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To Evaluate Importance of Coagulation Factors and Septic Screen Parameters in Prognosis of Surgical Necrotizing Enterocolitis

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ABSTRACT

Background: Necrotizing enterocolitis is an ongoing acquired inflammatory disease condition affecting the entire gut especially during the neonatal period, particularly preterm and low birth weight infants. NEC is notorious for its rapid onset, diagnostic challenges, and high mortality rate, posing a severe threat to neonatal life.

Aims-Relating parameters of coagulation and septic screen at the time of NEC diagnosis undergoing different surgical interventions and its applicability in further prognosis and outcome.

Methods and materials: A prospective observational study done in the department of pediatrics surgery, SMS Medical college Jaipur, in 70 patients from April 2023 to April 2024 with patients living between day1 to live day 28 were included. All had preoperative clinical -radiological features consistent with NEC and with intraoperative findings of NEC, were initially resuscitated, were taken a detailed history with demographic data and investigated with baseline and specific coagulation profile and sepsis screen and then were operated. An analysis of outcome and prognosis was done based on altered specific/predictive parameters taken into consideration.

Results: a total of 70 patients that underwent surgical procedure it was found that not only platelets count, but PT INR, APTT, CRP and D-DIMER were independently associated with surgical NEC. APTT and D-DIMER could be identified raised high significantly in poor prognostic neonates with 90 % specificity, 91 % sensitivity and 54.50% specificity 68.6% sensitivity respectively. Coagulopathy was found in almost 90% of cases of surgical NEC and 92% of those dyed to NEC.

Conclusion: Coagulation profile and septic screen parameters at the time of surgical NEC, are facilitative in predicting poor prognosis and likely deaths related to NEC. Hence, they should be scrutinized closely and can be used in future as conducive decision-making tools of surgical management and predict whether the outcome would be bad or good irrespective of intervention.

Keywords: *necrotizing enterocolitis, platelets count, septic screen, obstruction, complications, exploratory laparotomy.*

1. INTRODUCTION

Necrotizing enterocolitis (NEC) is an ongoing acquired inflammatory disease condition affecting the entire gut especially during the neonatal period, particularly preterm and low birth weight infants [1]. NEC is notorious for its rapid onset, diagnostic challenges, and high mortality rate, posing a severe threat to neonatal life.

The incidence of NEC has been estimated in population studies to be approximately 1 to 3 per 1,000 live births. Although the etiopathogenesis of NEC remains unclear and confusing, the current evidence supports a complex, multifactorial mode of disease with prematurity, mucosal injury, ischaemic-hypoxic insults, genetic factors, maternal infection, enteral feeds as old and known factors. Many predictive factors have been defined for NEC with variable sensitivity and specificity with no single entity holding promise for predicting prognosis before and after surgery for survival.

The treatment for NEC depends on the severity of the condition. Medical treatment for mild to moderate cases includes cessation of enteral feeds, empirical antibiotic therapy, supportive care, and close monitoring of vital signs. Severe cases require surgical intervention, such as intestinal resection, peritoneal drainage, and supportive medical treatment [2]. Accumulating clinical and basic research evidence supports a complex interplay between coagulation and inflammation [3], [4], [5]. Although abnormalities of coagulation and fibrinolysis system are involved in the pathogenesis of NEC, hematological abnormalities related to NEC are rarely reported, and the results remain controversial [6], [7], [8], [9].

This study aims for the predictive significance of these parameters at the time of surgical NEC diagnosis and further identify the serial trend of changes in the same affecting the outcome of the neonates with different surgical methods adopted/done.

2. MATERIAL AND METHODS:

This is a prospective observational study of 70 patients from April 2023 to April 2024(1 year) in the department of Pediatrics Surgery SMS Medical College Jaipur, with patients living between day1 to day 30, i.e. neonatal period to be taken into consideration. The main aim behind this study is to inter-relate parameters for coagulation and sepsis in pathophysiology and outcome in surgical NEC patients referred to our institute so that prognostication and, accordingly, management can be modified.

All neonates taken into inclusion had preoperative clinical -radiological features consistent with NEC (based on modified BELL'S CRITERIA) and with an intraoperative picture of NEC (grade 3 and above). However, cases of neonatal perforation due to Ileal atresia, Meconium ileus, Hirschsprung disease, Gastroschisis, Meckel's diverticulum, Malrotation with volvulus, Traumatic etiology, focal gastrointestinal perforation with no signs of necrosis, spontaneous pneumoperitoneum/bacteremia, neonatal sepsis were excluded from the study.

