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Abstract

Objective: Frailty is a multi-dimensional vulnerability due to age-associated decline. The impact of frailty on outcomes was assessed in a cohort of vascular surgical patients.

Methods: Patients aged over 65 years with length of stay (LOS) > 2 days admitted to a tertiary vascular unit over a single calendar year were included. Demographics, mode of admission, diagnosis, mortality, LOS and discharge destination were recorded, as well as a variety of frailty-specific characteristics. The impact of frailty on LOS, discharge destination, survival and readmission rate was assessed using multivariate regression techniques. The ability of such frailty models to predict these outcomes was also assessed.

Results: In total, 413 patients (median age 77 years) were followed up for a median of 18 months (range 12-24). In-hospital, 3- and 12-month mortality was 3.6%, 8.8%, and 15.4% respectively. ROC curve analysis revealed that frailty-based regression models were excellent predictors of 12-month mortality (area under ROC curve (AUC) = 0.81), prolonged LOS (AUC = 0.79) and discharge to a care institution (AUC = 0.84). A simple additive ‘frailty score’ using 6 key features retains strong predictive power for 12 month mortality (AUC = 0.83), discharge to a care institution (AUC = 0.78) and prolonged LOS (AUC = 0.74). This frailty score is also strongly associated with readmission (P<.001).

Conclusions: Frailty in vascular surgery patients predicts a multiplicity of poorer outcomes. Optimal treatment should include identification of “at risk” patients and management of modifiable risk factors.

Key words: Frailty, vascular surgery, mortality, readmission.

Introduction

Throughout most of the Western world, the proportion of the population aged over 60 increased significantly over the second half of the twentieth century, from around 12% in 1950 to around 20% in 2000[1]. This changing demographic is predicted to continue for the first half of the twenty-first century, with the proportion of the population aged over 60 reaching 33% in 2050.[1] This change brings with it huge challenges for healthcare providers, as older people use a disproportionately large amount of medical resources[2].

As people age, their burden of chronic disease inevitably increases, leaving them with less physiological reserve to overcome the acute physiological stress encountered following surgical intervention. Concurrent to this, advances in surgical and anaesthetic practice mean that the physiological impact of surgery is reduced, so that even procedures that were historically contemplated in only the fitter patients (eg. abdominal aortic aneurysm (AAA) repair), can now be undertaken in older patients with significantly increased comorbidity[3,4]. This combination of changing patient demographics and perioperative risk makes the development of modern tools for surgical risk assessment essential, and has generated a variety of scoring tools for specific procedures such as coronary artery bypass grafting and AAA repair[5,6]. Such procedure specific tools are important, but the development of a more generic tool assessing the degree of physiological reserve or frailty of a patient would be more powerful as it would have the potential to be employed across a number of procedures / disease pathologies.

The concept of frailty, defined by some as a multi-dimensional vulnerability due to age-associated decline in physiological reserve, is therefore of increasing interest to surgeons[3,7,8]. While some generic frailty scores exist, vascular surgery in particular has the potential to be affected by patient frailty, with around 60% of vascular surgical patients older than 65 so it is natural, therefore, that vascular surgeons have begun to examine this issue[3,9-11]. The literature concerning vascular-specific frailty, however, has thus far been either rather simple, or focussed on patients undergoing a single procedure.

The aims of the current study were therefore threefold. Firstly, frailty characteristics were assessed in a cohort of vascular surgical patients, to determine whether frailty predicted adverse short and mid-term outcomes in this population. Secondly, the frailty characteristics which were most predictive of poorer outcomes were determined. This was achieved by measuring a large number of frailty relevant characteristics and using statistical techniques to select the best predictors. Thirdly, these insights were used to develop a simple tool which predicts outcomes by incorporating information from a small number of key frailty characteristics. The primary outcome measure was mortality at 12 months following the start of the index admission. Secondary outcomes included discharge to a care facility, length of hospital stay during the index admission and readmission-free survival.

Methods

Patients

All patients admitted to the Cambridge Vascular Unit during the period 1st January 2012 to 31st December 2012 were screened for inclusion in the study. The inclusion criteria were age ≥ 65 years and length of stay ≥ 2 days. These were chosen pragmatically in order to focus attention on a subset of patients who were more likely to suffer a degree of frailty, admitted with conditions which were more likely to be associated with a significant risk of adverse outcomes. In this way the collection of large amounts of data about young, healthy individuals undergoing minor procedures including venous intervention and therapeutic peripheral endovascular treatments requiring an overnight stay was avoided. Data were collected retrospectively on all patients meeting the inclusion criteria by interrogating both electronic and paper medical records. Patient demographics, mode of admission (elective or emergency, which was defined as an unplanned admission either from an outpatient clinic, through the emergency department or an inter-hospital transfer), diagnosis, management, in-hospital mortality, length of stay (LOS) and discharge destination were recorded, along with the frailty-specific characteristics recorded in Table 1.[7] Readmission and mortality data were also collected for a further year of follow-up until 31st December 2013. The hospital electronic records system is linked to the United Kingdom Office for National Statistics for collection of mortality data.

