· Original article ·

Risk factors for congenital nasolacrimal duct obstruction in children under two years of age

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2 岁以下儿童先天性鼻泪管阻塞的危险因素 分析

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摘要

目的:确定可能在先天性鼻泪管阻塞(CNLDO)发展中发挥重要作用的各种危险因素。

方法: 观察性病例对照研究。纳入 2022-06/2024-06 于伊朗阿瓦士 Imam Khomeini 医院眼科诊断为 CNLDO 的 2 岁以下接受泪道探通加冲洗的患儿 122 例,以及 122 名年龄相匹配的无 CNLDO 的对照组儿童,收集所有儿童的医疗记录。

结果:研究发现 CNLDO 的发生与多种母体因素存在显著相关性,如子痫前期、使用左旋甲状腺素、甲状腺功能减退、怀孕 3 次以上(妊娠>3)、自然妊娠和妊娠期糖尿病。此外,在儿童中,氧疗、贫血、反流、黄疸和一级亲属的CNLDO 家族史等因素与 CNLDO 相关,母体子痫前期和甲状腺功能减退显著增加儿童患 CNLDO 的风险。

结论:鉴于 CNLDO 会影响早产儿和足月儿,这些发现可能 有助于早期识别有鼻泪管阻塞风险的儿童和婴儿,从而预 防慢性泪囊炎的发生。

关键词:危险因素;先天性鼻泪管阻塞;儿童

Abstract

• AIM: To identify various risk factors that may play a significant role in the development of congenital nasolacrimal duct obstruction (CNLDO).

- METHODS: This observational case control study included a case group of 122 children less than two years of age with CNLDO who underwent probing and irrigation treatment at the ophthalmology department of Imam Khomeini Hospital in Ahvaz, Iran, from June 2022 to June 2024. A control group of 122 age-matched children without CNLDO was also included for comparison. Data was collected from the children's medical records.
- RESULTS: The study found a significant correlation between the occurrence of CNLDO and several maternal factors, such as preeclampsia, the use of levothyroxine, hypothyroidism, having more than three pregnancies (gravidity > 3), natural pregnancy, and gestational diabetes mellitus. Additionally, in children, factors, such as oxygen therapy, anemia, reflux, jaundice, and a family history of CNLDO in first degree relatives were associated with CNLDO, and maternal preeclampsia and hypothyroidism were found to significantly increase the risk of developing CNLDO in children.
- CONCLUSION: Given that CNLDO affects both premature and full term children, the present findings may potentially facilitate the early identification of children and infants at risk of nasolacrimal duct obstruction, thereby preventing the onset of chronic dacryocystitis.
- KEYWORDS: risk factors; congenital nasolacrimal duct obstruction; children

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INTRODUCTION

ongenital nasolacrimal duct obstruction (CNLDO) is a common illness in the pediatrics, instigating failure in the nasolacrimal duct drainage system. It is existing clinically with the overflow of tears, which also called "epiphora" [1]. Studies report that the prevalence of CNLDO varies from 5% to 20% in the early phase of childhood [2-3]. In the cohort study by MacEwen and Young [3] of 4 792 infants in Britain, the prevalence of epiphora was around 20% in the first year of life, and nearly 95% of this population presented symptoms at one month of age. The pathogenesis of CNLDO lies in a mechanical obstruction situated distally in the nasolacrimal duct (NLD) at Hasner's valve [4]. Moreover, most of the

evidence showed the main reasons of obstruction as either a pathological persistence of the membrane at the distal portion of the NLD, some bone abnormalities, or a stenosis of the inferior meatus leading to a narrowing in the lacrimal drainage system^[5-6]. Interestingly, in about one—third of cases, it is bilateral, affecting both eyes^[7]. Moreover, the higher occurrence of CNLDO stated in premature infants compared with full—term ones recommends the importance of the physiological development of the nasolacrimal drainage system throughout intrauterine life, in order to ensure the patency of the NLD^[8].

The initial treatment for CNLDO typically involves massaging the lacrimal sac. If this approach does not lead to any improvement, probing and irrigation of the lacrimal ducts may be beneficial $^{[9]}$. If left untreated, the patient may develop chronic dacryocystitis $^{[10]}$. Also, more recently, a higher prevalence (10%-12%) of anisometropic amblyopia demonstrated in children with CLNDO $^{[11-12]}$.

