

Correlation of Anaemia and Restless Legs Syndrome in Elderly: A Cross-sectional Study

ABHIJIT AGRAWAL¹, JAHNABI BHAGAWATI², SUNIL KUMAR³



ABSTRACT

Introduction: Restless Legs Syndrome (RLS) also known as Willis Ekbohm Disease (WED) which manifests as a neurologic disorder among patients with anaemia, particularly with iron deficiency anaemia.

Aim: To find the association of anaemia with RLS in the elderly population.

Materials and Methods: In this cross-sectional study, 100 patients of age ≥ 60 years were enrolled and categorised into mild, moderate, and severe anaemia as per World Health

Organisation (WHO) criteria. Every participant was enquired about RLS via a questionnaire based on the International RLS Study Group Rating Scale (IRLSSGRS) for its Severity and for the diagnosis (Essential clinical criteria for the diagnosis of RLS).

Results: The study showed that patients with anaemia had a statistically significant correlation with RLS ($p=0.04$) and severity of RLS ($p=0.032$). Serum ferritin levels too showed a statistically significant correlation with RLS ($p=0.032$).

Conclusion: Patients with severe anaemia and lower serum ferritin levels were more prone to RLS and had more RLS severity.

Keywords: Ferritin, Geriatric, Iron deficiency, Severity, Willis ekbohm disease

INTRODUCTION

The Restless Legs Syndrome (RLS) also known as WED is a disorder characterised by neurologic features like the urge of rhythmic limb movement, which can either decrease or stop on limb motion. There is a creepy-crawly sensation along with itchiness and pins and needles like feeling [1-3]. The patients are likely to be misdiagnosed and physicians need to keep a comprehensive approach towards RLS to recognise, investigate, diagnose, and manage RLS. The prevalence of RLS is from 5% to 10% among adults and increases with age [4,5]. It is far more common in females, especially multiparous women [6,7]. Usual age of onset of RLS symptoms is around the fourth to the fifth decade, however, studies had shown more prevalent among the elderly population with 20% of people above the age of 65 years [2,8].

Primary and secondary RLS is indistinguishable at the initial presentation. Primary idiopathic RLS is not age-specific. Primary RLS often has genetic predilection whereas secondary RLS is often triggered by drugs or conditions like anaemia, Chronic Kidney Disease (CKD), etc., [9-11]. The mechanism behind it is said to be linked to an inherited defect in dopamine metabolism. In dopamine production, iron is a cofactor for tyrosine hydroxylase, a rate-limiting enzyme that undergoes hydroxylation [12-14]. Even RLS secondary to CKD, pregnancy, and anaemia involves alterations in iron metabolism. The pathology lies in the substantia nigra showing reduced iron storage visualised by the MRI brain of RLS patients. The reduced levels of iron are found to be proportionate to RLS severity.

Serum iron is lower at night and the RLS severity too increases by evening which coincides with lower serum iron values. Serum iron according to a study is central in RLS [13,14]. Even iron deficiency anaemia is 4 to 5 folds more in RLS patients [15]. This study aimed to find the prevalence of RLS in a rural population of Wardha district of Maharashtra in central India, as it remains an underdiagnosed entity especially in anaemic elderly.

MATERIALS AND METHODS

This cross-sectional study was conducted at Department of Medicine, Jawaharlal Nehru Medical College, Wardha, central India,

after obtaining permission from the Institutional Ethics Committee {Reg No. DMIMS (DU)/IEC/2019/4074}.

Inclusion criteria: All consecutive patients of age ≥ 60 years, diagnosed with anaemia (iron deficiency anaemia), and admitted in rural teaching hospital Wardha from October 2019 to December 2019. Patients with a history of diabetes mellitus (for not more than 10 years), hypertension and smoking were also included in this study.

