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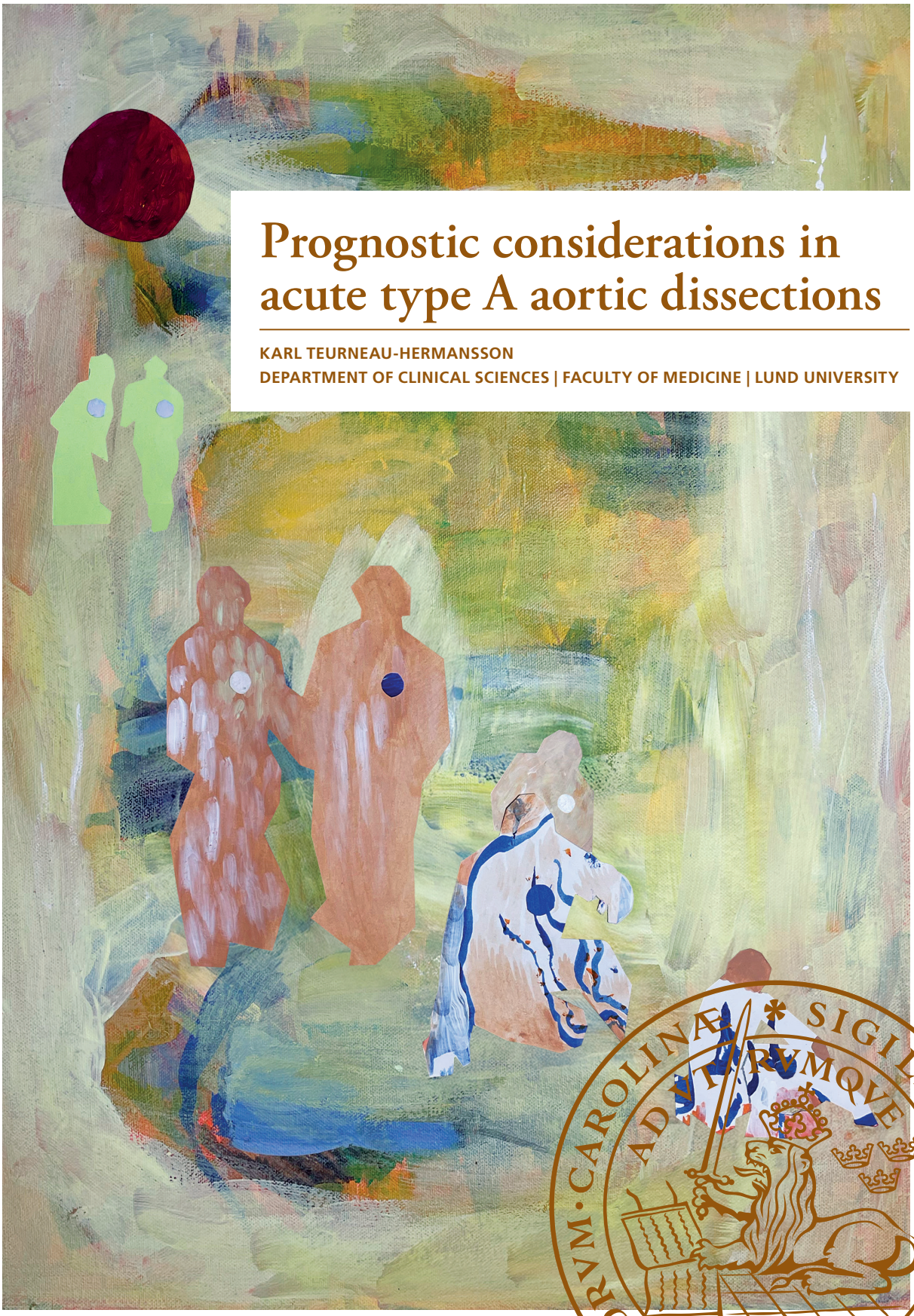

Prognostic considerations in acute type A aortic dissections

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Abstract:

Background: Acute type A aortic dissection (ATAAD) is an emergent condition with a high mortality rate. Initial misdiagnosis is common due to variation in clinical presentation. Even with adequate surgical treatment, approximately one third of the patients suffer complications, including neurological injuries.

Aims: I: To provide contemporary data on mortality following non-surgically treated (NST) ATAAD and to describe surgical decision rationale. II: To assess the frequency, and clinical impact, of misdiagnosis and delayed diagnosis of ATAAD. III: To determine whether the D-dimer/fibrinogen ratio could be used to improve risk assessment for ATAAD in the emergency department. IV: To study whether S100B could be used to predict neurological injury following ATAAD repair.

Methods: All studies had a retrospective design. Study I included 184 patients with NST ATAAD who were identified via a comprehensive search in all available registries in our region. Study II included 556 patients with ATAAD, out of whom 418 were surgically treated (ST) and 138 NST. Study III included 93 patients with ATAAD and 202 controls that were recruited from the Skåne Emergency Medicine cohort. Study IV included 393 patients that were ST for ATAAD.

Results: Study I: The mortality of NST ATAAD was 47.3 ±4.4%, 55.0 ± 4.4%, 76.7 ± 3.7% and 83.9 ± 4.3% at 24 h, 48 h, 14 days and 1 year, respectively. The hourly mortality rate during the first 24h after symptom onset was 2.6%. Study II: 45.3% of the patients were initially misdiagnosed. Female sex was an independent predictor of misdiagnosis (OR: 1.748; 95% CI 1.145–2.668; P = 0.010), but neither misdiagnosis nor delayed diagnosis were independent predictors of 30-day mortality. Patients without signs of malperfusion subjected to diagnostic delay were less likely offered surgical treatment (74.0 vs. 91.5%; P < 0.001) and had higher 30-day mortality (21.3 vs. 10.8%; P = 0.040). Study III: The AUC for the ability of D-dimer and fibrinogen to discriminate ATAAD from other diagnoses was 0.784 (95% CI 0.733-0.836) and 0.756 (95% CI 0.701-0.811), respectively. The AUC for the D-dimer/fibrinogen ratio was 0.812 (95% CI 0.764-0.860). Study IV: Multivariable logistic regression identified S100B ≥ 0.23 µg/l at 24h as an independent predictor for neurological injury (OR 4.71, 95% CI 2.59–8.57; p < 0.01) along with preoperative cerebral malperfusion (OR 4.23, 95% CI 2.03–8.84; p < 0.01).

Conclusions: In study I we observed higher mortality than has previously been reported. In study II, misdiagnosis and delayed diagnosis did not influence overall 30-day mortality, although delayed diagnosis led to significantly higher 30-day mortality in patients presenting without signs of malperfusion, likely caused by the observed higher risk of being denied surgical treatment. In study III, we could show that the D-dimer/fibrinogen ratio increased the ability to predict ATAAD compared to the biomarkers alone. The improvement in discriminative ability was small, however, and needs further validation to be clinically useful. In study IV we demonstrated that S100B, 24h after surgery was an independent predictor for neurological injury and 30-day mortality after ATAAD repair

Key words: Aortic dissection; Mortality; Diagnostic Errors; D-dimer; Fibrinogen; S100B

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Till Far – jag vet att du hade varit stolt.

Vendela, Astrid, Ingrid och Magnus – ni betyder allt.

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List of publications

This thesis is based on the following publications which are referred to in the text by their Roman numerals (I-IV).

I. **Teurneau-Hermansson K,** Ede J, Larsson M, Linton G, von Rosen D, Sjögren J, Wierup P, Nozohoor S, Zindovic I. Mortality after non-surgically treated acute type A aortic dissection is higher than previously reported. Eur J Cardiothorac Surg. 2024 Feb 1;65(2):ezae039. doi: 10.1093/ejcts/ezae039. PMID: 38310329; PMCID: PMC10871943.

II. **Teurneau-Hermansson K,** von Rosen D, Ede J, Larsson M, Sjögren J, Wierup P, Nozohoor S, Zindovic I. Causes and clinical impact of initial misdiagnosis of acute type A aortic dissection. Eur Heart J Open. 2025 Mar 12;5(2):oeaf027. doi: 10.1093/ehjopen/oeaf027. PMID: 40134847; PMCID: PMC11935741.

III. **Teurneau-Hermansson K,** Norén E, Ede J, Larsson M, Björkelund A, Sjögren J, Nozohoor S, Ekelund U, Zindovic I. Could the combination of fibrinogen and D-dimer improve risk assessment for acute type A aortic dissection in the emergency department? Scand J Clin Lab Invest. 2026 Feb 13:1-7. doi: 10.1080/00365513.2026.2630321. Epub ahead of print. PMID: 41685423.

IV. **Teurneau-Hermansson K**, Ede J, Larsson M, Moseby-Knappe M, Bjursten H, Nozohoor S, Sjögren J, Zindovic I. S100B predicts neurological injury and 30-day mortality following surgery for acute type A aortic dissection: an observational cohort study. J Cardiothorac Surg. 2023 Feb 6;18(1):62. doi: 10.1186/s13019-023-02151-2. PMID: 36747206; PMCID: PMC9900954.

Populärvetenskaplig sammanfattning

Prognostiska överväganden vid akuta typ A aortadissektioner

Aortan är kroppens största pulsåder. Den transporterar syresatt blod från hjärtat, via förgrenande mindre pulsådror, till kroppens alla organ förutom lungorna. Aortans vägg består av tre lager med olika karaktäristika: Det innersta lagret, intiman, består av ett tunt membran och ett lager av specialiserade celler, vilka är i kontakt med det cirkulerande blodet. Det mellersta lagret, median, består av muskelceller och elastiska bindvävsfibrer som tillsammans har en förmåga att hantera det pulserande blodflödet. Det yttersta lagret, adventitian, består av tålig bindväv, vilken ger kärlet en förmåga att tåla mekaniska påfrestningar. Vid en aortadissektion uppstår en spricka i det innersta vägglagret varvid blodet tränger sig in i kärlväggen och spaltar upp, dissekerar, de olika lagren. När en aortadissektion omfattar aortans uppåtstigande del, direkt efter hjärtat, klassificeras den som en typ A-dissektion.

Akut typ A aortadissektion (ATAAD) är en dödlig sjukdom. Upp till 50% av dem som drabbas dör innan de hinner nå sjukvård och därtill dör 1-2% av patienterna på sjukhus var timme i väntan på adekvat behandling. Mekanismerna bakom dödsfallen är flera: Den dissekerade aortaväggen blir kraftigt försvagad, varför den riskerar att spricka med dödlig blödning som följd. Därutöver kan en ATAAD som når aortans rot ge upphov till en blödning in i den strama bindvävssäck som omger hjärtat. När en sådan blödning fortgått tillräckligt länge hindrar trycket i hjärtsäcken återvändande blod från kroppens vensystem att nå hjärtat, varvid blodcirkulationen till sist kollapsar. Vidare kan ATAAD förstöra geometrin, och funktionen, i den viktiga aortaklaffen som sitter i övergången mellan hjärtats vänstra kammare och aortan, vilket får till följd att hjärtats pumpförmåga kan upphöra. Slutligen, riskerar en ATAAD att stänga av blodflödet till kroppens olika organ såsom hjärnan, hjärtat, njurarna eller tarmarna, då blodets väg i aortans vägg kan hindra det från att nå de avsedda pulsådrorna för respektive organ.

Den viktigaste behandlingen för ATAAD är en akut operation där den uppåtstigande delen av aortan, belägen direkt efter hjärtat, ersätts med en konstgjord kärlprotes. Ingreppet är tekniskt komplicerat; det kräver alltid hjärt-lung-maskin och det kräver oftast att patienten kyls till en kroppstemperatur mellan 20 och 32°C varefter blodcirkulationen helt stoppas. Trots adekvat kirurgisk behandling och eftervård dör ytterligare omkring 18% av patienterna.

ATAAD har ibland kallats för ”den stora imitatören” eftersom symtomen kan variera och ofta vara identiska med kardinalsymtomen för andra allvarliga, och betydligt vanligare åkommor såsom stroke, hjärtinfarkt och akuta bukåkommor. Det breda spektret av symtom förklaras av dissektionens inneboende natur där blodförsörjningen till olika organsystem påverkas. Då man betänker att ATAAD är relativt ovanligt är det inte förvånande att feldiagnostik är ett återkommande problem.

Initial feldiagnos drabbar ca 50% av ATAAD-patienterna. Den viktigaste metoden för att nå korrekt diagnos är datortomografi (DT), vilket i folkmun ibland benämns skiktröntgen. Förutom att bekräfta diagnosen ger DT värdefull information om dissektionens utbredning och kan därtill avslöja om det föreligger blodbrist i olika organsystem. I diagnostiken används även algoritmer med poängsystem, så kallade kliniska beslutsstöd, för att hjälpa den undersökande läkaren att värdera risken för ATAAD och avgöra om patienten bör genomgå DT eller ej. Studier har visat att tillägget av blodprovet D-dimer till de kliniska beslutsstöden skärper diagnostiken ytterligare. D-dimer är ett vanligt förekommande blodprov som speglar aktiviteten i patientens blodlevringssystem. Vid ATAAD blir D-dimer förhöjt eftersom den blodvolym som cirkulerar i aortans kärlvägg exponeras för ämnen som orsakar en kraftig aktivering i blodets levringssystem. Detta fenomen – aktiveringen av blodets levringssystem – orsakar flera andra rubbningar i vanliga blodprover såsom sänkta blodplättar, höjt INR (vilket vanligen används för att övervaka blodförtunnande behandling) och sänkt fibrinogen (ett ämne bidrar till blodlevring och därmed konsumeras vid processen).

Postoperativa komplikationer uppkommer hos mer än en tredjedel av dem som överlever en operation för ATAAD. Neurologiska skador anses ensamma stå för upp till 15% av den postoperativa dödligheten och är därmed bland de mest fruktade av komplikationer. Neurologiska skador orsakar ofta ett svårt lidande för dem som drabbas, då skadorna kan ha stor inverkan på den postoperativa funktionsnivån. Det finns ett antal blodprover som kan hjälpa till att identifiera neurologiska skador exempelvis S100B, NSE och NFL men de har ännu ingen etablerad roll vid ATAAD.

De övergripande målen med denna avhandling var att undersöka dödligheten vid ATAAD i en vidare kontext än vad som gjorts tidigare, att undersöka hur feldiagnostik påverkar dödlighet och att utvärdera blodprover som kan bidra i diagnostik av ATAAD, samt i upptäckandet av postoperativa komplikationer. En nyckelfaktor för att nå målen var att identifiera en studiepopulation som ej begränsas till patienter som nått thoraxkirurgiska kliniker, vilket varit en svaghet med tidigare publicerade studier.

Delarbete I var baserat på 184 patienter som diagnostiserats med ATAAD under perioden 1998 till 2021, men ej erhållit kirurgisk behandling. Patienterna identifierades med hjälp av en fullständig, systematisk datasökning i alla tillgängliga medicinska register i vår region. Dödligheten undersöktes och patienterna som ej genomgick kirurgisk behandling jämfördes med de 547 patienter som opererades för ATAAD på Thoraxkirurgiska kliniken, Skånes Universitetssjukhus, Lund under samma period. Delarbete II inkluderade de 556 patienter som diagnosticerades med ATAAD i vår region under perioden 2001 till 2022 och hade tillgängliga inskrivningsjournaler. Av dessa genomgick 418 patienter operation på Thoraxkirurgiska kliniken, Skånes Universitetssjukhus, Lund medan 138 patienter ej erhöll kirurgisk behandling. Risken för feldiagnos, samt försenad diagnos

undersöktes. Därtill undersöktes vilken påverkan feldiagnos och försenad diagnos hade på dödligheten. Delarbete III undersökte om kombinationen av blodproverna D-dimer och fibrinogen skulle kunna skärpa diagnostiken av ATAAD på akutmottagningar. Studien inkluderade 93 patienter som opererats för ATAAD under perioden 2008 och 2023 på Thoraxkirurgiska kliniken, Skånes Universitetssjukhus, Lund vilka jämfördes med 202 patienter som sökt akutmottagningar i Skåne för andra åkommor under 2017 och 2018. Samtliga patienter som inkluderades hade tillgängliga värden för D-dimer och fibrinogen. I delarbete IV inkluderades 393 patienter som opererades för ATAAD på Thoraxkirurgiska kliniken, Skånes Universitetssjukhus, Lund under perioden 1998 och 2021 och hade tillgängliga värden för S100B. Förmågan för S100B att förutspå postoperativ neurologisk skada undersöktes.

I delarbete I rapporterade vi högre dödlighet vid icke kirurgiskt behandlad ATAAD än vad som tidigare visats. Vi tror att detta beror på vår unika metod för att identifiera fall, vilket sannolikt gett högre täckning än tidigare studier haft. Trots detta tror vi att den verkliga dödligheten är än högre, då vi är övertygade om att det finns fall där patienter dött i ATAAD utan att någonsin ha erhållit diagnos.

Delarbete II visade att nästan hälften av patienterna med ATAAD initialt feldiagnostiseras. Kvinnor löpte högre risk för feldiagnos. Trots att feldiagnos försenade den korrekta diagnosen, och därmed den kirurgiska behandlingen betydligt, var dödligheten inte signifikant högre i den feldiagnostiserade gruppen. Detta berodde sannolikt på det faktum, vilket också visades, att de feldiagnostiserade patienterna i stor utsträckning var de som hade lindrigast symtom.

I delarbete III undersöktes den nya hypotesen att kvoten mellan värdena på blodproverna D-dimer och fibrinogen skulle kunna skärpa riskbedömningen för ATAAD på akutmottagningar. Vi visade att den diagnostiska förmågan skärptes något vid användning av kvoten jämfört med de ingående blodproverna var för sig. Skärpningen i diagnostisk förmåga var dock liten och ej signifikant, varför den i nuläget ej kan sägas vara kliniskt relevant.

Delarbete IV visade att S100B mätt 24 timmar efter operation för ATAAD kan förutspå neurologisk skada med högre träffsäkerhet än alla andra, i studien undersökta, variabler. Fyndet kan vara kliniskt värdefullt då det kan vara besvärligt att erhålla bilddiagnostik över hjärnan tidigt i det postoperativa förloppet.

Sammanfattningsvis understryker avhandlingen allvarligheten vid ATAAD genom att visa högre dödlighet än i tidigare publicerad forskning. Behovet av ytterligare forskning för att minska risken för feldiagnos och motverka könsskillnader tydliggörs och blodprovers roll undersöks, såväl i diagnostik av själva åkomman som i upptäckten av komplikationer.

Abbreviations

AD	Aortic dissection
ACP	Antegrade cerebral perfusion
ACS	Acute coronary syndrome
ADD-RS	Aortic Dissection Detection Risk Score
AKI	Acute kidney injury
ATAAD	Acute type A aortic dissection
AUC	Area under the curve
CD40L	CD40 ligand
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CT	Computed tomography
CTAAD	Chronic type A aortic dissection
DD	Delayed diagnosis
DSD	Departmental surgical database
ECG	Electrocardiogram
ED	Emergency department
ER	Emergency room
ERTAAD	European Registry of Type A Aortic Dissection
FA	First assessment
GERAADA	German Registry of Acute Aortic Dissection Type A
GI	Gastrointestinal
HCA	Hypothermic circulatory arrest
ICD	International classification of diseases
ICU	Intensive care unit
IMH	Intramural hematoma
IQR	Interquartile range
IRAD	International Registry of Acute Aortic Dissection
MD	Misdiagnosis
MRI	Magnetic resonance imaging
NDD	Non-delayed diagnosis
NfL	Neurofilament light chain

NMD	Non-misdiagnosis
NORCAAD	Nordic Consortium for Acute Type A Aortic Dissection
NSE	Neuron-specific enolase
NST	Non-surgically treated
OR	Odds ratio
PAU	Penetrating atherosclerotic ulcer
PCI	Percutaneous coronary intervention
RCP	Retrograde cerebral perfusion
Ref	Reference variable
ROC	Receiver operating characteristics
ROSC	Return of spontaneous circulation
RR	Risk ratio
SD	Standard deviation
SEM	Skåne Emergency Medicine
sELAF	Soluble elastin-laminin-associated fragments
smMHC	Smooth muscle myosin heavy chain
sST2	Soluble ST2
ST	Surgically treated
TAAD	Type A aortic dissection
TEE	Transoesophageal echocardiography
TMAO	Trimethylamine N-oxide
TTE	Transthoracic echocardiography
VIF	Variance inflation factor

Introduction

History

On 25 October 1760, King George II of Great Britain, shortly after rising from bed, was seated on his closet stool, when he emitted a sound described by his valet as being "louder than the royal wind". Moments later, the valet found the king lifeless on the floor. An autopsy was performed the following day by Dr. Francis Nicholls, the king's private physician, who reported that:

"…the pericardium was found distended with a quantity of coagulated blood, nearly a pint […] the whole heart was so compressed as to prevent any blood contained in the veins from being forced into the auricles […] and in the trunk of the aorta we found a transverse fissure on its inner side, about an inch and a half long, through which some blood had recently passed under its external coat and formed an elevated ecchymosis." (1, 2)

Although this famous case is often cited, the first comprehensive description of aortic dissection (AD) is generally attributed to Dr. Giovanni Battista Morgagni, who published his observations in 1761 (3).

