The Diagnostic Performance of Coronary Artery Angiography with 64-MSCT and Post 64-MSCT: Systematic Review and Meta-Analysis

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Abstract

Purpose: To comprehensively investigate the diagnostic performance of coronary artery angiography with 64-MDCT and post 64-MDCT.

Materials and Methods: PubMed was searched for all published studies that evaluated coronary arteries with 64-MDCT and post 64-MDCT. The clinical diagnostic role was evaluated by applying the likelihood ratios (LRs) to calculate the post-test probability based on Bayes' theorem.

Results: 91 studies that met our inclusion criteria were ultimately included in the analysis. The pooled positive and negative LRs at patient level were 8.91 (95% CI, 7.53, 10.54) and 0.02 (CI, 0.01, 0.03), respectively. For studies that did not claim that non-evaluable segments were included, the pooled positive and negative LRs were 11.16 (CI, 8.90, 14.00) and 0.01 (CI, 0.01, 0.03), respectively. For studies including uninterruptable results, the diagnostic performance decreased, with the pooled positive LR 7.40 (CI, 6.00, 9.13) and negative LR 0.02 (CI, 0.01, 0.03). The areas under the summary ROC curve were 0.98 (CI, 0.97 to 0.99) for 64-MDCT and 0.96 (CI, 0.94 to 0.98) for post 64-MDCT, respectively. For references explicitly stating that the non-assessable segments were included during analysis, a post-test probability of negative results >95% and a positive post-test probability <95% could be obtained for patients with a pre-test probability of <73% for coronary artery disease (CAD). On the other hand, when the pre-test probability of CAD was >73%, the diagnostic role was reversed, with a positive post-test probability of CAD >95% and a negative post-test probability of CAD <95%.

Conclusion: The diagnostic performance of post 64-MDCT does not increase as compared with 64-MDCT. CTA, overall, is a test of exclusion for patients with a pre-test probability of CAD<73%, while for patients with a pre-test probability of CAD> 73%, CTA is a test used to confirm the presence of CAD.

Introduction

Coronary artery disease (CAD) is the leading illness threating human health in developed countries and it is increasingly becoming a significant public health problem in developing countries [1]. With the development of the 16-multi-detector CT (MDCT), a non-invasive approach of coronary CT angiography (CTA), it has been applied widely to avoid the complications of invasive coronary angiography (ICA), which is generally believed to be the gold standard in evaluating CAD [2].

Several meta-analysis studies have proven that single source 64-MDCT with improved parameters has a better ability to predict the stenosis of coronary artery lumen than that of 16-MDCT [3–5]. With the emergence and wider application of dual source 64-, 128-, 256-, and 320-MDCT it is hoped that the improvement will lead to a greater diagnostic accuracy than 64-MDCT. To our knowledge, no study has statistically proven that this claim is correct.

In particular, the CAD diagnosis is not only dependent upon the accuracy of CTA, but also upon pre-test probability, which is estimated according to the symptoms and examinations [3,6–8]. The pre-test probability categorization is important because of its significant impact on the post-test probability of disease and the selection of a diagnostic test [8]. Appropriate application of CTA may improve patients' clinical outcomes, while the inappropriate utilization of CTA may generate extra radiation exposure to patients and unwarranted costs. Since there are already a number of risk algorithms available to evaluate the detailed pre-test probability [9–12], we evaluated the diagnostic role of CTA based on the diagnostic performance of CTA and the precise pre-test probability to provide a more practical patient-relevant utility of CTA.

Materials and Methods

Generally, we followed a standard protocol based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [13].

Selection of Studies

PubMed was searched for all published studies that examined patients with 64-MDCT and post-64-MDCT. The language was limited to English and the search terms were, "computed tomography," "multi-slice computed tomography," "multi-section computed tomography," "multi-detector computed tomography," and "coronary angiography."

The literature search ranged from 2004 to 2013, as 64-MDCT was first introduced into clinical practice in 2004. The references of published systematic reviews and meta-analyses were also screened. Two readers examined the studies to exclude potential duplicate or overlapping data.

Study Eligibility

The title and abstract were reviewed first. If considered suitable or in doubt, the full text was screened. The inclusion criterion were listed as follows: 64-MDCT or post-64-MDCT was applied as a test to diagnose stenostic CAD (stenosis >50%); the absolute numbers of true-positive, false-positive, true-negative, and false-negative results were presented or can be calculated from the detailed data; and ICA served as the reference standard. Studies were excluded for the following reasons: they included patients who had undergone bypass graft surgery (CABG), percutaneous coronary intervention (PCI), or prior heart transplantation; they were retrospective studies.

Data Extraction

Two investigators extracted the data independently. The following information was extracted from each study: first author, year of publication, country, number of patients, sex, age, heart rate, calcium scoring, the type and brand of machine used, temporal resolution, electrocardiographic (ECG) triggered scanning protocols, prevalence of CAD as well as non-diagnostic segments, and numbers of true-positive, true-negative, false-positive, and false-negative values. While most studies applied a 15-segment scheme of the coronary artery tree, several articles used other alternative protocols, such as 13-, 14-, 16-, and 17-segment models. The scheme of the coronary arterial tree for stenostic analysis was also extracted. Two readers assessed methodological quality independently and according to the QUADAS items [14].

Data Synthesis and Statistical Analysis

Cohen κ test was conducted to evaluate the inter-observer agreement. The publication bias was assessed by the method developed by Deeks, et al. [15]. The heterogeneity across studies was evaluated by I^2 test [16] and the impact of potential covariates was examined using meta-regression. Possible sources of heterogeneity were predefined based on QUADAS items, average age, gender, vendor, temporal resolution, number of slices, the scheme used to evaluate the coronary arterial tree, non-assessable segments, calcium score, protocol of ECG-triggered scanning, prevalence of CAD, and study quality score. A hierarchical summary receiver operating characteristic curves (sROC) was conducted based on the parameters estimated by the bivariate model. The area under the sROC (AUROC) serves as a global measure of CTA performance [17].

The available data was synthesized by an exact binomial rendition of the bivariate mixed-effects regression model [18-20]. We mainly calculated the positive and negative likelihood ratios (LRs) and 95% confidence intervals (CIs) to eliminate the influence of the prevalence of CAD [21] and to compute post-test probability. The LRs indicate by how much a given test would raise or lower the probability of having the disease.

