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Clinical Heterogeneity in Coarctation of the Aorta: Data-Driven Morbidity Sub-Phenotypes from a Nationwide Registry

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Abstract

Background/Objectives: Coarctation of the aorta (CoA) is associated with lifelong risks of residual or recurrent arch obstruction, hypertension, ventricular remodeling, and aortic-valve disease. We characterized documented morbidity and procedure-entry burden in a nationwide CoA registry cohort and assessed recurring morbidity patterns and age-dependent sex differences. **Methods**: Patients with CoA as the primary congenital diagnosis were identified in the German National Register for Congenital Heart Defects (NRCHD). Congenital, acquired cardiovascular, and extracardiac diagnoses, composite morbidity indicators, and procedure-source entries were analyzed descriptively and by age, CHD complexity, documented bicuspid aortic-valve (BAV) status, and sex. Exploratory latent class analysis characterized recurring cross-sectional morbidity patterns, and logistic regression assessed sex-by-age interactions. **Results**: Among 2720 patients (61.1% male; median age 17.85 years), BAV was documented in 34.4%, and a specific aortic-valve morphology in 65.6%. Arch-obstruction and pressure-load burden were documented in 27.7% and 27.2%, respectively, and were more frequent in older age groups. At least one operation- or catheter-intervention-source entry was present in 82.1% of patients. Five latent classes were identified: low documented burden (51.8%), arch-hypertension/pressure-load (11.4%), complex multilevel (18.9%), BAV/valve-aortopathy (13.1%), and systemic-hypertension/recurrent-obstruction (4.7%). Classification entropy was 0.661, and 25.3% of patients had a maximum posterior class probability below 0.70. Male sex was associated with higher pressure-load burden, and the sex-by-age interaction was significant

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in restricted cubic spline models ($p = 0.004$), whereas corresponding interactions were not supported for arch-obstruction burden or aortic-valve dysfunction excluding BAV morphology. **Conclusions**: CoA in routine clinical care is not a uniform condition but encompasses recurring patterns of documented morbidity centered on valve-aortopathy, complex congenital anatomy, and pressure-load or recurrent-obstruction disease. Documented BAV marked a particularly strong valve-morbidity phenotype, while pressure-load morbidity showed a distinct age-dependent association with sex. These findings provide a clinically interpretable framework for phenotype-oriented lifelong follow-up and future longitudinal validation, while reflecting registry-documented rather than systematically screened morbidity.

Keywords: coarctation of the aorta (CoA); hypertension; bicuspid aortic valve (BAV); latent class analysis; morbidity sub-phenotypes; sex differences

1. Introduction

Coarctation of the aorta (CoA) is a congenital left-sided obstructive lesion with a broad clinical spectrum ranging from critical neonatal obstruction to later presentation with systemic hypertension, diminished femoral pulses, cardiac murmurs, or incidental imaging findings. Although traditionally conceptualized as narrowing of the proximal descending thoracic aorta, CoA is increasingly understood as part of a broader arch, vascular, and left-heart phenotype. Anatomy, age at presentation, associated lesions, treatment strategy, and long-term vascular biology all influence clinical outcome [1–3].

The congenital substrate of CoA frequently extends beyond the narrowed aortic segment. Bicuspid aortic valve (BAV), aortic-arch hypoplasia, patent ductus arteriosus (PDA), ventricular septal defects, and other left-sided obstructive or aortic-valve lesions are common associated malformations in CoA cohorts. The association between CoA and BAV is particularly important, reflecting a shared developmental and aortopathic context and contributing to later risks of aortic stenosis, aortic insufficiency, aortic dilation, and valve or aortic interventions [4,5].

Treatment strategies for CoA include surgical and catheter-based approaches, depending on the severity and anatomical characteristics. In addition, repair of CoA is not synonymous with cure. Long-term studies and reviews have consistently identified residual or recurrent obstruction, persistent or late-onset hypertension, aneurysm formation, aortic-valve dysfunction, left ventricular hypertrophy, and the need for re-intervention or re-operation as important late problems after repair [6–11]. Hypertension after CoA repair is common, may progress with longer follow-up, and may be underestimated when ambulatory or exercise blood pressure measurements are not systematically performed [3,12–14]. These long-term risks support guideline recommendations for lifelong surveillance, including assessment of blood pressure, imaging of the repaired or native arch and thoracic aorta, evaluation of ventricular remodeling, and monitoring of associated aortic-valve disease [2,15,16].

Sex-related differences are increasingly recognized across congenital and acquired cardiovascular disease, but sex-specific evidence in CoA remains limited and partly inconsistent. Registry-based adult data suggest that later interventions may differ by sex, whereas recent adult data in isolated CoA reported similar daytime blood pressure and atherosclerotic risk profiles in men and women but less nocturnal blood pressure dipping, higher pulmonary vascular indices, and higher all-cause and cardiovascular mortality in women [17,18]. These findings indicate that sex may influence different aspects of CoA

morbidity and outcome, while also underscoring the need for cautious interpretation of registry-based sex comparisons.

Large real-world registry datasets are valuable because much of the published evidence derives from single-center surgical, interventional, or adult congenital heart disease follow-up cohorts. Beyond a diagnosis-by-diagnosis description, we addressed two questions that have received little attention in CoA cohorts: whether heterogeneous registry-documented morbidity organizes into recurring data-driven patterns, and whether associations between sex and documented morbidity vary across age. We therefore examined demographic characteristics, congenital substrate, acquired and extracardiac morbidity, diagnostic burden, registry-coded morbidity composites, procedural history, and exploratory patterns by age group, CHD complexity, documented BAV status, and sex. We additionally performed a latent class analysis of documented morbidity patterns and examined age-by-sex interactions for composite morbidity. Because registry diagnoses reflect what is documented in routine care rather than what systematic screening would detect, we also considered what the gap between registry-documented and intensively screened morbidity implies.

2. Materials and Methods

2.1. Data Source and Study Design

This registry-based observational study used data from the National Register for Congenital Heart Defects (NRCHD) in Germany. The analytical dataset comprised patients with plausibility-checked date variables and available registry diagnosis fields. The present study used a database snapshot extracted on 1 April 2026. The source dataset comprised 46,994 registered individuals. For the present analysis, inclusion was restricted to patients in whom coarctation of the aorta (CoA) was coded as the primary congenital diagnosis, hereafter referred to as the CoA-primary-diagnosis cohort.

Before application of the prespecified historical date-plausibility criterion, 2976 patients had CoA documented as the primary congenital diagnosis. Patients were excluded if at least one of the checked diagnosis or event dates preceded the recorded date of birth; missing dates alone did not trigger exclusion. This criterion identified 256 patients, leaving 2720 patients in the final analytical cohort. A further 1117 registry participants had CoA documented as an associated congenital diagnosis but not as the primary congenital diagnosis and were not included in the primary analyses. Patients without any documented coarctation diagnosis were likewise not included. The cohort-selection process is illustrated in Figure 1.

The National Register for Congenital Heart Defects

The NRCHD is an ongoing, nationwide, person-based registry for patients with congenital heart disease (CHD) in Germany and has enrolled patients since its establishment in 2003. It supports clinical, epidemiological, health-service, and long-term outcome research across the full spectrum of CHD. Registration is voluntary and based on informed consent. Patients may enter the registry during childhood or adulthood, and registry information can be updated over time when new documentation is provided.

Previous work has assessed the clinical representativeness of the NRCHD overall and has used the registry for nationwide studies of CHD populations and procedure-related outcomes [19–21]. However, representativeness of the specifically selected CoA-primary-diagnosis cohort cannot be assumed. In this manuscript, the term nationwide registry cohort refers to the geographic scope of the NRCHD rather than complete population-based ascertainment of all patients with CoA in Germany.

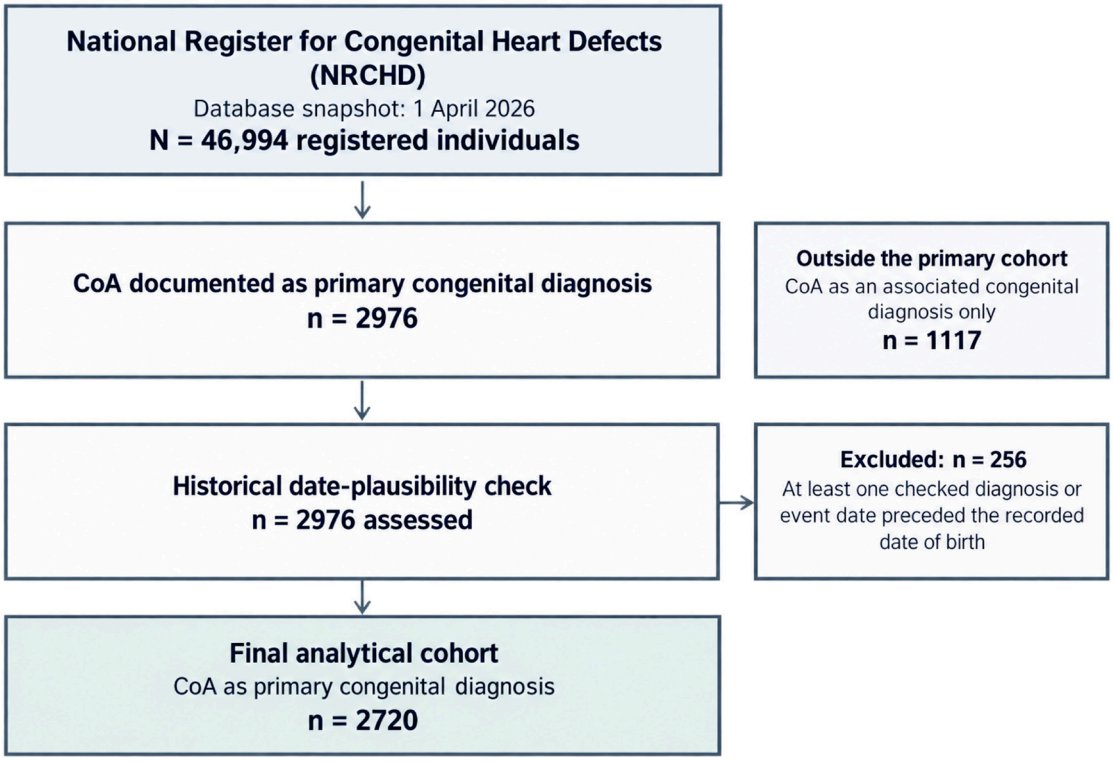


Figure 1. Cohort-selection flow diagram. Only patients with coarctation of the aorta (CoA) coded as the primary congenital diagnosis were eligible for the primary analysis. A further 1117 patients had CoA documented only as an associated congenital diagnosis and were not included. Patients were excluded if at least one checked diagnosis or event date preceded the recorded date of birth; missing dates alone did not trigger exclusion.

For the present study, a pseudonymized analytical extract from the NRCHD medical database was used. The analysis included registry master variables, diagnosis-specific coded fields, and repeated procedure fields. Treating-center or site identifiers were not available in the analytical dataset and were not analyzed; such information may also change over time as patients change physicians or institutions and is not necessarily updated completely in a voluntary registry. Because registry participation and diagnostic documentation are not equivalent to systematic population screening, all diagnosis and procedure variables were interpreted as documented registry information.

2.2. Variables and Cohort Characteristics

Sex, vital status, CHD complexity, and main congenital diagnosis group were obtained from registry master variables. Sex was coded as male or female according to the medical database entries. Vital status was coded as alive or deceased. CHD complexity was assigned according to the Warnes classification [22] using the registry complexity variable. The classification reflects the overall congenital phenotype rather than the isolated primary lesion: a simple lesion may be assigned to a moderate or complex category and a moderate lesion to a complex category when the overall congenital phenotype warrants a higher classification, whereas a severe/complex lesion is not downgraded to a lower complexity category. Analyses by CHD complexity were therefore interpreted descriptively as comparisons of registry-defined phenotypes rather than as estimates of an independent exposure effect.

Age at observation was calculated from date of birth to a patient-specific reference date. For deceased patients, the date of death was used as the reference date. For all other patients, the date of last documented contact was used. Age was expressed in years. These

cross-sectional age measures were used to describe age-associated documentation patterns and do not represent longitudinal follow-up duration or time since CoA repair.

2.3. Diagnostic Coding and Diagnosis Domains

Documented diagnoses were derived from the diagnostic fields available in the registry master dataset. For congenital cardiac diagnoses, each diagnosis entry could include an IPCCC-based code, the corresponding diagnosis text, and, where available, the date of diagnosis. Acquired cardiac or cardiovascular diagnoses were documented analogously using diagnosis code fields, diagnosis-text fields, and optional diagnosis dates. Extracardiac diagnoses were documented using ICD-10-based code fields, diagnosis-text fields, and optional diagnosis dates. A valid documented code was retained even when the accompanying diagnosis-text field was empty.

