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Early Haemodynamic Outcomes of Pulmonary Thrombo-endarterectomy: Experience of a Tertiary Referral Center in Egypt

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ABSTRACT
Background: Chronic thromboembolic pulmonary hypertension is a potentially curable condition via pulmonary thromboendarterectomy (PTE) which involves surgical removal of the thromboembolic material through endarterectomy. This is a technically demanding surgery and better results could be achieved only in experienced centers worldwide. The present study aimed to document the hemodynamic outcomes of PTE focusing on the degree of improvement in exercise capacity and hemodynamic parameters after surgery.
Subjects and Methods: an interventional prospective and retrospective study was undertaken in the Cardiothoracic Surgery Department at Kasr El-Aini University Hospitals, including 20 patients who underwent PTE.
Results: After excluding the 3 mortality cases, all the 15 cases with preoperative NYHA-FC III and IV improved to a better FC while the 2 cases with preoperative NYHA-FC II remained unchanged. Mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) decreased by 33.5 (range 35.6 - 31.3) mmHg and 542.6 (range 604 - 481.1) dyn.sec.cm^{-5} respectively.
Conclusion: PTE results in a dramatic improvement in the hemodynamic parameters in patients with chronic thromboembolic pulmonary hypertension.
Keywords: Chronic thromboembolic pulmonary hypertension, Pulmonary thromboendarterectomy, pulmonary vascular resistance, Venous thromboembolism, Pulmonary embolism.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is classified as "group (4) pulmonary hypertension" in the clinical classification of pulmonary hypertension (PH) **(1, 2, 3)**.

It is caused by obstruction of the pulmonary arteries with an organized thromboembolic material. Since the majority of confirmed cases of CTEPH had a history of acute pulmonary embolism, many studies related this disorder to venous thromboembolism and pulmonary embolism **(4-6)**.

Other factors, such as hypercoagulable states and pro-thrombotic conditions, could also have a role in the development of CTEPH **(7-9)**.

The predominant symptom of CTEPH is dyspnea that is non-specific. Therefore, it might result in misdiagnosis or delayed diagnosis which is implicated in the development of distal pulmonary vasculopathy, causing more rise in pulmonary vascular resistance (PVR) and worsening of symptoms **(6)**. If this condition left untreated, it eventually associated with 30% five year survival rate for patients with mean pulmonary artery pressure (mPAP) more than 40 mmHg and reaches 10% if mPAP exceeds 50 mmHg **(10)**.

Although CTEPH is life- threatening disease, it is potentially curable by performing pulmonary thrombo-endarterectomy (PTE) which restores exercise capacity and improves the patients' quality of life.

This operation is technically challenging and unfortunately not every patient with CTEPH can benefit from it **(11, 12)**.

Furthermore, it may expose the patients to various life-threatening complications such as reperfusion lung injury, residual pulmonary hypertension, and neurologic complications. So that, early detection of factors associated with good/ adverse outcomes is of extreme importance for both the surgeon and patient **(13)**.

The aim of the present study was to document the hemodynamic outcomes of PTE focusing on the degree of improvement in exercise capacity and hemodynamic parameters after surgery.

PATIENTS AND METHODS

Between June 2019 and April 2021, an interventional prospective and retrospective study was undertaken in the Cardiothoracic Surgery Department at Kasr El-Aini University Hospitals, including 20 patients who underwent pulmonary thromboendarterectomy (PTE).

Inclusion criteria:

The study included patients who had the following criteria:

- History of venous thromboembolism (VTE)/ pulmonary embolism sequelae with unexplained dyspnea (NYHA functional class II, III and IV) after ≥ 3 months despite receiving effective anticoagulation.
- Echocardiography revealed estimated pulmonary artery pressure ≥ 25 mmHg with or without presence of right ventricular (RV) dilatation or tricuspid regurgitation. But these changes were not attributed to cardiac or lung diseases.

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- Ventilation/perfusion lung scan showed mismatched major perfusion defects whether unilateral or bilateral.
- Multislice CT (MSCT) pulmonary angiography confirmed obstruction of one or the two major pulmonary arteries or their lobar branches with concomitant absent/diminished pulmonary vasculature distal to the level of obstruction.
- Right sided heart catheter (RHC) revealed mPAP of more than 30 mmHg and PVR ≥ 300 dyn.s.cm^{-5}.

