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Introduction

Dependence to opiates is a chronic relapsing brain disease that can cause major health, social and economic problems [1]. Dependence vulnerability is a ected by environmental factors, drug-induced factors

e genotypes CT and TT are 3.7 and 13.9 times more likely to be linked to drug dependence than genotype CC; respectively. In addition, the presence of allele T is associated with increased likelihood of dependence compared to allele C (OR=4.1; CI=2.8-5.96) (Table 3).

(Table 4) shows that the CT and TT genotypes have a signi cantly longer duration of dependence, higher severity score, more relapse, and larger dose of daily Heroin intake and higher percent of positive family history compared to genotype CC. e same pattern was observed in allele T compared to allele C. ese data are not deviated from Hardy-Weinberg equilibrium.

	Control (192) N (%)	Cases (178) N (%)	6 L J Q L ¿ F D Q F H
Age: <30 30- 40 & more Mean ± SD	49(25.5) 97(50.5) 46(24.0) 34.4 ± 9.6	48(27.0) 91(51.1) 39(21.9) 35.5 ± 8.7	²=0.23, P=0.88 t=1.1,P=0.3
Gender: Female Male	60(31.2) 132(68.8)	55(30.0) 123(69.1)	²=0.01, P=0.9
Religion: Muslim Christian	185(96.4) 7(3.6)	171(96.1) 7(3.9)	²=0.02, 3 ”
Marital status: Married Divorced Single Widow	 54(28.1) 9(4.7) 117(60.9) 12(6.2)	 48(27.0) 7(3.9) 114(64.0) 9(5.1)	 ²=0.5, P=0.9
Education *: literate Primary-preparatory Secondary school Faculty education	 64(33.3) 46(24.0) 68(35.4) 14(7.3)	 50(28.1) 40(22.5) 80(44.9) 8(4.5)	 ²=4.2, P=0.24
Work *: Not working Student Semi-skilled Skilled worker	 94(49.0) 71(37.0) 16(8.3) 11(5.7)	 66(37.1) 97(54.5) 13(7.3) 2(1.1)	 ²=14.96, P=0.002
Residence : Rural Urban	93(48.4) 99(51.6)	89(50.0) 89(50.0)	²=0.1, P=0.76

7KLV FODVVL¿FDWLRQ LV DFFRUGLQJ WR WKH 2I¿FH RI 3RSXODWLRQ &HQVXVHV DQG 6XUYH\V

(Table 5) shows that homocysteine level is signi cantly higher in cases than control. Among control homocysteine level does no signi cant variation according to genotype and allele type. On the other hand, in cases the homocysteine level is signi cantly higher in genotype CT and TT compared to CC and with allele type T compared to C.

Discussion

Present study revealed that cases and control were matched regarding their age, gender, religion, marital status, education and residence. However, they di er signi cantly in their working status which could be explained by the e ect of substance use and its hazard on social and occupational function.

In the current study, MTHFR C677T genotype CC was more prevalent in the control group (75%) with low prevalence of CT and TT (21% and 3%, respectively) while CT represented the most common genotype in the cases group (42%) then CC (38%) and lastly TT (19%). (P=0. 19 for the control group and 0.10 for cases group). ere are statistically signi cant increases in CT & TT genotypes as well as T allele in the cases group when compared to the control group. ese results con rm the idea recently emerged that opioid abuse is closely related to genetic polymorphism of some opioid receptor genes apart from MTHFR gene, [23]. For our knowledge, it is the rst study to investigate the association of MTHFR C677T gene polymorphism and Heroin dependence. Previous studies showed that T allele and T carrier genotypes (TT & CT) were more prevalent in nicotine smoker [11] alcohol [12] and cocaine dependent patients [13] than in the control group. Yuferov et al., [1] found that there is a strong association between Heroin and cocaine addiction and polymorphism in genes. e similarity of the present study results and other drug dependence (cocaine, alcohol, and nicotine) could return back to the fact that these drugs share common nal neurotransmitter release (dopamine) in the same brain area (brain reward system) and many other genotype polymorphism [1,23].

e current study shows statistically signi cant increase in plasma homocysteine level in the cases group than the control group. Also, there is increase in the TT genotype of MTHFR C677T gene and T allele frequency in comparison to other genotypes (CT and CC) and C allele frequency in the cases group but not in the control group. ese results are in agreement with Tomedi et al. [24]. eir study showed that the plasma homocysteine level is statistically higher in the opiate drug addict group even the treated subjects of them than that of their control group. e hyperhomocysteinemia associated with T allele and T