In the modern era, Hirst et al. published a series of 505 cases in 1958, describing the high mortality associated with aortic dissection (4). This period coincided with the development of cardiopulmonary bypass (CPB) technology, which facilitated surgical repair techniques. This work was pioneered by Dr. Michael DeBakey, who was the first to perform a successful repair of an aortic dissection in 1954 (5). Somewhat ironically, Dr. DeBakey himself suffered an aortic dissection at age 97. After initial ethical deliberation, his long-term associate Dr. George Noon performed the surgical repair, which Dr. DeBakey remarkably recovered from despite his advanced age. He lived for two more years. (6)

Anatomy

The aorta is the largest artery in the body, and it delivers blood from the left ventricle of the heart to all the organs in the body except for the lungs. Several anatomical classifications are used to divide the aorta into segments. Most commonly, the level of the diaphragm serves as the boundary between the thoracic aorta and the

abdominal aorta. The thoracic aorta may be further divided into the aortic root, ascending aorta, aortic arch, and descending aorta (7). A more detailed classification, the Ishimaru zoning system, divides the aorta into twelve segments or zones. The first six zones are located within the thoracic aorta. Zone 0 comprises the ascending aorta; zones 1 and 2 include the aortic arch and are separated by the left carotid artery. Zone 3 consists of the first 2 centimetres of the descending aorta, and zone 4 extends to approximately the level of the sixth thoracic vertebrae (Th6). Zone 5 then continues from this level to the diaphragm (8, 9).

The aortic wall consists of three layers: the tunica intima, tunica media, and tunica adventitia. The innermost layer, the tunica media, is a thin layer containing a single layer of endothelial cells and a basal membrane. The tunica intima is the thickest layer, and it consists of bundles of smooth cells surrounded by collagen fibres and elastic fibres in an extracellular matrix. With its flexible structure, the tunica media plays an important physiological role in bearing the load of the pulsatile blood flow. Lastly, the tunica adventitia is the outermost layer of the aorta. It consists of thick strains of collagen fibres giving it a high tensile strength. It also holds the vasa vasorum, the blood vessels that supply the aortic wall itself (10, 11, 12).

Pathophysiology

An aortic dissection occurs when an intimal tear allows blood to flow from the true lumen into the aortic wall creating a separation between the three wall layers. This creates a false lumen that may propagate along the aorta, both in the antegrade direction as well as in the retrograde direction. This process causes end-organ malperfusion as the false lumen may obstruct the branch vessels or allow blood to bypass them (13, 14).

Classifications

Aortic dissections are classified according to anatomical extent and symptom duration. Generally, aortic dissections with a symptom duration of less than 14 days are regarded as acute. Chronic dissections have longer symptom duration, although the term subacute dissection has been proposed for dissection with a symptom duration of 15-90 days (9, 13).

Stanford

The Stanford classification, introduced in 1970, is the most widely used classification system for aortic dissections (15). A Stanford A dissection involves the ascending aorta irrespective of the location of the primary intimal tear or the distal extent of the dissection. A Stanford B dissection is restricted to the descending

aorta distal to the left subclavian artery. A non-A non-B dissection is a small subset that involves the aortic arch but not the ascending or descending aorta (9).

DeBakey

The DeBakey classification subdivides aortic dissections into three types: DeBakey type I affects both the ascending and the descending aorta, DeBakey type II affects only the ascending aorta, and DeBakey type III affects only the descending aorta (16).

This thesis discusses Stanford A (DeBakey types I and II) dissections only as Stanford B (DeBakey type III) dissections are primarily treated medically or endovascularly (9, 17).

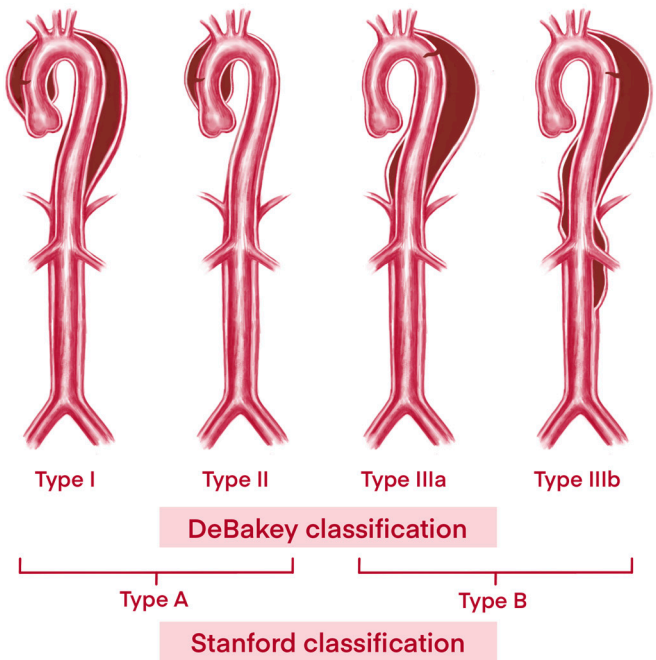

Figure 1. Classification of aortic dissections. ©Anni Tuikka

Intramural hematomas and penetrating atherosclerotic ulcers

Intramural hematomas (IMH) and penetrating atherosclerotic ulcers (PAU) represent distinct entities within the spectrum of acute aortic conditions that are often discussed in parallel with aortic dissection. Both IMHs and PAUs may be seen as precursors to dissection, and although they are not true dissections per se, they are generally treated similarly with acute surgical repair (9, 17).

An intramural hematoma (IMH) is defined as a bleeding within the aortic wall with or without an intimal tear. The IMH may be caused by a bleeding in the vasa vasorum, trauma, or microscopic tears in the intima (18, 19).

Penetrating atherosclerotic ulcers (PAUs) are atherosclerotic lesions that derive from the tunica intima and progress into the tunica media. They typically occur in patients with high atherosclerotic burdens. The ulceration causes a weakness in the aortic wall making it susceptible to aortic rupture as well as IMH or dissection (20).

Complications

Type A aortic dissections (TAADs) are associated with several life-threatening complications: The dissection severely impairs the tensile strength of the aortic wall making it prone to rupture. Retrograde propagation into the aortic root may cause a bleeding into the pericardium leading to hemopericardium and subsequently cardiac tamponade. In addition, a TAAD that affects the aortic root may disrupt the geometry and function of the aortic valve causing life-threatening aortic regurgitation (21).

As mentioned earlier, a propagating false lumen in an aortic dissection can result in the obstruction of branch vessels and lead to end-organ ischemia. This causes malperfusion syndromes, which may affect any vascular bed. The clinical consequences are often severe and may include myocardial, cerebral, renal, or mesenteric ischemia (22, 23).

Patients with AD are also at risk of developing severe coagulopathy. This occurs as the circulating blood within the false lumen is exposed to extracellular tissue, triggering widespread activation of the coagulation system. The resulting consumption of coagulation factors can lead to a haemostatic imbalance and increased risk of bleeding complications (24).

Incidence and risk factors

Aortic dissections are more common than PAUs and IMHs, with an approximate ratio of 4.4:2.1:1.2 (25). Type A aortic dissections make up 58-62% of all dissections (1, 13, 26). As many patients succumb to the disease before reaching medical care and thus remain undiagnosed, the true incidence of TAAD is difficult to determine. Reported incidence rates range from 2-16 cases per 100,000 patient-years, with a clear incidence increase with advancing age (26, 27, 28, 29, 30).

The incidence of TAAD is higher in males than females. Acosta et al. reported the incidence in males to be 3.9 cases per 100,000 patient-years and 2.9 cases per 100 000 patient-years in females. Moreover, men develop TAAD at a younger age,

with an incidence of 20.8 cases per 100,000 patient-years in the 65 to 74-year age group as compared to 5.0 cases per 100,000 patient years in the same age group in women (29).

Hypertension is the most significant risk factor for developing TAAD, and it is present in 67-86% of patients (1, 13, 14). Smoking and atherosclerosis are also independent predictors of aortic dissection (13).

Aortic aneurysms increase the risk of dissection as the increased aortic diameter leads to significantly elevated stress on the aortic wall (31). Aneurysms of the ascending aorta are more frequently associated with hereditary disorders while aneurysms of the descending aorta are more commonly related to hypertension, age, and atherosclerosis (13). A family history of aortic dissection can be found in 8% of TAAD patients, and 20% have a first-degree relative with a dilated thoracic aorta (32, 33).

Marfan syndrome is an autosomal dominant disorder that affects patients' ability to synthesize fibrillin. The lack of normal fibrillin causes degeneration of the tunica media and predisposes patients to dissections in medium- and large-sized arteries, including the aorta. Marfan syndrome is present in 3-7% of patients with AD (9, 13). Loeys-Dietz syndrome and vascular Ehler-Danlos are two additional hereditary syndromes that cause structural weakness of the aortic wall and increase dissection risk (14). Bicuspid aortic valve is also a known risk factor, present in approximately 6% of AD patients, compared to 2% in the general population (34).

Iatrogenic dissections, typically caused by coronary artery catheterization or surgical procedures involving arterial cannulation, account for 1-5% of all aortic dissections (1, 32, 35).

Mortality

It is widely accepted that an untreated acute type A aortic dissection (ATAAD) has an hourly mortality rate of 1-2% during the first 24 hours after symptom onset (13, 36, 37). These figures originate primarily from a study by Hagan et al., which analysed 81 patients with non-surgically treated (NST) ATAAD from the International Registry of Acute Aortic Dissection (IRAD) published in 2000 (1). All patients in the cohort were denied surgical repair as they were too old or had too severe comorbidities.

A 2013 IRAD update by Booher et al. included 186 patients with NST ATAAD, and reported a 24-hour mortality of 18%, 7-day mortality of 49%, 30-day mortality of 60%, and 60-day mortality of 62% (38).

In 2022, Haris et al. published an additional IRAD-based study on NST ATAAD, reporting a 48-hour mortality of 23.7%, corresponding to an hourly mortality rate of 0.5%, measured from the time of hospital arrival (39).

A major limitation to IRAD-based studies is selection bias: the registry includes only patients who reach participating tertiary referral centres alive. Nearly 50% of patients with ATAAD die before even reaching a hospital (40). Furthermore, IRAD does not capture patients who die in their homes, during transport, in primary hospitals, or who are not referred to surgery at any of the participating centres. This limitation has been discussed by Evangelista et al., which reported that 60% of patients in IRAD are referred from outside hospitals (21).

The in-hospital mortality of NST ATAAD is reported to range between 50% and 69% (1, 38, 41, 42).

Clinical presentation

The majority of ADs occur during physical exertion (4). The classical presentation is sudden onset of sharp, tearing or ripping pain in the chest, abdomen, or back. However, the clinical manifestations are often variable, which can lead to diagnostic delay (43). A sudden onset of severe chest pain, often described as sharp or tearing in nature, is experienced by 83-85% of patients. The pain is often described as migratory, following the anatomical progression of the dissection. Pain radiating to or presenting in the posterior chest or abdomen is present in 33% of patients and 22% of patients, respectively. Pain in the jaw or throat is sometimes described (1, 44, 45, 46). Females are more likely to present with atypical symptoms without abrupt onset (47).

Syncope occurs in approximately 13% of ATAAD patients (1), and cardiac tamponade is present in 17-20%. Between 5% and 6% of patients undergo cardiopulmonary resuscitation prior to surgery. Overall, nearly half of patients are hemodynamically unstable at presentation to the hospital (48, 49, 50).

Malperfusion syndromes are present in 27-48% of patients and may result from branch vessel obstruction or global hypoperfusion due to shock. Malperfusion may occur at any vascular bed, thus giving rise to a wide variety of symptoms that mimic other severe diseases such as stroke, mental clouding, paresis, acute coronary syndrome, peripheral arterial embolism, or renal failure (22, 51, 52, 53, 54). Pulse deficits are present in 31% of patients (46).

Penn classification

The Penn classification, developed at the University of Pennsylvania, stratifies ATAAD patients into mortality risk groups by severity of clinical presentation.

Patients in Penn class Aa show no signs of end organ malperfusion or hypotension, patients in Penn class Ab show end organ malperfusion (cardiac malperfusion excluded), patients in Penn class Ac show signs of cardiac malperfusion and/or hypotension, and finally, patients in Penn class Ab+c shows both signs of end organ malperfusion and cardiac malperfusion and/or hypotension (51). The Penn classification has since been validated and may serve as a valuable tool for identifying high-risk patients (55, 56).

Diagnosis

Given the high mortality associated with untreated ATAAD, rapid diagnosis and management are of paramount importance. As aortic dissection remains rare in comparison to important differential diagnoses such as acute coronary syndromes, strokes, pulmonary emboli and peripheral arterial emboli, a high clinical suspicion accompanied by a thorough clinical investigation and consideration of key anamnestic details will be necessary to avoid misdiagnosis (9, 57).

Scoring system

Guidelines recommend the use of the Aortic Dissection Detection Risk Score (ADD-RS) to establish an a priori risk level for aortic dissection and to guide appropriate diagnostic workup (9). The ADD-RS assigns one point each for high-risk conditions (Marfan syndrome, family history of aortic disease, known aortic valve disease, recent aortic manipulation, known thoracic aortic aneurysm); high-risk pain features (chest, back, or abdominal pain described as abrupt in onset, ripping or tearing, and severe in intensity); and high-risk examination features (evidence of perfusion deficits, aortic murmur, or hypotension/shock) (58). The score ranges from 0 to 3. An ADD-RS of 2-3 points indicates intermediate to high probability of aortic dissection. The ADD-RS has been validated in multiple studies (59).

Imaging tests

Computed tomography

Computed tomography (CT), ideally with an aortic protocol or at least contrast enhancement, is the most common and preferred modality for diagnosing aortic dissection. A CT is available at almost all emergency hospitals and provides rapid, high-resolution imaging. In addition to establishing the diagnosis, CT offers valuable information about the extent of the dissection and whether branch vessels are involved. A contrast-enhanced CT test can also show whether the branch vessels are primarily supplied by the true or false lumen (9, 13, 14, 21, 60).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) can also diagnose aortic dissections. However, it is more time-consuming than CT and is generally less accessible in emergency settings (61).

Chest X-ray

A conventional chest X-ray can show indirect signs of an aortic dissection such as widened mediastinum or abnormal aortic contours. However, 21% of patients with aortic dissection lack both these signs (1). A conventional chest X-ray is most valuable when part of a standard workup for patients presenting with chest pain.

Angiography

An aortic angiography can reveal a dissection membrane in the ascending aorta and thus establish the diagnosis of ATAAD. This modality is mainly relevant to patients who had symptoms mimicking acute coronary syndrome or in cases of iatrogenic dissection following coronary artery catheterisation (13).

Echocardiography

Transthoracic echocardiography (TTE) is widely available in emergency settings and may therefore be performed early. TTE might detect a dissection membrane in the ascending aorta, an intimal flap, or indirect signs of AD such as hemopericardium/cardiac tamponade or aortic regurgitation. However, due to its poor imaging windows, the sensitivity is only 59%. However, transesophageal echocardiography (TEE) offers excellent sensitivity comparable to CT, at 95%, and is particularly useful in sedated patients and in the operating room (62).

Biomarkers

D-dimer

D-dimer is a widely used biomarker that reflects the level of activity in patients' fibrinolytic systems as it is a degradation product that arises from the cleavage of fibrin by plasmin (63). D-dimer is typically used to diagnose pulmonary embolism or venous thromboembolism, but it can be applied to many other settings (63).

As the consumption coagulopathy in ATAAD causes a marked increase in the fibrinolytic activity (24, 64), ATAAD patients will show elevated levels of D-dimer. Therefore, a normal D-dimer (< 500ng/mL) has been proven in many studies to be an excellent tool to rule out ATAAD (65, 66, 67, 68). Yao et al., who published a meta-analysis in 2021, reported a sensitivity of 96% and a specificity of 70% (67).

D-dimer has been proven to be a valuable diagnostic addition to the ADD-RS in patients with 0 or 1 points as the combination of ADD-RS 0-1 points and D-dimer

< 500ng/mL will miss only ≈1 aortic dissection in 300 cases (69). The combined use of ADD-RS and D-dimer is recommended in guidelines (9).

D-dimer levels have been shown to correlate with the anatomical extent of aortic dissection (70), suggesting that patients with normal D-dimer may have limited dissections or thrombosed false lumina (71). However, elevated D-dimer is also found in several major differential diagnoses, most notably pulmonary embolism (72) and acute coronary syndromes (73).

Novel biomarkers

Aggrecan is a proteoglycan that is primarily found in cartilage but also in the aortic wall. A study published by Köing et al. found that Aggrecan could predict ATAAD with a sensitivity of 97% and a specificity of 81% (74). The levels of Aggrecan were significantly higher in patients with ATAAD compared to patients with thoracic aneursyms, myocardial infarctions, and healthy volunteers.

Soluble ST2 (sST2) is another biomarker that shows promising results in diagnosing ATAAD. It is an interleukin receptor family member that is secreted in inflammatory conditions and due to heart disease. When compared in patients with ATAAD, myocardial infarction, pulmonary embolism, angina pectoris, and in healthy volunteers, sST2 yielded a sensitivity of 99.1% and a specificity of 84.9% (75).

Other potential biomarkers that have been suggested are smooth muscle myosin heavy chain (smMHC) (76), calponin (77), soluble elastin-laminin-associated fragments (sELAF) (78), CD40 ligand (CD40L) (79), and trimethylamine N-oxide (TMAO) (80).

All of these novel biomarkers share the problem that they are not readily available at most hospitals, have not been repeatedly validated, and do not have established cutoff values.

Fibrinogen

Fibrinogen is a soluble macromolecule that circulates in the blood. The cleavage of fibrinogen plays a vital role in hemostasis as the insoluble form fibrin acts to stabilise blood clots. Fibrinogen is also an acute phase reactant as its synthesis, and secretion is increased in response to inflammation (81, 82). The consumption coagulopathy in aortic dissection has been shown to reduce fibrinogen levels (24).

Misdiagnosis

ATAAD has sometimes been described as a “great masquerader,” because of the large number of conditions it can resemble at presentation (9).

Incidence

Misdiagnosis occurs in 18-78% of ATAAD cases (83, 84, 85, 86, 87). The wide variation partly reflects the absence of a standardised definition. Zaschke et al., who reported the highest frequency of misdiagnosis (78.3%), considered the *initial* diagnosis made by the first examining physician regardless of setting—from prehospital care to the ED (84). In contrast, Hansen et al., Hirata et al., and Chua et al. assessed diagnosis *after* evaluation in the ED, and the reported rates of misdiagnosis were in the range of 37-39% (85, 86, 87). Kurabayashi et al. found a lower misdiagnosis frequency (16%) as they allowed for completion of the full diagnostic workup in the ED before judging whether a misdiagnosis had occurred (83).

Acute coronary syndrome (ACS) is consistently reported as the most common misdiagnosis (83, 84, 85, 87). ACS is far more common than ATAAD and the two diseases share chest pain as the dominant symptom. Other misdiagnoses that frequently occur are neurological disease/cerebrovascular disease, respiratory disease, gastrointestinal disease and musculoskeletal strain. Some of these misdiagnoses may be attributed to malperfusion syndromes producing symptoms at various locations or migrating pain caused by the propagating false lumen. It is also likely that circulatory compromise due to hypotension or shock may contribute to misdiagnosis as it may cause mental clouding, confusion, or even unconsciousness.

