Do we need a clinical decision rule for Acute Aortic Syndrome?

Robert Ohle

Thesis submitted to the faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the M.Sc. degree in Epidemiology

Epidemiology and Community Medicine

Faculty of Medicine

University of Ottawa

ABSTRACT

Acute aortic syndrome (AAS) is a life threatening clinical syndrome resulting from three distinct diagnoses; acute aortic dissection, penetrating atherosclerotic ulcer and intramural hematoma. There are no widely accepted guidelines that are both safe and efficient to guide the clinician on when to suspect AAS. Our aim was to assess the need for a clinical decision rule to help improve diagnosis of AAS. We conducted a diagnostic accuracy systematic review and meta-analysis, a historical case control study and historical cohort study.

We found wide variation in practice with a perceived need by physicians for a clinical decision rule. In addition we found it feasible to risk stratify patients at risk for AAS by historical, clinical and laboratory features. Therefore we conclude there is a need for the development of a clinical decision rule for the risk stratification of patients with a clinical suspicion of AAS.

EXECUTIVE SUMMARY

Acute aortic syndrome (AAS) is a life threatening clinical syndrome as a result of 3 distinct diagnoses; acute aortic dissection, penetrating atherosclerotic ulcer and intramural hematoma. It can present with a variety of symptoms (e.g. chest pain, back pain or neurological findings) that overlap with numerous more common conditions. This often leads to a missed or delayed diagnosis. There are no widely accepted guidelines that have been shown to be both safe and efficient in guiding who we should investigate for AAS. Clinical decision rules have been proposed as a way of reducing variation in practice and improving efficiency. A clinical decision rule may be defined as a decision-making tool that is derived from original research and that incorporates 3 or more variables from the history, physical examination, or simple test. In order to justify the development of a clinical decision rule 4 questions must be answered: 1) Can individuals be stratified for the disease state in question by standard history, physical examination, and simple laboratory testing? 2) Is there substantial variation in clinical practice for the condition with an impact on diagnostic accuracy or efficiency of test usage? 3) Does unnecessary testing results in increased morbidity or increased cost? 4) Is there a perceived need for a clinical decision rule by clinicians for the disease state in question?

As part of the thesis, three manuscripts were prepared. The first manuscript was based on a diagnostic accuracy systematic review and meta-analysis of clinical examination for acute aortic syndrome. The objectives of this manuscript were: 1) Summarize diagnostic accuracy of history, physical exam and basic investigations for the diagnosis of AAS; 2) Assess the ability of history,

physical exam and basic investigations to risk stratify those with a suspicion for AAS. The review identified suspicion for AAS should be raised with hypotension, pulse deficit or neurological deficit in those presenting with acute pain or perfusion deficit. Conversely the absence of a widened mediastinum and a low American Heart Association acute aortic dissection detection (AHA ADD) risk score decreases suspicion. The AHA ADD risk score did not have sufficient diagnostic accuracy to be useful in isolation to decide who requires investigation for AAS. Clinical exam alone cannot absolutely rule out acute aortic syndrome, but it can help risk stratify for further testing.

The second manuscript was based on a historical case control study. The objective of this manuscript was to assess the diagnostic accuracy of high risk historical, examination and basic investigative features for AAS, in confirmed cases of AAS and a low risk control group in order to address the perceived spectrum bias in previous studies and improve generalizability of results. Our study found that previously reported high-risk features (e.g. acute onset chest pain, tearing pain, hypotension, neurological or pulse deficit) maintain their diagnostic accuracy in a low risk population. No single high-risk feature can accurately rule in or rule out acute aortic syndrome. Further research should focus on the ability of a combination of these factors to generate a reproducible assessment of pre test probability. This could be used to risk stratify those who warrant further investigation thus reducing miss rate, morbidity and mortality.

The third manuscript was based on a historical cohort study. The objectives of this manuscript were to assess: 1) Emergency physician use of computed tomography (CT); 2) Diagnostic yield of CT ordered to rule out AAS; 3) Variation in CT ordering among physicians in patients

presenting with pain for diagnosis of AAS. Our study identified that current rate of imaging for AAS is appropriately low but inefficient, with 98% of advanced imaging negative for AAS. There is significant variation in physician CT ordering without an increase in diagnostic yield. These findings suggest great potential for more standardized and efficient use of CT for the diagnosis of AAS.

The recommendations from this thesis can be summarized as follows.

1. High-risk clinical features reported in our thesis can be used in clinical practice to help risk stratify patients, however the absence or presence of any one of these features cannot absolutely rule in or out the diagnosis. Assessment should be based on a thorough history and physical exam documenting all relevant high and low risk features reported in our thesis and the generation of a clinical gestalt taking into account probability of alternative diagnosis.
2. We have an unacceptable high miss rate for AAS. There is need to standardize assessment and increase clinical suspicion. In suspected acute coronary syndrome, pulmonary embolism and stroke clinicians should use high-risk features of AAS to help risk stratify for the possibility of AAS.
3. Given the inefficient and increasing use of computed tomography to rule out AAS we need to standardize our assessment in order to decrease practice variation and reduce costs.

4. We need to conduct a prospective cohort study with standardized definitions of high-risk features for AAS in order to derive a clinical decision rule to help stratify patients for AAS.

CONTRIBUTIONS OF THE AUTHORS

Three manuscripts have been prepared for publication as part of this thesis. Dr. R. Ohle is the first author of all papers, having been primarily responsible for data collection, analysis and writing of the manuscripts. All manuscripts are co-authored by Dr. R. Ohle his supervisors, Dr. Jeffrey Perry and Dr. George Wells. Five medical students aided in primary data collection and chart review Mr. Justin Um, Ms. Helena Bleeker, Mr. Omar Anjum, Mr. Hashim Khaliq Kareemi and Ms. Lindy Luo. Drs. Perry and Wells provided valuable feedback throughout the process.

ACKNOWLEDGEMENTS

I would like to thank my primary thesis supervisor Dr. Jeffrey J Perry. Since being nominated as my interim supervisor 6 years ago he has been a source of support and guidance. He has given me immense opportunity and wisdom for which I will always be very grateful. Eventually I will remember that percentages are to be to one decimal place and not to use abbreviations.

I am honored to have Dr. George Wells as my methodology supervisor. His input has been integral in the molding of the three papers, the use of a statistic which he first used almost 40 years ago to calculate variation in fruit production was inspiring.

A special thank you to the other member of my thesis advisory committee Dr. Ian Stiell.

I would not have been able to secure the additional help needed without Jane Sutherland and her constant support in how to get things done.

My go to fixer without whom this thesis would have taken twice as long, thank you Angela Marcantonio.

Thank you to the Canadian Association of Emergency Physicians and the Ottawa Hospital Department of Emergency Medicine for their additional funding.

The rock on which this thesis was built is my wife Sarah. An exceptional mother whose support throughout this process allowed me to complete this thesis and also discover the joys of becoming a father.

TABLE OF CONTENTS

LIST OF TABLES

Chapter Three

Chapter Four

Chapter Five

LIST OF FIGURES

Chapter Three

Chapter Five

ABBREVIATIONS USED IN THE TEXT

AAS – Acute aortic syndrome

ED – Emergency Department

CT – Computed tomography

MRI – Magnetic resonance imaging

ECHO – Echocardiography

TEE – trans esophageal echocardiography

ACS – acute coronary syndrome

PE – Pulmonary embolism

PCI – percutaneous coronary intervention

ECG - electrocardiogram

LR – negative likelihood ratio

LR+ positive likelihood ratio

CI - confidence intervals

CI - confidence intervals

SAEM - Society of Academic Emergency Medicine

AHA ADD risk score - American heart association aortic dissection detection risk score

Chapter One : Introduction

Rationale

Acute aortic syndrome (AAS) is a life threatening clinical syndrome as a result of 3 distinct diagnoses; acute aortic dissection, penetrating atherosclerotic ulcer and intramural hematoma. The aorta is the main artery supplying blood to the entire body. In acute aortic syndrome there is a defect in the wall of the aorta, this can cause a blockage of the vessel or its branches and can result in rupture of the aorta, leading to catastrophic blood loss. It can present with a variety of symptoms such as chest pain or a neurological deficit. These symptoms can overlap with more common conditions such as a myocardial infarction or a stroke(1). There are no widely accepted guidelines that have been shown to be both safe and efficient in guiding whom we should suspect AAS over a more common diagnosis (2). This often leads to a missed or delayed diagnosis. Clinical decision rules have been proposed as a way of reducing variation in practice, improving efficiency and diagnostic accuracy(3, 4). A clinical decision rule may be defined as a decision-making tool that is derived from original research and that incorporates 3 or more variables from the history, physical examination, or simple test. The first step in developing a rule is defining its need(4). This is defined by 4 questions: 1) Can individuals be stratified for the disease state in question by standard history, physical examination, and simple laboratory testing? 2) Is there substantial variation in clinical practice for the condition with an impact on diagnostic accuracy or inefficient test usage? 3) Does unnecessary testing results in increased morbidity or increased cost? 4) Is there a perceived need for a clinical decision rule by clinicians for the disease state in question?(5)

A clinical decision rule for AAS could reduce variation in practice, lead to reduced healthcare costs, decrease morbidity and ultimately decreased mortality for this deadly diagnosis.

Outline and objectives

The objective of this thesis is to assess the need for a clinical decision rule to help improve diagnosis of AAS. This thesis has been formatted as a manuscript based thesis. Three manuscripts have been prepared, in addition to a background chapter (Chapter2) and a general discussion and recommendations chapter (Chapter 6).

The following is an overview of the objectives of each chapter

Chapter One

An introductory chapter meant to provide an overview of the organization of the thesis and the objectives of each chapter.

Chapter Two

In order to appreciate the rationale for the thesis, chapter 2 provides background information on AAS.

Chapter Three

A manuscript based on the results of the systematic review and meta-analysis. The objectives of the manuscript were: 1) Summarize diagnostic accuracy of history, physical exam and basic investigations for the diagnosis of AAS; 2) Assess the ability of history, physical exam and basic investigations to risk stratify those with a suspicion for AAS.

Chapter Four

A manuscript based on a case controls study. The objectives of the manuscript were to assess the diagnostic accuracy of high risk historical, examination and basic investigative features for AAS, in confirmed cases of AAS and a low risk control group in order to address the perceived spectrum bias in previous studies and improve generalizability of results.

Chapter Five

A manuscript based on a historical cohort study. The objectives of the manuscript were to assess: 1) Emergency physician use of computed tomography (CT); 2) Diagnostic yield of

CT ordered to rule out AAS; 3) Variation in CT ordering among physicians in patients presenting with pain for diagnosis of AAS.

Chapter Six

A summary chapter meant to bring together the results of the systematic review and meta-analysis, the historical case control study and the historical cohort study. We used Stiell's suggested guideline for justification of a clinical decision rule to guide our discussion.

Reference

1. Hagan, P.G., et al., *The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease.* Jama, 2000. **283**(7): p. 897-903.

2. Hiratzka, L.F., et al., *2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease.* Journal of the American College of Cardiology, 2010. **55**(14): p. e27-e129.

3. Stiell, I.G., et al., *Implementation of the Canadian C-Spine Rule: prospective 12 centre cluster randomised trial.* Bmj, 2009. **339**: p. b4146.

4. Stiell, I.G. and G.A. Wells, *Methodologic standards for the development of clinical decision rules in emergency medicine.* Annals of emergency medicine, 1999. **33**(4): p. 437-447.

5. Finnerty, N.M., et al., *Clinical decision rules for diagnostic imaging in the emergency department: a research agenda.* Academic Emergency Medicine, 2015. **22**(12): p. 1406-1416.

Chapter Two : Background

Introduction

Acute aortic syndrome is a rare but potentially fatal condition that is often misdiagnosed and inappropriately treated. We will outline the incidence, mortality and discuss the underlying pathophysiology of this clinical syndrome. In addition we will explore the reasons behind the consistently high rate of misdiagnosis in the age of modern medicine. Finally we will propose criteria to assess if a clinical decision rule is needed to help reduce the high number of missed cases.

Pathophysiology

The aorta is the main artery that carries blood from the heart to the rest of the body. It originates from the left ventricle and travels through the chest down to the lower abdomen where it splits into two smaller arteries. It supplies oxygenated blood to the entire body through its many branches. The aorta has three main layers: tunica externa (adventia), tunica media and tunica intima. The intima provides a smooth layer for blood to flow over. The media consists of the elastic lamella, this is a concentric musculoelastic layer made up of a smooth muscle and elastic matrix. This layer is responsible for the aortas ability to expand and contract and thus respond to increase or decreased blood pressure. Damage to this elastic layer reduces the aortas ability to withstand hemodynamic stressors. The adventia provides structure and

support to the aorta. The thickness of the aorta requires an extensive network of tiny blood vessels called the vasa vasorum that supply the adventia and media layers.

The primary pathological process associated with AAS is weakening of the aortic wall through cystic medial degeneration. This is a process characterized by disruption and loss of elastic fibers with increased deposition of proteoglycans. The loss of elastin fibers reduces the ability of the aorta to adapt to hemodynamic stressors. This can lead to a tear in the inner wall of the aorta (aortic dissection), bleeding between the layers of the aortic wall (intramural hematoma) or predispose to the development of a penetrating ulcer (penetrating atherosclerotic ulcer) within the wall of the aorta.

Acute aortic syndrome embraces a heterogeneous group of patients with a similar clinical profile that includes penetrating atherosclerotic aortic ulcer, intramural aortic hematoma, and the classic aortic dissection.

Acute aortic dissection requires a tear in the intimal (inner most layer) layer of the aorta. This allows blood enter and separate the intima from the media (middle layer) or adventia (outer layer). This false lumen can propagate proximal or distally. As the false lumen propagates it can involve any of the side branches of the aorta, leading to a reduction in blood flow to the target organ. This can give rise to a variety of malperfusion syndromes such as a myocardial infarction, stroke, and an ischemic limb or bowel ischemia. The cystic medial degeneration of the aortic wall may be a result of hemodynamic stressors, connective tissue disorders, or abnormal flow of blood through the aorta caused by anatomic abnormalities (e.g. an aortic valve with two versus the normal three leaflets).

Aortic intramural hematoma (IMH) is a variant of classic aortic dissection. It is characterized by blood separating the intima from the media but an absence of an entrance tear. It is thought to be due to the rupture of the intraluminal vas vasorum. The intramural hemorrhage results in a circumferential oriented blood containing space. These can progress to an aortic dissection.

The third entity on the spectrum of acute aortic syndrome is penetrating atherosclerotic aortic ulcer. An aortic atherosclerotic lesion that penetrates the intima into the media defines this condition. These ulcers can lead to aneurysm (an abnormal dilation of the aorta) formation through aortic remodeling or pseudo aneurysm by trans mural rupture. In addition they can result in the formation of an intramural hematoma and even progress to an aortic dissection.

Incidence

Acute aortic syndrome is a relatively uncommon disease with an estimated annual incidence of 2.9-4/100,00 person years. (6-8). In Meszaros's 27-year longitudinal study on a population of 106,500 they included pre hospital mortality and found an incidence of 4.04/100,000/year(9). Acute aortic dissection accounts for the majority (~85%) of AAS, with intramural hematoma (~10%) and penetrating aortic atherosclerotic ulcer (~5%) accounting for the rest(1).

There are 4.6 million emergency departments visit each year alone for acute chest pain. Upwards of 1/3 will be diagnosed with non cardiac chest pain or unspecified chest pain (10). The best estimate of emergency department prevalence of acute aortic syndrome is the prospective study by Von Kodolitsch. They tracked all patients presenting with acute onset chest and/or back pain and found that 1 in 2000 were ultimately diagnosed with AAS(11). Acute

aortic syndrome represents one of the deadly diagnoses that must be ruled out in each patient presenting with acute chest pain. Thus although the population incidence and emergency department prevalence is low, the question of "does my patient have acute aortic syndrome?" is more common.

Mortality

Although advances in operative treatment have occurred mortality still remains at 25%(1, 12). This number varies with some specialized centers reporting mortality as low as 6.3%, however the overall number of 25% is consistent across German, Swedish and international registries(1, 13, 14). This number does not take into account the 20-36% that will die before presenting to hospital(9). Untreated mortality increases by 1-2% per hour from initial presentation and can reach a high of 40% within the first 24hrs and 70% in 2 weeks(1, 9). This dramatic time sensitive mortality has not changed since initially reported in Hirst's 1958 case series on 505 acute aortic dissections(15). Once diagnosed both medical and surgical interventions achieve a significant reduction in mortality. AAS is defined according to the Stanford classification by the location of the lesion. If found in the ascending aorta it is referred to as a Type A lesion, and if in the descending aorta a Type B. Type A aortic dissections have a surgical versus nonsurgical mortality of 26% versus 58%. For Type B aortic dissections mortality is 10.7% for medical management and 31% for surgical management (performed in 20% of type B candidates). Of those who are successfully treated the 5-year survival rate is 75%. The 10-year survival rate for surgically repaired dissections is 40% to 60%. The largest driver of overall mortality is the delay in initial diagnosis and transfer to definitive care if none is available(1, 12). The mortality of an intramural hematoma is similar to an aortic dissection. The natural history of intramural

hematoma depends on the location of the lesion. Like an aortic dissection if found in the ascending aorta it is classified as a Type A intramural hematoma and caries similar mortality as a type A aortic dissection. If found in the descending aorta it has a similar mortality to a type B aortic dissection(16). Mortality from penetrating atherosclerotic ulcers is unclear and controversy surrounds the most appropriate treatment. As it stands those in the ascending aorta are felt to be at a similar risk as a type A aortic dissection and thus are treated in the same fashion(17).

Misdiagnosis

Literature regarding AAS often starts with a reference to the mortality of acute aortic dissection and the exceptionally high rate of misdiagnosis. It is likely that many physicians continue to pursue an aggressive diagnostic strategy even in low risk patients because of a concern for poor patient outcome and the medico legal consequences of a missed diagnosis.

The Canadian Medical Protection Agency reviewed all cases of aortic dissection from 1991-2005. They excluded all cases of intramural hematoma, penetrating atherosclerotic ulcer, and dissections arising from surgical complications. During the study time period, 32 cases were identified for an average of 2.1 cases per year. These 32 cases generated 34 medico-legal difficulties: 21 (62%) were legal actions and 13 (38%) were complaints to a regulatory authority (College). Of the legal actions 44% were either judged in favor of the plaintiff or settled out of court(18). The initial diagnosis in these patients was; acute coronary syndrome (ACS) (19%) musculoskeletal (20%) pneumonia/pulmonary embolism (PE) (20%), pericarditis (12%),

gastritis/esophageal spasm (GI) (9%) and other (20% - pharyngitis, thyroiditis, renal colic, upper respiratory infection). The variety of initial misdiagnosis in these cases underlies the varied presentation of AAS and the diagnostic dilemma facing the physician.

Case series dating back to 1934 report a staggering 98% of diagnoses made post mortem. From 1934 to 1957 this rate gradually increases to 60% in Hirst's 339 patient case series (15). With advent of modern imaging technologies this rate has decreased significantly. The two most up-to-date assessments of the rate of AAS diagnosed post mortem are a case series from 1980-1990 with a rate of 17%, and Spittel's case series from 1992-1996 of 14%. (19). Spittel's case series of aortic dissection is often misquoted as reporting a post mortem diagnosis rate of 28%. However 158 new cases were found and of these 27 were diagnosed post mortem, giving us a rate of 17%(20).

With the linear relationship of mortality and time, delayed and missed diagnoses can be fatal(1). The definition of missed diagnosis varies across studies. In a historical heath records review from 1992-1996, Sullivan looked at how often physicians suspect the diagnosis of AAS after initial encounter. They defined suspected as those who underwent diagnostic imaging to rule out AAS in the emergency department. They excluded those who were transferred from an outside hospital with a diagnosis of AAS, to rule out AAS, if AAS was known to be chronic (>2 weeks old by prior study), or if the patient had no vital signs on emergency department presentation. Emergency physicians did not suspect AAS in 57% of cases(19). This is higher then Spittel's case series (38%) that used lack of diagnosis within the emergency department as their marker of a missed cases/inappropriate initial clinical impression. In another retrospective

chart review from 2012, Chua reviewed charts over a 10-year period (January 1998 to December 2008). Records with a diagnosis of "dissection of aorta" (International Classification of Diseases, Ninth Revision code 441.0) from the hospital discharge database and hospital death register were selected. AAS was defined as missed if diagnostic imaging or cardiothoracic surgeon consults was not elicited while in the emergency department. 68 patients were included in the analysis during the study period, of which 38.2% had a missed diagnosis(21). This high rate of initial misdiagnosis was replicated in a combined retrospective and prospective study of missed AAS conducted by Hansen (39%) between 2000-2004 and a 2004 retrospective chart review by Asouhidou (31%)(22, 23). Hirata in 2015 look specifically at type A aortic dissections from 1982-2011 and found a similar misdiagnosis rate of 37%. Two more recent case series seem to support a reduction in this rate over time. Kurabayashi's 2005-2010 retrospective review reported that the incidence of misdiagnosis was 16%. Zhan reports on misdiagnosis rate based on 361 cases of AAS from 2003-2008, 15% were initially diagnosed with an alternative diagnosis.

Acute coronary syndrome accounts for the majority of misdiagnoses (19%-80%). Common alternative diagnosis include musculoskeletal pain (5-20%), pulmonary embolism (3-20%), pericarditis (12%), gastrointestinal (GI) pain (cholecystitis, pancreatitis, gastroenteritis, mesenteric ischemia) (9-18%), renal colic (6%), stroke (6-20%), pneumonia (14%) small bowel obstruction (6%), and syncope (17%)(19, 21-30). Electrocardiograms with ischemic changes and a positive troponin are associated with delayed diagnosis of AAS(22, 28, 31). This is understandable given that acute coronary syndrome is far more common then AAS. One would expect the delay in diagnosis to be as a result of ischemic changes on ECG, which can be found

in 25% of AAS. However in a study by Hansen most patients with an initial misdiagnosis of acute coronary syndrome had neither electrocardiographic nor cardiac biomarker abnormalities. Highlighting the need not to anchor on acute coronary syndrome in those with chest pain and a lack of objective confirmation. The misdiagnosis of AAS as acute coronary syndrome can lead to potentially fatal inappropriate treatment. In a study by Hansen, all patients with AAS diagnosed with acute coronary syndrome received acetylsalicylic acid and 4% received clopidogrel. Exposure to antithrombotic agents was associated with higher rates of major bleeding (38% Vs. 13%) and a trend toward greater in-hospital mortality (27% Vs. 13%) ($P < 0.02$ for combined end point). Antithrombotic agent administration was also associated with increased hemorrhagic pericardial fluid (50% Vs. 25%), hemorrhagic pleural effusion (15% Vs. 3%), and hemodynamic instability (30% Vs. 13%) ($P < 0.02$)(22). A significant proportion of patients also received fibrinolytics (12%). Inappropriate fibrinolysis in AAS has been associated with severe hemorrhagic complications and a case fatality rate of 71%, a rate similar to the natural history of untreated cases but markedly higher than modern surgical series(32, 33).

Hirata demonstrated that initial misdiagnosis can lead to a significant diagnostic and therapeutic delay (1.0 vs. 6.0 h, $P < 0.0001$)(25). Based on the database of the metropolitan acute aortic dissection network in Bologna, Italy, Rapezzi looked at diagnostic delay as their primary outcome in patients presenting with acute aortic dissection or intramural hematoma. It took >12hours to reach the diagnosis of AAS in 25% of the patients(28). Harris evaluated time to final diagnosis in the International Registry of Acute Aortic Dissection study and reported 25% remaining undiagnosed until>24hrs after initial presentation(31). The International Registry of Acute Aortic Dissection (IRAD) is a consortium of research centers that are

evaluating the current management and outcomes of acute aortic dissection. It was established in 1996, and currently has 30 large referral centers in 11 countries participating in the registry.

Age seems to play an important role in diagnostic delay. It appears to have a bimodal distribution in its effect on delayed diagnosis. In a study by Sullivan younger patients (ages 39-41) underwent multiple evaluations and discharges prior to diagnosis of AAS. This may indicate a lack of suspicion on the part of emergency physicians for AAS in younger patients(19). Then in the study by Rapezzi, patients >70 years of age appeared to have double the risk of late in-hospital diagnosis, with increasing age and anterior chest pain predicting initial misdiagnosis(28). One possibility is a high pretest probability of coronary artery disease may have distracted clinicians from AAS as a diagnostic possibility.

The classic presentation of AAS has been described as acute onset, severe, tearing, central chest pain, radiating to the back. However the weight placed on this classic presentation leads to a lack of suspicion in patients presenting with atypical symptoms. In a study by Chua only 2.9% of patients presented with the typical features of central tearing chest pain of acute onset, whereas 8.8% had their worst-ever pain(21). Although in this study a large proportion of patients were unable to characterize their chest pain, and most of them (66.7%) were in their seventh decade of life and above. This highlights the difficulties of risk stratifying an older population for a potentially life threatening illness based on historical features. Absence of classic features for AAS such as pulse deficit (odds ratio, 35.76; 95% CI 3.70-345.34) and widened mediastinum on chest radiography (odds ratio, 33.16; 95% CI 5.74-191.49) increase the odds of a missed diagnosis. There is a perception that all cases of AAS are hemodynamically

unstable and unwell thus the number of walk-in mode of admissions to the emergency department is greater (29% vs. 10%, *p*=0.042) in missed cases of AAS. In addition, non-classic location of pain (e.g. abdominal) is associated with an increased probability of missed diagnosis. Thirty percent of painful presentations in the review by Sullivan were abdominal pain, most frequently epigastric; only one of these patients was suspected of AAS(19). As early as 1958, Hirst described the frequent and confusing combination of abdominal pain, tenderness, nausea and vomiting in some cases of AAS(15, 19, 22). Other atypical features such as pleural effusion (odds ratio 3.96, 95%CI 1.80 to 8.69) and dyspneic presentation (odds ratio 3.33, 95% CI 1.93 to 8.59) also increase the odds of diagnostic delay(21, 25, 26, 31). AAS should be considered as part of the differential in those presenting with chest/abdominal pain or dyspnea.

An interesting study by Rosman in 1998 hypothesized that the quality of history taking contributes to the accuracy of the diagnosis in those with AAS. Of the 83 patients included, 52 had the correct initial impression of AAS. If 3 questions in regards the characteristics of pain were asked; quality, radiation, sudden onset, 91% of the time a correct initial diagnostic impression was noted(29). Thus performing a full history and physical exam is essential in the early diagnosis of acute aortic syndrome. In those presenting with pain who are unable to provide a reliable history, alternative diagnosis to AAS should not be anchored upon without objective evidence.

Understanding the common reasons for misdiagnosis and the common conditions initially diagnosed in those with AAS will help raise clinical suspicion and prevent early dismissal of this important clinical syndrome. However the issue lies in quantifying the usefulness of historical or

physical findings. It is difficult to decide at what point you can dismiss the diagnosis given that an absence of high-risk features increases your probability of a missed diagnosis but also lowers the likelihood that your patient has AAS. A clinical decision rule may help fill this knowledge gap.

