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Distributions and burden of coronary calcium in asymptomatic Saudi patients referred to computed tomography

Sumaya Al Helali *, Muhamed Abid Hanif, Nura Alshugair, Ahmad Al Majed, Abdullah Belfageih, Hamad Al Qahtani, Sameer Al Dulikan, Hussain Hamed, Adnan Al Mousa

Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia

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ABSTRACT

Background: Unlike Western and Asian populations, the prevalence and severity of coronary artery calcification (CAC) have not been adequately examined in Saudi Arabia and other nearby Arab Gulf countries.
Objectives: To estimate the age and gender specific percentiles of coronary calcium score (CCS) and to study the severity of CAC in relation to patient risk in a large sample of asymptomatic Saudi patients.
Methods: Retrospective cross-sectional study was conducted between July 2007 and December 2017 at a large Cardiac Centre in Riyadh, Saudi Arabia. The target was adult patients without pre-existing CAD referred to (64 multidetector spiral) computed tomography for standard indications.
Results: A total 2863 patients were included in the current analysis. The 90th percentile of CCS was 95.0 in males compared with 53.2 in females and was 823.95 in patients aged $\geq$ 75 years compared with zero in patients < 40 years. Extensive CAC (CCS > 400) were 3.1% in males compared with 1.6% in females and 14.0% in patients aged $\geq$ 75 years compared with 0.0% in patients < 40 years. CCS was steadily higher with increasing European systematic coronary risk evaluation; 3.1 $\pm$ 22.5 in mild risk, 37.1 $\pm$ 201.9 in moderate risk, 116.1 $\pm$ 256.1 in high risk, and 131.0 $\pm$ 222.0 in very high risk.
Conclusions: As expected, the findings confirm the higher burden of CAC in males, older age, and higher CAD risk. The burden of CAC in current patients is much lower than reported in US and other Western patients. Local cardiologist should consider using local rather than US percentiles of CCS.

1. Introduction

Coronary artery disease (CAD) is the most common type of cardiovascular disease [1]. CAD is the single most important cause of death in both developed and developing countries [2]. In Saudi Arabia, the prevalence of CAD has been estimated at 5.5% with higher rates in males than females (6.6% versus 4.4%) [3]. Additionally, the mortality of cardiovascular disease represents 17.2% of all deaths in Saudi Arabia, which represented 4,287 deaths in 2017 [4]. Unlike the observed decline in CAD in developed countries, there is increasing burden of CAD and its risk factors in developing countries [5]. In the same direction, the rapid economic development and urbanization in Saudi Arabia probably increased the burden of CAD risk factors, specially dyslipidemia and abdominal obesity [6].

Coronary artery calcification (CAC) is a well-recognized marker of atherosclerosis that can be easily measured using computed tomography (CT) [7]. The resulting coronary calcium score (CCS) is a non-invasive screening tool for predicting future cardiovascular morbidity and mortality [8]. There has been accumulating evidence indicating that CCS improves CAD risk classification in asymptomatic patients beyond the underlying CAD risk factors [9]. This is specially helpful in some patients groups with borderline to intermediate CAD risk but without clinical CAD [10].

Several studies reported a wide variation in CAC between different countries and populations [11,12]. This may reflect the role of race and ethnicity in the prevalence and severity of CAC [13]. Unfortunately, most of these data were focusing on Western and Asian populations [14], with very limited data on prevalence and severity of CAC in Saudi Arabia and other nearby Arab Gulf countries [15,16]. More importantly, comparing local prevalence and severity of CAC with international data has never been attempted. The objective of the current study was to estimate the age and gender specific percentiles of CCS and to study the

* Corresponding author at: Adult Cardiology Department, Prince Sultan Cardiac Center, Riyadh 12233, Saudi Arabia.
E-mail address: sumaya_harbi@yahoo.com (S. Al Helali).

