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Clinical insights into nonbacterial thrombotic endocarditis in cancer patients: A case-based systematic review

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Abstract

BACKGROUND: Nonbacterial thrombotic endocarditis (NBTE) is a rare yet critical complication in cancer patients, with high embolic risk and poor prognoses. This systematic review investigates the clinical presentation, valve involvement, embolic risk, vegetation management, and prognostic variability across cancer types in NBTE cases.

METHODS: Adhering to PRISMA guidelines, we conducted a comprehensive literature search in PubMed, Scopus, and Embase for studies from 2000 to September 2024. Extracted data included demographics; cancer type and site; NBTE diagnosis timing; valve characteristics; embolic events; and patient outcomes. Chi-square and regression analyses evaluated associations among clinical variables and outcomes. Quality was appraised using the Joanna Briggs Institute tool.

RESULTS: From 38 studies comprising 40 cases, the mean patient age was 50.5 years (±12.5), with equal gender distribution (20 males, 20 females). Pancreatic adenocarcinoma (17.5%) and lung adenocarcinoma (15.0%) were most frequently associated with NBTE. Mortality rates varied significantly by cancer type, with gastrointestinal and urogenital cancers showing the highest rates. A significant association was found between cancer type and vegetation management strategy ($\chi^2 = 24.41$, $p = 0.018$). Further correlations indicated that longer cancer histories necessitated more invasive management, and concurrent embolic events correlated with poorer prognoses. Quality assessment reinforced the findings' reliability (65% high quality).

CONCLUSION: NBTE in cancer patients shows distinct clinical and prognostic patterns, with cancer type impacting both management and outcomes. These insights highlight the importance of tailored management approaches and provide a basis for future research to enhance care and prognostic assessments in NBTE cases within oncology.

Keywords: Nonbacterial Thrombotic Endocarditis; Anticoagulants; Cancer; Prognosis; Embolic Events; Vegetation Management

Introduction

Nonbacterial thrombotic endocarditis (NBTE) is a rare but serious complication, particularly in patients with metastatic cancer. Characterized by sterile vegetations on the cardiac valves most frequently the mitral and aortic valves—NBTE arises from a hypercoagulable state induced by advanced malignancies, especially adenocarcinomas of the lung and pancreas[1]. Cancer-related NBTE is often linked to a combination of factors, including tumor-related hypercoagulability, systemic inflammation, and endothelial injury. The vegetations in NBTE consist of fibrin and platelet deposits, which can lead to serious complications such as systemic embolism, predominantly affecting the brain, kidneys, and spleen[2].

NBTE remains difficult to diagnose premortem, as the manifestations of the underlying malignancy often overshadow its symptoms. In many instances, the diagnosis is delayed until patients present with embolic events such as stroke, which are frequent in NBTE patients with metastatic cancer[3]. Imaging, particularly transesophageal echocardiography (TEE), is a critical tool in detecting vegetations in cancer patients with embolic phenomena[4].

Management of NBTE in this population primarily focuses on anticoagulation, with heparin being the preferred treatment to prevent further embolization. Direct oral anticoagulants (DOACs) are often insufficient in managing cancer-associated NBTE, as evidenced by recurrent thromboembolic events in patients despite their use[5]. Additionally, managing the underlying malignancy—often with targeted therapies—is essential for improving outcomes. For example, in lung cancer patients with driver mutations, combining cancer treatment with anticoagulation has been shown to improve prognosis and reduce valvular vegetation[6].

The time between the initial cancer diagnosis and NBTE detection varies widely but is often associated with advanced metastatic disease. In some cases, NBTE is identified months after the primary malignancy is diagnosed, often when metastatic disease progresses and embolic events occur. This delayed presentation highlights the need for early and proactive screening in high-risk cancer patients, particularly those with metastatic adenocarcinomas[1].

This systematic review addresses gaps in understanding how clinical variables—such as age, cancer type, time to NBTE diagnosis, and valve involvement—affect outcomes and management in metastatic cancer patients with NBTE. Using Pearson correlation and regression modeling, we aim to clarify the relationships between these factors and patient prognosis, guiding more effective treatment approaches.

Methods

Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7], we conducted a comprehensive search in PubMed, Scopus, and Embase from 2000 to 28 September 2024. Our strategy combined MeSH terms and keywords, including "Nonbacterial Thrombotic Endocarditis," "Libman-Sacks Endocarditis," "NBTE," and "Anticoagulants," to capture relevant studies on anticoagulant therapy in NBTE. Detailed search syntax for each database is available in Supplementary Table S1.

Eligibility Criteria and Study Selection

Eligibility for inclusion required studies to focus on (1) NBTE in cancer patients; (2) individuals aged 18 years and older; (3) those with metastatic tumors; (4) documented heart valve involvement; and (5) a cancer diagnosis coinciding with or preceding the onset of NBTE. Studies were excluded if they involved COVID-19 cases, concurrent antiphospholipid syndrome (APS), or systemic lupus erythematosus (SLE), as well as systematic reviews, meta-analyses, observational studies, and non-primary literature such as conference papers, abstracts, and letters to the editor. The screening process involved two independent reviewers [A.T.] and [H.D.], with any discrepancies resolved by a third reviewer [R.Z.].

Data Extraction

Data extraction was performed independently by two reviewers [A.T.] and [H.D.] and focused on study characteristics and clinical outcomes aligned with the research objectives. Study characteristics included patient demographics (sex, age); cancer type and location; duration from cancer diagnosis to NBTE diagnosis; and presence of antiphospholipid syndrome. Clinical outcomes covered primary clinical and laboratory findings; affected heart valves with regurgitation severity; systemic emboli occurrence; imaging and cardiac findings; vegetation management strategies; and patient prognosis, specifically evaluating mortality, embolic events, and therapeutic interventions.

Study Outcomes

Primary outcomes included mortality rates, incidence of systemic embolic events, and vegetation management strategies. Secondary outcomes assessed associations between clinical variables—such as valve involvement, cancer type and location, and duration from cancer to NBTE diagnosis—and patient prognosis. Statistical analyses across studies included Chi-square tests, regression models, and Pearson correlation to evaluate relationships and trends among key variables.

Data Synthesis and Statistical Analysis

Data synthesis included descriptive analysis of study characteristics, cancer types, valve involvement, and clinical outcomes, using measures of central tendency (mean, median) and dispersion (standard deviation, range). For inferential analysis, we applied Chi-square tests to evaluate categorical relationships; Pearson correlation to assess associations between continuous variables; and regression models to explore predictive factors for mortality, systemic embolism, and vegetation management outcomes. Results were synthesized across studies to identify patterns, with statistical significance set at $p < 0.05$. All statistical analyses were conducted using Python (version 3.10.12).

Quality assessment

Two reviewers [A.T.] and [M.T.] independently evaluated the included studies' quality using the Joanna Briggs Institute (JBI) Critical Appraisal tools for case reports. The answers to the questions included the alternatives "Yes," "No," "Unclear," and "Not Applicable," and were divided into three categories: high quality (Yes answers to ≥70% of questions), medium (Yes answers to 50–69% of questions), and low (Yes answers to <50% of questions). The total rank of each study based on the number of "Yes" responses was also calculated.

Results

The initial search yielded 1416 records. After the removal of duplicates and other exclusions, 1181 records remained. Title and abstract screening narrowed this to 283 records. A full-text review, applying exclusion criteria, reduced this number to 38 articles (40 cases) being selected for final analysis[8-45] (Figure 1). The demographic and clinical characteristics of these studies are detailed in Tables 1 and Table 2.

Demographic, Global distribution, and Patient's profile

The final dataset comprises case reports from 18 countries. The highest representation came from the USA, accounting for 18 cases (45.0%), followed by Japan with 6 cases (15.0%) and Switzerland with 4 cases (10.0%). Collectively, these three countries contributed 70.0% of the total case reports. The mean age of the patients was 50.5 years (±12.5), with an age range from 36 to 81 years. There was an equal representation of male and female patients, with 20 cases (50.0%) for each gender.

The most common cancer types represented were pancreatic adenocarcinoma (7 cases; 17.5%), followed by lung adenocarcinoma (6 cases; 15.0%) and breast cancer (5 cases; 12.5%). In terms of the years between the diagnosis of cancer and the diagnosis of NBTE, the mean time was approximately 1.3 years (±2.3), ranging from 0 to 10 years.

