Scoping review of diagnostic strategies for suspected acute aortic syndrome (AAS)

We undertook a scoping review to identify primary or secondary research studies evaluating the accuracy of clinical scores, decision rules, algorithms, models, or biomarkers for AAS. We specifically aimed to determine the number of primary studies that would meet our proposed inclusion criteria for a systematic review (cohort and case-control studies) and meta-analysis (cohort studies only).

We searched Medline from inception to 7 April 2022 using terms for AAS + (decision rules OR biomarkers OR risk models OR algorithms) + (SIGN diagnostic filter OR "ROC" or "risk models and algorithms related terms") and retrieved 1816 citations. Review of the titles and abstracts identified 11 systematic reviews and 58 relevant primary research studies. The systematic reviews comprised seven reviews of D-dimer, and reviews of the ADD-RS, combined ADD-RS and D-dimer, and clinical features, and a review of all aspects of AAS diagnosis and management. The primary research studies comprised 40 studies of D-dimer, nine studies of the ADD-RS (four alongside D-dimer), three papers of other scores (one involving D-dimer), 28 studies of other biomarkers (20 alongside D-dimer), and three papers reporting the development of diagnostic models (Bayesian, machine learning, and deep learning).

Table 1 summarises the systematic reviews. Tsutsumi et al identified eight studies of the ADD-RS and four of the ADD-RS combined with D-dimer. Bima et al identified the same four studies of the ADD-RS combined with D-dimer. The seven reviews of D-dimer identified varying numbers of studies, depending upon the inclusion criteria, with more cohort studies being included in the recent reviews of Yao et al and Watanabe et al, although even these included seven and eight case-control studies respectively. The systematic reviews of clinical features (Ohle 2018) and all aspects of AAS diagnosis and management (Mussa 2016) are included for completeness, although they do not relate directly to the study question.

The systematic review of the ADD-RS (Tsutsumi 2020) identified one study that was not identified by our search, which was published only as an abstract (Kodera 2016). We identified one study (Kotani 2017) that was not included in the Tsutsumi review. Two of the studies (Nazerian 2014a, Nazerian 2014b) appear to report some of the same patients. Table 2 shows the studies of the ADD-RS. The systematic review of ADD-RS alongside D-dimer (Bima 2020) identified the same studies as our search, shown in Table 3. We therefore anticipate including eight cohort studies of ADD-RS alone and four cohort studies of ADD-RS with D-dimer in our meta-analysis, which is similar to the previous reviews (Tsutsumi 2020, Bima 2020).

The systematic reviews of D-dimer identified five studies that would be eligible for our systematic review but were not identified by our search (Xue 2007, Spinner 2006, Reeps 2010, Levcik 2013, Stanojlovic 2013), and one abstract (Li 2010) that appears to be an initial report of a study we identified (Li 2017). Table 4 shows all 45 studies of D-dimer. We anticipate that we will include data from 21 cohort studies in our meta-analysis, including 9404 patients (1873 with AAS). Six of these studies (4509 patients, 811 with AAS) were not included in previous meta-analyses, so we expect to produce a more robust estimate of D-dimer accuracy for diagnosing AAS.

Table 5 shows the studies reporting other biomarkers. The most widely studied biomarkers were C-reactive protein (10 studies), white cell count (6 studies), troponin (6 studies) and IL-6 (two studies), with two studies each of fibrin degradation products, fibrinogen, lactate dehydrogenase, matrix metalloproteinase 9, B-type natriuretic peptide and soluble ST2. There were 20 case-control studies and eight cohort studies (seven prospective). The only biomarker evaluated in more than one cohort study was soluble ST2 (two studies), so there is currently no potential for meaningful meta-analysis of studies with a low risk of bias.

Table 1: Systematic reviews of studies of diagnostic strategies for AAS

Author	Year	Test(s)	N (studies)	Designs included
Bima	2020	ADD-RS with D-dimer	4	3 retrospective cohort 1 prospective cohort
Tsutsumi	2020	ADD-RS alone ADD-RS with D-dimer	8 4 (9 total)	7 retrospective cohort 1 prospective cohort 1 case series
Yao	2021	D-dimer	16	7 retrospective cohort 2 prospective cohort 7 case-control
Watanabe	2016	D-dimer	22	8 retrospective cohort 6 prospective cohort 8 case-control
Asha	2015	D-dimer	5	3 retrospective cohort 1 prospective cohort 1 case-control
Cui	2015	D-dimer	5	1 retrospective cohort 1 prospective cohort 3 case-control
Shimony	2011	D-dimer	7	1 retrospective cohort 1 prospective cohort 5 case-control
Marill	2008	D-dimer	11	1 retrospective cohort 7 case-control 3 case series
Sodeck	2007	D-dimer	16	1 retrospective cohort 7 case-control 2 case series 6 case reports
Ohle	2018	Clinical features	9	6 prospective cohort 3 retrospective cohort
Mussa	2016	All AAs diagnosis and management	82	2 randomised trials 80 observational

