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ORIGINAL ARTICLE

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Long-term outcomes after aortic coarctation repair in Maltese patients: A population-based study

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Abstract

Objectives: To investigate survival and freedom from reintervention after aortic coarctation repair in Maltese patients and to compare cardiovascular mortality in coarctation repair survivors with that in the general population.

Design: All 72 aortic coarctation patients with any type of repair, born by end-1997 and logged in the local database were included. Trends in timing and type of repair were determined by comparing patients born before and after 1985. Kaplan-Meier analyses of survival and reintervention-free survival were performed on the 59 repair survivors with complete follow-up data (mean follow-up 26.13 ± 9.62 (range 1.05–44.55 years). Cardiovascular mortality in repair survivors was compared with that in 438 age- and sex-matched general Maltese controls.

Results: Patients born after 1985 underwent repair at a younger age (median age 0.18 vs 13.96 years; $P < .001$), with less patch aortoplasties in favor of end-to-end anastomosis or transcatheter stenting. Among the 59 long-term follow-up patients, there were 7 cardiovascular deaths and 10 patients needed reintervention. Estimated mean survival was 40.33 years (95% CI 37.71, 42.95) with a survival rate of 67.5% at 40 years from repair. Estimated mean reintervention-free survival was 38.13 years (95% CI 34.52, 41.75) with freedom from reintervention rate of 77% at 30 years. Patients repaired aged <10 years required earlier reintervention (estimated mean reintervention-free survival 35.12 years (95% CI 29.54, 40.71) vs 40.80 years (95% CI 37.16, 44.37); $P = .04$). There was an excess of cardiovascular deaths among repaired coarctation subjects compared to the general population (11.9% vs 1.4%; $P < .001$) and survival in coarctation patients was significantly lower (67.90 years (95% CI 60.28, 75.52) vs 85.78 years (95% CI 83.12, 88.44); $P < .001$).

Conclusions: Despite earlier diagnosis and repair, contemporary coarctation repair survivors remain at increased risk of cardiovascular death. An important proportion require repair site reintervention. Specialist follow-up and aggressive cardiovascular risk factor management are mandatory to improve long-term outcomes.

KEYWORDS

aortic coarctation, follow up studies, population-based, survival analysis

1 | INTRODUCTION

Aortic coarctation (CoA) refers to a narrowing of the aorta, most often near the ligamentum arteriosum adjacent to the origin of the left subclavian artery. It is associated with several other congenital heart defects (CHD), most commonly bicuspid aortic valve (BAV), as well as several syndromes including Turner and Williams-Beuren syndromes.[1] CoA has an incidence of about 1 in 2500 live births and is twice as common in males.[2] Since the first reported successful CoA repair in 1945,[3] there have been significant developments in surgical techniques. Transcatheter aortic stenting was first reported in the early 1990s[4] and has become the treatment of choice, particularly in adults with native or recurrent/residual coarctation.[1] CoA is part of a generalized arteriopathy, and, despite the improved survival after repair, long-term survival remains lower than in the general population due to cardiovascular complications and frequent incidence of arterial hypertension.[5]

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Malta is a group of islands in the Mediterranean Sea located 93km south of the Italian island of Sicily. Most inhabitants are native Maltese, who are genetically of Eastern Mediterranean descent with Greco-Roman and Arabic influences and a later European influence. The islands have a population of around 425 000 and a crude birth rate of 9.5/1000 in 2013.[6] Cardiovascular diseases were the leading cause of death in Malta in 2014, accounting for 38% of all deaths.[7] Epidemiological studies in the 1990s reported the overall incidence of CHD in Malta to be comparable to that in other European countries at 0.8% and rates of CoA were comparable to those reported in similar studies at the time.[8] They also confirmed a consistent decline in local mortality from CHD over time,[9] in line with trends worldwide. At the time of these studies, the Maltese Pediatric Cardiology Database (MAPCAD) was instituted and all known CHD cases have been included in it both prospectively and retrospectively since.[10] Virtually all congenital cardiac surgery on children and adults born in Malta is carried out in tertiary referral centers in the United Kingdom, through a reciprocal National Health Service agreement, while a number of structural cardiac interventions, including CoA stenting, are carried out locally by visiting specialists. Transfer of care from pediatric to adult services takes place at the age of 14–16 years. Transthoracic echocardiography was introduced in the mid-1980s and an on-site pediatric cardiology service started operating in the early 1990s, with adult congenital heart disease (ACHD) services starting some years later.[11]

This is the first report of the long-term outcomes of Maltese patients with repaired CoA and due to the nature of the population, constitutes a population-based study. The principal aims were to determine overall and reintervention-free survival from reparative surgery or intervention and to investigate cardiovascular mortality in CoA repair survivors when compared to the general Maltese population.

