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Are cardiovascular comorbidities always associated with a worse prognosis in patients with lung cancer?

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Many factors contribute to mortality in lung cancer, including the presence of concomitant cardiovascular disease. In the treatment of early stage of lung cancer, the presence of comorbidities and occurrence of cardiotoxicity may be prognostic. The effect of cardiotoxicity of radiotherapy and chemoradiotherapy on overall survival has been documented. Acute arterial and venous thromboembolic events seem to correlate with the degree of the histological malignancy, its clinical advancement, and even with optimal cardiac treatment, they may influence the survival time. In the case of high-grade and advanced lung cancer stage especially in an unresectable stadium, the prognosis depends primarily on the factors related to the histopathological and molecular diagnosis. Electrocardiographic and echocardiographic abnormalities may be prognostic factors, as they seem to correlate with the patient's performance status as well as tumor localization and size.

KEYWORDS

lung cancer, cardio-oncology, survival, prognosis, heart failure, thromboembolism

Introduction

Lung cancer is one of the most common malignancies worldwide and also the most common cause of cancer-related deaths in both men and women. The 5-year survival rates for all stages of lung cancer do not exceed 15–20% (1). There are multiple factors that influence mortality, including the presence of comorbidities. Depending on their duration, these conditions can be classified as chronic and acute.

The Charlson Comorbidity Index (CCI) is the most commonly used tool to assess the likelihood of death within a year for a patient with comorbidities, a score of ≥ 3 is associated with an 80% increase in the risk of death within a year (Table 1) (2). The CCI is important prognostic scale in oncology because it is independent of cancer stage and performance status. Other scale evaluating comorbidities is the Simplified Comorbidity Score (SCS) confirmed in lung cancer as independent determinant of a poor outcome (Table 1) (3). This validation study revealed the strong statistical concordance between CCI and SCS, by univariate analysis of large group of non-small-cell lung cancer (NSCLC) patients with long term follow up, CCI ≥ 3 and SCS > 9 were considered

TABLE 1 The comparison of the main mentioned indexes used for prognosis in lung cancer (2, 3).

Charlson comorbidity index (CCI)		Simplified comorbidity score (SCS)	
Myocardial infarction	1	Tobacco consumption	7
Congestive heart failure	1	Diabetes mellitus	5
Peripheral vascular disease	1	Renal insufficiency	4
Cerebrovascular disease	1	Respiratory comorbidity	1
Dementia	1	Cardiovascular comorbidity	1
Chronic pulmonary disease	1	Neoplastic comorbidity	1
Connective tissue disease	1	Alcoholism	1
Ulcer disease	1		
Mild liver disease	1		
Diabetes	1		
Hemiplegia	2		
Moderate or severe renal disease	2		
Diabetes with end organ damage	2		
Any tumor without metastasis	2		
Leukemia	2		
Lymphoma	2		
Moderate or severe liver disease	3		
Metastatic solid tumor	6		
AIDS	6		

as important for outcome ($p = 0.06$ and $p < 0.01$ respectively) with final suggestion of higher prognostic value of SCS. However both CCI and SCS were not predictable for survival, radiological response and toxicity during first-line chemotherapy due to advanced lung cancer (4). Similarly in patients with advanced and unrespectable NSCLC treated with radical sequential chemoradiotherapy CCI >4 or SCS >8 were not predictors of survival (5).

In patients with NSCLC, cardiovascular (CV) comorbidities, including coronary artery disease, hypertension, arrhythmias, and peripheral arteriosclerosis, increased the risk of death by 30% compared to patients without these conditions (6). However, some studies have shown no direct effect of concomitant diseases on overall survival (OS) in lung cancer in advanced inoperable stage (7). Retrospective cohort studies have shown that cancer-related mortality rates for biologically aggressive malignancies exceed those for comorbidities (8, 9).

Batra et al. showed that patients with lung cancer and CV diseases were less likely to receive oncological treatment, whether chemotherapy, targeted therapy or radiotherapy (10). It has also been shown that prior CV disease increases the risk of cancer-unrelated death (HR = 1.48; $p < 0.0001$) and does not contribute to cancer-related mortality. Disqualification from cancer treatment or use of less intensive and consequently less effective cancer treatment due to comorbidities, which may influence on overall survival, also seem an important problem.

