Incidentally identified coronary artery calcium on non-contrast CT scan of the chest predicts major adverse cardiac events among hospital inpatients

Christopher Yu 1,2, Austin C C Ng, 1,2 Lloyd Ridley, 1,2 Mekhala Anjaria, 2 Silvan Meier, 1,3 John Yiannikas, 1,2 Leonard Kritharides, 1,2 Christopher Naoum 1,2

ABSTRACT

Background Coronary artery calcium (CAC) identified on non-gated CT scan of the chest is predictive of major adverse cardiac events (MACE) in multiple studies with guidelines therefore recommending the routine reporting of incidental CAC. These studies have been limited however to the outpatient setting. We aimed to determine the prognostic utility of incidentally identified CAC on CT scan of the chest among hospital inpatients.

Methods and results Consecutive patients (n=740) referred for inpatient non-contrast CT scan of the chest at a tertiary referral hospital (January 2011 to March 2017) were included (n=280) if they had no known history of coronary artery disease, active malignancy or died within 30 days of admission. Scans were assessed for the presence of CAC by visual assessment and quantified by Agatston scoring. Median age was 69 years (IQR: 54–82) and 51% were male with a median CAC score of 7 (IQR 0–205). MACE occurred in 140 (50%) patients at 3.5 years median follow-up including 98 deaths. Half of all events occurred within 18 months. Visible CAC was associated with increased MACE (HR) 6.0 (95% CI: 3.7 to 9.7) compared with patients with no visible CAC. This finding persisted after adjusting for cardiovascular risk factors HR 2.4 (95% CI: 1.3 to 4.3) and with both absolute CAC score and CAC score ≥50th percentile.

Conclusion Incidental CAC identified on CT scan of the chest among hospital inpatients provides prognostic information that is independent of cardiovascular risk factors. These patients may benefit from aggressive risk factor modification given the high event rate in the short term.

INTRODUCTION

Coronary artery calcium (CAC) is an established predictor of future cardiovascular events.1-4 The relative risk posed by CAC scoring further improves risk stratification by traditional risk factor calculators including the Framingham risk score.5 6 Furthermore, data from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated CAC has a net reclassification improvement of 25% compared with traditional risk assessment for predicting major adverse cardiac events (MACE).7 The finding of zero calcium score has very high negative predictive value with a 10-year MACE risk of 1.1%.8

Traditionally, CAC has been identified using ECG-gated CT scan. However, CAC can be detected on a non-contrast, non-gated CT scan of the chest and is known to be under-reported despite being in the field of view and having the potential ability to identify patients at risk who could benefit from risk factor control and improve primary prevention of coronary events.9 Various methods have been examined for optimal CAC scoring on non-gated CT scan, with a meta-analysis demonstrating that a higher CAC score on non-gated CT scan of the chest is associated with an increased risk of MACE and does
not overestimate the CAC score.\textsuperscript{10} \textsuperscript{11} Accordingly, recent published guidelines recommend routine reporting of coronary calcium on such scans.\textsuperscript{12}

To date, studies have evaluated the prognostic role of CAC scoring on non-gated non-contrast CT scan of the chest only in the outpatient setting. The purpose of this study was to determine the medium-term prognostic value of incidentally identified CAC for predicting MACE among hospital inpatients without a history of coronary artery disease (CAD) undergoing CT scan of the chest who were discharged alive beyond 30 days.

METHODS

Patients who underwent non-contrast, non-gated CT scan of the chest between January 2011 and March 2017 as an inpatient of a tertiary referral hospital (Concord Repatriation General Hospital, Sydney, Australia) were retrospectively identified. Exclusion criteria included patients with a history of known CAD and those that died during the index admission or within 30 days of discharge. Active malignancy was an additional exclusion criterion because of limited survival in these patients. The index CT scan was used in cases where patients underwent multiple CT scans. The study complies with the 1975 Declaration of Helsinki.

Baseline demographic and clinical data were obtained using electronic medical records (PowerChart, Cerner, USA). Subsequent hospital admissions, vital status and cause of death data were obtained through data linkage performed by the Centre for Health Record Linkage (CHeReL), Sydney, Australia. In summary, CHeReL performed the population linkage of the study cohort with the NSW Admitted Patient Data Collection Registry and the NSW Registry of Births, Deaths and Marriages registrations databases. The primary outcome was MACE, a composite endpoint including all-cause death, non-fatal myocardial infarction, unstable angina requiring revascularisation, congestive cardiac failure and cerebrovascular events. Each admission diagnosis and cause of death code were categorised into CAC percentile groups: <50th percentile and 250th percentile and groups according to the following score: 0, 1–100, 101–400 and >400. CT scans were analysed by a single observer (CY) blinded to the clinical outcomes. A random selection of 30 patients was identified for secondary reads by an experienced Cardiac CT reader (CN) to determine interobserver variability.

