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ORIGINAL ARTICLE

Chest Computed Tomography for Lymphoma Staging: A Wasted Opportunity for Cardiovascular Risk Stratification?

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Aim Patients with a lymphoma diagnosis undergo non-gated chest computed tomography (CT) scans as part of cancer diagnosis or staging. Although coronary artery calcification (CAC) is traditionally evaluated on dedicated cardiac CT, CAC can also be detected on standard chest CT. This exploratory study aimed to determine the prognostic value of CAC detected on non-gated chest CT and to report its use on clinical practice.

Method Consecutive patients with a lymphoma diagnosis who performed non-contrasted non-gated chest CT for cancer diagnosis or staging were included and retrospectively evaluated. Coronary artery calcification was evaluated by quantitative (Agatston score) and qualitative (visual) assessment.

Results Fifty-seven patients were included in this study (mean age 61±15 years; 58% male). Coronary artery calcification was identified in 22 patients (39%), most of them with multi-vessel involvement. Coronary artery calcification was qualitatively classified as mild, moderate and severe in 11%, 19% and 9% patients, respectively. This study suggested that moderate or severe CAC was an independent predictor of all-cause mortality (odds ratio 3, 95% confidence interval 2–11; p=0.04) after adjusting for cardiovascular risk factors and lymphoma staging. Regarding quantitative evaluation, a higher CAC score was also associated with higher mortality. While significant CAC was identified in 22 patients, it was only reported in four patients.

Conclusions The preliminary findings of this hypothesis-generating study support the investigation of CAC identified by chest CT for diagnosis/staging of cancer as a risk modifier in the global risk assessment of patients with lymphoma. The unrecognition and underreporting of this finding may represent a wasted opportunity to detect subclinical coronary atherosclerosis in these patients and may help in guiding preventive cardiology care.

Keywords Lymphoma • Cardio-oncology • Risk stratification • Computed tomography

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Introduction

Lymphoma is the most prevalent blood cancer. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and commonly occurs in adults aged >64 years [1]. Treatment of B-cell lymphoma consists of a combination of chemotherapy, including cyclophosphamide, doxorubicin, vincristine and prednisone, and immunotherapy with rituximab, with or without radiotherapy. Among the different agents, anthracyclines are the most common cause of cardiotoxicity, particularly heart failure. These cardiotoxic effects can occur immediately or several weeks to months after chemotherapy administration. Previous studies have demonstrated that pre-existing cardiovascular (CV) diseases, including coronary atherosclerosis, increase the risk of heart failure development in these patients [2].

On the other hand, heart disease is the most common cause of non-cancer death among cancer patients. In addition to the traditional CV risk factors, both radiotherapy exposure and chemotherapy are associated with a subsequent increase in coronary artery calcification in patients with cancer [3,4]. A previous study demonstrated a 33% excess rate of myocardial infarction among patients with DLBCL compared with the general population [5].

Coronary artery calcification (CAC) scoring has been demonstrated to predict coronary events beyond the traditional CV risk factors. It was proposed as an alternative approach for CV risk stratification and to guide the implementation of preventive care, such as statin therapy. Coronary artery calcification is usually evaluated using specific protocols on electrocardiogram (ECG) gated non-contrasted cardiac computed tomography (CT) scans. However, CAC can also be identified on standard non-gated chest CT scans, and has been demonstrated to correlate well with traditional ECG-gated CAC scoring. This is of particular interest, considering that most patients with lymphoma perform CT scans as part of cancer staging or radiotherapy planning. Therefore, reporting CAC on cancer-staging CT scans may represent a unique opportunity for CV risk stratification and to identify patients at higher risk of cardiotoxicity.

This study aimed to assess the feasibility of CAC score severity assessment on standard cancer staging CT chest scans and to correlate its severity with mortality. As second objectives, it aimed to determine how often coronary calcium score is reported on lymphoma diagnosis or initial staging CT scans.