Risk factors

Arrival to the emergency room (ER) without ambulance transport has been identified as an independent predictor of misdiagnosis by several authors. Kurabayashi et al. reported an odds ratio (OR) of 4.8 (83) while Hirata et al. reported an OR of 2.6 (85). This likely reflects the fact that clinicians in the ER tend not to suspect ATAAD in patients in a clinically stable condition. The absence of pulse deficit also has been reported as a risk factor (86) and several authors have identified angina pectoris, or anterior chest pain, as a predictor of misdiagnosis (83, 84, 87), which again highlights ACS as the most important misdiagnosis.

Non-surgical treatment

The cornerstone of non-surgical treatment of ATAAD is blood pressure control, which reduces aortic wall stress and prevents further propagation of the dissection or the development of complications (9, 57). The general target is a systolic blood pressure below 120 mmHg, or even lower if tolerated without causing hypoperfusion. In addition, the heart rate should optimally be kept between 60 and 80 bpm. All patients who do not have contraindications should be treated with beta-blockers. Optimally, patients should be monitored in an intensive care unit (ICU)

setting with an arterial line for continuous blood pressure monitoring, and the patients should preferably have the beta-blockers administered intravenously for optimal dosage and effect. Patients who do not tolerate beta-blockers should be treated with calcium-channel blockers. If beta-blockers or calcium channel blockers do not suffice to reach the blood pressure target, intravenous vasodilators should be administered. They can, however, cause compensatory tachycardia and should, therefore, not be administered before beta-blockers or calcium channel blockers. In addition to blood pressure and heart rate control, adequate pain relief must be reached (9, 57).

Adequate blood pressure is also the cornerstone in long-term non-surgical treatment as inadequate blood pressure has been shown to correlate with exacerbations of the dissections (88). Patients not suitable for surgical treatment should receive beta-blockers and preferably angiotensin converting enzyme inhibitors. However, there is no solid evidence for adding statins (9, 57).

Surgical treatment

Open surgical repair remains the gold standard for ATAAD management (9, 57). The procedure has two principal aims: Firstly, to restore blood flow to the true lumen thus preventing malperfusion and the risk of rupture in the weakened, dissected, aortic wall. Secondly, to secure the aortic root to prevent cardiac tamponade and distortion of the valvular anatomy causing severe regurgitation. Resection of the intimal tear is desirable but not mandatory. The surgical procedure is done with the assist of extracorporeal circulation. A repair in hypothermic circulatory arrest (HCA) with an open distal anastomosis has been shown to be superior to a repair with a cross-clamped aorta (89).

Large, international registries (IRAD, European Registry of Type A Aortic Dissection (ERTAAD), German Registry of Acute Aortic Dissection Type A (GERAADA) and the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD)) report an early mortality rate following surgical repair in the range of 16.4-18.9% (21, 90, 91, 92). A trend towards lower mortality has been shown: IRAD reports a drop from 25% to 18% during two decades (21), and NORCAAD has been able to show a decrease in 30-day mortality from 24% to 13% from 2005 to 2014 (48).

There are scoring tools to predict the 30-day mortality following surgical treatment of ATAAD. Some authors promote the use of the widely used EUROSCORE II (93). It is, however, not specific to ATAAD but has been developed for assessment of mortality in heart surgery in general. In 2020, Czerny et al. introduced the GERAADA-score, a scoring tool specifically developed for ATAAD (94). The GERAADA-score is calculated from the following variables: age, sex, resuscitation

before surgery, previous cardiac surgery, intubation at referral, catecholamines at referral, aortic valve regurgitation, malperfusion, hemiparesis, extension of the dissection, and location of the primary tear with the aortic arch. The GERAADA-score has been validated in several studies, and it seems to outperform EUROSCORE II in the ATAAD-setting (95).

Cannulation

The extracorporeal circulation necessary for the surgical treatment of ATAAD requires both arterial and venous access. Cannulation of the venous system is not as controversial as where to access the arterial system (96). The difficulties in arterial cannulation in the ATAAD-setting lies in the necessity to reach the true lumen without causing an arterial rupture and, thereafter, to circulate the true lumen without flushing thromboembolic debris from the dissected aorta into end organs.

Peripheral cannulation

Femoral cannulation is the preferred method at many centres. It can be performed percutaneously under local anaesthesia in an awake patient and is generally safe (97), with few complications at the cannulation site (98). The theoretical downside to the technique is that the retrograde gradient through the aorta may aggravate the dissection via pressurization of the false lumen. It is also associated with the risk of embolic material reaching the brain or other end organs leading to cerebral or systemic embolisation. Another location accessible for peripheral cannulation is the axillary or right subclavian artery, and some authors advocate this approach because it allows antegrade flow through the descending aorta (99).

Central cannulation

Cannulation of the ascending aorta has several advantages, one of the most important being the circulation of blood in an antegrade direction throughout the arterial system. An aid to perform the cannulation as accurately and safely as possible is to use the Seldinger technique and to verify the location of the guidewire in the true lumen with ultrasound (100).

The optimal site of cannulation remains an area of debate. A large meta-analysis found no significant difference between central and peripheral cannulation with respect to operative mortality, long-term mortality, stroke, or renal failure (101). Nonetheless, international guidelines recommend axillary cannulation over femoral cannulation (9, 57), and American guidelines recognise ultrasound-guided central cannulation as an acceptable alternative to peripheral cannulation (57).

Hypothermic circulatory arrest

Hypothermia provides organ protection, particularly for the brain. The optimal target temperature for hypothermia is debated. Some centres prefer deep hypothermia with a core temperature below 20°C, while others use moderate hypothermia (20-28°C) (49). HCA is generally considered to be safe for 30-40 minutes, beyond which the risk of neurological injury increases (49, 102, 103).

Cerebral perfusion

Cerebral protection during HCA can be enhanced by methods of perfusing the brain. In antegrade cerebral perfusion (ACP), oxygenated blood is delivered to the cerebral parenchyma in an antegrade direction while retrograde cerebral perfusion (RCP) carrries blood to the brain in a retrograde direction via the superior vena cava (104). RCP provides little to no metabolic substrates to the cerebral tissues, and its primary protective effect is, therefore, considered to be mediated through topical cooling of the cerebral parenchyma and the flushing of thrombi and air from the supra-aortic branch vessels. ACP requires cannulation of one or more of the cervical vessels. The use of ACP allows for maintained cerebral protection with moderate HCA rather than deep HCA (105). A study by Samanidis et al. compared ACP and RCP and found no significant differences in 30-day mortality or neurological injury (106). Potential downsides of cerebral perfusion include increased procedural complexity and prolonged HCA and cardiopulmonary bypass time.

Proximal repair

The optimal extent of proximal repair remains debated. The least invasive approach is to replace the ascending aorta with a supracoronary graft with or without aortic valve resuspension depending on whether the dissection has affected the aortic valve commissures. The more extensive alternatives include aortic root replacement using composite grafts with prosthetic valves (Bentall procedure) or valve-sparing techniques such as the David or Yacoub procedures. The less aggressive approach, i.e. supracoronary grafts, is associated with fewer adverse events, less bleeding, shorter operating times, and lower short-term mortality (91, 107). However, evidence is mixed; some authors report lower mortality with root replacement (108). Proponents of more extensive repair argue that it does not significantly increase short-term risk and may reduce long-term reintervention rates (109, 110). Other studies show similar short- and long-term outcomes between supracoronary and root-replacement procedures (111).

Distal repair

The debate regarding the optimal extent of distal repair mirrors that of proximal repair. Surgeons must balance the goal of performing a safe, lifesaving procedure with the wish to achieve optimal long-term outcomes that reduce the need for further interventions (112, 113). The least extensive approach is to replace the ascending aorta and land the distal anastomosis proximal to the aortic arch. In very limited dissections, this may even be achieved with an aortic cross-clamp without the need for HCA. However, in most cases, it will be performed as an open distal anastomosis with HCA. More aggressive approaches will include total or partial replacement of the aortic arch. This is thought to reduce the risk of a circulated false lumen and to reduce the risk for reoperations. In a retrospective study, with propensity score-matched pairs, aortic arch-replacements led to higher in-hospital mortality (21% vs. 15% (p =0.008)) as well as a 10-year mortality (47% vs. 40% (p =0.001)) without decreasing the risk of distal aortic reoperation during ten years, following the primary surgery (9% vs. 7% (p =0.690)) (114). Therefore, when feasible, a limited repair seems to be favourable (115).

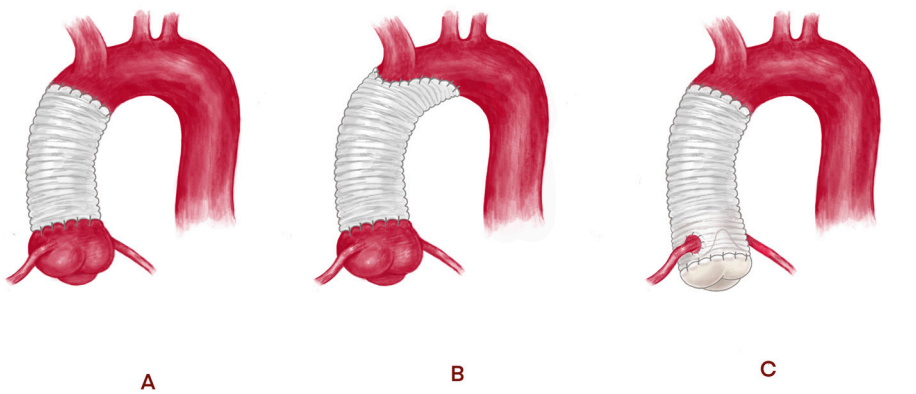

Figure 2. Surgical repair techniques for acute type A aortic dissections. (A) Supracoronary graft replacement of the ascending aorta. (B) Hemiarch repair with distal anastomosis in the aortic arch. (C) Bentall procedure with composite graft replacement of the aortic root and valve. ©Anni Tuikka

Complications

Complications following surgical repair of ATAAD are common and are reported to occur in 33-45% of patients (115). Due to the severe nature of the disease itself, and the complexity of the surgical repair, several serious adverse events may occur. Commonly, neurological injury is considered the most dreaded, but several others warrant attention:

Malperfusion syndrome, defined as malperfusion leading to end-organ malfunction, is associated with impaired outcomes with an elevated short-term

mortality rate reaching 43% (116). Due to the nature of an ATAAD, with a propagating false lumen, malperfusion syndrome may lead to ischemic injury in any organ system, including the brain, kidneys, intestines, and limbs (117, 118).

Acute kidney injury (AKI) may develop either preoperatively as a consequence of malperfusion or during the surgical repair. AKI is associated with a higher risk of 30-day mortality (risk ratio (RR) 3.98), stroke (RR 2.05), and re-exploration for bleeding (RR 2.46) (119).

Consumption coagulopathy may occur as an ATAAD with a circulating false lumen exposes a large proportion of the circulating blood to extra-endothelial tissues, thereby promoting coagulation (24). This poses significant challenges during surgical repair as well as in the immediate postoperative period and has been associated with both increased hospital stay and late mortality (120).

Neurological injury

Neurological injury occurs in 4-30% of patients who survive surgical repair for ATAAD (91, 118, 121, 122, 123, 124, 125). In the NORCAAD registry, the rate of postoperative stroke was 15.7% (126).

Neurological injury may occur preoperatively due to malperfusion or hypotension. It may also arise during surgical repair as a result of insufficient cerebral protection during HCA or because of dislodgement of emboli to the brain.

Apart from a potentially devastating effect on postoperative function level, neurological injury is an independent risk factor for postoperative mortality (91, 127). Chemtob et al. reported data from NORCAAD demonstrating an OR of 2.02 (1.34-3.05, $p<0.001$) for early mortality among patients with postoperative neurological injury.

Biomarkers

Several biomarkers may assist in predicting neurological injury in the context of ATAAD.

S100B

S100B is a calcium binding protein predominantly found in the glial Schwann cells of the brain, but it is also present in various other tissues such as muscles, adipocytes in fatty tissues, the liver, and melanocytes of the skin (128). S100B, in its soluble circulating form, is mainly eliminated by renal excretion, and it has a half-life of 30-60 minutes (128).

S100B has been proven to be a reliable biomarker to predict neurological injury following trauma (129). In a stroke setting, the level of S100B measured in blood correlates to the severity of the stroke and to the volume of affected brain tissue (130).

While previously thought to passively leak from damaged cells after injury, current understanding suggests S100B to play a pathophysiologic role as it seems to be actively released by the glial cells (131). In low concentrations, it acts neurotrophically, and in higher concentrations it becomes neurotoxic (128).

In routine cardiac surgery, S100B levels correlate with short- and long-term neurobehavorial impairment (132, 133, 134); with stroke and stroke volume (135); and, when measured 48 hours postoperatively, with long-term mortality (136).

Neurofilament light chain

Neurofilament light chain (NfL) is established as a biomarker for axonal damage across various neurological disorders, including traumatic injuries, as its levels increase proportionally in cerebrospinal fluid and blood following damage (137).

NSE

Neuron-specific enolase (NSE) is a highly specific marker for neurons and is shown to provide quantitative measures of brain damage and aid in the outcome evaluation of several neurological conditions, including ischemic stroke, intracerebral haemorrhage, and traumatic brain injury (138).

Aims

Study I

Study I aimed to provide contemporary data on mortality following non-surgically treated acute type A aortic dissection and describe surgical decision rationale.

Study II

In Study II, we aimed to assess the frequency of misdiagnosis and delayed diagnosis of acute type A aortic dissection, to identify independent predictors of misdiagnosis, and to assess the clinical impact of initial misdiagnosis.

Study III

The aim of Study III was to investigate whether the addition of fibrinogen to D-dimer could assist in the risk assessment for acute type A aortic dissection in the emergency department.

Study IV

Study IV aimed to examine whether S100B can be used to predict neurological injury following acute type A aortic dissection repair.

Material and methods

Patients and study design

Departmental surgical database

The Department of Cardiothoracic Surgery at Skåne University Hospital is a tertiary referral centre serving 1.9 million inhabitants (2023). Since January 1998, all patients undergoing surgery for TAAD have been prospectively entered into our departmental surgical database (DSD). The DSD covers background variables, intraoperative variables, and outcome variables. In total, the DSD holds more than 300 variables. Additional variables have been added through retrospective chart review when needed, while prospective registration remains ongoing. The DSD currently includes more than 660 patients. Data from the DSD were used in all studies in this thesis.

Non-surgically treated acute type A aortic dissection

All patients who received one of the following diagnoses: ICD-9 4410 (Aortic dissection), 4411 (Thoracic aneurysm, ruptured), 4415 (Aortic aneurysm of unspecified site, ruptured), 4416 (Thoracoabdominal aneurysm, ruptured) or ICD-10 I710 (Dissection of aorta), I711 (Thoracic aortic aneurysm, ruptured), I715 (Thoracoabdominal aortic aneurysm, ruptured), I718 (Aortic aneurysm of unspecified site, ruptured) from January 1998 to November 2021 at any health care facility in our region were assessed for inclusion (n=2325). The search was performed by the central data management department at Skåne University Hospital to ensure full regional coverage of eligible patients across all available medical registries. Consequently, the only patients potentially missed were those who died from ATAAD before receiving a diagnosis and did not undergo autopsy. All charts (including autopsy reports) and available imaging of each screened patient were then reviewed by a cardiothoracic surgeon to confirm or discard the diagnosis of ATAAD or chronic type A aortic dissection (CTAAD). In complicated cases, additional cardiothoracic surgeons and/or a thoracic radiologist was consulted. All patients with a confirmed diagnosis of ATAAD or CTAAD were included (n=735). The database was matched against our DSD, and the patients who had undergone surgical treatment for ATAAD were excluded (n=547). Patients who had undergone surgery for the TAAD outside of our department were also excluded (n=4). This resulted in 153 patients with NST-ATAAD. Additionally, 31 patients with CTAAD

were included. A flowchart of inclusion and exclusion is shown in Figure 3. Baseline and survival data on the NST-ATAAD patients were collected by retrospective chart review. Data from the NST-ATAAD database was used in studies I and II.

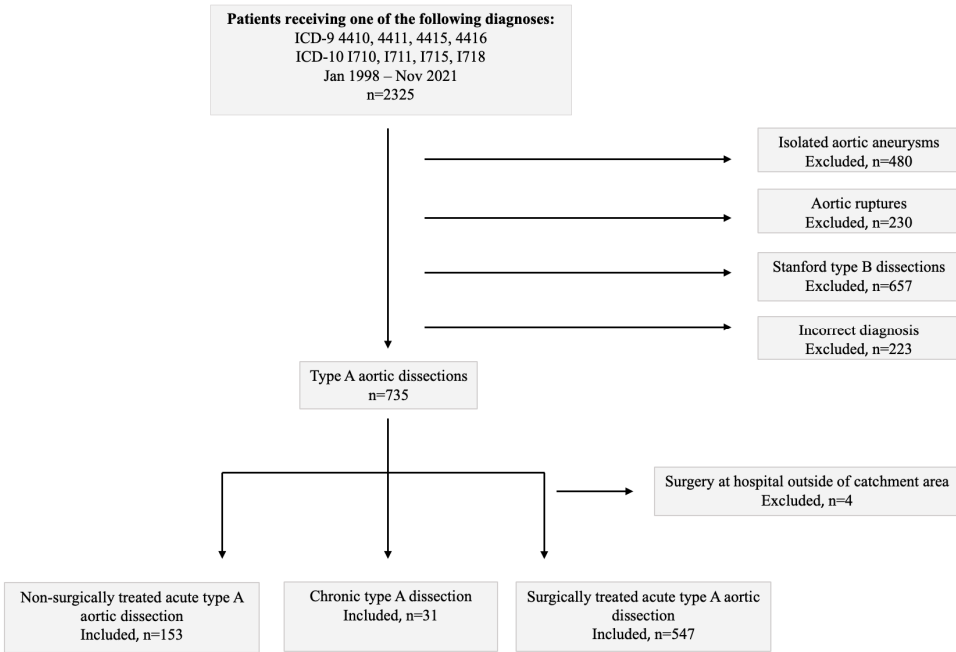

Figure 3. Flowchart of inclusion and exclusion of patients in the non-surgically-treated acute type A aortic dissection database..

Skåne Emergency Medicine

Skåne Emergency Medicine (SEM) is an emergency care database holding data on 630,275 visits by 325,539 patients to any of the eight EDs in the Skåne region during 2017-2018. A description of the database has been published (139). SEM includes baseline data on demographics and previous diseases, data about the visit to the ED including chief complaint, handling times, and test results, as well as outcome data with final diagnosis, treatments, and mortality among others. The database was established primarily to develop clinical decision systems.

Study I

Study I was a regional, retrospective, observational study.

All patients from the NST-ATAAD-database were included (n=184). Data on the patients who underwent surgery for ATAAD during the study period (January 1998 to November 2021) were obtained from our DSD (n=547).

Patients with NST-ATAAD were compared to ST patients. ATAAD was defined according to the Stanford classification with a symptom duration of less than 14 days. Intramural hematomas were included in the ATAAD group. CTAAD was defined as an aortic dissection with symptom duration exceeding 14 days. These patients were included in the NST cohort as they did not undergo surgery during the first 14 days after symptom onset and, therefore, by definition, were 14-day survivors of an ATAAD. All diagnoses were confirmed by computed tomography (CT), transthoracic echocardiography (TTE), transoesophageal echocardiography (TEE), aortic angiography, or autopsy. Survival follow-up was conducted on April 30, 2023. No patients were lost to follow-up.

The primary outcome measure was mortality.

Study II

This study was a single-centre, retrospective, observational study. We assessed for inclusion all patients who were diagnosed with ATAAD in our region between April 2001 and October 2021 (n=630). All patients who had available admission charts were included (n=556). Data on the ST patients (n=418) were collected from the DSD, and data on the NST patients (n=138) were obtained from the NST-ATAAD database. Additional data on the study population was collected by retrospective chart review.

