Derivation and Validation of Prognosis-Based Age Cutoffs to Define Elderly in Cardiac Surgery

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Background—The age cutoff to define elderly is controversial in cardiac surgery, empirically ranging from ≥65 to ≥80 years. Beyond semantics, this has important implications as a starting point for clinical care pathways and inclusion in trials. We sought to characterize the relationship between age and adverse outcomes in patients undergoing cardiac surgery and to derive and validate prognosis-based age cutoffs.

Methods and Results—Six thousand five hundred seventy one consecutive adult patients undergoing cardiac surgery at 3 hospitals in the United States and Canada were included in the cohort. Logistic regression models and generalized additive models with thin-plate splines were fit to the data. The age distribution was 50 to 59 years in 1244 (18.9%), 60 to 69 years in 2144 (32.6%), 70 to 79 years in 2000 (30.4%), ≥80 years in 1183 (18.0%) patients. After controlling for sex and type of operation, the relationship between age and 30-day operative mortality was found to be nonlinear. Receiver operating characteristic analysis showed that the optimal cutoffs to identify older patients at higher risk of operative mortality were greater than 74, 78, and 75 years for isolated coronary bypass, isolated valve surgery, and coronary bypass plus valve surgery, respectively. These age cutoffs were validated in an independent cohort.

Conclusions—The relationship between age and operative mortality is not linear, manifesting a steeper rise after age 75 for coronary bypass and approaching octogenarian age for isolated valve surgery. Rather than using arbitrary age cutoffs to define elderly, the outcomes-based cutoff of ≥75 years should be used to identify the population of older adults that has higher risk and may benefit from preoperative geriatric evaluation and optimization. (Circ Cardiovasc Qual Outcomes. 2016;9:424-431. DOI: 10.1161/CIRCOUTCOMES.115.002409.)

Key Words: aging ■ cardiac surgery ■ elderly ■ mortality ■ outcomes research

Age is one of the most robust risk factors for adverse outcomes in modern day cardiovascular epidemiology. The age-centric attitude is pervasive in cardiac surgery, where advanced age is the major driver of operative risk and the most frequently cited reason for not operating an otherwise eligible patient. Surprisingly, there is no consensus on how to define advanced age or elderly in the context of cardiac surgery. A survey of recent publications reveals that age cutoffs of ≥65, ≥70, ≥75, and ≥80 years have all been used. Adding to this uncertainty, there is ambiguity as to whether the relationship between age and adverse outcomes is linear or exponential; the Age, Creatinine, Ejection Fraction (ACEF) and European System for Cardiac Operative Risk Evaluation (EuroSCORE) risk models represent age as a linear continuous variable, whereas the Society of Thoracic Surgeons (STS) risk model represents it as a nonlinear function. Clinical intuition tends to support the latter because the incremental risk from age 45 to 55 is empirically trivial, whereas this is not the case from age 75 to 85 (despite the fact that both are 10 year increments).

Age is the starting point for many clinical care decisions in cardiovascular medicine. Age is a gatekeeper for finite resources, such as comprehensive geriatric assessment and multidisciplinary heart team evaluation. Age is also a gatekeeper for clinical trial protocols, one-quarter of which exclude or under-represent the elderly. Cardiologists and general practitioners may be less likely to refer for cardiac surgery above a certain age. Cardiac surgeons may be less likely to operate above a certain age if they view it to be futile. Although an integrated approach to risk prediction is clearly preferred and age alone should not be equated with operability, high-risk age cutoffs are needed to rapidly identify patient subsets that may benefit from more in-depth evaluation and optimization of frailty and other geriatric domains before surgery.

Thus, we sought to define the relationship between age and adverse outcomes after cardiac surgery in a diverse 3-center
WHAT IS KNOWN

- Advanced age is a major risk factor for mortality and morbidity after cardiac surgery.
- Although it is an imperfect measure of physiological resiliency, chronological age is commonly used to guide critical decisions about the operative approach and postoperative management of our patients.
- There is wide variability in the age cutoffs cited to denote elderly, ranging from ≥65 to ≥80 years in the medical and surgical literature.

WHAT THE STUDY ADDS

- The relationship between age and mortality after cardiac surgery is exponential rather than linear.
- The age cutoff of ≥75 years identifies older adults more likely to suffer adverse events that may benefit from preoperative geriatric evaluation and optimization.

