Predicting mid-term all-cause mortality in patients undergoing elective endovascular repair of a descending thoracic aortic aneurysm

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BP, MT and PH were involved in the conceptual design of the study. BP and AVD undertook statistical analysis. AB and SS oversaw collection and provided access to the external dataset. All authors were involved in interpretation of data as well as drafting the manuscript. Final Approval was by all authors but overall responsibility was MT.

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Abstract

Introduction

All-cause mortality in patients following repair of aortic aneurysms of the descending thoracic aorta (TEVAR) is relatively high at mid-term follow-up. The aim of this study was to derive and validate a system that could predict all cause mortality following TEVAR to aid with patient selection.

Methods

The MOTHER database contained 625 patients that underwent elective surgery for descending thoracic aortic aneurysms. Univariate analysis identified pre-operative factors associated with mid-term all-cause mortality, and a Cox's proportional hazards model was developed. The model was internally validated using Kaplan-Meier comparison of observed vs. predicted mortality. External validation was performed using a dataset from the University of Florida College of Medicine (UFCM).

Results

There were 625 patients that underwent TEVAR for descending thoracic aortic aneurysm in the MOTHER database and 231 in the UF validation set. The mid-term mortality rate at 6 years follow-up was 34.4% and 34% respectively. The all-cause mortality risk score was calculated using 0.0398*(age) + 0.516*(renal insufficiency) + 0.46*(previous cerebrovascular disease) + 0.352*(prior tobacco use) + 0.376*(number of devices > 2) + 0.016*(maximum aneurysm diameter). Using this score, low, medium and high-risk groups were defined, with predicted survival at 5 years of 80%, 60% and 40%. Patients at high risk of mid-term all cause death were identified in the validation cohort using the prediction rule.

Conclusion

Identifying patients with a limited life expectancy following TEVAR is possible using a pre-operative risk-stratification system. This information can be used to inform decision-making regarding when and whether to proceed with TEVAR.

Introduction

Endovascular repair of aneurysms of the descending thoracic aorta (TEVAR) has enabled treatment of patients who would previously have been considered unfit for extensive open surgery.[1,2] Patients with descending thoracic aortic aneurysms (DTAA) are generally elderly and frequently have multiple co-morbidities that may limit life expectancy, independent of aneurysm related mortality.[3] The principle of aneurysm repair is to prevent rupture, which often has a low annualized risk of occurring. Therefore, performing surgery on individuals who have a relatively short life expectancy independent of their aneurysm, is of limited utility.[4] Thus, a method of stratifying patients into groups based on their predicted survival at mid-term follow-up may help differentiate those who would benefit in terms of overall gain in life expectancy from those who may not.

Risk-stratification systems have been described extensively for the pre-operative assessment of patients undergoing elective abdominal aortic aneurysm repair.[5] Most of these systems were derived using logistic regression modelling and incorporated pre-operative physiological covariates to predict peri-operative mortality. Others have focused on one-year survival after AAA repair, placed in the context of rupture risk based on aneurysm diameter, which may be a more useful measure of utility of repair.[6]

Risk stratification models must be validated to prove that they are reliable before use in clinical practice,[7] and this validation can be internal, temporal or external,[8] Internal validation uses the same dataset that the models were initially developed from, and is the least stringent form of validation. Temporal validation utilizes the same source as

the original dataset, but uses new prospectively collected data acquired after the initial model has been developed. External validation is the most stringent form of validation and involves the testing of the model on an externally acquired dataset, ideally collected from a different institution or even geographical area, completely separate to the development sample.

The aim of this study was to derive and subsequently externally validate a model that could be used to stratify patients undergoing TEVAR into different groups depending on predicted life expectancy in order to inform pre-operative decision-making.

Methods

Data from five prospective trials were obtained from Medtronic (Santa Rosa, CA, USA) and collated with the addition of institutional data from a single UK centre. The collated data was termed the MOTHER Registry (MedtrOnic THoracic Endovascular Registry). The registry consists of the endovascular arm of one phase II/III trial (VALOR I[9]), the intervention arm of one randomised control trial (INSTEAD[10]) and three phase IV trials (VALOR II,[11] CAPTIVIA[12] and VIRTUE[13]), and patients who underwent TEVAR specifically for DTAA were selected for this study. Patients with a diagnosis of aortic dissection were excluded. The registry has been previously described[3]. Patients who suffered mid-term all-cause death were identified, and the cause of death was determined where possible. Time to death was determined as was censorship due to end of follow-up (**Table 1**).

