

 **Original Article** 

Isolated Distal Deep Vein Thrombus Detected before Orthopedic Surgery: Is Preoperative Anticoagulation Preferable?

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Objective: We evaluate the efficacy of anticoagulant administration for isolated distal deep vein thrombus (IDDDVT), detected before orthopedic surgery.

Materials and Methods: The study included 32 patients diagnosed with IDDDVT before orthopedic surgery in our hospital between October 2011 and October 2017. They were divided into two groups: the 'pre- and post-operative therapy group,' who were administered anticoagulants both pre- and post-operatively, and the 'post-operative therapy group,' who were administered anticoagulants only after surgery due to risk of bleeding judged by an orthopedic surgeon. We compared the primary efficacy (change in IDDDVT size) between the two groups.

Results: The proportion of patients with increased post-operative IDDDVT sizes was significantly larger in the post-operatively treated group than in the pre- and post-operatively

treated group (44.4% vs. 8.7%, $p=0.026$). No case demonstrated an IDDDVT extension proximal to the popliteal vein or presented with symptomatic pulmonary thromboembolism in this study.

Conclusion: Based on our findings, we recommend that, in patients with IDDDVT detected prior to orthopedic surgery and administered anticoagulant therapy only after the procedure because of a bleeding risk, a lower limb ultrasonography to re-evaluate the existing deep vein thrombus should be conducted before beginning rehabilitation.

Keywords: isolated distal deep vein thrombus, anticoagulation therapy, orthopedic surgery

Introduction

All major orthopedic surgical procedures, especially those involving the lower limbs, are considered a high-risk predisposing factor for deep vein thrombosis (DVT).^{1,2)} DVT may lead to a lethal pulmonary thromboembolism. Therefore, preventing DVT perioperatively is of great importance.

According to the 2016 American College of Chest Physicians guidelines,³⁾ infra-popliteal DVT of the lower limb (isolated distal DVT, also known as IDDDVT) is not a high-risk factor for fatal pulmonary embolism. Since there was no evidence of anticoagulant therapy's benefit in IDDDVT, expectant management was recommended. However, per the Japanese guidelines for preventing pulmonary thromboembolism,^{4,5)} a patient with a history of DVT who is undergoing major orthopedic surgery is judged to have the highest risk of perioperative thromboembolism. Therefore, anticoagulation is firmly recommended for such patients. These guidelines do not individually distinguish the level of risk between a supra-popliteal DVT of the lower limb and an IDDDVT. Therefore, there is much controversy surrounding IDDDVT treatment, which has lately come to be considered a relatively low risk factor.⁶⁻⁸⁾

For orthopedic surgery, especially in trauma patients, the risk of bleeding is a serious issue. In such high-risk

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cases, we administer anticoagulant therapy only after surgery, without offering preoperative coverage.

Our aim was to study anticoagulant administration efficacy in patients with an IDDVT detected before an orthopedic procedure by comparing the therapeutic outcome in patients who had undergone anticoagulation both before and after the surgery and in patients who had been administered anticoagulants only after the surgery (due to a risk of bleeding).

Materials and Methods

Study population and collection of data

The study subjects included patients who underwent orthopedic surgery at the Red Cross Kagoshima Hospital between January 2011 and October 2017. A lower extremity ultrasonography (USG) was performed for patients who presented with lower limb edema, or those detected with elevated D-dimer levels, during the preoperative work-up. Of the 636 consecutive patients who underwent the lower limb USG, 32 had a thrombus involving the infra-popliteal vessels of the lower limb. These 32 patients formed the study group (Fig. 1).

We collated all patients' background characteristics from their medical records (Table 1). Along with the pertinent physical characteristics and details of the impending orthopedic surgery, the preoperative investigation results were also documented. The lower extremity echogenic

findings (e.g., presence or absence of thrombus, localization, thrombus size, etc.) and details of anticoagulant administration were recorded in detail, along with the occurrence of bleeding complications (if any) in the post-operative period.

Exclusion criteria

We excluded the followings: a) patients with an IDDVT situated proximal to the popliteal vein, b) patients who received no anticoagulant therapy in the perioperative period, and c) the cases in which a lower limb USG was not repeated before the patient started walking after the surgery.

