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Original article

Adverse Cardiac Events Risks of Non-Obstructive Coronary Artery Disease by Cardiac CT Angiography at One-Year Follow-Up: Results of the Coronary Risk Determination in Intermediate Stratum Coronary CT Angiography (CORDISC) Study

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Abstract

We conducted a retrospective cohort study of the adverse events at one year post-cardiac computed tomography (cardiac CT) using data gathered from the Marshfield Clinic Health System (MCHS) Cardiac CT registry to compare non-fatal myocardial infarction (MI), revascularization, all-cause mortality, and composite major adverse cardiac events (MACE) one year following cardiac CT in patients with non-obstructive coronary artery disease (CAD) and normal coronary arteries. From 2009 to 2017, the records of 2,649 patients who underwent cardiac CT were reviewed. CAD detected by cardiac CT was defined as normal (0% luminal stenosis) and non-obstructive (1-49% luminal stenosis). Clinical outcomes were nonfatal MI, revascularization, including percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), all-cause mortality, and MACE. Cohorts were compared using t-tests and Fisher exact tests, and a logistic regression was performed to assess risk of clinical outcomes at one year. Compared with patients with normal coronary arteries, patients with non-obstructive coronary disease on cardiac CT had higher event rates of MACE (3.7% vs. 1.2%; P =0.006), revascularization (1.1% vs. 0.2%; P=0.033), and all-cause mortality (1.7% vs. 0.4%; P=0.012). After adjusting for baseline difference in demographics, risk factors, and medication use, the odds ratio of revascularization was 3.77 (95% CI: 1.03,13.79) and MACEs was 2.06 (95% CI: 0.94,4.51). Symptomatic congenital heart diseases accounted for about 50% of the non-death MACEs. Cardiac CT-defined non-obstructive CAD was associated with higher rates of revascularization, all-cause mortality and MACE compared to those with normal coronary arteries.

Keywords: ***Computed tomography; Cardiac CT angiography; Non-obstructive CAD, Major adverse cardiac events (MACE); Percutaneous coronary intervention (PCI)***

Introduction

Cardiac computed tomography (CT) has been a useful noninvasive modality to assess coronary artery disease (CAD) in intermediate risk patients with a high negative predictive value [1-3]. Its high diagnostic performance has been demonstrated in a meta-analysis with a sensitivity and specificity of 97.2% and 87.4%, respectively[2].

Several registry-based studies have demonstrated that patients with obstructive CAD, defined as ≥50% atherosclerotic coronary luminal diameter reduction, have a significantly higher major adverse cardiac event (MACE) rate than those with normal

or non-obstructive CAD and often receive invasive angiography and revascularization [4-13]. On the contrary, non-obstructive CAD (≤ 50% luminal stenosis) is usually managed medically with close follow-up, although in a 2014 multicenter retrospective study, individuals with non-obstructive disease had an increased risk of MACE compared to patients with normal cardiac CT defined coronary arteries at a 2.4 ± 1.2 year follow-up [14]. However, the prognostic value of non-obstructive stenosis in the first year following cardiac CT is not clear [5,8,12].

In this study, we evaluated the one year prognostic significance of cardiac CT for non-obstructive CAD by comparing the rate of non-fatal myocardial infarction (MI), revascularizations (as defined by an instance of percutaneous coronary intervention [PCI] or coronary bypass surgery), all-cause mortality, and composite MACE between patients with non-obstructive CAD and patients with normal cardiac CT findings after a 1-year follow-up using prospectively collected data from the Marshfield Clinic Health System (MCHS) cardiac CT registry. Our hypothesis was that there would be an increased risk among those with non-obstructive disease compared to those with normal coronary arteries by Cardiac CT.

Materials and Methods

This is a retrospective cohort study of prospectively collected data from the MCHS Cardiac CT registry from January 1, 2009 to December 31, 2017. This registry was created as part of quality improvement measures for cardiac CT procedures in the health system. Patient demographics, clinical data, pre-procedural, procedural, and follow-up data were carefully collected and entered prospectively by trained personnel in the cardiac CT quality assurance program. Up to 10% of registry entries were manually validated on a regular basis, and up to 10% of manually abstracted data were cross validated to assure data quality. The study was approved by the Marshfield Clinic Research Institute IRB.