The aim of this study was to review literature on the impact of cardiovascular comorbidities on the prognosis in

patients with lung cancer with special focus on the more common NSCLC.

Cardiac arrhythmias

The mechanism underlying cardiac arrhythmias and conduction disturbances in cancer patients consists of several elements: patient-related factors (comorbidities, age, genetic predisposition), tumor-related factors (invasion, autonomic system excitation, inflammation), cancer treatment-related factors (electrolyte abnormalities due to gastrointestinal toxicity, cardiac structural or electrical remodeling induced by chemotherapy, targeted therapy, immunotherapy, radiotherapy, supportive medications) (11).

Atrial fibrillation (AF) is the most common arrhythmia, affecting 2–4% of the general population, whose prevalence increases with age (up to 36% at the age of 85 years) (12). Cancer patients have many additional reasons to experience AF (13). The OPERA study (Oulu Project Elucidating Risk of Atherosclerosis) showed that cancer disease may be understood an independent risk factor of AF development, because authors recognized AF in 19% with cancer in comparison to only 9% of subject without cancer ($p < 0.001$, HR = 2.47; 95%CI: 1.57–3.88) (14). The new-onset AF may be associated with increased relative risk of a diagnosis of cancer disease of the lung, kidney, colon, ovary as well as non-Hodgkin's lymphoma: seven times increased risk for metastatic and 3.5 times for localized cancer

disease (15). The time relationship of 90 days between the recognition of AF and cancer is strongly interesting, because in this period the diagnosis of cancer can predict a 3.4 fold increased risk of new AF, however AF occurrence is related to a 1.85 times higher probability of coexisting cancer (16).

The large population-based study proved that not all types of cancer are associated with AF, but certainly hematological and intrathoracic malignancies are associated with AF (17). This study revealed the risk of AF development is more than doubled in patients with esophageal (HR = 2.69) and lung cancer (HR = 2.39), interestingly, lung cancer showed the strongest association with AF in patients aged > 50 years. Among women with new-onset AF the significant age-adjusted risk was observed for colon (HR = 2.36; $p < 0.001$), breast (HR = 1.35; $p = 0.04$) and lung cancer (HR = 1.69; $p = 0.04$) (18).

Particularly high AF percentages are observed among lung cancer patients. One of the Nationwide population-based study showed the highest incidence of AF as number per person years in lung cancer: 58.7/1000 in men and 35.3/1000 in women (19). The large analysis of cardiovascular admissions to hospital in US revealed AF as the main cause of hospitalization in lung cancer patients and significantly increased mortality was noted in lung cancer and AF (aOR = 4.69) (20).

However, the mechanisms underlying the high incidence of AF in cancer patients are not fully elucidated. In addition to classical risk factors present in the general population (hypertension, diabetes, heart failure, coronary artery disease, obesity, etc.), other factors, i.e., water-electrolyte disturbances, hypoxia, sympathetic over activity due to pain and emotional stress, have also been considered (21, 22). It can be additionally assumed that chronic pulmonary obstructive disease, often coexisting with lung cancer, is also a risk factor for AF, especially if there are episodes of infectious exacerbations and when the size of the left atrium is increased (23). A similar cause can be seen in AF with concomitant pulmonary hypertension associated with hypoxia in lung cancer (24). Compression or infiltration of the tumor mass or metastases to the heart may be another possible cause. AF can also be a complication of systemic treatment, radiotherapy or thoracic surgery (it occurs in 10–20% of patients 2–3 days after surgery) (25).

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 arrhythmia is another common type of rhythm abnormalities with possible impact on prognosis in the general population. Anker et al. assessed cancer patients free of

