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Original Article

Relationship Between Hardiness and Addiction Potential in Medical Students

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Abstract

Background: Hardiness as one of the personality traits is an important factor in predisposing risky behaviors including addiction. **Objectives:** This research examines the relationship between hardiness and addiction potential and identifies socio-economic determinants of hardiness and tendency to addiction among medical students in Iran.

Materials and Methods: In this study, 577 medical students selected based on the convenience sampling method were examined. They were selected from five faculties of Qazvin University of Medical Sciences. Data were collected on hardiness scale, addiction potential scale and demographic variables. Data analysis included descriptive and inferential statistics powered by SPSS (v. 22).

Results: Research results showed that there was a negative relationship between hardiness and addiction potential (r = -227, P < 0.001). Males had a higher level of hardiness (P < 0.05) and lower addiction potential than females (P < 0.01). Respondents who had an addicted person in their family showed a lower addiction potential than those who did not have an addicted family member (P < 0.01). Being in a family with cold relationships was associated with higher levels of hardiness; they showed less addiction potential compared to persons who enjoyed a warm family with friendly relationships (P < 0.01), but lower levels of hardiness.

Conclusions: Hardiness had a significant negative relationship with tendency to addiction. Regarding demographic factors that were found to be the predictors of hardiness and addiction potential, a consistent pattern was observed in which those who had high tendency for addition were low in hardiness. This is not surprising since hardiness is a shield that provides a defense mechanism for coping behavior when a person is faced with negative life events or adverse life conditions. Based on the results, individuals high in hardiness are perhaps less likely to resort to drugs. However, further researches are recommended on this subject.

Keywords: Addiction, Hardiness, Medical Students, Socio-Economic Factors

1. Background

Addiction is one of the main problems in all countries of the world (1, 2). In Iran, deaths related to drug abuse are considered as the second cause of abnormal death after traffic accidents (3, 4). Statistics of Iran drug control head-quarters show that in 2012, 2.65 percent of people in the 15-64 year old age group use drugs. It also estimated the approximate number of addicts to be 1.325 million in Iran (4, 5). Addiction among the youth has experienced an increasing trend. According to the Census 2005, 61.22 percent of addicts were between 20 and 29 years old (5). Alarmingly in the last two decades, the age of addicts and drug users has dropped below the age of 20 and in some cases even to 8 years old (6). This threatens social cohesion, affects economic activities and human capital formation and negatively affects the health care system.

Addiction has many negative consequences including the disintegration of families, loss of financial resources,

and other social deviations such as theft, murder, etc. The undesirable effects of this damaging social problem not only involve the addict, but also all those who are associated with the addicted person (7). Besides the physical adverse consequences of addiction including malnutrition, hypertension, and cancer, addicted individuals will be exposed to dangerous diseases such as AIDS and hepatitis. Research has shown that addicts suffer from lower psychological well-being because they often experience anxiety, irritability, depression, psychosis, loss of control, and lack of confidence (8). The addicted person also negatively affects the people around them, especially their immediate family members.

Easy access to drugs and the environment are two of the major reasons that spread addiction among the youth (6). It is common to find students affected by addiction. The community and family members hardly suspect that addiction could occur among students, since in their mind, students are supposed to be in school and engaged

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in learning with little or no opportunity for distraction to drugs (9).

Generally, factors that affect addiction potential in the youth are grouped into internal and external factors. Family (poor parent-child relationships), peer pressure (friends who are addicted), socio-economic condition (unemployment, growing urbanization, and geographical proximity to drug producing areas), community policies, feeling of loneliness as well as isolation are the main external factors that cause potential addiction (10). Internal factors that influence addiction include genetics, depression, stress, self-concept, self-esteem, mental health and personality traits, the lack of attention to religious affiliation, and not being powerful enough to say "no" to the demands of others had the greatest role in the addiction potential (11). Rezaei et al (2014) reported that the presence of an addicted person in the family is a factor for addiction potential (7). Moreover, the results of different studies suggested some factors such as gender (10), family relationships (12), poverty (13), and religious beliefs (14) in tendency to addiction.

