ORIGINAL ARTICLE

Examination and Validation of Neutrophil–Lymphocyte Ratio as a Perioperative Risk Assessment Biomarker in Major Noncardiac Surgical Patients: An Observational Cross-sectional Study

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Received: 11 January 2025; *Accepted:* 18 February 2026

Abstract

Background and aims: Neutrophil–lymphocyte ratio (NLR) can predict prognosis of disease in patients suffering from cerebrovascular accidents, ischemic heart disease, infectious diseases, sepsis, etc., that can cause increased postoperative morbidity and prolonged stay in hospital. So, NLR can be a potential preoperative risk assessment and stratification biomarker. Our study aims to estimate any correlation between preoperative NLR and coexisting medical and surgical disease and to validate NLR against American Society of Anesthesiologists Physical Status (ASA PS) Classification System, Revised Cardiac Risk Index (RCRI), Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score, and Gupta's postoperative respiratory failure risk in Indian patients.

Materials and methods: This observational, cross-sectional study was conducted in the preanesthesia check-up clinic. Information regarding sociodemographic profile, primary surgical disease, hematological investigations, that is, complete blood count, neutrophil count, lymphocyte count, NLR, and coexistent medical disease was collected, and ASA PS, RCRI, ARISCAT score, and Gupta's postoperative respiratory failure risk were calculated for each study subject. Data were analyzed using standard statistical tests.

Results: Age, congestive cardiac failure, smoking, malignancy, and beta blockers usage were associated with elevated NLR. NLR was found to have a significant relationship with anesthesia risk indices: ASA PS, RCRI, ARISCAT, and Gupta's postoperative respiratory failure risk.

Conclusion: Significant association has been observed between increased NLR and occurrence of systemic illness. NLR also has a significant association with ASA PS Classification System, RCRI, ARISCAT score, and Gupta's postoperative respiratory failure risk. So, NLR may serve as a valuable biomarker in preoperative risk stratification.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1462

Introduction

Patients undergoing major noncardiac surgery face a higher risk of adverse events.[1] Preoperative prediction of the severity of systemic illness and identifying the patients at a higher risk are important to plan safe intraoperative and postoperative care.[2] The use of risk stratification indices, like the American Society of Anesthesiologists Physical Status (ASA PS) classification system[3] as the sole risk stratification score, may not accurately predict the inflammatory processes underlying a patient's comorbid condition, and may not be appropriate for assessment and stratification of preoperative risk.[3] Considering the above facts, biomarkers may be used in preoperative risk stratification along with the perioperative risk stratification indices.

Neutrophil–lymphocyte ratio (NLR) has emerged as a novel marker in the prognostication and management of COVID-19.[4] NLR is an easily available ratio that can be calculated from routine preoperative complete blood count (CBC). As this study was conceived during full-blown COVID times, when we were trying our best to use resources judiciously everywhere, we planned to import this easily obtainable marker from COVID-19 to the perioperative scenario and see how this could be useful here. This is the concept behind conducting this study. So, we set out to investigate the normal levels and distribution of preoperative NLR to determine the frequency of patients who had an increased NLR among noncardiac surgical patients. Examination of the link between NLR and coexisting medical and primary surgical disease, and validation of NLR against the widely applied preoperative risk estimation tools, that is, ASA PS classification system,[3] Revised Cardiac Risk Index (RCRI),[5] Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score,[6] and Gupta's postoperative respiratory failure risk[7] in Indian patients were also aims of this study.

Materials and Methods

This observational, analytical, cross-sectional study was executed in the preanesthesia check-up (PAC) clinic of a tertiary care center from January 2021 to August 2022, in compliance with the Institutional Ethics Committee guidelines. Patients attending pre-anesthesia check-up clinics, aged 18 and above, planned for elective major noncardiac surgeries were enrolled in this study after getting their written informed consent.

The sample size of this cross-sectional study was calculated taking the assumption of sample size used in the previous study by Venkatraghavan et al.[8]

Here, sample size (n) = $Z(1 - \alpha/2)^2 pq/d^2$, where the confidence interval is assumed to be conventionally 95%, therefore, $\alpha = 0.05$ and $Z(1 - \alpha/2) = 1.96$ (2-sided test with a significance level of 0.05), p is the expected proportion in a population-based study. A prevalence of 26.6% was noted in the study by Venkatraghavan et al.,[8] thus $p = 0.266$ is taken in this study, q is $(1 - p) = 0.734$, and d is absolute precision, which is taken as 10% in this study. After applying the formula, n derived = 300. Considering 10% nonresponse or incomplete data, final sample size is calculated to be $n = 330$. Therefore, the final sample size on which the study was performed is $n = 330$.

