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Intraluminal thrombus effect on the progression of abdominal aortic aneurysms by using a multistate continuous-time Markov chain model

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Abstract

Objective: To investigate the relationship between the characteristics of intraluminal thrombus (ILT) with abdominal aortic aneurysm (AAA) expansion.

Methods: This retrospective clinical study applied homogeneous multistate continuous-time Markov chain models to longitudinal computed tomography (CT) data from Korean patients with AAA. Four AAA states were considered (early, mild, severe, fatal) and the maximal thickness of the ILT (max_{ILT}), the fraction of the wall area covered by the ILT ($area_{frac}$) and the fraction of ILT volume (vol_{frac}) were used as covariates.

Results: The analysis reviewed longitudinal CT images from 26 patients. Based on likelihood-ratio statistics, the $area_{frac}$ was the most significant biomarker and max_{ILT} was the second most significant. In addition, within AAAs that developed an ILT layer, the analysis found that the AAA expands relatively quickly during the early stage but the rate of expansion reduces once the AAA has reached a larger size.

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Conclusion: The results recommend surgical intervention when a patient has an $area_{frac}$ more than 60%. Although this recommendation should be considered with caution given the limited sample size, physicians can use the proposed model as a tool to find such recommendations with their own data.

Keywords
Abdominal aortic aneurysms, intraluminal thrombus, Markov chain model, survival analysis

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Introduction

Abdominal aortic aneurysm (AAA), the dilatation of an aorta at an abdominal level, is a common life-threatening disease that affects 9.5% of the elderly population (>65 years).[1] This dilatation of the abdominal aorta can cause death when it ruptures. The rupture occurs when the stress on the AAA wall overcomes the wall strength. Since the maximum diameter is positively associated with the wall stress[2] and with AAA expansion,[3] it has been used as a risk factor for AAA growth and subsequently for rupture. Current medical treatment suggests that once a patient is diagnosed with AAA, they should be kept under surveillance until the aneurysm reaches 5.5 cm in diameter in the US [4] Some studies, however, challenge the 5.5 cm threshold criterion since small AAAs still rupture. For example, 10–24% of ruptured AAAs were less than 5 cm in diameter, although more cases succumb to rupture prior to surgical intervention as the diameter increases.[5] In fact, the screening criterion varies from country to country.[6] Therefore, this current study took advantage of this association and investigated the statistical distribution of the maximum diameters of AAAs by quantitatively dichotomizing patients into four different prognostic groups: early, mild, severe and fatal.

In this current study, patients were observed over time and morphological characteristics of the AAA were recorded. With the time-to-event data, researchers and physicians usually like to make inferences on the progression path (e.g. deterioration or recovery) of the disease. Survival analysis is a commonly used statistical tool to achieve such a goal. However, usual survival analysis can only deal with binary events (e.g. alive or dead). Instead, a multistate model[7] is able to model longitudinal studies where individuals may experience several events; and then conduct forward or backward conversions between events. Therefore, this current study adopted a multistate continuous-time Markov chain model to estimate the transition from one state to another for patients with AAA. In this model, the transition intensities provide the hazards and the survival probabilities for AAA progression.[8] Then the mean sojourn time in a given state can be calculated.[9] In addition, this current study incorporated intraluminal thrombus (ILT) information as covariates into the model through transition intensities as ILT is strongly associated with AAA expansion rates.[10]

Choosing the appropriate covariate to predict AAA growth rate and time-to-event is an important task, because an accurate prediction can allow personalized