2 | METHODS

2.1 | Study protocol

All patients entered in MAPCAD with a main diagnosis of aortic coarctation and born before December 31, 1997 were extracted at end December 2013. Patients where CoA was part of more complex CHD and those with interrupted aortic arch were excluded. For long-term outcome analyses, only patients who survived the original repair and who had complete follow-up data till time of data extraction were included. Clinical data was obtained from MAPCAD and supplemented with information gathered from hospital notes. Mortality data was provided by the National Mortality Registry.

In a first analysis on all patients with repaired CoA, age at reparative surgery or intervention, mode of repair and perioperative/periprocedural mortality was compared between subjects born before and those born after 1985. The choice of timing for this division was based on the period when echocardiography was introduced in Malta.[12] Long-term outcome analyses among CoA repair survivors assessed were: (1) overall survival from reparative surgery/intervention with sub-analyses based on patient gender, age at repair ($<$10 years vs $>$10 years) and mode of repair, (2) comparison of cardiovascular mortality in CoA repair survivors with that in an age- and sex-matched general population cohort (control cohort), (3) reintervention-free survival with a further analysis based on mode of repair and age at repair. A cutoff age of 10 years at time of primary repair was chosen arbitrarily as it provided the most even split within the patient cohort. In view of the small number of patients represented in some repair categories, sub-analyses based on mode of repair concentrated only on the two commonest repair modalities represented in our cohort (Dacron patch aortoplasty and end-to-end anastomosis). The general population control cohort consisted of all 438 Maltese nationals with sex and date of birth matching those of each patient in the repaired CoA cohort. Non-Maltese nationals were excluded from the control group in view of potential differences in genetic predisposition for cardiovascular disease associated with other ethnic backgrounds.

Perioperative/periprocedural mortality was defined as death at, or within 30 days of, reparative surgery or intervention. The terms “CoA repair” and “reparative surgery or intervention” are used interchangeably and refer to the first surgical or transcatheter procedure during which CoA relief was achieved. “Cardiovascular mortality” was defined as death from any cardiac cause as declared on the death certificate (with or without prior postmortem studies), and included coronary artery disease (CAD), acute aortic syndromes, heart failure and death directly related to reinterventions. However, perioperative mortality related to the original repair was excluded. The term “reinterventions” refers to any repeat surgical or transcatheter interventions on the aorta directly related to the management of residual or recurrent pathology at/adjacent to the site of CoA repair. These included procedures to relieve recoarctation or correction of aneurysm formation adjacent to the repair site, but excluded repeat surgery/interventions performed within 30 days from, and directly related to, the primary reparative procedure and aimed to treat a complication of the repair itself. Electrophysiological studies and radiofrequency ablation of arrhythmias, implantation of permanent pacemakers and percutaneous coronary interventions or coronary artery bypass grafting needed to manage acquired coronary artery disease were excluded. In the case of patients requiring more than one reintervention, only the first procedure was taken into consideration. “Reintervention-free survival” refers to time in years between reparative surgery/intervention and the first reintervention. Clinical decision making regarding the timing of such reinterventions was in line with international recommendations.[1]

The study received institutional data protection clearance and was approved by the University of Malta Research Ethics Committee. It conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all participants or authorized representatives.

2.2 | Statistical methods

Categorical variables were analyzed using chi-square tests. Fisher’s exact test was applied in the case of smaller sample sizes. Comparison of all continuous variables was performed using Mann–Whitney *U* test after Shapiro-Wilk test determined a nonnormal distribution for all. Kaplan-Meier methodology was used to determine estimates of overall

