those persons with systemic febrile illnesses, immunosuppression, diarrheal illnesses, and dermatologic disorders[15-25]. Risk factors of ESBL infections in pediatrics have been determined to some extent; they include healthcare exposure, previous use or exposure of antibiotics, particularly cephalosporins, maternal transmission, and comorbid conditions such as urologic or neurologic conditions[26-29]. In addition, there have been several risk factors associated with the acquisition of ESBL and carbapenemase-producing Enterobacteriaceae in the community including age over 60 years, antibiotic treatment in the past 3 months, previous hospitalization in the past 3 months, within-household transmission, diabetes and some other underlying disorders, male gender, previous infection, nursing home stay and previous use of cephalosporins, penicillin, and quinolones[30-33]; thus, it is an urgent issue to increase knowledge, validate, and hinder the transmission of these multidrug-resistant species among children.

The aims of the current study were the statistical investigation of the worldwide prevalence and risk factors of ESBL and carbapemenase-producing Enterobacteriaceaee family members among pediatric population.

Information and Methods

We conducted a systematic review over the prevalence and risk factors associated with the acquisition and spread of ESBLs and carbapemase-producing species of Enterobacteriaceae and statistically analyzed them.

For this purpose, from October 1, 1995 to July 27, 2017, some keywords including “ESBLs”, “carbapenemase”, “pediatrics”, “children”, and “risk factor” were searched in the searching databases such as Google Scholar, Embase, Scopus, PubMed, and Web of Science among original research articles. The national publications were also considered to be used.

Inclusion and exclusion criteria: All publications regarding the prevalence of ESBLs and carbapenemases and risk factors among children (both patients and healthy population) conducted in all countries were considered. Pediatric patients from both healthcare and community were included. Pediatrics with ages between <1 year to 16 years were included. Furthermore, both colonization and infection by ESBL-producing and carbapenemase-producing Enterobacteriaceae members were included. All the infection sources caused by the Enterobacteriaceae family in children (UTI, fecal infection, respiratory tract sampling, etc.) and hospital wards (Pediatrics, NICU, ICU, Emergency, etc.) were included. Patients with asymptomatic status, who were colonized or infected with ESBL and carbapenemases-non producers, were excluded.

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Furthermore, case reports, review articles, systematic review papers, and those available only in the abstract form were excluded from this study.

Statistical analysis: The univariate and multivariate analysis of the collected data was performed by the Graph Pad Prism 6.1 software. The Mean±SD of factors, comparison of results, and possible relations were performed by the software. The unpaired t-test and one-way ANOVA tests were applied for the purpose of risk factor analysis and 95% confidence interval (95% CI) and p value<0.05 were considered the breakpoint for a significant result.

Findings

Risk factors for resistance development: A total of 8605 (5782 in the hospital and 2823 in the community) isolates were enrolled for ESBLPE and 1488 (all belonging to the hospital-associated infections) isolates were investigated for CPE prevalence among 51 publications in children population, which met the criteria. The mean percentage of ESBL production was 20.23±22.31 and the mean percentage of CPE was 1.81±2.77. Moreover, among ESBL producers, *E. coli* (N=991) and *K. pneumonia* (N=627) were the predominant ESBL-producers, followed by *Enterobacter cloacae* (N=53), *K. oxytoca* (N=19), *Proteus mirabilis* (N=19), *Citrobacter freundii* (N=9), *C. koseri* (N=7), Seratia spp (N=7*), morganella morganii* (N=6), and Salmonella spp (N=3) (Table1). The children age ranges were as follow: 0 to 1 year=2894, 1 to 5 years=3177, 5 to 10 years=2510, and >10 years=924. The majority of isolates (N=5005) were collected from children in Nephrology ward, followed by 1805 isolates in NICU, 817 isolates in ICU, 687 in Pediatric ward, and 301 isolates in infants units. The prevalence of ESBLs among hospital wards was shown (Figure 1, Table 1).

Table1) The prevalence of ESBL and carbapenemase producing Enterobacteriacea in hospital wards and infection and colonization sites, ESBL PE: ESBL-producing Enterobacteriacea, *CPE: carbapenem-producing E (percentage among the total of 1488 isolates), ND: not detected