The morphological data available varied depending on the specific parameters that were outlined in the original trial protocols. Participating centres measured their own patients CT scans using three dimensional central luminal line reconstructions where possible. The trial sponsors core laboratory then validated each centres measurements. For the institutional series, each scan was measured according to a combined protocol derived from all of the trials. For the St George's Vascular Institute group measurements were performed using 3-Mensio software (3-Mensio, Eindhoven, Netherlands) according to a protocol that was based on previous work validating a similar system for measuring the infra-renal aorta.[14,15]

Use of the data from the commercial trials was covered by the initial consent procedure, and approval from the local IRB was given for the St Georges' data.

Statistical analysis

Statistical analysis was performed using the SAS 9.3 statistical package and SPSS 20. Graphs were drawn with R 3.1.2 or SPSS 20. Univariate analysis was performed to determine which individual factors were associated with all-cause death at mid-term follow-up (6 years). Cox's proportional hazard's modelling was used to determine which variables were independently associated with mid-term adverse outcomes, and models were created to predict all-cause death at mid-term follow-up.

Univariate analysis

Univariate analysis for covariate association with mid-term outcomes was performed by plotting Kaplan-Meier curves for each pre-operative categorical variable (e.g. renal dysfunction) to determine if there was any significant difference in survival at follow-up between those with this characteristic and those without. This also enabled nominal (i.e. neck shape) or ordinal (access vessel tortuosity) variables with more than two categories to be visually assessed for association with poor outcomes. The Log-rank test was used to test for significance with a stringency of $p<0.05$. This test was also used for categorical anatomical variables with more than one category.
For continuous variables such as anatomical measurements, an independent two-tailed t-test was performed to compare the mean value for those that died with those that did not die during the follow-up period.

Selection of variables for multivariate modelling

As multiple univariate analyses were performed, selection of variables for the multivariable analysis was stringent to avoid entering too many variables into the automated process.

To select anatomical variables for consideration for use in multivariate analysis, a dendrogram was created which visually clustered those variables that were correlated according to Spearman's correlation coefficient. This allowed variables to be eliminated from further analysis on the basis that there was co-linearity and therefore only one from the cluster (in any) would not be eliminated during the derivation of a multivariate model. None of the trials included a complete set of anatomical variables in the minimum data set, so where possible the variable with the most complete data was selected from each cluster.

Categorical variables which were associated with a Chi-squared or Fisher's exact test p-value of $p<0.05$ were considered for multivariate analysis. Those which displayed a trend toward significance ($p<0.1$) were also considered if it was felt that it made clinical sense that they would contribute to a predictive model. Variables were excluded if they were less than 80% complete in the original dataset. If there were two variables that were considered to be potentially co-linear, the variable with the strongest association with the outcome in question was selected.
The "rule of thumb" which suggests that 5-9 variables per event should be used in logistic regression models was considered when selecting variables, to ensure as few variables as possible were entered into the backward selection process.[16]

Derivation of regression and proportional hazards models

The selected covariates were entered into an automated backwards selection process which used the Wald test for significance at each stage to determine if variables should be eliminated. The hazard ratio (HR) was calculated with 95% confidence intervals with a p-value for significance for the Wald test to assess the contribution of each covariate to the model.

Internal and external validation of Cox's regression model for all cause death

The dataset used to externally validate the risk-stratification systems was obtained from investigators from the University of Florida College of Medicine (UFCM), who maintain a prospective endovascular surgery database at their institution for all patients that have undergone TEVAR[6]. Institutional ethics board committee was applied for and approved for the use of these data in this study. Patients who had died during follow-up were identified and time to death from the procedure was calculated. Patients that were censored for other reasons, such as the end of the study period or loss to follow-up were identified.