Do we need a clinical decision rule for acute aortic syndrome?

Clinical prediction rules or clinical decision aids have been proposed as a means to standardize clinical assessment for important conditions. They incorporate elements of history and physical exam together with basic investigations to assist clinicians with diagnostic and therapeutic decisions. The advantage of clinical decision aids is that they transition decision making away from expert opinion towards evidence-based assessment. Clinical decision rules focus on reducing variation in practice to improve diagnostic accuracy and efficiency in the hope of reducing patient orientated adverse outcomes and rising health care costs.

Wasson, Feinstein, and Stiell separately describe methodological standards for the derivation of clinical decision rules(4, 34, 35). They focus on six pillars of rule development: 1) Is there a need for the decision rule? 2) Was the rule derived according to methodological standards? 3) Has the rule been prospectively validated and refined? 4) Has the rule been successfully implemented into clinical practice? 5) Would use of the rule be cost-effective? 6) How will the rule be disseminated and implemented?

Therefore the first question that needs to be addressed before attempting to derive a rule, is do we need a clinical decision rule? Combining a recent research agenda paper from the Society of Academic Emergency Medicine on clinical decision rules for diagnostic imaging in the emergency department and Stiell's definition of need, we propose four criteria which must be satisfied in order to justify the need for a clinical decision tool(4, 5): 1) Individuals can be stratified for the disease state in question by standard history, physical examination, and simple laboratory testing; 2) There is substantial variation in clinical practice for the condition with an impact on diagnostic accuracy or efficiency of test usage; 3) There is a perceived need for a clinical decision rule for the disease state in question by clinicians; 4) Unnecessary testing results in increased morbidity or increased cost.

Acute aortic syndrome is a rare clinical condition that is often misdiagnosed. Delayed or missed diagnosis results in a significant increase in mortality. A clinical decision rule could potentially reduce time to diagnosis, missed diagnosis and improve mortality.

References

1. Connection, B.H., *Contemporary Reviews in Cardiovascular Medicine.* Circulation, 2007. **116**: p. 77-84.

2. Clouse, W.D., et al. *Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture*. in *Mayo Clinic Proceedings*. 2004. Elsevier.

3. Fowkes, F., C. Macintyre, and C. Ruckley, *Increasing incidence of aortic aneurysms in England and Wales.* Bmj, 1989. **298**(6665): p. 33-35.

4. Lilienfeld, D., et al., *Epidemiology of aortic aneurysms: I. Mortality trends in the United States, 1951 to 1981.* Arteriosclerosis, Thrombosis, and Vascular Biology, 1987. **7**(6): p. 637-643.

5. Meszaros, I., et al., *Epidemiology and clinicopathology of aortic dissection: a population-based longitudinal study over 27 years.* CHEST Journal, 2000. **117**(5): p. 1271-1278.

6. Hagan, P.G., et al., *The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease.* Jama, 2000. **283**(7): p. 897-903.

7. Eslick, G., M. Jones, and N. Talley, *Non-cardiac chest pain: prevalence, risk factors, impact and consulting—a population-based study.* Alimentary pharmacology & therapeutics, 2003. **17**(9): p. 1115-1124.

8. von Kodolitsch, Y., A.G. Schwartz, and C.A. Nienaber, *Clinical prediction of acute aortic dissection.* Archives of Internal Medicine, 2000. **160**(19): p. 2977-2982.

9. Pape, L., M. Awais, and E. Woznicki, *Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: Seventeen-Year Trends From the International Registry of Acute Aortic Dissection*. Journal of Vascular Surgery, 2016. **63**(2): p. 552-553.

10. Boening, A., et al., *German Registry for Acute Aortic Dissection Type A: Structure, Results, and Future Perspectives.* The Thoracic and cardiovascular surgeon, 2016.

11. Olsson, C., S. Thelin, and E. Stahle, *Thoracic aortic aneurysm and dissection: Increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002.* Journal of Vascular Surgery, 2007. **46**(3): p. 609.

12. HIRST JR, A.E., J. VARNER J JOHNS, and S.W. KIME JR, *Dissecting aneurysm of the aorta: a review of 505 cases.* Medicine, 1958. **37**(3): p. 217.

13. von Kodolitsch, Y., et al., *Intramural hematoma of the aorta predictors of progression to dissection and rupture.* Circulation, 2003. **107**(8): p. 1158-1163.

14. Cho, K.R., et al., *Penetrating atherosclerotic ulcer of the descending thoracic aorta and arch.* The Journal of Thoracic and Cardiovascular Surgery, 2004. **127**(5): p. 1393-1401.

15. Canadian Medical Protection Agency. *Aortic dissections: "Tearing" apart the data*. 2008 [cited 2016 13 Jan]; Available from: https://www.cmpa-acpm.ca/-/aortic-dissections-tearing-apart-the-data.

16. Sullivan, P.R., et al., *Diagnosis of acute thoracic aortic dissection in the emergency department.* The American journal of emergency medicine, 2000. **18**(1): p. 46-50.

17. SPITTELL, P.C., et al. *Clinical features and differential diagnosis of aortic dissection: experience with 236 cases (1980 through 1990)*. in *Mayo Clinic Proceedings*. 1993. Elsevier.

18. Chua, M., et al., *Acute aortic dissection in the ED: risk factors and predictors for missed diagnosis.* The American journal of emergency medicine, 2012. **30**(8): p. 1622-1626.

19. Hansen, M.S., G.J. Nogareda, and S.J. Hutchison, *Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection.* The American journal of cardiology, 2007. **99**(6): p. 852-856.

20. Asouhidou, I. and T. Asteri, *Acute aortic dissection: be aware of misdiagnosis.* BMC research notes, 2009. **2**(1): p. 25.

21. Eagle, K.A., et al., *Spectrum of conditions initially suggesting acute aortic dissection but with negative aortograms.* The American journal of cardiology, 1986. **57**(4): p. 322-326.

22. Hirata, K., et al., *Clinical Predictors for Delayed or Inappropriate Initial Diagnosis of Type A Acute Aortic Dissection in the Emergency Room.* PloS one, 2015. **10**(11): p. e0141929.

23. Kurabayashi, M., et al., *Factors leading to failure to diagnose acute aortic dissection in the emergency room.* Journal of cardiology, 2011. **58**(3): p. 287-293.

24. Li, Y., et al., *Aortic Dissection and Sudden Unexpected Deaths: A Retrospective Study of 31 Forensic Autopsy Cases.* Journal of forensic sciences, 2015. **60**(5): p. 1206-1211.

25. Rapezzi, C., et al., *Usefulness of transesophageal echocardiographic monitoring to improve the outcome of stent-graft treatment of thoracic aortic aneurysms.* The American journal of cardiology, 2001. **87**(3): p. 315-319.

26. Rosman, H.S., et al., *Quality of history taking in patients with aortic dissection.* Chest, 1998. **114**(3): p. 793-795.

27. Zhan, S., et al., *Misdiagnosis of aortic dissection: experience of 361 patients.* The Journal of Clinical Hypertension, 2012. **14**(4): p. 256-260.

28. Harris, K.M., et al., *Correlates of Delayed Recognition and Treatment of Acute Type A Aortic Dissection The International Registry of Acute Aortic Dissection (IRAD).* Circulation, 2011. **124**(18): p. 1911-1918.

29. Tsai, T.T., et al., *Long-term survival in patients presenting with type B acute aortic dissection insights from the international registry of acute aortic dissection.* Circulation, 2006. **114**(21): p. 2226-2231.

30. Kamp, T.J., et al., *Myocardial infarction, aortic dissection, and thrombolytic therapy.* American heart journal, 1994. **128**(6): p. 1234-1237.

31. Feinstein, A.R., *Clinimetrics*. 1987: Yale University Press.

32. Wasson, J.H., et al., *Clinical prediction rules: applications and methodological standards.* New England Journal of Medicine, 1985. **313**(13): p. 793-799.

33. Stiell, I.G. and G.A. Wells, *Methodologic standards for the development of clinical decision rules in emergency medicine.* Annals of emergency medicine, 1999. **33**(4): p. 437-447.

34. Finnerty, N.M., et al., *Clinical decision rules for diagnostic imaging in the emergency department: a research agenda.* Academic Emergency Medicine, 2015. **22**(12): p. 1406-1416.

Chapter Three : Clinical examination for acute aortic syndrome: a systematic review and meta-analysis

Chapter overview

The following is a manuscript prepared for publication based on a systematic review and meta-analysis. The objectives of the manuscript were: 1) Summarize the diagnostic accuracy of history, physical exam and basic investigations for the diagnosis of AAS; 2) Assess the ability of history, physical exam and basic investigations to risk stratify those with a suspicion for AAS.

Dr. R. Ohle is the first author of this paper, having been primarily responsible for data collection, analysis and writing of manuscript. This manuscript was co-authored by Dr. R. Ohle his co-supervisors Dr. J. Perry and Dr. G. Wells in addition to a medical student Mr. H. Khaliq Kareemi. Dr. J. Perry and Dr. G. Wells provided valuable feedback throughout the process. Mr. H. Khaliq Kareemi was the second reviewer of eligible studies and second extractor of data to ensure accuracy.

Clinical examination for acute aortic syndrome: a systematic review and meta-analysis

Robert Ohle[1], Hashim Khaliq Kareemi[2], George Wells[3, 4], Jeffrey J Perry[4]

[1] The Department of emergency medicine, The Ottawa Hospital Research Institute, University of Ottawa

[2]Department of Undergraduate Medicine, University of Ottawa, Canada

[3]Department of Epidemiology and Community Medicine, University of Ottawa

[4] Cardiovascular Research Methods Centre, University of Ottawa Heart Institute

Correspondence to Robert Ohle E-mail:

Word Count: 3080

This manuscript includes five (5) figures and six (6) tables.

Abstract

Introduction

Acute aortic syndrome (AAS) is the clinical syndrome resulting from either acute aortic dissection, intramural hematoma or penetrating atherosclerotic ulcer. It is difficult to diagnose and if missed carries a significant mortality. Our aim was to assess the accuracy of history, physical exam and basic investigations compared to advanced imaging in adults presenting to the emergency department (ED) with a clinical suspicion for AAS.

Methods

We conducted a librarian assisted systematic review. Databases searched: Pubmed, Medline, Embase and the Cochrane database from 1968 to August 2016. No restrictions for language were imposed. Titles and abstracts were reviewed and data extracted by two independent reviewers. Disagreement was resolved by a thrid reviewer and agreement measured by Kappa statisitc. AAS was confirmed by computed tomographic angiography (CTA), magnetic resonance imaging (MRI) or trans esophageal echocardiography (TEE). Prospective and retrospective studies of patients presenting with a clinical suspicion of AAS were included. Case series were excluded. Studies were combined if appropriate as identified by low clinical and statstitical heterogeonity (I^2<30%). Study quality was assessed using the QUADAS-2 tool. Bivariate random effects meta analyses using Revman 5 and SAS 9.3 were performed.

Results

We identified 792 records: 60 were selected for full text review, 5 were included and a further 4 from reference searches. 9 studies with 2400 participants were included (overall QUADAS-2 low risk of bias, Kappa 0.89). Prevalence of AAS ranged from 21.9-76.1% (mean 39.1% SD 17.1%). Mean diagnosis in those without AAS varied between studies with ACS (30.3% SD 30.1%), aneurysm (12.4% SD 9.8%), chest wall pain (18.1% SD 13.3%) and PE (7.9% SD 7.85%) being the most common. The clinical findings most suggestive of AAS were: 1) neurological deficit (n=3, specificity 95%, LR+ 4.4 95%CI 3.3-5.7, I^2 0%), 2) hypotension (n=4, specificity 95%, LR+ 2.9 95%CI 1.8-4.6, I^2 42%) and 3) pulse deficit (n=3, specificity 91%, LR+ 2.5 95%CI 1.5-4.1, I^2 0%). The most useful for identifying patients less likely to have AAS were an absence of a widened mediastinum (n=4, sensitivity 76%-95%, LR- 0.14-0.60, I^2 93%) and an AHA aortic dissection detection risk score <1 (n=1 sensitivity 91%, LR- 0.22 95% CI 0.15–0.33).

Conclusions

Suspicion for AAS should be raised with hypotension, pulse or neurological deficit in the appropriate clinical setting. Conversely the absence of a widened mediastinum and a low AHA ADD score decreases suspicion. Clinical exam alone cannot rule out acute aortic syndrome but it can help risk stratify for further testing.

Introduction

Acute aortic syndrome (AAS) is a life threatening emergency, accounting for 1/2000 presentations of acute chest/back pain(1). It is a clinical spectrum of diagnoses including aortic dissection, intramural hematoma and penetrating atherosclerotic ulcer. If untreated, mortality increases by 1-2% every hour from initial presentation and may reach a high of 40% in the acute period and 70% in 2 weeks(2, 3). We fail to diagnose AAS in 38% of cases and in those we correctly identify 25% remain undiagnosed for greater than 24hrs(3-8).

Although 90% of AAS present with pain, it is difficult to identify these cases when taken in context of the millions of other patients also presenting with acute pain from an alternative cause(3). The varying location of the dissection and the involvement of branch vessels give rise to a myriad of associated symptoms. Given the rarity of AAS it is difficult to initiate your clinical suspicion, and secondly when suspicion is raised it is difficult to decide who needs advanced imaging.

Our objective was to conduct a systematic review and meta-analysis to assess the diagnostic accuracy in acute aortic syndrome of history, physical and plain radiographs compared to advanced imaging in adult patients presenting with acute pain to the emergency department with a clinical suspicion of AAS.

Methods

Data sources and search strategy

An electronic search was performed by a trained librarian on PubMed, EMBASE and Cochrane library databases (January 1968 to 4 August 2016). The search strategy is presented as a flow diagram in Figure 1. A combination of keywords and Medical Subject Headings (MeSH) terms were used, including; Aneurysm, dissecting, aortic dissection, medical history, Bayes theorem, sensitivity, specificity, reproducibility of results, physical examination, clinical exam, and diagnostic tests (Table 1.). (9) A citation search of included articles was undertaken using Google Scholar. The references of included studies were also hand searched for relevant papers. No language or age restrictions were placed on the searches. Where data were not clear from the published study materials, authors were contacted for clarification.

Study selection

Inclusion: We included studies that met the following criteria: (1) Adult patients presenting to an emergency department with suspected acute aortic dissection (2) Test - history, physical examination, basic investigations (chest x-ray, white blood cell count or electrocardiogram) or decision aid combining those elements described in adequate detail to generate 2x2 table (3) Reference standard – computed tomography (CT), magnetic resonance imaging (MRI) or trans esophageal echocardiography (TEE). (4) Outcome - diagnosis of AAS on advanced imaging.

Exclusion: The focus of this review was initial examination of the undifferentiated patient with potential acute aortic syndrome. Studies enrolling patients with a confirmed diagnosis of AAS were excluded, as accuracy and prevalence of clinical factors in this population will be overestimated. We did not exclude patients who had been transferred from the emergency department to a decision unit or coronary care unit (CCU) for work up of suspected AAS. We included only articles published in peer-reviewed literature, and did not seek unpublished data. Risk of bias was assessed using the QUADAS-2 (quality assessment of studies of diagnostic accuracy included in systematic reviews) tool as per Cochrane collaborative recommendations. Studies with a high risk of bias were excluded.

Two reviewers (RO and HK) completed the review process. The inclusion criteria were defined *a priori*. RO and HK independently reviewed titles and abstracts. After which each reviewers included studies were compared and measure of agreement was calculated using Kappa statistic. Agreed upon full text articles were retrieved and reviewed independently by RO and HK for inclusion. Each reviewer extracted data from included studies independently. .

Disagreements in included studies or data extraction were resolved through discussion and where agreement could not be reached through arbitration by a third reviewer (JP).

Quality assessment

Quality assessments of included papers were assessed using QUADAS-2 tool and the risk of bias table in Review Manager 5 software from the Cochrane collaboration (10, 11). A summary of the quality of included papers is presented in Figure 6. The quality assessment was independently performed by two investigators (RO and HK) and any disagreements were resolved by discussion.

Diagnostic accuracy – data extraction and statistical analysis

For the diagnostic accuracy (discrimination performance) of clinical exam, data were extracted and a 2 × 2 table constructed for diagnosis of AAS compared to a reference standard. Data extraction was carried out independently by two reviewers (RO and HK) using a standardized data collection tool and the data compared.

A bivariate random-effects model was used to compute summary diagnostic sensitivity and specificity and likelihood ratios, which allowed for heterogeneity beyond chance as a result of clinical and methodological differences between the studies.

Heterogeneity was assessed when 5 or more studies were included in analysis. Study heterogeneity is displayed through both confidence intervals and I^2. The I^2 statistic describes the percentage of total variation across studies that are due to heterogeneity rather than

chance. The broad quantification of heterogeneity using the I^2 statistic is low if <25%, moderate <50% and high if >75%(12). In addition heterogeneity was visually assessed with forest plots. Where heterogeneity was found, causes were explored by subgroup analysis and comparing nested models using meta-regression analysis. Studies were not pooled if significant clinical or statistical (I^2>50%) heterogeneity. Analyses were carried out using SAS software using the "metadas" command, in addition to REVMAN 5 and Meta-Disc (13, 14).

Results are presented as sensitivity and specificity as well as positive and negative likelihood ratios. When only 2 studies were found for a specific index test results are reported as ranges. Clinical predictors of AAS were defined as weak (LR+ 1-1.5, LR- 0.6-1), moderate (LR+ 1.5-2, LR- 0.2-0.5) or strong (LR+ >2, LR- <0.2)(15).

Results

The literature search was concluded in August 2016, yielding 792 titles and abstracts for screening. See table one for search strategy. The full text of 60 articles met the eligibility criteria, and these articles were retrieved (Figure 1). The Kappa value for included studies was 0.89(95%CI 0.82-0.95). Detailed characteristics of all included studies are presented in Table 7. For each variable evaluated, data were extracted from 1 to 7 studies; the total number of studies providing data for each variable, and the total number of patients enrolled in those studies are presented in Tables 2-6. Risk of bias for each included study is shown in Figure 6. All studies enrolled consecutive patients presenting to the emergency department with pain and a clinical suspicion for acute aortic syndrome.

Characteristics of included studies

Results of the quality assessment are shown in Figure 6. The overall quality of the included studies is considered acceptable for the majority of the quality items. The lowest rated item was the adequate description of the clinical features to allow reproducibility.

The rate of AAS ranged from 21.9-76.1% (mean 39.1% SD 17.1%). The majority of studies were prospective in design(n=6) with participants recruited from the emergency department(n=4)(Table 8).

Accuracy of clinical examination in diagnosing acute aortic syndrome

Risk factors

History of hypertension was a weak predictor of AAS (n=7, specificity 41.3%, LR+ 1.14 95% CI 1.008-1.297, $I^2$47%, sensitivity 68%, LR-0.749 95%CI 0.593-0.946, $I^2$84%). A history of Diabetes reduced the probability of AAS (n=3, specificity 87%, LR+ 0.32 95%CI 0.14-0.70, $I^2$48%). Connective tissue disease was a poor predictor (n=3, sensitivity 5%, LR- 1.11 95%CI 0.67-1.83, I^2 0% specificity 84-97%, LR+ 0.09-16.54, I^2 84%). History of ischemic heart disease did not predict AAS (n=1, Sensitivity 68.1%, LR- 0.39 95%CI 0.18-0.88, specificity 12-16%, LR+ 1.08-1.29)(Table 2, Figure 2).

History

Syncope was a weak predictor of AAS (n=4, Specificity 89%, LR+ 1.35 95%CI 1.04-1.76, I^2 35%)
There was significant statistical heterogeneity in included studies reporting of pain characteristics which prevented pooling of estimates. Severe pain (n=3, Sensitivity 46%-86%, LR- 0.31-0.68, specificity 45-80%, LR+ 1.47-2.29, I^2=95%), acute onset (n=4, sensitivity 34-88%,

LR- 0.30-0.98, specificity 22-83% LR+1.01-2.60, $I^2$95%) and back pain (n=5, sensitivity 32-56%, LR- 0.64-0.99, specificity 46-98%, LR+ 1.04-23.14) are associated with AAS but none had consistently reported positive or negative likelihood ratio to help differentiate AAS from alternative pathology. Chest pain, abdominal pain, tearing pain and migrating pain were not strong predictors of AAS (Figure 3, Table 3).

Physical examination

Findings suggestive of acute aortic syndrome were focal (motor and/or sensory) neurological deficits (n=3, specificity 95%, LR+ 4.34 95%CI 3.33-5.65, I^2 0%), pulse deficit (n=3, specificity 91%, LR+ 2.48 95%CI 1.51-4.09, I^2 0%) and hypotension (BP<90mmHg/signs of shock) (n=4 specificity 95%, LR+ 2.92 95%CI 1.84-4.62, I^2 42%). For identifying patients less likely to have AAS, no risk factor when absent conferred a negative likelihood ratio of 0.5 or lower. Hypertension on presentation (BP>150mmHg), murmur of aortic insufficiency and pulmonary edema were not strong predictors of acute aortic syndrome. No studies reporting the diagnostic accuracy of inter-arm blood pressure differential were found. Von Kodolitsch and Nazerian both indicated a high specificity (90%, 99%) and a poor sensitivity 23% 38% for the combination of pulse differential and/or bilateral BP differential of >20mmHg(1, 16). Three studies (Enia, Armstrong, Eagle) reporting on pulse differential alone had similar diagnostic accuracy (specificity 82-95%)(6, 17, 18)(Figure 4, Table 4).

Investigations

Patients with a normal mediastinal width were less likely to have acute aortic syndrome (n=5 sensitivity 76%-95% LR- 0.136-0.600 I^2 93%) heterogeneity prevented pooling of estimates.

Elevated white blood cell count (>15g/dl) reduced likelihood of AAS (n=1 specificity 78% LR+ 0.37 95%CI 0.20-0.68). Ischemic changes on EKG were not helpful (Figure 5,Table 5).

Clinical prediction rules

Two clinical prediction rules were found, the American heart association aortic dissection detection risk score (AHA ADD risk score) and Von Kodolitsch 3 variable rule. This rule included aortic pain (immediate onset tearing or ripping pain), mediastinal /aortic widening on chest x-ray, or pulse /blood pressure differential. The absence of all three variables reduced probability of AAS (n=1, sensitivity 96%, LR- 0.07 95%CI 0.03-0.18). The presence of all three variables increased the probability of AAS (n=1, Specificity 100%, LR+ 65.08 95%CI 4.03-1050). No validation studies of the rule were found (Figure 6, Table 6).

The second rule was the AHA ADD risk score (Figure 6, Table 6). This was derived by expert consensus. The AHA ADD risk score has been prospectively validated in one high quality study. A score of 0 yielded a sensitivity of 91.1% (87.2–94.1%), specificity 39.8% (36.8–42.9%) LR- 0.22 (0.15–0.33) LR+ 1.51 (1.42–1.61) and score of >1 sensitivity 32.7% (27.3–38.4%) specificity 85.7% (83.5–87.8%), LR-0.79 (0.72–0.85) LR+ 2.29 (1.83–2.86). Analysis of each variable in the rule found that only severe pain, BP/pulse differential, neurological deficit, hypotension/shock state and constant pain significantly contributed to the risk model.

Heterogeneity

Clinical heterogeneity: Alternative diagnosis was largely consistent between studies. Aneurysm without dissection, chest pain unspecified, acute coronary syndrome, pulmonary embolism, pericardial disease, mediastinal mass, syncope with no clear etiology were the most common diagnoses (Table 7.)

Statistical heterogeneity: Historical features of pain demonstrated significant heterogeneity which prevented combining studies. Due to the low number of studies included we were unable to perform any meaningful analysis of the cause of this heterogeneity.

Discussion

Principal findings

This systematic review and meta-analysis illustrates history and physical exam can be used to help increase the probability of AAS but in isolation cannot reduce the probability. Combining specific exam features can increase their ability to rule out AAS, but no rule has been prospectively validated with sufficient diagnostic accuracy to allow use in clinical practice.

Retrospective study of signs and symptoms is difficult

Diagnostic accuracy studies of history and physical exam are difficult. Definition of historical features such as characteristics of pain tends to vary between physicians and centers. This is reflected in the marked heterogeneity seen in our results of history or physical exam features being investigated. In addition the accuracy of classic pain features were likely at risk for inclusion bias, with high-risk features raising clinical suspicion and therefore prompting advanced imaging and thus inclusion in the studies. We can conclude from our results that

classically reported high risk pain features such as tearing/ripping pain, pain radiating to the back, acute onset pain are likely associated with AAS but it is difficult to define their diagnostic accuracy therefore cannot be used in isolation to risk stratify for AAS.

History and physical exam features are specific but not sensitive

Chua et al. performed a 10-year retrospective cohort study on cases of AAS that were initially misdiagnosed. They found absence of pulse differential increased the odds of a missed diagnosis of AAS(4). Pulse differential, neurological deficits and hypotension all have excellent specificity. However, the prevalence of each finding is rare, 31%, 25% and 8% respectively(3). Therefore although the presence of these findings helps increase clinical suspicion for AAS, the absence of these clinical findings cannot exclude AAS.

Combining history and exam features increases diagnostic accuracy

Overall elements of history and physical exam combined in the AHA ADD risk score performed better than in isolation. However 5.9% of patients classified as low risk (AHA ADD risk score 0) were diagnosed with AAS. Therefore it cannot be used in isolation to rule out AAS and further testing is required to reduce our posttest probability below an acceptable level. Nazerian investigated the addition of no widened mediastinum on chest x-ray to an ADD risk score of 0 but this only reduced the prevalence of AAS to 5.8%. Therefore absence of a widened mediastinum in a low risk group does not rule out AAS. Although we found absence of widened mediastinum showed some ability to reduce odds of AAS, the negative likelihood ratio ranged from 0.3-0.6 crossing the threshold of 0.5 indicating it may not be useful. The marked heterogeneity seen in included studies could partially be explained by varying methods of chest x-ray image acquisition. Studies did not report the number of portable Vs. non-portable x-rays.

Portable x-rays artificially increase the size of mediastinum width thus are unreliable for its assessment(19).

Gorla and Nazerian retrospectively studied the addition of D-dimer (Gorla - *Innovance D-Dimer, with a BCS coagulation analyzer; Dade Behring, Marburg, Germany*. Nazerian- ***Hemosil D-dimer HS, Bedford or STA LIATEST® D-DI, DiagnosticaStago, Mannheim***) to the AHA ADD risk score. In a low risk population, defined by an AHA ADD score of 0 (prevalence of AAS; Nazerian 5.9%, Gorla 0.5%), a negative D-dimer (< 500ng/ml) ruled out AAS with no missed cases.
The issue with applying this in clinical practice lies in the poor specificity of D-dimer and a lack of prospective validation of its use in decision-making. The varied prevalence of AAS in included studies indicates we do not have set reproducible criteria for defining who is at risk for AAS. Ease of access to advanced imaging appears to be the major driving force in deciding who is investigated for AAS. This is illustrated by the reduction in prevalence of AAS in included studies (78% in 1986 to 28% in 2014) as access to CT has improved(20). If we were to use a test that was even more readily available to rule out AAS such as D-dimer we can assume that use would be greater than that of CT. As with pulmonary embolism the crux lies in the question, is my patient at no risk or low risk? Without a clear answer to this question as in pulmonary embolism D-dimer will be applied to a lower and lower risk population thus increasing imaging without a proven reduction in miss rate or time to diagnosis.

