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The Association Between *Helicobacter pylori* Infection With Different Types of Colon Cancer and Children's Diseases: An Overview of Meta-analyses

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Abstract

Objectives: *Helicobacter pylori* is a gram-negative curved bacillus that assumes a significant role in colon cancer and children´s diseases. This study aimed to examine the association between *H. pylori* infection with colon cancer and children´s diseases in order to achieve a a comprehensive understanding of these associations and for future works.

Methods: Three main databases (i.e., Cochrane Central Register of Controlled Trials [CENTRAL], Scopus, and MEDLINE) were systematically searched by two reviewers from their inception date to 2022 in order to determine the association between the *H. pylori* infection with the colon cancer and children's diseases.

Results: The findings of two meta-analyses were similar regarding the positive association between the risks of colorectal neoplasm (pooled OR=0.18; 95% CI of 0.99–1.40; $P>0.05$) and colon neoplasia (pooled OR=0.41; 95% confidence interval 1.24–1.60; P=0.000). *H. pylori* was associated with an increased risk of colorectal adenoma, adenocarcinoma, and advanced adenoma. Also *H. pylori* infection was correlated with a high risk of iron deficiency anemia (IDA), otitis media with effusion (OME), Henoch-Schonlein purpura, and growth disorders in children.

Conclusions: In sum, the *H. pylori* infection may have been associated with an increased risk of colorectal cancer and children's diseases.

Keywords: *Helicobacter pylori* infection, Colon cancer, Children, Meta-analysis

Introduction

Helicobacter pylori infection, as a spiral-shaped gram-negative bacterium, has a global spread, with a mean colonization rate of approximately 58% and a higher prevalence in less-industrialized regions (1). According to the systematic reviews and meta-analyses, the global annual recurrence rate of the *H. pylori* infection is 4.3%. The lowest and highest prevalence rates of the *H. pylori* infection were 24.4% (in Oceania) and 79.1% (in Africa), respectively (2).

Helicobacter pylori plays a vital role in causing gastrointestinal diseases such as gastritis, peptic ulceration, gastric adenocarcinoma, and gastric lymphoma. The World Health Organization (WHO) has recognized *H. pylori* as a risk factor for stomach cancer (3-5). Gastrointestinal cancers (e.g., gallbladder, anal, pancreatic, esophageal, colon, small intestine, gastric, colorectal, and liver cancers) are among the deadliest cancers in the world (6). Various risk factors responsible for gastrointestinal cancers such as genetic characteristics, diet, diabetes mellitus, race, alcohol consumption, tobacco smoking, increasing age, blood groups, and family history negatively contribute to human gastrointestinal carcinoids (4,5). According to one hypothesis, *H. pylori* may provide the basis for the carcinogenicity via atrophic gastritis-mediated hypergastrinemia and, consequently, for the reduced acid secretion (1).

In the last decade, various evidence has been presented about the correlation of some gastrointestinal cancers with a colonization or an infection caused by the *H. pylori*, especially by *cagA* (i.e., cytotoxin-associated gene A) and *vacA* (i.e., vacuolating cytotoxin gene A) positive *H. pylori* strains (4-7).

According to the conclusive evidence, *H. pylori* contributes particularly to developing gastric cancer and extra-gastric gastrointestinal malignancies, such as colon and esophageal cancers (8). Colorectal carcinoma has been recognized as the third most prevalent malignancy and

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the fourth leading cause of cancer death worldwide (9). Risk factors involved in the development of cancer colon include external or environmental factors, inflammatory bowel diseases, obesity, alcohol consumption, and certain dietary patterns (10).

In this light, 6 meta-analyses addressed the associations between *H. pylori* and colorectal cancer (9-14), 5 meta-analyses examined the correlation of *H. pylori* with colorectal adenoma and adenocarcinoma (9,11,15-17), and two meta-analyses explored the relationship between *H. pylori* and risk of developing advanced colorectal adenoma (15,16).