Study population

The records of adult patients (>18 years) who underwent cardiac CT for cardiac symptomologies associated with CAD and listed in the MCHS Cardiac CT registry between 2009 and 2017 were eligible for study inclusion. Patients with cardiac symptomatology thought to be related to CAD including chest pain, shortness of breath, palpitations, pressure tightness, arm pain, squeezing pain, neck pain, jaw pain, dizziness, nausea, indigestion, abdominal pain, diaphoresis, or fatigue were clinically evaluated by experienced cardiologists who recommended further evaluation with cardiac CT according to the recommendations of the multi-society appropriate use criteria for cardiac CT.14 Patient records excluded were those that had obstructive coronary disease (> 50% luminal stenosis) on cardiac CT, as well as those with inconclusive cardiac CT readings due to poor image acquisition.

The study cohort was stratified into two subgroups: (1) Patients with normal or no CAD defined as 0% luminal stenosis; and (2) Patients with non-obstructive CAD defined as <50% luminal stenosis. All patients were followed up for one year post-cardiac CT for development of clinically relevant outcome events.

Cardiac CT Protocol, Image Reconstruction, and Interpretation

All patients underwent cardiac CT scans using a 128 or 326 slice scanner with retrospective or prospective electrocardiographic gating. Based on institutional protocol, heart rate was controlled with oral or intravenous beta-blocker (metoprolol) as indicated to keep heart rate < 60 beats per minute. A contrast enhanced scan was acquired using nonionic contrast medium injected in the peripheral forearm veins.

Radiation dose was controlled by vendor specific radiation reduction applications, reduction of the voltage when possible, and using prospective gating when applicable. Advanced post processing was performed with Tera-recon software. All cardiac CT images were interpreted by radiologists and cardiologists with special training and over 10 years of experience in noninvasive cardiac CT imaging.

Independent Variables

Coronary atherosclerosis was classified visually as normal coronary arteries (no evidence of luminal stenosis); mild CAD (1-49% luminal stenosis), moderate CAD (evidence of 50-69% luminal stenosis); or severe CAD (≥70% luminal stenosis). Patients with moderate and severe CAD (≥50% luminal stenosis) were classified as obstructive coronary disease and were excluded from the study.

Clinical Endpoints

The primary endpoints were nonfatal MI classified as ST-elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI), revascularization with PCI or coronary artery bypass surgery, all-cause mortality, and composite 3-point MACE.

Statistical Analysis

Statistical analysis was performed by the Office of Research Computing and Analytics of the Marshfield Clinic Research Institute (MCRI) using R version 3.6.0 [15].

Descriptive statistics were generated to define the cohort. Patient demographics (gender, race, and age) were described using means and standard deviation (SD) for continuous variables and counts and percentages for categorical variables. Data on comorbidities at the time of cardiac CT, specifically diabetes mellitus, hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), hyperlipidemia, cerebrovascular accident (CVA), and peripheral vascular disease, as well as medications (aspirin, beta blocker, and statin) at the time of cardiac CT and for one year following cardiac CT were described using counts and percentages. Reasons for revascularization were reported.

Comparisons between patients with normal cardiac CT and non-obstructive stenosis were made using t tests for normally distributed data and Fisher exact tests for categorical data. All comparisons were two-tailed with $p < 0.05$ considered significant.

Unadjusted and adjusted odds ratios (OR) were estimated using logistic regression. Adjustment variables were chosen a priori; models were adjusted for all patient demographics, comorbidities, and medications at time of cardiac CT. Normal cardiac CT result was selected as the reference group for OR estimation. Odds ratios, 95% CI, and p-values were presented.

Results and Discussion

Clinical characteristics of the study cohort

There were 2,649 unique patients who had a cardiac CT for intermediate risk CAD during the study period of January 1, 2009 until December 31, 2017. Of patients, 941 (36%0 were found to have obstructive coronary disease and were excluded, leaving 1,708 (64%) patient records for analysis. Of these patients, 1,366 (80%) had no atherosclerotic coronary arteries, while 342 (20%) had non-obstructive CAD and comprised 13% of the entire population (**Figure 1**).

