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Original Article

Serum Lactate – A Prognostic Marker of Early Post-Operative Outcome After Off Pump Coronary Artery Bypass Surgery: A Propensity Matched Study

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ABSTRACT

Objectives: Elevated blood lactate levels after on pump coronary artery bypass grafting is known to be an adverse prognostic marker. We proposed to assess the association between hyperlactatemia and early post-operative outcome after off pump coronary artery bypass (OPCAB) surgery.

Materials and Methods: 350 consecutive patients undergoing OPCAB surgery were studied retrospectively. Early postoperative serum lactate level was measured in all patients, upon shifting the patient to the ICU (0 hours), at 6 hours and 12 hours. The primary outcome was a composite of 30day all-cause mortality and severe morbidity. A propensity model was constructed to overcome the baseline differences between the group with and without complications.

Results: 32 (9.14%) patients had at least 1 complication, which was associated with significantly prolonged mechanical ventilation (38.6 h vs 12.8 h; p<0.001), and longer length of ICU stay (7.2 days vs 3.8 days; p<0.001).Propensity score matching yielded 23 pairs of cohorts with and without complications. Patients who developed complications, had higher serum lactate levels immediately after being shifted to the ICU (4.8 ± 0.6 Vs 2.9 ± 0.5; p < 0.001), at 6 hours (4.1 ± 0.5 Vs 2.3 ± 0.4; p < 0.001) and 12 hours (3.2 ± 0.5 Vs 1.8 ± 0.4; p < 0.001). Lactate levels of ≥ 3.65 mmol/L at 0 hours, ≥ 2.75 mmol/L at 6 hours and ≥ 2.25 mmol/L at 12 hours of ICU stay were associated with major post-operative complications. Amongst other intra- and post-operative variables, the rate of RBC transfusion was significantly higher in propensity matched cohort with complications (1.9 ± 0.3 Vs 1.1 ± 0.2; p < 0.001).

Conclusion: Hyperlactatemia is associated with worse outcomes after OPCAB surgery. Its detection, therefore, is an early and a very cost-effective marker in identifying patients at higher risk for adverse events.

Key words: Lactate; off pump coronary artery bypass (OPCAB) surgery; post-operative.

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INTRODUCTION

Hyperlactatemia is a well-documented marker of systemic hypoperfusion, tissue hypoxia and circulatory failure in the post-operative period following cardiac surgery[1]. Lactic acidosis after cardiopulmonary bypass (CPB) is indicative of low cardiac output syndrome (LCOS) and is significantly associated with poor prognosis and mortality[2]. Incomplete revascularization in coronary artery bypass graft (CABG) surgery, insufficient myocardial protection, and coagulation disorders are factors that affect hyperlactatemia[3].

Serum lactate level obtained by arterial blood gas (ABG) has been shown to play an important role in post-operative prognosis following on pump coronary artery bypass graft surgery[4]. However, the role of serum lactate in the setting of off pump coronary bypass (OPCAB) surgery has never been investigated. Therefore, in this study, we proposed to assess the association between hyperlactatemia and early postoperative outcome after OPCAB surgery.

METHODOLOGY

The necessary approval from the institutional review board was obtained. 350 consecutive patients who underwent OPCAB surgery in our institute from March 2015 to January 2017 were studied retrospectively. Patients requiring emergency surgery, re-operations, concomitant valve surgery, aneurysmectomy, those with pre-existing hepatic or renal dysfunction were excluded from the study. Early postoperative serum lactate levels were available in all patients, upon ICU admission (0 hours), at 6 hours and 12 hours from the arterial blood gas (ABG) analysis. Arterial lactate levels and blood gases were determined with the aid of Cobas b 221 Blood Gas System (Roche Diagnostics, Rotkreuz, Switzerland).

Outcome Measures

A composite end point for early post-operative complications was defined as a combination of 30-day all-cause mortality and severe morbidity (cardiogenic shock, adult respiratory distress syndrome (ARDS), or acute kidney injury (AKI) requiring renal replacement therapy). Cardiogenic shock was defined as the presence of tachycardia and hypotension associated with a central venous oxygen saturation < 65%, cardiac index ≤2.2 $Lmin^{-1}m^{-2}$, or metabolic acidosis (decrease in base deficit>4) ARDS was defined by standard criteria[5-7]. Renal function was evaluated daily using the RIFLE (renal risk, injury, failure, loss, end-stage kidney disease) classification[6].