Furthermore, the clinical, or patient-relevant, utility of the diagnostic test was evaluated by using the LRs and the pre-test probability of CAD to calculate the post-test probability based on Bayes' theorem [22]. The log-odds of the posterior probability, which show the chance to diagnose the disease after the test, is a linear function of the log-odds of prior probability and the log likelihood ratio of the target test, which is depicted visually with Fagan's nomogram [23]. The Fagan's nomogram plots an axis on the left with the prior log-odds, an axis in the middle representing the log likelihood ratio of the test, and an axis on the right representing the posterior log-odds. A straight line is drawn from the prior probability on the left axis through the likelihood ratios in the middle and extended to the posterior probability on the right. Thus, the posterior probability is estimated from the prior probability and the likelihood ratio of the test. The pre-test and post-test probabilities are both subjective estimates of the presence of a disease before and after a diagnostic test. The detailed pre-test probability of CAD could be calculated from clinical data and one or more proceeding tests [9,10]. The post-test probability, in turn, can be calculated, depending on whether CTA falls out as a positive test or a negative test. If the positive or negative post-test probability is larger than 95%, the test is treated as an effective tool to confirm or exclude CAD. The overall diagnostic role of CTA at artery and segment levels was represented graphically by an LR scattergram introduced by Stengel et al. [24].

The data was analyzed using STATA (version 12), MetaDiSc (version 1.4), as well as SPSS (version 16.0).

Results

The Characteristics of CT Studies

91 studies that met our inclusion criteria were finally included in the analysis (Figure 1 shows the literature search and selection algorithm). 48 studies performed CTA with single source, 64-MDCT; 26 studies with dual source, 64-MDCT; 6 with dual source, 128-MDCT; 9 with single source, 320-MDCT; 1 with single and dual source, 64-MDCT; and 1 with single source, 64-MDCT and 320-MDCT. 55 studies scanned the coronary artery with retrospective ECG gating, 21 studies with prospective protocol, 4 studies with retrospective and prospective ECG gating, and 11 studies did not report the detailed information. 36 studies reported a calcium score ranging from 47.7 to 821. The radiation dose ranged from 0.76 mSv to 21.4 mSv. Further information on the characteristics of each study is illustrated in Table 1.

Methodological Quality

The inter-observer agreement for assessing quality items was good (κ = 0.83). According to the QUADAS tool, 62 studies had a quality score of ≧10 and 29 studies had a quality score of <10. Table S1 demonstrates the QUADAS quality of the included studies.

Data Synthesis and Statistical Analysis

A total of 126,615 segments, 21,834 vessels, and 9,696 patients were analyzed. The publication bias was significant at the patient, artery and segment levels (P = 0.004, 0.001 and 0.005 respectively). The pooled positive and negative LRs at patient level were
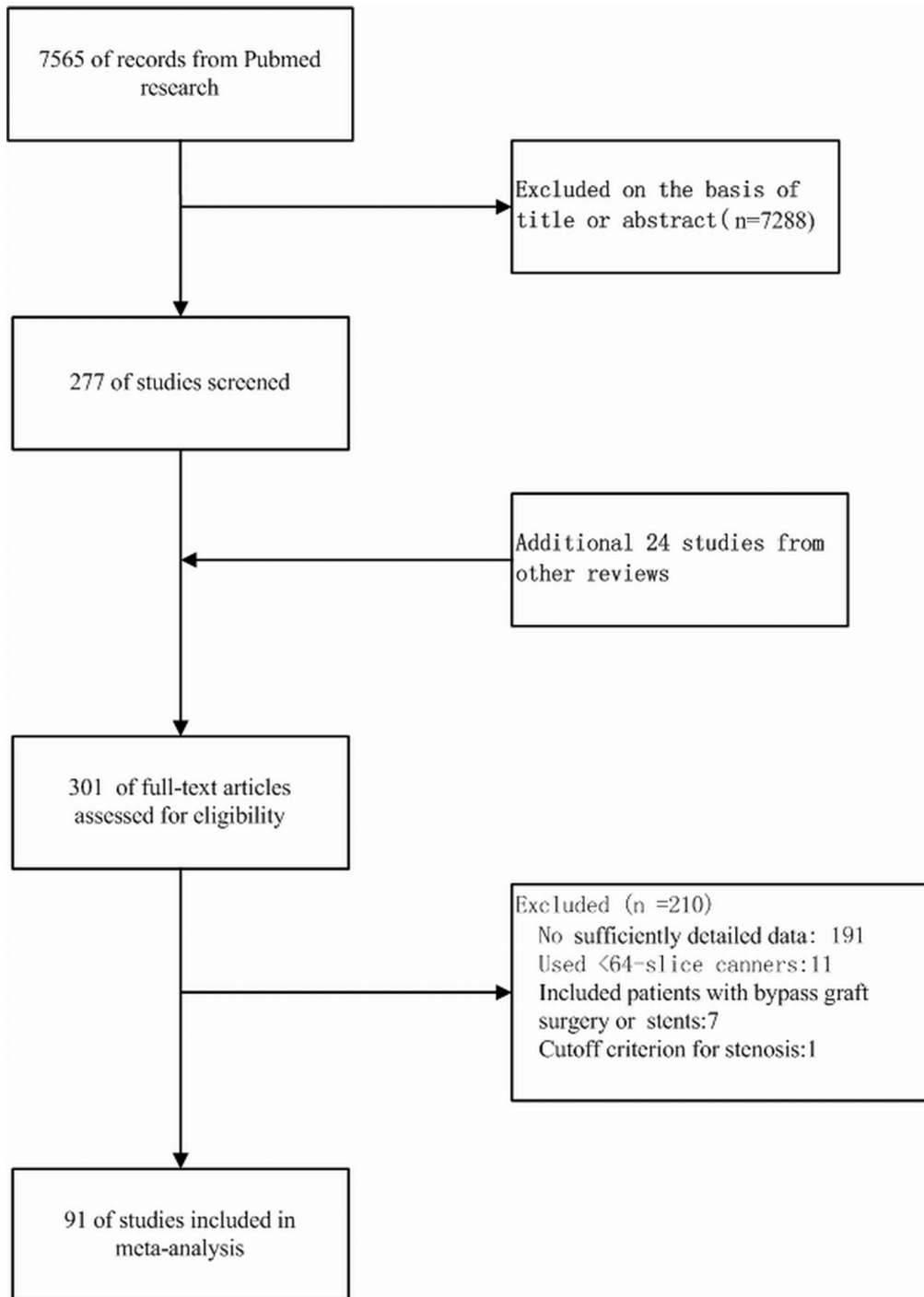
Figure 1. The flow chart for references searching and selection. After careful searching and selection, 91 studies were finally included in the analysis.
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8.91 (95% CI, 7.53, 10.54) and 0.02 (CI, 0.01, 0.03), respectively. At the patient level, significant heterogeneity was detected for positive and negative LRs (Q = 976.63; $P<0.001$; $I^2 = 88.58\%$ [CI, 88.58%, 91.55%]; Q = 476.01; $P<0.001$; $I^2 = 79.62\%$ [CI, 75.88%, 83.37%], respectively).