The primary congenital diagnosis was defined using IPCCC-based coding, and associated congenital cardiac diagnoses, acquired cardiac diagnoses, operations, and catheter interventions were likewise represented in structured registry fields [23]. Existing registry-based diagnosis mappings were retained. Valid code-only diagnosis entries were incorporated using the same analytical category definitions as text-documented entries; where a code-only value had not previously been mapped, the current IPCCC long list was used only to assign that value to an analytical category.

Because the diagnostic and procedural variables inform the clinical complexity classification, analyses by CHD complexity were interpreted descriptively as comparisons of registry-defined phenotypes rather than as analyses of independent risk factors.

Diagnosis entries were transformed into diagnosis-specific binary indicator variables. A patient was coded as documented for a given congenital cardiac, acquired cardiac or cardiovascular, or extracardiac category if the respective finding was identified by diagnosis text or by a valid mapped code in any corresponding diagnosis field. Multiple entries mapping to the same analytical category were counted once per patient. If no corresponding documentation was present, the indicator was coded 0; this denotes no registry documentation of the finding and not verified clinical absence. The denominator for documentation frequencies of binary diagnosis indicators was therefore the full CoA-primary-diagnosis cohort unless otherwise stated. For most binary diagnosis indicators, the available registry fields do not distinguish between a condition that was specifically assessed and found absent and a condition that was not assessed or documented. Consequently, variable-specific rates of true clinical missingness cannot be reliably estimated for these indicators, and the analyses are based on documentation frequencies rather than verified disease absence.

Aortic-valve morphology was handled separately from morbidity counts. Documented tricuspid aortic-valve morphology was retained as a morphology item but was not counted as an associated congenital diagnosis. For morphology-specific analyses, patients without a specific documented valve morphology were retained as an unspecified group rather than assumed to have a tricuspid valve; no morphology values were imputed. Missingness in analyses requiring timing primarily concerned diagnosis or procedure dates, and such analyses were restricted to patients with available and plausible dates. Throughout the manuscript, registry-derived frequencies are therefore interpreted as documented morbidity or findings rather than systematically screened prevalence.

2.4. Prevalence Analyses of Associated Diagnoses

Within the CoA-primary-diagnosis cohort, documentation frequencies were summarized separately for associated congenital cardiac diagnoses or morphology-coded findings, acquired cardiac or cardiovascular diagnoses, and extracardiac diagnoses. For each diagnosis-specific binary indicator, the numerator was the number of patients in

whom the respective diagnosis or finding was documented in at least one relevant registry field, using either a valid coded entry or the corresponding diagnosis text according to the registry-derived mapping. The denominator was the full CoA-primary-diagnosis cohort unless a more specific documentation denominator is stated explicitly. A value of zero therefore denotes that the diagnosis was not documented in the available registry fields and should not be interpreted as verified clinical absence.

Diagnosis variables were ranked in descending order by the number of patients with documentation of the respective finding. Main-manuscript tables focused on the most frequently documented findings, using presentation thresholds of at least 5% for associated congenital and acquired diagnoses and at least 1% for extracardiac diagnoses. These thresholds were used only for table presentation and did not determine whether a diagnosis was retained in the underlying analytical dataset.

2.5. Age-Stratified Analyses

For age-stratified analyses, patients were categorized according to age at death or last documented contact into five groups: 0–5 years, 6–11 years, 12–17 years, 18–29 years, and 30 years or older.

Age-stratified analyses focused on selected acquired cardiovascular diagnoses considered clinically relevant in CoA, including residual coarctation, recurrent coarctation, hypertension related to aortic-arch obstruction, arterial hypertension, left ventricular hypertrophy, and acquired aortic insufficiency. These analyses were interpreted as cross-sectional age-stratified patterns of registry-documented morbidity. They were not used to estimate incidence, within-patient progression, or longitudinal transition between morbidity states.

2.6. Analyses by Congenital Heart Disease Complexity

Selected congenital and acquired diagnosis indicators were compared descriptively across the registry-defined moderate and complex CHD categories. The congenital variables included documented BAV, aortic-arch hypoplasia, patent ductus arteriosus, ventricular septal defects, congenital valvular aortic stenosis, and congenital aortic insufficiency. The acquired variables included hypertension related to aortic-arch obstruction, arterial hypertension, residual coarctation, recurrent coarctation, left ventricular hypertrophy, and acquired aortic insufficiency.

Because the Warnes-based complexity classification reflects the overall congenital phenotype and may incorporate anatomical features that are also represented by the diagnosis indicators being compared, these analyses were treated as descriptive phenotype comparisons rather than as estimates of an independent effect of CHD complexity.

2.7. Bicuspid Aortic-Valve Subgroup Analysis

In the primary BAV subgroup analysis, patients with documented BAV were compared with patients without documented BAV with respect to selected congenital and acquired cardiovascular diagnoses. The latter group includes patients in whom a different valve morphology was documented as well as patients in whom no specific aortic-valve morphology was documented; it should therefore not be interpreted as a confirmed tricuspid-valve reference group.

The compared diagnoses included congenital valvular aortic stenosis, congenital aortic insufficiency, aortic-arch hypoplasia, acquired aortic insufficiency, residual coarctation, recurrent coarctation, hypertension related to aortic-arch obstruction, arterial hypertension, and left ventricular hypertrophy.

To address uncertainty in valve-morphology documentation, a sensitivity analysis was restricted to patients with documented BAV or documented tricuspid aortic-valve morphology. BAV was defined by the registry BAV indicator; documented tricuspid mor-

phology was defined by either the registry indicator for tricuspid aortic-valve morphology or the indicator for asymmetric opening of a tricuspid aortic valve. Patients with unicuspid morphology or without a specific documented morphology were not included in this sensitivity comparison. Unknown morphology was not imputed.

2.8. Composite Morbidity Indicators

Three composite morbidity indicators were derived as descriptive summaries of clinically related registry-documented findings and were not treated as validated clinical endpoints or formal severity scores.

The broad aortic-arch burden indicator was coded as documented if at least one of the following was documented: residual coarctation, recurrent coarctation, or hypertension related to aortic-arch obstruction. The pressure-load burden indicator was coded as documented if at least one of the following was documented: hypertension related to aortic-arch obstruction, arterial hypertension, or left ventricular hypertrophy. Thus, hypertension related to aortic-arch obstruction intentionally contributes to both composites, and the two outcomes are not statistically independent.

The broad aortic-valve burden indicator was coded as documented if BAV, congenital valvular aortic stenosis, congenital aortic insufficiency, or acquired aortic insufficiency was documented. Because this indicator contains BAV morphology by definition, a separate non-circular aortic-valve dysfunction indicator excluding BAV was used for analyses in which documented BAV served as an explanatory variable. This indicator comprised congenital valvular aortic stenosis, congenital aortic insufficiency, and acquired aortic insufficiency.

To evaluate whether findings involving the broad arch composite were driven by its shared hypertension component, an additional anatomic arch sensitivity outcome was defined by documented residual or recurrent coarctation only. This narrower outcome was used as a sensitivity analysis and did not replace the prespecified broad composite.

Exploratory logistic regression assessed associations with the composite outcomes using the prespecified covariates sex, age per 10 years, CHD complexity, and documented BAV where applicable. For the non-circular aortic-valve dysfunction outcome, BAV was retained as the morphology variable of interest. Sensitivity analyses restricted to documented BAV versus documented tricuspid morphology used the same outcome definitions while excluding patients with unspecified morphology.

2.9. Diagnostic Burden per Patient

For each patient, diagnostic burden was summarized separately for associated congenital, acquired cardiovascular, and extracardiac domains by counting distinct registry-documented analytical categories once per patient. A category could be established by the registry-derived text mapping or by a valid code-only entry mapped to the same analytical category. Repeated documentation of the same category did not increase the patient-level count.

The associated congenital count excluded documented tricuspid aortic-valve morphology because this variable represents valve morphology rather than an additional congenital disease. The resulting counts should therefore be interpreted as numbers of distinct registry-documented diagnostic or finding categories rather than as numbers of independent diseases.

2.10. Procedural History

Surgical and catheter-based interventions were assessed using the repeated procedure fields available in the registry dataset. Operation entries were identified from operation code fields and corresponding free-text fields; catheter-intervention entries were identified analogously. A procedure slot was counted as a documented entry if either its code field or

its corresponding free-text field was populated. These variables therefore represent registry-documented procedure entries and not adjudicated counts of unique clinical procedures.

For each patient, we derived indicators for any documented operation entry, any documented catheter-intervention entry, and any documented operation or catheter-intervention entry. We also counted operation entries, catheter-intervention entries, and combined entries. Multiple-entry indicators were defined as two or more documented entries within the corresponding source category. Entries with missing dates were not collapsed. Distinct entries recorded on the same calendar day were retained because they may represent separate components, procedures, or documentation elements and could not be clinically adjudicated from the registry fields alone. To assess potential duplicate documentation, an exact duplicate was defined as an entry with the same patient, procedure source, stored code, free-text entry after trimming leading and trailing spaces, and stored procedure date. Exact duplicates were collapsed only for this sensitivity assessment.

2.11. Timing of First and Second Documented Procedure

For the timing variables, the earliest documented operation date and the earliest documented catheter-intervention date were identified for each patient, and the earlier of these was defined as the first documented procedure date. Age at first documented operation, catheter intervention, and any procedure was calculated from date of birth and expressed in years. These timing variables should be interpreted as timing of documented procedure-date entries rather than clinically adjudicated timing of a unique index repair.

Second distinct documented procedure dates were derived analogously. For operations and catheter interventions separately, the second date was defined as the earliest documented date after the first documented date of the same procedure type. For combined procedural history, the second distinct documented procedure date was defined as the earliest operation or catheter-intervention date after the first documented operation or catheter-intervention date and could therefore represent a mixed sequence such as one operation followed by one catheter intervention, or vice versa.

Procedure dates were considered plausible if date of birth and procedure date were available, the calculated age at procedure was between 0 and 100 years, and the procedure date did not occur after the patient-specific reference date. For second procedure dates, the interval between the first and second distinct dates additionally had to be greater than zero. Because the registry fields do not reliably identify a clinically adjudicated index CoA repair or complete longitudinal treatment history, treatment era and time since repair were not derived.

2.12. Potential CoA-/Arch-Related Procedure Classification

In an exploratory procedure analysis, long-format operation and catheter-intervention datasets were created from the repeated procedure fields. For each documented entry, procedure code and free-text label were combined into a procedure key and summarized at entry and patient level.

Potential CoA-/aortic-arch-related operation entries were identified using the prespecified conservative code/text criteria indicating coarctation or aortic-isthmus disease, including the text strings “coarct”, “coarkt”, “aortenisthmus”, “isthmusstenose”, “recoarct”, or “re-coarct”, and the IPCCC procedure-code family “12.18.” Because the 12.18 family also contains aortic-arch procedures that are not necessarily isolated CoA repairs, these entries were labeled potential CoA-/aortic-arch-related rather than confirmed CoA procedures.

Potential CoA-related catheter-intervention entries were classified using the same CoA- and aortic-isthmus-specific text terms, without classifying nonspecific terms such as “balloon”, “stent”, or isolated “ista” as sufficient evidence. The resulting distinct code/text

keys were manually reviewed for plausibility. This classification was not used to infer index repair, reintervention, procedural success, or clinical indication.

2.13. Procedure Analyses

Within the CoA-primary-diagnosis cohort, we summarized the proportions of patients with any documented operation entry, catheter-intervention entry, or either type of entry; the number of documented entries; multiple-entry indicators; and plausible first and second documented procedure dates. Procedure-entry burden was described overall and by age group, CHD complexity, documented BAV status, and sex. Potential CoA-/aortic-arch-related operation entries and potential CoA-related catheter-intervention entries were summarized overall and in selected subgroups.

No proportion of entries was classified as index repair versus reintervention because the available information was insufficient for reliable adjudication.

2.14. Sex-Stratified and Age-by-Sex Analyses

Exploratory sex-stratified analyses compared male and female patients with respect to age, vital status, CHD complexity, selected congenital and acquired diagnoses, extracardiac obesity, composite morbidity indicators, diagnostic-category counts, procedural history, multiple documented procedure-entry indicators, and potential CoA-/arch-related procedure-entry indicators. Because this was a registry-based descriptive study, these comparisons were interpreted as exploratory associations with documented morbidity rather than evidence of biological sex effects.

To contextualize unadjusted sex-stratified findings, logistic regression models were fitted for the broad arch-obstruction burden, pressure-load burden, and the non-circular aortic-valve dysfunction outcome. The prespecified covariates were sex, age at death or last documented contact expressed per 10 years, registry-defined CHD complexity, and documented BAV where applicable. Age was entered without centering in the primary linear models. Results are reported as odds ratios with 95% confidence intervals.

To assess whether the association between sex and documented morbidity varied with age, the models were extended with a sex-by-age interaction term (male sex $\times$ age per 10 years). The interaction was evaluated using both the coefficient test and a likelihood-ratio comparison with the corresponding model without the interaction.