Demographics

Patient demographic characteristics were compared between the development registry dataset and the external dataset. Continuous variables were compared between the two groups using the independent samples t-test, and categorical variables were compared the Fisher's exact test. Where there was more than one category to compare, the Chi-squared test was used.

Internal validation of Cox's regression models for mid-term events

The accuracy of the Cox's proportional hazards models was tested using Kaplan-Meier plots that compared observed and predicted events. The "predicted" plot was created by determining the probability of each patient having died at a particular time point and taking the mean of every patients likelihood. 95% confidence intervals were generated from the mean for each point. To determine if the model was able to stratify patients into clinically useful groups according to predicted risk, quartiles and tertile cut-off points of the scores were calculated and a comparison of Kaplan-Meier curves made to determine if two, three or four risk groups were appropriate. Multiple log-rank tests with Sidak's adjustment for multiple comparisons of the log-rank test were used to determine if these were any differences between pairs of groups (i.e. 1^{st} and 2^{nd} quartile and 1^{st} and 3^{rd} quartile) etc. with a stringency of $p<0.05$. Cut-off values to stratify patients into groups could then be derived based.

These steps were repeated first for the original registry data for internal validation purposes and using the UFCM dataset for external validation.

Results

Patient demographics, co-morbidities and aneurysm morphology

671 TAA patients from the MOTHER registry were identified, of which 625 patients from the MOTHER registry were identified as having undergone elective repair. The UFCM validation set consisted of 256 patients that underwent TEVAR for DTAA between 2000 and 2010, of whom 224 underwent elective repair. The age and gender distribution of the development registry and the UFCM groups were statistically similar (**Table 1**). The mean follow-up period was 29.6 months (range 0-121 months) and the median was 26.4 months.

Outcomes

Of the 671 patients with a TAA in the MOTHER registry, 231 (34%) of patients had died during follow-up. Of the 256 patients in the UFCM dataset, 90 (35%) had died during follow-up. In the MOTHER group there were 275 (40%) patients entering the 3rd year of follow-up and 184 (27%) entering the 5th year. In the UFMC group there were 99 (39%) patients entering the 3rd year of follow-up and 36 (14%) entering the 5th year of follow-up.

Initial selection of anatomical covariates

Proximal neck diameter was selected for further univariate analysis as it was strongly correlated with all other diameter measurements in the aortic arch, and was the most complete (additional **figure 1**). Similarly, distal neck diameter was selected as it was correlated with other diameter measurements of the distal aorta and was the most complete. Maximum aneurysm diameter and aneurysm length were selected, as they were relatively complete and are known to be clinically relevant. Of the categorical variables, only iliac tortuosity was selected to enter into the selection process for the models, as it was the most complete. Unfortunately descriptions of neck shape, thrombus burden, calcification and access vessel calcification were not complete enough to use in the model.

Univariate associations with mid-term all cause death and covariate selection for multivariate modelling

Age >75 years was associated with all cause mortality (log-rank p<0.001), as was renal dysfunction (p<0.001), previous cerebrovascular disease (p=0.027), the requirement for >2 devices (p<0.001) and coverage of the left subclavian artery (p=0.005). Previous tobacco use displayed a trend toward significance (p=0.098). More proximal stent-graft landing zones (Ishimaru 0, 1 and 2) (p=0.033), and increasing burden of calcification in the distal neck (p=0.014) and access vessels (p=0.018 and p=0.008 for the right and left respectively) were also subject to increased mid-term mortality and patients with conical distal aneurysm necks showed a trend toward increased risk of mortality (p=0.062) (supplemental **table 1**) (see supplemental figure 2 for some example Kaplan-Meier plots).

Larger mean proximal (32mm vs. 33.5mm; p=0.001) and distal (31.6mm vs. 33.3mm; p=0.003) neck diameters, larger mean maximum aortic diameters (58.3mm vs. 63.mm; p<0.001) and more extensive aneurysms (mean lengths of 121.7mm vs. 135.5mm; p<0.001) were associated with a subsequent mid-term death (supplemental table 2).

Age, renal dysfunction, cerebrovascular disease, need for >2 devices, coverage of the LSA, tobacco usage and the four continuous anatomical variables were used in the multivariate modelling. Ishimaru zone was not used to avoid co-linearity of model variables as LSA coverage and aneurysm length showed a stronger association. ASA grade was not used as it was considered that this is decided on in a subjective manner and is likely subject to variation. Vessel calcification parameters and aneurysm neck shape could not be used due to incompleteness of these data.