	Genes			Alleles	
	CC Median (min-max)	CT Median (min-max)	TT Median (min-max)	C Median (min-max)	T Median (min-max)
Duration	14(12-26)[AB]	28(12-39)[A]	27.5(12-39)[B]	18(12-39)	28(12-39)
6 L J Q L ¿ F D Q F H		K W. Ƥ 3 ”		=	3 ”
Severity scor96e56D 6m 8.PS					

carrier genotypes of the MTHFR C677T gene could be explained by the following mechanism; MTHFR synthesizes 5-methyltetrahydrofolate, the major carbon donor in the remethylation of homocysteine to methionine. C to T mutation causes the substitution of valine for alanine at amino acid 223 and renders the enzyme less e cient (raised levels of homocysteine especially in TT genotype) and thermolabile [23,25].

Explanation for how hyperhomocysteinemia (associated with T carrier genotype of the MTHFR C677T gene in the current study) could harm brain and in uence Heroin dependence can be extracted from nding of previous studies. MTHFR C677T gene is linked with low folate levels and is associated with increased incidence of neural tube defects [26]. Moreover, in patients with severe MTHFR de ciency cerebral demyelination was detected [25]. In addition, MTHFR is involved in remethylation of homocysteine to methionine which is central for dopamine methylation and the synthesis of neurotransmitters [11]. In addition, hyperhomocysteinemia is associated with global DNA hypomethylation [27]. Major life events occurring before the onset of Heroin dependence and/or chronic Heroin use were found to modify DNA methylation [28]. e polymorphisms within the MTHFR gene also in uence homocysteine related neurotransmitters like taurine (play important in oxidative process). Homocysteine increase superoxide and hydrogen peroxidase by auto-oxidation leading to oxidative stress and reduce the expression of glutathione peroxidase (an antioxidant enzyme) thereby causing the accumulation of its neurotoxic oxidative products [29]. Moreover, homocysteine was found to provoke neuronal cell damage and brain atrophy by stimulating N-methyl-D-aspartate (NMDA) receptors [30]. erefore, it is not strange to nd that elevated homocysteine (Hcy) levels associated with neuro-degeneration, vascular diseases and brain atrophy [31].

In this study, the dependence severity was more associated with the presence of a positive family history. is was consistent with previous studies by Pickens et al., [32] found that family history of substance dependence is a good predictor for more opioid dependence symptoms and more likely to be classi ed as severely dependent patient. Moreover, the current study revealed an association between the severity of dependence as measured by duration of illness, number of relapses severity of dependence scale and the dose of the substance with genotyp and alleles. All these measures are higher in CT & TT genotypes than CC genotype as well as T allele than C allele. A similar increase in severity of dependence with an increase in gene polymorphism was noted in alcohol dependence by Lutz et al., [12]. ey found that the T - allele frequency increased from 0.28 in healthy control subjects to 0.33 in alcohol dependent patients su ering from mild withdrawal symptoms up to 0.40 in alcohol dependent men with a history of withdrawal seizure [12]. De Bree et al. [33] found that the frequency of substance abuse was associated with increase duration of dependence, averag Heroin daily dose, score on the severity of dependence scale, and more relapse. is may be explained by the results that put a link between MTHFR enzymatic activity and the polymorphism of the responsible gene. A recent cross sectional study based on Dutch, found a signi cant lower level of serum folate with 677CT and 677TT genotypes among individuals with self-reported low folate intake [33]. e 677TT genotype even conferred lower serum folate in individuals with high folate intake compared to other genotypes. Individuals with 677TT genotype had elevated homocysteine levels when folate status is low [33]. Finnell and associates [34]. Studies of the folic acid biosynthetic pathway led to the discovery of an association between elevated levels of homocysteine (Hcy). e thermo-labile form of the enzyme led to elevated (Hcy) which may be the mediator of the dependence case severity.

Limitation of the study

Although we tried hardly to exclude ethnicity in this study using through history taking but this may not surly true. Moreover, the present study population was accessed at two private hospitals this may excluded a large portion of the population who could not be treated in private hospital. In our locality no public hospital treating addiction is present.

Conclusion

MTHFR polymorphism may contribute to the incidence and severity of heroin dependence, but that numerous other factors may play an equal or more signi cant role. In addition, plasma homocysteine may have a role in pathogenesis of Heroin related disorders. Multicenter studies and larger samples are recommended in further research to con rm the result of this study.

References

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