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1 **Impact of cancer on the prevalence, management, and outcome of patients with chronic thromboembolic**
2 **pulmonary hypertension**

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22

23 **Abstract**

24 **Introduction**

25 Chronic thromboembolic pulmonary hypertension (CTEPH) results from unresolved thrombotic obstruction of
26 the pulmonary vasculature. Cancer is a known risk factor for CTEPH. This study aimed to determine the impact of
27 cancer on the prevalence, management, and outcomes of patients with CTEPH.

28 **Materials and methods**

29 In this retrospective study involving 99 patients sequentially diagnosed with CTEPH in our hospital, the
30 prevalence of 10 comorbid conditions including a past history of cancer at the time of CTEPH diagnosis were
31 calculated.

32 **Results**

33 Among the 99 patients, 17 (17%) had a history of cancer. Breast cancer (n=6) was the most common cancer type,
34 followed by gastrointestinal cancer (n=3), uterine cancer (n=2), and malignant lymphoma (n=2). Between patients
35 with and without cancer, there were no differences in the demographics, severity of CTEPH, and management;
36 however, the 5-year survival rate was lower for patients with cancer (65%) than for those without (89%). In addition,
37 patients with cancer had significantly worse survival than those without (p=0.03 by log-rank test). During follow-
38 up, nine patients developed cancer after the diagnosis of CTEPH. Among the 99 patients, 13 died during follow-up,
39 6 (46%) of whom died of cancer.

40 **Conclusions**

41 Seventeen percent of our patients with CETPH were diagnosed with cancer, with breast and gastrointestinal tract
42 cancers being the most common. Cancer comorbidity was associated with a poor prognosis and contributed to death
43 in 46% of deceased patients. The impact of cancer on CTEPH should be further evaluated in the future.

44

45 **Keywords:** Survival, Cause of death, Breast cancer, Gastrointestinal tract

46

47 **Key points**

- 48 • In the CTEPH cohort, 17% had a history of cancer, with breast and gastrointestinal tract cancers being the
49 most common.
- 50 • Of the 99 patients, 9 (9%) developed cancer after CTEPH diagnosis, indicating the need for careful cancer
51 surveillance in patients with CTEPH during follow-up.
- 52 • Cancer comorbidity was associated with a poor prognosis and contributed to death in 43% of deceased
53 patients.
- 54 • Future studies should evaluate the impact of cancer on CTEPH.

55

56 INTRODUCTION

57 Chronic thromboembolic pulmonary hypertension (CTEPH) is a condition wherein organic thrombi
58 formation in pulmonary arteries causes pulmonary hypertension [1]. The survival rate of patients with a mean
59 pulmonary artery pressure of >30 mmHg is poor [2]; however, recently, the management of CTEPH has
60 substantially progressed, and the prognosis is notably improving [3]. Therefore, proper management of
61 comorbidities will likely become more important to further improve the prognosis of patients with CTEPH.

62 CTEPH is known to be associated with various comorbid conditions, including a history of acute pulmonary
63 thromboembolism, deep vein thrombosis (DVT), and prothrombotic disorders such as protein C or S deficiency [4].
64 A history of cancer is also considered an important risk [4-6], with multicenter studies of CTEPH reporting a
65 frequency of 5–15% for a history of cancer [5, 7-10]. In addition, a European study reported that a history of cancer
66 increases the risk of developing CTEPH by approximately fivefold [5]. However, epidemiological data on cancer
67 vary widely by region and race, and studies focusing on cancer as a risk factor for CTEPH are scarce.

68 The most common cause of death in patients with CTEPH is right-sided heart failure [11, 12]. However,
69 recent advances in the treatment of CTEPH are likely to reduce deaths due to right-sided heart failure in the future.
70 Cancer is the second most common cause of death [11, 12], and a recent report documented that cancer was at least
71 partially responsible for death in 60% of CTEPH-related mortalities [13]. These findings suggest the importance of
72 early diagnosis and appropriate management of cancer to further improve the survival of patients with CTEPH.

73 This study aimed to analyze detailed information on cancer in patients with CTEPH and determine the
74 impact of cancer on the demographics, management, and outcome of these patients.

