

# Energy Loss Index as a Predictor of All-Cause Mortality after Transcatheter Aortic Valve Replacement: A 9-year follow-up

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## Abstract

**Background:** As transcatheter aortic valve replacement (TAVR) procedures become more widely available, there is a growing need to monitor and evaluate postoperative outcomes accurately. The energy loss index (ELI) of the ascending aorta has been commonly used to examine the agreement between the echocardiographic and Gorlin measurement of the aortic valve area. **Objectives:** This project aims to demonstrate a link between ELI values and mortality following implanted TAVR valves and determine an ELI cutoff value associated with post-TAVR events. **Method:** We retrospectively reviewed patients undergoing TAVR from 2012 – 2017. We calculated ELI values for patients immediately postoperative after a TAVR procedure. Using Receiver-Operator Characteristic and Cox Regression analyses, we identified a cutoff value to distinguish between high and low-risk patients. **Results:** This study showed ELI [?] 1.34 (hazard ratio, 1.783; 95% confidence interval 1.231-2.583,  $p=0.002$ ) as representative of patients with a high risk of mortality post-TAVR. Additionally, post-TAVR, ejection fraction increased by 3.5 percent ( $p<0.001$ ), and the aortic valve effective orifice area increased by 1.25 cm squared ( $p<0.001$ ) while the mean transvalvular gradient decreased by 33.6 mmHg ( $p<0.001$ ) and the peak transvalvular gradient decreased by 49.7 mmHg ( $p<0.001$ ). **Conclusion:** ELI is an additional prognostic factor that should be considered during risk assessment before TAVR. This study shows that patients with ELI [?] 1.34 had decreased cumulative survival post-TAVR. These patients had a fivefold increased risk of death following TAVR.

## INTRODUCTION

Degenerative aortic valve disease affects over 25% of all patients over 65<sup>1</sup>. However, most tend to be asymptomatic until the valve is severely restricted. After the onset of symptoms, survival rates decrease dramatically<sup>2</sup>. Patients with valvular heart disease will acquire noninvasive testing such as ECG or transthoracic echocardiography to evaluate the extent of the disease. However, the less invasive doppler echocardiogram is the standard for diagnosis<sup>3</sup>. If there is discordance between the symptoms and such testing, invasive evaluations may be utilized<sup>4</sup>. Transesophageal echocardiography is especially useful in patients with a poor transthoracic window or complex cardiac pathology. Although cardiac catheterization is no longer recommended for the purposes of aortic valve evaluation, it may be utilized for further evaluation and thus optimizes the treatment strategy.

Echocardiographic estimation of aortic stenosis performed typically correlates well with assessment by cardiac catheterization. However, catheterization may differ slightly from the echocardiographic assessment of certain individuals as echocardiography may overestimate aortic stenosis severity<sup>5</sup>. Because the peak aortic pressure is attained milliseconds later than the peak left ventricular pressure, a *peak-to-peak* gradient is not an actual physiological measurement during the catheterization procedure. On the other hand, doppler measurements reflect peak *instantaneous* gradients. Thus, doppler-derived gradients may be of a greater value and accuracy than catheter-derived gradients, where peak-to-peak gradients are reported.

To excavate this inconsistency, the fluid dynamics of aortic stenosis must be considered. Before the acceleration through the aortic valve, there is a low dissipation of pressure and high stability, and laminar flow of the blood as the static pressure (Potential Energy) is converted to dynamic force (Kinetic Energy). Once accelerated through the valve, there is much dynamic tension, which allows for the velocity through the vena contracta (VC). At this point, the continuity equation corresponds to the effective orifice area (EOA) or aortic valve area (AVA). Upon passage through this high-velocity point, a turbulent flow carries a high dynamic pressure that should be transformed back to static pressure upon deceleration. However, due to the instability and turbulence of blood downstream from VC, some energy is lost due to heat and shear force through the valve and the surrounding aorta. In valvular stenosis, there is an increase in flow acceleration and velocity, resulting in a higher-pressure gradient, as described by the Bernoulli Equation. The peak gradient differences, mainly upstream and downstream from VC, are measured using the Gorlin formula<sup>6-8</sup>.

