

**Study of the histopathologic samples of chronic thromboembolic pulmonary hypertension (CTEPH) patients and its relationship with mortality**

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**Abstract**

*Background:* Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive form of pulmonary hypertension. Although pulmonary hypertension is strongly associated with a high morbidity and mortality rate, this condition's prognosis and mortality rate are still unclear in Iran. This study aims to evaluate the correlation between the histopathologic findings in endarterectomy specimens of CTEPH patients and their mortality rate.

*Material and method:* In this study, 65 patients from Masih Daneshvari Hospital, Tehran, Iran, who were diagnosed with CTEPH and underwent endarterectomy were studied from 2008 until 2018. A questionnaire, including two main sections, was filled out for each patient. One section contained basic characteristics of patients, such as age, sex, etc. In contrast, the other section had the histopathologic findings of endarterectomy specimens, such as the presence of media, intima, atherosclerosis, and blood clots. The mortality rate was obtained by following up with patients by calling them or their families on the phone. Ultimately, the data analysis was performed using SPSS software version 16 and the ANOVA method.

*Results:* The patients' mean age was  $46.2 \pm 13.09$ , consisting of 43.1% women and 56.9% men. Intima, blood clots, media, and atherosclerosis were seen in 89%, 86%, 67%, and 27% of the specimens, respectively. The mortality rate was 27%.

*Conclusion:* The presence of the media of the vessel (muscular part of the vascular wall) in the histopathologic evaluation of samples of CTEPH patients who underwent endarterectomy was associated with an increased risk of mortality.

*keywords:* Chronic thromboembolic pulmonary hypertension, Pulmonary endarterectomy, Pathology, Mortality

## **Introduction**

Chronic thromboembolic pulmonary hypertension (CTEPH) is progressive but curable; therefore, it is an important type of pulmonary hypertension (PH)(1, 2). The World Health Organization (WHO) has classified PH into five clinical subgroups, and CTEPH is within subgroup 4 of this classification(3). It results from a fibrotic transformation of pulmonary artery clots obstructing pulmonary arteries. Associated vascular remodelling in the microvasculature and increased vascular pressure and resistance in the pulmonary vasculature eventually lead to right heart failure and premature mortality(4).

Once regarded as a rarer condition, CTEPH was reported to complicate 3.8% of acute pulmonary embolic events(5). In published prospective studies, with the confirmed diagnosis by right heart catheterization (RHC), the incidence of CTEPH after acute pulmonary embolisms, which were symptomatic, is reported to range from 0.4% to 6.2%, giving a pooled incidence of 3.4% (95% CI 2.1–4.4%)(6). In recent years, the prevalence of CTEPH is estimated at 3–30 per million in the general population(7).

The diagnostic criteria of CTEPH are as follows:

1. effective anticoagulant therapy for a minimum duration of 3 months.
2. a mean pulmonary pressure (mPAP) > 25 mmHg and a capillary wedge pressure

(PCWP) of 415 mmHg at the RHC.

3. pulmonary vascular resistance (PVR) > 3 Wood units (WU).
4. evidence of perfusion defect of at least one or two medium-high calliper vascular segments at the ventilation/perfusion scintigraphy and specific diagnostic signs observed on CT pulmonary angiography(8).

CTEPH is the sole cause of severe PH, which has the potential to be cured without performing lung transplantation, which turns it into an extraordinary condition(9). The surgical therapeutic procedure is Pulmonary endarterectomy (PEA). This surgery removes the obstructive thromboembolic material, resulting in significant improvements in the right ventricular function and hemodynamic in a good deal of cases, normalization (10).

For the past two decades, the number of PEA has steadily increased, showing an improved physician recognition of both CTEPH and PH. Even outside of reported experience and individual case series, there is still minimal information to support a good deal of the suppositions and theories regarding this condition(11).

The prognosis of patients with CTEPH after PEA depends on multiple factors, such as the occlusion degree of the small peripheral pulmonary arteries by thrombi(12, 13). While only a few studies, especially in Iran, have analyzed the relationship between histopathologic samples and the prognosis of CTEPH, this study aims to determine whether the histological findings of endarterectomy specimens of patients with CTEPH are related to the mortality rate of affected patients.

