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Factors associated with symptom-to-surgery time in patients undergoing surgical repair for acute type A aortic dissection: an exploratory analysis from a prospective cohort study

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ABSTRACT

Objectives The primary objective of this study was to investigate perioperative factors associated with symptom-to-surgery (STS) time in patients diagnosed with hyper-acute aortic dissection (AAD). The secondary objective was to develop a causal model to understand the relationship between STS times and hospital mortality in this population.

Design Prospective cohort study.

Setting Exploratory analysis of a national audit conducted by the Association of Cardiothoracic Anaesthesia and Critical Care.

Participants From a total of 270 participants diagnosed with AAD with an STS time <72 hours, 218 were included in the multivariate analysis, after excluding 52 participants with missing covariates.

Main outcome measures STS time, measured in hours. Hospital mortality at 30 days.

Results In the multivariate analysis, mean STS time for misdiagnosed patients was nearly twice as high when compared with patients who initially had the correct diagnosis (estimated proportion of change=1.9, 95% CI 1.5 to 2.3, p<0.001). STS time decreased when patients were accompanied by a medical doctor in the ambulance transfer, had mean arterial blood pressure below 70 mm Hg or presented to the emergency department (ED) with a Glasgow Coma Scale (GCS) <15. Estimated ED-to-surgery (ETS) times were 1.8 hours longer for women than for men (10.5 hours, 95% CI 9.0 to 12.0 hours vs 8.7 hours, 95% CI 7.8 to 9.6 hours). From a total of 334 patients, 64 (19.2%) died. Mortality was higher in older patients and when STS time was ≥6 and <24 hours, compared with STS time <6 hours.

Conclusions Potentially modifiable factors that may reduce STS times include avoidance of misdiagnosis and provision of a medical doctor for the ambulance transfer. Younger women had longer STS and ETS times, but further research is warranted to investigate the impact of age and sex on these times. The relationship between STS time and hospital mortality among these patients remains unclear.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The high mortality of patients with acute aortic dissection (AAD) undergoing emergency surgery continues to be a public health problem.

⇒ Due to the natural history and urgency of this condition, it requires immediate open-heart surgery; however, little is known about variables influencing symptom-to-surgery (STS) times in patients diagnosed with AAD.

WHAT THIS STUDY ADDS

⇒ STS times are twice as long if patients with AAD were misdiagnosed.

⇒ Conversely, STS times were decreased if patients were hemodynamically and neurologically unstable, and when a medical doctor was present during the transfer.

⇒ Once in the emergency department, men received their surgery quicker than women, particularly at older ages, thereby suggesting that symptoms tend to be less recognized in younger women.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICE

⇒ Promoting campaigns to include AAD in the differential diagnosis of chest pain, thus ensuring an accurate diagnosis, is crucial to decrease STS times.

⇒ The early recognition of AAD in the emergency setting is likely to be paramount for the survival of these patients.

⇒ The commissioning of critical care transfers with a medical doctor on board for all patients with AAD may help reduce STS times.

⇒ There is a suggestion that older men with a diagnosis of AAD may be likely to have their surgery quicker, as compared with younger women.

⇒ Clinicians may underestimate the symptoms of women presenting with AAD, thereby making women more prone to delays in receiving their surgery.

INTRODUCTION

Acute aortic dissection (AAD) is a relatively rare but life-threatening condition that primarily affects people in middle and advanced age. In the USA, the incidence of aortic dissection between 2000 and 2011 was about 10 cases per 100 000 person-years.[1] Howard *et al* estimated that in the UK, between 2002 and 2012, the incidence rate of AAD was seven cases per 100 000 person-years in men (95% CI 4 to 9), and five cases per 100 000 person-years in women (95% CI 3 to 7) at a mean age of 72 years.[2]

From the perspective of time elapsed from the onset of symptoms, aortic dissection can be classified into hyper-acute (<24 hours), acute (between 1 and 7 days), subacute (8–30 days), and chronic (>30 days),[3] with the highest mortality rate among acute cases (1%–2% per hour after symptoms onset, without undergoing surgical repair).[4,5]

The only life-saving treatment for patients presenting with AAD comprises prompt open-heart surgery repair, which in the UK is conducted in about 30 specialist centers. When left untreated, it can have devastating consequences, including acute myocardial ischemia, cardiac tamponade, stroke, organ malperfusion, and death.[4]

From 2016 to 2019, before the COVID-19 pandemic era, approximately 400 patients per year with a diagnosis of aortic dissection underwent emergency surgery for aorta repair in the UK. During this period, the overall postoperative in-hospital mortality of these patients was 17.7%.[6] In England, approximately 2500 cases of aortic dissection involving the proximal aorta are expected every year, from which about 20% will die before receiving any healthcare, and as many as half of them will die before reaching a cardiac center.[7] It has also been estimated that without surgical repair, the mortality of aortic dissection is 50% and 80% at 48 hours and 14 days, respectively.[6] Moreover, around 16%–40% of these patients can have a delayed diagnosis, with potentially serious consequences, including death.[7–9]

While it is clear that age is a determinant risk factor, the incidence of this condition in young people is unknown. Risk factors for AAD include age, previous vascular disease, history of aortic aneurysm, smoking, hypertension, and congenital abnormalities, among others.[2,4]

Furthermore, the similarity of AAD symptoms with acute coronary syndromes (including myocardial infarction), the possibility of having concomitant symptoms of myocardial ischemia[5] and the relatively low incidence of aortic dissection[7] make it difficult to diagnose AAD, thus requiring a high level of awareness of this condition among health providers.[10]

Despite the joint efforts of healthcare authorities to increase the awareness of AAD, the mortality of these patients has been estimated to be around 18%.[4,11,12] While such a high mortality is inherent to the complexity of this condition,[13] there exist some preventable factors influencing the prognosis of these patients. In particular, the impact of any delay in performing the surgical treatment in patients with AAD is well-known, but factors influencing this delay, and the implications in the mortality of these patients have yet to be established.[8,9]

Previous research has suggested that in the setting of patients diagnosed with acute myocardial infarction, the call-to-balloon time (ie, the time elapsed between the call for help and the start of the transcutaneous intervention) might better reflect service efficiency compared with the door-to-balloon time (ie, time elapsed between arrival to hospital and the initiation of the endovascular procedure). However, the correlation of these times with in-hospital and long-term mortality has not been consistent across studies.[14]

This prospective cohort study sought to explore factors influencing symptom-to-surgery (STS) times and mortality in patients with AAD undergoing surgery within 72 hours from the onset of symptoms, as well as the potential role of age and sex in this population, with the aim of identifying more vulnerable/under-represented populations, thus providing key information for patient and public involvement related to future research.