The frequency of the number of valves

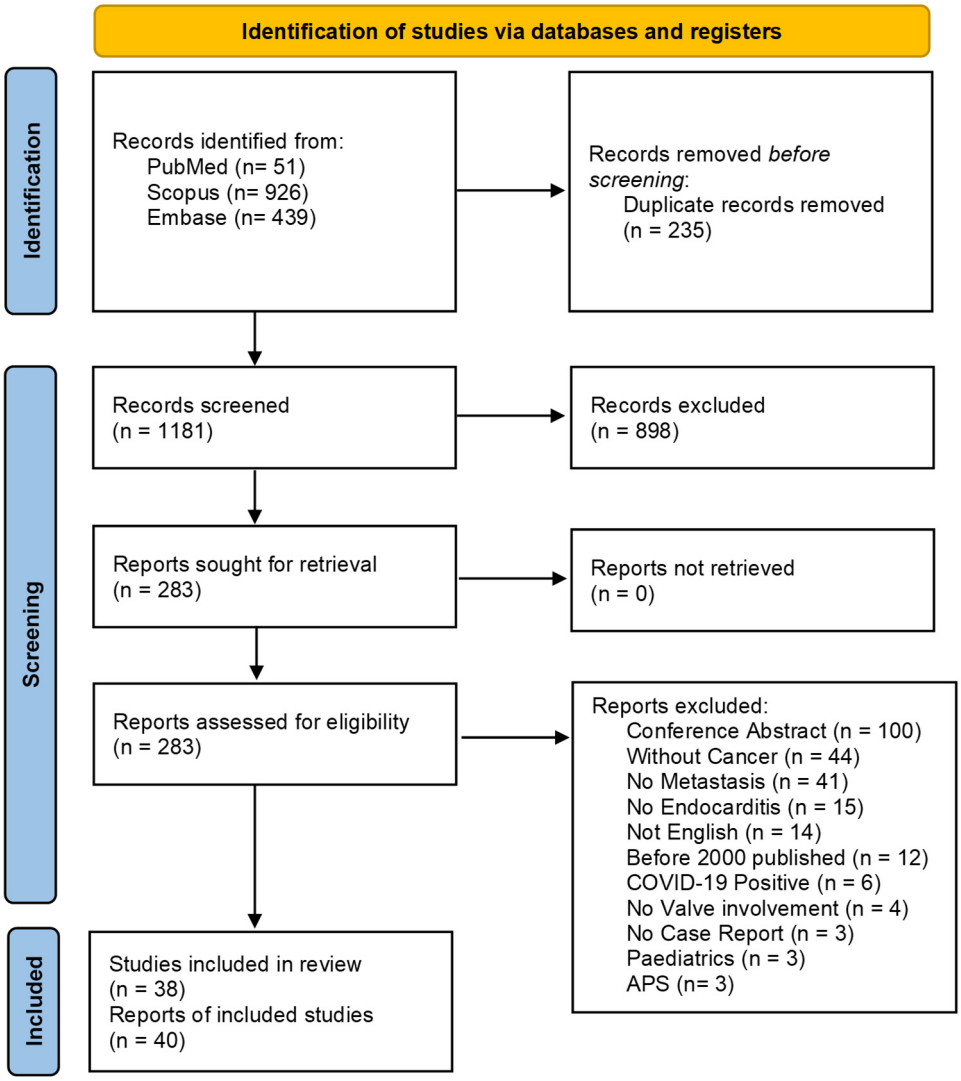

Figure 1. PRISMA Flowchart of the systematic review process.

affected by NBTE and the corresponding vegetation management strategies revealed that 24 cases (60.0%) involved one valve, indicating a relatively localized involvement of the condition. There were 7 cases (17.5%) with two valves, 3 cases (7.5%) with three valves, and 1 case (2.5%) with four valves.

The number of systemic emboli detected in patients showed 5 cases (12.5%) involving pulmonary embolism only, followed by 9 cases (22.5%) categorized as systemic emboli only, which included embolic events in organs such as the kidneys and spleen. Furthermore, 10 cases (25.0%) exhibited both pulmonary embolism and systemic emboli, excluding ischemic events. Lastly, 5 cases (12.5%) involved ischemic strokes or ischemic events, highlighting a significant concern for cerebrovascular complications associated with NBTE.

In terms of vegetation management, 19 cases (47.5%) employed low-invasive interventions, which included anticoagulation and palliative care. Meanwhile, 9 cases (22.5%) utilized medium-invasive interventions, where anticoagulation was combined with non-surgical therapies. Additionally, 8 cases (20.0%) required high-invasive interventions, indicating situations where anticoagulation was administered alongside surgical procedures.

The prognosis data revealed a diverse range

Table 1. Demographic and clinical features of NBTE-diagnosed patients with metastatic cancer.

Reference	Country	Sex	Age	PMH	Clinical findings	Lab findings	Type of Cancer	Years between Cancer to NBTE
Brooke Kania et al. 2022 (8)	USA	M	55	- Anxiety - Tobacco use - Polysubstance abuse	-Dyspnea on exertion -Orthopnea -Hypoxic respiratory failure -Epigastric pain -Bilateral lower extremity swelling -Diastolic and systolic murmur	-Troponin: Elevated -BNP: Elevated -CA-19-9: Elevated	Pancreatic adenocarcinoma	Coincidence
Erik R. Washburn et al. 2015[9]	USA	M	63	-Hypertension -Coronary artery disease	-Bilateral lower extremity claudication -Acute dysphagia and Dysarthria	-PSA: Not tested -Blood cultures: Multiple negative results	Prostatic ductal adenocarcinoma	Unknown (diagnosed upon autopsy)
Wilfred Ifeanyi Umeojiako et al. 2019[10]	United Kingdom	M	44	Hypertension	-Lower back pain -Pansystolic murmur at apex -Lumbar vertebral tenderness	-CRP: Elevated -ALP: Elevated -ALT: Elevated	small cell lung cancer	N/A
Madiha Makhdumi et al. 2021[11]	USA	F	48	-Ascites -Swollen legs -Obesity	-Dyspnea -Heart Murmur	-WBC: Normal -Hb: Normal -Plt: Normal	Ovarian cancer	4 years
Elias Akiki et al. 2023[12]	Italy	F	70	-Atrial fibrillation -Cardiac tamponade	-Headaches -Retrosternal chest pain -Multiple embolic strokes	-High-sensitivity troponin: Elevated -Blood cultures: Negative	Lung adenocarcinoma	N/A
Geeta Lal et al. 2003[13]	USA	M	59	-Thymus irradiation -Left thyroid lobectomy	-Headaches -Malaise -Night sweats -Weight loss -Migratory superficial thrombophlebitis -Aphasia	-Calcitonin: Elevated -CEA: Elevated -D-dimer: Elevated	Medullary Thyroid Cancer	N/A
Rogayeh Pourkia et al. 2022[14]	Iran	F	46	Surgical removal of breast cancer	-Left limb weakness -Mild left foot edema -Dyspnea	-Hb: Decreased -Plt: Decreased -WBC: Elevated -ESR: Elevated -CRP: Normal	Breast cancer	2 years
Hideki Yasutake et al. 2015[15]	Japan	M	67	-Aortic & mitral Valve Insufficiency -Atrioventricular Block -Cerebral Infarcts	-Abnormal mass on the prosthetic aortic valve -Acute cerebral infarction -Embolic stroke	-D-dimer Elevated -Blood cultures: Negative	Colorectal cancer	10 years
Takeshi Kawakami et al. 2023[16]	Japan	M	56	Asthma	-Lung adenocarcinoma -Pseudo-progression of brain tumor -Multiple thromboembolisms	Not explicitly mentioned	Lung adenocarcinoma	1 year
Vito Maurizio Parato et al. 2023[17]	Italy	F	37	Left popliteal deep vein thrombosis	-Dysarthria -Blurred vision -Cardio-embolic stroke	-Hb: Decreased -D-dimer: Elevated -CRP: Elevated	Uterine adenocarcinoma	N/A
Lugen Chen et al. 2004[18]	USA	F	81	-Hypertension -Type II diabetes mellitus -Mental status changes	-Comatose -Myocardial infarction -Cerebral infarction	-CK: Elevated -CK-MB: Elevated -Troponin T: Elevated -DIC markers: Present	Pancreatic adenocarcinoma	N/A

Continued Table 1. Demographic and clinical features of NBTE-diagnosed patients with metastatic cancer.

Reference	Country	Sex	Age	PMH	Clinical findings	Lab findings	Type of Cancer	Years between Cancer to NBTE
Maulin J Patel et al. 2020[19]	USA	F	66	- Tobacco use - Surgical removal of breast cancer	-Dizziness -Chest pain -Troponin elevation (NSTEMI) -Altered mental status -Hemiplegia -Dysarthria -Facial droop	-Troponin I: Elevated -Blood cultures: Negative	Pancreatic	N/A
Kazuko Norisada et al. 2011[20]	Japan	M	63	-Hypertension -Hyperlipidemia -Chronic rheumatoid arthritis	-Right lateroabdominal pain -Brain embolic infarctions -Aphasia	-D-dimer: Elevated -CEA: Elevated	Metastatic colon cancer	Coincidence
Kamran Amir Khan et al. 2019[21]	Pakistan	M	50	-Hypertension -Diabetes -TURP for BPH	-Recurrent ischemic strokes -Slurred speech	-Hb: Decreased Thrombocytopenia: Present DIC: Present -PSA: Elevated	Prostate Cancer	N/A
Wassim Shatila et al. 2014[22]	Lebanon	M	36	NL	-Presyncope -Chest pain -Dizziness -Mild tachycardia -Grade II/VI systolic murmur -Splinter hemorrhages	-D-dimer: Elevated -LDH: Elevated -Lupus anticoagulant: Positive -MTHFR mutation: Heterozygous	Gastric adenocarcinoma	N/A
Marissa K. Shoji et al. 2019[23]	USA	F	63	- Hypertension - Hyperlipidemia - Left lower extremity DVT and pulmonary embolism - Surgical removal of Sigmoid colon adenocarcinoma	-Left upper extremity weakness -Left facial droop -Recurrent strokes -Fever -Rash	-WBC: Elevated -CA 19-9: Elevated	Gallblader Non-mucinous biliary adenocarcinoma	4 months
JohannesWild et al. 2021[24]	Germany	F	67	-Left lower extremity deep vein thrombosis	-Metastatic pancreatic carcinoma -Severe venous and arterial thromboembolism -Critical ischemia in lower extremities	Thrombocytopenia: Present -D-dimer: Elevated DIC: Present	Pancreatic carcinoma	2 weeks
Jordi Recuero-Borau et al. 2024[25]	Spain	F	42	- Isolated brain metastasis - Pulmonary embolism and DVT in right lower limb	-Tetraplegia -Seizures -Left upper and lower limb weakness -Aphasia -Dysphagia	-Plt: Decreased -Fibrin: Decreased -D-dimer: Elevated Coagulation times: Prolonged	Lung adenocarcinoma with ROS1 rearrangement	1 year
		M	54	- Hypertension - Tobacco use	-Left hemiparesis -Numbness	-Hb: Decreased -ALP: Elevated	Lung adenocarcinoma with ROS1 rearrangement	2 months
Christoph C. Kaufmann et al. 2020[26]	Austria	F	44	Hypothyroidism	-Numbness -Visual impairments -Headaches -Strokes -Embolic events	-CRP: Elevated -NT-proBNP: Elevated -TSH: Normal -CYFRA 21-1: Normal	Non-small-cell lung adenocarcinoma	3 weeks
Daisuke Taniyama et al. 2013[27]	Japan	M	37	NL	-Chest pain -Fever -Dyspnea -Acute heart failure	-WBC: Decreased -Hb: Decreased -CRP: Elevated -D-dimer: Elevated	Lung Adenocarcinoma	4 months