In 2000, an article in circulation demonstrated the energy loss between the left ventricular outflow tract and the ascending aorta. These investigators established a relationship with the effective orifice area (EOA), the aortic cross-sectional area (AA), and the energy loss in terms of pressure difference across the valve instead of the transvalvular pressure gradient (TPG)<sup>7</sup>:

$$\frac{EOA \times AA}{AA - EOA} = \left( \frac{Q}{50\sqrt{EL}} \right)$$

Based on this equation, Energy loss (EL) is a squared function of flow rate. Therefore, at a given flow rate, energy loss (heat and other forces on the aorta and the valve) increases with decreasing EOA and increasing AA. The energy loss index (ELI) refers to the energy loss per square meter of body surface area (BSA).<sup>9</sup>:

$$\frac{EOA \times AA}{AA - EOA} \div BSA$$

Based on this theory, previous studies have shown the efficacy of ELI in stratifying and reclassifying aortic stenosis patients in high, moderate, or low-risk categories (ELI of <0.6cm<sup>2</sup>/m<sup>2</sup> signifying severe aortic stenosis). Interestingly, such studies highlighted the overestimation of stenosis by doppler echocardiogram<sup>9</sup>. Furthermore, given the significance of energy loss to the shear forces and turbulence through the valve, we aim to study the longevity of the implanted transcatheter aortic replaced valves and use it to predict post-transcatheter aortic valve replacement outcome. We, therefore, hypothesized that one could predict the likelihood of all-cause mortality utilizing ELI in patients who have undergone the TAVR procedure.

## METHODS

### Experimental Design and Study Population:

This study was a retrospective cohort investigation with a longitudinal follow-up. We collected the study data by reviewing patients' electronic medical records who had undergone TAVR at the structural Heart unit of Gates Vascular Institute in Buffalo, NY. This unit is one of the busiest structural cardiology centers in the US and performs over 600 TAVR procedures per year. The University of Buffalo Institutional Review Board reviewed and approved this study. We took extreme caution to minimize the risk of the privacy leak of the participants during data collection and not to impact the rights and welfare of these patients adversely.

We screened 677 patients who underwent TAVR from 2012 -to 2017. Based on inclusion criteria, we included 272 patients for further analysis. Patients were identified from the locally collected national database registry and had if they did not meet the exclusion criteria. Follow-up echocardiographic data (postoperative, six months, then annual follow-ups) pertinent to ELI calculation and hemodynamic properties of the prosthesis were collected. Patients were followed after the procedure until the primary endpoint was met. The relevant clinical information was collected along the way. ELI values were compared to these post-procedural events to identify a trend and a cutoff ELI value at which these events become more likely to occur. Inclusion criteria were all patients who had undergone a successful TAVR procedure at the Gates Vascular Institute

from 2012 to 2017. Exclusion criteria applied to patients who passed away due to vehicular accidents, homicide, suicide, pre-procedural terminal illnesses, and patients who were lost to follow-up.

### Primary and Secondary Endpoints:

The primary endpoint for this study was overall mortality throughout the follow-up period extending to 9 years after the TAVR procedure. Secondary endpoints included aortic valve revision, myocardial infarction, newly recognized arrhythmia, new-onset angina, cardiac arrest, coronary artery bypass grafting, coronary angioplasty, stroke, endocarditis, and prosthetic valve insufficiency.

The independent variables included: ELI values calculated based on the native aortic valve and the effective aortic orifice area (EOA) after TAVR, demographic data, type of prosthesis, and presence of preoperative aortic valve insufficiency.

Clinical and demographic baseline characteristics and routine preoperative hemodynamic variables were collected from the medical records and existing preoperative trans-thoracic echocardiography (TTE), trans-esophageal echocardiography (TEE), and left/right cardiac catheterization database. The ELI value was calculated using the formula  $(AVA * A_{STJ} / (A_{STJ} - AVA)) / (\text{body surface area in } M^2)$ , where AVA is the aortic valve area and  $A_{STJ}$  is the aortic area at the sinotubular junction<sup>5</sup>. The AVA for the native valves were the values obtained by TTE before the TAVR procedure. The EOA replaced this value for any individual implanted with TAVR in postoperative TTE exams. Prosthetic aortic valve characteristics, including the prosthesis diameter, height, bovine/porcine-derived, trans-femoral/apical/aortic implantation, and sheath size, were obtained by reviewing the manufacturer manual.