Statistical analysis

Statistical analyses were performed on SPSS V.24 (IBM, USA). Continuous data are described as median and IQR if not normally distributed or mean±SD otherwise. Categorical data are reported as percentages. Continuous variables were compared using independent sample t-test and categorical variables using $\chi^2$ test. Kaplan-Meier analysis was used to estimate event-free survival and compared using the log-rank test. A Cox proportional hazards model was used to analyse time to a primary event and estimate HRs between age and sex-specific adjusted CAC score categories and groups by CAC score after adjusting for cardiovascular risk factors (age, sex, smoking history, hypertension, chronic kidney disease and diabetes). The proportional hazards assumption was checked with log-minus-log plots. Cohen’s kappa ($\kappa$) was used to assess interobserver agreement of categorical data and a two-way random intraclass correlation for continuous data. We defined a two-sided $p$ value $<$0.05 as statistically significant.

RESULTS

A total of 810 inpatient non-contrast non-gated CT scans of the chest were performed on 740 patients between January 2011 and March 2017. Of these, 530 scans were excluded, with most excluded due to a known history of coronary heart disease (n=181), death during index admission (n=156) and malignancy (n=80) (figure 1). A total of 280 scans were included in the analysis. The primary indications for the CT scan of the chest were chronic obstructive pulmonary disease (n=56), lung nodule assessment (n=49) and interstitial lung disease (n=36).

Baseline characteristics of the overall cohort are shown in table 1. The median age of the study patients was 69 years
Coronary artery disease

Yu C, et al. Open Heart 2021;8:e001695. doi:10.1136/openhrt-2021-001695

Coronary artery disease

Visible CAC was identified in 172 (61%) of the patients. Patients with visible CAC were older and had a higher prevalence of diabetes, hypertension and hyperlipidaemia. However, among the 65 patients who had no known cardiovascular risk factors, 17 (26%) patients had visible CAC. Conversely, among patients with two or more risk factors, 23 (17%) had no visible CAC.

On quantitative assessment, the cohort’s overall median CAC score was 7 (IQR 0–205). There were 120 (43%) patients with a CAC score of 0, 109 (39%) with a CAC score of 1–399 and 51 (18%) with a CAC score ≥400. There were 12 (7%) patients who had a CAC score of 0 despite there being visible calcium on visual assessment, consistent with prior studies.15 16 Using MESA-based percentiles correcting for age, sex and race, 187 (67%) patients had a CAC <50th percentile and 93 (33%) patients had a CAC ≥50th percentile. Despite this adjustment, older patients (≥median age of 69 years) were still more likely to have a CAC score ≥50th percentile compared with younger patients (62 (44%) vs 31 (22%), p<0.001).

Outcomes

Median follow-up was 3.5 years (IQR 2.0–5.5). There were 140 MACE events (50%), with a median time to MACE of 1.5 years (IQR 0.6–3.2 years) including 98 deaths (35%), which occurred at a mean age of 77±14 years (table 2). Of the 98 deaths, 30 patients (31%) suffered cardiovascular death, with heart failure being the most common cause of cardiovascular death (n=30, 33%). Respiratory death was the most common cause of non-cardiovascular mortality (n=23, 23%) and causes included pneumonia, respiratory failure and pulmonary embolism. The cause of death was unclassified in 20 cases due to lack of death certificate information.

MACE-free survival was significantly higher in patients with no visible CAC compared with those with visible CAC (82% vs 30%, log-rank p<0.001; figure 2). For patients with visible CAC, the unadjusted HR for MACE was 6.0 (95% CI: 3.7 to 9.7, p<0.001) compared with patients with no visible CAC (table 3). After adjusting for age, sex and cardiovascular risk factors, visible CAC was associated with increased risk of MACE compared with non-visible CAC with a HR of 3.2 (95% CI: 1.8 to 5.6, p<0.001).