Neonates were initially received either directly from referral centers or from our medical neonatal ICCU. Initially, they were resuscitated with fluids and decompression done by nasogastric tube insertion and catheterization and blood samples withdrawn post resuscitation for baseline workup and special investigations pertaining to study as coagulation parameters (PT/APTT/INR) sepsis parameter (CRP qualitative, D-DIMER).

With initial informed consent taken from the relatives (available more preferably father, mother or from first degree relative) was followed by detailed history of type of birth, birth weight, NICU admission (if referred from outside), feeding history, history of presenting complaints and other demographic details. Radiological investigations were then ordered as baseline BABYGRAM for documentation of the pathology and, in doubtful and moderately stable cases, were further investigated with ultrasonography of the abdomen.

For frank pneumoperitoneum and vitally unstable patients, no further investigations were planned, and they were taken for operative intervention with necessary blood products in hand [PRBC and PC] and were explored after initial resuscitation and with minimal anesthesia. For some, direct peritoneal drain placement was done initially for stabilization and dealing with locally overwhelming sepsis, to be later explored if survived this phase. As per intraoperative bowel condition, overall neonatal conditions also, to minimize operative time and anesthetic complications, surgical intervention was done to either resecting necrosed part with anastomosing to healthy bowel (if present), or resection of gangrenous gut with proximal ostomy, simple proximal diversion as ostomy with or without drain placement.

3. STATISTICAL ANALYSIS:

Data collection was done through medical records maintained manually. Excel sheets were used for data entry. Statistical Package for Social Sciences (SPSS) 28.0 software was used for statistical assessments. Chi square tests were used for categorical variables with contingency tables and depicted in pie charts and bar graphs and with tables for data and ROC curves. Independent t tests were used for continuous variables also depicted in bar graphs and with tabular representation of data and ROC curves.

4. RESULTS:

In this study there were 40 male and 30 female patients and the male to female ratio was 1.34. The mean weight was 2.1 kg and ranged between 0.9 kg to 3.2 kg. The mean age of presentation was 6.4 days and ranges between 4 days to 11 days. Signs and symptoms are present in 25 patients who have both local and abdominal and 45 patients have only locally. [table-1, figure-1,2]

Figure-1 **figure-2**

Figure 1: BABYGRAM: Pneumoperitoneum: football sign: Grade 3b (bell's staging)
Figure 2: USG: Sealed off perforation showing loculated collection in pelvic cavity extending to epigastrium with air foci

C-reactive protein (CRP):

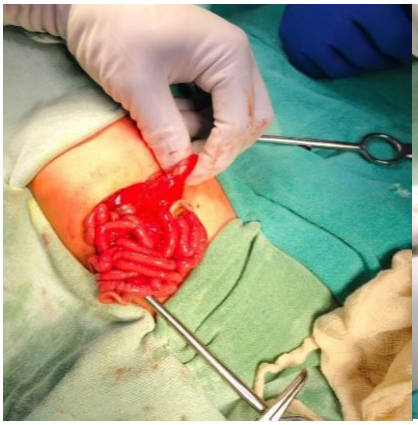
Among patients with negative CRP (12.8%), 31.8% were discharged, and 4.2% died. In contrast, 68.2% of CRP-positive patients (87.14%) were discharged, and 95.8% died. This difference was statistically significant (chi-square = 10.295, p = **0.001**).

Table- 1 epidemiological and clinicopathological summary.

	Categories	N	Outcome		Chi square	P value
			DISCHARGE (N (%))	DEATH (N (%))		
Gender	Female	30	9 (40.9)	21 (43.8)	0.05	0.824
	Male	40	13 (59.1)	27 (56.2)		
Clinically sign and symptoms	Both (local+ Abdominal)	25	7 (31.8)	18 (37.5)	0.212	0.645
	Local	45	15 (68.2)	30 (62.5)		
Radiological	BABYGRAM	46	16 (72.7)	30 (62.5)	3.02	0.221
	Both (xray+usg)	18	6 (27.3)	12 (25)		
	USG	6	0 (0)	6 (12.5)		