Variables	ESBL-PE No (%)	OR	95% CI	p value	*CPE No (%)	OR	95% CI	p value
Hospital ward								
Nephrology (N=5005)	158 (3.81)		1.124-3.141		4 (2.69)		1.111-3.141	
NICU (N=1805)	155 (8.56)		1.421-5.574		11 (7.39)		2.132-6.162	
ICU (N=817)	11 (1.34)	0.9832	0.982-2.111	<0.0001	12 (8.06)	0.849	2.211-5.415	0.0035
Pediatrics (N=687)	134 (19.50)		11.187-15.596		ND		-	
Infants (N=301)	81 (26.9)		12.271-19.519		ND		-	
Sampling site								
Fecal (N=5939)	400 (6.73)		2.141-3.207		21 (3.53)		2.829-5.133	
Urinary tract (N=3789)	123 (3.24)		1.569-3.161		5 (1.58)		4.837	
Blood (N=599)	14 (2.33)	0.9276	1.508-2.433	<0.0001	1 (1.6)	0.968	4.838	<0.0001
Respiratory (N=63)	2 (3.17)		2.642-3.111		ND		-	
Other (N=15)	ND		ND		ND		-	

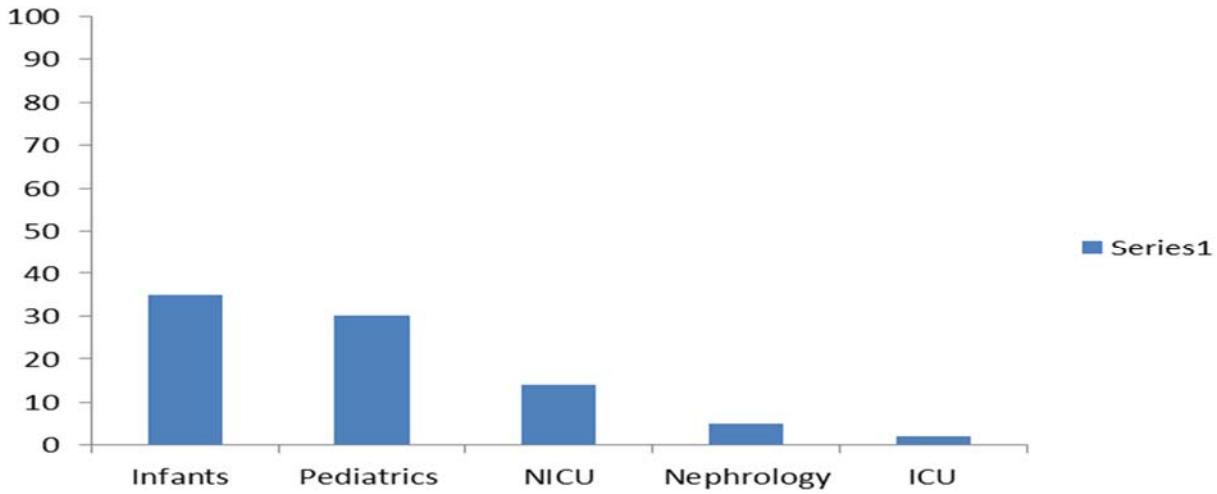

Figure1) The prevalence of ESBL-producing Enterobacteriacea among hospital wards

ESBL-PE had significantly higher prevalence in the infants unit (OR=0.9832, 95% CI=12.271-19.519; p<0.001), which can be considered as an independent risk factor for spread of ESBL-PE (Figure 1, Table 1). Moreover, ICU ward was a significant and independent risk factor for CPE acquisition (OR=0.849, 95% CI=2.211-5.415; p=0.0035).

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Furthermore, fecal samples (N=5939) were mostly investigated, followed by urine specimens (N=3789), blood samples (N=599), respiratory samples (N=63) and other (N=15). The prevalence of ESBL and carbapenemase-producing species among both infection and colonization sites were depicted (Table1).

ESBL-PE and CPE were significantly isolated from blood samples (OR=0.9276, 95% CI=1.508-2.433, p<0.0001) and fecal specimens (OR=0.968, 95% CI=2.829-5.133, p<0.0001), respectively.

Among various risk factors, previous hospitalization and prolonged antibiotic use, especially cephalosporins, are independent risk factors for the acquisition of HA-ESBL-PE among pediatrics (Table 2).

Table2) The significant risk factors found among hospital acquired (HA) ESBL-PE, Community-acquired (CA) ESBL-PE, and CPE

