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ORIGINAL ARTICLE

Predictors of intraoperative intracranial aneurysm rupture in patients with subarachnoid hemorrhage: a retrospective analysis

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Abstract

Purpose Intraoperative cerebral aneurysm rupture (IOR) is a common phenomenon with a frequency of around 19%. Research regarding IOR lacks an analysis of its predictors.

Methods We retrospectively examined all saccular aneurysms, in 198 patients with subarachnoid hemorrhage, surgically treated from 2013 to 2019. Operative reports, patient histories, blood test results, discharge summaries, and radiological data were reviewed. IOR was defined as any bleeding from the aneurysm during surgery, preceding putting a clip on its neck, regardless of how trivial.

Results The frequency of IOR was 20.20%. Patients with IOR had higher aneurysm dome size (9.43 ± 8.39 mm vs. 4.96 ± 2.57 mm; $p < 0.01$). The presence of blood clot on the aneurysm dome was significantly associated with IOR (12.50% vs. 2.53%; $p < 0.01$). We also associated lamina terminalis fenestration during surgery (7.50% vs. 21.52%; $p = 0.04$) and multiple aneurysms (5.00% vs. 18.35%; $p = 0.038$) with a lower risk of IOR. Glucose blood levels were also elevated in patients with IOR (7.47 ± 2.78 mmol/l vs. 6.90 ± 2.22 mmol/l; $p = 0.04$). Multivariate analysis associated that urea blood levels (OR 0.55, 0.33 to 0.81, $p < 0.01$) and multiple aneurysms (OR 0.04, 0.00 to 0.37, $p = 0.014$) were protective factors against the occurrence of IOR.

Conclusion Large dome size of an aneurysm, a blood clot on the aneurysm dome and elevated glucose blood levels can be IOR predictive. Lamina terminalis fenestration, the appearance of multiple aneurysms, and high urea blood levels may be associated with a lower risk of such an event.

Keywords Intracranial aneurysm · Surgical instruments · Subarachnoid hemorrhage · Neurosurgical procedures

Introduction

Intracranial aneurysm rupture is an unpredictable danger that may lead to an unfavorable outcome. Intraprocedural rupture is a well-known complication of intracranial aneurysm treatment that has been profoundly studied for coiling procedures, but there is less research on operative cerebral aneurysm treatment. Intraoperative rupture (IOR) is a much more common issue in comparison to endovascular methods—19% to 5%, respectively [1]. The most dangerous bleeding may be the effect of IOR occurring before proximal vascular control [2]. Despite larger sack size, location on an anterior communicating artery (ACoA) being independent predictors of IOR, many preoperative risk factors such as elevated systolic blood pressure, previous aneurysm rupture, temporary artery occlusion, blood glucose level, ventricular opening, modified Fischer grade, brain swelling, World Federation of Neurosurgical Societies (WFNS) scale, Glasgow Coma Scale (GCS) upon admission still need more research [3–5]. Possible causes of IOR also include craniotomy drilling vibration and dural opening transmural pressure changes [2]. When studying factors associated with IOR drugs taken before surgery and laboratory blood parameters results are often overlooked. This study aimed to seek new predictors of IOR with special attention of above mentioned.

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Methods

In this retrospective study, we analyzed patients with surgically treated, ruptured saccular cerebral aneurysms, hospitalized between January 2013 and July 2019 due to aneurysmal subarachnoid hemorrhage (SAH). A total of 198 patients have met the study inclusion criteria. All patients were operated by neurosurgeons working in the same center. All the neurosurgeons, who were main operators, were experts in field with at least 6 years of experience. SAH was diagnosed by assessing computed tomography (CT) scan performed upon admission. All patients were operated within 24 h after first symptoms of aneurysm rupture. The presence of IOR was determined based on operative records, which were written by neurosurgeons shortly after surgery. We additionally obtained factors such as aneurysm visual appearance, with special consideration of the presence of blood clot on the aneurysm dome, and whether the patient had lamina terminalis fenestration before putting clip on aneurysm neck (during obtaining access to aneurysm or directly after opening the dura mater). Aneurysm characteristics such as its number, location, dome, and neck size were obtained from an assessment of CT angiography on coronal and sagittal planes. Measurements were performed on dedicated workstation running IMPAX 6 Software (Agfa Healthcare nV, Belgium). From patients' medical records, we also acquired data regarding medical history—diseases, current medication, and blood test results preceding surgery. On admission, patients were assessed with GCS, Hunt and Hess scale, modified Fischer grading scale, and WFNS scale. Upon discharge, patients were assessed using the modified Rankin Scale (mRS). The intraoperative rupture was defined as any bleeding from the aneurysm preceding putting a clip on its neck during surgery [6]. The study protocol was approved by the local bioethical committee and all patients gave informed consent. The database management and statistical analysis were performed with RStudio version 8.5 for Windows (RStudio, Inc, USA). We used the Shapiro–Wilk test to assess normality. For comparisons of continuous variables, we used the *t* test for normally distributed variables and Mann–Whitney *U* test for non-normally distributed variables. We used the $\chi 2$ test for dichotomized variables. We express continuous variables as mean ± standard deviation. To find factors independently associated with risk of IOR we employed logistic regression analysis, with and without adjustment for possible confounders. All significance tests are two-tailed and p value < 0.05 are considered statistically significant.