While the focus of attention in previous meta-analyses was on the association between *H. pylori* and colorectal cancer, recent meta-analyses—studies published between 2020-2022, in particular—have focused on the association between the *H. pylori* infection and the children's diseases, and have found that the *H. pylori* infection may adversely affect the growth disorders (18) and pose higher risks of otitis media with effusion (OME) (19) and Henoch-Schonlein purpura (20). A meta-analysis by Hamdan et al showed that the *H. pylori* infection was associated with a high risk of iron deficiency anemia (IDA) in children (21). This overview aimed to examine the association between *H. pylori* infection and different types of colon cancer and children's diseases.

Search Strategy

Four main electronic databases, namely Scopus, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, were systematically searched by two reviewers from their inception date to 2022 in order to determine the association between the *H. pylori* infection and different types of colon cancer. The search keywords in English were ("Helicobacter pylori" OR "H pylori" OR "H. pylori" OR "Helicobacter species" OR "Helicobacter spp" OR "Helicobacter" OR "Helicobacter pylori" OR "Helicobacter bilis" OR "Helicobacter hepaticus" OR "Helicobacter pullorum" OR "H. pylori" OR "Campylobacter pylori" OR "Helicobacter species") AND ("colorectal adenocarcinoma" OR "colorectal adenoma" or "cancer" OR "colorectal" OR "tumors" OR "neoplasm" OR "malignancy" OR "adenocarcinoma" OR "carcinoma" OR "Children") AND (meta-analysis). The reference lists of all identified meta-analyses were hand-searched to detect the missed met-analyses. Figure 1 depicts the meta-analyses selected for inclusion in this overview.

Inclusion Criteria

1) All meta-analyses on cohort or case-control studies;
2) Studies published in English;
3) Studies examining the association among the colon cancer, children´s diseases, and *H. pylori* infection;
4) Exposure to *H. pylori* infection confirmed by at

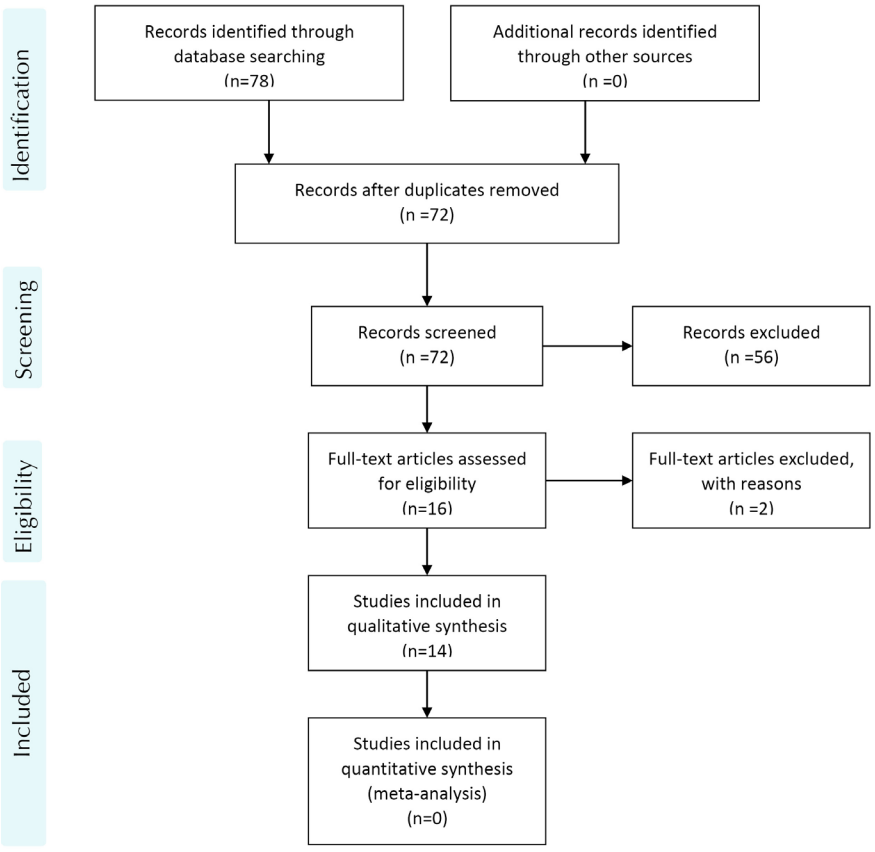

Figure 1. Meta-analyses Selected for Inclusion in This Overview.