METHODS

Data

We analyzed prospectively collected data from a national audit, involving patients attending emergency department (ED) services from 34 hospitals in England and undergoing surgery for AAD.[12] Patients with a diagnosis of AAD were recruited from May 1, 2021 to April 30, 2022. Outcome variables included mortality and STS time. Independent variables were collected and classified into the following categories: variables collected before arrival to cardiac centers, variables collected on arrival to cardiac centers, and variables collected during in-hospital admission to cardiac center. A summary of the variables included in this study is provided in table 1, and a detailed description of the variables collected can be found in the online supplemental table S1.

This analysis was focused on type A hyper-AAD. We considered the time elapsed between symptoms onset and surgery in the following periods:

1. STS time: defined as the time elapsed between symptoms onset and the start of surgery.
2. Symptom-to-ED (STE) time: defined as the time elapsed between symptoms onset and arrival to the ED services.
3. ED-to-surgery (ETS) time: defined as the time elapsed between arrival to the emergency department services and the start of surgery.

For the purposes of the present study, we define AAD as the aortic dissection with STS time ≤72 hours.

Statistical analysis

For the description of data, all patients who underwent surgery were included irrespective of their time to surgery. For subsequent data analyses, we only included patients with STS time ≤72 hours. Accordingly, patients with potentially contained, chronic or type B aortic

Table 1 Description of the covariates included in this study

Variable	Description
Age	Age (in years) at the time of admission to the ED.
Sex	Binary variable for sex of the patient.
MBP	Mean blood pressure (given in mm Hg) measured on arrival to ED.
Misdiagnosis	Binary variable for whether the patient has been misdiagnosed at ED.
Medic	Binary variable for the presence of any medical doctor during the ambulance transfer.
Endotracheal tube	Binary variable for the need for endotracheal tube to secure the patient's airway, before arrival to OR.
GCS	Binary variable for the degree of consciousness of the patient (15, <15).
High-volume center	Binary variable for the number of patients recruited in the cardiac center (≤5, >5).
Echocardiogram	Binary variable for whether the patient had an echocardiogram before surgery.
CT	Binary variable for whether the patient had a CT before surgery.
High-volume center	Binary variable for the number of patients recruited in the cardiac centre (≤5, >5).
Delay arrival to ED	Binary variable for the time between symptoms onset and ED arrival ≥24 hours.
Delayed arrival to OR	Binary variable for a delay in arrival to the OR ≥1 hour.

ED, emergency department; GCS, Glasgow Coma Scale; OR, operating room.

aneurysms were excluded.[15 16] Complete-case analyses were used to construct all multivariate models, excluding missing observations where relevant.

The distribution of the variable STS time was evaluated with histograms. In addition, the continuous independent variables age and mean blood pressure (MBP, measured on arrival to ED services) were categorized, as shown in table 2. MBP was also centered at 90 mm Hg for all analysis purposes to facilitate the clinical interpretation of data. The most appropriate functional forms for the variables age and MBP (ie, continuous, categorical and quadratic) were evaluated with log-likelihood ratio tests and accordingly included in the multivariate models. STS time and mortality were described and presented for the total sample and for each one of the 43 independent variables included in this study (online supplemental table S1).

To investigate the factors associated with STS time, a log-linear model was constructed incorporating independent variables taken from a large pool of available variables. Variables collected after the start of surgery were not considered, as they were not associated with STS time. The details of the methodology used to evaluate factors associated with STS time and the association between STS time and mortality are provided in the online supplemental material.[17]

With the aim of describing the survival times of patients with AAD undergoing surgical repair with STS time ≤24 hours as compared with those having STS time >24 hours, a binary variable for STS time was generated. Subsequently, a Kaplan-Meier survival curve was plotted after removing observations with STS time >72 hours, and a log-rank test was calculated to compare the unadjusted survival between these two groups.

All analyses were conducted using Stata V.17.0 (StataCorp, College Station, Texas, USA).

Patient and public involvement

Patients and patient carers were involved in the design of the audit questionnaire and in outcome measures. In addition, the study was conceived and designed with the purpose of identifying more vulnerable populations, thus potentially providing key information for future research involving patient and public involvement.

RESULTS

From a total of 334 patients, 270 were included in the univariate analysis with known STS time ≤72 hours, and 218 were included in the multivariate models (figure 1). The distribution of the outcome variable STS time was approximately normal after logarithmic transformation, as illustrated in figure 2. All covariates included in this study had missing observations <10%, with the exception of the variables MBP (20.96%) and presence of a medical doctor (20.66%).

Factors associated with STS time

In the descriptive analysis among all 334 patients, median STS time was higher in women (15.5 hours) compared with men (11.5 hours), as well as in conscious patients (GCS=15, 13.2 hours) compared with patients with impaired consciousness (GCS <15, 9.5 hours), and in misdiagnosed patients (33.5 hours) when compared with patients correctly diagnosed (11.4 hours) (table 2). These findings were similar when analyzing 270 patients with STS time ≤72 hours (online supplemental table S2).

For all univariate and multivariate analyses, the variable MBP was centered at 90 mm Hg. All estimates were obtained for every MBP increase in 10 mm Hg, and a quadratic MBP term was incorporated, as it substantially improved the goodness of fit of the model (online supplemental figure S1).