Results

Our study group consisted of 125 (63.13%) females. The mean age of patients was 55.68 ± 13.77 years. Most of the aneurysms were located on the middle cerebral artery (MCA) (54.04%), on ACoA (30.80%), and internal carotid artery (ICA) (6.06%) (Fig. 1). The average GCS score upon admission was 11.66 ± 4.71 and the average mRS score upon discharge was 3.02 ± 2.02. Most of the aneurysms were right-sided—84 (61.31%) and 53 (38.69%) remained left-sided, while 61 were located on a single ACoA. Multiple aneurysms were present in 31 (15.66%) cases. We established the frequency of IOR at 20.20%. The dome size of an aneurysm was observed to

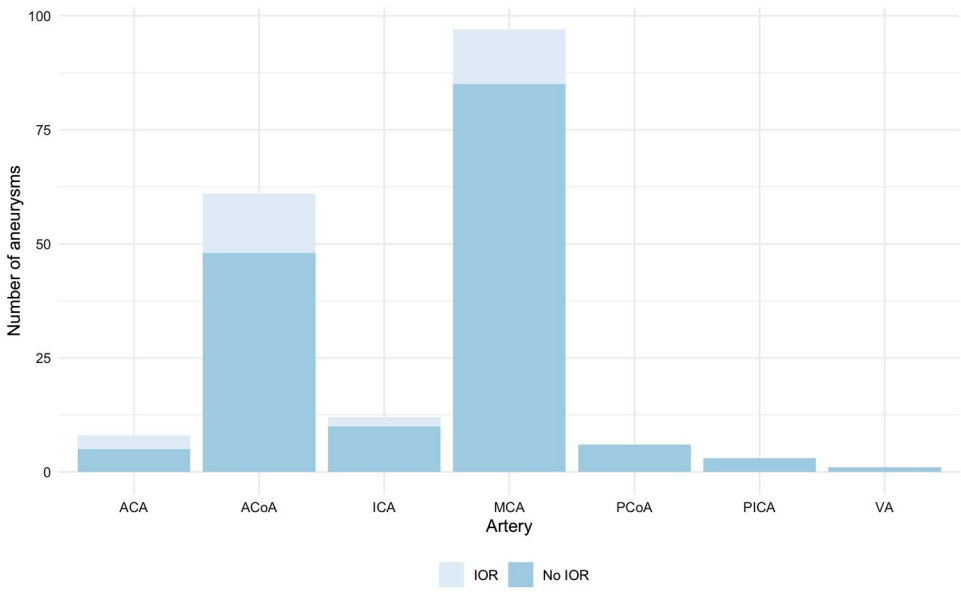

Fig. 1 Distribution of surgically clipped aneurysms' rupture rates by location. *ACA* anterior cerebral artery, *ACoA* anterior communicating artery, *ICA* internal carotid artery, *IOR* intraoperative cerebral aneurysm rupture, *MCA* middle cerebral artery, *PCoA* posterior communicating artery, *PICA* posterior inferior cerebellar artery, *VA* vertebral artery

