REVIEW ARTICLES

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CARDIOVASCULAR RISK IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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Summary
Objectives. To systematically review the complex relationship between cardiovascular comorbidities and lung cancer, focusing on their impact on patient prognosis, treatment outcomes, and quality of life, with special emphasis on non-small-cell lung cancer (NSCLC).
Methods. A comprehensive literature search was conducted across databases such as PubMed, MEDLINE, and Google Scholar. A total of 137 studies examining the following aspects were included: Prevalence of cardiovascular comorbidities (e.g., coronary artery disease, heart failure, arrhythmias, valvular disease, thromboembolic events) in lung cancer patients; Prognostic implications of cardiovascular comorbidities across different stages of lung cancer; Impact of cardiovascular complications arising from cancer treatments (chemotherapy, radiotherapy); Assessment of quality of life in lung cancer patients with cardiovascular comorbidities.
Results. The prevalence of various cardiovascular comorbidities in lung cancer patients across different stages remains high. Prognostic impact of pre-existing cardiovascular comorbidities, especially in early-stage lung cancer remains negative. Cancer therapies can exacerbate existing cardiovascular conditions or induce new complications, significantly reducing the quality of life in patients with both lung cancer and cardiovascular comorbidities.
Conclusions. To mitigate the risk of cardiovascular complications in lung cancer patients with comorbidities, a comprehensive approach is necessary. This includes proactive cardiovascular risk assessment and management throughout all stages of lung cancer treatment, the development of treatment strategies tailored to individual patient risk profiles, and continued research into the underlying mechanisms of cardiovascular complications in lung cancer.
Keywords: lung cancer, cardiovascular comorbidities, non-small-cell lung cancer, prognosis, treatment, quality of life

Introduction

Lung cancer stands as the most prevalent malignancy globally, concurrently holding the grim distinction of being the leading cause of cancer-related mortality in both genders [1]. The dismal 5-year survival rates for lung cancer, hovering around 15-20% across all stages, highlight the urgency for improved therapeutic strategies [1]. A multitude of factors influence its mortality rate, with comorbidities playing a significant role.

Charlson Comorbidity Index (CCI) is the most widely employed tool for assessing a patient's one-year mortality risk in the presence of comorbidities. Notably, a score of ≥3 translates to an 80% increased risk of death within a year [2]. Its significance in oncology stems from its independence from both cancer stage and performance status. Another established comorbidity assessment scale is the Simplified Comorbidity Score (SCS), validated as an independent predictor of poor outcomes in lung cancer [3]. This validation study demonstrated a strong statistical correlation between CCI and SCS through univariate analysis of a large cohort of non-small-cell lung cancer (NSCLC) patients with long-term follow-up. Scores of CCI ≥ 3 and SCS > 9 were identified as significant for prognosis ($p = 0.06$ and $p < 0.01$, respectively) with the study suggesting a potentially superior prognostic value for SCS [3]. However, it is noteworthy that advancements in lung cancer treatment have rendered both CCI and SCS unreliable for predicting survival, radiological response, and toxicity during first-line chemotherapy regimens [4]. Similarly, in patients with advanced and unresectable NSCLC, treated with radical sequential chemoradiotherapy, neither a CCI >4 nor an SCS >8 emerged as a reliable predictor of survival [5].

In patients with NSCLC, cardiovascular (CV) comorbidities – encompassing coronary artery disease, hypertension, arrhythmias, and peripheral arterial disease – have been associated with a 30% increased risk of death compared to patients without such co-existing conditions [6]. However, this association appears less prominent in advanced, unresectable stages of NSCLC. Studies employing a retrospective cohort design suggest that for these aggressive malignancies, cancer-related mortality rates may overshadow those attributable to comorbidities [7, 8, 9]

Batra et al. demonstrated that the presence of CV comorbidities significantly reduces the likelihood of receiving curative oncological interventions, encompassing chemotherapy, targeted therapy, and radiotherapy [10]. This phenomenon likely stems from concerns regarding treatment tolerability in patients with pre-existing CV conditions. Furthermore, studies have shown that a history of CV disease elevates the risk of death from non-cancerous causes (hazard ratio [HR] = 1.48; $p < 0.0001$) but does not necessarily influence cancer-specific mortality rates [11].

Disqualification from potentially curative treatments or the administration of less intensive, potentially less effective regimens, due to comorbidity burden, emerges as a significant concern, potentially impacting overall survival in this patient population.

This study aims to conduct a comprehensive review of the literature examining the prognostic implications of cardiovascular comorbidities in lung cancer, with a particular emphasis on the prevalent NSCLC subtype.