The counter argument is we use our clinical acumen on a daily bases to decide who requires further testing. There are no set criteria for deciding who to start investigating for deep vein thrombosis, we use clinical judgment to say who is no or some risk and then apply Wells criteria

+/- D-dimer to investigate. However a diagnostic algorithm combining D-dimer and clinical acumen for AAS has not been prospectively validated nor its impact assessed.

Limitations

The strength of included studies is that all patients underwent the reference standard to confirm the diagnosis of AAS. The prevalence of AAS varied across studies reflecting a variation in practice of imaging for AAS but also the increased access to imaging over time. Prevalence decreased from 76% in 1986 to 28% in 2014.

We included only studies of high methodological quality, excluding those that artificially inflate diagnostic accuracy (case control studies, case series). The low number of included studies reduced our ability to investigate sources of heterogeneity and publication bias.

We performed an extensive search of the literature using a librarian assisted search strategy of multiple databases. However five of the final studies were found on reference search of included studies. We performed a second broader search strategy which did not find any additional papers therefore we are confident that no high quality relevant papers were missed. We did not search conference proceedings or grey literature, as the material is not peer reviewed. We did not perform funnel plots because we did not have sufficient included studies (i.e. >10 per variable analyzed) to generate meaningful results.

Description of how the index tests (historical feature, examination finding or basic investigation) were performed was lacking in most studies. This lack of clarity could account for some of the heterogeneity found in pain characteristics.

Future research

Future research should focus on multi center prospectively collected data on those with a suspicion for AAS. Clear definitions of clinical and exam features need to be decided upon. Accuracy of history and physical exam needs to be confirmed in a broader population including those who do not undergoing advanced imaging. This will allow application to a broader population including cases that are not imaged initially, resulting in diagnostic delay or failure to diagnose.

The largest challenge lies in how we define suspicion for AAS. As we have seen with pulmonary embolism a lack of clarity in regards whom to suspect AAS can lead to applying criteria to a lower risk population then intended. Previous studies have used the threshold of imaging to define suspicion, however in order to help decrease our miss rate we need to expand future study populations in which we have a suspicion for AAS to those who ultimately do not undergo advanced imaging.

Conclusion

In the appropriate clinical setting, suspicion for AAS should be raised with hypotension, pulse deficit or neurological deficit. Conversely the absence of a widened mediastinum and a low AHA ADD score decreases likelihood of AAS. Clinical exam alone cannot rule out AAS but it can help risk stratify for further testing.

References

1. Von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. Archives of Internal Medicine. 2000;160(19):2977-82.

2. HIRST JR AE, VARNER J JOHNS J, KIME JR SW. Dissecting aneurysm of the aorta: a review of 505 cases. Medicine. 1958;37(3):217.

3. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. Jama. 2000;283(7):897-903.

4. Chua M, Ibrahim I, Neo X, Sorokin V, Shen L, Ooi SB. Acute aortic dissection in the ED: risk factors and predictors for missed diagnosis. The American journal of emergency medicine. 2012;30(8):1622-6.

5. Asouhidou I, Asteri T. Acute aortic dissection: be aware of misdiagnosis. BMC research notes. 2009;2(1):25.

6. Eagle KA, Quertermous T, Kritzer GA, Newell JB, Dinsmore R, Feldman L, et al. Spectrum of conditions initially suggesting acute aortic dissection but with negative aortograms. The American journal of cardiology. 1986;57(4):322-6.

7. Hansen MS, Nogareda GJ, Hutchison SJ. Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection. The American journal of cardiology. 2007;99(6):852-6.

8. Hirata K, Wake M, Takahashi T, Nakazato J, Yagi N, Miyagi T, et al. Clinical Predictors for Delayed or Inappropriate Initial Diagnosis of Type A Acute Aortic Dissection in the Emergency Room. PloS one. 2015;10(11):e0141929.

9. Wilczynski NL, Haynes RB. EMBASE search strategies for identifying methodologically sound diagnostic studies for use by clinicians and researchers. BMC Med. 2005;3:7.

10. Review Manager (RevMan). 5 ed. Copenhagen,The Nordic Cochrane Centre: The Cochrane Collaboration; 2008.

11. P RA Whiting RJ, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3(25).

12. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. Cochrane handbook for systematic reviews of diagnostic test accuracy. Version 09 0 London: The Cochrane Collaboration. 2010.

13. Takwoingi Y GB, Deeks JJ. Metadas: an SAS macro for meta-analysis of diagnostic accuracy studies. In: Deeks JJ, Glasziou P, Irwig L, eds Methods for evaluating medical tests symposium; University of Birmingham2008.

14. Zamora J AV, Muriel A, Khan KS, Coomarasamy A. Meta-DiSc: A software for meta-analysis of test accuracy data. . BMC Med Res Methodol (2006) 6(31).

15. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. Bmj. 2004;329(7458):168-9.

16. Nazerian P, Giachino F, Vanni S, Veglio MG, Castelli M, Lison D, et al. Diagnostic performance of the aortic dissection detection risk score in patients with suspected acute aortic dissection. European Heart Journal: Acute Cardiovascular Care. 2014;3(4):373-81.

17. Armstrong WF, Bach DS, Carey LM, Froehlich J, Lowell M, Kazerooni EA. Clinical and echocardiographic findings in patients with suspected acute aortic dissection. American heart journal. 1998;136(6):1051-60.

18. Enia F, Ledda G, Lo Mauro R, Matassa C, Raspanti G, Stabile A. Utility of echocardiography in the diagnosis of aortic dissection involving the ascending aorta. Chest. 1989;95(1):124-9.

19. Gleeson C, Spedding R, Harding L, Caplan M. The mediastinum—Is it wide? Emergency Medicine Journal. 2001;18(3):183-5.

20. (CIHI) CIfHI. MIT (Medical Imaging Technology) 2012 Data Release - Static Figures & Tables.

Figures

Figure 1. Flow diagram for selection of included studies.

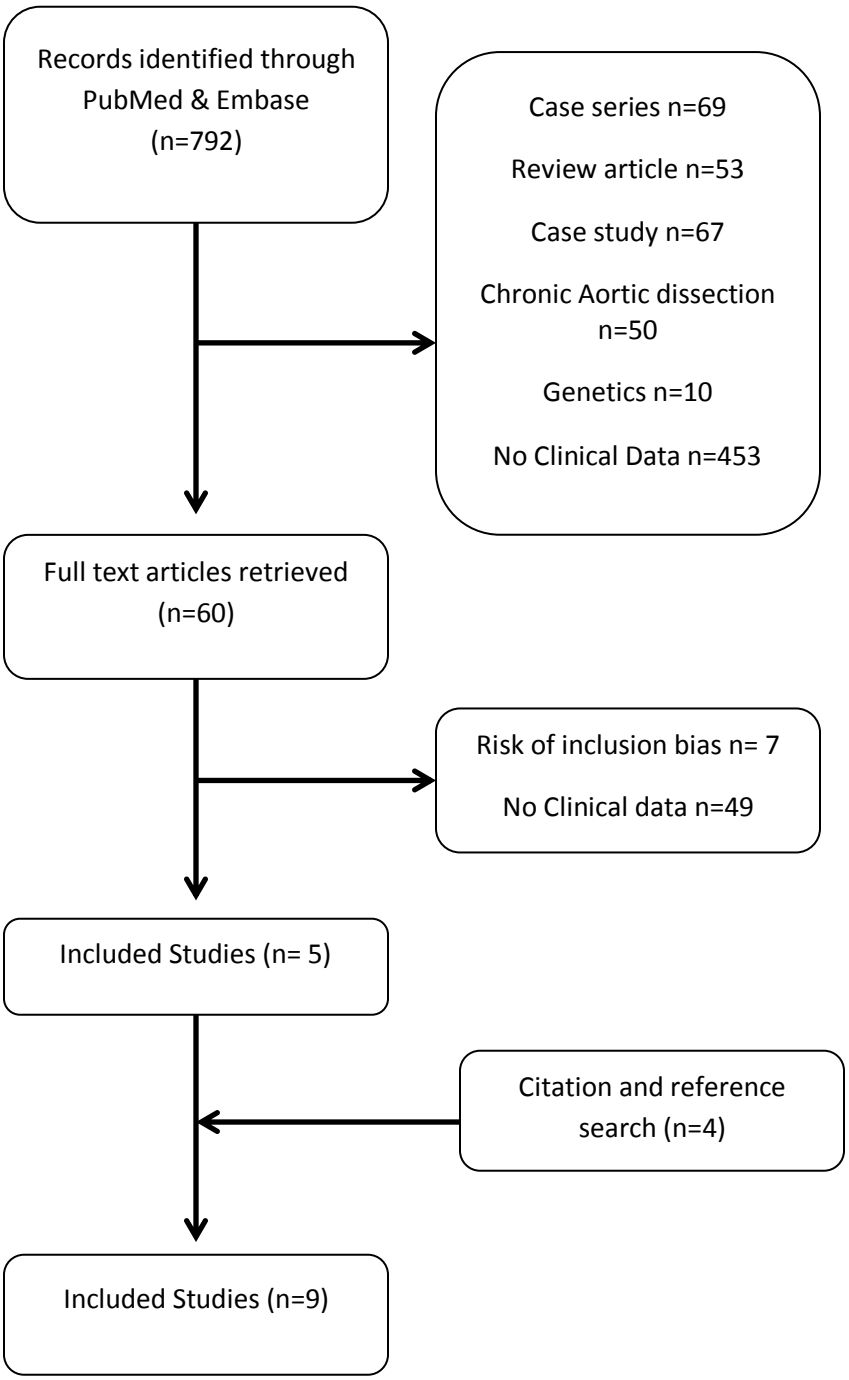
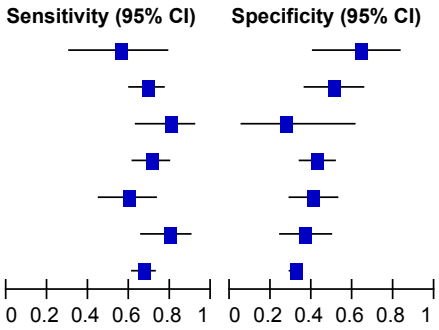


Figure 2. Forest plot of sensitivity and specificity of risk factors for diagnosis of AAS

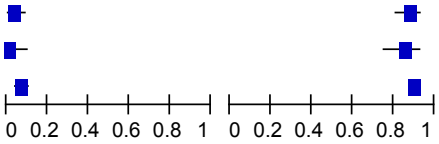
History of Hypertension

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chan 1991	10	8	8	14	0.56 [0.31, 0.78]	0.64 [0.41, 0.83]
Eagle 1986	86	25	39	26	0.69 [0.60, 0.77]	0.51 [0.37, 0.65]
Enia 1989	28	8	7	3	0.80 [0.63, 0.92]	0.27 [0.06, 0.61]
Fan 2010	76	78	31	58	0.71 [0.61, 0.79]	0.43 [0.34, 0.51]
Giachino 2013	31	44	21	30	0.60 [0.45, 0.73]	0.41 [0.29, 0.53]
Keren 1996	39	40	10	23	0.80 [0.66, 0.90]	0.37 [0.25, 0.50]
Nazerian 2014	195	703	96	334	0.67 [0.61, 0.72]	0.32 [0.29, 0.35]



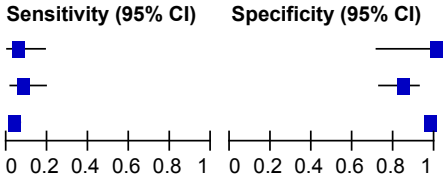
History of Diabetes

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fan 2010	4	17	103	119	0.04 [0.01, 0.09]	0.88 [0.81, 0.93]
Giachino 2013	1	11	51	63	0.02 [0.00, 0.10]	0.85 [0.75, 0.92]
Nazerian 2014	21	108	270	929	0.07 [0.05, 0.11]	0.90 [0.88, 0.91]



History of Connective tissue disorder

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Enia 1989	2	0	33	11	0.06 [0.01, 0.19]	1.00 [0.72, 1.00]
Keren 1996	4	10	45	53	0.08 [0.02, 0.20]	0.84 [0.73, 0.92]
Nazerian 2014	12	27	279	1010	0.04 [0.02, 0.07]	0.97 [0.96, 0.98]



History of Ischemic heart disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Keren 1996	6	20	43	43	0.12 [0.05, 0.25]	0.68 [0.55, 0.79]

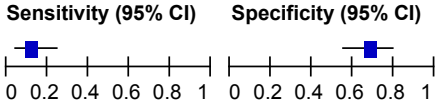


Figure 3. Forest plot of sensitivity and specificity of pain location for diagnosis of AAS

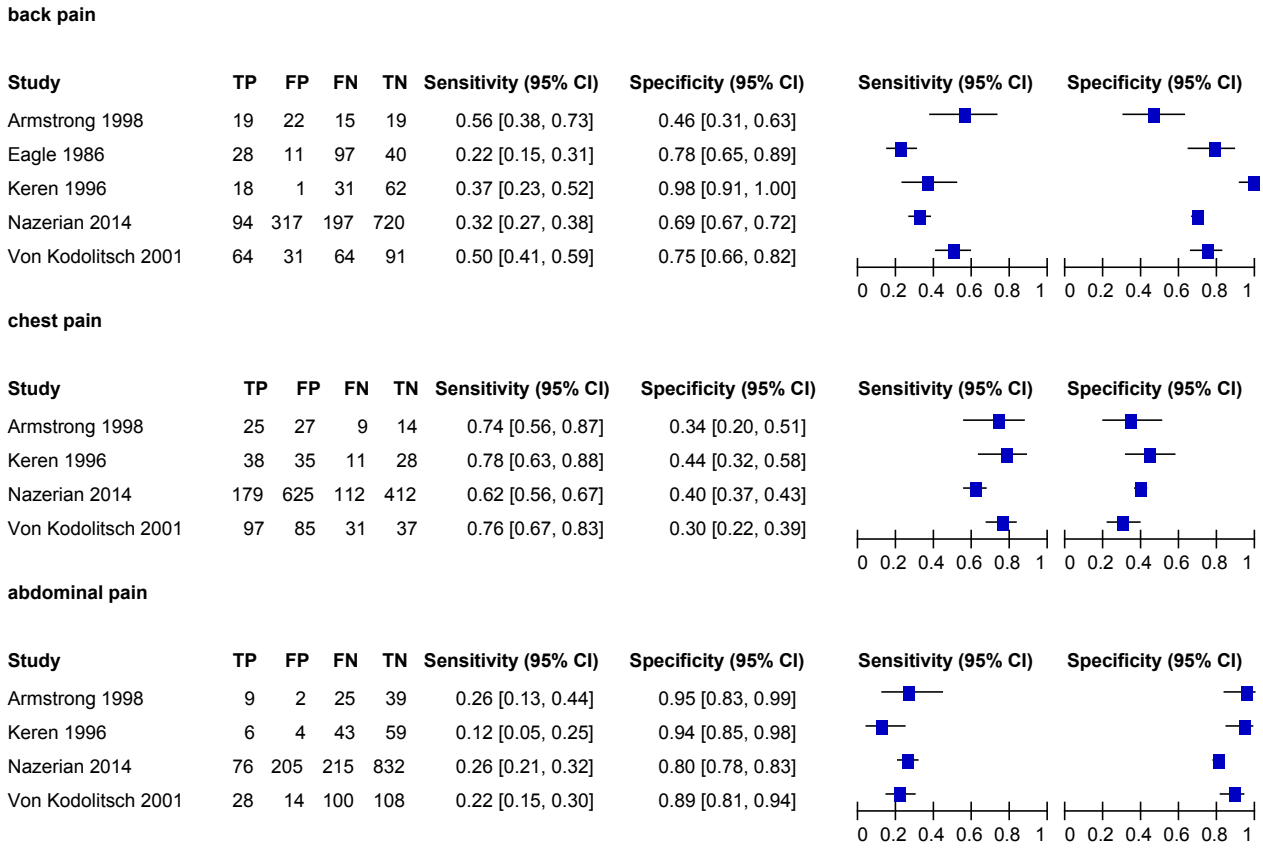


Figure 4. Forest plot of sensitivity and specificity of pain characteristics for diagnosis of AAS

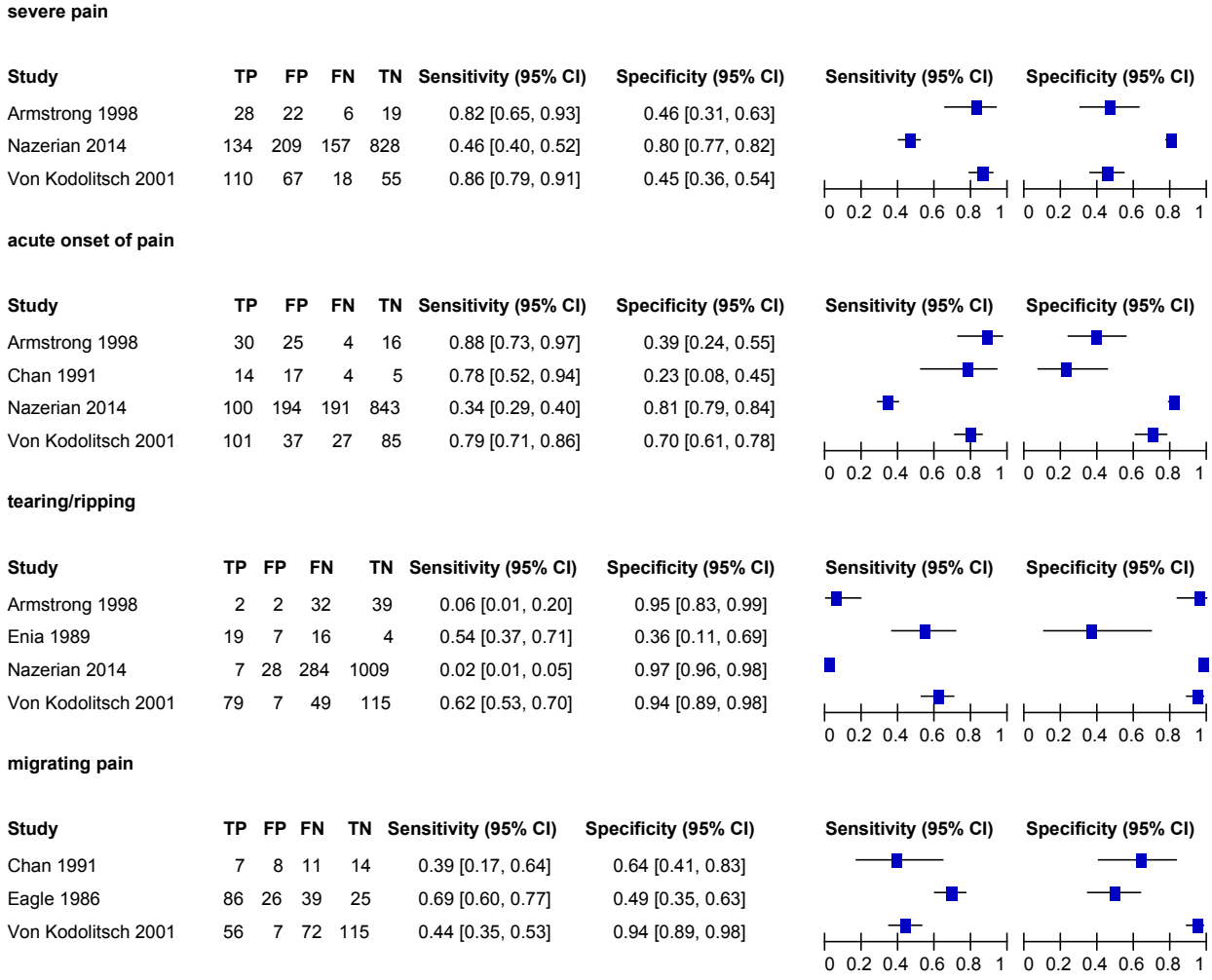


Figure 5. Forest plot of sensitivity and specificity of investigations for diagnosis of AAS

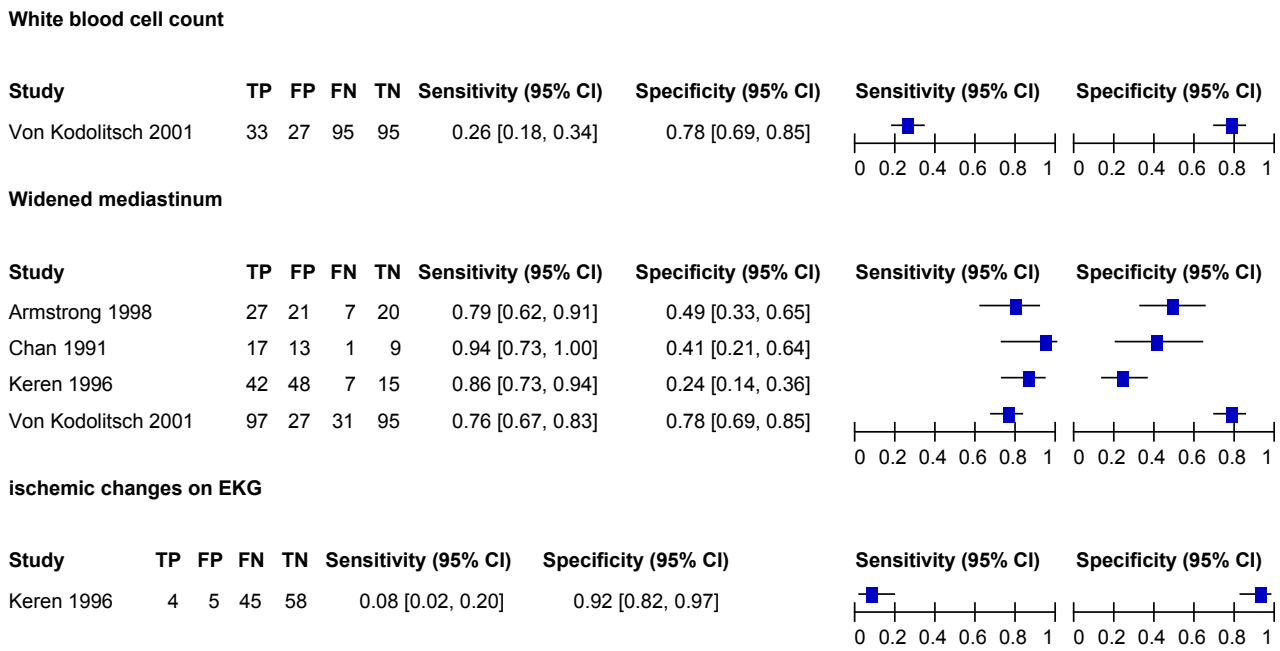
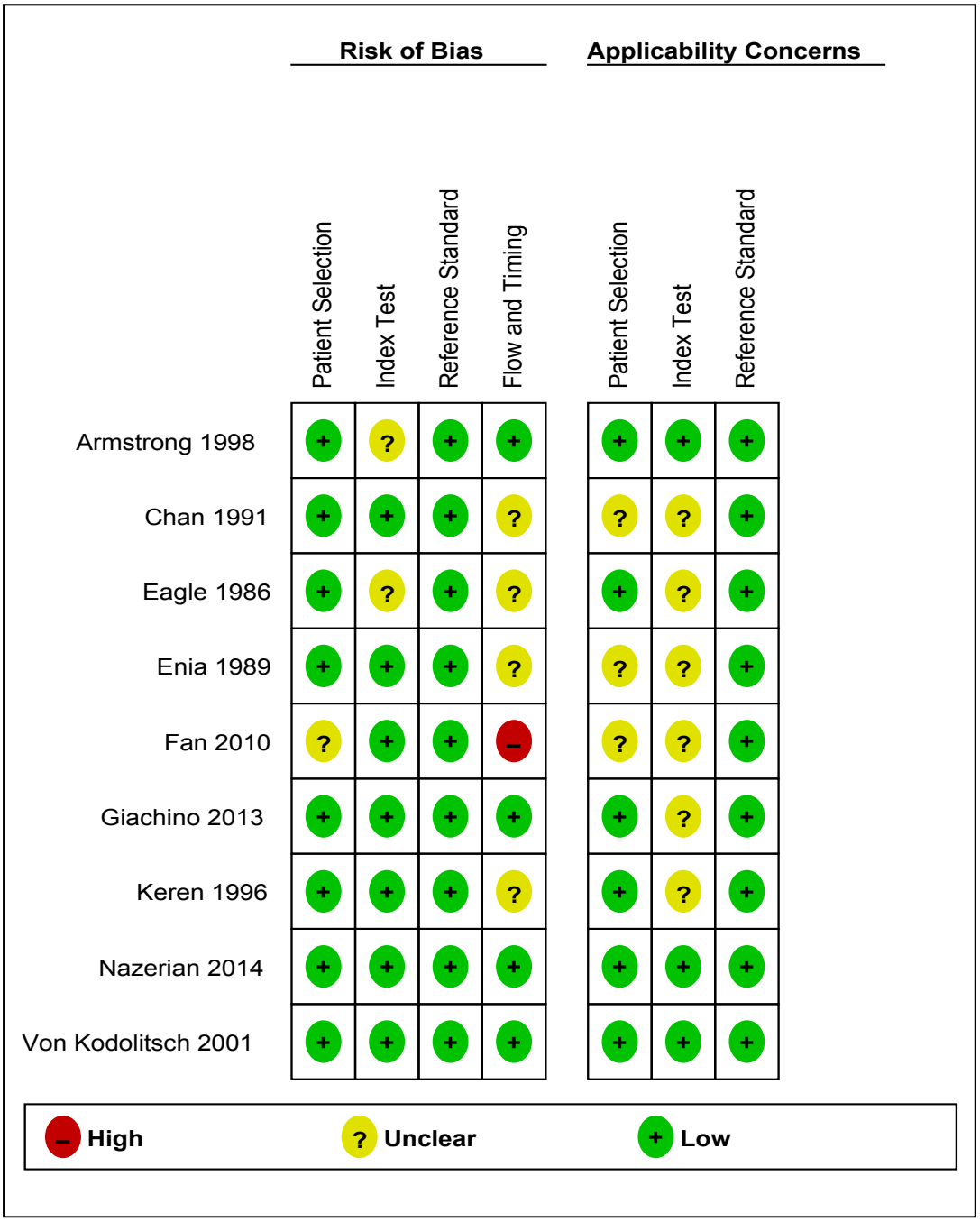


Figure 6. Risk of bias and applicability of concerns summary


Risk of Bias
Applicability Concerns
Patient Selection
Index Test
Reference Standard
Flow and Timing
Patient Selection
Index Test
Reference Standard
Armstrong 1998
Chan 1991
Eagle 1986
Enia 1989
Fan 2010
Giachino 2013
Keren 1996
Nazerian 2014
Von Kodolitsch 2001
High
Unclear
Low