Numerous studies have been conducted on the treatment of blocked tear ducts, acknowledging that a variety of factors can contribute to this condition. Some research has specifically investigated the correlation between the mode of childbirth (cesarean section or natural delivery) and the incidence of $CNLDO^{[13-14]}$.

Dacryocystitis is a condition characterized by the inflammation of the lacrimal sac. This inflammation is typically secondary to the obstruction of the lacrimal duct, which is responsible for naturally draining tears from the surface of the $eye^{\left[15\right]}$. In children, the obstruction of the lacrimal duct is predominantly congenital. Often, this blockage spontaneously resolves through the massage of the lacrimal sac within the first year of life $^{\left[16-17\right]}$. The congenital form of dacryocystitis, which can arise due to improper formation of the lacrimal drainage ducts, occurs in 2%-6% of infants $^{\left[16,18-19\right]}$. Generally, dacryocystitis exhibits a bimodal age distribution. One peak occurs in infancy, typically due to congenital defects in the lacrimal drainage system. The other peak is observed in adulthood, usually in individuals over 40 years of age, and is often attributable to secondary causes.

Untreated infections of the lacrimal system can potentially lead to endophthalmitis and vision loss, particularly if cataract and glaucoma surgeries are performed. If an infection of the lacrimal system is present, it is advisable to postpone any planned surgeries. Therefore, timely diagnosis and appropriate treatment of infection in the lacrimal duct system are of paramount importance^[20].

If a child experiences a blockage of the tear duct, they may exhibit symptoms, such as excessive tearing, formation of dry crusts on the eyelids, and redness and itching of the eyes or eyelids, which may be associated with the child rubbing their eyes excessively. In the event of an infection of the tear duct, additional symptoms may include the presence of yellow or green mucus discharging from the eyes, redness of the eyes, and swelling of the eyelids^[21].

Given the scarcity of studies on the epidemiological and risk factors associated with CNLDO, this research was performed on children with CNLDO, who were referred to the Department of Ophthalmology of Imam Khomeini Hospital in Ahvaz, Iran. The objective of this study was to identify various epidemiological and risk factors contributing to the development of CNLDO in children. The present findings can potentially facilitate the early identification of children and infants at risk of NLD obstruction, thereby preventing the onset of chronic dacryocystitis.

SUBJECTS AND METHODS

Ethical Approval The study adhered to rigorous ethical standards, which included obtaining an ethical code (IR. AJUMS. HGOLESTAN. REC. 1401. 188), ensuring confidentiality of patient information, and maintaining objective reporting of results.

Subjects This observational case – control study was conducted at the ophthalmology department of Imam Khomeini Hospital in Ahvaz, Iran, from June 2022 to June 2024. The study comprised a case group of 122 children less than two years of age diagnosed with CNLDO who underwent probing and irrigation treatment. A control group of 122 age—matched children without CNLDO was also included for comparison.

The study adhered to the ethical principles outlined in the Declaration of Helsinki. The inclusion criteria for the control group consisted of healthy children aged below two years who attended the ophthalmic outpatient department without any history of excessive tearing or discharge. The control group also excluded children with other congenital ophthalmic disorders, such as congenital glaucoma, retinal or corneal abnormalities. In contrast, the case group included children presenting with symptoms of CNLDO, characterized by excessive tearing, ocular matting, and mucopurulent discharge.

The diagnosis of CNLDO was established through the fluorescein dye disappearance test, which evaluates the clearance of the dye from the tear meniscus in both eyes over a five-minute interval. Children were excluded from the study if they had other causes of lacrimation, such as infantile glaucoma, foreign body presence, or corneal infections. Informed consent was obtained from the parents for their children's participation in the study.

Data Collection Prior to the commencement of the study, informed consent was secured from the parents. Mothers of the children in both the case and control groups engaged in structured interviews, responding to a series of designed questions aimed at identifying potential risk factors.

