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Research Article

# Alteration in the expression of *PELP1* and *c-Src* genes in tumor tissue of colorectal cancer patients

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## ABSTRACT

**Objectives:** The genetic and environmental factors have crucial role in colorectal cancer (CRC) pathogenesis. Due to important role of proline , glutamic acid, and leucine-rich protein 1 (*PELP1*) and *c-Src* genes in different types of malignancy, this study aimed to investigate the expression levels of the *PELP1* and *c-Src* genes in tumor versus matched non-cancerous margin tissues of patients with CRC, and further evaluate their capacity as potential diagnostic biomarkers.

**Methods:** The gene expression of *PELP1* and *c-Src* in 31 tumor tissues and 31 non-cancerous margin tissues of CRC subjects was analyzed by the Real-Time PCR. Moreover, Receiver Operating Characteristic (ROC) curve analysis was utilized for the determination of these genes' RNA levels as potential biomarkers.

**Results:** Our findings indicated the increased *PELP1* (P=0.016) and *c-Src* (P=0.006) gene expression in tumor tissues, compared to non-cancerous margin tissues in CRC. The result of ROC analysis showed that the area under the curve (AUC) for *PELP1* and *c-Src* were 0.673 (Cut off:7.74, sensitivity:0.714, specificity:0.615) and 0.731 (Cut off:16.04, sensitivity: 0.857, specificity: 0.653), respectively.

**Conclusion:** The higher expression of *c-Src* and *PELP1* genes in tumor tissues compared to non-cancerous margin tissues indicated that these genes are critical components of the signaling pathways involved in CRC pathogenesis. Furthermore, the findings revealed that studied genes can have a potential for diagnosis purposes in CRC.

**Keywords:** *c-Src*, *PELP1*, Colorectal cancer, gene expression

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## Introduction

Colorectal cancer (CRC), a major health issue, is highly frequent around the world (1). Similar to other types of malignancy, the CRC results from a combination of genetic and environmental variables that can occur due to mutations in tumor suppressor, proto-oncogenes, growth factors and their receptor genes. Therefore, a wide system of diverse genes can play a role in the development of CRC; thus, it is crucial to identify the genes that have role in the path of CRC and also their regulatory factors (2, 3). *PELP1* and *c-Src* are among the effective genes in CRC.

Proline, glutamic acid, and leucine-rich protein 1 (PELP1) is involved in many normal and physiological processes as well as in many malignancies (4-6). Previous researchers have shown that PELP1 plays a key role in various types of tumors (7). PELP1 is known to interact with several signaling pathways that are crucial for cancer cell proliferation and survival. Research indicates that PELP1 may modulate the response to hormonal signaling and contribute to the development of resistance against typical therapies, such as chemotherapy (8). This gene acts as an oncogene by upregulating c-Src, a critical protein involved in the proliferation and invasion of cancer cells. Silencing *PELP1* leads to a reduction in c-*Src*, thereby inhibiting the proliferation, migration and invasion of CRC cells (3).

c-Src is a non-receptor tyrosine kinase that becomes aberrantly activated in CRC, contributing to various cellular processes such as proliferation, survival, migration, and invasion. It activates multiple downstream signaling pathways, including the PI3K-AKT and Ras-MAPK pathways, which are crucial for cancer cell growth and metastasis (9). In a large number of patients with CRC, Src activity is increased and the data show that c-Src can act as a mediator of cell signaling (10). In addition, increased expression of this gene enhances cell invasion and migration (11).

Considering the importance that CRC has gained all over the world today due to the increasing rate of incidence and death, early diagnosis of this disease is very important for patients. It is therefore pertinent to investigate PELP1 and c-Src in CRC, given their significant role in tumor growth, metastasis, and resistance to treatment. The inhibition of oncogenic pathways and facilitation of sensitivity to existing treatments imply novel therapeutic strategies aiming to improve patient outcomes in CRC through the targeting of these proteins. Continued research into their mechanisms will be vital for developing effective interventions against this malignancy. Therefore, in the present work, we decided to study the expression levels of these two important genes, *c-Src* and *PELP1*, which might be important in CRC pathway and pathogenesis, and evaluate them in terms of their biomarker capacity.

