





Frailty leads to poor long-term survival in patients undergoing elective vascular surgery

Banning, Louise B D; El Moumni, Mostafa; Visser, Linda; van Leeuwen, Barbara L; Zeebregts, Clark J; Pol, Robert A

Published in: Journal of Vascular Surgery

DOI: 10.1016/j.jvs.2020.10.088

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version Publisher's PDF, also known as Version of record

Publication date: 2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA): Banning, L. B. D., El Moumni, M., Visser, L., van Leeuwen, B. L., Zeebregts, C. J., & Pol, R. A. (2021). Frailty leads to poor long-term survival in patients undergoing elective vascular surgery. *Journal of Vascular Surgery*, *73*(6), 2132-2139.e2. https://doi.org/10.1016/j.jvs.2020.10.088

Copyright Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverneamendment.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Frailty leads to poor long-term survival in patients undergoing elective vascular surgery

Louise B. D. Banning, BSc,^a Mostafa El Moumni, MD, PhD, MSCE,^b Linda Visser, MD,^a Barbara L. van Leeuwen, MD, PhD,^c Clark J. Zeebregts, MD, PhD,^a and Robert A. Pol, MD, PhD,^a *Groningen, The Netherlands*

ABSTRACT

Objective: Frailty has persistently been associated with unfavorable short-term outcomes after vascular surgery, including an increased complication risk, greater readmission rate, and greater short-term mortality. However, a knowledge gap remains concerning the association between preoperative frailty and long-term mortality. In the present study, we aimed to determine this association in elective vascular surgery patients.

Methods: The present study was a part of a large prospective cohort study initiated in 2010 in our tertiary referral teaching hospital to study frailty in elderly elective vascular surgery patients (Vascular Ageing Study). A total of 639 patients with a minimal follow-up of 5 years, who had been treated from 2010 to 2014, were included in the present study. The Groningen Frailty Indicator, a 15-item self-administered questionnaire, was used to determine the presence and degree of frailty.

Results: Of the 639 patients, 183 (28.6%) were considered frail preoperatively. For the frail patients, the actuarial survival after 1, 3, and 5 years was 81.4%, 66.7%, and 55.7%, respectively. For the nonfrail patients, the corresponding survival was 93.6%, 83.3%, and 75.2% (log-rank test, P < .001). Frail patients had a significantly greater risk of 5-year mortality (unadjusted hazard ratio, 2.09; 95% confidence interval, 1.572-2.771; P < .001). After adjusting for surgical- and patient-related risk factors, the hazard ratio was 1.68 (95% confidence interval, 1.231-2.286; P = .001).

Conclusions: The results of our study have shown that preoperative frailty is associated with significantly increased long-term mortality after elective vascular surgery. Knowledge of a patient's preoperative frailty state could, therefore, be helpful in shared decision-making, because it provides more information about the procedural benefits and risks. (J Vasc Surg 2021;73:2132-9.)

Keywords: Frail elderly; Frailty; Mortality; Vascular surgical procedure

At present, the mean population of vascular surgery patients consists mainly of elderly patients with numerous chronic diseases and physical disabilities. Studies have demonstrated that neither chronologic age nor multimorbidity, most often defined as "the coexistence of at least three chronic conditions over a span of at least one year," can be used to distinguish between a fit and frail patient.^{1,2} Frailty is a complex state of a decreased physiologic reserve, resulting in increased susceptibility to stressors that is separate from the natural process of

Additional material for this article may be found online at www.jvascsurg.org.

Correspondence: Robert A. Pol, MD, PhD, Division of Vascular Surgery, Department of Surgery, University Medical Center Groningen, PO Box 30.001, Groningen 9700 RB (e-mail: pol.chirurgie@gmail.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest. 0741-5214

Copyright © 2020 The Authors. Published by Elsevier Inc. on behalf of the Society for Vascular Surgery. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

https://doi.org/10.1016/j.jvs.2020.10.088

aging. Thus, it is considered a geriatric syndrome composed of several domains (ie, physical, cognitive, and psychosocial) describing the weakest adults.³

The prevalence of frailty in the surgical setting has varied from 16% to 53%, because various studies have used different frailty measurement tools. At present, no reference standard of the available instruments is considered the most reliable in determining the level of frailty.^{4,5} A number of instruments can be used to measure multiple frailty domains, such as the Fried Frailty Index, G8 questionnaire, Groningen Frailty Indicator (GFI), and Edmonton frail scale.^{3,6,7}

