CT-Defined Coronary Artery Calcification as a Prognostic Marker for Overall Survival in Lung Cancer: A Systematic Review and Meta-analysis

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Rationale and Objectives: Coronary artery calcification (CAC) can be quantified by computed tomography (CT). It is an important predictive and prognostic imaging marker for cardiovascular disease. The prognostic role for CAC in oncological patients is provided in preliminary studies, especially in lung cancer patients. The aim of the present study was to establish the effect of CAC score on overall survival (OS) in lung cancer patients based on the published literature

Materials and Methods: Literature databases were screened for papers analyzing the association between CAC and overall survival in lung cancer patients up to June 2024. The primary endpoint of the present systematic review was the OS. Overall, seven studies were suitable for the analysis and were included.

Results: The included studies comprised 2292 patients undergoing curative treatment. The pooled hazard ratio for the association between CAC score and OS was HR = 1.42 (95% CI = (1.19; 1.69), $p < 0.0001$) in the univariable analysis and HR = 1.56 (95% CI = (1.25; 1.94), $p < 0.0001$) in the multivariable analysis. The pooled odds ratio for the association between CAC score and major cardiovascular events was OR = 1.97 (95% CI = (1.24; 3.13)], p = 0.004.

Conclusion: CT-defined CAC has a meaningful impact on overall survival and prediction of major cardiovascular events in lung cancer patients undergoing curative treatment. The sole presence of CAC on staging CT should be reported as an important prognostic marker in these patients.

Key Words: Meta-analysis; Systematic review; Coronary calcification; Lung cancer.

INTRODUCTION

Lung cancer is still the leading cause of both incidence and mortality, with 2.1 million new cases and 1.8 million deaths in 2018 for cancer (1,2). This leads to nearly one in five (18.4%) cancer deaths caused by lung cancer (2,3). It is a well-established fact that tobacco smoking is the most important risk factor for lung cancer occurrence and every histological subtype has been associated with tobacco use (1,4).

Computed tomography (CT) is used for diagnosis and staging in lung cancer patients, but harbors also prognostic factors, comprising the tumor size and sarcopenia as an important body composition parameter (5–7). However, there is need to extract further parameters from the acquired CT images.

Coronary artery calcification (CAC) can be diagnosed and quantified using computed CT (8–10). There is a growing body of literature demonstrating the prognostic importance of CAC in patients with coronary artery disease (8–10).

The Framingham Heart Study has shown a strong association between CAC score and major cardiovascular events in asymptomatic individuals (9).

In addition, CAC has been shown to be a good predictor of general vascular status and has been associated with outcome in

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patients with ischemic stroke and acute pulmonary embolism (11,12). In addition, there are recent promising results regarding the associations between CAC and survival outcomes in oncology patients (13,14). The rationale is that CAC may indicate poor cardiac status, presumably before clinical symptoms are present, and may therefore stratify patients at risk for poorer outcome.

In general, the widely used Agatston score is used to quantify CAC (8). This score is calculated on cardiac-gated CT images, which are not used in oncology patients.

However, with the advent of artificial intelligence algorithms and semi-quantitative scores, such as the Weston score, CAC can also be calculated from routinely acquired staging CT images (15,16).

In lung cancer patients, the CAC score may be particularly relevant, as most patients are heavy tobacco users and therefore at risk for cardiovascular disease (3,4). However, there is still a paucity of data on the prognostic relevance of CT-determined CAC in lung cancer patients.

Therefore, the aim of the present systematic review and meta analysis was to elucidate the associations between CT-determined CAC and overall survival (OS) in lung cancer.

PATIENTS AND METHODS

Literature Search

The MEDLINE library, Google Scholar, and SCOPUS databases were searched for articles on CAC score in lung cancer up to June 2024 by two raters in consensus. The literature acquisition was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (17). The literature search is demonstrated in Figure 1.

