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Aortic centres should represent the standard of care for acute aortic syndrome

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Abstract

Background

Existing evidence suggests that patients affected by acute aortic syndromes (AAS) may benefit from treatment at dedicated specialized aortic centres. The purpose of the present study was to perform a meta-analysis to evaluate the impact aortic service configuration has in clinical outcomes in AAS patients.

Methods

The design was a quantitative and qualitative review of observational studies. We searched *PubMed/MEDLINE*, *EMBASE*, and *Cochrane Library* from inception to the end of December 2017 to identify eligible articles. Areas of interest included hospital and surgeon volume activity, presence of a multidisciplinary thoracic aortic surgery program, and a dedicated on-call aortic team. Participants were patients undergoing repair for AAS, and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were adopted for synthesizing hospital/30-day mortality.

Results

A total of 79,131 adult patients from a total of 30 studies were obtained. No randomized studies were identified. Pooled unadjusted ORs showed that patients treated in high-volume centres or by high-volume surgeons were associated with lower mortality rates (OR 0.51; 95% CI 0.46–0.56, and OR 0.41, 95% CI 0.25–0.66, respectively). Pooled adjusted estimates for both high-volume centres and surgeons confirmed these survival benefits (adjusted OR, 0.56; 95% CI 0.45–0.70, respectively). Patients treated in centres that introduced a specific multidisciplinary aortic program and a dedicated on-call aortic team also showed a significant reduction in mortality (OR 0.31; 95% CI 0.19–0.5, and OR 0.37; 95% CI 0.15–0.87, respectively).

Conclusions

We found that specialist aortic care improves outcomes and decreases mortality in patients affected by AAS.

Keywords [Acute aortic syndrome](#), [aortic dissections](#), [meta-analysis](#), [hospital volume](#), [surgeon volume](#), [quality of health care](#)

Introduction

The prevalence of diseases of the thoracic aorta has steadily increased in the last decade, with an overall global death rate of 2.78 per 100,000 inhabitants.¹ The highest rates have been observed in Australasia and Western Europe (8.38 and 7.68 per 100,000 inhabitants, respectively).¹ Admissions for acute aortic syndrome (AAS) have also increased worldwide, although the epidemiology is difficult to establish since these entities may only be diagnosed after a long period of subclinical development.²⁻⁵ Their natural history remains poorly understood, and errors in the diagnostic process may account for deaths otherwise attributed to other pathological conditions.^{2,3} In the face of this increasing problem, however, the optimal service configuration for the management of AAS patients has not been defined.⁶ Across centres and regions, a wide variation in treatment and outcomes has been reported.^{2,3,6-12} In Europe and the wider world, mortality for operated type A dissection ranges from 6% to 47.6%,^{3-10,11} whereas high-volume centres in the United States (US) have documented lower mortality rates, ranging from 2.8% to 12.1%.^{2,7,8} It is therefore critical that diseases of the thoracic aorta are recognized promptly and surgical care is expedited. International guidelines recommend that affected patients could benefit from high-volume surgical centres with focused multidisciplinary expertise in thoracic aortic surgery.^{2,3} Existing evidence suggests that AAS patients treated in multidisciplinary specialized aortic centres demonstrate significantly improved outcomes and decreased mortality.⁶ The purpose of the present review was to summarize the existing literature that relates to the organization of aortic services and the impact this may have on clinical outcomes in patients affected by AAS.

Methods

Search strategy and outcome measures

Electronic databases (*PubMed/MEDLINE*, *EMBASE*, and *Cochrane Library*) without date or language restriction were searched from inception to the end of December 2017. To supplement the electronic search, the 'first generation' reference lists of pertinent articles were reviewed. Search criteria, adopted keywords and MeSH terms used in relevant combinations are reported in the Supplementary Methods.

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Supplementary Material).¹³

Areas of interest included hospital volume activity, generally defined as annual number of major aortic operations performed, subdivided into low- or high-volume, surgeon volume, presence of a multidisciplinary thoracic aortic surgery program and a dedicated aortic team.⁶ The primary outcome of interest was all-cause mortality in hospital or within 30 days from index admission or procedure. Other secondary outcomes were not considered due to heterogeneity definitions.