As methodological quality may significantly influence diagnostic accuracy, we investigated the impact of QUADAS items on the heterogeneity. We found that item 13 was the only key factor for heterogeneity (P = 0.02). In the present study, item 13 was defined as, "How authors handled uninterpretable results." For studies that did not claim that non-evaluable segments were included, the pooled positive and negative LRs at patient level were 11.16 (CI, 8.90, 14.00) and 0.01 (CI, 0.01, 0.03), respectively. Slight heterogeneity was detected for positive and negative LRs (Q = 67.06; $P<0.001$; $I^2 = 89.78\%$ [CI, 89.78%, 92.36%]; Q = 78.23; $P<0.001$; $I^2 = 38.64\%$ [CI, 17.37%, 59.91%], respectively).

Table 1. Characteristics of Included Studies.

Authors	Year	Country	Male/female	Mean age(y)	Scanner	Temporal resolusion(ms)	ECG triggered protocol	NO. of slice	HR(bpm)	Calcium score	Undiagnosis segments	Scheme to evaluate coronary tree	Radiation dose(mSv)
Leber[41]	2005	Germany	...	64	Siemens	165	R	64	62	...	0	15	10–14
Leschka[42]	2005	Switzerland	2.84	60	Siemens	165	R	64	66	...	0	15	...
Mollet[43]	2005	Netherlands	1.89	58	Siemens	165	R	64	58	231	0	16	15.2–21.4
Pugliese[44]	2005	Netherlands	1.5	61	Siemens	165	R	64	58	...	0.03	17	15–20
Raff[45]	2005	United States	3.12	59	Siemens	165	R	64	65	326	0.12	15	13–18
Ehara[46]	2006	Japan	3.06	67	Siemens	165	R	64	72	...	0.05	14	...
Ghostine[47]	2006	France	1.54	69	Siemens	165	R	64	67	...	0.06	15	7
Meijboom[48]	2006	Netherlands	2.33	63	Siemens	165	R	64	60	214	...	17	15.2 –21.4
Nikolaoui[49]	2006	Germany	4.54	63	Siemens	165	R	64	61	...	0.1	15	8.8–13.6
Plass[50]	2006	Switzerland	3.54	66	Siemens	165	R	64	65	...	0.03	11	...
Ropers[51]	2006	Germany	1.63	58	Siemens	83	R	64	59	...	0.04	17	7.45–10.24
Scheffel[52]	2006	Switzerland	4	63.1	Siemens	83	R	64	70.3	821	0.014	...	...
Schuijf[53]	2006	Netherlands	3.29	60	Toshiba	200	R	64	60	423	0.014	...	...
Cademartiri[54]	2007	Italy	1.12	53.9	Siemens	165	R	64	60.6	47.7	0.004	17	15.2–21.4
Herzog[55]	2007	Germany	1.12	67	Siemens	165	R	64	64	...	0.076	15	...
Herzog[56]	2007	Germany	1.22	61	Siemens	165	R	64	72	...	...	15	...
Heuschmid[57]	2007	Germany	2.64	64	Siemens	83	R	64	65	779	0.046	13	...
Johnson[58]	2007	Germany	2.18	60	Siemens	83	R	64	68	...	0.02	15	4.6–7.8
Leber[59]	2007	Germany	1.73	58	Siemens	83	R	64		...	...	13	9.6
Meijboom[60]	2007	Netherlands	2.06	56.2	Siemens	165	R	64	59	...	...	17	13.4–17
Meijboom[61]	2007	Netherlands	2.59	58	Siemens	165	R	64	58	450	...	17	15.2–21.4
Oncel1[62]	2007	Turkey	3.21	56	Siemens	165	R	64	58	...	0	15	...
Ropers[63]	2007	Italy	1.70	61	Siemens	83	R	64	64	...	...	...	15.3
Scheffel[64]	2007	Switzerland	3.17	54	Siemens	165	...	64	65.5	136	0.018	15	8.8–13.6
Schlosser[65]	2007	Germany	1.86	62.4	Siemens	165	...	64	57	...	0.01	15	...
Weustink[66]	2007	Netherlands	3.76	61	Siemens	83	R	64	68	...	0.06	17	11.1–14.4
Achenbach[67]	2008	Germany	0.8	65	Siemens	165	R	64	64.5	...	0.12	17	12.6
Achenbach[67]	2008	Germany	1.78	61	Siemens	83	R	64	64.3	...	0.04	17	14.7
Alkadhi[68]	2008	Switzerland	2.19	62.9	Siemens	83	R	64	68.5	309	0.019	16	7–9
Brodoefel[69]	2008	Germany	4	62	Siemens	83	R	64	64.9	786.5	0.098	15	...
Han[70]	2008	Taiwan	...	59.64	GE	175	R	64	...	...	...	15	...
Herzog[71]	2008	Switzerland	1.73	58.8	GE	175	P	64	55.7	...	0.04	16	2.1
Leschka[72]	2008	Switzerland	0.54	64.1	Siemens	165	R	64	63.9	...	0.014	15	...
Leschka[73]	2008	Switzerland	2.077	61.9	Siemens	83	R	64	67.7	720	0.021	15	7–9

Table 1. Cont.