Because a linear age term may be insufficient across the broad age range, a sensitivity analysis modeled age using a restricted cubic spline with four knots at the 5th, 35th, 65th, and 95th percentiles of the age distribution. The same knots were used across outcomes and in the morphology-restricted BAV-versus-tricuspid-valve sensitivity subset. The joint sex-by-age interaction was evaluated across the linear and two nonlinear spline interaction terms using a three-degree-of-freedom likelihood-ratio test. Individual spline coefficients were not interpreted as clinical odds ratios.

A separate sensitivity model additionally included the number of other documented acquired diagnoses after excluding the components of the pressure-load composite. This variable was treated only as a limited proxy for documentation intensity and not as proof that documentation bias had been removed, because documentation depth may itself be related to age, morbidity, and healthcare contact. Such adjustment may also introduce overadjustment or collider bias.

2.15. Vital Status Analyses

Among deceased patients in the CoA-primary-diagnosis cohort, age at death was summarized descriptively using mean, median, and interquartile range. Vital status was also cross-tabulated by CHD complexity with counts and row percentages. The corre-

sponding Pearson chi-square test was exploratory and was not included in the prespecified multiplicity families used for the main categorical subgroup comparisons.

2.16. General Statistical Analysis

Categorical variables were summarized as counts and percentages. Continuous variables were summarized using means, standard deviations, medians, interquartile ranges, and 95% confidence intervals where appropriate. Categorical subgroup comparisons were evaluated using Pearson chi-square tests. Diagnosis and procedure-entry counts were summarized descriptively. Independent-samples t tests were used only for age at the patient-specific reference date and age at the first plausible documented procedure date.

For two-group categorical comparisons, absolute prevalence differences are reported in percentage points with 95% Newcombe–Wilson hybrid confidence intervals without continuity correction. For five-level age-group comparisons, Pearson chi-square tests remained omnibus tests and no post hoc pairwise testing was performed.

Benjamini–Hochberg false-discovery-rate correction was applied separately within the five predefined exploratory comparison families: age-group comparisons, CHD-complexity comparisons, BAV-documentation comparisons, sex comparisons, and potential CoA-/arch-related procedure comparisons. Adjusted q values were calculated from unrounded p values and are reported in Supplementary Table S1. Confidence intervals were not multiplicity-adjusted. All subgroup analyses were considered exploratory.

All non-LCA analyses were conducted using IBM SPSS Statistics (version 25; IBM Corp., Armonk, NY, USA). Statistical significance was not used as a criterion for variable inclusion, exclusion, or post hoc model selection.

2.17. Latent Class Analysis of Morbidity Sub-Phenotypes

To examine whether registry-documented morbidity organized into recurring cross-sectional patterns, we performed an exploratory latent class analysis using a latent class mixture model for binary indicators. The analysis was intended to characterize patterns of documented morbidity and not to define fixed biological phenotypes or longitudinal disease stages.

The input comprised 17 prespecified, clinically selected congenital and acquired indicators reflecting major structural and acquired domains relevant to CoA: bicuspid aortic valve, aortic-arch hypoplasia, patent ductus arteriosus, congenital valvular aortic stenosis, congenital aortic insufficiency, patent foramen ovale, secundum atrial septal defect, perimembranous and muscular ventricular septal defects, hypertension related to aortic-arch obstruction, residual coarctation, recurrent coarctation, left ventricular hypertrophy, arterial hypertension, acquired aortic insufficiency, complete right bundle branch block, and ascending aortic dilation. For each indicator, a value of zero denoted no documentation of the respective finding in the available registry fields and did not imply verified clinical absence.

Models with one to six classes were estimated by maximum likelihood using the expectation–maximization algorithm. For models with two to six classes, 100 random starts were used to reduce the risk of local optima. Models were estimated with a maximum of 20,000 iterations and a convergence tolerance of 1×10^{-8}. The number of classes was selected by considering the Bayesian information criterion (BIC), classification entropy, convergence, recovery of the best log-likelihood across random starts, class size, and clinical interpretability [24].

Patients were assigned to the class with the highest posterior probability for descriptive presentation. Classification uncertainty was assessed using the distribution of maximum posterior probabilities, including the proportion of patients with a maximum posterior probability below 0.70. Because class assignment was probabilistic, class-based compar-

isons were interpreted descriptively. As a sensitivity check, class characteristics were also reviewed among patients with a maximum posterior probability of at least 0.70. This threshold was used to assess classification uncertainty and not as an inferential correction or external validation.

Two sensitivity analyses were performed to assess the robustness of the class structure. First, models with four and five classes were re-estimated after excluding patent foramen ovale and complete right bundle branch block from the indicator set. Second, four- and five-class models were estimated in the subgroup with documented bicuspid or tricuspid aortic-valve morphology. These analyses were used to examine whether the class structure depended materially on the two relatively nonspecific indicators or on incomplete valve-morphology documentation.

Age, sex, CHD complexity, vital status, and procedure-entry burden were not included as latent class indicators. These variables were summarized descriptively across modal classes to aid clinical interpretation.

Latent class models were estimated in R (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria) and the poLCA package (version 1.6.0.1) [25]. All other analyses were conducted using IBM SPSS Statistics (version 25; IBM Corp., Armonk, NY, USA).

2.18. Ethical Statement

Participation in the NRCHD is voluntary and based on written informed consent obtained at the time of registration from the patient and/or the parents or legal guardians, as applicable. This consent includes the use of medical data stored in the registry for scientific analyses and for publication of the resulting research findings. The present study did not involve the recruitment of a new cohort, and no participants were contacted or enrolled specifically for this analysis. Instead, a secondary analysis of anonymized data from the NRCHD was performed. Analyses of data collected within the NRCHD are covered by the currently valid general ethics approval of the registry issued by the Ethics Committee of Charité-Universitätsmedizin Berlin, Ethics Committee at Campus Virchow-Klinikum. The relevant protocol number is EA2/040/23. The ethics vote was issued on 6 March 2023; fulfillment of the corresponding requirements was confirmed by the Ethics Committee on 26 May 2023.

3. Results

3.1. Cohort Characteristics

The source registry dataset comprised 46,994 individuals. Before application of the prespecified historical date-plausibility criterion, 2976 patients had CoA documented as the primary congenital diagnosis. Of these, 256 met the date-plausibility exclusion criterion, resulting in the final analytical cohort of 2720 patients. A further 1117 registry participants had CoA documented as an associated congenital diagnosis but not as the primary congenital diagnosis and were not included in the primary cohort.

The study cohort comprised 2720 patients with CoA documented as the primary congenital diagnosis. Of these, 1661 patients were male (61.1%) and 1059 were female (38.9%). At the time of last documented observation, 2667 patients (98.1%) were alive and 53 patients (1.9%) were deceased.

The mean age at the patient-specific reference date, defined as age at death for deceased patients and age at last documented contact for all others, was 18.25 years, with a median of 17.85 years. Age ranged from birth to 88.40 years. According to CHD complexity classification, 2090 patients (76.8%) were classified as having moderate CHD and 630 patients (23.2%) as having complex CHD. Further details are presented in Table 1.

Table 1. Baseline characteristics of the CoA-primary-diagnosis cohort.

Characteristic	Value
Total patients, n	2720
Male sex, n (%)	1661 (61.1)
Female sex, n (%)	1059 (38.9)
Alive, n (%)	2667 (98.1)
Deceased, n (%)	53 (1.9)
Mean age at reference date, years	18.25
95% CI of mean age	17.68 to 18.82
Median age at reference date, years	17.85
Interquartile range of age at reference date, years	5.85 to 25.53
Moderate CHD complexity, n (%)	2090 (76.8)
Complex CHD complexity, n (%)	630 (23.2)

3.2. Associated Congenital Diagnoses

The most frequently documented associated congenital diagnosis was BAV (34.4%). The specific registry item ACD149 for documented tricuspid aortic-valve morphology was present in 805 patients (29.6%). Other frequent associated congenital findings included PDA in 574 patients (21.1%). The ten most frequently documented associated congenital diagnoses are shown in Table 2.

Table 2. Most frequent associated congenital or morphology-coded findings.

Variable (IPCCC)	Diagnosis	n (%)
ACD150 (09.15.22)	Bicuspid aortic valve	937 (34.4)
ACD149 (09.15.23)	Documented tricuspid aortic-valve morphology	805 (29.6)
ACD062 (09.27.21)	Patent ductus arteriosus	574 (21.1)
ACD163 (09.29.11)	Aortic-arch hypoplasia	462 (17.0)
ACD060 (05.03.01)	Patent foramen ovale	363 (13.4)
ACD005 (07.10.01)	Perimembranous ventricular septal defect	311 (11.4)
ACD151 (09.15.01)	Congenital valvular aortic stenosis	286 (10.5)
ACD135 (05.04.02)	Secundum atrial septal defect	247 (9.1)
ACD153 (09.15.07)	Congenital aortic insufficiency	224 (8.2)
ACD006 (07.11.01)	Muscular ventricular septal defect	145 (5.3)

Values are n (% of the total CoA-primary-diagnosis cohort, n = 2720), unless otherwise indicated. Diagnosis indicators were derived from registry documentation. A finding not identified by diagnosis text or a valid mapped code was interpreted as not documented. Documented tricuspid aortic-valve morphology is shown as a registry documentation item and should not be interpreted as an associated lesion.

3.3. Acquired Diagnoses and Extracardiac Comorbidity

The most frequent acquired diagnosis was hypertension related to aortic-arch obstruction, documented in 344 patients (12.6%). Residual coarctation was documented in 329 patients (12.1%), and left ventricular hypertrophy in 305 patients (11.2%). Additional frequent acquired diagnoses are shown in Table 3.

Table 3. Most frequent documented acquired diagnoses.

Variable (IPCCC)	Diagnosis	n (%)
AD192 (10.14.04)	Arterial hypertension due to aortic-arch obstruction	344 (12.6)
AD160 (15.37.05)	Residual coarctation of the aorta	329 (12.1)
AD117 (07.06.05)	Left ventricular hypertrophy	305 (11.2)
AD193 (10.14.01)	Arterial hypertension	246 (9.0)
AD131 (11.06.23)	Complete right bundle branch block	240 (8.8)
AD159 (10.14.72)	Recurrent coarctation of the aorta	229 (8.4)
AD207 (10.36.04)	Acquired aortic insufficiency	186 (6.8)

Values are n (% of the total CoA-primary-diagnosis cohort, n = 2720), unless otherwise indicated. Diagnosis indicators were derived from registry documentation. A finding not identified by diagnosis text or a valid mapped code was interpreted as not documented.

Extracardiac diagnoses were less frequent overall. The most commonly documented extracardiac comorbidity was obesity, present in 136 patients (5.0%). Four other extracardiac diagnoses reached the predefined 1% presentation threshold (Table 4).

Table 4. Most frequent extracardiac diagnoses.

Variable (ICD-10)	Diagnosis	n (%)
ED2050 (E66)	Obesity	136 (5.0)
ED1793 (J45)	Bronchial asthma	39 (1.4)
ED1258 (E03.9)	Hypothyroidism	38 (1.4)
ED927 (F79)	Unspecified intellectual disability	37 (1.4)
ED593 (M41)	Scoliosis	29 (1.1)

Values are n (% of the total CoA-primary-diagnosis cohort, n = 2720), unless otherwise indicated. Diagnosis indicators were derived from registry documentation; absence of a coded diagnosis was interpreted as absence of documentation.

3.4. Age-Related Patterns of Acquired Morbidity

Age-stratified analyses showed clear differences in the cross-sectional distribution of documented acquired morbidity across age groups. The cohort included 687 patients aged 0–5 years, 326 aged 6–11 years, 368 aged 12–17 years, 847 aged 18–29 years, and 492 aged 30 years or older.

Hypertension related to aortic-arch obstruction was documented in 1.9% of patients aged 0–5 years and in 26.2% of patients aged 30 years or older. Arterial hypertension showed a similar age-associated pattern, with documented frequencies of 2.3% in the youngest group and 22.6% in patients aged 30 years or older. Acquired aortic insufficiency was documented in 0.4% of patients aged 0–5 years and in 15.7% of those aged 30 years or older.

Residual coarctation was documented in 6.1% of patients aged 0–5 years, reached 16.0% in patients aged 12–17 years, and was documented in 11.0% of patients aged 30 years or older. Recurrent coarctation was documented in 4.4% of the youngest age group and 11.8% of patients aged 30 years or older. Left ventricular hypertrophy was documented in 6.4% of patients aged 0–5 years and in 18.5% of patients aged 30 years or older.

All selected acquired morbidity variables differed significantly across age groups in exploratory chi-square analyses (see Table 5).

Table 5. Age-stratified prevalence of key documented acquired diagnoses.