Among the internal factors, personality traits are lesser-known factors while they play an important role in the formation of addiction and are regarded as strong predictors (10). Personality traits consist of neuroticism, extroversion, openness to experience, agreeableness as well as conscientiousness (15). Hardiness is another personality trait proposed by Kobasa et al. (1979) that could explaine resistance to addiction (16). They believe that hardiness acts as a source of resistance to encounter stressful life events. This personality trait has three components: commitment, control, and challenge. An individual who has high commitment believes in the importance and value of his/her existence and action. Similarly, an individual with the proper control has faith in his/her ability. Thus, the level of control in a person indicates his/her ability to accept life changes as normal life features and path. Being able to take challenges (whether positive or negative) is considered as an opportunity for personal growth which contributes to hardiness (17). Moreover, individuals who are high in hardiness often possess certain characteristics such as high intelligence, lack of substance abuse and delinquency, independency, empathy, commitment to work, and have good relationships with peers (18). In short, hardiness makes a defense mechanism to addiction since individuals who score high on hardiness are less susceptible to addiction.

Whilst it is important to understand barriers to addiction, it is equally important to identify factors that contribute to addiction potential. Some of the common contributing factors for addiction among the younger population as explained earlier are geographical proximity to locations of drug producing regions and hence the con-

venient access to drugs. Some studies have also pointed out the importance of the relationship between addiction and the psychosocial, cultural, and genetic factors that affect tendency towards addiction (19, 20). Up to now, no research has been directly conducted to examine the relationship between addiction and hardiness, an important personality trait to predict addiction potential among university students (21, 22).

The main purpose of this study is to examine the relationship between hardiness and addiction potential among Iranian university students. This group of people is different from their peers in terms of their position, thinking ability as well as social respect in the present and the future. This ability and prestige deter them from addiction (10). We hypothesize a negative relationship between hardiness and tendency to addiction, and hence the higher the hardiness score, the lower the addiction potential in a sample of medical students. The second objective of this research is to determine if socio-demographic factors (i.e. age, sex, marital status, economic status, education level, religious beliefs, living arrangement, and type of family relationship) are predictors of hardiness and addiction potential among medical students.

2. Materials and Methods

2.1. Participants

The present study was conducted on the students of Qazvin University of Medical Sciences selected based on convenience sampling. Students were selected from the medical, dental, paramedical, hygiene, and nursing and midwifery schools. The inclusion criteria were the length of study (at least a semester), and the age (18 years or older). Data collection was carried out from October to December 2015. All participants were informed about the voluntary nature of participation, with the option to withdraw from the study. A total of 577 respondents participated in the survey.

2.2. Measures

The survey instrument consisted of a questionnaire that had been approved by the associated university's Medical Sciences ethics committee. Collected data included the socio-economic variables of students: age, sex, marital status, economic status, living arrangement, educational level, religious beliefs, and type of family relationship. The second section of the questionnaire collected data on respondents' orientation towards hardiness using the Hardiness Scale (HS), and their propensity towards addiction using the addiction potential scale (APS).

2.3. Variables

Hardiness Scale (HS) was measured using the 50-item scale designed by Kobasa et al. (1979) to measure subjective evaluation of hardiness among individuals (16). The hardiness scale consists of three sub-scales: commitment, control, and challenge. Hardiness was measured using a four-point Likert-type scale that ranged from not true (0) to completely true (3). A higher score indicates higher hardiness. The validity and reliability of the HS has been well established (19). The Cronbach's alpha coefficient for the HS was also reported as 0.71(23). In this study, internal consistency reliability, using Cronbach's alpha, was 0.813.

Addiction potential scale (APS) designed by Weed and Butcher (1992) was adopted for the purpose of this study. This scale consists of 36 items. A four-point Likert scale ranging from completely disagree (0) to completely agree (3) was applied, with the possible total scores ranging from 0 to 108. A higher score indicates higher desire to addiction (24). Upon examining the criterion validity of the APS, Zargar et al. (2008) found that it could differentiate well between addicts and non-addicts (22). In addition, the reliability of this scale using Cronbach's alpha was estimated 0.90 (25). In this study, Cronbach's Alpha for the 36-item APS scale was 0.95, indicating a good internal consistency.

2.4. Ethical Consideration

Our study was approved by our main affiliated university's medical sciences ethics committee (QUMS.REC.1394.108). In addition, students were fully informed about the various aims of the study and procedures. We also emphasized the fact that participation was voluntarily before signing an informed consent form. All personal data were anonymized by assigning generic codes to record the responses of participants.