Exclusion criteria: Patients suffering from thyroid disorders, Parkinson's disease, peripheral neuropathy (ruled out by clinical evaluation as Nerve Conduction Velocity (NCV) was not done due to financial constraint (deep tendon reflex examination was the cornerstone to examine neuropathies, a focal loss of deep tendon reflex, absent ankle jerks with preserved reflex at other sites suggests length-dependent axonopathies). Patients on antipsychotics, antidepressants, anticonvulsants, statins, and steroids, and alcohol consumers were also excluded.

Power analysis was done in G*Power (point biserial correlation) and an adequate sample size was taken with power (0.80), alpha (0.05), a small effect size ($p=0.1$), and two tails. Based on the above-mentioned assumptions, the desired sample size was 100.

Detailed information regarding the patient's past medical disorders and pharmacological interventions were taken. All participants were subjected to general and systemic examination. Anaemia was further classified into mild (haemoglobin between 10-10.9 mg/dL), moderate (haemoglobin between 7-9.9 mg/dL) and severe when (haemoglobin < 7 mg/dL) according to WHO criteria, VMNIS 3 [16]. Spectrophotometry (CLIA) was used for ferritin studies, 4 mL serum from 1 Serum Separating Tube (SST) was taken and haemolysis was avoided. An overnight fasting sample was preferred.

Each patient was provided with a RLS/WED diagnostic criteria: Updated IRLSSG consensus criteria [6,17-19] by a third person who was oblivious to the nature of the study and its possible outcome, to avoid bias. The diagnosis of disease status was exclusively based upon the patient's medical history alone.

Patients under study were questioned for RLS diagnosis. The questions were as follows:

1. The presence of an urge for leg movement is sometimes associated with or due to an unpleasant/uncomfortable leg sensation.
2. Presence of an urge for leg movement with unpleasant sensation while lying down/sitting that starts or aggravates during rest or period of inactivity.
3. Presence of an urge for leg movement with the unpleasant sensation which may resolve completely or incompletely on stretching of the limb/walking till the movement persists.
4. Presence of an urge for leg movement along with an unpleasant sensation that starts or aggravates at night or evening more than daytime, during a period of rest or absence of limb movement.
5. Excluding the presence of such features solely because of other medical or behavioural states like arthritis, habitual foot tapping, myalgia, oedema, venous stasis, leg cramps, etc.,

RLS severity was assessed using the IRLSSG, RLS rating scale for severity in which patients were inquired via the mentioned questions:

1. Rate the discomfort due to RLS in arms and legs
2. Rate the need for moving due to RLS.
3. Quantify the relief achieved on movement in the discomfort in arms and legs due to RLS.
4. How much disturbance in sleep is present due to RLS?
5. How much tired or sleepless do you feel due to RLS?
6. Describe the RLS severity in total.
7. What is the frequency of RLS features?
8. On an average day, describe the RLS Severity if symptoms occur?
9. How impactful is RLS over your work, school, family, and social life?
10. Describe the severity of disturbance in mood, irritability, anxiety, depression, anger, or sadness due to RLS.

The study group was categorised into 5 groups based on their respective scores: patients with score=0 into "none" group, patients with a score between 1 to 10 into "mild" group, patients with a score between 11 to 20 into "moderate" group, patients with a score between 21 to 30 into the "severe" group and patients with a score between 31 to 40 into "very severe" group [17]. The general examination was done for all patients and vitals checked, blood pressure was measured in the right arm, supine position by the auscultatory method.

STATISTICAL ANALYSIS

Statistical analysis was done by using descriptive and inferential statistics using the chi-square test and one way ANOVA and software used in the analysis were Statistical Package for the Social Sciences (SPSS) 24.0 version and GraphPad Prism 7.0 version and $p < 0.05$ was considered as the level of significance.

RESULTS

In this study, out of 100 elderly patients of age ≥ 60 years, the majority (75) were in the age group of 60 to 69 years. The mean age of patients was 66.27 years and there were 76 males. The majority (83) patients did not have RLS symptoms. The mean Hb% was 7.39, mean MCV was 73.63, and mean serum Ferritin was 103.95 [Table/Fig-1].