Exclusion criteria:

The study excluded patients who had the following criteria:

- Surgically inaccessible disease.
- Concomitant other pulmonary conditions such as severe parenchymal lung diseases contributing also to pulmonary hypertension or lung malignancies.
- Concomitant other cardiac conditions that may need combined cardiac surgeries or making the patients inoperable.

Pre-operative assessment:

After CTEPH have been confirmed, assessment of surgical candidacy was done based on inclusion and exclusion criteria. For each patient enrolled in the study, full history and clinical examination had been taken. Investigations were done in the form of laboratory tests, chest X-ray, echocardiography, ventilation/perfusion scan, MSCT pulmonary angiography and right heart catheter.

- Routine laboratory tests were CBC, ALT, AST, Urea, creatinine, total and direct bilirubin, and coagulation profile.

- Chest X-ray was done to detect enlarged major pulmonary arteries and rapid peripheral pruning (decreased broncovascular markings). Echocardiography was also used to measure estimated pulmonary artery pressure, RV size and function, and to detect tricuspid valve regurge as well as concomitant other cardiac problems.

- Echocardiography was also used to measure estimated pulmonary artery pressure ((PAP), RV size and function, and to detect tricuspid valve regurge as well as concomitant other cardiac problems.

- V/Q scan was obtained to detect areas of perfusion defects and V/Q mismatch. MSCT pulmonary angiography was done to demonstrate obstruction sites caused by the thromboembolic material and to show the degree of pulmonary affection from the disease process. Finally, right heart catheter (RHC) was done to accurately measure mPAP, PVR, and CI.

The oral anticoagulant (warfarin) was discontinued 4 days before surgery and bridged with low molecular weight heparin. When INR reached 1.3 surgery could be done.

The procedure PTE:

Anesthetic management:

In the operating room, proper monitoring lines were applied for patients involving pulse oximeter, radial arterial line for invasive blood pressure monitoring and urinary catheter insertion. Then induction of anesthesia was followed by endotracheal intubation subsequently Swann-Ganz catheter was inserted to measure right sided pressures, PAP as well as to calculate cardiac index. Final preparations for the surgery were the insertion of intraoperative TEE and thermal probes.

The operative technique:

The patient is laid supine on table, then routine prepping and draping as standard open cardiac procedures. Hereafter that median sternotomy and pericardiotomy were done. Full heparinization was accomplished using intravenous unfractionated heparin (400 units/kg) with target activated clotting time >400 seconds, then full CPB was instituted with aorto-bicaval cannulation. LV vent, pulmonary artery vent, and venae caval snares were all inserted.

Systemic hypothermia was allowed down to 20°C and the head was placed inside a head cooling jacket. Aortic cross clamp was applied and cardioplegia was given with antegrade cold blood cardioplegia to arrest the heart and achieve good myocardial protection. During cooling the patient and giving cardioplegia, dissection between the ascending aorta, superior vena cava, and right pulmonary artery (RPA) could be done. Before making the right pulmonary arteriotomy, the surgeon stood on the left side of the patient and retracted the ascending aorta and SVC away from each other to work on the RPA.

The arteriotomy extended under the SVC and as far as the take-off of the middle lobe artery. Any loose thrombus detected now was removed. Circulatory arrest commenced once core temperature reached the deep hypothermic levels and arteriotomy had been made to create a bloodless field suitable for complete and effective endarterectomy.

This procedure usually continued for at most 20 minutes before the circulation was re-allowed for 10 minutes. Next, the surgeon stands on the right side of the patient to start another 20 minute DHCA period to work on the left PA in the same manner as used in the right pulmonary endarterectomy.

After finishing each side, the specimen was arranged on a table to examine if it took the shape of inner branches and configuration of the pulmonary artery segment, wrapping it till its distal small tail ends.

During stitching of the left pulmonary arteriotomy, rewarming was allowed gradually to euthermic levels within 15– 20 minutes. Cross-clamp could be removed after deairing the heart, then weaning from CPB was allowed gradually, followed by the removal of CPB lines. Subsequently, adequate hemostasis was done, followed by inserting two mediastinal chest drains, and finally, sternotomy and wound closure could be done.