Study selection, participants and interventions

Only studies considering the impact of aortic service configuration on outcome of patients affected by AAS were included, with no restriction on ethnicity or age. The target disease was an AAS involving the thoracic aorta as per definition of the international guidelines on diagnosis and management of patients with thoracic aortic disease (TAD).^{2,3} Studies with quantitative, qualitative and mixed-method approaches were included in order to obtain a comprehensive overview of the existing literature, while publications without such study design, including conference abstracts, reviews, editorials, and letters were excluded. Inclusion and exclusion criteria for qualitative/quantitative analyses were summarized according to the PICOS approach (Supplementary Table 1).

Titles, abstracts, and full-text articles were independently reviewed by two investigators against the specified inclusion criteria. Discrepancies were resolved through consensus and consultation with a third investigator.

Data collection, extraction and analysis

All included articles were independently appraised by two investigators, and study quality was assessed using the Newcastle–Ottawa Scale.¹⁴ Disagreements about critical appraisal were resolved by discussion. Overall, two reviewers extracted key data from the selected studies using standard dedicated proforma, while a third reviewer checked the collected data for completeness and accuracy. Full details on key study characteristics, including design, year of publication, sample size, aortic centre configuration, baseline patient demographics and outcome results were summarized.

Statistical analysis

Treatment effect on hospital/30-day mortality outcome is reported as an odds ratio (OR) with a 95% confidence interval (CI). Individual ORs and variance were computed using

number of events and sample size and pooled by using an inverse-variance method and random-effects model.¹⁵ Finally, to account for inherent patient selection bias related with an observational study design, individual risk-adjusted ORs for hospital/30-day mortality were obtained when reported, and pooled adjusted risk estimates were computed by using logarithmic transformation and a generic inverse-variance weighting method.^{6,16} The I^2 statistic was used to estimate the percentage of total variation across studies attributed to heterogeneity rather than chance. Suggested thresholds for heterogeneity were used, with I^2 values of 25% to 49%, 50% to 74%, and $\geq 75\%$, indicative of low, moderate, and high heterogeneity.¹⁷ Publication bias was evaluated using visual inspection of funnel plot asymmetry and by Egger's test.¹⁸ A p -value < 0.05 was used as the level of significance and 95% CIs were reported where appropriate. Statistical analysis was conducted using meta package for R (version 4.3-2; R Foundation for Statistical Computing, Vienna, Austria).^{19,20}

Results

Study design, selection and quality assessment

Among the 11,552 identified records, 90 were fully assessed for eligibility. A total of 30 studies that met all the eligibility criteria were finally considered for the qualitative systematic review, and 24 studies were included for the quantitative synthesis (meta-analysis). The PRISMA diagram is shown in [Figure 1](#). All the identified records (14 multi-centre and 16 single-centre) were retrospective observational studies, published between 1994 and 2017, comprising 79,131 patients (sample size range: 30 to 15,641).²¹⁻⁵⁰ No randomized nor prospective observational studies were retrieved. The main study characteristics are summarized in [Table 1](#) and in Supplementary Tables 2–4.

Among the studies included in the meta-analysis, seven analysed the impact of hospital volume on mortality, eight the impact of surgeon volume, and one the impact of both. However, the threshold definition for high- and low-volume hospital/surgeon volumes were observed widely heterogeneous, and in six cases no threshold definition was even provided ([Table 1](#)). A total of nine papers investigated the role of a specific aortic multidisciplinary program in improving the outcome following the AAS diagnosis, and three the role of a dedicated on-call aortic team.

Quality assessment indicated that 80% studies were at significant risk of bias (Newcastle-Ottawa scale (NOS) < 8 ; Supplementary Table 5).