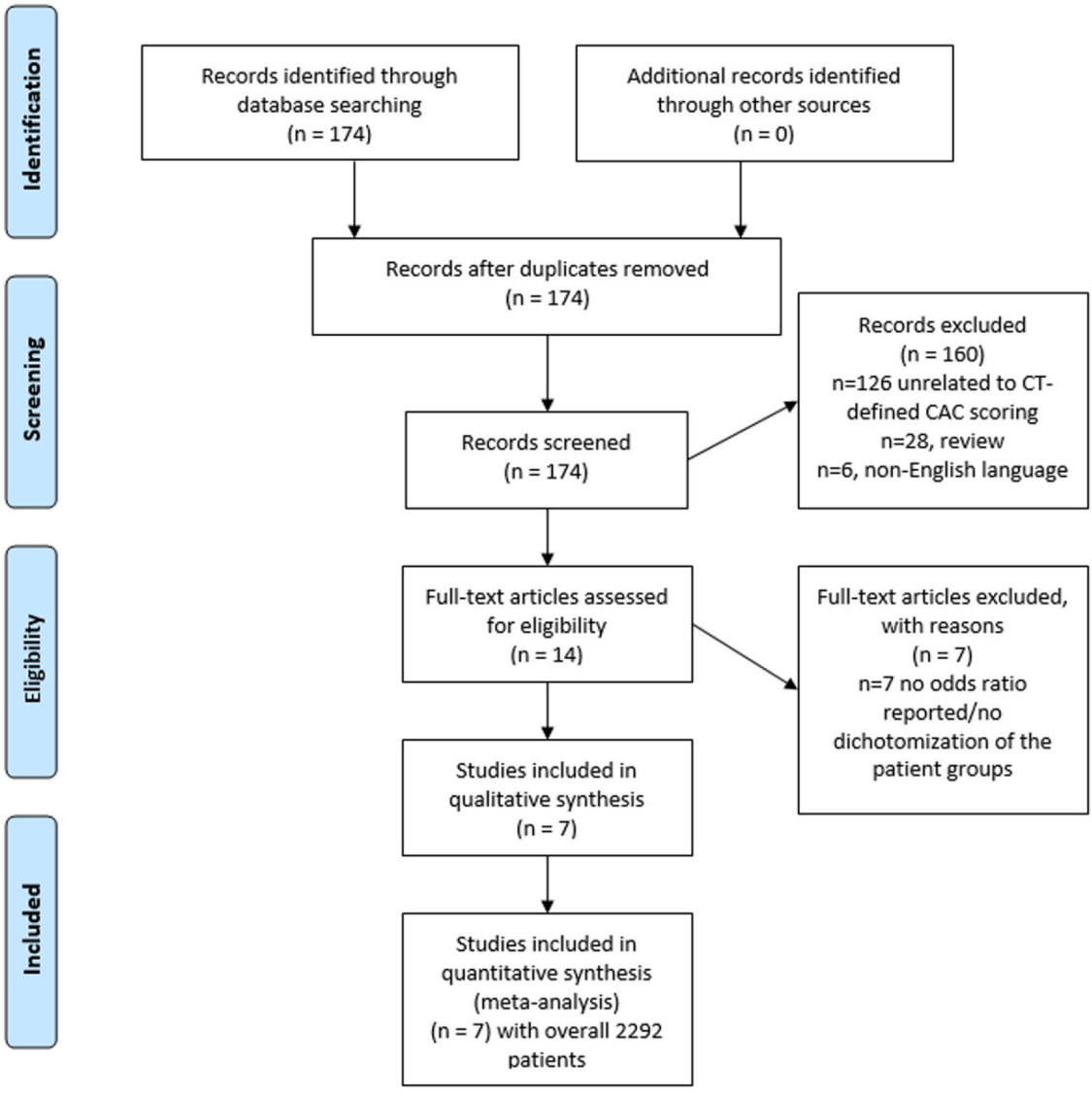

Figure 1. PRISMA flow chart provides an overview of the paper acquisition. Overall, seven studies with 2292 patients with lung cancer were suitable for the analysis.

The search terms "lung cancer" OR "lung carcinoma" AND "coronary artery calcification" OR "CAC" were used to extract the papers.