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How to cite this article: Nangalia S, Dasgupta S, Choudhury A, *et al.* Examination and Validation of Neutrophil–Lymphocyte Ratio as a Perioperative Risk Assessment Biomarker in Major Noncardiac Surgical Patients: An Observational Cross-sectional Study. J Assoc Physicians India 2026;74(4):69–74.

Patient's demographic data, primary surgical disease, hematological investigations (CBC, neutrophil count, lymphocyte count, NLR), coexistent medical disease, anesthesia risk indices, that is, ASA PS, RCRI, ARISCAT score, Gupta's postoperative respiratory failure were collected.

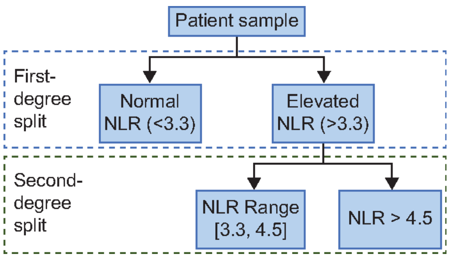

Fig. 1: Distribution of NLR in the study population

Data were entered into a Microsoft Excel spreadsheet and subsequently analyzed statistically by Python statistical analysis tool (version 3.9.6, Python.org). Data had been summarized as mean and standard deviation (SD) for numerical/continuous variables, and for categorical variables, data were expressed as count and percentages. For multivariate and univariate regression analysis, an NLR value of >3.3 and >4.5, respectively, have been found in prior research to be predictive of an increased risk of major adverse cardiovascular events (MACEs) in postsurgical as well as asymptomatic populations.[8–10] So, patients were classified as having normal or high NLR based on 2 defined cutoff values.[8] A *p*-value of <0.25 (*p*-value < 0.25) in univariate analysis served as the criterion for including the potential variables in the multivariate analysis. To identify independent determinants of a higher NLR, multiple logistic regressions were carried out.[8]

During the analysis of the collected data, the data was segregated based on the threshold value of NLR > 3.3, and a thorough data exploration, comparison, and hypothesis testing were performed to check for variables' significance and correlation. Now, to check what factors are responsible for increased risk in patients with elevated NLR, a second-degree dichotomous comparison was made taking the threshold of 3.3 ≤ NLR < 4.5 and NLR > 4.5 during multivariate and univariate regression analysis (Fig. 1). To choose the potential predictors for the multivariate model, a screening was performed using univariate analysis, and the criterion for inclusion was set at $p < 0.25$. To identify independent determinants of a higher NLR, multiple logistic regressions were carried out. A *p*-value of <0.05 was the criterion for statistical significance (*p*-value < 0.05).