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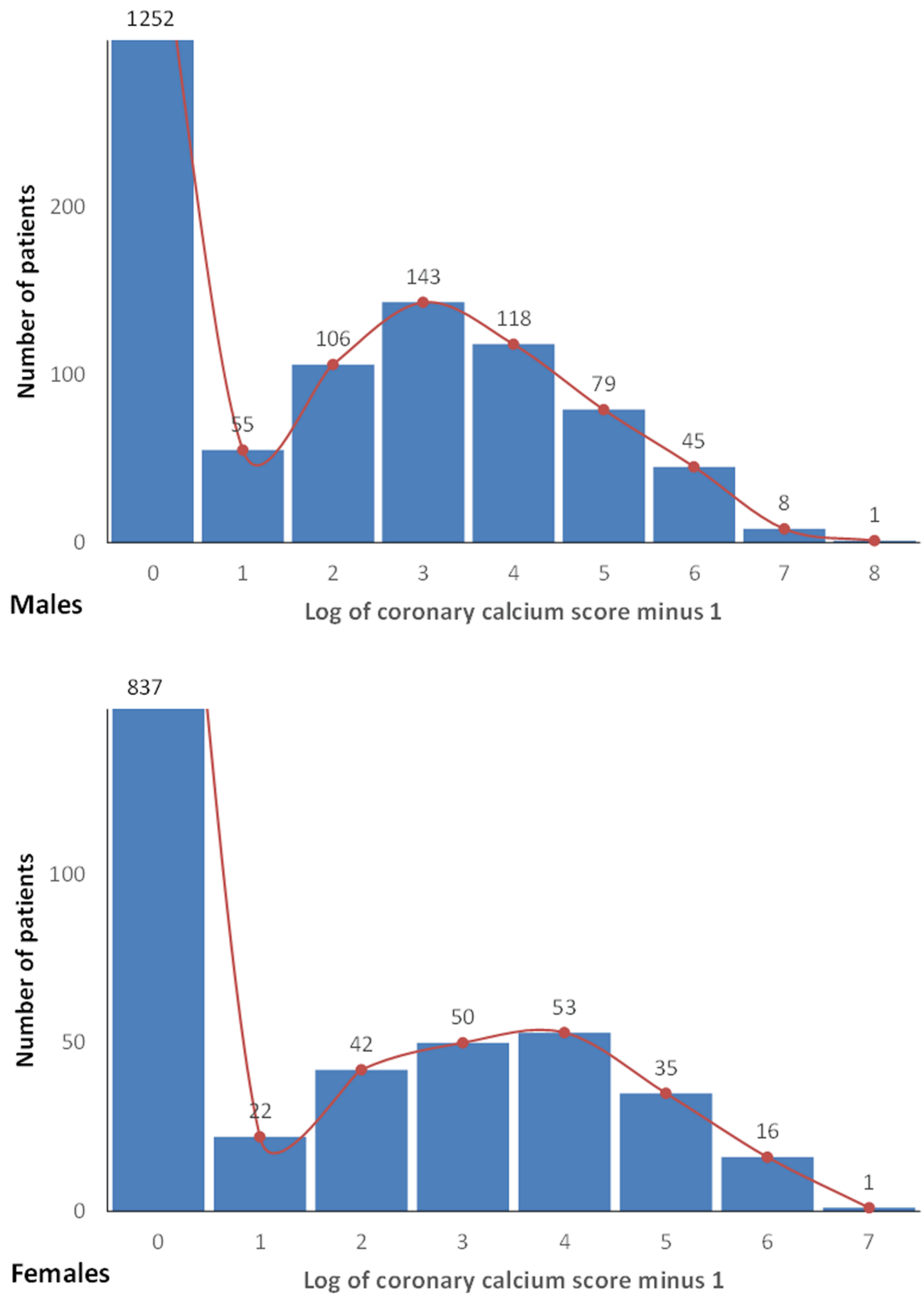

Fig. 1. Distribution of coronary calcium score among male and female asymptomatic patients (N = 2863). Note: The bar for zero calcium score was severed (while keeping the actual number of patients) to allow better view of the distribution of patients with non-zero coronary calcium score.

severity of CAC in relation to patient risk in a large sample of asymptomatic Saudi patients. Additionally, to compare the study findings with similar studies done internationally.