Among the 270 patients with known STS time ≤72 hours, the distribution of the outcome variable STS time showed a marked positive skewness, and therefore this variable was transformed to a logarithmic scale (figure 2).

Table 3 outlines the results obtained for the univariate analysis. To facilitate the interpretation of results, all coefficients and 95% CIs have been transformed back to

Table 2 STS time (given in hours) and crude mortality (given in percentage) stratified by covariates collected before arrival to cardiac center

Variable	Total N (%)*	STS† median time in hours (IQR)	Mortality N (%)‡
All patients	334 (100.0)	12.5 (9.0 to 26.7)	64 (19.2)
Age (years)	334 (100.0)		
<45	46 (13.8)	14.9 (9.0 to 35.4)	7 (15.2)
46–55	61 (18.3)	11.9 (7.8 to 18.5)	11 (18.0)
56–65	68 (20.4)	14.5 (9.8 to 27.5)	12 (17.7)
66–75	96 (28.7)	11.0 (8.2 to 27.7)	20 (20.8)
>75	63 (18.9)	15.0 (9.6 to 27.2)	14 (22.2)
Sex	334 (100.0)		
Male	208 (62.3)	11.5 (8.5 to 23.9)	42 (20.2)
Female	126 (37.7)	15.5 (9.4 to 42.2)	22 (17.5)
High-volume center	334 (100.0)		
No (≤5 patients recruited)	22 (6.6)	10.1 (6.8 to 21.3)	4 (18.2)
Yes (>5 patients recruited)	312 (93.4)	12.9 (9.1 to 27.6)	60 (19.2)
STS time	308 (100.0)		
≤6 hours	25 (8.2)	4.8 (4.0 to 5.5)	5 (20.0)
>6 hours, ≤12 hours	123 (40.2)	9.5 (7.8 to 10.9)	29 (23.6)
>12 hours, ≤24 hours	75 (24.5)	16.7 (14.6 to 19.4)	16 (21.3)
>24 hours, ≤72 hours	47 (15.4)	38.5 (28.0 to 49.2)	5 (10.6)
>72 hours	36 (11.8)	137.2 (107.8 to 240.3)	3 (8.3)
Symptom-to-ED time	299 (100.0)		
≤1 hour	60 (20.1)	10.8 (6.9 to 24.3)	10 (16.7)
>1 hour, ≤2 hours	80 (26.8)	11.1 (8.0 to 15.8)	15 (18.8)
>2 hours, ≤3 hours	49 (16.4)	10.1 (8.8 to 13.4)	15 (30.6)
>3 hours, ≤6 hours	48 (16.1)	12.7 (10.2 to 19.5)	11 (22.9)
>6 hours	62 (20.7)	44.8 (21.5 to 112.2)	5 (8.1)
ED-to-surgery time	312 (100.0)		
≤6 hours	73 (23.4)	6.8 (5.3 to 9.8)	16 (21.9)
>6 hours, ≤12 hours	111 (35.6)	10.9 (9.2 to 12.0)	26 (23.4)
>12 hours	128 (41.0)	30.3 (18.8 to 72.0)	16 (12.5)
MBP (mm Hg)§	264 (100.0)		
<70	56 (21.2)	9.5 (7.4 to 11.6)	9 (16.1)
70–90	83 (31.4)	14.3 (9.4 to 25.8)	22 (26.5)
>90	125 (47.4)	15.8 (9.8 to 34.2)	19 (15.2)
GCS§	329 (100.0)		
<15	28 (8.5)	9.5 (6.7 to 13.4)	12 (42.9)
15	301 (91.5)	13.2 (9.3 to 26.7)	51 (16.9)
Misdiagnosis	334 (100.0)		
No	282 (84.4)	11.4 (8.5 to 19.8)	55 (19.5)
Yes	52 (15.6)	33.5 (16.1 to 69.2)	9 (17.3)
Delay arrival to ED¶	334 (100.0)		
No	297 (88.9)	11.5 (8.6 to 19.7)	61 (20.5)
Yes	37 (11.1)	117.3 (62.3 to 210.3)	3 (8.1)
Cardiac center**	334 (100.0)		
No	322 (96.4)	12.8 (9.0 to 27.7)	64 (19.9)
Yes	12 (3.6)	8.2 (5.1 to 11.5)	0 (0.0)

Continued

Table 2 Continued

Variable	Total N (%)*	STS† median time in hours (IQR)	Mortality N (%)‡
Medic††	334 (100.0)		
No	284 (85.0)	13.4 (9.5 to 27.9)	53 (18.7)
Yes	50 (15.0)	10.2 (7.4 to 18.9)	11 (22.0)
Delay arrival to OR ≤1 hour	334 (100.0)		
No	127 (38.0)	9.8 (7.0 to 12.5)	25 (19.7)
Yes	207 (62.0)	18.3 (10.9 to 43.5)	39 (18.8)

*Column percentages.
†Time between onset of symptoms and surgery (figure 2).
‡Row percentages.
§On arrival to the ED.
¶Delay defined as time between symptoms onset and ED attendance >24 hours.
**Cardiac centre as the first hospital of attendance.
††Presence of any medical doctor during ambulance transfer.
ED, emergency department; GCS, Glasgow Coma Scale; MBP, mean blood pressure; OR, operating room; STS, symptom-to-surgery.

a linear scale. Hence, the figures presented in this table represent the estimated proportion of change in STS times (EPC) with respect to the reference category. The results from the multivariate analysis are summarized in table 4. In the multivariate analysis, after adjusting for sex, MBP, quadratic MBP, misdiagnosis, presence of a medical doctor during ambulance transfer and ETT, STS time decreased by 20% when comparing patients aged >75 years with patients aged <45 years (EPC 0.80, 95% CI 0.58 to 1.08). Similar results were obtained for the remaining categories of age (p value for trend=0.072). When comparing STS times for men with respect to women, there was weak evidence for an increased STS time in women compared with men (EPC 1.13, 95% CI 0.94 to 1.35, p=0.186). This is in contrast with the observed STS time change for the covariates MBP, misdiagnosis, presence of a medical doctor and ETT, where there was strong evidence for an association between STS times and these variables (table 4).