### **Methods and Materials**

This study was conducted in Masih Daneshvari Hospital, Tehran, Iran. 65 patients (37 men and 28 women patients) with an established diagnosis of CTEPH who underwent endarterectomy from July 2008 to June 2018 were included in the study. Exclusion criteria were the presence of chronic pulmonary disease without pulmonary hypertension and also patients with pulmonary angiosarcoma.

The endarterectomy specimens of these patients were fixed in 10% formalin and were divided into 3 blocks or more in each case. For the next step, the pathologic evaluation of endarterectomy specimens was performed by searching for the presence of intima, media(muscle), atherosclerosis, and blood clots in the samples.

Furthermore, the examiner filled out a questionnaire for each patient composed of two sections. Section one included the basic characteristics of patients, such as sex and age, while section two included the pathologic features of samples, particularly the presence of the intima, media(muscle), atherosclerosis, and blood clots. The presence of intima and media(muscle) was confirmed by immunohistochemistry staining (CD31 and CD34) and trichrome staining, respectively.

The mortality rate of patients was evaluated by calling them or their families on the phone one month after the procedure.

The data was analyzed using Chi-square and ANOVA by SPSS software version 16.

### **Statistical analysis**

The morphological data of histology findings, including blood clots, intima, muscle, and atherosclerosis, as qualitative variables were described with Yes/No based on their presence or absence, respectively. The death of the patients was determined by calling their families on the phone. Data was analyzed by one-way ANOVA using SPSS software version 16, and the p-value < 0.05 was regarded as significant.

### **Results**

The mean age of patients was  $46.2 \pm 13.09$ , comprised of 43.1% women and 56.9% men. The mortality rate was 18 out of 65 or 27.3%.

Based on the data presented in Table 1, it was observed that 89.2% of the 58 individuals had intima present in their samples. In addition, 86.2% of the patients' specimens contained blood clots, as seen in 56 individuals. The presence of muscle was observed in 67.7% of the samples, accounting for 44 cases. Furthermore, atherosclerosis was present in 27.7% of the specimens, observed in 18 individuals.

Figure 1 indicates the histopathological characteristics of patients as well as their gender and mortality rate. Table 2 revealed that blood clots, intima, and atherosclerosis rate of presence did not have a meaningful relationship with mortality. However, media presence in the endarterectomy specimens had a meaningful relationship with mortality ( $P<0.01$ ). Therefore, the presence of media in the histopathologic evaluation of endarterectomy samples from CTEPH patients was associated with an increased mortality risk in these individuals.

## **Discussion**

Newer translational and pathological studies have enhanced our understanding of CTEPH. However, only a few studies have compared histopathological findings from pulmonary endarterectomy of CTEPH patients with their prognosis after the procedure. It is worth noting that there is a lack of information concerning the mortality rate and pathologic findings in CTEPH patients undergoing endarterectomy in Middle Eastern countries, particularly Iran. To address this issue, this study has been designed to investigate the relationship between the mortality rate and pathologic findings in CTEPH patients who underwent endarterectomy at Masih Daneshvari Hospital in Tehran, Iran. The results of this study will provide valuable insights into the outcomes of this procedure in this particular patient population.

Our research evaluated 65 patients (28 males and 37 females) over ten years (2008-2018). The mean age of patients was  $46.26\pm 13.09$ . In the histopathologic evaluation of samples after endarterectomy, the number of samples that included blood clot, intima, media and evidence of atherosclerosis were 56 (86.2%), 58 (89%), 44 (67.7%), and 18 (27%), respectively. Surprisingly, patients with media in the pathologic assessment of their endarterectomy samples had the most significant mortality rate ( $p<0.001$ ). On the other hand, no significant relationship was seen between the presence of atherosclerosis, thrombosis, or intima in the samples and the mortality rate ( $P>0.05$ ).