Table 2: Studies evaluating the accuracy of the ADD-RS for identifying AAS

Author	Year	N	Population	Reference standard	Design
Gorla	2017	85/376 (22.6%)	Chest pain with suspected AAS	CTA (unclear)	Retrospective cohort
Kodera*	2016	105/162 (64%)	Suspected AAS	Unclear	Retrospective cohort
Kotani**	2017	123/545 (13.9%)	Acute chest pain + admission to hospital + DD available	CTA	Retrospective cohort
Nazerian***	2014	233/1035 (22.5%)	Chest/back/abdo pain, syncope or perfusion deficit + no alternative diagnosis + clinical suspicion leading to CTA + D-dimer measured	CTA (all)	Retrospective analysis of prospective registry
Nazerian***	2014	291/1328 (21.9%)	Chest/back/abdo pain, syncope or perfusion deficit + no alternative diagnosis + clinical suspicion leading to CTA	CTA (all)	Retrospective analysis of prospective registry
Nazerian	2018	241/1848 (13.0%)	Chest/back/abdo pain, syncope, or perfusion deficit + clinical suspicion	CTA, TEE, MRA, surgery or autopsy; or 14-day clinical FU	Prospective cohort
Ohle	2018	12/370 (3.2%)	ED attendances undergoing CTA for suspected AAS	CTA (all)	Retrospective cohort
Rotella	2018	5/200 (2.5%)	ED attendances undergoing CTA for suspected AAS	CTA (all)	Retrospective cohort
Wang	2018	239	Hospital admissions with AAD confirmed by CTA (analysis evaluated accuracy of ADD-RS for type A AAD)	CTA (all)	Case series
Yamashita	2018	361/22075 (1.6%)	EMS transfers with chest/back/abdo pain, syncope or perfusion deficit	CTA (selected cases)	Retrospective analysis of EMS records

*Not detected by our search
**Not detected by Tsutsumi
***Report patients in common

Table 3: Studies evaluating the accuracy of the ADD-RS in combination with D-dimer for identifying AAS

Author	Year	n/N (%)	Population	Reference standard	Design
Gorla	2017	85/376 (22.6%)	Chest pain + DD measured at presentation	Unspecified advanced imaging	Retrospective cohort
Kotani	2017	123/545 (13.9%)	Acute chest pain + admission to hospital + DD available	CTA	Retrospective cohort
Nazerian	2014	233/1035 (22.5%)	Chest/back/abdo pain, syncope or perfusion deficit + no alternative diagnosis + clinical suspicion leading to CTA	CTA (all)	Retrospective analysis of prospective registry
Nazerian	2018	241/1848 (13.0%)	Chest/back/abdo pain, syncope, or perfusion deficit + clinical suspicion	CTA, TEE, MRA, surgery or autopsy; if unavailable, 14-day clinical follow-up	Prospective cohort