2. Methods

2.1. Setting

The current study was conducted at Prince Sultan Cardiac Center (PSCC). It is 200-bed specialized cardiac center located in Riyadh that provides a major portion of the diagnostic and therapeutic cardiac services in Saudi Arabia. The PSCC has several departments including adult and pediatric cardiology, adult and pediatric cardiac surgery, cardiac anesthesia, and advanced imaging. The current study was done at the advanced imaging unit of adult cardiology.

2.2. Design

A retrospective cross-sectional study was conducted between July 2007 and December 2017. The study design obtained all required ethical approvals from the ethical committee of PSMMC.

2.3. Population

The study targeted adult patients (age $>$ 18 years) referred to (64 multidetector spiral) CT for standard indications. Those with pre-existing CAD were excluded from the study. Pre-existing CAD was defined as myocardial infarction, angioplasty, stent placement, aortic valve replacement, and coronary artery bypass grafting. Low-quality CT with artifacts and CT scanning that was done for aortic reasons or pericardial assessment were excluded from the study. Stratification of

Table 1
Age and gender specific percentiles of coronary calcium score among asymptomatic patients.

Age groups	<40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	≥75	Total
Males										
Number	377	287	312	283	234	148	80	52	34	1807
Percentiles										
10th	0	0	0	0	0	0	0	0	0	0
25th	0	0	0	0	0	0	8.5	0.23	6.75	0
50th	0	0	0	0	0.95	4.5	61.5	44.5	94	0
75th	0	0	1.06	18	38.5	60.75	188.25	222.75	323.25	11
90th	0	14	43.4	99.2	130	220.5	533.8	470	674	95
95th	0	35.2	82.2	229.6	234.25	408.25	1062.3	580.4	2164.75	226.2
Females										
Number	134	116	201	193	162	107	78	41	24	1056
Percentiles										
10th	0	0	0	0	0	0	0	0	0	0
25th	0	0	0	0	0	0	0	0	0	0
50th	0	0	0	0	0	0	8.5	31	35.5	0
75th	0	0	0	0	5	10	58.5	96	190	0
90th	0	0	0	35.38	30	139.6	218.9	677.6	535	53.2
95th	0	8.3	33.5	124.8	69.55	338	387.4	1032.09	659	142.35
Total										
Number	511	403	513	476	396	255	158	93	58	2863
Percentiles										
10th	0	0	0	0	0	0	0	0	0	0
25th	0	0	0	0	0	0	0	0	1.63	0
50th	0	0	0	0	0	0	24	37	65	0
75th	0	0	0	10	23	49	136.25	184	300.75	5
90th	0	10	32	77.3	77.3	187.4	433	500.6	538.1	77.6
95th	0	29.8	67.9	193.2	186.6	392	690.85	682.7	823.95	198.8

the CAD risk was done using the number of risk factors and the systematic coronary risk evaluation (SCORE) of the European Society of Cardiology (ESC). Risk factors for CAD were defined as history of hypertension, diabetes, dyslipidemia, smoking, family history of premature CAD (before the age of 65 years), and obesity (BMI > 30). History of hypertension, diabetes, and dyslipidemia was documented based on previous physician diagnosis and/or receiving relevant treatment. SCORE estimating the 10-year risk of developing fatal cardiovascular disease in populations with high cardiovascular disease risk was calculated according to the standard methodology [17].

2.4. CT scanning protocol

Patients were scanned during a single breath-hold using a 64 (multidetector spiral) CT scanner (Philips Brilliance). A retrospective gating protocol was used with thickness of 0.5 to 2.5, FOV of 220, and average radiation dose of 6–9 mSv. The scanning protocol was designed to minimize radiation dose based on BMI. Indications of coronary CT scanning included chest pain in patients with intermediate risk of CAD, impaired left ventricular function in asymptomatic patient, before non-coronary cardiac surgery in patients with intermediate risk of CAD, to rule out coronary anomaly, and in case of arrhythmia with atypical chest pain.