Materials and Methods

A comprehensive literature search was conducted across databases such as PubMed, MEDLINE, and Google Scholar. A total of 137 studies examining the following aspects were included: Prevalence of cardiovascular comorbidities (e.g., coronary artery disease, heart failure, arrhythmias, valvular disease, thromboembolic events) in lung cancer patients; Prognostic implications of cardiovascular comorbidities across different stages of lung cancer; Impact of cardiovascular complications arising from cancer treatments (chemotherapy, radiotherapy); Assessment of quality of life in lung cancer patients with cardiovascular comorbidities

Cardiac arrhythmias

The pathophysiology of cardiac arrhythmias and conduction disturbances in cancer patients arises from a multifaceted interplay of factors. These include patient-specific characteristics (comorbidities, age, genetic susceptibility), tumor-related mechanisms (direct tissue invasion, autonomic system dysregulation, inflammation), and iatrogenic effects stemming from cancer treatment modalities (electrolyte imbalances secondary to gastrointestinal toxicity, adverse cardiac remodeling induced by chemotherapy, targeted therapy, immunotherapy, radiotherapy, and supportive medications) [11].

Atrial fibrillation (AF), the most prevalent arrhythmia, affects 2-4% of the general population with its incidence increasing markedly with age (up to 36% at age 85) [12]. Cancer patients face an elevated risk of AF due to a confluence of factors [13]. The OPERA study (Oulu Project Elucidating Risk of Atherosclerosis) established cancer as an independent risk factor for AF development, demonstrating a significantly higher prevalence of AF in cancer patients (19%) compared to non-cancer controls (9%) ($p<0.001$, HR=2.47; 95% CI: 1.57–3.88) [14]. Furthermore, new-onset AF may signal an increased relative risk of subsequent diagnosis with malignancies affecting the lung, kidney, colon, ovary, and non-Hodgkin's lymphoma. This association is particularly strong for metastatic disease (seven-fold increased risk) and remains significant for localized cancers (3.5-fold increased risk) [15]. Intriguingly, a 90-day period surrounding a new AF diagnosis exhibits a bidirectional relationship with cancer risk. During this timeframe, not only does a cancer diagnosis predict a 3.4-fold increased risk of new AF, but AF occurrence is also associated with a 1.85-fold higher likelihood of coexisting cancer [16].

Large-scale, population-based investigations have demonstrated that the association between cancer and atrial fibrillation (AF) varies by tumor type, with hematological and intrathoracic malignancies exhibiting a particularly strong link [17]. One such study revealed a more than doubled risk of AF development in patients with esophageal cancer (HR = 2.69) and lung cancer (HR = 2.39). Notably, lung cancer displayed the most robust association with AF in individuals over 50 years of age [17]. Among women with new-onset AF, statistically significant age-adjusted risk elevations were observed for colon cancer (HR = 2.36; $p < 0.001$), breast cancer (HR = 1.35; $p = 0.04$), and lung cancer (HR = 1.69; $p = 0.04$) [18].

Lung cancer exhibits a particularly strong association with AF. A nationwide population-based study demonstrated the highest incidence of AF among cancer types, with rates of 58.7/1000 person-years in men and 35.3/1000 person-years in women with lung cancer [19]. Furthermore, a large-scale analysis of US cardiovascular hospitalizations identified AF as a leading driver of admission for lung cancer patients. Crucially, the presence of AF was associated with a significantly elevated mortality risk in this patient population (adjusted odds ratio [aOR] = 4.69) [20].

While established risk factors like hypertension, diabetes, and heart failure contribute to AF in the general population, their presence in cancer patients likely represents just one piece of the puzzle [21, 22]. The oncological milieu introduces a unique set of contributors potentially influencing AF development:

- Derangements in Electrolyte Homeostasis: Disruptions in electrolyte balance, a potential consequence of paraneoplastic syndromes or treatment-induced side effects, can directly influence cardiac electrical activity and promote arrhythmias [21].
- Hypoxia: Reduced oxygen availability, either due to lung dysfunction associated with lung cancer or the high metabolic demands of tumors, can alter cardiac electrophysiology, creating a substrate for AF [22].
- Neurohormonal Dysregulation: Elevated sympathetic tone triggered by pain, inflammation, or psychological stress related to cancer can destabilize cardiac rhythm and increase AF susceptibility [22].
- Chronic Obstructive Pulmonary Disease (COPD) and Pulmonary Hypertension: The frequent coexistence of COPD with lung cancer synergistically elevates AF risk. Infectious exacerbations of COPD and left atrial enlargement further contribute to this phenomenon [23, 24]. Similarly, pulmonary hypertension caused by lung cancer and resulting hypoxia can also promote AF development [24].
- Direct Tumor Effects: Infiltration or compression of the heart by tumor masses or metastases can create a physical substrate that predisposes to AF [25].
- Treatment-Related Cardiotoxicity: Certain cancer treatments, such as radiotherapy or thoracic surgery, can have cardiotoxic effects, with post-surgical AF occurring in 10-20% of patients within 2-3 days of the procedure [25].