Post-operative care:

Patients were transferred to the ICU on mechanical ventilation and, if needed, on proper inotropic support or IV milrinone. The intensivist continues monitoring of the invasive blood pressure, oxygen saturation, central venous pressure, Swann-Ganz readings, and urine output that reflect the systemic perfusion status.

Ethical approval:

The study was approved by the Ethics Board of Cairo University and an informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data was collected, coded, clustered in groups when needed, and analyzed using Medcalc 18.9.1, IBM SPSS 21 and Microsoft Excel 2016. Parametric data are described as mean and standard deviation (SD), non-parametric data are described as median and interquartile ranges and categorical data are described as percentages and frequencies when appropriate. Paired t- test was used for comparing 2 paired means, Mann-Whitney test was used to compare two independent medians. Friedman and Wilcoxon tests were used to compare medians of paired multivariables. Chi-squared and Fisher's exact tests were used to analyze categorical variables. For all the statistical tests, the level of significance was set at 5% level. A p value > 0.05 indicated that there was no significant value. A p value ≤ 0.05 indicated presence of a significant value. When p value was <0.01 this indicated that it was highly significance value.

RESULTS

Baseline characteristics

There were 11 males (55%) and 9 females (45%). The age ranged from 20 to 62 years, with a mean age of 41.7 (SD 10.14) years. The mean body mass index was 22.5 (SD 5.3). There were 18 patients (90%) with a previous history of VTE. The average duration between the last episode of VTE and the diagnosis of CTEPH was 14.9 (SD 4.8) months. The median time between CTEPH diagnosis and having surgery was 11.5 (10-14.5) months.

Concerning the preoperative hemodynamic and respiratory status, eleven patients (55%) had FC-III, seven patients (35%) had FC-IV, and two patients (10%) had FC-II. The mean resting respiratory rate was 17.3 (SD 1.9) breaths/min. The respiratory rate after exercise was measured in all patients except in the seven cases with FC-IV, the respiratory rate reached a mean of 31.6 (SD 3.4) breaths/minute. The mean arterial oxygen tension (PaO_2) was 71.7 (SD 9.4) mmHg.

Before surgery, echocardiography identified 4 patients (20%) with normal RV dimensions, 5 cases (25%) with mild RV dilatation, 7 cases (35%) with moderate RV dilatation, and 4 cases (20%) with significantly dilated RV. The mean tricuspid annulus plane systolic excursion (TAPSE) was 2.36 (SD 0.39). Four cases (20%) presented to surgery with no tricuspid regurge. Another four cases (20%) had mild degree of tricuspid valve regurge. Moderate tricuspid regurgitation was present in 4 cases (20%). Eight patients had a severe degree of tricuspid regurge before they underwent PTE.

The Right heart catheter (RHC) revealed a median mean pulmonary artery pressure (mPAP) of 57.7 (53.1-62.9) mmHg. The mean pulmonary vascular resistance was 758.7 (SD 177.3) dyn.sec.cm-5. The cardiac index was 2.4 (SD 0.5) L/min/m^2 on average. The mean mixed venous oxygen saturation (SVO2) was 53.9 (SD 10.6) %. Three patients (15%) had an IVC filter inserted prior to surgery.

Table (1): Patients demographics before surgery

Total number		N=20
Clinical review	Age (years)	41.7 ±12.6
	Sex • Male • Female	 11 (55%) 9 (45%)
	BMI	22.5 ± 5.3
	Previous VTE	18 (90%)
	Time between VTE and CTEPH symptoms (ms)	14.9 ± 3.43
	Time between CTEPH diagnosis and PTE (ms)	11.5 (10-14.5)
Hemodynamic status	NYHA functional class • Class II • Class III • Class IV	 2 (10%) 11 (55%) 7 (35%)
Respiratory status	Resting respiratory rate (BPM)	17.3 ± 1.9
	Respiratory rate after exercise*	31.6 ± 3.4
	P_aO_2 (mmHg)	71.1 ± 9.4
Echocardiography	Right ventricle size • Normal sized • Mildly dilated • Moderately dilated • Severely dilated	 4 (20%) 5 (25%) 7 (35%) 4 (20%)
	Degree of tricuspid regurge • Normal valve • Mild regurge • Moderate regurge • Severe regurge	 4 (20%) 4 (20%) 4 (20%) 8 (40%)
	Tricuspid annulus plane systolic excurtion	2.36 ± 0.39
Right heart catheter	mPAP (mmHg)	57.7 (53.1 - 62.9)
	PVR (dyn.sec.cm^{-5})	758.7 ± 177.3
	CI (L/min/m^2)	2.1 ± 0.5
	SVO_2 (%)	53.9 ± 10.6
IVC filter		3 (15%)