Intraoperative findings: -

For those with colon perforation (14.2%), 27.3% were discharged, and 8.3% died. Among patients with ileal perforation (37.1%), 40.9% were discharged, and 35.4% died. For jejunal perforation (20%), 27.3% were discharged, and 16.7% died. Only 4.5% of those with jejunoileal perforation (8.6%) were discharged, and 10.4% died. None of the non-operated patients were discharged, and 29.2% i.e. all died. This was statistically significant (chi-square = 11.782, **p = 0.019**). [table no. -2, figure- 3,4,5]



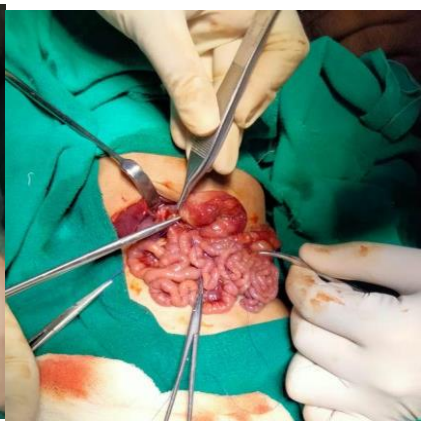


Figure-3 **figure-4** **figure-5**

Figure 3: Multiple ileal perforations (hand pointing largest one) with pre-gangrenous changes
Figure 4: Single transverse colon perforation with relatively healthy bowel
Figure 5: Jejunal perforation with pre-gangrenous changes elsewhere in the bowel

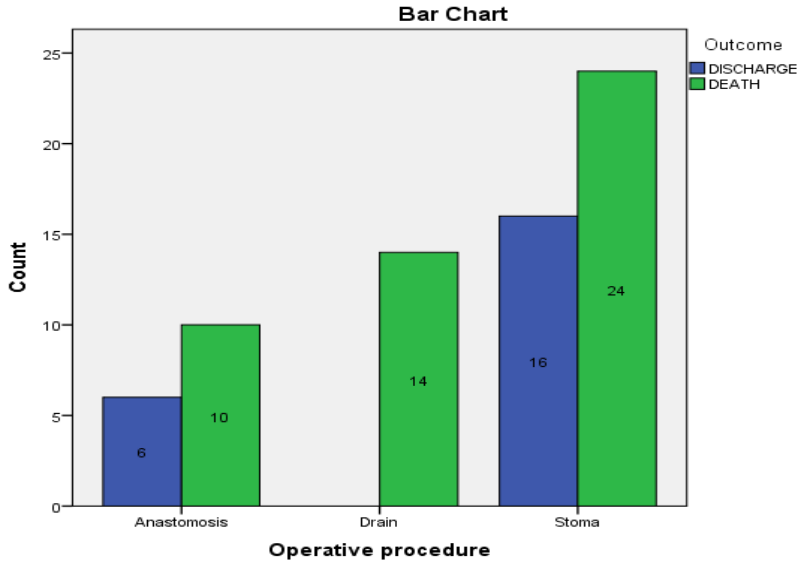
Table -2 site of perforation and surgical managements

			Outcome			
	Categories	N	DISCHARGE (N (%))	DEATH (N (%))	Chi square	P value
Intraoperative findings	Colon perforation	10	6 (27.3)	4 (8.3)	11.782	**0.019**
	Ileal perforation	26	9 (40.9)	17 (35.4)		
	Jejunal perforation	14	6 (27.3)	8 (16.7)		
	Jejunoileal perforation	6	1 (4.5)	5 (10.4)		
	Not Operated (drain placement)	14	0 (0)	14 (29.2)		
Operative procedure	Anastomosis	16	6 (27.3)	10 (20.8)	8.054	**0.018**
	Drain	14	0 (0)	14 (29.2)		
	Stoma	40	16 (72.7)	24 (50)		

Operative procedure:

Among patients who underwent anastomosis (22.9%), 27.3% were discharged, and 20.8% died. None of the patients who had a drain (20%) were discharged, while 29.2% died. In the stoma group (57.1%), 72.7% were discharged, and 50% died. This was statistically significant (chi-square = 8.054, **p = 0.018). [table no-2, figure- 6, graph- 1]**

Figure 6: Diverting ileostomy (with transverse colon distal mucous fistula)