Statistical analysis

Relationships between the complications and potential risk factors were assessed using a chi^2 test, Fisher's exact test, likelihood ratio test, t test, or MannWhitney U test as appropriate. All tests were 2-tailed. A propensity score model was constructed to overcome the effects of confounding variables between the complications and no complications group. The nearest neighbor matching was used.

Receiver operating characteristic (ROC) curves were constructed from the propensity matched pairs, and the area under the ROC curve (AUC) was determined to assess the discriminant ability of the lactate concentration measured at ICU admission (0 hours), 6 hours, and 12 hours to predict complications as done previously by Hajjar et al.[8]. The ROC curves were then used to determine the cutoff values of lactate to predict complications. An AUC of 1 would indicate 100% accuracy in predicting complications, while an AUC of 0.5 would show a complete worthlessness of the test. Statistical analyses were performed using SPSS version 19 (SPSS, Inc, Chicago).

RESULTS

Of the 350 patients included in the study, 32 (9.14%) patients had at least 1 complication. Fourteen (4.0%) patients had 2 or more complications. Cardiogenic shock was encountered in 21 (6.0%) patients, AKI requiring renal replacement therapy in 12 (3.43%), and ARDS in 9 (2.57%) patients. Eight deaths (2.29%) patients occurred in the study.

Pre-operative characteristics presented in Table 1, shows significantly higher number of complications in older population (64.5 ± 11.4 years Vs 57.7± 11.8 years; p=0.002) and those with low LVEF (≤ 40%) (p = 0.01). Propensity matching extracted 23 pairs of cohorts, those with and those without complications. Upon propensity matching the pre-operative variables of both the age and low LVEF were found to be statistically insignificant.

The group with complications had a significantly prolonged mechanical ventilation (38.6 h vs 12.8 h; p<0.001), and a longer length of ICU stay (7.2 days vs 3.8 days; p<0.001) as compared to the group without complications. This difference continued to remain statistically significant in the propensity matched cohorts as shown in Table 2.

Amongst intra-operative variables as shown in Table 3, the group with complications received more units of red blood cells (RBC) transfusions during surgery than the group without complications (2.1 ± 0.3 Vs 0.9 ± 0.2; P < 0.001). Also, the group that encountered complications received higher fresh frozen plasma (FFP) transfusions (25% Vs 16.4%), though it was not statistically significant (p = 0.22). The rate of RBC transfusions remained significantly higher after propensity score matching (1.9 ± 0.3 Vs 1.1 ± 0.2; p < 0.001).

Patients who developed complications, received more units of red blood cells (RBC) transfusions in the early post-operative period than the group without complications (2.4± 0.3 Vs 1.1 ± 0.3; P < 0.001), as depicted in Table 4.This difference remained statistically significant in the propensity matched pairs (2.2± 0.3 Vs 1.2 ± 0.3; P < 0.001). Post-operative fresh frozen plasma (FFP) transfusions did not have a statistically significant impact on the two groups. Patients developing complications were noted to have higher serum lactate levels immediately after being shifted to the ICU (4.8 ± 0.6 Vs 2.9 ± 0.5; p < 0.001). The higher serum lactate in these patients, persisted at 6 hours (4.1 ± 0.5 Vs 2.3 ± 0.4; p < 0.001) and 12 hours (3.2 ± 0.5 Vs 1.8 ± 0.4; p < 0.001), as given in Table 4. The table also shows that, the significant higher lactate levels were noted in each of the three early post-operative time periods in the propensity matched cohorts.

Lactate levels of ≥ 3.65mmol/L at 0 hours,≥ 2.75mmol/L at 6 hours and ≥ 2.25 mmol/L at 12 hours of ICU admission were associated with major post-operative complications, resulting in an area under the ROC curve (AUC) of 0.898 (95% confidence interval [CI], 0.811-0.985; p<0.001), 0.901 (95% CI, 0.815-0.987; p < 0.001) and 0.922 (95% CI, 0.850-0.995; p < 0.001) as shown in Figures 1-3. The cut-off serum lactate level of ≥ 2.75 mmol/L at 6 hours had the highest sensitivity (95.7%) in predicting major post-operative complications, while the cut-off level of ≥ 2.25 mmol/L at 12 hours was associated with the highest specificity (87.0%), as presented in Table 5.