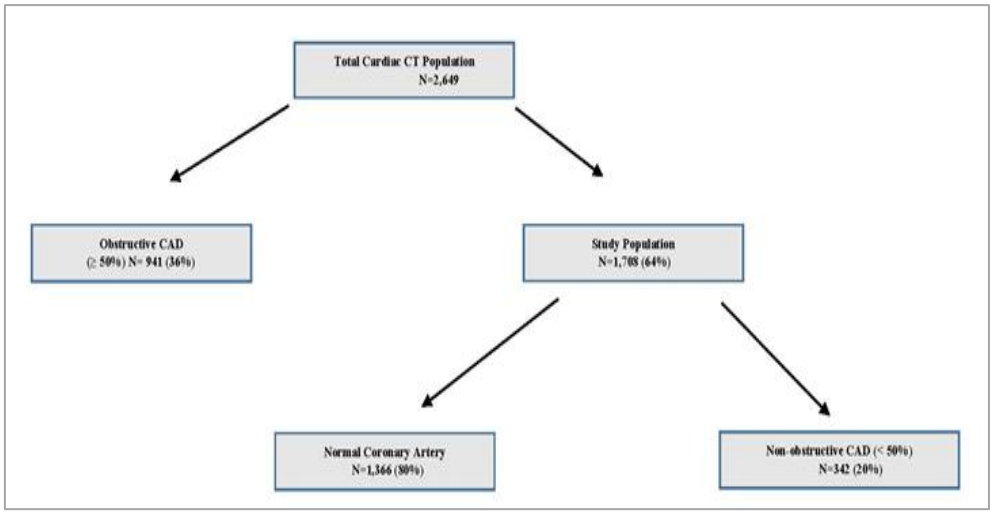

Figure 1: Study cohort distribution.

There were 1,708 unique patients who had a total of 1,742 cardiac CT procedures at least one year apart. The study population was predominantly white (91.5%) with a mean age of 54 years. Patients with non-obstructive coronary disease were older with a mean age of 61 years, compared to 52 years from the normal coronary cohort (p=0.001). Females were more likely to have normal coronary arteries (60.5% versus 48.0%; p <0.001; Table 1). The patients with non-obstructive CAD had a significantly higher frequency of cardiovascular risk factors including diabetes, hypertension, CHF, CKD, and hyperlipidemia than patients with normal coronary arteries (Table 2). They were also more likely to be medically managed with aspirin, beta-blockers, and statin at the time of cardiac CT and for one year afterwards.

Table 1: Demographic characteristics of unique patients who underwent Cardiac CT

	All N = 1,708[a] (%)	**Normal Cardiac CT N = 1,366**	**Non-obstructive Stenosis (<50%) N = 342**	**p-value**
Gender				**<0.001**
Women	991 (58.0)	827 (60.5)	164 (48.0)	
Men	717 (42.0)	539 (39.5)	178 (52.0)	
Race				0.986
White	1562 (91.5)	1248 (91.4)	314 (91.8)	
Other	56 (3.3)	45 (3.3)	11 (3.2)	
Age at first Cardiac CT	54 (14)*	52 (14)*	61 (11)*	**<0.001**

[a] There are 1,708 unique patients with 1,742 Cardiac CT procedures. Thirty patients had two Cardiac CTs. Two patients had three Cardiac CTs.
* +/- One standard deviation from the mean age

Table 2: Baseline comorbidities and medications of patients who underwent Cardiac CT