According to international CTEPH registry records on 386 patients who underwent PEA, the hospitals with the annual number of 1-10, 11-50, and  $>50$  PEAs being performed documented in-hospital mortality rates of 8.8%, 4.5%, and 3.4%, respectively(15). In another study from the UCSD, the in-hospital mortality rate for the more recent 500 cases

of PEA was documented to be 2.2% compared with the earlier 1000 cases rate of 5.2%, indicating the importance of institutional experience increase(16).

In our center, the endarterectomy procedure for CTEPH patients had just become operational a few years ago, and the mortality rate was 27.7%, which is higher than the previous studies.

Blauwet et al. studied 54 patients with the bilateral distribution of disease who had undergone PEA. In almost all cases, organized or organizing thrombi were seen in conjunction with fresh red thrombi. The intima was composed of myofibroblast cells as well as collagen and the extracellular matrix containing collagen (100%), elastin (67%), hemosiderin (56%), atherosclerosis (32%), or calcification (15%). All specimens contained partial-thickness portions of media, and only one specimen contained a small amount of adventitia (17). A second study by Bernard et al. on 200 consecutive PEAs revealed similar findings regarding the distribution of lesions and noted a predominance of organizing or organized thrombi compared to fresh fibrinous clots (99.2% vs. 0.8%) (18).

The findings of our study regarding the presence rate of intima (89.2%), atherosclerosis (27.7%), and thrombotic lesion (86.2%) were very close to the research mentioned above. The only exception was the proportion of media in our samples, which was considerably lower than in the previous studies.

This study found that the presence of media in endarterectomy samples of CTEPH patients is associated with a higher mortality rate. This is likely the reason for the high mortality rate observed in CTEPH patients who underwent endarterectomy in surgical centers with less experience and fewer similar surgeries compared to the global statistics. However, a closer look at the histopathologic findings reveals the lower rate of presence of media (muscle) in our study compared with others.

Furthermore, although resection of media should logically lead to a decrease in vascular resistance and improvement of patients' conditions, it seems an inappropriate deep resection of the media could result in interstitial edema, respiratory distress syndrome, and a high mortality rate by increasing the permeability of vessels. In other words, proper

detection and resection of the superficial layer of media can significantly decline mortality and morbidity rates.

### **Conclusion**

The mortality rate of CTEPH in our center was higher than that of the more experienced centers (19, 20). Furthermore, detecting muscle in the endarterectomy samples of patients with CTEPH was associated with an increased mortality risk. It seems that a thinner layer of tissue should be excised during the surgery of these patients.

A larger sample size and a longer patient follow-up are recommended.

### **Ethics declaration**

#### Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Ethics approval and informed consent

All patients participating in this study provided written informed consent, and the study was approved by the ethical committees of participating centers.

#### Statement of Human and Animal Rights

The study was performed in accordance with the declaration of Helsinki and the ethical standards of the institutional and national research committee.

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### **Authors' contribution**

Najmeh Assadinia was responsible for the study concept and design. All authors intercepted the data, drafted the manuscript, approved the final manuscript, and agreed to be accountable for all aspects of the work.

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Table 1: Frequency of presence of blood clot, intima, muscle, and atherosclerosis in the endarterectomy samples

	Frequency	percent
<u>Blood clot</u>		
Yes	56	86.2
no	9	13.8
<u>Intima</u>		
Yes	58	89.2
no	7	10.8
<u>Muscle</u>		
Yes	44	67.7
No	21	32.3
<u>Atherosclerosis</u>		
Yes	18	27.7
no	47	72.3

Table2: Association of variables of CTEPH patients with mortality

	Alive	Death	p-value
<u>Sex</u>			
Female	20	8	0.893
Male	27	10	
<u>Blood clot</u>			
Yes	42	14	0.233

No	5	4	
<u>Intima</u>			
Yes	41	17	0.409
No	6	1	
<u>Muscle</u>			
Yes	27	17	0.004
No	20	1	
<u>Atherosclerosis</u>			
Yes	13	5	0.993
No	34	13	

Figure 1 Histopathological characteristics, gender, and mortality rate of patients