Continued Table 1. Demographic and clinical features of NBTE-diagnosed patients with metastatic cancer.

Reference	Country	Sex	Age	PMH	Clinical findings	Lab findings	Type of Cancer	Years between Cancer to NBTE
Olivier Wigger et al. 2016[28]	Switzerland	M	66	Coronary heart disease	-Nausea -Vomiting -Headache -Blurred vision -Hemianopsia	Consumption coagulopathy: Present -Fibrinogen: Decreased -D-dimer: Elevated	Non-small cell lung cancer	N/A
Naruchorn Kijpaisalratana et al. 2020[29]	Thailand	F	66	-Hypertension -Diabetes mellitus	-Visual loss -Hemineglect -Hemihypesthesia -Apraxia	-D-dimer: Elevated	Uterine Adenocarcinoma	1 year
Sohiub N. Assaf et al. 2023[30]	USA	M	76	-Diastolic heart failure -Atrial fibrillation -Coronary artery disease	-Jugular vein distention -Pitting edema	-Sodium: Decreased	Pancreatic adenocarcinoma	N/A
Lusha W. Liang et al. 2016[31]	USA	F	68	- Surgical removal of the cancer -Pulmonary emboli	-Shortness of breath -Headaches -Visual changes -Left homonymous hemianopsia -Confusion	-CRP: Elevated -Hb: Decreased -CA-125: Elevated	Ovary Clear cell carcinoma	3 years
Panagiotis J. Vlachostergios et al. 2010[32]	Greece	F	74	- Recurrent abdominal pain - Surgical removal of the cancer	-Acute dyspnea -Chest pain -Cachexia -Tachycardia	-CEA: Elevated	Colorectal adenocarcinoma	1 year
Hiroki Mine et al. 2004[33]	Japan	F	59	-Deep venous thrombosis -Stroke	-Shortness of breath	-WBC: Normal -CRP: Normal -Plt: Decreased -PT-INR: Elevated -D-dimer: Elevated	Breast Cancer	4 years
Ricky Patil et al. 2024[34]	USA	F	76	Aortic and mitral valve insufficiency.	-Shortness of breath -Malaise	Pulmonary emboli: Multiple	Metastatic breast cancer	N/A
		M	60	-CVA -COPD -DM -HTN -DVT -Heart transplantation	Dyspnea	None reported	Pancreatic adenocarcinoma	Coincidence
Valentin Gabelmann et al. 2022[35]	Germany	F	52	- Surgical removal of the cancer -Pulmonary Embolism	-Tachycardia and hypotension -Respiratory distress	-CRP: Elevated -Troponin I: Elevated -BNP: Elevated -D-dimers: Elevated Thrombocytopenia: Mild -Hb: Decreased	Clear cell cervical cancer (FIGO IV4A)	1 year
Marcel Pina Ciuffo Almeida et al. 2019[36]	Brazil	M	46	Cancer	Seizure	-Blood cultures: Negative	Pancreatic Adenocarcinoma	N/A
Boris Adjibodou et al. 2018[37]	Switzerland	M	74	N/A	STEMI	Thrombocytopenia: Present -Hb: Decreased -CRP: NL	Biliary adenocarcinoma	N/A
Angel A Mitma et al. 2016[38]	USA	M	68	N/A	-Sudden chest discomfort -Confusion -Dysarthria -Expressive aphasia	NL	Lung Adenocarcinoma (EGFR-mutated)	N/A

Continued Table 1. Demographic and clinical features of NBTE-diagnosed patients with metastatic cancer.

Reference	Country	Sex	Age	PMH	Clinical findings	Lab findings	Type of Cancer	Years between Cancer to NBTE
Carmen Tisch et al. 2024[39]	Switzerland	F	70	- Arterial hypertension - Hashimoto thyroiditis - Vitamin B-12 deficiency - Pulmonary embolism, renal and splenic arterial infarctions (paraneoplastic coagulopathy) - Deep vein thrombosis	-Memory deficits -Personality changes -Left homonymous hemianopia	Thrombocytopenia: Moderate -CRP: Elevated -Cr: Elevated -Troponin: Elevated	Duodenal adenocarcinoma	1 year
Wael Zaher et al. 2023[40]	Belgium	F	74	- Persistent fever and lymphadenopathy - Arterial hypertension	-Persistent dyspnea -Amaurosis fugax -Transient diplopia -Febrile (38.1°C)	-Factor VIII: Elevated -CRP: Elevated -Blood cultures: Negative	Non-small cell lung carcinoma	3 months
Abdolhamid Bagheri et al. 2023[41]	Iran	F	54	-Deep venous thrombosis	-Dyspnea -Early-diastolic murmur	-Hb: Decreased -D-dimer: Elevated -WBC: Normal -CRP: Elevated -Blood cultures: Negative	Metastatic colorectal adenocarcinoma	3 months
Saki Ito et al. 2013[42]	Japan	F	60	Cancer	-Supraclavicular lymphadenopathy -Systolic heart murmur -Slight chest congestion	-CA19-9: Elevated -CEA: Elevated -CA125: Elevated -D-dimer: Elevated -TAT: Elevated -Blood cultures: Negative	Uterine adenocarcinoma	N/A
Theodore E. Warkentin et al. 2003[43]	Canada	F	61	- Raynaud's phenomenon - Severe aortic insufficiency - Transient visual disturbance	Ischemia of fingers and toes	-INR: Elevated -TAT: Elevated -Prothrombin fragment F1.2: Elevated	Breast adenocarcinoma	N/A
Kelsey Margaret Gray et al. 2021[44]	USA	M	66	- Chronic hepatitis C - Chronic obstructive lung disease - Hypertension	-Nausea and vomiting -Atrial fibrillation -Non STEMI	-Troponin: Elevated -Sodium: Decreased	Small cell lung carcinoma	Coincidence
Maxence Lepour et al. 2022[45]	Belgium	M	60	- Paroxysmal atrial fibrillation -Hypertension	-Dysphasia -Apraxia -Dyspnea -NYHA III -Diastolic aortic murmur (2/6) -Systolic mitral murmur (3/6) -Bilateral hypoventilation -Lower extremities pitting edema	-Hb: Decreased -DIC: Present -INR: Elevated -Fibrinogen: Decreased -Thrombocytopenia: Present -Haptoglobin: Decreased	Pancreatic adenocarcinoma	N/A

Table 2. Clinical findings and management of NBTE-diagnosed patients with metastatic cancer.

