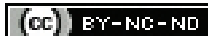


# Serum Kynurenine Levels in Patients of Depression with and without Suicidality: A Case-control Study

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## ABSTRACT

**Introduction:** Depression is a common mental health disorder and suicide is one of the most dreaded outcomes of depression. In India, the suicide rate is reported to be 12.91 of 100,000 population and as per the estimates, it is further going to increase in time to come. Several potential biomarkers for suicidality have been identified over the last years in an effort to devise an investigational test to detect suicidality. Kynurenine, a tryptophan metabolite, is one of the potential biomarkers as it has been found to be elevated in patients with suicidality.

**Aim:** To assess the levels of kynurenine in patients of severe depression with and without suicidal attempt.

**Materials and Methods:** This was a case-control study conducted in MGM Medical college, Indore from April 2020 to March 2021. Socio-demographic parameters like age, gender, residence, marital status were collected along with Hamilton depression rating score, suicidal behaviour questionnaire score. Blood samples of sixty patients with depression having suicide attempt (case group) were compared to the similar parameters of the 60 patients with depression not having any history of the suicide attempt (control

group). Data obtained was analysed using Statistical Package for Social Sciences (SPSS) version 23.0 and relevant statistical tests were applied with the p-value <0.05 was considered as statistically significant.

**Results:** Mean age of the case group was 39.03±11.58 years and in control group was 41.92±11.62 years. The mean serum kynurenine for depression with suicidal attempt was 464.05±89.11 ng/mL which is considered a high value as per the criteria for cut-off for normal level. While for depression without suicidal attempt was 420.78±69.66 ng/mL which is low. The present study had a positive correlation of serum kynurenine levels with the suicidal behaviour questionnaire (r-value=0.48, p-value=0.001) but not with the Hamilton depression rating scale (r-value=-0.243, p-value=0.061).

**Conclusion:** Case group has shown higher mean serum kynurenine than control group, which was statistically significant. This study concluded that, serum kynurenine was not correlated with the severity of depression which makes it a good prospective for further research as a biomarker for early prediction of suicidality.

**Keywords:** Biological markers, Psychiatry suicide, Suicide prevention

## INTRODUCTION

Depression is a common mental disorder that permeates across all age groups, sex, and socio-economic status. Approximately 280 million people across the world have depression, in turn bringing its prevalence to 5.0%. As per the 2020 survey by World Health Organisation (WHO), depression was found to be 12<sup>th</sup> highest cause of Disability-Adjusted Life Years (DALYs) globally. In India, the prevalence of depression was reported to be 3.3% with about as many as 45.1 million suffering from depression and it contributed most to DALYs of all the mental disorders [1,2].

Suicide attempt stands as one of the most dreaded outcomes of the disorder which necessitates aggressive management and remission of symptoms as quickly as possible. As per WHO, every year about seven lakh people die due to suicide of which 77% of suicides are from low to middle-income countries. Unfortunately, suicide forms the 4<sup>th</sup> leading cause of death among 15-29 years old which encompasses the young generation and the productive age groups of a nation, thus suicidality at such age can have catastrophic outcomes [3].

In India, the suicide rate is reported to be somewhere around 12.91 per 100,000 population of which males had a higher rate of 14.69 compared to females at a rate of 11.12 per 100,000 population [4]. As per a report by National Crime Research Bureau (NCRB) the suicide rates in India increased by 8% and are forecasted to still increase over the next few years [5,6].

Several biomarkers associated with suicide risks such as indices of serotonergic function, inflammation, neuronal plasticity, and lipids

have been identified and are being investigated [7,8]. Kynurenine (2-amino-4-(2-aminophenyl)-4-oxobutanoic acid), a tryptophan metabolite, is also being studied as a possible biomarker for suicide. Initially, the importance of the kynurenine pathway, which accounts for about 99% of catabolism of the tryptophan, was linked to the synthesis of Nicotinamide Adenine Dinucleotide (NAD) [9]. However, recent studies have linked the pathway to several neurodegenerative disorders, tumour proliferation, inflammation, and depression as well. As the role of the kynurenine pathway in the neurobiology of depression became more and more apparent, it was conceptualised that, upon activation, the kynurenine pathway diverts even more tryptophan away from the serotonin production. This diversion could be in response to the activation of enzyme Indoleamine 2,3-dioxygenase, by increased proinflammatory cytokines, which mediates the conversion of tryptophan to kynurenine.