### Statistical Analysis and Sample Size Determination:

A model was constructed to test the predictive value of ELI on post-procedural outcomes. We calculated the ELI value for each patient and then examined its accuracy and value in predicting all-cause mortality/cardiac events. Sample size determination for this prediction model accepted a minimum area under the curve (AUC) of 0.7 on C statistics. A global shrinkage factor of 0.9 has been used to estimate the minimum number of events ( $E = 46$ ) to fit the newly established model in predicting the primary endpoint using a time-to-event multivariable survival (Cox Regression) analysis<sup>10</sup>. Recently, we reported 4-year mortality of 32% following the TAVR procedure at our institution<sup>11</sup>. To include an adequate sample size of 46 events, a total of 144 patients to achieve enough power for properly fitting the predictive model of ELI. We increased the global shrinkage factor by including 272 subjects in our review to 0.95.

A Kaplan Meier curve was constructed to perform univariate, and the Cox regression model was used for multivariable survival analyses. Since no similar study has been identified in our literature search, we used a receiver operating characteristic curve (ROC curve) to determine the cutoff point for ELI. A ROC curve was also used to calculate the best discrimination threshold, which balanced sensitivity and specificity. The plotted points were then used to create a ROC curve to identify the best entry for distinguishing high-risk from low-risk sub-groups. The positive and negative predictive values, sensitivity, specificity, and accuracy of the prediction model were then calculated for this cutoff value of ELI. The value of the ELI was used for grouping the patients for comparison. The relative risk determined the probability of mortality in the high-risk group to mortality in the low-risk group. This relative risk may be used to predict post-procedural outcomes of patients based on their ELI value. Furthermore, this ROC curve method may highlight differences in threshold values between different patient demographics and types of prosthesis. All analyses were performed using the Statistical Program for Social Sciences version 26.0 on the Mac OS platform (SPSS-IBM Inc. Chicago, IL).

## RESULTS

Our study population included 272 patients: 140 (51%) were men, and 132 (49%) were female. The average patient age was  $85.6 \pm 7.8$  years. Most of the patients were Caucasian: 259 (95%) Caucasian vs. 8 (3%) Black vs. 3 (1%) American Indian vs. 2 (1%) Other. The average patient BMI was  $28.2 \pm 6$ . The majority of patients received the newer generation SAPIEN 3 valve: 14% SAPIEN vs 14% SAPIEN XT vs 56% SAPIEN

3 vs 5% CoreValve vs 8% CoreValve Evolut vs 3% Evolut Pro. A majority of the patients had hypertension, hyperlipidemia, and a smoking history: 246 (90%) HTN vs. 203 (75%) HLD vs. 145 (53%) smokers. 95 (35%) patients had diabetes mellitus type II. 59% of this sample did not have coronary revascularization procedures before TAVR. Average left ventricular ejection fraction, aortic valve area, mean gradient, and peak gradient before TAVR were as follows:  $55 \pm 13.3$ ,  $0.68 \pm 0.21$ ,  $42.1 \pm 16.7$ , and  $67.3 \pm 26.8$ . 70% of the sample had some degree of aortic insufficiency before TAVR. (Table 1).

Following TAVR, ejection fraction ( $p < 0.001$ ) as well as aortic valve effective orifice area ( $p < 0.001$ ) increased while both mean transvalvular ( $p < 0.001$ ) and peak transvalvular gradients ( $p < 0.001$ ) decreased. The ejection fraction increased by 3.5 percent, and the aortic valve effective orifice area increased by 1.25 cm squared. The mean transvalvular gradient decreased by 33.6 mmHg, and the peak transvalvular gradient decreased by 49.7 mmHg. (Table 2).