The primary endpoints were initial misdiagnosis, delayed diagnosis and 30-day mortality. Misdiagnosis was defined as one or a combination of the following: (1) initial misdiagnosis based on the patient chart; (2) misdiagnosis on imaging referral or a computed tomography referral without aortic pathology as a differential diagnosis; (3) holding or admitting a patient for observation; or (4) an unjustified or unmotivated delay of more than 120 minutes from initial assessment to diagnosis. Delayed diagnosis was defined as a period of more than 120 minutes from initial assessment to diagnosis. However, when unpreventable circumstances (e.g. cardiopulmonary resuscitation) caused a delay in diagnosis, the 120-minute limit was disregarded as long as the medical team had already formed a high suspicion of ATAAD. Similarly, the 120-minute limit was not applied in cases where primary care physicians referred patients to the emergency department with high suspicion of ATAAD. Time of first assessment was defined as either the arrival time to the primary care physician or to the emergency department. For inpatients, the first assessment was defined as the time medical personnel detected symptom onset. The time of diagnosis was defined as follows: (1) the point at which an imaging modality capable of diagnosing ATAAD revealed the first probable suspicion of ATAAD; or (2) in more complex cases, the time at which an imaging procedure was conducted providing the basis for the surgical decision. In cases where the exact time points were unknown, they were approximated if within an estimated accuracy of ± 30 minutes.

The specific misdiagnoses of patients were denoted and divided into groups to facilitate statistical analysis. Misdiagnosed cases lacking information regarding specific diagnoses were labelled "unclear," less frequent diagnoses were grouped together as "other," and cases of multiple incorrect differentials were labelled as "multiple diagnoses." Patients were grouped by clinical presentation according to the Penn classification, which has been defined previously (51).

Study III

Study III was an exploratory, retrospective, single-region, observational study. All patients in the DSD who had undergone surgery for ATAAD from January 1998 to August 2023 were assessed for inclusion (n=567), and the patients who had available values for preoperative D-dimer and fibrinogen were included (n=93). ATAAD was defined as a Stanford type A dissection with a symptom duration of less than 14 days. Data on the non-ATAAD patients were collected from SEM. All patients in the SEM-cohort (n=325 539) were assessed for inclusion, and the patients whose D-dimer and fibrinogen values were obtained within 24 hours of arrival to the ED were included (n=287). Non-ATAAD patients who were admitted to the ED because of multi-trauma or circulatory arrest (n=85) were excluded from the analyses as these patients have a severely disrupted coagulation and are unlikely to be diagnosed as ATAAD patients.

The primary outcome of the study was to determine the discriminative ability of the D-dimer/fibrinogen ratio to predict ATAAD, measured as the area under the curve (AUC) on receiver operating characteristics (ROC) curves. This was then compared to AUC of D-dimer and fibrinogen alone.

Study IV

Study IV was a single-centre, retrospective, observational study. Data was retrieved from our DSD and the study period spanned from January 1998 to December 2021. All patients from the study period were assessed for inclusion (n=538). All patients with recorded S100B values were included (n=393). Missing values were collected by retrospective chart review. An AD was regarded as acute if the time from symptom onset to surgery was less than 14 days.

The primary outcome measure was neurological injury, which was defined as focal neurological deficit or coma, with a symptom duration of more than 24 hours, diagnosed by clinical assessment by a neurologist with or without radiological confirmation by computed tomography or magnetic resonance imaging. Thirty-day mortality and postoperative complications were secondary outcome measures. Transient cerebral events (transient ischemic attack or transient stroke) were defined as neurological deficits with symptom duration of less than 24 hours diagnosed by clinical assessment regardless of radiological findings. Hypotensive shock was defined as a preoperative period of systolic blood pressure <90mmHg, and preoperative cerebral malperfusion was defined as impaired consciousness or

presence of clinical focal neurological symptoms preoperatively. Postoperative stroke was defined as focal neurological symptoms with a duration of more than 24 hours postoperatively, while postoperative coma was defined as a state of unconsciousness (Glasgow Coma Scale Motor Score <6) persisting more than 48 hours without pharmacological sedation.

The blood samples were collected during routine lab monitoring using a central venous line at the following time points: T0 – preoperatively at arrival to the operating theatre; T1 – within the first 12 hours after surgery; T2 – 24 hours after surgery; T3 – 48 hours after surgery; and T4 – 72 hours after surgery. S100B was analysed by a monoclonal sandwich immune assay primarily using the Cobas 6000/8000 analyser (Roche) but also using the Sangtec 100 analyser (LIAISON) and Hitachi Modular-E analyser (Roche).

Ethical aspects

All studies complied with the principles of the Helsinki Declaration of Human Rights and were approved by the Swedish Ethical Review Agency (ref 2019-05783; ref 2021-01185; ref 2023-05843-02). Permission to access data was granted by the Institutional Review Board of Skåne University Hospital (ref 144-21). Informed consent was waived.

Surgical technique

The principles of surgical repair for ATAAD at our institution have been described previously (24). Briefly, general anaesthesia was routinely induced with propofol, fentanyl, and rocuronium bromide and maintained with propofol and remifentanil. Median sternotomy was used for surgical access. CPB and intermittent cold blood cardioplegic cardiac arrest were used in all cases. Bicaval cannulation or two-stage atrial cannulation was used for venous access. Arterial cannulation was most often performed in the femoral artery, or by direct aortic cannulation using the Seldinger-technique with TEE to ensure access to the true lumen. In cases of limited dissections, a distal anastomosis with a cross-clamped aorta was performed; however, in most cases, distal repair was performed under HCA and sometimes with the adjunct of antegrade or retrograde cerebral perfusion. Both deep hypothermia (core temperature <20°C) and moderate hypothermia (core temperature 20-32°C) were used. A neuroprotective strategy including topical cooling of the head, and thiopental (1g) and hydrocortisone (500mg) were administered before circulatory arrest. After completion of the distal anastomosis, perfusion was restarted using a side-branch of the vascular prosthesis with the patient in a Trendelenburg position

to enable de-airing before clamping the vascular graft. Proximal repair was performed during rewarming. An aortic root replacement was performed when the coronary ostia or aortic valve were affected by the ATAAD or in the presence of an aortic root aneurysm. Surgery on the aortic arch was performed in selected cases with an entry tear within the aortic arch, involvement of supra-aortic branch vessels, significant aortic arch dilation, or distal malperfusion. Other concomitant procedures were performed when necessary. Specific surgical techniques were left to the discretion of each responsible surgeon.

Statistical analysis

Categorical data were presented as numbers and percentages. Normally distributed continuous variables were presented as mean ± standard deviation (SD), and non-normally distributed variables were presented as median and interquartile range (IQR). Normal distribution was assessed with skewness and kurtosis. Variables with skewness and kurtosis within the range of ± 1 were considered normally distributed except for Study I where skewness and kurtosis of ± 2 was allowed. Intergroup comparisons between continuous values were performed with two sample T-tests if normally distributed and with Mann-Whitney U-tests if non-normally distributed. Intergroup comparison between categorical variables was conducted with Chi-Square tests unless the expected cell count was less than 5 when Fisher's exact test was used for 2x2 contingency tables and Fisher-Freeman-Halton's exact test for contingency tables exceeding 2x2. Missing values were excluded when calculating differences between groups.

In Study II and Study IV, uni- and multivariable regression analyses were performed. Multicollinearity was assessed using Spearman and Pearson correlation, and variables with a correlation coefficient >0.5 were deemed collinear. In Study IV, linear regression yielding a variance inflation factor (VIF) was also used, and variables with a VIF >3.0 were considered collinear. The goodness of fit of the multivariable models was assessed using the Omnibus Tests for Model Coefficients and the Hosmer-Lemeshow goodness of fit. The regression analyses relied on complete case-analysis. The results from regression analyses were presented as odds ratios (OR) with corresponding 95% confidence intervals (95% CI) and p-values.

A p-value <0.05 was considered statistically significant for all tests unless otherwise stated. Statistical analyses were performed using IBM® SPSS® Statistics version 27.0.1.0 for MacOS® (IBM Corp, Armonk, NY, USA) and IBM® SPSS® Statistics version 29.0.2.0 for MacOS® (IBM Corp, Armonk, NY, USA). The 95% confidence intervals for Kaplan–Meier survival curves in Study I were constructed with GraphPad Prism® version 9.5.1 for MacOS® (GraphPad Software, Boston, MA, USA).

Study I

Kaplan-Meier graphs were generated to analyse survival. The Kaplan-Meier survival curves included only the patients with known exact times for symptom onset and death. The hourly mortality rates were generated by calculating the average hourly mortality rate resulting from the known Kaplan-Meier survival estimates at 24 h, 48 h, and 7 days, respectively. The equation used for calculating hourly mortality was: $Mortality\ rate_{hourly} = 1 - \left(1 - Mortality\ rate_{daily}\right)^{\frac{1}{24}}$.

Patients with CTAAD were, by definition, considered to have survived 14 days and were censored at the time of surgical repair.

Study II

A p-value <0.1 in the univariable regression analyses was used as an inclusion criterion in the multivariable models.

The multivariable analysis on misdiagnosis excluded the variables 'intramural haematoma,' 'DeBakey type 1,' and 'surgically treated' as they were variables that could not be known at first assessment. Also, 'Time from first assessment to diagnosis' was excluded from the multivariable model for misdiagnosis because it was a logical consequence of the outcome. Finally, 'Penn class' was excluded as it was colinear with 'hypotensive shock' and the malperfusion variables, which were considered more clinically relevant at first assessment. The variables 'ECG signs' and 'cerebral malperfusion' were forced into the multivariable model despite their univariable p-values exceeding the inclusion criterion of 0.1. This decision was made due to their importance as key clinical signs for the two most common misdiagnoses: ACS and cerebrovascular insult.

The malperfusion variables and the variable 'hypotensive shock' were excluded from the multivariable analysis on 30-day mortality as they are colinear with 'Penn class,' which was considered a better-suited variable to stratify the mortality risk with regards to the severity of ATAAD. Furthermore, 'preoperative lactate' was excluded due to the excess of missing data. As the variables 'initial misdiagnosis' and 'diagnostic delay' were colinear, the multivariable analysis on 30-day mortality was run as a core model including diagnostic delay. The model was then run with the variable 'initial misdiagnosis' replacing the variable 'diagnostic delay,' and the OR for 'initial misdiagnosis' was reported separately without adjusting the other ORs from the core model.

Study III

We assessed the discriminative capacity of each predictor for ATAAD using ROC curves and AUCs with 95% CI. We reported the cutoff values that corresponded to a sensitivity of >95% and the matching specificity. For D-dimer, the cutoff 0.5 mg/L was also reported as this value is used in clinical routine (65, 66). As D-dimer and

fibrinogen were collected over the period 2008-2023 for the ATAAD patients versus 2018-2019 for the non-ATAAD patients, we investigated whether time trends in the D-dimer/fibrinogen ratio were present by truncating the ATAAD patients into three different periods: 2008-2012, 2013-2017, and 2018-2023 and reviewing whether there was a difference between the ratios.

Study IV

ROC curves with AUCs and 95% CIs were generated at each time point to determine the optimal S100B cutoff value for predicting neurological injury. The cutoff yielding the most favourable Youden's index was then used as our grouping variable for postoperative outcomes.

A p-value <0.2 in the univariable regression analyses served as the inclusion criterion for the multivariable models.

A core multivariable model using the optimal S100B cutoff was generated to identify independent predictors of neurological injury. To generate an odds ratio for S100B as a continuous variable, an additional analysis was performed where the optimal cutoff for S100B was replaced by S100B as a continuous variable. In the multivariable analysis, adjusted p-values were generated using the Bonferroni correction for multiple testing.

Results

Study I

Study population, baseline characteristics and diagnosis

For inclusion in the study, we assessed 2,325 patients in our catchment area between January 1998 and November 2021 who received one of the following diagnoses: ICD-9 4410, 4411, 4415, 4416 or ICD-10 I710, I711, I715, I718. We excluded 480 patients with isolated aortic aneurysm, 230 patients with aortic rupture, 657 patients with Stanford Type B aortic dissection, and 223 patients with incorrect diagnosis. A total of 551 patients had undergone surgery for ATAAD (547 of at our department while the 4 remaining patients were excluded as they underwent surgery at other hospitals). The remaining 184 patients were included as NST-ATAAD patients. Of these, 153 patients (83%) presented with an ATAAD and were NST, and 31 (17%) presented with CTAAD and underwent surgery.

Baseline characteristics are shown in Table I.1. The ST patients were younger than the NST patients (64.4 ± 11.8 years vs. 74.7 ± 13.3 years, $p<0.01$) and were less often female (36.2% vs. 50.5% ($p<0.01$)). Cardiac arrest with return of spontaneous circulation (ROSC) was more frequent in the NST group (11.8% vs. 3.8% ($p<0.01$)), as was syncope (26.2% vs. 17.2% ($p=0.01$)). Furthermore, the NST patients more often presented with cerebral malperfusion (23.6% vs. 14.5% ($p<0.01$), and there were fewer patients with DeBakey type 1 dissections in the NST group than in the ST group (65.8% vs. 78.3% ($p<0.01$)).

Table I.2 shows how the diagnosis of ATAAD was confirmed. The most frequent method was CT (71.7%) followed by autopsy (20.1%). TEE and TTE were equally common (3.3%, respectively), and 1.6% were diagnosed by aortic angiography.

Table I.1. Baseline characteristics of the study population.

	All patients n= 731	Non-surgically treated n=184	Surgically treated n=547	*p*	Missing
Age (years)[a]	67.0 ± 13.0	74.7 ± 13.3	64.4 ± 11.8	<0.01	0 (0)
Female[b]	291 (39.8)	93 (50.5)	198 (36.2)	<0.01	0 (0)
Hypertension[b]	381 (52.6)	105 (59.0)	276 (50.5)	0.05	6 (0.8)
Diabetes Mellitus[b]	108 (14.9)	11 (6.2)	97 (17.7)	<0.01	7 (1.0)
COPD[b]	48 (6.6)	18 (10.1)	30 (5.5)	0.03	6 (0.8)
Coronary artery disease[b]	90 (12.4)	37 (20.6)	53 (9.7)	<0.01	4 (0.5)
Known thoracic aneurysm[b]	82 (11.2)	22 (12.0)	60 (11.0)	0.72	1 (0.1)
Marfan syndrome[b]	29 (4.0)	0 (0)	29 (5.3)	<0.01	6 (0.8)
Family history of dissection[b]	25 (3.4)	1 (0.5)	24 (4.4)	0.01	0 (0)
Previous cardiac surgery[b]	26 (3.6)	13 (7.2)	13 (2.4)	<0.01	6 (0.8)
Previous aortic surgery[b]	21 (2.9)	4 (2.2)	17 (3.1)	0.54	6 (0.8)
Syncope[b]	139 (19.4)	45 (26.2)	94 (17.2)	0.01	13 (1.8)
Hypotensive shock[b]	181 (25.6)	47 (28.0)	134 (24.8)	0.41	23 (3.1)
Cardiac arrest with ROSC[b]	41 (5.7)	20 (11.8)	21 (3.8)	<0.01	15 (2.1)
Any malperfusion[b]	257 (36.2)	62 (37.8)	195 (35.7)	0.63	21 (2.9)
Cerebral malperfusion[b]	117 (16.6)	38 (23.6)	79 (14.5)	<0.01	25 (3.4)
Cardiac malperfusion[b]	84 (12.0)	25 (15.8)	59 (10.8)	0.09	29 (4.0)
Intramural hematoma[b]	85 (11.6)	18 (9.8)	67 (12.3)	0.36	1 (0.1)
Debakey type 1[b]	530 (75.5)	104 (65.8)	426 (78.3)	<0.01	29 (4.0)
Preoperative Creatinine (µmol/l)[c]	89 (73-111)	89.5 (74-114)	89 (73-111)	0.78	57 (7.8)
Preoperative Lactate (mmol/l)[c]	1.8 (1.2-3.4)	1.9 (1.15-3.9)	1.8 (1.2-3.3)	0.53	208 (28.5)
Assessed by cardiothoracic surgeon[b]	665 (91.0)	118 (64.1)	547 (100)	<0.01	0 (0)
Accepted for acute surgery[b]	569 (77.8)	22 (12.0)	547 (100)	<0.01	0 (0)
Misdiagnosed[b]	321 (50.2)	101 (55.8)	220 (48.0)	0.08	92 (12.6)

Values are presented as n (%), mean ± SD or median (interquartile range). *p*-values represent comparison between surgically treated patients and non-surgically treated patients. COPD: Chronic obstructive pulmonary disease. ROSC: Return of spontaneous circulation. a: Two-sample T-test, b: Chi-square test, c: Mann-Whitney U-test

Table I.2. Diagnostic modality for non-surgically treated patients with ATAAD.

	Non-surgically treated patients n= 184	Missing
CT	132 (71.7)	0 (0)
TEE	6 (3.3)	0 (0)
TTE	6 (3.3)	0 (0)
Aortic angiography	3 (1.6)	0 (0)
Autopsy	37 (20.1)	0 (0)

Values are presented as n (%). CT: computed tomography. TEE: transoesophageal echocardiography. TTE: transthoracic echocardiography.

Survival

The study population was divided into 14-day survivors (n=58) and non-14-day survivors (n=108). There was no significant difference in gender distribution, but the non-survivors were significantly older than the 14-day survivors (76.2±11.1 years vs. 70.9±16.2 years, p=0.01). The non-survivors were more likely to suffer from hypotensive shock, syncope, cardiac arrest with ROSC, any malperfusion, cerebral malperfusion, and cardiac malperfusion. Intramural hematomas were more frequent among 14-day survivors (24.1% vs. 2.8%, p<0.01) and DeBakey type 1 dissections were less frequent (44.2% vs. 72.7%, p<0.01). The comparison between 14-day survivors and non-survivors is shown in Table I.4.

Table I.3. Baseline characteristics of patients with non-surgically treated ATAAD. Comparison of 14-day survivors and non-survivors.

	All patients n= 166	**Non-survivors n=108**	**14-day survivors n=58**	***p***	**Missing**
Age (years)[a]	74.4 ± 13.3	76.2 ± 11.1	70.9 ± 16.2	0.01	0 (0)
Female[b]	85 (51.2)	59 (54.6)	26 (44.8)	0.23	0 (0)
Hypertension[b]	100 (61.0)	62 (57.9)	38 (66.7)	0.28	2 (1.2)
Diabetes Mellitus[c]	10 (6.1)	5 (8.9)	5 (4.7)	0.31	3 (1.8)
COPD[b]	17 (10.4)	8 (14.0)	9 (8.4)	0.26	2 (1.2)
Coronary artery disease[b]	32 (19.6)	15 (14.0)	17 (30.4)	0.01	3 (1.8)
Known thoracic aneurysm[b]	21 (12.7)	14 (13.0)	7 (12.1)	0.87	0 (0)
Marfan syndrome	0 (0)	0 (0)	0 (0)	N/A	3 (1.8)
Family history of dissection[c]	1 (0.6)	0 (0)	1 (1.7)	0.35	0 (0)
Previous cardiac surgery[c]	12 (7.4)	3 (2.8)	9 (16.1)	<0.01	3 (1.8)
Previous aortic surgery[c]	4 (2.5)	1 (0.9)	3 (5.4)	0.12	3 (1.8)
Syncope[b]	43 (26.5)	39 (36.4)	4 (7.3)	<0.01	4 (2.4)
Hypotensive shock[b]	46 (28.6)	44 (41.5)	2 (3.6)	<0.01	5 (3.0)
Cardiac arrest with ROSC[b]	20 (12.3)	18 (17.0)	2 (3.6)	0.01	4 (2.4)
Any malperfusion[b]	59 (37.8)	56 (54.9)	3 (5.6)	<0.01	10 (6.0)
Cerebral malperfusion[b]	35 (22.9)	35 (34.7)	0 (0)	<0.01	13 (7.8)
Cardiac malperfusion[b]	25 (16.6)	23 (23.0)	2 (3.9)	<0.01	15 (9.0)
Intramural hematoma[b]	17 (10.2)	3 (2.8)	14 (24.1)	<0.01	0 (0)
Debakey type 1[b]	91 (64.1)	72 (72.7)	19 (44.2)	<0.01	14 (8.4)
Chronic dissection[b]	31 (18.7)	0 (0)	31 (53.4)	<0.01	0 (0)
Preoperative Creatinine (µmol/l)[d]	89.5 (74-114)	91 (75-111)	86 (67-114)	0.30	18 (10.8)
Preoperative Lactate (mmol/l)[d]	1.9 (1.2-3.9)	2.9 (1.7-4.8)	1.05 (0.7-1.7)	<0.01	61 (36.7)
Assessed by cardiothoracic surgeon[b]	115 (69.3)	66 (61.1)	49 (84.5)	<0.01	0 (0)
Accepted for acute surgery[b]	22 (13.3)	22 (20.4)	0 (0)	<0.01	0 (0)
Misdiagnosed[b]	94 (56.6)	51 (47.2)	43 (74.1)	<0.01	0 (0)

Values are presented as n (%), mean ± SD or median (interquartile range). *p*-values represent comparison between 14-day survivors and non-survivors. COPD: Chronic obstructive pulmonary disease. ROSC: Return of spontaneous circulation. a: Two-sample T-test, b: Chi-square test, c: Fisher's exact test, d: Mann-Whitney U-test

The exact times of symptom onset and death were known for 129 NST patients. Their 14-day survival is shown in Figure I.1A and their 48-hour survival is shown in Figure I.1B. The Kaplan-Meier estimates of mortality were 47.3%±4.4% at 24 hours, 55.0%±4.4% at 48 hours, 67.4%±4.1% at 7 days, 76.7%±3.7% at 14 days, 78.9%±3.9% at 30 days, 81.2%±4.1% at 90 days, and 83.9%±4.3% at 1 year. For NST patients, the hourly mortality rate during the first 24 hours after symptom onset was 2.6%. The hourly mortality rate from 24-48 hours was 0.7%, and the hourly mortality rate from 48 hours to 7 days was 0.3%.