* Tests were done only in 13 cases as the remaining cases had dyspnea at rest.

BMI: body mass index, VTE: venous thromboembolism, BMP, breaths/min CTEPH: chronic thromboembolic pulmonary hypertension PTE: pulmonary thromboendarterectomy, ms: months, N: total number, n: number of cases, mPAP: mean pulmonary artery pressure, CI: cardiac index, SVO_2: mixed venous oxygen saturation, PaO_2 partial arterial oxygen pressure.

Intra-operative data:

The mean **cardiopulmonary bypass time** was 114.2 (SD 47.81) minutes. It took about 30–60 minutes to cool the patients down to (20°C) and rewarm them to normal body temperature. In 10 cases (50%), the CPB time was ≤ 100 minutes in 10 cases (50%), while in 2 cases (10%), the CPB time of ≥ 180 minutes.

The mean **deep hypothermic circulatory arrest time** for both pulmonary arteries together was 36 (SD 4.7) minutes. In 15 cases (75%), the DHCA time was less than or equal to 40 minutes, while in 5 patients (15%), the DHCA time was longer than 40 minutes (See **Table 2**).

During surgery, one patient died from a catastrophic pulmonary haemorrhage. This patient was orthopneic with massive pericardial effusion and hypoxia (PaO_2 of 62.6 mmHg), which necessitated urgent intervention.

Table (2): Intraoperative variables

Parameters	Results (n=20)
CPB time (mins)	**114.2 ± 47.8**
• ≤ 100 min	10 (50%)
• 101 – 140 mins	4 (20%)
• 141 – 180 mins	4 (20%)
• > 180 mins	2 (10%)
DHCA time (mins)	**36 ± 4.7**
• DHCA ≤ 40 mins	15 (75%)
• DHCA > 40 mins	5 (25%)
Intraoperative mortality	1(5%)

CPB: cardiopulmonary bypass, DHCA: deep hypothermic circulatory arrest, PTE: pulmonary thromboendarterectomy, mins: minutes.

Early postoperative outcomes:

The median **length of stay in the ICU** after surgery was 3 (3-4) days. The median **duration of MV** was 15 (10.25 – 25.5) hours. 13 cases (68.4%) had been extubated within one day, while the remaining 6 cases (31.6%) had prolonged mechanical ventilation. The mean **hospital stay** was 10.9 (SD 2.12) days.

Concerning ICU and in-hospital mortality, there were two cases (10.5%) of postoperative mortality. One of them died as a result of severe RLI. The other case had protein C and protein S deficiency and died as a consequence of recurrent pulmonary embolism.

In terms of **hemodynamic outcomes**, six cases (35.3%) had NYHA-I, nine cases (52.9%) had NYHA-II, and two cases (11.8%) had NYHA-III. The mPAP was 24.3 (SD 5.8) mmHg. The mean cardiac index was 3.4 (SD 0.5) L/min/m2. The mean PVR was 201.9 (SD 55.7) dyn.sec.cm-5.

Table (3): Post-operative (ICU and in-hospital) outcomes

Parameter		Results (n=19)
Duration of MV (hours)		15 (10.25 – 25.5)
	≤24 hours	13 (68.4%)
	>24 hours (prolonged)	6 (31.6%)
ICU stay (days)		3 (3 – 4)
Hospital stay (days)		10.9 ± 2.12
ICU mortality		2 (10.5%)
Hemodynamic outcomes		
NYHA on discharge (n=17)	• Class I	6 (35.3%)
	• Class II	9 (52.9%)
	• Class III	2 (11.8%)
• mPAP (mmHg)		24.3 ± 5.8
• CI before discharge		3.4 ± 0.5
• PVR before discharge ($dyn.s.cm^{-5}$)		201.9 ± 55.7

MV: mechanical ventilation, ICU: intensive care unit, NYHA: New York heart association, mPAP: mean pulmonary artery pressure, CI: cardiac index, PVR: pulmonary vascular resistance.