The normal range of serum lactate is 0.4 to 2.0 mmol/L. Lactate levels between >2 mmol/L and ≤ 4.0 mmol/L is considered as mild to

Table 1: Pre-operative characteristics.

PRE-OPERATIVE CHARACTERISTICS					
I. ENTIRE COHORT (n = 350)					
Sl.No.	Characteristics	Complications (n = 32)	No complications (n = 318)	Total (n = 350)	p value
1	Age	64.5 ± 11.4	57.7 ± 11.8	58.3 ± 11.8	0.002*
2	Male sex	19 (59.4%)	177 (55.7%)	196 (56.0%)	0.69
3	BMI	25.1 ± 3.1	24.5 ± 3.2	24.6 ± 3.2	0.31
4	Comorbidity :				
	i. Hypertension	27 (84.4%)	260 (81.8%)	287 (82.0%)	0.71
	ii. Diabetes mellitus	12 (37.5%)	107 (33.6%)	119 (34%)	0.66
	iii. Dyslipidemia	21 (65.6%)	193 (60.7%)	214 (61.1%)	0.59
	iv. Previous MI	10 (31.3%)	91 (28.6%)	101 (28.9%)	0.75
	v. NYHA III/IV	9 (28.1%)	83 (26.1%)	92 (26.3%)	0.80
	vi. COPD	3 (9.4%)	20 (6.3%)	23 (6.6%)	0.50
5	LVEF ≤ 40%	15 (46.9%)	84 (26.4%)	99 (28.3%)	0.01*
6	Laboratory Parameters:				
	i. Hemoglobin	11.4 ± 1.2	11.6 ± 1.2	11.6 ± 1.2	0.37
	ii. Hematocrit	35.3 ± 3.7	35.6 ± 3.8	35.6 ± 3.8	0.67
	iii. Serum Creatinine	1.06 ± 0.3	1.02 ± 0.3	1.02 ± 0.3	0.47
II. PROPENSITY MATCHED COHORT (n = 46)					
SL. NO.	Characteristics	Complications (n = 23)	No complications (n = 23)	Total (n = 46)	p value
1	Age	63.8 ± 11.7	62.9 ± 11.8	63.35 ± 11.8	0.68
2	Male sex	13 (56.5%)	12 (52.1%)	25 (54.3%)	0.77
3	BMI	25.2 ± 3.2	24.9 ± 3.2	25.1 ± 3.2	0.75
4	Comorbidity :				
	i. Hypertension	20 (87.0%)	19 (82.6%)	39 (84.8%)	0.68
	ii. Diabetes mellitus	9 (39.1%)	8 (34.8%)	17 (37%)	0.76
	iii. Dyslipidemia	15 (65.2%)	14 (60.9%)	29 (63.0%)	0.76
	iv. Previous MI	7 (30.4%)	7 (30.4%)	14 (60.9%)	1.00
	v. NYHA III/IV	7 (30.4%)	6 (26.1%)	13 (56.5%)	0.74
	vi. COPD	3 (13.0%)	3 (13.0%)	6 (26.1%)	1.00
5	LVEF ≤ 40%	10 (43.5%)	5 (21.7%)	15 (32.6%)	0.12
6	Laboratory Parameters:				
	i. Hemoglobin	11.5 ± 1.2	11.6 ± 1.2	11.6 ± 1.2	0.78
	ii. Hematocrit	35.5 ± 3.8	35.6 ± 3.8	35.5 ± 3.8	0.93
	iii. Serum Creatinine	1.08 ± 0.3	1.04 ± 0.3	1.06 ± 0.3	0.65

*statistically significant, BMI – body mass index (Kg.m^{-2}), MI – myocardial infarction, NYHA – New York Heart Association, COPD – chronic obstructive pulmonary disease, LVEF – left ventricular ejection fraction