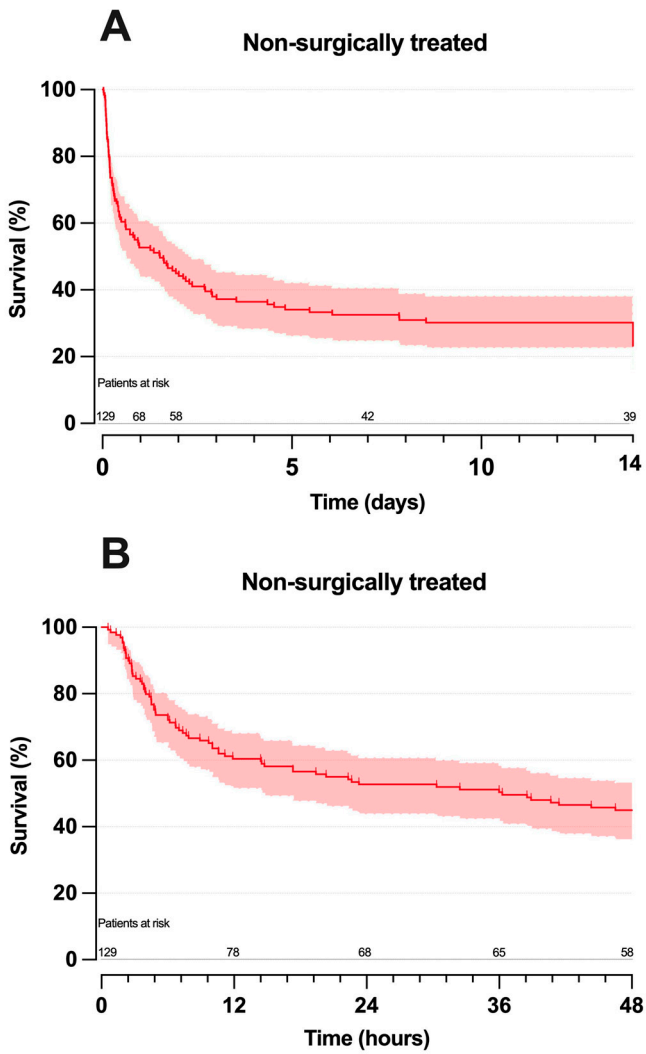

Figure I.1A and I.1B. Kaplan-Meier estimates of 14-day and 48-hour survival in patients with non-surgically treated ATAAD. Upper and lower bands display 95% confidence interval.

The 14-day survival in the ST patients (n=422) is shown in Figure I.2. The Kaplan-Meier estimates of mortality for ST patients were 3.8%±0.9% at 24 hours, 5.0%±1.0% at 48 hours, 6.6%±1.2% at 7 days, 9.2%±1.4% at 14 days, 10.9%±1.5% at 30 days, 13.5%±1.7% at 90 days, and 14.9%±1.7% at 1 year.

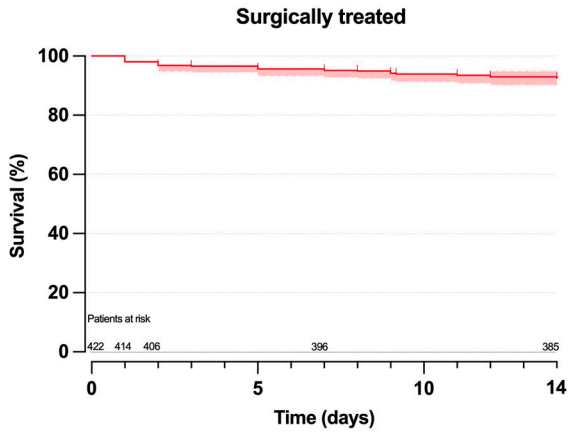

Figure I.2. Kaplan-Meier estimates of 14-day survival in patients with surgically treated ATAAD. Upper and lower bands display 95% confidence interval.

Reasons not to perform surgery

Figure I.3 shows the reasons for not performing surgery on the 86 NST patients who were assessed by a cardiothoracic surgeon. In descending order, the most common reason was severe comorbidity (32.6%) followed by death during transfer to surgery (25.6%), altered state of consciousness at time of assessment (17.4%), poor prognosis (11.6%), other (9.3%), and limited dissection (3.5%).

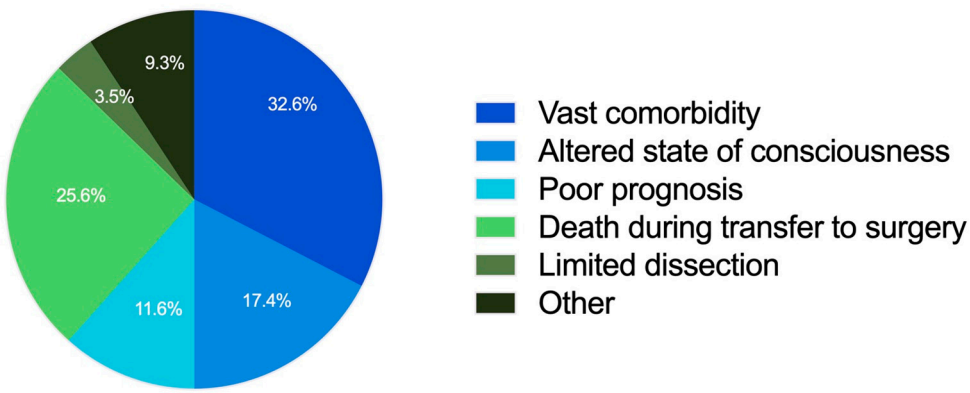

Figure I.3. Reasons not to perform acute surgery after cardiothoracic surgeons' assessment of patients with ATAAD (n=86).

Study II

Study population and baseline characteristics

During the study period April 2001 to October 2021, a total of 630 patients were diagnosed with ATAAD in our region. Admission charts were unavailable for 74 patients and, therefore, the study included 556 patients. Of these, 418 patients underwent surgical repair at our institution, and 138 patients were NST.

Table II.1 shows the baseline characteristics of the study population. Initial misdiagnosis occurred in 252 (45.3%) patients, and 219 (39.4%) patients received a delayed diagnosis. There were significantly more females in the misdiagnosed group (47.6% vs. 35.9%; p=0.005) but fewer patients who presented with syncope (17.7% vs. 28.7%; p=0.003), hypotensive shock (19.9% vs. 38.5%; p<0.001), or malperfusion (37.6% vs. 49.5%; p=0.005). The levels of lactate (1.6 (1.1-3.0) mmol/L vs. 2.2 (1.4-3.9) mmol/L; p< 0.001) and creatinine (85 (70-110) µmol/L vs. 91 (77-111) µmol/L; p=0.024) were significantly lower in the misdiagnosed patients. Furthermore, misdiagnosed patients were less likely to have DeBakey type I dissection (70.3% vs. 79.1%; p=0.020) and were also less likely to have undergone previous aortic surgery (1.2% vs. 4.0%; p=0.048) or to have a known thoracic aneurysm (7.8% vs. 14.4%; p=0.021). The misdiagnosed patients had longer time from symptom onset to first assessment (01:25 hrs:min (01:06-02:46) vs. 01:10 hrs:min (00:50-01:45); p<0.001) as well as time from first assessment to diagnosis (04:08 hrs:min (01:52-14:57) vs. 00:59 hrs:min (00:41-01:29); p<0.001). There were more patients presenting without pain (16.1% vs. 7.9%; p=0.003) among the misdiagnosed patients, and they were more often categorised in a lower Penn class (Penn Aa 50.6% vs. 33.4%, Penn Ab 19.4% vs. 23.6%, Penn Ac 19.4% vs. 14.6%, Penn Ab+c 10.5% vs. 22.6%; p<0.001).

Table II.1 Baseline characteristics of the study cohort.

	All (n=556)	Misdiagnosis (n=252)	No misdiagnosis (n=304)	*p*	Missing
Age[a]	68.0 ± 12.8	68.5 ± 13.3	67.6 ± 12.3	0.414	0
Female[b]	229 (41.2)	120 (47.6)	109 (35.9)	0.005	0 (0)
Hypertension[b]	299 (54.0)	131 (52.4)	168 (55.3)	0.501	2 (0.4)
Diabetes mellitus[b]	85 (15.4)	44 (17.7)	41 (13.5)	0.175	3 (0.5)
COPD[b]	40 (7.2)	21 (8.4)	19 (6.3)	0.331	2 (0.4)
History of smoking[b]	152 (28.7)	66 (27.5)	86 (29.7)	0.585	26 (4.7)
Coronary artery disease[b]	56 (11.2)	29 (13.4)	27 (9.5)	0.170	54 (9.7)
Known thoracic aneurysm[b]	58 (11.5)	17 (7.8)	41 (14.4)	0.021	52 (9.4)
Marfan syndrome[b]	26 (4.7)	14 (5.6)	12 (3.9)	0.355	3 (0.5)
Other connective tissue disease[c]	3 (0.6)	1 (0.5)	2 (0.7)	1.000	54 (9.7)
Family history of dissection[b]	16 (2.9)	7 (2.8)	9 (3.0)	0.898	0 (0)
Previous cardiac surgery[b]	17 (3.1)	8 (3.2)	9 (3.0)	0.875	5 (0.9)
Previous aortic surgery[b]	15 (2.7)	3 (1.2)	12 (4.0)	0.048	5 (0.9)
Creatinine (µmol/L)[d]	89 (73-110)	85 (70-110)	91 (77-111)	0.024	28 (5.0)
Lactate (mmol/L)[d]	1.9 (1.3-3.5)	1.6 (1.1-3.0)	2.2 (1.4-3.9)	<0.001	123 (22.1)
Syncope[b]	131 (23.8)	44 (17.7)	87 (28.7)	0.003	5 (0.9)
Hypotensive shock[b]	163 (30.1)	49 (19.9)	114 (38.5)	<0.001	14 (2.5)
Cardiac arrest with ROSC[b]	33 (6.1)	10 (4.0)	23 (7.7)	0.074	11 (2.0)
Any malperfusion[b]	239 (44.1)	92 (37.6)	147 (49.5)	0.005	14 (2.5)
Cerebral malperfusion[b]	116 (21.4)	50 (20.4)	66 (22.3)	0.594	15 (2.7)
Cardiac malperfusion[b]	87 (16.2)	42 (17.2)	45 (15.3)	0.550	18 (3.2)
Gastrointestinal malperfusion[b]	20 (3.7)	9 (3.7)	11 (3.8)	0.961	18 (3.2)
Renal malperfusion[b]	29 (5.4)	13 (5.3)	16 (5.5)	0.937	18 (3.2)
Peripheral malperfusion[b]	105 (19.5)	27 (11.0)	78 (26.6)	<0.001	18 (3.2)
Spinal malperfusion[c]	10 (1.9)	3 (1.2)	7 (2.4)	0.385	19 (3.4)
Intramural hematoma[b]	74 (14.7)	32 (14.6)	42 (14.7)	0.982	51 (9.2)
DeBakey type 1[b]	402 (75.1)	168 (70.3)	234 (79.1)	0.020	21 (3.8)
Not presenting with pain[b]	64 (11.6)	40 (16.1)	24 (7.9)	0.003	4 (0.7)
Time symptom to FA[d]	01:16 (00:55-02:00)	01:25 (01:06-02:46)	01:10 (00:50-01:45)	<0.001	102 (18.3)
Time FA to diagnosis[d]	01:25 (00:48-03:47)	04:08 (01:52-14:57)	00:59 (00:41-01:29)	<0.001	66 (11.9)
Surgically treated[b]	418 (75.2)	182 (72.2)	236 (77.6)	0.142	0 (0)
ECG Signs[e]				0.483	71 (12.8)
No signs	345 (71.1)	145 (66.8)	200 (74.6)		
ST elevation	28 (5.8)	16 (7.4)	12 (4.5)		
ST depression	36 (7.4)	17 (7.8)	19 (7.1)		
T-wave inversion	18 (3.7)	9 (4.1)	9 (3.4)		
New branch block	10 (2.1)	4 (1.8)	6 (2.2)		
New atrial fibrillation	18 (3.7)	11 (5.1)	7 (2.6)		
Multiple signs	30 (6.2)	15 (6.9)	15 (5.6)		
Penn class[e]				<0.001	13 (2.3)
Aa	224 (41.3)	125 (50.6)	99 (33.4)		
Ab	118 (21.7)	48 (19.4)	70 (23.6)		
Ac	108 (19.9)	48 (19.4)	60 (20.3)		
Ab+c	93 (17.1)	26 (10.5)	67 (22.6)		

Values are presented as numbers (%), mean ± standard deviation, median (interquartile range). Times are presented as median (interquartile range) on the format hh:mm. [a] Two-sample T-test, [b] Chi-square test, [c] Fisher's exact test, [d] Mann-Whitney U-test, [e] Fisher-Freeman-Halton exact test. COPD: chronic obstructive pulmonary disease; ROSC: return of spontaneous circulation; FA: first assessment; ECG: electrocardiogram

Misdiagnosis, diagnostic delay and mortality

The most frequent misdiagnosis was acute coronary syndrome (ACS) (13.5%), followed by cerebral infarction/hemorrhage (8.1%), and pulmonary embolism (5.0%) as shown in Table II.2. All categories of misdiagnoses except for cerebral infarction/hemorrhage, gastritis/gastrointestinal bleeding, and multiple diagnoses were significantly associated with diagnostic delay. Patients who received a delayed diagnosis did not have significantly higher 30-day mortality nor significantly lower likelihood of receiving surgical treatment. Table II.3 shows the frequency of all occurring misdiagnoses allowing more than one diagnosis per patient.

Table II.2 Diagnostic delay and initial misdiagnosis.

	All (n=556)	**Diagnostic delay (n=219)**	**No delay (n=337)**	***p***	**Missing**
Initial misdiagnosis[a]	252 (45.3)	192 (87.7)	60 (17.8)	<0.001	0 (0)
ACS[a]	75 (13.5)	59 (26.9)	16 (4.7)	<0.001	0 (0)
Cerebral infarction/ Hemorrhage	45 (8.1)	21 (9.6)	24 (7.1)	0.297	0 (0)
Pulmonary Embolism[a]	28 (5.0)	22 (10.0)	6 (1.8)	<0.001	0 (0)
Pneumonia[b]	7 (1.3)	7 (3.2)	0 (0)	0.001	0 (0)
Gastritis/GI Bleeding[b]	10 (1.8)	6 (2.7)	4 (1.2)	0.203	0 (0)
Limb Ischemia[b]	5 (0.9)	5 (2.3)	0 (0)	0.009	0 (0)
Multiple diagnoses[b]	3 (0.5)	2 (0.9)	1 (0.3)	0.565	0 (0)
Other[a]	34 (6.1)	27 (12.3)	7 (2.1)	<0.001	0 (0)
Unclear[a]	45 (8.1)	43 (19.6)	2 (0.6)	<0.001	0 (0)
Time FA to diagnosis[c]	01:25 (00:48-03:47)	06:21 (03:12-22:09)	00:56 (00:41-01:19)	<0.001	62 (11.2)
Surgically treated	418 (75.2)	157 (71.7)	261 (77.4)	0.125	0 (0)
30-day mortality	155 (28.8)	57 (27.1)	98 (29.8)	0.508	17 (3.1)

Values are presented as numbers (%). Times are presented as median (interquartile range) on the format hh:mm. [a] Chi-square test; [b] Fisher's exact test; [c] Mann-Whitney U test. ACS: acute coronary syndrome; GI: gastrointestinal; FA: first assessment

Table II.3 Frequency of all misdiagnoses allowing for multiple diagnoses per patient.

Initial misdiagnosis	n
Cardiovascular conditions:	
Acute coronary syndrome	75 (25.3)
Limb ischemia	6 (2.0)
Congestive heart failure	3 (1.0)
Pericardial effusion of unknown origin	2 (0.7)
Pericarditis	2 (0.7)
Abdominal aortic aneurysm	2 (0.7)
Atrial fibrillation	1 (0.3)
Perimyocarditis	1 (0.3)
Stent related pain after PCI	1 (0.3)
Endocarditis	1 (0.3)
Cerebral and cerebrovascular conditions:	
Cerebrovascular insult	46 (15.5)
Subarachnoid hemorrhage	5 (1.7)
Epilepsy	2 (0.7)
Basilary artery occlusion	1 (0.3)
Syncope	1 (0.3)
Sinus thrombosis	1 (0.3)
Pulmonary and respiratory conditions:	
Pulmonary embolism	30 (10.1)
Pneumonia	7 (2.4)
Pneumothorax	5 (1.7)
Pneumomediastinum	2 (0.7)
Upper respiratory tract infection	2 (0.7)
Exacerbation of COPD	1 (0.3)
Obstructive bronchitis	1 (0.3)
Intercostal bleeding	1 (0.3)
Pleuritis	1 (0.3)
Gastrointestinal conditions:	
Gastritis	12 (4.1)
Cholecystitis	3 (1.0)
Bowel obstruction	3 (1.0)
Intestinal perforation	2 (0.7)
Acute abdomen	2 (0.7)
Biliary colic	2 (0.7)
Esophagitis	2 (0.7)
Unspecified abdominal infection	2 (0.7)
Gastroenteritis	1 (0.3)
Gastrointestinal bleeding	1 (0.3)
Pancreatitis	1 (0.3)
Other conditions:	
Unclear	45 (15.2)
Musculoskeletal injury	6 (2.0)
Sepsis	3 (1.0)
Unspecified fever	3 (1.0)
Vagal reaction	2 (0.7)
Vertebral compression fractures	1 (0.3)
Sciatica	1 (0.3)
Vertigo	1 (0.3)
Urinary tract infection	1 (0.3)
Unspecified hemorrhage	1 (0.3)
Mediastinal abscess	1 (0.3)

Values presented as numbers (%).

Figure II.1 shows mortality stratified per Penn class and NST- vs. ST patients. The 30-day mortality in the NST group was 82.7% (62.2%, 95.8%, 88.0%, and 91.9% in Penn class Aa, Ab, Ac, and Ab+c, respectively) and 12.1% (7.3%, 12.1%, 11.0%, and 30.2% in Penn class Aa, Ab, Ac and Ab+c, respectively) in the ST group.