be increased in patients with IOR (9.43 ± 8.39 mm vs. 4.96 ± 2.57 mm; $p < 0.01$). Statistical analysis showed that the presence of blood clot on the aneurysm dome is significantly associated with IOR (12.50% vs. 2.53%; $p < 0.01$). We additionally observed that patients who had lamina terminalis fenestration during surgery are at a lower risk of IOR (7.50% vs. 21.52%; $p = 0.04$), as well as those with multiple aneurysms (5.00% vs. 18.35%; $p = 0.038$) (Table 1). We found no correlation between IOR and intake of anti-hypertensive and anti-diabetic drugs. (Table 2). In terms of blood test results upon admission, patients with longer activated partial thromboplastin time (APTT) (31.44 ± 5.73 s vs. 28.73 ± 4.56 s; $p = 0.02$) and prothrombin time (PT) through International Normalized Ratio (INR) (1.15 ± 0.47 vs. 1.03 ± 0.10; $p = 0.05$) had increased risk of IOR. Glucose blood levels were also higher in patients with IOR (7.47 ± 2.78 mmol/l vs. 6.90 ± 2.22 mmol/l; $p = 0.04$). APTT, INR and glucose above norms were not predictive for IOR. IOR was also associated with lower urea blood levels (4.18 ± 1.34 vs. 5.57 ± 3.53; $p = 0.048$). Multivariate analysis associated that urea blood levels (OR 0.55, 0.33–0.81, $p < 0.01$) and multiple aneurysms (0.04, 0.00–0.37, $p = 0.014$) were protective factors against the occurrence of IOR. Such analysis also revealed that APTT (1.18, 1.03–1.38, $p = 0.026$) was IOR predictive (Table 3). Rupture occurred the most (61.11%) when surgeon was dissecting cerebral structures to access to the aneurysm. Second most common moment was putting clip on aneurysm neck (22.22%), third—after dural opening (1.11%), and fourth was when dissecting the aneurysm from encasing tissues and vessels (5.56%).

Discussion

The study group in our research consisted mostly of female patients. Articles by Chen et al., Krzyżewski et al. and the CARAT study [1, 3, 7] have explicitly shown that aneurysms occur more often in women than in men. Vast evidence supports our results that aneurysms mostly appear in anterior cerebral circulation with the dominance of MCA and ACoA [7]. ICA appeared to be the third most popular location of an aneurysm, which also appeared in research by Korja M et al. [8], that considered only ruptured aneurysms. Some studies show that ICA aneurysms or ACoA aneurysms are the most popular ones, but it may be dependent on the number of female patients in study group [1, 3]. One in five patients had an aneurysm rupture during the clipping procedure. IOR frequency varies in different studies from 3% to 19% [1, 3]. IOR present in 19% of patients was observed in the CARAT study, which observed 711 patients during clipping procedure due to SAH being in our opinion the most accurate estimation of IOR frequency among literature [1]. Chen S.F. et al. [3] study has compared IOR rates in patients with unruptured and ruptured aneurysms. In patients with unruptured aneurysms prior to surgery IOR rate was 0.57%, which is much lower than in the ruptured aneurysms IOR ratio of 9.6%. The first of the factors associated with the increased risk of IOR in our study was higher aneurysm dome size. Lakićević et al. [9] study shared an idea that aneurysm size may have an influence but that research could not prove such an association. CARAT study has also suggested that IOR is not associated with aneurysm size [1]. However, a pooled analysis of six prospective cohort studies conducted by Greving et al. [10] described aneurysm size as a predictor of overall aneurysm rupture. Similarly, irregular aneurysm shape, which is associated with aneurysm size,

Table 1 Differences in aneurysm characteristics between patients with and without IOR

	IOR ($n = 40$)	No IOR ($n = 158$)	p value
Dome size [mm] ± SD	9.43 ± 8.39	4.96 ± 2.57	< 0.01
Neck size [mm] ± SD	3.00 ± 1.00	2.89 ± 1.23	0.89
Blood clot on aneurysm dome [%]	12.50 (5)	2.53 (4)	< 0.01
Lamina terminalis fenestration [%]	7.50 (3)	21.52 (34)	0.04
Multiple aneurysms [%]	5.00 (2)	18.35 (29)	0.038
Dome/neck ratio ± SD	1.57 ± 0.60	1.74 ± 0.43	0.56
Anterior cerebral artery [%]	7.50 (3)	3.16 (5)	0.43
Anterior communicating artery [%]	32.50 (13)	30.38 (48)	0.80
Internal carotid artery [%]	5.00 (2)	6.33 (10)	1.00
Middle cerebral artery [%]	55.00 (12)	53.80 (85)	0.89
Posterior inferior cerebellar artery [%]	0 (0)	1.90 (3)	0.88
Posterior communicating artery [%]	0 (0)	3.80 (6)	0.46
Vertebral artery [%]	0 (0)	0.63 (1)	1.00