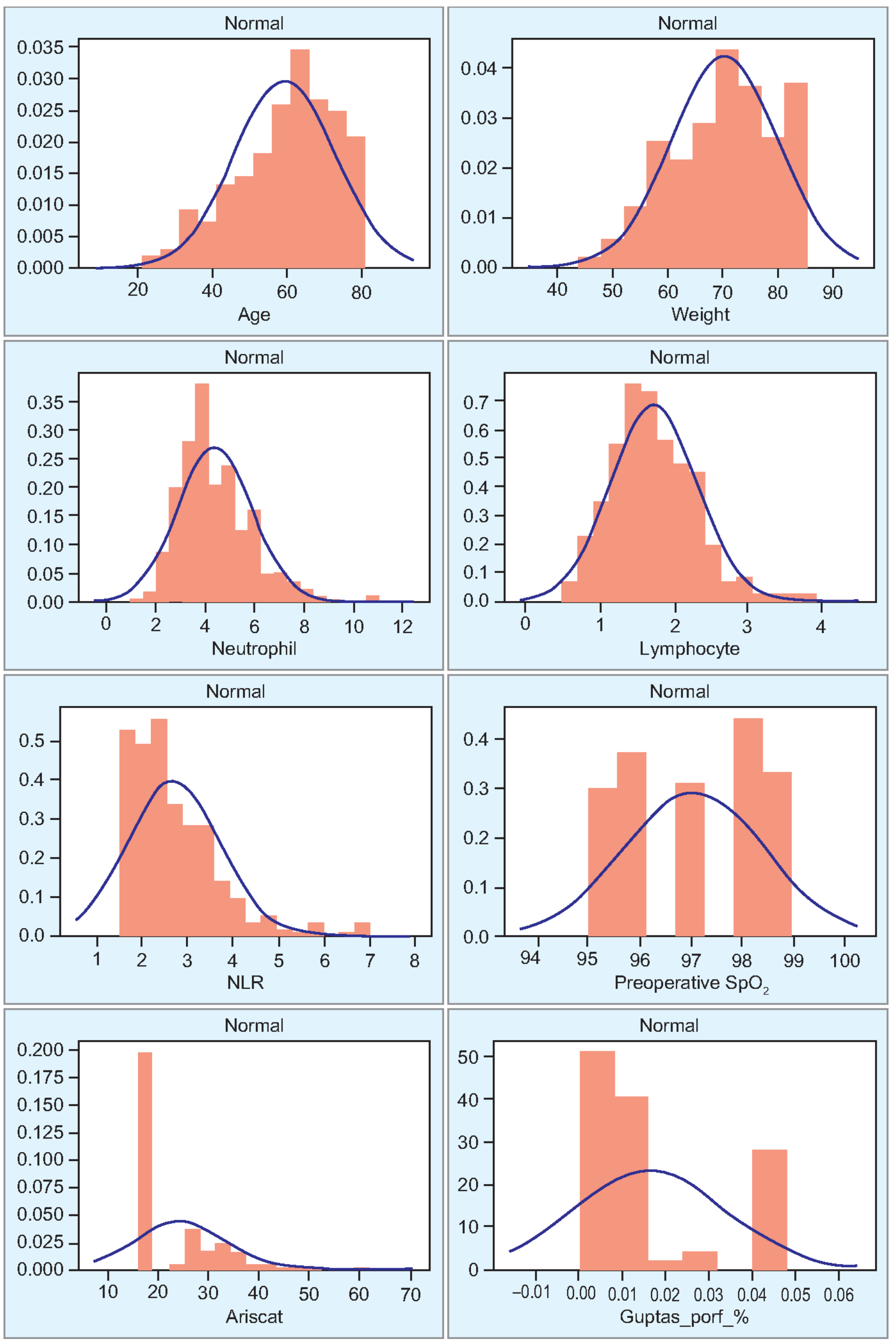

Fig. 2: Distributions of continuous variables

Results

From Table 1, it can be observed that in the present study, mean age (± SD) of the participants is 60 years (±13.5), weight 70.3 kg (±9.5), NLR 2.7 (±1). Continuous variables were also checked for skewness by checking the distribution of each of the variables.

Upon looking at the distribution in Figure 2, all the continuous variables follow a normal distribution except for NLR with a median of 2.5, GUPTA score with a median of 1.02, and ARISCAT with a median of 19.

In Table 2, we compared the distribution of each categorical variable with elevated NLR values. The test is used in conjunction with the goodness-of-fit test to assess whether 2 categorical variables are independent of one another or whether they are connected. The condition of elevated NLR was considered as NLR > 3.3; therefore, NLR > 3.3 were labeled as 1 and NLR < 3.3 was labeled as 0. Out of 330 patients, 212 (64%) are male, whereas 118 (36%) are female. Among all the variables, a statistically significant association was observed between CCF, smoking, beta blocker intake, and any form of malignancy with elevated NLR value.

From Table 3, we can derive the results of univariate logistic regression for NLR > 3.3 as a threshold. Table 3 depicts that age,

Table 1: Statistics on continuous variables

Parameters	*Mean (SD)*	*Minimum*	*Maximum*
Age	60.4 (13.5)	22	82
Weight	70.3 (9.5)	43.8	85.6
Neutrophil	4.4 (1.5)	0.9	11.1
Lymphocyte	1.7 (0.6)	0.5	3.9
NLR	2.7 (1.0)	1.5	7.0
Pre-op SpO_2	97.1 (1.4)	95	99

CCF, smoking, and malignancy were highly associated with NLR > 3.3 and stood out as statistically significant variables. However, after multivariate analysis, malignancy and use of beta blockers were highly associated with elevated NLR.