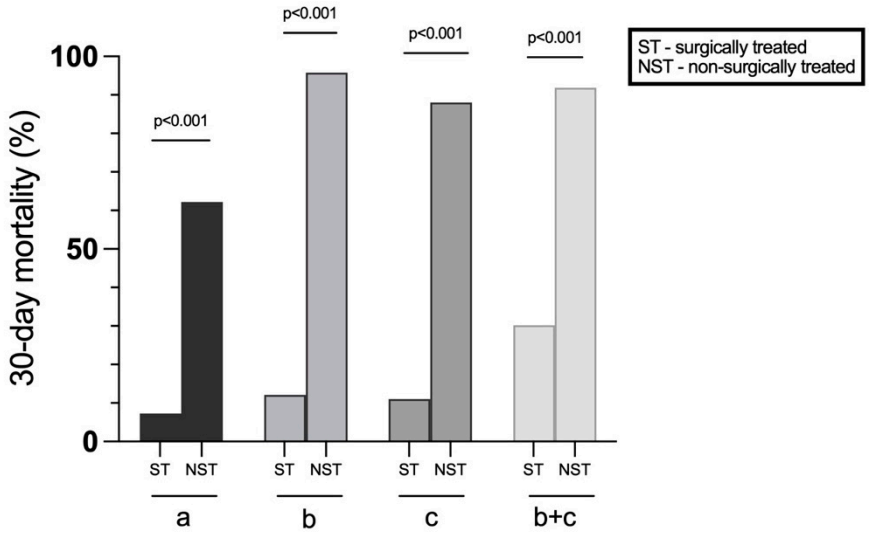

Figure II.1. 30-day mortality per Penn class in surgically and non-surgically treated patients

The 30-day mortality in misdiagnosed vs. non-misdiagnosed patients stratified per Penn class is shown in Figure II.2. Misdiagnosed patients in Penn class Ab had significantly higher 30-day mortality compared to accurately diagnosed patients in the same class (40.4% vs. 22.1%; p=0.034), but there were no statistically significant differences in the other Penn classes. Furthermore, the 30-day mortality was significantly higher for patients in Penn class Aa with delayed diagnosis (21.3% vs. 10.8%; p=0.040) while there were no significant differences in 30-day mortality in the other Penn classes as shown in Figure II.3.

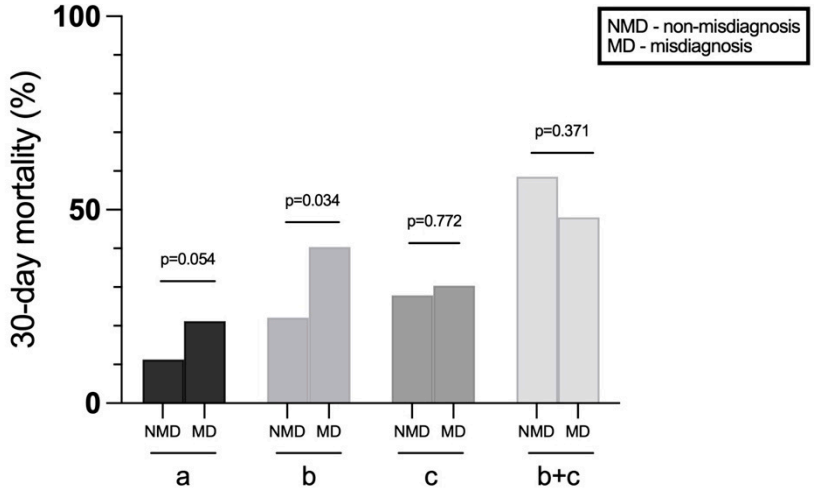

Figure II.2. 30-day mortality per Penn class in non-misdiagnosed and misdiagnosed patients

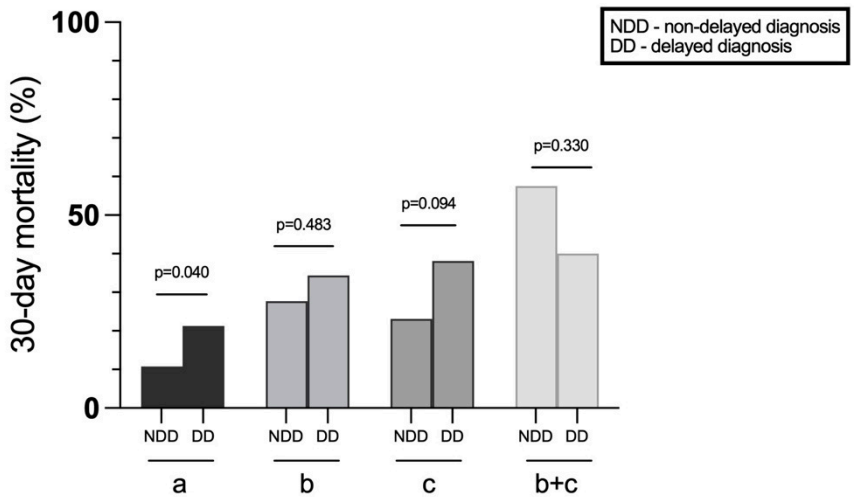

Figure II.3. 30-day mortality per Penn class in patients with non-delayed and delayed diagnosis

The risk of misdiagnosis differed significantly between the different Penn classes (Penn Aa 55.8%, Penn Ab 40.7%, Penn Ac 44.4%, and Penn Ab+c 28.0%; $p<0.001$). Patients in Penn class Aa who had been misdiagnosed had a significantly lower likelihood of receiving surgical treatment as compared to non-misdiagnosed patients (75.6% vs. 88.8%; $p=0.012$) (Figure II.4) as had patients with delayed diagnosis in Penn class Aa (74.0% vs. 91.5%; $p<0.001$) compared to patients without delayed diagnosis (Figure II.5).

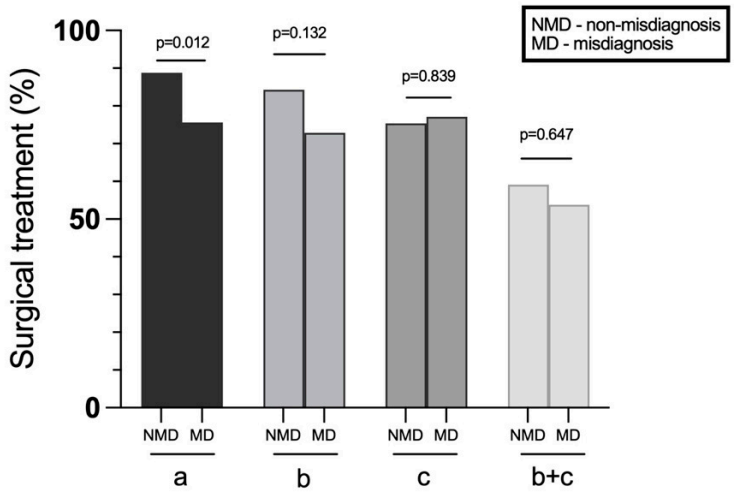

Figure II.4. Surgical treatment per Penn class in non-misdiagnosed and misdiagnosed patients

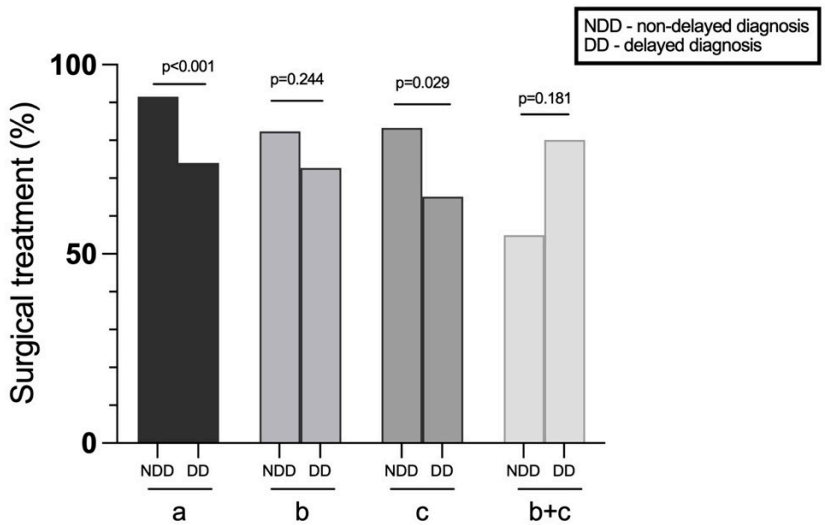

Figure II.5. Surgical treatment per Penn class in patients with non-delayed and delayed diagnosis

Female sex (OR: 1.748; 95% CI 1.145-2.668; p=0.010) and not presenting with pain (OR: 2.576; 95% CI 1.175-5.648; p=0.018) were identified as predictors of increased likelihood of misdiagnosis (Table II.4) whereas known thoracic aneurysm (OR: 0.294; 95% CI 0.133-0.651; p=0.003) and peripheral malperfusion (OR: 0.279; 95%CI 0.157-0.498; p< 0.001) were identified as predictors of decreased likelihood of misdiagnosis. However, neither misdiagnosis nor delayed diagnosis were identified as independent predictors of 30-day mortality (Table II.5).

Table II.4 Uni- and multivariable logistic regression analysis of variables associated with misdiagnosis.

	Univariable analysis			Multivariable analysis		
	Odds Ratio	95% CI	*p*	Odds Ratio	95% CI	*p*
Female	1.626	1.157-2.286	0.005	1.748	1.145-2.668	0.010
Known thoracic aneurysm	0.501	0.276-0.908	0.023	0.294	0.133-0.651	0.003
Previous aortic surgery	0.297	0.083-1.064	0.062	0.648	0.148-2.828	0.563
Syncope	0.535	0.355-0.807	0.003	0.620	0.343-1.120	0.113
Hypotensive shock	0.397	0.269-0.587	<0.001	0.476	0.274-0.825	0.008
Preoperative cardiac arrest	0.504	0.235-1.081	0.079	0.956	0.360-2.534	0.927
Cerebral malperfusion	0.894	0.591-1.352	0.594	1.416	0.782-2.564	0.251
Peripheral malperfusion	0.341	0.212-0.550	<0.001	0.279	0.157-0.498	<0.001
Not presenting with pain	2.225	1.301-3.806	0.004	2.576	1.175-5.648	0.018
ECG signs						
No signs	Ref.		Ref.	Ref.		Ref.
ST Elevation	1.839	0.844-4.006	0.125	2.783	1.054-7.347	0.039
ST Depression	1.234	0.620-2.456	0.549	1.368	0.626-2.990	0.432
T-wave inversion	1.379	0.534-3.561	0.506	1.467	0.520-4.133	0.469
New branch block	0.920	0.255-3.317	0.898	1.971	0.393-9.882	0.409
New atrial fibrillation	2.167	0.820-5.726	0.119	1.862	0.623-5.561	0.266
Multiple signs	1.379	0.654-2.911	0.399	1.345	0.579-3.128	0.491

ECG: electrocardiogram; Ref: Reference variable

Table II.5 Uni- and multivariable logistic regression analysis of variables associated with 30-day mortality

	Univariable analysis			Multivariable analysis		
	Odds Ratio	95% CI	*p*	Odds Ratio	95% CI	*p*
Age per year increment	1.051	1.033-1.070	<0.001	0.993	0.961-1.027	0.686
Female	1.441	0.989-2.099	0.057	1.326	0.629-2.797	0.459
COPD	2.042	1.052-3.961	0.035	4.782	1.454-15.732	0.010
History of smoking	0.375	0.230-0.610	<0.001	0.912	0.410-2.026	0.820
Marfan syndrome	0.206	0.048-0.884	0.034	0.707	0.141-3.533	0.673
Preoperative creatinine per mmol increment	1.004	1.000-1.008	0.058	1.003	0.994-1.012	0.541
Syncope	2.460	1.622-3.732	<0.001	1.085	0.445-2.647	0.857
Preoperative cardiac arrest	5.721	2.700-12.124	<0.001	1.669	0.404-69.896	0.479
Intramural hematoma	0.240	0.112-0.514	<0.001	0.063	0.014-0.289	<0.001
Not presenting with pain	4.773	2.694-8.455	<0.001	1.241	0.394-3.908	0.712
Surgically treated	0.029	0.017-0.050	<0.001	0.015	0.005-0.043	<0.001
ECG signs						
No signs	Ref.		Ref.	Ref.		Ref.
ST Elevation	1.337	0.564-3.170	0.510	0.859	0.184-4.016	0.847
ST Depression	1.587	0.760-3.318	0.219	1.141	0.297-4.388	0.848
T-wave inversion	0.397	0.089-1.763	0.225	0.861	0.112-6.608	0.885
New branch block	1.361	0.344-5.385	0.661	3.074	0.518-18.260	0.217
New atrial fibrillation	3.572	1.334-9.564	0.011	2.629	0.532-12.993	0.236
Multiple signs	2.117	0.978-4.583	0.057	0.804	0.210-3.072	0.750
Penn class						
Aa	Ref.		Ref.	Ref.		Ref.
Ab	2.122	1.241-3.630	0.006	2.471	0.913-6.684	0.075
Ac	2.090	1.205-3.623	0.009	1.875	0.624-5.636	0.263
Ab+c	6.165	3.571-10.646	<0.001	8.086	2.437-26.831	<0.001
Initial misdiagnosis	1.064	0.732-1.548	0.746	1.170	0.571-2.394	0.668
Diagnostic delay	0.878	0.597-1.291	0.508	1.164	0.519-2.613	0.713

COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; Ref: Reference variable

Study III

Study population and baseline characteristics

In total, 567 patients underwent surgical repair for ATAAD at our institution between January 1998 to August 2023 and were assessed for inclusion. The inclusion criteria were met by 93 patients, and they had surgery performed from August 2008 to April 2023. We assessed all patients in the SEM-cohort (n=325,539) for inclusion. A total of 287 patients had available D-dimer and fibrinogen lab values, but 85 were excluded because they were admitted to the ED for either circulatory arrest or multi-trauma. Therefore, the study included 202 non-ATAAD patients.

Table III.1 shows baseline data for the study population. There was no significant difference in gender distribution between the ATAAD patients and the non-ATAAD patients (33.3% females vs. 40.6% females ($p=0.233$)), but the ATAAD patients were significantly older than the non-ATAAD patients (64.3±10.9 vs. 58.6±18.2 ($p<0.001$)). Hypotensive shock was present in 31.1% of the ATAAD patients, and 2.2% of them suffered cardiac arrest with ROSC. Furthermore, 45.2% of the ATAAD patients showed signs of malperfusion. The most frequent type of dissection was DeBakey type 1 (83.9%), while 13.0% of the aortic pathologies were IMHs.

Arrival to the ED by ambulance was the case for 56.9% of the non-ATAAD patients, and 75.2% of them were admitted to the hospital after assessment in the ED. The most common main complaint was dyspnoea followed by infection/fever, neurological symptoms, abnormal laboratory value, chest pain, and abdominal pain (15.1%, 14.1%, 10.9%, 10.4%, 9.9%, and 9.4%, respectively).

Table III.1 Baseline characteristics of the study population

	ATAAD (n=93)	Missing ATAAD	Non-ATAAD (n=202)	Missing non-ATAAD	*p*
Age[a]	64.3 ± 10.9	(0)	58.6 ± 18.2	0 (0)	<0.001
Female[b]	31 (33.3)	0 (0)	113 (38.3)	0 (0)	0.233
Hypertension	55 (59.1)	0 (0)			
Diabetes mellitus	12 (12.9)	0 (0)			
COPD	5 (5.4)	0 (0)			
History of smoking	28 (32.6)	7 (7.5)			
Coronary artery disease	5 (5.4)	0 (0)			
Known thoracic aneurysm	17 (18.5)	1 (1.1)			
Marfan syndrome	4 (4.3)	0 (0)			
Family history of dissection	3 (3.2)	0 (0)			
Previous cardiac surgery	2 (2.2)	1 (1.1)			
Previous aortic surgery	4 (4.3)	1 (1.1)			
Creatinine (µmol/L)	90 (76-116)	1 (1.1)			
Lactate (mmol/L)	2.0 (1.3-3.6)	2 (2.2)			
Syncope	15 (16.1)	0 (0)			
Hypotensive shock	28 (31.1)	3 (3.3)			
Cardiac arrest with ROSC	2 (2.2)	0 (0)			
Any malperfusion	42 (45.2)	0 (0)			
Cerebral malperfusion	11 (11.8)	0 (0)			
Cardiac malperfusion	15 (16.3)	1 (1.1)			
Gastrointestinal malperfusion	6 (6.5)	0 (0)			
Renal malperfusion	8 (8.6)	0 (0)			
Intramural hematoma	12 (13.0)	1 (1.1)			
DeBakey type 1	78 (83.9)	0 (0)			
Arriving by ambulance			115 (56.9)	0 (0)	
Admitted to hospital			152 (75.2)	0 (0)	
Reason for visit				10 (5.0)	
Dyspnea			29 (15.1)		
Infection / Fever			27 (14.1)		
Neurological symptoms			21 (10.9)		
Abnormal laboratory result			20 (10.4)		
Chest pain			19 (9.9)		
Abdominal pain			18 (9.4)		
Musculoskeletal injury			11 (5.7)		
Unspecified disease			11 (5.7)		
Extremity pain			9 (4.7)		
Poisoning			9 (4.7)		
Anemia			8 (4.2)		
GI-bleed			3 (1.6)		
GI-tract symptoms			2 (1.0)		
Arrythmia			1 (0.5)		
Ascites			1 (0.5)		
Edema			1 (0.5)		
Surgical complication			1 (0.5)		
Urinary tract symptoms			1 (0.5)		

Values are presented as numbers (%), mean ± standard deviation, median (interquartile range). [a]Two-sample T-test, [b]Chi-square test. ATAAD: acute type A aortic dissection, COPD: chronic obstructive pulmonary disease; GI: gastrointestinal; ROSC: return of spontaneous circulation.

D-dimer and fibrinogen

The D-dimer levels were significantly higher in the ATAAD patients compared to the non-ATAAD patients (2.90 (1.30-10.00) vs. 0.53 (0.20-2.28) (p<0.001)), and the levels of fibrinogen were significantly lower (2.3 (1.8-2.9) vs. 3.3 (2.5-4.4) (p<0.001)) as shown in Table III.2. Furthermore, the ATAAD group showed a significantly higher D-dimer/fibrinogen ratio than the non-ATAAD group (1.26 (0.51-5.02) vs. 0.14 (0.06-0.56) (p<0.001)).

Table III.2 D-dimer, fibrinogen and D-dimer/fibrinogen ratio

	All (n=295)	ATAAD (n=93)	No ATAAD (n=202)	*p*	Missing
Fibrinogen (g/L)[a]	3.0 (2.1-4.2)	2.3 (1.8-2.9)	3.3 (2.5-4.4)	<0.001	0 (0)
D-dimer (mg/L)[a]	1.00 (0.28-4.10)	2.90 (1.30-10.00)	0.53 (0.20-2.28)	<0.001	0 (0)
D-dimer/fibrinogen ratio [a]	0.32 (0.08-1.53)	1.26 (0.51-5.02)	0.14 (0.06-0.56)	<0.001	0 (0)

Values are presented as median (interquartile range). [a] Mann-Whitney U-test. ATAAD: acute type A aortic dissection.

Figure III.1 shows ROC-curves with the discriminative capacity of D-dimer, fibrinogen and D-dimer/fibrinogen-ratio to differentiate ATAAD from other diagnoses. The AUC of D-dimer was 0.784 (95% CI 0.733-0.836) and the cutoff point that corresponded to a sensitivity ≥95% was D-dimer >0.38 mg/L with a specificity of 43%. D-dimer > 0.5 mg/L had a sensitivity of 92% with a matching specificity of 50%. The AUC of Fibrinogen was 0.756 (95% CI 0.701-0.811). A sensitivity of ≥95% was seen at a level of 0.9 g/L, and the matching specificity was 2%. The D-dimer/fibrinogen ratio showed an AUC of 0.812 (95% CI 0.764-0.860) and the level of D-dimer/fibrinogen ratio that provided a sensitivity ≥95% was 0.130 at a matching specificity of 52%.