2.5. Statistical Analysis

The demographic profile of the respondents was captured using socio-economic measures including age, sex, education level, marital status, parent's education level, living arrangement, economic situation, and faculty. The presence of religious belief was measured using a single item which measured the perceived level of religious belief. This item asked the students to select their perceived level of religious belief from 1 to 4 (1 = do not believe at all, 4 = strong belief). For living arrangement, respondents were asked to indicate: "with family", "in dormitory", or "alone". For type of family relationship, the respondents were asked to choose the option that applied: "a family with warm and friendly relationships", "a family with cold relationships", and "having divorced parents". All demographic variables were summarized using frequencies and

percentages for categorical variables as well as mean and standard deviation (SD) for ratio scale variables. Pearson correlation analysis was run to examine the relationship between the main variables of this study including hardiness, challenge, commitment, control, and addiction potential. The mean scores of hardiness and addiction potential were compared. Univariate ANOVA was performed to compare the means of hardiness and addiction potential among socio-demographic factors. Moreover, univariate linear regression analysis was utilized to estimate unadjusted regression coefficients. The predictors of hardiness and addiction potential were determined using general linear model with Bonferroni correction for pair-wise comparisons to calculate multivariate-adjusted means for hardiness and addiction potential scores across sociodemographic factors. The multivariate-adjusted models included sex, education level, marital status, parent's education, economic situation, living arrangement, religious belief, presence of an addicted person in family, type of family, and faculty. All statistical tests were 2-tailed, and a P value of equal to or less than 0.05 was the sign of significance.

3. Results

Table 1 shows the demographic profile of respondents. Slightly more than one quarter of the students were from the medical faculty, 22% from paramedical faculty, 20% from nursing and midwifery faculty, and up to 15% from dental and hygiene faculty. The sample consisted of 234 male (40.6%) and 342 female (59.3%) medical students, aged 15 - 48 (Mean = 21.32, SD = 2.75). Majority of the respondents were single (87.7%) and living in families with warm and friendly relationship (85.6%). Almost 95% of the students placed in the middle class families to good economic background ones. An equal percentage of the parents had at least a diploma degree in terms of education, indicating a good socio-economic background. Only 6.9% (N = 40) of the respondents had an addicted person in their family.

Table 2 shows the results of Pearson correlation analysis for addiction, hardiness, and hardiness dimensions. The results showed a significant negative relationship between hardiness and addiction potential (r = -227, P < 0.001). In addition, among the dimensions of hardiness, commitment (r = -320, P < 0.001) and control (r = -272, P < 0.001) had a significant negative relationship with addiction potential, while the challenge dimension had no significant relationship with hardiness (r = 0.020, ns).

Tables 3 and 4 provide detailed information about the univariate results and general linear modeling results for hardiness and addiction potential in medical students, respectively. The results indicate that males had higher level

Dem	ographic characteristics	No. (%)
Sex		
	Male	234 (40.6)
	Female	342 (59.3)
	Missing	1(.2)
Educ	ation	
	Degree	332 (57.5)
	Master	9 (1.6)
	PhD	233 (233)
	Missing	3 (.5)
Mari	ital Status	
	Single	506 (87.7)
	Married	69 (12.0)
	Missing	2(0.3)
Moth	her's Education	
	No Formal Education	30 (5.2)
	Under Diploma	139 (24.1)
	Upper Diploma	220 (38.1)
	College	186 (32.2)
	Missing	2 (0.3)
Fath	er's Education	
	No Formal Education	17(2.9)
	Under Diploma	106 (18.4)
	Upper Diploma	209 (36.2)
	College	243 (42.1)
	Missing	2(0.3)
Livin	ng Arrangement	
	With Family	277 (48)
	Dormitory	267(46.2)
	Lonely	33 (5.7)
Fami	ily's Economic Situation	
	Poor	11 (1.9)
	Average	314 (54.4)
	Good	229 (39.7)
	Excellent	20 (3.5)
	Missing	3 (0.5)
Keng	gious Belief Do not believe at All	10 (2.2)
	Do not belief	19 (3.3)
		61(10.6)
	Moderate belief	404 (70.0)
	Strong belief	92 (15.9)
	Missing icted Person in the Family	1(0.2)
Addi		10 (5 0)
	Yes	40 (6.9)
	No	531 (92.0)
	Missing	6 (1.0)
lype	of Family	
	With warm and friendly relations	494 (85.6)
	A family with cold relationships	64 (11.1)
	Parents are divorced	13 (2.3)
E2	Missing	6 (1.0)
Facu		255 (27.0)
	Medical Poptal	156 (27.0)
	Dental	87 (15.1)
	Paramedical	129 (22.4)
	Hygiene	90 (15.6)
	Nursing and midwifery	115 (20)
Age,	Mean (SD)	
	·	21.32 (2.75)