Clinical Implications and Prognostic Significance

The increased prevalence of AF in cancer patients carries substantial clinical implications. AF is an independent risk

factor for stroke, heart failure, and overall mortality [26, 27]. This heightened vulnerability underscores the importance of early detection and effective management of AF in this high-risk population. However, treatment decisions in patients with coexisting cancer and AF require careful consideration of potential interactions between anticoagulant medications and anticancer therapies, particularly those that increase the risk of bleeding complications [28].

The prevalence of new onset AF (i.e., first occurrence after the cancer diagnosis) is associated with a higher tumor grade and thus a worse prognosis and higher cardiovascular mortality [26]. Poor prognosis has been demonstrated in patients undergoing thoracic surgery for lung cancer who developed AF: increased hospital mortality (6.7% vs. 1.0%, p = 0.024) and higher long-term mortality (HR = 3.75) [27]. A significant negative prognostic value of AF (HR = 2.39 for mortality, p = 0.02) in lung cancer patients qualified for systemic cancer treatment has also been demonstrated [7].

Ventricular arrhythmias represent another class of rhythm disturbances potentially influencing prognosis in cancer patients. Anker et al. investigated the prevalence of ventricular arrhythmias using 24-hour Holter electrocardiograms (ECG) in a cohort of cancer patients free from pre-existing cardiovascular disease, compared to healthy controls [28]. They observed a significantly increased frequency of non-sustained ventricular tachycardia (nsVT) in 6% of patients with NSCLC. Notably, the presence of nsVT was associated with a worsened overall survival (HR = 2.68; p = 0.005) and demonstrated independent prognostic significance across various cancer types. Interestingly, frequent premature ventricular contractions (PVCs), detected in 42% of NSCLC patients (with 21% exhibiting ≥50 PVCs/24 hours), did not adversely affect survival in this specific population. However, patients with pancreatic or colorectal cancers harboring frequent PVCs did display a poorer prognosis. The authors postulate that the more frequent use of beta-blockers in NSCLC patients might explain the lack of association between frequent PVCs and prognosis in this group, as beta-blockers are known to suppress PVCs [28].

Supporting the link between ventricular arrhythmias and mortality in cancer, a larger study analyzing 24-hour ECG recordings over a 6-year period (2012-2018) identified the highest prevalence of nsVT (33%) in lung cancer patients without underlying cardiac dysfunction [29]. Furthermore, over half (52%) of the lung cancer patients exhibited a minimum of 20 PVCs during monitoring. A multivariate analysis of the entire cancer cohort revealed that nsVT events of ≥4 beats or a daily PVC burden of ≥20 were independently associated with a heightened risk of all-cause mortality (HR = 1.81, p = 0.016 and HR = 1.6, p = 0.0088, respectively) [28].

Beyond the established role of atrial fibrillation, elevated resting heart rate itself has emerged as a potential independent risk factor for mortality in patients with stable cardiovascular disease [30]. Interestingly, a similar association between heart rate and survival has been observed in specific oncological settings, independent of factors like hemoglobin levels or tumor grade [31]. Hemu et al. demonstrated that the development of sinus tachycardia (heart rate ≥100 bpm) during cancer treatment significantly increases the risk of cardiovascular events and mortality over a 10-year follow-up period [32]. Furthermore, a prospective lung cancer study revealed the prognostic significance of heart rate, irrespective of the underlying rhythm (sinus rhythm or atrial fibrillation). In this study, a resting heart rate exceeding 90 bpm predicted a higher risk of death (HR = 1.67; p = 0.03) [7]. One potential explanation for this association could be the impact of tumor growth on the cardiovascular system. The same study demonstrated a correlation between higher right ventricular systolic pressure (RVSP) (>39 mmHg) and poorer survival (HR = 2.01; p = 0.0045), suggesting that tumor burden might adversely affect cardiac function and contribute to worse outcomes [7].

On the other hand, asymptomatic sinus bradycardia, defined as a heart rate below 50 beats per minute, emerges as an intriguing side effect associated with ALK inhibitor therapy (such as crizotinib). Importantly, this bradycardia may positively correlate with clinical response, serving as a potential indirect marker of drug efficacy [33, 34]. This highlights a distinct scenario where drug-induced bradycardia is not viewed as an adverse effect but rather an indicator of a favorable therapeutic response.