In receiver-operator curve (ROC) analysis, we determined the ELI cutoff value to be 1.34 ( $p < 0.001$ ), using all-cause mortality as the primary outcome. (Figure 1). Multivariate cox regression showed an increased cumulative survival time for nine years post-TAVR in patients with  $ELI > 1.34$  ( $p = 0.002$ ). (Figure 2). All patients were assigned to one of two groups based on their calculated ELI.

Patient characteristics are shown in Table 3. One hundred and seventy-three patients had  $ELI > 1.34$ , and ninety-nine patients had  $ELI \leq 1.34$ . There was no significant difference between both ELI groups in the following demographic and comorbid conditions: gender, race, age, BMI, hypertension, diabetes mellitus, hyperlipidemia, or smoking status. Additionally, there was no significant difference in prior coronary revascularization, aortic valve area, mean transvalvular gradient, peak transvalvular gradient, and left ventricular ejection fraction before TAVR between both ELI groups. 86 (61%) men compared to 87 (66%) women had elevated  $ELI > 1.34$ . Patients with  $ELI > 1.34$  were  $82.6 \pm 8.2$  years, while those with  $ELI \leq 1.34$  were  $82.1 \pm 6.5$  years ( $p = 0.634$ ). BMI was  $27.7 \pm 6.1$  in patients with  $ELI > 1.34$  compared to  $28.9 \pm 5.7$  for patients with low ELI ( $p = 0.055$ ). Patients with  $ELI > 1.34$  had ejection fraction of  $55.8 \pm 14.2$  while patients with  $ELI \leq 1.34$  had ejection fraction of  $53.5 \pm 13.1$  ( $p = 0.09$ ). SAPIEN valves were most commonly associated with  $ELI \leq 1.34$  ( $p = 0.014$ ): 62% of SAPIEN vs 35% of SAPIEN XT vs 29% of SAPIEN 3 vs 46% of CoreValve vs 35% CoreValve Evolut vs 44% CoreValve Evolut Pro (Table 3).

All-cause mortality was higher in patients with lower ELI (95% confidence interval, 5.59 (3.25 - 9.62);  $p < 0.001$ ). Patients with  $ELI \leq 1.34$  had a fivefold increased risk of death following TAVR. 71 (71.7%) patients with  $ELI \leq 1.34$  compared to 53 (31.2%) patients with  $ELI > 1.34$  were deceased within nine years following TAVR. There was no significant difference between ELI groups in the following clinical outcomes following TAVR: cerebrovascular events, congestive heart failure, prosthetic thrombosis, bacterial endocarditis, prosthetic regurgitation, myocardial infarction, new onset dysrhythmias, cardiac arrest requiring CPR, post-TAVR coronary intervention, TAVR revision or hospital readmission. (Table 4).

In total, one hundred and twenty-five patients died within nine years post-TAVR. Univariate analysis was performed on demographic and patient-related factors that may contribute to death following TAVR. Hypertension was associated with increased mortality in this univariate analysis (95% confidence interval, 3.12 (1.21 - 8.03);  $p = 0.021$ ). While 48.4% of all patients had hypertension, 95.2% of deceased patients had hypertension. Each valve type was associated with different mortality rates within 9 years post-TAVR ( $p = 0.027$ ): 64.8% SAPIEN vs 53.3% CoreValve vs 51.7% SAPIEN XT vs 37.9% SAPIEN 3. Although not statistically significant, age and aortic valve area were other factors that were borderline. The age of the deceased patients was  $83.3 \pm 6.8$  (95% confidence interval, 1.02 (0.99 - 1.06);  $p = 0.07$ ). The aortic valve area of the deceased patients was  $0.70 \pm 0.19$  (95% confidence interval, 1.96 (0.88 - 4.34);  $p = 0.098$ ). The following factors were not associated with mortality post-TAVR: gender, race, BMI, diabetes mellitus, hyperlipidemia, smoking status, prior coronary revascularization, moderate/severe aortic insufficiency, mean transaortic gradient or left ventricular ejection fraction. (Table 5).