Table 2. The Relationship between Hardiness and Tendency to Addiction in Medical Students^a

	Mean (SD)	1	2	3	4	5
1. Hardiness	62.082 (14.000)	1.000				
2. Challenge	24.619 (5.786)	0.776 ^b	1.000			
3. Commitment	17.392 (5.805)	0.867 ^b	0.463 ^b	1.000	000	
4. Control	20.069 (5.254)	0.852 ^b	0.454 ^b	0.696 ^b	1.000	
5. Addiction potential	105.720 (24.800)	-0.227 ^b	0.020ns	-0.320 ^b	-0.272 ^b	1.000

Abbreviation: ns, non-significant at 95% confidence level.

of hardiness than females (P < 0.05); thus, making them less susceptible to addition. Since females had lower level of hardiness, they also scored higher on addiction potential than males (P < 0.01), indicating a negative significant relationship between hardiness and tendency for addiction. Students staying in dormitory had lower hardiness than those staying with their family (P < 0.05). Respondents who had an addicted person in their family had lower addiction potential (and higher level of hardiness) compared to those who did not have an addicted person in the family (P < 0.01). Importantly, being in a family with cold relationship was associated with less addiction potential than a warm family with friendly relationships (P < 0.01). This further supported the significant relationship between hardiness and tendency for addiction because those who came from home with warm family relationship had lower levels of hardiness and therefore tended to be more susceptible to drug addiction.

4. Discussion

The primary aim of this study was to examine the relationship between hardiness and addiction potential and factors that predict these two factors among medical students in Iran. The findings suggest that there is a negative significant relationship between addiction potential and hardiness as well as its two components, commitment and control, since hardiness is regarded as a defense mechanism that provides a barrier against addiction. These findings were similar to the results of other studies conducted in Iran on high school students (21) as well as on the employees of an industrial factory in Ahvaz, Iran (22). It seems that having a certain goal in the life, resistance to the life problems and the pressure, and having positive relationship with others may lead persons to avoid drugs and tendency to addiction (10).

Indeed, while drug abuse can be seen as an avoidance coping strategy, hardiness and its subscales guide students

to adopt coping strategies that help them solve their problems. People with high hardiness tend to deal directly with life events rather than denying or attempting to avoid problems caused by the occurrence of life events. In contrast, people with lower hardiness feel a sense of helplessness, alienation, and threat in the face of adversities in life. Also, they tend to have less control over the problems and events (26). Therefore, young people with higher hardiness have great tolerance or resistance against the inevitable life pressures that threaten their well-being including social environment (e.g. relationships with partners). They are able to manage their emotions perhaps by adopting more problem solving approaches rather than using emotion coping strategies such as turning to drugs that will lead to addiction (27).

The results of this study show that men reported higher hardiness in comparison with women. This contrasted with the study results of Barton et al. (2001) that stated women experience a greater hardiness than men (28). Several other studies did not find significant genderbased differences (29, 30). The difference between men and women in hardiness can be attributed to perceptions and stereotyping about genders. In fact, beliefs about the characteristics and different roles of men and women are formed during socialization which has an early beginning in the family environment and is strengthened through school environment, media, etc. (31, 32). Women are seen as weaker gender, which could explain their lower level of hardiness, especially in an Eastern society where women tend to be more protected. As a result of such attitudes and beliefs, women show lower hardiness than men. In addition to cultural and social factors, biological and physiological differences between men and women can also explain the results of the present study. Testosterone hormone and having higher physiological endurance and strength in men may lead to higher psychological hardiness (33).