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76

77 MATERIAL AND METHODS

78 This retrospective observational study analyzed the electronic medical records of consecutive patients
79 diagnosed with CTEPH at the Hokkaido University Hospital between 2001 and 2023. This study was approved by
80 the Institutional Review Board of the Hokkaido University Hospital (016-0461), and informed consent was waived
81 owing to the retrospective nature of the study.

82 CTEPH was diagnosed using dedicated examinations based on the guidelines at that time [14, 15]. For
83 example, the diagnostic criteria for CTEPH included mean pulmonary arterial pressure of ≥ 25 mmHg, pulmonary
84 arterial wedge pressure of ≤ 15 mmHg during right heart catheterization, and ventilation-perfusion mismatch by
85 nuclear examination. We excluded those who were diagnosed with CTEPH where the exact results of the diagnostic
86 right heart catheterization were unclear. The following 10 comorbid conditions at the time of CTEPH diagnosis
87 were investigated: (1) history of venous thromboembolism (VTE), including DVT and acute pulmonary embolism;
88 2) use of intravenous devices such as inferior vena cava filters and pacemakers; 3) history of cancer; 4) use of
89 antipsychotic medications or antidepressants; 5) prothrombotic diseases such as protein C/S or antithrombin
90 deficiency and antiphospholipid antibody syndrome; 6) hypothyroidism; 7) use of steroids; 8) varicose veins; 9) use
91 of oral contraceptives/female hormone replacement; and 10) inflammatory bowel disease (ulcerative colitis or
92 Crohn's disease). These 10 factors are derived from the comorbid conditions surveyed in the nationwide registry of
93 Japan on CTEPH [16]. Among these, however, some were deleted when the validity was considered low based on
94 the results of multicenter registries on CTEPH [4, 5]. Regarding cancer, we investigated the organ of origin and

date of diagnosis and compared the clinical pictures including demographics, management, and survival between patients with and without a history of cancer. We also investigated the development of cancer after the diagnosis of CTEPH and the cause of death in patients who died during follow-up using the method described by Tonelli et al. [16].

Statistical analysis

The data are presented as median [25th and 75th percentiles]. The prevalence of the 10 comorbid conditions at the time of CTEPH diagnosis were calculated. The rates of history of cancer and the primary organ were investigated separately for men and women. Clinical data were compared between those with and without a history of cancer using the χ^2 test or Wilcoxon test. The 5-year survival rate was calculated separately in patients with and without a history of cancer, and the survival was compared between the two groups using Kaplan–Meier curves and log-rank test, and with a Cox proportional hazard model (univariate, and age- and sex-adjusted comparisons).

RESULTS

There were 100 patients diagnosed with CTEPH during the analysis period; the detailed data on CTEPH were missing in 1 patient; thus, the data of 99 patients were analyzed in this study.

Table 1 shows the characteristics of the study participant. Among the 99 patients, 37 (37%) were men, and the median age was 63 years (57 years for men and 67 years for women). The median mean pulmonary arterial pressure was 41 mmHg and the median pulmonary vascular resistance was 8.8 Wood units.

Among the 10 comorbid conditions, the prevalence was highest for a history of VTE (46%), followed by use of intravenous devices (31%), history of cancer (17%), use of antipsychotic medications or antidepressants (16%), prothrombotic diseases (8%), hypothyroidism (7%), use of steroids (6%), varicose veins (6%), use of oral contraceptives/female hormone replacement (0%), and inflammatory bowel disease (0%). In the 17 patients with a history of cancer, the prevalence of a history of cancer was 16.2% in men and 17.7% in women. In the six men with a history of cancer, the most common primary organ affected was the stomach (n=2), followed by the esophagus, thyroid gland, bladder, and lymphatic system (malignant lymphoma) with one case each. In contrast, among the 11 women, the primary organ affected was the breast (n=6), followed by the uterus, ovary, kidney, and lymph system with one case each. The time from the diagnosis of cancer to the diagnosis of CTEPH was 6.1 [2.6, 9.0] years, and four patients (24%) were diagnosed with cancer within 1 year before the diagnosis of CTEPH.