Methods

Study Design and Setting

A cohort of consecutive adult patients undergoing cardiac surgery was assembled at 3 university hospitals between 2007 and 2013: Massachusetts General Hospital (Boston, MA), Beth Israel Deaconess Medical Center (Boston, MA), and Jewish General Hospital (Montreal, QC). The cohort was divided into derivation and validation subsets, with the primary aim being to model the relationship between age and postoperative outcomes and determine the age cutoff for each type of surgical procedure that would yield a balanced combination of sensitivity and specificity to screen elderly patients at higher risk of postoperative mortality and major morbidity. The study complied with the ethics committee regulations at participating hospitals, which waived written informed consent.

Participants

Inclusion criteria were (1) coronary artery bypass graft surgery (CABG), valve repair or replacement surgery, or combined CABG plus valve surgery performed during the study timeframe; (2) case captured by the STS Adult Cardiac Surgery Database for the Boston sites or by the Pre-Operative Surgical Stratification by Echocardiography (POSSE) database for the Montreal site; and (3) age ≥50 years at the time of surgery. Elective, urgent, and emergent surgeries were included. Pediatric and younger adult patients were excluded because of their heterogeneous assortment of congenital pathologies and premature presentations of noncongenital pathologies.

Predictor and Outcome Variables

The primary predictor was chronological age at the time of the index surgical procedure. Age was represented in years without decimals or rounding. The primary outcome was 30-day all-cause mortality. Secondary outcomes were long-term all-cause mortality and the composite end point of in-hospital mortality or major morbidity defined as stroke, acute kidney failure (RIFLE stages III–IV), need for reoperation, or prolonged intubation (>48 hours). Data were extracted from the STS Adult Cardiac Surgery Database, the POSSE database, and hospital-level medical records. Extended vital status was available for patients operated at the Massachusetts General Hospital from the National Social Security Database via the Research Patient Data Registry.

Covariates

The covariates of interest were sex and type of cardiac surgery procedure. Cardiac surgery procedures were grouped as follows: (1) isolated CABG, (2) isolated valve repair or replacement, and (3) combined CABG plus valve repair or replacement. For ease of interpretation, the combined CABG and valve group was used as the reference group. Because the aim was to determine the global predictive impact of age for the purposes of initial screening, that is, encompassing all associated comorbidities and cardiovascular disease–related factors, adjustment for individual comorbidities was not desired and, therefore, not performed in the main analysis (this distinction between predictive modeling versus causal modeling has been reviewed elsewhere16). Adjustment for comorbidities and for surgical urgency (elective versus urgent/emergent surgery, defined according to the STS data dictionary) was explored in a sensitivity analysis. The data definitions used in the POSSE data set mirrored those used in the STS data set.

Statistical Approach

Logistic regression models were fit to the data for the primary analysis. Generalized additive models were also fit to the data as a secondary analysis to test the appropriateness of the assumption of a linear relationship between age and log-odds of mortality. For the generalized additive models, thin-plate splines were used as basis functions and optimal tuning parameters were selected using generalized cross validation statistics. Logistic and generalized additive models contained age, sex, and type of surgery as predictors, as well as interactions between them (age and sex, age and type of surgery). The Akaike information criterion and C statistic were compared for models with and without these interaction terms to determine if they contributed incremental predictive value. All hypothesis tests were performed using a Type I error rate of 0.05.

Receiver operating characteristic (ROC) curves were generated to determine the sensitivity and specificity of all possible age cutoffs for postoperative outcomes, stratified by type of procedure. The optimal balanced age cutoff was defined a priori as that which maximized the sum of sensitivity and specificity. ROC analysis was conducted in the derivation cohort (N=3220 from Massachusetts General Hospital) and then independently repeated in the validation cohort (N=3351 from the Beth Israel Deaconess Medical Center and Jewish General Hospital). Finally, Kaplan–Meier survival plots were generated to inspect the effect of age treated as a categorical variable on long-term mortality. All analyses were performed using R (version 3.2.2). The generalized additive models for the secondary analysis were fit using the mgcv package in R.12

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Figure 1. Flow diagram. The final cohort consisted of 8571 cardiac surgery patients from 3 hospitals. CABG indicates coronary artery bypass graft.
Results