cardiovascular diseases in comparison to healthy controls using 24-h ECG (28). They showed an increased frequency of non-sustained ventricular tachycardia (nsVT) observed in 6% of NSCLC patients and associated with negative impact on survival (HR = 2.68; $p = 0.005$). Prognostic value of nsVT was significant independently of type of cancer. Although in the same study single premature ventricular contractions (PVCs) were observed in 42% of NSCLC patients (in 21% in number of 50 or more per 24 h) this arrhythmia did not affect the prognosis for NSCLC patients, but surprisingly it had an effect on the survival of patients with pancreatic and colorectal cancer. As one of possible explanation may be a fact that NSCLC patients receive beta-blockers more frequent which could inhibit PVCs. In the larger study where 24-h ECG recordings from the period of 6 years (2012–2018) were reviewed, the highest frequency of nsVT (33%) was observed in lung cancer patients without cardiac dysfunction (29). Moreover 52% of lung cancer patients had at least 20 PVCs during monitoring. The analysis in whole group of cancer patients revealed the arrhythmias nsVT ≥ 4 beats or PVCs ≥ 20 /day were independently associated with higher risk of all-cause mortality (HR = 1.81, $p = 0.016$ and HR = 1.6, $p = 0.0088$, respectively in multivariate adjusted analysis).

Elevated resting heart rate alone may be an independent risk factor for death in stable cardiovascular disease in general cardiology (30). In selected cancer diseases irrespective of hemoglobin levels or tumor grade, a similar relationship has been observed (31). Hemu et al. showed that sinus tachycardia (heart rate ≥ 100 /min.) occurring during cancer treatment is associated with an increase in cardiovascular events and mortality over a 10-year period (32). The prospective study in lung cancer demonstrated the prognostic significance of heart rate, regardless of whether it was sinus rhythm or atrial fibrillation, heart rate > 90/min predicted a higher risk of mortality (HR = 1.67; $p = 0.03$) (7). The tumor growth effect can be considered a potential explanation, as shorter survival was also observed in patients with right ventricular systolic pressure (RVSP) higher than 39 mmHg (HR = 2.01; $p = 0.0045$).

On the other hand, asymptomatic sinus bradycardia, defined as heart rate < 50/min, is an adverse effect of ALK inhibitor treatment (such as crizotinib) and may positively correlate with clinical response to treatment (33, 34). However it should be remembered that this slowing of the heart rate is an effect of the cancer drug activity and therefore appears to correlate with its efficacy.

Arterial hypertension

Hypertension (HT) is one of the major single risk factors for cardiovascular (CV) diseases and increased CV mortality (35). A worldwide survey among 1.5 million adults performed in May 2019 showed that 32% of the population had never had their blood pressure measured, 34% had HT of whom

23.3% had untreated or sub-optimally treated HT (36). It is also the most common comorbidity among cancer patients, regardless of the type of malignancy identified in 38% of patients (37). Prospective multicenter study documented HT in 43% of NSCLC patients (38). Similarly Polish study based on one center experience identified HT in 42.3% of metastatic NSCLC EGFR positive patients (39).

There are no papers clearly demonstrating the negative impact of pre-existing HT as a single prognostic factor in lung cancer. Moreover, there are no evidences that lung cancer (except for neuroendocrine type) may lead to HT development.

Lung cancer patients usually experience increase in blood pressure related to cancer therapy. Cisplatin is the most commonly used alkylating agent in various treatment regimens for both NSCLC and small cell lung cancer (SCLC). It increases blood pressure at varying rates, depending on the observation of patients with testicular cancer: 39% in 10-year follow-up (40) or 53% in 11-year follow-up (41). The main mechanisms leading to increased blood pressure include endothelial cell dysfunction or damage, excessive platelet aggregation and reduced nitric oxide availability (42). Anti-VEGF agents, such as bevacizumab and ramucirumab, are other drugs used in the treatment of these tumors that also may contribute to the increase in blood pressure. Yan et al. showed that HT in the treatment with bevacizumab-based regimens for metastatic NSCLC was associated with higher response rates (43). This is a next clear confirmation that HT as effect of cancer drug activity correlate positively with outcome. Supportive therapies, such as steroids, non-steroidal anti-inflammatory drugs or erythropoietin, are also implicated in hypertension (44). Reduction of angiotensin-converting enzyme (ACE) activity in tumor tissue correlating with poor prognosis and tumor metastasis is yet another problem. One retrospective paper has shown a positive effect of RAAS blockers on survival, whereas none has shown its negative effect (45).

Coronary artery disease

Coronary artery disease (CAD) is a condition associated with the formation of atherosclerotic plaques in the coronary arteries, which runs with periods of clinical stability (chronic coronary syndrome) and destabilization (acute coronary syndrome). According to population-based studies, the CAD prevalence increases with age and is 10–12% in women aged 65–84 years, and 12–14% in similarly aged men (46). The prevalence in lung cancer patients seems to be higher because ranges from 10.3% (10) to 33.7% (47), depending on the source. Every third patient (33%) from those with cardiovascular disease had previous myocardial infarction (10).