Multivariate Cox regression was performed on select variables with p values  $< 0.15$ . Increased age (hazard ratio, 1.037; 95% confidence interval 1.006 - 1.069,  $p = 0.019$ ),  $ELI < 1.34$  (hazard ratio, 1.783; 95% confidence

interval 1.231 - 2.583,  $p=0.002$ ) and SAPIEN valve (hazard ratio, 1.861; 95% confidence interval 1.025 - 3.382,  $p=0.041$ ) were associated with increased mortality within 9 years after TAVR. Patients with ELI [?] 1.34 had a 78% chance of all-cause mortality following TAVR. Unlike the univariate analysis, the following variables no longer were associated with mortality: hypertension ( $p=0.188$ ), CoreValve ( $p=0.301$ ), or SAPIEN XT ( $p=0.813$ ). Although not statistically significant, the preoperative aortic valve area remained borderline (hazard ratio, 2.387; 95% confidence interval 0.961 - 5.931,  $p=0.061$ ). (Table 6).

## DISCUSSION

This work is the first study to determine an ELI cutoff value associated with postoperative mortality. When using all-cause mortality as the primary outcome, our analysis found increased cumulative survival time in patients with  $ELI > 1.34$  for nine years post-TAVR. We discovered that ejection fraction and aortic valve effective orifice area increased post-TAVR while mean transvalvular, and peak transvalvular gradients decreased post-TAVR. Multivariate analysis indicated that advanced age and SAPIEN valves were associated with increased mortality post-TAVR.

Over 276,000 patients have undergone the TAVR procedure in the United States<sup>12</sup>. TAVR has been widely available in the US since 2011 and has surfaced as an alternative to SAVR. Although the PARTNER I trial demonstrated similar valve performance and cardiac hemodynamics post-TAVR and SAVR implantation<sup>13</sup>, TAVR has grown in popularity. One key difference between the two procedures is that in TAVR, the native aortic leaflets are not removed. Instead, they are displaced into the Valsalva sinus, reducing the sinus volume and blood velocity in the sinus<sup>14</sup>. This decrease in speed may increase the chances of thrombus formation. Despite these risks, TAVR has been proven much safer based on one-year follow-up than surgical valve replacement<sup>15</sup>. While enough time elapsed to examine the longevity of the prosthesis, there was no significant increased risk of thrombotic events post-TAVR in our sample.

Our study corroborates prior research showing ELI offers clinical benefits and provides additional prognostic information in classifying aortic stenosis. One study reported that decreases in ELI predicted increased aortic events and increased total mortality and hospitalizations for heart failure. However, after reclassification analysis, ELI improved the prediction of aortic valve events but no longer predicted total mortality or hospitalizations<sup>16</sup>. Other research found that patients with small aortic roots or aortic sinotubular junctions were associated with higher rates of ischemic cardiovascular events, non-hemorrhagic stroke, and mortality<sup>17</sup>.

Blood pressure in the left ventricular outflow tract (LVOT) is high while the velocity is low, and the pressure in the aortic valve area is low while the velocity is high. The pressure in the receiving aorta is again high while the velocity is low. This decrease in velocity in the aorta and subsequent increase in pressure is known as pressure recovery<sup>18</sup>. The amount of pressure recovery increases with more severe aortic stenosis. A more accurate fluid dynamics model considers the third variable outside of velocity and pressure, which is the heat. The turbulent flow or friction through a valve can cause energy to be lost as heat. This loss of energy due to heat will decrease the pressure recovery in the aorta. Thus, patients who have higher energy losses are more likely to survive following TAVR as they experience less turbulent or shear forces.

As the aortic valve becomes increasingly stenotic, turbulent flow increases in a non-linear fashion<sup>19</sup>. Patients with increased turbulent flow experience more shear forces, which in turn cause structural instability<sup>20</sup>.

We concluded that ELI should be used as an additional factor when considering all-cause mortality following TAVR. It is reasonable to implement this factor during the pre-op risk assessment process as we have shown lower ELI values predictive of increased post-op mortality. ELI is indirectly related to body surface area and body weight. Therefore, delaying TAVR in non-emergent cases to allow patients to engage in weight reduction strategies may improve patient outcomes post-TAVR. Additionally, ELI may be used to highlight the efficacy of different prostheses in different patient populations.