## Material and Methods

### Sample collection

This case-control study utilized 31 fresh frozen CRC samples as the case group and 31 non-cancerous margin tissues as the control group which were obtained from 31 patients with CRC at the Iran Tumor Bank/ Tehran University of Medical Sciences (Iran). Sample selection adhered strictly to ethical standards and required informed consent from participants. The CRC was confirmed by histopathological examination, furthermore, control tissues confirmed as non-cancerous via histopathological examination (the histopathological information were obtained from Iran National Tumor Bank). Crucially, the study implemented rigorous exclusion criteria, systematically excluding patients with a history of Inflammatory Bowel Disease (IBD), patients who had received chemotherapy or radiotherapy, those using anti-inflammatory drugs, and individuals presenting with metastatic CRC originating from other primary sites were also excluded from the analysis. The present study was confirmed by Research Ethical Committee of Islamic Azad University of Shahrood (IR.IAU.SHAHROOD.REC.1401.027).

### Gene expression analysis

To gene expression analysis, total RNA was extracted from cancerous and non-cancerous margin tissues. Brifily, up to 50 mg of fresh frozen tissue was crushed using liquid nitrogen and RNX plus solution (Sinaclon, Iran) was used for RNA extraction. Then, the quality of total RNA was assessed by 1% Tris-acetate EDTA-agarose gel electrophoresis. Subsequently, cDNA was synthesized using cDNA synthesis kit (Cat No: YT4500, Yekta Tajhiz Azma, Iran). The primers were obtained from Sinaclon company (Sinaclon, Iran) and sequence of forward and reverse primers in present study were: *β-actin* (forward 5′- CATGTACGTTGCTATCCAGGC-3′, and reverse: 5′- CTCCTTAATGTCACGCACGAT-3′), *PELP1* (forward TCAGTAATGCACGTCTCAGTTC and reverse CTCCGAAGCCAAGACACACAG), and *c-Src* (forward TGTTCGGAGGCTTCAACTCC and reverse CAGTAGGCACCTTTCGTGGT). The gene expression analysis was carried out using quantities RT-PCR by the Real Q plus 2x maser mix Green (Ampliqon) on Applied Biosystems, Step One Plus, USA. The fold change of the *PELP1* and *c-Src* was calculated based on $2^{-\Delta\Delta Ct}$ formula (the *β-actin* was applied as housekeeping gene).

### Statistical analysis

Statistical analysis of the collected data was performed using SPSS software (version 16). The Kolmogorov-Smirnov test was initially employed to assess the normal distribution of the data.

To determine statistical differences between the

studied groups, Student's paired t-tests were utilized (paired t-test). Pearson's correlation coefficient was applied to examine any potential bivariate correlation between the variables. Furthermore, the Chi-Square test ($\chi$ 2) was used for further data analysis. Ultimately, the Receiver Operating Characteristic (ROC) curve was applied to asses possible potential of studied genes as biomarkers to diagnosis CRC. Data are presented as mean ± standard deviation (SD). A *P* value of less than 0.05 ($P < 0.05$) was considered to be statistically significant.

## Results

### Demographic information of patients

As presented in Table 1, 80.6% of patients were over 50 years of age, while 19.4% of participants were under 50 years of age. The clinical characteristics of patients are listed in Table 1; as shown, most tumors were of the adenocarcinoma type with Grade II differentiation.

### Clinicopathological information of patients

Pathological information of the patients including tumor size, histology, tumor grade, vascular and lymphatic invasion, tumor staging (primary tumor, lymph node involvement, and metastasis) and TNM staging is presented in Table 2. Our finding showed that tumor size was less than 3 cm in 16.1% of patients and more than 3 cm in 83.9% (Table 2). We observed that 80.6% of the tumors were adenocarcinoma, while 16.1% were mucinous adenocarcinoma. Histological grade was I or II in 80.7% of the tumors, and Grade III or IV in 16.2%.

### The results of gene expression analysis

Gene expression analysis showed that *PELP1* expression in tumor tissues of patient with CRC was significantly higher (1.38-fold higher) than matched non-cancerous margin tissues ($P$=0.016) (Fig 1a). Our observations also revealed that the expression of *c-Src* in tumor tissues increased up to two-fold compared to the matched non-cancerous margin tissues ($P = 0.006$) (Fig. 1b).