The high prevalence of CAD and lung cancer is due to common aetiological factors: cigarette smoking (48), advanced age, obesity (49) and the same pathomechanism associated with

oxidative stress and chronic inflammation (50, 51). During lung cancer screening by a low-dose CT scan, coronary microcalcifications indicative of atherosclerotic lesions have been additionally found as often coexisting clinical problem (52, 53). Sun et al. demonstrated a relationship between the severity of CAD (degree of coronary stenosis) and lung cancer, which may broaden the diagnostic scope for this malignancy in the future (54).

The coexistence of CAD can worsen the prognosis of patients undergoing surgery for stage I and II NSCLC (55, 56). On the other hand, other studies have shown no significant effect of CV disease on mortality during primary surgery (57, 58). Assuming that CAD is the most common cause of CV diseases, the conflicting data may reflect the thoracic perioperative risk and prognosis may depend on the severity of CAD and control of ischemic symptoms through effective cardiac treatment.

Acute coronary syndromes (ACS) are another problem. Approximately 15% of patients treated for ACS have a coexisting cancer (59). Non-ST-segment elevation myocardial infarction (NSTEMI) accounted for the majority of ACS in cancer patients, as in the general population (60). The clinical picture of ACS in cancer patients is atypical, with only 33% of patients experiencing chest pain, 44% reporting dyspnoea and 23% developing hypotension (61). ACS can also be triggered by anti-cancer treatment. Cisplatin, gemcitabine and bevacizumab are highly thrombogenic (62). Treatment guidelines for cancer patients are missing, and it is believed that this group should be treated like other patients.

Many studies show a worse prognosis for patients with ACS and cancer (63–65). In particular, lung cancer patients are at risk of arterial thromboembolism like myocardial infarction and in this way the risk of mortality is increased three times (66). Lung cancer is one of the four most common types of cancer disease with highest frequency of myocardial infarction, only 21.0% of those patients were treated by coronary intervention, lung cancer was associated with the highest in-hospital mortality, major adverse cardiovascular and cerebrovascular complications (67). The large “real world” data on prognosis after STEMI presented lung cancer as one of the strongest independent determinants of all-cause mortality (HR = 2.04), next advanced peripheral artery disease (HR = 1.78), metastasis (HR = 1.72), previous stroke (HR = 1.44) (68).

Heart failure

Heart failure (HF) affects 1–2% of adults in the general population, and its prevalence increases with age (69). There are 23 million people worldwide with HF (70) and many of them may experience of lung cancer.

Current treatment of HF improves patients’ survival, which means that more of these patients will have cancer. In an analysis performed by the Women’s Health Initiative, in postmenopausal

women HF was shown to be associated with an increased incidence of obesity-related cancers (HR = 1.24), and even more with the risk of developing lung cancer (HR = 1.58) (71). The prevalence of HF in patients with lung cancer is estimated between 7.6% (72) and 17.5% (47), depending on the source.

HF patients were less likely to undergo surgery and chemotherapy than patients without HF. HF is significantly correlated with increased perioperative mortality in lung cancer (OR = 6.0) (73). More and more aggressive anticancer treatment will increase the number of patients with newly diagnosed HF (74). Both old and newer drugs recommended in lung cancer seem to predispose to HF development through different pathomechanism (75, 76).

Patients with known lung cancer hospitalized for HF have a higher mortality rate (5.9%) compared to those cancer-free (3.3%) (77). In the same study, as a very optimistic observation, it should be considered that over the years from 2003 to 2014, mortality among patients hospitalized due to HF decreased, but very importantly, the decrease in mortality was the highest among patients with accompanying lung cancer (8.1 to 4.6%; $p < 0.001$).

Valvular heart disease

Valvular heart disease (VHD) may occur in cancer patients for several reasons: due to pre-existing valvular defects and as a complication of anti-cancer treatment: after radiotherapy, due to infective endocarditis in the course of chemotherapy-induced severe infection and secondary to cardiac dysfunction (78, 79).