Diagnosis	Total (N = 2720)	0–5 Y (n = 687)	6–11 Y (n = 326)	12–17 Y (n = 368)	18–29 Y (n = 847)	≥30 Y (n = 492)	*p* Value
Hypertension due to arch obstruction	344 (12.6)	13 (1.9)	26 (8.0)	43 (11.7)	133 (15.7)	129 (26.2)	<0.001
Arterial hypertension	246 (9.0)	16 (2.3)	22 (6.7)	26 (7.1)	71 (8.4)	111 (22.6)	<0.001
Residual coarctation	329 (12.1)	42 (6.1)	42 (12.9)	59 (16.0)	132 (15.6)	54 (11.0)	<0.001
Recurrent coarctation	229 (8.4)	30 (4.4)	31 (9.5)	30 (8.2)	80 (9.4)	58 (11.8)	<0.001
Left ventricular hypertrophy	305 (11.2)	44 (6.4)	51 (15.6)	39 (10.6)	80 (9.4)	91 (18.5)	<0.001
Acquired aortic insufficiency	186 (6.8)	3 (0.4)	13 (4.0)	20 (5.4)	73 (8.6)	77 (15.7)	<0.001

Values are n (% within subgroup). Diagnosis indicators were derived from registry documentation. A finding not identified by diagnosis text or a valid mapped code was interpreted as not documented.

3.5. Congenital Heart Disease Complexity

Patients classified as having complex CHD showed a broader documented congenital and cardiovascular phenotype than those classified as having moderate CHD. Among the 630 patients with complex CHD, aortic-arch hypoplasia was documented in 462 (73.3%), BAV in 228 (36.2%), patent ductus arteriosus in 201 (31.9%), perimembranous ventricular septal defect in 140 (22.2%), and muscular ventricular septal defect in 67 (10.6%). These findings were not mutually exclusive and describe the congenital anatomy documented within the registry-defined complex-CHD subgroup rather than individual diagnostic criteria for complexity classification. Aortic-arch hypoplasia was not documented in the moderate-CHD group, while patent ductus arteriosus and ventricular septal defects were also more frequent among patients classified as having complex CHD (Table 6).

Table 6. Selected diagnoses by CHD complexity.

Diagnosis	Moderate CHD (n = 2090)	Complex CHD (n = 630)	*p* Value
Bicuspid aortic valve	709 (33.9)	228 (36.2)	0.294
Aortic-arch hypoplasia	0 (0.0)	462 (73.3)	<0.001
Patent ductus arteriosus	373 (17.8)	201 (31.9)	<0.001
Perimembranous VSD	171 (8.2)	140 (22.2)	<0.001
Muscular VSD	78 (3.7)	67 (10.6)	<0.001
Congenital valvular aortic stenosis	207 (9.9)	79 (12.5)	0.059
Congenital aortic insufficiency	188 (9.0)	36 (5.7)	0.009
Hypertension due to arch obstruction	269 (12.9)	75 (11.9)	0.523
Arterial hypertension	201 (9.6)	45 (7.1)	0.058
Residual coarctation	244 (11.7)	85 (13.5)	0.220
Recurrent coarctation	152 (7.3)	77 (12.2)	<0.001
Left ventricular hypertrophy	231 (11.1)	74 (11.7)	0.629
Acquired aortic insufficiency	145 (6.9)	41 (6.5)	0.708

Values are n (% within complexity group). *p* values are Pearson chi-square tests and are interpreted descriptively. CHD complexity reflects the overall congenital and cardiovascular phenotype and is not an independent exposure variable; therefore, differences by complexity should be interpreted as descriptive phenotype differences within the CoA-primary-diagnosis cohort.

In contrast, documented BAV frequency was similar between moderate and complex CHD groups (33.9% vs. 36.2%; $p = 0.294$). For acquired morbidity, several pressure-load and obstruction-related diagnoses were broadly similar between moderate and complex CHD. For example, hypertension related to aortic-arch obstruction was documented in 12.9% of moderate and 11.9% of complex CHD patients ($p = 0.523$). Detailed data are presented in Table 6.

3.6. Bicuspid Aortic-Valve Subgroup

BAV was documented in 937 patients (34.4% of the full cohort). A specific aortic-valve morphology was documented in 1784 patients (65.6%), comprising 937 patients with BAV, 844 with documented tricuspid morphology, and three with documented unicuspid morphology. The count of 844 patients with documented tricuspid morphology was based on either the specific registry item for tricuspid aortic-valve morphology (ACD149; n = 805, as shown in Table 2) or the additional indicator for asymmetric opening of a tricuspid aortic valve, as defined in Section 2.7. BAV therefore accounted for 52.5% of patients with a specific documented valve morphology. The remaining 936 patients (34.4%) had no specific aortic-valve morphology documented. Patients with documented BAV showed higher frequencies of several aortic valve and pressure-load diagnoses compared with patients without documented BAV.

Congenital valvular aortic stenosis was present in 19.9% of patients with BAV compared with 5.6% of those without BAV. Congenital aortic-valve insufficiency was present in 14.2% versus 5.1%, and acquired aortic insufficiency in 9.8% versus 5.3%.

Patients with BAV also had higher frequencies of several obstruction-related and pressure-load diagnoses. Residual coarctation was documented in 14.6% of patients with BAV compared with 10.8% of patients without documented BAV. Hypertension related to aortic-arch obstruction was present in 17.3% versus 10.2%. Detailed data are shown in Table 7.

Table 7. Selected diagnoses by documented BAV status.

Diagnosis	No Documented BAV (n = 1783)	Documented BAV (n = 937)	*p* Value
Congenital valvular aortic stenosis	100 (5.6)	186 (19.9)	<0.001
Congenital aortic insufficiency	91 (5.1)	133 (14.2)	<0.001
Aortic-arch hypoplasia	288 (16.2)	174 (18.6)	0.111
Acquired aortic insufficiency	94 (5.3)	92 (9.8)	<0.001
Residual coarctation	192 (10.8)	137 (14.6)	0.003
Recurrent coarctation	131 (7.3)	98 (10.5)	0.005
Hypertension due to arch obstruction	182 (10.2)	162 (17.3)	<0.001
Arterial hypertension	145 (8.1)	101 (10.8)	0.022
Left ventricular hypertrophy	159 (8.9)	146 (15.6)	<0.001

Values are n (% within BAV group). *p* values are Pearson chi-square tests and are interpreted descriptively.

Because the main aortic-valve burden indicator included BAV morphology by definition, an additional non-circular aortic-valve dysfunction indicator excluding BAV was analyzed. This indicator comprised congenital valvular aortic stenosis, congenital aortic insufficiency, and acquired aortic insufficiency. Overall, 608 patients (22.4%) had documented aortic-valve dysfunction excluding BAV morphology. This non-circular indicator was more frequent in patients with documented BAV than in those without documented

BAV (37.8% vs. 14.2%, $p < 0.001$). In an exploratory logistic regression adjusted for age, sex, and CHD complexity, documented BAV was associated with higher odds of aortic-valve dysfunction excluding BAV morphology (adjusted OR 3.41, 95% CI 2.81 to 4.13).

In the sensitivity analysis restricted to patients with documented BAV or documented tricuspid aortic-valve morphology (n = 1781), BAV remained associated with aortic-valve dysfunction excluding BAV morphology (adjusted OR 3.19, 95% CI 2.54 to 4.02). In contrast, BAV was not clearly associated with the broad arch-obstruction burden (adjusted OR 1.12, 95% CI 0.92 to 1.38) or pressure-load burden (adjusted OR 0.87, 95% CI 0.71 to 1.06) in this morphology-restricted comparison.

3.7. Composite Morbidity Indicators

Composite morbidity indicators highlighted the cumulative burden of clinically related morbidity. An arch-obstruction burden, defined as residual coarctation, recurrent coarctation, or hypertension related to aortic-arch obstruction, was documented in 753 patients (27.7%). A pressure-load burden, defined as hypertension related to aortic-arch obstruction, arterial hypertension, or left ventricular hypertrophy, was documented in 741 patients (27.2%). An aortic-valve burden, defined as BAV, congenital valvular aortic stenosis, congenital aortic insufficiency, or acquired aortic insufficiency, was documented in 1191 patients (43.8%).

The arch-obstruction and pressure-load composites overlapped substantially: 484 patients fulfilled both definitions, and hypertension related to aortic-arch obstruction was a shared component in 344 patients.

These composite indicators differed significantly across age groups. Arch-obstruction burden was documented in 10.9% of patients aged 0–5 years and in 41.3% of patients aged 30 years or older. Pressure-load burden was documented in 9.5% of the youngest age group and in 53.7% of patients aged 30 years or older. Aortic-valve burden was documented in 27.2% of patients aged 0–5 years and in 56.1% of patients aged 30 years or older. An overview is provided in Table 8.

Table 8. Composite morbidity-burden indicators overall and by age group.

Composite Indicator	Total (n = 2720)	0–5 Y (n = 687)	6–11 Y (n = 326)	12–17 Y (n = 368)	18–29 Y (n = 847)	≥30 Y (n = 492)	*p* Value
Arch-obstruction burden	753 (27.7)	75 (10.9)	87 (26.7)	110 (29.9)	278 (32.8)	203 (41.3)	<0.001
Pressure-load burden	741 (27.2)	65 (9.5)	81 (24.8)	95 (25.8)	236 (27.9)	264 (53.7)	<0.001
Aortic-valve burden	1191 (43.8)	187 (27.2)	139 (42.6)	159 (43.2)	430 (50.8)	276 (56.1)	<0.001

Values are n (% within column age group unless otherwise indicated). *p* values are Pearson chi-square tests and are interpreted descriptively. Arch-obstruction burden was defined as residual coarctation, recurrent coarctation, or hypertension related to aortic-arch obstruction; pressure-load burden as hypertension related to arch obstruction, arterial hypertension, or LV hypertrophy; and aortic-valve burden as BAV, congenital valvular aortic stenosis, congenital aortic insufficiency, or acquired aortic insufficiency. The arch-obstruction and pressure-load composites were not mutually exclusive and shared hypertension related to aortic-arch obstruction as one component.

Composite burden also differed according to documented BAV status. Arch-obstruction burden was documented in 34.7% of patients with BAV compared with 24.0% of those without documented BAV. Pressure-load burden was present in 35.4% versus 22.9%. By definition, all patients with documented BAV met the aortic-valve burden criterion, whereas 14.2% of patients without documented BAV had aortic-valve burden due to other aortic-valve diagnoses.

3.8. Diagnostic Burden per Patient

The median number of distinct registry-documented associated congenital diagnoses or finding categories per patient, excluding tricuspid aortic-valve morphology, was two [IQR 1–3]. The median number of documented acquired diagnoses was one [IQR 0–2], and the median number of documented extracardiac diagnosis categories was 0 [IQR 0–1] (see Table 9).

Table 9. Number of distinct registry-documented diagnosis or finding categories per patient.

Diagnostic Burden Measure	Overall Mean (SD); Median [IQR]	Moderate CHD Mean (SD); Median	Complex CHD Mean (SD); Median
Associated congenital diagnosis/finding categories, excluding TAV morphology	1.90 (1.63); 2 [1–3]	1.47 (1.33); 1	3.33 (1.70); 3
Acquired diagnosis categories (AD)	1.34 (1.94); 1 [0–2]	1.18 (1.83); 1	1.88 (2.18); 1
Extracardiac diagnosis categories (ED)	0.73 (1.42); 0 [0–1]	0.67 (1.36); 0	0.95 (1.56); 0

Counts represent distinct registry-documented diagnosis or finding categories rather than adjudicated numbers of diseases. Tricuspid aortic-valve morphology was excluded from the associated congenital category count.

When stratified by sex, male patients had a lower mean number of documented associated congenital diagnoses or finding categories than female patients (1.80 vs. 2.06), but a higher mean number of acquired diagnosis categories (1.46 vs. 1.16). The mean number of extracardiac diagnosis categories was similar between male and female patients (0.71 vs. 0.77).

3.9. Procedural History and Timing

At least one documented operation-source entry was present in 1898 patients (69.8%), at least one catheter-intervention-source entry in 1027 patients (37.8%), and at least one entry from either source in 2232 patients (82.1%). The median number of operation entries was one [IQR 0–2], the median number of catheter-intervention entries was 0 [0–1], and the median total number of operation or catheter-intervention entries was two [1–3]. These registry source fields represent documented entries rather than clinically adjudicated counts of unique procedures.

A plausible first operation date was available in 1823 patients (67.0%), a plausible first catheter-intervention date in 996 patients (36.6%), and a plausible first operation or catheter-intervention date in 2153 patients (79.2%). The median age at first documented operation was 0.19 years [0.04–3.21], at first catheter intervention 4.89 years [0.36–14.90], and at first operation or catheter intervention overall 0.28 years [0.04–4.88].

Multiple documented procedure entries were common (see Table 10). Two or more operation entries were present in 1033 patients (38.0%), two or more catheter-intervention entries in 460 patients (16.9%), and two or more operation or catheter-intervention entries in 1484 patients (54.6%). A plausible second distinct operation date was available in 627 patients (23.1%), and a plausible second distinct catheter-intervention date in 401 patients (14.7%). When operations and catheter interventions were considered jointly, 1170 patients (43.0%) had a plausible second distinct documented procedure date; this combined measure also includes mixed sequences such as one operation and one catheter intervention.

Table 10. Documented procedural history, multiplicity, and timing.