least one of the invasive tests (i.e., histopathology, endoscopy, and biopsy), and non-invasive tests (i.e., polymerase chain reaction, immunoglobulin G detection, stool antigen, and the 13C-urea breath test).

Exclusion Criteria

1) Cell culture and animal studies:
2) Article types such as letter, abstract, original article, and systematic review without meta-analysis.

Data Extraction

A predesigned form was used by the two reviewers to perform data extraction. The following variables were collected: publication year, authors and main results and subgroup (Tables 1 and 2).

Methodological Assessment of Meta-analysis

Measurement Tool Assess Reviewer (AMSTAR) approach was used to evaluate the meta-analyses in this overview. This checklist includes 12 questions (Table 3).

Results

The Association Between Colon Cancer and *H. pylori* Infection

Two meta analyses investigated the relationship between *H. pylori* and colorectal neoplasia and colon neoplasia, and found a positive relationship between *H. pylori* and colorectal neoplasia chances (pooled odds ratio [OR] = 0.18; 95% C: 0.99–1.40; $P > 0.05$) (9) and colon neoplasia (pooled OR = 0.41; 95% CI: 1.24–1.60; $P = 0.000$) (8). Six meta-analyses assessed the associations between colorectal cancer and *H. pylori*. Positive associations were detected between *H. pylori* and colorectal cancer in all meta-analyses, including meta-analyses by Wu et al (OR = 1.39; 95% CI: 1.18–1.64; Heterogeneity = 0.057; $I^2 = 35.8\%$) (11), Yang et al (OR = 1.27; 95% CI: 1.17-1.37; $P < 0.001$) (12), Njei et al (OR = 1.49; 95% CI: 1.22-1.82; $P < 0.001$) (13), Guo et al (OR = 1.08; 95% CI: 0.89–1.68; $P > 0.05$) (9), Zuo et al (pooled OR = 1.70; 95% CI: 1.64–1.76) (14), and Chen et al (1.49; 95% CI: 1.30-1.72) (10). *H. pylori* was discovered to be associated with an increased risk of colorectal adenoma in 4 meta-analyses including meta-analyses by Hong et al (OR = 1.36; 95% CI: 1.10–1.68) (15), Choi et al (pooled OR: 1.49; 95% CI: 1.37–1.62) (16), Wu et al (OR = 1.66; 95% CI: 1.39 1.97; heterogeneity $P = 0.008$; $I^2 = 54.3\%$) (11), and Guo et al (OR = 1.83; 95% CI: 1.35–2.51; $P < 0.01$) (9). The relationship between colorectal adenocarcinoma and *H. pylori* was investigated by one meta-analysis, according to which *H. pylori* was associated with an increased risk of colorectal adenocarcinoma (OR = 1.24; 95% CI: 1.12–1.37; $P = 0.66$) (17). The association between *H. pylori* and risk of developing colorectal advanced adenoma was confirmed by two meta-analyses including those by Choi et al (pooled OR = 1.50; 95% CI: 1.28–1.75) (16) and Hong et al (OR = 2.21; 95 % CI: 1.41–3.48) (15).