Arterial hypertension

Hypertension (HT) stands as a leading risk factor for CV disease and associated mortality [35]. Alarmingly, a 2019 global survey of 1.5 million adults revealed inadequate HT awareness and management, with 32% never having their blood pressure measured and 23.3% of those with diagnosed HT remaining untreated or sub-optimally treated [36]. This underscores the urgent need for improved management of hypertension. Cancer patients exhibit a disquietingly high prevalence of HT, identified in approximately 38% of individuals across various malignancies [37]. Specifically, within the NSCLC population, prospective multicenter studies document HT in up to 43% of patients [38]. This trend is consistent with findings from a Polish single-center study that identified HT in 42.3% of patients with metastatic EGFR-positive NSCLC [39].

The impact of pre-existing HT as a sole prognostic factor in lung cancer remains an area of ongoing investigation. While some studies haven't established a clear negative impact, the overall body of evidence is not conclusive. Similarly, the potential for lung cancer itself (excluding neuroendocrine tumors) to directly induce HT development lacks definitive evidence [40]. Further research is necessary to elucidate the complex interplay between HT and lung cancer prognosis.

Lung cancer patients frequently experience elevated blood pressure as a side effect of various therapeutic interventions. Cisplatin, a widely used alkylating agent in both NSCLC and SCLC treatment, has been associated with hypertension at differing rates over time: 39% in a 10-year follow-up of testicular cancer patients [40] and 53% in an 11-year follow-up [41]. Proposed mechanisms for cisplatin-induced hypertension include endothelial dysfunction, increased platelet aggregation, and reduced nitric oxide availability [42]. Anti-VEGF agents, like bevacizumab and ramucirumab, also

commonly employed in lung cancer treatment, contribute to elevated blood pressure. Intriguingly, Yan et al. demonstrated a correlation between bevacizumab-induced hypertension and improved response rates in metastatic NSCLC [43]. This finding further supports the concept that treatment-induced hypertension may paradoxically serve as a positive prognostic marker. It's important to note that supportive therapies like steroids, NSAIDs, and erythropoietin can also contribute to hypertension in this patient population [44].

An additional consideration is the potential impact of reduced angiotensin-converting enzyme (ACE) activity in tumor tissue, which has been associated with poor prognosis and metastasis in some studies. While one retrospective analysis suggests a potential survival benefit from RAAS blockers, no studies have conclusively demonstrated a negative effect of these agents in cancer patients [45].

Pulmonary hypertension

Lung cancer and pulmonary hypertension (PH) exhibit a complex, multifactorial relationship. Autopsy studies and animal models have identified pulmonary tumor thrombotic microangiopathy (PTTM) as a key contributor, characterized by microscopic tumor cell emboli and intimal proliferation [46]. Additionally, chronic thromboembolism stemming from venous thromboembolism can lead to PH. Certain chemotherapeutic agents [47] and the rare condition, pulmonary veno-occlusive disease (PVOD) [48], also contribute to the development of PH in cancer patients. Histological evidence of vascular remodeling in lung cancer tissue and in mouse models suggests a direct role of the malignancy in triggering PH [49]. Exploring the connection from a metabolic perspective, both PH and lung cancer cells exhibit a "Warburg effect" – a shift towards aerobic glycolysis for energy production [50]. This altered metabolic state provides the necessary building blocks for the rapid proliferation and apoptosis resistance characteristic of both diseases [51].

An analysis of 562 lung cancer patients with long-term follow-up revealed elevated pulmonary artery systolic pressure (PASP) as a common finding in this unselected cohort (19.8%). This finding highlights a significantly higher prevalence compared to the general population where PH occurs at a rate of 11 to 26 cases per million adults [52]. Several studies indicate that approximately 1.4% of cancer patients develop pulmonary tumor thrombotic microangiopathy (PTTM), a condition that frequently leads to pulmonary hypertension. Lung cancer constitutes a significant portion of these cases (16.7%), with adenocarcinoma being the predominant histological subtype (93.3%) [53].

Coronary artery disease

Coronary artery disease (CAD) arises from atherosclerotic plaque buildup within the coronary arteries, manifesting in alternating periods of clinical stability (chronic coronary syndrome) and destabilization (acute coronary syndrome) [54]. Population-based studies demonstrate an age-related increase in CAD prevalence, with estimates ranging from 10-12% in women and 12-14% in men aged 65-84 years [54]. However, lung cancer patients appear to exhibit a significantly higher burden of CAD, with prevalence rates reported between 10.3% and 33.7% across various studies [10, 55]. Myocardial infarction is a frequent comorbidity, identified in up to one-third of lung cancer patients with pre-existing cardiovascular disease [10].