2.5. Data collection tool

Study data collection sheets were initiated for patients who underwent coronary CT and meeting the study eligibility criteria. Clinical information including medical history, traditional risk factors, and cardiac comorbidity were then abstracted from the electronic patient chart system.

Table 2
Age and gender specific groups of coronary calcium score (CCS) among asymptomatic patients.

Age groups	<40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	≥75	Total
Males										
Number	377	287	312	283	234	148	80	52	34	1807
CCS groups										
0	96.3%	84.7%	74.5%	63.1%	49.6%	46.9%	17.5%	25.5%	12.1%	68.4%
1–100	3.7%	13.9%	21.9%	27.7%	38.4%	34.7%	40.0%	33.3%	36.4%	22.3%
101–400	0.0%	1.0%	2.3%	5.7%	8.6%	13.6%	25.0%	29.4%	36.4%	6.3%
>400	0.0%	0.3%	1.3%	3.5%	3.4%	4.8%	17.5%	11.8%	15.2%	3.1%
Females										
Number	134	116	201	193	162	107	78	41	24	1056
CCS groups										
0	98.5%	93.1%	92.0%	80.7%	72.2%	67.3%	40.3%	40.0%	37.5%	78.3%
1–100	1.5%	6.9%	6.0%	14.1%	24.1%	19.6%	40.3%	40.0%	25.0%	15.4%
101–400	0.0%	0.0%	2.0%	4.2%	3.7%	9.3%	15.6%	7.5%	25.0%	4.7%
>400	0.0%	0.0%	0.0%	1.0%	0.0%	3.7%	3.9%	12.5%	12.5%	1.6%
Total										
Number	511	403	513	476	396	255	158	93	58	2863
CCS groups										
0	96.9%	87.1%	81.4%	70.3%	58.9%	55.5%	28.7%	31.9%	22.8%	72.1%
1–100	3.1%	11.9%	15.7%	22.2%	32.5%	28.3%	40.1%	36.3%	31.6%	19.7%
101–400	0.0%	0.7%	2.2%	5.1%	6.6%	11.8%	20.4%	19.8%	31.6%	5.7%
>400	0.0%	0.2%	0.8%	2.5%	2.0%	4.3%	10.8%	12.1%	14.0%	2.5%

Table 3
Risk-stratified levels of coronary calcium score (CCS) among asymptomatic patients.

Gender	Males		Females		Total	
Levels of CCS	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Number of patients	1798	1798	1053	1053	2851	2851
Number of risk factors*						
None	19.5 ± 77.8	0 (0–0)	12.3 ± 53.6	0 (0–0)	17.4 ± 71.7	0 (0–0)
Single	27.4 ± 118.5	0 (0–2)	18.4 ± 68.9	0 (0–0)	24.0 ± 102.9	0 (0–0)
Two	69.1 ± 361.9	0 (0–28)	23.8 ± 125.2	0 (0–0)	50.6 ± 290.0	0 (0–10)
Three or more	85.2 ± 217.8	0 (0–52)	53.0 ± 154.0	0 (0–15)	71.7 ± 194.2	0 (0–34)
P-value1		<0.001		<0.001		<0.001
P-value2		<0.001		<0.001		<0.001
Number of patients	1420	1420	905	905	2325	2325
ESC SCORE						
Mild (<1%)	2.7 ± 16.5	0 (0–0)	3.4 ± 25.3	0 (0–0)	3.1 ± 22.5	0 (0–0)
Moderate (1%-<5%)	41.9 ± 242.9	0 (0–10)	28.3 ± 88.4	0 (0–5)	37.1 ± 201.9	0 (0–10)
High (5%-<10%)	108.3 ± 246.2	15 (0–95)	156.1 ± 302.2	67 (0–140)	116.1 ± 256.1	18 (0–102)
Very high (≥10%)	131.0 ± 222.0	41 (0.5–154)	–	–	131.0 ± 222.0	41 (0.5–154)
P-value1		<0.001		<0.001		<0.001
P-value2		<0.001		<0.001		<0.001

SD, standard deviation; IQR, interquartile range; ESC, European Society of Cardiology; SCORE, systematic coronary risk evaluation.
*Risk factors included hypertension, diabetes, dyslipidemia, obesity, smoking, and family history of premature coronary artery disease.
P-value1 was derived from Kruskal–Wallis test (simple difference between groups) and p-value2 was derived from Jonckheere-Terpstra test (linear difference between groups).