Of the 100 elderly patients, in the age group of 60 to 69 years, 1.33% have severe RLS. In the age group 70 to 79 years, 4.35% have severe RLS. In the age group ≥ 80 years, 50% have severe RLS. The correlation between age and severity of RLS was statistically ($p=0.002$) as shown in [Table/Fig-2].

Variables	No. of patients
Age (Years)	
60-69	75
70-79	23
≥ 80	2
Mean \pm SD	66.27 \pm 5.45 (60-85 year)
Gender	
Male	76
Female	24
H/O DM	
Present	22
Absent	78
H/O HTN	
Present	49
Absent	51
H/O Smoking	
Present	24
Absent	76
RLS	
Present	17
Absent	83
Severity of RLS	
None	83
Mild	3
Moderate	11
Severe	3
Very severe	0
Hb (gm%)	7.39 \pm 1.98 (3.20-12)
MCV (fl)	73.63 \pm 13 (50-110)
Ferritin (ng/mL)	103.95 \pm 89 (7-300)
Ferritin (RLS present)	61.58
Ferritin (RLS absent)	112.62
Anaemia	
Mild	15
Moderate	36
Severe	49

[Table/Fig-1]: Baseline characteristics of study participants.

RLS: Restless legs syndrome; Hb: Haemoglobin; MCV: Mean corpuscular volume; H/O: History of; HTN: Hypertension; DM: Diabetes mellitus; SD: Standard deviation

Out of 100 patients, 15 had mild anaemia, of which 6.67% patient had severe RLS. 36 patients had moderate anaemia, of which 2.78% patient had severe RLS. Out of 49 patients with severe anaemia, 2.04% patient had severe RLS, as shown in [Table/Fig-3,4].

Out of 100 patients, 3 patients had mild RLS and their mean serum ferritin was 13.0, 11 patients had moderate RLS and their mean serum ferritin was 78.09 and 3 patients had severe RLS with their mean serum ferritin value being 49.66. The correlation of serum ferritin with the severity of RLS was statistically significant ($p=0.032$) as shown in [Table/Fig-5].

Multiple logistic regression analysis showed that age was the main factor that was associated with RLS ($p=0.041$) [Table/Fig-6].

DISCUSSION

Anaemia has an impact on RLS as well as its severity specifically among the elderly population. The primary outcome of the study was to find the strength of association between anaemia and RLS and the secondary endpoint was to determine, if RLS symptoms increased with the severity of anaemia. Various other factors are already known

Age (Years)	Severity of RLS					Total	Chi-square value
	None	Mild	Moderate	Severe	Very severe		
60-69	66 (88%)	1 (1.33%)	7 (9.33%)	1 (1.33%)	0 (0%)	75 (%)	21.05 p=0.002
70-79	16 (69.57%)	2 (8.70%)	4 (17.39%)	1 (4.35%)	0 (0%)	23 (%)	
≥80	1 (50%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	2 (%)	
Total	83 (83%)	3 (3%)	11 (11%)	3 (3%)	0 (0%)	100 (100%)	

[Table/Fig-2]: Correlation of age in years with the severity of RLS. Chi-Square was applied; RLS- Restless legs syndrome; p<0.05 was considered as the level of significance

Anaemia	RLS		Total	Chi-square value
	Present	Absent		
Mild	1 (6.67%)	14 (93.33%)	15 (15%)	6.20 p=0.04
Moderate	3 (8.33%)	33 (91.67%)	36 (36%)	
Severe	13 (26.53%)	36 (73.47%)	49 (49%)	
Total	17 (17%)	83 (83%)	100 (100%)	

[Table/Fig-3]: Correlation of anaemia with Restless Legs Syndrome (RLS). Chi-Square test was applied; p<0.05 was considered as the level of significance