The concerning co-occurrence of CAD and lung cancer can be attributed to shared risk factors. Cigarette smoking stands out as the most prominent culprit, acting synergistically with other factors like advanced age and obesity to promote both conditions [56, 57]. Mechanistically, chronic inflammation and oxidative stress appear to play a key role in the pathogenesis of both diseases [58, 59]. This overlap extends to the clinical realm, with studies demonstrating the frequent detection of coronary microcalcifications (indicative of atherosclerotic plaques) during lung cancer screening using low-dose CT scans [60, 61]. Interestingly, Sun et al. observed a potential correlation between the severity of CAD (degree of coronary stenosis) and lung cancer, suggesting a possible avenue for future diagnostic strategies that consider both conditions [62].

The presence of pre-existing CAD can complicate the surgical management of early-stage (stage I and II) NSCLC. While some studies suggest a negative impact of CAD on patient prognosis following surgery [63, 64], others have not observed a significant influence on mortality during primary lung cancer resection [65, 66]. This apparent discrepancy in findings may be attributable to variations in the severity of CAD and the effectiveness of pre-operative cardiac management. Given that CAD represents the most prevalent cardiovascular comorbidity, it is plausible that the thoracic surgery risk profile and long-term prognosis are significantly influenced by the extent of CAD and the adequacy of treatment for ischemic symptoms [65, 66]. Future studies that incorporate stratification based on CAD severity and pre-operative cardiac optimization strategies are warranted to definitively elucidate the impact of CAD on surgical outcomes in this patient population.

Acute coronary syndromes (ACS), encompassing conditions like non-ST-segment elevation myocardial infarction (NSTEMI), pose another challenge in cancer care. A concerning number of patients (approximately 15%) undergoing ACS treatment are concurrently diagnosed with cancer [67]. Similar to the general population, NSTEMI represents the most prevalent form of ACS in patients with cancer [68]. However, a significant diagnostic hurdle is the atypical presentation of ACS in this population. Unlike typical presentations, chest pain is only reported by 33% of cancer patients with ACS, while dyspnea (44%) and hypotension (23%) emerge as more frequent presenting features [69]. Furthermore, certain anti-cancer treatments, such as cisplatin, gemcitabine, and bevacizumab, can directly trigger ACS due to their pro-thrombotic properties [70]. The lack of established treatment guidelines specifically tailored for cancer patients with ACS necessitates a management approach that mirrors best practices for the general population, while acknowledging the potential for atypical presentations and drug-induced cardiotoxicity.

The presence of ACS significantly worsens prognosis in cancer patients, as evidenced by multiple studies [71-73]. Lung cancer, in particular, confers a heightened risk of arterial thromboembolic events like myocardial infarction, with a reported three-fold increase in mortality risk [74]. This vulnerability is further underscored by findings from a large, real-world study demonstrating that among various cancer types, lung cancer patients with ST-segment elevation myocardial infarction (STEMI) had the lowest rates of coronary intervention (21.0%), the highest rates of in-hospital mortality, and the most frequent major adverse cardiovascular and cerebrovascular complications [75]. Similarly, another large-scale study analyzing outcomes following STEMI identified lung cancer as one of the most potent independent predictors of all-cause mortality (HR = 2.04), surpassing even advanced peripheral artery disease (HR = 1.78), metastasis (HR = 1.72), and previous stroke (HR = 1.44) [76]. These findings collectively highlight the critical importance of early diagnosis and aggressive management of ACS in patients with underlying cancer, given their heightened susceptibility to poor clinical outcomes.

Heart failure

Heart failure (HF), a complex clinical syndrome characterized by the heart's reduced ability to pump blood effectively, affects a substantial portion of the adult population (1-2%), and its prevalence increases markedly with age [77]. Globally, an estimated 23 million individuals live with HF [78]. Given the considerable overlap in risk factors and the aging population, heart failure and cancer frequently coexist, posing an additional layer of complexity to the management of these patients.

Advances in HF management have translated into improved survival for affected patients. This positive trend suggests that a growing number of HF patients will experience concurrent cancer diagnoses throughout their lifespan. Data from the Women's Health Initiative highlights a concerning link between HF and an increased incidence of obesity-related cancers (HR = 1.24), with lung cancer exhibiting a particularly strong association (HR = 1.58) [79]. Studies investigating the prevalence of heart failure in lung cancer patients present a range of estimates, from 7.6% [80] to 17.5% [55], underscoring the variability across populations.