clinical management and proper timing of surgery.[11] Patient-specific prediction of AAAs have been performed via Bayesian methods combining sequential CT images[12] and biomedical and computational models[13] without taking into account the ILT. There has been, however, substantial heterogeneity of AAA expansion rates and accurate growth prediction remains a top priority to improve the prediction capability. Numerous variables have been suggested as potential predictors for growth and AAA rupture[14] and, among them, the ILT is being recognized as a potential metric of AAA growth.[15]A previous study obtained a set of follow-up CT images from four patients and estimated AAA growth along with geometrical characteristics of ILT.[16] The study found that the intraluminal ILT volume and maximum ILT thickness were correlated with AAA volume growth.[16] Another study that evaluated 14 patients classified scan images of AAAs into two groups of AAAs by the ILT area fractions and found that AAAs grew significantly faster in the group with larger ILT compared with the group with lower ILT.[10] These studies of the effect of ILT on AAA growth were based on small AAA datasets. Only a few studied which geometrical characteristics of ILT were linked to the prediction of AAA expansion.[10,13] Therefore, using a larger dataset of follow-up AAAs, this current study investigated which geometrical characteristics of ILT can enhance the prediction of AAA expansion and their transition probabilities. In particular, the current study measured the association between AAA growth and ILT by considering a homogeneous multistate continuous-time Markov chain model with covariates related to ILT.

Generally, the progression of AAA growth is related to other factors such as age, sex, smoking and vascular diseases.[17] The retrospective data used in the current study were originally obtained for characterizing relevant morphological parameters so that the clinical and biochemical data were not available. As the focus of the current study was the influence of ILT characteristics on AAA progression, ILT thicknesses, percentage of the luminal area covered during the AAA progression and the volume of ILT per each scan were extracted and applied in a statistical model to predict AAA expansion based on these geometrical characteristics of ILT. By incorporating contributing factors such as ILT volume or fraction, a fitted model could be used to predict the progression of AAA and its rate of transition from one state to another state.

Materials and methods

Study population

This retrospective study reviewed longitudinal computed tomography (CT) images from de-identified Korean patients each with up to seven surveillance scans in the Department of Radiology, Seoul National University Hospital, Seoul, Republic of Korea between January 2000 and December 2016. Inclusion criteria were as follows: (i) patients diagnosed with AAA; (ii) CT imaging at a minimum of two different time-points.

The study was reviewed and exempted by the Internal Review Board at Michigan State University East Lansing, MI, USA where the statistical analyses were undertaken.

Scan data collection

For each scan, a maximum spherical diameter D was measured and used to categorize the AAAs into four stages:[18](i) early ($D < 40$ mm); (ii) mild (40 mm $\leq D < 47$ mm); (iii) severe (47 mm $\leq D < 58$ mm); (iv) fatal ($D \geq 58$ mm). A previous study proposed a diameter measurement called

the spherical diameter that the largest sphere fits within the aorta and found that the spherical diameter measurement has the lowest uncertainty compared with other measurements, which has an advantage for the growth prediction, although the spherical diameters are slightly smaller than the traditional orthogonal diameters (mean 4 mm with the maximum value of 9 mm).[18] Note that there are variations in AAA screening among countries. However, the typical orthogonal diameter criterion for surgical recommendation is 50 mm or 55 mm.[4,6] Given such variations in criterion and the use of spherical diameter in this current study, it was reasonable to assume that a patient in a severe state was recommended for surgical intervention and a patient in a fatal state should be guided toward prompt surgery.

Data collection

For each CT scan, the maximal thickness of the ILT (max_{ILT}), the fraction of the wall area covered by the ILT ($area_{frac}$) and the fraction of ILT volume (vol_{frac}) were measured using an approach described previously.[10]

Multistate continuous-time Markov chain model

Multistate continuous-time Markov chain models can be used to model the progression of diseases, as previously described,[19] which can provide information about disease progression by determining the transition probabilities between different states and the mean sojourn time at one state. Specifically, this current study used a homogeneous model by assuming a transition intensity (the rate of a transition probability) that was independent of time. This model allows a transition probability that changes over time but the rate remains constant. In addition, the ILT information was incorporated into the model by considering the logarithm of an intensity as a linear function of explanatory variables from the ILT. To investigate which model fits the data best, the study considered the likelihood ratio (LR) statistics given the proposed statistical model. The LR statistics was the ratio of two likelihoods (or –2 log [likelihood ratio]), which was used to perform a statistical hypothesis test for model comparison. The likelihood in the numerator was from the null model and the likelihood in the denominator was from the alternative model. Thus, a larger value of the likelihood ratio statistics (or a smaller value of –2 log [likelihood ratio]) indicates the data support the null model. The algorithm for the estimation was converged and produced stable results.