Authors	Year	Country	Male/female	Mean age(y)	Scanner	Temporal resolusion(ms)	ECG triggered protocol	NO. of slice	HR(bpm)	Calcium score	Undiagnosis segments	Scheme to evaluate coronary tree	Radiation dose(mSv)
Maruyama[74]	2008	Japan	2.73	69.1	GE	175	R	64	56.1	...	0.045	15	21.1
Maruyama[74]	2008	Japan	1.62	69.9	GE	175	P	64	54.6	...	0.034	15	4.3
Miller[75]	2008	Multi-countries	2.83	59	Toshiba	200	R	64	60	80	...	19	13.8–15.2
Pugliese[76]	2008	Netherlands	3.25	59	Siemens	165	R	64	58	440	0.026	17	15–20
Pundziute[77]	2008	Netherlands	0.98	60	Toshiba	200	R	64	...	216	...	17	...
Ravipati[78]	2008	United States	1.94	66	Siemens	83	...	64	...	...	...	...	...
Scheffel[79]	2008	Switzerland	1.44	68	Siemens	83	P	64	59	238	0.017	...	1.6
Stolzmann[80]	2008	Switzerland	0.72	65.8	Siemens	83	P	64	60.7	316	0.04	16	2.6
Dewey[81]	2009	Germany	2.63	61	Toshiba	175	P	320	59.9	384	0	16	4.2
Gaudio[82]	2009	Italy	1.68	65	Siemens	165	R	64	...	...	...	...	10.6
Herzog[83]	2009	Switzerland	2.23	62	GE	165	P	64	55.4	...	0.0282	16	2.1
Leschka[84]	2009	United States	4	62	Siemens	75	P	128	58	...	0.01	16	0.9
Meng[85]	2009	China	1.66	63	Siemens	83	...	64	71.8	821	0.02	15	...
Pontone[86]	2009	Italy	7	64.8	GE	175	P	64	54.7	375	0.04	15	5.7
Pontone[86]	2009	Italy	4.33	64.3	GE	175	R	64	57.4	334	0.03	...	20.5
Reimann[87]	2009	Germany	2.75	62	Siemens	83	R	64	62.7	707	0	13	...
Rixe[88]	2009	Germany	1.62	65	Siemens	83	R	64	68	337	0.007	16	13.8–14.3
Sheikh[89]	2009	Kuwait	4.62	60	GE	165	R	64	...	...	...	13	...
Weustink[29]	2009	Switzerland	2.24	61.5	Siemens	165	R	64	69.8	...	...	17	14.2
Weustink[29]	2009	Switzerland	2.21	61.9	Siemens	165	P	64	68.8	...	...	17	10.7
Alkadhi[33]	2010	Switzerland	3.17	62	Siemens	75	P	128	58	...	0.014	16	1.4
Alkadhi[33]	2010	Switzerland	2.57	63	Siemens	75	P	128	56	...	0.011	16	0.9
Andreini[90]	2010	Italy	7.08	65.4	GE	165	R	64	61.2	479	...	15	14.3
Andreini[90]	2010	Italy	7.08	63.3	GE	165	R	64	58	356	...	15	...
Cademartiri[91]	2010	Italy	1.13	53.6	Siemens	165	R	64	58	151	...	15	15–21
Cademartiri[92]	2010	Italy	0.52	48	Siemens	165	R	64	59.4	...	...	17	15–22
Carrascosa[93]	2010	United States	1.94	62.4	Philips	200	P	64	54.9	...	0.021	17	3.4
Chen[94]	2010	China	1.62	60.7	Siemens	83	...	64	86.4	...	0.014	15	...
de Graaf[95]	2010	Netherlands	1.13	61	Toshiba	175	P	320	60	184	0.01	17	3.9–6
Donati[96]	2010	Switzerland	4.22	64	Siemens	83	R	64	60	...	0.005	16	2.5
Fang[97]	2010	China	1.78	59.6	Siemens	83	R	64	88	...	0.012	15	...
Husmann[98]	2010	Switzerland	1.54	61	GE	175	P	64	56	481	...	16	2.1
Kajander[99]	2010	Finland	1.49	63.5	GE	175	R	64	...	...	...	17	7.6
Nasis[100]	2010	Australia	1.52	63.2	Toshiba	175	P	320	65	...	0.02	17	5.4

Table 1. Cont.

Authors	Year	Country	Male/female	Mean age(y)	Scanner	Temporal resolusion(ms)	ECG triggered protocol	NO. of slice	HR(bpm)	Calcium score	Undiagnosis segments	Scheme to evaluate coronary tree	Radiation dose(mSv)
Nazeri[101]	2010	Iran	1.68	58	Siemens	165	R	64	62	...	0	15	...
Ovrehus[102]	2010	Denmark	1.28	61	Siemens	83	...	64	61	...	0.025	16	8.4
Sato[103]	2010	Japan.	2.33	67	Toshiba	200	R	64	...	...	...	...	...
Scheffel[104]	2010	Switzerland	2.45	56	Siemens	83	...	64	67.3	126	0.009	16	...
Scheffel[105]	2010	Switzerland	3.78	64	Siemens	83	P	64	61	...	0.014	16	...
Xu[106]	2010	China	2.23	64.6	Siemens	83	R	64	71.4	...	...	15	16.1
Yang[107]	2010	China	3.6	62	Siemens	83	...	64	59	...	...	15	...
Zhang[108]	2010	China	2.65	64	Siemens	165	R	64	76	136.7	0.038	15	16.51
Achenbach[109]	2011	Germany	2.13	59	Siemens	75	P	128	71	...	0	...	0.76
Bamberg[110]	2011	Multi-countries	...	68.1	Siemens	75	P	128	72.2	...	0.04	17	3.1
Gang[111]	2011	China	1.73	68	Toshiba	175	R	320	73.7	653	0.021	15	12.5
Kerl[112]	2011	United States	1.31	65	Siemens	165	R	64	66	...	0.028	15	...
Moon[113]	2011	Korea	1.85	60.5	Siemens	83	R	64	58.9	...	0.02	15	5.8
Stolzmann[114]	2011	Switzerland	1.38	68	Siemens	83	P	64	58	...	0.016	16	2.2
van Velzen[115]	2011	Netherlands	1.78	57	Toshiba	175	P	320/64	...	...	0.04	17	3.2–7.1
van Velzen[116]	2011	Netherlands	2.03	57	Toshiba	175	P	320	58	139	0.036	17	6–12
Vavere[117]	2011	Multi-countries	3.03	61	Toshiba	175	R	64	61	...	0.096	19	...
Xu[118]	2011	China	0.76	60.4	Toshiba	175	P	320	60.4	...	0.03	15	13
Zhang[119]	2011	China	...	...	Toshiba	200	R	64	60.5	...	...	15	19.88
Zhang[119]	2011	China	...	...	Toshiba	175	P	320	60.9	...	...	15	4.27
Dharampal[120]	2012	Netherlands.	1.18	58	Siemens	165	...	128	66	252	...	17	12
Kadokami[121]	2012	Japan.	2.5	70	Toshiba	200	...	640	70	...	...	15	16.
Kerl[122]	2012	Germany	1.08	67	Siemens	165	R	64	64	...	...	15	...
Maffei[123]	2012	Italy	1.13	61.2	Siemens	75	R	128	64.3	178	...	17	8.9
Maffei[124]	2012	Italy	1.8	59.3	Siemens	75	...	64	58	444	...	17	...
Sohns[125]	2012	Germany.	2.18	57	Siemens	...	R	64	84	...	...	15	...
Uehara[126]	2012	...	2.12	64.4	Toshiba	175	...	320	65.2	180	...	15	...
van Velzen[127]	2012	Netherlands.	2.03	57	Toshiba	175	P	64	58	...	0.04	17	12.0
Gueret[128]	2013	France	2.44	61	GE/Philips	...	...	64	63	396	...	...	17.2
Pelliccia[129]	2013	Italy	1.95	61	Toshiba	175	P	64	...	...	...	16	...