The cohort consisted of 6571 patients ≥50 years of age who underwent cardiac surgery (Figure 1). The age distribution was as follows: 50 to 59 years (N=1244, 18.9%), 60 to 69 years (N=2144, 32.6%), 70 to 79 years (N=2000, 30.4%), and ≥80 years (N=1183, 18.0%). Overall, the mean age was 69.1±9.9 years, with 30.3% females. The surgical procedure performed was isolated CABG (N=3292, 50.1%), isolated valve (N=2011, 30.6%), and combined CABG plus valve (N=1268, 19.3%). The mean STS Predicted Risk of Mortality (STS-PROM) and Predicted Risk of Mortality or Major Morbidity (STS-PROMM) were 3.3±4.7% and 18.2±13.1%, respectively, whereas observed 30-day mortality was 2.1% and mortality or major morbidity was 19.3%.

Advancing age was associated with a higher proportion of females, combined CABG plus valve procedures, prior cardiac surgery, heart failure within 2 weeks, elevated creatinine, and elevated STS-PROM (Table 1). Among patients undergoing valve procedures, age <60 years was associated with a lower proportion of aortic valve replacements, whereas age ≥80 years was associated with a lower proportion of mitral valve surgeries. The prevalence of most comorbid conditions increased from age 50 to 65 years and then plateaued from age 65 to 80 years and above. There was no association between age and left ventricular ejection fraction. The distributions of age and sex were similar in the STS and POSSE data sets, although the proportion of valve surgery and the predicted and observed mortality rates were slightly higher in the former.

Nonsurvivors had a higher median age and a skewed left-shifted age distribution for isolated CABG, isolated valve, and combined CABG plus valve procedures (Figure 2). The relationship between age and 30-day mortality was modeled using logistic regression and was found to be nonlinear. The nonlinear relationship between age and 30-day mortality persisted in multivariable logistic regression models controlling for type of cardiac surgery procedure and sex (Figure 3). Furthermore, when age was categorized by 5-year age increments in the logistic regression models, the same nonlinear relationship was observed, with a step-up in adjusted odds of mortality observed as of ≥75 years (Table 2). There was a significant interaction between age and type of surgery (P=0.029) but not between age and sex (P=0.20). Model selection via the Akaike information criterion and C statistic indicated that the model with the interaction term for age and type of surgery was preferred over the model without.

ROC analysis in derivation and validation subsets revealed that the age cutoffs with the highest sum of sensitivity and specificity to discriminate between survivors and nonsurvivors were >74 years, >78 years, and >75 years for isolated CABG, isolated valve, and CABG plus valve procedures, respectively (Figure 4; Table 3). Surgery-specific age cutoffs were chosen because of the significant interaction between age and type of surgery. The same cutoffs were obtained when ROC analysis was stratified by sex and by surgical urgency. Age was more useful to discriminate risk in the setting of isolated CABG (C statistic 0.72–0.73) compared with valve surgeries (C statistic 0.50–0.66). For the secondary outcome of in-hospital mortality or major morbidity, the ROC age cutoffs were not consistently replicated in the derivation and validation subsets (Table 4).

Inspection of Kaplan–Meier survival curves (Figure 5) revealed a sharp decline in initial survival for the 75- to 79-year, 80- to 84-year, and ≥85-year groups during the first 3 to 6 months after surgery. Survival curves for the 75- to 79-year and 80- to 84-year groups stabilized thereafter and assumed a more gradual decline parallel to other age groups; however, the ≥85-year group continued its sharp decline in survival throughout the first 1 to 2 years after surgery. Thus,
patients \( \geq 75 \) years had an amplified early hazard period, whereas those \( \geq 85 \) years had the most marked risk profile protracted throughout the intermediate and late phases.

**Sensitivity Analyses**

A generalized additive model containing age, sex, and type of surgery as predictors confirmed the appropriateness of the assumption of a linear relationship between age and log-odds of mortality. Moreover, a logistic regression model containing age, sex, type of surgery, as well as comorbid conditions and surgical urgency confirmed a similar step-up in adjusted log-odds of mortality as of \( \geq 75 \) years (Table 2).