Variable	Result
Any documented operation	1898 (69.8%)
Any documented catheter-based intervention	1027 (37.8%)
Any documented operation or intervention	2232 (82.1%)
Plausible first operation date	1823 (67.0%)
Plausible first catheter-intervention date	996 (36.6%)
Plausible first operation/intervention date	2153 (79.2%)
Plausible second distinct operation date	627 (23.1%)
Plausible second distinct catheter-intervention date	401 (14.7%)
Plausible second distinct documented procedure date, considering OP and catheter interventions jointly	1170 (43.0%)
Documented operation entries, median [IQR]	1 [0–2]
Documented catheter-intervention entries, median [IQR]	0 [0–1]
Documented operation/intervention entries, median [IQR]	2 [1–3]
≥2 documented operation entries	1033 (38.0%)
≥2 documented catheter-intervention entries	460 (16.9%)
≥2 documented operation/intervention entries	1484 (54.6%)
Age at first documented operation, median [IQR], years	0.19 [0.04–3.21]
Age at first documented catheter intervention, median [IQR], years	4.89 [0.36–14.90]
Age at first documented operation/intervention, median [IQR], years	0.28 [0.04–4.88]
Age at second distinct operation, median [IQR], years	2.19 [0.35–11.80]
Age at second distinct catheter intervention, median [IQR], years	11.61 [2.02–18.37]
Age at second distinct operation/intervention, median [IQR], years	3.25 [0.32–13.64]
First-to-second operation interval, median [IQR], years	1.50 [0.23–7.17]
First-to-second catheter-intervention interval, median [IQR], years	1.37 [0.43–5.06]
First-to-second operation/intervention interval, median [IQR], years	1.03 [0.20–7.91]

Values are n (%) unless otherwise indicated. Operation and catheter-intervention entries were counted across all available registry source slots using non-empty code or text fields and represent documented entries rather than adjudicated unique procedures. First dates were defined as the earliest plausible date across all corresponding date slots. Timing summaries include only patients with plausible dates. The combined operation/catheter-intervention variable identifies the second distinct documented procedure date of either type and may therefore include mixed sequences such as one operation followed by one catheter intervention, or vice versa. It is not the sum of second operation and second catheter-intervention dates.

Among patients with a plausible second operation date, the median age at second operation was 2.19 years [0.35–11.80], and the median first-to-second operation interval was 1.50 years [0.23–7.17]. For second catheter interventions, the corresponding values were 11.61 years [2.02–18.37] and 1.37 years [0.43–5.06]. For the combined second procedure date, the median age was 3.25 years [0.32–13.64], and the median first-to-second procedure interval was 1.03 years [0.20–7.91].

In an additional sensitivity analysis, exclusion of exact dated duplicate entries reduced the number of operation-source entries from 4641 to 4640 and catheter-intervention-source entries from 1923 to 1915. The number of patients with at least two operation entries remained unchanged at 1033, whereas the corresponding number for catheter interventions

decreased from 460 to 458. In a separate analysis, multiple plausible entries on the same calendar day were documented in 782 patients for operation-source fields and 151 for catheter-intervention-source fields.

3.10. Multiple Documented Procedure Entries by Subgroup

Multiple documented procedure entries differed mainly by age group, CHD complexity, and BAV status. Two or more operation or catheter-intervention entries were present in 38.1% of patients aged 0–5 years and in 65.0% of patients aged 30 years or older. Patients with complex CHD more frequently had multiple documented entries than those with moderate CHD, with two or more operation or catheter-intervention entries in 78.4% versus 47.4%. Similarly, two or more operation or catheter-intervention entries were documented in 63.9% of patients with BAV compared with 49.6% without documented BAV.

Sex differences in multiple procedure entries were small. Two or more operation or catheter-intervention entries were almost identical between male and female patients (54.6% vs. 54.5%). Borderline unadjusted sex differences in multiple operation entries and multiple catheter-intervention entries did not remain significant after FDR correction. Detailed subgroup results are shown in Table 11.

Table 11. Multiple documented procedure entries by subgroup.

Subgroup	≥2 OP Entries	≥2 Catheter-Intervention Entries	≥2 OP/Catheter-Intervention Entries
Total cohort (N = 2720)	1033 (38.0)	460 (16.9)	1484 (54.6)
0–5 years (n = 687)	198 (28.8)	54 (7.9)	262 (38.1)
6–11 years (n = 326)	138 (42.3)	51 (15.6)	193 (59.2)
12–17 years (n = 368)	112 (30.4)	76 (20.7)	188 (51.1)
18–29 years (n = 847)	350 (41.3)	174 (20.5)	521 (61.5)
≥30 years (n = 492)	235 (47.8)	105 (21.3)	320 (65.0)
Moderate CHD (n = 2090)	642 (30.7)	318 (15.2)	990 (47.4)
Complex CHD (n = 630)	391 (62.1)	142 (22.5)	494 (78.4)
No documented BAV (n = 1783)	625 (35.1)	245 (13.7)	885 (49.6)
Documented BAV (n = 937)	408 (43.5)	215 (22.9)	599 (63.9)
Male (n = 1661)	606 (36.5)	300 (18.1)	907 (54.6)
Female (n = 1059)	427 (40.3)	160 (15.1)	577 (54.5)

Values are n (% within subgroup). OP indicates operation; BAV, bicuspid aortic valve. Entries represent registry-documented source entries rather than adjudicated unique procedures.

3.11. Potential CoA-/Arch-Related Procedure Entries

In the long-format procedure analysis, the most frequent operation keys were CoA-/aortic-arch-related procedures, including CoA resection with end-to-end anastomosis, patch enlargement, operative CoA correction, aortic-arch operations, graft interposition for long-segment CoA, subclavian flap repair, and aortic-arch patch enlargement. The catheter-intervention keys classified as potential CoA-related were specific to native CoA balloon dilation, recoarctation balloon dilation, and stent implantation in the aortic isthmus.

Any potential CoA-/aortic-arch-related operation-source entry was documented in 1841 patients (67.7%), and two or more such entries in 289 patients (10.6%). Any potential CoA-related catheter-intervention-source entry was documented in 890 patients (32.7%), and two or more such entries in 290 patients (10.7%). Multiple potential CoA-/aortic-arch-related operation entries were more frequent in patients with complex than moderate

CHD and were similar between sexes, whereas multiple potential CoA-related catheter-intervention entries were more frequent in patients with documented BAV and somewhat more frequent in males. These analyses were exploratory and describe documentation-entry patterns rather than clinically adjudicated reintervention rates (see Table 12).

Table 12. Potential CoA-/arch-related documented procedure entries.

Variable	Result
Any potential CoA-/aortic-arch-related operation entry	1841 (67.7%)
≥2 potential CoA-/aortic-arch-related operation entries	289 (10.6%)
Any potential CoA-related catheter-intervention entry	890 (32.7%)
≥2 potential CoA-related catheter-intervention entries	290 (10.7%)
≥2 potential CoA-/aortic-arch-related operation entries, male vs. female	177/1661 (10.7%) vs. 112/1059 (10.6%)
≥2 potential CoA-related catheter-intervention entries, male vs. female	195/1661 (11.7%) vs. 95/1059 (9.0%)

Values are n (%) unless otherwise indicated. Potential CoA-/aortic-arch-related operation-source entries were identified using conservative code/text criteria including CoA, aortic isthmus, recoarctation, and the 12.18 IPCCC procedure-code family. Potential CoA-related catheter-intervention-source entries were identified using conservative CoA/aortic-isthmus-specific code/text criteria. These variables represent registry-documented entries rather than adjudicated unique procedures or reinterventions.

3.12. Sex-Stratified Analyses

Male and female patients had similar age distributions, vital status, and CHD complexity. Mean age was 18.06 years in males and 18.54 years in females. Complex CHD was documented in 22.1% of male and 24.8% of female patients. Documented BAV was present in 35.3% and 33.1%, respectively.

Several acquired pressure-load and residual-obstruction variables were more frequently documented in males. Hypertension related to aortic-arch obstruction was documented in 14.8% of males and 9.3% of females, arterial hypertension in 10.3% versus 7.1%, residual coarctation in 14.3% versus 8.7%, and left ventricular hypertrophy in 13.5% versus 7.6%. Recurrent coarctation and obesity were similar between sexes. Arch-obstruction burden was documented in 31.5% of males and 21.7% of females, and pressure-load burden in 31.2% and 21.0%, respectively. Aortic-valve burden was similar between sexes (44.1% vs. 43.2%).

Documented procedure-entry history was broadly similar between sexes. At least one operation-source entry was documented in 69.7% of males and 70.0% of females, and at least one operation or catheter-intervention entry in 82.8% and 80.8%, respectively. At least one catheter-intervention-source entry was somewhat more frequent in males (39.8% vs. 34.6%). Multiple operation or catheter-intervention entries were nearly identical between sexes (54.6% vs. 54.5%). Borderline unadjusted sex differences in multiple operation and catheter-intervention entries were not significant after FDR correction. Age-stratified male-versus-female odds ratios for the three morbidity outcomes are shown in Figure 2.

3.13. Sensitivity Analyses

In exploratory logistic regression models adjusted for age at death or last documented contact, CHD complexity, and documented BAV status, male sex was associated with higher arch-obstruction burden (adjusted OR 1.74, 95% CI 1.45 to 2.10) and pressure-load burden (adjusted OR 1.88, 95% CI 1.55 to 2.28). Age was also associated with both outcomes, whereas complex CHD was associated with arch-obstruction burden but not clearly with pressure-load burden. Documented BAV was associated with arch-obstruction burden (adjusted OR 1.50, 95% CI 1.25 to 1.79) and pressure-load burden (adjusted OR 1.60, 95%

CI 1.33 to 1.92) in the full cohort. For the non-circular aortic-valve dysfunction outcome, documented BAV showed a stronger association (adjusted OR 3.41, 95% CI 2.81 to 4.13), whereas male sex was not clearly associated with this outcome (see Table 13).

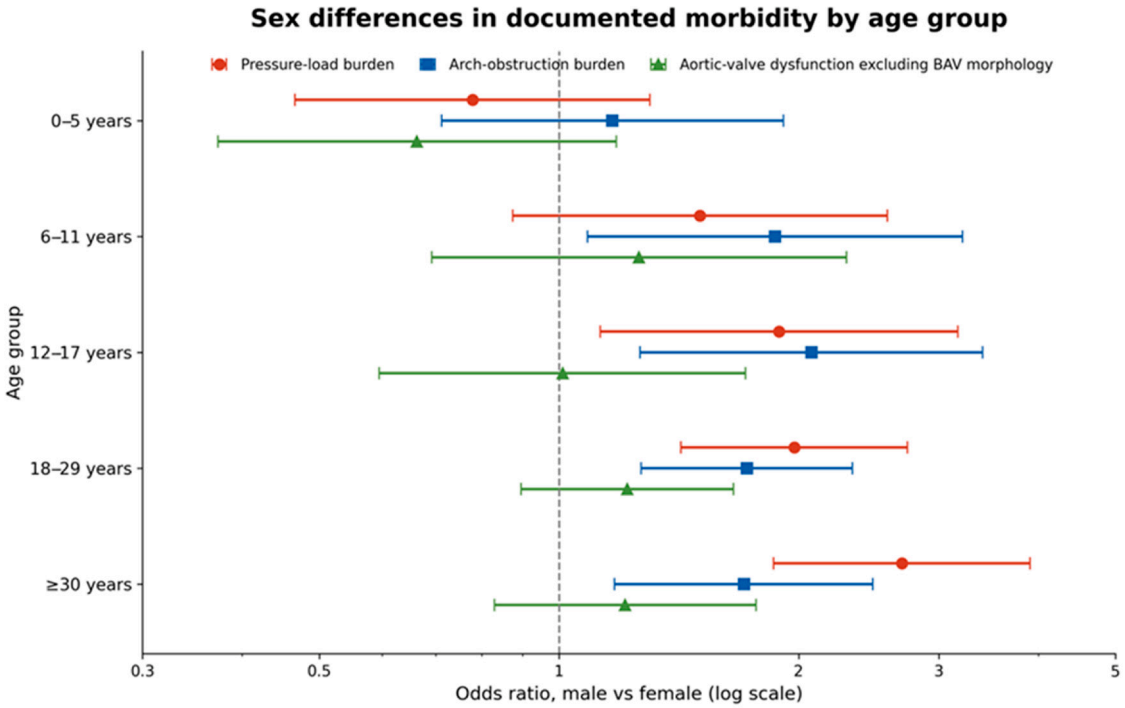


Figure 2. Age-stratified sex differences in documented morbidity. Male-versus-female odds ratios with 95% confidence intervals are shown for pressure-load burden, arch-obstruction burden, and aortic-valve dysfunction excluding BAV morphology. The vertical dashed line indicates no sex difference (OR = 1). In adjusted restricted cubic spline models, the joint sex-by-age interaction was significant for pressure-load burden (p = 0.004), but not for arch-obstruction burden (p = 0.487) or aortic-valve dysfunction excluding BAV morphology (p = 0.436).

