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Elevated neutrophil-to-lymphocyte ratio is associated with poor outcomes in patients with chronic thromboembolic pulmonary hypertension

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Abstract:

BACKGROUND AND AIM: Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by pulmonary artery obstruction due to persistent organized thrombus and remodeling of pulmonary vascular structures. The treatment of CTEPH is considered a multimodal approach, including pulmonary endarterectomy (PEA) surgery, balloon pulmonary angioplasty, and medical therapy. We aimed to report our 12-year experience with CTEPH patients and identify risk factors for mortality in a real-life setting.

METHODS: Patients older than 18 years, evaluated by a multidisciplinary expert team between July 1, 2011 and July 1, 2023, and diagnosed with CTEPH, were included in the study.

RESULTS: The study population comprised 32 CTEPH patients with a mean age of 61.0±13.8 years and a median follow-up duration of 28 months. At the end of the follow-up period, 13 (40.6%) patients had died. A high neutrophil-to-lymphocyte ratio (NLR) and elevated B-type natriuretic peptide (BNP) levels at the time of diagnosis, along with low BNP levels and pulmonary artery pressure (PAP) changes within the first year, were observed in patients with mortality. Survival analysis, including NLR, BNP, pulmonary endarterectomy, and hematocrit (Hct) demonstrated that a high NLR and the absence of surgical treatment were independently associated with mortality.

CONCLUSIONS: Our study underscores the critical role of PEA surgery in treatment of CTEPH, in addition to the importance of BNP trajectories and the neutrophil-to-lymphocyte ratio as prognostic biomarkers. Further research is needed to evaluate the reliability of easily obtained measurements, such as NLR, in categorizing high-risk patients.

Keywords:

B-type natriuretic peptide (BNP), chronic thromboembolic pulmonary hypertension, mortality, neutrophil-to-lymphocyte ratio

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by pulmonary artery obstruction, persistent organized thrombus, and remodeling of pulmonary vascular structures.[1] According to the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines, CTEPH is defined as a mean pulmonary arterial pressure (mPAP) >20 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 WU, combined with evidence of chronic thromboembolism in pulmonary arteries.[2]

The treatment of CTEPH involves a multimodal approach including pulmonary endarterectomy (PEA) surgery, balloon pulmonary angioplasty (BPA), and medical therapy.[1,2] Despite advances in diagnostic and therapeutic options, there unanswered questions remain regarding long-term follow-up and risk factors associated with worse outcomes.[1] Both PEA surgery and BPA have been shown to improve quality of life and survival. High serum levels of B-type natriuretic peptide (BNP) are also associated with poor outcomes. However, the prognostic value of other laboratory measurements and echocardiographic assessments are still under investigation. Factors such as right ventricular strain and remodeling,[3,4] as well as the severity of tricuspid valve regurgitation,[5] are potential imagining indicators, while endothelial progenitor cells[6] represent possible laboratory measurements related to prognosis. However, these novel prognostic factors require advanced techniques, such as magnetic resonance imaging, 2D-speckle tracking echocardiography, or flow cytometry. In contrast, the neutrophil-to-lymphocyte ratio (NLR) is an easily obtainable parameter that reflects heightened inflammation or depressed adaptive immunity. NLR can be used to evaluate the balance between inflammation and systemic endothelial dysfunction.[7,8] NLR is associated with adverse outcomes in cardiovascular diseases and chronic obstructive lung disease,[9,10] and it is suggested to be related to CTEPH surgery outcomes.[11]

We aimed to share our 12-year experience with CTEPH patients and identify risk factors for mortality in a real-life setting.