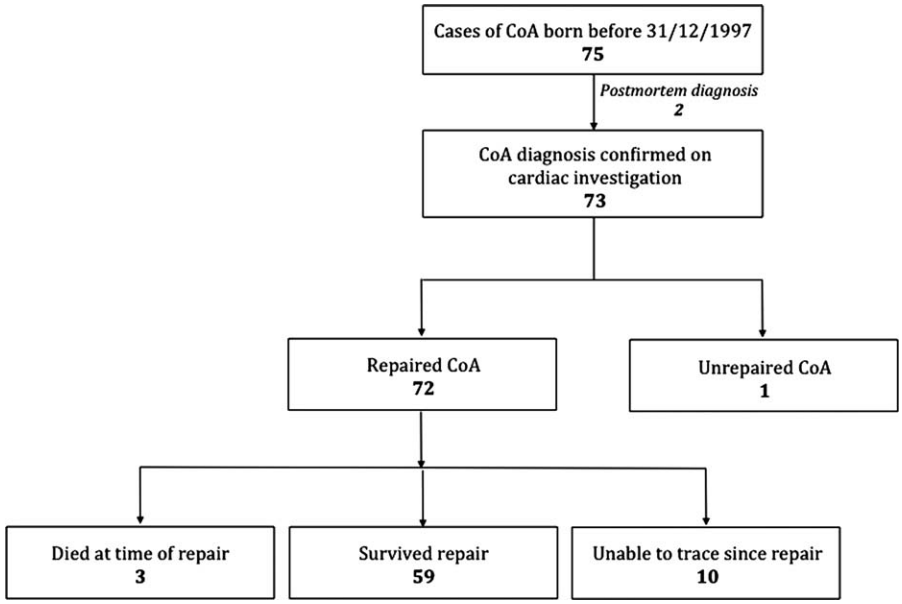

FIGURE 1 Cohort of Maltese patients with aortic coarctation (CoA) included in institutional database. In our study, unoperated CoA patients were excluded. For the purposes of long-term outcome analyses, only repair survivors with complete follow-up data were included (n = 59)

and reintervention-free survival from repair for CoA patients and survival for all repaired patients and their matched controls. The statistical significance of comparisons between Kaplan-Meier curves was calculated using a log-rank test. All analyses were performed using SPSS 21 (IBM SPSS 21, SPSS Inc., Chicago, IL). Statistical significance was defined as $P \leq .05$.

3 | RESULTS

Seventy-five patients with CoA born before end December 1997 were extracted from MAPCAD at end December 2013. Of these, 72 cases (26 born before 1985) had undergone repair. CoA repairs were carried out between 1968 and 2012. Analyses of overall survival were performed on the 59/72 (81.9%) CoA repair survivors with complete follow-up data, with 1/59 patients being excluded from estimates of reintervention-free survival due to lack of accurate data on the timing of his first reintervention (Figure 1). Table 1 summarizes the baseline characteristics of the 72 patients in the repaired CoA cohort. Forty-five patients (62.5%) were male and an underlying genetic syndrome was present in 4 (5.6%) patients. The commonest associated congenital cardiac lesion was bicuspid aortic valve (BAV), which featured in 30 (41.7%) patients, followed by ventricular septal defect (VSD) in 11 (15.3%) patients. The distribution of different types of repair within the repaired cohort is shown in Table 2.

3.1 | Trends in management of aortic coarctation over time

The 26/72 patients born after 1985 underwent repair at a significantly younger age (mean 2.35 ± 5.18 years, median 0.18 years) compared to the 46 patients born before 1985 (mean 16.03 ± 11.63 years, median 13.96 years) ($P < .001$). There were also significant differences in the repair methods utilized in the two subgroups, with a move away from Dacron patch aortoplasty (pre-1985 34.8% vs post-1985 0%) in favor of resection with end-to-end anastomosis (pre-1985 39.1% vs post-1985 84.6%) or transcatheter stenting (pre-1985 2.2% vs post-1985 11.5%) in the younger subgroup ($P < .001$). Mortality at repair in the two subgroups was similar, with 2/46 (4.3%) deaths for patients born before 1985 and one death (3.8%) among those born after 1985 ($P = 1.00$).