Statistical analysis

The impacts of frailty on survival; readmission-free survival; prolonged LOS, defined as a LOS greater than or equal to 1 week; and discharge destination, quantified by whether or not a patient was discharged to a care facility (DTC). P-values for univariate analysis were then corrected for multiple testing using the Bonferroni-Holm method[12]. Optimal multivariate models were developed by performing stepwise minimisation of Akaike's Information Criterion[13], and fine-tuned by then removing terms with Wald P-values greater than 0.1.

For survival and readmission-free survival, univariate P-values were calculated using the log-rank test, while multivariate analysis made use of Cox regression analysis[14]. The relationship of frailty to prolonged LOS and DTC was investigated using Fisher's exact test for binary predictors and the Mann-Whitney U test for continuous predictors. Multivariate analysis for these outcomes was then performed using logistic regression analysis[15].

In order to facilitate rapid assessment of frailty in the clinical environment, the terms of the Cox model for mortality were then used to construct a simple additive score, and receiver operating characteristic curve analysis[16,17] was used to assess the ability of this score and the full multivariate models developed using the above techniques to predict prolonged LOS, DTC, 12-month mortality and 12-month readmission-free survival. Bootstrap using 1000 replicates was also used to correct bias attributable to overfitting[18]. Throughout the analysis, adjusted P-values less than 0.05 were considered significant.

Analysis was performed using the R statistical software version 3.0.1 (The R Foundation for Statistical Computing, http://www.r-project.org/foundation)[19] together with the 'survival'[20] and 'pROC'[21] packages.

Results

There were nine-hundred and forty-seven admissions to the Vascular Unit between 1st January 2012 and 31st December 2012, involving 823 patients. Seven-hundred and twenty-five patients were admitted to the unit once, 79 patients were admitted twice, 13 were admitted three times, 5 patients were admitted four times and one patient was admitted five times. Five-hundred and sixty-one patients were aged 65 years or older on their first admission to the unit, of whom four-hundred and thirteen patients had a length of stay greater than or equal to 2 days, and therefore met both of the inclusion criteria (Figure 1). Data was incomplete for three patients, so these were excluded from the analysis. Weight, BMI and serum albumin were not available for a significant number of patients and so were excluded from the multivariate analysis, but data on the remaining parameters was complete.

Development of the Addenbrookes Vascular Frailty Score

After correction for multiple testing, 12-month mortality was significantly higher ($P<0.01$) in patients who were anaemic on admission, not independently mobile on admission, those with polypharmacy or raised Waterlow score, those with a history of multiple falls or depression, and those admitted as an emergency (Table 2, column 2). Multivariate Cox regression modeling revealed that, other than a history of falls, these were independent discriminators of increased mortality (Table 2, columns 3 & 4). As can be seen from Table 2, the coefficients of the six significant variables are quite similar, so these six features were used to create an additive Addenbrookes Vascular Frailty Score (AVFS - scored from 0-6 with one point given for each of the six variables each patient had). Out of

410 patients analysed, 60 had a frailty score of zero, 104 had a frailty score of one, 93 had a score of two, 74 had a score of three, 54 had a score of four, and 24 had a score of five. Only one patient had a frailty score of six.

Mortality

The in-hospital mortality rate was 3.6%. This rose to 8.5% and 13.8% at 3 and 12 months respectively. In total, 81 patients died during follow-up. The commonest causes of death were cardiac disease (24%), cancer (19%) and sepsis (15%). Seven patients died of ruptured aortic aneurysms, of whom three were treated operatively. Four patients died of severe chronic limb ischaemia, all of whom were treated palliatively. The cause of death was not ascertained in 7 cases. ROC curve analysis revealed that both the full Cox regression model shown in Table 2 and the AVFS were excellent predictors of 12-month survival (Figure 2, area under ROC curve (AUC) 0.81, 95% confidence interval (0.76-0.86) for full model; 0.83, 95% confidence interval (0.78,0.87) for AVFS). Patients with 0-5 of these characteristics had 12-month mortality of 0%, 1.9%, 11.8%, 21.6%, 38.9% and 58.3% respectively (Figure 3). Bootstapping with 1000 replicates revealed no significant need for bias correction of the AUC (bias-corrected AUCs 0.81 and 0.83 respectively).