Cox's proportional hazard's models for mid-term events

The backwards selection process eliminated aneurysm length, proximal neck diameter and distal neck diameter from the final model which contained age (HR 1.041 per year, 95% CI 1.021-1.061; p<0.001), renal insufficiency (HR 1.675, 95% CI 1.208-2.324; p=0.002), previous history of stroke (HR 1.584 95% CI 1.111-2.259; p=0.0111), the requirement for a placement of >2 devices into the aorta (HR 1.456, 95% CI 1.068-1.985; p=0.0176), tobacco use (HR 1.422, 95% CI 0.99-2.043,p=0.0569) and maximum aneurysm diameter (HR 1.016 per mm 95% CI 1.004-1.028; p=0.01).

The risk score produced was:

All-cause mortality score = 0.0398*(age) + 0.516*(renal insufficiency) + 0.46*(previous history of cerebrovascular disease) + 0.352*(prior tobacco use) + 0.376*(number of devices > 2) + 0.016*(maximum aneurysm diameter)

For categorical variables such as renal insufficiency, when a risk factor is present "1" is used and when it is not "0" is used.

Validation of Cox's proportional hazard's models for mid-term all-cause death

The model for mid-term all-cause death appeared to predict death well when applied to the development group based only on the variables in the model (**Figure 1 and supplemental table 3**). Patients were stratified according to the risk score using tertiles (33rd and 66th centiles), quartiles and a high-risk and low-risk group (over 75th centile = high risk) group (**Figure 2 and supplemental table 4**). Division into a high and low-risk groups resulted in a highly significant log-rank test ($p<0.001$), whereas division into quartiles showed that the two medium risk groups were not significantly different. The group could be separated into a low, medium and high-risk group successfully ($p<0.05$ for comparisons between each group) with a 80%, 63% and 43% 5-year freedom from death respectively. Low risk was defined as a score of < 4.10325, medium risk 4.10325 - 4.67375 and high risk > 4.67375 (Supplemental **table 3)**.

When the all-cause death model was applied to the UFCM dataset, there appeared to be a clearly identified low-risk group with a 79% freedom from mortality at 5 years (**Figure 3**). The medium-risk group had a freedom from mortality of 57%, and the high-risk group only 24% (Supplemental **table 4**). There was no significant difference between the medium and high-risk Kaplan-Meier curves, as the medium risk group appeared to suffer from a high rate of mortality than the development registry patients in the first three years. When split into two groups, the group predicted to be in the highest quartile of risk had a 21% freedom from mortality at 5 years compared to the rest of the group which had 63% freedom from mortality.

Discussion

Univariate analysis of pre-operative physiological and anatomical variables revealed several factors that were associated with mortality at mid-term follow-up after endovascular repair of DTAA. A risk stratification model was derived, and was validated internally meaning the proportion of observed events would likely have been predicted using only the covariates contained in the models. The models were able to identify different risk strata in the development registry, and when applied to the University of Florida group, also placed patients into clinically useful risk strata.

Age, renal dysfunction, previous cerebrovascular disease and a history of tobacco use were all associated with mid-term all-cause death, and these are factors that would be expected to impact on the life-expectancy of the general population regardless of surgical intervention. Patients with aneurysms that extended more proximally and required >2 devices to repair were less likely to survive to follow-up, which is consistent with other work that has suggest more proximal pathology is associated with increased mortality at one year.[6] Increasing maximum aneurysm diameter and diameter of the proximal and distal neck was also associated with poor survival, as was severe calcification of the distal aorta and access vessels. Advanced, generalised aneurysmal and calcific arterial disease is associated with a combination of risk factors that would increase the risk of death from various causes, and has been demonstrated in previous work.[17]

The multivariate model stratified the patients from the development registry into three groups that had approximately an 80%, 60% and 40% freedom from all-cause mortality at 5 years. The model was based on several covariates that intuitively would be likely to predict a limited life expectancy. When applied to the UFCM group, it appeared that only two distinct groups were visible. This was due to the fact that although the mid-term all-cause death rate was comparable in both groups (34% vs. 35%), the patients in the "medium-risk" UFCM group tended to see a sharper decline in survival at an earlier time in the follow-up period and had a poorer overall survival at 5 years (49%). The rate of death in the high-risk group was such that only 23% of patients were left alive after 5 years. It would appear therefore that the model under-predicted 5-year survival in the UFCM group, but it should be noted that there were relatively more patients in the "high-risk" group than in the development registry.