In the present study, females had great addiction po-

a Control variables: sex, age, marital status, education level, mother's education, father's education, religious beliefs, economic situation, and addiction person.

b Adjusted P value < 0.001

Table 3. Predictors of Hardiness in Medical Students

	Mean	SD	Multiple Comparison Adjusted P Value	P Value	Partial Eta Squared
Sex				0.023	0.010
Male	63.578	13.173	0.023		
Female	61.058	14.488			
Education				0.050	0.011
Degree	62.613	14.203	Ref		
Master	62.070	18.537	0.853		
PhD	61.428	13.580	0.091		
Marital Status			0.067	0.067	0.006
Single	62.351	13.809			
Married	60.187	15.472			
Mother's Education				0.203	0.009
No Formal Education	59.567	13.175	.609		
Under Diploma	62.942	12.534	1.000		
Upper Diploma	60.763	14.724	0.445		
College	63.367	14.270	Ref		
Father's Education				0.310	0.007
No Formal Education	63.527	15.077	Ref		
Under Diploma	61.797	12.803	1.000		
Upper Diploma	62.329	14.403	1.000		
College	61.913	14.201	1.000		
Economic situation				0.545	0.004
Poor	61.455	7.866	Ref		
Average	61.757	13.884	1.000		
Good	62.330	14.523	1.000		
Excellent	65.153	13.684	1.000		
Living arrangement				0.014	0.016
With Family	63.740	14.135	0.012		
Dormitory	60.194	13.998	Ref		
Lonely	64.204	10.555	0.804		
Religious Belief				0.880	0.001
Do not believe at All	63.437	10.989	Ref		
Low belief	62.053	11.509	1.000		
Moderate belief	61.690	14.490	1.000		
Strong belief	63.542	14.014	1.000		
Addicted Person			0.354	0.354	0.002
Yes	64.756	12.209			
No	61.908	14.153			
Type of Family				0.065	0.011
With warm and friendly relationships	61.638	13.880	Ref		
A family with cold relationships	66.583	13.634	0.250		
Parents are divorced	54.672	17.149	0.479		
Faculty				0.903	0.000
Medical	62.058	13.438	Ref		
Dental	61.364	13.684	1.000		
Paramedical	61.756	14.556	1.000		
Hygiene	62.144	14.361	1.000		
Nursing and midwifery	62.981	14.321	1.000		

tential and lower level of hardiness compared to males, whereas the results of many past studies were in contrast with the present study findings (10, 34). The lower level of

hardiness in women may make them vulnerable; hence, contributing to addiction or more tendencies to addiction, which results in greater addiction potential (10). In ad-

Table 4. Predictors of Tendency to Addiction in Medical Students

	Mean	SD	Multiple Comparison Adjusted P Value	P Value	Partial Eta Squared
Sex			0.002	0.002	0.018
Male	102.244	24.868			
Female	108.098	24.544			
Education				0.048	0.012
Degree	104.744	24.555	0.051		
Master	100.561	30.624	0.921		
PhD	107.161	25.034	Ref		
Marital Status			0.629	0.629	0.000
Single	105.249	24.832			
Married	109.068	24.834			
Mother's Education				0.966	0.001
No Formal Education	93.627	33.059	Ref		
Under Diploma	101.898	25.716	1.000		
Upper Diploma	107.946	22.743	1.000		
College	107.752	24.282	1.000		
Father's Education				0.154	0.010
No Formal Education	85.410	28.753	Ref		
Under Diploma	98.104	28.328	1.000		
Upper Diploma	108.782	22.319	0.265		
College	107.766	23.776	0.438		
Economic situation				0.159	0.010
Poor	92.091	29.931	1.000		
Average	104.273	23.975	0.297		
Good	108.643	24.366	0.149		
Excellent	100.993	35.596	Ref		
Living arrangement				0.413	0.003
With Family	106.401	24.414	0.640		
Dormitory	106.426	24.915	0.556		
Lonely	93.474	25.646	Ref		
Religious Belief	33.1,1	-5		0.064	0.014
Do not believe at All	89.825	23.805	0.323	0.004	0.014
Low belief	94.775	24.388	0.125		
Moderate belief	107.455	23.151	1.000		
Strong belief	108.639	29.332	Ref		
Addicted Person	100.033	25.552	0.007	0.007	0.014
Yes	86.279	26.637	0.007	0.007	0.014
No	107.047	24.134			
Type of Family	/10 1/			0.008	0.019
With warm and friendly relations	108.114	24.584	Ref		
A family with cold relations	89.883	21.444	0.007		
Parents are divorced					
Faculty	97.231	19.214	1.000	0.011	0.000
-	405	05.4==	D. C.	0.811	0.000
Medical	106.219	25.175	Ref		
Dental	105.156	26.560	1.000		
Paramedical	108.184	23.090	1.000		
Hygiene Nursing and midwifery	105.255 103.045	24.324 25.380	1.000		

dition, there is a more hidden form of addiction among women compared to men (22), perhaps due to the negative social attitude towards addiction and the socio-cultural en-

vironment in Iran that view addiction among women as promiscuous.