Materials and Methods

Patients and standard care

Patients aged 18 years or older, evaluated by a multidisciplinary expert team between July 1, 2011 and July 1, 2023, and diagnosed with CTEPH, were included in this study. Diagnosis and treatment decisions for all patients were made based on the current ESC/ERS Guidelines.[2] Symptomatic patients with ongoing mismatched perfusion defects or chronic, organized, fibrotic clots on computed tomography (CT) after at least three months of anticoagulation therapy were evaluated. In summary, patients suspected of having CTEPH underwent transthoracic echocardiography (TTE), pulmonary angiography CT, and ventilation/perfusion (V/Q) scintigraphy. The diagnosis was confirmed via right heart catheterization (RHC) and catheter-based pulmonary angiography. A history of previous pulmonary embolism was defined as known and treated acute pulmonary embolism prior to diagnosis.

Echocardiography was performed in accordance with international guidelines[12] using a General Electric Vivid T8 echo device (General Electric Company, Boston, MA, USA). Patients were positioned supine with a left lateral rotation. Measurements included tricuspid annular plane systolic excursion (TAPSE), maximum tricuspid regurgitation velocity (TRV), derived systolic pulmonary artery pressure (sPAP), inferior vena cava dimensions, and inspiratory collapsibility to estimate right atrial pressure (RAP) and left ventricular (LV) ejection fraction (EF). The estimated pulmonary vascular resistance (PVR) was calculated using the formula (TRVmax/RVOT TVI)10+0.16.[12–14]

Right heart catheterization was performed through the right femoral vein using a multipurpose pulmonary artery catheter under local anesthesia. Hemodynamic parameters measured included right atrial pressure, right ventricular pressure, sPAP, diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP), cardiac output (calculated using Fick's method), oxygen saturations (including vena cava, right atrium, right ventricle, pulmonary artery, and mixed venous oxygen saturation [SvO2]), and cardiac index (CI).[15,16] The Fick method was applied for the measurement of cardiac output, using the formula CO=VO2/Cao2−CVo2, where Cao2 is arterial oxygen content and CVo_2 is mixed venous blood content.[17,18] PVR was calculated using Ohm's law: PVR=MPAP−LAP or PCWP/Qp.[19]

The results were presented to a multidisciplinary expert team consisting of specialists in cardiology, thoracic surgery, cardiovascular surgery, pulmonology, rheuma-

tology, and radiology. Treatment decisions were tailored individually for each patient. Pulmonary endarterectomy was performed by an experienced thoracic and cardiovascular surgery team. Balloon pulmonary angioplasty was not available at the study center. Medical treatment primarily consisted of lifelong anticoagulation with a vitamin K antagonist and, since 2015, riociguat, a guanylate cyclase stimulator. Treatment response was evaluated every 3 to 6 months, and any necessary adjustments were decided by the multidisciplinary expert team.

Study design and outcome measures

This study was designed as a retrospective observational study. Demographic and clinical data were obtained from the hospital's clinical database. Laboratory measurements were recorded prior to right heart catheterization. The follow-up period was defined as the time between the CTEPH diagnosis and the last recorded control in outpatient or inpatient clinics. Follow-up protocols included repeated TTE, 6-minute walking tests, serum BNP levels, and routine blood measurements. Mortality was recorded as all-cause mortality based on hospital database records and national health records.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics 26.0) (IBM Corp., Armonk, NY, USA). Means and standard deviations were reported for normally distributed continuous data, while medians and interquartile ranges (IQR) were used for non-normally distributed continuous data. Differences in means and medians between two groups in independent samples were analyzed using the Student's t-test and the Mann-Whitney U test, respectively. Categorical variables were compared using the chi-square test. Univariate analysis of risk factors for mortality was conducted, and parameters with a p-value less than 0.30 were included in the multivariate analysis. The Cox regression model was applied to identify independent predictors of mortality. Kaplan-Meier curves were used to illustrate survival differences between surgical intervention groups. Values of $p<0.05$ were considered statistically significant. Artificial intelligence-assisted technologies were not used in this study or during the manuscript preparation.