Evaluation and treatment of DVT

The venous thrombus was located using bilateral whole-leg USG examination⁹⁾ (Aloka prosound[®] α 10: Hitachi-Aloka Medical Corp., Tokyo, Japan). The patients were divided into two groups; one received both pre- and post-operative anticoagulant therapy, while the other group was only administered the same post-operatively. The patients diagnosed with DVT before the surgery underwent a post-surgical re-evaluation of the DVT. The repeat lower limb USG was performed before starting rehabilitation after the surgery. Intermittent pneumatic compression was not used on the DVT limb. However, all patients wore elastic compression stockings on both lower limbs. The dual anticoagulant dosage was determined according to each

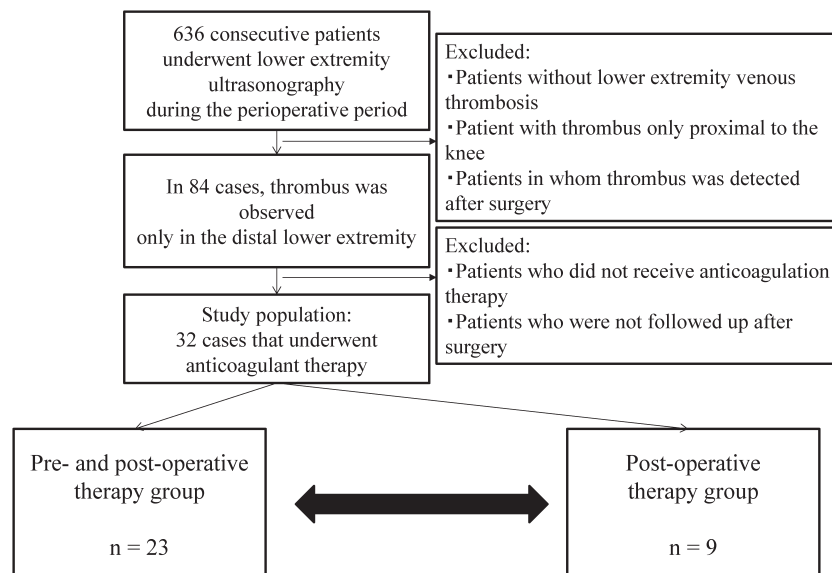


Fig. 1 Study population.

The study population is shown. There were 32 patients who were detected with a thrombus involving the infra-popliteal vessels of the lower limb before orthopedic surgery. We divided the subjects into two groups, the 'pre- and post-operative therapy group,' in which patients underwent anticoagulation before and after the operation, and the 'post-operative therapy group' in which patients were administered anticoagulants only after the surgery since they had a higher risk of bleeding.

Table 1 Patient background characteristics

Age (year)		78.4±14.4
Sex	Male/female	4/28
BMI		23.6±4.6
Diagnosis (n (%))	Lower extremity	21 (65.6%)
	Femoral neck fracture	5
	Femoral trochanteric fracture	5
	Osteoarthritis of the knee	4
	Osteoarthritis of the hip	2
	Septic arthritis of the hip	2
	Infected joint replacement arthroplasties	1
	Spontaneous osteonecrosis of the knee	1
	Fractures of the distal part of the fibula	1
	Spine	10 (31.3%)
	Lumbar spinal canal stenosis	3
	Ossification of the posterior longitudinal ligament	2
	Cervical spondylosis myelopathy	2
	Lumbar disc herniation	1
	Cervical dislocation	1
	Vertebral fractures	1
	Upper extremity	1 (3.1%)
	Cubital tunnel syndrome	1
Fracture cases		12 (37.5%)
D-dimer (µg/mL)		5.5 [2.8–13.8]
	Fresh thrombus	20 (62.5%)
	Old thrombus	12 (37.5%)
Side of thrombosis	Bilateral	9 (28.1%)
	Unilateral	23 (71.9%)
Site of thrombosis	Soleal vein	29 (90.6%)
	Peroneal vein	3 (9.4%)
Symptomatic cases		7 (21.9%)
LVEF (%)		68.3±7.2
BNP (pg/mL)		46.7 [18.5–89.0]
Cardiac rhythm	Sinus rhythm	32 (100%)
	Atrial fibrillation	0 (0%)
GFR (mL/min/1.73 m ²)		59.7±22.6
HbA1c (%)		5.9±0.6
Preoperative hemoglobin value (g/dL)		11.6±1.9
History of bleeding		5 (15.6%)
Combination of antiplatelet drug		9 (28.1%)
Bleeding volume during surgery (mL)		354 [30–460]