Results

This retrospective study reviewed longitudinal CT images from 26 de-identified Korean patients each of whom had up to seven follow-up scans. The maximum spherical diameter of the AAAs of all of the patients at different scan times are shown in Figure 1. There were cases where the status of the AAA growth moved to another state (e.g. it moved from an 'early' state to a 'mild' state or from a 'mild' state to a 'severe' state). One patient (patient 14) experienced a decrease of the maximum spherical diameter before an expansion in the diameter. There were also cases in whom scan times were relatively short. One patent (patient 21) had a much smaller diameter AAA compared with the other patients. The measurements of this patient could be an outlier or due to the characteristics of the spherical diameter measurement (i.e. smaller than that of the traditional orthogonal diameter).[18] As patient 21 remained in the early state according to the study criterion, the results were unlikely to be affected by the inclusion

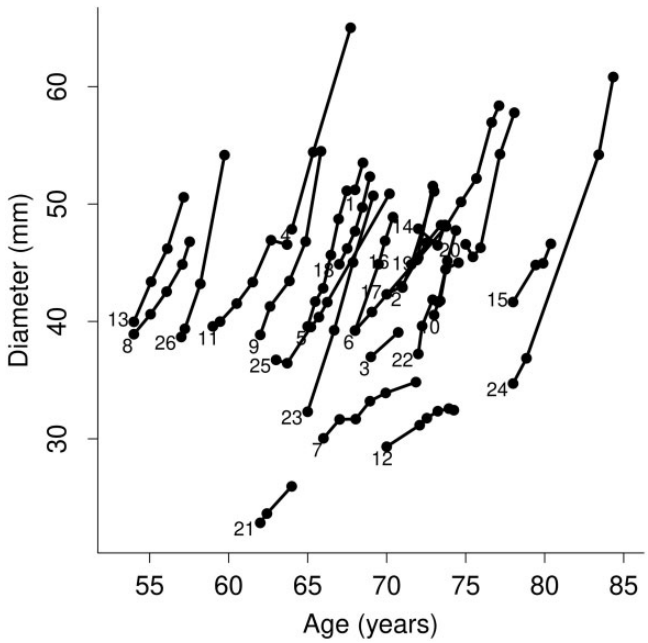

Figure 1. The maximum spherical diameter of the abdominal aortic aneurysms (AAAs) for each patient over time based on the age of the patient. Each line corresponds to one patient that is identified by the number shown on the lower left corner of each line. The dots on each line indicate when the computed tomography image was taken.

or exclusion of this patient, so the decision was made to keep the patient in the analysis.

The current study considered the $\max_{ILT}$, $area_{frac}$ and vol_{frac} as covariates in the model. These variables are continuous variables and it should be noted that they are highly correlated with each other. In particular, the correlation between the $area_{frac}$ and vol_{frac} was 0.89. High correlation between covariates can lead to unstable estimates if they are included in the model together. Thus, the model was used with one covariate only. Although the three ILT variables were highly correlated (Figure 2), they had different effects on the transition probability curves at different times. The current study investigated which variable was a significant biomarker for AAA progression.

With regard to model comparisons, Table 1 shows likelihood ratio statistics (–2 log [likelihood ratio]) and the corresponding *P*-value for each model when the null model was the model without covariates. This result showed that the model with one of the covariates was overall statistically significant. Although it was not possible to directly determine which covariate fits the data better compared with the two covariates by a hypothesis test as they were not nested models. The larger LR statistics could imply a better fit as the LR statistics of each model was calculated with the same null model.