TABLE 1 Basic characteristics of the patients with repaired coarctation (N = 72)

Characteristic	Number (%) N = 72
Gender	
Male	45 (62.5)
Female	27 (37.5)
Underlying genetic syndrome	
Cornelia de Lange	1 (1.4)
Turner	1 (1.4)
Unspecified	2 (2.8)
Other congenital cardiac lesions	
VSD	11 (15.3)
ASD	5 (6.9)
BAV	30 (41.7)
PDA	9 (12.5)
Head & neck vessel abnormalities	4 (5.6)
Other abnormalities[a]	5 (6.9)

[a]Other abnormalities = tricuspid valve anomaly; vascular ring, subaortic stenosis, persistent left superior vena cava, partial anomalous pulmonary venous drainage, abnormal systemic venous drainage.
Abbreviations: ASD = atrial septal defect; BAV = bicuspid aortic valve; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

TABLE 2 Distribution of aortic coarctation reparative techniques within the repaired cohort (all repaired; n = 72) and the repair survivors with complete long-term follow-up (repair survivors; n = 59)

Repair type	All repaired *Number (%)*	Repair survivors *Number (%)*
Resection & end-to-end anastomosis	40 (55.6)	35 (59.3)
Dacron patch aortoplasty	16 (22.2)	12 (20.3)
Subclavian flap aortoplasty	5 (6.9)	3 (5.1)
Gore-tex patch repair	4 (5.6)	3 (5.1)
Transcatheter stenting	4 (5.6)	4 (6.8)
Resection & Dacron tube graft	3 (4.2)	2 (3.4)

The terms "repair" and "reparative technique" refer to any surgical or transcatheter procedure used to achieve CoA relief.

3.2 | Overall survival after aortic coarctation repair and comparison of cardiovascular mortality with the general Maltese population

There were 38 males and 21 females in the 59-patient cohort of CoA repair survivors with complete long-term data. Thirty-two patients (54.2%) were operated before age 10 years and 27 patients (45.8%) were over 10 years of age at time of repair. Mean length of follow-up from initial repair was 26.13 ± 9.62 years (range 1.05–44.55 years). CoA relief techniques represented in this cohort are summarized in Table 2. Hypertension (HT) was documented in 16 patients (27.1%).

There were 7 cardiovascular deaths (5 males) during follow-up: 4 deaths in patients with Dacron patch aortoplasty, and 1 death each in a patient with resection and Dacron tube graft, resection with end-to-end anastomosis and subclavian flap aortoplasty. No deaths occurred during the first 20 years, with most deaths (6/7) occurring between 20 and 40 years from repair. The estimated mean survival from initial CoA repair was 40.33 years (95% CI 37.71, 42.95). Kaplan-Meier estimates of survival rates were 90.5% at 30 years and 67.5% at 40 years from repair (Figure 2). Mean age of cardiovascular death was 50.33 ± 16.29 years and median age was 56.73 years. Although estimated mean survival was better for females, patients operated at age <10 years and in those with resection with end-to-end anastomosis, none of the comparisons in survival reached statistical significance as follows: males 40.00 years (95% CI 36.63, 43.37) vs females 41.81 (95% CI 37.69, 45.94) ($P = .77$); repair <10 years old 43.06 years (95% CI 40.25, 45.87) vs repair >10 years old 39.05 years (95% CI 35.50, 42.59) ($P = .21$); Dacron patch aortoplasty 40.05 years (95% CI 36.40, 43.71) vs resection with end-to-end anastomosis 43.51 years (95% CI 41.50, 45.51) ($P = .21$).

There was a significant excess of cardiovascular deaths in the repaired CoA cohort (6/59, 11.9%) when compared to the general population control group (6/438, 1.4%) ($P < .001$). Although repaired CoA patients were younger at time of cardiovascular death compared to age- and sex-matched controls (median age 56.37 years vs 64.90 years), this difference failed to reach statistical significance ($P = .63$). Estimated mean survival for CoA repair patients (67.90 years [95% CI 60.28, 75.52]) was significantly lower than that for general population subjects (85.78 years [95% CI 83.12, 88.44]) ($P < .001$) (Figure 3). Though the difference in survival estimates was significant in both sexes, it was more marked among male CoA patients. In males, estimated mean survival was 59.45 years (95% CI 54.28, 64.62) compared to 81.34 years (95% CI 80.06, 82.62) in the general population ($P < .001$), while female CoA repair patients had an estimated mean survival of 73.05 years (95% CI 64.23, 81.87) compared to 86.49 years (83.86, 89.12) in general population females ($P = .002$) (Figure 4).