When based on CAC score, patients with higher CAC scores had higher risk for MACE (unadjusted HR 1.001, 95% CI: 1.001 to 1.001, p<0.001). When CAC score was

Table 1 Baseline clinical characteristics stratified by the presence of visible CAC

|                          | All patients (n=280) | Non-visible CAC (n=108) | Visible CAC (n=172) | P value |
|--------------------------|----------------------|-------------------------|---------------------|---------|
| Age (years)—median (IQR)| 69 (54–82)           | 51 (37–63)              | 78 (66–86)          | <0.001  |
| Male, n (%)              | 142 (51)             | 50 (46)                 | 92 (54)             | 0.241   |
| Diabetes, n (%)          | 78 (28)              | 14 (13)                 | 64 (37)             | <0.001  |
| Hypertension, n (%)      | 149 (53)             | 28 (26)                 | 121 (70)            | <0.001  |
| Hyperlipidaemia, n (%)   | 90 (32)              | 17 (16)                 | 73 (42)             | <0.001  |
| Smoking history, n (%)   | 93 (33)              | 30 (28)                 | 63 (37)             | 0.126   |
| Chronic airways disease, n (%) | 79 (28) | 27 (25) | 52 (30) | 0.344 |
| Chronic kidney disease, n (%) | 78 (28) | 15 (14) | 63 (37) | <0.001 |
| CAC score per Agatston—median (IQR) | 7 (0–205) | 0 (0–0) | 95 (14–498) | <0.001 |
| CAC percentile—median (IQR) | 18 (0–67) | 0 (0–0) | 55 (23–79) | <0.001 |

CAC percentile refers to the age and sex adjusted percentile as per Multi-Ethnic Study of Atherosclerosis.
CAC, coronary artery calcium.

Table 2 Major adverse cardiac events (MACE) and causes of death

|                          | Number of events (%) |
|--------------------------|----------------------|
| MACE (n=140)             |                      |
| All-cause death          | 98 (70)              |
| Non-fatal myocardial infarction | 23 (16)           |
| Unstable angina requiring revascularisation | 5 (4)        |
| Congestive cardiac failure | 7 (5)               |
| Cerebrovascular events   | 7 (6)                |
| All-cause death (n=95)   |                      |
| Cardiovascular death (n=30) |                    |
| Acute myocardial infarction | 3 (18)            |
| Cardiac arrest           | 5 (17)               |
| Cerebrovascular accident | 6 (20)               |
| Congestive cardiac failure | 10 (33)            |
| Ischaemic heart disease  | 4 (13)               |
| Other cardiovascular     | 2 (7)                |
| Non-cardiovascular death (n=48) |            |
| Malignancy               | 6 (13)               |
| Chronic obstructive pulmonary disease | 7 (15)        |
| Respiratory failure      | 2 (4)                |
| Pneumonia                | 5 (10)               |
| Pulmonary embolism       | 3 (6)                |
| Other sepsis (UTI, cholecystitis, etc) | 6 (13)        |
| Other respiratory causes (asthma, bronchiectasis, ILD) | 6 (13) |
| Other cause              | 13 (27)              |
| Cause of death unknown (n=20) |                      |

ILD, interstitial lung disease; UTI, urinary tract infection.
divided into groups by scores of 0, 1–100, 101–400 and >400, those in the >400 CAC score group had higher MACE (unadjusted HR 5.01, 95% CI: 3.1 to 8.1, p<0.001). After adjusting for age, sex and cardiovascular risk factors, CAC score remained predictive of MACE with an adjusted HR of 1.0004 (95% CI: 1.0002 to 1.001, p=0.001) per Agatston unit. The CAC by group analysis despite showing a trend for increasing CAC score group had higher risk for MACE, it was only predictive in the >400 CAC group after adjusting for age, sex and cardiovascular risk factors 2.17 (95% CI: 1.23 to 3.84, p=0.008).

MACE-free survival was significantly higher among patients in the <50th CAC percentile group (60% for patients <50th CAC percentile and 29% for patients ≥50th CAC percentile (log-rank p<0.001, figure 3). The unadjusted HR for MACE was 2.6 (95% CI: 1.9 to 3.7, p<0.001) in the ≥50th CAC percentile group. After adjusting for cardiovascular risk factors, the HR was 1.9 (95% CI: 1.4 to 2.7, p<0.001). For each percentile increase in CAC, the unadjusted HR was 1.01 (95% CI: 1.01 to 1.02, p<0.001) and the adjusted HR was 1.01 (95% CI: 1.01 to 1.02, p<0.001).

**Interobserver variability of visual CAC on non-gated CT scan of the chest**

Among the 30 (11%) scans that were randomly selected for secondary reads, the Cohen’s k value was 0.85, p<0.001 between observers for assessing visible CAC. Interclass correlation for CAC score was 0.97, p<0.001.