Methods

Study Population

This single-centre, retrospective study reviewed patients who performed a standard (non-ECG gated) chest CT scan for lymphoma diagnosis or initial staging between 2016 and 2018 in a tertiary hospital. Inclusion criteria were adult patients (aged ≥18 years) with an established lymphoma diagnosis who had available chest CT scans at the time of cancer diagnosis. The CV risk factors, comorbidities and cancer-related information (subtype of lymphoma, staging and treatment characteristics) were obtained by a comprehensive review of the electronic medical records. Due to the study's retrospective nature, informed consent was waived by the institution.

Endpoints

The primary endpoint was all-cause mortality. The second endpoint was prevalence of reported CAC score on chest CT final report.

Image Acquisition

The CT scans were performed on commercially available 64-slide or 16-slice multi-detector CTs (Siemens Medical Solutions, Germany). Images were non-ECG-gated chest CT scans without contrast enhancement. Slice thickness varied according to the CT protocol employed. All studies were reviewed for study purposes using patient Sectra Picture Archiving and Communications system (PACS) software (Sectra AB, Linköping, Sweden).

Coronary Artery Calcification Quantification

Coronary artery calcification was evaluated by an investigator blinded to the clinical information and quantified using two methods:

a) Qualitative (visual) assessment, in which CAC was qualitatively quantified according to the global extent of coronary calcification as absent (0 points), mild (1 point), moderate (2 points) or severe (3 points). For statistical analysis purposes, patients were further stratified into two risk categories: no or mild CAC and moderate to severe CAC.
b) Quantitative assessment, in which CAC was obtained by using the Agatston method with the traditional 130-Hounsfield unit threshold. Based on the total Agatston score, patients were further stratified into two risk categories, which have been used in previous studies [6–8]: no or mild CAC (<100), and moderate to severe CAC (≥100).

A second investigator evaluated all CT scans to determine interobserver reliability.

Computed Tomography Report

Reports from the CT chest studies were obtained from the patient's electronic medical records by an investigator blinded for CAC quantification analysis. Report of CAC was considered if any mention of coronary calcification or atherosclerosis was made. Reporting of valvular or non-coronary vascular calcification was not considered indicative of reporting CAC.

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Table 1 Comparison of demographics for patients with no or mild coronary artery calcification and with moderate or severe coronary artery calcification at the time of chest computed tomography.

Variable	No or mild CAC (n=41)		Moderate or severe CAC (n=16)		p-value
Mean age – years	56	(15)	71	(11)	p=0.002[a]
Gender – female	19	(46)	5	(31)	p=0.300
Lymphoma characterisation					
Diffuse B-cell lymphoma	28	(68)	8	(50)	p=0.435
Stage I	5	(12)	2	(13)	p=0.144
Stage II	8	(20)	3	(19)	p=0.948
Stage III	6	(15)	6	(38)	p=0.057
Stage IV	10	(24)	3	(19)	p=0.648
Comorbidities					
Arterial hypertension	13	(32)	12	(75)	p=0.003[a]
Dyslipidaemia	6	(15)	5	(31)	p=0.153
Diabetes mellitus	3	(7)	5	(31)	p=0.019[a]
Chronic kidney disease					p=0.401
Obesity	2	(5)	0	(0)	p=0.368
Smoking	4	(10)	3	(19)	p=0.353
Cerebrovascular disease	1	(2)	1	(6)	p=0.482
Peripheral arterial disease	0	(0)	1	(6)	p=0.106
Atrial fibrillation	3	(7)	1	(6)	p=0.887
HIV infection	7	(17)	1	(6)	p=0.290
Outcomes					
All-cause mortality	21	(51)	13	(81)	p=0.038[a]

Data are shown as n (%) or mean ±SD.

[a]A p-value that is statistically significant.

Abbreviations: CAC, coronary artery calcification; HIV, human immunodeficiency virus.