Tables

Table 1. Search strategy for MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:	
1	Aneurysm, Dissecting/ or dissecting.tw.
2	aortic aneurysm/ or aortic aneurysm, thoracic/
3	1 and 2
4	aortic dissection.tw.
5	dissecting aorta.tw.
6	**3 or 4 or 5**
7	medical history taking/ or history taking.tw.
8	Observer Variation/
9	Bayes Theorem/ or (Bayes or Bayesian).tw.
10	exp "sensitivity and specificity"/
11	"Reproducibility of Results"/
12	physical examination/ or physical exam$.tw.
13	clinical exam$.tw.
14	Diagnostic Tests, Routine/
15	diagnostic test$.tw.
16	**or/7-15**
17	**6 and 16**
18	**limit 17 to yr="1966 -Current"**

Table 2. Performance of risk factors in the diagnosis of acute aortic syndrome

Test	No.		% (95%CI)		LR+(95%CI)	I^2, %	LR- (95%CI)	I^2, %
	Studies	Patients	Sensitivity	Specificity				
Hypertension[24, 43, 45, 48-51]	7	2071	68(64-73)	41(34-49)	1.14 (1.01-1.30)	46	0.75 (0.60 -0.95)	85
Diabetes[43, 49, 51]	3	1697	6(4-9)	87 (83-90)	0.32 (0.14-0.70)	48	1.07(0.72-1.57)	0
Connective tissue disease[43, 45, 50]	3	1486	5(3-8) 96(58-100) 84(73-91) 97(96-98)		0.09(0.02-0.36) 0.51(0.17-1.54) 1.58(0.81-3.09)	84	1.11(0.68-1.83)	0
Ischemic heart disease[50]	1	112	12(5-25)	68(55-79)	0.39(0.18-0.88)	-	1.29(1.14-1.45)	-

Table 3. Performance of historical features in the diagnosis of acute aortic syndrome

Test		No.		% (95%CI)		LR+(95%CI)	I^2, %	LR- (95%CI)	I^2, %
		Studies	Patients	Sensitivity	Specificity				
Characteristics of P	Severe[11, 43, 44]	3	1653	82(66-92) 46(40-52) 86(78-91)	46(32-62) 80(77-82) 45(37-54)	1.54(1.11-2.12) 2.29(1.92-2.72) 1.57(1.31-1.87)	86	0.38(0.28-0.53) 0.68(0.57-0.80) 0.31(0.26-0.37)	90
	Tearing/Ripping[11, 43, 48]	4	1699	6(2-21) 54(38-70) 2(1-5) 62(53-70)	95(83-99) 36(14-66) 97(96-98) 94(89-97)	1.21(0.18-8.12) 0.85(0.50-1.46) 0.89(0.39-2.02) 10.76(5.17-22.37)	89	0.99(0.15-6.66) 1.26(0.73-2.16) 1.00(0.44-2.27) 0.41(0.20-0.84)	34
	Migrating[11, 24, 48]	3	466	39(20-62) 69(60-76) 44(35-52)	64(42-81) 49(36-63) 94(86-97)	1.07(0.48-2.38) 1.35(1.01-1.81) 7.63(3.62-16.07)	84	0.96(0.43-2.14) 0.64(0.47-0.85) 0.60(0.28-1.26)	0
	Acute onset[11, 43, 44, 48]	4	1693	88(72-95) 79(54-91) 34(29-40) 79(71-85)	39(25-54) 23(10-44) 81(79-84) 70(61-77)	1.45(1.10-1.90) 1.01(0.72-1.41) 1.84(1.50-2.25) 2.6(1.96-3.45)	92	0.30(0.23-0.40 0.98(0.70-1.37) 0.81(0.66-0.99) 0.30(0.23-0.40)	95
Location of pain	Abdominal[11, 43, 44, 50]	4	1765	27(14-44) 12(6-25) 26(21-32) 22(16-30)	95(83-99) 94(84-98) 80(78-83) 89(82-93)	5.43(1.26-23.44) 1.93(0.58-6.46) 1.32(1.05-1.66) 1.91(1.06-3.45)	46	0.92(0.75-1.13)	0
	Chest[11, 43, 44, 50]	4	1765	74(57-86) 78(64-87) 62(56-67) 76(68-82)	34(21-50) 44(33-57) 40(37-43) 30(23-39)	1.12(0.83-1.51) 1.40(1.07-1.82) 1.02(0.92-1.13) 1.09(0.93-1.27)	56	0.78(58-1.05) 0.51(39-0.66) 0.97(87-1.07) 0.80(69-0.93)	87
	Back[11, 24, 43, 44, 50]	5	1941	56(39-71) 22(16-31) 37(25-51) 32(27-38) 50(41-59)	46(32-62) 78(65-88) 98(90-1) 69(67-72) 75(66-82)	1.04(0.69-1.57) 1.04(0.56-1.92) 23.14(3.20-167.41) 1.06(0.87-1.28) 1.97(1.39-2.80)	79	0.91(0.78-1.05)	0
Syncope[11, 43-45]		4	1699	12(8-19)	89(84-93)	1.35(1.04-1.76)	35	0.95(0.73-1.24)	0

Table 4. Performance of physical exam in the diagnosis acute aortic syndrome

Test	No.		% (95%CI)		LR+(95%CI)	I^2, %	LR- (95%CI)	I^2, %
	Studies	Patients	Sensitivity	Specificity				
Neurological deficit[11, 43, 44]	3	1653	18(11-30)	95(93-97)	4.34(3.33-5.65)	0	0.78(0.60-1.01)	0
Pulse deficit[24, 44, 45]	3	297	24(13-41)	92(86-96)	2.48(1.51-4.09)	0	0.83(0.51-1.37)	0
Hypotension[11, 24, 43, 50]	4	1866	15(10-23)	95(93-96)	2.92(1.84-4.62)	42	0.85(0.64-1.13)	0
Aortic Insufficiency [11, 24, 43-45]	6	1915	19(8-39)	90(71-97)	1.70(1.29-2.24)	0	0.85(0.65-1.13)	0
Pulmonary Edema[45, 50]	2	158	7(2-21) 22(13-36)	96(58-1) 87(77-94)	1.68(0.9-32.22) 1.77(0.77-5.06)	86	0.97(0.05-18.4) 0.89(0.39-2.04)	76
BP>150mmHg[11, 24]	2	426	5(2-10) 41(33-50)	57(43-70) 69(60-76)	0.11(0.05-0.26) 1.33(0.95-1.86)	92	1.68(0.72-3.89) 0.85(0.61-1.19)	55

Table 5. Performance of basic investigation in diagnosing acute aortic syndrome

Test	No.		% (95%CI)		LR+(95%CI)	I^2, %	LR- (95%CI)	I^2, %
	Studies	Patients	Sensitivity	Specificity				
Widened mediastinum[11, 44, 48, 50]	4	477	80(63-90) 94(69-99) 86(72-93) 76(68-82)	49(34-64) 41(23-62) 24(15-36) 78(70-84)	1.55(1.10-2.19) 1.60(1.11-2.30) 1.13(0.94-1.35) 3.42(2.42-4.84)	89	0.42(0.30-0.60) 0.14(0.09-0.20) 0.60(0.50-0.72) 0.31(0.22-0.44)	93
Ischemic changes on EKG[50]	1	112	14(10-19)	94 (92-96)	1.03(0.29-3.63)	-	1(0.28-3.52)	-
Elevated White blood cell count [11]	1	250	26(18-34)	78(69-85)	0.37(0.20-0.68)	-	1.09(0.84-1.41)	-

Table 6. Performance of clinical decision aids in diagnosing acute aortic syndrome

Risk Level	Threshold	LR+(95%CI)	LR- (95%CI)
High			
AHA ADD risk score[43]	>1	2.29(1.83-2.86)	0.79(0.72-0.85)
Von Kodolitsch score[11]	>2	65.79(4.08-1061.41)	0.74(0.05-11.97)
Low			
AHA ADD risk score[43]	0	1.51(1.42-1.61)	0.22(0.15-0.33)
Von Kodolitsch score[11]	0	2.06(1.70-2.49)	0.07(0.06-0.09)

Table 7. Final diagnoses of patients with and without acute aortic syndrome

Diagnosis	Armstrong 1998	Chan 1991	Fan 2010	Eagle 1986	Enia 1989	Giachino 2013	Keren 1996	Nazerian 2014	Von Kodolitsch 2000
AAS group n	34	18	107	125	35	52	49	291	128
Non-AAS group n	42	23	-	55	11	124	63	1037	122
Aneurysm	15	2	-	4	1	16	33	-	-
Angina	-	-	-	3	2	-	-	-	-
Chest pain syndrome	-	-	-	18	3	-	-	383	18
Acute coronary syndrome	8	5	118	9	-	5	-	120	18
Gastrointestinal (i.e. Gastritis/GERD/Pancreatitis)	-	-	-	-	-	-	-	100	12
Atrial fibrillation	-	-	-	-	-	1	-	-	-
Pulmonary embolism	-	-	18	-	1	1	-	14	6
Pericardial disease	-	1	-	3	4	3	4	34	7
Pulmonary disease	-	-	-	1	-	-	-	-	1
Valvular pathology	-	-	-	5	-	-	-	-	-
Neuroradicular	-	-	-	-	-	-	-	-	1
Hypertensive crisis	-	-	-	-	-	-	-	-	11
Pneumothorax	-	-	-	-	-	-	-	-	2
Pleuritis	-	-	-	1	-	-	-	-	5
Chronic dissection	-	-	-	4	-	-	-	-	-
Acute arterial occlusion	-	-	-	-	-	-	-	-	-
Mediastinal mass	-	2	-	4	-	-	-	-	-
Cholelithiasis	-	-	-	2	-	-	-	-	-
Ischemic stroke	-	-	-	-	-	-	-	25	-
Syncope unspecified	-	-	-	-	-	-	-	71	-
Organ/limb ischemia	-	-	-	-	-	-	-	21	-
Undiagnosed	-	-	-	-	-	34	-	-	4
Other	19	13	-	1	-	14	26	269	37

Table 8. Characteristics of included studies

Study	Armstrong 1998	Chan 1991	Fan 2010	Eagle 1986	Enia 1989	Giachino 2013	Keren 1996	Nazerian 2014	Von Kodolitsch, 2000
Study period	June 1992 to October 1994	September 1987 to April 1989	January 2007 to September 2008	1963 to 1983	May 1981 to June 1987	June 2010 to August 2012	April 1991 to June 1994	January 2008 to December 2012	January 1988 to December 1996
Number of Patients	74	41	243	180	46	126	112	1328	250
Study design	Retrospective	Prospective	Prospective	Retrospective	Prospective	Prospective	Prospective	Retrospective study on prospective registry	Prospective
Country	USA	Canada	China	USA	Italy	Italy	USA	Italy	Germany
Setting	Inpatient/Emergency Department	Inpatient	Inpatient	Inpatient/Out patient	Inpatient	ED	ED/ICU	ED	ED
Study population	Patients identified with an admitting diagnosis, discharge diagnosis, indication for surgery, or echocardiographic study of aortic dissection or aneurysm.	Referred to regional cardiac center for investigation of suspected aortic dissection as defined by treating clinician	Admitted patients presenting with either chest pain, back pain, abdominal pain, myocardial ischemia and with suspected aortic dissection, excluded if diagnosis other than aortic dissection made or if no clear diagnosis found	All patients undergoing aortogram to rule out aortic dissection	Patients admitted for work up of suspected aortic dissection	Clinical presentation suggestive of AAS and a CT thorax and abdomen ordered	Consecutive patients undergoing trans esophageal echo for a evaluation of aortic dissection	Chest pain, back pain, abdominal pain, syncope or symptoms of perfusion deficit, no alternative diagnosis after investigation and CT or trans esophageal echo ordered to rule out aortic dissection	Acute onset chest or back pain without an alternative diagnosis on investigation and a CT/Echo ordered to rule out aortic dissection
Acute aortic syndrome (N,%)	24 (45%)	18 (44%)	107(44%)	125 (69%)	35 (76)	52 (41)	49(44)	291 (22)	128 (51)
Gold standard	Trans esophageal Echocardiography	Angiography, autopsy, CT or surgery	Trans thoracic or trans esophageal echocardiography, CT, and/or MR	Aortography, autopsy or surgery	Aortography and Trans esophageal echocardiography	CT	Angiography, autopsy, CT or surgery	CT angiography or Trans esophageal echocardiography	CT or Trans esophageal echocardiography
Age (mean and range)	59 +/- 16	59 +/- 11	-	58 +/-13	64	-	60.6 +/-16.8	68 +/- 1	54 +/- 15
Male, %	49(62.8)	11(61.1)	166(70.3)	-	39(84.7)	89(70.6)	80(71.4)	446(33.6)	173(69.2)
Type A, %	31	50	38(30.6)	-	23(65.7)	32(61.5)	30(61.2)	185(63.6)	78(60.9)
Type B, %	3	50	86(69.4)	-	12(34.3)	20(38.5)	19(38.8)	67(23.1)	50(39.1)

Appendix

Figure A-1. Summary receiver operating characteristics of high-risk features on history for acute aortic syndrome

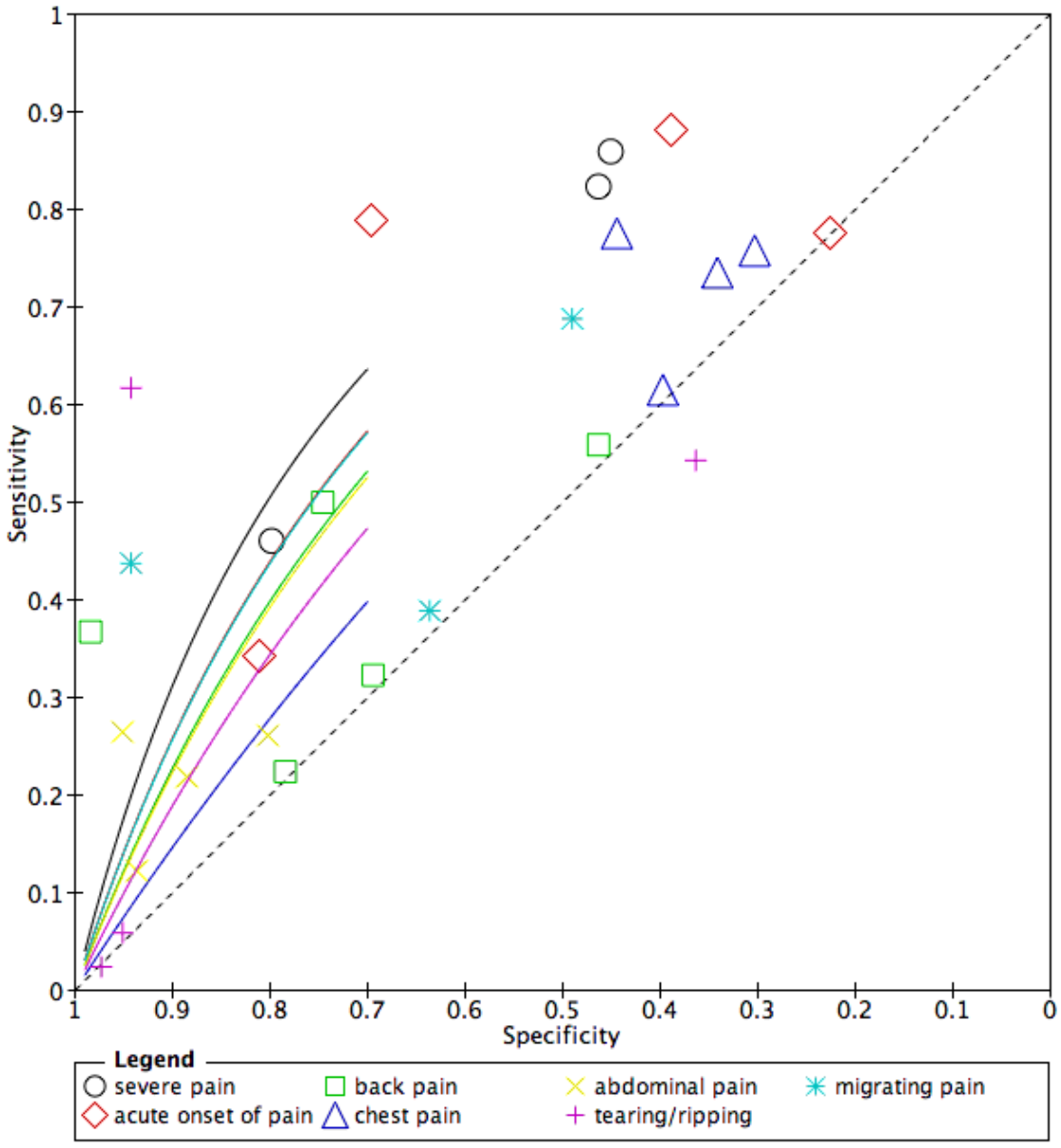


Figure A-2. Summary receiver operating characteristic of risk factors for acute aortic syndrome

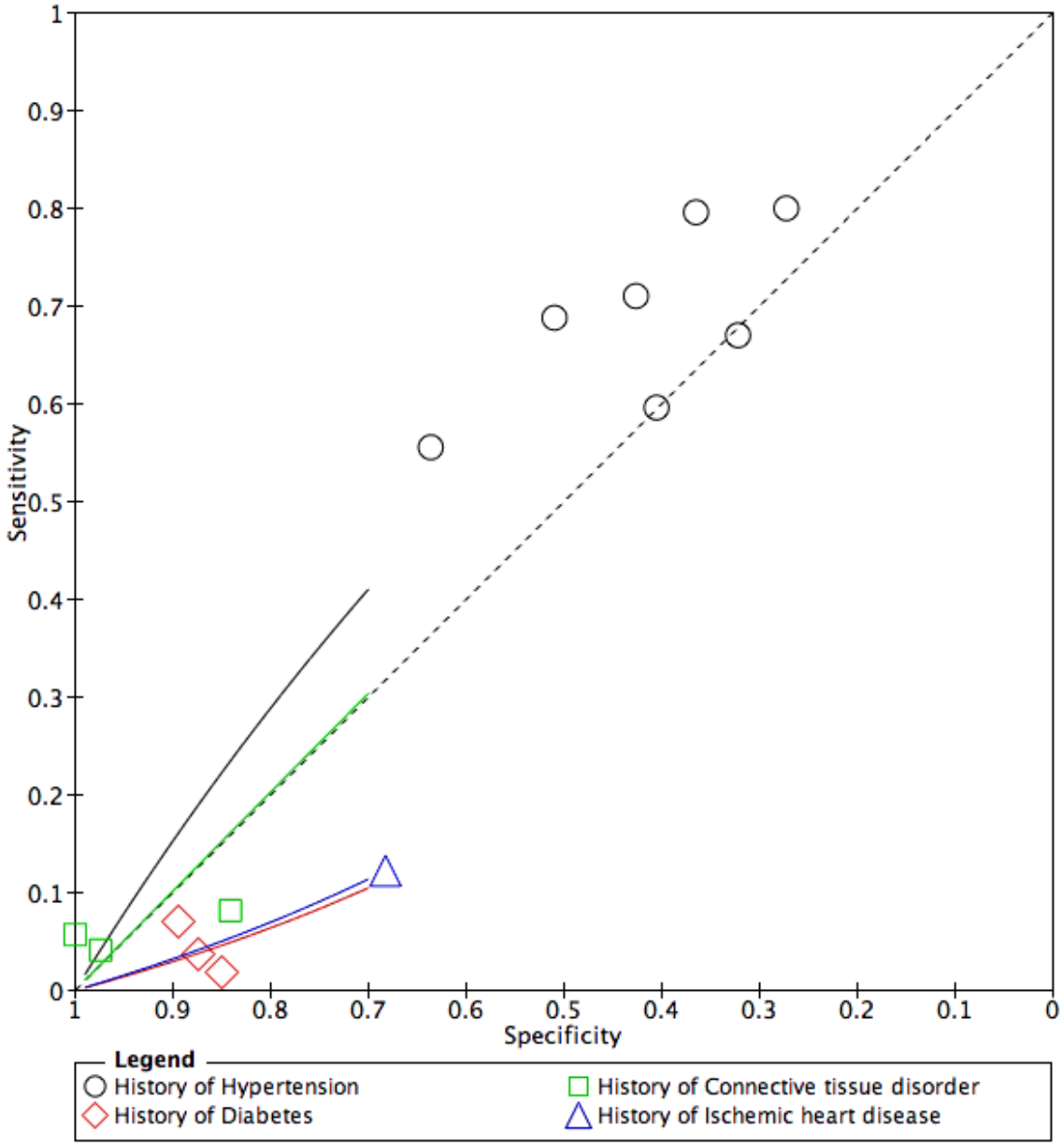
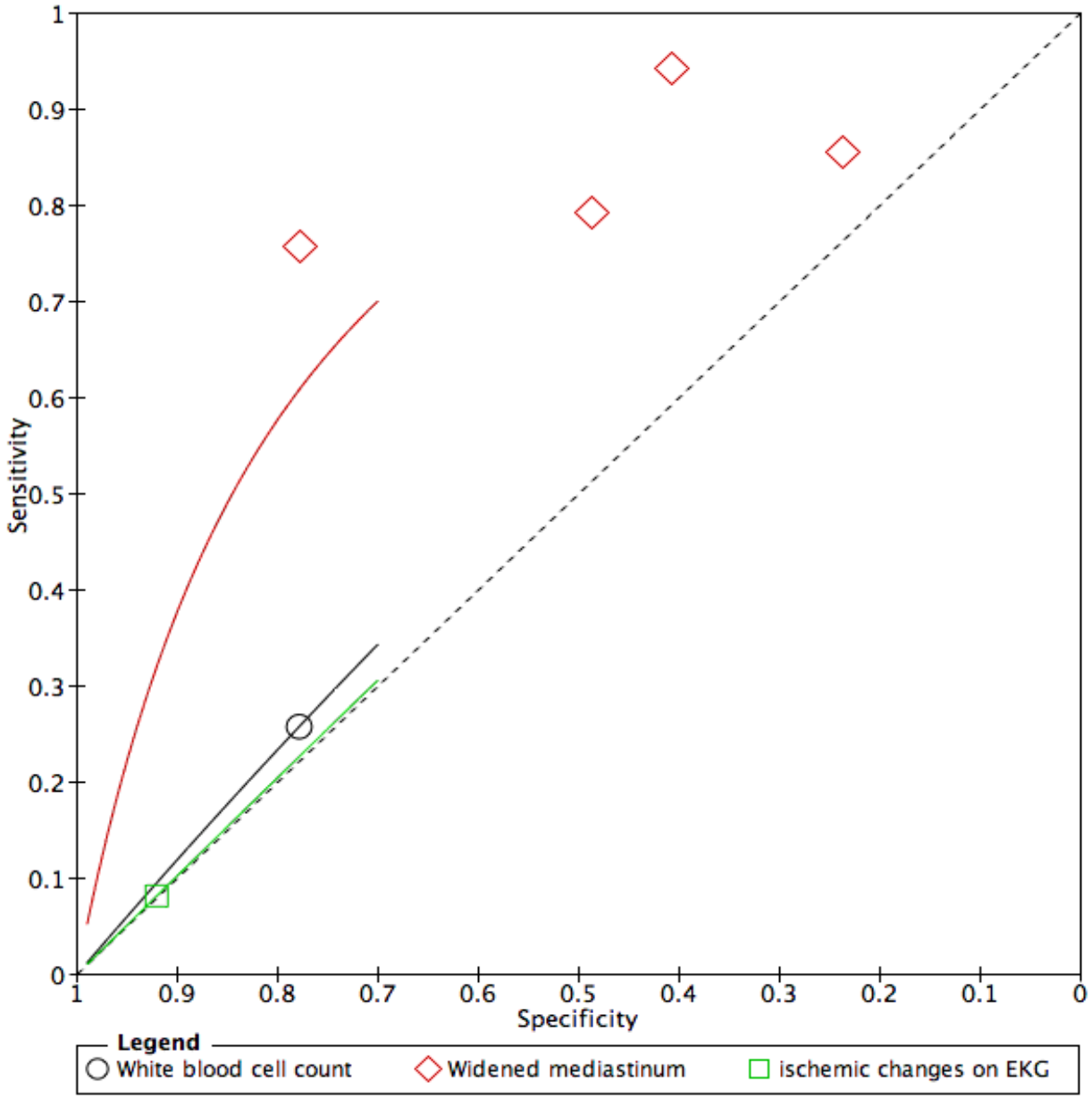


Figure A-3. Summary receiver operating characteristics of basic investigations for acute aortic syndrome



* EKG = electrocardiogram

Chapter Four : High risk clinical features for acute aortic syndrome: a case control study

Chapter overview

The following is a manuscript prepared for publication based on a historical case control study. The objective of the manuscript was to assess the diagnostic accuracy of high risk historical, examination and basic investigative features for AAS, in confirmed cases of AAS and a low risk control group in order to address the perceived spectrum bias in previous studies and improve generalizability.

Dr. R. Ohle is the first author of this paper, having been primarily responsible for data collection, analysis and writing of manuscript. This manuscript was co-authored by Dr. R. Ohle, his co-supervisors Dr. J. Perry and Dr. G. Wells. Dr. J. Perry and Dr. G. Wells provided valuable feedback throughout the process. Mr. Justin Um contributed to data extraction and to a lesser degree Mr. Omar Anjum, Ms. Helena Bleeker and Ms. Lindy Luo also contributed to data extraction.

See Appendix A for data collection sheet and Appendix B for ethics board approval

High risk clinical features for acute aortic syndrome: a case control study

Robert Ohle[1], Justin Um[2], Omar Anjum[2], Helena Bleeker[2], Lindy Luo[2], George Wells[3, 4] Jeffrey J. Perry[1]

[1] The Department of emergency medicine, The Ottawa Hospital Research Institute, University of Ottawa, Canada

[2]Department of Undergraduate Medicine, University of Ottawa, Canada

[3]Department of Epidemiology and Community Medicine, University of Ottawa, Canada

[4] Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Canada

Correspondence to Robert Ohle E-mail:

Word Count: 5958

This manuscript includes five (5) tables.

Abstract

Introduction

Acute aortic syndrome (AAS) is a rare clinical syndrome with a high mortality encompassing acute aortic dissection, intramural hematoma and penetrating atherosclerotic ulcer. Previous studies assessing the usefulness of clinical exam were performed in a population with a high prevalence of AAS. This does not represent the low prevalence population we are attempting to risk stratify in the emergency department. The objective of our study was to assess the performance of high risk historical, examination and basic investigative features for AAS, in confirmed cases of AAS and a low risk control group in order to address the perceived spectrum bias in previous studies and improve generalizability.