In the linear interaction models, evidence for age-related variation in the association between sex and morbidity was observed for pressure-load burden (sex-by-age OR 1.23 per 10 years, 95% CI 1.08 to 1.39, p = 0.001), but not for arch-obstruction burden (OR 1.02, 95% CI 0.91 to 1.15, p = 0.707) or aortic-valve dysfunction excluding BAV morphology (OR 1.05, 95% CI 0.93 to 1.19, p = 0.414). Because age effects were nonlinear across the cohort, restricted cubic spline models were also fitted. The joint sex-by-age interaction remained significant for pressure-load burden (likelihood-ratio p = 0.004), but not for arch-obstruction burden (p = 0.487) or aortic-valve dysfunction excluding BAV morphology (p = 0.436).

Additional adjustment for the number of other documented acquired diagnoses produced a similar linear sex-by-age interaction estimate for pressure-load burden (OR 1.23 per 10 years, 95% CI 1.09 to 1.40, p = 0.001). This variable was used only as a limited proxy for documentation intensity and does not exclude residual documentation bias.

In the morphology-restricted analysis of patients with documented BAV or documented tricuspid morphology (n = 1781), BAV remained associated with aortic-valve dysfunction excluding BAV morphology (adjusted OR 3.19, 95% CI 2.54 to 4.02), whereas associations with arch-obstruction burden (adjusted OR 1.12, 95% CI 0.92 to 1.38) and pressure-load burden (adjusted OR 0.87, 95% CI 0.71 to 1.06) were not clearly supported. The joint spline-based sex-by-age interaction remained significant for pressure-load burden in this subset (p = 0.002), but not for arch-obstruction burden (p = 0.826) or aortic-valve dysfunction excluding BAV morphology (p = 0.195).

Table 13. Exploratory adjusted logistic regression models for documented morbidity outcomes.

Outcome	Predictor	Adjusted OR	95% CI	*p* Value
Arch-obstruction burden	Male sex	1.74	1.45–2.10	<0.001
	Age per 10 years	1.38	1.31–1.47	<0.001
	Complex CHD	1.55	1.27–1.91	<0.001
	Documented BAV	1.50	1.25–1.79	<0.001
Pressure-load burden	Male sex	1.88	1.55–2.28	<0.001
	Age per 10 years	1.62	1.52–1.72	<0.001
	Complex CHD	1.18	0.95–1.47	0.131
	Documented BAV	1.60	1.33–1.92	<0.001
Aortic-valve dysfunction excluding BAV	Male sex	1.11	0.91–1.35	0.311
	Age per 10 years	1.37	1.29–1.46	<0.001
	Complex CHD	1.10	0.87–1.39	0.415
	Documented BAV	3.41	2.81–4.13	<0.001

Logistic regression models were fitted separately for each outcome and adjusted for sex, age at death or last documented contact per 10 years, CHD complexity, and documented BAV status. Odds ratios for sex refer to male versus female patients, odds ratios for CHD complexity refer to complex versus moderate CHD, and odds ratios for BAV refer to documented BAV versus no documented BAV. These models use a linear age term. Nonlinear age effects and sex-by-age interactions were evaluated separately using restricted cubic splines.

In the anatomic arch sensitivity analysis restricted to documented residual or recurrent coarctation, male sex remained associated with the outcome in the full cohort (adjusted OR 1.503, 95% CI 1.225 to 1.844) and in the morphology-restricted subset (adjusted OR 1.575, 95% CI 1.234 to 2.011). The corresponding estimates for documented BAV were 1.388 (95% CI 1.139 to 1.692) and 1.298 (95% CI 1.031 to 1.634). The linear sex-by-age interaction was not supported in either analysis ($p = 0.616$ and $p = 0.550$, respectively).

Age-group associations for acquired morbidity, composite morbidity indicators, and multiple procedure entries remained FDR-significant. Most BAV-status comparisons also remained FDR-significant. In sex comparisons, pressure-load burden, arch-obstruction burden, left ventricular hypertrophy, hypertension related to arch obstruction, residual coarctation, arterial hypertension, and any catheter-intervention entry remained FDR-significant. In contrast, the unadjusted sex differences in multiple operation entries and multiple catheter-intervention entries were not significant after FDR correction (q = 0.095 for both).

3.14. Vital Status

Among the 53 deceased patients, the mean age at death was 29.09 years, and the median age was 21.80 years, with an interquartile range of 8.30 to 44.86 years. Mortality differed by CHD complexity in exploratory analysis: 31 of 2090 patients with moderate CHD (1.5%) and 22 of 630 patients with complex CHD (3.5%) were deceased.

3.15. Morbidity Sub-Phenotypes (Latent Class Analysis)

A latent class analysis of the 17 documented congenital and acquired indicators was evaluated in the full CoA-primary-diagnosis cohort using models with one to six classes. Among these models, the five-class solution had the lowest BIC (31,349.2), compared with 31,365.7 for four classes and 31,362.3 for six classes (see Table 14). Entropy for the five-class model was 0.661. All 100 random starts converged for the two- through six-class models,

and the best five-class log-likelihood was recovered in 31 of 100 starts. The five-class solution was therefore used for the primary descriptive class characterization. Model-estimated class proportions and modal class sizes for all one- to six-class full-cohort models are provided in Supplementary Table S2.

Table 14. Latent class model fit and summary of the five documented morbidity sub-phenotypes.

Panel A. Model Fit in the Full CoA-Primary-Diagnosis Cohort

Number of Classes	Log-Likelihood	AIC	BIC	Entropy	Random Starts	Best-Likelihood Recoveries	Converged Starts
1	−16,085.3436	32,204.6872	32,305.1298	—	—	—	—
2	−15,773.0609	31,616.1218	31,822.9154	0.592	100	38	100
3	−15,480.9837	31,067.9675	31,381.1120	0.555	100	99	100
4	−15,402.0944	30,946.1888	31,365.6843	0.644	100	6	100
5	**−15,322.6983**	**30,823.3966**	**31,349.2430**	**0.661**	**100**	**31**	**100**
6	−15,258.0274	30,730.0549	31,362.2523	0.694	100	62	100

Panel B. Summary of the five-class solution

Class	N (%)	Median age, years	Male, %	Complex CHD, %	Defining documented findings, model-estimated probability	≥2 documented procedure entries, %	Median documented procedure entries
C1 Low documented burden	1410 (51.8)	14.5	59.0	11.6	Low probabilities across all indicators	36.8	1
C2 Arch-hypertension/ pressure-load	311 (11.4)	23.8	69.8	20.3	HTN related to arch obstruction 63.7%; residual CoA 25.2%; LVH 23.8%	65.3	2
C3 Complex multilevel	515 (18.9)	12.4	53.4	60.6	PDA 47.0%; arch hypoplasia 43.7%; perimembranous VSD 38.6%; ASDII 35.2%	82.5	4
C4 BAV/valve-aortopathy	355 (13.1)	22.5	68.2	17.2	BAV 86.5%; congenital valvular aortic stenosis 42.3%; congenital aortic insufficiency 29.2%; ascending aortic dilation 19.8%	66.5	2
C5 Systemic-hypertension/ recurrent-obstruction	129 (4.7)	24.0	73.6	23.3	Arterial hypertension 100%; recurrent CoA 43.7%; LVH 39.3%; residual CoA 26.9%	78.3	3

The five-class solution is highlighted in bold because it had the lowest BIC among the evaluated models. Class sizes are based on modal assignment to the class with the highest posterior probability. Defining findings are model-estimated probabilities of registry documentation within each class. Age, sex, CHD complexity, vital status, and procedure-entry burden were not used as latent class indicators. Because class assignment was probabilistic, class descriptors are interpreted descriptively. Entropy is not defined for the one-class model.

The five modal classes were: C1, a low documented-burden group (1410 patients, 51.8%); C2, an arch-hypertension/pressure-load group (311, 11.4%) characterized particularly by hypertension related to aortic-arch obstruction (model-estimated probability 63.7%), residual coarctation (25.2%), and left ventricular hypertrophy (23.8%); C3, a complex multilevel group (515, 18.9%) characterized by aortic-arch hypoplasia (43.7%), patent ductus arteriosus (47.0%), and septal defects; C4, a BAV/valve-aortopathy group (355, 13.1%) characterized by bicuspid aortic valve (86.5%), congenital valvular aortic stenosis (42.3%), congenital aortic insufficiency (29.2%), and ascending aortic dilation (19.8%); and C5, a systemic-hypertension/recurrent-obstruction group (129, 4.7%) characterized by

arterial hypertension (100%), recurrent coarctation (43.7%), left ventricular hypertrophy (39.3%), and residual coarctation (26.9%).

Age, sex, CHD complexity, vital status, and procedure-entry burden were not used to estimate the classes and were summarized descriptively. Median age ranged from 12.4 years in C3 to 24.0 years in C5. Complex CHD was most frequent in C3 (60.6%), whereas the proportion of male patients was highest in C5 (73.6%). The median number of documented procedure entries was 1 in C1, 2 in C2, 4 in C3, 2 in C4, and 3 in C5. The class-specific morbidity patterns and descriptive characteristics are illustrated in Figure 3.

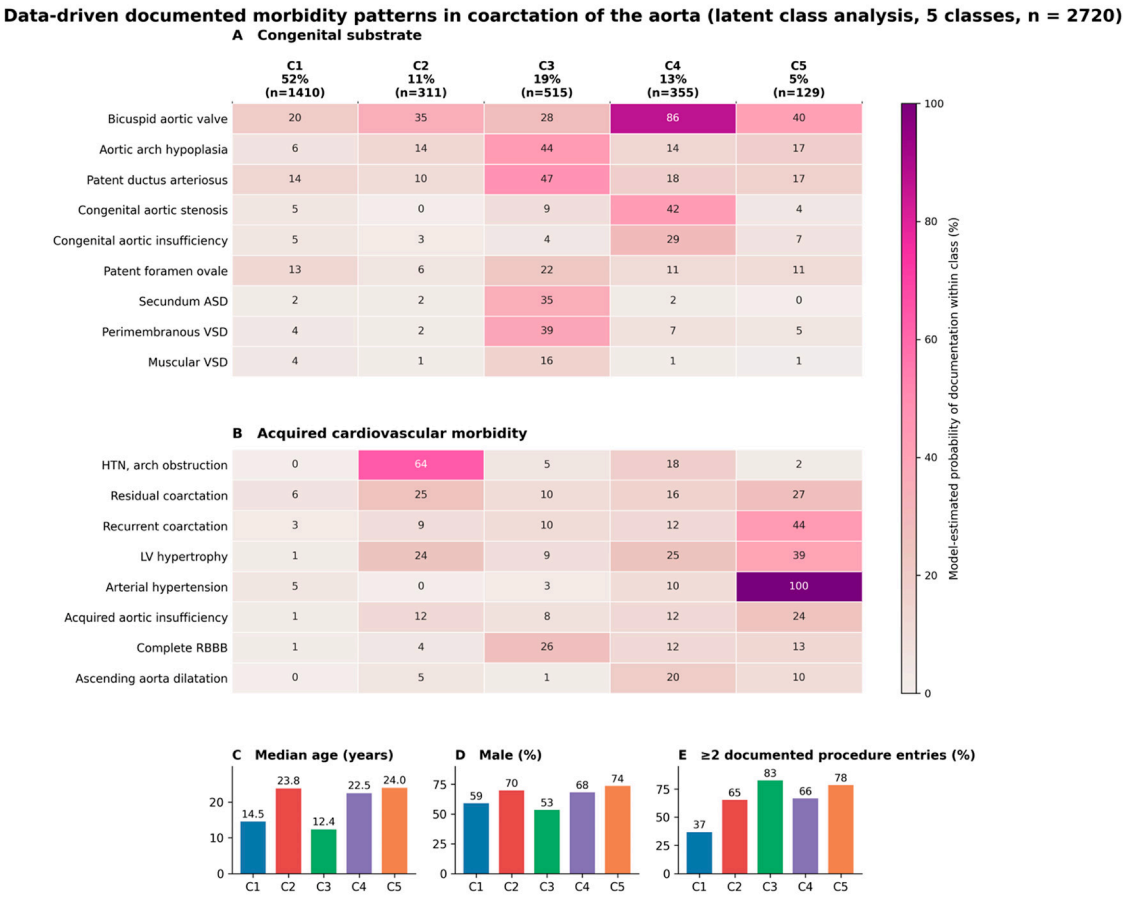


Figure 3. Data-driven documented morbidity patterns identified by latent class analysis. Panels (**A**) and (**B**) show model-estimated probabilities of documented congenital and acquired morbidity indicators within each class. Panel (**C**) shows median age, panel (**D**) the proportion of male patients, and panel (**E**) the proportion with at least two documented procedure entries. Class sizes are based on modal assignment to the class with the highest posterior probability. Age, sex, CHD complexity, and procedure-entry burden were not used as latent class indicators and are shown descriptively.

Classification uncertainty was non-negligible. A maximum posterior probability below 0.70 occurred in 689 of 2720 patients (25.3%). Among patients with a maximum posterior probability of at least 0.70, 1108 were assigned to C1, 241 to C2, 384 to C3, 193 to C4, and 105 to C5. The overall class profiles remained recognizable in this higher-certainty subset. Classification uncertainty varied across classes and was highest in the BAV/valve-aortopathy class (C4), where 162 of 355 patients (45.6%) had a maximum posterior class probability below 0.70.