Irrespective of the measure used, frailty, in general, has persistently been associated with unfavorable postoperative outcomes after vascular surgery, such as an increased complication risk, higher readmission rate, and discharge to a nursing home.⁸⁻¹² In addition, frailty has been associated with greater short-term mortality after vascular surgery.^{9,13,14} Studies of other populations, such as cardiac patients, have demonstrated that frailty is also associated with poor long-term survival.¹⁵⁻¹⁷ It is difficult to extend these results to the long-term outcomes after vascular surgery, because the association of frailty and mortality can vary by a factor of 40 among the different surgical populations.¹⁸ One study of patients

From the Division of Vascular Surgery,^a Division of Trauma Surgery,^b and Division of Surgical Oncology,^c Department of Surgery, University of Groningen, University Medical Center Groningen.

Author conflict of interest: none.

undergoing endovascular aortic aneurysm repair showed that sarcopenia, used as a surrogate for frailty, increased the likelihood of 5-year mortality.¹⁹ However, sarcopenia alone does not capture the whole multidimensional frailty syndrome. Consequently, a knowledge gap remains concerning the association between preoperative frailty and long-term mortality in vascular surgery patients. Providing insight of the frailty-related mortality risk will help to improve the outcomes of frail patients.

Therefore, the aim of the present study was to determine the association between preoperative frailty and 5-year mortality for elective vascular surgery patients. Second, we sought to determine how this association might be affected by surgical- and patient-related risk factors.

METHODS

Study design. The present study was a part of a large prospective cohort study initiated in 2010 in frail and elderly elective vascular surgery patients (Vascular Ageing Study), conducted at our tertiary referral teaching hospital.²⁰ The total cohort of the Vascular Ageing Study consisted of 1306 patients. For our study, patients were included if they had undergone open or endovascular thoracic, aortic, iliac, or popliteal procedures, peripheral bypass surgery, carotid endarterectomy, and elective major limb amputation (transfemoral, through knee exarticulation, and transtibial). Single procedures, which were usually performed as day-care surgery (ie, arteriovenous access surgery, percutaneous transluminal angioplasty interventions, including coil embolization, and minor amputations [eg, digits and wound revisions]) were excluded from the present analysis. The follow-up period after intervention was ≥ 5 years (intervention performed between 2010 and 2014). Thus, 639 patients formed the basis for the present study. All the patients provided written informed consent. The medical ethical institutional review board granted dispensation for the Vascular Ageing Study from the Medical Research Involving Human Subjects Act obligation (registration no. METC 2016/322). Patient data were processed and electronically stored, in agreement with the ethical principles of the Declaration of Helsinki for medical research involving human subjects.²¹ The data were stored and analyzed anonymously.

Frailty assessment. The GFI was used to determine the presence and degree of frailty.^{22,23} Preoperatively, the GFI was completed by the patients, under supervision of specially trained nurses at the outpatient clinic. The decision to schedule a patient for surgery was independent of the GFI score obtained. However, if a patient was frail according to the GFI, a geriatrician was consulted. Several studies, including a pilot study of vascular surgery patients, had previously tested and validated the feasibility, sensitivity, and specificity of the

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, prospective cohort study
- **Key Findings:** A total of 639 patients were included, of whom 183 (28.6%) were considered frail preoperatively. The frail elective vascular surgery patients had a significantly greater risk of 5-year mortality compared with nonfrail patients (hazard ratio, 2.09; P < .001). Even after adjustment for surgical- and patient-related risk factors, the risk remained almost twice as high (hazard ratio, 1.68; P = .001).
- **Take Home Message:** Preoperative frailty led to significantly greater 5-year mortality in vascular surgery patients, a finding that can be used to optimize the preoperative risk prediction.