Degenerative aortic valve stenosis is the most common primary valvular heart defect in the general population (80). The majority of patients with active cancer are disqualified from classical cardiac surgery (surgical aortic valve replacement, SAVR) due to the high risk of perioperative complications such as bleeding, arrhythmias, infections or coagulation disorders (81). Transcatheter aortic valve replacement (TAVR) seems to be an alternative solution. According to current European recommendations, the procedure should be performed in patients with expected survival of at least 1 year (82), but only a small percentage of patients with advanced lung cancer meets such criteria. In a study by Landes et al. compared the survival of patients with and without cancer who underwent TAVR, lung cancer patients constituted a small group - only 11% (83). The authors showed a worse prognosis in oncology patients, with tumor stage being the strongest predictor of late mortality. Similar findings were also published in several other papers (84–86). However it is worth to consider concomitant cardiac surgery as treatment option for valvular defects in patients with early stage lung cancer scheduled for thoracic surgery (87).

The prevalence of radiotherapy-induced VHD is described as frequent, affecting approximately 10% of treated patients (88, 89), but it occurs late (median time to diagnosis is 22 years)

(90). The short expected survival time of lung cancer patients does not allow for the manifestation of late cardiac toxicity, which is a typical complication of radiation therapy.

Cancer patients have a higher risk of developing infective endocarditis (IE) due to immunosuppression (e.g., secondary to chemotherapy) or the presence of a central line or a vascular port (91). In most studies, *Staphylococcus aureus* was the predominant aetiological agent, with one native valve (aortic or mitral, less frequently tricuspid) most frequently involved (92). A higher mortality in the course of IE was also demonstrated in all cancer patients in comparison to the control group (also associated with tumor progression). Cardiac surgery was performed in approximately 50% of patients (93, 94).

Venous thromboembolism

Venous thromboembolism (VTE) as deep vein thrombosis (DVT) and pulmonary embolism (PE) is the common clinical worldwide problem in general population, because last data showed the annual incidence rate of VTE in Europe ranged from 104 to 183 per 100000 person-years (95). Prevalence of VTE varies greatly from region to region but generally fluctuates 39–115/100000 for PE, and 53–162/100000 for DVT (96). Acute PE remains the third most common cause of acute cardiovascular syndromes, its incidence increases (97, 98).

Major surgery (OR = 18.95) and active cancer (OR = 14.64) belong to the strongest independent risk factors for DVT or PE (99). Lung cancer is the sixth most frequent reason of PE among malignancies (100). Lung cancer, especially adenocarcinoma, predisposes to PE more than other malignancies, especially within 3 months of the diagnosis (101). It has also been shown that lung cancer patients are six times more likely to develop PE than those cancer-free in the 12 months preceding the diagnosis (102). Risk of PE diagnosis correlates with a moment of cancer occurrence: for NSCLC: HR = 9.7 during 6 months prior to cancer diagnosis, HR = 20.0 during 6 months after cancer diagnosis and HR = 17.4 during 12 months after cancer diagnosis and for SCLC: HR = 6.9 and HR = 14.8 and HR = 16.1 respectively (103).

PE most often accompanies advanced-stage lung cancer (stages III to IV) (104). The Vienna Cancer and Thrombosis Study by multivariable Cox proportional hazards analysis confirmed that lung is one of the high risk tumor site associated with VTE (HR = 4.3; $p < 0.001$) together with high tumor grade, tumor histology (adenocarcinoma) and elevated D-dimer level (105). PE is diagnosed in a high percentage of cancer patients incidentally as unprovoked PE or asymptomatic PE (the increased risk of incidental PE in cancer was calculated as OR = 1.80) (106). PE can be recognized during diagnostic imaging for staging or evaluation of response to cancer treatment. In lung cancer such correlation with asymptomatic/incidental PE ranges from 29.4 to 63% of patients

(107). Colorectal cancer and lung cancer appears to be two cancer diseases with the most frequent incidental VTE (108).

Lung cancer treatment can induce new episodes of VTE (107). PE developed during lung cancer treatment rather does not affect survival ($p = 0.206$) (101). Subsequent cancer remission resulted from cancer therapy and control of cancer-related coagulation state seem to reduce the occurrence of VTE important for prognosis (109).