Comorbidities at time of Cardiac CT	**All N = 1,742[a] (%)**	**Normal Cardiac CT N = 1,393 (%)**	**Non-obstructive Stenosis (<50%) N = 349 (%)**	**p-value**
Diabetes Mellitus Type I or II	191 (11.1)	134 (9.7)	57 (16.6)	**<0.001**
Hypertension	625 (35.9)	461 (33.1)	164 (47.0)	**<0.001**
Congestive Heart Failure	94 (5.4)	62 (4.5)	32 (9.2)	**0.001**
Chronic Obstructive Pulmonary Disease	86 (4.9)	62 (4.5)	24 (6.9)	0.071
Chronic Kidney Disease	40 (2.3)	26 (1.9)	14 (4.0)	**0.026**
Lipidemia	649 (37.3)	479 (34.4)	170 (48.7)	**<0.001**
Cerebral Vascular Accident	20 (1.2)	16 (1.2)	4 (1.1)	1.000
Peripheral Vascular Disease	16 (0.9)	12 (0.9)	4 (1.2)	0.542
Medications at time of Cardiac CT				
Aspirin	838 (48.1)	630 (45.2)	208 (59.6)	**<0.001**
Beta Blocker	812 (46.6)	627 (45.0)	185 (53.0)	**0.008**
Statin	626 (35.9)	457 (32.8)	169 (48.4)	**<0.001**
Medications 1 year after Cardiac CT				
Aspirin	854 (49.0)	619 (44.4)	235 (67.3)	**<0.001**
Beta Blocker	665 (38.2)	492 (35.3)	173 (49.6)	**<0.001**
Statin	686 (39.4)	473 (34.0)	213 (61.0)	**<0.001**

Average age (SD) is reported. Counts (percentages) are reported for categorical variables.
[a] Count of Cardiac CT procedures at least 1 year apart. Not a count of unique patients. There are 1,708 unique patients. Thirty patients had 2 Cardiac CTs. Two patients had 3 Cardiac CTs.

Clinical outcomes

Over a one year follow-up duration, a total of 34 (1.9%) composite MACEs were recorded, which differed significantly between the normal (21 [1.5%]) and non-obstructive (13 [3.7%]) cohorts, respectively (p=0.015). There were 16 (0.9%) non-fatal MI events documented, which did not differ significantly between the two groups (0.9% each; p=1.00). However, there were 11 (0.6%) revascularization events that significantly differed between the normal cardiac CT and non-obstructive groups (0.4% versus 1.7%; p= 0.012), respectively. One-year all-cause mortality was also significantly different between the two groups (0.2% versus 1.1%; p=0.033) (Table 3).

Table 3: MACE frequencies

	Total N = 1,742[a]	**Normal Cardiac CT N = 1,393**	**Nonobstructive Stenosis (<50%) N = 349**	**P-value.**
Frequency, N[b]				
MI	16	13 (0.9%)	3 (0.9%)	1.00
STEMI	5	5	0	
NSTEMI	11	8	3	
Revascularization	11	5 (0.4%)	6 (1.7%)	**0.012**
CABG	8	4	4	
PCI	3	1	2	
Death	7	3 (0.2%)	4 (1.1%)	**0.033**
MACE	34	21 (1.5 %)	13 (3.7%)	**0.015**

[a] Count of Cardiac CT procedures at least 1 year apart. There are 1,708 unique patients. Thirty patients had 2 Cardiac CTs. Two patients had 3 Cardiac CTs.

[b] Total number of events.

Abbreviations: MACE, Major adverse cardiac events; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTEMI, Non-ST-elevation myocardial infarction; CABG, Coronary artery bypass graft; PCI, Percutaneous coronary intervention

Analysis of OR for the two cohorts suggests that patients in the non-obstructive cardiac CT group had significantly higher odds of having revascularization, all-cause mortality, and composite MACE over a one-year period in the unadjusted model (Table 4). After adjusting these findings for baseline differences in patient demographics, comorbidities, and medication use at the time of cardiac CT, the OR of revascularization remained significant at 3.77 (95% CI: 1.03,13.79; p= 0.045), and the MACE OR was marginally non-significant at 2.06 (95% CI: 0.94, 4.51; p= 0.071). Table 5 demonstrates the event OR in all the adjusted models. Figure 2 illustrates the differences between the unadjusted and the adjusted OR for all models.