Table 2: **ICU course.**

ICU COURSE					
I. ENTIRE COHORT (n=350)					
SL. NO.	Characteristics	Complications (n = 32)	No complications (n = 318)	Total (n = 350)	p value
1	Duration of mechanical ventilation (h)	38.6 ± 8.2	12.8 ± 6.3	15.2 ± 6.8	< 0.001*
2	Length of ICU stay (days)	7.2 ± 1.8	3.8 ± 1.1	4.1 ± 1.3	< 0.001*
II. PROPENSITY MATCHED COHORT (n=46)					
Sl. No.	Characteristics	Complications (n = 23)	No complications (n = 23)	Total (n = 46)	p value
1	Duration of mechanical ventilation (h)	34.6 ± 8.0	15.1 ± 6.7	24.9 ± 6.9	< 0.001*
2	Length of ICU stay (days)	6.8 ± 1.6	4.2 ± 1.3	5.5 ± 1.4	< 0.001*
*statistically significant					

Table 3: **Intra-operative characteristics.**

INTRA-OPERATIVE CHARACTERISTICS					
I. ENTIRE COHORT (n = 350)					
Sl. No.	Characteristics	Complications (n = 32)	No complications (n = 318)	Total (n = 350)	p value
1	Number of grafts				
	1	1 (3.1%)	23 (7.2%)	24 (6.9%)	0.38
	2	4 (12.5%)	59 (18.6%)	63 (18.0%)	0.40
	3	22 (68.8%)	203 (63.9%)	225 (64.3%)	0.58
	>3	5 (15.6%)	33 (10.4%)	38 (10.9%)	0.36
2	ITA graft	30 (93.8%)	314 (98.7%)	344 (98.3%)	0.04*
3	RBC transfusion units	2.1 ± 0.3	0.9 ± 0.2	1.0 ± 0.2	< 0.001*
4	FFP transfusion	8 (25%)	52 (16.4%)	60 (17.1%)	= 0.22
II. PROPENSITY MATCHED COHORT (n=46)					
Sl. No.	Characteristics	Complications (n = 23)	No complications (n = 23)	Total (n = 46)	p value
1	Number of grafts				
	1	1 (4.3%)	2 (8.7%)	3 (6.5%)	0.55
	2	2 (8.7%)	3 (13.0%)	5 (10.9%)	0.64
	3	19 (82.6%)	17 (73.9%)	36 (78.3%)	0.47
	>3	1 (4.3%)	1 (4.3%)	2 (4.3%)	1.0
2	ITA graft	22 (95.7%)	22 (95.7%)	44 (95.7%)	1.0
3	RBC transfusion units	1.9 ± 0.3	1.1 ± 0.2	1.5 ± 0.2	< 0.001*
4	FFP transfusion	6 (26.1%)	4 (17.4%)	10 (21.7%)	0.47
*statistically significant, ITA – internal thoracic artery, RBC – red blood cells, FFP – fresh frozen plasma					

Table 4: **Post-operative characteristics.**

POST-OPERATIVE CHARACTERISTICS					
I. ENTIRE COHORT (n = 350)					
Sl. No.	Characteristics	Complications (n = 32)	No complications (n = 318)	Total (n = 350)	p value
1	RBC transfusion units	2.4 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	< 0.001*
2	FFP transfusion	5 (15.6%)	24 (7.5%)	29	0.11
3	Serum lactate				
	0 h	4.8 ± 0.6	2.9 ± 0.5	3.1 ± 0.5	< 0.001*
	6 h	4.1 ± 0.5	2.3 ± 0.4	2.5 ± 0.4	< 0.001*
	12 h	3.2 ± 0.5	1.8 ± 0.4	1.9 ± 0.4	< 0.001*
II. PROPENSITY MATCHED COHORT (n=46)					
Sl. No.	Characteristics	Complications (n = 23)	No complications (n = 23)	Total (n = 46)	p value
1	RBC transfusion units	2.2 ± 0.3	1.2 ± 0.3	1.7 ± 0.3	< 0.001*
2	FFP transfusion	4 (17.4%)	3 (13.0%)	7 (15.2%)	0.17
3	Serum lactate				
	0 h	4.6 ± 0.6	3.0 ± 0.5	3.8 ± 0.5	< 0.001*
	6 h	4.1 ± 0.6	2.5 ± 0.4	3.3 ± 0.5	< 0.001*
	12 h	3.2 ± 0.5	1.9 ± 0.4	2.6 ± 0.4	< 0.001*
*statistically significant, RBC – red blood cells, FFP – fresh frozen plasma					

Table 5: Cut-off levels of serum lactate.