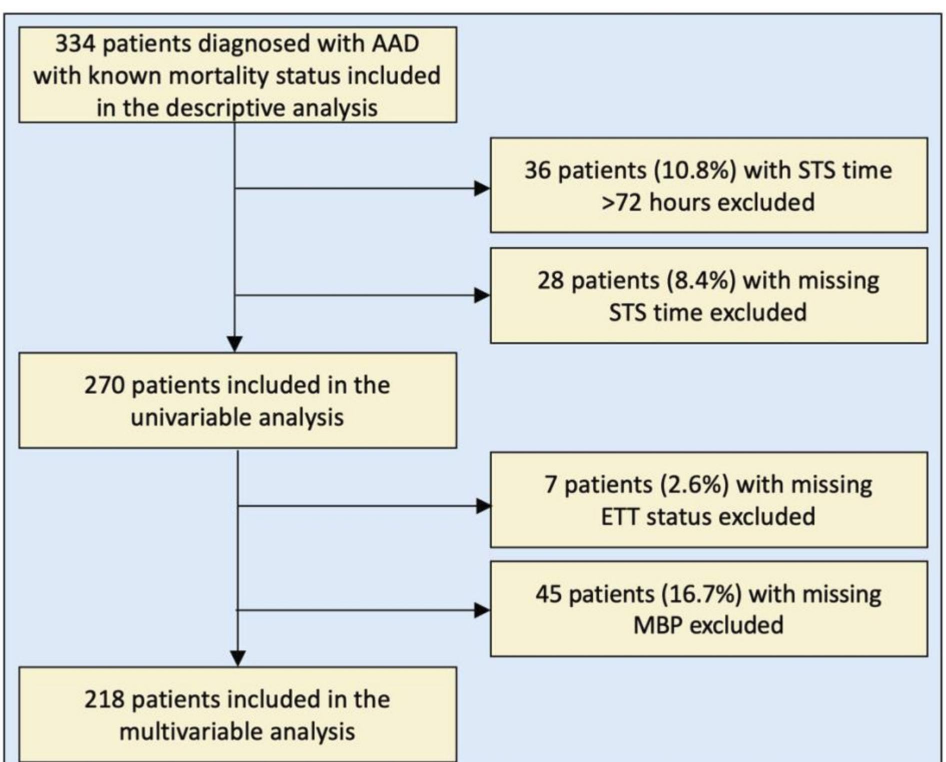

Figure 1 Flow chart illustrating patients included and excluded from this study for the analysis of the relationship between STS time ≤72 hours and mortality of patients diagnosed with AAD. AAD, type A acute aortic dissection; ETT, endotracheal tube placed on arrival to the operating room; MBP, mean blood pressure; STS, symptom-to-surgery time.

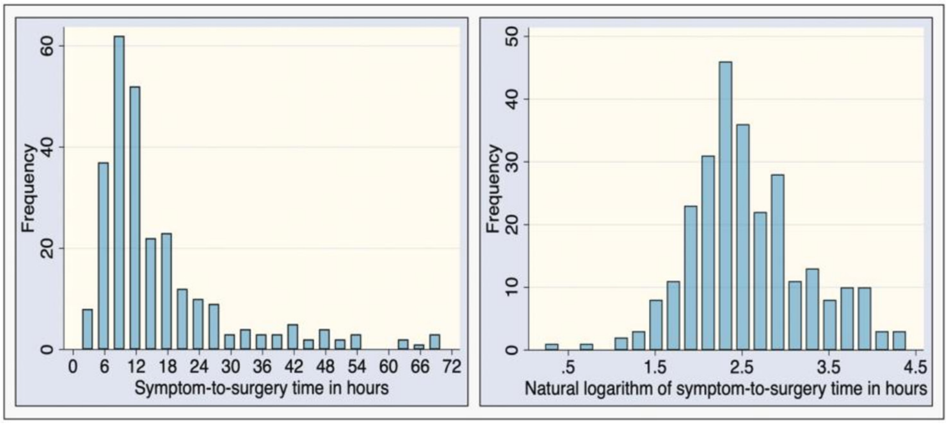

Figure 2 Histograms for the variable symptom-to-surgery time (given in hours) before and after logarithmic transformation, excluding patients undergoing surgery after 72 hours of symptoms onset.

Among patients with MBP of 90 mm Hg, after adjusting for age, sex, misdiagnosis, presence of a medical doctor and ETT, the EPC was 1.07 (95% CI 1.04 to 1.11, p<0.001). There was very strong evidence that this EPC changed according to the level of MBP (p<0.001), as shown in table 4 and online supplemental figure S1.

Two additional multivariate analyses were conducted to investigate whether the variables identified in the multivariate model were associated with STE time or ETS time (table 4). According to these models, the variable ETT was strongly associated with STE time, whereas the variables MBP and misdiagnosis were equally associated with

Table 3 Univariate analysis exploring factors influencing STS time—given in hours—among patients with STS ≤72 hours

	Univariate analysis			
Variable	**N**	**EPC**	**95% CI**	**P value**
Age (years)	270			0.317*
<45	39	1.00	–	–
46–55	52	0.78	0.59 to 1.05	–
56–65	55	0.92	0.70 to 1.22	–
66–75	74	0.77	0.58 to 1.00	–
>75	50	0.88	0.66 to 1.16	–
Sex (0=male, 1=female)	270	1.12	0.95 to 1.33	0.163
MBP (per 10 mm Hg)†	225	1.08‡	1.05 to 1.11‡	<0.001
Quadratic MBP (per 10 mm Hg)	225	0.984	0.978 to 0.991	<0.001
Misdiagnosis (0=no, 1=yes)	270	2.01	1.62 to 2.50	<0.001
Medic (0=no, 1=yes)§	270	0.82	0.66 to 1.00	0.055
ETT (0=no, 1=yes)¶	263	0.48	0.26 to 0.90	0.022
Glasgow Coma Scale (0≤15, 1≥15)†	268	1.45	1.02 to 2.07	0.037
High-volume center (0=≤5, 1≥5)**	270	1.16	0.86 to 1.55	0.332
Echocardiogram (0=no, 1=yes)†	270	1.07	0.89 to 1.28	0.488
CT (0=no, 1=yes)†	270	1.13	0.77 to 1.66	0.527