The Association Between Children's Diseases and *H. pylori* Infection

Xu et al showed that *H. pylori* infection may have strongly influenced the children's height-for-age Z scores ($P < 0.01$), and reported that the *H. pylori* infection was statistically and significantly associated with the ponderal growth disorders ($P = 0.02$) and linear growth disorders ($P = 0.01$) (18). Wei et al also documented a significant correlation between the H pylori infection and the delayed childhood growth (OR = 1.51; 95% CI: 1.28-1.78). This correlation was statistically significant in both type of studies, namely the cross-sectional (OR = 1.43; 95% CI: 1.18-1.73) and the case-control (OR = 1.81; 95% CI; 1.23-2.67) studies (22). Wu reported a significant association between the H pylori infection and the OME, which was statistically significant for both adenoid samples from the case group ($P = 0.002$) and middle ear fluid samples from the case group ($P < 0.00001$) (19). The meta-analysis by Hamdan et al revealed that the *H. pylori* infection was correlated with a high risk of IDA (OR = 1.70; 95% CI: 1.21–2.38) in children (21). Xiong et al, moreover, discovered a relationship between Helicobacter pylori infection and Henoch-Schonlein purpura in Chinese children (pooled OR = 3.80; 95% CI: 2.54–5.68; $P < 0.001$) (20), and detected a correlation of pylori infection with a high risk of IDA, OME, Henoch-Schonlein purpura, and growth disorders in children.

Discussion

The associations between some cancers with viral and bacterial infections have been confirmed by the literature (3). This systematic review aimed to examine the relationship between *H. pylori* and the risk of colorectal cancer using a variety of data sources and then incorporating the findings into a meta-analysis. It was revealed that the *H. pylori* infection was associated with a high risk of IDA, OME, Henoch-Schonlein purpura, and growth disorders in children.

Colorectal cancer is the fourth deadliest cancer in the world and its rate, unfortunately, is increasing rapidly in some areas (23,24). Thus, controlling and monitoring the infection progress effectively may prove useful in preventing the cancer (25). *H. pylori*, as a gram-positive bacterium, can enter the human digestive tract, infect gastric mucosa, and cause gastric adenocarcinoma, peptic ulcer, and chronic gastritis (26-28). According to recent studies, the *H. pylori* infection associated with the stomach-related disorders may induce a prolonged inflammation of the stomach and impact other organs systemically, notably by developing extra gastric lesions (23). Moreover, the frequency of some disorders such as respiratory, cardiovascular, digestive, extra gastroduodenal, nervous, and other autoimmune diseases is closely related to seropositive for the *H. pylori* infection

Table 1. Characteristic of Meta-analyses Examining the Association Between Colon Cancer and *H. pylori* Infection

Study	Sample size	Association between *H. pylori* Infection and Adenomatous Polyp	Association between *H. pylori* Infection and Colorectal Adenocarcinoma	Association between *H. pylori* Infection and Colorectal Adenomas	Association between *H. pylori* Infection and Colorectal Hyperplastic Polyps	Association between *H. pylori* Infection and Colorectal Neoplasm	Association between *H. pylori* Infection and Colon Cancer	Association between *H. pylori* Infection and Colon Polyps	Association between *H. pylori* Infection and colorectal Adenoma	Association between *H. pylori* Infection and Advanced Adenoma	Association between *H. pylori* Infection and Colorectal Cancer
Rokkas et al (8)	33 studies	-	-	-	-	-	OR = 1.3 (1.07–1.59, *P* = 0.01)	OR = 1.5 (95% 1.26–1.79; *P* = 0.000)	-	-	-
Guo et al (9)	Colorectal neoplasm patients n=2081, Healthy controls (n=5598)	-	-	OR = 1.83 (95% CI: 1.35–2.51, *P*<0.01)	OR = 0.72 (95% CI: 0.44–1.18, *P*>0.05)	OR=0.18 (95% CI: 0.99–1.40, *P*>0.05)	Cancer (OR= 1.08, 95% CI: 0.89–1.68 *P*>0.05)	-	-	-	-
Hong (15)	2195 subjects	-	-	-	-	-	-	-	OR=1.36 (95% CI: 1.10–1.68)	OR=2.21 (95% CI: 1.41–3.48).	-
Njei et al (13)	16 studies	-	-	-	-	-	OR: 1.49 (95% CI: 1.22-1.82; *P*<0.001)	-	-	-	-
Yang et al (12)	27studies	-	-	-	-	-	-	-	-	-	OR=1.27 (95% CI: 1.17-1.37 (*P*<0.001)
Wang et al (17)	27 studies	OR=1.87, 95% CI (1.53–2.28, *P*=0.81)	OR=1.24 (95% CI 1.12–1.37, *P*=0.66)	-	-	-	-	-	-	-	-
Zuo et al (14)	47 studies	-	-	-	-	-	-	-	-	-	OR=1.70 (95% CI: 1.64–1.76)
Wu et al (11)	27 studies	-	-	-	-	-	-	-	OR = 1.66 (95% CI: 1.39-1.97)	-	OR= 1.39 (95% CI 1.18–1.64)
Choi et al (16)	48 studies	-	-	-	-	-	-	-	OR = 1.49 (95% CI: 1.37–1.62)	OR=.50 (95% CI: 1.28–1.75)	OR=1.44 (95% CI: 1.26–1.65)
Chen et al (10)	22 studies	-	-	-	-	-	-	-	-	-	OR=1.49 (95% CI: 1.30-1.72).