Risk factor	p value: HA-ESBL-PE	p value: CA-ESBL-PE	p value: CPE (HA)
Previous hospitalization	0.05	-	0.001
Prolonged antibiotic use 1886	0.002	0.001	0.001
Nursery	0.007	-	-
Day care home 1886	0.013	0.003	-
Travel history 1886	0.003	0.001	0.01
prolonged out residence	-	0.041	-
Gestational age/birth weight	0.02	0.02	0.001
Previous cephalosporin	<0.001	<0.001	<0.001
Previous stay	0.001	0.001	0.001
Previous UTI	0.001	0.001	0.001
Previous nitrofurantoin	<0.001	-	-
Previous quinolones	<0.001	-	0.001
Previous use of carbapenems	0.007	0.01	0.001
Neurologic comorbidity	0.01	-	-
central venous catheters	-	0.035	-
ESBL-E-positive mother	0.002	-	-
Underlying disease	0.006	0.006	0.004
Gastrointestinal comorbidity	0.006	-	-
tracheostomy or gastrostomy	0.018	-	-
Birth in hospital	-	-	0.027
Cesarean birth	0.036	-	-
Male gender	0.035	-	-
cephalosporin plus aminoglycoside	0.02	-	-
central vascular catheter	0.003	-	-
Previous colonization	0.002	0.003	0.001
Lower age	0.02	-	-
History of infection (last 3 month)	0.001	0.001	0.001
Suppression	0.001	-	-
Septicemia	0.001	-	-
Systemic infection	0.001	-	-
Renal abnormality	0.001	0.002	-
Recurrent UTI	0.004	0.004	-
TMP/SMX-nitrofurantoin	0.003	-	-

Trends in ESBL and carbapenemase enzymes development: Pediatrics population is important regarding the acquisition of ESBL-PE and CPE for several reasons including vulnerability of them, unawareness of children about the issue, and, thus, rare observing the hygiene and having more contact among them and other populations.

For neonates, mother colonization with ESBL producing Enterobacteriaceae (p<0.001) and length of stay in hospital (0.037) were significant risk factors[26].

The presence of wound or drain and the use of cephalosporins, carbapenems, and PPIs (p=0.005) in the preceding 6 months were independent risk factors in the multivariable analysis.

Discussion

The aims of the current study were the statistical investigation of the worldwide prevalence and risk factors of ESBL and carbapemenase producing Enterobacteriaceaee family members among pediatric population. In Chinese pediatric hospitals, among pediatric patients, the DHA-1 type AmpC enzymes had the highest prevalent rate without any risk factor stated, which were mainly isolated from neonatology ward and respiratory medicine ward (41.2% and 20.5% for *K. pneumonia* and 24.4% and 27.9% for *E. coli*, respectively) [34]. Increasing age has also been stated as a risk factor for the development of carbapenem-resistant Enterobacteriaceae and

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likewise antimicrobials can enhance these strains acquisition[35].

Among 1- to 17-year-old pediatrics in a study, a recent hospital exposure was compared to the control group (90% vs. 63%; p=.008) and having a comorbid gastrointestinal (60% vs. 18.3%, p<.001) or neurologic (53% vs. 20% p=.01) impair were potential risk factors. However, a comorbid gastrointestinal illness was the only significant risk factor associated with non-ESBL infection (43.3% vs. 18.3%, p=.012); most of the children were diagnosed in NICU (37%) and PICU wards (23%) and 30% of pediatrics were outpatients[29].

A study among children between 0 to 18 years old, on multivariate analysis showed that the significant risk factors for ESBL acquiring were Asian race (OR=2.56, 95% CI=1.34-4.89; p=0.005), international travel (OR=8.93, 95% CI=2.92-27.78; p<0.001), prior UTI (OR=8.06, 95% CI=3.47-18.87; p<0.001), and comorbid GI condition (OR=2.65, 95% CI=1.36-5.15; p=0.002) [36].

In a study on pediatrics, tracheostomy or gastrostomy (OR=3.62, 95% CI=1.24-10.53; p=0.018) and antibiotic therapy in previous 3 months (OR=4.07, 95% CI=1.29-12.81; p=0.016) were the significant risk factors of ESBL spread[37].

In a study in Lebanon, of 117 rectal swabs collected from 1- to 12-year-old pediatrics in the community, 58 (49.6%) of them were carriers of ESBL-PE. The male gender, caesarean delivery, hospital birth, and being formula-fed were the significant determined risk factors for colonization of ESBL-producing Enterobacteriaceae. Moreover, CTX-M9 and CTX-M15 were the most ESBL-encoding genes[38].

In a study conducted in NICU among infected Brazilian children, of 383 neonates screened for the presence of ESBL-KP, the prevalence of infection and colonization of ESBL-KP was 13 (3.4%) and 206 (53.8%), respectively. The associated risk factors of colonization and infection were combination therapy with cephalosporin and aminoglycoside (HR=4.60; 95% CI=1.48±14.31), previous colonization (HR=5.19; 95% CI=1.58-17.08), and presence of central vascular catheter (HR=13.89; 95% CI=2.71±71.3), respectively[39].