Table 4: Studies evaluating the accuracy of D-dimer for identifying AAS

Author	Year	N	Population	Reference standard	Design
Akutsu	2005	30/78 (38.5%)	Suspected AAD requiring CTA	CTA (all)	Retrospective cohort
Dong	2017	202:150	202 cases with AAD, 150 controls with MI (45), PE (51) and AAA (54)	CTA	Case-control
Eggebrecht	2004	16:80	16 cases with AAD, 60 controls (32 chronic AD, 16 NCCP, 16 MI, 16 PE)	CTA, MR, TOE	Case-control
Ersel	2010	30/99 (30.3%)	30 cases with AAD, 69 controls with other chest pain (ICD R07)	CTA	Case-control
Fan	2010	107/260 (41.1%)	Suspected AAD undergoing imaging	CTA, MR or TOE (all)	Retrospective cohort
Forrer**	2021	34:33	34 cases with AAD, 33 controls with NSCP	CTA	Case-control
Giachino	2015	52/126 (41.3%)	Suspected AAD undergoing CTA	CTA (all)	Prospective cohort
Gorla	2017	231:291	231 cases with AAS, 291 controls with chest pain and AAS ruled out	Imaging, surgery, or autopsy	Case-control
Gorla	2017	85/376 (22.6%)	Chest pain + DD measured at presentation	Unspecified advanced imaging	Retrospective cohort
Guo**	2013	35:303	ED attendances with MI (327), PE (76) or AAD (35)	Unclear	Case-control
Hagiwara**	2013	94:776	94 cases with AAD, controls with AMI (187), angina (142), CVA (353), or TIA (94)	CTA	Case-control
Han**	2021	78:77	78 cases with AAD, 77 healthy controls	CTA	Case-control
Hazui	2005	29:49	29 cases with AAD, 49 controls with MI	CTA	Case-control
Kotani**	2017	123/887 (13.9%)	Admitted to hospital with acute chest pain	Unclear	Retrospective cohort
Lee**	2022	82/204 (40.2%)	ED attendances undergoing CTA for suspected AAS with ADD-RS>0	CTA (all)	Retrospective cohort
Levcik*	2013	41/76 (53.9%)	Suspected AAD undergoing imaging	CTA, TOE or aortography	Retrospective cohort
Li**	2017	202/790 (25.6%)	Admitted to hospital with acute chest pain	Unclear	Prospective cohort
Li**	2018	88:88	88 cases with AAD, 88 controls without	Unclear	Case-control
Liu**	2018	43:43	43 cases with AAD, 43 matched controls	Unclear	Case-control
Morello	2018	104/313 (33.2%)	Suspected AAS with red flag symptoms	CT (selected)	Prospective cohort

				and clinical FU	
Morello	2020	88/297 (29.6%)	Suspected AAS with red flag symptoms	CT (selected) and clinical FU	Prospective cohort
Morello**	2021	49/447 (11%)	Suspected AAS with red flag symptoms	CT (selected) and clinical FU	Prospective cohort
Nazerian	2014	233/1035 (22.5%)	Chest/back/abdo pain, syncope or perfusion deficit + no alternative diagnosis + clinical suspicion leading to CTA	CTA (all)	Retrospective analysis of prospective registry
Nazerian**	2018	241/1848 (13.0%)	Chest/back/abdo pain, syncope, or perfusion deficit + clinical suspicion	CTA, TEE, MRA, surgery or autopsy; Or 14d clinical	Prospective cohort
Ohlmann	2006	94:94	94 cases with AAD, 94 with AAD ruled out	CTA	Case-control
Okazaki	2014	15:115	15 cases with AAS, 115 controls with stroke	?	Case-control
Pan**	2021	86:118	86 cases with AAD, 60 with MI, 28 with PE and 30 healthy controls	CTA (all)	Case-control
Peng	2015	35/76 (46.1%)	Suspected AAD undergoing CTA	CTA (all)	Prospective cohort
Reeps*	2010	18	18 patients with acute (9), symptomatic progressive (2), or known chronic stable (7) type B AD	CTA	Case series
Sakamoto	2011	35:228	35 cases with AAD, 22 controls with PE and 206 with MI	CTA	Case-control
Sakamoto	2016	5/240 (2.1%)	Patients with suspected stroke	Unclear	Retrospective cohort
Sbarouni	2007	18:29	18 cases with AAD, 21 dilated aorta, 8 normal	Unclear	Case-control
Sbarouni	2015	120:121	120 cases with AAD, 121 controls with chronic aneurisms	CTA	Case-control
Shao	2014	89/368 (24.2%)	Suspected AAD	CTA, TOE or MR (unclear)	Retrospective cohort
Spinner*	2006	26/82 (37.1%)	Acute chest pain r/o STEMI	CTA, TOE, angio	Retrospective cohort
Stanojlovic*	2013	29/54 (53.7%)	Not specified (abstract)	CTA, TOE	Retrospective cohort

Suzuki	2009	87/220 (39.5%)	220 patients with symptoms requiring imaging for AAD	Imaging for AAD	Prospective cohort
Tokuda**	2018	24:812	Stroke or TIA with and without AAD	Unclear	Augmented cohort
Wang**	2018	114/333 (34.2%)	Suspected AAS receiving imaging	Definitive imaging (all)	Prospective cohort
Weber	2003	24:35	24 AAD, 35 controls without AAD	?	Case-control
Xiao	2016	60:60	60 cases with AAD, 60 controls with chest pain but no AAD	CTA	Case-control
Xue*	2007	16:27	16 cases with AAD, 27 with no AAD	TOE, MRI, or CT	Case-control
Yoshimuta	2015	9/1236 (0.7%)	Stroke diagnosed on CT or MR, and AAD not suspected	CTA (unclear)	Retrospective cohort
Yuan**	2011	20:9:20	20 cases with AAD, 9 with aortic aneurism, 20 with CAD	Surgery	Case-control
Zeng**	2020	19:20	19 cases with AAD, 20 healthy controls	Unclear	Case-control