IOR intraoperative aneurysm rupture, *SD* standard deviation

Table 2 Comparison of patients' medical history and current medications in subjects with and without IOR

	IOR ($n=40$)	No IOR ($n=158$)	p value
Age [years] ± SD	57.37 ± 13.67	55.25 ± 13.8	0.38
Female gender [%]	55.00 (22)	65.19 (103)	0.23
Glasgow coma scale ± SD	10.6 ± 5.18	11.92 ± 4.57	0.11
Hunt & hess scale ± SD	2.80 ± 1.68	2.51 ± 1.53	0.30
WFNS scale ± SD	2.75 ± 1.79	2.35 ± 1.63	0.17
Fisher grade ± SD	2.5 ± 1.24	2.34 ± 1.31	0.57
Modified Rankin Scale ± SD	3.55 ± 2.00	2.89 ± 2.01	0.06
Hypertension [%]	45.00 (18)	34.18 (54)	0.20
Diabetes mellitus [%]	5.00 (2)	3.80 (6)	0.73
Cigarette smoking [%]	25.00 (10)	12.66 (20)	0.051
Ischemic heart disease [%]	2.50 (1)	1.27 (2)	0.57
History of heart attack [%]	5.00 (2)	1.90 (3)	0.26
History of ischemic stroke [%]	10.00 (4)	12.66 (20)	0.65
Atrial fibrillation [%]	2.50 (1)	0 (0)	0.046*
Lungs disease [%]	0 (0)	1.90 (3)	0.38
Hypothyroidism [%]	0 (0)	3.16 (5)	0.25
Hypercholesterolemia [%]	0 (0)	3.16 (5)	0.25
Acetylsalicylic acid [%]	5.00 (2)	3.16 (5)	0.57
Beta-blockers [%]	12.50 (5)	15.19 (24)	0.67
Angiotensin-converting-enzyme inhibitors [%]	17.50 (7)	12.66 (20)	0.43
Calcium channel blockers [%]	10.00 (4)	8.86 (14)	0.82
Diuretics [%]	12.50 (5)	5.06 (8)	0.09
Insulin [%]	2.50 (1)	0.63 (1)	0.29
Anticoagulants [%]	5.00 (2)	0 (0)	< 0.01*
Statins [%]	2.50 (1)	1.90 (3)	0.81

IOR intraoperative aneurysm rupture, *SD* standard deviation, *WFNS* World Federation of Neurosurgical Societies

*Sample size not large enough to consider statistically significant

has been shown to increase the risk of IOR [11]. Additionally, according to a study by Zhu et al. [12], aneurysm size is independently associated with aneurysm wall enhancement that is considered a rupture risk factor. Our research has shown that the presence of a blood clot on the aneurysm dome significantly increases the risk of IOR. Experimental models have demonstrated that continuous exposure of the unorganized thrombus to the circulation can promote the recruitment of neutrophils and inflammatory cells [13, 14]. There is also evidence that the presence of thrombus in the aneurysm lumen is associated with the inflammation process in the aneurysm wall [15]. That leaves us with a question if IOR risk correlates with the inflammatory process beginning prior to SAH/during/after SAH. Lamina terminalis fenestration (LTF) appeared as another protective factor against the occurrence of IOR as well as the presence of multiple aneurysms. In our study LTF was performed after cranial and dural opening or at the beginning of aneurysm access cerebral dissection. All neurosurgeons in operative records described that performing LTF gave them better operating conditions and more procedural space. Neurosurgeons often perform LTF to create an additional way for cerebrospinal fluid to outflow and reduce intracranial pressure (ICP) which allows better operating conditions. To the best of our knowledge, there is no research assessing the lamina terminalis fenestration effect on IOR frequency. Although, LTF was associated with a better outcome in patients who underwent surgery due to SAH. This procedure was also associated with a lower risk of vasospasm [16]. Reducing the risk of vasospasm by performing LTF may influence outcome after SAH, because it was associated as one of the main contributors to SAH mortality and morbidity [17]. LTF has also been associated with a lower risk of hydrocephalus which may occur during SAH [18]. It may allow us to suggest that performing LTF can lead to improved functional outcomes [19]. Our study also associated IOR with multiple aneurysms putting them forward as a possible protective factor. Such association was also supported by the multivariate analysis result. A study conducted by Ho et al. [20] has also shown that patients with unruptured aneurysms were more likely to