Data were collected in two phases: 1) Maternal data collection: utilizing a structured questionnaire, information was gathered from the mothers regarding the pregnancy type (natural or IVF), gravida status, medication use (notably levothyroxine), history of preeclampsia, mode of delivery, and any history of maternal diabetes or other specific diseases,

including hypothyroidism and hypertension. Confirmations for diabetes, hypothyroidism, and hypertension, along with other medical conditions and medication usage, were validated through laboratory test reports or digitally documented medical records; 2) Child-specific data collection: factors related to the child were assessed, which included gender, gestational age, birth weight, and medical history (*i.e.*, apnea, anemia, oxygen therapy, birth trauma, gastroesophageal reflux, sepsis, jaundice) as well as any familial history of NLD obstruction in first-degree relatives. This data collection was performed through a review of the child's medical records and interviews with the parents and time frame for data collection was 6 mo.

Statistical Analysis Data analysis was guided by the specific study objectives, the researchers' perspectives, and literature. Sample sizedetermination parameters such as $\alpha = 0.05$, $\beta = 0.9$, d = 8, and s = 9.5, aiming for a confidence interval (CI) of 95%. All data were initially entered into SPSS Version22. Descriptive statistical methods were employed to summarize data, utilizing frequency distribution tables and graphical representations to illustrate the study variables. Categorical variables were compared employing the Chi-square test, while continuous variables were analyzed using the t-test for normally distributed data. For non - normally distributed continuous variables, the Mann-Whitney U test was applied. Additionally, Pearson's correlation coefficient test was utilized to evaluate correlations between quantitative variables. This structured approach facilitated a comprehensive analysis of the data, contributing to the understanding of risk factors associated with CNLDO in the pediatric population. Mantel-Haenszel stratified methods, Logistic regression, or conditional logistic regression used to estimate adjusted odds ratios.

RESULTS

This study included 244 children under the age of two years, with 122 children in the case group and 122 in the control group. The results revealed that in the case group, 46.7% (n=57) of children were female, while 53.3% (n=65) were male. In the control group, 49.2% (n=60) of children were female, while 50.8% (n=62) were male. The results indicated that there was no significant difference in terms of gender between the groups (P=0.39, OR=0.9).

Regarding the history of CNLDO in first-degree relatives, in the case group, 18.9% (n=23) had a history of CNLDO in first-degree relatives, while 81.1% (n=99) did not have

such a history. In the control group, 4.9% (n=6) had a history of CNLDO in first-degree relatives, while 95.1% (n=116) did not. The results indicated a significant difference between the groups (P=0.001, OR=4.49; Table 1).

In terms of preeclampsia, 10.7% (n=13) of mothers in the case group had experienced preeclampsia, while the remaining 89.3% (n=109) had not. In the control group, 4.1% (n=5) of mothers had experienced preeclampsia during their pregnancy, while 95.9% (n=117) had not, in which the results indicated a significant difference between the groups (P=0.042, OR=2.79; Table 2).

In terms of levothyroxine use during pregnancy, 11.5% (n=14) of mothers in the case group had used levothyroxine, while 88.5% (n=108) had not. In the control group, 24.6% (n=30) of mothers had used levothyroxine during their pregnancy, while 75.4% (n=92) had not. The results indicated a significant difference between the groups (P=0.006, OR=0.39; Table 2).

Regarding gravidity, 72.1% (n=88) of mothers in the case group had fewer than three pregnancies, while 27.9% (n=34) had more than three pregnancies. In the control group, 52.5% (n=64) of mothers had fewer than three pregnancies, while 47.5% (n=58) had more than three pregnancies. The outcomes indicated a significant difference between the groups (P=0.002, OR=2.34; Table 2).

With respect to the mode of delivery, 62.3% (n=76) of mothers in the case group had a natural delivery, while 37.7% (n=46) had a cesarean section. In the control group, 54.9% (n=67) of mothers had a natural delivery, while 45.1% (n=55) had a cesarean section. The Chi – square test results revealed no statistically significant difference (P=0.149; Table 2).

Regarding the method of pregnancy, 100.0% (n=122) of mothers in the case group had a natural pregnancy, while none of them (n=0) had undergone in vitro fertilization (IVF). In the control group, 93.4% (n=114) of mothers had a natural pregnancy, while 6.6% (n=8) had undergone IVF, in which the results indicated a significant difference between the groups (P=0.003, OR=2.34; Table 2).

With respect to diabetes mellitus (DM), 5.7% (n=7) of mothers in the case group had DM, while 94.3% (n=115) did not. In the control group, 3.3% (n=4) of mothers were diagnosed with DM, while 96.7% (n=118) were not. The Chi-square test results indicated no statistically significant difference (P=0.27; Table 2).