3.3 | Reintervention-free survival after aortic coarctation repair

Ten patients (17.2%) underwent reintervention during follow-up, with time to reintervention ranging between 0.92 years and 44.55 years

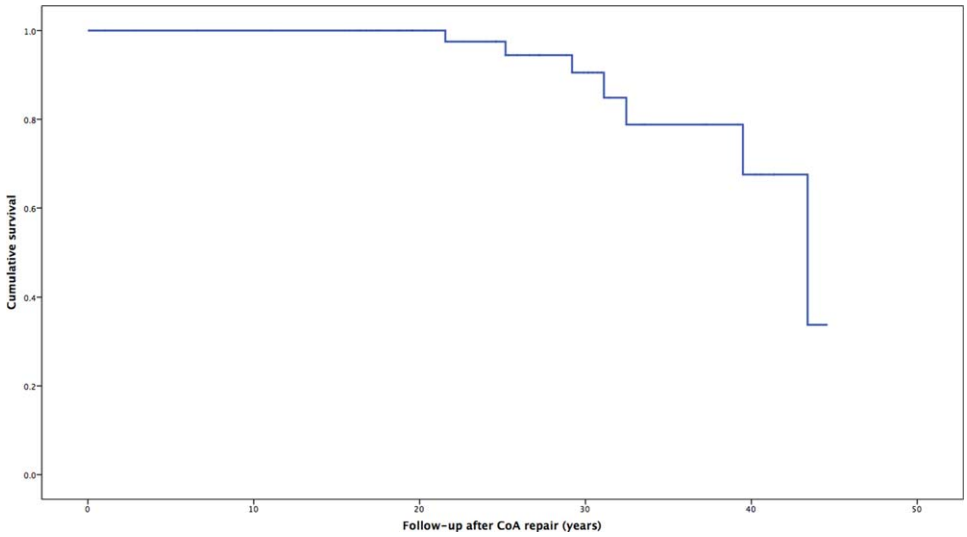

FIGURE 2 Kaplan-Meier curve showing overall survival from original repair for all CoA repair patients with complete follow-up data (n = 59). Estimated mean survival was 40.33 years (95% CI 37.71, 42.95). There were 7 deaths from cardiovascular causes during follow-up, with 6 occurring between 20 and 40 years from repair

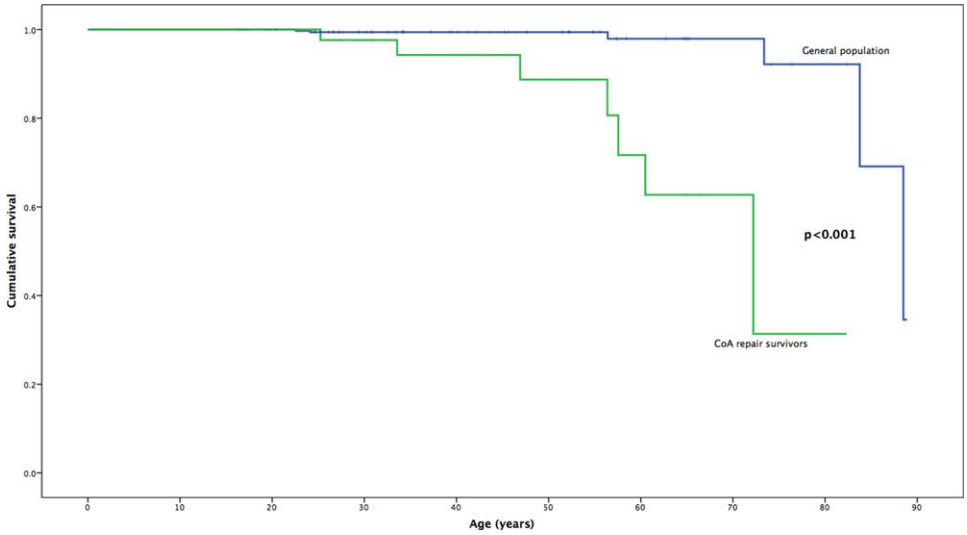

FIGURE 3 Kaplan-Meier curves comparing survival in CoA repair survivors with an age- and sex-matched general Maltese population control cohort. A statistically significant difference in cardiovascular mortality was demonstrated