Graph- 1 operative procedures

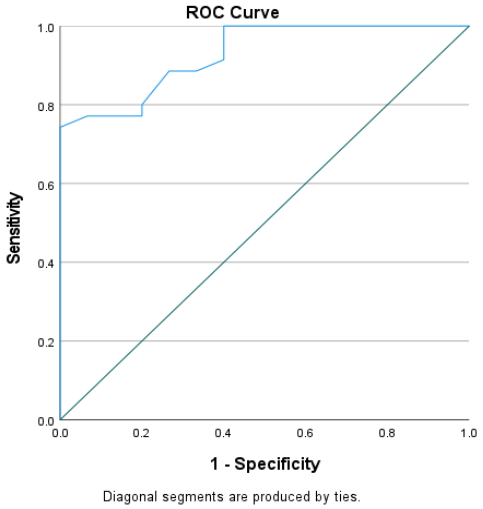
5. PLATELET COUNTS

Comparison of the Platelet (in thousands) between the two groups shows that Platelet (in thousands) is higher in discharge group with a t value of 2.451 and is statistically significant with a **p value of 0.017. AUC:0.929** showing excellent association (sensitivity 74.4% ,30-50K) of increasing trend in platelets count in surgical NEC patients showing survival dealt with any modality of intervention. [table-3, graph-2]

Table -3 outcomes with various parameters

	DISCHARGE(n=22)	DEATH(n=48)		P VALUE
	Mean ± sd	Mean ± sd	T	
Age in days	9.59±6.25	10.96±7.18	-0.769	0.444
Weight (in Grams)	1656.82±302.09	1710±570.51	-0.509	0.613
HB	14.51±2.93	13.09±4	1.489	0.141
Platelet (in thousands)	56.82±18.68	43.92±21.18	2.451	**0.017**

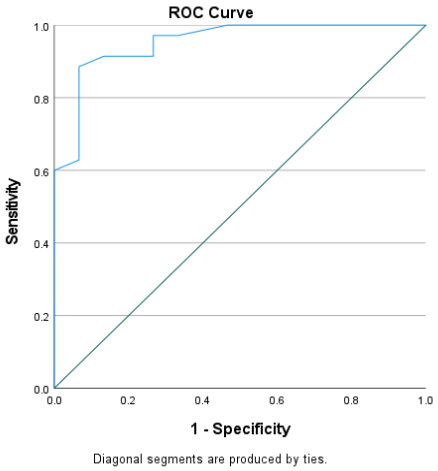
PT	15.6±2.27	16.9±2.2	- -2.27	**0.026**
INR	1.42±0.21	1.51±0.29	-1.382	0.171
APTT	31.36±4.5	40.73±7.13	6.659	**<0.001**
D Dimer	6.35±2.08	9.58±5.71	-3.448	**0.001**



Graph no-2

PT

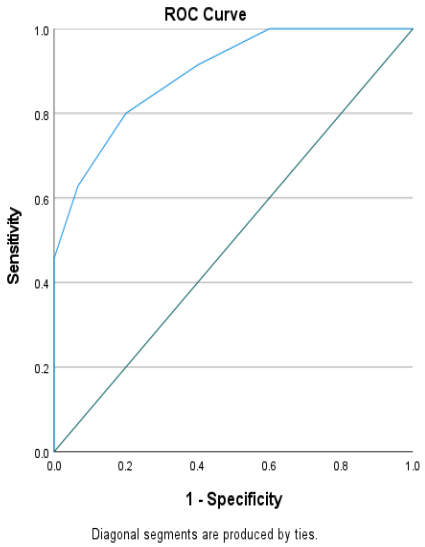
Comparison of the PT between the two groups shows that PT is higher in death group with a t value of 2.27 and is statistically significant with a p value of **0.026. AUC: 0.952** showing excellent association (sensitivity 97.1% >17s or above) of increasing trend in values of PT in surgical NEC patients progressing to death dealt with any modality of intervention. [table-3, graph-3]