BMI: body mass index; LVEF: left ventricle ejection fraction; BNP: brain natriuretic peptide; GFR: glomerular filtration rate; HbA1c: hemoglobin A1c

patient's renal function. Warfarin was administered at a dose that maintained the prothrombin time-international normalized ratio (PT-INR) level between 1.5 and 2.0, and dose-controlled heparin was adjusted and administered at a dose at which the activated partial thromboplastin time was maintained at 1.5–2.0 times the normal upper limit.⁴⁾

Endpoint

We divided the subjects into two groups, the 'pre- and post-operative therapy group,' which underwent antico-

agulation before and after the operation, and the 'post-operative therapy group,' who received anticoagulants only after the surgery since orthopedic surgeons judged they had a risk of bleeding (Fig. 1). The primary efficacy outcome measure was the change in DVT size.

Definition of thrombus expansion

We defined 'thrombus expansion' as an increase in the size of the existing thrombus by ≥ 2 mm,^{10,11)} or the appearance of a new thrombus on the USG after surgery. We

also classified cases that had responded favorably to the anticoagulant therapy into two groups; one included patients whose thrombi had regressed in size by ≥ 2 mm and the other included patients whose thrombi had completely disappeared.^{10,11)}

Definition of bleeding

The patients whose hemoglobin levels fell >2 g/dL after surgery were classified as having excessive bleeding. This group also included patients who required a red blood cell transfusion of >2 units. The remaining patients were classified as those with minor bleeding.¹²⁾

Statistical analysis

All normally distributed data were expressed as mean \pm standard deviation. The non-normally distributed data (brain natriuretic peptide [BNP], D-dimer levels, and bleeding volume during surgery) were indicated as a median with the inter-quartile range. Pearson's Chi-square test or Fisher's exact test was used to evaluate IDVT's response to the various anticoagulants. To assess the correlation of the patient's background with anticoagulant therapy, a t-test was performed for parameters such as age, glomerular filtration rate, glycosylated hemoglobin, pre-operative hemoglobin value, and cardiac ejection fraction. The Wilcoxon test was used for non-normally distributed parameters such as D-dimer level, BNP level, and bleeding volume during surgery. Pearson's Chi-square test was applied to comparisons based on sex, surgical site, thrombotic state, thrombus localization, history of bleeding, and combination of antiplatelet drug. Finally, a logistic regression analysis was performed to delineate factors influencing the outcome with respect to thrombosis. All analyses were conducted using JMP 14.1 (SAS Institute Inc., Cary, NC, USA). The significance level was set at $p < 0.05$.

Ethics

This study complied with the standards of the Declaration of Helsinki and current ethical guidelines. It was approved by the institutional ethics board at the Kagoshima Red Cross Hospital.

Results

Patient background

The baseline characteristics of all patients included in our study are shown in **Table 1**. The mean age of the subjects was 78.4 ± 14.4 years. Of the 32 included patients, 21 (65.6%) and 10 (31.3%) underwent lower extremity surgery and spinal surgery, respectively, while one patient (3.1%) underwent an upper limb operative procedure. A thrombus was freshly detected in 20 patients (62.5%) with lower limb DVT, while 12 patients (37.5%) had

known cases of DVT. Additionally, nine patients (28.1%) were diagnosed with bilateral thrombi, while 23 patients (71.9%) had a thrombus involving a single lower limb. A soleal vein thrombus was identified in 29 cases (90.6%). Seven patients (21.9%) had symptomatic IDVT. All patients included in the study had a sinus rhythm.

Post-operative thrombus evaluation

In 19 cases (59.4%), the extent of thrombosis remained unchanged after surgery. The thrombi contracted in size or completely disappeared in eight cases (25.0%). Conversely, in five patients, the thrombi were found to have expanded in size post-operatively (15.6%).

The thrombosis was significantly fresh in those cases where the thrombi had completely disappeared compared to those cases in which the thrombi remained unchanged, contracted in size, or expanded in size ($p = 0.005$ vs. $p = 0.092$, $p = 0.251$, $p = 0.814$).