Several of the kynurenine pathway metabolites are known to be neurotoxic agents like 3-hydroxyanthranilic acid and quinolinic acid which further cause downstream glutamatergic changes which in turn are hypothesised to lead to depression and in turn increased suicidality. Thus, this increase in depression and suicidality can be due to the depletion of serotonin due to its conversion to kynurenine or due to the influence of neurotoxic metabolites of the kynurenine pathway [9,10]. Hence, in this study, authors aim to assess serum kynurenine levels in depressive patients with and without suicidality and determine if there is any correlation between serum kynurenine and suicidality in depressive patients. To offset a possible confounding, authors are comparing serum kynurenine levels in patients of suicide attempt with non suicidal attempt while

keeping depression common to both the groups. To the best of authors knowledge no such study on serum kynurenine levels has been conducted in Central India which makes it to be the first of its kind.

## MATERIALS AND METHODS

The case-control study was conducted over the duration of one year from April 2020 to March 2021 in the Department of Psychiatry, MGM Medical College, Indore, Madhya Pradesh, India. Institutional Ethics Committee clearance was obtained before initiating this study (No. EC/MGM/Feb-20/64). All eligible patients fulfilling the inclusion criteria and who were present during the study period were enrolled for the study after obtaining appropriate informed consent.

The study recruited 154 participants by convenient sampling method based out of which 34 declined to consent so they were excluded from the sample. The final sample had 120 participants which consisted of 60 depressed patients diagnosed with depression on the basis of a clinical interview and diagnostic criteria described in Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition (DSM 5) [11]:

- Case group (n=60): Patients admitted to a tertiary care centre following a suicide attempt as described by the criteria described in DSM 5.
- Control group (n=60): Depressed patients without suicide attempt.

**Inclusion criteria:** Patients aged 18-65 years belonging to either sex and suffering from major depressive disorders according to the criteria in DSM 5 [11]. Patients with suicide attempt defined as per criteria described in DSM 5 were taken for the case group while patients without suicide attempt were taken for the control group. Only those patients who were willing to give written, informed consent were enrolled for the study.

**Exclusion criteria:** Patients below 18 years of age or above 65 years of age, suffering from any neurodegenerative disorder and currently on treatment with any anti-inflammatory drugs, antidepressants, antipsychotics, and mood stabilisers were excluded from the study because of the possibility of these drugs interfering with serum kynurenine levels.

### Study Procedure

After explaining the procedure to the patient and the caregivers, written informed consent was obtained. A semi-structured proforma was used to obtain socio-demographic details of the patients such as age, gender, educational status, marital status and occupational status [12]. Hamilton depression rating scale and Suicide Behaviour Questionnaire were used subsequently.

**Serum kynurenine levels:** Blood samples were collected using a 5 mL syringe and serum was extracted using a 1200 RPM centrifuge machine (Remi centrifuge R8C DX). Serum kynurenine levels were assessed within a maximum one month of obtaining the sample and as care was taken to minimise the duration between obtaining the sample and analysis, as all samples could not be assessed simultaneously. Samples were assessed using an automated analyzer using enzyme-linked immune assay. Normal cut-off was considered to be 460 ng/mL which is the value as reported in the available literature [13].

**Hamilton Depression Rating Scale (HDRS):** Also abbreviated as HAM-D [14]. Hamilton originally published the scale in 1960. It consists of 17 items rated by a clinician. Eight of the items rated on a 3-pointer scale from 0 to 2:

- Insomnia
  - Initial
  - Middle
  - Delayed

- Somatic symptoms
  - Gastrointestinal
  - General,
- Genital symptoms,
- Weight loss and insight

Nine of the items like:

- Depressed mood,
- Feelings of guilt,
- Agitation,
- Suicide,
- Work and interests,
- Retardation,
- Anxiety
  - Psychic,
  - Somatic
- Hypochondriasis

Rated on a 5-pointer scale from 0 to 4. A score up to seven is considered to be normal while the maximum possible score is of 52 [14].