Further evidence that these three covariates contribute to the progress of AAA enlargement is the comparison of transition probability curves under different models (Figure 2). The fitted transition probability

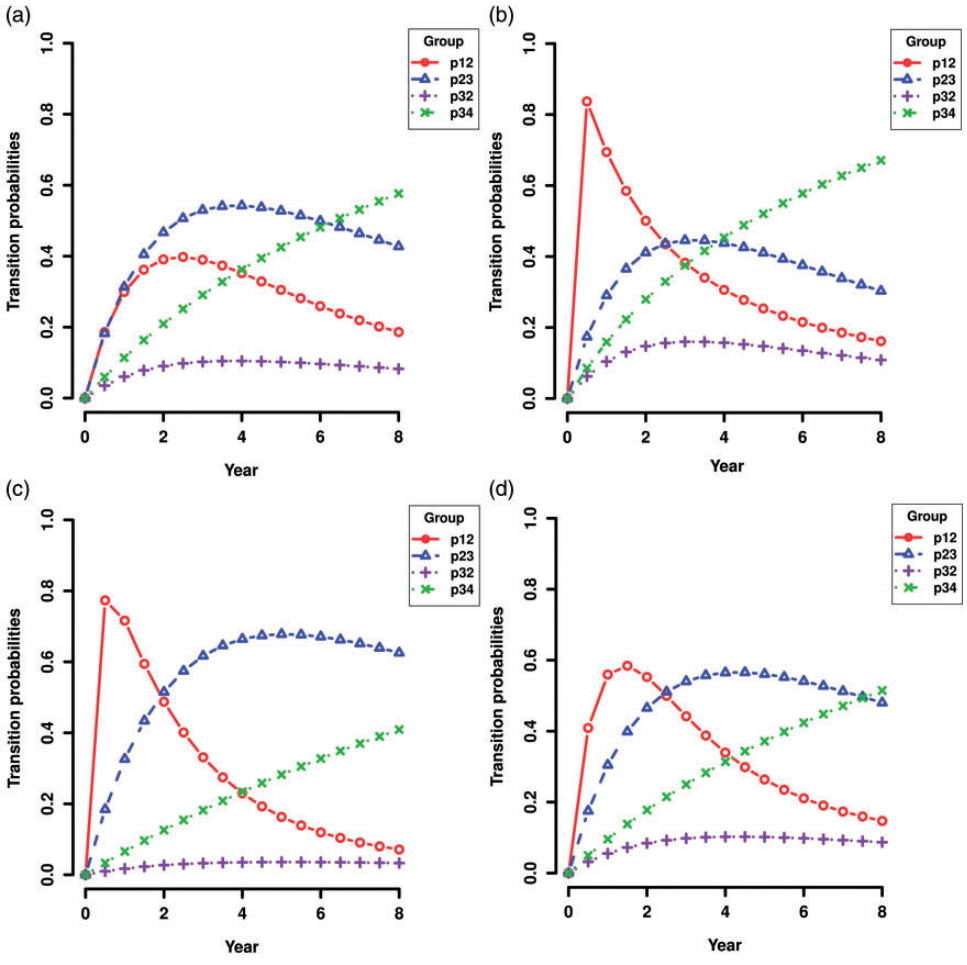

Figure 2. Fitted transition probability curves at different years. (a) The homogeneous Markov model without covariates. (b) The homogeneous Markov model with a covariate: max_{ILT}, when max_{ILT} is fixed at its mean value 14.34 mm. (c) The homogeneous Markov model with a covariate: $area_{frac}$, when $area_{frac}$ is fixed at its mean value 0.31. (d) The homogeneous Markov model with a covariate: vol_{frac}, when vol_{frac} is fixed at its mean value 0.38. In each graph, the red circle line denotes the transition probabilities of moving from an 'early' state to a 'mild' state (p12); the blue triangle line denotes the transition probabilities of moving from a 'mild' state to a 'severe' state (p23); the purple plus line denotes the transition probabilities of moving from a 'severe' state to a 'mild' state (p32): and the green cross line denotes the transition probabilities of moving from a 'severe' state to a 'fatal' state (p34). The colour version of this figure is available at: http://imr.sagepub.com.

curve without covariates (Figure 2a) has relatively lower peaks than the other three transition probability curves, especially when the transition is from an 'early' state to a 'mild' state. In addition, by finding the peak of the curves for p12 and p23, the model shows that patients in an 'early' state are most likely to move to a 'mild' state between 1 and 2 years, while patients in a 'mild' state are most likely to move to a 'severe' state at around 4 years. The model with $area_{frac}$ has the highest transition

probability from a 'mild' state to a 'severe' state among the three models given the severe criterion within 3 years (Figures 2b–2d). This may indicate that the progression from a 'mild' state to a 'severe' state is sensitive to the changes of $area_{frac}$. In other words, when a patient already has a mild AAA, $area_{frac}$ can be a useful biomarker to predict their state after a certain time period.