Note. —ECG = electrocardiographic, R = retrospective, P = prospective, HR = heart rate.
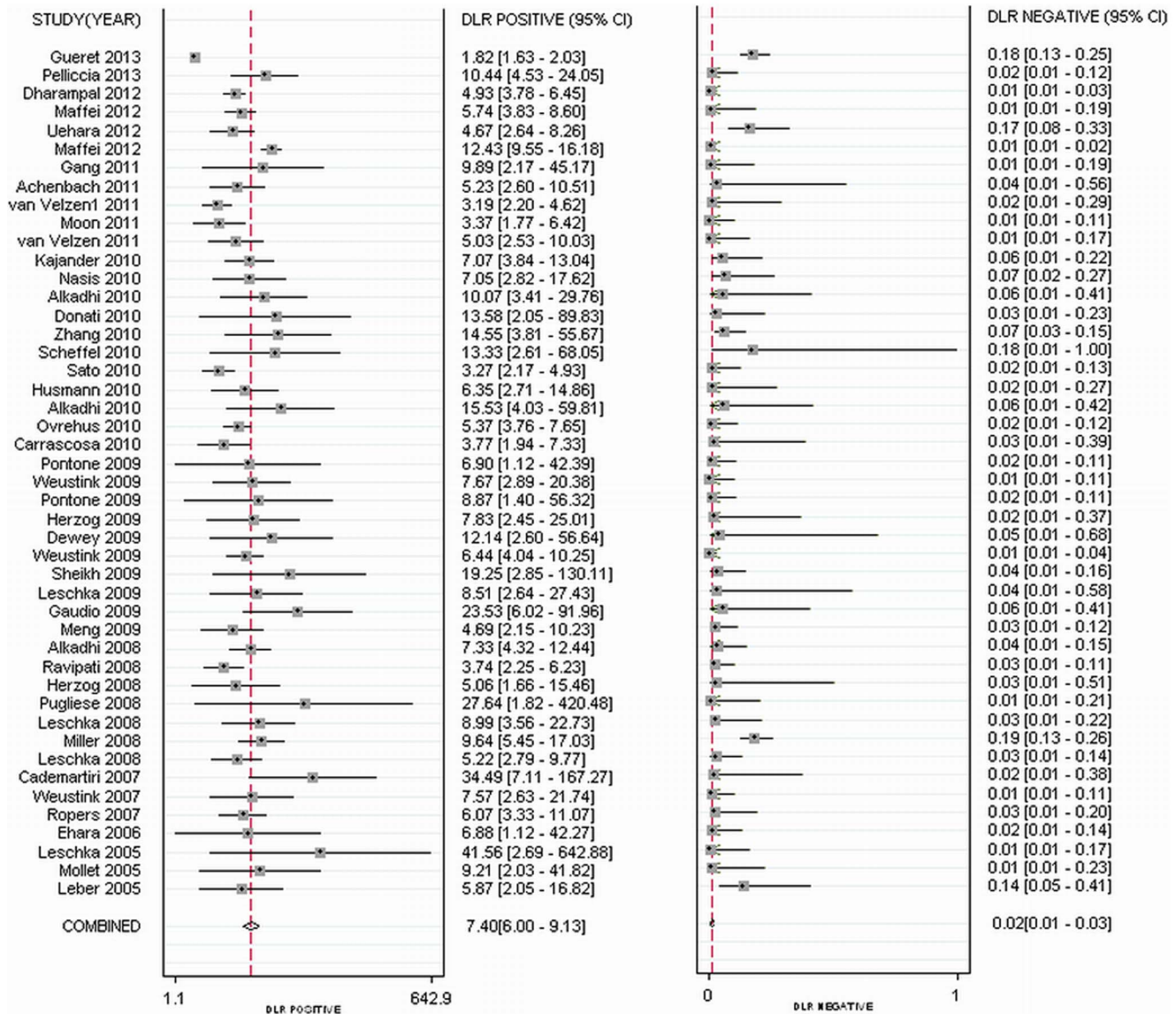doi:10.1371/journal.pone.0084937.t001

Figure 2. Forest plots showing positive and negative LRs at the patient level. For studies including uninterpretable results, the pooled positive LR was 7.40 (CI, 6.00, 9.13) and negative LR was 0.02 (CI, 0.01, 0.03), respectively.
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For studies including uninterpretable results, the diagnostic performance decreased, with the pooled positive LR 7.40 (CI, 6.00, 9.13) and negative LR 0.02 (CI, 0.01, 0.03). Moderate heterogeneity was found for positive LR (Q = 705.71; $P<0.001$; $I^2 = 91.75\%$ [CI, 91.75%, 94.37%]) and significant heterogeneity for negative LR (Q = 346.89; $P<0.001$; $I^2 = 85.87\%$ [CI, 82.59%,

Table 2. Overall Diagnostic Performance of CT Angiography.

	All references		References excluding non-diagnostic image		References including non-diagnostic image	
	Positive LR (95% CI)	Negative LR (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Patient level	8.91(7.53, 10.54)	0.02 (0.01, 0.03)	11.16(8.90, 14.00)	0.01(0.01, 0.03)	7.40(6.00, 9.13)	0.02(0.01, 0.03)
Artery level	15.22(12.44, 18.64)	0.05(0.04, 0.07)	16.27(12.37, 21.42)	0.05(0.03, 0.08)	14.45(10.83, 19.27)	0.05(0.04, 0.08)
Segment level	31.57(26.92, 37.02)	0.08(0.07, 0.10)	39.76(31.84, 49.63)	0.08(0.06, 0.11)	23.91(19.62, 29.14)	0.08(0.07, 0.11)

Note. —LR = likelihood ratio.
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Table 3. Pooled Summary Results by Subgroups.