GFI.²⁴⁻²⁷ In brief, the GFI is a 15-item screening instrument classified into the four domains of functioning: physical (mobility function, 0-4 points; vision, 0-1 point; hearing, 0-1 point; nutritional status, 0-1 point; comorbidity, 0-1 point; and physical fitness, 0-1 point), cognitive (history of delirium, 0-1 point; and cognitive dysfunction, 0-1 point), and social and psychological (psychosocial condition, 0-5 points). The GFI yields a score of 0 to 15 points, and patients with a score of \geq 4 are classified as frail.²²

Outcome parameters. The demographics of the patients and clinical data, such as age, sex, body mass index, medical history, American Society of Anesthesiologists (ASA) score, smoking status, and type of surgery, were extracted from the Vascular Ageing Study cohort. Comorbidity was determined using the Charlson Comorbidity Index, a weighted score that predicts the 1-year mortality of patients according to their medical condition and age.²⁸ We used the calculator developed by Hall et al²⁹ to calculate the index. Postoperatively collected data included the length of hospital length of stay, intensive care unit admittance, postoperative complications, and the occurrence of delirium. The postoperative complications were registered and analyzed using the Comprehensive Complication Index, a tool that considers all postoperative complications stratified by severity, in agreement with the Clavien-Dindo classification of surgical complications.^{30,31} The Comprehensive Complication Index uses a specific calculation that yields a score from 0 to 100, thereby giving a detailed assessment for a single patient. For our primary outcome, 5-year mortality, the date of death was formally requested from the personal records database, recorded by the Dutch municipalities.³² The cause of death was extracted from the electronic medical records or by contacting the general practitioner. Our secondary outcomes (admission to the hospital, admittance to the intensive care

Table I. Baseline characteristics

| Variable | Total (N = 639; 100.0%) | Frail ^a (n = 183; 28.6%) | Nonfrail (n = 456; 71.4%) | P value |
|--|-------------------------|-------------------------------------|---------------------------|---------|
| Age, years | 69.4 ± 10.0 | 69.8 ± 11.3 | 69.2 ± 9.5 | .524 |
| Sex | | | | <.001 |
| Male | 497 (77.8) | 122 (66.7) | 375 (82.2) | |
| Female | 142 (22.2) | 61 (33.3) | 81 (17.8) | |
| BMI, kg/m ² | 27.1 ± 4.6 | 27.4 ± 5.0 | 27.0 ± 4.4 | .339 |
| Smoking ^b | 428 (67.0) | 114 (62.3) | 314 (68.9) | .117 |
| Hypertension | 336 (52.6) | 99 (54.1) | 237 (52.0) | .627 |
| Comorbidities ^c | 5.1 ± 1.9 | 5.6 ± 2.2 | 4.9 ± 1.8 | <.001 |
| Type of surgery | | | | |
| Endovascular aneurysm repair | 185 (29.0) | 43 (23.5) | 142 (31.1) | .054 |
| Open aneurysm repair | 105 (16.4) | 23 (12.6) | 82 (18.0) | .095 |
| Peripheral bypass | 128 (20.0) | 34 (18.6) | 94 (20.6) | .561 |
| Carotid | 155 (24.3) | 42 (23.0) | 113 (24.8) | .626 |
| Major limb amputation | 66 (10.3) | 41 (22.4) | 25 (5.5) | <.001 |
| ASA ^d score | | | | |
| 1-2 | 238 (37.2) | 49 (26.8) | 189 (41.4) | .001 |
| 3-4 | 401 (62.8) | 134 (73.2) | 267 (58.6) | .001 |
| Hospital stay, days | 6 (6-9) | 6 (4-10) | 6 (4-8) | .016 |
| Postoperative complications ^e | 0 (0-8.7) | 0 (0-20.9) | 0 (0-8.7) | .028 |
| Delirium during hospital stay | 44 (6.9) | 17 (9.3) | 27 (5.9) | .128 |
| History of delirium | 66 (10.3) | 39 (21.3) | 27 (5.9) | <.001 |
| Admittance to ICU | 180 (28.2) | 49 (26.8) | 131 (28.7) | .620 |

ASA, American Society of Anesthesiologists; BMI, body mass index; ICU, intensive care unit.

Data presented as mean \pm standard deviation, number (%), or median (interquartile range). Boldface *P* values represent statistical significance. ^aGroningen Frailty Indicator score of \geq 4.

^bHistory of smoking.

 $^{
m c}$ Charlson Comorbidity Index (a weighted index that predicts 1-year mortality from the number of comorbidities; range, 0-19).

^dFitness of patients before surgery (score range, 1-5).

^eComprehensive Complication Index, which considers complications after a procedure and their severity (score range, 0-100).

unit, and surgical procedures during follow-up) were obtained from the electronic medical records.