For the NLR threshold of NLR > 4.5, malignancy was highly associated with *p*-values < 0.05 in the univariate analysis and was statistically significant. Furthermore, individuals with any sort of malignancy had a substantially higher NLR than patients without malignancy (Table 4).

NLR was found to have a significant relationship with comparative biomarkers like ASA PS, RCRI, ARISCAT, and GUPTA's risk index. According to Table 5, increased value of NLR exhibits a statistically significant association with the aforementioned biomarkers.

Discussion

The NLR is a biomarker that can be useful for diagnosing systemic inflammation.[11] NLR as a preoperative risk stratification tool can be beneficial since NLR is derived from routine complete blood count (CBC), which is a part of preoperative and postoperative workup.[8] The usefulness of NLR for evaluating the prognosis of various diseases, including cancer, community-acquired pneumonia (CAP), hemorrhagic stroke, sepsis, and recently acute coronary syndrome, has been investigated.[1114] Elevated preoperative NLR is also known to be associated with increased morbidity and mortality in cardiac and major vascular surgeries postoperatively.[15,16] However, NLR has not been adequately investigated for assessment and stratification of preoperative risk among patients scheduled for noncardiac surgical procedures.

In our study, most of the patients attending the preadmission clinic were scheduled for orthopedic surgery (51%), followed by neurosurgery (28%), general surgery (11%), and the rest (9%) for urology and other noncardiac surgeries. Among the study subjects, 21.5% patients had an elevated NLR value (>3.3). An independent association was observed between CCF and NLR values of >3.3. This finding confirms the fact that NLR serves as a useful predictor of long-term prognosis in acute decompensated heart failure.[16] In our study, a strong association has also been observed between the occurrence of malignancy and NLR values of >3.3 and 4.5. This reaffirms the established role of NLR in prognosis, and predicting mortality and recurrence in patients with cancer.[17] After univariate analysis, age, CCF, smoking, and malignancy were increasingly associated with NLR > 3.3. However, after multivariate analysis, malignancy and use of beta blockers were highly associated with elevated NLR. For the NLR threshold of NLR > 4.5, malignancy was associated with elevated NLR. NLR was also found to be significantly associated with ASA physical status, ARISCAT score, RCRI, and Gupta's postoperative respiratory failure risk.

In the present study, increased medication usage, which indicates the presence of multiple comorbidities, was associated with NLR values >4.5. This emphasizes the relationship of increased NLR and presence of multiple comorbidities in the study population. In a study on NLR in patients with community-acquired pneumonia by de Jager et al., pneumonia severity (CURB-65 score), clinical characteristics, complications, and outcomes were related to the NLR and compared with C-reactive protein (CRP), neutrophil count, and white blood cell (WBC) count, and it was found that NLR value exhibits superior prognostic accuracy for assessment of the severity and outcome of CAP relative to the conventional markers of infection. This aligned with the result of the current study, where it has been observed that increased NLR is related to the presence of systemic illness.[18] A study by Kuikel et al. on NLR to predict the adverse outcomes in 3,340 patients suffering from community-acquired pneumonia observed that NLR was more useful in predicting mortality than C-reactive protein levels, white blood cell count, neutrophil count, or lymphocyte level alone, Pneumonia Severity Index (PSI) level, PSI class, procalcitonin, and CURB-65. So, this study found NLR as an easy-to-measure and simple marker to predict outcomes in patients having CAP, and likewise our study observed NLR as a potential perioperative risk assessment biomarker.[12] NLR and its relation with the occurrence of atherosclerotic events were observed in a study by Adamstein et al. In the CANTOS, JUPITER, SPIRE-1, SPIRE-2, and CIRT trials, baseline and on-treatment NLRs were obtained from 60,087 randomized participants and were followed to determine the incidence of major adverse cardiovascular events. As per this study, NLR could predict the risk of cardiovascular events and all-cause mortality independently.[19] Our study also showed an association of NLR with perioperative risk. Imtiaz and colleagues found a significant correlation between the raised NLR value and increased risk of being diagnosed with hypertension and diabetes mellitus, and likewise our study showed the presence of various systemic illnesses to be associated with raised NLR.[20]