Readmission-free survival

The majority (54%) of patients were re-admitted during the study follow-up period. The 3 month readmission-free survival was 70%, which fell to 48% at 12 months. After correction for multiple testing, overall re-admission-free survival was significantly worse ($P<0.01$) in patients who were older, not independently mobile, those with a raised Katz score on admission, those with polypharmacy or raised Charlson comorbidity index, those with a history of multiple falls or with a limb-related admission, and those admitted as an emergency (Supplementary Table 1).

Multivariate Cox regression modelling revealed that only lack of independent mobility, polypharmacy, raised Charlson comorbidity index and emergency admission were independent discriminators of reduced readmission-free survival (Supplementary Table 1). The AVFS described in the previous section was an excellent predictor of readmission free survival at 12 months when used as a predictor in Cox regression: patients with a AVFS of 0-6 had 12-month readmission-free survival rates of 68%, 60%, 50%, 38%, 30%, 17% and 0% respectively (Supplementary Figure 1, P<.001). The AVFS provided average discrimination for prediction of readmission-free survival at 12 months, which was similar to the level of discrimination achieved by the full Cox model for readmission-free survival shown in Supplementary Table 1 (Supplementary Figure 4, AUC=0.67 and 0.71 respectively). Bootstapping with 1000 replicates again revealed no significant need for bias correction of the AUC (bias-corrected AUCs 0.67 and 0.71 respectively).

Length of hospital stay

Overall median LOS was 6 days, with an interquartile range of 3-12 days. Predictors of increased LOS were sex, emergency admission, Charlson comorbidity index, polypharmacy, poor admission mobility, Katz score, Waterlow score, evidence of malnutrition, memory problems and a positive falls history (Supplementary Table 2). Stepwise model selection found a combined model for prolonged LOS

(Supplementary Table 2) that also showed excellent discrimination (Supplementary Figure 2, AUC=0.79, 95% CI 0.74-0.83). Although not as good as the optimal model shown in Supplementary Table 2, the AVFS was also a good predictor of prolonged LOS (Supplementary Figure 2, AUC=0.74). Bootstapping with 1000 replicates revealed minimal need for bias correction (bias-corrected AUCs 0.78 and 0.74 respectively).

Discharge destination

The majority of patients (84%) were discharged to home from hospital. Of the remainder, 21% died during their index admission and 79% were discharged to a care facility (DTC). After correction for multiple testing, predictors ($p<0.01$) for DTC included age, emergency admission, Charlson comorbidity index, polypharmacy, Katz score, poor admission mobility, Waterlow score, memory problems and positive falls history (Supplementary Table 3). Stepwise model selection found a combined logistic regression model for DTC using five frailty characteristics (Supplementary Table 3) with excellent discrimination (Supplementary Figure 3: AUC=0.84, 95% CI 0.77-0.90). The AVFS was also a good predictor of discharge destination (Supplementary Figure 3, AUC=0.78). Bootstapping with 1000 replicates again revealed no significant need for bias correction (bias-corrected AUCs 0.84 and 0.78 respectively).

Discussion

Population ageing makes the need for reliable quantification of frailty within a surgical population essential for determination of operative and non-operative risk. The present work shows that collection of a relatively small number of frailty characteristics combined with admission mode creates a powerful predictor of morbidity and mortality, irrespective of diagnosis and treatment, in a broad vascular surgical cohort representative of everyday practice. This is consistent with work in cardiac and colorectal surgery, where frailty has been found to influence mortality[22], discharge institutionalisation[8] and healthcare-related costs[23]. It is also concordant with a recent study in vascular surgical patients, which looked only at 30-day mortality and major post-operative complications[24].