Statistical Analysis

Categorical variables were presented as frequency rates/percentages, and continuous variables as median with interquartile range. Categorical and continuous variables were compared using Pearson Chi-square and Mann-Whitney tests, respectively. The differences in demographics and traditional CV risk factors were evaluated using *t*-tests or Wilcoxon Rank Sum tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. The comparison of means was performed using analysis of variance (ANOVA). The comparison of non-normally distributed continuous variables was reported as medians and interquartile ranges, and analysed using the Mann-Whitney test. Receiver operating characteristic (ROC) curve analysis was performed. Cox regression was used for the multivariate-adjusted factor analysis to study the impact of CAC severity on survival. Agreement between visually estimated (qualitative assessment) CAC was determined, using weighted kappa statistics and percentage agreements. Statistical significance was defined as $p<0.05$.

Results

A total of 57 patients with lymphoma were included in the study. The mean age was 61±15 years, 58% were male. The most prevalent subtype was diffuse large B-cell lymphoma (DLBCL) (n=36, 63%). Regarding staging, seven patients (12%) had stage I, 11 patients (19%) had stage II, 12 patients (21%) had stage III, 13 patients (23%) had stage IV, and it was not possible to define staging by reviewing medical records in 16 patients (28%). Regarding medical treatment, most patients (n=42, 74%) were submitted to R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride [Hydroxydaunomycin], Vincristine Sulfate [Oncovin] and Prednisone). Seven patients (12%) were submitted to radiotherapy in association with chemotherapy.

Coronary artery calcification was identified in 22 patients (39%). The most common artery to be involved was the right coronary artery (n=18, 82%) followed by the left anterior descending artery (n=15, 68%) and circumflex (n=9, 41%). Most patients had multi-vessel coronary involvement, and four patients had single-vessel disease.

By visual assessment, 34 patients (60%) had no CAC, seven patients (12%) had mild CAC, 11 patients (19%) had moderate CAC, and five patients (9%) had severe CAC. The demographic and clinical features of patients with no or mild CAC and patients with significant CAC (moderate to severe CAC) are shown in Table 1. Patients with significant (moderate to severe) CAC were older and with a higher prevalence of hypertension and diabetes. No

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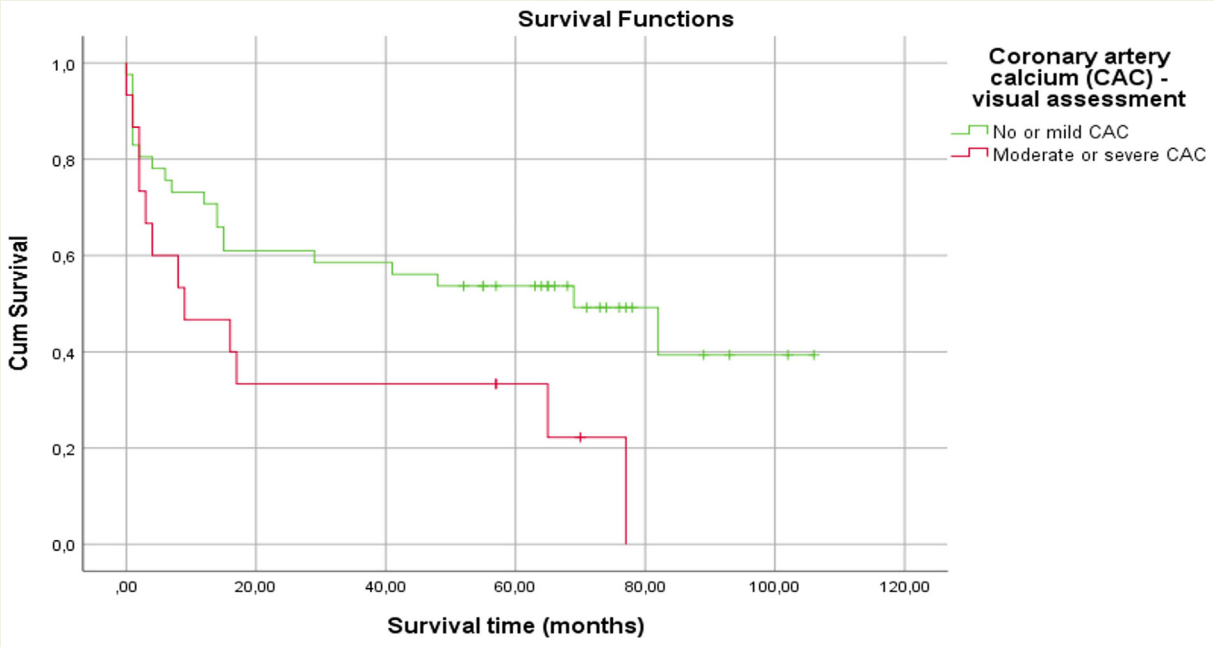