Table 1: Characteristics of the study participants

	Entire cohort	Patients with a history of cancer	Patients without a history of cancer	P value (patients with vs. without a history of cancer)
N	99	17	82	
Age	63 [54, 70]	61 [57, 69]	63 [54, 71]	0.738
Men/women	37/62	6/11	31/51	0.846

Smoking history	41/46/8/4	5/11/1/0	36/35/7/4	0.371
(never/past/current/unknown)				
Pack year	2.5 [0, 31]	13.5 [0, 40.5]	0.2 [0, 22.5]	0.078
History of alcohol consumption	30/67/2	6/11/0	24/56/2	0.737
(yes/no/unknown)				
WHO functional class (I/II/III/IV)	2/30/57/10	1/4/10/2	1/26/47/8	0.596
Right heart catheterization				
Mean pulmonary arterial pressure (mmHg)	41 [33, 47]	40 [36, 51]	41 [33, 47]	0.603
Cardiac output (L/min)	3.8 [3.0, 4.4]	3.3 [2.9, 4.8]	3.9 [3.1, 4.4]	0.379
Pulmonary vascular resistance (Wood units)	8.8 [6.3, 11.2]	8.4 [6.9, 12.6]	8.8 [6.1, 11.2]	0.344
Treatment for CTEPH				
Use of pulmonary vasodilator, n (%)	88 (89%)	15 (88%)	73 (89%)	0.925
Balloon pulmonary angioplasty, n (%)	37 (37%)	7 (41%)	30 (37%)	0.722
Pulmonary endarterectomy, n (%)	24 (24%)	4 (24%)	20 (24%)	0.940
Number of patients who died during follow up	13 (13%)	4 (24%)	9 (11%)	0.229
Main cause of death				
Right heart failure	2	0	2	
Cancer	6	4	2	
COVID 19	1	0	1	
Others or multiple factors	4	0	4	

WHO World Health Organization, CTEPH chronic thromboembolic pulmonary hypertension

Figure 1 shows the survival curves of patients with CTEPH, with or without a history of cancer. The 5-year survival rates were 65% for patients with a history of cancer and 90% for those without, and there was a significant difference between the two groups ($p=0.03$, log-rank test). In the Cox proportional hazard model, the difference in the survival between those with and without a history of cancer did not reach a statistical significance (univariate analysis, $p=0.123$; age- and sex-adjusted analysis, $p=0.308$).