Table 4: MACE unadjusted odds ratios

	Nonobstructive Stenosis		
	OR	**95% CI**	***p***
Myocardial Infarction	1.00	(0.28, 3.56)	0.997
Revascularization	4.86	(1.47, 16.01)	**0.009**
Death	5.37	(1.20,24.11)	**0.028**
MACE	2.80	(1.37, 5.72)	**0.005**
Normal Cardiac CT (Reference)	1.00	--	--

Logistic regression model with MACE Event (MI, Revascularization, Death, or MACE) as the dependent variable and coronary artery condition (normal or nonobstructive) as the main predictor.

Abbreviations: MACE, Major adverse cardiac events; MI, myocardial infarction; CTA, computed tomographic angiography; Cardiac CT, cardiac computed tomography

Table 5: MACE adjusted odds ratios

	MI			**Revascularization**			**Death**			**MACE**		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Model A												
Nonobstructive Stenosis	0.80	(0.21,3.03)	0.745	3.72	(1.02, 13.50)	**0.046**	2.90	(0.60, 14.01)	0.184	2.00	(0.93, 4.30)	0.075
Normal coronary CTA (Reference)	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Model B												
Nonobstructive Stenosis	0.83	(0.22, 3.13)	0.779	3.83	(1.05, 14.02)	**0.042**	2.47	(0.51, 12.11)	0.263	1.96	(0.91, 4.23)	0.087
Normal Cardiac CT(Reference)	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Model C												
Nonobstructive Stenosis	0.85	(0.22, 3.22)	0.807	3.94[c]	(1.07, 14.45)	**0.039**	2.45	(0.47, 12.66)	0.286	1.97	(0.91, 4.29)	0.087

Normal Cardiac CT(Reference)	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Model D												
Nonobstructive Stenosis	0.85	(0.22, 3.25)	0.813	3.77[c]	(1.03, 13.79)	**0.045**	2.70	(0.47, 15.39)	0.264	2.06	(0.94, 4.51)	0.071
Normal Cardiac CT (Reference)	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--

Logistic regression model with MACE (MI, Revascularization, Death, or MACE) as the dependent variable and coronary artery condition (normal or nonobstructive) as the main predictor adjusted for other variables as follows:
Model A: Age and sex
Model B: Age, sex and diabetes
Model C: Age, sex, diabetes, hypertension, CHF, CKD, lipidemia
Model D: Age, sex, diabetes, hypertension, CHF, CKD, lipdemia, and medications at time of Cardiac CT
[c] No revascularizations for patients with CKD or CHF
Abbreviations: MACE, Major adverse cardiac events; MI, myocardial infarction; CTA, computed tomographic angiography; Cardiac CT, cardiac computed tomography; CHF, congestive heart failure; CKD, chronic kidney disease