Anaemia	Severity of RLS					Total	Chi-square value
	None	Mild	Moderate	Severe	Very severe		
Mild	13 (86.67%)	0 (0%)	1 (6.67%)	1 (6.67%)	0 (0%)	15 (15%)	6.85 p=0.032
Moderate	31 (86.11%)	1 (2.78%)	3 (8.33%)	1 (2.78%)	0 (0%)	36 (36%)	
Severe	39 (79.59%)	2 (4.08%)	7 (14.29%)	1 (2.04%)	0 (0%)	49 (49%)	
Total	83 (83%)	3 (3%)	11 (11%)	3 (3%)	0 (0%)	100 (100%)	

[Table/Fig-4]: Correlation of anaemia with the severity of RLS. Chi-Square was applied; RLS- Restless legs syndrome; p<0.05 was considered as the level of significance

Severity of RLS	N	Mean	Std. deviation	Std. error mean	F-value
None	83	112.62	86.11	9.45	3.05 p=0.032
Mild	3	13.00	6.24	3.60	
Moderate	11	78.09	109.93	33.14	
Severe	3	49.66	63.51	36.67	
Very severe	-				
Total	100	103.95	89.00	8.90	

[Table/Fig-5]: Correlation of Sr. ferritin with of severity of RLS. ANOVA was applied; RLS: Restless legs syndrome; Sr. ferritin is represented in ng/mL. p<0.05 was considered as the level of significance

Parameters	B	SE	p-value	Exp (B)	95% CI for EXP (B)	
					Lower	Upper
Age	-0.141	0.069	0.041	0.869	0.760	0.994
Gender	-0.030	0.673	0.965	0.971	0.260	3.628
Hb	0.210	0.190	0.268	1.234	0.851	1.791
MCV	0.013	0.037	0.730	1.013	0.942	1.089
Ferritin	0.008	0.005	0.100	1.008	0.998	1.018
DM	0.745	0.798	0.350	2.107	0.441	10.059
HTN	0.514	0.622	0.409	1.672	0.494	5.660
Smoking	-1.379	0.925	0.136	0.252	0.041	1.543
Constant	8.319	5.818				

[Table/Fig-6]: Multiple logistic regression analysis for RLS. Hb: Haemoglobin; MCV: Mean corpuscular volume; HTN: Hypertension; DM: Diabetes mellitus; SE: Standard error; p<0.05 was considered as the level of significance

to predispose a patient towards RLS, factors like ferritin levels in iron deficiency anaemia, diabetes mellitus, hypertension, and smoking. It was found that RLS has a statistically significant correlation to anaemia and serum ferritin, although no such correlation was found with other variables like Mean Corpuscular Volume (MCV), diabetes mellitus, hypertension, and smoking. The correlation between age and severity of RLS was statistically significant (p=0.002). Similarly in another study, the authors showed a higher prevalence of RLS among the elderly population (24.2%). However, they did not divide the severity group of RLS as in the index study [19,20]. In

the present study, correlation of anaemia to RLS was statistically significant (p=0.04). It was also found that RLS severity increased with the severity of anaemia (p=0.032). Other studies also showed patients having anaemia had a significantly higher risk of developing RLS [21,22].

In the present study, patients with RLS had lower mean serum ferritin levels (61.58) than patients who did not have RLS (112.62). Lower serum ferritin levels were found to be associated with more severe RLS symptoms (p=0.032). Some studies showed that there

was decreased serum ferritin in the elderly population associated with RLS and among other RLS patients [21,23,24]. In this study, no significant relationship was found between MCV, diabetes mellitus, hypertension, and smoking. In a study, the authors included 110 consecutive patients from age 34 to 87 years having type 2 diabetes. RLS was detected in 27 patients, however relation was not significant (p=0.31) [25]. In another study, the authors found that RLS was present in 22 diabetic patients (17.7%) and only 5 controls (5.5%) and that RLS was independently associated with type 2 diabetes (p<0.04) [26]. Another study confirmed a positive relationship and a high prevalence of RLS among patients with T2DM visiting primary healthcare [27].