Table 3 Comparison of blood test results preceding surgery in patients with and without IOR

	IOR ($n=40$)	No IOR ($n=158$)	p value
Red blood cells count [10^3/µl] ± SD	3.93 ± 0.71	3.93 ± 0.62	0.98
White blood cells count [10^3/µl] ± SD	12.70 ± 4.90	11.97 ± 4.14	0.44
Platelets count [10^3/µl] ± SD	253.40 ± 95.72	228.3 ± 85.78	0.20
Haemoglobin [g/dl]	11.99 ± 2.15	11.71 ± 1.93	0.52
Activated partial prothrombin time [s] ± SD	31.44 ± 5.73	28.73 ± 4.56	0.02
International normalized ratio ± SD	1.15 ± 0.47	1.03 ± 0.10	0.05
Creatinine [µmol/l] ± SD	61.11 ± 14.94	79.14 ± 146.11	0.52
Glucose [mmol/l] ± SD	7.47 ± 2.78	6.90 ± 2.22	0.04
Mean corpuscular volume [μm^3] ± SD	89.62 ± 4.43	88.12 ± 5.84	0.23
Mean corpuscular haemoglobin [pg] ± SD	30.75 ± 1.53	29.99 ± 2.42	0.10
Mean corpuscular haemoglobin concentration [g/dl] ± SD	34.17 ± 0.84	33.93 ± 1.32	0.36
Urea [mmol/l] ± SD	4.18 ± 1.34	5.57 ± 3.53	0.048
Sodium [mmol/l] ± SD	141.47 ± 3.74	140.74 ± 5.27	0.48
Potassium [mmol/l] ± SD	3.98 ± 0.47	3.91 ± 0.52	0.47
Prothrombin Time [s] ± SD	11.48 ± 0.70	11.81 ± 0.98	0.20
Haematocrit [%] ± SD	35.66 ± 5.90	34.42 ± 5.28	0.26
Glucose above 5.6 mmol/l [%]	69.23% (18)	68.54% (61)	1.0
Activated partial prothrombin time above 36.0 s [%]	14.29% (3)	7.69% (6)	0.395
International normalized ratio above 1.2 [%]	14.29% (3)	5.13% (4)	0.162

IOR intraoperative aneurysm rupture, *SD* standard deviation

have multiple aneurysms in comparison to those with ruptured aneurysms. Such association was also supported by long-term study by Juvela et al. [21] which suggested that presence of multiple aneurysms does not elevate rupture risk. Study by Sai Kirian et al. [22] has shown that successful occlusion and similar outcomes can be achieved after both single and multiple aneurysms microsurgical clipping procedures. Patients with multiple aneurysms have also been studied for specific rupture risk factors. Researchers found out that aspect ratio and irregular shape of multiple aneurysms have been associated with a higher risk of aneurysm rupture [23]. Until now, there has been no evidence that the presence of multiple intracranial aneurysms may be a factor reducing the risk of IOR. There was evidence that multiplicity raises the risk of subarachnoid hemorrhage and endovascular treatment of one aneurysm may also trigger a formation of another aneurysm elsewhere [24]. We consider that association between multiple aneurysms and lower risk of IOR may be an effect of higher surgeon attention during multiple aneurysm microsurgery, being a possible high-risk scenario. What is more hemodynamic study of single patient with multiple aneurysms has shown that aneurysms affect each other's flow rates which may affect rupture risks preoperatively and during surgery [25]. As it comes to drugs association with IOR, only two patients in our study had taken anticoagulants prior to SAH and both had consecutive IOR, but due to small sample size the statistical difference is likely to be spurious. A large randomized control trial on antithrombotic agents (anticoagulants included) influence on intracranial hemorrhage risk has proved such association [26]. On the other hand, Tarlov et al. [27] study has shared an idea that aneurysm rupture is not influenced by anticoagulants. Lack of such association in that research, as authors admitted, may have been caused by the small sample size and retrospective aspect of the study. Coagulation parameters by the mean of Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR) appeared to be higher in patients with IOR, although APTT and INR above normal levels—> 36.0 s and > 1.2, respectively—showed no relationship to IOR. Our multivariate analysis has also supported such a theory. INR elevation in aneurysm surgery had been previously studied by Can et al. [28] and provided us with an association of intracranial aneurysm rupture and higher INR values. APTT to the best of our knowledge has not been researched for impact on intracranial aneurysms, although a study on abdominal aortic aneurysms shows that APTT increases in patients admitted to ICU due to its rupture [29]. Such an effect on IOR is yet to be researched more profoundly. Despite not finding a link between IOR and anti-diabetic drugs, increased blood glucose levels were a factor that increased the risk of an IOR. Presence of glucose blood level above norm—over 5.8 mmol/L was not found significantly predictive for IOR. Hyperglycemia develops in one-third of SAH patients. Hyperglycemia is associated with a poor clinical condition on admission and is independently associated with poor outcome [30–33]. In American Guidelines for management of aneurysmal, SAH prevention of hyperglycemia is classified