**Suicide Behaviour Questionnaire (Revised) (SBQ-R):** It was developed by Osman A et al., in 2001. It is used to assess:

- Suicide threats rated upto 3,
- Suicidal ideation rated upto 4,
- Suicide expectancies rated upto 5,
- Suicidal behaviour rated upto 6.

Total score is calculated by adding up all the individual scores. The maximum possible score cut-off score is considered to be >7 for the adult general population and >8 for adult psychiatric inpatients. The scale has high sensitivity and specificity [15,16].

## STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 23.0. All values were expressed as mean±standard deviation. Continuous variables were assessed using an Independent t-test. Chi-square test was performed to test the relationship between categorical variables. A p-value <0.05 was considered to be statistically significant at a confidence limit of 95%.

## RESULTS

Mean age of the case group was 39.03±11.58 years and of control group was 41.92±11.62 years. The minimum age in the case group was 19 years while in the control group it was 25 years. The maximum age in the case group was 62 years while in the control group it was 63 years [Table/Fig-1].

Age (years)	Case group (n=60)	Control group (n=60)
Minimum	19	25
Maximum	62	63
Mean age	39.03	41.92
Standard deviation	11.58	11.62

**[Table/Fig-1]:** Description of age of study participants in case and control group (N=120).

The study had a male preponderance in both the groups, case and control with 63.3% and 66.7% belonging to the male gender, respectively. In the description of the marital status, the case group and the control group had 55% and 65% married participants, respectively. The majority in both groups were Hindu by religion. In the case group, 50% were unemployed of which majority were housewives [Table/Fig-2].

[Table/Fig-3] shows an Independent t-test comparison of serum kynurenine levels between case group and control group with

Socio-demographic parameters		Case group (n, %)	Control group (n, %)
Gender distribution	Male	38 (63.3%)	40 (66.7%)
	Female	22 (36.7%)	20 (33.3%)
	Male: Female	1.7:1	2:1
Marital status	Married	33 (55%)	39 (65%)
	Single	13 (21.7%)	7 (11.7%)
	Separated	7 (11.7%)	7 (11.7%)
	Divorced	5 (8.3%)	4 (6.7%)
	Widowed	2 (3.3%)	3 (5%)
Religion	Hindu	50 (83.7%)	39 (65%)
	Muslim	10 (16.3%)	21 (35%)
Educational status (as per modified Kupuswami)	Illiterate	4 (6.7%)	7 (11.7%)
	Primary	22 (36.7%)	30 (50.0%)
	Middle school	0	0
	High School	22 (36.7%)	16 (26.7%)
	Intermediate or post high school diploma	0	0
	Graduate or Postgraduate	12 (20.0%)	7 (11.7%)
Occupational status (as per modified Kupuswami)	Unemployed	30 (50.0%)	24 (40.0%)
	Unskilled	9 (15.0%)	16 (26.7%)
	Semi-skilled	15 (25.0%)	19 (31.7%)
	Skilled	3 (5.0%)	1 (1.7%)
	Clerical	0	0
	Semi-professional	0	0
	Professional	3 (5.0%)	0

**[Table/Fig-2]:** Description of other socio-demographic parameters of study participants in case and control groups.

significant p-value <0.05. The mean serum kynurenine for case group was 464.05±89.11 ng/mL which was considered a high value as per the study criteria for cut-off. While for was 420.78±69.66 ng/mL which was low. The means differed significantly with a t-value of 2.96 and a p-value of 0.04. Case group has shown higher mean serum kynurenine than the control group, which was statistically significant.

Serum Kynurenine levels	Case group	Control group
Mean	464.05	420.78
Standard deviation	89.11	69.66
Minimum	337.62	332.82
Maximum	598.47	771.35
t-value	2.96	
p-value	<b>0.04</b>	

**[Table/Fig-3]:** Independent t-test comparison of serum Kynurenine between case and control group.  
p-value <0.05 was considered as statistically significant

[Table/Fig-4] shows the Chi-square analysis of patients with serum kynurenine with above or below cut-off as per the case or control group. The significant p-value was considered to be <0.05 at 95% confidence interval. The cut-off was 460 ng/mL [14]. The test was significant with Pearson Chi-square value 10.47 and p-value of 0.001 implying that the serum kynurenine levels are associated with case group.

