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Selection for early surgery in asymptomatic mitral regurgitation: A Markov model

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ABSTRACT

Background: Current guidelines propose mitral valve repair in asymptomatic chronic mitral regurgitation (MR) when the likelihood of repair is 90% or more. As this figure is not evidence-based, we sought whether the results of a decision-analytic model could facilitate the selection between early surgery (ES) and watchful waiting (WW) based on current guidelines.

Methods: A Markov model was developed to reflect the anticipated health states in MR (pre-operative, post-operative, post-complication and death). Risks and transitions were informed by the literature. Implications of the strategies for survival, quality-adjusted life years (QALYs), cost and cost-effectiveness were calculated from a US healthcare provider perspective.

Results: In the reference case (90% repair), QALY with ES was superior to WW (11.2 [0.4–21.3] vs 10.7 [95%CI: 1.0–21.3]) at an incremental cost-effectiveness of $54,659 ($45,030–$64,288) per QALY. Sensitivity analyses of health benefit showed the main variables influencing outcome were repair rate, operative mortality and risks of heart failure and death with medical management. At the registry repair rate (50%), outcomes of ES were worse than WW, and threshold analysis showed that a repair rate of 84% was required for ES to be superior. High medical risk (yearly heart failure risk 5.6 ± 6.6% and mortality 2.5 ± 4%) was the most favorable scenario for surgery; ES was more effective when mortality in the WW group was >3.5%/year.

Conclusion: A Markov model might be used to guide the selection of asymptomatic patients for mitral repair, based on local variations in risk and complications as well as repair rate.

1. Introduction

Mitral regurgitation (MR) is the most common regurgitant heart valve lesion, and degenerative valve disease is the most common etiology [1]. Early surgery is often considered for severe MR in asymptomatic individuals, because volume loading eventually has irreversible effects on LV function and has been associated with sudden death [2]. The main disadvantage of ES is failure to repair the mitral valve, which exposes the patient to the health burden of valve replacement, as well as the morbidity of surgery. Moreover, although the guidelines emphasize the performance of ES if there is a 90% likelihood of repair, registry data suggest that the repair rate is closer to 50%. The outcome and cost-effectiveness of ES across a spectrum of peri-operative risk and repair rate is undefined.

The alternative approach to ES for managing the asymptomatic patient with severe MR and normal LV function is "watchful waiting (WW)" [1]. This involves ensuring that echocardiographic findings are below the thresholds for surgery and following the patient at least yearly for the development of symptoms or echocardiographic evidence of progression (cardiac enlargement, LV dysfunction, pulmonary hypertension), any of which could be used as a trigger to proceed to surgery. A recent European study has supported the safety of this approach [3]. Proponents of this strategy point out that the evidence base for heart failure and sudden death in medically-managed patients that supports ES includes symptomatic individuals, who should not be followed medically [2,4–7]. The potential problems of the WW strategy are the risk of patients failing to attend for follow-up and the risk of irrecoverable LV damage (which may subsequently progress to heart failure).

Outside of centers that perform mitral surgery in high volumes, both clinicians and patients find the decision to operate in a completely asymptomatic patient to be a difficult one because of the potential for adverse outcome from operation (especially if replacement is performed rather than repair). Not only is the timing of such intervention controversial on an individual basis, but the cost-effectiveness of doing this on a population-wide basis is unknown. The latter issue is important, as the prevalence of asymptomatic moderate–severe MR is approximately 8% in those ≥65 years old [8]. As the question is unlikely to be submitted to clinical trial, we sought to assess the cost-effectiveness, from a perspective of costs to a healthcare provider, of early (immediate) surgery for asymptomatic severe MR compared with WW, and to estimate the best decision under various assumptions.