The presence of HF significantly influences treatment decisions and outcomes in patients with lung cancer. Studies have shown that HF patients are less likely to undergo potentially curative surgical interventions or chemotherapy compared to those with normal cardiac function [81]. This reluctance to administer aggressive therapy is likely due, in part, to the well-established association between HF and increased perioperative mortality in lung cancer surgery (odds ratio [OR] = 6.0) [81]. Paradoxically, the evolving landscape of lung cancer treatment, with the introduction of increasingly potent targeted and immune-oncology therapies, may inadvertently contribute to a rise in the HF population [82]. Both established and emerging drugs used in lung cancer treatment have been linked to the development of HF through various mechanisms [83, 84]. Therefore, a critical challenge lies in optimizing treatment strategies for lung cancer patients with coexisting HF, balancing the potential benefits of anticancer therapies against the risk of cardiotoxicity.

Hospitalizations due to HF exacerbations portend a worse prognosis in patients with coexisting lung cancer. Data demonstrates a higher in-hospital mortality rate in this population (5.9%) compared to HF patients without cancer (3.3%) [85]. However, this same study provides an encouraging observation: between 2003 and 2014, while in-hospital mortality due to HF declined overall, patients with concurrent lung cancer experienced the most significant reduction (from 8.1% to 4.6%; $p < 0.001$). This finding suggests that advancements in the management of both heart failure and lung cancer might be contributing to improved outcomes, even in this complex patient population.

Valvular heart disease

Valvular heart disease (VHD) in patients with cancer can arise from several distinct mechanisms. Pre-existing valvular abnormalities represent one significant risk factor. Additionally, VHD can develop secondary to various cancer treatments: radiation-induced valvular damage, infective endocarditis in the context of chemotherapy-induced immunosuppression, or VHD resulting from treatment-related cardiac dysfunction [86, 87]. This multifaceted etiology highlights the importance of careful cardiac evaluation before, during, and after cancer treatment to ensure early detection and appropriate management of VHD.

Degenerative aortic valve stenosis (AVS), the most prevalent primary valvular heart defect among the general population, presents a unique challenge in lung cancer patients [88]. While surgical aortic valve replacement (SAVR) remains the gold standard treatment for AVS, the majority of patients with active lung cancer are deemed inoperable due to the high risk of perioperative complications like bleeding, arrhythmias, and infections, often compounded by underlying coagulopathies [89]. Transcatheter aortic valve replacement (TAVR) has emerged as a promising alternative for these patients. Current European guidelines recommend TAVR for individuals with a life expectancy exceeding one year [90]. However, this criterion excludes a significant portion of patients with advanced lung cancer, a population often characterized by limited lifespans. Landes et al., in a study investigating survival outcomes following TAVR, reported that lung cancer patients comprised only 11% of the study population, with tumor stage identified as the strongest determinant of late mortality [91]. Several other studies corroborate these findings [92-94]. In contrast, for patients with early-stage lung cancer undergoing thoracic surgery, concomitant cardiac surgery to address valvular defects appears to be a feasible and potentially beneficial treatment option [87]. This strategy warrants further exploration to determine its role in optimizing outcomes in this specific patient subgroup.

While radiotherapy-induced VHD is a recognized complication, with an estimated prevalence of 10% among treated patients [96, 97], its clinical manifestation is often

delayed, with a median time to diagnosis of 22 years [98]. This long latency period, coupled with the short life expectancy associated with advanced lung cancer, generally minimizes the risk of clinically significant radiation-induced VHD within the lifespan of lung cancer patients. However, consideration should be given to this potential complication for long-term lung cancer survivors treated with thoracic radiotherapy, particularly those with younger age at diagnosis.

Patients with cancer face an elevated risk for infective endocarditis (IE), primarily due to treatment-related immunosuppression and the frequent presence of central venous catheters [99]. Staphylococcus aureus emerges as the predominant causative agent in the majority of cases, typically affecting native heart valves (aortic or mitral, less commonly tricuspid) [100]. Alarmingly, studies have demonstrated an association between IE and higher overall mortality in cancer patients, often compounded by underlying tumor progression. While approximately 50% of cases may necessitate cardiac surgery, the management of IE in the context of active cancer presents a complex and challenging scenario [101, 102].