2.6. Statistical analysis

The distribution of CCS (minus one) was plotted after transforming to logarithmic value. Age specific percentiles of CCS for both males and females were calculated at standard percentiles. The severity of CAC was categorized as none (zero CCS), minimal/mild (CCS 1–100), moderate (CCS 101–400), and extensive (CCS > 400). The severity of CAC was presented as percentage by age and gender groups. The levels of CCS by the risk of CAD (number of risk factors and SCORE) were presented by age and gender groups as mean and standard deviation (SD) and median and inter-quartile range (IQR). Difference in the level of CCS was assessed using Kruskal–Wallis test for any difference and Jonckheere-Terpstra test for linear difference. Age and gender specific percentiles of CCS were plotted for Saudi (this study) against Western, and Asian patients (published data [14]). Similarly, the severity of CAC was plotted for Saudi (this study) against patients from different countries (published data [18–21]). All P-values were two-tailed. P-value < 0.05 was considered as significant. SPSS software (release 25.0, Armonk, NY: IBM Corp) was used for all statistical analyses.

3. Results

A total 2863 patients have been included in the current analysis. The distributions of CCS in males and females are shown in Fig. 1. The majority of males (68.4%) and females (78.3%) had zero CCS. The patients without zero CCS in both genders had approximately normal distribution.

Age and gender specific percentiles of CCS are shown in Table 1. The percentiles were clearly higher in males than females and in older ages than younger ages. For example, 90th percentile in all patients was 77.6, with higher numbers in males than females (95.0 versus 53.2, respectively). Additionally, 90th percentile was 823.95 in patients 75 years and older compared with zero in patients younger than 40 years. In all patients, 10th, 25th, and 50th percentiles of CCS were zero. However, they were higher than zero among older patients, including males 55 years or more and females 65 years or more.

Age and gender specific groups of CCS are shown in Table 2. Patients who had extensive CAC (CCS > 400) were higher in males than females and in older ages than younger ages. They represented 2.5% in all patients, with higher percentages in males than females (3.1% versus 1.6%, respectively). Additionally, those who had extensive CAC represented 14.0% in patients 75 years and older but were absent in patients younger than 40 years.

Risk-stratified levels of CCS are shown in Table 3. The levels of CCS were steadily higher with increasing number of traditional risk factors in all patients and in both genders (p-value < 0.001 for all). For example, the average CCS in all patients was 17.4 ± 71.7 in those with no risk factor, 24.0 ± 102.9 in those with one risk factor, 50.6 ± 290.0 in those with two risk factors, and 71.7 ± 194.2 in those with three or more risk factors. Similarly, the levels of CCS were steadily higher with increasing SCORE in all patients and in both genders (p-value < 0.001 for all). For example, the average CCS in all patients was 3.1 ± 22.5 in those with low SCORE (<1%), 37.1 ± 201.9 in those with moderate SCORE (1%-<5%), 116.1 ± 256.1 in those with high SCORE (5%-<10%), and 131.0 ± 222.0 in those with very high SCORE (≥10%).

Fig. 2 shows the comparisons of percentiles of CCS between Saudi, Western, and Asian patients. The percentiles of CCS in Saudi patients of both genders were almost always lower than Western percentiles and the difference clearly widen with increasing age. On the other hand, the percentiles of CCS in Saudi patients of both genders were generally overlapping or slightly lower than Asian percentiles. Fig. 3 shows the comparisons of groups of CCS between Saudi and international patients. Saudi patients of both genders who had extensive CAC were less frequent than US white and black patients but general similar to patients from Brazil, Korea, and Japan.