Statistical analysis. Categorical variables, presented as numbers and percentages, were analyzed using the Fisher exact test or χ^2 test. A normal distribution was assumed with help from a Q-Q plot and a histogram. Differences in continuous variables, presented as the mean \pm standard deviation when normally distributed, were tested using the Student t test. The Mann-Whitney U test was used for non-normally distributed variables, which are presented as the median and interguartile range. Five-year survival was calculated using the Kaplan-Meier method, and differences in survival between frail and nonfrail patients were determined using the log-rank test. Hazard ratios (HRs), with the corresponding 95% confidence intervals (CIs), of the association between frailty and 5-year survival were derived using Cox proportional hazard survival models. The covariates included in the first multivariate model (ie, age, sex, history of smoking, Charlson Comorbidity Index, ASA score, type of intervention, postoperative complications) were selected

in accordance with existing data and subject matter knowledge or when the regression coefficient of the unadjusted Cox regression analysis had changed by >10%. A history of delirium was added to these confounders in the second multivariate model, because frailty is a proven predisposing factor for delirium.³³ A *P* value of \leq .05 was considered statistically significant. All statistical analyses were performed using SPSS, version 22.0 (IBM Corp, Armonk, NY).

RESULTS

Baseline characteristics. The patient characteristics and clinical data are summarized in Table I. A total of 639 patients were included, of whom 183 (28.6%) were considered frail preoperatively. The mean age of the total cohort was 69.4 \pm 10.0 years. Frail patients had a greater comorbidity burden (Charlson Comorbidity Index, 5.6 vs 4.9; *P* < .001), a higher ASA score (73.2% vs 58.6%; *P* = .001), and a greater incidence of a history of delirium (21.3% vs 5.9%; *P* < .001). In the frail group, significantly more patients had required a major limb amputation (22.4% vs 5.5%; *P* < .001). More nonfrail patients had

| Follow-up variable | Total (N = 639) | Frail [®] (n = 183) | Nonfrail (n = 456) | <i>P</i> value |
|--|--|------------------------------|--------------------|----------------|
| Hospital admission | 327 (51.2) | 100 (54.6) | 227 (49.8) | .239 |
| ICU admission | 92 (14.4) | 20 (10.9) | 72 (15.8) | .186 |
| Surgical intervention | 233 (36.5) | 67 (36.6) | 166 (36.4) | .563 |
| Death | 196 (30.7) | 82 (44.8) | 114 (25.0) | < .001 |
| <i>ICU,</i> Intensive care unit. Data presented as number (%) | . Boldface <i>P</i> values represent sta | tistical significance. | | |

^aGroningen Frailty Indicator score of ≥ 4

undergone an endova scular aortic procedure (31.1% vs 23.5%; P = .054).

Five-year follow-up. A total of 327 patients (51.2%) had been readmitted to the hospital at least once during follow-up, with no statistically significant differences between the two groups (Table II). Overall, the 5-year mortality was 30.7% (n = 196). After a follow-up of 5 years, 44.8% of the frail patients had died compared with 25.0% of the nonfrail patients (P < .001). In the total cohort, the most common cause of death was cardiac (14.8%; Table III). In frail patients, the most common cause of mortality was cardiac (18.3%); for nonfrail patients, the most common cause was malignancy (14.9%).

Survival outcomes and frailty. For frail patients, the actuarial survival after 1, 3, and 5 years was 81.4%, 66.7%, and 55.7%, respectively (Fig 1). For the nonfrail patients, the corresponding survival was 93.6%, 83.3%, and 75.2% (log-rank test, P < .001). Patients who had undergone a major limb amputation had significantly lower survival compared with the other patients (Supplementary Fig 1, online only; log-rank test, P < .001). After excluding these patients, the difference in actuarial survival between the frail and nonfrail patients remained significant (log-rank test, P = .012; Fig 2). After stratifying the long-term survival per vascular procedure by frailty status, the frail patients who had undergone endovascular aneurysm repair had had significantly worse long-term survival (Supplementary Fig 2, online only, A; log-rank test, P = .038). The results of the Cox proportional hazards analysis for the complete cohort are summarized in Table IV. In the unadjusted analysis, frail patients had a significantly greater risk of 5-year mortality (HR, 2.09; 95% CI, 1.572-2.771; P < .001). After adjusting for the previously stated confounders in model 2, the HR for 5-year mortality was 1.68 (95% CI, 1.231-2.286; P = .001). After inclusion of a history of delirium as a confounder (model 3), the HR was 1.53 (95% CI, 1.110-2.113; P = .010). The results of the Cox proportional hazards analysis for the complete cohort, excluding the patients who had undergone a major limb amputation, are also presented in Table IV. In the unadjusted analysis, the frail patients still had a significantly greater risk of 5-year mortality (HR, 1.82; 95% CI, 1.302-2.542; P < .001). After adjusting for the confounders included in model 2, the HR

for 5-year mortality was 1.75 (95% CI, 1.220-2.512; P = .002). In model 3, the HR was also 1.75 (95% CI, 1.212-2.523; P = .003).