**DISCUSSION**

We report that among hospitalised inpatients undergoing non-gated CT scan of the chest, both visible CAC and a CAC score ≥50th percentile provide independent prognostic information at medium-term follow-up, with

**Table 3** HRs for MACE based on CAC assessment

|                          | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* |
|--------------------------|------------------------|------------------------|
| Qualitative CAC assessment |                        |                        |
| No visible CAC           | Reference              | Reference              |
| Visible CAC              | 6.0 (3.69 to 9.57)     | 3.2 (1.8 to 5.6)       |
| Quantitative CAC assessment |                       |                        |
| CAC score†               | 1.001 (1.001 to 1.001) | 1.0004 (1.0002 to 1.001) |
| CAC percentile‡          | 1.01 (1.01 to 1.02)    | 1.01 (1.01 to 1.02)    |
| CAC percentile group     |                        |                        |
| <50th percentile         | Reference              | Reference              |
| ≥50th percentile         | 2.6 (1.88 to 3.67)     | 1.9 (1.4 to 2.7)       |
| CAC by groups            |                        |                        |
| CAC score 0              | Reference              | Reference              |
| CAC score 1–100          | 2.97 (1.9 to 4.7)      | 1.49 (0.88 to 2.54)    |
| CAC score 101–400        | 3.60 (2.1 to 6.2)      | 1.64 (0.89 to 3.03)    |
| CAC score >400           | 5.01 (3.1 to 8.1)      | 2.17 (1.23 to 3.84)    |

*Adjusted for age, sex, diabetes mellitus, smoking history, hypertension and dyslipidaemia.
†HR for each incremental CAC score value.
‡HR for each incremental CAC percentile.
CAC, coronary artery calcium; MACE, Multi-Ethnic Study of Atherosclerosis.

![Figure 2](Kaplan-Meier graph for visible versus non-visible coronary artery calcium (CAC).)

![Figure 3](Kaplan-Meier graph for <50th coronary artery calcium (CAC) percentile versus ≥50th CAC percentile.)
half of the events occurring within 18 months. The simple, pragmatic assessment of visible CAC could potentially identify patients at increased risk of cardiac events before hospital discharge and facilitate commencement of primary prevention therapy.

Prevalence of CAC in non-gated inpatient chest CT

Despite the high prevalence of incidental CAC, it remains under-reported.17 Multiple large outpatient cohorts have shown a prevalence of incidentally visualised CAC of approximately 70%.11 18 There is only one report on incidental CAC prevalence in inpatients cohorts, reporting a prevalence of 63%.19 Our study found a similar prevalence of 61% despite none of our included patients having a known history of CAD. Furthermore, among patients with no cardiac risk factors, just over a quarter (26%) had visible CAC, and conversely, among patients with seemingly increased risk based on traditional risk assessment (two or more cardiac risk factors), 17% had no visible CAC. These findings highlight the ability of CT scan of the chest to reclassify patients into high-risk and low-risk groups independent of baseline traditional risk assessment. Additionally, we found that CAC could be assessed reproducibly with excellent interobserver reliability between two readers for both visual CAC and CAC score. This finding emphasises the ease at which simple CAC assessments can be done in non-gated CT scans of the chest.

Prognostic value of CAC in non-gated inpatient chest CT scan

Our results show that visible CAC and ≥50th CAC percentile on non-gated CT scan of the chest are independent predictors of MACE in the medium term among hospital inpatients without a known history of coronary artery disease and remained significant after adjusting for cardiovascular risk factors. The current literature on the prognostic role of CAC in non-gated CT scan of the chest is primarily based on lung cancer screening outpatient scans.11 20–22 These studies have all consistently shown that CAC can be identified on non-gated CT scan of the chest and identification of CAC is associated with poorer cardiovascular outcomes.11 20–22 More recently, Shao et al demonstrated the prognostic utility of visible CAC among all comers presenting for outpatient CT scans of the chest requested by respiratory physicians.15 This has been reaffirmed by Xie et al’s systematic review and meta-analysis.19 The Society of Cardiovascular Computed Tomography/Society of Thoracic Radiology guidelines now support the use of visual assessment of CAC as an alternative to Agatston scoring.18 Our study uniquely involves hospital inpatients, which has not been reported previously. As a result, there was a wider variation in scan indications, such as trauma and foreign bodies (n=25, 9%). We found that CT scan of the chest is still predictive of prognosis in this group of inpatients independent of cardiovascular risk factors. The fact that incidental visible CAC was independently predictive of MACE in an acute inpatient population, with half of the MACE events occurring within 18 months of discharge, indicates that intervention to reduce the risk of cardiovascular events may be temporally relevant in these populations.