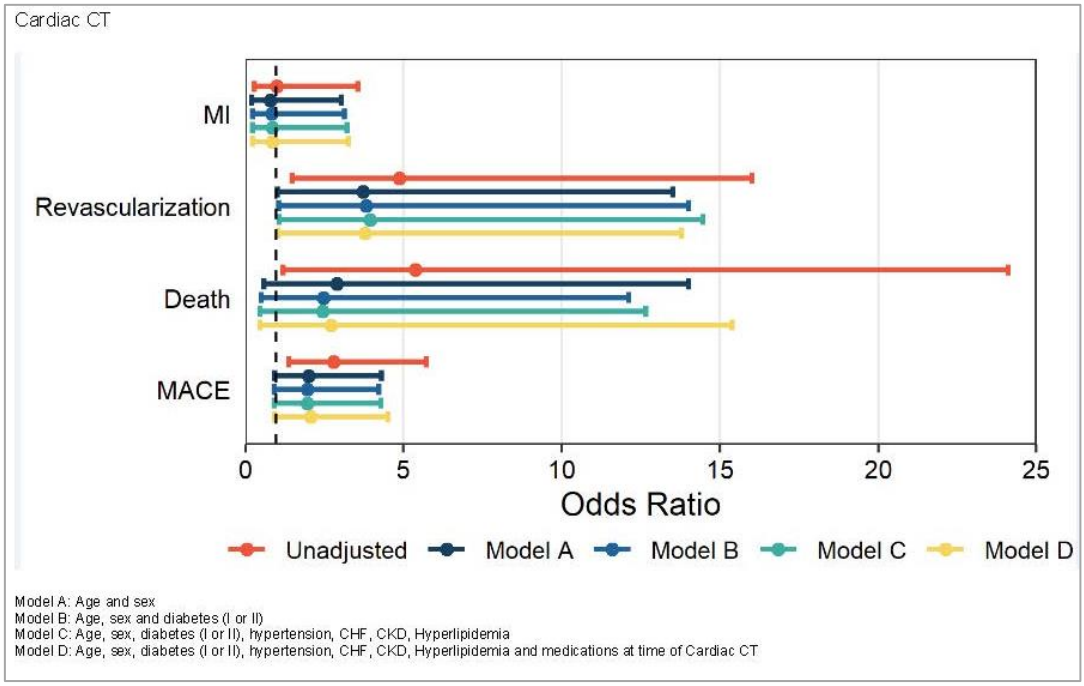

Figure 2: Comparison between the unadjusted and adjusted odds ratios for non-obstructive stenosis versus normal

Clinical outcome etiologies

Further evaluation of the etiologies of the specific primary outcome events showed that congenital heart diseases accounted for nearly 50% of non-death related MACE in the study, as demonstrated in Table 5. All MACEs were either due to congenital heart disease with anomalous coronary artery with malignant course, coronary aneurysms, or coronary artery spasms. There were seven coronary artery bypass surgeries attributed to congenital heart disease with malignant anomalous coronary artery course or aneurysm. In the study, NSTEMI accounted for 40% of non-death related MACE, though all NSTEMI events occurred where type II MI secondary to supply demand mismatch in the settings of several systemic conditions like anemia, severe hypertension, and cardiac arrhythmias. Only three (10%) non-death related MACEs were due to progressive symptomatic coronary disease and resulted in PCI; six out of the seven deaths reported were due to non-coronary artery related conditions.

Discussion

In this study, we examined the clinical outcomes (nonfatal MI, revascularization, all-cause mortality, and composite MACE) of patients who underwent cardiac CT for various cardiac symptomatology and had non-obstructive CAD versus patients with normal appearing coronary arteries at one-year follow-up. Individuals with non-obstructive CAD had significantly higher rates of revascularization, all-cause mortality, and composite MACE compared to those with normal appearing arteries. These differences were similarly represented in the unadjusted ORs. However, after adjusting for differentials in demographics, comorbidities, and medication use at the time of cardiac CT, the OR of revascularization remained significant, and the MACE OR was marginally non-significant.

Though the absolute overall event rate was small, over the one-year period, about 50% of non-death MACE and 73% of revascularizations mainly occurred in individuals with congenital heart disease and symptomatic coronary artery anomalies. This finding, not reported in the literature, may be explained by the fact that our institution is a referral center for patients with congenital heart diseases in the health system. To the best of our knowledge, this is one of the largest single center studies to investigate the one-year clinical outcomes of cardiac CT-defined non-obstructive CAD using a real-time prospectively collected database with further

delineation of the different etiologies of observed MACE [1,11-13,16-18].

Given the high diagnostic accuracy of cardiac CT in the detection and delineation of coronary artery lesions [1-3,19-22], this study suggests a potential clinical utility of cardiac CT in the initial investigation of patients presenting with chest pain or other symptoms indicative of CAD. This is especially prudent for intermediate risk patients who may have negative functional assessment warranting no further invasive coronary angiography that can otherwise reveal a coronary abnormality. The findings of this study are supported by prior studies that demonstrated increased mortality risk, revascularization, and composite MACE of individuals with cardiac CT-defined non-obstructive disease and also demonstrates the high negative predictive value of cardiac CT-reported normal coronary arteries for adverse clinical events [16-18].

However, there are conflicting findings regarding the clinical significance of non-obstructive CAD as defined by cardiac CT. After a follow-up evaluation of 959 patients who presented with chest pain and underwent cardiac CT evaluation over a mean follow-up of 27 ± 11 months, Beigel et al. [1] reported benign clinical outcomes with no difference in events of nonfatal MI and overall MACE between the non-obstructive and normal coronary artery cohorts over the study duration. In contrast, other multiple single and multicenter studies have observed findings to the contrary [17,23]. In a systematic review and meta-analysis of 18 published studies with a total of 9,592 patients and a median follow-up of 20 months, Hulten et al. [23] observed an incrementally increased risk of adverse events (MI, revascularization, and death) with an annual event rate of 0.17% for patients with normal cardiac CT and 1.41% for patients with non-obstructive Cardiac CT, which achieved statistical significance.