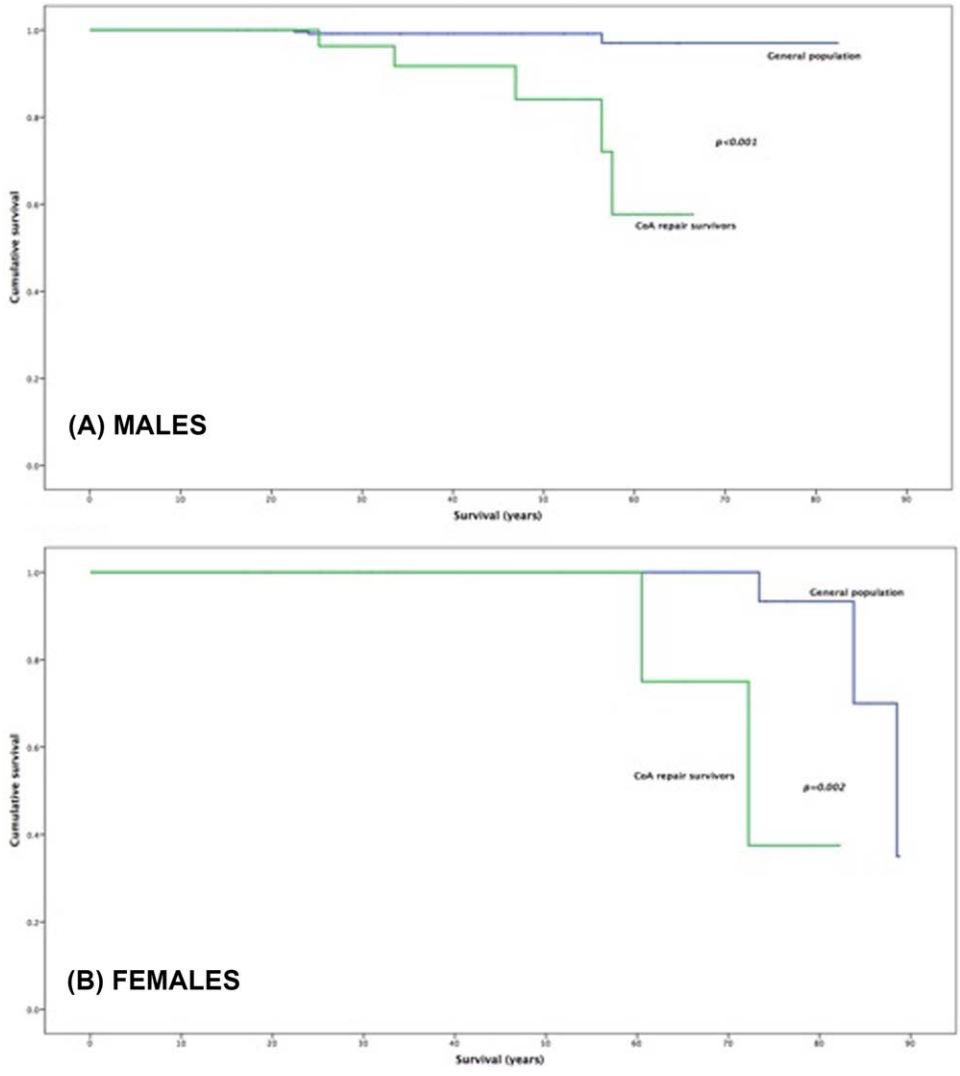

FIGURE 4 Kaplan-Meier curves comparing survival in (A) male and (B) female CoA repair patients with age-matched general population controls. Though the difference in survival estimates was significant in both sexes, it was more marked among male CoA patients