In a Korean study, of 157 blood isolates at the Seoul Children's Hospital, 17.9% and 52.9% of the *E. coli* and 52.9% of the *K. pneumoniae* isolates were ESBL producers and the fatality rate since ESBL producers was significantly higher (26.7% vs 5.7%) than those non-ESBL producers[40].

Another study conducted among 225 children in Hong Kong demonstrated a high prevalence of ESBL-producing *E. coli* and *K. pneumonia* fecal carriage among both 0– to 5-year-old children at hospital admission and household members and showed both intra- and inter-household transmission. CTX-M14 and 15 were detected higher than other types[33]. Among pediatrics with urinary tract infection (UTI), the presence of an underlying disease, infections, hospitalization, and use of antibiotics within the prior 3 months were potential risk factors of acquisition of ESBL-bearing *K. pneumonia* and *E. coli* (p<0.001). In addition, *E. coli* was mostly isolated from UTI, but *K. pneumonia* was isolated more frequently from ESBL-positive children than ESBL-negative UTI[31].

The associated risk factors among a 4 cases outbreak in an NICU caused by *K. pneumonia* and *K. oxytoca* isolates, which produced ESBLs, were low gestational age and exposure to third-generation cephalosporins[41]. The low birth weight and low gestational age and combination therapy using cephalosporins and aminoglycosides have been demonstrated in several other studies as significant risk factors for ESBL colonization and infection in children[39, 42, 43].

In a recent study among pediatrics admitted to an NICU ward, gestational age, NICU stay time, and birth weight were associated with infection or colonization with ESBLPE[44]. In France, of 1886 rectal samples from children, 7.60% of *E. coli* isolates were ESBL producers and risk factors for the acquisition of the strains included being cared for at home, recent antibiotic use, and travel history[45].

In another study in Guinea Bissau, of 408 <5 years children, 133 (32.6%) were ESBL-PE, and bed sharing and crowded population was shown as a potential risk factor for ESBL-PE spread[46].

Another study in Spain among 8- to 16-year-old healthy children showed that 10.7% of 318 *E. coli* isolates from fecal samples were ESBL producers and the SHV-12, CTX-M-1, CTX-M-14, and TEM-52 were the predominant enzyme encoding genes[47].

A study assessed the risk factors among carbapenem-resistant Enterobacteriaceae and concluded that previous hospitalizations within a 3 month period, use of carbapenem, first generation cephalosporin antibiotics and β-Lactamase inhibitor, and use of a central catheter of peripheral insertion are significant risk factors[48].

Among the risk factors of acquisition of CPE isolates, age <1 year, presence of underlying chronic diseases, nasogastric tube placement, surgical intervention, ampicillin usage, and carbapenem use were significant among children population[49].

In a study conducted in Ethiopia, a high rate of ESBL-PE was determined among neonates and children (74% and 69%, respectively), who were higher than that of adults mostly due to *K. pneumonia* (76%) and *E. coli* (46%). In addition 1.9% of them produced carbapenemases[50].

Most of the risk factors between ESBL producer and carbapenemase producer species of

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Enterobacteriaceae are similar, including previous hospitalization, prolonged use of antibiotics, especially cephalosporins, previous colonization, and last 3 month stay in hospital. Other possible potential risk factors that should be considered include the presence of catheters and travel history. It seems that use of fluoroquinolones and nitrofurantoin should also be cautious.

Identifying the associated risk factor of ESBL-PE and CPE carriage in infant populations would help to define the population requiring more control measures to prevent the in-hospital dissemination of ESBL-PE and CPE. Although more studies are needed for the empirical therapy in children, cephalosporins and carbapenems should be used cautiously; likewise, response to the treatment must be followed closely. Limitations of this study were lack of other age groups for the assessment of the risk factors.

Conclusion

Tracking the risk factors associated with ESBL-PE and CPE acquisition among pediatrics has important implications on empiric antibiotic consumption as well as infection control management. The significant emergence of ESBL-PE and CPE pathogens among children populations indicate a serious health threat, which requires the implementation of control measures and surveillance at hospital and outside.

Acknowledgments: This study was performed by the authors.

Ethical Permissions: No ethical permission was stated by the authors.

Conflict of Interests: None declared by authors.

Authors Contribution: Ghasemian A (First author), Original researcher (20%); Norouzi F (Second author), Introduction author (20%); Shokouhi Mostafavi SK (Third author), Introduction author (20%); Hasanvand F (Fourth author), Introduction author (20%); Nojoomi F (Fifth author), Introduction author/ Methodologist/ Original researcher or Assistant/ Statistical analyst/ Discussion author (20%).

Funding/Support: This study was supported by AJA University of Medical Sciences, Tehran, Iran.

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