The primary endpoint of the systematic review was OS presented as hazard ratio for CAC with reported 95% confidence interval and p-value in univariable and multivariable analyses. In addition, the odds ratio for CAC on major cardiovascular events (MACE) was extracted as a secondary endpoint.

Eligibility Criteria

The following criteria were used for the inclusion: (1) lung cancer patients, (2) CAC defined by CT, (3) reported hazard ratio for CAC on overall survival or reported odds ratio on MACE.

Exclusion criteria were (1) systematic reviews, (2) case reports, (3) non-English language.

After thorough review, seven studies were eligible for analysis and included in the present study (18–24).

Data Extraction

Data extraction from the papers was performed by one author (HJM) followed by an independent evaluation of extractions for correctness by a second author (AS).

For each study, details regarding study design, year of publication, country of origin, patient number, patient age, diagnosis, treatment, CAC measurement, overall survival, MACE, and adjustment factors were extracted.

Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) (25). The quality assessment of the studies was performed by two authors (H.J.M., A.S.) and mainly included the selection of cases, the comparability of the cohort and the outcome assessment of risk exposure. Each study was given a score of 0–9, and a study with a score ≥ 6 was considered to be of high quality. Table 1 provides an overview of the study quality.

Statistical Analysis

The meta-analysis was performed using RevMan 5.4 (2020; Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was calculated by means of the inconsistency index I^2 (26,27). DerSimonian and Laird random-effect models with inverse-variance weights were performed without any further correction (28).

RESULTS

Quality of the Included Studies

Table 2 gives an overview of the included studies. Most studies had a retrospective single-center design ($n = 5$, 71.4),

TABLE 1. The Quality of the Studies by NOS Scale

Study	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Quality Score
Atkin et al., 2022(18)	*	*	*	*	*	*	*	*	8
Haseltine et al., 2023(19)	*	*	*	*	*	*	*	*	8
Koutroumpakis et al., 2022(20)	*	*	*	*	*	*	*	*	8
Nardone et al., 2023(21)			*	*		*	*	*	5
Olloni et al., 2023(22)	*	*	*	*	*	*	*	*	8
Osawa et al., 2020(23)	*		*	*	*	*	*	*	7
Tahir et al., 2022(24)	*	*	*	*	*	*	*	*	8

NOS, Newcastle-Ottawa Scale

TABLE 2. Overview of the Included Studies.

Authors	Country	Study design	Included patients, *n* (% female)	Mean age, years	Histology	Tumor stage	Treatment	Patients with CAC = 0, *n* (%)	Patients with CAC ≥ 1, *n* (%)	Quantification of CAC
Atkins et al., 2022 (18)	USA	Retrospective	428 (48.5)	59 for CAC = 0, 69 for CAC ≥ 1	189 adenocarcinoma135 squamous cell 104 others	46 I 235 IIIa 147 IIIb	Definitive radiotherapy	165 (38.5)	263 (61.5)	Non-ECG gated CT, deep-learning based quantification
Haseltine et al., a 2023 (19)	USA	Retrospective	130 (52)	66	NSCLC, not other specified	67 IIIa 63 IIIb	Definitive radiotherapy	Not specified	Median plaque volume of 0.75	Non-ECG gated CT without contrast media, deep-learning based quantification
Haseltine et al., b 2023 (19)	USA	Retrospective	133 (63)	67	NSCLC, not other specified	21 Ia 15 Ib 10 IIa 5 IIb 78 IIIa 4 IIIb	Surgery with postoperative radiotherapy	Not specified	Median plaque volume of 0.03	Non-ECG gated CT without contrast media, deep-learning based quantification
Koutroumpakis et al., 2022 (20)	USA	Substudy of an RCT	193 (45)	64	95 adenocarcinoma 70 squamous cell 28 other	16 II 79 IIIa 78 IIIb 8 IV	photo-radiation or proton therapy with concurrent chemotherapy in curative intent	51 (26.4)	142 (73.6)	Non-ECG gated CT without contrast media, commercial software
Nardone et al., 2023 (21)	Italia	Retrospective	173 (31.8)	18–50 10 (5.8%) 51–65(43.3%) 80 66–75 75 (46.2%) ≥76 8 (4.7%)	NSCLC, not other specified	Not specified	Not specified	40 (23.1)	133 (76.9)	Non-ECG gated CT without contrast media, non commercial software
Olloni et al., 2023 (22)	Denmark	Multicenter observational cohort	644 (47)	68	NSCLC, not other specified	80 ≤ IIb 529≥ IIIa	Definitive radiotherapy with concurrent chemotherapy	172 (26.7)	472 (73.3)	Non-ECG gated CT without contrast media, commercial software
Osawa et al., 2020 (23)	Japan	Retrospective	309 (39.2)	67.4	258 adenocarcinoma 35 squamous cell 16 other	21 0 181 Ia 49 Ib 16 IIa 18 IIb 24 IIIa	surgery	175 (56.6)	134 (43.4)	Non-ECG gated CT without contrast media, commercial software
Tahir et al., 2022 (24)	USA	Retrospective	282 (59.6)	75	74 adenocarcinoma 29 squamous cell 8 NSCLC, not other specified 171 no pathology	282 I	Sterotactic radiotherapy	75 (26.5)	207 (73.5)	Non-ECG gated CT with and without contrast media, commercial software