Table 1 Evaluation of epidemiological factors in the case and control groups

(n, %)

Variables	Control group	Case group	P/Odds ratio (OR)
Gender			
Male	62 (50.8)	65 (53.3)	P = 0.39 / OR = 0.9
Female	60 (49.2)	57 (46.7)	
History of nasolacrimal duct obstruction in first-degree relatives			
Yes	6 (4.9)	23 (18.9)	P = 0.001/OR = 4.49
No	116 (95.1)	99 (81.1)	

In terms of gestational diabetes mellitus (GDM), 8.2% (n =10) of mothers had GDM in the case group, while 91.8% (n=112) did not. In the control group, 17.2% (n=21) of mothers were diagnosed with GDM, while 82.8% (n = 101) were not. The test's significance level, indicated a significant difference between the groups (P = 0.049, OR = 0.42; Table 2).

Regarding hypothyroidism, 11.5% (n=14) of mothers in the case group had hypothyroidism, while 88.5% (n = 108) did not. In the control group, 23.8% (n = 29) of mothers were diagnosed with hypothyroidism, while 76.2% (n = 93) were not. The Chi - square test results, suggesting a significant difference between the groups (P=0.009, OR=0.41; Table 2). In terms of hypertension (HTN), 6.6% (n=8) of mothers in the case group were diagnosed with HTN, while 93.4% (n =114) were not. In the control group, 4.1% (n=5) of mothers had HTN, while 95.9% (n = 117) did not. The results indicated no significant difference between the groups (P =0.28; Table 2).

With respect to apnea, 17.2% (n=21) experienced apnea in the case group, while 82.8% (n = 101) did not. In the control group, 10.7% (n = 13) experienced apnea, while 89.3%

(n = 109) did not. The results indicated no statistically significant difference (P = 0.098; Table 3).

In terms of birth trauma, none of the children in the case group had experienced a birth trauma. In the control group, 3.3% (n = 4) of children had experienced a birth trauma, while 96.7% (n = 118) had not. The Chi-square test results revealed no statistically significant difference between the groups (P = 0.06; Table 3).

Regarding reflux, 54.1% (n = 66) of children in the case group experienced reflux, while 45.9% (n = 56) did not. In the control group, 22.9% (n = 28) of children experienced reflux, while 77.1% (n = 94) did not. The test's results indicated a significant difference between the groups (P =0.001, OR = 2.33; Table 3).

In terms of sepsis, it was observed that none of the children in either the case or control group had experienced sepsis. In relation to jaundice, 41.0% (n=50) of children had jaundice in the case group, while 59.0% (n = 72) did not. In the control group, 19.7% (n = 24) of children had jaundice, while 80.3% (n = 98) did not. The results indicated a significant difference between the groups (P=0.001), and the OR was calculated to be 2.83 (Table 3).

Table 2	Evaluation of maternal factors in	(n, %)	
Variables	Control group	Case group	P/OR
Preeclampsia			
Yes	5 (4.1)	13(10.7)	P = 0.042/OR = 2.79
No	117 (95.9)	109(89.3)	
Levothyroxine use			
Yes	30 (24.6)	14 (11.5)	P = 0.006/OR = 0.39
No	92 (75.4)	108 (88.5)	
Gravidity			
>3	58 (47.5)	34 (27.9)	P = 0.002/OR = 2.34
€3	64 (52.5)	88 (72.1)	
Mode of delivery			
Natural birth	67 (54.9)	76 (62.3)	P = 0.149
Cesarean section	55 (45.1)	46 (37.7)	
Type of pregnancy			
Natural birth	114 (93.4)	122 (100.0)	P = 0.003/OR = 2.34
IVF	8 (6.6)	0 (0)	
Diabetes mellitus			
Yes	4 (3.3)	7 (5.7)	P = 0.27
No	118 (96.7)	115 (94.3)	
Gestational diabetes mellitus			
Yes	21 (17.2)	10 (8.2)	P = 0.049 / OR = 0.42
No	101 (82.8)	112 (91.8)	
Hypothyroidism			
Yes	29 (23.8)	14 (11.5)	P = 0.009 / OR = 0.41
No	93 (76.2)	108 (88.5)	
Hypertension			
Yes	5 (4.1)	8 (6.6)	P = 0.28
No	117 (95.9)	114 (93.4)	

IVF: In vitro fertilization.