Figure 1 Cox regression survival analysis stratified by severity of coronary artery calcium (CAC) evaluated by visual/qualitative assessment (no or mild CAC, and moderate or severe CAC); log-Rank p=0.034.

difference in lymphoma subtype or staging was found between patients with no or mild CAC and patients with significant CAC.

Thirty-four patients (60%) died during a mean follow-up time of 39±34 months. Patients with no or mild CAC scores had longer survival rates compared with those with significant CAC (51% vs 81%; p=0.038). The CAC qualitative score stratified by non-significant (no or mild) and significant (moderate to severe) CAC was found to be associated with reduced survival (log-rank test p=0.034), according to survival proportion by Cox regression analysis adjusted for age, traditional risk factors and lymphoma staging (Figure 1).

Regarding the quantitative evaluation of CAC, 40 patients (70%) had CAC <100 and 17 patients (30%) had CAC ≥100 (five of whom had CAC between 100–399, and 12 had ≥400). The presence of moderate or severe CAC was an independent predictor of all-cause mortality (OR 3; 95% CI 2–11; p=0.04]. The survival Cox-regression analysis stratified according to CAC is represented in Figure 2 (log-rank p=0.042).

Most of the patients died due to the progression of oncological disease (22 patients, 65%). Nine patients (27%) died from related complications, such as infectious diseases. The cause of mortality was undetermined in three patients. None of the patients died due to CV disease. None of the patients had a myocardial infarction, were submitted to coronary angiography or had a stroke during the follow-up period.

Since both qualitative and quantitative analyses were performed on all patients, the relationship between both classifications according to the severity of CAC is represented in Table 2. The agreement between qualitative and quantitative assessment was 100% for patients with no or severe calcification. Considering the 34 patients classified as having an absence of coronary calcification on visual assessment, most (n=31, 91%) had a quantitative score of 0, and the remaining three patients had a score <50. All patients classified as having severe coronary artery calcification by visual assessment had a quantitative score ≥400. The more considerable heterogeneity was verified for patients classified with moderate CAC on qualitative assessment (n=11); of these, four patients (36%) had a quantitative score between 100–399, and the other seven patients (64%) had a score ≥400.

Regarding interobserver reliability, agreement was 100% for the presence/absence of coronary calcium. For the qualitative assessment of CAC (mild/moderate/severe), interobserver agreement was excellent ($_K$ 0.89; 95% CI 0.86–0.91; p<0.001), and similar for both 64- and 16-slice multi-detector CT scans.

While CAC was identified by simple visual assessment in 39% of the reviewed CTs, it was reported in four patients. When considering patients with moderate to severe CAC by visual assessment, four of 16 reports (25%) mentioned it; none of the chest CT reports referred to the absence of CAC.

Of the 11 patients with the diagnosis of dyslipidaemia, nine were under statin treatment at baseline (82%), and five (46%) had evidence of moderate to severe CAC by visual assessment. Considering all patients with moderate to severe CAC by visual assessment (n=16), five (31%) were under statin treatment at the time of CT scan, and none of the remaining patients initiated statin therapy during the follow-up period.