Table 2. Characteristic of Meta-analyses Examining the Association between Children´s Diseases and *H. pylori* Infection

Study	Sample Size	Association between *H. pylori* Infection and Henoch-Schönlein Purpura	Association between *H. pylori* Infection and IDA	Association between *H. pylori* Infectionn and Media with Effusion	Association between *H. pylori* Infection and Delayed Childhood Growth	Association between *H. pylori* Infection and Growth Outcomes
Xiong et al (20)	749 Henoch-Schonlein purpura children and 560 controls	Pooled OR= 3.80 (95% CI: 2.54-5.68, *P*<0.001)	-	-	-	-
Hamdan et al (21)	3434 cases and 4455 control		OR = 1.70, (95% CI: 1.21-2.38)	-	-	-
Wu et al (19)	11 studies	-	-	OR = 2.75; (95% CI: 1.43-5.30; *P*=0.002)	-	
Wei et al (22)	4199 subjects	-	-	-	OR = 1.51; (95% CI: 1.28-1.78)	-
Xu et al (18)	9384 subjects					OR = 2.47 (95% CI: 1.13=5.37; *P*=0.02)

(29,30). Hence, it seems that *H. pylori* indirectly causes cancer. Gastritis related to *H. pylori* is also associated with an increased risk of colorectal cancer and is found in the malignant tissues (31). The particular relationship between the *H. pylori* infection and an increased risk of colorectal cancer has not been determined. However, the *H. pylori* inflammation may disrupt the cell cycle and start a mechanism of carcinogenesis. The *H. pylori*'s cytotoxin-associated gene A (*cagA*), on the other hand, has been linked to an increased risk of gastric cancer. Since CagA can directly bind to and activate the human phosphatase (SHP2), it can act as a tumor marker for promoting the cell growth. Hypergastrinemia may be associated with hyper- or hypo-chlorhydria, and a prolonged exposure to *H. pylori* could start a cascade of hyperplasia to neoplasia, with carcinogenic potential. Chen et al reported the increased circulating gastrin levels in individuals colonized with *H. pylori* and affected by a developed colorectal cancer. In a meta-analysis study including 55,811 cases of control and 17,416 cases of colorectal cancer, Zuo et al showed that the *H. pylori* infection had the potential to increase the risk of colorectal cancer (7). Moreover, Epplein et al demonstrated that the patients with high amounts of antibodies specific to *H. pylori* proteins may have faced a greater risk of colon cancer (32). However, these results were not consistent with the findings from some other studies regarding the relationship between colorectal cancer and *H. pylori* infection (33,34). According to de Fernández de Larrea-Baz et al, for instance, *H. pylori* seropositivity to the virulence factor *cagA* is not linked to an increased risk of colorectal cancer (35). In addition, some *H. pylori* strains that may express the *cagA* gene have been linked to an increased inflammatory response and, consequently, to a raised blood gastrin level, raising the risk of gastric cancer (36). Further investigations are still required to examine the chaperonin GroEL, *Helicobacter* cysteine-rich protein C, and the vacuolating toxin (VacA), known as the potential relevance of further virulence factors. According to Zhang et al, the *H. pylori* infection is linked to a minor but relevant risk increase in the left colorectum (36). These contradictions might be attributed to several factors such as different methodologies, differences in the age distribution, educational level, smoking status, sex, physical activity, country of birth, average lifetime, and immunity status of the individuals. Furthermore, most meta-analysis studies only include English language reports. A study on 29 meta-analyses assessing language bias has provided evidence that OR estimated in meta-analyses from non-English publications are on average 0.8 (95% CI, 0.7–1.0) times those from English-written publications (37). However, the notion presuming the association between the *H. pylori* infection and the colorectal cancer is only a theory at this stage. Furthermore, experimental findings have shown that some potential carcinogenic interactions between colonic mucosa and *H. pylori* might contribute to the tumor formation (38,39). In agreement with the findings from previous studies, our results showed a positive correlation between the risk of colorectal cancer and the *H. pylori* infection in different populations worldwide. One of the limitations of our study was its failure to investigate the treatment effect of the *H. pylori* infection on reducing the incidence of colorectal cancer. Therefore, it was recommended that further research should be carried out to arrive at more reliable conclusions and obtain enough information on possible confounding variables. It should be noted that the IDA occurs as a result of the *H. pylori* infection in patients with gastric cancer due to active hemorrhage and iron utilization by bacteria for colonization (40).