The study was conducted in accordance with the Declaration of Helsinki. Uludağ University Faculty of Medicine Clinical Research Ethics Committee approved the study protocol (Approval Number 2022-11/4, Date: 25.05.2022). Due to the retrospective design of the study, patient consent was not obtained.

Table 1: Clinical characteristics of the study population (n=32)

	n	%
Age	61.0±13.8	
Male gender	13	40.6
Comorbidities	27	84.4
Hypertension	15	46.9
Airway disease	13	40.6
Diabetes	8	25.0
Smoking status, ever smoker	13	40.6
Pulmonary embolism history	29	90.6
Echocardiography upon diagnosis		
EF (%)	57.3±9.5	
PAP (mmHg)	80.0 (46.5–107.5)	
TAPSE (mm)	16.1±5.2	
PVR (WU)	2.97±0.90	
Right heart catheterization (n=26)		
mPAP (mmHg)	41.6±12.0	
PVR (WU)	5.5 (3.3–9.3)	
PCWP (mmHg)	12.7±3.5	
CO (L/dk)	4.7±1.5	
CI (L/dk/m^2)	2.6±0.8	
Qp/Qs	1.0 (0.8–1.0)	
6-minute walking distance (meters)	289.6±95.7	
BNP at time of diagnosis (pg/mL)	196.0 (80.0–443.0)	
Creatinine (mg/dL)	0.98 (0.80–1.17)	
Hct	39.3±8.0	
RDW	17.4±3.86	
NLR	2.42 (1.50–4.02)	
Pulmonary endarterectomy surgery performed	11	34.4
Follow-up duration (months)	28.0 (7.0–82.0)	
All-cause mortality	13	40.6

EF: Ejection fraction, PAP: Pulmonary arterial pressure, TAPSE: Tricuspid annular plane systolic excursion, PVR: Pulmonary vascular resistance, mPAP: Mean pulmonary arterial pressure, PCWP: Pulmonary capillary wedge pressure, CO: Cardiac output, CI: Cardiac index, BNP: Brain natriuretic peptide, Hct: Hematocrit, NLR: Neutrophil-to-lymphocyte ratio

Results

The study population included 32 patients with CTEPH, with a mean age of 61.0±13.8 years and a median follow-up duration of 28 months. Within the cohort, 29 (90.6%) patients had a prior history of pulmonary embolism, and the median time between pulmonary embolism diagnosis and CTEPH diagnosis was 5.5 months. Thoracic computed tomography revealed mosaic attenuation in 16 (50.0%) cases, partial obstruction of pulmonary arteries in 12 (37.5%) cases, and pericardial effusion in 2 (6.3%) patients. Clinical characteristics and laboratory parameters at the time of diagnosis are presented in Table 1.

Table 2: Comparison between mortality groups

	Alive (n=19)		Exitus (n=13)		p
	n	%	n	%	
Age (years)	58.8±14.5		64.2±12.8		0.28
Male gender	7	36.8	6	26.0	0.72
Any comorbidity	15	78.9	12	92.3	0.62
Hypertension	6	31.5	9	69.2	0.07
Echocardiography					
PAP upon diagnosis, (mmHg)	80.0 (49.0–109.0)		83.5 (46.2–106.5)		0.77
PAP at 1st year (mmHg)	48.0 (40.0–98.0)		70.0 (48.0–90.2)		0.51
PAP change at 1st year (%)	25.9 (14.2–60.0)		-14.0 (-18.9–12.2)		0.14
Right heart catheterization (n=26)					
mPAP (mmHg)	42.2±13.1		39.7±10.8		0.79
PVR (WU)	5.7 (3.6–13.0)		4.5 (3.1–6.0)		0.31
PCWP (mmHg)	11.9±2.9		13.9±4.1		0.17
CO (L/dk)	4.8±1.3		4.7±1.9		0.89
CI (L/dk/m^2)	2.64±0.76		2.65±0.96		0.97
6-minute walking distance (meters)	315.4±101.9		244.5±74.1		0.22
BNP at time of diagnosis (pg/mL)	90.0 (40.0–290.0)		458.5 (115.5–1454.7)		**0.01**
BNP change at 1 year[a] (%)	-26.4 (-78.2–1.78)		75.8 (3.6–271.0)		0.07
Hct	41.5±8.0		36.1±7.2		0.059
NLR	1.81 (1.20–3.07)		3.26 (2.11–5.22)		**0.03**
Pulmonary endarterectomy surgery performed	8	42.1	3	23.0	0.27
Hospitalization during follow-up, median (IQR 25–75)	4.0 (1.5–9.5)		4.0 (1.0–9.0)		0.97