Changes in the haemodynamic outcomes after PTE: After excluding the 3 mortality cases, a comparison was made between baseline and postoperative haemodynamic measurements. This comparison included NYHA-FC changes, mean pulmonary artery pressure changes, and pulmonary vascular resistance changes:

NYHA functional class changes (NYHA-FC): When we compared the distribution of NYHA -FC across patients before and after surgery, we discovered the following: **For the 6 patients with preoperative FC-IV,** 4 cases (66.7%) became FC-II, and 2 cases (33.33%) became FC-III after surgery. **For the 9 patients with preoperative FC-III,** 6 cases (66.7%) became FC- I, and 3 cases (33.3%) became FC-II after surgery. **The 2 patients with preoperative FC-II** remained in FC-II as they were before surgery.

DISCUSSION

CTEPH is one of the causes of pulmonary hypertension that is categorised as "group 4" in numerous pulmonary hypertension clinical classifications. It is characterized by occlusion of pulmonary arteries by an organized thromboembolic material [1, 3].

The exact cause of CTEPH is still unknown, but in a large European study, a history of acute pulmonary embolism was found in 74.8% of patients with CTEPH [14]. Other studies correlated prothrombotic and hypercoagulable states (such as protein C and protein S deficiencies, and antiphospholipid syndrome) with the development of the disease process [7, 9]. Although pulmonary embolism constituted a major risk factor for CTEPH, the cumulative incidence of CTEH was 0.1-0.5% following acute pulmonary embolism [10].

One major problem in CTEPH is misdiagnosis, underdiagnosis, and delayed diagnosis before undergoing for surgery. It may be difficult to distinguish some cases of CTEPH from other conditions that cause pulmonary hypertension. Hence, these cases should be referred to pulmonary hypertension expert centers [6, 15, 16].

The best option and the only curative measure for CTEPH is PTE. Other options (such as BPA and medical treatment) can only be offered if these patients are deemed inoperable [1, 12, 17, 18].

The University of California–San Diego (UCSD) medical centre provided the majority of the current surgical experience and techniques for PTE. Braunwald founded the UCSD PTE programme in 1970, and it now has over 4000 cases with the best success rate and outcomes in the world [19].

The purpose of this research was to investigate and document the early haemodynamic outcomes of PTE. It investigated the early outcomes of PTE concerning operative time, deep hypothermic arrest time, intraoperative risks and complications. The ICU and in-hospital outcomes were also assessed.

According to the NYHA functional class system, 2 patients (10%) were classified as FC–II, 11 patients (55%) as FC–III, and 7 patients (35%) as FC–IV. The results of this study were compared to those of **Chen *et al.*** [20], who performed PTE on 12 patients (63%) with FC – III and 7 patients (37%) with FC – IV.

In this study, the **average time for cardiopulmonary bypass** (CPB) was 114.2 (SD 47.8) minutes. CPB time was less than or equal to 100 minutes in ten cases (50%), and 180 minutes or more in two cases (10%). It took between 100 and 180 minutes for the remaining 8 individuals (40%). The **mean deep hypothermic circulator arrest time** was 36 (SD 4.7) minutes, 15 cases (75%) of them were less than or equal to 40 minutes, while only 5 cases (25%) exceeded 40 minutes.

These results were compared with those of **Madani *et al.*** [5], who worked on 500 patients. They reported a CPB time of 265.4 ± 37.9 minutes and a DHCA time of 36.3 (SD 12.5) minutes. Whereas **Chen *et al.*** [20] reported 226 (SD 83) and 60 (SD 31) minutes for CPB time and DHCA time, respectively.