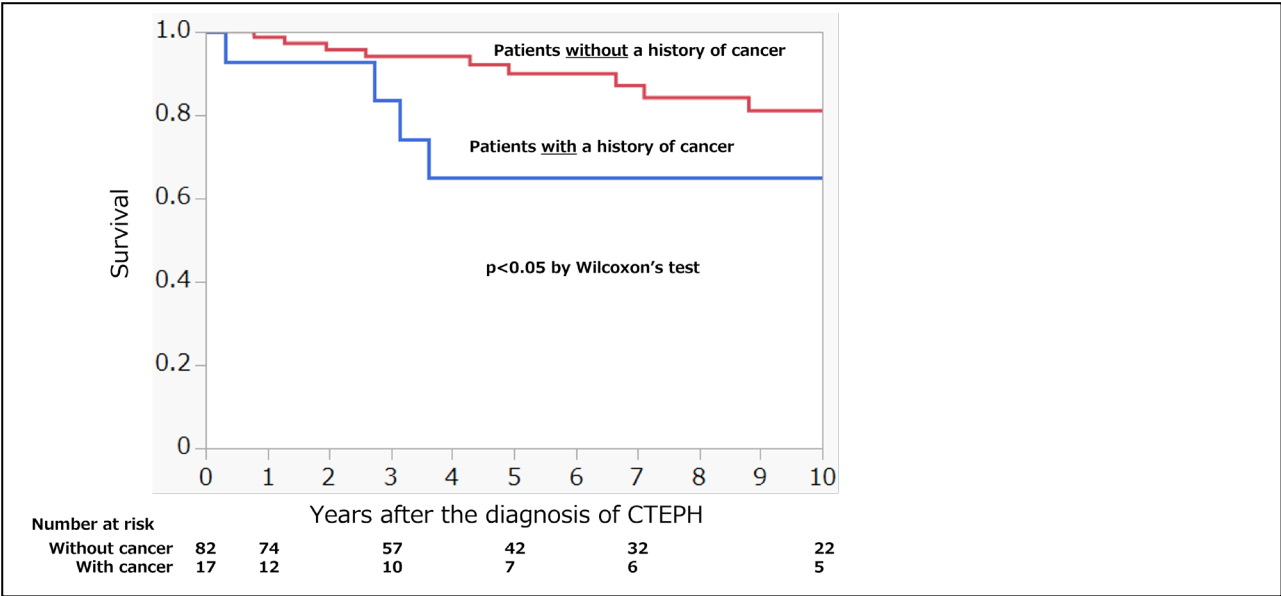


Fig. 1 Kaplan–Meier curves of patients with CTEPH with or without a history of cancer. Five-year survival was 65% for those with a history of cancer and 90% for those without a history of cancer. The difference in survival between patients with CTEPH with or without a history of cancer was statistically significant as revealed by Wilcoxon’s test ($p=0.03$)

During follow-up after the diagnosis of CTEPH, 9 patients (5 men and 4 women) developed cancer. Three of the nine cases had already been diagnosed with cancer at the time of CTEPH diagnosis; that is, these patients had a second primary cancer. The time from CTEPH diagnosis to cancer diagnosis was 56 [4.5, 111] months, and 3 of the 9 patients were diagnosed with cancer within 1 year of CTEPH diagnosis.

During a median observation period of 4.7 years, 13 of the 99 patients died. Analysis of the cause of death showed that right heart failure mainly contributed to death in two, cancer mainly contributed to death in six, and other or multiple factors contributed to death in five patients. Of the six cancer deaths, four had a cancer diagnosis prior to the CTEPH diagnosis, and two had a cancer diagnosis after the diagnosis of CTEPH.

DISCUSSION

This study retrospectively investigated detailed information related to cancer in 99 patients with CTEPH. The main findings of our study revealed that the prevalence of a history of cancer was 17% in our population and that the most common primary site was the breast (35%), followed by the gastrointestinal tract (24%). Patients with and without a history of cancer had similar demographics and were managed similarly; however, the survival of patients with cancer was significantly worse than that of patients without cancer. The present study focused on the prevalence/incidence of cancer and their clinical impact in CTEPH. Notably, the clinical relevance of cancer will become increasingly important as the management and outcomes of patients with CTEPH improve.

In previous studies investigating the demographics of patients with CTEPH, the prevalence of cancer was reported to be 5–15%. The results of the present study were consistent with these data; that is, a certain subset of patients with CTEPH had a history of cancer. Notably, a previous study reported that the prevalence of a history of cancer was approximately fourfold higher than that of pulmonary arterial hypertension [5], indicating a possible

link between preceding cancer and CTEPH. Notably, however, various factors such as age, sex, and ethnicity significantly impact the epidemiological data of cancer. In this regard, few multicenter studies on the prevalence of cancer in CTEPH have been reported in Asian countries. In addition, the methods of investigation were not standardized across studies. Thus, larger studies including variable ethnicities with standardized methodologies are warranted to accurately investigate the relationship between preceding cancer and CTEPH.

In Japan, the “cumulative risk of cancer” has been reported based on the results of a nationwide survey. This index indicates the percentage of Japanese people of a certain age who will develop cancer [17]. Using this data sheet where the estimated cumulative cancer risk at certain ages is provided, we first identified the estimated cumulated risk of cancer in each of the 99 participants and then calculated the mean values separately in men and in women, which were 4.4 [2.6, 7.7] and 15.4 [8.5, 25.2], respectively. Compared to these, the currently reported incidence of 16.2% in men and 17.7% in women were both high, especially in men. This suggests that the presence of cancer may be associated with an increased incidence of CTEPH particularly in men. However, it should be noted that the sample size of the present study is remarkably small and the comparison of cancer prevalence in our cohort with the national database needs to be done with great caution. In addition, the “cumulative risk” has a different meaning from the actual rate of prior cancer, and the numbers cannot be directly comparable. Whether a history of cancer is truly a risk factor for CTEPH development needs to be verified by prospective long-term studies with a relevant control group.