Methods

We performed a historical matched case-control study: participants were adults >18 years old presenting to two tertiary care emergency departments (ED) or one regional cardiac referral center. Cases were selected based on an ED or in-hospital diagnosis of non-traumatic AAS confirmed by computed tomography or echocardiography. Cases were excluded if no pain or known AAS. Controls were selected based on a triage diagnosis of truncal pain and an absence of a clear diagnosis (e.g. urinary tract infection pneumonia, pneumothorax, acute fracture) on basic investigation or pain >14 days/no pain. We matched cases and controls in a 4:1 ratio by gender and age (within 5 years). A sample size of 165 cases and 660 controls was calculated based on 80% power and confidence interval of 95% to detect an odds ratio of greater than 2.

Results

Data were collected from 2002-2014 yielding 194 cases of acute aortic syndrome and 776 controls with a mean age of 65(SD 14.1) and 66.7% male. Of the 194 cases of AAS, 32(16.5%)

were missed on initial assessment. Chest pain unspecified (20.7%), abdominal pain unspecified (9.9%), acute coronary syndrome (8.7%) and renal colic (6.4%) were the top four diagnoses in the control population. Absence of acute onset pain (Sensitivity 95.9% (91.7-98.3), negative likelihood ratio (LR-) 0.07(0.03-0.14)), history of ischemic heart disease (Specificity 78% (74.9-80.8), positive likelihood ratio (LR+) 0.44(0.28-0.7)), diabetes (Specificity 81.8% (78.9-84.5), LR+0.4(0.23-0.67)) and a negative D-dimer (Sensitivity 96.7% (88.7-99.6), LR- 0.05(0.01-0.18)) can help rule out acute aortic syndrome. Presence of acute onset pain (Specificity 61.3%(57.5-65.1), LR+ 2.48(2.24-2.74)) tearing/ripping pain (Specificity 99.7% (98.8-99.9), LR-42.07 (9.97-177.49), a history of aortic aneurysm (Specificity 97.8%(96.5-98.7), LR+6.35(3.54-11.42)), hypotension (Specificity 98.7%(97.6-99.4), LR+ 17.2(8.8-33.61)), pulse deficit (Specificity 99.3(98.3-1), LR+ 31.14(11.20-86.62)), neurological deficits (Specificity 96.9% (95.2-98.1), LR+ 5.26(2.98-9.30)), new murmur (Specificity 97.8%(96.5-98.7), LR+ 9.41(5.46-16.24))or a widened mediastinum/absence of aortic notch on chest x-ray (Specificity 94.9% (92.5-96.7), LR+ 10.23(6.75-15.50)) can help rule in the diagnosis of acute aortic syndrome.

Conclusion

Previously reported high-risk features maintain their diagnostic accuracy in a low risk population. No single high-risk feature can accurately rule in or rule out acute aortic syndrome. Further research should focus on the ability of a combination of these factors to generate a reproducible assessment of pre test probability. This could be used to risk stratify those who warrant further investigation thus reducing miss rate, morbidity and mortality.

Introduction

Acute (<14 days) non-traumatic pain is a common presenting complaint in emergency departments, accounting for about 20% of all visits. Acute aortic syndrome is defined by aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer. Although acute aortic syndrome (AAS) accounts for only 0.05% of these visits(1), emergency physicians need to rule out this life threatening diagnosis. These patients typically present with sudden onset and severe pain(1-3). Perfusion/neurological deficits or hemodynamically unstable patients with acute pain make the decision to investigate some patients relatively straightforward. However the majority of patients presenting with AAS do not present with high risk features such as neurological/pulse deficit or hypotension making it difficult to decide who warrants further investigation (3). These are the patients who are often missed but would benefit the greatest from earlier diagnosis(4-7).

Many physicians do not consider AAS in their initial differential, which is in part why 25% are not diagnosed until 24 hours after presenting to the emergency department(3, 8-10). Mortality follows a linear increase with diagnostic delay and can be as high as 2% per hour(3, 11). Prognosis is most favorable when patients are treated early, while they are clinically well(12). Miss diagnosis rate (patients not diagnosed during initial ED visit, i.e. admitted for an alternative diagnosis and later diagnosed as AAS, discharged and represent with a diagnosis of AAS, diagnosed on post mortem) for AAS is thought to be as high as 38%(4-10, 13-16). These patients with minimal symptoms but a potential deadly condition epitomize the challenges of emergency medicine; the condition is uncommon and difficult to diagnose and yet they have the most to lose by a missed diagnosis.

Patients with suspected AAS are typically investigated with enhanced computed tomography(3). Not surprisingly, current use of these investigations in patients with a clinical suspicion for AAS is inefficient(17). Computed tomography (CT) is a high volume imaging technology, unnecessary use leads to a direct increase in health care costs but can also result in an indirect increase with contrast associated complications (nephrotoxicity, allergic reactions), increased length of ED stay or incidental findings requiring further follow up and additional imaging. Over 98% of CT scans to rule out AAS, however, yield negative results(17, 18). Although it would be ideal to investigate only high or intermediate risk patients, no previous research has safely and rigorously identified this population(19). Previous studies investigating high-risk clinical features for AAS focus on a high-risk population as demonstrated by their high prevalence of AAS (25-78%)(1, 2, 6, 19-24). This leads to spectrum bias where the performance of a diagnostic test (i.e. history, clinical exam and basic investigations) may vary in different clinical settings because each setting has a different mix of patients. The population in practice that we are attempting to risk stratify is low risk as illustrated by the 2% prevalence of AAS in Lovy's study on CT use for AAS. Thus our population in practice is different than previous studies used to assess diagnostic accuracy of clinical exam, this limits the generalizability to the low risk patient population we wish to risk stratify.

The objective of our study was to assess the performance of high risk historical, examination and basic investigative features for AAS, in confirmed cases and a low risk control group in order to address the perceived spectrum bias in previous studies and improve generalizability.

Methods

Study Population

The study population in this historical case control study was enrolled from two urban academic tertiary care emergency departments and a regional cardiac referral centre.

Inclusion criteria: Adults >18 years who presented to the emergency department of the Civic or General Hospital campus of The Ottawa Hospital or the University of Ottawa Heart Institute with acute (<14days) onset non traumatic abdominal/back/chest/flank pain. AAS cases were identified and enrolled via emergency department, in hospital or death certificate diagnosis of aortic dissection, intramural hematoma or penetrating atherosclerotic ulcer. Patient controls were enrolled via ED triage diagnosis of chest, back, abdominal, flank pain.

Exclusion criteria: Trauma within 24hrs of pain onset or known AAS. Those presenting with chest pain without radiological imaging confirming lack of pneumonia, pneumothorax or fracture. Those presenting with abdominal, back, flank pain and suspected (dysuria/frequency) or confirmed urinary tract infection. Those with back pain and the presence of risk factors for fracture (>65 years old, corticosteroid use, history of malignancy (within 10 years), symptoms of cauda equine (urinary retention, bowel incontinence, intravenous drug use, night pain) without imaging (either plain radiograph, computed tomography (CT) or magnetic resonance imaging (MRI)) of the appropriate area proving no fracture.

We generated a potential control population from a triage diagnosis of truncal pain and our case population as described above. Triage diagnosis was not consistently recorded every year from 2002-2014. Therefore our control population was derived from 2010 and 2011, these were the most recent years that had triage diagnosis available for all patients presenting to the

emergency department. Each patient was assigned a random number (random number generation (RAND function SAS University Edition)). Both populations were then ordered by random number starting from lowest to highest. In a sequential fashion we matched a case with a potential control based on gender and age within 5 years. The control patients chart was then reviewed, if patient satisfied inclusion criteria and had no exclusion criteria clinical data was extracted. One case was matched with four controls. Data was extracted as per guidelines put forward by Jansen et al.(25). Data extracted was verified in multiple sources; emergency department record of treatment, consultant notes and integrated progress notes. Four trained reviewers extracted data by standardized paper data sheets. Data sheet was trialed on 50 patient charts, refined and trialed on a further 50 charts. Training included 50 chart data extraction by all four reviewers, data was compared and kappa calculated, clarification and oversight was provided by fifth reviewer (RO). In addition 40% of total charts were reviewed by at least two reviewers and Kappa calculated. Reviewers were not blind to study objective but had no knowledge regards the direction of association of clinical variables.

Outcome measures

Acute aortic syndrome was defined by radiological evidence of aortic dissection, intramural hematoma or penetrating atherosclerotic ulcer on CT, MRI or trans esophageal echocardiography (TEE). The absence of acute aortic syndrome was confirmed on imaging. In those who were discharged without imaging charts were reviewed up to 6 months post encounter confirming no new diagnosis of AAS. Repeat hospital visits without diagnosis of AAS or future imaging without diagnosis of AAS were used as confirmation. In those who did not return to study hospitals or did not undergo additional imaging, publicly available obituaries

were searched to ascertain death. A missed case of AAS was defined by failure to diagnose within the emergency department or treatment for an alternative diagnosis (i.e. anticoagulation for a pulmonary embolism) within the emergency department, or representation within 14 days of initial visit with a new diagnosis of AAS.

Variables

We extracted 33 variables extracted from the case and control charts. These variables were chosen following a comprehensive systematic review of the literature for statistically significant clinical/investigation findings and the consensus of the study team that the variables were clinically significant. (Appendix)

Data Analysis

Extracted clinical variables were entered into an electronic database. Results outside of a predefined range were flagged and reviewed. First descriptive statistics including means, medians, standard deviation for continuous variables and percentages for dichotomous variables were calculated. Variables were assessed for association with AAS with univariate analysis. The continuous variables were compared using the two-sided Student t test for normal distributions and the Mann-Whitney U test for non-normal distributions. The categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

We conducted multivariable logistic regression with stepwise selection for those variables found to be associated with acute aortic syndrome on univariate analysis ($p<0.05$) and deemed

clinically important. So as not to over fit the model, one independent variable per 10 dependant variables was decided a priori(26). Odds ratios, sensitivity, specificity, positive and negative likelihood ratios with 95% confidence intervals were calculated. Missing data were expected, after analysis of the pattern and prevalence of missing data we used multiple imputations to account for this. Analysis was performed using SAS 9.4 University edition.

Sample Size

Sample size was calculated on the basis of an 80% power and confidence interval of 95% to detect an odds ratio of greater than 2. Based on a minimum of 10% of controls with any of the independent variables, our sample size consisted of 165 cases and 660 controls. In order to maximize our statistical power we matched controls and cases in a 4:1 ratio. A larger ratio was not used as minimal statistical power is added with a greater number of controls(27).

Results

Data were collected from 2002-2014 yielding 194 cases of acute aortic syndrome and 776 controls with a mean age of 65(SD 14.1) and 66.7% male. The Kappa after chart training was 0.85 and for study data extraction 0.91. Of the 194 cases of AAS, 32 (16.5%) were missed on initial assessment. Controls were extracted from a random sample of 64,402 patients presenting with triage diagnosis of truncal pain over two calendar years (2010 and 2011). Chest pain unspecified (20.7%), abdominal pain unspecified (9.9%), acute coronary syndrome (8.7%) and renal colic (6.4%) were the top four diagnoses in the control population.

Family history was only reported in 7.1% of study population. Hypertension was prevalent with 48.6% of the population reporting a history. D-dimer (12.8%) was not often measured. The overall mortality was 4% all but 0.3% due to complications of acute aortic syndrome. Outcome data was not available for 6 (0.6%) patients. No obituary was found for any of these patients. They were excluded from the analysis and a further 6 controls were recruited.

All previously reported high-risk clinical exam findings and investigations were significantly different between cases and controls. With the exception of previous cardiac surgery (p <0.678, pain less intense then at onset (p<0.208), hypertension (>150 mmHg) at presentation (p<0.372) and signs of heart failure (bibasilar crackles) (p<0.501). In addition factors which increased the likelihood of an alternative diagnosis were significantly different between case and controls; history of ischemic heart disease (p<0.001), renal colic (p<0.015), biliary colic (p<0.025), diabetes (p<0.001), palpable tenderness (p<0.001 and ischemic changes on ECG (p<0.003).

Risk factors

After adjusting for all historical, physical and investigation findings, known aortic aneurysm (OR 13.9 (4.6-41.4), history of hypertension (OR 2.9(1.3-6.1)), increased odds of AAS. A history of ischemic heart disease (OR 0.09(0.02-0.32)), diabetes (OR $0.35(0.20\text{-}0.62)$) and renal colic (OR 0.20(0.04-0.91)) decreased the odds of AAS. A history of ischemic heart disease (specificity 78 LR+0.44(0.28-0.7)) and history of diabetes (specificity 81.8%, LR+0.4(0.23-0.67)) were useful in ruling out AAS. A history of aortic valve disease (specificity 98.5%, LR+3.3(1.5-7.6)), history of aortic aneurysm (specificity 97.8%, LR+ 6.4(3.5-11.4) and connective tissue disease (specificity 99.7%, LR+14(2.9-66.9)) were useful in ruling in AAS.

History

Acute onset, tearing/ripping, pleuritic, other, and migrating/radiating pain were independently associated with AAS when adjusting for other historical and physical exam findings. The presence of acute onset pain (specificity 61.3%, LR+ 2.5(2.2-2.7)) increases likelihood of AAS and its absence decreases likelihood (sensitivity 95.9%, LR- 0.07(0.03-0.14)). When present tearing/ripping pain (specificity 99.7%, LR+42.1(9.9-177.5)), syncope (specificity 98.7% LR+ 6.8(3.2-14.6)) and subjective neurological deficits (specificity 92.1%, LR+ 3.5(2.5-4.9)) all increased likelihood of AAS.

Physical examination

Hypotension, new murmur and pulse deficit, were independently associated with AAS when adjusting for other historical and physical exam findings. Hypotension (specificity 98.7%, LR+ 17.2 (8.8-33.6)), pulse deficit (specificity 99.3%, LR+ 31.1 (11.2-86.6)), new murmur (specificity 97.8%, LR+9.4(5.5-16.2)), or focal neurological deficit (specificity 96.9%, LR+ 5.3 (2.9-9.3)) all increased likelihood of AAS when present. Palpable tenderness decreased likelihood of AAS (specificity 53.2%, LR+ 0.48 (0.35-0.64)).

Basic investigations

A negative D-dimer can help decrease likelihood of AAS (sensitivity 96.7%, LR- 0.05 (0.01-0.18)). A widened mediastinum or absence of aortic knob (specificity 94.9%, LR+ 10.23 (6.75-15.50)), aortic root dilation on echocardiography (TEE or transthoracic) (specificity 93.9%, LR+ 10.03(2.59-38.78)), positive D-dimer (specificity 71.7%, LR+ 3.41(2.28-5.12)), and elevated

white blood cell count (specificity 72.1%, LR+ 2.11(1.78-2.49)) were clinically useful, increasing likelihood acute aortic syndrome.

The variables with the highest proportion of missing values were pain resolving (26.1%), character of pain (20.3%), location of migration of pain (54.2%), D-dimer (88.4%), echocardiographic findings (86%) and electrocardiogram ischemic changes (33%).

Discussion

Clinical history and physical exam together with basic investigations can help risk stratify patients in need of further investigation to rule out acute aortic syndrome. Although multiple high-risk features are associated with acute aortic syndrome, only 14 are independently associated. Of these only the absence of acute onset pain, history of ischemic heart disease, history of diabetes and a negative D-dimer have sufficient diagnostic accuracy to help rule out acute aortic syndrome. The presence of tearing/ripping pain, a history of an aortic aneurysm, hypotension, pulse/neurological deficits, new murmur or a widened mediastinum/absence of aortic notch can help rule in the diagnosis.

The majority of those with acute aortic syndrome presented with abrupt onset chest pain. This underlines the diagnostic dilemma in acute aortic syndrome given the overlap with more common diagnoses such as acute coronary syndrome and pulmonary embolism. A study by Halsted found an initial misdiagnosis rate of 39% and a third of these were treated as acute coronary syndrome with anti-platelet agents or fibrinolytics. Of the 32 cases misdiagnosed in our study half were initially diagnosed as acute coronary syndrome.

The absence of high-risk features is often the decision point to discard acute aortic syndrome from a physician's differential diagnosis. However the classically reported high risk features for acute aortic syndrome; tearing/ripping pain (14%) hypotension (22%), neurological deficit (13%), pulse deficit (17%) were all uncommon in our study. Acute onset pain is a more common high-risk feature in patients with AAS and its absence is of greater use in decreasing probability of AAS. It was present in 96% of AAS versus 39% of our control population. Our prevalence was higher then found in the review by Hagan of the international registry of acute aortic dissection (IRAD) (86%). This is an international collaborative study that prospectively and retrospectively collects data on all patients ultimately diagnosed with acute aortic syndrome. Our prevalence was also higher than in studies of those undergoing imaging to rule out AAS such as Armstrong's retrospective study (88%), Lovy's 2013 case control (83%) and two prospective studies (Von Kodolitsch (77%) & Nazerian (34%)). We had 130 (13.4%) missing values with this variable. It is possible that physicians did not record acute onset pain in patients when it was not present. Our prevalence is more in keeping with other studies if this was the case (84.5%). Another possibility could be the varying definition of abrupt or acute onset pain between studies, and underlies the difficulty of assessing diagnostic accuracy of historical features. Acute onset pain in our study was defined as physicians described the pain as acute, abrupt, sudden, documenting a specific time of onset and which was maximal severity at onset. Definitions of acute onset pain are not provided in previous studies therefore our definition may vary, this could explain our increased prevalence. In order for reported diagnostic accuracy's of abrupt onset pain to be used in clinical practice, clinicians' must be aware of how each study defines

this variable. We found our definition of abrupt onset pain to be useful in ruling out AAS with a negative likelihood ratio of 0.07. This is markedly lower than previous studies (0.26-0.98).

A novel finding in our study was that a history of ischemic heart disease decreased the probability of AAS. This is less likely due to an underlying process that is protective for AAS and more due to it being a risk factor for an alternative diagnosis such as acute coronary syndrome. Kerens 1996 prospective study found a similar association (sensitivity 68% and LR+ 0.4)(22). We also found a history of diabetes to be associated with a reduced probability of AAS. Three previous studies have found a similar association (n=3, specificity 87%, LR+ 0.32 95%CI 0.14-0.70)(19, 23, 24). Again this likely speaks to the fact that diabetes is a risk factor for multiple alternative diagnoses. However multiple population-based studies have shown a decreased incidence of diabetes in those who develop AAS or abdominal aortic aneurysm (AAA)(28-31). These findings suggest that diabetes may play a protective role in the development of AAS. The precise mechanism of this negative association is unknown. Whilst a number of studies have supported the hypothesis that protection is a function of diabetes-mediated changes in the vascular extracellular matrix biology, there is also support for the idea that the treatment regimens used in diabetes may afford protection against AAS and AAA (31).

D-dimer was only measured in a minority of the study population. Given the extent of the missing data we did not use multiple imputations. We analyzed the diagnostic accuracy of D-dimer in the subset of cases and controls that had data available. This is a biased sample, as factors that impact whether a clinician orders a D-dimer will dictate the prevalence of high-risk historical and physical exam findings. However our assessment of its diagnostic accuracy

(sensitivity 96.7%, LR- 0.05 (0.01-0.18), specificity 71.7%, LR+ 3.41 (2.28-5.12)) is consistent with two recent meta-analyses of D-dimer to rule out acute aortic syndrome, albeit with a slightly higher specificity(32, 33). The negative likelihood ratio of 0.05 suggests that this test can be used to rule out acute aortic syndrome in a low risk population. In order to define this low risk population we must first answer two questions. Number one, what is our acceptable miss rate and thus highest pre test probability of a patient in which we can use D-dimer. Number two, how do we define that pre test probability. The expert consensus derived AHA AAD detection risk score is the only prospectively validated system for assessing pretest probability. Combining this screening tool with D-dimer yields a miss rate of 0.8%-1.1% and has been proposed as a means of defining a pretest probability for use with D-dimer. There is no consensus as to an acceptable miss rate for AAS. However, Taylor et al performed a decision analysis and found the test threshold for computed tomographic angiography (CTA) versus D-dimer was 0.6%. These studies were conducted in a population whose prevalence of AAS was >20% which does not reflect the population we are ordering CT's to rule out AAS(18). The potential reduction in imaging with use of this pathway varied between studies from 8.9%-31%. Thus it needs to be prospectively validated in a lower risk population in order to assess its impact and validity.

Tearing or ripping is a classic descriptor of the pain associated with acute aortic syndrome. However it was only present in 14% of patients with AAS in our study. The marked lower prevalence compared to previous studies (20-91%) is likely a consequence of the retrospective nature of this study and our inclusion criteria (1, 20). Retrospective data collection relies on the documentation of the treating physician and character of pain was missing in 20% of patient

charts. The inclusion criterion for all previous prospective studies on AAS was based on clinician suspicion. With classic high-risk features generating this clinical suspicion, they will likely be over represented in the study population leading to a spectrum bias. Our case inclusion criteria was all those who were ultimately diagnosed with acute aortic syndrome independent of initial presenting symptoms. In a retrospective study by Armstrong et al with similar inclusion criteria the prevalence of tearing/ripping pain was only 6% (1, 20). In Nazerian's 2014 retrospective review of prospectively collected data they found tearing pain in only 2.3% of AAS. Ultimately the varying prevalence of this symptom in prospectively collected data is likely a result of the difficulty in standardizing definitions across physicians, patients and centers. The association of tearing pain with AAS is consistent across studies; however the diagnostic accuracy of this symptom varies. In our study in comparison to a low risk control group it showed excellent ability (LR+ 42.07(9.97-177.49)) to help increase the probability of AAS. However given the low prevalence of this symptom and its negative likelihood ratio >0.5 (LR- 0.87(0.81-0.92)) the absence of this finding should not alter your probability of AAS.

With the expansion of an intimal dissection down the aorta branch vessels can be occluded leading to perfusion deficit syndromes. Arteries supplying the spinal cord can be affected leading to focal sensory or motor deficits. We looked at patient reported neurological deficit versus a clinician physical finding of a neurological deficit. Both were useful in increasing probability of AAS (LR+ 3.54 (2.54-4.93) Vs. 5.26 (2.98-9.30)) and not surprisingly focal neurological deficit on physical exam was more specific (96.9% (95.2-98.1) Vs. 92.1%(90-93.9). Subjective neurological deficits were present in 28% of those with AAS Vs. 13% on physical exam. Previous studies report on the excellent diagnostic power of a neurological

deficit to help rule in AAS, but the usefulness of this sign is reduced by its low prevalence. Expanding the definition of neurological deficit to include subjective patient reported deficits could increase the applicability of this clinical finding in practice.

Similar to a neurological deficits pulse deficit has an excellent ability (Specificity 99.3(98.3-1) LR+ 31.14 (11.20-86.62)) to help rule in AAS but its low prevalence (15%) also reduces its usefulness in clinical practice.

The propagation of an aortic dissection proximally can result in aortic insufficiency (AI). The usefulness of the murmur of aortic insufficiency on examination is questionable with a positive likelihood ratio varying between studies (LR+ 0.9-4.8)(1, 2, 6, 19-21, 24). These studies do not differentiate between an old or new murmur. Prevalence of new or old murmur of AI in the IRAD database was 31.6%. Our study looked at new or presumed new murmur and had prevalence of 25%. A new murmur was independently associated with AAS and had good diagnostic accuracy (specificity 97.8 (96.5-98.7) LR+ 9.41 (5.46-16.24)). In our cohort auscultation for a new murmur had greater diagnostic accuracy for AAS then echocardiographic evidence of a valvular abnormality. This is likely due to the fact that an increased number of valvular abnormalities were diagnosed on echo in those with AAS (52% Vs. 25%) and in those without (33% Vs. 4%). Thus although echocardiography has increased sensitivity (52% Vs. 20%) it leads to a reduced specificity (98% Vs. 67%).

Chest x-ray has been proposed as a readily available adjunct to clinical assessment to help increase the probability of AAS. Diagnostic accuracy of chest x-ray varies markedly between studies (LR- 0.1-0.7, LR+ 1.1-4)(1, 2, 21, 22, 34). This may be in part due to the mediastinum

appearing artificially wide if the film is from a portable x-ray, the number of which is not reported in any study of chest x-ray accuracy for AAS(34). In addition the inter rater reliability of chest x-ray interpretation is poor (35). Widened mediastinum and/or absence of aortic notch were present in 52% of AAS in our study. Nazerian looked at the addition of chest x-ray to a clinical risk score (AHA ADD risk score) but found that a low risk group and a negative chest x-ray did not rule out the diagnosis of AAS(19). We found a negative likelihood ratio of 0.5(0.43-0.59) indicating a very low change in probability of AAS if chest x-ray is negative. However a widened mediastinum or absence of the aortic notch (LR+ 10.23 (6.75-15.50) has the ability to significantly increase the probability of AAS. Chua et al prospective study found that an absence of mediastinal widening was associated with an increased rate of missed diagnosis, further highlighting that a chest x-ray is only helpful if there is a positive finding(5).

Connective tissue diseases are a risk factor for acute aortic syndrome(3, 36). It has been hypothesized that significant decrease and fragmentation of the elastic fibers observed in patients leads to a progressive dilatation of the aortic root. This is most prominent at the sinuses of Valsalva, leading to dissection and/or rupture if left untreated. The prevalence of connective tissue disorders in those who suffer an acute aortic syndrome ranges in previous studies from 4-15%(1, 3, 19, 22). In Kerens 3 year emergency department and intensive care study on all those undergoing investigation to rule out AAS, there was actually a higher prevalence of Marfan's syndrome in the alternative diagnosis group (15% Vs. 8%). The negative likelihood ratio for connective tissue disease ranges from 0.5-1.3. In Nazerian's validation of the AHA ADD risk score they found that Marfan's syndrome in isolation was associated with AAS, however in conjunction with other high risk features it was not independently associated

with AAS, this is consistent with our findings. This lack of independent association may be due in part to the low prevalence of these conditions. This limits their clinical usefulness but given their specificity (Table 5) if present the diagnosis of AAS should be considered.

As we age the aorta increases in size. This is due to the normal process of cystic media degeneration, where the media displays loss of smooth muscle cells and fragmentation of elastic fibers leading to a loss of compliance and an increased stiffness. This increase in size is pathological when it reaches 1.5 times the normal diameter of the aorta. The incidence of abdominal aortic aneurysms is around 2%, thoracic aortic aneurysms are more rare (16 per 100,000) but are steadily increasing(37). The loss of aortic compliance increases risk for aortic dissection or rupture. A patient presenting with acute truncal pain and a history of an aortic aneurysm should increase the probability for AAS (specificity 97.8(96.5-98.7) LR+ 6.35(3.54-11.42). However like connective tissue diseases, aortic aneurysms are relatively rare in those with AAS (14%). Pape examined 591 type A dissection patients enrolled in the international registry of acute aortic dissection between 1996 and 2005 and found that 98% of type A dissections had a diameter <5.5cm. We found a sensitivity of 9.8% (6-14.9%) and a negative likelihood ratio of 1.16 (1.09-1.23), thus the absence of a previously diagnosed aortic aneurysm should not alter you suspicion for AAS(38).

A bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality with a population incidence of approximately 1-2 %(39, 40). Historically it has been considered a risk factor for AAS due to its increase in shear stress on the proximal aorta above the sinotubular junction (the point in the ascending aorta where the aortic sinuses end and the aorta becomes

a tubular structure) leading to weakening of the wall and aneurysmal dilation. However in recent times it has become unclear if this dilation is secondary to shear stress or a result of aortic malformation during embryonic development. Either way patients with AAS and a bicuspid valve tend to be younger with an average age of 49 Vs. 64. The rupture rate of aneurysms associated with bicuspid valves is 14.1% for those >6cm. In a study of aortic dissections in people under the age of 40, 24 % were associated with BAV (41-43). The pathophysiology for aortic dilation and dissection with BAV is shared with other abnormalities of the aortic valve such as aortic stenosis. Thus our definition of aortic valve disease included BAV and stenosis. Although aortic valve disease was associated with AAS, it was not an independent risk factor. Like connective tissue diseases the lack of association could be due to low numbers in our study. Thus a history of aortic valve disease should prompt AAS to be included in the differential (specificity 98.5 LR+3.33(1.46-7.6)) but its low prevalence and lack of independent associated limits its usefulness.

Syncope can be the presenting symptom in up to 9% of AAS. Prevalence of syncope in AAS ranges from 5-17%. It is more commonly found in type A aortic dissections (12.7%), likely representing the increased incidence of dangerous complications, such as cardiac tamponade, obstruction of cerebral vessels or activation of cerebral receptors. An IRAD study found that syncope, coma, and altered consciousness were three times more common in patients with tamponade (33 vs. 11 %)(44). In Nallamothu's 2002 analysis of the IRAD database patients with syncope were more likely to die in hospital when compared to those without syncope (34 % vs. 23 %) (45). While patients presenting with syncope had significantly higher rates of important complications including cardiac tamponade, stroke, coma, and spinal cord ischemia, nearly half

had none of these complications as an explanation for their loss of consciousness. In our study we found a prevalence of 9% of syncope, it was independently associated with AAS and had a good positive likelihood ratio of 6.8 (95%CI 3.16-14.61). Therefore in those presenting with acute truncal pain and syncope, the clinician should have high index of suspicion for AAS. This patient population would benefit from bedside echocardiography to help rule out tamponade. Although cardiac tamponade is absent in 70% of cases, when present bedside ECHO can reduce time to diagnosis and improve mortality(46).

Trans esophageal echocardiography has similar accuracy to computed tomography in diagnosis of acute aortic syndrome, however the need for a skilled operator decreases its use in the emergency department(3, 47-50). With increasing use of beside ultrasound by emergency physicians it has been proposed that transthoracic echocardiography might prove useful in diagnosing acute aortic syndrome. There are direct (intimal flap, intramural hematoma) and indirect signs (ascending aorta enlargement (diameter >4 cm), pericardial effusion or tamponade and aortic valve regurgitation) of AAS. We looked at trans esophageal echocardiographic measurement of ascending aorta dilation and found a good specificity (93.9%, LR+10.03(2.59-38.78)) significantly higher then transthoracic echocardiography in Nazerian's study (specificity 75%, LR+ 2.8 (2.1–3.8)), but a lower sensitivity (60.8% (50.6-70.3%) Vs. 70% (55–82%)). Nazerian as part of a larger prospective cohort study on acute aortic syndrome looked at the accuracy of emergency physician with 2 years experience focused trans thoracic echocardiography to help risk stratify those with a clinical suspicion of Type A acute aortic dissection. They found 50 of a possible 291 patients underwent bedside echocardiography. The presence of any direct or indirect sign had a sensitivity of 88% (76–

95%), specificity 56% (49–62), LR+ 2 (1.7–2.4) and LR- 0.2 (0.1–0.5)(51). A direct flap or intramural hematoma was visualized in only 54% of patients. Pare et al in a retrospective review of Type A aortic dissections found that assessment of aortic root diameter was associated with a reduced time to diagnosis by computed tomographic angiography and a reduced number of missed diagnoses. (46). Although useful, assessment for direct signs of AAS, aortic root diameter or aortic valve abnormality are likely beyond the skill set of most emergency physicians. However as part of an assessment in undifferentiated shock bedside echocardiography to rule out cardiac tamponade should be performed and if present suspicion for AAS should be raised.

Strengths

Most studies investigating association of clinical factors with AAS are performed in high-risk populations with a prevalence of upwards of 25%. These studies in a higher risk population likely suffer from spectrum bias. In practice the prevalence of AAS in those we are considering the diagnosis of acute aortic syndrome is likely very low. This is supported by Lovy's study looking at all those who underwent CT to rule out AAS and found a prevalence of 2%. These results were replicated in a review of local prevalence of acute aortic syndrome in those undergoing CT to rule out the diagnosis (2%). A strength of our study is that we include patients who are at a lower risk of acute aortic syndrome. This allows us to confirm the accuracy of previously reported high-risk findings in a lower risk population increasing the external validity and applicability.

Limitations

The data collected were retrospective in nature. This could potentially lead to misclassification

bias with each physician defining the clinical variables according to their own criteria. However in prospective studies examining historical and physical exam findings inter rater reliability is often reported as only fair to moderate. We used strict definitions for our data extraction so as to not further introduce bias. Our inter rate reliability for data extraction was excellent (Kappa 0.91). Misclassification is also a potential issue in defining our cases. However it is unlikely that any case was misclassified as we reviewed the radiology reported generated by staff radiologist and also confirmed the documentation of an assessment by consult service in regards the new diagnosis of AAS.

The aim of this study was to confirm in a lower risk population that classically reported high-risk features maintained their power to differentiate between acute aortic syndrome and an alternative diagnosis. Thus our population was less severely ill then previous studies on acute aortic syndrome. This is apparent in the number presenting with shock (8.4%) in comparison with the IRAD database (22%). This could lead to a reverse spectrum bias artificially increasing the diagnostic accuracy of high-risk features of AAS by including a low risk population with a lower prevalence of these high-risk features. However the inclusion of low risk patients likely represents the population that we are risk stratifying for AAS in daily practice, illustrated by the low prevalence of AAS in all those undergoing CT to rule out the diagnosis(17).

We found that a history of ischemic heart disease and diabetes reduced odds that a patient had acute aortic syndrome. A possible explanation is that the medical history of a specific illness may not have been sought or documented if the clinician felt it not to be relevant to their working differential diagnosis. For example a history of ischemic heart disease or diabetes was

sought in a patient whom the clinician had a higher suspicion for acute coronary syndrome versus acute aortic syndrome. An alternative hypothesis is that both are risk factors for atherosclerosis and it has been reported that atherosclerosis is not associated with acute aortic dissection or intramural hematoma. This is based on the fact that the majority of dissections are found in the ascending aorta where atherosclerosis is less common in addition to the low prevalence of coronary artery disease in perioperative angiograms in those undergoing repair for type A dissections(52, 53).

Our study was retrospective and case control in nature. The prevalence of acute aortic syndrome was fixed, this could artificially inflate the diagnostic accuracy of classically reported high-risk features. However the prevalence of common alternative diagnosis to acute aortic syndrome was comparable to prospective studies investigation high-risk clinical features (ACS 7.2% Vs. Von Kodolitsch et al 7.5% Vs. Nazerian et al 8.7%). We chose not to exclude conditions such as renal colic which clinicians may feel are obviously diagnosed by history. Previous studies looking at the misdiagnosis of AAS found that 2-5% of patients were initially diagnosed with renal colic(8-10, 15). In our cohort 5% of AAS patients presented with flank pain versus 10% in our control population indicating that although uncommon it is important to consider AAS in the differential of renal colic.

There was a high degree of missing data for characteristics of pain. After analyses of the pattern of missing data to account for this we used multiple imputation. We compared the summary odds ratios in the imputed and unimputed datasets they were not significantly different. This indicates that even though a high prevalence of missing data existed it is less likely to have a

significant impact on the reliability of our results.

Clinical and Research Implications

This study adds to the body of literature describing the diagnostic accuracy of high-risk clinical features. It further defines the clinical usefulness of these findings to differentiate a low risk from a high-risk population. Educational strategies focusing on disseminating this information in a small scale has been shown to reduce time to diagnosis by 43%(54).

Further research should focus on the ability of a combination of these factors in the assessment of a patient for acute aortic syndrome, specifically focusing and generating a reproducible assessment of pre test probability. Prospective data collection is needed to address the reproducibility of subjective historical features and the accuracy of D-dimer in a lower risk population.

Conclusion

No single high-risk feature can accurately rule in or rule out acute aortic syndrome. However absence of acute onset pain, history of ischemic heart disease, diabetes and a negative D-dimer can decrease the probability of acute aortic syndrome. The presence of tearing/ripping pain, a history of aortic aneurysm, hypotension, pulse or neurological deficits, new murmur or a widened mediastinum on chest x-ray can increase the probability of acute aortic syndrome.

References

1. Von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. Archives of Internal Medicine. 2000;160(19):2977-82.

2. Armstrong WF, Bach DS, Carey LM, Froehlich J, Lowell M, Kazerooni EA. Clinical and echocardiographic findings in patients with suspected acute aortic dissection. American heart journal. 1998;136(6):1051-60.

3. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. Jama. 2000;283(7):897-903.

4. Asouhidou I, Asteri T. Acute aortic dissection: be aware of misdiagnosis. BMC research notes. 2009;2(1):25.

5. Chua M, Ibrahim I, Neo X, Sorokin V, Shen L, Ooi SB. Acute aortic dissection in the ED: risk factors and predictors for missed diagnosis. The American journal of emergency medicine. 2012;30(8):1622-6.

6. Eagle KA, Quertermous T, Kritzer GA, Newell JB, Dinsmore R, Feldman L, et al. Spectrum of conditions initially suggesting acute aortic dissection but with negative aortograms. The American journal of cardiology. 1986;57(4):322-6.

7. Hansen MS, Nogareda GJ, Hutchison SJ. Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection. The American journal of cardiology. 2007;99(6):852-6.

8. Rosman HS, Patel S, Borzak S, Paone G, Retter K. Quality of history taking in patients with aortic dissection. Chest. 1998;114(3):793-5.

9. Sullivan PR, Wolfson AB, Leckey RD, Burke JL. Diagnosis of acute thoracic aortic dissection in the emergency department. The American journal of emergency medicine. 2000;18(1):46-50.

10. Zhan S, Hong S, Shan-shan L, Chen-ling Y, Lai W, Dong-wei S, et al. Misdiagnosis of aortic dissection: experience of 361 patients. The Journal of Clinical Hypertension. 2012;14(4):256-60.

11. HIRST JR AE, VARNER J JOHNS J, KIME JR SW. Dissecting aneurysm of the aorta: a review of 505 cases. Medicine. 1958;37(3):217.

12. Lilienfeld D, Gunderson P, Sprafka J, Vargas C. Epidemiology of aortic aneurysms: I. Mortality trends in the United States, 1951 to 1981. Arteriosclerosis, Thrombosis, and Vascular Biology. 1987;7(6):637-43.

13. Rapezzi C, Rocchi G, Fattori R, Caldarera I, Ferlito M, Napoli G, et al. Usefulness of transesophageal echocardiographic monitoring to improve the outcome of stent-graft treatment of thoracic aortic aneurysms. The American journal of cardiology. 2001;87(3):315-9.

14. Kurabayashi M, Miwa N, Ueshima D, Sugiyama K, Yoshimura K, Shimura T, et al. Factors leading to failure to diagnose acute aortic dissection in the emergency room. Journal of cardiology. 2011;58(3):287-93.

15. Hirata K, Wake M, Takahashi T, Nakazato J, Yagi N, Miyagi T, et al. Clinical Predictors for Delayed or Inappropriate Initial Diagnosis of Type A Acute Aortic Dissection in the Emergency Room. PloS one. 2015;10(11):e0141929.

16. Li Y, Li L, Mu HS, Fan SL, He FG, Wang ZY. Aortic Dissection and Sudden Unexpected Deaths: A Retrospective Study of 31 Forensic Autopsy Cases. Journal of forensic sciences. 2015;60(5):1206-11.

17. Lovy AJ, Bellin E, Levsky JM, Esses D, Haramati LB. Preliminary development of a clinical decision rule for acute aortic syndromes. The American journal of emergency medicine. 2013;31(11):1546-50.

18. Lovy AJ, Rosenblum JK, Levsky JM, Godelman A, Zalta B, Jain VR, et al. Acute aortic syndromes: a second look at dual-phase CT. AJRAmerican journal of roentgenology. 2013;200(4):805-11.

19. Nazerian P, Giachino F, Vanni S, Veglio MG, Castelli M, Lison D, et al. Diagnostic performance of the aortic dissection detection risk score in patients with suspected acute aortic dissection. European Heart Journal: Acute Cardiovascular Care. 2014;3(4):373-81.

20. Enia F, Ledda G, Lo Mauro R, Matassa C, Raspanti G, Stabile A. Utility of echocardiography in the diagnosis of aortic dissection involving the ascending aorta. Chest. 1989;95(1):124-9.

21. Chan K-L. Usefulness of transesophageal echocardiography in the diagnosis of conditions mimicking aortic dissection. American heart journal. 1991;122(2):495-504.

22. Keren A, Kim CB, Hu BS, Eyngorina I, Billingham ME, Mitchell RS, et al. Accuracy of biplane and multiplane transesophageal echocardiography in diagnosis of typical acute aortic dissection and intramural hematoma. Journal of the American College of Cardiology. 1996;28(3):627-36.

23. Fan Qk, Wang Ww, Zhang Zl, Liu Zj, Yang J, Zhao Gs, et al. Evaluation of D-dimer in the diagnosis of suspected aortic dissection. Clinical chemistry and laboratory medicine : CCLM / FESCC. 2010;48(12):1733-7.

24. Giachino F, Loiacono M, Lucchiari M, Manzo M, Battista S, Saglio E, et al. Rule out of acute aortic dissection with plasma matrix metalloproteinase 8 in the emergency. 2013.

25. Jansen AC, van Aalst-Cohen ES, Hutten BA, Büller HR, Kastelein JJ, Prins MH. Guidelines were developed for data collection from medical records for use in retrospective analyses. Journal of clinical epidemiology. 2005;58(3):269-74.

26. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. Journal of clinical epidemiology. 1995;48(12):1503-10.

27. Hennessy S, Bilker WB, Berlin JA, Strom BL. Factors influencing the optimal control-to-case ratio in matched case-control studies. American Journal of Epidemiology. 1999;149(2):195-7.

28. Theivacumar NS, Stephenson MA, Mistry H, Valenti D. Diabetics are less likely to develop thoracic aortic dissection: a 10-year single-center analysis. Annals of vascular surgery. 2014;28(2):427-32.

29. Prakash SK, Pedroza C, Khalil YA, Milewicz DM. Diabetes and reduced risk for thoracic aortic aneurysms and dissections: a nationwide case-control study. Journal of the American Heart Association. 2012;1(2):jah3-e000323.

30. Tsai CL, Lin CL, Wu YY, Shieh DC, Sung FC, Kao CH. Advanced complicated diabetes mellitus is associated with a reduced risk of thoracic and abdominal aortic aneurysm rupture: a population-based cohort study. Diabetes/Metabolism Research and Reviews. 2015;31(2):190-7.

31. Torsney E, Pirianov G, Cockerill GW. Diabetes as a negative risk factor for abdominal aortic aneurysm–does the disease aetiology or the treatment provide the mechanism of protection? Current vascular pharmacology. 2013;11(3):293-8.

32. Asha SE, Miers JW. A Systematic Review and Meta-analysis of D-dimer as a Rule-out Test for Suspected Acute Aortic Dissection. Annals of emergency medicine. 2015;66(4):368-78.

33. Cui Js, Jing Zp, Zhuang Sj, Qi Sh, Li L, Zhou Jw, et al. D-dimer as a biomarker for acute aortic dissection: a systematic review and meta-analysis. Medicine. 2015;94(4):e471.

34. Hartnell GG, Wakeley CJ, Tottle A, Papouchado M, Wilde RP. Limitations of chest radiography in discriminating between aortic dissection and myocardial infarction: implications for thrombolysis. Journal of thoracic imaging. 1993;8(2):152-5.

35. Jagannath AS, Sos TA, Lockhart SH, Saddekni S, Sniderman KW. Aortic dissection: a statistical analysis of the usefulness of plain chest radiographic findings. American Journal of Roentgenology. 1986;147(6):1123-6.

36. Klompas M. Does this patient have an acute thoracic aortic dissection? JAMA : the journal of the American Medical Association. 2002;287(17):2262-72.

37. Olsson C, Thelin S, Ståhle E, Ekbom A, Granath F. Thoracic Aortic Aneurysm and Dissection Increasing Prevalence and Improved Outcomes Reported in a Nationwide Population-Based Study of More Than 14 000 Cases From 1987 to 2002. Circulation. 2006;114(24):2611-8.

38. Pape LA, Tsai TT, Isselbacher EM, Oh JK, O'Gara PT, Evangelista A, et al. Aortic diameter≥ 5.5 cm is not a good predictor of Type A aortic dissection observations from the International Registry of Acute Aortic Dissection (IRAD). Circulation. 2007;116(10):1120-7.

39. Hoffman JI, Kaplan S. The incidence of congenital heart disease. Journal of the American college of cardiology. 2002;39(12):1890-900.

40. Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. The American journal of cardiology. 2005;96(5):718-21.

41. Elefteriades JA. Natural history of thoracic aortic aneurysms: indications for surgery, and surgical versus nonsurgical risks. The Annals of thoracic surgery. 2002;74(5):S1877-S80.

42. Davies RR, Kaple RK, Mandapati D, Gallo A, Botta DM, Elefteriades JA, et al. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. The Annals of Thoracic Surgery. 2007;83(4):1338-44.

43. Gore I. Dissecting aneurysms of the aorta in persons under forty years of age. AMA archives of pathology. 1953;55(1):1-13.

44. Girdauskas E, Kuntze T, Borger MA, Falk V, Mohr F-W. Surgical risk of preoperative malperfusion in acute type A aortic dissection. The Journal of Thoracic and Cardiovascular Surgery. 2009;138(6):1363-9.

45. Nallamothu BK, Mehta RH, Saint S, Llovet A, Bossone E, Cooper JV, et al. Syncope in acute aortic dissection: diagnostic, prognostic, and clinical implications. The American journal of medicine. 2002;113(6):468-71.

46. Pare JR, Liu R, Moore CL, Sherban T, Kelleher MS, Thomas S, et al. Emergency physician focused cardiac ultrasound improves diagnosis of ascending aortic dissection. The American journal of emergency medicine. 2015.

47. Nicosia A, Greco G, Felis S, Drago A, Deste W, Tamburino C, et al. [Diagnostic accuracy of transesophageal echocardiography in the diagnosis of aortic dissection: comparison with computerized axial tomography]. Cardiologia (Rome, Italy). 1995;40(5):329-39.

48. Nienaber CA, von Kodolitsch Y, Brockhoff CJ, Koschyk DH, Spielmann RP. Comparison of conventional and transesophageal echocardiography with magnetic resonance imaging for anatomical mapping of thoracic aortic dissection. A dual noninvasive imaging study with anatomical and/or angiographic validation. International journal of cardiac imaging. 1994;10(1):1-14.

49. Nienaber CA, von Kodolitsch Y, Nicolas V, Siglow V, Piepho A, Brockhoff C, et al. The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. The New England journal of medicine. 1993;328(1):1-9.

50. Penco M, Paparoni S, Dagianti A, Fusilli C, Vitarelli A, De Remigis F, et al. Usefulness of transesophageal echocardiography in the assessment of aortic dissection. The American journal of cardiology. 2000;86(4A):53G-6G.

51. Nazerian P, Vanni S, Castelli M, Morello F, Tozzetti C, Zagli G, et al. Diagnostic performance of emergency transthoracic focus cardiac ultrasound in suspected acute type A aortic dissection. Internal and emergency medicine. 2014;9(6):665-70.

52. Coady MA, Ikonomidis JS, Cheung AT, Matsumoto AH, Dake MD, Chaikof EL, et al. Surgical management of descending thoracic aortic disease: open and endovascular approaches a scientific statement from the American Heart Association. Circulation. 2010;121(25):2780-804.

53. Motallebzadeh R, Batas D, Valencia O, Chandrasekaran V, Smith J, Brecker S, et al. The role of coronary angiography in acute type A aortic dissection. European journal of cardio-thoracic surgery. 2004;25(2):231-5.

54. Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management Part I: from etiology to diagnostic strategies. Circulation. 2003;108(5):628-35.

Tables

Table 1. Characteristics of clinical features of 970 patients enrolled in the study

Characteristics	**N (%)**
Family history recorded	68(7.1)
Past Medical History	
Cardiac surgery	77(8.3)
Aortic valve disease	22(2.2)
Known aortic aneurysm	44(4.6)
Ischemic heart disease	190(19.8)
Connective tissue disease (Marfans, Ehlers Danlos)	9(0.9)
Radiculopathy	38(4)
Percutaneous coronary intervention	58(6)
Hypertension	467(48.6)
Diabetes	155(15.2)
Deep vein thrombosis/Pulmonary embolism	36(3.7)
Renal Colic	69(7.1)
Biliary disease	48(4.9)
Chronic kidney injury	115(11.8)
Symptom	
Acute onset pain	423(50.1)
Pain resolving	363(51.2)
Location of pain	
Back	143(14.7)
Abdomen	384(39.5)
Chest	501(51.6)
Flank	88(9.1)
Character of pain	771(79.4)
Tearing/ripping	23(2.9)
Sharp	297(38.5)
Squeeze/pressure	311(40.3)
Pleuritic	106(13.8)
Other	128(16.6)
Migrating/radiating of pain	456(47)
Syncope	27(2.8)
Presyncope	118(12.2)
Subjective Neurological deficits	115(11.8)

Physical Exam	
Bilateral blood pressure measurement	250(25.8)
Bilateral blood pressure differential (>20mmHg)	56(22.1)
Hypertension (>140mmHg)	419(43.2)
Hypotension	53(5.5)
Bibasilar crackles	60(6.2)
New murmur	57(5.9)
Pulse deficit	37(3.8)
Focal Neurological deficit	44(4.5)
Palpable tenderness	364(37.5)
Investigation	
D-dimer	125(12.8)
D-dimer >500ng/dl	76(63)
Creatinine elevated	287(34.1)
White blood cell count elevated	311(34.5)
Liver function tests (AST, ALT, GGT) elevated	47(110.5)
Widened mediastinum or absence of aortic notch	110(18.3)
Electrocardiogram ischemic changes	95(14.7)
Computed tomography	380(39.2)
Echocardiography	135(14.1)
Outcome	
Admitted to hospital	323(33.3)
Surgery	137(14.1)
Died	39(4)
Returned confirming no death	267(27.5)
Discharged	
Return >14days confirming no death	638(65.8)

Table 2. Characteristics of 970 patients enrolled in the study

Characteristics	N (%)
Mean (SD) age (years)	65(14.1)
Age range (years)	24-93
Male	640(66.7)
Hospital Site	
Civic Hospital	312(32.5)
General Hospital	571(59.5)
University of Ottawa Heart Institute	87(9.1)
Arrival status	
Arrival by ambulance	363(37.8)
Transferred from another emergency department	92(9.5)
Acute aortic syndrome	194(20)
Type A	114(59)
Type B	80(41)
Missed cases of acute aortic syndrome	32(16.7)
No Acute aortic syndrome	776(80)
Chest pain unspecified	201(20.7)
Abdominal Pain unspecified	96(9.9)
Acute coronary syndrome	84(8.7)
Renal Colic	62(6.4)
Biliary disease	26(2.7)
Mechanical back pain	25(2.6)
Diverticulitis	24(2.5)
Pancreatitis	18(1.9)
Constipation	17(1.8)
Back pain unspecified	14(1.4)
Cancer	13(1.3)
Musculoskeletal chest pain	12(1.2)
Gastroenteritis	10(1)
Gastritis/Gastro esophageal reflux disease	10(1)
Other	174(17.9)

Table 3. Univariate correlation of variables with acute aortic syndrome

Characteristics	**AASN (% of AAS)** 194(20)	**No AAS N (% of No AAS)** 776(80)	**P value**
Family history	24(12.4)	44(5.8)	P<0.001
Past Medical History			
Cardiac surgery	14(7.2)	63(8.1)	P<0.678
Aortic valve disease	10(5.2)	12(1.6)	P<0.002
Known aortic aneurysm	27(13.9)	17(2.2)	P<0.001
Ischemic heart disease	19(9.7)	171(22)	P<0.001
Connective tissue disease	7(3.6)	2(0.3)	P<0.001
Radiculopathy	7(3.6)	31(3.9)	P<0.803
Percutaneous coronary intervention	5(2.6)	53(6.8)	P<0.001
Hypertension	125(64.4)	342(44.1)	P<0.001
Diabetes	14(7.2)	141(18.2)	P<0.001
Deep vein thrombosis/Pulmonary embolism	7(3.6)	29(3.7)	P<0.932
Renal Colic	6(3.1)	63(8.2)	P<0.015
Biliary disease	5(32.6)	43(5.5)	P<0.025
Chronic kidney injury	31(15.9)	84(10.8)	P<0.047
Symptom			
Acute onset Pain	164(95.7)	259(38.6)	P<0.001
Pain resolving	71(56.4)	292(50.2)	P<0.208
Location of pain			
Back	53(27.3)	90(11.6)	P<0.001
Abdomen	55(28.4)	329(42.4)	P<0.001
Chest	135(69.6)	366(47.2)	P<0.001
Flank	10(5.2)	78(10.1)	P<0.034
Character of pain	153(78.8)	618(79.7)	P<0.8
Tearing/ripping	21(13.6)	2(0.3)	P<0.001
Sharp	73(47.4)	224(36.3)	P<0.01
Squeeze/pressure	54(35.1)	257(41.6)	P<0.14
Pleuritic	32(20.8)	74(11.9)	P<0.005
Other	4(2.6)	124(20.1)	P<0.001
Migrating/radiating pain	146(75)	310(40)	P<0.001
Neck	32(21.9)	55(17.7)	P<0.37
Arm	22(15.1)	123(39.8)	P<0.001
Leg	20(13.7)	34(11)	P<0.46
Back	53(36.3)	90(29)	P<0.001
Flank	10(6.8)	78(22.6)	P<0.03
Abdomen	22(15.1)	26(8.4)	P<0.001
Chest	17(11.6)	17(5.5)	P<0.001
Syncope	17(8.8)	10(1.3)	P<0.001
Presyncope	30(15.5)	88(11.3)	P<0.12
Subjective Neurological deficits	54(27.8)	61(7.9)	P<0.001