In respect of birth weight, in the case group, 18.0% (n=22) of children had a birth weight of less than 2 500 g, while 82.0% (n=100) weighed more than 2 500 g. In the control group, 19.7% (n=24) of children weighed less than 2 500 g, while 80.3% (n=98) weighed more than 2 500 g. The results indicated no significant difference between the groups (P=0.31; Table 3).

Regarding gestational age, in the case group, 17.2% (n=21) of the children were born before 37 weeks of gestation, while 82.8% (n=101) were born after 37 weeks of gestation. In the control group, 16.4% (n=20) of the children were born before 37 weeks of gestation, while 83.6% (n=102) were born after 37 weeks of gestation. The Chi-square test results suggested no significant difference between the groups (P=0.5; Table 3).

In relation to oxygen therapy, in the case group, 22.1% (n=27) of the children had undergone oxygen therapy, while 77.9% (n=95) had not. In the control group, 23.0% (n=28) of the children had undergone oxygen therapy, while 77.0% (n=94) had not. The results indicated a significant difference between the groups (P=0.049; Table 3).

In terms of anemia, in the case group, 6.6% (n=8) of the children had anemia, while 93.4% (n=114) did not. In the control group, 13.9% (n=17) of the children had anemia,

while 86.1% (n=105) did not. The results indicated a significant difference between the groups (P=0.045; Table 3).

DISCUSSION

CNLDO is a common pediatric condition characterized by the failure of the NLD to properly canalize during embryonic development. This developmental aberration leads to impaired tear drainage, resulting in epiphora and a heightened risk of conjunctival infections due to stagnant tears. The pathophysiology of CNLDO is not only limited to anatomical anomalies but also encompasses a complex interplay of physiological factors that may be influenced by prenatal and perinatal conditions [1-2].

In recent years, there has been increasing interest in understanding how delivery methods may impact the occurrence of CNLDO. Notably, cesarean delivery is hypothesized to disrupt the biomechanical forces that facilitate normal duct development. Evidence suggests that the absence of vaginal delivery's compressive forces could potentially hinder the proper morphological changes necessary for optimal NLD maturation. Recent studies have begun to elucidate this relationship, indicating that infants born *via* cesarean section may exhibit a higher incidence of CNLDO compared to those delivered vaginally. This finding has important implications for

Table 3 Evaluation of pediatric related factors in the case and control groups

(n, %)

1	able 3 Evaluation of pediatric related fa	groups $(n, \%)$	
Variables	Control group	Case group	P/OR
Apnea			
Yes	13 (10.7)	21 (17.2)	P = 0.098
No	109 (89.3)	101 (82.8)	
Birth trauma			
Yes	4 (3.3)	0 (0)	P = 0.06
No	118 (96.7)	122 (100.0)	
Reflux			
Yes	28 (22.9)	66 (54.1)	P = 0.001/OR = 2.33
No	94 (77.1)	56 (45.9)	
Sepsis			
Yes	0 (0)	0 (0)	_
No	122 (100.0)	122 (100.0)	
Jaundice			
Yes	24 (19.7)	50 (41.0)	P = 0.001/OR = 2.83
No	98 (80.3)	72 (59.0)	
Birth weight			
>2 500 g	98 (80.3)	100 (82.0)	P = 0.31
<2 500 g	24 (19.7)	22 (18.0)	
Gestational age			
>37 w	102 (83.6)	101 (82.8)	P = 0.5
<37 w	20 (16.4)	21 (17.2)	
Oxygen therapy			
Yes	28 (23.0)	27 (22.1)	P = 0.049
No	94 (77.0)	95 (77.9)	
Anemia			
Yes	17 (13.9)	8 (6.6)	P = 0.045
No	105 (86.1)	114 (93.4)	

obstetric practices and reinforces the need for further investigations into the perinatal factors that may affect the risk of this condition, ultimately informing strategies for prevention and management^[22].