4. Discussion

The current study reported the percentiles and severity of CCS by age, gender, and CAD risk groups, among asymptomatic patients without clinical CAD in Saudi Arabia. Consistent with previous studies done in different populations, the current findings confirm the higher level of CCS and severity of CAC in males than females and among older compared with younger patients [14,18–23]. For example, detection of any CAC and the burden of extensive CAC were observed approximately 10 years younger in males than females in the current and previous studies [14,19]. Additionally, steady increase of percentiles of CCS with increasing age groups (irrespective of gender) was consistent in all studies including current study [14,22,23]. Moreover, extensive CAC was almost lacking or negligible before the age of 50 years but very high in those aged 75 years or more in the current and previous studies [19,23]. Finally, the traditional non-normal distribution of CCS was approximately normalized after excluding those with zero score in the current and previous studies [24,25].

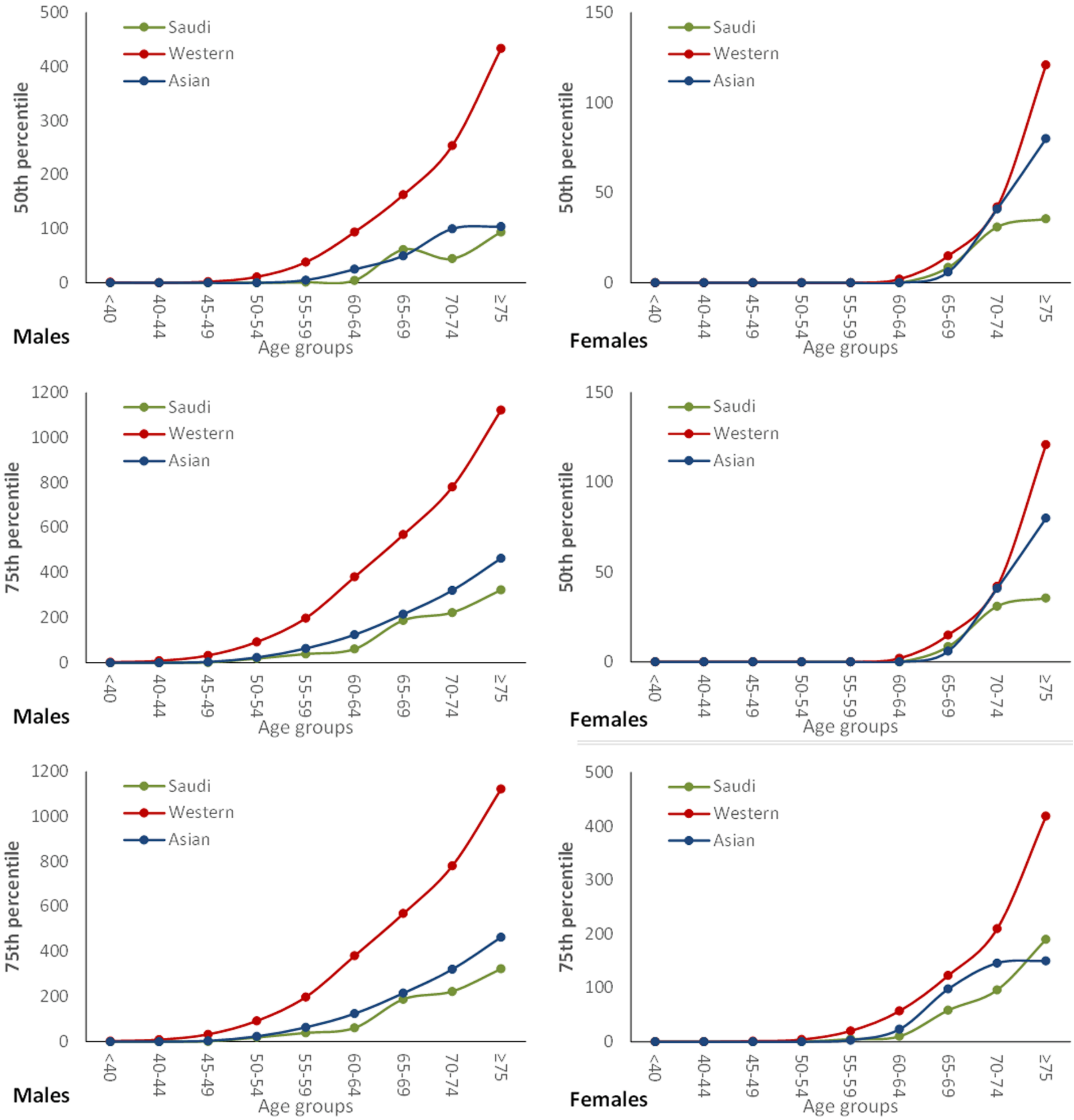

Fig. 2. Comparisons of age and gender specific percentiles of coronary calcium score between Saudi, Western, and Asian patients. Note: Percentiles of CCS in Western and Asian patients were derived from de Ronde, et al [14].

As expected, the current findings confirm the higher level and severity of CCS in patients with higher compared with lower CAD risk. For example, the levels of CCS in the current study were increasing with increasing risk, irrespective of gender or the method used. This has been observed in previous studies using the number of risk factors [22,26] and SCORE [27] as methods of risk stratification. The European SCORE for population with high risk was used in the current study as there is lack of locally validated tool. Additionally, SCORE has been shown to better correlate with cardiovascular risk in Arab populations than other tools including Framingham risk score [28,29].