Reference	Valve(s) with NBTE	Severity of Regurgitation in Valves	Systemic Emboli	Imaging/Cardiac Findings	Vegetation management	Prognosis
Brooke Kania et al. 2022[8]	Aortic valve	Severe aortic regurgitation	Pulmonary embolism	- CXR: Bilateral hazy opacities, possible pulmonary embolism - CTA of chest: Hypodense cystic mass in distal pancreatic body and tail, complex liver masses with concern for metastatic disease - 2D echocardiogram: Aortic thickening, possible aortic vegetation, severe aortic regurgitation, left ventricular ejection fraction of 35% - TEE: Thickening of aortic valve leaflets, small vegetation, left ventricular ejection fraction of 40%-45% - CT of head: No acute intracranial abnormality or metastatic disease	Anticoagulation	Favorable
Erik R. Washburn et al. 2015[9]	Mitral valve	Not specified	Cerebral, renal, mesenteric, lower extremity ischemia	-Brain Imaging: Demonstrated multiple acute cerebral infarctions. -TTE: Revealed bilateral mitral leaflet mobile masses consistent with endocarditis. -CT Scan of Abdomen: a 3 × 2 cm lytic lesion in the left iliac bone concerning malignancy.	Hospice care	Expired
Wilfred Ifeanyi Umeojiako et al. 2019[10]	Mitral valve	Mitral regurgitation	No systemic emboli reported	MRI whole spine: -Widespread low T1 and high T2 signal changes throughout the spinal column -Suspicious for widespread bone metastases CT scan of thorax, abdomen, and pelvis: -Multiple cavitating and subpleural lesions in hemithoraces -Widespread liver lesions -Lytic lesions in the spine -Para-aortic adenopathy	-Radiotherapy -Targeted therapy	Palliative Care
Madiha Makhdumi et al. 2021[11]	Aortic valve	Moderate to severe	None reported	- TTE (3.5 months prior): Mild aortic regurgitation, LVEF ~65% - Cardiac Catheterization: LV and aortic pressures 112/2 and 102/63 mmHg, respectively - CT Imaging: Small pleural effusions bilaterally - TEE (3 days prior): Moderate aortic regurgitation, LVEF ~35%, small mass on the ventricular aspect of left coronary cusp	Surgical replacement	Not specified
Elias Akiki et al. 2023[12]	Mitral valve	Moderate mitral regurgitation	Multiple embolic strokes	-CT Head (ED): New brain hypodensities, suspicious for brain metastasis -MRI Brain: Multifocal embolic infarcts in cerebral and cerebellar hemispheres, largest in left cerebellar hemisphere and right temporal lobe -TTE: 7–8 mm soft mobile echodensity on the atrial surface of mitral leaflet tips -TEE: "Kissing-lesion" appearance of echodensity at mitral leaflet tips, measuring 1.1 cm in width, with moderate mitral valve regurgitation -Cardiac MRI: Evidence of myopericarditis	Anticoagulation	Favorable
Geeta Lal et al. 2003[13]	Mitral valve (posterior leaflet)	Not mentioned	Recurrent strokes, acute infarcts	CT Scan: -7-cm mass in the right thyroid lobe -Bilateral neck and supraclavicular lymphadenopathy -Additional lymphadenopathy at right thoracic inlet, aortopulmonary window, precarinal and subcarinal space, and left axilla MRI:	-Surgical replacement -Anticoagulation	Expired

Continued Table 2. Clinical findings and management of NBTE-diagnosed patients with metastatic cancer.

Reference	Valve(s) with NBTE	Severity of Regurgitation in Valves	Systemic Emboli	Imaging/Cardiac Findings	Vegetation management	Prognosis
				-Scattered T2 hyperintensity in bilateral white matter -5-mm focus in left cerebellum (acute ischemia) Head MRI (on readmission): -Acute infarcts in left parietal and right occipital lobes -Smaller, bilateral punctate infarcts in frontal lobes TEE: -0.5-cm mobile marantic vegetation on the posterior leaflet of the mitral valve		
Rogayeh Pourkia et al. 2022[14]	Tricuspid and mitral valves	Moderate regurgitation	Pulmonary embolism and ischemic stroke	- Brain MRI: Acute ischemic infarct in right basal ganglia and temporoparietal region - Carotid Doppler ultrasound: Normal - Lower limb Doppler ultrasound: Acute DVT in popliteal veins, chronic DVT in left femoral veins - TTE & TEE: Large, irregular, mobile shaggy mass on tricuspid and mitral valves with moderate regurgitation - Pulmonary CT angiography: Bilateral acute pulmonary embolism	Anticoagulation	Favorable
Hideki Yasutake et al. 2015[15]	Prosthetic aortic valve	Not mentioned	Multiple old cerebral infarcts	TTE: -1 year before admission: 0.6 cm x 0.3 cm echo-dense mass on the prosthetic aortic valve sewing ring -Follow-up TTE (admission year): Mass increased to 1.2 cm x 0.9 cm, mobile, no interference with valve motion Chest X-ray: No pulmonary congestion or pleural fluid Brain CT (on admission): Multiple old cerebral infarcts, no acute infarction on onset of right hemiparesis	-Anticoagulation -Surgical replacement -Left hemicolectomy	Favorable
Takeshi Kawakami et al. 2023[16]	Aortic valve	Not mentioned	Arterial emboli in spleen, kidney	Echocardiography revealed 3 mm vegetation on aortic valve	Anticoagulation	Favorable
Vito Maurizio Parato et al. 2023[17]	Aortic, mitral	Aortic: mild regurgitation; Mitral: moderate regurgitation	Cerebral, splenic, limb ischemia	TEE: vegetations on aortic and mitral valves	-Anticoagulation -Surgical replacement -Chemotherapy	Expired
Lugen Chen et al. 2004[18]	Mitral valve	Not reported	Multiple infarcts (brain, lung, spleen, kidney, myocardium) recurrent embolic strokes	- Cranial CT (initial): Left posterior parietal infarction - Cranial CT (2 days later): Right anterior cerebral artery occlusion	Anticoagulation	Expired
Maulin J Patel et al. 2020[19]	Mitral, Aortic	Severe mitral regurgitation, severe aortic stenosis		- Cardiac catheterization: Non-obstructive coronary disease - TTE: Reduced LVEF (33%), mobile echodensities on mitral valve, severe mitral regurgitation, and severe aortic stenosis - TEE: Multiple mobile masses on mitral and aortic valves - CT (chest, abdomen, and pelvis): 2.3 cm mass in the pancreas head with celiac artery encasement, multiple splenic and renal infarcts, and liver metastases - Brain MRI: Large right middle cerebral artery stroke	Anticoagulation	Expired
Kazuko Norisada et al. 2011[20]	Mitral valve (anterior and posterior leaflets)	No significant regurgitation	Brain infarctions	- Colon contrast enema and colonoscopy: Stenosis of rectum and transverse colon - Endoscopic ultrasonography: Tumor invasion in the muscular layer of rectum, intact mucosa and submucous layer - Brain MRI: Multiple embolic infarctions - TEE: Two mobile, echo-dense masses on mitral valve leaflets (3 × 7 mm and 6 × 4 mm), no mitral stenosis or regurgitation; thrombus (12 × 8 mm) in left auricular appendage	Anticoagulation	Expired

Continued Table 2. Clinical findings and management of NBTE-diagnosed patients with metastatic cancer.

Reference	Valve(s) with NBTE	Severity of Regurgitation in Valves	Systemic Emboli	Imaging/Cardiac Findings	Vegetation management	Prognosis
Kamran Amir Khan et al. 2019[21]	Mitral, Aortic valves	Mild regurgitation on aortic valve	Multiple infarcts in bilateral occipital and parietal regions	- MRI Brain: Multiple infarcts in bilateral occipital and parietal regions - Brain CT: Infarcts in multiple arterial territories - Echocardiography: Mitral valve vegetation (5 mm x 4 mm) with regurgitation, multiple vegetations on aortic valve with mild regurgitation, EF 56% - Abdomen/Pelvis CT: Multiple enlarged lymph nodes (para-aortic and pelvic), bladder diverticulum - Bone Scan: Extensive metastasis	-Anticoagulation -GnRH analogue -Bicalutamide -Leuprolide	Favorable
Wassim Shatila et al. 2014[22]	Mitral valve	Not specified	multi-organ infarctions, including brain stroke	- TTE: Mitral valve vegetation (0.8 cm × 0.6 cm) - CT Abdomen/Pelvis: Multiple lytic bone lesions, splenic and renal infarcts, malignant ascites, omental caking - Brain MRI: Acute right middle cerebral artery stroke	Anticoagulation	Poor
Marissa K. Shoji et al. 2019[23]	Mitral and aortic valves	Not specified	Recurrent embolic infarcts	- Brain MRI: Multiple acute infarcts in right frontal, parietal, and basal ganglia; left frontal, parietal - CTA head and neck: Filling defect at right internal carotid artery, anterior and middle cerebral arteries - TEE: Small echodensities on mitral and aortic valves (suggestive of endocarditis) - Brain MRI (follow-up): Acute infarcts in right frontal, parietal, insular cortex, basal ganglia, corona - CT abdomen/pelvis: Enlarged porta hepatis lymph node, abnormal gallbladder wall thickening - PET/CT: FDG uptake near liver, suspicious for malignancy	Anticoagulation	Palliative Care
JohannesWild et al. 2021[24]	Tricuspid valve	Initially non-severe, progressed to severe tricuspid regurgitation	Arterial thrombosis in lower extremities	- TTE: Large masses adherent to tricuspid valve leaflets, suspected NBTE - CT scan: Hypodense lesion (28 × 20 mm) predominantly in the right ventricle with a small intra-atrial portion - Echocardiography (follow-up): Increased tricuspid valve masses with severe tricuspid insufficiency	-Anticoagulation -Chemotherapy	Expired
Jordi Recuero-Borau et al. 2024[25]	Mitral valve	Not specified	Cerebral ischemic emboli	- Brain MRI: Multiple small metastases, hemorrhage, multiple ischemic lesions consistent with cardioembolic disease - TTE: Cardiac vegetation on the mitral valve, NBTE diagnosis	-Anticoagulation -Targeted therapy - Radiotherapy	Palliative Care
	Aortic valve	Not specified	Cerebral ischemic emboli	- Brain CT: Capsule-thalamus stroke - Follow-up brain CT: Larger ischemic area	-Anticoagulation -Targeted therapy	Palliative Care
Christoph C. Kaufmann et al. 2020[26]	Aortic valve (right and left coronary cusps)	Moderate aortic regurgitation	Multiple strokes, renal and splenic infarction, pulmonary embolism	- Initial brain MRI: Bilateral supratentorial hyperintensity, suggestive of stroke - Chest CT and X-ray: Peripheral pulmonary embolism and incidental suspect pulmonary lesion - TTE (initial): Mild-to-moderate tricuspid regurgitation - Follow-up MRI: Bilateral supratentorial and infratentorial strokes (progressed) - TOE: 8x4 mm vegetation on right coronary cusp of aortic valve with moderate aortic regurgitation - Abdominal MRI: Renal and splenic infarctions - Follow-up TOE: Resolution of aortic valve vegetation and reduced aortic regurgitation - Final TTE: New 5x3 mm vegetation on left coronary cusp	- Anticoagulation -Targeted therapy	Favorable
Daisuke Taniyama et al. 2013[27]	Aortic valve	Not mentioned	Pulmonary embolism, potential cerebral embolism	-CXR: Mass detected in the left lung apex. -CT Scan (Chest): Irregular 55 mm mass in the left lung apex with pulmonary artery involvement (pulmonary thromboembolism).	-Anticoagulation -Chemotherapy -Radiotherapy	Expired

Continued Table 2. Clinical findings and management of NBTE-diagnosed patients with metastatic cancer.