as probably indicated [19]. Hyperglycemia could be a secondary phenomenon to a transient stress reaction inflicted by the insult. Indeed, previous studies showed that the release of catecholamines and levels of glucose relates to the clinical magnitude of SAH [34]. Such associations are yet to be established for IOR. Strikingly, blood urea levels were found to be lower in patients with IOR. The multivariate analysis we performed has also exposed such association. This is the first study to connect urea and intracranial aneurysms, however, elevated serum urea levels were previously associated with calcification in intracranial arteries [35]. To the best of our knowledge, calcification has also beenconnected with higher aneurysm size which has been associated, as stated above, with increased risk of IOR [36]. Despite such association staying in contrary with our research, enteral urea dosage has also been reported to decrease ICP [37]. Managing increased ICP may decrease the risk of IOR, but such studies are yet to be performed [38]. As in both groups, mean urea levels were within normal range, the simplest association may be the fact that higher urea levels are associated with higher protein intake [39]. High-protein diet has been found to improve systemic microvascular health in patients with heart failure, while low-protein diet was found to increase inflammation and vascular calcification in rats [40, 41].

Several factors were identified to increase and decrease the risk of aneurysm rupture during the clipping procedure. Specifically, a large dome size of an aneurysm, a blood clot on the aneurysm dome and elevated glucose blood levels were found to be associated with IOR in our study. Performing lamina terminalis fenestration, the appearance of multiple aneurysms, and high urea blood levels may be associated with a lower risk of such an event. These parameters were available through imaging, patients' data and, although further analysis and validation of these parameters is necessary, they could add to the surgeon's ability to assess the rupture risk more accurately before or in surgery.

Limitations

Due to retrospective character of this study may present inferior level of evidence compared with prospective studies as it is a "chart-based study". Our research was limited by the size of the study group. Further research should be performed on larger and more varied study groups. Factors like fluctuation of blood pressure, use of tranexamic acid, sharp or blunt dissection, transmural pressure gradient, multilobulated sac, number of previous bleeds, irregular shapes, pre-emptive trapping, or proximal control, use of pilot clip, presence of calcification or atherosclerosis were not possible to discuss and analyze due to retrospective character of the study. Missing data for different laboratory tests may have also influenced results of our study. Despite using operative reports to determine IOR, we would like to emphasize that those reports were standardized and high-quality with specific description of every part of surgery. Despite our limitations, this is the first study which analyzes such a wide spectrum of factors possibly influencing IOR frequency.

Author contribution All authors contributed to the study conception and design. Material preparation was done by KMK. Data collection and analysis were performed by MJF, MJB and KMK. The first draft of the manuscript was written by MJF and all authors commented on previous versions of the manuscript. Supervision of the article and guidance—Roger: MK, JP, KS, BMK. All authors read and approved the final manuscript.

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Data availability No data and materials are going to be available publicly.

Code availability Not applicable.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards Study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, with local ethics committee approval and informed consent obtained from patients about using their blinded data in medical research.

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