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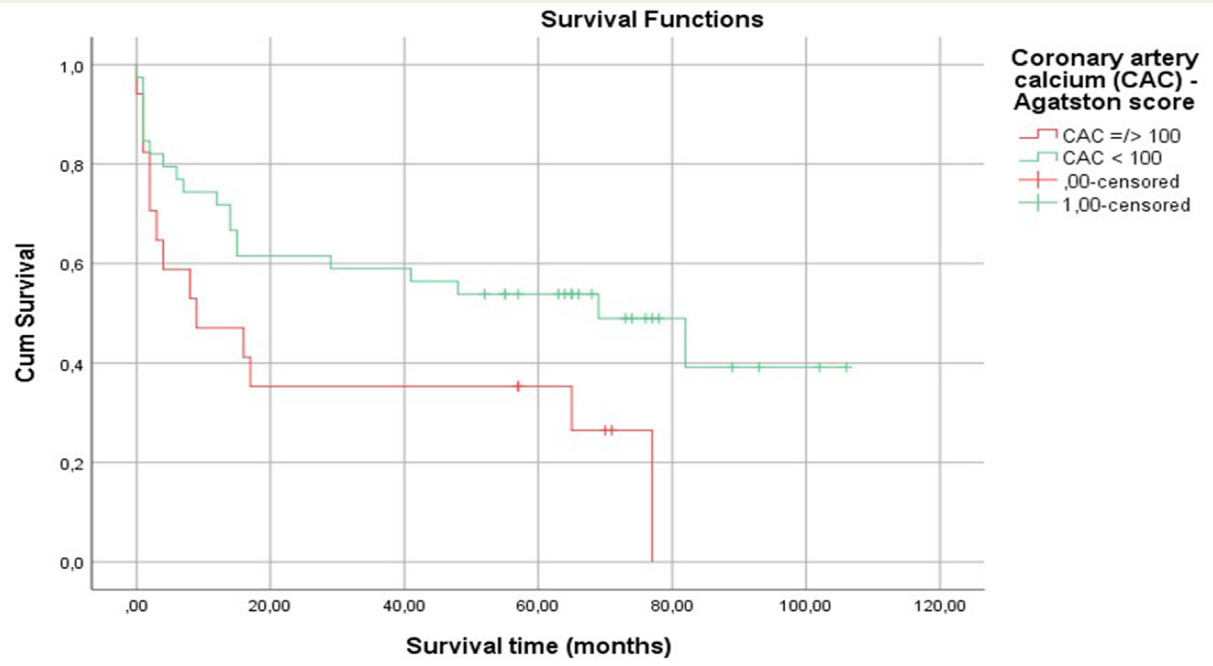

Figure 2 Cox regression survival analysis stratified by severity of coronary artery calcium (CAC) evaluated by quantitative assessment – Agatston score: no or mild CAC (<100) and moderate or severe (100); log-Rank p=0.042.

Regarding antiplatelet therapy, two patients were under acetylsalicylic acid during the baseline and follow-up period.

Discussion

This study demonstrated a high prevalence of CAC on standard chest CT and highlights the potential utility of CAC identification on chest CT performed for lymphoma diagnosis or staging as a predictor of mortality. These findings are hypothesis-generating and should be used to direct future studies.

It is known that patients with cancer have a greater burden of CV risk factors and are at higher risk of CV disease compared with the general population, highlighting the importance of implementing preventive measures to reduce morbidity and mortality in these patients [9–11]. This may be attributed to shared risk factors between both cancer and CV disease, but also to underdiagnosis and undertreatment of CV risk factors and comorbidities in cancer patients, as cancer treatment is often prioritised. However, due to earlier diagnoses and modern therapies, cancer survival is increasing, and nowadays, these patients are as likely to die from other comorbid conditions as from cancer, particularly CV disease [12]. Thus, a combined focus on cancer treatment and CV prevention may be crucial to achieving the best outcomes in cancer patients.