*Not detected by our search
**Not included in previous reviews

Table 5: Papers reporting evaluation of other biomarkers

Author	Year	Biomarkers	n/N (%)	Population	Reference standard	Design
Cheng	2020	Multiple proteins	20:20	20 AAD cases, 20 controls	Unclear	Case-control
Dong	2017	FDP	202:150	202 cases with AAD, 150 controls with MI (45), PE (51) and AAA (54)	CTA	Case-control
Dong	2017	Multiple microRNAs	37:66	37 cases with AAD, 66 controls with chronic AD (26), healthy (17), without AAD (23)	CTA	Case-control
Eggebrecht	2004	WBC, CRP, fibrinogen	16:80	16 cases with AAD, 60 controls (32 chronic AD, 16 NCCP, 16 MI, 16 PE)	CTA, MR, TOE	Case-control
Forrer	2021	PAI-1, IL-6, IL-10, HSTnT	34:33	34 cases with AAD, 33 controls with NSCP	CTA	Case-control
Giachino	2013	MMP8, MMP9	52/126 (41.3%)	Suspected AAD undergoing CTA	CTA (all)	Prospective cohort
Hagiwara	2013	FDP	94:776	94 cases with AAD, controls with AMI (187), angina (142), CVA (353), or TIA (94)	CTA	Case-control
Han	2021	S100A, hsCRP, cTnT	78:77	78 cases with AAD, 77 healthy controls	CTA	Case-control
Konig	2021	ACAN, CKMB, cTnT	33:43	33 cases with type A AAD, 13 MI, 18 thoracic aneurism, 12 healthy volunteers		Case-control
Li	2018	MMP9, TRL4, CRP	88:88	88 cases with AAD, 88 controls without	Unclear	Case-control
Liu	2018	Plasma resistin, WBC, glucose, hs-CRP, IL-6, TNF-alpha	43:43	43 cases with AAD, 43 matched controls	Unclear	Case-control
Morello	2016	LDH	201/999 (20.1%)	Suspected AAD	Aortic imaging	Prospective cohort
Morello	2017	WBC, platelet, fibrinogen	271/1210 (22.4%)	Suspected AAD	CTA	Retrospective cohort

Morello	2018	copeptin	104/313 (33.2%)	Suspected AAS with red flag symptoms	CT (selected) and clinical FU	Prospective cohort
Morello	2020	sST2	88/297 (29.6%)	Suspected AAS with red flag symptoms	CT (selected) and clinical FU	Prospective cohort
Ohlmann	2006	CRP, troponin, LDH, WBC	94:94	94 cases with AAD, 94 with AAD ruled out	CTA	Case-control
Okazaki	2014	BNP	15:115	15 cases with AAS, 115 controls with stroke	Unclear	Case-control
Pan	2021	LPA	86:118	86 cases with AAD, 60 with MI, 28 with PE and 30 healthy controls	CTA (all)	Case-control
Peng	2015	alpha-SMA, smMHC, sELAF, PC1	35/76 (46.1%)	Suspected AAD undergoing CTA	CTA (all)	Prospective cohort
Sbarouni	2007	WBC, CRP, BNP	18:29	18 cases with AAD, 21 dilated aorta, 8 normal	Unclear	Case-control
Sbarouni*	2015	WBC, CRP, neutrophil to lymphocyte ratio	120:121	120 cases with AAD, 121 controls with chronic aneurisms	CTA	Case-control
Sbarouni*	2018	platelet-lymphocyte (PLR), red cell distribution width (RDW) and RDW/PLT's (platelets) (RPR	120:121	120 cases with AAD, 121 controls with chronic aneurisms	CTA	Case-control
Suzuki	2008	calponin	87/220 (39.5%)	220 patients with symptoms requiring imaging for AAD	Imaging for AAD	Prospective cohort
Wang	2018	sST2, cTnI	114/333 (34.2%)	Suspected AAS receiving imaging	Definitive imaging (all)	Prospective cohort
Xiao	2016	CRP, multiple proteins	60:60	60 cases with AAD, 60 controls with chest pain but no AAD	CTA	Case-control
Xu	2017	Multiple microRNAs	16:27	16 cases with AAD, 27 with no AAD	TOE, MRI, or CT	Case-control

Yuan	2011	CRP	20:9:20	20 cases with AAD, 9 with aortic aneurism, 20 with CAD	Surgery	Case-control
Zeng	2020	CRP, IL-6, metabolomics	19:20	19 cases with AAD, 20 healthy controls	Unclear	Case-control

*Papers reporting different biomarkers from the same study

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