In sensitivity analyses excluding patent foramen ovale and complete right bundle branch block from the indicator set, the five-class model again had a lower BIC than the four-class model (27,706.7 vs. 27,728.2), and the optimally label-aligned modal class assignment agreed with the primary five-class solution in 93.2% of patients. In the morphology-

restricted subset of patients with documented BAV or documented tricuspid aortic-valve morphology (n = 1781), a targeted comparison of four- and five-class models yielded a lower BIC for the four-class model (22,940.5 vs. 22,957.6). Because only four- and five-class models were evaluated in this subset, this analysis was interpreted as a sensitivity assessment of class-number stability rather than as a separate class-selection analysis.

3.16. Completeness of Routine Documentation

Several internal indicators demonstrated incomplete and variable registry documentation. A specific aortic-valve morphology was documented in 1784 patients (65.6%), comprising 937 patients with BAV (34.4% of the full cohort), 844 with documented tricuspid morphology (31.0%), and three with documented unicuspid morphology (0.1%). No specific aortic-valve morphology was documented in the remaining 936 patients (34.4%). Among patients with a specific documented morphology, BAV accounted for 52.5%.

A plausible first documented operation or catheter-intervention date was available in 2153 patients (79.2%), whereas 567 patients (20.8%) had no plausible first procedure date available. In addition, 488 patients (17.9%) had no documented operation or catheter-intervention entry. These patterns illustrate that absence of registry documentation should not be interpreted as verified clinical absence and that documentation completeness differed across data domains.

4. Discussion

Registry data cannot replace detailed imaging, hemodynamic, ambulatory blood pressure, or longitudinal event analyses, but they can characterize the documented clinical phenotype observed across a broad national cohort. The specific contribution of this study is therefore not to estimate systematically screened disease prevalence or adjudicated reintervention risk, but to characterize the registry-documented morbidity and procedure-entry burden of patients with CoA as the primary congenital diagnosis.

4.1. Principal Findings

This nationwide registry analysis describes a large cohort of patients with CoA as the primary congenital diagnosis and demonstrates substantial heterogeneity in registry-documented morbidity. Seven main findings emerge. First, acquired cardiovascular morbidity, particularly obstruction-related hypertension, arterial hypertension, LV hypertrophy, and acquired aortic insufficiency, was more frequently documented in older age groups. Second, registry-documented arch-obstruction and pressure-load composites were present in more than one quarter of patients and showed marked differences across age groups. Third, documented BAV identified a subgroup with substantially greater valve-related morbidity. Associations between BAV and the broader arch-obstruction and pressure-load composites observed in the full cohort were not clearly supported in the morphology-restricted BAV-versus-tricuspid-valve sensitivity analysis. Fourth, complex CHD was characterized mainly by a broader congenital substrate and higher procedure-entry burden rather than uniformly greater acquired pressure-load morbidity. Fifth, most patients had a documented operation or catheter-intervention entry, and multiple procedure entries were common. Sixth, latent class analysis identified five recurring cross-sectional patterns of documented morbidity: low documented burden, arch-hypertension/pressure-load, complex multilevel, BAV/valve-aortopathy, and systemic-hypertension/recurrent-obstruction. Classification was probabilistic and showed moderate uncertainty. Seventh, the association between sex and documented pressure-load morbidity varied with age, whereas corresponding sex-by-age interactions were not supported for arch-obstruction burden or aortic-valve dysfunction excluding BAV morphology. Together, these findings characterize

documented morbidity and procedure-entry patterns rather than systematically screened disease prevalence, longitudinal disease progression, or adjudicated reintervention risk.

4.2. CoA as a Lifelong Vascular and Left-Heart Phenotype

The present findings support the concept that CoA is not merely a localized narrowing of the aorta but part of a broader left-heart, arch, and vascular phenotype. In this nationwide registry cohort, the documented congenital substrate was dominated by BAV, aortic-arch hypoplasia, PDA, ventricular septal defects, and other aortic-valve findings, while the acquired morbidity pattern was characterized by residual or recurrent obstruction, hypertension, LV hypertrophy, and acquired aortic insufficiency. This combination is consistent with previous cohort studies and reviews describing the developmental association between CoA, BAV, arch abnormalities, and other left-sided obstructive lesions [4,5].

The registry data complement long-term outcome studies by showing how clinically expected CoA-related morbidities appear as documented diagnoses across a broad multicenter cohort. Adult survivors of CoA repair continue to show excess cardiovascular burden compared with reference populations, including hypertension, residual or recurrent obstruction, aortic and valve interventions, and late mortality [10]. In the present study, this pattern was reflected in the frequent documentation of arch-obstruction and pressure-load burden, supporting the interpretation of CoA as a lifelong vascular and left-heart condition rather than a defect that is fully resolved after initial repair.

4.3. Age-Related Morbidity Patterns

Documented acquired morbidity was more frequent in older age groups, particularly hypertension related to aortic-arch obstruction, arterial hypertension, LV hypertrophy, and acquired aortic insufficiency. Hypertension related to aortic-arch obstruction was documented in 1.9% of patients aged 0–5 years and in 26.2% of patients aged 30 years or older. Arterial hypertension and acquired aortic insufficiency showed similar age-group-associated patterns. These findings are concordant with systematic reviews and adult follow-up studies showing that hypertension after CoA repair is common, may become more frequent with longer follow-up, and may be underdetected when ambulatory or exercise blood pressure measurements are not systematically used [3,12–14].

These age-stratified findings should be interpreted as cross-sectional patterns of registry documentation rather than as longitudinal incidence, progression, or within-patient change. This distinction is important because some variables, such as residual coarctation, did not show a strictly monotonic pattern across age groups. Residual coarctation was most frequently documented in adolescents and young adults, which may reflect timing of follow-up imaging, transition to adult congenital heart disease care, coding practices, or the clinical period in which residual obstruction becomes most actively documented.

Despite these limitations, the observed age-group-associated documentation patterns are consistent with the clinical need for follow-up beyond childhood and adolescence. The distribution of documented hypertension, LV hypertrophy, residual or recurrent obstruction, and acquired aortic insufficiency is consistent with the guideline and review literature emphasizing lifelong surveillance after CoA diagnosis or repair [2,15,16].

4.4. Pathophysiological Considerations

The age-group differences in documented pressure-load morbidity are clinically plausible in light of the multifactorial pathophysiology of CoA-associated hypertension. Persistent or late-onset hypertension after CoA repair is not explained solely by residual anatomical obstruction. Proposed mechanisms include residual or recurrent arch narrowing, altered arch geometry, increased arterial stiffness, reduced vascular compliance, impaired endothelial function, abnormal vasoreactivity, baroreflex dysfunction, and neuro-

humoral activation [3,12,26,27]. Masked and exercise-induced hypertension may further contribute to under-recognized pressure load [13,14].

These mechanisms provide a framework for the observed co-documentation of hypertension, LV hypertrophy, residual or recurrent obstruction, and acquired aortic insufficiency. The registry data cannot determine whether LV remodeling was driven by residual obstruction, systemic hypertension, vascular stiffness, aortic-valve disease, or their combination. However, prior studies linking LV hypertrophy after CoA repair to blood pressure burden and hypertensive exercise response support the importance of systematic hemodynamic follow-up [28–31].

The association between documented BAV and valve-related morbidity is also consistent with a broader left-heart and aortic developmental phenotype. BAV and CoA are related manifestations of left-sided obstructive and aortopathic disease, and both may be associated with altered vascular wall biology and abnormal aortic mechanics [4,5,32]. These mechanisms were not directly assessed here but support the biological plausibility of the strong association between documented BAV and aortic-valve dysfunction. Associations between BAV and the broader arch-obstruction and pressure-load composites were less consistent in the morphology-restricted sensitivity analysis and should therefore be interpreted more cautiously.

4.5. Procedural Documentation, Multiplicity, and CoA-/Arch-Related Procedure-Entry Burden

The procedural data support the clinical plausibility of the cohort. More than two thirds of patients had a documented operation-source entry, more than one third had a documented catheter-intervention-source entry, and 82.1% had at least one entry of either type. First documented operation dates occurred predominantly early in life, whereas first catheter-intervention dates occurred later. This pattern is compatible with early surgical treatment in many patients and later catheter-based procedures in a subset, although the available registry fields did not permit reliable adjudication of repair type, indication, unique index procedures, or reinterventions.

Multiple procedure entries were frequent: more than one third of patients had two or more operation-source entries, approximately one sixth had two or more catheter-intervention-source entries, and more than half had two or more entries of either type. These findings indicate substantial documented procedural history but should not be interpreted as direct estimates of the number of unique procedures or reinterventions.

The potential CoA-/aortic-arch-related procedure analysis further supports the CoA-centered nature of the documented procedural history. Potential CoA-/arch-related operation entries were documented in 67.7% of patients, and potential CoA-related catheter-intervention entries in 32.7%. The catheter-intervention keys were specific for native CoA balloon dilation, recoarctation balloon dilation, and aortic-isthmus stenting. The operation category was intentionally labeled CoA-/aortic-arch-related because it included aortic-arch procedure codes in addition to classic CoA repair codes.

These findings complement surgical and interventional series showing excellent early survival after repair but persistent late morbidity, including recoarctation, aneurysm formation, hypertension, and later procedures [17,33,34]. The present registry analysis adds a nationwide perspective on documented procedure-entry patterns, but it cannot replace adjudicated longitudinal analyses of reintervention or freedom from reintervention.

4.6. Congenital Substrate: Valve Morphology and Arch Phenotype

Documented BAV was present in 34.4% of the full cohort and accounted for 52.5% of patients with a specific documented aortic-valve morphology. This finding is consistent with the established association between CoA and BAV [4,5]. The observed frequency

should be interpreted as registry documentation rather than systematic echocardiographic ascertainment because a specific aortic-valve morphology was documented in only 65.6% of patients. Documented tricuspid aortic-valve morphology should likewise be understood as a registry documentation item rather than an associated lesion.

The BAV subgroup analysis showed higher frequencies of congenital valvular aortic stenosis, congenital aortic insufficiency, acquired aortic insufficiency, obstruction-related hypertension, and LV hypertrophy. Importantly, valve-related morbidity remained more frequent in patients with BAV even when BAV morphology itself was excluded from the composite definition. This association remained strong in the sensitivity analysis restricted to patients with documented BAV or tricuspid aortic-valve morphology. Thus, documented BAV appears to identify a subgroup with greater valve-related morbidity rather than merely contributing to a circular composite indicator.

4.7. CHD Complexity and Phenotype Heterogeneity

The complexity analysis illustrates the heterogeneity of patients with CoA as the primary diagnosis. CHD complexity should not be interpreted as an independent causal determinant, because the registry classification reflects the overall congenital phenotype rather than the primary lesion alone. Patients may therefore be assigned to a higher complexity category when associated congenital anatomy warrants up-classification. Accordingly, the 630 patients classified as complex CHD represent a selected subset of the broader spectrum of patients with CoA and complex congenital anatomy, because the present cohort was restricted to patients in whom CoA was coded as the primary congenital diagnosis.

Patients classified as complex CHD had a broader congenital substrate, including more frequent aortic-arch hypoplasia, PDA, and VSD. In contrast, several acquired pressure-load diagnoses, including hypertension related to arch obstruction, arterial hypertension, LV hypertrophy, and acquired aortic insufficiency, were broadly similar between moderate and complex CHD. The procedural findings reinforce this interpretation: complex CHD was associated with higher procedure-entry burden, likely reflecting broader congenital anatomy, associated lesions, staged procedures, and greater documentation depth rather than isolated CoA severity.

4.8. Data-Driven Morbidity Sub-Phenotypes

Beyond describing individual diagnoses, the latent class analysis identified five recurring cross-sectional patterns of registry-documented morbidity within the CoA-primary-diagnosis cohort. The largest class was characterized by low documented morbidity burden. The remaining classes reflected an arch-hypertension/pressure-load pattern, a complex multilevel congenital pattern, a BAV/valve-aortopathy pattern, and a systemic-hypertension/recurrent-obstruction pattern. These classes differed descriptively in age, sex, CHD complexity, and documented procedure-entry burden, although none of these variables was used to estimate the latent classes.

The class structure was clinically interpretable but should not be viewed as evidence of fixed biological phenotypes or longitudinal disease stages. Classification uncertainty was moderate, with an entropy of 0.661 and a maximum posterior probability below 0.70 in 25.3% of patients. Nevertheless, the main class profiles remained recognizable among patients with higher posterior classification certainty. In addition, exclusion of patent foramen ovale and complete right bundle branch block produced a closely similar five-class structure, with 93.2% agreement in optimally aligned modal class assignment.