Serum lactate	AUC (95 % ci)	Cut-off level (mmol/l)	Sensitivity (%)	Specificity (%)
0 h	0.898 (0.811 – 0.985)	3.65	87.0	73.9
6 h	0.901 (0.815 – 0.987)	2.75	95.7	73.9
12 h	0.922 (0.850 – 0.995)	2.25	82.6	87

AUC – area under curve, CI – confidence interval

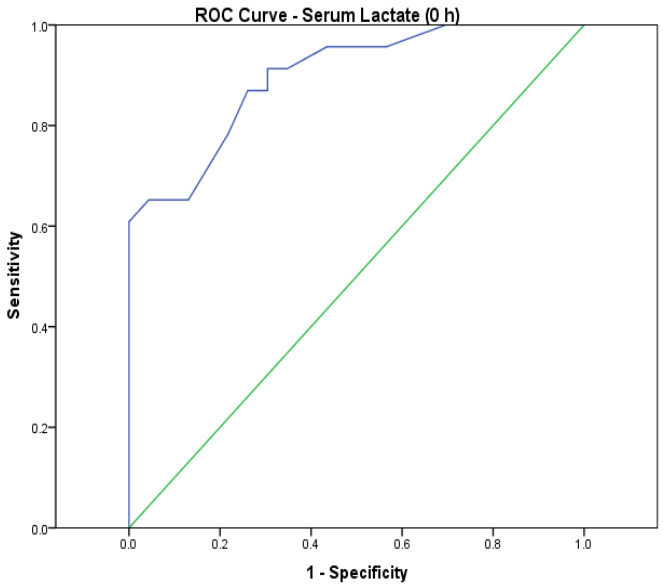

FIGURE 1: Receiver operating characteristic (ROC) curve illustrating the ability of immediate postoperative serum lactate levels (at 0hours) after ICU admission in predicting major complications following OPCAB surgery.

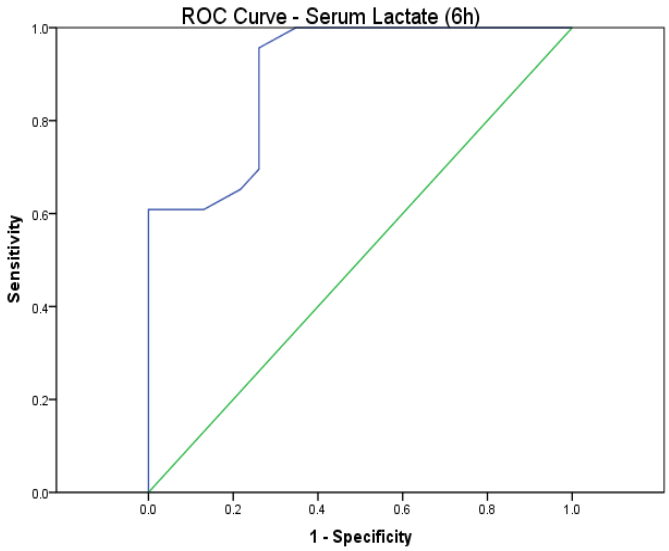

FIGURE 2: Receiver operating characteristic (ROC) curve illustrating the ability of postoperative serum lactate levels (at 6 hours) after ICU admission in predicting major complications following OPCAB surgery.

moderate hyperlactemia and blood lactate >4.0 mmol/L is classified as severe hyperlactemia[9]. In 2003, one of the earliest studies evaluating the implications of early post-operative hyperlactatemia after cardiac surgery, Maillet JM et al. showed that, elevated serum lactate was frequent, and a threshold of 3 mmol/L at ICU admission aided in identifying patients with a poorer outcome and a higher mortality risk. However, OPCAB surgery was an exclusion criterion in this study[10].