	Patient level (95% CI)		Artery level (95% CI)		Segment level (95% CI)	
	Positive LR	Negative LR	Positive LR	Negative LR	Positive LR	Negative LR
Temporal resolution						
<100ms	7.23(5.74, 9.09)	0.02(0.01, 0.03)	14.21(9.86, 20.48)	0.05(0.03, 0.07)	25.55(19.49, 33.50)	0.08(0.06, 0.10)
>100ms	7.83(6.03, 10.16)	0.02(0.01, 0.03)	15.61(10.29, 23.66)	0.05(0.03, 0.10)	23.01(17.60, 30.09)	0.08(0.06, 0.12)
ECG-triggered protocol						
Retrospective	8.41(5.83, 12.13)	0.02(0.01, 0.04)	17.10(10.71, 27.30)	0.06(0.03, 0.12)	23.74(18.79, 30.00)	0.08(0.05, 0.12)
Prospective	5.95(4.52, 7.84)	0.03(0.02, 0.06)	12.41(8.22, 18.72)	0.05(0.03, 0.08)	25.64(17.895, 36.77)	0.107(0.07, 0.13)
Gender						
Male/female<3	7.01(5.59, 8.80)	0.02(0.01, 0.03)	16.52(12.43, 21.95)	0.05(0.03, 0.08)	25.148(19.58, 32.30)	0.08(0.06, 0.12)
Male/female>3	11.02(6.56, 18.52)	0.02(0.01, 0.04)	9.43(4.49, 19.82)	0.05(0.03, 0.09)	19.87(14.20, 27.81)	0.08(0.05, 0.12)
Scheme of coronary tree						
≦16-segments	7.82(6.17, 9.93)	0.02(0.01, 0.04)	16.75(11.07, 25.34)	0.06(0.04, 0.08)	24.89(18.81, 32.93)	0.09(0.07, 0.12)
>16-segments	7.33(5.53, 9.72)	0.01(0.00, 0.03)	12.28(8.65, 17.44)	0.05(0.02, 0.12)	22.50(16.57, 30.54)	0.06(0.05, 0.08)
Heart rate						
<65bpm	7.55(5.52, 10.34)	0.02(0.01, 0.04)	13.09(9.32, 18.40)	0.06(0.04, 0.11)	21.79(17.46, 27.19)	0.10(0.07, 0.14)
>65bpm	6.89(5.28, 8.98)	0.02(0.01, 0.04)	18.07(9.48, 34.47)	0.03(0.02, 0.07)	26.11(18.36, 37.14)	0.06(0.05, 0.09)
Calcium score						
<400	7.23(5.86, 8.92)	0.02(0.01, 0.03)	13.97(8.22, 23.72)	0.06(0.03, 0.15)	22.36(15.31, 32.65)	0.08(0.04, 0.15)
>400	11.51(9.13, 14.53)	0.01(0.01, 0.02)	16.37(7.00, 38.30)	0.04(0.02, 0.09)	19.43(12.28, 30.72)	0.06(0.03, 0.12)
Prevalence of CAD						
<0.5	7.50 (5.32, 10.58)	0.05(0.02, 0.08)	18.27(13.11, 25.48)	0.06(0.03, 0.11)	28.35(21.32, 37.71)	0.09(0.06, 0.15)
>0.5	7.18(5.62, 9.17)	0.01(0.01, 0.02)	11.48(7.473, 17.64)	0.05(0.03, 0.07)	20.06(15.36, 26.21)	0.08(0.06, 0.11)
Prevalence of non-assessable segments						
<0.02	9.12(6.41, 12.96)	0.03(0.01, 0.05)	18.73(13.76, 25.50)	0.05(0.03, 0.08)	33.303(25.574, 43.369)	0.08(0.05, 0.11)
>0.02	6.36(4.32, 9.36)	0.01(0.01, 0.04)	12.21(7.19, 20.74)	0.04(0.02, 0.07)	17.62(14.14, 21.94)	0.09(0.06, 0.12)

Note. —TP = true-positive, FP = false-positive, TN = true-negative, FN = false-negative, LR = likelihood ratio, ECG = electrocardiographic, bpm = beat per minute, BMI = body mass index, CAD = coronary artery disease.
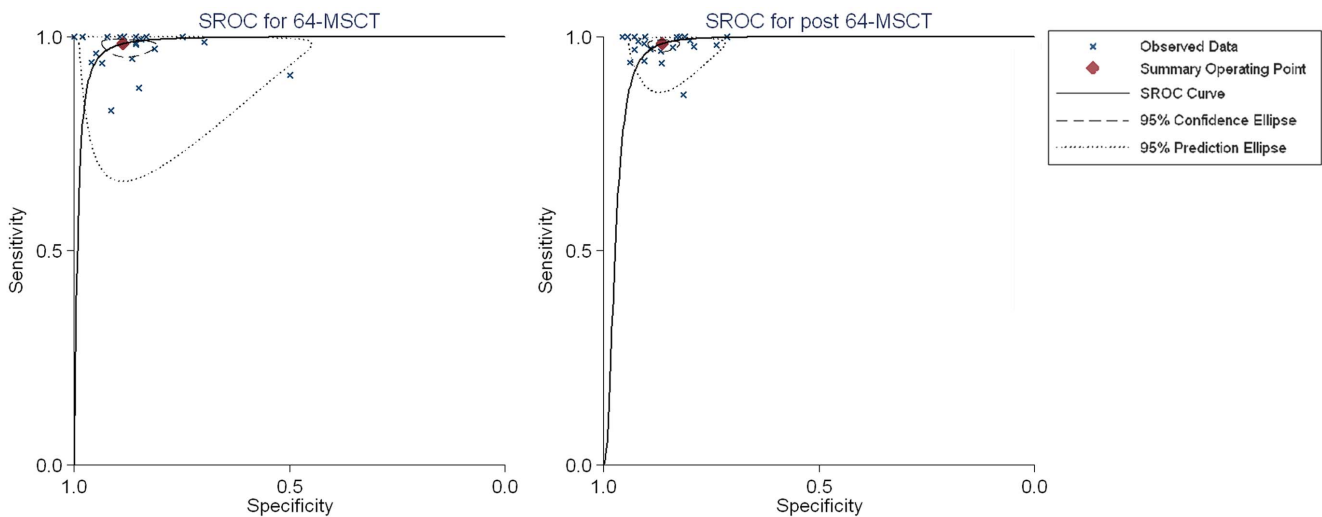
doi:10.1371/journal.pone.0084937.t003

Figure 3. sROC for 64-MDCT and post 64-MDCT. sROC demonstrated the diagnostic performance of 64-MDCT and post 64-MDCT at the patient level (sROC = summary receiver operating characteristic).
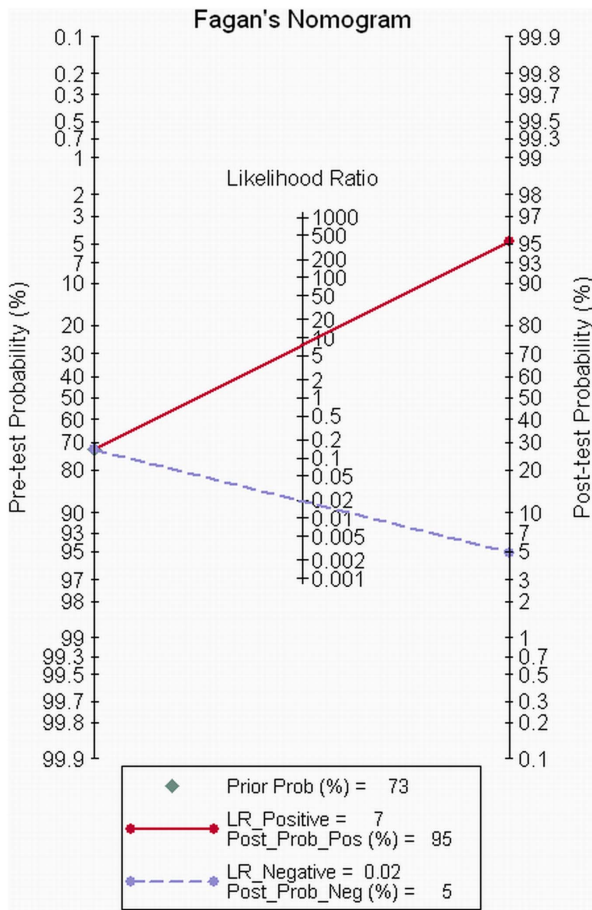doi:10.1371/journal.pone.0084937.g003