The mid-term all-cause mortality observed amongst patients that have undergone TEVAR is relatively poor, a finding which consistently observed in the published literature. A recent study of UK administrative data showed that freedom from mortality at 5 years was only 65% after TEVAR, compared to 89% in matched controls, which suggests that this group has a generally poorer life expectancy to that of the normal population.[18] Other prospective studies of mid-term mortality in patients undergoing TEVAR for aneurysm revealed a similarly poor rate of survival as the two cohorts studied here.[19,20] This finding has been confirmed by analysis of large administrative datasets in the UK and the US.[1,21]

This risk stratification system is able to identify a group of patients who might not be offered TEVAR unless their aneurysm is felt to be at imminent danger of rupturing, as

they are unlikely to see any benefit in terms of life expectancy. This is an important finding given reports of the increasing numbers of procedures being performed in relatively older, sicker patients than in the era of purely open surgical repair.[1,21,22] Ultimately, TEVAR does not change the natural history of these patients with the exception of decreasing their risk of aneurysm rupture. Thus, due care must be applied when selecting which patients are to undergo TEVAR, given the potential for early serious morbidity and mortality in high-risk patients. If the procedure is not adding significantly to life expectancy, subsequent surveillance and re-intervention may be costly to healthcare systems for little or no benefit at all. Importantly, these risk-stratification systems should not be used to make final decisions about patients, but they can certainly be used to assist in peri-operative decision-making.

Limitations of this study include the fact that some pre-operative information was not available in the development registry, such as some morphological data and information regarding secondary prevention medications. Although the external dataset was similar statistically to the development registry, the UFCM dataset was smaller meaning there were less events that could be used for validation of the peri-operative events. The MOTHER registry is made up of many patients that were enrolled into clinical studies with exclusion and inclusion criteria, whereas the UFCM dataset was an institutional case series. Despite this the two groups were from similar time periods, and to a certain extent differences in institutional practice is important if external validation is to be successful.

Conclusion

Identifying patients who have a limited life expectancy despite successful endovascular treatment of a thoracic aortic aneurysm appears to be possible using an externally validated pre-operative risk-stratification system. A variety of physiological and morphological factors are associated with adverse peri-operative and mid-term outcomes following thoracic endovascular aneurysm repair. Patients can potentially be grouped into risk strata that will inform their risk of mid-term all cause mortality. This knowledge could be used to target patients who stand to gain the most from treatment, and potentially counsel some against intervention.

Figure legends

Figure 1 KM curves for mid-term all-cause death model internal validation

Figure 1 showing internal validation of the Cox's proportional hazards model for all-cause death. The red points or (KM estimates) represent the actual occurrence of death in sample population. The blue line (PH model fit) represents a line drawn through the predicted deaths that would have occurred based on the predictions of the proportional hazards model with 95% confidence intervals.

	0	1	2	3	4	5
No. at risk	631	456	364	279	228	164
Observed Deaths	119	39	28	17	22	2
Expected deaths	113	38	26	17	20	1

Figure 2 KM curves for mid-term all-cause death stratification groups

Figure 2 showing different ways of stratifying risk of all cause death according to grouping. When the group was divided into three, there was a significant difference between all groups ($p<0.001$ for group 1 vs. 3 and 2 vs. 3 and $p = 0.014$ for 1 vs. 2) (see supplemental table 3 for life-tables)

Figure 3 KM curves for mid-term all-cause death - validation of stratification groups

Figure 3 showing the Kaplan-Meier showing groups of patients at low-risk, medium-risk and high-risk according to the model for predicting mid-term all-cause death applied to the validation cohort (UFCM group) (see supplemental table 3 for life-tables).

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