Venous thromboembolism

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a major public health concern globally. Recent European data indicates an annual VTE incidence rate ranging from 104 to 183 per 100,000 individuals [103]. Worldwide prevalence varies considerably, with figures generally fluctuating between 39–115/100,000 for PE and 53–162/100,000 for DVT [104]. Of particular concern, acute PE, the third most common acute cardiovascular syndrome, is experiencing a rising incidence [105, 106]. This alarming trend underscores the need for heightened awareness and effective preventive strategies to address this significant healthcare challenge.

Major surgery (OR = 18.95) and active cancer (OR = 14.64) stand out as the most potent independent risk factors for deep vein thrombosis (DVT) or PE [107]. Among malignancies, lung cancer ranks sixth as a leading contributor to PE [108]. Notably, lung cancer, particularly the adenocarcinoma subtype, predisposes individuals to PE more strongly than other cancers, with an especially pronounced risk within the first three months following diagnosis [109]. Studies have demonstrated that lung cancer patients are six times more likely to experience PE compared to cancer-free individuals in the year prior to diagnosis [110]. Moreover, the risk of PE correlates with the stage of cancer progression, with an elevation in hazard ratio (HR) at various timepoints: for NSCLC - HR = 9.7 six months prior to diagnosis, HR = 20.0 within six months post-diagnosis, and HR = 17.4 during the 12 months following diagnosis; for SCLC - HR = 6.9, HR = 14.8, and HR = 16.1, respectively [111].

PE exhibits a strong association with advanced stages (III and IV) of lung cancer [112]. The Vienna Cancer and Thrombosis Study employed multivariable Cox proportional hazards analysis to identify lung cancer as a high-risk tumor site for VTE (HR = 4.3; $p < 0.001$), alongside factors such as high tumor grade, adenocarcinoma histology, and elevated D-dimer levels [113]. Furthermore, a significant proportion of PE diagnoses in cancer patients are incidental or asymptomatic (increased risk of incidental PE in cancer: OR = 1.80) [114]. These asymptomatic PEs are often identified during routine imaging procedures for cancer staging or treatment response evaluation. In lung cancer patients specifically, the prevalence of incidental/asymptomatic PE ranges from 29.4% to 63% [115]. Among malignancies, colorectal cancer and lung cancer appear to have the highest rates of incidental VTE [116]. These findings underscore the crucial need for heightened vigilance for PE in patients with lung cancer, particularly in advanced stages, given their significantly elevated risk and the potential for asymptomatic presentations.

Lung cancer treatment itself can paradoxically increase the risk of new thromboembolic events [115]. While PE occurring during active lung cancer treatment may not directly influence survival ($p = 0.206$) [109], subsequent cancer remission appears to lower the risk of recurrent VTE [117]. This suggests that the successful management of the underlying malignancy, along with the subsequent resolution of prothrombotic states associated with active cancer, plays a crucial role in improving prognosis for patients with cancer-related VTE.

Post-mortem studies by Nichols et al. revealed that PE directly caused death in 10% of lung cancer patients, with the possibility that PE may contribute to mortality in a broader range of cases based on pathophysiological considerations [118]. Significantly, PE has been demonstrably associated with a poorer prognosis in lung cancer ($p < 0.0005$) [119]. The authors suggest that this correlation might be attributable to factors such as more advanced disease stages (III or IV) and a higher prevalence of patients receiving only supportive care, excluding anti-cancer therapies. A prospective cohort study investigating older lung cancer patients (aged ≥ 65 years) corroborated these findings. Patients with PE experienced a statistically significant reduction in overall survival (4.3 vs. 9.2 months, $p = 0.0015$). While PE-related mortality was significantly higher in the PE subgroup (15.1% vs. 0%), there were no statistically significant differences observed in tumor-related mortality rates (75.5% vs. 66.0%) [120]. Furthermore, PE diagnosed concurrently with lung cancer diagnosis appears to be associated with a shorter lifespan [121]. These findings collectively underscore the detrimental impact of PE on prognosis in lung cancer patients.

Studies have shown no significant difference in mortality between symptomatic and asymptomatic PE in lung cancer patients. However, both presentations worsen prognosis due to potential complications like hemorrhagic events and recurrent VTE episodes, with these patient groups exhibiting similar characteristics in terms of age and metastatic disease burden [122]. Alarmingly, data suggests that as many as 55% of lung cancer patients with undiagnosed PE do not receive anticoagulation therapy, a circumstance associated with a substantially increased risk of premature death (HR = 4.1) [123]. These findings underscore the importance of

maintaining a high index of suspicion for PE in lung cancer patients, even in the absence of overt symptoms, to ensure timely diagnosis and potentially life-saving anticoagulation therapy.