Figure 4. Fagan's nomogram for CTA. For patients with a pre-test probability of CAD<73%, the post-test probability of negative results was larger than 95%. However, when the pre-test probability was larger than 73%, the diagnostic role was reversed, with a positive post-test probability of larger than 95% and a negative post-test probability of less than 95%.
doi:10.1371/journal.pone.0084937.g004

89.16%]) (Figure 2). The detailed diagnostic accuracy at patient, artery and segment levels is presented in Table 2 as well as in Table S2.

Using the pre-specified potential sources of heterogeneity as covariates in the random effects models, we found that gender, heart rate, scheme of the coronary arterial tree for stenostic analysis, temporal resolution, calcium score, the proportion of non-assessable segments, and the protocol of ECG-triggered scanning were significant predictors, while age did not impact diagnostic accuracy (Table S3). The results for the subgroups in patient-based analyses are shown in Table 3.

We added the generation of CT scanners as a covariate to the bivariate model to compare the performance of 64-MDCT and post 64-MDCT. The result showed that, with new techniques used in the newer generations of CT scanners, the overall accuracy of post 64-MDCT at the patient level decreased (P<0.001, the area under the summary ROC curve were 0.98 [CI, 0.97 to 0.99] for 64-MDCT and 0.96 [CI, 0.94 to 0.98] for post 64-MDCT, respectively) (Figure 3). Further analysis indicated that the decreased index was positive LRs (8.71 [5.76, 13.12] versus 7.24 [5.92, 8.85]), while the negative LRs were similar (0.02 [0.01, 0.04] versus 0.02 [0.01, 0.03]). Importantly, the heterogeneity of 64-MDCT was larger than that of post 64-MDCT ($I^2 = 96.26\%$

versus 30.2%; 91.89% versus 56.79% for positive and negative LRs, respectively).

We evaluated the post-test probability for studies that explicitly stated that the non-assessable segments were included during analysis, as it is common practice to classify a segment as diseased if there is any doubt. The relationship between pre-test probability and post-test probability was depicted by visual Fagan's nomogram [23]. As we can see from Figure 4, for patients with a pre-test probability of CAD<73%, the post-test probability of negative results was larger than 95%, while the post-test probability of positive results was less than 95%, which indicated that the CT angiography was only an effective tool to exclude patients with CAD. On the other hand, when the pre-test probability was larger than 73%, the diagnostic role was reversed, with a positive post-test probability of larger than 95% and a negative post-test probability of less than 95%, which implied that when there was a pre-test probability of CAD >73%, the role of CTA changed from a test of exclusion to a confirmatory tool.

The likelihood ratio scattergram showed that at the artery and segment levels, the likelihood ratio profile of CTA was both a test of exclusion and a confirmatory test tool to diagnose stenosis > 50% (positive likelihood ratio >10; negative likelihood ratio <0.1), while CTA was generally a test of exclusion to rule out significant stenosis at the patient level (positive likelihood ratio <10; negative likelihood ratio <0.1) (Figure 5) [24].

The sensitivity analysis was conducted at the patient level to investigate the influence of each individual study on the overall meta-analysis summary estimate. No study influenced the pooled sensitivity and specificity larger than 0.02 (Figure S1).

Discussion

The present study analyzed studies of 64-MDCT and post 64-MDCT to shed new light on the following critical questions: (1) What is the role of CTA in patients with different pre-test probabilities? (2) Can post 64-MDCT lead to a better diagnostic accuracy than 64-MDCT?

The hypothesis, which states that CTA can exclude individuals with suspected CAD for patients with low to intermediate pre-test likelihood, has been argued widely in previous studies [3,20]. The present study showed that not all patients with an intermediate pre-test likelihood of CAD could be excluded by CTA. After assessing the precise analysis based on Bayes' theorem, the results show that the pre-test probability of 73% is the cut off value for the diagnostic role of CTA. When pre-test probability is <73%, CTA is an effective tool to exclude CAD. Of note, the positive LR is comparatively low and CTA may be still applied to determine the presence of obstructive CAD in patients with a pre-test probability of CAD>73%. The confirmatory application of CTA also plays an important role for clinical diagnosis, especially for patients with stable angina when revascularization is not preferred at the present time [25]. CTA, therefore, may provide more evidence to confirm the presence of CAD and avoid the major complications associated with ICA [2,25]. As there are several studies providing detailed algorithms to quantify pre-test risk [9–12], a precise evaluation of the diagnostic role of CTA according to pre-test probability will improve the cost-effectiveness of CTA. Moreover, the present analysis demonstrates that CTA is both a test of exclusion and confirmatory test on both artery and segment levels, which provides detailed information for prognostic evaluation [26,27] or for the selection of a revascularization strategy [28].