Graph n-3

APTT

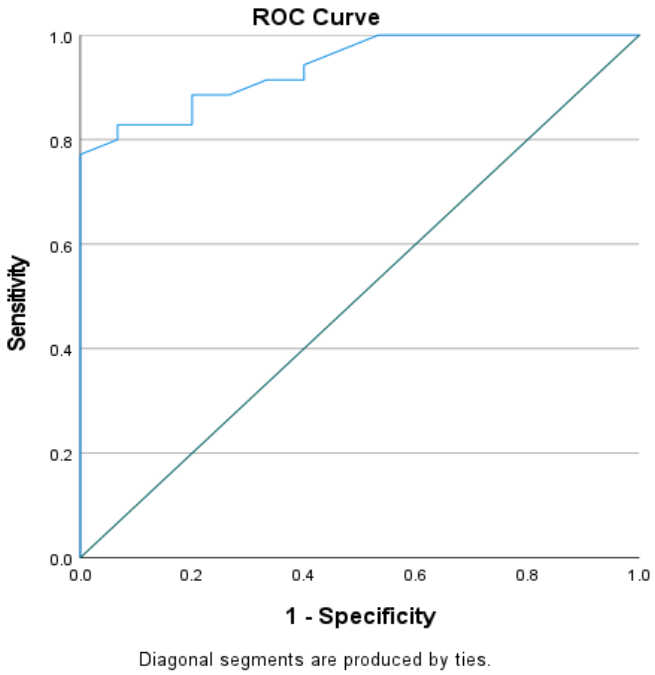
Comparison of the APTT between the two groups shows that APTT is higher in death group with a t value of 6.659 and is statistically significant with a p value of **<0.001. AUC: 0.894** showing excellent association (sensitivity 91.1% >40s or above) of increasing trend in values of APTT in surgical NEC patients progressing to death dealt with any modality of intervention. [table-3, graph-4]



Graph no-4

D -DIMER

Comparison of the D Dimer between the two groups shows that D Dimer is higher in death group with a t value of 3.448 and is statistically significant with a p value of **0.001. AUC:0.939** showing excellent association (sensitivity 97.7% >7mg/dl) of increasing trend in values of D DIMER in surgical NEC patients progressing to death dealt with any modality of intervention. [table-3, graph-5]



Graph no-5

Table -4 various blood parameter and their association

Parameter	True negative i.e. Outcome: discharge & test: negative	True positive i.e. Outcome: death & test: positive	False negative i.e outcome: death & test: negative	False positive i.e outcome: discharge & test: positive	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy	P value
Platelets (Cutoff 30k)	20	12	36	2	74.00%	90.90%	85.70%	35.70%	45.71%	0.0170
PT (Cutoff >17s)	18	29	19	4	97.1%	81.80%	87.90%	48.60%	67.14%	0.0020
APTT (Cutoff >40s)	20	35	13	2	91.1%	90.90%	94.60%	60.60%	78.57%	<0.001
D dimer (Cut off >7)	12	33	15	10	97.7%	54.50%	76.70%	44.40%	64.29%	0.007

On comparison of the 2-test group (death and discharge), platelet counts (Cutoff 30k) have a sensitivity of 74% and specificity of 90.9%. The test has a positive predictive value of 85.7% and a Negative predictive value of 35.7%.

On comparison of the 2-test group (death and discharge), PT (Cutoff >17s) has a sensitivity of 97.1 % and specificity of 81.8%. The test has a positive predictive value of 87.9% and a Negative predictive value of 48.6%.

On comparison of the 2-test group -(death and discharge), APTT (Cutoff >40s has a sensitivity of 91.1 % and specificity of 90.9%. The test has a positive predictive value of 94.6% and a Negative predictive value of 60.6%.

On comparison of the 2-test group (death and discharge), D-Dimer (Cutoff> 7) has a sensitivity of 97.7 % and specificity of 54.5%. The test has a positive predictive value of 76.7% and a Negative predictive value of 44.4%.

Hence, to summarize the demographic parameters of significant importance among those who died of the disease and the intervention included low birth weight(<1500gram), delayed presentation (>15 days), preterm delivery (<32 weeks) and history of NICU admission before referral. Hematological parameters included low platelet counts (<30000), low hemoglobin levels(<10gm/dl), leukopenia (<3000) and specific SEPSIS PARAMETERS: CRP (POSITIVE), D DIMER(>7mg/dl) and COAGULATION PARAMETERS:PT (>17s) APTT(>40s) were present in all cases of surgical NEC that ultimately led to dismal outcome.

6. DISCUSSION

There have been a number of studies predicting parameters suggesting severity of NEC as it is an ongoing process managed both medically and surgically. However, those suggesting prognosis on serological indicators before operating on a surgically treated NEC are very limited. Our study specifically targets these surgical neonates' cohorts by correlating these specific hematological factors associated with pathogenesis of NEC and its impact on the outcome of operated cases.