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2. Methods

2.1. Model development

We developed a Markov model to evaluate the morbidity, mortality and costs associated with two strategies for the management of patients with severe but asymptomatic MR. The typical clinical setting would correspond to an asymptomatic patient in whom a systolic murmur is a coincidental finding, and in whom an echocardiogram confirms the presence of severe MR with preserved systolic function and LV size below the current guidelines for surgery [2]. The two strategies were i) early surgery and ii) WW — comprising yearly clinical and echocardiographic review and performance of surgery with the development of symptoms, LV dysfunction (ejection fraction <0.60) or LV size exceeding current guideline thresholds (end-systolic dimension >40 mm) [1]. Atrial fibrillation and pulmonary hypertension are Class IIa indications for surgery.

A Markov model with Monte Carlo simulations [9] (TreeAge Pro 2008, TreeAge, Williamstown, MA) was used to follow a hypothetical cohort of 10,000 patients through a number of health states that arose as consequences of WW, surgery or their combination (Fig. 1). The model was used to estimate quality-adjusted life-years (QALY) and lifetime cost, with the most efficient as the strategy that created QALYs and had an incremental cost-effectiveness ratio (ICER) less than the societal threshold. We anticipated the latter "willingness to pay" threshold (the societal acceptance of how much can reasonably be spent to save each QALY) as be $50,000 and $100,000 per QALY. We used a healthcare provider perspective by including all medical care costs and costs incurred due to increased survival associated with cardiac disease. All future costs and outcomes were discounted at 3.0% per year, with costs estimated in 2006 US dollars [10]. Discounting is a standard strategy applied in cost-effectiveness analysis to enable the comparison of present and future costs and health consequences. Cycle length represents the time-frame of transition from one state to the next, during which period all information is held constant — for the purposes of this analysis, this was assumed to be 1 year, with half-cycle correction to adjust for the implicit time-related bias of assuming that transitions occurred at the end or beginning of the cycle. It was anticipated that there was an equal gender distribution, that the initial age was 50 years and the rest of life was simulated.

2.2. Health states and transitions

Data on transitions between health states were obtained from the literature. The following health states and transitions were defined (Table 1).

2.2.1. Asymptomatic MR

All patients entered the model with asymptomatic MR. Application of current guidelines has shown 6% of patients per year to progress to a surgical indication [3]. A variety of mortality rates have been reported, varying from 0.4% through 2.5%, up to 6.3% per year [3,5,6], giving a weighted average of 2.2% per year (Table 1). Background age-specific mortality was also applied in the model for non-cardiac death (see below).

2.2.2. Heart failure

The development of heart failure (HF) during medical therapy has also varied between studies; we used a weighted average of 3.3% from previous reports (Table 1) [3–]. The highest recorded rate (5.6% in medical patients with preserved systolic function, ejection fraction >60%) [7] was used in a scenario analysis. The weighted annual average development of HF after surgery was 1.9% [3,5,7].

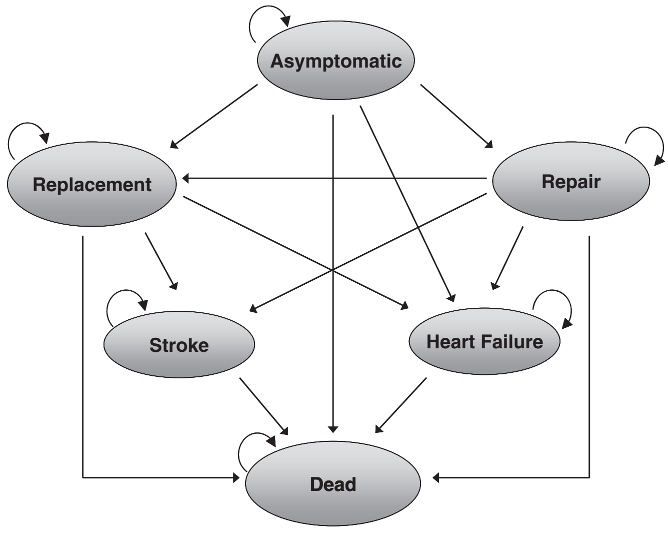

Fig. 1. Markov process for comparing early surgery and watchful waiting.

Table 1
Annual transition probabilities and mortality rates (± standard error).