Nichols et al. showed in their post-mortem studies in lung cancer patients that PE was the direct cause of death in 10% of cases, however from a pathophysiologic perspective, PE may be an additional contributing cause of death in many other cases (110). PE significantly worsens the prognosis in lung cancer ($p < 0.0005$) and as a possible explanation authors discussed more advanced stage of cancer disease (III or IV) and more frequent used only supportive care without anticancer therapy (111). In the prospective cohort study in older patients (age ≥ 65 years) with lung cancer it was documented significantly shorter survival in subgroup with PE (4.3 vs. 9.2 months, $p = 0.0015$), there were significant differences in PE-related mortality (15.1 vs. 0%) but insignificant differences in tumor-related mortality (75.5 vs. 66.0%) (112). It should be highlighted that PE is associated with shorter survival when is recognized synchronous with lung cancer (113).

No difference in mortality between symptomatic vs. asymptomatic PE in lung cancer was documented, with both forms worsening the prognosis due to haemorrhagic complications and VTE recurrences (there were similar patients' age and frequency of metastatic disease) (114). There are data that even 55% of lung cancer with unsuspected PE did not receive anticoagulation therapy which led to premature death (HR = 4.1) (115).

Comorbidity or multi-morbidity

The outcome and quality of life in lung cancer can be determined not only by coexisting cardiovascular diseases, the importance of other age-, obesity- and tobacco-related diseases should be taken into account. Number of comorbidities in lung cancer is so high that authors from Spain proposed the term multi-morbidity when at least two chronic diseases coexist with lung cancer and documented the highest mortality in patients with multi-morbidity ($p = 0.002$) in comparison to patients with one or no comorbidity (40% higher mortality) (116). It is worth emphasizing that the prevalence of multi-morbidity correlated with older patients' age and history of smoking.

Apart from cardiovascular diseases, chronic obstructive pulmonary disease is most often associated with lung cancer (117). Among other serious co-morbidities another cancer (10–20%) and diabetes mellitus (5–25%) seem to be essential for prognosis (118). Generally, mortality in lung cancer was defined as 1.1–1.5 times higher for patients with comorbidity (119). In lung cancer 19 comorbidities were found as independent

predictors of survival (72). The Nebraska Hospital Discharge Data showed survival in lung cancer may negatively depend on congestive HF, diabetes, liver disease, dementia, renal disease, cerebrovascular disease, the greatest difference in survival in patients with and without comorbidities was seen at low grades: HR = 1.316 for localized, HR = 1.228 for regional and HR = 1.075 for metastatic lung cancer (120). Due to frequent follow-up, patients with comorbidities were more likely to be diagnosed at an early stage of each cancer disease.