Recent research reported that more than 30% of neonates with NEC require surgical intervention, and the mortality rate among surgical NEC cases is estimated to be 20% ~ 30%. But in our cohort, estimated mortality among surgical patients was likely to be above 60%.It's probably due to the fact that our institute is the largest tertiary referral center in the state and hence, the quality of neonates referred to has already been compromised and pathogenesis, leading it to be a surgical case worse, hence despite all improvements in pre-operative care and stabilization and in being into expert hand surgical and anesthetic technique prognosis remains miserable [10], [11].

Sepsis is a well known risk factor for NEC which leads to systemic inflammation and microvascular thrombosis. Hence, coagulation profiles may provide useful insights and basic hints into the actual pathogenesis of surgical NEC. Evidently there is literature available showing interlinks between inflammation and coagulation which later assist in identifying severity and guide for diagnostic and therapeutic interventions [12], [13], [14].

Coagulation parameters suggestive of an indirect reflection of coagulation status and have been reported clinically to make preliminary judgements about condition and prognosis, to develop coping strategies [15], [16]. Giuliani et al. suggested that coagulation status could serve as a potential biomarker for disease progression in NEC [17].

NEC, a gastrointestinal emergency being inflammatory bowel necrosis of neonates, is characterized by severe inflammatory response in the gut and systemic, intestinal ischemia, thrombocytopenia, and DIC, a procoagulant state, reduction of fibrinolysis and debarred endothelial regeneration. Hutter et al. noted signs of DIC in 35% of neonates with NEC [18]. Many of these patients showed changes in coagulation parameters as follows: plasma Fib and PLT levels decreased, FDP tested positive, and APTT elevated [19]. Also, studies have been found to promote some nonspecific and sensitive markers such as C-reactive protein for necrotizing enterocolitis, whereas platelet-activating factor and intestinal fatty acid binding protein were both sensitive and specific [20], [21], [22].

As in this study it was noted that altered platelet counts, CRP, D dimer, Pt, APTT in patients diagnosed as surgical NEC were independently associated with poor outcome even if treated surgically by any method. APTT values found greater than or equal to 40 seconds showed 90.9 % specificity in predicting death and so are PT values found greater than or equal to 17 seconds showing 81.8% specificity, likely pointing to a severely compromised procoagulant phase in a surgical NEC cohort. Moreover, APTT values were found more sensitive 91.1% in predicting a dismal outcome as per our study. Also, qualitative POSITIVE CRP and D-Dimer with 54.5% specificity also show significant impact on septic screen parameters too.

Hence, Coagulopathy could increase the risk of death and even grave morbidity in survival and thus could be an effective predictor. If early coagulation assessment can be done and correct coagulopathy timely, it may be beneficial to reduce the mortality of NEC even in higher surgical cases. This study not only described the independent risk factors for surgical NEC, but confirmed that coagulopathy and septic screen parameters can effectively predict the outcome of surgical NEC and prognosis.

7. CONCLUSION

This study is one of the first kinds of at our institute where we tried to inter relate the already known factors and parameters of etiopathogenesis of an ever evolving and complicated diagnosis of NEC especially the later stages of surgical importance.

We intentionally took only surgical patients to find out that coagulation factors, especially PT APTT and sepsis factors, especially D DIMER, with other already known serological parameters of thrombocytopenia and leukopenia, as corroborative evidence was significantly altered in all the patients. Predictable at the critical values, we found pre-operatively ultimately affected the outcome irrespective of the surgical procedure and although all pre-operative and post-operative factors were kept the same in all the neonates.

Hence, coagulopathy could be instrumental in predicting the natural outcome of surgical NEC. Accordingly, in a resource-limited setup, triage of these neonates is imperative, and appropriate counseling of the parents and relevant guidance is necessary.

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Declaration of financial other relationship- The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the

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Authors contributions- All authors participated in the conception and design of the work or the collection, interpretation or analysis of the study data, and in the drafting, critical revision, and approval of the final version of the manuscript

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Ethical statement- All participants were thoroughly informed about the study and provided written informed consent. The study received approval from the Academic Ethics Committee of sawai man singh medical college and hospital and adhered to the principles outlined with the Declaration of Helsinki.

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