Outcome measures

A total of 6864 and 9893 patients affected by AAS underwent surgery in high- and low-volume centres, respectively. Pooled unadjusted ORs showed that high-volume centres were associated with a 49% relative risk reduction in mortality when compared with low-volume centres with no heterogeneity among studies ($I^2 = 0\%$), and publication bias ($p = 0.10$; [Figure 2](#) upper panel and Supplementary Figure 1). Similarly, 1707 and 2961 patients were operated on by high-volume and low-volume surgeons, respectively. Pooled unadjusted ORs showed that patients treated by high-volume surgeons had a 59% relative risk reduction in mortality with a moderate heterogeneity among studies ($I^2 = 74\%$), and no publication bias ($p = 0.30$; [Figure 2](#) lower panel and Supplementary Figure 1). Overall, eight studies reported on adjusted effect size of hospital and surgeon volume on mortality, and pooled adjusted estimates of individual logarithmic ORs confirmed that both high-volume centres and high-volume surgeons were independently associated with a significantly reduced incidence of mortality (adjusted OR 0.66; 95% CI 0.45–0.96; $p = 0.031$, and OR 0.32; 95% CI 0.11–0.93; $p = 0.037$, respectively; [Figure 3](#)).

CI: confidence intervals; OR: odds ratio.

Centres that introduced a specific multidisciplinary aortic program also reported a significant reduction in mortality in comparison with the prior patient management (OR 0.31; 95% CI 0.19–0.51). A moderated heterogeneity was observed ($I^2 = 50\%$), but no publication bias ($p = 0.67$; [Figure 4](#) upper panel). Finally, better survival after AAS surgery was also observed in centres that introduced a dedicated on-call aortic team (OR 0.37; 95% CI 0.15–0.87). A significant heterogeneity was noted, but no publication bias ($I^2 = 83\%$ and $p = 0.18$, respectively) ([Figure 4](#) lower panel).

Ao: aortic; CI: confidence intervals; OR: odds ratio.

Discussion

Our results suggest that designated specific aortic centres reduce the mortality of patients undergoing surgical repair for AAS, and should represent the standard of care in this population setting. Our data also demonstrated that mortality varies widely across

hospitals and surgeons, and centres with and without a dedicated specialized aortic program.

However, despite this large body of evidence, patients affected by complex aortic diseases are still predominantly treated at hospitals where few complex aortic procedures are performed and where a low level of expertise is present. An analysis of data from the UK national cardiac surgery database clearly demonstrates higher mortality rates in centres where the volume of cases is low, even for elective aortic surgery.⁶ Currently, there is no accepted minimum service specification for the delivery or commissioning of care for patients with aortic disease, especially those affected by AAS.^{3,4}

In 1984, Albrink et al.²¹ firstly demonstrated the importance of designated thoracic programs in reducing mortality after traumatic aortic transection. Operations performed by designated high-volume thoracic surgeons produced a dramatic reduction in mortality (7% versus 50%) when compared with low-volume general surgeons. More recently, Andersen et al.³³ analysed the outcomes following acute type A aortic dissection repair after the implementation of a multidisciplinary thoracic aortic surgery program, confirming even more significantly the above survival benefits. Operative mortality after this implementation fell from 33.9% to 2.8%, thereby approximating the results observed after conventional elective cardiac surgery.³³

Operations on the thoracic aorta (mainly on the aortic arch and descending thoracic aorta) are certainly challenging surgical procedures, with prolonged learning curves, for individuals and surgical teams.^{22,33,34} Previous data on patients with abdominal aortic aneurysm, a complex pathology with subsequent morbidity and mortality similar to aortic disease, have confirmed that volume and centre experience are of crucial importance to subsequent outcomes, with a 13% estimated reduction in the odds of mortality for each additional 20 cases performed.⁵¹ However, if hospital volume and surgeon experience are intuitive factors influencing postoperative outcomes, other important factors should not be neglected. Our systematic review showed that availability and coordination of critical care, imaging and other treatment modalities are additional crucial elements in the care of AAS patients. Specifically, the availability of a designated 'aortic team' for the treatment of AAS patients has been proved to influence clinical postoperative results.⁴⁸⁻⁵⁰ Bashir et al.⁴⁹ revising their experience after the introduction of dedicated on-call rota for acute type A aortic dissection observed that this surgical reorganization resulted in lower early and late mortality. Patients who underwent surgical repair in the post-dissection rota era