CAC, coronary artery calcification; ECG, electrocardiography; NSCLC, non-small cell lung cancer; RCT, randomized controlled study

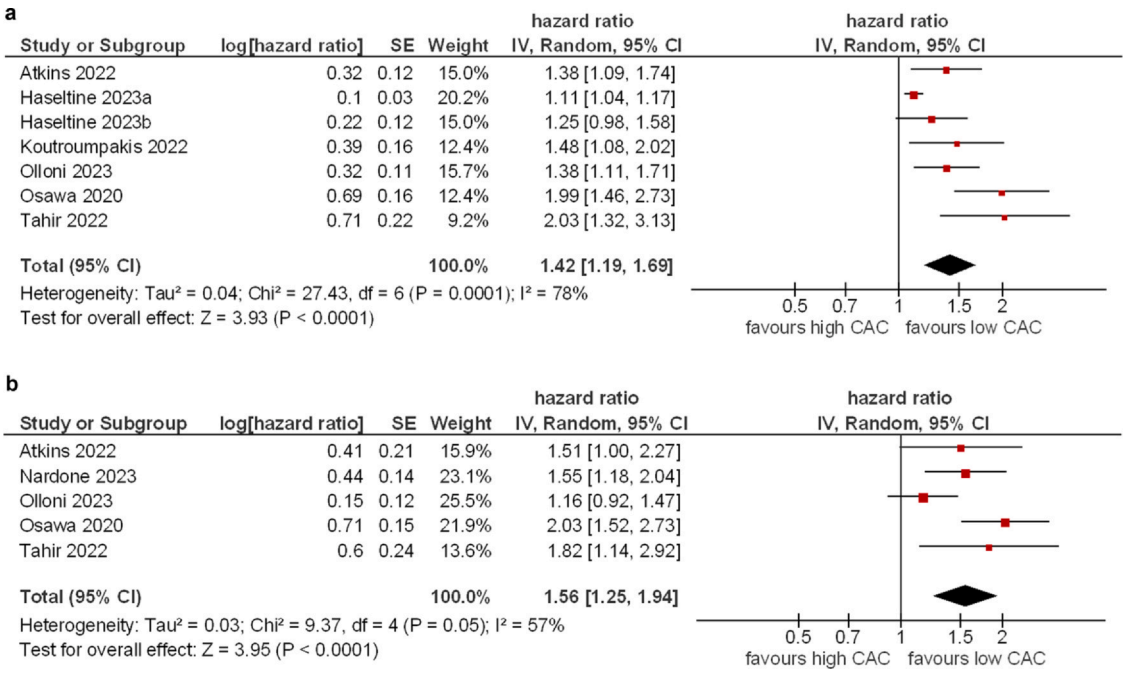

Figure 2. **(a)** Forrest plots of the effect of CAC score on overall survival in univariable analysis. The pooled hazard ratio was HR = 1.42 (95% CI = (1.19; 1.69), p < 0.0001). **(b)** In multivariable analysis, the pooled hazard ratio of the effect of CAC score on overall survival was HR= 1.56 (95% CI = (1.25; 1.94), p < 0.0001).

one study was a subanalysis of a randomized controlled trial (20) and one study (22) was a multicenter observational cohort study.