Reference	Valve(s) with NBTE	Severity of Regurgitation in Valves	Systemic Emboli	Imaging/Cardiac Findings	Vegetation management	Prognosis
Olivier Wigger et al. 2016[28]	Aortic valve	Severe	Intracerebral hemorrhage, ischemic brain lesions	-CT Scan (Adrenal and Brain): Metastases found in adrenal glands and brain. -CT Head: Parieto-occipital intracerebral hemorrhage (approx. 25 ml) -MRI Brain: Multiple bilateral ischemic lesions, additional intracerebral hemorrhages -TOE (initial): 6 x 6 mm mobile structure on the right coronary cusp of the aortic valve; moderate aortic regurgitation -TOE (follow-up): Severe aortic regurgitation; new echo-dense structure on the noncoronary cusp -Thoracic and Abdominal CT: Enlarged mediastinal lymph nodes, unclear pulmonary consolidation in the left lower lobe -PET CT: Left hilar lymph node metastases, osteolytic lesions in the left acetabulum	Palliative care	Expired
Naruchorn Kijpaisalratana et al. 2020[29]	Aortic valve	Not mentioned	Multiple cerebral emboli (ischemic stroke)	-MRI Brain: Acute to subacute infarctions in the right parietal lobe, right temporo-occipital lobe, right supramarginal gyrus, right anterior frontal lobe, and medial left occipital lobe -CT Angiography: Occlusion of the right distal branch of the middle cerebral artery, no significant luminal stenosis in other intracranial and extracranial arteries -TEE: Thickened trileaflet aortic valve with multiple small oscillating masses on all leaflets -FDG-PET Scan: Multiple pulmonary metastases	Anticoagulation	Expired
Sohiub N. Assaf et al. 2023[30]	Mitral and Tricuspid	Severe mitral regurgitation, moderate tricuspid regurgitation	Not mentioned	Chest X-ray: Findings consistent with pneumonia TTE: - Normal left ventricular cavity size - Mildly reduced systolic function (LVEF 45%-50%) - Septal flattening (RV pressure/volume overload) - Left atrial enlargement - Suspected mitral valve vegetation with severe mitral regurgitation - Elevated RV systolic pressure (RVSP = 53 mmHg) TEE: - Normal left ventricular size and function (LVEF 60%-65%) - Two large vegetations on mitral valve leaflets - Large vegetation on tricuspid valve leaflet (1.6 x 1.1 cm) with tricuspid regurgitation - RVSP 47 mmHg CT Head: To rule out intracerebral hemorrhage due to embolic disease	Anticoagulation	Expired
Lusha W. Liang et al. 2016[31]	Mitral valve	Mild-to-moderate mitral regurgitation	Cerebrovascular accidents (infarcts in occipital and temporal lobes)	-TTE: Normal EF -TEE: 1.8 × 0.8 cm mass on mitral valve -Brain MRI: acute infarcts	Anticoagulation	Expired
Panagiotis J. Vlachostergios et al. 2010[32]	Right atrium, tricuspid valve, atrial septum, later mitral valve	Not documented	Pulmonary embolism (suspected)	CXR: Bilateral pleural effusions. CT Scan of Chest: - Moderate cardiomegaly. - Multiple borderline (1 cm) mediastinal lymph nodes. - Confirmed presence of bilateral pleural effusions.	-Anticoagulation -Chemotherapy	Favorable

Continued Table 2. Clinical findings and management of NBTE-diagnosed patients with metastatic cancer.

Reference	Valve(s) with NBTE	Severity of Regurgitation in Valves	Systemic Emboli	Imaging/Cardiac Findings	Vegetation management	Prognosis
				CT Scan of Abdomen and Pelvis: Postoperative changes. Echocardiogram: Intracardiac lesions; transesophageal ultrasound indicated three heterogeneous friable masses fixed to the right atrial wall, tricuspid valve, and atrial septum. PET-CT scan: Increased uptake at mediastinal lymph nodes, spleen, sigmoid anastomosis, peritoneum, and common/internal iliac lymph nodes (no heart involvement).		
Hiroki Mine et al. 2004[33]	Mitral and Tricuspid Valves	Severe mitral and tricuspid regurgitation	Stroke (systemic emboli)	-TTE & TEE: Severe mitral and tricuspid regurgitation with mobile vegetations	-Anticoagulation -Surgical replacement	Expired
Ricky Patil et al. 2024[34]	Aortic and mitral valves	Severe aortic and mitral regurgitation	Multiple pulmonary emboli	- TTE: Ejection fraction of 55% with severe aortic and mitral regurgitation, moderate aortic stenosis, new pulmonary hypertension (pulmonary artery pressure of 85 mm Hg). - CTA Chest: Multiple pulmonary emboli. - TEE: Irregular echogenic densities on aortic and mitral valves, suggestive of non-bacterial endocarditis.	-Anticoagulation -Surgical replacement	Poor
	Aortic and mitral valves	Severe regurgitation in both	None	- TTE: Ejection fraction of 65% with severe aortic regurgitation and severe mitral regurgitation (increased compared to prior TTE). - Coronary Catheterization and Endocardial Biopsy: Negative for acute pathology. - TEE: New vegetative growths on aortic and mitral valves; all aortic leaflets markedly thickened with mobile echo-density attached to the left coronary cusp. - Cross-Sectional Imaging: New pancreatic, liver, and pulmonary lesions concerning for malignancy.	None	Poor
Valentin Gabelmann et al. 2022[35]	Aortic, mitral, tricuspid, pulmonary	Moderate insufficiencies	Stroke, pulmonary embolism	- TEE: Large vegetations on the aortic, mitral, and tricuspid valves; large floating masses in the right ventricle extending over the pulmonary valve into the pulmonary artery; moderate valve insufficiencies; vegetations on the right atrial septum. - CT Scan of Pulmonary Arteries: Bilateral pulmonary embolism. - Bedside TTE: Suggested large vegetations affecting the aortic valve.	Anticoagulation	Expired
Marcel Pina Ciuffo Almeida et al. 2019[36]	Mitral valve	Moderate mitral regurgitation	CNS embolization (ischemic stroke)	CT Scan of the Brain: Excluded intracranial bleeding MRI of the Brain: Revealed ischemic lesions likely due to cardiac embolism TEE: - Two slightly mobile echogenic foci on the native mitral valve - Associated with moderate mitral regurgitation	Anticoagulation	Favorable
Boris Adjibodou et al. 2018[37]	Aortic, Mitral	Severe	Coronary, cerebral emboli	- Coronary Angiogram: Thrombotic occlusion of the distal segment of the right coronary artery; normal coronaries. - TTE: Dilated left ventricle with LVEF of 30%; vegetations on aortic and mitral valves; severe aortic and mitral regurgitation. - Brain MRI: Three probably acute ischemic lesions with small hemorrhagic transformation.	Anticoagulation	Palliative Care
Angel A Mitma et al. 2016[38]	Mitral valve (anterior leaflet)	Mild mitral regurgitation	Multiple cerebral and cerebellar infarcts	- PET/CT: 4.5×3.3 cm fluorodeoxyglucose-avid mass in right upper lobe (adenocarcinoma) - Head CT: Negative	-Anticoagulation -Targeted therapy	Favorable

Continued Table 2. Clinical findings and management of NBTE-diagnosed patients with metastatic cancer.