Our results are in concordance with findings from a recent prospective, large-scale, multicenter, international study by Nakazato et al.,16 which involved 15,187 patients and was designed to examine the relationship of the extent and severity of CAD as diagnosed by cardiac CT to the risk of incidence of MACE. They found an independent prognostic value of both non-obstructive and obstructive CAD as a predictor for future MACE at 2.4 ± 1.2 years follow-up on a per-patient, per-vessel, and per-vessel-segment basis and demonstrated an increasing risk for adverse cardiac events in individuals < 65 years-of-age versus individuals ≥ 65 years-of-age. An increased risk of MACE was also observed for individuals with non-obstructive CAD with a hazard ratio (HR) of 2.43 (p =0.001) when compared to patients with normal cardiac CT.16 Another large multicenter, multinational study of 24,775 stable patients from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) registry reported similarly higher rates of mortality for non-obstructive CAD diagnosed by cardiac CT (HR: 1.60; 95% CI: 1.18 to 2.16; p =0.002) for the prediction of all-cause mortality at 2.3 ± 1.1-year follow-up compared to patients without evidence of CAD, with differing risk profiles for age and sex. However, the results of our study suggest that MI, death, and MACE at one year post-cardiac CT may be due in part to the overall increased risk for adverse cardiac events for individuals diagnosed with congenital heart disease and anomalous cardiothoracic abnormalities.24,25 This finding requires validation from a larger multicenter study.

Since our study is a single center retrospective cohort study, it is subject to the inherent limitations of retrospective design, such as missing data. Secondly, because of the overall low event counts, there was a sub-optimal model fit for the adjusted models. As a result, our findings with the unadjusted models may have been affected by the significantly differing baseline risk comorbidities of the non-obstructive cohort. Furthermore, the etiologies for the all-cause mortality events seen were mainly non-cardiovascular in nature, which limits the clinical significance of different mortality numbers seen in the two groups and limits the risk predictive power of the cardiac CT findings. Lastly, the generalizability of our findings to other settings are limited by the homogenous nature of our target population. However, as our cohort is from a predominantly rural population that receives most of their health care from our health system, this lack of diversity is balanced by the strengths of standardized reporting procedures within our center and minimal patient loss to follow-up.

Conclusions

Patients with normal coronary arteries and non-obstructive CAD by cardiac CT have a low number of adverse clinical events (MI, revascularization, death, and MACE) at one year post-procedure. However, those with non-obstructive CAD have a significantly higher rate of revascularization, death, and composite MACE compared to those with normal coronary arteries. Factors such as congenital heart disease, anomalous coronary arteries, and supply-demand mismatch may be a more common etiology for MACE within the first year and may warrant close follow-up by cardiologists.

Ethics approval and consent to participate

The study was approved by the Marshfield Clinic Research Institute Institutional Review Board.

List of abbreviations

CAD, coronary artery disease
CHF, congestive heart failure
CKD, chronic kidney disease
COPD, chronic obstructive pulmonary disease
CT, computed tomography
CVA, cerebrovascular accident
MACE, major adverse cardiac event
MCHS, Marshfield Clinic Health System
MCRI, Marshfield Clinic Research Institute
MI, myocardial infarction
NSTEMI, non-ST segment elevation myocardial infarction
OR, odds ratio
PCI, percutaneous coronary intervention
SD, standard deviation
STEMI, ST-elevation myocardial infarction

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Conflicts of Interest

The authors have no personal or financial conflicts of interest to disclose

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Authors' contributions

SN, CZ, PU, PYLW, RG, BC, SR, and RR designed the research, collected and analyzed the data; SN, PU, and RR wrote the first draft; SN, CZ, PU, PYLW, RG, BC, SR, and RR edited the paper. All authors read and approved the final manuscript.

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