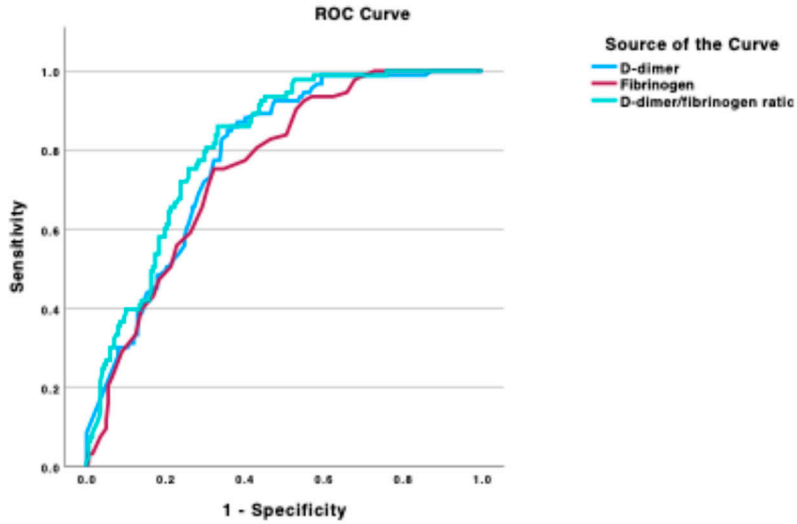

Figure III.1. ROC-curves with D-dimers-, fibrinogens-, and D-dimer/fibrinogen ratio's discriminative capacity for ATAAD D-dimer AUC 0.784 95% CI (0.733-0.836), fibrinogen AUC 0.756 95% CI (0.701-0.811), D-dimer/fibrinogen ratio AUC 0.812 95% CI (0.764-0.860)

The D-dimer/fibrinogen ratio showed no apparent time trend.

Study IV

Study population and preoperative characteristics

During the study period January 1998 to December 2021, 538 patients underwent surgery for ATAAD at our institution and were assessed for inclusion. A total of 393 patients had recorded S100B values and were included. Intraoperative death occurred for 3 patients who had recorded preoperative S100B-values, and their exclusion resulted in S100B being available for 60 patients at T0, 299 patients at T1, 312 patients at T2, 183 patients at T3, and 76 patients at T4.

Table IV.1 shows the baseline variables of the study population. The mean age was 64.4 ± 11.1 years, and 34% were female. There were no significant differences in age or gender distribution between the neurological injury and no neurological injury groups. Patients were more likely to end up in the neurological injury group as compared to the no neurological injury group if they had preoperative cerebral malperfusion (29% vs. 11% ($p<0.01$)), other malperfusion (48% vs. 32% ($p<0.01$)), or cardiac tamponade (21% vs. 12% ($p=0.04$)). Patients in the neurological injury group had significantly higher preoperative creatinine and lactate levels compared to the patients in the no neurological injury group, but there was no significant difference in preoperative S100B levels.

Table IV.1 Baseline characteristics of the study population

	All patients n=393	Neurological Injury* n= 94	No Neurological Injury* n= 296	*p*	Missing
Age (years)	64.4 ± 11.1	65.5 ± 10.1	64.0 ± 11.5	0.26	0 (0)
Female	135 (34.4)	28 (29.8)	107 (36.1)	0.26	0 (0)
Hypertension	208 (52.9)	54 (57.4)	152 (51.4)	0.30	0 (0)
Diabetes mellitus	80 (20.4)	27 (28.7)	52 (17.6)	0.02	0 (0)
COPD	26 (6.6)	4 (4.3)	21 (7.1)	0.33	0 (0)
Smoking	133 (35.5)	35 (40.2)	97 (34.0)	0.29	18 (4.6)
Coronary artery disease	24 (7.0)	5 (5.8)	19 (7.5)	0.60	50 (12.7)
Known thoracic aneurysm	37 (10.8)	7 (8.2)	30 (11.8)	0.36	51 (13.0)
Marfan syndrome	22 (5.6)	4 (4.3)	18 (6.1)	0.50	0 (0)
Other connective tissue disease	5 (1.3)	1 (1.2)	4 (1.6)	1.00	50 (12.7)
Family history of dissection	16 (4.1)	3 (3.2)	13 (4.4)	0.77	0 (0)
Previous cardiac surgery	7 (1.8)	2 (2.1)	5 (1.7)	0.68	1 (0.3)
Previous aortic surgery	12 (3.1)	2 (2.1)	10 (3.4)	0.74	1 (0.3)
Syncope	61 (17.8)	21 (24.4)	39 (15.4)	0.06	50 (12.7)
Hypotensive shock	81 (24.0)	26 (30.6)	54 (21.6)	0.01	55 (14.0)
Preoperative cardiac arrest	16 (4.7)	6 (7.0)	10 (3.9)	0.25	50 (12.7)
Cardiac tamponade	49 (14.3)	18 (20.9)	30 (11.8)	0.04	50 (12.7)
Any malperfusion	142 (36.1)	45 (47.9)	95 (32.1)	<0.01	0 (0)
Cerebral malperfusion	58 (14.8)	27 (28.7)	31 (10.5)	<0.01	1 (0.3)
Carotid dissection				0.26	26 (6.6)
None	185 (50.4)	38 (42.7)	145 (52.7)		
Unilateral	73 (19.9)	21 (23.6)	52 (18.9)		
Bilateral	109 (29.7)	30 (33.7)	78 (28.4)		
Intramural hematoma	51 (14.9)	10 (11.6)	41 (16.2)	0.31	51 (13.0)
Debakey type 1	300 (76.7)	71 (76.3)	226 (76.6)	0.96	2 (0.5)
Preoperative creatinine (µmol/l)	89 (73-110)	93.5 (77-125)	87 (72-106)	<0.01	8 (2.0)
S100B T_0 (µg/l)	0.27 (0.06-0.89)	0.27 (0.11-0.93)	0.21 (0.05-0.89)	0.41	330 (84.0)

* Patients who died intraoperatively (n=3) were excluded from analysis. Values are presented as n (%), mean ± SD or median (interquartile range). T_0: Preoperative. COPD: Chronic obstructive pulmonary disease.

Intraoperative data

The patients in the neurological injury group had longer CBP time than patients in the no neurological injury group (201 min (160-252) vs. 189 min (152-227), p=0.04), but there was no significant difference in cross-clamping time or duration of HCA. In terms of cannulation and surgical technique, no differences were observed between the groups; femoral cannulation and supracoronary graft with a distal anastomosis in the ascending aorta was most common in both groups. The intraoperative data are shown in Table IV.2.

Postoperative data

Postoperative data are shown in Table IV.3. Postoperative bleeding was more pronounced in the neurological injury group compared to the no neurological injury group as is seen with larger bleeding in the chest tubes during the first 24 hours following surgery (760 ml (550-1370) vs. 660 ml (446-900, p=0.01)); more reoperations due to bleeding (21% vs. 13%, p=0.05), and significantly more transfusions of red blood cells as well as plasma and platelets. Furthermore, prolonged ventilatory support was more frequent in patients with neurological injury (66% vs. 35 %, p<0.01). Patients with neurological injury had significantly higher 30-day mortality and in-hospital mortality (21.5% vs. 3.8%, p<0.01) and 23.7% vs. 4.4%, p<0.01, respectively).

Table IV.2 Intraoperative data of the study population

	All patients n=393	**Neurological Injury* n=94**	**No Neurological Injury* n=298**	***p***	**Missing**
CPB time (min)	191 (155-235)	201 (160-252)	189 (152-227)	0.04	0 (0)
Cross-clamping time (min)	88 (60-130)	92.5 (61-140)	84 (60-128)	0.44	0 (0)
HCA technique				0.22	3 (0.8)
Aortic cross-clamp	19 (4.9)	3 (3.2)	16 (5.5)		
Circulatory arrest	193 (49.5)	52 (55.3)	140 (47.8)		
ACP	30 (7.7)	10 (10.6)	20 (6.8)		
RCP	148 (37.9)	29 (30.9)	117 (39.9)		
HCA time (min)	22 (17-29)	22 (16-32)	22 (17-29)	0.78	25 (6.4)
HCA temperature (°C)	18.0 (16.9-20.0)	18.0 (17.0-21.0)	18.0 (16.7-20.0)	0.24	3 (0.8)
Arterial cannulation site				0.68	0 (0)
Femoral	290 (73.8)	68 (72.3)	220 (74.3)		
Axillary	10 (2.5)	2 (2.1)	8 (2.7)		
Direct aortic	83 (21.1)	20 (21.3)	62 (20.9)		
Other/Unknown	10 (2.5)	4 (4.3)	6 (2.0)		
Distal surgical technique				0.11	0 (0)
Ascending	318 (80.9)	69 (73.4)	246 (83.1)		
Hemiarch	52 (13.2)	17 (18.1)	35 (11.8)		
Arch	23 (5.9)	8 (8.5)	15 (5.1)		
Proximal surgical technique				0.26	0 (0)
Supracoronary graft	278 (70.7)	70 (74.5)	205 (69.3)		
Bentall procedure	85 (21.6)	15 (16.0)	70 (23.6)		
Isolated aortic valve replacement	23 (5.9)	8 (8.5)	15 (5.1)		
Root replacement/Aortic valve repair	7 (1.8)	1 (1.1)	6 (2.0)		

* Patients who died intraoperatively (n=3) were excluded from analysis. Values are presented as n (%) or median (interquartile range). CPB: Cardiopulmonary bypass, HCA: Hypothermic circulatory arrest, ACP: Antegrade cerebral perfusion, RCP: Retrograde cerebral perfusion.

Table IV.3 Postoperative data of the study population

	All patients n=395	Neurological Injury* n=94	No Neurological Injury* n=298	*p*	Missing
Recombinant Factor VII	83 (37.9)	23 (43.4)	60 (36.1)	0.34	174 (44.3)
Fibrinogen substitution (g)	4.0 (3.0-8.0)	4.5 (4.0-8.0)	4.0 (3.0-7.0)	0.13	174 (44.3)
Bleeding during first 24 hours (ml)	680 (450-940)	760 (550-1370)	660 (446-900)	0.01	178 (45.3)
Reoperation due to bleeding	58 (14.9)	20 (21.3)	38 (12.8)	0.05	3 (0.8)
Red blood cell units	4 (2-8)	5 (2-12)	4 (2-7)	<0.01	56 (14.2)
Plasma units	4 (0-6)	4 (1-9)	4 (0-6)	0.05	56 (14.2)
Platelet units	4 (2-6)	4 (2-6)	4 (2-4)	<0.01	56 (14.2)
Ventilation >48h	163 (41.9)	61 (65.6)	102 (34.5)	<0.01	4 (1.0)
Renal replacement therapy	39 (10.0)	13 (13.8)	26 (8.8)	0.16	3 (0.8)
Postoperative MI	15 (14.3)	7 (29.2)	8 (9.9)	0.04	288 (73.3)
Multiple organ failure	7 (2.8)	4 (6.6)	3 (1.6)	0.06	145 (36.9)
Postoperative CKMB	30.0 (19.6-62.3)	34.7 (23.0-75.3)	28.75 (18.0-55.0)	0.03	121 (30.8)
Postoperative Creatinine (µmol/l)	121 (90-201)	153 (102-248)	116 (87-180)	<0.01	5 (1.3)
Intraoperative death	3 (0.8)	0 (0)	0 (0)	N/A	0 (0)
30-day mortality	34 (8.7)	20 (21.5)	11 (3.8)	<0.01	4 (1.0)
In-hospital mortality	38 (9.7)	22 (23.7)	13 (4.4)	<0.01	2 (0.5)

* Patients who died intraoperatively (n=3) were excluded from analysis. Values are presented as n (%) or median (interquartile range).

S100Bs discriminative capacity for neurological injury

Figures IV.1A-E show ROC curves with corresponding AUC values. The AUC for the discriminative capacity of S100B to detect neurological injury was 0.687 (95% CI 0.615-0.759), 0.688 (95% CI 0.599-0.777), and 0.692 (95% CI 0.568-0.816) at T2, T3, and T4, respectively. We chose to use S100B at T2 as we aimed to identify the earliest possible biomarker cutoff to predict neurological injury. The best Youden's index was 0.349, which corresponded to a S100B of 0.225 µg/l and yielded a sensitivity of 60.2% and a specificity of 74.7% for predicting neurological injury.

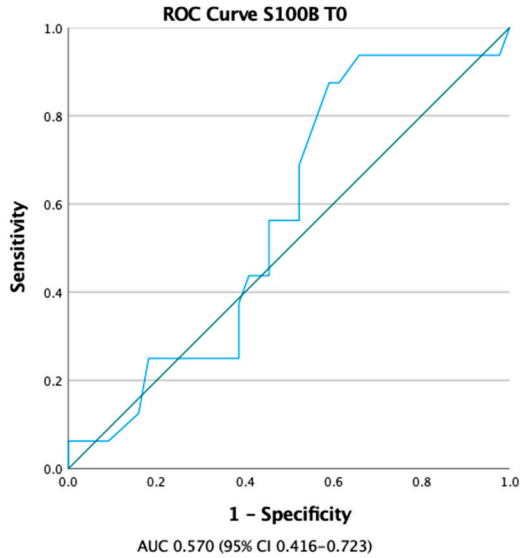

Figure IV.1A. Receiver operating characteristics curve for prediction of neurological injury for S100B at T_0 (preoperatively)

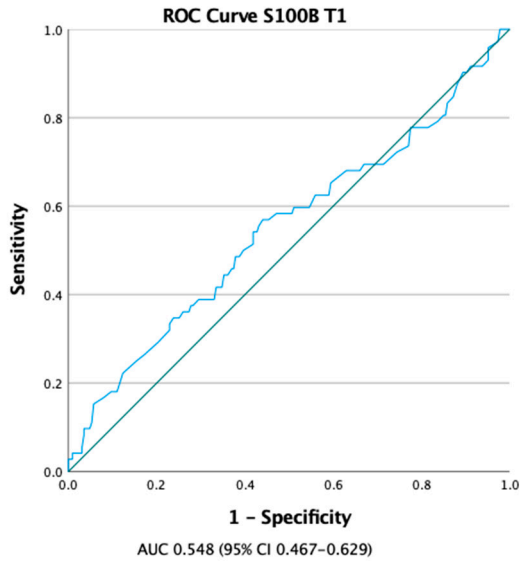

Figure IV.1B. Receiver operating characteristics curve for prediction of neurological injury for S100B at T_1 (within 12 hours postoperatively)

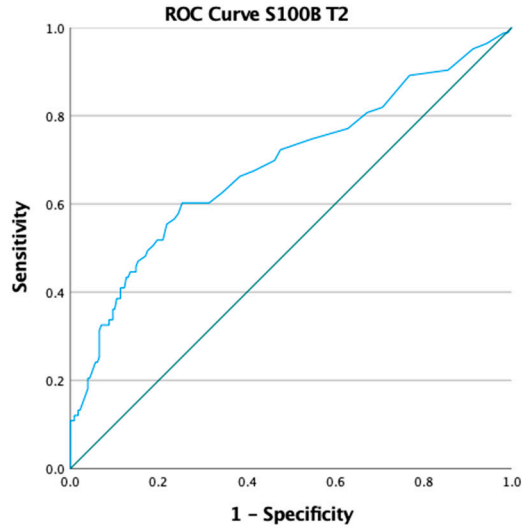

Figure IV.1C. Receiver operating characteristics curve for prediction of neurological injury for S100B at $T_{2.}$ (24 hours postoperatively)

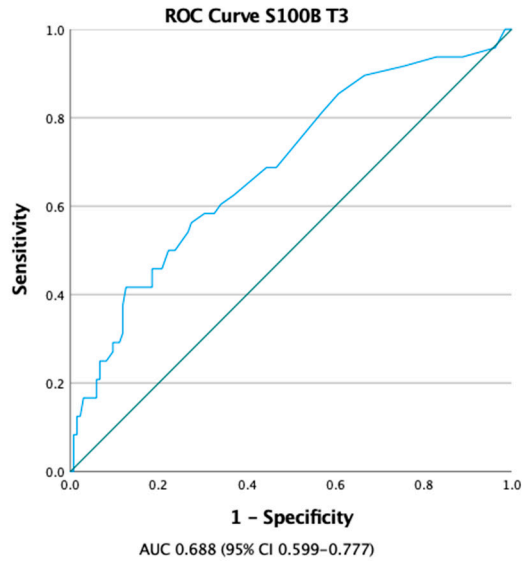

Figure IV.1D. Receiver operating characteristics curve for prediction of neurological injury for S100B at $T_{3.}$ (48 hours postoperatively)

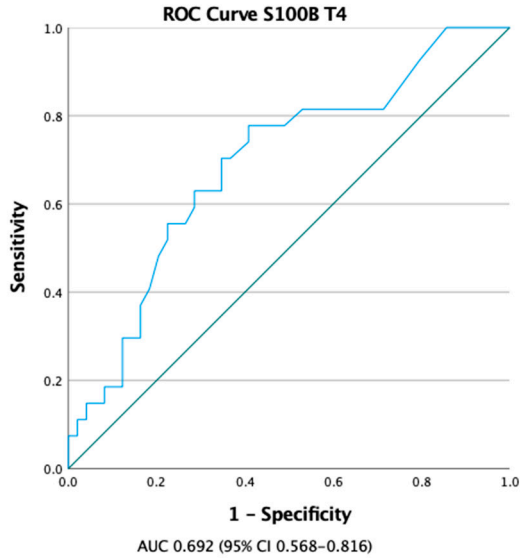

Figure IV.1E. Receiver operating characteristics curve for prediction of neurological injury for S100B at T_4 (72 hours postoperatively)

Neurological outcomes and mortality

The neurological outcomes for the whole study population are shown in Table IV.4 and the neurological outcomes for all patients with recorded S100B values at T2 are shown in Table IV.5. The patients are divided into two groups based on a cutoff for S100B of 0.23 µg/l. Neurological injury was more frequent among patients with S100B ≥ 0.23 µg/l compared to patients with S100B < 0.23 µg/l (46% vs. 16% ($p<0.01$)), as were 30-day mortality and in-hospital mortality (15.7% vs. 3.5% ($p<0.01$) and 17.6% vs. 4.4% ($p<0.01$), respectively).

Table IV.4 Neurological outcomes in the study population

	All n=393	Neurological Injury* n=94	No Neurological Injury* n=298	*p*	Missing
Neurological injury	94 (23.9)	94 (100)	0 (0)	N/A	3 (0.8)
Postoperative stroke	74 (19.0)	74 (79.6)	0 (0)	<0.01	4 (1.0)
Postoperative coma	31 (8.0)	31 (33.3)	0 (0)	<0.01	4 (1.0)
Transient cerebral event	6 (1.5)	0 (0)	6 (2.0)	0.34	4 (1.0)
S100B T_1 (µg/l)	0.58 (0.34-1.00)	0.68 (0.32-1.28)	0.56 (0.34-0.95)	0.22	94 (23.9)
S100B T_2 (µg/l)	0.16 (0.10-0.31)	0.29 (0.13-0.73)	0.14 (0.10-0.23)	<0.01	81 (20.6)
S100B T_3 (µg/l)	0.16 (0.09-0.32)	0.24 (0.13-0.60)	0.14 (0.09-0.23)	<0.01	210 (53.4)
S100B T_4 (µg/l)	0.18 (0.08-0.34)	0.31 (0.17-0.40)	0.11 (0.08-0.27)	<0.01	317 (80.7)

*Patients who died intraoperatively were excluded from analysis. Values are presented as n (%) or median (interquartile range) T_1: within 12 hours postoperatively, T_2: 24 hours postoperatively, T_3: 48 hours postoperatively, T_4: 72 hours postoperatively.

Table IV.5 Neurological outcomes – groupwise comparison between S100B $T_2 \geq 0.23$ and S100B $T_2 < 0.23$

	All n=312	S100B $T_2 \geq 0.23$ n=108	S100B $T_2 < 0.23$ n=204	*p*	Missing
Neurological injury	83 (26.6)	50 (46.3)	33 (16.2)	<0.01	0 (0)
Postoperative stroke	65 (20.9)	35 (32.7)	30 (14.7)	<0.01	1 (0.)
Postoperative coma	29 (9.3)	24 (22.4)	5 (2.5)	<0.01	1 (0.3)
Transient cerebral event	5 (1.6)	0 (0)	5 (2.5)	0.17	1 (0.3)
Ventilation >48h	141 (45.3)	68 (63.0)	73 (36.0)	<0.01	1 (0.3)
Renal replacement therapy	34 (10.9)	22 (20.4)	12 (5.9)	<0.01	0 (0)
Multiple organ failure	6 (3.0)	5 (8.9)	1 (0.7)	<0.01	111 (35.6)
30-day mortality	24 (7.7)	17 (15.7)	7 (3.5)	<0.01	2 (0.6)
In-hospital mortality	28 (9.0)	19 (17.6)	9 (4.4)	<0.01	1 (0.3)

Values are presented as n (%). *p*-values represent comparison between S100B $T_2 \geq 0.23$ group and S100B $T_2 < 0.23$ group. T_2: 24 hours postoperatively

S100B ≥ 0.23 µg/l at T2 was identified as an independent predictor for neurological injury (OR 4.71, 95% CI 2.59-8.57; p<0.01, adjusted p<0.01) along with preoperative cerebral malperfusion (OR 4.23, 95% CI 2.03-8.84; p<0.01, adjusted p<0.01) as is shown in Table IV.6. Furthermore, S100B ≥ 0.23 µg/l at T2 was identified as an independent predictor for 30-day mortality (OR 4.57, 95% CI 1.18-11.70; p<0.01, adjusted p=0.02) (Table IV.7).