A prevalence plot could also show the goodness of fit for a multistate continuous Markov chain model and Pearson tests can provide the goodness of fit for the models. These results indicate that the Markov model with max_{ILT} or $area_{frac}$ as the covariate passed the test of the goodness of fit (data not shown). Among the models with ILT characteristics as a covariate, the model using $area_{frac}$ was investigated in more detail and the results of the other two models (max_{ILT} and vol_{frac}) are available at: www.medrxiv.org/content/10.1101/2020.08.31.20185330v1.

Table 1. Likelihood ratio (LR) statistics of different multistate continuous-time Markov chain models when the null model was the model without covariates.

	max_{ILT}	$area_{frac}$	vol_{frac}
–2 log (LR)	17.9	23.33	10.51
P-value	$P = 0.0013$	$P = 0.0001$	$P = 0.0326$

The value of $area_{frac}$ ranged from 0.00 to 0.74 and approximately the third quartile of the values of $area_{frac}$ were less than 0.4. So, the value 0.4 was used as a criterion for the severity of the ILT. As an extreme case, the analysis also considered 0.6, which was the 95% quantile. With these values for $area_{frac}$, the analysis estimated transition probabilities for the duration of 3 years and the mean sojourn time (Table 2). According to the estimated transition probability, there was no chance that a patient with $area_{frac}$ being 0.4 was in an 'early' state. In addition, such a patient will instantly transit to or already stay in either a 'mild' or 'severe' state within 3 years. By comparing transition probabilities when $area_{frac}$ was 0.6 with those when $area_{frac}$ was 0.4, the data indicate that the disease state of AAA progresses more with the increase of $area_{frac}$. Also, the estimated mean sojourn time for an 'early' state was relatively small compared with those for the other states. Although the range of AAA size for each state was rather different, this still implies that a patient stays at an 'early' state for a shorter time with an $area_{frac}$ of 0.4.

To investigate the effects of $area_{frac}$ on the survival probability, the Kaplan–Meier method was used to plot survival probability curves.[20] By comparing Figure 3a with Figure 3b, the data indicate that the model

Table 2. Results from multistate continuous-time Markov chain models with the covariate $area_{frac}$ showing the estimated transition probabilities (ETP) at the different values of the covariate and time and the estimated mean sojourn time (EMST).

	ETP for each state when $area_{frac}$ is 0.4 at 3 years				ETP for each state when $area_{frac}$ is 0.6 at 3 years				EMST (year) for each state when $area_{frac}$ is 0.4	
	Early	Mild	Severe	Fatal	Early	Mild	Severe	Fatal	Estimates	95% Confidence interval
Early	0.000	0.236	0.630	0.134	0.000	0.323	0.374	0.302	0.052	0.007, 0.415
Mild	0.000	0.231	0.631	0.138	0.000	0.323	0.374	0.303	1.754	0.226, 13.602
Severe	0.000	0.075	0.673	0.252	0.000	0.282	0.330	0.388	5.845	0.831, 41.087