Reference	Valve(s) with NBTE	Severity of Regurgitation in Valves	Systemic Emboli	Imaging/Cardiac Findings	Vegetation management	Prognosis
				- CT angiogram: Negative - MRI: Acute ischemic infarct in left MCA territory, scattered infarcts in left temporal, parietal, occipital, and cerebellar lobes - TTE: No emboli source - TOE: 6×6 mm mobile echodensity on anterior mitral valve leaflet, mild mitral regurgitation, no LV/atrial thrombi, no intracardiac shunting or aortic pathology		
Carmen Tisch et al. 2024[39]	Mitral valve, tricuspid valve	Severe mitral regurgitation, moderate tricuspid regurgitation	Cerebral infarctions (bihemispheric)	Mitral valve vegetation (11x6 mm) on TTE, cerebral infarctions on MRI	-Anticoagulation	Expired
Wael Zaher et al. 2023[40]	Mitral valve (posterior and anterior leaflets)	No stenotic or regurgitant complications	Ischemic stroke, pulmonary embolism	- Initial TTE: Mass in the right atrium - TEE and cardiac MRI: Filamentous 15 × 15 × 19 mm mass originating from the inferior vena cava, extending to the interatrial septum; interpreted as Chiari's network - CT Angiography: Bilateral pulmonary embolism - Follow-up TEE: Increase in right atrium mass, two new masses on mitral valve - Cerebral MRI: Multiple bilateral ischemic embolic lesions	-Anticoagulation -Immunotherapy -Chemotherapy	Favorable
Abdolhamid Bagheri et al. 2023[41]	Mitral, aortic, and tricuspid valves	Mild to moderate mitral, aortic, and tricuspid regurgitation	Pulmonary artery thrombus	-TTE and TEE showing vegetations on mitral, aortic, and tricuspid valves - Pulmonary CT Angiography: Thrombus in the left lower lobe pulmonary artery	Anticoagulation	Expired
Saki Ito et al. 2013[42]	Mitral valve	Severe mitral regurgitation	Cerebral, renal, and splenic embolisms	- Chest X-ray: Slight congestion - Venous ultrasound: Thrombosis in right soleus vein - Lung perfusion scintigraphy: No pulmonary embolism - TTE and TEE: Vegetation on mitral valve with severe regurgitation (largest area 13 mm) - MRA: No carotid artery obstruction - Cerebral, renal, and splenic infarctions detected	-Anticoagulation -Total hysterectomy -Bilateral salpingo-oophorectomy -Chemotherapy	Palliative Care
Theodore E. Warkentin et al. 2003[43]	Aortic valve	Severe aortic insufficiency	Right posterior parietal lobe infarct, left hemiparesis, new infarct in right frontal lobe	Nonbacterial thrombotic endocarditis involving aortic valve, thrombus in right superficial femoral and popliteal veins - CT (pre-surgery): Right posterior parietal lobe infarct - Duplex ultrasound (postoperative): DVT in right superficial femoral and right popliteal veins - CT (postoperative day 18): New infarct in right frontal lobe's precentral gyrus	-Surgical replacement -Anticoagulation	Expired
Kelsey Margaret Gray et al. 2021[44]	Mitral valve	Severe mitral regurgitation	Coronary and systemic	- Thoracic and Abdominal CT: Right hilar mass with lymphangitic spread to right lung's middle and lower lobes; obstructive lobar pneumonia; hepatic metastases - CT Angiogram (Day 5): No evidence of pulmonary embolism - Initial TTE: Left ventricular diastolic dysfunction; very mild mitral regurgitation - Repeat TTE (Day 9): Severe eccentric mitral regurgitation (regurgitant fraction: 65%) - TOE (Day 10): Thickening of mitral valve leaflet tips, multiple small valvular vegetations, severe mitral regurgitation (regurgitant fraction: >60%)	-Surgical replacement -Anticoagulation -Chemotherapy	Expired
Maxence Lepour et al. 2022[45]	Aortic and mitral valves	Severe mitral regurgitation, moderate aortic regurgitation	Multiple ischemic strokes	TTE & TEE: Vegetations on aortic and mitral valves - Severe mitral regurgitation (56 mL, regurgitating orifice of 37 mm^2) - Moderate aortic regurgitation; largest vegetation: 1.4 cm (aortic), 1 cm (mitral)	-Anticoagulation -Chemotherapy	Expired

of outcomes. Specifically, 10 cases (25.0%) were considered favorable, indicating a positive prognosis. In contrast, 12 cases (30.0%) resulted in death, highlighting a significant proportion of patients facing mortality. Additionally, there were 8 cases (20.0%) that required palliative care, suggesting the need for supportive measures rather than curative treatment. Moreover, 5 cases (12.5%) were classified as having a poor prognosis.

Heatmap Correlation Analysis

The heatmap Pearson analysis revealed specific correlations among clinical factors. A moderate positive correlation (0.32) between cancer type and vegetation management interventions suggested that certain cancers (e.g., endocrine, respiratory) were more often associated with invasive management (anticoagulation with valve surgical repair or targeted/chemotherapy). Similarly, a 0.32 correlation between years since diagnosis and vegetation management indicated that longer-diagnosed patients were likely to undergo more intensive interventions. A mild positive correlation (0.23) between prognosis and intervention type showed that patients with poorer prognoses may receive more aggressive treatment. The negative correlation (-0.23) between gender and cancer type implied some gender-based differences in cancer distribution (breast and endocrine cancers more common in females, and gastrointestinal and urogenital cancers more common in males). Lastly, a moderate negative correlation (-0.23) between prognosis and emboli/ischemia suggested that patients with a poorer prognosis had a higher risk of embolic events (coincidence of pulmonary and systemic emboli, ischemic strokes, or ischemic events) (Figure 2).

The correlation matrix visualizes the relationships between key variables, including cancer type, years since diagnosis, patient age, gender, prognosis, included valves, vegetation management, and emboli or ischemia presence. The most notable correlations include the relationship between cancer type and vegetation management (r = 0.32), years since diagnosis and vegetation management (r = 0.32), and prognosis with years since diagnosis (r = –0.27). This matrix aids in identifying patterns and potential interactions within the dataset, providing insights into the factors influencing prognosis and management outcomes.

Association between paired variables

The chi-squared analyses revealed that most clinical and demographic variables showed no significant associations with each other, including factors such as age, gender, and prognosis. However, a significant association emerged between the type and location of cancer diagnosis and vegetation management (chi-squared = 24.41, p = 0.018), suggesting a potential link between cancer classification and approaches to managing vegetation.

Prognosis Variability Across Cancer Types

Prognosis distribution differs markedly among cancer groups. Gastrointestinal and urogenital cancers generally show worse outcomes, predominantly clustering around “Expired.” Respiratory cancers demonstrate significant heterogeneity, with outcomes ranging widely and including some extreme outliers. Breast cancers tend to have more favorable prognoses, while endocrine cancers consistently show poorer outcomes. Overall, these variations underscore the diverse prognostic profiles associated with different cancer types (Figure 3).

The boxplot shows the variability in prognosis across different types of cancer, highlighting the central tendency and spread within each group. The respiratory cancer group (3) demonstrates the widest range of prognosis outcomes, indicating greater variability compared to other cancer types. Outliers are present in multiple groups, particularly in the gastrointestinal (1) and breast (5) cancer groups, suggesting individual cases with prognosis values differing significantly from the group medians. This visualization aids in identifying prognosis trends and outliers within cancer subtypes.

Prognosis categories are defined as follows: Favorable (1), Expired (2), Palliative Care (3), and

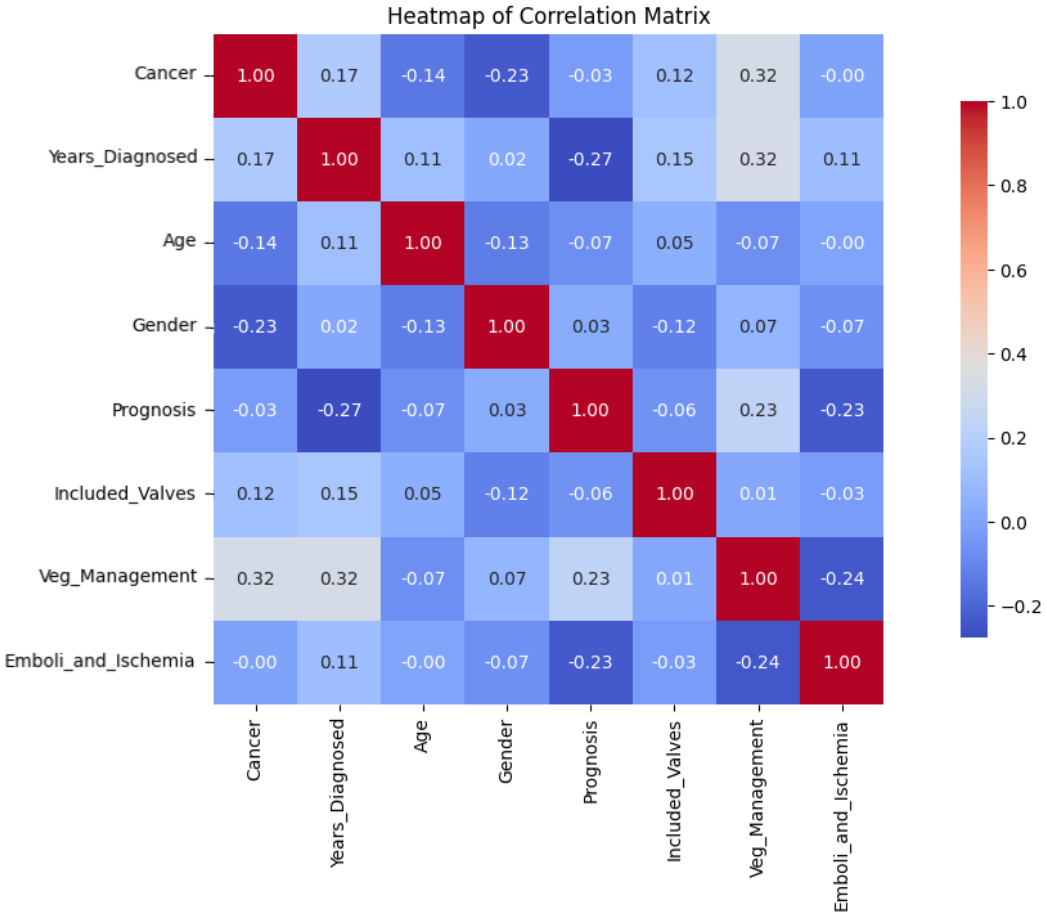

Figure 2. Correlation Matrix Heatmap of Clinical Variables in Cancer Patients with NBTE