Table IV.6 Uni- and multivariable analysis on neurological injury

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Diabetes Mellitus	1.89	1.10-3.24	0.02	2.48	1.25-4.91	<0.01
Cerebral malperfusion	3.43	1.92-6.14	<0.01	4.23	2.03-8.84	<0.01
CPB time (per 1 min increment)	1.00	1.00-1.01	0.04	1.00	1.00-1.01	0.23
Proximal surgical technique						
Supracoronary graft	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Bentall procedure	0.63	0.34-1.17	0.14	0.42	0.19-0.93	0.03
Isolated aortic valve replacement	1.56	0.64-3.84	0.33	1.03	0.33-3.21	0.96
Root replacement/Aortic valve repair	0.49	0.06-4.13	0.51	0.38	0.04-3.84	0.41
S100B T_2 (per 0,1 µg/l increment)	1.15	1.07-1.23	<0.01	1.22	1.01-1.35	<0.01
S100B $T_2 \geq 0.23$ µg/l	4.47	2.63-7.60	<0.01	4.71	2.59-8.57	<0.01

CPB: Cardiopulmonary bypass, T_2 = 24 hours postoperatively.

Table IV.7 Uni- and multivariable analysis on 30-day mortality.

	Univariable analysis			Multivariable analysis		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***
COPD	2.36	0.75-7.36	0.14	3.50	0.95-12.88	0.06
Any malperfusion	3.14	1.48-6.69	<0.01	3.40	1.37-8.42	0.01
Preoperative Creatinine (per 1 µmol/l increment)	1.01	1.00-1.01	0.04	1.01	1.00-1.02	0.28
Reoperation due to bleeding	3.05	1.35-6.86	<0.01	2.75	1.03-7.34	0.04
S100B $T_2 \geq 0.23$ µg/l	5.20	2.09-12.99	<0.01	4.57	1.18-11.70	<0.01

COPD: Chronic obstructive pulmonary disease, T_2 = 24 hours postoperatively.

Discussion

ATAAD is a lethal condition in which up to 50% of patients die before reaching the hospital (40, 91). The gold standard of care is immediate surgical repair (9, 17, 57). The generally accepted hourly mortality rate of 1-2% during the first 24 hours of untreated ATAAD (13, 36, 37) underscores the need for swift management and accurate diagnostics to expedite surgery. Even after surgical repair and intensive care, approximately 18% of patients succumb to the disease (21, 90, 91, 92).

ATAAD has been described as a "great masquerader" because its symptoms vary greatly and often mimic other severe and more common diseases such as stroke, myocardial infarction, pulmonary embolism, acute abdomen, peripheral arterial embolism, and others. The broad spectrum of symptoms stems from the inherent nature of the disease, in which the propagating false lumen may cause end-organ ischemia in any vascular territory (51, 52, 53, 54). Given its relatively low incidence of 2-16 cases per 100,000 patient-years (26, 27, 28, 29, 30), it is unsurprising that misdiagnosis is common.

Misdiagnosis occurs in 18-78% of ATAAD cases (83, 84, 85, 86, 87), a range partly explained by the lack of a uniform definition for misdiagnosis in the ATAAD-setting. CT is the most common method for obtaining a correct diagnosis. Scoring systems such as the ADD-RS (58) can assist clinicians in EDs by stratifying the likelihood of ATAAD and guiding appropriate tests for definite diagnosis. While ADD-RS can be improved by the addition of D-dimer, an established rule-out marker for ATAAD (69), there are currently no readily available biomarkers to indicate ATAAD. Some novel biomarkers such as aggrecan and ST2 have been proposed (74, 75).

Postoperative complications occur in 33-45% of patients who survive surgical repair for ATAAD (115). Neurological injury is among the most feared complications and alone accounts for up to 15% of postoperative mortality (140). Several biomarkers, including S100B, NSE, and NfL can predict neurological injury (130, 137, 138), but they have not been thoroughly studied with respect to ATAAD.

The overarching aim of this thesis was to investigate ATAAD mortality in a broader cohort than previously studied, to examine the impact of misdiagnosis on mortality, and to evaluate biomarkers that may aid in diagnosing ATAAD and predicting adverse postoperative outcomes. A key component to achieving this aim was not

restricting the cohort of ATAAD patients to only those arriving at cardiothoracic surgical units, a limitation that has affected most previous studies.

Mortality in non-surgically treated ATAAD

In Study I, we assessed mortality of NST ATAAD and found a higher mortality than has previously been reported (1, 13, 21, 36, 37, 38, 141). We found a 24-hour mortality of 47.3%, 48-hour mortality of 55.0%, 14-day mortality of 76.7%, and 1-year mortality of 83.9%. The hourly mortality rate during the first 24 hours after symptom onset was 2.6%.

We believe that the primary reason for the higher mortality observed in our study is the Swedish system of personal identification numbers combined with access to regional population and medical registries. This enabled identification of all patients diagnosed with ATAAD across all healthcare facilities, including emergency and pathology departments in addition to our cardiothoracic surgical department. Despite this comprehensive approach, the true mortality rate is likely even higher as not all patients in our region underwent autopsy. Thus, patients who died at home or in the hospital without undergoing autopsy may not have been captured.

The NST patients were older and were more likely to have developed complications such as syncope, cardiac arrest with ROSC, or cerebral malperfusion. These results are consistent with previous studies (1, 38, 141). Furthermore, significantly more females were in the NST group compared to the ST group (51% vs. 36% ($p<0.01$)). A possible explanation is that females tend to develop ATAAD at an older age and are more likely to present with atypical symptoms (47, 142, 143), increasing the risk of misdiagnosis or diagnostic delay.

In the 86 NST patients who were assessed by a cardiothoracic surgeon, 26% were accepted for surgery but died during transfer to the operating centre. This stresses the need for timely diagnosis and rapid management.

Misdiagnosis

In Study II, we found that 45.3% of ATAAD patients were initially misdiagnosed and that female gender was associated with a higher risk of misdiagnosis. Although misdiagnosis delayed correct diagnosis by a median of almost five hours, there was no significant difference in overall 30-day mortality compared with accurately diagnosed patients. However, patients without signs of malperfusion (Penn class Aa) who experienced diagnostic delay were less likely to be ST and had a higher 30-day mortality compared with timely diagnosed patients.

After showing that the hourly mortality rate in NST ATAAD was 2.6% in Study I, we expected diagnostic delay to increase mortality. Surprisingly, diagnostic delay—

despite prolonging time to diagnosis by almost five hours—did not increase overall 30-day mortality. This aligns with previous studies where no difference in in-hospital or 30-day mortality was observed between misdiagnosed and correctly diagnosed patients (83, 84, 87). Two prior studies also indicated that misdiagnosed patients often present in a clinically more favourable condition (84, 87), validating our decision to stratify patients by severity of clinical presentation.

Misdiagnosed patients in Study II were less likely to present with hypotensive shock, syncope, or malperfusion, and their preoperative levels of creatinine and lactate were lower compared to non-misdiagnosed patients. Consequently, when stratifying the patients according to Penn classes, the misdiagnosed patients were significantly more likely to belong in the less severe classes. When comparing the patients in the different Penn class strata, we could show that misdiagnosed patients in Penn class Ab had significantly higher 30-day mortality compared to their accurately diagnosed counterparts, as did patients with delayed diagnosis in Penn class Aa. A plausible explanation to the higher mortality for patients with delayed diagnosis in Penn class Aa was the observed significantly lower likelihood of being offered surgical treatment after delayed diagnosis. Generally, our results pointed towards misdiagnosis and delayed diagnosis being associated with higher 30-day mortality rates across all Penn classes, but the results did not reach the level of statistical significance in all Penn classes, possibly due to the study being under-powered.

Consistent with previous studies, the most common misdiagnosis in our study population was ACS, followed by cerebral infarction or haemorrhage (84, 85).

One of the most important findings was that female gender was an independent predictor of misdiagnosis, with an OR of 1.7 (95% CI 1.1-2.7 ($p = 0.01$)). A gender-based disparity in timely, accurate diagnosis and treatment of ACS and stroke (144, 145) is well-documented, but to our knowledge, no gender-based disparity in diagnosis of ATAAD has been previously shown. A possible explanation, in line with our explanation in Study I of why more females were NST, could be that females tend to display more atypical symptoms when suffering ATAAD (47). They also tend to be older, have more comorbidities, and are more prone to have less extensive ATAADs such as DeBakey type II (142, 143). Increasing the use of objective diagnostic tools such as the ADD-RS or biomarkers may help counteract this disparity.

D-dimer / fibrinogen ratio for prediction of ATAAD

After demonstrating a high hourly mortality rate in NST ATAAD (Study I), and high rate of misdiagnosis leading to higher mortality in less clinically severe ATAAD patients (Study II), we sought to evaluate whether combining two widely available biomarkers—D-dimer and fibrinogen—could improve ATAAD risk

assessment in the ED. We hypothesised that the combination of D-dimer and fibrinogen would benefit from the sensitivity of an elevated D-dimer and the speculated high specificity of a low fibrinogen. With our highly selected cohort, we found that the combination of the two biomarkers generated a slight increase in discriminative capacity but with questionable clinical relevance compared to using only one of the biomarkers.

The increased risk for females to be denied surgical treatment (Study I) and the increased risk for females to be misdiagnosed (Study II) obviates the need for objective methods to assess the risk of ATAAD.

We could show a significant difference in the D-dimer/fibrinogen ratio between ATAAD and non-ATAAD patients (1.26 (0.51-5.02) vs. 0.14 (0.06-0.56), respectively ($p<0.001$). However, the AUC for the D-dimer/fibrinogen ratio was 0.81 compared to 0.78 for D-dimer and 0.76 for fibrinogen. The confidence intervals of the AUCs were overlapping. The increase in discriminative capacity was slight and non-significant when using the D-dimer/fibrinogen ratio rather than one of the biomarkers alone. A possible explanation is that both biomarkers reflect the same pathophysiological process in ATAAD: consumption coagulopathy. This means that patients with limited dissections, thrombosed false lumen, or unrelated moderate activation of the coagulation cascade will show normal or near normal levels of both biomarkers.

S100B and postoperative neurological injury

In Study IV, we evaluated whether S100B could be used to predict neurological injury following surgical treatment for ATAAD. We showed that S100B sampled 24 hours after surgery could predict neurological injury with an OR of 4.7 and 30-day mortality with an OR of 4.6. We, therefore, believe that S100B could serve as a tool for detection of postoperative neurological injury.

Although S100B has been studied in routine cardiac surgery, where it can predict neurological injury as well as mortality (135, 136), the ATAAD setting is more complex because of HCA, the complicated nature of the surgery, and the risk of preoperative neurological injury. Thus, a dedicated assessment in ATAAD was warranted.

At T1, mean S100B levels were highest in both groups, with no significant difference between the groups. However, previous studies have shown that a significant portion of S100B measured in the blood after heart surgery might be of extracerebral origin, presumably from mediastinal fat and other mediastinal tissues (146). This phenomenon is exaggerated by cardiotomy suction and autotransfusion. Given the relatively short half-life of S100B, it has been suggested that measurements 24-48 hours after surgery are less influenced by contamination from

the surgical site (128). Therefore, elevated levels at T1 likely reflect contamination rather than cerebral injury.

The S100B values were significantly higher in the neurological injury group at timepoints T2, T3, and T4 compared to the no neurological injury group. As early recognition of neurological injury is known to be critical for implementing neuroprotective strategies and optimising treatment (147, 148), we focused on T2, the earliest timepoint with meaningful discriminative capacity. In multivariable regression analysis, S100B was the strongest independent predictor of neurological injury, stronger than preoperative cerebral malperfusion.

Our results may have some clinical implications. Neurological injury is preferably diagnosed by imaging tests such as CT or MRI. To perform radiological tests on patients who are sedated or under intensive care is, however, not only logistically challenging, but also dangerous as intrahospital transfers of intensive care patients has been shown to increase the risk of complications such as pulmonary dysfunction, hemodynamic alteration, and nosocomial infection (149). Therefore, a biomarker that can help identify patients more likely to need further assessment is obviously useful.

Limitations

All studies in this thesis were retrospective and therefore share the inherent limitations associated with retrospective design. Data were incomplete or missing in several cases. Selection bias may have been introduced as we do not know the rationale behind certain variables being available for some patients but not for others. The challenges of translating information from medical records into strict research protocols may have affected the validity of our data. Additionally, clinical routines likely evolved during the extended study period, possibly leading to inconsistencies in the study populations.

Furthermore, all studies were conducted within a single region or single-centre, raising concerns about the generalisability of the findings.

Study I

The patients who were selected for non-surgical treatment were deemed unfit for the gold-standard treatment: surgery. This is a clear selection bias and although the outcomes of non-surgical treatment may not be representative of all ATAAD patients, the data presented represent a real-life scenario. Furthermore, it is likely that the results underestimated the true mortality rates because of the difficulty of identifying all ATAAD patients. Considering the emergent nature of the disease, it is likely that some patients died before they could ever be diagnosed, and not all patients were autopsied.

Study II

The frequency of misdiagnoses may have been underestimated as misdiagnosed patients who died from the disease before conclusive diagnostic tests could be performed and did not undergo autopsy could not be identified for inclusion. The lack of an established definition of misdiagnosis of ATAAD may impact the generalisability of our results, but as discussed previously, our results are in line with prior studies. The 120-minute threshold from first assessment to diagnosis may be viewed as arbitrary; however, we believe it adds necessary objectivity, as the absence of a time limit could allow subjective reinterpretation of medical records. Another limitation of the study is the estimation of time points not possible to be established exactly, although restricting the margin of error to 30-minutes likely minimized the effect on our results.

Study III

Study III has several significant limitations. First, the study was performed on a historical database of ATAAD patients who underwent surgery and ED all-comers who had a D-dimer and fibrinogen analyses performed during their first 24 hours of hospital stay. Thus, our analyses rely on a control group where only 202 of more than 300,000 patients were eligible for inclusion, and this is likely to introduce a strong selection bias as it is reasonable to assume that the analyses on the non-ATAAD patients were performed due to suspected disturbance of the coagulation system, which is not reflective of the general ED population. Furthermore, the cohort does not represent the optimal differential diagnostic spectrum for ATAAD patients, and it is not possible to exclude the risk of the non-ATAAD group containing undiagnosed cases of ATAAD that were misdiagnosed and discharged. Another limitation to the study is that the blood samples in the non-ATAAD group were not always collected at presentation but during the first 24 hours after presentation, which makes them susceptible to reflect events that have occurred after presentation rather than before, or at, presentation.

Study IV

A limitation to Study IV is that biomarker analyses were performed using point-of-care assays, which varied across the study period. Additionally, because our definition of neurological injury did not require confirmation by imaging tests, the rate of neurological injury may have been overestimated.

Conclusions

Study I

In Study I, we observed higher mortality after NST ATAAD than has previously been reported. The results emphasise the need for timely diagnosis, swift management, and emergent surgical treatment for patients suffering an ATAAD.

Study II

In this study, we could show that almost half of ATAAD patients were initially misdiagnosed. The risk of misdiagnosis was significantly higher for female patients, a finding that highlights the need for accurate diagnostic algorithms to objectively assess the patients in the EDs to counteract gender disparities. Overall mortality was not significantly higher in misdiagnosed patients or those with delayed diagnosis, which is likely a reflection of these patients presenting with less severe symptoms and, therefore, having a lower risk of mortality. Stratification of the study population on the severity of symptoms at clinical presentation did, however, reveal that patients with delayed diagnosis and no end-organ malperfusion (Penn class Aa) were significantly more likely denied surgical treatment and had a significantly higher 30-day mortality.

Study III

In this exploratory study of a highly selected cohort, we demonstrated a non-significant increase in discriminative capacity when using the D-dimer/fibrinogen ratio compared with either biomarker alone. The confidence intervals in the AUCs generated by the ROC curves did, however, overlap, suggesting that the improvement is of limited clinical utility, at least based on the current data. We encourage further exploration of the hypothesis and suggest prospective sampling, with samples drawn at presentation, of a larger number of patients with suspected ATAAD.

Study IV

In Study IV, we demonstrated that S100B measured 24 hours after surgery is an independent predictor of neurological injury and 30-day mortality following surgical repair of ATAAD. Postoperative S100B may serve as a tool for detection of neurological injury and assist clinicians in identifying ATAAD patients with the highest need for further diagnostic evaluation.

Future perspective

In Study I, we showed that mortality in NST ATAAD is higher than previously reported. Efforts to decrease mortality must focus on immediate recognition, correct diagnosis, and rapid management of ATAAD patients to get as many patients as possible to surgical treatment in the timeliest manner. Attempts to lower mortality by optimising non-surgical treatment alone are unlikely to succeed, as the ability to counteract the devastating effects of a propagating dissection without surgery is limited.

Interesting approaches to optimize the handling time of ATAAD patients do exist. One such example is the "Aortentelefon" in the Berlin-Brandenburg region of Germany, which is explained in a publication by Zschaler et al. (150). The Deutsches Herzzentrum Berlin operates a phoneline that is open 24 hours per day with a corresponding website. As soon as an ATAAD is diagnosed in the region, the Aortentelefon can be activated whereby all accessible prehospital resources such as intensive care ambulances, police departments, and fire departments can be directed to as swiftly and safely as possible transport the patient to surgical treatment. The Aortentelefon has been shown to decrease the time from symptom onset to surgical treatment by up to 40% (27). Projects like the Aortentelefon are highly dependent on local conditions such as geographical and demographic settings, the proximity to cardiothoracic surgical centres, the ability to mobilize prehospital resources, and others. Therefore, although the Aortentelefon sets an inspiring example, it is not generalisable. Similar projects must, however, be encouraged. They should be adapted to local conditions and evaluated.

The results of Study II, showing that almost half of ATAAD patients are initially misdiagnosed, clearly motivates further efforts to reduce diagnostic error. As discussed in this thesis, the rarity of the disease combined with the wide variety of presenting symptoms contributes substantially to diagnostic error.

Among the most important findings in this thesis is the gender-related differences in both the likelihood of receiving surgical treatment shown in Study I and the risk of misdiagnosis shown in Study II. Although many studies have explored gender-related differences in the treatment of ATAAD (47, 142, 143), severe inequalities obviously remain and must be addressed in further research. A possible approach to mitigate sex-related differences could be an increased use of objective risk-assessment scores such as the ADD-RS (58, 69) for detection of ATAAD and the

GERAADA-score (94) for prediction of postoperative 30-day mortality. Although both scoring systems have been validated (59, 95), further research to promote their use and possibly enhance their performance is warranted.

Another potential mechanism to improve the performance of diagnostic algorithms is the addition of biomarkers. This has already been shown as D-dimer is recommended as an addition to ADD-RS (69). In Study III, we explored the combined use of D-dimer and fibrinogen. The hypothesis is grounded in the unique pathophysiological feature of aortic dissections with circulating false lumen causing consumption coagulopathy. Our study is flawed by the highly selected study population. Further studies on the combination of D-dimer and fibrinogen and other promising candidate biomarkers are needed, and they should preferably be performed with prospective sampling on larger numbers of patients with suspected ATAAD.

As postoperative neurological injury remains one of the most feared complications of ATAAD, severely impacting function level as well as postoperative survival, many studies have been or are to be published, to optimise aspects of the ATAAD treatment to prevent neurological injury (49, 125, 151). Early, and effective, recognition of postoperative neurological injury remains a clinical challenge as ATAAD patients need intensive care during the early postoperative period, and obtaining the high-resolution neuroimaging required for the diagnosis of neurological injury is logistically difficult and potentially hazardous. Therefore, biomarkers that could diagnose neurological injury, particularly in the immediate postoperative period and with a sensitivity and specificity similar to CT and MRI, would be of substantial clinical value.

“Gå nu unge man, att med arbete förkovra ditt välstånd.”

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