	Early surgery	Watchful waiting [1]
Surgery	100% at outset	6.1% ± 0.9% [3]
Rate of repair surgery	49.9% ± 1.65% [13]	
Heart failure rate	1.9% ± 3.7%[a][3,5,7]	3.3% ± 4.4% [3–7]
Stroke — 1st year post-surgery	2% ± 5%[b][11]	
Tissue MVR — median time to reoperation (years); Weibull distribution	14.4 ± 2.2 [17,29]	
Mechanical MVR — reoperation	0.47% ± 0.13% [17,29]	
Repair — reoperation	0.76% ± 0.28% [16]	
Annual mortality in patients with[c]		
Cardiac death in asymptomatic MR[d]	2.2% ± 2.7% [3–7]	
Heart failure	10% ± 7% [31]	
Stroke	1st year: 11% ± 2%, Subsequent years: 11% ± 11% [21]	
Post-MVR	Operation 5% 1st year: 5.8% ± 7.1% [14,24] Subsequent years: 4.1% ± 0.7% [14,24,29]	
Post-repair	Operation 1% 1st year: 1.7% ± 1.6% [5,14,15,24] Subsequent years: 1.4% ± 0.5% [5,14,24]	

[a] Post surgery HF rate.

[b] 2% at age 50 years linearly increasing to 7% at age 80 years.

[c] Adjusted for age-specific all-cause mortality [18].

[d] Adjusted for age by multiplying the rate by current age and dividing the product by mean age at death. This gives a linear increase from 1.7% at age 50 years to 2.7% at age 80 years.

2.2.3. Stroke

The risk of stroke from mitral surgery is 1–2%, reaching 7% at more advanced age. The other main cause of stroke in chronic MR is atrial fibrillation, which is represented as part of the disease burden of both valve disease and valve surgery.

2.2.4. Mitral valve surgery

We investigated 2 health states — post-repair and post-mitral valve replacement (MVR). The relative frequencies of repair and MVR are variable — registry data show the frequency of repair to be approximately 50% [11,12], but at sites with a specialty interest in repair, rates of 80–93% have been reported [5,7,13]. We therefore selected a repair rate of 90% for the reference case and used a repair rate of 50% for a scenario analysis. For non-repaired valves, we anticipated mechanical replacements for patients <65 years old and tissue valves for those ≥65.

Although the 30-day mortality of mitral repair at high volume centers is often reported to be close to 0%, a more representative figure of 0.7% has been reported in a recent multicenter study [5], and reports of peri-operative mortality range to 1.8% [14]. We used a weighted average of 1.4% for peri-operative mortality, with a mortality rate of 1.7% and 1.4%/year for the 1st year and subsequently [5,13,14,24]. The performance of MVR carries a mortality risk of 5% [11]. Re-operation rates after MVR were anticipated to be 0.25% per year for mechanical valves [15] and to follow a previously described Weibull distribution for tissue valves [16]. Recurrent MR may occur after repair, with a reoperation rate of 0.8% per year [17].

2.2.5. Death

The background mortality rate was calculated from USA life tables [18]. Further details regarding mortality in each health state is provided in the next section.

2.3. Health outcome information

Information regarding health outcomes was obtained from the literature, by performing searches with the words "utility" and "quality of life" in conjunction with the health states. Utilities are values obtained from preferences associated with health-related quality of life where full health = 1.0 and dead = 0.0; the findings for utilities are listed in Table 2. Utility weights were multiplied by the duration in each health state to calculate quality-adjusted life years (QALYs).

2.3.1. Asymptomatic MR

Age-specific utility data, drawn from the Medical Expenditure Panel Survey of 38,678 individuals with valid responses, has been used to define QOL in the general population [19]. We expected asymptomatic patients to have the same QOL as the general USA population of 0.842 for the age range 50–59 years and expected to decline with age to 0.790 for the range 70–79 years.

2.3.2. Heart failure

Utility weight from the Cardiovascular Outcomes Research Consortium, measured with the EQ-5D (the most widely used utility instrument) was 0.67 in heart failure