The findings of this study reveal that among children diagnosed with CNLDO, 46.7% are female, with multiple maternal and infant characteristics associated with an increased risk for this condition. Specifically, 18.0% of the children within the case group were born with a birth weight below 2 500 grams, 17.2% were delivered preterm (before 37 weeks of gestation), and 22.1% required oxygen therapy. 10. 7% of mothers reported experiencing preeclampsia during their pregnancies, while 11.5% indicated the use of levothyroxine. Furthermore, 27.9% of mothers stated they had undergone more than three pregnancies, with 62.3% having delivered via natural childbirth. Other relevant factors observed included 54.1% of children presenting with reflux, 41.0% exhibiting jaundice, and 18.9% possessing a familial history of CNLDO.

In our investigation of potential risk factors related to CNLDO, no significant associations were identified with the mode of delivery, DM, HTN, apnea, birth trauma, birth weight, gestational age, or gender. In contrast, significant correlations were found between CNLDO and various factors, including maternal preeclampsia, levothyroxine use, gravidity greater than three, natural conception, GDM, hypothyroidism, oxygen therapy, anemia, reflux, and jaundice (P < 0.05). Subsequently, Logistic regression analysis indicated that a family history of CNLDO, maternal preeclampsia, gravidity greater than three, natural conception, reflux, and jaundice were notable predictors of increased risk for CNLDO. Importantly, the adjusted odds ratios demonstrated that hypothyroidism preeclampsia and significant contributors to the development of CNLDO in infants.

These findings are consistent with the results of other studies. For instance, Valchva $et\ al^{[7]}$ conducted a case – control study, which identified maternal use of antibiotics and levothyroxine as independent risk factors for CNLDO. Our findings corroborate the association between levothyroxine and CNLDO but did not assess maternal antibiotic use due to a lack of documented cases for this variable.

Ulutaş and Uçan Gündüz^[23] conducted a retrospective study assessing the impact of cesarean delivery on the incidence of CNLDO in 173 children from 2016 to 2020 and concluded that cesarean delivery could represent an independent risk factor for this condition. This conclusion aligns with the findings from Kuhli–Hattenbach *et al*^[24], who examined the mode of delivery, birth weight, and incidence of CNLDO in a cohort of 2 591 children, further suggesting cesarean delivery as a risk factor. Interestingly, our study did not find a significant correlation between cesarean deliveries and CNLDO, potentially attributable to the low number of cesarean cases in

our sample.

Moreover, Aldahash et $al^{[25]}$ conducted a cross – sectional study encompassing 756 children, indicating that infections during pregnancy might represent an independent risk factor for CNLDO. Nevertheless, the present study did not investigate maternal infections, which should be assessed in future studies in combination with other pertinent risk factors. Additionally, Kasaei et al^[26] conducted a study on 60 newborns, reporting no significant relationship between CNLDO and factors such as gender and gestational age, which aligns with our results. Conversely, a retrospective study by Lorena et al^[8] involving 400 newborns from 2004 to 2009 concluded that prematurity could be an independent risk = factor for CNLDO. Similarly, Sathiamoorthi et al^[2] reported findings from a study of 17 713 children from 1995 to 2004, which also indicated that prematurity may increase the risk for CNLDO. In contrast, our study did not find a significant association between prematurity and CNLDO, which may be a consequence of the reduced number of premature infants in our cohort or improvements in medical management that have diminished associated risks.

In summary, our findings highlight the complex interplay of maternal and infant factors contributing to CNLDO. Specifically, maternal health conditions, particularly preeclampsia and hypothyroidism, emerge as critical risk factors. Future research should further explore the influence of maternal infections and antibiotic use. alongside advancements in neonatal care, to provide comprehensive understanding of CNLDO risk factors.

In conclusion, CNLDO can affect both premature and fullterm children. Therefore, identification and prevention or proper control of risk factors is crucial as it can lead to advancements in preventing this condition. For these purposes, early standard diagnostic screenings for CNLDO, especially in high-risk groups may be recommended. Also, the present findings may potentially facilitate the early identification of children and infants at risk of NLD obstruction, thereby preventing the onset of chronic dacryocystitis. Future studies may focus on combined comparison of found significant risk factors of present study with previous ones such as antibiotic use, cesarian and prematurity in addition to more cases to achieve better view for prevention and management of CNLDO.

Conflicts of Interest: Kasiri R, None; Khataminia G, None; Kasiri A, None; Mirdehghan MS, None; Kasiri MA, None.

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