[a]: n=12 for BNP measurement at one year. PAP: Pulmonary arterial pressure, mPAP: Mean pulmonary arterial pressure, PVR: Pulmonary vascular resistance, PCWP: Pulmonary capillary wedge pressure, CO: Cardiac output, CI: Cardiac index, BNP: Brain natriuretic peptide, Hct: Hematocrit, NLR: Neutrophil-to-lymphocyte ratio, IQR: Interquartile ranges

Table 3: Risk factors related to mortality

	Univariate analysis			Multivariate Cox regression analysis		
	HR	95% CI	p	HR	95% CI	p
PAP upon diagnosis (via echocardiography)	0.99	0.97–1.10	0.45	–	–	–
mPAP (mmHg)	0.98	0.92–1.05	0.74	–	–	–
BNP at time of diagnosis (pg/mL)	1.00	0.99–1.00	0.08	1.00	0.99–1.00	0.47
NLR (%)	1.20	0.86–1.68	0.27	1.22	1.04–1.43	0.01
Hct	0.85	0.75–0.96	0.01	0.94	0.97–1.02	0.16
Receiving only medical treatment	4.57	0.90–23.1	0.06	9.80	1.16–82.6	0.03

HR: Hazard ratio, CI: Confidence interval, PAP: Pulmonary arterial pressure, mPAP: Mean pulmonary arterial pressure, BNP: Brain natriuretic peptide, NLR: Neutrophil-to-lymphocyte ratio, Hct: Hematocrit

During follow-up, 11 (34.3%) patients underwent pulmonary endarterectomy surgery at a median of 7.0 months [2.0–14.0] after diagnosis. Postoperative pulmonary artery pressure (PAP), measured via transthoracic echocardiography, was significantly reduced compared to preoperative values (105.4±30.4 vs. 58.2±22.2, p=0.01). Among the patients who underwent surgery, 3 out of 11 (27.3%) died, and the total follow-up duration was 74.0 [42.0–91.0] months.

Across all participants, at the 6-month follow-up, 18 (56.3%) patients continued with the same treatment regimen initiated at diagnosis. By the first-year follow-up, 22 (68.8%) patients remained on the same treatment. However, by the second year, 8 (25%) patients were lost to follow-up, and their treatment status could not be determined. By the end of the follow-up period, 13 patients had died. Clinical and laboratory parameters were compared based on mortality status (Table 2). A high neutrophil-to-lymphocyte ratio and elevated BNP levels at the time of diagnosis, as well as low BNP levels and PAP reductions in the first year, were observed in patients who experienced mortality. The trajectories of repeated BNP measurements differed between groups, as shown in Figure 1. Survival analysis, including NLR, BNP, pulmonary endarterectomy, and