[Table/Fig-5] depicts the Pearson correlation of Hamilton Depression rating score, and Suicidal Behaviour Questionnaire- Revised, with serum kynurenine levels in the patient having suicide attempt with depression. It was revealed that serum kynurenine levels had negligible correlation with HAM-D scores with Pearson correlation

Serum Kynurenine		Suicide attempt		Total
		No	Yes	
Above cut-off (>460 ng/mL)	Count	13	30	43
	Expected count	21.5	21.5	43.0
Below cut-off (<460 ng/mL)	Count	47	30	77
	Expected count	38.5	38.5	77.0
Total		60	60	120
Pearson $\chi^2$		10.47		
p-value		<b>0.001</b>		

**[Table/Fig-4]:** Chi-square test for Kynurenine samples between case and control group.  
p-value <0.05 was considered as statistically significant

coefficient r-value=-0.243 and a p-value of 0.61 while there was moderate positive correlation between serum kynurenine levels with SBQ score with Pearson correlation coefficient r-value=0.48 (p-value=0.001).

Serum Kynurenine	HAM-D score	SBQ score
Pearson correlation	-0.243	0.48
Sig. (2-tailed)	0.061	0.001

**[Table/Fig-5]:** Pearson correlation of HAM-D, and SBQ with serum Kynurenine levels in depressive patients with suicide attempt.  
p-value <0.05 was considered as statistically significant

## DISCUSSION

This is a novel study in Central India assessing serum kynurenine levels of patients of depression with and without suicide attempt in 120 patients. The mean age of the case group was 39.03 years. The finding is similar to Mudgal V et al., and Runeson B et al., who reported the mean age of suicide attempter to be 33.08 years and 37 years, respectively [8,17]. The mean age of the control group i.e., individuals having depression without suicidal attempt was 41.92 years. The finding is in concordance with a study by Gupta C et al., who reported the mean age of depression to be 41.5 years and Mathias K et al., who reported the mean age to be 39.4 years [18,19].

The gender-wise distribution revealed a male preponderance in both case and control group in the present study. The case group had about 63.3% males and 36.7 females. The finding is in concordance with the study by Mishra K et al., which reported suicide preponderance in males at 63.20% compared to females at 36.80% [20]. Other investigators like Srivastava A, reported 70% male preponderance in suicide attempters, and Vijayakumar L, also reported similar result [21,22]. The male to female ratio was 1.7:1 which is in accordance with a study by Gururaj G et al., who reported the male to female ratio in suicide attempters to be 1.4:1 in the Indian population [23]. The male to female ratio reported in different countries appears to be higher at 3.8, 3.9, 4.1, and 3.4 in Australia, Canada, the United States, and the UK, respectively although literature also reports it to be lower in Asian countries [24,25].

The present study observed a higher percentage of the married individual constituting both groups i.e., case and control group in the present study. Among case group patients, about 55% of individuals were married while in the control group 65% of the participants were married. Marriage is generally considered to be a protective factor against suicide but it has also been noted that this does not stand true for developing countries [26]. Other studies have also shown similar results such as Srivastava A et al., [21] reported 68% of individuals to be married. Study by Latha KS et al., [27], Hegde PS et al., [28] Vijayakumar L [22] and Kumar PS [29] showed no individuals were unmarried in their study. The observation is contrary to those of western authors like Heikkinen ME et al., [30], Castle K et al., [31] and Appleby L et al., [32]. Further, this finding can also be corroborated with the data on suicide made available by National

Crime Research Bureau (NCRB) which observed 66.7% (92,757 out of 1,39,123) individuals to be married [6]. It has been surmised that marital status, per se, is not a protective factor rather quality of the marital relationship, warmth and intimacy shared between the couple, ability to bear the stresses and responsibilities of married life are more important factors that determine protection against suicide in a married individual [27]. Additionally, the concept of marriage is more deeply ingrained in Indian culture compared to the west. Also, owing to the prevalence of arranged marriages often times marital partners are almost strangers to each other. Hence, several conflicts and adjustment problems could arise among married couples and their families, especially if mental illness is present in either partner. Divorce being social taboo, suicide provides the only escape for such frustrated married partners [21].