The results indicate that students living in dormitories

reported less hardiness compared to the group of students who lived with their families but there was no significant difference between them in terms of tendency to addiction. The present study is the first that included living arrangement and hence it is not possible to make comparison with the previous studies. It could be said that students living in dormitories receive less emotional support from their family and are less prepared to deal with life problems (29). Results of a previous study showed that social support and hardiness are two influencing factors in facing with problems (35). Considering the key role of social support and emotional support, and their effect on hardiness, students who live away from their families experience less hardiness perhaps due to insufficient emotional support especially in the freshman year.

The results of the previous studies show that presence of addicted person in the family is an important factor in addiction potential (36, 37). Contrary to expectation, this study shows that students who have addicted person in the family reported lower extents of addiction potential compared to those who did not have an addicted family member. It appears that students with addicted person in their family have greater hardiness and less addiction potential probably due to their exposure to problems associated with addiction. They may also have lower sense of curiosity and risk (7).

In this study, students who lived in a family with warm relationships were more likely to report higher addiction potential as they also scored lower on hardiness. The findings of different studies previously conducted were opposite to the present one (12, 38). This could be due to the influence of hardiness since lower level of hardiness creates a lower barrier to drug tendency. While parents as influential individuals in the youth's life can help them move in the right direction through effective communication, warm families may also allow children to have more freedom or leeway which could result in less desirable consequences. We expect children from family with warm relationships to have good relationship with their parents and a stronger sense of belonging. However, when faced with life crisis or problems, it is unclear to what extent they are willing to share their problems and seek guidance from their parents. Due to their low level of hardiness, these children may not be able to cope and hence turning to drug addiction may seem to be a good coping strategy. In addition, peer influence may outweigh the influence of warm family relationships especially among the younger age groups (39).

4.1. Conclusions

Based on the research findings, a negative significant correlation existed between hardiness and addiction po-

tential, and the subscales of hardiness, commitment, and control indicating that individuals high in hardiness have fewer tendencies to addition. In other words, people who have high tendencies to addition report low level of hardiness, showing reduced defense mechanism. In addition, some of the individual characteristics, family and social environment, and also gender were determining factors in addiction potential and hardiness. Contrary to the results of previous studies, the present study found that the youth from families with warm relationships have a higher tendency to addition. It suggests that hardiness which provides barriers to addiction is a personality trait that could explain addiction potential since the results of the present study show that those who have lower levels of hardiness tend more towards addiction.

4.2. Limitation of Study

One of the limitations of this study was adopting a convenience sampling procedure which limits the generalizability of the research findings. Moreover, the cross-sectional nature of the study limits our ability to determine the causal relationships among the constructs. Although the study was carried out on a completely voluntary basis and students were given assurances of confidentiality of information (according to the importance of stigmatization), participants may not have answered in a completely non-biased manner due to the sensitivity of their condition.

4.3. Recommendation for Future Studies

The demographic variables chosen for this study were sex, living location/place, presence of an addicted person in the family, and type of relationship in the family that predicted addiction potential and hardiness, further empirical study is warranted, especially in other age groups. In addition, future research should include peer influence and parental relationship as third variables to provide a deeper understanding of the influence of hardiness and tendency towards addiction.

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Footnotes

Author's Contribution: Mohammad Ali Soleimani and Ameneh Yaghoobzadeh conceived and designed the evaluation and helped draft the manuscript. Ameneh Yaghoobzadeh collected the clinical data. Mohammad Ali Soleimani and Ameneh Yaghoobzadeh re-evaluated and interpreted the clinical data. Saeed Pahlevan Sharif performed the statistical analysis. Saeed Pahlevan Sharif, Ameneh Yaghoobzadeh and Fon Sim Ong revised the manuscript. All authors read and approved the final manuscript.

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