### Association of *PELP1* and *c-Src* expression with clinicopathological characteristics

As indicated in Table 3, the tumor size ($P = 1.00$), histology grade ($P = 0.287$), TNM staging ($P = 1.00$), vascular invasion ($P = 1.00$) and lymphatic invasion ($P = 1.00$) had no significant association with the *PELP1* gene expression. Table 4 presents the association of *c-Src* gene expression with clinicopathological characteristic of patients. As indicated in Table 4, the tumor size ($P = 0.634$), histology grade ($P = 0.304$), TNM staging ($P = 0.676$), vascular invasion ($P = 1.00$) and lymphatic invasion ($P = 1.00$) also had no significant association with the *c-Src* gene expression.

**Table 1.** Demographic and Clinical Characteristics of the 31 Patients with CRC (Tumor Tissues n=31 and Matched Margin Tissues n=31)

| Characteristic | Categorization | N (%) |
|---|---|---|
| Age | < 50 ≥ 50 | 6 (19.35) 25 (80.64) |
| Alcohol | Drinker Non-Drinker | 0 (0) 31 (100) |
| Smoking Status | Non smoker DX-Smoker at Diagnosis but Discontinued Smoker | 22 (70.96) 5 (16.12) 4 (12.90) |
| Family History | Yes No | 13 (41.93) 18 (58.06) |

**Table 2.** Frequency of Clinicopathological Information of Tumor Tissues (n=31) from Patients with CRC

| Characteristic | Categorization | N (%) |
|---|---|---|
| Tumor Size | < 3 cm ≥ 3 cm | 5 (16.12) 26 (83.87) |
| Tumor Histology | Adenocarcinoma Mucinous (Colloid) adenocarcinoma Other | 25 (80.64) 5 (16.12) 1 (3.22) |
| Histology grade | Grade I (Well Differentiated) Grade II (Moderately Differentiated) Grade III (Poorly Differentiated) Grade IV (Undifferentiated) Grade X(Unknown) | 6 (19.35) 19 (61.29) 3 (9.67) 2 (6.45) 1 (3.22) |
| Pathological T | T2 T3 T4 | 4 (12.90) 23 (74.19) 4 (12.90) |
| Pathological N | Nx N0 N1 N2 | 1 (3.22) 12 (38.70) 11 (35.48) 7 (22.58) |
| Clinical Metastasis | M0 (the primary tumor) M1 (manifest metastasis) N/A | 27 (87.09) 3 (9.67) 1 (3.22) |
| TNM staging | Stage I Stage IIA Stage IIB Stage IIIB Stage IIIC Stage IV | 3 (9.67) 8 (25.80) 1 (3.22) 10 (32.25) 6 (19.35) 3 (9.67) |
| Vascular invasion | Yes No | 30 (96.77) 1 (3.22) |
| Lymphatic invasion | Yes, No Unknown | 29 (93.54) 1 (3.22) 1 (3.22) |

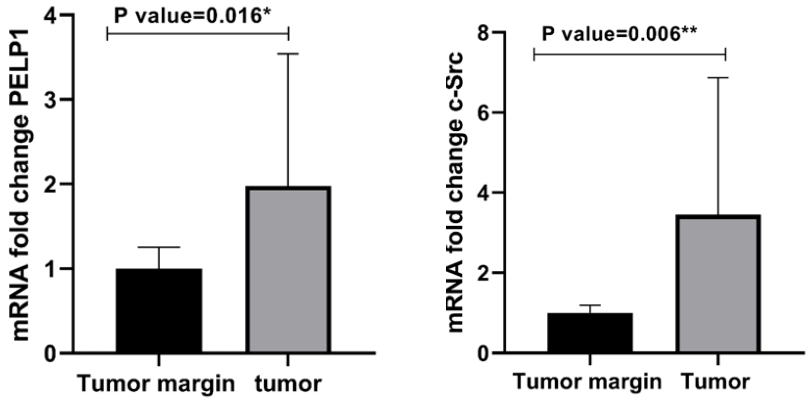


**Figure 1.** *PELP1* and *c-Src* genes expression levels (fold change) in patients with CRC.

**A:** *PELP1* gene expression: The relative mRNA expression of *PELP1* was significantly increased by 1.38-fold in tumor tissues compared to matched non-cancerous margin tissues ($P = 0.016$). **B:** *c-Src* gene expression: The relative mRNA expression of *c-Src* was significantly increased by 2.00-fold in tumor tissues compared to matched non-cancerous margin tissues ($P = 0.006$).