Limitations

The first limitation of our study is selection bias as patients were primarily referred for non-contrast CT scan of the chest for lung disease. Moreover, a significant number of patients were excluded due to malignancy and death during the index admission. The applicability of the results is therefore limited to similar patients. Second, although non-gated CT scan of the chest was used for calcium scoring, there was excellent interobserver reliability for this method. Third, our study was a single-centre retrospective cohort study with a small sample size, thus leading to underpowering when CAC was divided into ordinal groups. Future studies are needed to prospectively evaluate the prognostic role of incidentally identified CAC on non-gated CT scan of the chest among hospital inpatients.

CONCLUSION

CAC is frequently observed among hospital inpatients undergoing non-gated CT scan of the chest who otherwise have no known history of CAD. Simple visual assessment of the CAC on non-gated CT scan of the chest in hospital inpatients provides independent prognostic information beyond traditional cardiovascular risk factors. This may provide an opportunity to identify patients who may benefit from aggressive risk factors modification.

Twitter Christopher Yu @drchrisyu

Contributors All authors contributed to the manuscript. ACCN assisted with the ethics application. CY, LR and CN performed coronary artery calcium analysis. MA performed data collection.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by New South Wales Population and Health Services Research Ethics Committee (Reference HREC/18/CIPH/62) with a waiver for informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Christopher Yu http://orcid.org/0000-0003-1025-5480

REFERENCES

1 Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med Overseas Ed 2008;358:1336–45.
2 Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.
3 Kondos GT, Hoff JA, Sevrakov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 2003;107:2571–6.
4 Shaw LJ, Raggi P, Schisterman E, et al. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228:826–33.
5 Hecht HS. Coronary artery calcium scanning: past, present, and future. JACC Cardiovasc Imaging 2015;8:579–96.
6 Lloyd-Jones DM, Braun LT, Nidumolu CE, et al. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease. J Am Coll Cardiol 2019;73:3153–67.
7 Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010;303:1610–6.
8 Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation 2000;101:850–5.
9 Uretsky S, Chokshi N, Kobrinski T, et al. The interplay of physician awareness and reporting of incidentally found coronary artery calcium on the clinical management of patients who underwent noncontrast chest computed tomography. Am J Cardiol 2015;115:1513–7.
10 Xie X, Zhao Y, de Bock GH, et al. Validation and prognosis of coronary artery calcium scoring in nontriggered thoracic computed tomography: systematic review and meta-analysis. Circ Cardiovasc Imaging 2013;6:514–21.
11 Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the National lung screening trial: a comparison of scoring methods. Radiology 2015;276:82–90.
12 Hecht HS, Cronin R, Blaha MJ, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: a report of the Society of cardiovascular computed tomography and society of thoracic radiology. J Cardiovasc Comput Tomogr 2017;11:74–84.
13 Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
14 McClelland RL, Chung H, Detrano R, et al. Distribution of coronary artery calcium by race, gender, and age: results from the multi-ethnic study of atherosclerosis (MESA). Circulation 2006;113:30–7.
15 Shao L, Yan AT, Lebovic G, et al. Prognostic value of visually detected coronary artery calcification on unenhanced non-gated thoracic computed tomography for prediction of non-fatal myocardial infarction and all-cause mortality. J Cardiovasc Comput Tomogr 2017;11:196–202.
16 Huang Y-L, Wu F-Z, Wang Y-C, et al. Reliable categorisation of visual scoring of coronary artery calcification on low-dose CT for lung cancer screening: validation with the standard Agatston score. Eur Radiol 2013;23:1226–33.
17 Williams KA, Kim JT, Holohan KM. Frequency of unrecognized, unreported, or underreported coronary artery and cardiovascular calcification on noncardiac chest CT. J Cardiovasc Comput Tomogr 2013;7:167–72.
18 Shemesh J, Henschke CI, Farooqi A, et al. Frequency of coronary artery calcification on low-dose computed tomography screening for lung cancer. Clin Imaging 2006;30:181–5.
19 Haller C, Vandehei A, Fisher R, et al. Incidence and implication of coronary artery calcium on non-gated chest computed tomography scans: a large observational cohort. Cureus 2019;11:e6218.
20 Taix RAP, Isgum I, Willeminck MJ, et al. Quantification of coronary artery calcium in non-gated CT to predict cardiovascular events in a lung cancer screening participants: results of the Nelson study. J Cardiovasc Comput Tomogr 2015;9:50–7.
21 Jacobs PC, Gondrie MJA, van der Graaf Y, et al. Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. AJR Am J Roentgenol 2012;198:505–11.
22 Mets OM, Vliegenthart R, Gondrie MJ, et al. Lung cancer screening CT-based prediction of cardiovascular events. JACC Cardiovasc Imaging 2013;6:899–907.