Conclusions

Despite the contradictory results reported by various studies and their limitations, it was found that an infection with *H. pylori* was associated with a higher risk of colorectal cancer in adults. *H. pylori* was correlated with deficiency

Table 3. Methodological Quality Assessment of Meta-analysis Using the AMSTAR Rating

Questions	Studies														
	Wang et al (17)	Zuo et al (14)	Wu et al (11)	Choi et al (16)	Yang et al. (12)	Njei et al (13)	Rokkas et al (8)	Guo et al (9)	Hong et al (15)	Chen et al. (10)	Xiong et al (20)	Hamdan et al (21)	Wu et al (19)	Wei et al (22)	Xu et al (18)
1) To address a straightforward question	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2) Comprehensive search	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
3) Systematic and reproducible search	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4) Has prevention of publication bias	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
5) Definition inclusion and exclusion criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6) Methodological quality	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
7) Description of key features	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8) Correct meta-analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9) Results similar from study to study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10) Effect size	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11) CIs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12) Results be applied to your organization?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

anemia, OME, Henoch-Schonlein purpura, and growth disorders in children. However, it was recommended that a more randomized controlled trial with an internal and external validity should be conducted in order to confirm these findings. It was also suggested that more valid and confirmative explorations should be carried out to identify the underlying biological mechanisms of this relation.

Authors' Contribution

Conceptualization: Masumeh Ghazanfarpour, Davood Kalantar-Neyestanaki, and Bahar Banasaz.
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Funding acquisition: Masumeh Ghazanfarpour and Davood Kalantar-Neyestanaki
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Methodology: Masumeh Ghazanfarpour, Bahar Banasaz and Davood Kalantar-Neyestanaki.
Project administration: Masumeh Ghazanfarpour and Davood Kalantar-Neyestanaki.
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Supervision: Masumeh Ghazanfarpour and Davood Kalantar-Neyestanaki.
Validation: Masumeh Ghazanfarpour, Bahar Banasaz and Davood Kalantar-Neyestanaki
Visualization: Ghazanfarpour, Bahar Banasaz, and Davood Kalantar-Neyestanaki.
Writing–original draft: Masumeh Ghazanfarpour, Davood Kalantar-Neyestanaki, Bahar Banasaz and Hossein Zarrinfar.
Writing–review & editing: Masumeh Ghazanfarpour, Davood Kalantar-Neyestanaki, Mahmood Barani, and Hossein Zarrinfar Bahar Banasaz.

Conflict of Interests

None.

Ethical Issues

None.

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