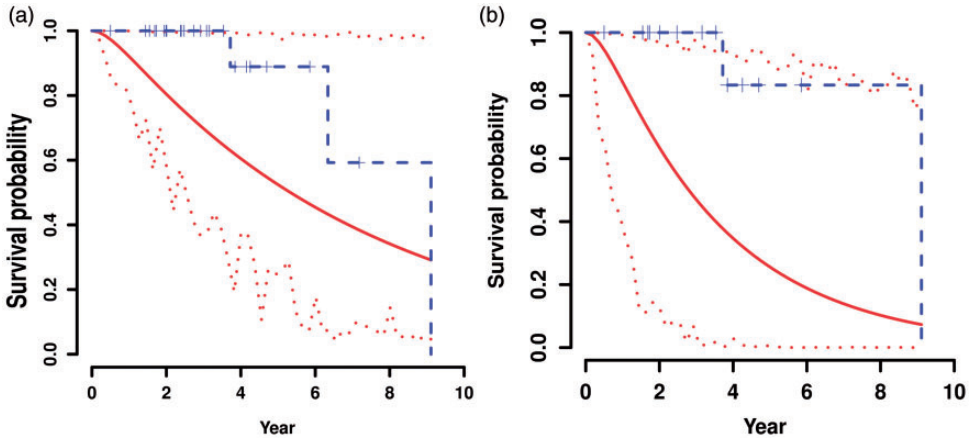

Figure 3. Comparison of the empirical and fitted survival probability for two multistate continuous-time Markov chain models with $area_{frac}$. (a) The multistate continuous-time Markov chain model with covariate $area_{frac}$, when $area_{frac}$ is 0.4. (b) The multistate continuous-time Markov chain model with covariate $area_{frac}$, when $area_{frac}$ is 0.6. In each graph, the red solid line denotes the fitted survival curve. The blue dashed line denotes the empirical survival. The red dotted line denotes the 95% confidence interval of the fitted survival. The colour version of this figure is available at: http://imr.sagepub.com.

with the larger $area_{frac}$ as a covariate had a lower survival probability, which implies that a patient with a larger $area_{frac}$ is exposed to a higher risk of entering into the last stage (i.e. a 'fatal' state). The two survival curves, the one with an $area_{frac}$ of 0.4 and the other with an $area_{frac}$ of 0.6, were compared using the two-sample Kolmogorov–Smirnov test.[21] This test demonstrated that the two curves were significantly different ($P < 0.0001$).

A larger patient data set should be investigated in order to reach a stronger conclusion. However, despite the fact that a small data set was used in the current study, a trend was clearly seen. If it is assumed that a surgical intervention should be recommended when survival probability is lower than 40% at 4 years, Figure 3b suggests that a patient with 0.6 of $area_{frac}$ was being considered for such a recommendation. It is also possible to find a criterion using max_{ILT} or vol_{frac}. For example, with the survival probability was lower than 40% at 4 years, a patient with a max_{ILT} of 30 mm was being considered for surgical intervention. Note that depending on the physician's criterion on the survival probability (e.g. 40%) and the time period (e.g. 4 years), the recommendation will change. However, the model that was used can provide such information adaptively.

Discussion

In this current study, a homogeneous multistate continuous-time Markov chain model was used for the analysis of AAA progression to investigate the transition of progression from one state to another state in terms of AAA growth. The model determines the estimated mean sojourn time for a patient being in each state. Given the estimated mean sojourn times for 'mild' and 'severe' states from the model with $area_{frac}$, it was possible to state that an approximate time for a 1-mm increase in the 'mild' state was shorter than that for the 'severe' state, which implies that the AAA expands relatively quickly at an early stage but the rate

slows down once the AAA has reached a larger size. The model with $area_{frac}$ had the highest transition probabilities among the three models within 3 years at the value of the third quartile ('severe' condition). This finding may imply that the progression from a 'mild' state to a 'severe' state was sensitive to the changes of $area_{frac}$. In other words, when someone already has a mild AAA, the $area_{frac}$ might be a useful biomarker to predict their AAA state after a certain period of time.