Comorbidity or multi-morbidity

Cardiovascular comorbidities significantly impact outcome and quality of life in lung cancer patients. However, it is crucial to recognize the compounding influence of other age, obesity, and tobacco-related conditions. The prevalence of multiple chronic diseases alongside lung cancer is so high that experts have coined the term "multimorbidity". A study from Spain demonstrated significantly higher mortality in lung cancer patients with multimorbidity (40% greater mortality) compared to patients with one or no chronic comorbidities ($p = 0.002$) [124]. Unsurprisingly, the prevalence of multimorbidity correlated strongly with older age and a history of smoking. These findings emphasize the need for a holistic approach to managing lung cancer patients, taking into account the cumulative burden of multiple chronic conditions and their potential impact on treatment outcomes.

Previous findings demonstrating a strong correlation between multimorbidity, older age, and smoking history are essential considerations when addressing lung cancer management. These factors underscore the importance of a comprehensive approach that accounts for the impact of multiple chronic conditions on treatment outcomes. In addition to cardiovascular diseases, other highly prevalent comorbidities in lung cancer include chronic obstructive pulmonary disease (COPD) [125], secondary malignancies (10-20%), and diabetes mellitus (5-25%) – all of which carry significant prognostic implications [126]. Studies generally indicate a 1.1-1.5-fold increase in mortality for lung cancer patients with comorbidities [127], with an analysis identifying 19 specific comorbidities as independent predictors of survival [80]. Data from the Nebraska Hospital Discharge database further highlights how conditions such as congestive heart failure, diabetes, liver disease, dementia, renal disease, and cerebrovascular disease can negatively impact lung cancer survival rates. Interestingly, the greatest survival disparities between patients with and without comorbidities were observed in lower grade cancers: HR = 1.316 (localized), HR = 1.228 (regional), HR = 1.075 (metastatic) [128]. It's important to note that the more frequent follow-up experienced by individuals with comorbidities might contribute to earlier cancer detection.

Conclusion

Acute cardiovascular events, such as pulmonary embolism and myocardial infarction, significantly worsen the prognosis for lung cancer patients. Importantly, the risk of both venous and arterial thromboembolic complications in lung cancer strongly correlates with advancing tumor stage [113, 129]. Furthermore, thromboembolic events often coincide with the initial presentation of the malignancy [130, 131]. This complex interplay highlights the urgent need for proactive assessment and management of cardiovascular risks in lung cancer patients, especially in more advanced stages of the disease.

Lung cancer treatment modalities, including systemic therapy and radiotherapy, can themselves induce cardiovascular complications [132, 133]. Studies have shown an increased risk of developing CAD or HF in patients over 65 years of age receiving chemotherapy [132]. Similarly, radiotherapy, particularly when directed at the left lung, has been associated with a higher incidence of cardiac disorders [133]. The risk of cardiotoxicity appears to be greatest in patients undergoing combined chemo-radiotherapy [134]. Furthermore, the ARIC Study demonstrated an increased risk of cardiovascular disease development, particularly HF, even in lung cancer survivors who lacked traditional cardiovascular risk factors [135]. These findings underscore the importance of considering the potential long-term cardiovascular effects of treatment when developing therapeutic strategies for lung cancer patients.

Lung cancer exhibits the highest prevalence of cardiovascular comorbidities compared to other malignancies [136]. A study documented concomitant cardiovascular disease in at least 67.2% of NSCLC patients [137]. The impact of pre-existing cardiac comorbidities on mortality appears to be most significant in early-stage lung cancer. Extensive data analysis involving 95,167 NSCLC patients revealed that cardiovascular disease increased mortality across stages I-IIIB, while losing prognostic significance in stage IV [10]. Specific cardiac conditions such as heart failure, myocardial infarction, and arrhythmias were associated with a poorer prognosis during follow-up. However, the magnitude of risk varied according to disease stage and treatment modality, with concomitant cardiovascular diseases increasing mortality risk by up to 2.59-fold ($p < 0.001$) for chemotherapy alone and 2.20-fold ($p < 0.001$) for combined chemotherapy and radiotherapy in stages I-IIIB.

The prognostic influence of pre-existing cardiovascular comorbidities appears to be diminished in advanced stages of lung cancer. At this stage, cardiac arrhythmias, particularly atrial fibrillation, and echocardiographic findings suggestive of pulmonary hypertension (increased right ventricular systolic pressure) and right ventricular dysfunction are more likely attributable to the neoplastic process itself, correlating with a decline in performance status and predicting a shorter overall survival [7]. These observations highlight the complex interplay between advanced lung cancer and cardiovascular complications, where pre-existing comorbidities may take a backseat to the direct effects of tumor progression on the heart.

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