The percentiles of CCS and severity of CAC among Saudi patients in the current study was much lower than similar US patients but comparable with Korean, Japanese, and Brazilian patients. This striking finding will probably have some clinical implications. Local cardiologists who use CAC in risk stratification for their patients usually use US numbers which represents the bulk of international data [30]. For example, Abazid and colleagues used CAC > 400 and 75th percentile of CCS obtained from Multi-Ethnic Study of Atherosclerosis (MESA) done in the US to compare CAC risk stratification in a Saudi population [30]. On the other side, a study that compared the 50th and 90th percentiles of CCS in Saudi and US women concluded that CCS levels were higher in Saudi Arabia [15]. The later finding was derived from Saudi females with high burden of CAD risk factors, which might have distorted the comparison. Additionally, the authors set a reference obtained from a single relatively old US study with lower CCS values [15,31]. Finally, the 50th percentile difference reported in that study has been probably exaggerated by the inaccurate transcription of the figures of the US reference study [15,31]. Nevertheless, as Saudi Arabia is currently experiencing an increased burden of CAD risk factors [6,32], the lower burden of CAC observed in the current study compared with the US may change in the future. The economic development, urbanization, consumption of Western food, and limited activity in Saudi population is only few decades long [6,32]. The impact on of these factors on CAC is a cumulative process that start early in life [33] and is expected to