Likelihood ratio statistics demonstrated that a model with any one of three covariates fitted the data better than the model without the ILT information. This may suggest that when AAA growth is being considered, ILT information such as max_{ILT}, $area_{frac}$ and vol_{frac} from patients should not be ignored. More specifically, if it is assumed that a patient with a fitted survival probability lower than 40% at 4 years should be recommended for surgical intervention, these current data suggest that any patients with an $area_{frac}$ more than 60% should be highly recommended for surgical intervention, considering the low survival probabilities in these two progression stages. This recommendation could be changed depending on the threshold of survival probability and the time. Also, the results would be different to those reported due to the dependency of the chosen stages threshold criteria. More detailed analysis on the appropriate threshold should be conducted with a larger cohort before reaching stronger conclusions. Despite this limitation, these current results were in agreement with other previous studies.[22,23]

Thrombus accumulation is an ongoing process that is present in 75% of detected AAAs and the prevalence of thrombus accumulation increases as the size of the aneurysm increases.[24] Therefore, it is expected to observe AAAs without ILT at the early stage ('early') of this disease. This current study found that most of the AAAs remained without ILT accumulation during the 'early' stage and a significant ILT accumulation was observed when they transitioned to the following stage. Over this 'early' stage, a faster AAA expansion in comparison with other stages was observed. This could suggest that the faster growth may promote ILT accumulation. Additionally, this observation and the fact that the ILT accumulation rate was found to be the same as the AAA expansion rate[10] would explain the proposed idea of using a sudden increase of thrombus as a potential predictor of a rupture.

Once the initial ILT accumulation occurs (usually in the transition between the 'early' to 'mild' state), these current results have shown that the next transition stage would be sensitive to the amount of lumen area covered by the thrombus ($area_{frac}$). The intraluminal thrombus is a complex biological entity composed of many inflammatory cells, including macrophages and neutrophils,[25] which not only interfere with the direct wall shear stress and strain relationship between the lumen wall and blood flow, but they also interact biochemically (promoting wall thinning, cell inflammation, degradation of the extracellular matrix[26]) and biomechanically (modifying wall shear stress[27]) with the arterial wall. It is then understandable that a larger area covered by thrombus would have a greater impact on the AAA growth process and thus in the transition time. Furthermore, these current results may indicate that the risk of a patient transitioning to the 'fatal' last stage is outweighed as a larger ILT thickness (max_{ILT}) is observed. These results agree with signs of a lower pO_2 levels and signs of hypoxia in aneurysms with an ILT thickness greater than 4 mm.[28]

This current study had several limitations. First, these current data were originally obtained for characterizing relevant morphological parameters so the clinical

and biochemical data such as smoking habits and blood pressure were not collected. Secondly, there were only three female patients in the cohort so it was not possible to investigate the effects of sex. It was not possible to add more patient-specific information. Thirdly, with more observations from a control group (individuals with no AAA) and patients whose AAA had ruptured or those that had received surgical treatment, it would be possible to provide more reliable estimates of transition probabilities as well as mean sojourn times. A thorough investigation of the effects of the ILT parameters, as well as other patient-specific characteristics, on the AAA growth could be undertaken with a larger sample size. Finally, the growth rate/expansion rate could be an informative criterion to determining the stages of AAA. However, this study used the maximum spherical diameter because it is the clinically important metric to assess the onset, progression and risk of AAA rupture. The use of this widely known relationship to stratify AAAs severity makes it easier for the reader to compare these current results with those of other cohorts or to patients in clinical practice. These current findings provide an interesting hypothesis that should be verified by further studies with larger groups of patients with AAA.

To the best of our knowledge, there are only a few studies with morphological data obtained from follow-up patients.[10,27] This current study was one of the largest data sets in terms of characterizing morphological parameters in a follow-up study. The reason for the scarcity of such data could be due to the need for manual, time-consuming segmentation or the lack of development of an automatic process for quantifying the morphological parameters of an ILT. Despite the small sample size in the current study, it has been possible to demonstrate the use of a new statistical tool in determining the role of thrombus development in the prediction AAA progression. Future research will include clinical data associated with various risk factors and the development of an automatic morphological quantification system that will extract ILT data easily, which will help to produce a larger dataset for analysis.

In conclusion, these current results recommend surgical intervention when a patient has an $area_{frac}$ more than 60%. Although this recommendation should be considered with caution given the limited sample size, physicians could use the proposed model as a tool to find such recommendations with their own data.

Acknowledgements

All of the codes were written and performed in R (r-project.org; version 3.4.4.). The R package that was mainly used was 'msm' and usage was introduced previously.[29]

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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