**Discussion**

In this multicenter study, we demonstrated that the relationship between age and operative mortality is not linear and becomes steeper as of 75 years for patients undergoing isolated or combined CABG surgery and closer to 80 years for patients undergoing isolated valve surgery. The outcomes-driven age cutoffs derived and validated in this study are preferable to the arbitrary and variable age cutoffs currently used to define elderly in day-to-day practice and in clinical trials. Although advanced age should not be overemphasized as a sole predictor for risk stratification, it remains the starting point for many clinical decisions in cardiovascular medicine, which, to-date, had yet to be objectively defined. Thus, the implications of our findings are to equip clinicians and researchers with a prognostically meaningful definition of elderly in the context of cardiac surgery, which they can use as an upfront screening criterion to broadly identify older adults at higher risk of operative mortality that benefit from comprehensive geriatric assessment to better assess their risk and individualize their therapeutic plan.

There are at least 3 general reasons why advancing age is associated with adverse events. The first is that older patients have more severe and diffuse cardiovascular disease. Our selected group of patients is notable in that all had de facto severe coronary or valvular heart disease that required surgical intervention, making this less relevant to explain the findings in our specific cohort. The second reason is that older patients are less likely to receive adjunctive medical therapies. The third reason is that older patients have accrued more comorbid conditions and, importantly, subclinical impairments in multiple organ systems that render

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**Figure 2.** Age distribution in 30-day survivors and nonsurvivors. In the violin plots, white circles denote the median age, thick black bars denote the interquartile range, and thin black lines denote the lower and upper range.
them vulnerable to the iatrogenic stress or surgery—this constitutes the geriatric syndrome known as frailty. Frail patients are at 2- to 3-fold greater risk of mortality and morbidity after cardiac surgery. That said, the absolute risk of mortality remains quite low in most older adults undergoing cardiac surgery irrespective of frailty and comorbidity, as shown in a prior report.

The accumulation of subclinical deficits is exponential rather than linear in relation to age. Accordingly, the prevalence of frailty is 3.9% at 65 to 74 years and rises steeply to 11.6% at 75 to 84 years and 25.0% at ≥85 years. The exponential rise in frailty corresponds with the observed exponential rise in mortality at advancing ages; however, this link remains hypothesis-generating at the present time because frailty status was not directly measured in our cohort. The steeper rise in postoperative mortality observed at 75 to 80 years did not temporally correspond with the rise in prevalence of comorbidities observed at 65 to 70 years.

The high-risk age cutoff was a few years older for patients undergoing isolated valve surgery compared with those undergoing CABG with or without valve surgery. One of the major differentiating features is that isolated valve patients do not have significant coronary artery disease, and additionally, we and others found that they have a 10% to 20% lower likelihood of manifesting concomitant cerebrovascular or peripheral arterial disease. In fact, isolated valve patients 80 to 84 years had a similar prevalence of noncoronary vascular disease as CABG patients 75 to 79 years. We hypothesize that the decreased/delayed manifestation of vascular disease in coronary and noncoronary beds seen in isolated valve patients may explain why these patients have a later step-up in age-associated risk. It is also worth noting that vascular disease is a strong risk factor for frailty.

### Table 2. Effect of Age on Risk of 30-Day Mortality in the Multivariable Model

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>1.00</td>
<td>Referent</td>
<td>…</td>
</tr>
<tr>
<td>60–64</td>
<td>1.19</td>
<td>0.50–2.81</td>
<td>0.694</td>
</tr>
<tr>
<td>65–69</td>
<td>1.32</td>
<td>0.58–3.04</td>
<td>0.508</td>
</tr>
<tr>
<td>70–74</td>
<td>1.39</td>
<td>0.6–3.19</td>
<td>0.444</td>
</tr>
<tr>
<td>75–79</td>
<td>3.08</td>
<td>1.49–6.38</td>
<td>0.002</td>
</tr>
<tr>
<td>80–84</td>
<td>4.66</td>
<td>2.28–9.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>85+</td>
<td>4.32</td>
<td>1.92–9.73</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Surgical procedure

| CABG+valve   | 1.00                | Referent    | …       |
| Isolated CABG | 0.51                | 0.33–0.77   | 0.003   |
| Isolated valve | 0.44                | 0.28–0.69   | <0.001  |