The D-dimer level after surgery was not significantly different between the patients with an increased IDVT and those without (7.7 ± 2.0 vs. 6.8 ± 0.9 ; $p = 0.671$). Furthermore, there was no difference in the D-dimer level before surgery between patients with decreased IDVT and those with increased or unchanged IDVT (10.1 ± 7.0 vs. 15.1 ± 4.1 ; $p = 0.540$).

In our study, no case demonstrated an IDVT extension proximal to the popliteal vein, or presented with symptomatic pulmonary thromboembolism.

Comparison between the two groups

Table 2 shows the comparison between the 'pre- and post-operative therapy group' and 'post-operative therapy group.' There was no significant difference in the backgrounds of the patients in both groups, except that there were significantly more fracture cases in the 'post-operative therapy group.'

The anticoagulants administered to the patients in each group were as follows: In the pre- and post-operatively treated group, heparin was used in five cases, warfarin in seven cases, and edoxaban in 10 cases before surgery. Furthermore, heparin was utilized in one case, enoxaparin in one case, warfarin in one case, and edoxaban in 10 cases after surgery. In the post-operatively treated group, warfarin was used in one case, edoxaban in five cases, and rivaroxaban in three cases after surgery.

There was no significant difference between the pre- and post-operatively treated group and the post-operatively treated group with respect to the percentage of cases in which IDVT size remained unchanged (65.2% vs. 33.3%, $p = 0.10$; **Fig. 2**). Moreover, no significant difference was observed in the proportion of cases in which the IDVT decreased in size or disappeared (26.1% vs. 22.2%, $p = 0.82$; **Fig. 2**). However, the proportion of

Table 2 Comparison between pre- and post-operative therapy group and post-operative therapy group

		Pre- and post-operative therapy group (n=23)	Post-operative therapy group (n=9)	p value
Age (year)		79.4±6.0	75.7±26.2	0.51
Sex (male/female)		4/19	0/9	0.09
BMI		24.0±4.8	22.6±3.9	0.47
Surgical site	Upper extremity	1	0	0.43
	Lower extremity	13	7	
	Spine	9	2	
Fracture cases		5	7	0.003
D-dimer (µg/mL)		4.9 [3.3–12.3]	12.3 [2.25–20.75]	0.59
Properties of thrombus	Fresh thrombus	13	7	0.25
	Old thrombus	10	2	
Side of thrombosis	Unilateral	16	7	0.64
	Bilateral	7	2	
LVEF (%)		67.9±7.4	69.1±7.0	0.69
BNP (pg/mL)		46.7 [20.4–105.4]	37.4 [9.8–85.1]	0.30
GFR (mL/min/1.73m ²)		59.2±23.7	61.0±18.8	0.84
HbA1c (%)		6.0±0.6	5.8±0.5	0.43
Preoperative hemoglobin value (g/dL)		11.7±0.4	11.4±0.6	0.69
History of bleeding		4	1	0.65
Combination of antiplatelet drug		8	1	0.15
Bleeding volume during surgery (mL)		300.0 [30.0–460.0]	75.0 [35.0–572.5]	0.70

BMI: body mass index; LVEF: left ventricle ejection fraction; BNP: brain natriuretic peptide; GFR: glomerular filtration rate; HbA1c: hemoglobin A1c

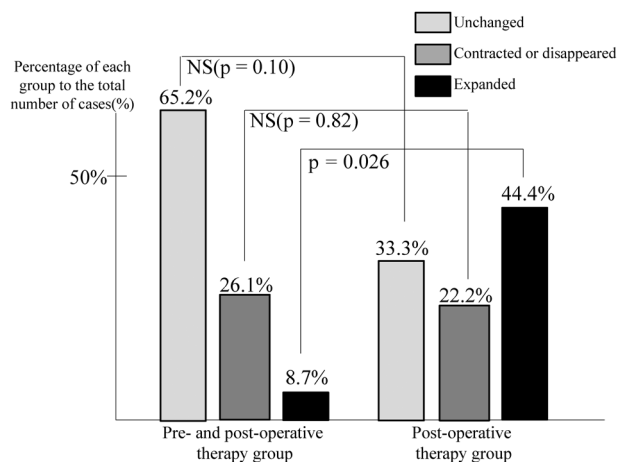


Fig. 2 Comparison of post-operative thrombus evaluation between the 'pre- and post-operative therapy group' and 'post-operative therapy group.'