The overall risk of bias can be considered as low, indicated by the high NOS values throughout the studies (Table 1). The only concern for bias was one study with lack of information for the tumor stage and treatment performed (21).

The included studies comprised overall 2292 patients with a mean age of 68 years of all studies.

Two studies investigated patient cohorts with curative resection, one study with stereotactic radiotherapy for stage I patients, three studies with radiotherapy in curative intent and one study with unclear treatment.

Two studies used novel deep-learning algorithms for CAC quantification and five studies used conventional commercial and non-commercial software.

Overall Survival

For the effect of CAC score on overall survival, six studies comprising overall 2119 patients were suitable for analysis. The pooled hazard ratio for the associations between CAC score and overall survival in univariable analysis was HR = 1.42 (95% CI = (1.19; 1.69), p < 0.0001, Tau^2 = 0.04, Chi^2= 27.43, df = 6, I^2 = 78%) (Fig 2a).

Furthermore, five studies with 1836 patients were suitable for a multivariable analysis. The pooled hazard ratio on overall survival was HR = 1.56 (95% CI = (1.25; 1.94), p < 0.0001, Tau^2 = 0.03, Chi^2= 9.37, df = 4, I^2 = 57%) (Fig 2b).

Effect of CAC Score on MACE

The analysis of the effect of CAC score on MACE included two studies with 502 patients. The pooled odds ratio for the associations between CAC score and MACE was OR = 1.97 (95% CI = (1.24; 3.13), p = 0.004, Tau^2 = 0.0, Chi^2= 0.07, df = 1, I^2 = 0%) (univariable analysis) (Fig 3). As there was no heterogeneity in this analysis, the data was also analyzed with a fixed-effects model. The pooled odds ratio with this model demonstrated the same results with an OR = 1.97 (95%CI 1.23; 3.13), p = 0.004, Chi^2= 0.07, df = 1, I^2= 0%).

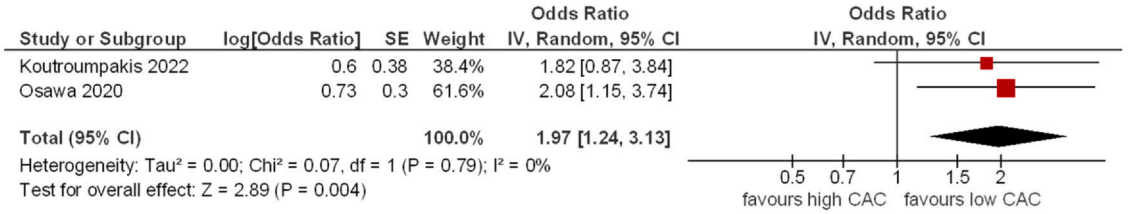

Figure 3. Forrest plots of the effect of CAC score on major cardiovascular events. The pooled odds ratio was OR = 1.97 (95% CI = (1.24; 3.13), p = 0.004).

DISCUSSION

The present analysis investigated associations between CT-defined CAC score and overall survival in lung cancer patients. In short, there was a meaningful impact of the CAC score on overall survival and was associated with the occurrence of major cardiovascular events. This was demonstrated in a comprehensive analysis of curative-treated lung cancer patients.

It is a well-established fact that CAC score is a good predictor of general vessel status of the body (8–10). Besides its prognostic and predictive role in coronary heart disease, it was also demonstrated to be of prognostic relevance in other diseases, such as acute ischemic stroke and acute pulmonary embolism (8–12).

However, the general prognostic role of CAC score in oncological patients is still under investigated. In a comprehensive study of over 66,636 asymptomatic adults, CAC score was higher in patients with cancer related deaths (29).