were less likely to suffer in-hospital mortality (30% versus 13.3%), and similar benefits were observed in the 5-year survival rate.⁴⁹ Implementation of diagnostic aortic protocols, regionalization of services, and inter-hospital coordination are other important factors in the care of AAS patients.^{26,27,29,50} Davies et al.²⁶ firstly observed a significant increase in volume (referrals) and reduction in time to definitive treatment for AAS patients after initiation of an acute aortic treatment centre, and a prompt diagnosis and proper treatment is crucial since patients with acute type A dissection who do not receive treatment die at a rate of 1–2% per hour during the first day and almost half die by one week.⁵² Similarly, Harris et al., after the introduction of a standardized protocol within a regional hospital network, observed a drastic reduction in the length of time to both diagnosis and surgical repair (median time reduction of 30% and 50%, respectively) with improved survival postoperative outcomes.²⁷ The rate of follow-up care in the outpatient setting also improved, from 75% before the protocol to 85% after the protocol.²⁷

Similar data have been observed in other cardiovascular procedures, where hospital and surgical expertise has been increasingly recognized as an important contributor to operative outcomes.⁵³

As a matter of fact, an evidence-based hospital referral as a key part of safety standards to reduce nationwide mortality for several procedures, including coronary artery bypass grafting and aortic valve replacement has been adopted by the Leapfrog Group (Washington, DC, USA).^{54,55} Improved surgical results and outcomes have been also observed in specialized centres for mitral valve diseases, leading international guidelines to recommend having mitral valve repairs at heart valve centres of excellence where the likelihood of successful repair is high and comorbidity low.^{56–59}

Limitations

The present study has limitations. First, owing the emergent nature of AAS, no randomized trials of abdominal aortic aneurysm interventions were retrieved, therefore limiting our qualitative and quantitative analysis to retrospective observational studies only, often with a limited sample size.^{21–50} Retrospective studies are subject to confounders and bias, possibly resulting in a decline in the power of our meta-analysis. The majority of collected data were derived from a simple univariate comparison analysis, therefore limiting the opportunity to perform sub-group analysis, especially with reference to the different entities included in the wide definition of AAS. It is well known that

management, and treatment approaches with related outcomes largely vary among acute type A and B dissections, intramural hematoma, and penetrating ulcers.¹² Second, due to the nature of these life-threatening diseases, several patients who died before the diagnosis or those felt inappropriate for high-risk surgical approaches were not considered in the included studies, therefore limiting the recommendation of the present study for this subgroup of individuals, which is not negligible. Bottle et al.⁶ in their nationwide analysis of patients affected by thoracic diseases showed that 30% of aortic patients are refused surgery. Third, definitions of high- and low-volume centres and/or surgeons are heterogeneously defined across the included studies, and the great majority of these reports originate from small centre experiences. Unfortunately, international guidelines are lacking in terms of agreed service specification for TAD, and of recognized recommendations for aortic service organizations, hindering the establishment of clear and well accepted definitions of high- and low-volume thresholds.^{3,4} The present systematic review with meta-analysis is an attempt to overcome this knowledge gap.

Conclusion

Specialist aortic care improves outcomes and decrease mortality in patient affected by AAS. Aortic centres with multidisciplinary expertise should constitute the standard of care for this population of patients.

Author contribution

GM and DM contributed equally to this work. GM and BVD had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Other contributions were as follows: Study concept and design: GM, AM, DM and BVD; Acquisition of data: GM and BVD; Analysis and interpretation of data: GM and BVD; Drafting of the manuscript: GM and AM; Critical revision of the manuscript for important intellectual content: GM, RG, FN, UB; Paper supervision: GM, FN; Language revision: AA.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Characteristics of the studies included in the qualitative systematic review.

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram regarding article selection for the systematic review and meta-analysis.

Figure 2. Forest plot with unadjusted risk estimates for in-hospital/30-day mortality in high-volume versus low-volume hospitals (upper panel) and in high-volume versus low-volume surgeons (lower panel).

Figure 3. Forest plots with adjusted risk estimates for in-hospital/30-day mortality in high-volume versus low-volume hospitals (upper panel) and low-volume surgeons (lower panel).

Figure 4. Forest plots with unadjusted risk estimates for in-hospital/30-day mortality in hospitals with dedicated multidisciplinary standardized care for acute aortic syndromes (before and after implementation, upper panel) and hospitals with dedicated on-call aortic team (lower panel).