A study showed patients with higher systolic and diastolic blood pressure had higher RLS frequency. Hypertension was more prevalent among women and RLS frequency increased with hypertension. Among the RLS group with higher frequency (15 episodes per month), hypertension was more prevalent (33%), patients with RLS frequency of 5 to 14 episodes per month had a prevalence of hypertension of about 26% and the prevalence was the lowest (21.4%) among patients without RLS [28]. Another study showed that patients with hypertension, hypertension with diabetes mellitus, and only diabetes mellitus had a higher frequency of RLS (30%, 30%, and 21%, respectively) [29]. This was contradictory to the present study finding which could have been because all the patients were elderly while the stated study included patients below 60 years. Another study concluded the consistent and-long term improvement of RLS symptoms by cigarette smoking possibly due to stimulation of nicotine acetylcholine receptors in a similar neuronal dopaminergic population [30]. However in the present study, no significant correlation was found between smokers and RLS symptoms.

Limitation(s)

No objective methodology could be used for excluding the conditions as mentioned in the exclusion criteria of the study, due to financial constraints.

CONCLUSION(S)

Restless Legs Syndrome (RLS) is a commonly occurring, but a frequently underdiagnosed and neglected condition among elderly patients, as it showed significant correlation to age, anaemia, and serum ferritin level in this study. RLS severity increased with age and with severity of anaemia. Patients with severe anaemia and lower serum ferritin levels are more prone to RLS and had more severity of RLS. This article gives an insight into why physicians must focus on symptoms of RLS to improve patient care and must have a background knowledge about RLS to diagnose and manage it.