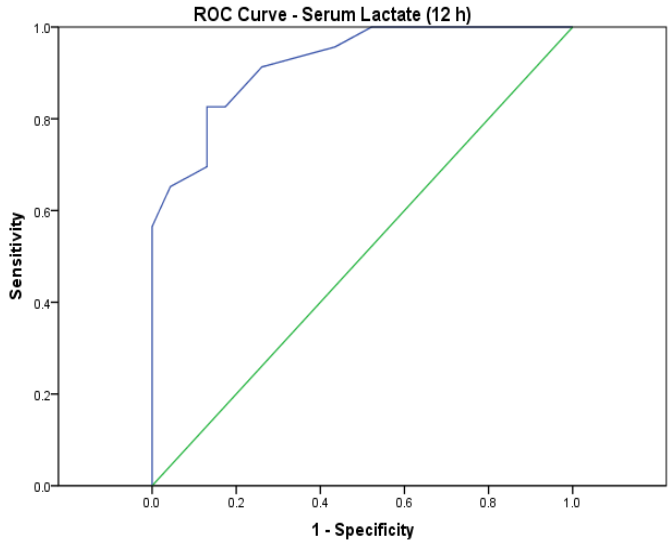

FIGURE 3: Receiver operating characteristic (ROC) curve illustrating the ability of postoperative serum lactate levels (at 12 hours) after ICU admission in predicting major complications following OPCAB surgery.

In a large study comprising 1820 patients in 2012, Kogan A et al showed that, a maximal lactate threshold ≥4.4 mmol/l post-operatively in the first 10 hours, was associated with prolonged ventilation time, longer ICU stay, and increased mortality[11]. In a more recent study in 2016, Sanfilippo F et al. showed that the incidence of arterial hyperlactemia was similar in on pump coronary artery bypass grafting and OPCAB surgery at all-time points during the first 24 hours after surgery[12].

While, hyperlactatemia in the early post-operative period has been shown to carry an adverse prognosis in on pump coronary artery bypass graft surgery, with significant post-operative morbidity and increased risk of 30-day mortality, a study evaluating the direct association between hyperlactemia and the early post-operative outcome, following OPCAB surgery has never been done before[4]. Our study brings in a new perspective in assessing the role of arterial lactate monitoring after off pump bypass surgery, in contrast to all the previous studies which have focused their attention on the utility of lactate monitoring in cardiac surgery involving cardiopulmonary bypass (CPB). Therefore, ours is the first such study involving a cohort entirely of OPCAB surgery, aimed at evaluating the role of early arterial lactate monitoring.

The present study found a strong correlation between hyperlactetemia and adverse events following OPCAB surgery. The overall incidence of complications in our study was comparable with that of Hajjar et al (9.1% Vs 10%)[8]. As shown by Kogan et al.[11] previously in their study, we found that, patients who developed complications after OPCAB surgery, had a significantly prolonged mechanical ventilation (38.6 h vs 12.8 h; p<0.001), and a longer length of ICU stay (7.2 days vs 3.8 days; p<0.001). Similar to the study performed by Hajjar et al. we deduced the cut-off value of serum lactate that predicted complications. Our study however, was an exclusive cohort of OPCAB surgery, in contrast to a diverse mix of CABG, valve and combined procedures included by Hajjar et al.[8]. We found that hyperlactemia ≥ 3.65 mmol/L at 0 hours, ≥ 2.75 mmol/L at 6 hours and ≥ 2.25 mmol/L at 12 hours post-operatively,

predicted major post-operative complications. The incorporation of a propensity score matched model further adds strength to our findings.

Therefore, in the early post-operative management of OPCAB surgery, the detection of hyperlactatemia is an early, reliable and a very cost-effective marker in identifying patients at higher risk for adverse events. An elevated serum lactate level in accordance with our cut-off values calls for heightened vigilance to optimize outcomes in these subsets of patients.

LIMITATIONS

Our study has the limitation of being a single-centre retrospective study, with a relatively small number of propensity matched patients. Larger, multi-centre randomized controlled studies are therefore necessary to further validate our findings and to evaluate the possible benefits of any strategy that would aim at normalizing the serum lactate levels after OPCAB surgery.

CONCLUSION

Hyperlactatemia is associated with more number of adverse events after OPCAB surgery. It, therefore, serves as an early and a very cost-effective marker in identifying patients at higher risk for worse outcomes.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE :

Approval from institutional review board (Staff & Research Society, Sion, Mumbai) was obtained.

CONSENT FOR PUBLICATION:

Not applicable

AVAILABILITY OF DATA AND MATERIALS:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS:

The authors declare that they have no competing interests

FUNDING :

None.

AUTHORS CONTRIBUTIONS:

GKKA conceptualized the study and wrote the manuscript. He also analyzed the data and drew conclusions. He was ably supported in analyzing the data and drawing conclusions equally by PM and JVK.

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Not applicable

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