### Sex

| Female       | 1.56                | 1.08–2.24   | 0.01    |

A sensitivity analysis was performed adding individual covariates to the model (diabetes mellitus, chronic kidney disease, chronic lung disease, myocardial infarction, congestive heart failure, prior cardiac surgery, and urgent or emergent surgery), and the adjusted odds ratio for each age strata was similar to that in the main analysis: 1.79, 1.45, 1.09, 3.22, 4.47, and 4.35, for ages 60–64, 65–69, 70–74, 75–79, 80–84, and 85+, respectively. CABG indicates coronary artery bypass graft surgery; and CI, confidence interval.
Discrimination of postoperative complications as a function of age was modest, implying that it is more difficult to predict individual complications than it is to predict survival. The same has been shown for discrimination of complications as a function of risk scores, where the C statistic for cardiac surgery risk scores is in the range of 0.7 to 0.8 to predict mortality as compared with 0.6 to 0.7 to predict complications. Postulated reasons include larger component of surgeon- and procedure-related factors responsible for complications, chance, and measurement issues in ascertaining complications. We attempted to minimize ascertainment error by using standardized data definitions from the STS. Discrimination of mortality as a function of age was modest in patients undergoing isolated or combined valve surgery, particularly in the validation data set. One reason for this may be the greater complexity and heterogeneity of valve surgery patients, necessitating more granular measures of risk stratification beyond chronological age.

There are several limitations. First, the outcome measures analyzed were limited to postoperative mortality and major complications.
morbidty, whereas recovery time and quality of life would have been of interest but were not recorded. Second, although this was not the aim of our study, we could not prove that the step-up in risk was related to accumulated deficits and frailty because these were not captured in our data sets. That said, the STS database has recently started collecting a frailty measure which would allow us to test this hypothesis in the future.

Third, our findings cannot be extrapolated to surgeries other than CABG and valve repair or replacement because other types were excluded (eg, aortic surgery and congenital heart disease surgery).

Conclusions

The relationship between age and postoperative outcomes is not linear, as evidenced by a nonlinear increase in mortality across age strata and an additional layer of variability across surgical

<p>| Table 3. Optimal Age Cutoffs to Screen for Risk of 30-Day Mortality (ROC Analysis) |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Optimal Age Cutoff</th>
<th>C Statistic</th>
<th>Derivation Site</th>
<th>Validation Site</th>
<th>Derivation Site</th>
<th>Validation Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated CABG</td>
<td>&gt;74&gt;74</td>
<td>0.72</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated valve</td>
<td>&gt;78&gt;78</td>
<td>0.65</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG+valve</td>
<td>&gt;75&gt;75</td>
<td>0.66</td>
<td>0.50</td>
<td></td>
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</tr>
</tbody>
</table>

Combining data from all sites, the optimal age cutoffs and C statistics (with their 95% confidence intervals) were 74 y (68, 77) and 0.73 (0.65, 0.81) for isolated CABG, 78 y (63, 80) and 0.62 (0.52, 0.72) for isolated valve, 75 y (48, 86) and 0.61 (0.53, 0.69) for CABG plus valve, respectively. CABG indicates coronary artery bypass graft; and ROC, receiver operating characteristic.

<p>| Table 4. Optimal Age Cutoffs to Screen for Risk of In-Hospital Mortality or Major Morbidity (ROC Analysis) |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Optimal Age Cutoff</th>
<th>C Statistic</th>
<th>Derivation Site</th>
<th>Validation Site</th>
<th>Derivation Site</th>
<th>Validation Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated CABG</td>
<td>&gt;73&gt;69</td>
<td>0.63</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated valve</td>
<td>&gt;73&gt;78</td>
<td>0.57</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG+valve</td>
<td>&gt;71&gt;65</td>
<td>0.56</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The composite end point of in-hospital mortality or major morbidity is defined as all-cause death, stroke, acute kidney failure, need for reoperation, or prolonged intubation. CABG indicates coronary artery bypass graft; and ROC, receiver operating characteristic.

Figure 5. Age strata and long-term mortality. Kaplan–Meier curves for long-term survival data available in patients operated at the Massachusetts General Hospital via the Research Patient Data Registry.
procedures. Despite being one of the most powerful predictors of outcomes in cardiovascular medicine, chronological age should not be viewed as a singular determinant of risk or operability. To the contrary, the health status of older adults is complex, necessitating granular assessments of comorbidity and frailty. However, the current climate requires us to implement these types of resource-consuming assessments judiciously. By using the prognosis-driven age cutoffs validated in this study, as opposed to subjective age cutoffs, clinical care pathways and research protocols have a better starting point to target the elderly patients who may benefit from preoperative comprehensive geriatric assessment and optimization.24,25

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Disclosures
None.

References
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