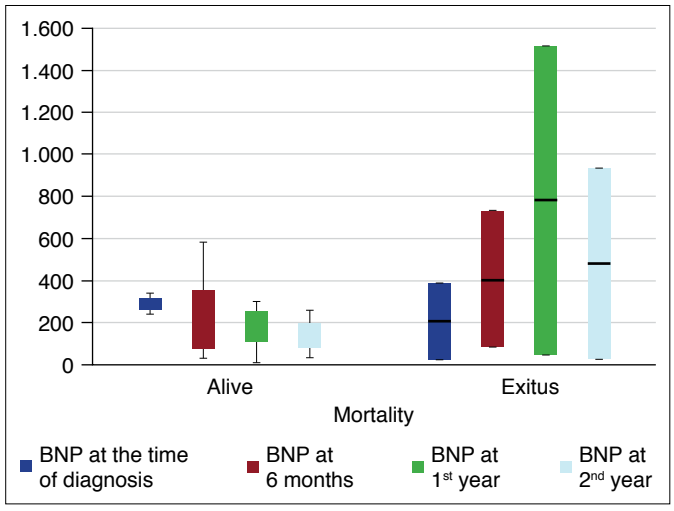

Figure 1: Brain natriuretic peptide (BNP) trajectories in patient groups

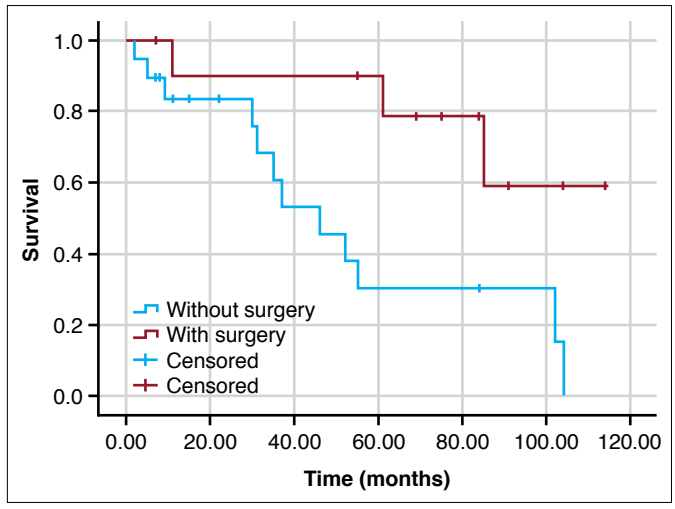

Figure 2: Kaplan-Meier curves illustrating survival differences between treatment groups

hematocrit (Hct), demonstrated that a high NLR and the absence of surgical treatment were independently associated with mortality (Table 3) [Fig. 2].

Discussion

Our observational study demonstrated that mortality in patients with chronic thromboembolic pulmonary hypertension is independently associated with the neutrophil-to-lymphocyte ratio and surgical intervention. Baseline and follow-up serum BNP levels were identified as significant prognostic indicators. No differences were observed between mortality groups in terms of echocardiographic or hemodynamic measurements of PAP and PVR at diagnosis.

In our cohort, patients receiving only medical treatment had a 9.80 times higher risk of mortality. This finding aligns with recent real-world data. A report from a United Kingdom referral center, which included 683 patients diagnosed with CTEPH, showed significant differences in survival rates between operated and non-operated patients at the first, third, and fifth years. The survival probabilities at the first, third, and fifth years were 98%, 91%, and 83% in operated patients, whereas in non-operated patients, they were 85%, 63%, and 49%, respectively.[20] In addition to improved survival, surgery led to better health-related quality of life without differences in healthcare-related costs. Jansa et al.[21] reported the first-year mortality rates for operated and non-operated patients as 26.6% and 50.2%, respectively. Contrary to our findings, their analysis revealed that hospitalization due to CTEPH-related complications nearly doubled the risk of mortality. Similarly, data from the Swedish Pulmonary Hypertension Registry demonstrated higher survival rates for surgically treated CTEPH patients at the first, third, and fifth years, with rates of 95%, 91%, and 87%, respectively, compared to 92%, 77%, and 61% in medically treated patients.[22] Ruaro et al.,[23] in a study involving 65 patients with a three-year follow-up, also demonstrated that PEA is the cornerstone of CTEPH treatment by reporting mortality exclusively in the medical treatment group.