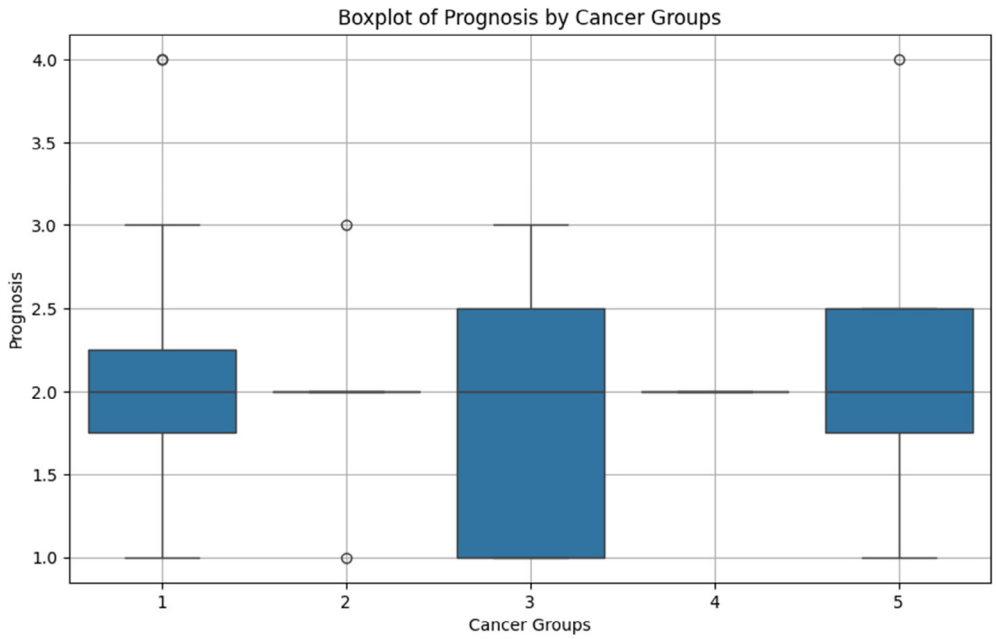

Figure 3. Boxplot of Prognosis Outcomes by Cancer Type in Patients with NBTE

Table 3. JBI quality assessment of included studies

Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total Quality
Brooke Kania et al. 2022	Y	Y	Y	Y	N	N	N	N	Medium
Erik R. Washburn et al. 2015	Y	Y	Y	Y	Y	Y	Y	N	High
Wilfred Ifeanyi Umeojiako et al. 2019	Y	Y	Y	Y	Y	Y	U	N	High
Madiha Makhdumi et al. 2021	Y	U	Y	Y	Y	N	N	N	Medium
Elias Akiki et al. 2023	Y	Y	Y	Y	Y	Y	U	N	High
Geeta Lal et al. 2003	Y	Y	Y	Y	Y	Y	Y	Y	High
Rogayeh Pourkia et al. 2022	Y	Y	Y	Y	Y	Y	Y	Y	High
Hideki Yasutake et al. 2015	Y	Y	Y	Y	Y	Y	Y	Y	High
Takeshi Kawakami et al. 2023	Y	Y	Y	Y	Y	Y	Y	Y	High
Vito Maurizio Parato et al. 2023	Y	U	Y	Y	Y	U	Y	U	Medium
Lugen Chen et al. 2004	Y	U	Y	Y	Y	U	Y	U	Medium
Maulin J Patel et al. 2020	Y	U	Y	Y	Y	Y	Y	U	High
Kazuko Norisada et al. 2011	Y	Y	Y	Y	Y	Y	Y	U	High
Kamran Amir Khan et al. 2019	Y	Y	Y	Y	Y	Y	U	Y	High
Wassim Shatila et al. 2014	Y	Y	Y	Y	Y	Y	U	Y	High
Marissa K. Shoji et al. 2019	Y	Y	Y	Y	Y	Y	Y	Y	High
JohannesWild et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	High
Jordi Recuero-Borau et al. 2024	Y	Y	Y	Y	Y	Y	Y	U	High
Jordi Recuero-Borau et al. 2024	Y	Y	Y	Y	Y	Y	U	U	High
Christoph C. Kaufmann et al. 2020	Y	Y	Y	Y	Y	Y	Y	U	High
Daisuke Taniyama et al. 2013	Y	Y	Y	Y	Y	Y	Y	Y	High
Olivier Wigger et al. 2016	Y	Y	Y	Y	Y	Y	Y	U	High
Naruchorn Kijpaisalratana et al. 2020	Y	Y	Y	Y	Y	Y	Y	Y	High
Sohiub N. Assaf et al. 2023	Y	Y	Y	Y	Y	U	N	U	Medium
Lusha W. Liang et al. 2016	Y	Y	Y	Y	Y	Y	Y	Y	High
Panagiotis J. Vlachostergios et al. 2010	Y	Y	Y	Y	Y	Y	Y	U	High
Hiroki Mine et al. 2004	Y	U	Y	Y	Y	Y	Y	U	High
Ricky Patil et al. 2024	Y	Y	Y	Y	Y	Y	Y	U	High
Ricky Patil et al. 2024	Y	U	Y	Y	U	N	Y	U	Medium
Valentin Gabelmann et al. 2022	Y	Y	Y	Y	Y	Y	Y	U	High
Marcel Pina Ciuffo Almeida et al. 2019	Y	U	Y	Y	Y	Y	N	U	Medium
Boris Adjibodou et al. 2018	Y	N	Y	Y	Y	N	U	U	Medium
Angel A Mitma et al. 2016	Y	U	Y	Y	Y	Y	N	U	Medium
Carmen Tisch et al. 2024	Y	U	Y	Y	Y	Y	U	U	Medium
Wael Zaher et al. 2023	Y	Y	Y	Y	Y	Y	U	U	High
Abdolhamid Bagheri et al. 2023	Y	U	Y	Y	Y	U	U	U	Medium
Saki Ito et al. 2013	Y	U	Y	Y	Y	Y	Y	Y	High
Theodore E. Warkentin et al. 2003	Y	Y	Y	Y	Y	Y	Y	Y	High
Kelsey Margaret Gray et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	High
Maxence Lepour et al. 2022	Y	U	Y	Y	Y	Y	N	U	Medium

Q1: "Were patient's demographic characteristics clearly described?"; Q2: "Was the patient's history clearly described and presented as a timeline?"; Q3: "Was the current clinical condition of the patient on presentation clearly described?"; Q4: "Were diagnostic tests or assessment methods and the results clearly described?"; Q5: "Was the intervention(s) or treatment procedure(s) clearly described?"; Q6: "Was the post-intervention clinical condition clearly described?"; Q7: "Were adverse events (harms) or unanticipated events identified and described?"; Q8: "Does the case report provide takeaway lessons?"
JBI: Joanna Briggs Institute; N: No; Q: Question; U: Uncertain; Y: Yes.

Poor (4). Cancer groups include Gastrointestinal (1), Urogenital (2), Respiratory (3), Endocrine (4), and Breast (5).

Quality assessment

The findings of the JBI quality assessment demonstrate a favorable evaluation of the overall quality of the studies reviewed. The majority (65%) of studies were rated as high quality, strengthening the reliability of the conclusions drawn from this body of literature. The presence of 35% of studies rated as medium quality highlights the need for ongoing research improvements and adherence to rigorous methodological standards in future investigations (Table 3).

Discussion

This systematic review analyzed 38 articles (40 cases) from 18 countries, focusing on the

relationship between cancer type, vegetation management, and prognosis in NBTE patients. Key findings include: (1) pancreatic and lung adenocarcinomas were most commonly associated with NBTE; (2) cancer type correlated with vegetation management strategy, with more invasive interventions for certain cancers; (3) prognosis varied across cancer types, with gastrointestinal and urogenital cancers showing poorer outcomes; and (4) poorer prognosis was linked to increased embolic events.

Types of Cancer Associated with NBTE

NBTE frequently occurs in patients with underlying malignancies, particularly those with adenocarcinomas. The most common cancer types associated with NBTE are mucin-producing tumors such as pancreatic, lung, and gastric adenocarcinomas. In one meta-analysis, lung cancer was the most prevalent, accounting for nearly 30% of cancer-associated NBTE cases, followed by pancreatic cancer at 19% and other gastrointestinal malignancies. Advanced cancer stages and metastatic disease also significantly increase the likelihood of NBTE development, with a strong correlation seen in tumors that express pro-coagulant factors such as tissue factor and inflammatory cytokines, promoting a hypercoagulable state (e.g., lung adenocarcinoma, ovarian cancer)[46,47]. Similarly, the findings of our study also indicate that pancreatic adenocarcinoma, lung adenocarcinoma, and breast cancer, respectively, had the highest prevalence among all patients diagnosed with NBTE.