The variable STS time has been transformed to the natural logarithmic scale, and subsequently, the coefficients and 95% CIs have been transformed back to a linear scale to facilitate the interpretation of results.
All p values and 95% CI are based on robust SEs.
*From log-likelihood ratio test.
†Measured on arrival to the emergency department.
‡Estimated after including a quadratic BMP term in the model, for every 10 mm Hg of MBP increase.
§Presence of any medical doctor during ambulance transfer.
¶On arrival to operating rooms.
**Based on the number of patients recruited per centre.
††P value for trend test.
EPC, estimated proportion of change in STS times, with respect to the category of reference; ETT, endotracheal tube; MBP, mean blood pressure, centered at 90 mm Hg; STS, symptom-to-surgery.

Table 4 Multivariate analyses examining factors associated with (i) STS time, (ii) STE time, and (iii) ETS time, among patients with STS time ≤72 hours

	STS time (n=218)			STE time (n=218)			ETS time (n=218)		
	EPC	95% CI	P value	EPC	95% CI	P value	EPC	95% CI	P value
Age (years)			0.072*			0.689*			0.162*
<45	1.00	–	–	1.00	–	–	1.00	–	–
46–55	0.84	0.63 to 1.11	–	1.05	0.65 to 1.70	–	0.85	0.62 to 1.17	–
56–65	0.80	0.61 to 1.06	–	1.24	0.78 to 1.99	–	0.69	0.51 to 0.94	–
66–75	0.77	0.57 to 1.02	–	0.95	0.57 to 1.57	–	0.74	0.54 to 1.02	–
>75	0.80	0.58 to 1.08	–	1.13	0.67 to 1.89	–	0.73	0.53 to 1.01	–
Sex (0=male, 1=female)	1.13	0.94 to 1.35	0.186	0.94	0.69 to 1.29	0.706	1.20	1.00 to 1.44	0.050
MBP (per 10 mm Hg)†	1.07	1.04 to 1.11	<0.001	1.03	0.97 to 1.09	0.397	1.09	1.06 to 1.13	<0.001
Quadratic MBP (per 10 mm Hg)	0.985	0.979 to 0.992	<0.001	0.99	0.98 to 1.01	0.331	0.98	0.98 to 0.99	<0.001
Misdiagnosis (0=no, 1=yes)	1.86	1.49 to 2.31	<0.001	1.14	0.78 to 1.67	0.489	2.07	1.64 to 2.61	<0.001
Medic (0=no, 1=yes)‡	0.82	0.67 to 0.99	0.049	0.89	0.66 to 1.18	0.406	0.86	0.71 to 1.05	0.133
ETT (0=no, 1=yes)§	0.42	0.21 to 0.85	0.016	0.44	0.27 to 0.74	0.002	0.65	0.39 to 1.09	0.105

In this analysis, STS time has been broken down into STE time and ETS time.
The corresponding point estimates have been transformed to the natural logarithmic scale, and subsequently, the coefficients and 95% CIs have been transformed back to a linear scale.
STS, STE and ETS times were introduced in the model in hours. All p values and 95% CIs are based on robust SEs.
*P value for trend test.
†Measured on arrival to the emergency department.
‡Presence of any medical doctor during ambulance transfer.
§On arrival to the operating room.
ED, emergency department; EPC, estimated proportion of change, with respect to the category of reference; ETS, ED-to-surgery ; ETT, endotracheal tube; STE, symptom-to-ED; STS, symptom-to-surgery.

ETS time, but not with STE time. After adjusting for age, sex, MBP, misdiagnosis, and presence of a medical doctor, there was strong evidence for a decrease in STE time, with an observed decrease of 56% in patients requiring ETT before arrival to the operating room, compared with patients who did not undergo this procedure (EPC 0.44, 95% CI 0.27 to 0.74, p=0.002). Similarly, after adjusting for age, sex, MBP, presence of a medical doctor, and ETT, there was strong evidence for an increase in ETS time—nearly twice as much—when comparing misdiagnosed patients with those who were correctly diagnosed (EPC 2.07, 95% CI 1.64 to 2.61, p<0.001). In regard to the variable sex, ETS time increased 1.2 times in women as compared with men (95% CI 1.00 to 1.44, p=0.050) (table 4).

Relationship between STS time, age, and sex

After adjusting for the variables sex, MBP, misdiagnosis, presence of a medical doctor and ETT, older patients with a diagnosis of AAD had their surgical procedure quicker, with estimated STS time ranging from 11.9 to 15.6 hours, and ETS time ranging from 8.2 to 11.9 hours (figure 3). After adjusting for age, quadratic MBP, misdiagnosis, medic and ETT, women had to wait on average longer to undergo surgical repair for AAD compared with men (STS and ETS times 1.6 hours and 1.8 hours longer for