In our study, only one-third of the patients underwent PEA surgery, which contrasts with practices at some other centers. While the benefits of PEA are well-established, there are several reasons for choosing for medical treatment in patients with CTEPH. Commonly observed reasons include surgically inaccessible disease, such as involvement of distal branches; mild disease that could benefit from intervention; the presence of comorbidities that contraindicate surgery; and patient refusal to undergo the procedure.[21]

In our study population, baseline BNP levels and BNP trajectories during follow-up were significantly associated with mortality. Çolak et al.[24] conducted a study of 56 patients who received only medical treatment over a follow-up period of 27 months. They found that mortality was associated with higher baseline BNP levels, higher PVR measured invasively, and a shorter 6-minute walking distance. However, similar PAP values were observed in both echocardiographic and hemodynamic

measurements. Multivariate analyses in their study revealed that only the combination of TAPSE/sPAP ratio and functional status was independently associated with mortality. Similarly, Samouco et al.,[25] in their 10-year study from a Portuguese referral center, reported that high serum BNP and creatinine levels at diagnosis were independently associated with worse outcomes.

The neutrophil-to-lymphocyte ratio is a simple calculated biomarker that reflects the balance between inflammation and adaptive immunity. NLR has been shown to correlate with disease progression and outcomes in various conditions, including cardiac events, cerebrovascular diseases, sepsis, infectious diseases, and cancer.[7] In our study, NLR was found to be associated with mortality. Yanartaş et al.[11] identified NLR as a potential biomarker for risk stratification after PEA surgery in CTEPH patients. Consistent with this, Yogeswaran et al.[26] demonstrated the predictive value of NLR in CTEPH patients undergoing PEA surgery, particularly those requiring extracorporeal membrane oxygenation (ECMO) support. Furthermore, a recent study proposed a scoring system that incorporates NLR, the aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, and gamma-glutamyl transferase (GGT) levels at diagnosis and during follow-up, which can achieve a predictive power comparable to ESC/ERS risk stratification.

Limitations

The primary limitation of our study is the small sample size and its retrospective nature. Despite this limitation, our center serves as a regional reference center with an experienced multidisciplinary expert team, ensuring reliable results concerning patient care. Due to the limited number of patients, both surgically treated and non-surgically treated patients were included in the mortality analysis. However, the multivariate analysis demonstrated that the relationship between NLR and mortality is independent of surgical treatment.

Conclusion

Our study highlights the importance of PEA surgery in the treatment of CTEPH, along with the significance of BNP trajectories and the neutrophil-to-lymphocyte ratio as prognostic biomarkers. Further research could assess the accuracy of easily obtainable measurements, such as NLR, in categorizing high-risk patients.

Ethics Committee Approval

The study was approved by the Uludağ University Faculty of Medicine Clinical Research Ethics Committee (No: 2022-11/4, Date: 25/05/2022).

Authorship Contributions

Concept – N.A.A.Ö., Ş.G.P., O.E.T., M.B., B.N.C., F.C.; Design – N.A.A.Ö., Ö.A.G., A.Ö., A.S.B., D.Y., S.G., F.C.; Supervision – Ş.G.P., A.Ö., M.B., A.S.B., D.Y., S.G.; Funding – Ö.A.G., O.E.T., A.S.B., B.N.C., D.Y.; Materials – N.A.A.Ö., O.E.T., Y.P., S.G., F.C.; Data collection &/or processing – N.A.A.Ö., Ö.A.G., O.E.T., A.Ö.; Analysis and/or interpretation – N.A.A.Ö., Ö.A.G., B.N.C.; Literature search – N.A.A.Ö., Y.P., D.Y., S.G.; Writing – N.A.A.Ö., Ö.A.G., M.B., Y.P., D.Y., F.C.; Critical review – N.A.A.Ö., Ş.G.P., Ö.A.G., O.E.T., A.Ö., A.S.B., B.N.C., S.G.

Conflicts of Interest

There are no conflicts of interest.

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No AI technologies utilized.

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