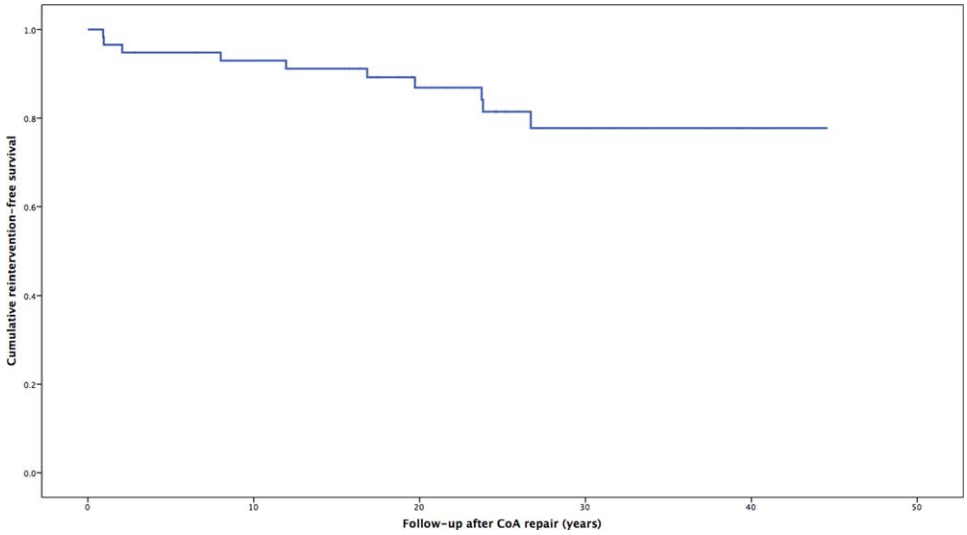

FIGURE 5 Kaplan-Meier curve showing reintervention-free survival from original repair (n = 58). Estimated mean reintervention-free survival from repair was 38.13 years (95% CI 34.52, 41.75) with an estimated survival rate of 77% at 30 years

from the original repair. Recoarctation was the main indication (90%) for repeat intervention, with 6 patients undergoing balloon angioplasty, while 2 were stented and 1 patient underwent Dacron patch repair. The remaining patient underwent surgical repair of an aneurysm at the previous repair site. The estimated mean reintervention-free survival from repair was 38.13 years (95% CI 34.52, 41.75) with Kaplan-Meier estimates of survival rates of 93% at 10 years, 86.9% at 20 years, and 77% at 30 years (Figure 5). Patients who underwent repair aged <10 years underwent reintervention significantly earlier compared to those operated at age >10 years (estimated mean reintervention-free survival 35.12 years (95% CI 29.54, 40.71) vs 40.80 years (95% CI 37.16, 44.37); $P = .04$). Comparison of reintervention-free survival between patients with Dacron patch aortoplasty and resection with end-to-end anastomosis showed the latter to require aortic reintervention at a younger age after repair, although the difference failed to reach statistical significance (estimated mean reintervention-free survival 41.72 years (95% CI 38.62, 44.82) vs 36.99 years (95% CI 31.99, 41.99); $P = .20$)).

4 | DISCUSSION

Our study is the first to investigate long-term outcomes in Maltese patients with repaired CoA, with follow-up in excess of 40 years from original repair in some patients. Our initial analysis of all local cases that underwent CoA repair demonstrates a move towards earlier repair, aided by earlier diagnosis through wider access to imaging, particularly the introduction of echocardiography. This study also documents a change in repair technique with a move away from prosthetic patch aortoplasty in favor of end-to-end anastomosis and, later, transcatheter aortic stenting particularly in older patients. These trends in diagnosis and surgical management had previously been documented in an observational study on a smaller cohort of CoA patients born in Malta between 1925 and 1994.[12] As endovascular stenting is only a recent addition to the management armamentarium of native CoA,[13] most longer-term outcome studies in the literature to date have concentrated on patients corrected surgically. Furthermore, the length of follow-up for patients with stented native CoA is inevitably much shorter.[14] Our study is unique in that it includes patients with all modalities of CoA relief.

Despite satisfactory CoA relief, patients remain at increased risk of premature cardiovascular death.[1] In our repaired cohort followed long-term, the estimated mean survival was 40.33 years (95% CI 37.71, 42.95), with a survival rate of 67.5% at 40 years from repair. Most deaths (6 of 7) occurred between 20 and 40 years from repair, with a mean age of cardiovascular death of 50.33 ± 16.29 years (median age = 56.37 years). Long-term outcome studies in recent years reported somewhat lower survival rates among repaired CoA patients. In 2013, Brown et al reported a mean age at death among surgically-repaired patients in a single high-volume institution of 34.2 ± 20.1 years and an actuarial survival rate of 73.5% at 30 years.[2] while, more recently, Bambul Heck et al reported a median age of death of 46 years (range 30–64 years).[15]

Although survival in the Maltese cohort appears to be better compared to that in recent papers, this difference should be interpreted with caution, particularly considering the small number of subjects in our study. Among our repaired subjects, survival was better in females, patients operated at age <10 years and in patients with end-to-end anastomosis (compared to Dacron patch aortoplasty), though none of the differences reached statistical significance. Older age at repair[2,16,17] and male gender[16] have previously been found to be predictive of decreased survival after CoA repair. Other factors associated with reduced survival include preoperative hypertension,[2] postoperative hypertension,[16,18] and associated cardiac malformations.[18] Repaired CoA patients showed a strongly significant excess of death from cardiovascular causes when compared to the age- and sex-matched general Maltese population, which finding is in line with what has been previously reported by several authors from different institutions.[1,2,19,20]

Furthermore, our findings suggest that the discrepancy in survival between CoA patients and general population counterparts could be even more marked in males (Figure 4).