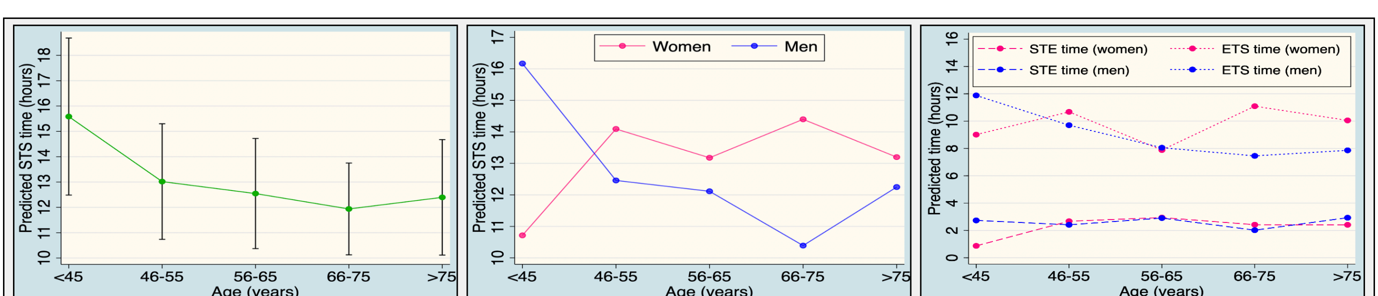

Figure 3 Left: estimated symptom-to-surgery (STS) time according to age, obtained from the multivariate model described in table 4, without including an interaction between age and sex. The vertical lines represent the 95% CIs. Center: estimated STS times for women and men according to age, after including an interaction between age and sex (p=0.058). Right: estimated symptom-to-ED (STE) time and ED-to-surgery (ETS) time (dashed and dotted lines, respectively) for women and men according to age, after including an interaction between age and sex (p=0.284 and p=0.071, respectively). ED, emergency department.

women, respectively). The estimated STS time for men was 12.3 hours (95% CI 11.1 to 13.5) and for women was 13.9 hours (95% CI 12.0 to 15.8). This corresponds to an EPC increased by 12.7% when comparing women with men (95% CI 8.0% to 16.6%). The estimated ETS time for men was 8.7 hours (95% CI 7.8 to 9.6 hours) and for women was 10.5 hours (95% CI 9.0 to 12.0). Thus, the EPC for ETS time increased by 20% when comparing women with men (95% CI 14.7% to 24.3%). All estimated times were calculated with the remaining covariates set to their mean values.

When including an interaction term between age and sex in the multivariate model presented in table 4 for STS time, men tended to have their surgical repair quicker than women (p=0.050), with the exception of patients aged <45 years (figure 3).

Mortality

The overall mortality of the cohort included in the descriptive analysis was 19.2%. The relationship between (i) STS time and mortality, (ii) STE time and mortality, and (iii) ETS time and mortality was non-linear (online supplemental figure S2).

Mortality was consistently higher in older (aged 75 years) than in younger (aged <45 years) patients (22.2% vs 15.2%, respectively), in men than in women (20.2% vs 17.5%), and in patients with impaired consciousness (GCS <15) compared with conscious patients (GCS=15) (42.9% vs 16.9%, respectively), as shown in table 2.

From a total of 261 patients included in the Kaplan-Meier analysis, 53 (20.3%) died, and the 30-day mortality was 24.4% (online supplemental figure S3). In examining patients with STS time ≤24 hours (n=215) and STS time between 24 and 72 hours (n=46), the crude 30-day mortality was 26.1% and 15.2%, respectively (online supplemental figure S3).

Association between STS time and mortality

A causal diagram was drawn to identify variables influencing the relationship between STS time and mortality (online supplemental figure S4). After adjusting for age, sex, MBP, whether the patient was misdiagnosed, and whether the patient needed ETT before arrival to the operating room, the observed hazard of mortality for patients undergoing surgical repair for AAD increased 42%, when comparing patients with STS time between 6 and 12 hours with those with STS time <6 hours (HR 1.42, 95% CI 0.42 to 4.79), although numbers were small and the evidence was weak. This increased HR was only 10% higher when the comparison was between STS time 12–24 hours, and STS time <6 hours (95% CI 0.29 to 4.16). By contrast, the HR suggested a lower risk when comparing STS time between 24 and 72 hours and STS time <6 hours (HR 0.59, 95% CI 0.12 to 2.91). This is likely due to different baseline characteristics of patients with STS times >24 hours (table 5).

Sensitivity analysis

The complete-case analysis strategy used for all univariate and multivariate analyses presented in this study is based on the assumption that missing data are non-informative. Stated in a different way, we assumed that the mechanism of missing data was 'missing completely at random' (MCAR).[18]

A sensitivity analysis was conducted to support the MCAR assumption for the variables MBP and STS time, by comparing the outcomes obtained for the sample included in this study with those obtained for observations with missing data. The median STS time for those with observed and missing MBP was similar (11.4 vs 12.5 hours, p value for Mann-Whitney U test=0.524). There was no evidence for a difference in mortality when comparing patients with observed MBP with those who had missing MBP (p value Fisher's exact test=0.543). Similarly, there was no evidence for a different mortality in patients with observed STS time, as compared with those with missing STS time (p value Fisher's exact test=0.805) (online supplemental table S3).

DISCUSSION

This study sought to investigate perioperative factors associated with STS times and identify variables influencing STS times in patients with AAD undergoing surgery within 72 hours from the onset of symptoms. In addition, factors associated with mortality and a potential causal relationship between STS times and hospital mortality within the same time frame were evaluated. We demonstrated that in patients with AAD, modifiable factors for a reduction of STS times include avoidance of misdiagnosis and provision of a medical doctor for the critical care transfer.[12] Furthermore, women and young patients tended to have longer STS times. Importantly, the observed differences in STS times for age, sex, and misdiagnosis seemed to be related primarily to ETS times, thus suggesting that designing strategies to decrease the time elapsed between arrival to ED and start of surgery may be crucial to decrease STS times. These strategies could make an impact on the mortality of these patients.