In terms of **ICU and in-hospital outcomes**, a recent study by **Kratzert *et al.*** [13] reported that the **ICU stay** usually takes 2 to 3 days for uncomplicated cases. Another study by **Cannon *et al.*** [21] reported a median stay in ICU lasted for 3 days. A third study by **D'Armini *et al.*** [22] reported a median stay in ICU for 4 days. In this study, the median **ICU stay** continued for 3 – 4 days, which was comparable to the three previous studies' results.

Related to the duration of mechanical ventilation (MV) in this study, the median MV time was 15 (10.25 – 25.5) hours. While thirteen cases (68.4%) of patients had been extubated within 24 hours, the remaining six cases (31.6 %) had prolonged mechanical ventilation. Reperfusion lung injury occurred in four cases (66.66%).The above results were comparable to those of **Kratzert *et al.*** [13]**,** who reported that 50% of patients were usually extubated within 24 hours and 80-90 % within 48 hours after surgery. In their study, the most common reason for prolonged mechanical ventilation was reperfusion lung injury.

Concerning the mean **hospital stay** in this study, it was 10.9 (SD 2.12) days which was comparable to the study of **Jamieson and Kapelanski** [23] who reported 11 (SD 4) days. Other studies by **Chen *et al.*** [20]**, Cannon *et al.*** [21] **and D'Armini *et al.***[22] reported the mean hospital stay as 16, 13, and 19 days, respectively.

Regarding the **hemodynamic outcomes** of this study, PTE was associated with a strong improvement in exercise capacity and the partial arterial oxygen pressure after surgery. **Exercise capacity**, had been assessed by NYHA- functional class. There was a statistically significant improvement in NYHA-FC after PTE, as the prevalence of FC- I and FC- II increased to 88.2% after surgery, while it was only 11.8 % before surgery. This result was similar to that of the study by **Madani *et al.*** [12] who reported an 83 % prevalence of FC- I and II among survivors of PTE in the early postoperative period.

In this study, there was a statistically significant drop in the **mPAP** by about 37 mmHg, which was similar to the drop in the study of **Cannon *et al.*** [21] which was 20 mmHg. This drop was also noticed in the results of **Reesink *et al.*** [24] which was 19 mmHg. This drop in the mPAP also happened in the PVR after PTE. Not only did the **PVR** decrease by 557 dyn.sec.cm^{-5} in this study, but it also decreased by 434 dyn.sec.cm-5 in the study of **Reesink *et al.*** [24] and 513 dyn.sec.cm^{-5} in the study of **Cannon *et al.*** [21].

In terms of **mortality,** there were 3 operative mortality cases (15%) in this study. One of them had intra-operative massive pulmonary hemorrhage. Another case died from a severe degree of reperfusion pulmonary edema. The remaining case died as a consequence of recurrent pulmonary embolism.

Chen *et al.* [20] reported a mortality rate of 10.5% in 19 patients, which was similar to the results of this study. They suggested that the degree of preoperative hemodynamic compromise, prolonged CPB, and DHCA time were all important factors correlated with high mortality. They linked the relatively small sample size to the mortality rate.

The above mortality rates in the study of **Chen *et al.*** [20] and the current one were consistent with the early results of the UCSD programme for PTE. The programme documented 16.8% mortality rate in 143 patients who underwent PTE. Recently, the programme has released a number of publications documenting the outcomes of PTE in a significant number of patients, with decreased mortality rates reaching 4.4% and 2.2% following surgery. **Madani *et al.* [5] and Jamieson *et al.* [25]**. Thus, **Madani[26], Mayer *et al.* [27]**, **Jenkins *et al.* [28] and Lankeit *et al.* [29],** emphasized that a low mortality rate <5% is achieved only when surgery is conducted in high-volume expert centers such as the UCSD medical center.

LIMITATIONS: The main limitation of this study was the small sample size, which was caused by low disease incidence and a low rate of CTEPH diagnosis. Although ECMO has been recommended by many studies, it was not used in this study due to financial constraints. This made postoperative care problematic in some cases. The delay for undergoing surgery after diagnosis, was another factor that made our overall survival still unsatisfactory.

CONCLUSIONS

PTE significantly and dramatically improves the hemodynamic status in patients with CTEPH in terms of functional class, PAP and PVR.

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Author contribution: Authors contributed equally in the study.

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