Regarding the cancer types in CTEPH, in a multicenter study in Europe, breast cancer was the most common at 23%, followed by cancer of the digestive tract 17% [5]. These results are consistent with the results of the present study, which reported an incidence rate of 35% and 18% for breast and gastrointestinal tract cancers, respectively. However, the sample size of the present study was remarkably small. Consequently, further studies are needed to examine the possible association between specific cancer types and the risk of CTEPH.

In the survival analysis, the 5-year survival rate of patients with CTEPH was 65% in the subset with a history of cancer, which was significantly lower than that of patients without a history of cancer (90%), as determined by the Log-rank test. A recently published study reported a 5-year survival rate of 92% among Japanese patients with CTEPH [18]. Compared to this rate, the prognosis of patients with a history of cancer is considered poor. There were no differences in background factors or hemodynamic indices between the two groups with or without a history of cancer in the present study, suggesting that the cancer itself contributed to poor prognosis. In fact, 4 of 17 patients with a history of cancer died during the course of the study, and all deaths were attributed to cancer. The impact of cancer on the survival of patients with CTEPH should be further investigated in future studies.

Several reports have addressed the development of cancer after the diagnosis of CTEPH, and Bravos et al. [19] reported that 7 (10.9%) of 64 patients with CTEPH developed cancer after the diagnosis of pulmonary hypertension. In the present study, 8 of the 99 patients (8%) developed cancer after CTEPH diagnosis, a value similar to that reported by Bravos et al. In addition, Sørensen et al. reported that CTEPH increased the risk of developing cancer by 1.4-fold [20]. These findings suggest that CTEPH practitioners should always consider the possibility of cancer complications during follow-up.

The most common cause of death in CTEPH is right heart failure, with a rate of approximately 60% [11, 12]. Cancer is the second most common cause of death after right-sided heart failure, as reported by Gall et al. [11] (9%) and Barco et al. [12] (7%). In the present study, 13 of the 99 patients died. Among the 13 deceased patients, 6

201 (46%) died of cancer, a higher number than in previous reports. This difference may be due to recent advances in
202 the treatment of CTEPH. In particular, recent advances in medical therapy and balloon pulmonary angioplasty may
203 have decreased the rate of death from right heart failure and increased the rate of death from other causes, including
204 cancer. It is assumed that early diagnosis and appropriate treatment of cancer will become even more important to
205 improve the prognosis of patients with CTEPH in the future.

206 This study has several limitations. First, it was based on a small number of cases. A total of 99 cases were
207 not sufficient for a detailed epidemiological analysis. The statistical power was insufficient, especially for
208 comparisons between men and women, those with and without a history of cancer, and on survival and the cause of
209 death. Second, it was conducted at a single institution. The epidemiology of cancer is strongly influenced by country,
210 race, geographic region, and exposure to risk. Therefore, there are various problems in generalizing the results of
211 single-center analyses. Third, the study design was retrospective. Therefore, the results of the investigation of the
212 prevalence of cancer and the cause of death might have been biased. Fourth, the 10 comorbid conditions analyzed
213 in the present study were not established independent risks for CTEPH. Fifth, the mutational status was not analyzed
214 in this study and, thus, its possible contributions to the development of cancer and CTEPH were not investigated.

215 In conclusion, this unique retrospective observational study focused on the impact of cancer in patients
216 with CTEPH. The analysis showed that approximately one in six patients with CTEPH had a history of cancer and
217 that gastrointestinal and breast cancers were more common in men and women, respectively. The prognosis of
218 patients with CTEPH with a history of cancer was poor, and cancer was the cause of death in nearly half of the
219 patients with CTEPH. With further advances in CTEPH treatment, the importance of cancer complications in
220 CTEPH is expected to increase; thus, both basic and clinical studies should clarify the etiologic relationship between
221 CTEPH and cancer, as well as clinical considerations, which are expected to improve the outcomes in patients with
222 CTEPH.

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224

225 **Author contributions**

226 • Conceptualization: JN, IT, TS; Methodology: JN, IT, TS; Formal analysis and investigation: JN, HS, TN, AS, TW,
227 HO, IY; Writing - original draft preparation: JN; Writing - review and editing: IT, MS, SK; Funding acquisition:
228 NA; Resources: NA; Supervision: SK

229

230 **Declarations**

231 **Conflict of interest**

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235

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239

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