At the same time, the morphology-restricted sensitivity analysis showed that class-number selection was not completely stable across analytical subsets, because the four-class model had a lower BIC than the five-class model among patients with documented BAV or

tricuspid aortic-valve morphology. The latent classes should therefore be interpreted as exploratory patterns of co-documented morbidity rather than as validated clinical entities. Their clinical relevance requires confirmation in independent cohorts with systematic phenotyping, longitudinal follow-up, and outcome data.

4.9. Pressure-Load Morbidity, Hypertension, and Ventricular Remodeling

The documented acquired morbidity pattern was consistent with the established long-term CoA literature. Hypertension related to arch obstruction, residual coarctation, LV hypertrophy, arterial hypertension, recurrent coarctation, and acquired aortic insufficiency are recognized persistent or late problems after CoA treatment [3,6,28,29].

The registry data cannot determine temporal sequence or causality. LV hypertrophy, for example, cannot be attributed to a specific mechanism without blood pressure measurements, gradients, imaging, and treatment history. Nevertheless, the frequent co-documentation of hypertension, residual or recurrent obstruction, and LV hypertrophy indicates that pressure-load-related cardiovascular morbidity represents an important component of the documented clinical burden in this CoA-primary-diagnosis cohort.

4.10. Sex-Stratified Findings in the Context of the Emerging Outcome Literature

Male patients showed higher documented frequencies of obstruction-related hypertension, residual coarctation, LV hypertrophy, and the arch-obstruction and pressure-load composites, consistent with the male predominance of CoA and with evidence that sex is associated with intervention patterns and outcomes after repair [17]. In the present cross-sectional analyses, the association between male sex and documented pressure-load morbidity varied by age. The male-versus-female difference was small in early childhood and larger in older age groups, whereas corresponding sex-by-age interactions were not supported for arch-obstruction burden or aortic-valve dysfunction excluding BAV morphology. This pattern was also observed in the morphology-restricted sensitivity analysis.

These findings should not be interpreted as evidence that female patients with CoA are at lower clinical risk. A recent adult study of isolated CoA reported similar daytime blood pressure and atherosclerotic risk profiles in men and women, but less nocturnal blood pressure dipping, higher pulmonary vascular indices, and higher all-cause and cardiovascular mortality in women [18]. The registry-documented pattern observed here may therefore reflect differences in phenotype, surveillance intensity, treatment history, documentation, or other unmeasured factors rather than a biological sex effect. The adjusted and interaction models were intended to characterize associations with documented morbidity, not to estimate causal effects.

Additional adjustment for a limited proxy of documentation intensity did not materially change the linear sex-by-age interaction for pressure-load burden. However, because documentation depth may itself be related to age, morbidity, and healthcare contact, this sensitivity analysis cannot exclude residual documentation bias or other forms of confounding. The observed sex-by-age pattern should therefore be regarded as hypothesis-generating and as a target for future longitudinal studies with systematic blood pressure, imaging, treatment, and outcome data.

4.11. Extracardiac Comorbidity and Obesity

Extracardiac comorbidity was comparatively modest. Obesity was the most frequently documented extracardiac diagnosis, affecting 5.0% of the cohort. This finding should be interpreted in light of the young age distribution and potential underdocumentation of extracardiac diagnoses in a cardiology-centered registry. In the German KiGGS Wave 2 survey [35], measured obesity prevalence was 5.9% among children and adolescents aged 3 to 17 years, increasing from 2.0% at ages 3 to 6 years to 8.5% at ages 14 to 17 years. Because

the present cohort spans a much broader age range and obesity was derived from routine registry documentation rather than standardized anthropometric assessment, these figures are not directly comparable. Nevertheless, the comparison suggests that the observed 5.0% registry frequency cannot by itself be interpreted as evidence of either unusually low obesity burden or complete ascertainment. The comparatively low documentation frequencies of other extracardiac diagnoses further support cautious interpretation of extracardiac morbidity estimates in this dataset.

4.12. Clinical Implications

The findings are consistent with the established need for structured lifelong follow-up in patients with CoA. Because this registry analysis did not include measured blood pressure values, imaging measurements, gradients, medication exposure, repair type, or procedural indications, it cannot define optimal screening intervals, treatment thresholds, or individualized surveillance strategies. The documented morbidity patterns observed here are therefore hypothesis-generating and should be interpreted in the context of existing guideline-based follow-up recommendations focused on blood pressure, residual or recurrent arch obstruction, ventricular remodeling, and associated aortic-valve disease [2,15,16].

Blood pressure surveillance remains clinically important because hypertension after CoA repair may be present at rest, masked during routine office measurements, or unmasked during exercise testing. Ambulatory blood pressure monitoring and exercise blood pressure assessment may therefore provide clinically relevant information beyond resting measurements [3,12–14]. Long-term imaging is likewise important for assessment of the repaired or native arch, thoracic aorta, residual or recurrent narrowing, aneurysm formation, ventricular remodeling, and associated aortic-valve disease.

Patients with documented BAV may warrant particular attention to valve function and aortic dimensions. Patients classified as moderate CHD should not be considered free of long-term risk solely because they lack complex associated anatomy, as pressure-load morbidity was also documented in this group. The sex-related and latent-class findings should be regarded as hypothesis-generating and used to inform future studies rather than to alter surveillance intensity on their own.

4.13. Multiple Testing and Robustness of Exploratory Findings

Because this was a descriptive registry study with multiple exploratory subgroup comparisons, unadjusted p values were not interpreted as confirmatory hypothesis tests. Benjamini–Hochberg FDR correction was used as a robustness assessment within predefined comparison families. The major patterns were largely retained, including age-group differences in documented acquired morbidity and composite morbidity, higher procedure-entry burden in patients with documented BAV and in patients with complex CHD, and higher documented pressure-load and arch-obstruction morbidity in males. In contrast, borderline sex differences in multiple operation and catheter-intervention entries did not remain significant after FDR correction.

These findings support a conservative interpretation of the exploratory subgroup analyses. In particular, the more robust sex-related findings concern documented pressure-load and residual-obstruction morbidity, whereas sex differences in multiple procedure entries were weaker. FDR correction does not address residual confounding, incomplete documentation, center-level variation in coding or ascertainment, or missing hemodynamic and imaging data. All FDR-adjusted findings should therefore remain descriptive and hypothesis-generating.

4.14. Documented Morbidity as a Distinct, Real-World Measure

A recurring theme of this study is that registry-coded diagnoses represent documented morbidity rather than systematically screened prevalence. The incompleteness of registry documentation is directly illustrated by aortic-valve morphology, a universal clinical attribute for which no specific morphology was documented in 34.4% of patients. This documentation gap is important for interpretation of all diagnosis-based analyses.

The gap is best understood as a systemic feature of clinical documentation rather than as a shortcoming of individual clinicians or centers. Hospital correspondence and routine records are generated primarily for immediate, lesion-focused communication; comorbidities such as obesity or mood disorders are frequently managed by other providers and may not be consolidated into the cardiac record [36], while acquired and extracardiac morbidity may be under-captured in cardiology-centered documentation [37]. This matters particularly in congenital heart disease, where patients are multimorbid [38,39] and require lifelong, cross-disciplinary follow-up that may itself be interrupted [40]. Comprehensive history-taking and structured recording of the broader clinical picture, not only the index cardiac lesion, are therefore particularly important in this population.

Two complementary interpretations of the gap between registry-documented and intensively screened morbidity are possible. First, incomplete routine documentation may lead the registry to underestimate true morbidity; the relatively low documented frequency of conditions such as obesity [41] is compatible with this possibility. Second, much published CoA morbidity derives from single-center or specialist cohorts in which selected patients undergo intensive ascertainment using ambulatory or exercise blood pressure monitoring and cross-sectional imaging. Because more intensive ascertainment detects additional disease, including post-coarctation hypertension [3,42], prevalence estimates from such cohorts are not directly comparable with frequencies derived from routine registry documentation. These interpretations are not mutually exclusive, and the present data cannot determine their relative contribution because no within-cohort gold-standard screening or center-level information was available.

Recognizing these limitations does not diminish the value of registry data but defines the level at which they can be interpreted. The registry captures a broad spectrum of information recorded during routine care, while completeness varies across data domains. For example, a specific aortic-valve morphology was documented in 65.6% of patients, whereas a plausible first documented procedure date was available in 79.2%. The principal value of these data is therefore their ability to characterize patterns of documented morbidity and procedure-entry history across a large nationwide registry cohort and, at the same time, to make limitations of routine documentation visible. Future linkage to protocolized clinical assessment or targeted source-record validation could help quantify the extent to which documented registry morbidity corresponds to systematically ascertained disease.

4.15. Strengths

The major strength of this study is the large nationwide multicenter registry cohort. Many CoA studies derive from single-center surgical, interventional, or adult congenital heart disease cohorts, whereas the present dataset provides a broad real-world profile of patients with CoA recorded as the primary congenital diagnosis across Germany. The analysis adds clinical granularity by combining congenital substrate, acquired morbidity, diagnostic burden, registry-documented morbidity composites, documented procedural history, procedure-entry multiplicity, potential CoA-/aortic-arch-related procedure entries, and exploratory age-, BAV-, complexity-, sex and latent-class-related patterns. This allows a detailed characterization of the documented CoA-centered phenotype while preserving the distinction between registry-documented morbidity and procedure-entry burden on

the one hand and systematically screened prevalence or adjudicated clinical event rates on the other.

4.16. Limitations

Several limitations should be considered. As a registry-based observational study, the analyses depend on the completeness and consistency of routine clinical documentation. An absence of a coded diagnosis or procedure cannot be equated with an absence of disease or treatment. Accordingly, the reported frequencies reflect registry-documented morbidity and procedure-entry burden rather than systematically screened prevalence or adjudicated event or reintervention rates. Registration in the NRCHD is voluntary and does not provide population-complete ascertainment of all patients with CoA in Germany. In addition, the present analysis was restricted to patients with CoA coded as the primary congenital diagnosis. A further 1117 registry participants had CoA documented only as an associated congenital diagnosis and were not included. The findings therefore characterize a CoA-primary-diagnosis cohort and should not be generalized to the full spectrum of patients with CoA, particularly those with complex CHD in whom another lesion may define the primary diagnosis.

Cross-sectional age-group comparisons cannot establish temporal sequence, incidence, progression, or within-patient change and may additionally reflect differences in treatment era, follow-up duration, survival, referral patterns, and opportunities for diagnostic documentation. Treating-center identifiers, reliable treatment era, time since CoA repair, and individual duration of registry follow-up were not available for analysis. Granular clinical information such as repair type and indication, measured or ambulatory blood pressure, imaging and hemodynamic data, medication exposure, and procedural outcomes was also unavailable, limiting assessment of underlying mechanisms and treatment effects. Procedure-source entries could not be reliably adjudicated as unique procedures, index repairs, or reinterventions.

The latent class and sex-by-age analyses were exploratory and should be regarded as hypothesis-generating. Latent class separation was moderate, and classification uncertainty was non-negligible. Although the main five-class structure was robust to the exclusion of patent foramen ovale and complete right bundle branch block, the morphology-restricted sensitivity analysis favored four over five classes in the targeted comparison, indicating some sensitivity of class-number selection to the analytical subset. The derived morbidity patterns therefore require validation in independent cohorts with systematic phenotyping, longitudinal follow-up, and clinical outcomes. Similarly, the observed sex-by-age association with documented pressure-load morbidity cannot distinguish biological effects from differences in surveillance, treatment, or documentation.

5. Conclusions

This nationwide registry study shows that CoA as the primary congenital diagnosis is associated with substantial but structured heterogeneity in documented morbidity. Rather than representing a single uniform clinical phenotype, the cohort comprised recurring morbidity patterns centered on low documented burden, arch-related hypertension and pressure load, complex multilevel congenital anatomy, BAV-associated valve and aortic disease, and systemic hypertension with recurrent obstruction. These patterns were accompanied by marked differences in age, CHD complexity, sex distribution, and documented procedure-entry burden.

Three clinically relevant themes emerge. First, documented BAV identified a strong valve-morbidity phenotype, even when BAV morphology itself was excluded from the valve-dysfunction outcome. Second, complex CHD was characterized predominantly by

broader congenital anatomy and greater procedure-entry burden rather than uniformly greater acquired pressure-load morbidity. Third, pressure-load morbidity represented a major acquired component of the CoA phenotype and showed an age-dependent association with sex that was not observed for the other morbidity domains.

Taken together, these findings move the description of CoA beyond aggregate diagnosis frequencies toward a phenotype-oriented view of lifelong morbidity. The identified patterns should not yet be used as fixed clinical categories, but they provide a clinically interpretable framework for longitudinal validation and for studying whether different CoA morbidity profiles warrant different surveillance priorities. Registry-based ascertainment necessarily reflects documented rather than systematically screened morbidity, but within that scope these data provide a broad real-world picture of how CoA-associated morbidity is organized across the life course.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/medsci14070708/s1, Table S1: Exploratory categorical subgroup comparisons, effect sizes, and Benjamini–Hochberg FDR-adjusted q values; Table S2: Model-estimated class proportions and modal class sizes for the one- to six-class full-cohort LCA models (N = 2720).

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the NRCHD.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

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