In order to prompt the diagnosis of AAD, several strategies have been proposed to increase the awareness of this condition among healthcare providers,[10 11 19] underscore the high mortality of this condition,[7 12] and emphasize the crucial role of a rapid CT scan to confirm the diagnosis.[11] In our study, misdiagnosed patients had ETS and STS times increased nearly twice as high when compared with patients who had the right diagnosis. This finding reinforces the need for initiatives promoting prompt, accurate diagnosis of AAD and encourages policy-makers to develop strategies to prompt the early recognition of AAD in ED services.[20]

Our results suggest that age and sex may be associated with STS time, and specifically ETS time, although the statistical power for these findings is limited. Despite there not being strong evidence for this association, older men tended to have their surgical repair quicker than younger women. In addition, there was weak evidence of an interaction of age and sex for the relationship between

Table 5 Three separate multivariate analyses for the association between (i) STS time and mortality, (ii) STE time and mortality, and (iii) ETS time and mortality, in patients undergoing surgical repair for type A acute aortic dissection within the first 72 hours of symptoms onset

	STS time (n=214)			STE time (n=211)			ETS time (n=211)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
STS time			0.427*						
≤6 hours	1.00	–	–	–	–	–	–	–	–
>6 hours, ≤12 hours	1.42	0.42 to 4.79	–	–	–	–	–	–	–
>12 hours, ≤24 hours	1.10	0.29 to 4.16	–	–	–	–	–	–	–
>24 hours, ≤72 hours	0.59	0.12 to 2.91	–	–	–	–	–	–	–
STE time						0.145*			
≤1 hour	–	–	–	1.00	–	–	–	–	–
>1 hour, ≤2 hours	–	–	–	1.12	0.41 to 3.04	–	–	–	–
>2 hours, ≤3 hours	–	–	–	2.08	0.72 to 6.03	–	–	–	–
>3 hours, ≤6 hours	–	–	–	2.14	0.74 to 6.24	–	–	–	–
>6 hours, ≤72 hours	–	–	–	0.59	0.14 to 2.47	–	–	–	–
ETS time									0.178*
≤6 hours	–	–	–	–	–	–	1.00	–	–
>6 hours, ≤12 hours	–	–	–	–	–	–	0.89	0.43 to 1.84	–
>12 hours, ≤72 hours	–	–	–	–	–	–	0.45	0.18 to 1.15	–
Age (years)			0.840*			0.688*			0.926*
<45	1.00	–	–	1.00	–	–	1.00	–	–
46–55	1.69	0.52 to 5.55	–	1.48	0.45 to 4.88	–	1.48	0.45 to 4.86	–
56–65	1.30	0.38 to 4.38	–	1.13	0.33 to 3.84	–	1.08	0.32 to 3.65	–
66–75	1.75	0.55 to 5.57	–	1.82	0.57 to 5.89	–	1.42	0.44 to 4.62	–
>75	1.30	0.37 to 4.59	–	1.04	0.29 to 3.80	–	1.16	0.33 to 4.08	–
Sex (0=male, 1=female)	1.00	0.50 to 2.01	0.990	0.97	0.49 to 1.92	0.942	1.09	0.54 to 2.17	0.824
Mean blood pressure (mm Hg)†			0.048*			0.060*			0.029*
<70	1.00	–	–	1.00	–	–	1.00	–	–
70–90	2.90	1.17 to 7.18	–	2.78	1.12 to 6.89	–	3.17	1.28 to 7.83	–
>90	1.71	0.69 to 4.28	–	1.63	0.65 to 4.08	–	1.85	0.73 to 4.66	–
Misdiagnosis (0=no, 1=yes)	1.33	0.54 to 3.24	0.534	1.05	1.49 to 2.43	0.917	1.43	0.59 to 3.47	0.431
ETT (0=no, 1=yes)‡	6.85	2.27 to 20.71	0.001	10.70	3.52 to 32.57	<0.001	6.47	2.23 to 18.82	0.001

All p values are provided from Wald test, unless otherwise indicated.
*From log-likelihood ratio test.
†On arrival to ED.
‡On arrival to the operating room.
ED, emergency department; ETS, ED-to-surgery; ETT, endotracheal intubation; STE, symptom-to-ED; STS, symptom-to-surgery.

age and STS time. These results are in agreement with previous research on ST-elevation myocardial infarction, in which men received surgical procedures more quickly.[14] However, it is uncertain whether these differences significantly affect patient mortality.

While our results did not demonstrate strong evidence for an association between STS time and mortality, caution must be exercised when interpreting these findings, because the study was underpowered to address this research question. Furthermore, the severity of the disease was not quantified in this cohort, thus rendering the analysis of patients with severe AAD unexplored. In fact, one possible explanation for these results is that STS time may not be crucial in the mild spectrum of AAD, but it can be important when the manifestations of the disease are life-threatening. About half of patients with AAD die before they arrive in hospital[7]; therefore, the complete cohort with acutely life-threatening disease, including those who die before arrival in the hospital, could not be assessed in this audit, which may have skewed the correlation between STS times and mortality. Thus, further research is warranted to elucidate the role of STS time in these patients.

It is readily apparent that risk of death for patients with severe AAD before undergoing surgical repair increases with longer STS times. Paradoxically, this increased preoperative mortality may have a 'dilution' effect on in-hospital mortality (calculated from deaths occurring after the surgical procedure and before discharge), potentially creating a false impression of improved in-hospital mortality with long STS times. This type of selection bias, known as survivor bias, has long been recognized in other medical fields[21 22] and might explain why in the Kaplan-Meier curve analysis patients with STS time between 24 and 72 hours seemed to survive more, when compared with patients with STS time ≤24 hours.

The decision to establish a cut-off of 72 hours for STS time was made on the basis of previous subject-matter knowledge of the topic and clinical considerations of the baseline characteristics of patients. Factors associated with a surgical repair of AAD delayed >72 hours can be divided into clinical, surgical, and logistic factors. The clinical factors may include severity and chronicity of the disease.[16] From this perspective, patients with prolonged STS times may have a contained aortic dissection, in which case the condition may behave similarly to type B (abdominal) aneurysms, whose evolution can be chronic.[15] Surgical factors involve complex clinical decisions to postpone a surgical procedure in the best interests of the patient.[16] Finally, logistic factors refer to difficulties in transferring patients living in remote areas to a tertiary referral hospital, the availability of cardiac surgeons to carry out the procedure, and the day of the week that the patient is presenting to ED.[12] Thus, patients experiencing AAD with STS time >72 hours represent a different spectrum of the disease, and the exploration of this subpopulation of patients was beyond the scope of this study.