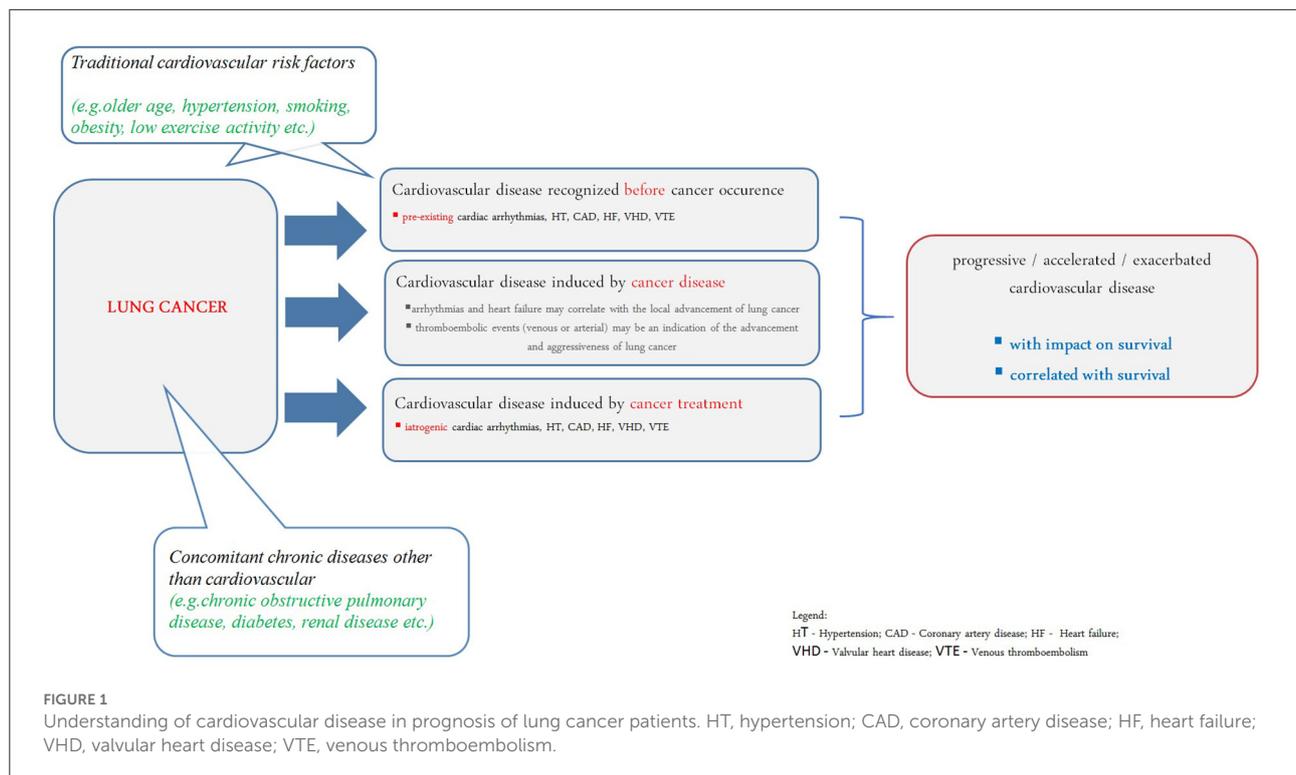
Conclusion

Acute cardiac conditions, such as pulmonary embolism or myocardial infarction, clearly worsen the prognosis in lung cancer. Lung cancer belongs to such malignancies where the risk of venous and arterial thromboembolic complications correlates with tumor advancement (Figure 1) (105, 121). Often an arterial or venous thromboembolic event occurs at the onset of the neoplastic disease (122, 123).

Systemic treatment and radiotherapy in lung cancer may cause cardiovascular complications (124, 125). It has been shown that in patients over 65 years of age undergoing chemotherapy, the risk of developing CAD or HF was increased; cardiac disorders were also more common in patients undergoing radiotherapy, especially if the left lung was irradiated. The greatest risk of cardiotoxicity was found in patients undergoing chemo-radiotherapy (126). ARIC Study revealed that lung cancer survivors have higher risk of cardiovascular disease development (especially HF) even they do not have traditional cardiovascular risk factors (Figure 1) (127).

Lung cancer patients have the highest prevalence of cardiovascular comorbidities compared to other cancers (128). At least one concomitant cardiovascular disease was present in 67.2% of patients with NSCLC (129). The hypothesis that the effect of chronic cardiac comorbidities on mortality is dominant in early stages of lung cancer seems most plausible. Data on 95 167 NSCLC patients showed that cardiovascular disease can increase mortality when the cancer stage is in the range I-III B, while it is not important for survival in stage IV (10). Worse prognosis was associated with concomitant heart failure, myocardial infarction, and arrhythmias diagnosed during follow-up, although the risk still varied depending on the stage of the disease and the treatment method. For stage I-IIIB disease, concomitant cardiovascular diseases increased the risk of mortality by as much as 2.59 ($p < 0.001$) for chemotherapy and by 2.20 ($p < 0.001$) for chemotherapy and radiotherapy.

The impact of cardiovascular comorbidities on prognosis is limited in advanced stages of lung cancer. Cardiac arrhythmias (especially atrial fibrillation) and echocardiographic changes suggesting the development of pulmonary hypertension (right ventricular systolic pressure increase) and dysfunction of the right ventricle rather result from the advancement of neoplastic



disease, correlate with decreased performance status and predict shorter overall survival (Figure 1) (7).

Author contributions

All authors have design and conception, writing of manuscript, editing and reviewing the manuscript and final approval of the version to be published.

Conflict of interest

SS declares speaker fee or advisory board fee or travel and meeting support: Angelini, Amgen, Astra-Zeneca, Bayer, BMS, Gilead, Pfizer, TEVA (all outside of this study).

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