In religion-wise distribution [Table/Fig-2] of study participants, it was observed that individuals belonging to the Hindu religion made up 83.7% of the entire sample in the case group and 65% of the sample in the control group. The finding is in corroboration with multiple studies by Mudgal V et al., Gupta C et al., Mathias K et al., Raju SS et al.,. The finding can be explained by the fact that Hinduism is professed by the most of the people in India [8,18,19,33,34].

The study observed [Table/Fig-2] 6.7% of the study participants had received no formal education while 36.7% had received education upto primary level or secondary level. About 20% had received education upto college level. The findings were in concordance with Latha KS et al., who reported that upto 46% had received education less than the primary level [27]. Whereas Srivastava A et al., who reported only less than 30% suicide attempters had received education higher than the primary level [21]. The findings could be reflective of the educational status of the population in general rather than reflecting the educational status of the suicide attempters. Any inference to be drawn from this result would require a more robust understanding of the educational status of the Indian general population.

The occupational distribution of the study sample revealed that housewives had highest representation (28.3%) in suicide attempt group and second highest representation (26.7%) in the depression without suicide attempt group. The finding is similar to the study by Raju SS et al., who studied the socio-demographic factors of depressive disorders in India and revealed a preponderance of housewives at 33.9% with unipolar depression while 46.6% with bipolar depression [33]. This could be the result of multiple reasons stemming from the social architecture of our society. Housewives have lesser freedom, monotonous unrewarding work and several roles to be played at the same time. Also, girls in our society get married at an early age and without their own consent in many cases which adds to the problem statement [34]. Another caveat in the current study was that it had strikingly low level of representation by skilled and professional workers which could be due to lesser incidence of depression and suicide attempt among them. But at the same time it should not be overlooked that this study was done at a government-run tertiary care centre which mostly caters to people belonging to lower socio-economic status being located in such a locality.

Depression with suicidal attempt patient group [Table/Fig-3,4] has shown higher mean serum kynurenine than the non suicidal group of depression which was statistically significant. The finding is in agreement with Sublette ME et al., who also reported that serum kynurenine levels were raised in individuals having depression with suicide attempt as compared to depression without suicidal attempt individuals and healthy volunteers [35]. Bradley KA et al., also reported similar results with alteration of KYN/TRP ratio in suicidal patients [36]. This could be because tryptophan instead of making serotonin is getting diverted to the kynurenine pathway resulting in serotonin depletion and as per monoaminergic hypothesis serotonin depletion leads to depression and suicidality. To add, many of

the kynurenine pathway metabolites have their neurotoxic effects leading to increased neuroinflammation [10,37].

On correlating serum kynurenine levels with HAM-D scores, and SBQ scores this study reveals a positive correlation with SBQ which again indicates serum kynurenine to be a marker of suicidality rather than depression. Similar results have been reported in other studies involving suicidality and kynurenine pathway metabolites. In a recent study by Achtyes E et al., on women suffering from peripartum depression with suicidality it was concluded that there was dysregulation of the kynurenine pathway resulted in tryptophan getting diverted to make more kynurenine metabolites as compared to serotonin [38]. Similarly, Messaoud A et al., in their study reported depletion of tryptophan levels and an increase in serum KYN/TRP levels which correlated with suicidality rather than depression [39].

The present study included a control group also, which can be seen as an advantage of the study. Another advantage was that the research is novel study, especially in central India. Patients who suffered from other neurodegenerative diseases or were on drugs that could have influenced the kynurenine levels were excluded. Serum samples taken from the suicidal and non suicidal patients were analysed quickly not allowing the marker levels under assessment to get disturbed. Serum kynurenine levels could serve as a biomarker for suicidality in near future.

### Limitation(s)

As the present study has small sample size, so there is a need for more extensive studies with a larger sample size from a variety of geographical locations and with more ethnic diversity to allow for any generalisability of the results. Also the present study concentrate only on comparing serum kynurenine levels in patients of suicide attempt, there is a requirement to study other kynurenine pathway metabolites and to look for similar associations.

### CONCLUSION(S)

Depression with suicidal attempt patient group has shown higher mean serum kynurenine than the non suicidal group of depression which was statistically significant. Serum kynurenine levels were also found to be higher in patients with higher SBQ scores as compared to HAM-D scores which indicates a possibility of its correlation with suicidality rather than depression. It was also found that the serum kynurenine was not correlated with the severity of depression which makes it a good prospective for further research.

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