The present study has several strengths. The independent variables were collected prospectively from 34 cardiac centers across the UK, and most of them were measured objectively, thus improving the external validity of results. In view of the departures from normality and homoscedasticity of the linear model, a log-linear model with robust SEs was conducted. Furthermore, we introduced the concepts of STS time, STE time, and ETS time in the context of patients diagnosed with AAD, thereby establishing a benchmark for future studies.

Limitations of this study include the small sample size, which rendered some of the study results underpowered. Thus, further studies will need to be conducted to confirm or controvert these results. The severity of AAD may be influenced by the size, location, and extension of the aortic dissection.[13 16] Similarly, the hospital size and structure may be associated with ETS times. Unfortunately, none of these variables were collected in this study. Hence, the exploration of these aspects in relation to the mortality of patients and STS times is desirable for future research. In addition, other important aspects of the disease were not considered in this study, including surgeon's experience[20] and the day of the week on which the procedure was performed, thereby increasing the probability of residual confounding.

Non-informative censoring was assumed for the observations missing MBP and STS time, and therefore, no attempts at multiple imputation were made to replace missing data. Although the MCAR assumption is often unrealistic in many clinical scenarios, our sensitivity analysis did not show any evidence against this assumption. Moreover, the proportion of missing data was low (15.3% and 8.4% including all observations for MBP and STS time, respectively).

In summary, our results demonstrate that STS times were approximately doubled when patients with AAD had been misdiagnosed, and they were reduced when patients had reduced consciousness and medical doctors were present during transfer. Furthermore, younger patients and female patients tended to arrive slower at cardiac surgical centers, when compared with older and male patients, respectively. These differences remained significant for ETS times, but not for STE times.

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REFERENCES

1 Yin J, Liu F, Wang J, *et al*. Aortic dissection: global epidemiology. *Cardiology Plus* 2022;7:151–61.
2 Howard DPJ, Banerjee A, Fairhead JF, *et al*. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. *Circulation* 2013;127:2031–7.
3 MacCarrick G, Black JH 3rd, Bowdin S, *et al*. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med* 2014;16:576–87.
4 Isselbacher EM, Preventza O, Hamilton Black III J, *et al*. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;80:e223–393.
5 Flower L, Arrowsmith JE, Bewley J, *et al*. Management of acute aortic dissection in critical care. *J Intensive Care Soc* 2023;1 to 10.
6 National Cardiac Audit Program, NCAP. 2020 annual report for patients and the public. https://www.nicor.org.uk/wp to content/uploads/2020/12/NCAP to Patient to and to Public to Report to 2020 to FINAL.pdf, 2023.
7 Mahase E. Half of patients with acute aortic dissection in England die before reaching a specialist centre. *BMJ* 2020;368:m304.
8 Gilbey T, Milne B, Kunst G, *et al*. Time critical diagnosis and transfer of patients with acute type a aortic dissection in the United Kingdom – a need to define standards? *J Cardiothorac Vasc Anesth* 2020;34:S54–5.
9 The Healthcare Safety Investigation Branch HSIB. Transfer of critically ill adults. 2023. Available: https://hsib to kqcco125 to media.s3.amazonaws.com/assets/documents/hsib_report_transfer_of_critically_ill_adults.pdf
10 The Royal College of Emergency Medicine (RCEM) & the Royal College of Radiologists (RCR UK) best practical guideline. Diagnosis of thoracic aortic dissection in the emergency departmen. Available: https://www.thinkaorta.net/_files/ugd/e855b1_574a8a5390e34557b36f59a13d1afae0.pdf [Accessed 14 Nov 2023].
11 The Healthcare Safety Investigation Branch, HSIB. Delayed recognition of acute aortic dissection. Available: https://www.england.nhs.uk/north to west/wp to content/uploads/sites/48/2020/02/hsib to report to delayed to recognition to acute to aortic to dissection.pdf [Accessed 14 Nov 2023].
12 Gilbey T, Milne B, Agarwal S, *et al*. Time critical diagnoses and transfers of patients with acute type A aortic dissection in the UK: national audit of current practice. *Anaesthesia* 2024;80:248–58.
13 Czerny M, Rylski B. Acute type A aortic dissection reconsidered: it's all about the location of the primary entry tear and the presence or absence of malperfusion. *Eur Heart J* 2021;43:53–5.
14 Varcoe RW, Clayton TC, Gray HH, *et al*. Impact of call-to-balloon time on 30-day mortality in contemporary practice. *Heart* 2017;103:117–24.
15 Oyama S, Ohuchi S, Arai T, *et al*. Chronic contained rupture of abdominal aortic aneurysm that developed from chronic abdominal aortic dissection. *J Vasc Surg Cases Innov Tech* 2021;7:280–2.
16 Carrel T, Sundt TM 3rd, von Kodolitsch Y, *et al*. Acute aortic dissection. *Lancet* 2023;401:773–88.
17 Greenland S, Daniel R, Pearce N. Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. *Int J Epidemiol* 2016;45:565–75.
18 Haukoos JS, Newgard CD. Advanced statistics: missing data in clinical research--part 1: an introduction and conceptual framework. *Acad Emerg Med* 2007;14:662–8.
19 Baliyan V, Parakh A, Prabhakar AM, *et al*. Acute aortic syndromes and aortic emergencies. *Cardiovasc Diagn Ther* 2018;8:S82–96.
20 Benedetto U, Sinha S, Dimagli A, *et al*. Decade-long trends in surgery for acute Type A aortic dissection in England: A retrospective cohort study. *Lancet Reg Health Eur* 2021;7:100131.
21 Sy RW, Bannon PG, Bayfield MS, *et al*. Survivor treatment selection bias and outcomes research: a case study of surgery in infective endocarditis. *Circ Cardiovasc Qual Outcomes* 2009;2:469–74.
22 Carvalho MC, Hochman SM, Milne WK, *et al*. Immediate Versus Delayed Cardiac Catheterization in Post-Arrest Patients Without ST Elevation Myocardial Infarction: Is Survivorship Bias an Important Influence?: March 2022 Annals of Emergency Medicine Journal Club. *Ann Emerg Med* 2022;79:315–6.