Physical Exam			
Bilateral BP differential (>20mmHg)	39(29.8)	17(13.8)	P<0.002
Hypertension (>150mmHg)	88(45.4)	331(42.6)	P<0.372
Hypotension	43(22.2)	10(1.3)	P<0.001
Bibasilar crackles	14(7.2)	46(5.9)	P<0.505
New murmur	40(20.6)	17(2.2)	P<0.001
Pulse deficit	33(20.6)	4(0.7)	P<0.001
Focal Neurological deficit	25(12.9)	19(2.5)	P<0.001
Palpable tenderness	37(22.3)	327(46.8)	P<0.001
Investigation			
D-Dimer >500ng/dl	59(96.7)	17(28.3)	P<0.001
Creatinine elevated	103(55.7)	184(28.4)	P<0.001
WBC elevated	112(58.9)	119(27.9)	P<0.001
LFTs elevated	18(14.9)	29(9.4)	P<0.101
Widened mediastinum or absence of aortic notch	86(52.4)	24(5.1)	P<0.001
ECG ischemic changes	36(21.8)	59(12.3)	P<0.003
CT	181(93.3)	199(25.9)	P<0.001
ECHO	101(52.1)	34(4.4)	P<0.001
Valve abnormality	53(51.9)	11(33.3)	P<0.063
Aortic root dilation	62(60.8)	2(6.1)	P<0.001
Outcome			
Admitted	192(98.9)	131(16.9)	P<0.001
Surgery	106(54.7)	31(3.4)	P<0.001
Died	36(18.5)	3(0.3)	P<0.001
Returned confirming no death	146(75.3)	121(15.6)	P<0.001
Discharged			
Return >14days confirming no death	0	633(81.6)	
Missed	32(16.8)	0	P<0.001

Table 4. Unadjusted and adjusted odds of historical, examination and investigations for acute aortic syndrome

Characteristics	Odds ratio (95%CI) Unadjusted	Odds ratio (95%CI) adjusted	Missing values N (%)
Past Medical History			
Cardiac surgery	0.88(0.48-1.61)	-	
Aortic valve disease	3.46(1.47-8.13)	0.97(0.08-11.63) ^	
Known aortic aneurysm	7.22(3.85-13.55)	**13.86(4.63-41.38)^**	
Ischemic heart disease (Angina or previous acute coronary syndrome)	0.38(0.23-0.64)	**0.09(0.02-0.32)^**	
Connective tissue disease	14.49(2.99-70.30)	3.36(0.39-29.07)^	
Radiculopathy	0.90(0.39-2.08)	-	
Percutaneous coronary intervention	0.36(0.14-0.92)	-	
Hypertension	2.30(1.66-3.19)	**2.91(1.34-6.12)^**	
Diabetes	0.35(0.20-0.62)	**0.35(0.16-0.79)^**	
Deep vein thrombosis/Pulmonary embolism	0.96(0.42-2.24)	-	
Renal Colic	0.36(0.15-0.85)	**0.20(0.04-0.91)^**	
Biliary disease	0.45(0.18-1.15)	-	
Chronic kidney injury	1.57(1.00-2.45)	1.91(0.67-5.43)^	
Symptom			
Acute onset pain	37.18(17.18-80.48)	**25(10.32-60.63)***	129(13)
Pain resolving	1.28(0.87-1.88)	-	256 (26)
Location of pain			
Back	2.87(1.95-4.21)	-	
Abdomen	0.54(0.38-0.76)	-	
Chest	2.56(1.83-3.59)	-	
Flank	0.49(0.25-0.96)	-	
Character of pain			
Tearing/ripping	48.55(11.25-209.58)	**37.26(3.84-361.65)***	198(20)
Sharp	1.59(1.11-2.26)	0.93(0.54-1.73)*	198(20)
Squeeze/pressure	0.76(0.53-1.10)	-	198(20)
Pleuritic	1.93(1.22-3.05)	**2.17(1.05-4.51)***	198(20)
Other	0.11(0.04-0.29)	**0.26(0.1-0.66)***	198(20)

Migrating/radiating pain	2.5(1.3-4.31)	**3.1(1.7-5.65)***	524(54)
Neck	1.25(0.77-2.04)	-	
Arm	0.26(0.15-0.43)	-	
Leg	1.25(0.69-2.25)	-	
Back	2.55(1.70-3.82)	-	
Flank	0.71(0.29-1.71)	-	
Abdomen	1.88(1.02-3.44)	-	
Chest	2.20(1.09-4.45)	-	
Syncope	7.36(3.31-16.34	0.46(0.15-1.43)*	
Presyncope	1.43(0.91-2.24)	-	
Subjective Neurological deficits	4.52(3.01-6.81)	-	
Physical Exam			
Hypertension (>150mmHg)	1.12(0.81-1.53)	-	
Hypotension	21.81(10.73-44.36)	**12.84(3.23-51.01)***	
Bibasilar crackles	1.23(0.66-2.30)	-	
New murmur	11.60(6.41-20.99)	**5.24(1.97-13.92)***	2(<1)
Pulse deficit	39.56(13.83-113.21)	**21.01(5.31-83.27)***	
Focal Neurological deficit	5.90(3.17-10.95)	**3.33(1.5-6.91)***	
Palpable tenderness	0.33(0.22-0.48)	0.63(0.30-1.34)*	105(11)
Investigations			
D-Dimer >500ng/dl	74.62(16.37-340.13)	-	849(88)
Creatinine elevated	3.17(2.27-4.44)	-	136(14)
White blood cell count elevated	3.70(2.66-5.16)	-	68(7)
Liver function tests (AST, ALT, GGT) elevated	1.69(0.90-3.17)	-	535(55)
Widened mediastinum or absence of aortic notch on chest x-ray	20.40(12.22-34.05)	-	339(35)
Electrocardiogram ischemic changes	2.00(1.26-3.16)	-	324(33)
Valve abnormality	74.62(16.37-340.13)	-	835(86)
Aortic root dilation	3.17(2.27-4.44)	-	835(86)

*Adjusted for acute onset pain migrating tearing, sharp pleuritic other palpable tenderness syncope subjective neurological deficits hypotension murmur pulse deficit focal neurological deficit

^Adjusted for acute onset pain migrating tear sharp pleuritic other tender hypotension murmur pulse deficit focal neurological deficit history of hypertension aortic valve disease diabetes known aneurysm ischemic heart disease history of renal colic known connective tissue disease

Table 5. Diagnostic accuracy of high-risk clinical features and investigations for acute aortic syndrome

Characteristics	Sensitivity (95%CI)	Specificity (95%CI)	LR- (95%CI)	LR+ (95%CI)
Family history	87.6(82.2-92)	5.7(4.2-7.5)	**2.18(1.36-3.5)**	0.93(0.88-0.98)
Past Medical History				
Cardiac surgery	7.2(4-11.8)	91.9(89.7-93.7)	1.01(0.97-1.06)	0.89(0.51-1.55)
Aortic valve disease	5.2(2.5-9.3)	98.5(97.3-99.2)	0.96(0.93-1)	**3.33(1.46-7.6)**
Known aortic aneurysm	13.9(9.4-19.6)	97.8(96.5-98.7)	0.88(0.83-0.93)	**6.35(3.54-11.42)**
Ischemic heart disease (Angina, previous acute coronary syndrome)	9.8(6-14.9)	78(74.9-80.8)	1.16(1.09-1.23)	**0.44(0.28-0.7)**
Connective tissue disease	3.6(1.5-7.3)	99.7(99.1-1)	0.97(0.94-0.99)	**14(2.93-66.86)**
Radiculopathy	3.6(1.5-7.3)	96(94.4-97.3)	1(0.97-1.04)	0.9(0.4-2.02)
Percutaneous coronary intervention	2.6(0.8-5.9)	93.2(91.2-94.8)	1.05(1.01-1.08)	**0.38(0.15-0.93)**
Hypertension	64.4(57.3-71.2)	55.9(52.4-59.5)	0.64(0.52-0.78)	1.46(1.28-1.67)
Diabetes	7.2(4-11.8)	81.8(78.9-84.5)	1.13(1.08-1.19)	**0.4(0.23-0.67)**
Deep vein thrombosis/Pulmonary embolism	3.6(1.5-7.3)	96.3(94.7-97.5)	1(0.97-1.03)	0.97(0.43-2.17)
Renal Colic	3.1(1.1-6.6)	91.9(89.7-93.7)	1.05(.02-1.09)	0.38(0.17-0.87)
Biliary disease	2.6(0.8-5.9)	94.5(92.6-96)	1.03(1-1.06)	0.27(0.19-1.16)
Chronic kidney injury	16(11.1-21.9)	89.2(86.8-91.3)	0.94(0.88-1.01)	1.48(1.01-2.16)
Symptom				
Acute onset pain	95.9(91.7-98.3)	61.3(57.5-65.1)	**0.07(0.03-0.14)**	**2.48(2.24-2.74)**
Pain resolving	55.9(46.8-64.7)	50.3(46.1-54.4)	0.88(0.71-1.08)	1.12(0.94-1.34)
Location of pain				
Back	26.9(20.9-33.7)	88.4(85.9-90.6)	0.83(0.76-0.90)	**2.32(1.72-3.13)**
Abdomen	28.4(22.1-35.3)	57.6(54-61.1)	1.24(1.12-1.38)	0.67(0.53-0.85)
Chest	69.6(62.6-76)	52.8(49.3-56.4)	0.58(0.46-0.72)	1.48(1.31-1.66)
Flank	5.2(2.5-9.3)	90(87.6-92)	1.05(1.01-1.10)	0.51(0.27-0.97)
Character of pain				
Tearing/ripping	13.6(8.6-20.1)	99.7(98.8-99.9)	0.87(0.81-0.92)	**42.07(9.97-177.49)**
Sharp	47.4(39.3-55.6)	63.8(59.8-67.6)	0.83(0.70-0.97)	1.31(1.07-1.59)
Squeeze/pressure	35.1(27.6-43.2)	58.4(54.4-62.3)	1.11(0.97-1.27)	0.84(0.67-1.07)
Pleuritic	20.8(14.7-28.1)	88.03(85.2-90.5)	0.90(0.83-0.98)	**1.74(1.19-2.53)**
Other	2.6(0.7-6.5)	79.9(76.6-83)	1.22(1.16-1.28)	0.13(1.05-0.34)
Migrating/radiating pain	60.1(56.5-63.5)	75.3(68.6-81.2)	**1.88(1.67-2.12)**	0.41(0.32-0.53)

Neck	21.9(15.5-29.5)	81.7(76.8-85.9)	0.96(0.86-1.06)	1.20(0.81-1.76)
Arm	15.1(9.7-21.9)	59(53.2-64.6)	1.44(1.28-1.63)	0.37(0.24-0.55)
Leg	13.7(8.6-20.4)	88.7(84.6-92.1)	0.97(0.90-1.05)	1.21(0.72-2.03)
Back	56.9(48.4-65)	65.9(60.3-71.2)	0.65(0.53-0.80)	1.67(1.35-2.06)
Flank	4.8(1.9-9.6)	93.4(89.9-95.9)	1.02(0.97-1.07)	0.72(0.31-1.67)
Abdomen	15.1(9.7-21.9)	91.4(87.6-94.3)	0.93(0.86-1)	**1.74(1.02-2.97)**
Chest	11.6(6.9-18)	94.4(91.1-96.7)	0.94(0.88-1)	**2.06(1.08-3.92)**
Syncope	8.8(5.2-13.7)	98.7(97.6-99.4)	0.92(0.88-0.97)	**6.8(3.16-14.61)**
Presyncope	15.5(10.7-21.3)	88.7(86.2-90.8)	0.95(0.89-1.02)	1.36(0.93-2)
Subjective Neurological deficits	27.8(21.7-34.7)	92.1(90-93.9)	0.78(0.72-0.86)	**3.54(2.54-4.93)**
Physical Exam				
Bilateral BP differential (>20mmHg)	30.2(22.5-38.9)	86.2(78.8-91.7)	0.81(0.71-0.93)	**2.19(1.31-3.65)**
Hypertension (>150mmHg)	45.4(38.2-52.7)	57.4(53.8-60.9)	0.95(0.83-1.27)	1.06(0.89-1.27)
Hypotension	22.2(16.5-28.7)	98.7(97.6-99.4)	0.79(0.7300.85)	**17.2(8.8-33.61)**
Bibasilar crackles	7.2(4-11.8)	94.1(92.2-95.6)	0.99(0.94-1.03)	1.22(0.68-2.17)
New Murmur	20.6(15.2-27)	97.8(96.5-98.7)	0.81(0.75-0.87)	**9.41(5.46-16.24)**
Pulse deficit	20.6(14.6-27.7)	99.3(98.3-1)	0.8(0.74-0.86)	**31.14(11.20-86.62)**
Focal Neurological deficit	16.3(10.9-23.2)	96.9(95.2-98.1)	0.86(0.80-0.93)	**5.26(2.98-9.30)**
Palpable tenderness	22.3(16.2-29.4)	53.2(49.4-57)	1.46(1.31-1.63)	**0.48(0.35-0.64)**
Investigation				
D-Dimer >500ng/dl	96.7(88.7-99.6)	71.7(58.6-82.6)	**0.05(0.01-0.18)**	**3.41(2.28-5.12)**
Creatinine elevated	55.7(48.2-63)	71.7(68-75.1)	0.62(0.52-0.73)	**1.96(1.64-2.35)**
	40(32.9-47.4)	82.3(79.1-85.1)	0.73(0.64-0.82)	**2.26(1.77-2.87)**
White blood cell count elevated	59(51.6-66)	72.1(68.6-75.3)	0.57(0.48-0.68)	**2.11(1.78-2.49)**
	23.7(17.8-30.4)	91.4(89.1-93.4)	0.83(0.77-0.91)	**2.76(1.95-3.92)**
Liver function tests (AST, ALT, GGT) elevated	14.9(9.1-22.5)	90.6(86.8-93.6)	0.94(0.86-1.02)	1.59(0.92-2.75)
Widened mediastinum or absence of aortic notch on chest x-ray	52.4(44.5-60.3)	94.9(92.5-96.7)	**0.5(0.43-0.59)**	**10.23(6.75-15.50)**
Electrocardiogram ischemic changes	21.8(15.8-28.9)	87.7(84.5-90.5)	0.89(0.82-0.97)	**1.78(1.22-2.59)**
Echocardiography	24.03(5.45-105.98)	339(35)	24.03(5.45-105.98)	
Valve abnormality	52(41.8-62)	66.7(48.2-82)	0.72(0.53-0.99)	1.56(0.93-2.62)
Aortic root dilation	60.8(50.6-70.3)	93.9(79.8-99.3)	**0.42(0.32-0.54)**	**10.03(2.59-38.78)**

Appendix

Case – Health records search of ICD 9 code for acute aortic dissection. Database searched emergency department diagnosis, hospital discharge diagnosis and death certificates. Cases randomized by computer generated random number Cases reviewed for relevant exclusion criteria. Acute aortic syndrome confirmed on imaging - Computed tomography, MRI or trans esophageal echocardiography report stating aortic dissection, intramural hematoma or penetrating atherosclerotic ulcer.

Control – Health record search of triage diagnosis for chest, abdominal, flank, and back pain. Controls randomized by computer generated random number. Sequentially reviewed by random number and matched with case by age and sex then assessed for exclusion criteria.

Dissection type – Type – Aortic pathology located in the ascending aorta, type B located in the descending aorta.

Arrive by ambulance – Pre printed standardized triage document contains tick box for method of arrival. Arrive by ambulance positive if box ticked. If other mode of presentation or no tick present defined as not arriving by ambulance.

Referral for acute aortic syndrome – If Emergency department record of treatment mentions transfer from other facility. Documentation from an emergency department other than the Civic or General campus emergency department. All patients seen at the heart institute were considered referrals given the institution does not have an emergency department.

Ischemic heart disease – documented previous myocardial infarction or angina.

Past medical history – if a specific condition was not documented in the nursing triage note, emergency department record of treatment, consultant notes or integrated progress notes it was deemed not to be present.

Acute onset pain – documented as acute, sudden or starting at a defined time and reaching maximal intensity at onset.

Pain resolving – pain less intense at presentation or over the stay in the emergency department, does not take into account if analgesia was received.

Character pain – other = burning, cramping or indescribable.

New murmur – any new murmur heard on auscultation not specified if diastolic or systolic. If murmur was not known to be new or old it was defined as new.

Subjective neurological deficits – patient described focal weakness or altered sensation, resolved or ongoing.

Inter limb pulse differential – documented difference in character or volume of pulse between either right and left arm or right and left leg at any location. If not specifically mentioned as abnormal assumed to be normal.

Bilateral blood pressure measurement – recorded measure within 12hrs of presentation, if more than one measurement first documented blood pressure differential was recorded.

Hypertension (<150mmHg) – earliest documented blood pressure, most often the blood pressure taken by the triage nurse.

Hypotension (<90mmHg) – any documented hypotension within the emergency department.

Chapter Five : Variation in emergency department use of computed tomography for investigation of acute aortic syndrome

Chapter overview

The following is a manuscript prepared for publication based on a historical cohort study. The objectives of the manuscript were to assess: 1) Emergency physician use of computed tomography (CT) for the investigation of AAS; 2) Diagnostic yield of CT ordered to rule out AAS; 3) Variation in CT ordering among physicians in patients presenting with pain for diagnosis of AAS.

Dr. R. Ohle is the first author of this paper, having been primarily responsible for data collection, analysis and writing of manuscript. This manuscript was co-authored by Dr. R. Ohle, his co-supervisors Dr. J. Perry and Dr. G. Wells. Dr. J. Perry and Dr. G. Wells provided valuable feedback throughout the process. Mr. Omar Anjum and Ms. Helena Bleeker contributed to data extraction.

See Appendix B for ethics board approval

Variation in emergency department use of computed tomography for investigation of acute aortic syndrome

Robert Ohle[1], Omar Anjum[2], Helena Bleeker[2], George Wells[3, 4], Jeffrey J. Perry[1]

[1] The Department of Emergency Medicine, The Ottawa Hospital Research Institute, University of Ottawa, Canada

[2]Department of Undergraduate Medicine, University of Ottawa, Canada

[3]Department of Epidemiology and Community Medicine, University of Ottawa, Canada

[4]Cardiovascular Research Methods Center, University of Ottawa Heart Institute, Canada

Correspondence to Robert Ohle E-mail:

Word Count: 2515

This manuscript includes one (1) figure and four (4) tables.

Abstract

Introduction

Acute aortic syndrome (AAS) is a life threatening condition making early diagnosis critical. Although 90% present with acute pain, the myriad of associated symptoms can make investigation and diagnosis a challenge. Our objectives were: 1) assess the rate of CT ordering for AAS in those presenting with truncal pain; 2) calculate the diagnostic yield of CT's ordered; 3) quantify variation in ordering among physicians.

Methods

This historical cohort study of consecutive adult patients presenting to two tertiary academic care emergency departments over one calendar year included patients with a primary complaint of non-traumatic chest, back, abdominal or flank pain. Patients were excluded if clear diagnosis (e.g. pneumonia, urinary tract infection abscess, cellulitis, arrhythmia) was made by basic investigations (e.g. plain x-ray, urinalysis) or exam. Data were abstracted in a standardized fashion by trained researchers. Primary outcome was rate of CT Thorax or CT Thorax/Abdomen ordered to rule out AAS as per clinical indication on diagnostic requisition. Secondary outcome was variation in CT ordering. Variation was measured using the Gini coefficient; modeling physician CT usage (high user>12CT/yr., low user<12CT/yr.) adjusting for training (5 year residency (FRCPC) versus family medicine residency with 1 year subspecialty training (CCFP-EM)), gender, and years in practice. Sample size of 12 per group was calculated based on an expected delta in mean CT ordered of 5 and a within group SD of 3.

Results

31,201 patients presented with chest abdominal, back, or flank pain during the study period.

8,472 were excluded based on a diagnosis made by clinical exam or basic investigations. 22,776 were included (Mean 47years SD 18.5yrs 56.2% Female). Most common diagnoses; Chest pain unspecified (23.3%), Abdominal pain unspecified (20.8%), Lower back pain unspecified (10.5%), Renal Colic (5.3%), Female reproductive pathology (3.0%) and Acute coronary syndrome (2.9%). CT was ordered to rule out AAS in 175 (0.7%) patients (Mean 62 years SD 16.5, 50.6% Female). Only 4(2.3%) were found to have an AAS. There was a large variation in CT's ordered between physicians (Gini coefficient 0.42). No AAS were missed.

Conclusions

Current rate of imaging for AAS is appropriately low but inefficient, with 98% of advanced imaging negative for AAS. There is considerable variation in physician CT ordering without an increase in diagnosis. These findings suggest great potential for more standardized and efficient use of CT for the diagnosis of AAS.

Introduction

Acute aortic syndrome (AAS) is the clinical syndrome resulting from acute aortic dissection, intramural hematoma and penetrating atherosclerotic ulcer. It is a life threatening condition making early diagnosis critical(1). Although 90% present with acute pain the myriad of associated symptoms can make investigation and diagnosis a challenge(1-3). The most common modality for investigating AAS is computed tomography (CT)(1). There is no accurate Canadian data available for the use and yield of CT for the diagnosis of AAS. However the American College of Emergency Physicians (ACEP) and the American Heart Association (AHA) guidelines on investigation for AAS state that clinicians must maintain a high index of suspicion in those presenting with chest, back, abdominal pain and/or a perfusion deficit. If no alternative diagnosis is found for a patient's symptoms they should undergo advanced imaging(4, 5). We know there are 4.6million visits per year to American emergency departments for chest pain alone, and up to 1/3 of these will remain undiagnosed(6). Although these recommendations likely have good sensitivity, they may lead to over investigation.

Lovy's 2013 case control study in the United States, shows 97.3% of all CT's to rule out AAS are negative(7). Guidelines that could lead to even a modest reduction in imaging could lead to large savings in health care expenditure. Unnecessary usage of this modality exposes patients to radiation, risk of contrast complications and morbidity related to incidental findings.

Our objectives were: 1) assess the rate of CT ordering for AAS in those presenting with truncal pain; 2) calculate the diagnostic yield of CT's ordered; 3) quantify variation in ordering among physicians. This information, in turn, would suggest the potential for improved efficiency and standardization of patient care through guidelines or a clinical decision rule.

Methods

This historical cohort study of consecutive adult patients presenting to two tertiary academic care EDs over one calendar year included patients with a primary complaint of non-traumatic chest, back, abdominal or flank pain. Our initial study population was generated through a search for a triage diagnosis of truncal pain (non-traumatic chest, back, abdominal or flank pain). The discharge diagnoses of these patients were screened and patients were excluded if a clear diagnosis could be made (i.e. pneumonia, pneumothorax, urinary tract infection, acute fracture, abscess or cellulitis, pharyngitis, herpes zoster, viral infection, arrhythmia) by basic investigations or initial clinical exam. For included patients who underwent CT thorax or thorax and abdomen, the ordering physician and indication for imaging were recorded. Data were extracted from the electronic radiology requisitions. Data were abstracted in a standardized fashion by 2 trained researchers. A standardized electronic data collection form was used. The form was trialed on 20 patient charts, refined and re trialed on a further 20 charts. To confirm accurate data extraction a proportion of data (20%) were reviewed by the 2 trained researchers and a third reviewer (RO). Agreement was measured using the Kappa statistic and disagreement was resolved through discussion, were consensus could not be researched final decision was made by third reviewer (RO). The primary outcome was the frequency of CT Thorax or Thorax/Abdomen ordered to rule out AAS. Secondary outcome was variation in CT ordering. Variation was measured with the Gini coefficient.

The Gini coefficient is a measure of statistical dispersion intended to represent the distribution of a variable across a population. It is most commonly used as a measure of unequal income distribution(8). A coefficient of 0 indicates that the variable is distributed evenly among a

population. A theoretical Gini coefficient of 1 indicates that the variable is distributed to one individual. There is no agreed upon definition of what constitutes mild, moderate or high levels of inequality. The United Nations defines the Gini coefficient related to income distribution as; low<0.25, moderate=0.25-0.35, high =0.35-0.5 extremely high >0.5(9). We used this definition given that most studies, using the Gini coefficient to describe distribution of resources use the United Nations grading(10).

In our study a Gini coefficient of 0 represents no variability and a coefficient of 1 represented marked variability in CT ordering per physician adjusting for training, years in practice and gender. (11, 12). We expected the number of patients included to be greater than 20,000 therefore it was not deemed feasible to review all patients to ascertain the rate of CT's ordered by each physician per number of patients seen. Therefore we used the proportion of CT's ordered per hours worked as a surrogate for number of patients seen. We calculated expected number of CT's per year based on their actual number ordered per hours worked. Calculated CT's per year was based on a physician working 15 shifts of 8hrs per month over 1 year (full time at our institution). Physicians were divided into high-test users (>12 CT/year) or low-test users (<12 CT/year). The Gini coefficient was used to measure unequal distribution of CT usage amongst physicians accounting for confounding factors such as training (CCFP-family physicians with an extra 1 year training in emergency medicine versus FRCPC-a dedicated 5 year emergency medicine training program), gender and years in practice. Logistic regression was used to model CT usage per physician adjusting for confounding factors. Sample size of 12 physicians per group was calculated based on an expected delta in mean CT ordered of 5 and a within group SD of 3.

Missed AAS was defined by a positive case that had been seen in the emergency department in the proceeding 14 days and discharged without a diagnosis of AAS. We additionally searched the database of the University of Ottawa Heart Institute, which is the regional referral center for cardiac pathology for missed cases. Acute aortic syndrome was defined as computed tomography, magnetic resonance imaging or trans esophageal echo evidence of either penetrating atherosclerotic ulcer, intimal hematoma or aortic dissection. Research board ethics approval was sought and obtained.

Results

A total of 26,932 out of 31,201 were included (Mean 47years, SD 18.5years; 56.2% Female). Most common diagnoses; Chest pain unspecified (23.3%), Abdominal pain unspecified (20.8%), Lower back pain unspecified (10.5%), Renal Colic (5.3%), Female reproductive pathology (3.0%), Biliary disease (2.3%), ACS (2.9%), Colitis/diverticulitis (2.3%)(Table 2). CT was ordered to rule out acute aortic syndrome in 175 (0.7%) (Mean age 62years, SD 16.5 years; Female 50.6%).

Only 4(2.3%) patients were found to have an AAS. They were predominantly male presenting with chest pain and were diagnosed with CT thorax and abdomen (Table 1). Kappa for data extracted by 3 reviewers was 0.82.

There was a significant difference in number of CT ordered per year in low test users (n=22 mean 6.5 (STD 3)) and high test users (n=28 mean 29.1 (STD 22.8) but no difference in the number of AAS diagnosed (high users n=2, low users n=2). Low-test users were more likely to be male and FRCPC trained. Adjusting for gender, training and years in practice high variation

was still found in distribution of CT across the physician group (Gini coefficient 0.42)(Table 3). No AAS were missed.

Discussion

Our study shows that the prevalence of AAS in a population presenting with pain is low. Imaging to rule out AAS is also appropriately low but inefficient with 98% being negative for the diagnosis of AAS. There is significant variation in the rate of ordering among physicians. This variation could not be accounted for by difference in specific physician characteristics. These findings suggest great potential for more standardized and efficient use of CT for the diagnosis of AAS.

Our study showed that the prevalence of acute aortic syndrome is very low (2.3%) in those with suspected AAS undergoing advanced imaging. We found significant variation in the rate of CT ordering between physicians (Figure 1). Accounting for specific physician characteristics such as years in practice or subspecialty training did not account for this variation (Table 3). Variation in emergency physician use of diagnostic imaging has been previously demonstrated(13-15). Wennberg believes true variation is strongly affected by individual physician practice and lack of agreement on optimal management for many medical problems(16). Kassierer has suggested that variations in patterns of care should lead to the development of clinical practice guidelines(17). We believe that the large variation among physicians in our study may be explained by the lack of consensus in the literature regarding who is at sufficiently low risk for AAS to warrant no further imaging.