The CAC score describes the extent and burden of coronary calcification, and it has been extensively demonstrated as an independent CV risk factor. In addition, it has been shown to predict adverse CV outcomes beyond traditional CV risk factors, and it is recommended as an approach to identify patients at higher risk of CV events who could benefit from more aggressive preventive care, such as statin therapy. Although CAC scoring is traditionally performed on dedicated ECG gated-CT scans with standardised parameters, this investigation is not always available and, particularly in cancer patients, it will not only increase radiation exposure but also add a new scheduled imaging study in patients who are frequently overwhelmed with the burden of examinations. However, the assessment of coronary calcification is feasible on standard non-gated chest CTs, and it correlates well with the traditional gated CAC scoring of cardiac CT, having similar prognostic value [13]. Thus, the use of the standard chest CT scans, performed for cancer diagnosis or staging, may be useful to extract information about coronary calcification and help on CV risk-stratification of these patients.

By analysing standard non-gated non-cardiac chest CT, this study reported a prevalence of 39% of CAC in patients with lymphoma diagnosis. The high prevalence of CAC is in line with previous studies that demonstrated many underlying shared risk factors in both conditions. In addition to the documentation of a high prevalence of CAC, this study documented that most of those patients had multivessel coronary disease and moderate to severe CAC (82% and 73%, respectively), which has, in earlier studies, been associated with the worst prognosis. This is relevant, considering that many oncological therapies are associated with cardiotoxicity.

Chest radiotherapy is associated with a long-term effect on coronary arteries and has been extensively associated with

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Table 2 Relationship between qualitative (visual) and quantitative assessment of coronary artery calcification.

		Quantitative assessment		
		<100	100–399	≥400
Qualitative assessment	Absent	34	0	0
	Mild	6	1	0
	Moderate	0	4	7
	Severe	0	0	5

the presence and extent of coronary artery calcification on calcium-scoring CT, even after controlling for conventional risk factors for coronary disease [3]. Although more established for radiation exposure, the impact of chemotherapy on coronary atherosclerosis has also been investigated. El-Sabbagh et al. documented an average increase of 35% in CAC from baseline to last chemotherapy treatment in a population of patients with lymphoma who were not exposed to thoracic radiation therapy [4]. This suggests that such patients have both a short-term and long-term higher risk of CV events. A previous study reported that significant coronary artery disease occurred in 10% of patients who underwent radiotherapy for Hodgkin's lymphoma at a median of 9 years of follow-up [14]. In addition, it has been demonstrated that coronary atherosclerosis increases the risk of heart failure in patients undergoing chemotherapy treatment [15]. Thus, identifying patients with a high risk of coronary events at baseline may help signal those who need closer follow-up and more aggressive control of CV risk factors.

Previous studies have reported that CV risk factors are less aggressively managed in cancer patients [16,17]. Although various risk models are available for coronary artery disease prediction in the general population, they focus on traditional risk factors, and do not include cancer therapies as part of the risk stratification, leading to risk underestimation [18]. Thus, early identification of subclinical coronary atherosclerosis could better risk-stratify patients and guide the implementation of preventive measures. This is particularly interesting considering that statins have shown some promise in mitigating radiation-induced atherosclerosis [19].

The global prevalence of dyslipidaemia was 19% in the current study, with nearly half of those patients with documented moderate to severe coronary artery calcification on CT. However, although most of the patients with the diagnosis of dyslipidaemia were under statin therapy, if all patients with documented moderate to severe CAC on chest CT are considered (n=16), five patients (31%) had the diagnosis of dyslipidaemia and were under statin therapy. This means that 69% of patients considered to be at very high CV risk according to current guidelines were not under appropriate statin treatment, and not following the target LDL level of <55 mg/dL for this subset of very high-risk patients. A multidisciplinary team, including both cardiologist and haematologist, may be crucial to define the baseline CV risk of the patient at the time of lymphoma diagnosis, define preventive measures to decrease CV risk and to avoid drug-to-drug interactions and bleeding complications. Preventive therapies can be recommended for patients with moderate or severe CAC, and statin therapy can be considered through shared decision-making even in patients with mild CAC [20].