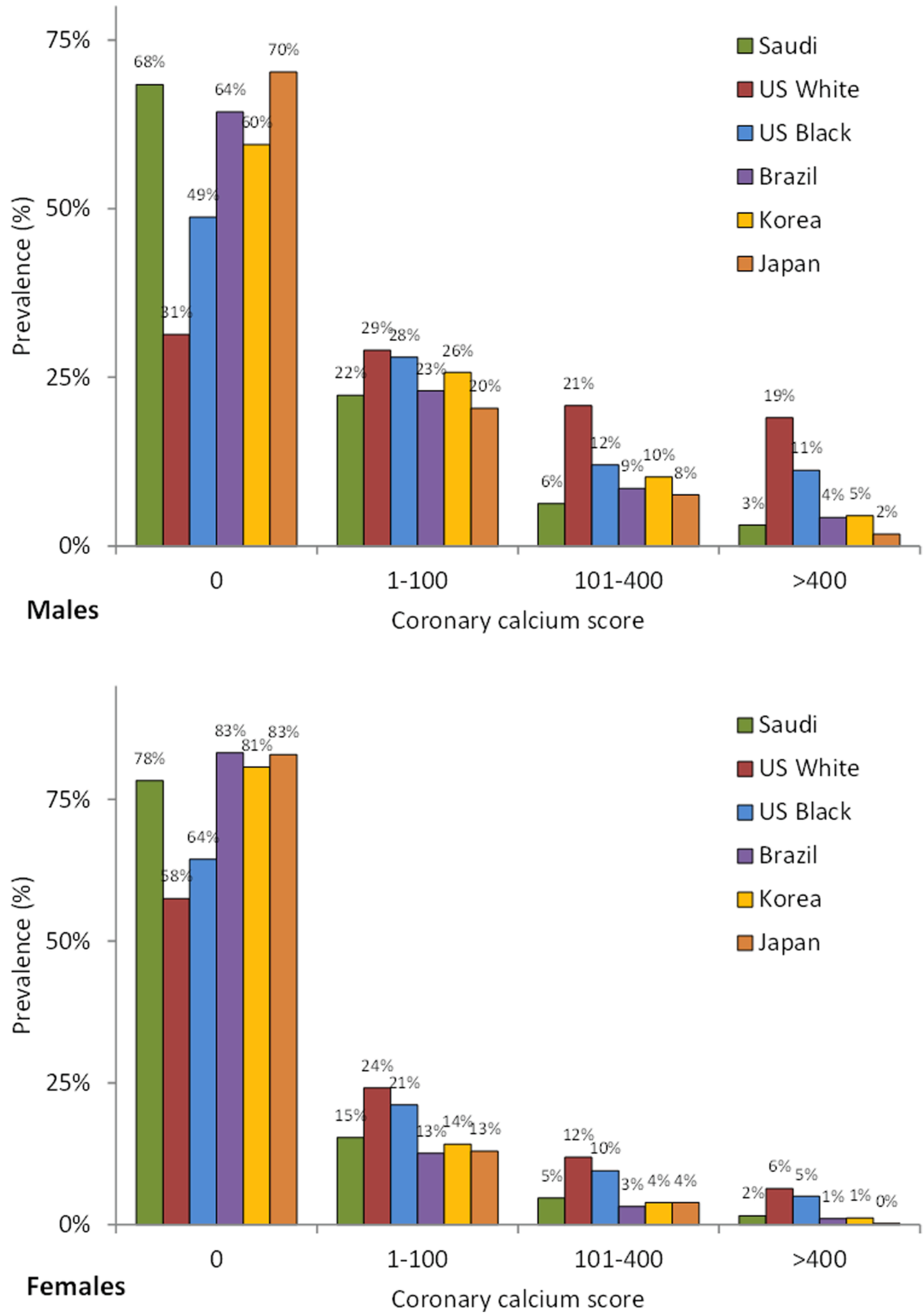

Fig. 3. Comparisons of age and gender specific groups of coronary calcium score (CCS) between Saudi and international patients. Note: CCS groups in international patients were derived from published literature [18–21].

progress with increasing age of the cohort.

The current study is considered the first study in Saudi Arabia and region to report the distribution and levels of CAC in both genders. The study examined a large number of patients seen over 10 years in a large referral center. This allowed for detailed age, gender, and risk specific analysis. Nevertheless, we acknowledge few limitations. The cross-sectional design determines association but not causation. Being a single center experience may limit the generalizability of the findings to the larger Saudi population. However, we believe that these limitations have minor impact on the study finding (if any).

In conclusion, the current findings confirm the higher level of CCS and severity of CAC in males than females, among older compared with younger patients, and those with higher compared with lower CAD risk in asymptomatic patients without clinical CAD in Saudi Arabia. The percentiles of CCS and severity of CAC among Saudi patients in the current study was much lower than similar US patients and other Western patients. Given the fact that the US numbers are used locally in clinical practice, local cardiologist should consider using local rather than US percentiles of CCS.

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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Statement

All authors have been acknowledged as contributors of submitted work and fulfill the standard criteria for authorship. All authors have read and approved the submission of the current version of the manuscript. The material included in this manuscript is original and it has been neither published elsewhere nor submitted for publication simultaneously.

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