There have been three clinical decision aids derived to aid in risk stratification of those suspected to have AAS. Von Kodolitsch conducted a prospective study enrolling patients with acute chest or back pain and a clinical suspicion for AAS, with an AAS prevalence of 20%. They found that patients with an absence of aortic pain (immediate onset/tearing/ ripping character), mediastinal widening/aortic widening on chest radiography, and pulse differentials/blood pressure differentials had a 7% probability of AAS(3). This has not been prospectively validated. Lovy's 2013 case control study with a prevalence of 2.7% derived a two-step rule: first screen for ongoing pain; if present, screen for acute chest pain or an abnormal chest radiograph. This approach achieved a 54% (84/155) reduction in CT usage with a sensitivity for AAS of 96% (95% CI: 89%-100%), negative predictive value of 99.8% (99.4%-100%) and a false negative rate of 1.7% (1/84)(7). This rule has also not been prospectively validated. The AHA derived a clinical algorithm by expert consensus in 2010 and this was streamlined into the AHA acute aortic dissection detection (ADD) risk score(5). It includes elements of history and physical exam. In 2014 Nazerian retrospectively validated the rule in a prospectively collected database. They found that a score of 0 had a sensitivity of 91.1% (95% confidence interval (CI) 87.2–94.1%) and a specificity of 39.8% (95% CI 36.8–42.9%). The prevalence of AAS in the population with a score of 0 was 5.9% and therefore was not sufficiently sensitive to rule out the diagnosis of AAS(2). Thus all previously derived rules are not sufficiently sensitive to rule out AAS or have not been prospectively validated.

The three main guidelines for the work up of AAS are the American heart association 2010 guidelines, the American college of emergency physicians (ACEP) policy statement on the diagnosis of acute thoracic aortic dissection and the European society for cardiology (ESC)

diagnosis and management of aortic disease. The American and European guidelines are based around the ADD risk score. AHA 2010 guidelines incorporate the ADD risk score and suggest considering AAS in any patients presenting with chest, back or abdominal pain, syncope, or symptoms consistent with a perfusion deficit (ischemic stroke, mesenteric ischemia, acute coronary syndrome or limb ischemia). If an alternative diagnosis is not found on electrocardiogram, chest x-ray or further testing they suggest imaging of the aorta even in the absence of any high risk factors. If >2 high risk features are present they suggest expedited imaging(5). In our population over 50% of patients left the emergency department with chest pain, abdominal pain or back pain of unspecified origin. Therefore rigid application of these guidelines would lead to over testing.

In the ESC 2014 guidelines on the diagnosis and treatment of aortic diseases they suggest, "every patient with suspected aortic dissection should undergo diagnostic imaging…..to rule out the disease". They suggest an algorithm incorporating the ADD risk score to evaluate pre test probability, in those of low risk with a score of 0 or 1 they suggest the use of ECG, chest x-ray and D-dimer to divide the population further into no argument for AAS and further imaging recommend(18). Nazerian found that the addition of chest x-ray to a low risk ADD score could not rule out AAS(2). In a separate study the addition of a negative D-dimer to a low risk score of 0 could effectively rule out AAS. However use of the risk score and D-dimer would only reduce imaging by 8.8%, thus would have limited benefit in clinical practice(19). No study has looked at the combination of chest x-ray with D-dimer and the ADD risk score. ACEP 2015 gives level c recommendations "In an attempt to identify patients at very low risk for acute non-traumatic thoracic aortic dissection, do not use existing clinical decision rules alone. The decision to

pursue further workup for acute non-traumatic aortic dissection should be at the discretion of the treating physician"(4). Thus AHA guidelines have failed prospective validation; ESC guidelines will lead to over investigation and ACEPs recommendations are to rely solely on physician gestalt. Without reliable guidelines with an accurate reproducible diagnostic pathway many physicians are likely to over investigate given the catastrophic outcome of a missed case of AAS.

The findings of our study may be limited by several factors. We did no adjust for case severity. However over the course of a year we would expect that the acuity of patients seen would balance out amongst the physician group, as staff schedules are a fixed ratio of acute vs. non acute care shifts. We could not calculate the rate of CT ordered by a physician per number of patients seen. We estimated the number of CT ordered per physician per year working a full time schedule. Therefore the estimated CT/year may not truly represent the actual number each physician would have ordered. Our inclusion criterion was a triage diagnosis of pain. This did not differentiate between acute or chronic pain. In a study of patients presenting to an emergency department with complaints of pain, 39% reported an underlying chronic pain syndrome.(20) Therefore our rate of CT ordering is likely an underestimation of the rate of CT ordering to rule out AAS in a population presenting with acute pain. Retrospective chart studies may suffer from problems with unclear or missing data or with inconsistencies in data abstraction. We believe that these problems were minimized by our use of a standardized data form and the careful, independent review of all cases by 2 reviewers. Finally, we cannot be absolutely certain that no missed AAS occurred in patients who may have been followed up at a different hospital. We believe that this is unlikely because the study hospitals represented the

main referral area for community emergency departments, and the regional cardiac referral center manages all AAS diagnosed in the adjacent community hospitals. However we could have missed cases that were undiagnosed and died in the community.

We believe that our study strongly supports the need for a clinical decision rule for the use of CT in the investigation of AAS. Current practice is inefficient with 98% of CT being negative for AAS. There is significant variation in the rates of CT ordering. Our results show that physicians with lower ordering rates are no more likely to miss a case of AAS. A reliable highly sensitive decision rule for CT and AAS would permit physicians to provide more standardized and efficient care of patients presenting with pain and no obvious alternative diagnosis. Such a decision rule would lead to improved patient care and considerable savings for health care systems(21).

Conclusion

Our study demonstrated considerable variation among individual physicians in the ordering of CT for patients presenting with truncal pain and no obvious diagnosis on initial assessment. None of the physicians with low ordering rates missed a patient with AAS. The yield of CT for AAS was extremely low. These findings suggest great potential for more efficient use of CT, possibly through the use of a clinical decision rule.

References

1. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. Jama. 2000;283(7):897-903.

2. Nazerian P, Giachino F, Vanni S, Veglio MG, Castelli M, Lison D, et al. Diagnostic performance of the aortic dissection detection risk score in patients with suspected acute aortic dissection. European Heart Journal: Acute Cardiovascular Care. 2014;3(4):373-81.

3. von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. Archives of Internal Medicine. 2000;160(19):2977-82.

4. Diercks DB, Promes SB, Schuur JD, Shah K, Valente JH, Cantrill SV. Clinical policy: critical issues in the evaluation and management of adult patients with suspected acute nontraumatic thoracic aortic dissection. Annals of Emergency Medicine. 2015;65(1):32-42. e12.

5. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. Journal of the American College of Cardiology. 2010;55(14):e27-e129.

6. Ghaemmaghami CA, Brady WJ. Pitfalls in the emergency department diagnosis of acute myocardial infarction. Emergency medicine clinics of North America. 2001;19(2):351-69.

7. Lovy AJ, Bellin E, Levsky JM, Esses D, Haramati LB. Preliminary development of a clinical decision rule for acute aortic syndromes. The American journal of emergency medicine. 2013;31(11):1546-50.

8. Yitzhaki S. Relative deprivation and the Gini coefficient. The quarterly journal of economics. 1979:321-4.

9. Luebker M. Inequality, income shares and poverty: the practical meaning of Gini coefficients. International Labour Organization, 2010.

10. Munga MA, Mæstad O. Measuring inequalities in the distribution of health workers: the case of Tanzania. Human Resources for Health. 2009;7(1):1.

11. Song P, Ren Z, Chang X, Liu X, An L. Inequality of Paediatric Workforce Distribution in China. International Journal of Environmental Research and Public Health. 2016;13(7):703.

12. Hatam N, Zakeri M, Sadeghi A, Darzi Ramandi S, Hayati R, Siavashi E. Equity analysis of hospital beds distribution in Shiraz, Iran 2014. Medical Journal of The Islamic Republic of Iran (MJIRI). 2016;30(1):667-72.

13. Stiell IG, Clement CM, McKnight RD, Brison R, Schull MJ, Rowe BH, et al. The Canadian C-spine rule versus the NEXUS low-risk criteria in patients with trauma. New England Journal of Medicine. 2003;349(26):2510-8.

14. Stiell IG, Wells GA, Vandemheen KL, Clement CM, Lesiuk H, De Maio VJ, et al. The Canadian C-spine rule for radiography in alert and stable trauma patients. Jama. 2001;286(15):1841-8.

15. Stiell IG, Wells GA, Vandemheen K, Laupacis A, Brison R, Eisenhauer MA, et al. Variation in ED use of computed tomography for patients with minor head injury. Annals of emergency medicine. 1997;30(1):14-22.

16. JE. W. Dealing with medical practice variations: a proposal for action. Health Aff. 1984(4):6-32.

17. Kassirer JP. The quality of care and the quality of measuring it. New England Journal of Medicine. 1993;329(17):1263-5.

18. Erbel R, Aboyans V, Boileau C, Bossone E, Di Bartolomeo R, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. European heart journal. 2014;35(41):2873-926.

19. Nazerian P, Morello F, Vanni S, Bono A, Castelli M, Forno D, et al. Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection. International journal of cardiology. 2014;175(1):78-82.

20. Neighbor M, Puntillo K, Homel P, Todd K. Chronic pain in the emergency department. Academic Emergency Medicine. 2007;14(5S):S112-S.

21. Stiell IG, Clement CM, Grimshaw J, Brison RJ, Rowe BH, Schull MJ, et al. Implementation of the Canadian C-Spine Rule: prospective 12 centre cluster randomised trial. Bmj. 2009;339:b4146.

Tables

Table 1. Characteristics of included patients

Characteristics	**AAS (N=4)**	**Alternative diagnosis (N=171)**	**P value**
Male	3(75)	84(49.1)	P<0.31
Age	58(16.2)	62(16.5)	P<0.53
Campus			
General	2(50)	69(40.4)	P<0.69
Civic	2(50)	102(59.6)	
Presenting complaint			P<0.01
Flank pain	-	4(2.3)	
Chest pain	3(75)	109(63.7)	
Shortness of breath	-	2(1.2)	
Back pain	-	20(11.7)	
Lower extremity pain	1(25)	-	
Abdominal pain	-	26(15.2)	
Imaging			
Thorax	-	31(18.1)	P<0.0001
Thorax and abdomen	4(100)	140(81.9)	P<0.43

Table 2. Diagnoses of included and excluded patients presenting with truncal pain

Diagnosis	**N, %**
Included	
Chest pain unspecified	6264 (23.3)
Abdominal pain unspecified	5617(20.8)
Lower back pain	2833(10.5)
Renal Colic	1413(5.3)
Female reproductive pathology	809(3.0)
GERD	807(3.0)
Acute coronary syndrome	773(2.9)
Biliary disease	628(2.3)
Colitis/diverticulitis	614(2.3)
Appendicitis	491(1.8)
Pulmonary embolism	89(0.3)
Excluded	
Urinary tract infection	510(1.6)
Pneumonia	213(0.7)
Arrhythmia	197(0.6)
Acute fracture	104(0.3)
Acute pharyngitis	101(0.3)
Viral infection	66(0.2)
Herpes zoster	43(0.1)

Table 3. Characteristics of high test users (>12 computed tomography's per year) and low test users (<12 computed tomography's per year))

	High User (N=22) **N (%, STD)**	**Low User (N=28)** **N (%, STD)**	**P value**
Computed tomography per year (actual number)	5(4.2)	2.25(1.2)	P<0.001
Computed tomography per year (if worked full time)	29.1(22.8)	6.5(3)	P<0.001
Male	11(50)	24(85)	P<0.006
Training			
Fellow of the Royal College of Physicians of Canada (FRCPC) (5 year emergency medicine training)	5(26.3)	14(73.7)	P<0.049
Canadian College of Family Physicians – Emergency Medicine certificate (CCFP-EM) (2 year family medicine residency +1 year emergency medicine training)	17(54.8)	14(45.2)	P<0.20
Years practicing	13.5(6.4)	16.7(8.5)	P<0.18

Table 4. Significant variation in CT ordering between physicians adjusting for gender, training and years in practice

	OR	**95% CI**	**P value**
Gender (Male Vs. Female)	0.18	0.04 - 0.72	P<0.015
Training (FRCPC Vs. CCFP-EM)	0.32	0.08 - 1.2	P<0.094
Years in practice	1.0	0.95 - 1.0	P<0.862
Gini Coefficient	0.42		

Figures

Figure 1. Relative standard deviation of number of CT ordered per physician, above horizontal axis indicates increased deviation, below indicates decreased deviation

Chapter Six : Discussion & recommendations

Introduction

The purpose of this thesis was to answer the question of do we need a clinical decision rule for acute aortic syndrome. This final chapter will bring together the results of the systematic review and meta-analysis of high risk clinical features for AAS (Chapter 3), the historical case control study of high risk features for AAS (Chapter 4) and the historical cohort study describing computed tomography use for the diagnoses of AAS (Chapter 5). This discussion will be framed by the specific questions that need to be answered in order to decide if a clinical decision rule is needed.

Can individuals be stratified for the disease state in question by standard history, physical examination, and simple laboratory testing?

In chapter 3 we discussed a review of the literature and synthesis of the results of previous studies in a meta-analysis. We found that suspicion for AAS should be raised with hypotension, pulse or neurological deficit in the appropriate clinical setting. Conversely the absence of a widened mediastinum and a low AHA ADD score decreases suspicion. Specific clinical exam findings could be used to alter a clinician's probability for AAS. In addition a consensus derived clinical decision tool (AHA ADD score), which was a combination of historical, and physical exam

findings could successfully be used to risk stratify patients into a high, intermediate and lower risk group. This consensus derived tool does not fall under the definition of a clinical decision rule as it was not derived through accepted methods from original research, but it confirms that it should be possible to construct a clinically useful rule.

The major limitation of previous studies investigating the diagnostic accuracy of high-risk features for AAS was spectrum bias. Prevalence of AAS was often greater than 20%. Evidence from Lovy's case control study and our historical cohort study indicates that the population in which we are considering AAS has a prevalence of 2%. Thus previous studies may overestimate the usefulness of high-risk features. In chapter 4 we confirmed that high-risk features maintained their diagnostic accuracy within a lower risk control population. Specifically, absence of acute onset pain, history of ischemic heart disease, diabetes and a negative D-dimer could help rule out acute aortic syndrome. Presence of tearing/ripping pain, a history of aortic aneurysm, hypotension, pulse or neurological deficits, new murmur or a widened mediastinum on chest x-ray could help rule in the diagnosis of acute aortic syndrome. Therefore although no single high-risk feature could accurately rule in or rule out AAS, certain features could alter your probability of AAS and therefore had the ability to help stratify patients.

The limitations of both the systematic review and the case control study were that they included retrospective data and a varying definition of historical features across studies. These limitations need to be addressed in future prospective studies with standardized definitions leading to improved external validity of these high risk features to help risk stratify for AAS

We conclude from our systematic review and meta-analysis in addition to our case control

study that it is possible to stratify patients at risk for acute aortic syndrome by standard history, physical examination and simple laboratory testing.

Is there substantial variation in clinical practice for the condition with an impact on diagnostic accuracy or efficiency of test usage?

Chapter 5 discussed the substantial variation in computed tomography use in the diagnosis of acute aortic syndrome. There was no difference in the number of AAS diagnosed in high versus low-test users. There were no missed cases in the year the study was performed but the diagnostic yield of advanced imaging was extremely low with 98% of CT's negative.

In chapter 2 we discussed the prevalence of misdiagnosed acute aortic syndromes. There seems to be a decrease over time, possibly as a result of increased access to advanced imaging, but the misdiagnosis rate remains unacceptably high at 17%. Given that there are no guidelines that are sufficiently efficient and accurate to aid in the diagnosis of AAS it is understandable that there is a variation in practice and thus CT ordering. It is likely that this variation in practice is contributing to the unacceptably high miss rate.

Thus from review of the literature and our historical cohort study we conclude that there is substantial variation in practice, inefficient use of diagnostic imaging and a potential to improve diagnostic accuracy.

Is there a perceived need for a clinical decision rule by clinicians for the disease state in question?

There has been no formal survey of physicians answering this specific question. However as part of the 2015 Society of Academic Emergency Medicine (SAEM) consensus conference on clinical decision rules (CDR) for diagnostic imaging in the emergency department, physicians discussed specific clinical conditions that may be amenable to the development of decision rules. After discussion with the 65 participants at the breakout group of the consensus conference, a list of candidate CDR's was generated (20 adult and eight pediatric) and attendees were surveyed regarding their prioritization. The number one priority was non-traumatic chest pain defined by pulmonary embolism and acute aortic syndrome.

From the results of this limited survey we can conclude that there is a potential need amongst physicians for the development of a clinical decision rule for acute aortic syndrome.

Does unnecessary testing results in increased morbidity or increased cost?

Clinical decision rules have the greatest utility when they address a prevalent disease, a high-risk clinical problem or a condition for which there is inefficient use of testing. AAS is relatively rare within the emergency department. The best estimate of incidence is 0.05% of those presenting with chest and/or back pain. However given the undiagnosed mortality of 70% at 2 weeks it represents a high-risk problem. In addition although the condition itself is rare the clinical question is potentially common given that nearly 20% of patients presenting to the emergency department have acute truncal pain (Chapter 5).

The self-pay cost for computed tomography thorax and abdomen at our institution is $1065. In Chapter 5 we saw that in 2010 at our institution we performed 175 CT thorax and abdomen to rule out AAS. On review of our imaging ordering within the emergency department at both campuses of the Ottawa Hospital in 2015, that number increased to 358 and the diagnostic yield decreased to 1.6%. Total cost for imaging to rule out AAS in 2015 was $381,270. This represents an area of potential cost reduction within our hospital and the Canadian health service.

We also found that 61(16.1%) of these negative CT's resulted in incidental findings that required further work up including repeat imaging and/or consultation. Taking into account only the cost of additional imaging this adds an addition $65,000 to the yearly cost of investigations for AAS resulting in a total nearing half a million dollars. This does not take into

account the additional radiation exposure to patients with unnecessary testing and the additional anxiety provoked from incidental findings requiring further investigation.

Thus investigation for AAS is inefficient resulting in increased morbidity and increased cost. Standardization of investigation has the potential for substantial cost savings.

Recommendations

This thesis project comprised a systematic review, meta-analysis and case control study of high risk historical, exam and basic investigations for AAS, in addition to quantifying the use of CT within the emergency department to rule out AAS. These studies have allowed us to conclude that we need to derive a clinical decision rule to help risk stratify patients at risk for AAS.

In summary our recommendations are as follows:

1. High-risk clinical features reported in our thesis can be used in clinical practice to help risk stratify patients, however the absence or presence of any one of these features cannot absolutely rule in or out the diagnosis. Assessment should be based on a thorough history documenting all relevant high and low risk features reported in our thesis and the generation of a clinical gestalt taking into account probability of alternative diagnosis.
2. We have an unacceptable high miss rate for AAS. There is need to standardize assessment and increase clinical suspicion. In suspected acute coronary syndrome, pulmonary embolism and stroke clinicians should use high-risk features of AAS to help risk stratify for the possibility of AAS.

3. Given the inefficient and increasing use of computed tomography to rule out AAS we need to standardize our assessment in order to decrease practice variation and reduce costs.
4. We need to conduct a prospective cohort study with standardized definitions of high risk features for AAS in order to derive a clinical decision rule to help stratify patients for AAS

Although there is need for a clinical decision rule to risk stratify patients for AAS, the feasibility of prospectively deriving this rule is yet to be addressed. With an incidence of 0.05% and a need for 100 cases of AAS to derive a 10 variable rule, the study population would be in excess of 200,000. Alternative derivation strategies such as retrospective derivation with a prospective validation and adjustment should be explored. Another option is the development of an evidence informed expert consensus diagnostic algorithm based on a retrospective derivation of a clinical decision rule. This algorithm could be studied in a prospective randomized step wedge trial to assess its accuracy and impact on diagnostic imaging.

In spite of the challenges in derivation we are confident that a CDR is needed and that it will have a real and meaningful impact on health care cost, physician practice and most importantly patient outcomes.

APPENDICES

Appendix A. Letter of approval from the Ottawa Hospital Research Ethics Board

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

uOttawa

University of Ottawa Heart Institute
Institut de cardiologie de l'Université d'Ottawa

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
http://www.ohri.ca/ohsn-reb

May 29, 2015

Dr. Robert Ohle
Department of Emergency Medicine
University of Ottawa / The Ottawa Hospital - Civic Campus
1053 Carling Ave, E-Main, Room EM-206, Box 227
Ottawa, Ontario, K1Y 4E9

Dear Dr. Ohle:

Re: Protocol # 20150343-01H **A retrospective case control study to identify high risk clinical factors for aortic dissection**

Protocol approval valid until - May 28, 2016

Thank you for the email of May 26, 2015. I am pleased to inform you that your Application for Chart Review underwent expedited review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB), and is approved to begin on June 1, 2015. No changes, amendments or addenda may be made to the protocol without the OHSN-REB's review and approval.

PLEASE NOTE: THE APPROVAL OF THIS PROTOCOL IS CONDITIONAL UPON A FULLY-SIGNED STUDY CONTRACT/AGREEMENT BETWEEN THE OTTAWA HOSPITAL RESEARCH INSTITUTE, THE PRINCIPAL INVESTIGATOR AND THE SPONSOR (OR AS OTHERWISE REQUIRED). YOU CANNOT START THE STUDY, OR BEGIN TO RECRUIT RESEARCH PARTICIPANTS INTO THE STUDY UNTIL THE STUDY CONTRACT/AGREEMENT HAS BEEN SIGNED BY ALL PARTIES, AND HAS BEEN RECEIVED BY THE OTTAWA HOSPITAL RESEARCH INSTITUTE'S CONTRACTS OFFICE. FOR FURTHER DETAILS, PLEASE CONTACT CHRISTINE LAFONTAINE , CONTRACTS ADMINISTRATOR AT CHRILAFONTAINE@OHRI.CA OR AT 613-798-5555 EXT. 19690.

Approval is for the following:
- Electronic OHSN-REB Application
- AD Case Control Study Protocol (Version 2) dated May 26, 2015
- Aortic Dissection - Case Control Study Data Collection Form (Version 2) dated May 26, 2015

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHSN-REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) was created by the merger of both the Ottawa Hospital Research Ethics Board (OHREB) and the Human Research Ethics Board (HREB) for meetings held at the University of Ottawa Heart Institute.

...2

Appendix B. Data Collection Sheet

Aortic Dissection – Case control Study — Data Collection

Subject #:_____

O Control **O** Case - Dissection type **O** Thoracic ----**O** A ----**O** B **O** Abdominal

Site: O TOH–Civic O TOH–General **Date of Visit (yy/mm/dd)** ___/_____/_____

Sex: O Male O Female **Age:** _____

Arrived by Ambulance: O Yes O No

Referred for investigation of Aortic dissection O Yes O No

ED diagnosis_____ **Hospital discharge diagnosis**_____

Exclusion criteria: if yes to any exclude

1. Pain Onset >14 days **O Yes O No**
2. Trauma at onset of pain **O Yes O No**
3. Chest pain
   a. No imaging(Chest x-ray, CT,MRI) to exclude pneumonia/pneumothorax **O YesO No**
   b. Radiological evidence of pneumonia/pneumothorax **O YesO No**
4. Abdominal Pain
   a. Dysuria/frequency & positive urinalysis(leucocytes + nitrites) R/M(>20wbc) **O YesO No**
   b. Dysuria and frequency and no urinalysis **O Yes O No**
   c. Radiological evidence of bowel obstruction (>3 air fluid levels)/report **O YesO No**
5. Back Pain
   a. Radiological evidence of fracture **O Yes O No**
   b. Risk factors for fracture – (IVDU/Ca/>65/corticosteroid use or prev vertebral #) and no imaging **O YesO No**
   c. Positive urinalysis and dysuria or frequency **O Yes O No**
   d. No urinalysis and dysuria and frequency **O Yes O No**
6. Flank pain
   a. Positive urinalysis and dysuria or frequency **O Yes O No**
   b. No urinalysis and dysuria and frequency **O Yes O No**
7. Known aortic dissection **O Yes O No**

Diagnosis
1. Aortic Dissection A
2. Aortic dissection B
3. Chest Pain NYD
4. Pneumonia
5. PE
6. Gastritis/GERD
7. Pericarditis
8. ACS
9. Valvular pathology
10. Other

Symptoms

O Maximal pain intensity < 2min from onset

O Pain less intense at time of assessment then at initial onset

O Location **O** ant. chest **O** post. Chest **O** back **O** abdomen **O** flank

O Character

O tearing/ripping **O** sharp **O** squeeze/pressure **O** pleuritic

O Migrating/radiating

O Neck O arm **O** leg **O** back **O** flank **O** abdomen **O** chest

O Syncope

O Past Medical History, if yes:

O Cardiac surgery **O** HTN

O Aortic valve disease **O** Diabetes

O Known aneurysm **O** DVT/PE

O Ischaemic Heart disease **O** Renal Colic

O Connective tissue disease **O** Bilairy colic/gallstones

O Radiculopathy/disc protrusion prev imaging? **OYes O No**

O Percutaneous coronary intervention **O** CRF

O Family History, if yes:

O Non traumatic death <50

O AD

O connective tissue disease

Physical Exam

O Bi-lat BP **If yes, O** BP differential **if yes**:

Rt____mmHg **Lt**____mmHg

O Hypertension systolic _____mmHg

O Hypotension systolic _____mmHg

O Bibasilar crackles

O Murmur if yes : **O** New **O** Old **O** Unknown

- Pulse differential: **O Yes O No O Not recorded**

- Focal neurological deficit:

O sensory, **O** motor **O** other **O None O Not recorded**

- Palpable tenderness: **O Yes O No O Not recorded**

Outcome

O Admitted, if yes:

O Surgery

O Died

O Return confirming no death

O Discharged, if yes:

O Return <14days and diagnosed with aortic dissection

O Return >14 days confirming no death

Investigations

O D-Dimer **if yes O** elevated **if yes: level**_____**g/dl**

O Creatinine **if yes O** elevated **if yes:** creatinine level: _____**umol/L**

O WBC **if yes O** elevated **if yes**: _____g/dl

O LFT **if yes O** Transaminitis **if yes**: ALT____AST____ GGT____

O CXR **if yes : O** Mediastinal widening **O** absence of aortic notch

O ECG **if yes :** Ischemic changes(St elevation/depression, t wave inversion,new q waves)? **O** Yes **O** No

O CT **if yes : O IV contrast** if yes **O** thorax if yes: O PE study **O** abdomen **O** both

O No IV contrast if yes: **O** thorax **O** abdomen **O** both

O ECHO **if yes : O** transthoracic **O** bedside **O** trans oesophageal **O** valve abnormality **O** Aortic root dilation