The results indicate that the exclusive performance of post 64-MDCT does not increase. Rather, the confirmatory accuracy of post 64-MDCT decreases. The main reason may be that the
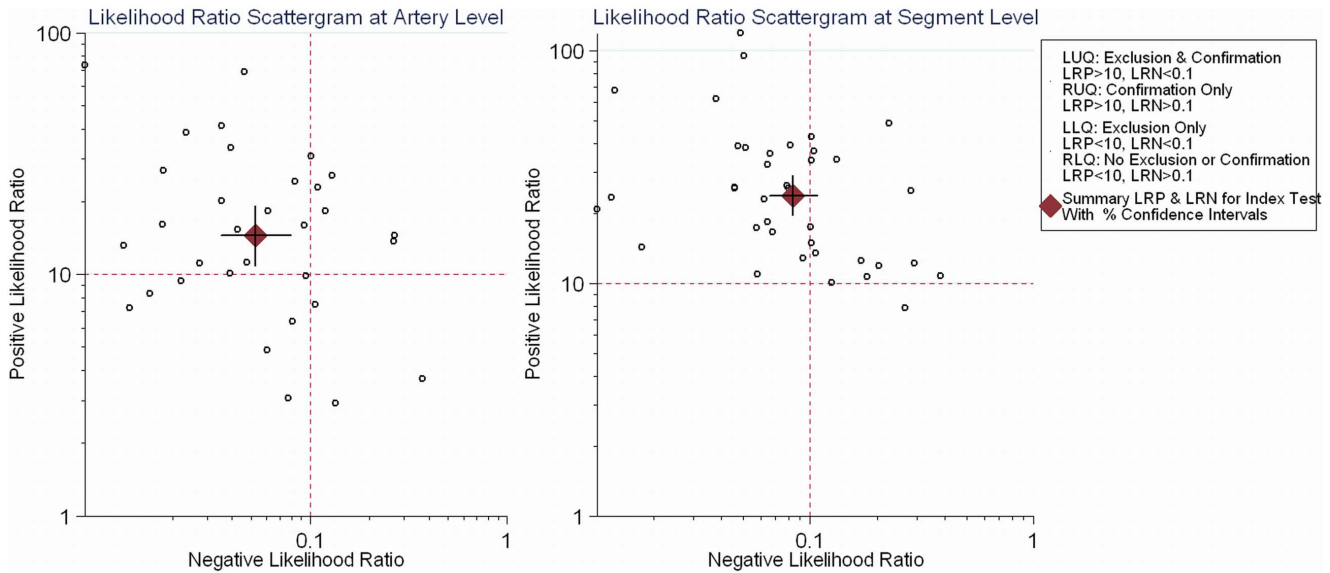
Figure 5. Illustration chart indicating the diagnostic role for accuracy of CTA at the artery and segment levels. At the artery and segment levels, the likelihood ratio profile of CT was both an exclusion and s confirmation test to diagnose stenosis >50% (positive likelihood ratio > 10; negative likelihood ratio <0.1), while CTA was generally a test of exclusion to rule out significant stenosis at the patient level (LRP = positive likelihood ratio, LRN = negative likelihood ratio, LLQ = left lower quadrant, LUQ = left upper quadrant, RLQ = right lower quadrant, RUQ = right upper quadrant).

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improved techniques mainly focuses on the motion artifacts. For example, DSCT, with two detectors arranged at angles of 90°, effectively doubles the temporal resolution [29]. Additionally, 320-MDCT, with 16-cm wide volume coverage, enabled whole coronary arteries covered with one heartbeat, which eliminated the motion artifact effectively [30]. The spatial resolution, however, is not improved and the beam hardening artifacts still present a primary shortcoming of CTA. As is apparent from the results, the heterogeneity of post 64-MDCT was significantly larger than that of 64-MDCT. The decreased positive LR of post 64-MDCT may be caused by a different prevalence of calcified plaques, which are not, however, provided by most studies. Further analysis with information regarding the individual may illustrate the question more clearly. Another potential reason for the decreased pooled positive LR may be that with an improved technique of post 64-MDCT, the inclusion criteria of patients was broader than that of 64-MDCT. With dual-source, 64-slice CT, it could be theoretically possible to scan without lowering the heart rate [31]. Nevertheless, in reality, the heart rate still needs to remain low for good image quality since the temporal resolution of this scanner is still too low. In addition, a low heart rate is also suggested for 128-MDCT or 320-MDCT due to the technical specifications of the scanners. Nevertheless, with wider detection, prospective ECG gating is more feasible. Combined with iterative construction, the radiation dose of post 64-MDCT was significantly lower than that of 64-MDCT [32,33].

Schueler et al. reported that item referring to how authors handled ''Uninterpretable Results'' (QUADAS item 13) had a significant influence on diagnostic accuracy values and that exclusion of uninterpretable results may overestimate the diagnostic abilities of the method being investigated[34], which has also been proven by our analysis. Salavati et al., on the other hand, did not detect a difference between studies including and excluding uninterpretable segments[35]. The potential reason might be the lower proportion of uninterpretable segments achieved by DSCT[35]. The present study, with 64- and post

64-MDCT included, evaluates the diagnostic performance mainly through studies that clearly claim that coronary arterial segments with non-diagnostic image quality were treated as positive for disease, as it is a common practice to classify a segment as diseased if it is non-diagnostic, which guarantees the validity of the conclusion reached.

Our meta-analysis has limitations. First, we did not analyze the diagnostic accuracy of CTA for stable angina and ACS respectively, as most studies include all symptomatic patients without further classification of clinical features. In addition, though the clinical diagnoses were different, the morphologic images of angiography were both indicative of stenosis of the coronary lumen. Second, although the present study is aimed at illustrating the diagnostic role of CTA by pre-test probability, information on symptoms, however, are not provided by most references. However, the main conclusion was not impacted as we mainly used Bayes' theorem and the positive and negative LRs, instead of the sensitivity and specificity, to evaluate the diagnostic role of CT angiography. Such LRs have advantages for the following reasons: they are less likely to change with the prevalence of CAD and they can be calculated for several levels of the symptom/sign. Third, the conclusion was conducted by using ICA as standard references. Recent studies indicate that fractional flow reserve (FFR)-guided treatment may lead to a better prognosis than that of an ICA-guided strategy [36,37]. Several studies, however, demonstrate that the accuracy to diagnose ischemic stenosis, with FFR as a reference, was poor [38-40]. Further meta-analysis is therefore required to explore the different capacities of CTA for detecting morphological and functional stenosis.

In conclusion, the diagnostic performance of post 64-MDCT does not increase as compared with 64-MDCT. CTA, overall, is a test of exclusion for patients with a pre-test probability of CAD< 73%, while for patients with a pre-test probability of CAD>73%, CTA is a test used to confirm the presence of CAD.

Supporting Information

Figure S1 The Serrbar Illustrating a Sensitivity Analysis in which the Meta-Analysis was Re-estimated by Omitting Each Study in Turn. The sensitivity analysis indicates that no study influenced the pooled sensitivity and specificity larger than 0.02. (TIF)

Table S1 Quality Assessment of Studies Enrolled to Diagnostic Accuracy.
(DOCX)

Table S2 Detailed Diagnostic Information for Each Study.
(DOCX)

Table S3 Results of the Multivariate Meta-Regression Analysis for Identifying Covariates to Explain Heterogeneity at Patient Level.
(DOCX)

Checklist S1 PRISMA Checklist.
(DOC)

Author Contributions

Conceived and designed the experiments: ML XD. Analyzed the data: ML XD ZJ. Contributed reagents/materials/analysis tools: ZJ JD. Wrote the paper: ML XD ZJ JD ZP LL.

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