There was no significant difference between the pre- and post-operatively treated group and the post-operatively treated group with respect to the percentage of cases in which the IDDVT size remained unchanged (65.2% vs. 33.3%, $p=0.10$) and decreased in size or disappeared (26.1% vs. 22.2%, $p=0.82$). However, the proportion of patients with a documented increase in the size of IDDVT after surgery was significantly larger in the post-operatively treated group than in the pre- and post-operatively treated group (44.4% vs. 8.7%, $p=0.026$).

Table 3 The logistic regression analysis of factors influencing post-operative thrombotic outcome

Variable	Odds ratio (95% confidence interval)	p value
Method of anticoagulation therapy	8.40 (1.28–59.49)	0.026
Use of direct oral anticoagulants	0.53 (0.09–3.18)	0.488
History of thromboembolism	5.00 (0.27–93.96)	0.299
History of malignant tumor	1.53 (0.13–17.97)	0.740
Lower extremity surgery	1.25 (0.19–8.13)	0.814
Fresh thrombus	1.25 (0.19–8.13)	0.814
Value of D-dimer	1.01 (0.99–1.03)	0.200
Localization of thrombus	0.74 (0.11–4.96)	0.756
Fracture	1.89 (0.31–11.34)	0.488

patients with a documented increase in IDDVT size after surgery was significantly larger in the post-operatively treated group than in the pre- and post-operatively treated group (44.4% vs. 8.7%, $p=0.026$; Fig. 2).

No significant difference in the incidence of bleeding complications due to anticoagulant therapy was observed between the two groups (17.4% vs. 11.1%, $p=0.65$).

Factors affecting post-operative thrombosis

Table 3 shows the results of logistic regression analyses

of factors influencing the post-operative thrombosis outcome. In the present study, the method of anticoagulation therapy, that is, whether anticoagulation therapy was administered only after or both before and after the operation was found to be the only significant factor (odds ratio [OR]: 8.40, 95% confidence interval [CI] 1.28–59.49, $p=0.026$). Other factors were not found to have a significant effect.

Discussion

In our study, we found that the size of an IDDVT detected before orthopedic surgery had significantly increased post-operatively in patients who were administered anticoagulant therapy only after the procedure compared to those who had been similarly treated in both the pre- and post-operative period. Based on our findings, we suggest that patients who can be administered anticoagulant therapy only after surgery should undergo a re-evaluation of the DVT post-operatively before beginning rehabilitation.

Recently, administering anticoagulant therapy for IDDVT has become a controversial issue, since it is unknown whether the risk of subsequent symptomatic pulmonary embolism is higher in patients with an isolated lower limb thrombus, even in cases where the thrombus has expanded in size following surgery. Some reports have suggested that an IDDVT does not warrant anticoagulant therapy and only expectant management is recommended.^{3,5} In our study, there were no cases in which the thrombus had post-operatively extended proximal to the popliteal vein. The frequency with which lower thrombi develop above the knee differs between reports.⁸ In past reports, there was a tendency for the thrombus to increase in size without anticoagulation. In our study, we think that there were few cases where the thrombus had progressed to the knee because cases without anticoagulation were excluded. Furthermore, none of our study patients developed symptomatic pulmonary embolism. However, there have been reports of IDDVT having progressed proximally, converting into a free-floating thrombus, and leading to a lethal pulmonary thromboembolism.¹³ Moreover, the risk of DVT varies depending upon individual patient history and characteristics,⁸ which makes it difficult to establish a uniform management protocol for IDDVT. As described above, the effect of anticoagulation on IDDVT detected in the preoperative period is unclear. However, based on our finding, we think that pre- and post-operative anticoagulant therapy may suppress the expansion of IDDVT detected before an orthopedic surgery, thus suppressing pulmonary embolism. Further study to clarify this point is needed in the future.