The promising results of the current analysis regarding lung cancer patients can be discussed that smoking is both a risk factor for lung cancer and for cardiovascular diseases (3,4). The identified association between CAC score and overall survival in lung cancer patients should, therefore, also be discussed by a possible confounding smoking status.

A recent recommendation article promotes the value of CAC score to screen for coronary heart disease in cancer survivors using the already existing CT images (30).

Another interesting aspect could be to predict patients at risk to develop cardiac toxicity due to the chemotherapy and use the CAC score to better stratify the patients (31).

Mais et al. could demonstrate in a mixed oncological cohort of 266 patients that patients with positive CAC score had worse outcome than those without (13). CAC was associated with the primary endpoint on univariable and multivariable analysis (OR = 2.6 (95% CI = (1.42; 4.77), $p < 0.01$) in this study (13). In breast cancer patients, the effect of CAC was also established (32). For this tumor, the association between cardiac radiation exposure and cardiotoxicity was mediated by the CAC score (32). Presumably, same relationships can be presumed with the current results of radiotherapy studies on lung cancer. Yet, more explorative data is needed for this hypothesis.

CAC score was only quantified by cardiac-gated CT studies caused by the motion artefacts (8). With the advent of larger numbers of detectors and faster gantry speeds of the current CT technology, non-cardiac-gated images can be quantified in a semi-quantitative (ordinal scores) or quantitative CAC (Agatston scoring) manner, which was highly correlated to gated CT studies and cardiovascular outcomes (15,16). This is the reason why it can now be reliably used on staging CT used for oncological purposes.

One must acknowledge that the CAC score is in general slightly higher in male patients compared to female patients, which should further be assessed in lung cancer patients (33). Another important aspect of CAC scoring is that also cases of patients with amnestic known coronary heart disease exist without calcified plaques, which are not covered by this CAC scoring method and would result in a CAC score of 0 (33). Notably, the CAC score in oncology patients might not differ compared to the general patient population (34).

For clinical routine in lung cancer screening, it has to be considered that coronary calcifications in 34% of cases, which leads to under prescription of statins and even in 9% of cases further radiological evaluation with stress testing (35). This highlights the importance of the correct reporting of coronary calcifications by the radiologist in every CT investigation. Similar results were even reported for abdominal CT images with only partial display of the heart (36).

Presumably, the inclusion of CAC scoring into prognostic scores for lung cancer patient could increase the prognostic stratification in these patients. The inclusion of CAC score would include a parameter of an important cardiovascular risk factor in these patients. However, prospective studies are needed to provide reliable data of the prognostic relevance of CAC score for clinical routine in lung cancer patients. Especially, as it was not able to adjust for different chemotherapy regiments in the current study due to insufficient reporting in the included studies. Presumably, lung cancer patients with cisplatin-included chemotherapy might show higher cardiotoxicity with a higher CAC score than patients without visible calcifications on CT images.

The present meta-analysis has some limitations to address. First, it is comprised of published studies with inhomogeneities between studies. Possible reasons are different treatments and compositions of the investigated patient cohorts. Second, there is the restriction to English language. Third, the investigated studies included only patients with curative intent. The role of CAC score in palliative setting remains unclear to this date. Further analyses are needed in palliative lung cancer patients. Fourth, the CAC scoring was performed on non-cardiac gated CT. The gold standard is the Agatston score calculated on cardiac gated CT. However, due to the advent of deep-learning algorithms and semi-quantitative methods, the measurements used in the included studies can be considered as representative. Fifth, we could not test for potential publication bias in our analysis, as a funnel plot analysis is suggested with at least 10 included studies.

CONCLUSIONS

CT-defined CAC score has a meaningful impact on overall survival and prediction of major cardiovascular events in lung cancer patients undergoing curative treatment. The sole presence of CAC on staging CT should be reported as an important prognostic marker in these patients.

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None.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

AS, AW, and HJM designed the study. AS and HJM collected the data. AW analyzed and interpreted the data. HJM and AS contributed to the writing of the manuscript.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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