Regarding clinical outcomes, this study documented a high mortality rate. This may be related to the significant burden of comorbidities of the study population and the fact that 44% of patients had advanced-stage lymphoma (III or IV). The latter may play an important role, as most patients die from the progression of oncological disease or related complications.

None of the patients had a documented CV event during the follow-up period, namely myocardial infarction or stroke. However, after a patient dies, the Portuguese health platform (Plataforma de Dados de Saúde) does not allow consultation of medical processes of institutions other than the current one, which may lead to underreporting of those events. In addition, the high mortality rate due to advanced oncological disease in a relatively short follow-up may also contribute to the absence of CV adverse events. Despite the absence of CV events, this study demonstrated an increased global mortality risk of patients with CAC. However, due to the small sample size, larger observational studies should corroborate these results.

This study found excellent interobserver reliability regarding the presence and grading of CAC severity. In addition, the agreement of qualitative (visual) and quantitative assessment was 100% for patients without coronary calcification and those with severe CAC. The major heterogeneity was verified for patients with moderate CAC by visual assessment, although all had a CAC score >100 by quantitative assessment.

The mention of CAC in the CT report was 7% in this study. Even when considering only patients with moderate to severe CAC by simple visual assessment, 25% of the cases were reported. The under-recognition and under-reporting of CAC on standard chest CT were also demonstrated in previous studies. A recent survey showed that 17% of non-cardiothoracic radiologists in Canada were aware of the correlation between CAC scores on gated and non-gated thoracic CT [21]. Considering that coronary calcification documentation may impact these patients' prognostic and treatment decisions, it is important to request that radiologists report this finding.

Limitations

Several limitations may warrant further consideration. This was a retrospective, single-centre, chart-review study with small sample size, which limited statistical power to correct multiple comparisons. Thus, the findings should be considered hypothesis-generating and warrant further investigation.

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This study aimed to report the CAC detected on non-gated chest CT scans performed for diagnosis or staging of lymphoma. For this reason, the inclusion criteria did not define a specific CT protocol, particularly with a wide range of slice thickness and no control of heart rate during the exam, which may have impacted the sensitivity and specificity for CAC detection. Nevertheless, it intended to demonstrate the feasibility and prognostic impact of CAC detection, irrespective of CT protocol, reflecting its possibility of applicability in everyday practice.

This study reported a high cancer-related mortality rate, which may have been related to the advanced lymphoma staging of the participants and also due to the chest CT being performed in radiology clinics. Only the most severe cases are selected to be performed in the current hospital, which corresponds to the patients included in this study.

As previously discussed, the adverse CV events could have been underreported, considering that the information about hospitalisation or adverse events in other institutions is unavailable after a patient's death.

Future Directions

The relationship between the identification of CAC on non-gated chest CT at the time of lymphoma diagnosis and mortality should be confirmed in a larger sample size study. It may also be advantageous to explore the relationship between CAC identification and the occurrence of CV events, such as stroke and coronary syndromes. Such an approach would clarify the impact of CAC detection on lymphoma patients' prognosis. It could lead to implementing preventive measures and defining strategies for cardiovascular surveillance in patients with a higher risk of cardiovascular events receiving potentially cardiotoxic therapies.

Conclusion

The findings of this study suggest that baseline CAC screening in patients undergoing non-gated chest CT for lymphoma diagnosis or staging presents an opportunity to detect subclinical coronary atherosclerosis. This observational study was largely hypothesis-generating. Future better-powered studies may shed more light on using CAC as a modifier in the risk assessment of lymphoma patients.

Declarations of Interest

None.

Authors' Contribution

BVS conceived the idea, analysed the data and took the lead in writing the manuscript. BVS, DA, IM: collected data. AM, MNM, DA, MF, FJP: supported and reviewed the manuscript.

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