In our study, there was no significant difference in the occurrence of hemorrhagic complications between the

two groups. In this study, orthopedic surgeons decided whether or not to perform anticoagulation based on their subjective judgment, without clear criteria. In the group treated with anticoagulation only after surgery, there were significantly more fracture cases, which may have affected orthopedic decision making. However, comparing the two groups retrospectively, in addition to the general patient background, indicated no significant differences in bleeding history, presence or absence of antiplatelet drugs, and preoperative hemoglobin values. Thus, in fact, there were no significant differences in the bleeding risk between the two groups. Therefore, the safety between pre- and post-operative anticoagulant therapy and only post-operative anticoagulant therapy should be discussed in a future study. Moreover, currently, there is no method for objectively evaluating the risk of bleeding when anticoagulation therapy is indicated before an orthopedic surgery. A tool or scale (such as the HAS-BLED score¹⁴) in atrial fibrillation) is urgently required to objectively evaluate the risk of bleeding in patients before administering anticoagulants prior to any major orthopedic surgery.

In our study, the method of anticoagulation, that is, whether anticoagulants for an IDDVT detected before an orthopedic surgery were administered both pre- and post-operatively or only post-operatively, was the only significant differentiating factor influencing the expansion of the lower limb venous thrombus following the surgery. In our study, most thrombi were found in the soleal vein. The soleus muscle is involved in exerting an antigravity force while standing up. For this reason, exercise in the supine position is not useful to induce contraction of this muscle, and the muscle pump action of the soleus muscle remains unused.¹⁵ Since rehabilitation exercises in a standing position could be started only after the initial post-operative recovery, it was considered that an expansion of a lower limb thrombus in the perioperative period could not be effectively suppressed using only elastic stockings or mechanical compression via a foot pump.¹⁶

In our study, we excluded patients who did not undergo anticoagulation therapy at the perioperative stage, even though IDDVT was pointed out before surgery. Orthopedic surgery, especially lower limb surgery, is considered a high-risk factor for DVT, and not performing anticoagulation in the perioperative period is rare unless there are special circumstances. There are few reports on IDDVT outcomes when anticoagulation therapy was not enforced, but Wang et al. reported that IDDVT cases without anticoagulation therapy were significantly more symptomatic than those with anticoagulation therapy, which was consistent with our research results.¹⁷

Our study had a few limitations. First, this was a single-center study with a relatively small number of subjects. Furthermore, since it was a retrospective observational

study, the influence of unknown confounding factors cannot be ruled out. In addition, the average age of patients in our study was relatively high, so the results might be overestimated and may not be applicable across all age-groups. Second, the preoperative lower extremity venous ultrasonography had been performed in patients with lower limb swelling or elevated D-dimer levels. Therefore, not all cases included in the study had symptomatic DVT. In our study, there are two reasons why anticoagulation therapy was performed in those symptomatic or asymptomatic patients: Firstly, cases that were treated with anticoagulation therapy for symptomatic IDDVT, and secondly, asymptomatic IDDVT cases with a history of thrombosis and anticoagulation were administered anticoagulant therapy for the purpose of perioperative prophylactic administration. As anticoagulant therapy for an asymptomatic thrombotic thrombus is not recommended in recent years; future research on anticoagulant therapy in the orthopedic surgery period should be conducted for preventive or therapeutic purposes, separately. Third, the post-operative absence of a pulmonary embolism was determined based on a lack of subjective patient symptoms and by an evaluating oxygen saturation. An objective assessment with investigations such as echocardiography, contrast computerized tomography, and ^{99m}Tc-macroaggregated albumin scintigraphy had not been performed in all patients after the surgery to definitively rule out pulmonary embolism.

Conclusion

In conclusion, the proportion of patients with an increased IDDVT sizes post-operatively was significantly larger in the post-operatively treated group than in the pre- and post-operatively treated group. Therefore, we recommend that, for patients with an IDDVT detected prior to an orthopedic surgery who are administered anticoagulant therapy only after the procedure because of a risk of bleeding, a lower limb USG for re-evaluation of the existing DVT should be conducted before beginning rehabilitation. Furthermore, in the future, we should clarify whether patients with IDDVT detected prior to an orthopedic surgery, who do not have a significant bleeding risk, should be administered preoperative anticoagulant therapy or not. A prospective study on a much larger scale would establish a definite protocol for perioperative prophylactic anticoagulant administration.

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Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

Study conception: all authors

Data collection: KH, ATe, TM, SO, KS

Analysis: KH, ATo, ATe

Investigation: KH, ATo, TM, SO, KS, NS, ET

Writing: KH, ATo, ATe, TM, KS, MO

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Accountability for all aspects of the work: all authors

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