A study to determine NLR as a predictive marker of metabolic syndrome (MS) by Liu et al. concluded that as NLR increases, the risk of MS also increases, and NLR values can be a valuable tool to predict the development of MS. Similarly, our study found an independent association between malignancy and NLR.[21]

Park et al. investigated the incidence of MACEs 5 years after STEMI and observed an association between elevated NLR and higher mortality rates among patients surviving 30 days following successful coronary intervention; this was in uniformity with our study, where the prognostic value of NLR was examined.[22] Similar findings have been observed in the study by Shah and colleagues, where they observed that an NLR value above 4.5 was independently associated with coronary heart disease (CHD)-related death in the general healthy population. They also showed that the study participants who were in the intermediate risk category of the Framingham Risk Score (FRS), NLR permitted reclassification of those patients as having a lower or higher risk of cardiovascular mortality, and also NLR could independently predict CHD-related death in asymptomatic patients.[15] In a study conducted by Adamsson et al. to find any correlation between coronary events and blood neutrophil and lymphocyte counts, it was found that neutrophil counts were associated with increased incidence of coronary events.[23] Venkatraghavan et al.

Table 2: Categorical variable analysis

		NLR < 3.3	*NLR > 3.3*	*Total*	*p-value*
		0	*1*		
Gender	0	168	44	212	0.62
	1	90	28	118	
IHD	0	231	61	292	0.3
	1	27	11	38	
CCF	0	252	68	320	0.003*
	1	4	6	10	
HT	0	152	39	191	0.5
	1	106	33	139	
Smoker	0	164	33	197	0.009
	1	94	39	133	
Resp. infection	0	232	62	294	0.48
	1	26	10	36	
COPD	0	243	65	308	0.36
	1	15	7	22	
OSA	0	235	65	300	1
	1	23	7	30	
Resp. malign.	0	256	72	328	1
	1	2	0	2	
GI. malign.	0	253	69	322	0.5
	1	5	3	8	
CKD	0	255	70	325	0.6
	1	3	2	5	
Urin. malign.	0	254	68	322	0.12
	1	4	4	8	
Anemia	0	236	68	304	0.56
	1	22	4	26	
CVA.TIA	0	246	67	313	0.63
	1	12	5	17	
Breast and gyne. malign.	0	250	69	319	0.94
	1	8	3	11	
Diabetes	0	237	67	304	0.93
	1	21	5	26	
Insulin	0	255	69	324	0.23
	1	3	3	6	
OHA	0	238	69	307	0.4
	1	20	3	23	
HT. meds	0	183	52	235	0.94
	1	75	20	95	
NSAIDs	0	147	45	192	0.4
	1	111	27	138	
	1	16	10	26	
Beta blocker	0	230	58	288	0.05*
	1	28	14	42	
Diuretics	0	235	67	302	0.7
	1	23	5	28	
Malignancy	0	220	52	272	0.001
	1	35	18	53	
	2	3	2	5	

*IHD, ischemic heart disease; CCF, congestive cardiac failure; HT, hypertension; Resp. infection, respiratory infection; COPD, chronic obstructive pulmonary disease; Resp. malign., respiratory malignancy; GI malign., gastrointestinal malignancy; CKD, chronic kidney disease; Urin. malign., urinary malignancy; CVA, cerebrovascular accident; TIA, transient ischemic attack; Breast and gyne. malign., breast and gynecological malignancy; OHA, oral hypoglycemic agent; HT meds., medication for hypertension

Table 3: Results—univariate logistic regression for the threshold = (3.3 ≤ NLR < 4.5)

	Univariate logistic regression analysis			Multivariate logistic regression results		
Variables	*Odds ratio*	*95% CI range*	*p-value*	*Odds ratio*	*95% CI range*	*p-value*
Age	1.02	(0.9–1.041)	0.04	1.02	(0.99–1.04)	0.075
Surgery	1.2	(0.95–1.51)	0.11	0.97	(0.53–1.79)	0.934
IHD	1.54	(0.72–3.28)	0.22	1.01	(0.41–2.47)	0.978
CCF	2.55	(1.24–5.25)	0.003	1.84	(0.85–4.03)	1.12
Smoker	2.06	(1.21–3.49)	0.007	2.33	(1.30–4.19)	0.004
COPD	1.7	(0.68–4.45)	0.24	0.99	(0.35–2.77)	0.992
Insulin	3.69	(0.7–18.71)	0.11	1.68	(0.28–10.09)	0.568
Beta blocker	1.98	(0.98–4.00)	0.05	1.43	(0.65–3.15)	0.366
Malignancy	1.99	(1.15–3.44)	0.01	2.19	(1.22–3.924)	0.008