The association between the time from cancer diagnosis to the development of NBTE is well documented, emphasizing that NBTE often manifests in the later stages of cancer progression. Research shows that as cancer advances, the hypercoagulable state becomes more pronounced, leading to a higher risk of NBTE. Tumors such as pancreatic and lung adenocarcinomas, which are aggressive and metastasize quickly, are more likely to lead to NBTE shortly after cancer diagnosis. The timing varies, but embolic risks peak as tumors secrete more pro-thrombotic factors and inflammatory markers[48]. Our analysis found a mean time of 1.3 years (±2.3 years), with a wide range from 0 to 10 years, illustrating the variability based on cancer type, disease progression, and other factors.

Valvular Engagement

Cardiac involvement in NBTE typically manifests as sterile vegetations located on the heart valves, most commonly the mitral and aortic valves. Echocardiographic studies highlight that the mitral valve is affected in approximately 55% of cases, followed by the aortic valve in about 42% of patients. Vegetations can be small and friable, often resulting in regurgitation. Transesophageal echocardiography (TOE) is more sensitive than transthoracic echocardiography (TTE) in detecting these valvular abnormalities, with TOE able to identify subtle vegetations that may otherwise be missed. Multiple valves can be involved, though single-valve involvement is more common[46,49]. Moreover, we observed the frequency of valvular involvement as follows: single-valve, dual-valve, triple-valve, and four-valve cases were reported in 60%, 17.5%, 7.5%, and 2.5% of NBTE-detected patients, respectively.

Embolic Events

Embolic complications are a hallmark of NBTE, occurring when vegetations dislodge and travel to the systemic circulation. These events often involve the brain, leading to strokes, or affect other organs such as the spleen, kidneys, or extremities. In one large review, embolic stroke was the most frequent initial presentation, reported in 88% of cases. This underscores the need for prompt identification, as embolic events can result in significant morbidity. The hypercoagulable state induced by malignancies contributes to a high risk of embolic phenomena, especially when multiple or large vegetations are present[47,50]. In line with previous literature, our findings emphasize the variation in presentation; pulmonary and systemic emboli had the highest frequency, while ischemic strokes/events were less commonly reported overall.

Vegetation Management

Management of vegetations in NBTE among cancer patients necessitates a multifaceted approach, focusing on anticoagulation, treatment of the underlying malignancy, and, in select cases, surgical intervention[51].

Anticoagulation Therapy

Systemic anticoagulation is a cornerstone in NBTE management, particularly to prevent thromboembolic events. LMWH is often preferred over warfarin in cancer-associated NBTE due to its efficacy in hypercoagulable states linked to malignancy. However, anticoagulation alone may not suffice, as recurrent embolic events have been reported despite adequate therapy[52].

These sterile valvular vegetations—primarily composed of fibrin and platelets—are highly prone to embolization, particularly to the brain, spleen, kidneys, and extremities[53]. LMWH is generally favored over vitamin K antagonists (e.g., warfarin) in cancer-associated NBTE due to its more predictable pharmacokinetics, fewer drug interactions, and superior efficacy in malignancy-associated thrombosis (Trousseau syndrome). Moreover, the hypercoagulable state in cancer is driven by tumor-associated tissue factor expression, cytokines, and mucin-producing tumors—all of which contribute to ongoing thrombus formation that LMWH seems better equipped to mitigate[53].

Recent studies have also explored the use of direct oral anticoagulants (DOACs), such as apixaban and rivaroxaban, for malignancy-associated thromboembolism. However, evidence regarding their effectiveness specifically in NBTE remains limited and controversial. Some case series and retrospective reviews suggest possible benefit, but concerns persist regarding DOACs' ability to prevent embolic complications from valvular vegetations due to differences in their mechanism of action compared to heparin[54].

Despite adequate anticoagulation, recurrent embolic events are frequently reported, underscoring the limitations of pharmacologic management alone. Research by El-Shami et al.[55] and subsequent case series[56] highlighted multiple instances where patients continued to experience embolic phenomena despite therapeutic doses of LMWH or warfarin. This suggests that the ongoing prothrombotic stimulus from the underlying malignancy may override the protective effects of anticoagulation in some cases.

In practice, many experts recommend initiating LMWH promptly once NBTE is suspected, particularly in patients with confirmed or suspected cancer, and continuing it indefinitely or until the malignancy is controlled. In terminally ill patients, goals of care and bleeding risk must also be considered, balancing embolic prevention with quality of life.

Treatment of Underlying Malignancy

Effective treatment of the underlying cancer is essential in managing NBTE, as malignancy-driven hypercoagulability is a primary trigger for valvular thrombus formation. Tumors—especially mucin-producing adenocarcinomas—promote thrombosis through tissue factor expression, cytokine release, and platelet activation. Clinical improvement of NBTE has been documented following successful oncologic therapy. For instance, in a patient with advanced EGFR-mutated lung adenocarcinoma, targeted therapy with osimertinib led to rapid resolution of DIC and marked regression of mitral valve vegetations, as seen on echocardiography[57]. Similarly, NBTE resolution has been reported after chemotherapy or surgical resection in pancreatic, gastric, and gynecological cancers, though outcomes depend on cancer type, stage, and responsiveness to treatment. Additionally, close coordination between oncology and cardiology is vital, especially when combining anticoagulation with cytotoxic or targeted therapies, due to bleeding risk and overlapping complications[55].

Surgical Intervention

Surgical management, including valve repair or replacement, is considered in select NBTE

cases—particularly when there are large, mobile vegetations, recurrent embolic events despite adequate anticoagulation, or severe valvular dysfunction leading to heart failure or hemodynamic compromise[56,58]. While NBTE is typically managed medically, surgery becomes necessary when the embolic risk is high or when vegetations impair valve function. The timing of surgery is critical and must be individualized, weighing the patient's cardiovascular stability, cancer prognosis, and operative risk. Surgery may be deferred in patients with poor oncologic prognosis or active metastatic disease unless life-threatening complications arise[59]. Notably, in a reported case, a patient with NBTE and previously undiagnosed endometrioid adenocarcinoma underwent successful valve surgery for mitral regurgitation caused by vegetations, followed by definitive oncologic resection—highlighting the potential benefit of a coordinated surgical-oncologic approach in carefully selected patients[59].

Prognosis and Variability Across Cancer Types in NBTE

The prognosis for patients with NBTE significantly varies depending on the type and stage of the associated malignancy. In general, the overall prognosis for NBTE is poor, largely because it typically occurs in the setting of advanced or metastatic cancer. However, some distinctions exist between different cancer types.

NBTE is most commonly associated with highly aggressive cancers such as lung and pancreatic adenocarcinomas. These cancers are often in advanced stages by the time NBTE is diagnosed, contributing to a particularly poor prognosis. For instance, a meta-analysis revealed that patients with lung cancer had a median survival of just 1.3 months after NBTE diagnosis. The six-month survival rate was also lower compared to other cancers, emphasizing the aggressive nature of lung and pancreatic malignancies associated with NBTE[47,60].

Other cancer types, such as ovarian and gastrointestinal malignancies, also carry a risk of NBTE but may be associated with slightly better outcomes if the cancer is diagnosed and treated earlier. Nonetheless, the overall prognosis remains guarded. The systemic embolic complications that often accompany NBTE—such as strokes or peripheral emboli—further complicate management and survival outcomes in these groups[61,62].

The prognosis worsens considerably in cases where NBTE occurs in the context of metastatic cancer. Studies have shown that patients with metastases have an increased risk of mortality, and the effectiveness of interventions such as anticoagulation or surgery is limited in advanced cases. In general, NBTE associated with adenocarcinomas tends to have worse outcomes compared to other cancer types, owing to the pro-thrombotic environment these cancers create[50,63]. Our pooled data demonstrated that 30% of patients had expired, followed by 25% with favorable outcomes, 20% required palliative care, and 12.5% had poor outcomes.

Study limitations

Our study has limitations. Firstly, the reliance on case reports and case series introduces a risk of publication bias, as cases with unique or severe presentations are more likely to be reported. This could skew the observed associations and outcomes. Secondly, the retrospective nature of the included studies limits the ability to establish causation or temporal relationships between cancer types, anticoagulant therapy, and clinical outcomes in NBTE.

Additionally, variability in reporting quality and completeness across case reports may introduce inconsistencies in the data, particularly regarding patient demographics, clinical interventions, and outcomes. Despite attempts to standardize data extraction, the lack of uniform diagnostic criteria and management protocols across cases may affect the robustness of statistical comparisons. Finally, this review excludes non-English language studies, which may lead to geographical bias, limiting the study's applicability to diverse patient populations.

Conclusion

Our study showed that pancreatic and lung adenocarcinomas were the most frequently associated with NBTE, with gastrointestinal and urogenital cancers exhibiting the highest mortality rates. Invasive management strategies—including anticoagulation combined with surgical interventions—were more common in patients with longer cancer histories and those presenting with embolic events. Prognosis varied significantly across cancer types, with gastrointestinal and urogenital cancers showing the worst outcomes. These findings underscore the importance of tailored management strategies based on cancer type and disease progression. Further research is needed to better understand the mechanisms underlying NBTE in cancer patients and to optimize treatment approaches.

Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: MT; RZ
Data Acquisition: AT; HD
Data Analysis or Interpretation: AT; MT
Manuscript Drafting: AT; HD
Critical Manuscript Revision: MT
All authors have approved the final manuscript and are responsible for all aspects of the work.

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