**Table 3.** The association between PELP1 with clinicopathological characteristics in patients with CRC

| | | Expression of PELP | | | |
|---|---|---|---|---|---|
| **Parameter** | **Number** | **Low Expression (%)** | **High Expression (%)** | **$\chi^2$** | **P-value*** |
| Histology Grade I&II | 25 | 8 (32) | 17 (68) | 2.18 | 0.28 |
| III&IV | 5 | 0 (0) | 5 (100) | | |
| Tumor size(cm) < 3 ≥ 3 | 6 | 1 (16.7) | 5 (83.3) | 0.32 | 1 |
| | 25 | 7 (28) | 18 (72) | | |
| TNM Staging I&II | 12 | 3 (25) | 9 (75) | 0.007 | 1 |
| III&IV | 19 | 5 (26.3) | 14 (73.7) | | |
| Tumor Type Adenocarcinoma | 25 | 6 (24) | 19 (76) | 0.54 | 0.58 |
| Mucinous | 5 | 2 (40) | 3 (60) | | |
| Vascular Invasion Yes | 30 | 8 (26.7) | 22 (73.3) | 0.35 | 1 |
| No | 1 | 0 (0) | 1 (100) | | |
| Lymphatic Invasion Yes | 29 | 8 (27.6) | 21 (72.4) | 0.37 | 1 |
| No | 1 | 0 (0) | 1 (100) | | |

### The results of *PELP1* and *c-Src* as potential biomarker

For evaluating the expression of *PELP1* and *c-Src* as potential biomarker for CRC diagnosis, ROC curve was uesed. As indicated in Fig 2a, the Area Under Curve (AUC) area for *PELP1* expression was 0.673 (Cut off: 7.74, sensitivity: 0.714, specificity: 0.615). Additionally, our analysis indicated that the AUC area for *c-Src* was 0.731(Fig 2b) (Cut off: 16.04, sensitivity: 0.857, specificity: 0.653). Correlation analysis revealed a positive and significant correlation between *PELP1* and *c-Src* expression (r=0.3855, *P*=0.0075).

## Discussion

We found that the expression of the *PELP1* and *c-Src* genes were significantly increased in the tumor tissue of patients with CRC compared to non-cancerous margin tissues. This study also assessed the clinicopathological characteristics of the patients' tumor tissues. The majority of samples showed a histological grade of I and II, the tumor size greater than 3 cm, and were classified as adenocarcinoma. Furthermore, vascular and lymphatic invasion were observed in most of the cancer tissue samples. Another part of our findings also indicated that based on ROC analysis, both *PELP1* and

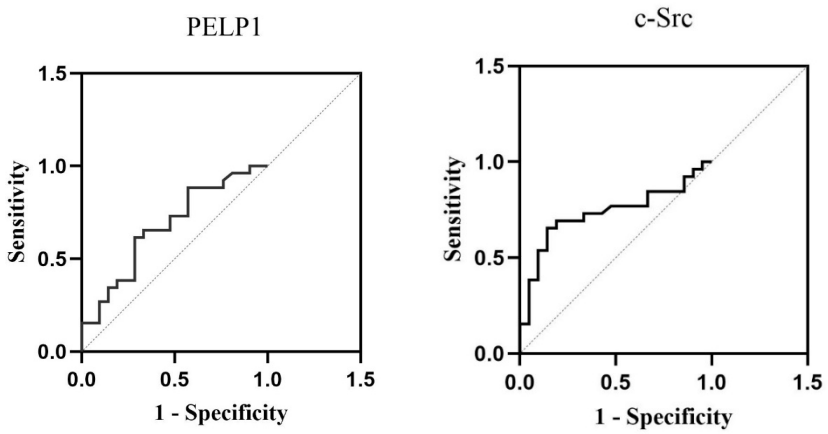


**Figure 2.** ROC curve analysis for assessing the diagnostic potential of *PELP1* and *c-Src* mRNA expression in CRC.

**A:** *PELP1* biomarker potential: The AUC for *PELP1* was 0.673 (95% Confidens Interval: 0.533-0.813), with a sensitivity of 0.714 and specificity of 0.615 at the optimal cut-off value of 7.74. **B:** *c-Src* biomarker potential: The AUC for *c-Src* was 0.731 (95% Confidens Interval: 0.607-0.855), with a sensitivity of 0.857 and specificity of 0.653 at the optimal cut-off value of 16.04.