Table 4: Results—univariate logistic regression for the threshold = (NLR > 4.5)

	Univariate logistic regression results			Multivariate logistic regression results		
Variables	*Odds ratio*	*95% CI range*	*p-value*	*Odds ratio*	*95% CI range*	*p-value*
Smoker	1.05	(1.00–1.11)	0.036	3.05	(1.06–8.76)	0.037
COPD	1.08	(0.98–1.20)	0.1	1.85	(0.44–7.58)	0.396
Beta blocker	1.102	(1.02–1.18)	0.01	3.4	(1.14–10.12)	0.028
Malignancy	1.07	(1.01–1.13)	0.016	3.27	(1.36–7.85)	0.008

Table 5: Results—logistic regression on other biomarkers with elevated NLR

Variables	*Odds ratio*	*95% CI range*	*p-value*
Gupta's Index	3.11	(2.89–53.68)	0.019
RCRI	2.55	(0.27–3.47)	0.022
ASA PS	1.88	(1.16–3.05)	0.01
ARISCAT	0.83	(0.50–1.39)	0.04

found that 26.6% of their study population had an NLR value of >3.3. They also observed a correlation between NLR and the preoperative risk stratification indices, like ASA PS, and RCRI score. Our study also observed a significant relationship between NLR and the preoperative risk stratification indices, like ASA PS, RCRI, ARISCAT score, and Gupta's postoperative respiratory failure risk.[8]

Shibutani and associates found that higher value of preoperative NLR is related to poor survival in patients suffering from colorectal cancer. It was found that cancer-specific mortality was significantly ($p < 0.001$) more in the patients with a high NLR, which was an independent risk factor for poor survival. It was concluded that preoperative NLR measurement is a convenient biomarker and predictor of a poor prognosis after surgery for colorectal cancer.[24]

However, we acknowledge certain limitations in our study. This study is not formulated to evaluate the usefulness of preoperative NLR to assess and stratify perioperative risks and predict perioperative major cardiovascular adverse events and mortality. Instead, this cross-sectional study is intended to give a "snapshot" of the distribution and prevalence of NLR in a subset of the patients during their pre-anesthesia check-up before their operation and to link this biomarker to the occurrence and prevalence of comorbidities of those patients. Further research is required to establish the ideal function of this biomarker as a perioperative risk stratification tool. The present study sets the platform for the evaluation of the role of NLR in future research considering the optimal cutoff value of NLR and the association between increased NLR and adverse health outcomes in the perioperative period.

In conclusion, elevated value of NLR is associated with increased occurrence of systemic illness, and the association is statistically significant. Congestive cardiac failure and malignancy had a significant relationship with increased NLR at >3.3 and >4.5, respectively. NLR has also been found to have a significant association with the comparative anesthesia risk indices, like the American Society of Anesthesiologists Physical Status (ASA PS) Classification System, Revised Cardiac Risk Index (RCRI), Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score, and Gupta's postoperative respiratory failure risk.

Hence, NLR, an easily available and measurable biomarker, may be useful as a preoperative anesthetic risk stratification tool. It would be particularly appropriate for tertiary care hospitals where the patient load is huge and patients often have multiple comorbidities.

Author Contributions

SDG2, SN1, KKP3, AC4: conceptualization, visualization, design of study, and literature search, investigation, methodology, project administration. KKP3, SN1: data curation, software, formal analysis. SN1, SDG2, AC4: writing the original draft. SDG2, KKP3, AC4: supervision, validation, manuscript editing, and manuscript review.

Acknowledgments

The authors wish to thank all the participating investigators and patients for their contributions to this study.

CTRI number: Registration not done as it is an observational study.

Ethics declaration: Approval from the Ethics Committee of our institution was taken. Written informed consent was obtained from

every participant after providing a detailed explanation of the purpose and procedure of our study.

IEC approval number and date: RKC/412; 09/03/2021.

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