This excess of cardiovascular mortality is thought to be multifactorial. Hypertension (HT) is very common, becoming more prevalent with increasing patient age, and could lead to accelerated atherosclerosis. A systematic review of the literature from 2013 reported a median prevalence of HT of 32.5% (range 25–68%) developing late after anatomically satisfactory CoA repair.[21] The prevalence of HT in our cohort was 27.12%, though this could be an underestimate due to difficulty to access the notes of the 7 patients that died prior to data extraction. Although recoarctation is a recognized contributor, it accounts for only a small proportion of cases of HT late after CoA repair,[20,22] and other factors, including use of prosthetic material during CoA repair, male sex and older age at follow-up have been identified as independent risk factors associated with development of HT.[22] In the absence of significant recoarctation, medical treatment of HT in this setting often follows the same algorithms applied for essential HT.[23] An increase in left ventricular (LV) mass has been observed in several patients even in the absence of HT and is thought to be related to central aortic stiffness.[24–26] This can in turn result in diastolic dysfunction and increase the risk of subendocardial ischemia and arrhythmias.[2] While CAD is a main contributor of increased mortality among repaired CoA patients, it is still uncertain whether there is an independent association between the two[27,28] or whether it is the result of the higher prevalence of atherosclerosis risk factors coupled with other factors such as endothelial dysfunction and increased proinflammatory cytokines.[29] Interestingly, some authors reported little improvements in long-term survival after CoA repair over time despite progress in surgical management and better care of cardiovascular risk factors and concomitant cardiac malformations, suggesting that other factors might play a role.[2]

In our cohort, the estimated mean reintervention-free survival from repair was 38.13 years (95% CI 34.52, 41.75) with an estimated survival rate of 77% at 30 years. The majority of reinterventions (90%) were performed to address significant recoarctation. In their larger-scale outcome study, Brown et al reported better rates of freedom from reintervention on the descending aorta with rates of 89.4% at 30 years.[2] Once again, this difference is difficult to interpret considering possible differences in surgical techniques, as well as a marked difference in patient populations under study. Our observation that younger age at repair (in our case defined as $<$10 years old) was associated with significantly earlier reintervention on the descending aorta is in line with that reported by other studies,[2,17,18] even though in the latter studies the age cutoff was lower. The smaller size of the anastomosis in smaller children and a more severe nature of CoA calling for early surgery could predispose to recoarctation requiring earlier reintervention.[2]

4.1 | Limitations

The small number of patients in our cohort represents the main limitation of this study, which is an inevitable consequence of the small Maltese population. However, the small geographical area coupled with the structure of the Maltese healthcare system, where cardiovascular specialist care is effectively centralized in our institution, allows for population-based studies like the current one, which in turn should offer a more realistic picture of the unnatural history of this condition. Furthermore, every effort was made to include all known patients in our system, and subdivision of the study population was limited to as few categories as possible to avoid reducing the numbers further during statistical analyses. Similarly, assessment of reinterventions was purposefully limited to those involving the descending aorta in relation to previous repair, and excluded interventions related to concomitant congenital malformations. The retrospective nature of the study led to incomplete or unavailable data on a few occasions, particularly for the patients that died during follow-up.

5 | CONCLUSIONS

Our study consolidates the notion that despite significant advances leading to earlier diagnosis and wider access to specialist surgical or transcatheter CoA relief, CoA repair survivors remain at increased risk of cardiovascular mortality and an important proportion require at least one further intervention to the descending aorta in their lifetime. Better long-term outcomes can only be ensured through regular clinical and imaging follow-up, every 1 to 2 years,[1] coupled with aggressive traditional cardiovascular risk factor management, particularly HT control. Our findings also suggest that male CoA patients might be at an even higher risk of cardiovascular morbidity and mortality, calling for even stricter follow-up and risk factor management.

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CONFLICTS OF INTEREST

The authors report no relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

The final article was approved by both authors.

Data collection, analysis and interpretation and drafting of the article: Caruana

Inception of MAPCAD and data entry, critical revision of this article: Grech

Concept and design and statistical analysis of the data: Caruana and Grech

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