**Table 4.** The association between c-Src with clinicopathological characteristics in patients with CRC

| | | Expression of c-Src | | | |
|---|---|---|---|---|---|
| **Parameter** | **Number** | **Low Expression (%)** | **High Expression (%)** | **$\chi^2$** | **P-value*** |
| Histology Grade I&II III&IV | 25 | 7 (28) | 18 (72) | 1.82 | 0.30 |
| | 5 | 0 (0) | 5 (100) | | |
| Tumor size(cm) < 3 ≥ 3 | 6 | 2 (33.3) | 4 (66.7) | 0.22 | 0.63 |
| | 25 | 6 (24) | 19 (76) | | |
| TNM Staging I&II III&IV | 12 | 4 (33.3) | 8 (66.7) | 0.57 | 0.67 |
| | 19 | 4 (21.1) | 15 (78.9) | | |
| Tumor Type Adenocarcinoma Mucinous | 25 | 6 (24) | 19 (76) | 0.54 | 0.58 |
| | 5 | 2 (40) | 3 (60) | | |
| Vascular Invasion Yes No | 30 | 8 (26.7) | 22 (73.3) | 0.35 | 1 |
| | 1 | 0 (0) | 1 (100) | | |
| Lymphatic Invasion Yes No | 29 | 7 (24.1) | 22 (75.9) | 0.31 | 1 |
| | 1 | 0 (0) | 1 (100) | | |

*c-Src* suggested a reasonable biomarker potential. This investigation yielded interesting results regarding the potential biomarker role of these two genes. Our results also revealed a positive and significant correlation between the *PELP1* and *c-Src* gene expressions. However, the *PELP1* and *c-Src* gene expressions showed no significant correlation with tumor size, histological grade, TNM staging, vascular invasion, or lymphatic invasion.

In parallel with our study, research has shown that PELP1 is upregulated in various CRC cell lines compared to normal colorectal epithelial cells. In a study conducted by Zhifeng Nin et al. (3) they investigated PELP1 expression in several CRC cell lines using Western blotting and bioinformatics analyses. In this study, they silenced *PELP1* by short hairpin RNA, which increased senescence and inhibited proliferation, colony formation, migration, invasion, and tumor formation of the CRC cell line HT-29 xenograft. Therefore, high levels of PELP1 can be said to be associated with increased malignant

behaviors, including enhanced proliferation, migration, and invasion of CRC cells. Furthermore, silencing of *PELP1* using short hairpin RNA (shRNA) has been shown to inhibit these malignant traits and promote cellular senescence in CRC cell lines. In continuation of the results of our study, Gravis et al. investigated the expression of ERα, ERβ and PELP1/MNAR proteins by immunohistochemistry in normal colorectal mucosa, adenoma and adenocarcinoma of 113 patients with CRC (12). They identified ERβ and PELP1/MNAR in the nuclei of epithelial, endothelial, inflammatory, smooth muscle, and myofibroblast cells, and also, based on staining intensity, the expression of both proteins was significantly increased in carcinoma epithelial cells compared to normal mucosa. Therefore, based on the studies conducted, it can generally be concluded that PELP1 may have an oncogenic function in CRC. On the other hand, there is still debate in this field, as Tzelpi et al.(13), stated that PELP1 expression decreases from normal to cancerous colorectal epithelium.