Frailty is recognized as a multi-dimensional, multi-system impairment across numerous physiologic domains[25]. As such, the analysed frailty characteristics that were measured covered six domains: burden of co-morbidity, function, nutrition, cognition/mental, geriatric syndromes and extrinsic frailty in keeping with the paper by Robinson et al.[7] The data were easy to collate from routine medical and nursing documents. This has resulted in a broad range of frailty characteristics analysed in a large cohort. We then selected those characteristics which best predicted adverse outcomes using rigorous statistical methodology. This has enabled us to discover the most significant characteristics and to develop a novel frailty score, which uses a small number of these characteristics but is nonetheless a powerful predictor of multiple adverse outcomes. What is striking of the AVFS is that five of the predictors come from three of the frailty domains (comorbidity, physical function, nutrition) suggesting that poor outcome is multifactorial in nature and not purely for example related to the burden of co-morbidity. Furthermore, it may be that some of these predictors can be positively modified either prior to or on admission to improve outcome. Indeed, our results suggest that negating just one of the predictors may result in significant long-term improvements in mortality. The AVFS also predicts other important patient and healthcare related outcomes – namely discharge destination, length of stay and readmission free survival - which adds weight to its role as an overall outcome measure in older vascular patients. Multivariate analysis was also performed using the six frailty domains for the other outcome measures and the results show some constant features (polypharmacy, independent mobility and emergency admission). What we have not been able to elucidate is whether the polypharmacy is reflective of co-morbidity or whether the poorer outcomes are a consequence of the side effects of over medication. However, rationalisation of medication and targeted physiotherapy aimed at improving physical ability may help to improve patient related outcomes.

The data for this study were retrospectively collected, though patients were selected using the prospectively collected hospital coding system, which should reduce any recall bias. Model generation and testing were performed on the same data, which can lead to overfitting, though the use of the Schwarz-Bayes criterion for parameter selection should reduce this risk somewhat. Some parameters which were specified in the study protocol were excluded from the study as they were not measured for all patients (for example, serum albumin). Multiple imputation methodology[26] was applied to compensate for this, but as none of these parameters were selected during stepwise multivariate analysis, this data and analysis has not been presented.

While mortality is a universal outcome which is transferrable between healthcare systems, the remaining outcomes (length of stay, discharge destination and to some extent readmission-free survival) are all somewhat dependent upon local healthcare provision. In addition, cultural issues such as the likelihood that frail elderly family members may be looked after at home by their younger relatives despite significant requirement for nursing care will also modify these outcomes. This was part of the reason for basing the AVFS upon mortality and then testing its applicability to the other measures.

The requirement for care following discharge, whether institutional or within the home, is naturally related to the amount of care in place on admission. In fact only 6 patients were discharged to a care facility who were not in a care facility on admission. It would be interesting to look at increasing care requirements, for example an increase in care from once a day care at home to two times or more a day care at home, but these details were poorly recorded in the notes so we were not able to assess this in the current work.

The exclusion criteria were determined so as to exclude patients admitted overnight for observation after minor procedures such as angioplasty or varicose vein procedures as well as to concentrate on frailty as an age-associated decline. The definition of prolonged LOS as greater than or equal to one week, irrespective of diagnosis, was chosen firstly as the median LOS was 6 days, and secondly as this was considered to be more than expected for most admissions. Similarly, we performed little subgroups analysis, specifically with regard to admission diagnosis, as the number of patients in each group were too small to make sound statistical analysis, although we already know that infrainguinal revascularisation for severe limb ischaemia contributes to poor post-operative mobility and increased risk of DTC[27,28].

Ultimately, this study strengthens the evidence for the need of in hospital multidisciplinary teams to address frailty incorporating medical, nursing and allied health professionals. Although the AVFS can be used within the emergent setting, the score has potential to be used as a vital part of pre-operative patient assessment, as it is relatively easy to quantify and has a major impact on multiple key outcomes. This is important firstly for appropriate patient counselling about individual perioperative risk, as length of stay, discharge destination and mortality risk are all factors which patients may use in coming to a decision about the merits of elective surgery. Secondly, it is important in surgical audit given the increasing drive towards publication of surgeon-specific outcomes.[29] There has been much concern about the validity of such statistics, both because only the most crude risk-adjustment has been employed and also because surgeons do not typically perform a large enough number of these procedures each year for there to be very much power to detect poor performance[30]. As frailty is a characteristic that translates across all specialties, it would be a natural choice to use to improve risk adjustment. Such data may also empower healthcare providers to provide appropriate resources to improve outcomes such as LOS and prevention of readmission, with an associated overall reduction in hospital costs.

One potential criticism of the AVFS is that it is 'obvious' that patients with poor mobility, polypharmacy due to multiple comorbidities, those admitted emergently and so forth will do worse, and that calculation of the score will add nothing to a subjective assessment from an expert clinician. We would challenge this notion, as care within our institution is consultant-led and every inpatient is seen by a consultant every day of their admission. Despite this context, the AVFS succeeds in identifying patients with poor outcomes.