The external validity of this study was low, given that most patients were Caucasians living in the western New York area who received newer generation valves. Additionally, the location at which the sinotubular junction measurement was obtained from an echocardiogram may have differed slightly between patients due

to human error. It is important to consider patients' native anatomy as patients with a smaller ascending aorta have a more significant pressure recovery and thus a larger ELI. Future studies may be designed to improve the longevity of these prosthetics by deciding on the appropriate size of the valve according to the established ELI criterion.

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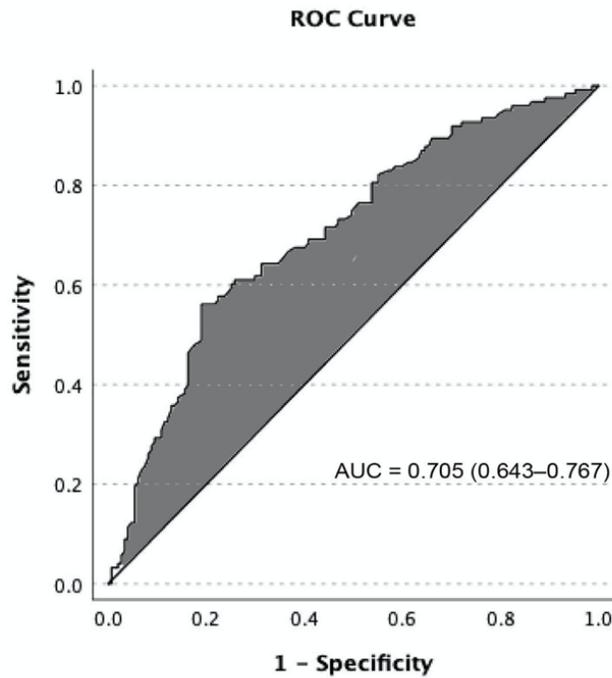


Figure 1: Receiver-operator characteristic analysis revealed a cutoff point of 1.34 for ELI. At this value, the sensitivity of the model was 59% with a specificity of 81%. P-value for this model was < 0.001.

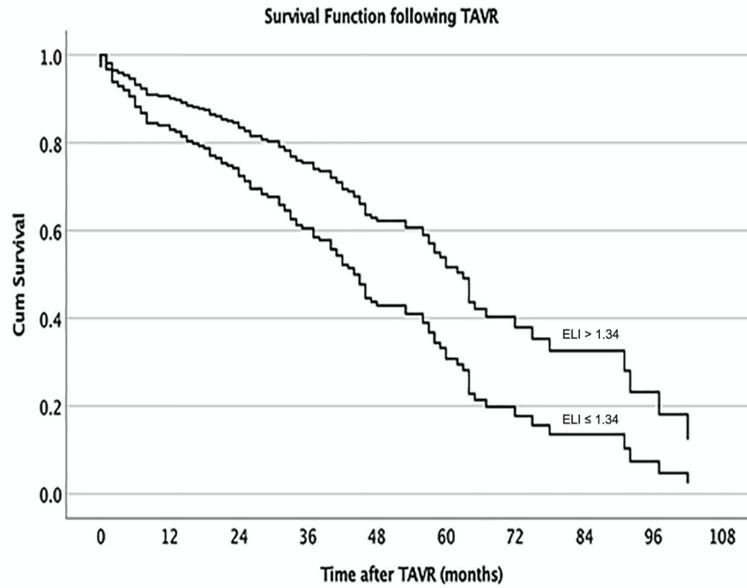


Figure 2: Multivariable Cox regression survival of patients graphed for a period of 9 years after trans-catheter aortic valve replacement according to the cutoff value of energy loss index of 1.34. P-value for this factor was 0.002.

	Year-1	Year-2	Year-3	Year-4	Year-5	Year-6	Year-7	Year-8	Year-9
ELI $\geq$ 1.34	172	142	96	70	37	13	5	3	1
ELI < 1.34	97	79	62	46	28	17	6	4	2

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