Extensive research into the molecular biology and genetics of Rous sarcoma virus identified v-Src as a viral oncogene responsible for malignant transformation. Simatou A et al.(14) subsequently showed that v-Src has a cellular counterpart, thus identifying the first *c-Src* proto-oncogene. c-Src is a non-receptor tyrosine kinase that is abnormally expressed in many human cancers and is associated with malignant biological behavior related to proliferation, adhesion, migration, invasion, and metastasis(15). The results of the present study showed that *c-Src* gene expression in tumor tissue was significantly increased compared to the control group. Another interesting result was that vascular and lymphatic invasion was observed in a large proportion of tumor tissues exhibiting increased *c-Src* expression. *c-Src* expression is reported to be elevated in approximately 80% of CRC specimens compared to normal colonic epithelium. In metastatic lesions, such as those in lymph nodes and liver, c-Src activity is even higher than in primary tumors, indicating a progressive increase as the disease advances (16, 17). Consistent with the results of our study, Zhang et al.(18) in a study examined the expression levels of miR-654-3p and c-*Src* in 103 CRC tissues and matched normal colorectal tissues by qRT-PCR. They showed that some microRNAs, such as miR-654-3p, negatively regulate c-*Src* expression. Decreased miR-654-3p in CRC tissues is associated with increased c-Src levels and promotes malignant behaviors such as proliferation and migration. This suggests that in addition to the loss of tumor suppressor microRNAs, Src may also play an important role in tumorigenesis. Also in this regard, Julia Martínez-Pérez et al.(19) investigated whether c-Src activity is a marker for poor clinical prognosis in colon cancer patients. Their findings suggested that high expression of active Src (phospho-Src) in Stage II and III colon cancer patients is associated with significantly reduced disease-free survival and overall survival and is an independent prognostic factor. Therefore, Src activity is recognized as an important biomarker for predicting clinical malignancy in colon cancer and could be a therapeutic target to improve patient outcomes. Similar to *PELP1*, analyses showed that samples with increased *c-Src* gene expression mostly had adenocarcinoma-type tumors and also exhibited vascular and lymphatic invasion.

Several researchers have identified the fact that there is an interaction between PELP1 and c-Src. In this regard, another interesting finding from our study was that *PELP1* gene expression was positively and significantly correlated with *c-Src* expression. This relationship is biologically plausible, as *c-Src* is known to activate several downstream signaling pathways that promote cell survival and proliferation, including the PI3K/AKT and MAPK/ERK pathways(11, 15, 20). When c-Src levels are elevated after PELP1 silencing, these pathways can be reactivated, leading to enhanced tumor cell growth and invasive capabilities (3). *c-Src* is known to be a critical proto-oncogene involved in various signaling pathways that promote cell growth and survival (21). Based on our findings in the present study, *c-Src* expression is also increased in CRC along with *PELP1*. Notably, when *PELP1* is silenced, there is a negative regulation of *c-Src* expression. This suggests that *PELP1* may exert its oncogenic effects in part through the regulation of *c-Src* (3). The interaction between PELP1 and c-Src is critical. Upregulation of c-Src can reduce the inhibitory effects on CRC cell malignancy induced by silencing *PELP1*. This relationship highlights the potential of targeting these pathways in therapeutic strategies against CRC (3).

ROC curve analysis further highlighted the diagnostic potential of both *PELP1* and *c-Src*, evidenced by respectable AUC values alongside satisfactory sensitivity and specificity metrics. Moreover, a positive and statistically significant correlation between the expression levels of *PELP1* and *c-Src* suggests a coordinated regulatory mechanism that may contribute to tumor progression. These findings advocate for the consideration of *PELP1* and *c-Src* as promising biomarkers for early detection of CRC, and they also emphasize the therapeutic potential of targeting these molecules to inhibit tumor growth and metastasis. Nonetheless, further validation at the protein level and in larger cohorts is warranted to substantiate their clinical applicability and prognostic relevance.

In conclusion, the results of our study showed that *PELP1* and *c-Src* can be considered as biomarkers in the diagnostic process of CRC. While the present study successfully identified the increased expression of *PELP1*and *c-Src* and their diagnostic potential in CRC, it is essential to acknowledge certain limitations. First, the relatively small sample size necessitates caution when generalizing these findings; therefore, future

studies with a larger cohort are warranted. Secondly, our investigation was limited to the mRNA level using Real-Time PCR, and the results were not confirmed at the protein level (e.g., by Western Blot or IHC). Finaly, the cross-sectional design of this study, based on archived samples, does not allow for a definitive correlation between the observed gene expression alterations and patient clinical outcomes or prognosis. These findings, therefore, lay the groundwork for subsequent functional and prospective studies that should address these limitations.

## Authors' Contribution

Nina Lotfi, Fatemeh Babajani, Seyed Askar Roghani, Atefeh Kakavand, Mohammad Taghi Goodarzi, Soheila Asadi contributed to the Conceptualization, Writing, Reviewing, Study design, data analysis and interpretation.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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