REFERENCES

- [1] Sales S, Sanghera MK, Klocko DJ, Stewart RM. Diagnosis and treatment of restless legs syndrome. *J Am Acad Physician Assist.* 2016;29(7):15-20.
- [2] Ekblom KA. Restless legs syndrome. *Neurology.* 1960;10(9):868-68.
- [3] Bhagawati J, Kumar S, Agrawal A, Acharya S, Wanjar A, Kamble TK. Impact of different stages of chronic kidney disease on the severity of Willis-Ekbom disease. *Journal of Family Medicine and Primary Care.* 2019;8(2):432-36.
- [4] Zhu XY, Wu TT, Wang HM, Li X, Ni LY, Chen TJ, et al. Correlates of nonanaemic iron deficiency in restless legs syndrome. *Front Neurol.* 2020;11:298. Published 2020 Apr 30.
- [5] Zucconi M. Epidemiology and clinical findings of restless legs syndrome. *Sleep Med.* 2004;5(3):293-99.
- [6] Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelmann JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: Updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria-history, rationale, description, and significance. *Sleep Med.* 2014;15(8):860-73.
- [7] Hanly P. Sleep disorders and end-stage renal disease: *Curr Opin Pulm Med.* 2008;14(6):543-50.
- [8] Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: The MEMO Study. *Neurology.* 2000;54(5):1064-68.
- [9] Kushida CA. Clinical presentation, diagnosis, and quality of life issues in restless legs syndrome. *Am J Med.* 2007;120(1):S4-12.
- [10] Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: A systematic review and new concept. *Neurology.* 2016;86(14):1336-43.
- [11] Sunil K, Abhijit A, Jahanvi B, Sachin A. Exploring the relationship between the platelet indices and psychosocial morbidity in elderly patients at a rural medical college hospital. *Gerontol & Geriatric Stud.* 2018;3(2).
- [12] Patrick LR. Restless legs syndrome: pathophysiology and the role of iron and folate. *Altern Med Rev J Clin Ther.* 2007;12(2):101-12.
- [13] Lyu S, DeAndrade MP, Mueller S, Oksche A, Walters AS, Li Y. Hyperactivity, dopaminergic abnormalities, iron deficiency and anaemia in an in vivo opioid receptors knockout mouse: Implications for the restless legs syndrome. *Behav Brain Res.* 2019;374:112123.
- [14] Telarović S, Čondić L. Frequency of iron deficiency anaemia in pregnant and non-pregnant women suffering from restless legs syndrome. *Hematology.* 2019;24(1):263-67.
- [15] Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anaemia. *Am J Hematol.* 2013;88(4):261-64.
- [16] WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. *Vitamin and Mineral Nutrition Information System.* Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1) (<http://www.who.int/vmnis/indicators/haemoglobin.pdf>, accessed [date]). last assessed on August, 2020.
- [17] Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003;4(2):121-32.
- [18] Gupta R, Goel D, Lahan V. Translation and validation of International Restless Leg Syndrome Study Group rating scale in Hindi language. *Ann Indian Acad Neurol.* 2011;14(4): 257-61.
- [19] Kumar S, Jain S, Wanjar A, Mandal S. Development and validation of a modified Frailty Risk Index as a predictor of mortality in rural elderly people. *Asian Journal of Gerontology and Geriatrics.* 2019;14(1):15-22.
- [20] Celle S, Roche F, Kerleroux J, Thomas-Anterior C, Laurent B, Rouch I, et al. Prevalence and clinical correlates of restless legs syndrome in an elderly french population: the synapse study. *J Gerontol A Biol Sci Med Sci.* 2010;65A(2):167-73.
- [21] Banerji NK, Hurwitz LJ. Restless Legs Syndrome, with Particular Reference to its Occurrence After Gastric Surgery. *BMJ.* 1970;4(5738):774-75.
- [22] Rangarajan S, D'Souza GA. Restless legs syndrome in Indian patients having iron deficiency anaemia in a tertiary care hospital. *Sleep Med.* 2007;8(3):247-51.
- [23] O'Keefe ST. Iron deficiency with normal ferritin levels in restless legs syndrome. *Sleep Med.* 2005;6(3):281-82.
- [24] Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep.* 1998;21(4):371-77.
- [25] Lopes LA, Lins CdMM, Adeodato VG, Quental DP, de Bruin PFC, Montenegro RM, et al. Restless legs syndrome and quality of sleep in type 2 diabetes. *Diabetes Care.* 2005;28(11):2633-36.
- [26] Merlino G, Fratticci L, Valente M, Giudice AD, Noacco C, Dolso P, et al. Association of Restless Legs Syndrome in Type 2 Diabetes: A Case-Control Study. *Sleep.* 2007;30(7):866-71.
- [27] Bener A, Al-Hamaq AOAA, Ağan AF, Öztürk M, Ömer A. The prevalence of restless legs syndrome and comorbid condition among patient with type 2 diabetic mellitus visiting primary healthcare. *J Fam Med Prim Care.* 2019;8(12):3814-20.
- [28] Batool-Anwar S, Malhotra A, Forman J, Winkelmann J, Li Y, Gao X. Restless legs syndrome and hypertension in middle-aged women. *Hypertension.* 2011;58(5):791-96.
- [29] Sabic A, Sinanovic O, Sabic D, Galic G. Restless legs syndrome in patients with hypertension and diabetes mellitus. *Med Arch.* 2016;70(2):116.
- [30] Oksenberg A. Alleviation of severe restless legs syndrome (RLS) symptoms by cigarette smoking. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med.* 2010;6(5):489-90.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Science (Deemed to be University), Wardha, Maharashtra, India.
2. Assistant Professor, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Science (Deemed to be University), Wardha, Maharashtra, India.
3. Professor, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Science (Deemed to be University), Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Sunil Kumar,
Professor, Department of Medicine, Jawaharlal Nehru Medical College,
Datta Meghe Institute of Medical Science (Deemed to be University),
Wardha, Maharashtra, India.
E-mail: sunilkumarmed@gmail.com

PLAGIARISM CHECKING METHODS: [\[Jan H et al.\]](#)

- Plagiarism X-checker: Jul 01, 2020
- Manual Googling: Sep 29, 2020
- iThenticate Software: Dec 13, 2020 (11%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 01, 2020**
Date of Peer Review: **Aug 17, 2020**
Date of Acceptance: **Oct 06, 2020**
Date of Publishing: **Dec 15, 2020**