Going forward, further studies are underway to validate the AFVS in independent cohorts of vascular and non-vascular patients, including disease-specific subgroups such as patients requiring revascularisation for severe lower limb ischaemia. In addition, previous studies have demonstrated that frailty phenotypes can be applied in a community-dwelling cohort as well as in hospital to assess mortality and morbidity.[31, 32] It would be interesting to apply our frailty score in this context, as this would facilitate enhanced patient counselling in the elective setting. Finally, although the AVFS identifies prognostic features, it is not clear what rôle modification of these features might play in improving outcomes. While it is natural to suspect that a medication review to reduce unnecessary polypharmacy, or intensive pre-operative physiotherapy to improve muscle strength and stamina might improve outcomes, aggressive treatment of anaemia is less likely to be beneficial. Further clarification of these issues will require further interventional studies.

In conclusion, our study demonstrates that frailty has significant effects on multiple key outcomes for vascular surgical patients. The ageing population makes this an area of increasing importance in the majority of surgical specialties. Further work is required to validate the tools we have developed both within and outside vascular surgery.

Disclosures

None.

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Captions for Figures

Figure 1: Patients included in the study.

Figure 2: ROC curves for 12 month mortality. Solid line: full multivariate Cox regression model; dashed line: AVFS.

Figure 3: Kaplan-Meier survival curves according to the value of the AVFS. Curves are plotted to 18 months, as the numbers at risk beyond this time were small. The symbol '+' represents a censoring point.

Supplementary Figure 1: ROC curves for 12 month readmission-free survival. Solid line: full multivariate Cox regression model; dashed line: AVFS.

Supplementary Figure 2: ROC curves for prolonged length of stay. Solid line: full multivariate logistic regression model; dashed line: AVFS.

Supplementary Figure 3: ROC curves for discharge to a care institution. Solid line: full multivariate logistic regression model; dashed line: AVFS.

Supplementary Figure 4: Kaplan-Meier survival curves for readmission-free survival according to the value of the AVFS. Curves are plotted to 18 months, as the numbers at risk beyond this time were small. The symbol '+' represents a censoring point.

Captions for Tables

Table 1: Frailty characteristics.[12] Laboratory measurements such as serum albumin were based on samples taken within 12 hours of admission to hospital. If multiple samples were available, the first was used. All of the remaining items below are routinely documented on admission as part of the standard medical and/or nursing proforma in our institution.

Table 2: Parameters associated with survival on univariate and multivariate analysis. For the multivariate analysis, parameters were selected by stepwise minimisation of Akaike's Information Criterion as independently associated with survival in multivariate Cox model, and coefficients stated are those for Cox regression. P: Wald P-value for predictor. These six factors form the Addenbrookes Vascular Frailty Score (AVFS).

* Significant at 1% level after Bonferroni-Holm correction.

†Significant at 5% level after Bonferroni-Holm correction.

Supplementary Table 1: Parameters associated with readmission-free survival on univariate and multivariate analysis. For the multivariate analysis, parameters were selected by the stepwise minimisation of Akaike's Information Criterion as independently associated with readmission-free survival in multivariate Cox model, together with removal of parameters not significant at 10% level on the basis of Wald's test. P: Wald P-value for predictor.

* Significant at 1% level after Bonferroni-Holm correction.

†Significant at 5% level after Bonferroni-Holm correction.

Supplementary Table 2: Parameters associated with length of stay greater than or equal to seven days on univariate and multivariate analysis. For the multivariate analysis, parameters selected by the stepwise minimisation of Akaike's Information Criterion as independently associated with prolonged length of stay (>= 1 week) in multivariate logistic regression model. P: Wald P-value for predictor. Parameters with Wald P-values greater that or equal to 0.1 were removed from the model even if they were selected on the basis of Akaike's information criterion. Only the most significant parameter from each frailty domain was used.

* Significant at 1% level after Bonferroni-Holm correction.

†Significant at 5% level after Bonferroni-Holm correction.

Supplementary Table 3: Parameters associated with discharge to a care facility on univariate and multivariate analysis. For the multivariate analysis, parameters selected by the stepwise minimisation of Akaike's Information Criterion as independently associated with discharge to a care facility in multivariate logistic regression model. P: Wald P-value for predictor. Parameters with Wald P-values greater that or equal to 0.1 were removed from the model even if they were selected on the basis of Akaike's information criterion. Only the most significant parameter from each frailty domain was used.

* Significant at 1% level after Bonferroni-Holm correction.

†Significant at 5% level after Bonferroni-Holm correction.