DISCUSSION

The results from the present study have shown that preoperative frailty is associated with a significantly increased long-term mortality risk after elective vascular surgery. After adjusting for important confounders, frail patients continued to have a significantly greater 5-year mortality risk compared with nonfrail patients.

In accordance with the present results, previous studies of vascular surgery patients have demonstrated that frailty is associated with many adverse outcomes, including mortality. However, most of these studies had focused on the short-term outcomes only. A recently reported systematic review on frailty and outcomes after vascular surgery showed a significant association between frailty and 30-day mortality (unadjusted odds ratio, 4.81). After adjusting for important confounding variables, this association persisted (odds ratio, 2.77).³⁴ Smaller studies have previously shown an association between frailty and mid- to long-term mortality in vascular surgery patients.^{8,20} One study found that frailty was an independent predictor of 2-year survival for patients who had undergone surgical and medical management for vascular disease, although in a more heterogeneous vascular patient group than that in our study.³⁵ In another study, frailty proved to be independently associated with poor 2-year overall survival for patients with critical limb ischemia. The 2-year survival rate was 80.5%, 63.1%, and 49.3% for patients with a low, an intermediate, and a high clinical frailty scale score, respectively.³⁶ The unadjusted HR of 1.64 in that study was lower than the unadjusted HR in our study (HR, 2.09). We also found that patients who had undergone a major limb amputation were more often frail and had significantly worse 5-year survival compared with those who had undergone other vascular interventions, a previously reported finding.³⁷ Therefore, we decided to perform a survival analysis in which we excluded the patients who had undergone a major limb amputation. After excluding these patients, the association between frailty and 5-year mortality remained significant.

Frail

| Course of death | | Engil (m. 02) | | Dualua |
|-------------------------------|--|-----------------------|------------------------|----------------|
| Cause of death | 10tal (N = 196) | Frail $(n = 82)$ | Nontrall ($n = 114$) | <i>P</i> value |
| Aneurysm related | 13 (6.6) | 5 (6.1) | 8 (7.0) | .798 |
| Neurologic | 9 (4.6) | 2 (2.4) | 7 (6.1) | .309 |
| Cardiac | 29 (14.8) | 15 (18.3) | 14 (12.3) | .242 |
| Pulmonary | 18 (9.2) | 10 (12.2) | 8 (7.0) | .216 |
| Malignancy | 25 (12.8) | 8 (9.8) | 17 (14.9) | .286 |
| Multiple organ failure | 26 (13.3) | 10 (12.2) | 16 (14.0) | .708 |
| Other | 27 (13.8) | 13 (15.9) | 14 (12.3) | .474 |
| Unknown | 49 (25.0) | 19 (23.2) | 30 (26.3) | .616 |
| Data presented as number (%). | Boldface <i>P</i> values represent stati | istical significance. | | |

Table III. Differences in causes of death stratified by frailty status

Groningen Frailty Indicator score of ≥4





Although frail surgical patients have a greater risk of readmission, we found no significant differences in the admission rates between the frail and nonfrail patients during the 5 years of follow-up in our study.³⁸ A possible explanation could be that hospitals in the Netherlands do not have a national medical record system. Because of privacy laws, we could not receive this information without approval of the ethical committee and written informed consent, the latter being impossible when a patient has died if not previously provided. Because we are a tertiary referral center for the northern part of the Netherlands, the primary physicians of our patients prefer to send their patients to our academic hospital for readmission and treatment. Thus, we expected that the number of significant readmissions to other hospitals was low.

We found that frail patients more often had a history of delirium. After adjusting for this factor, the HR of frailty on 5-year mortality had decreased slightly. Although

frailty and delirium share many common aspects, such as possible overlapping pathophysiology and adverse outcomes, frailty is more a chronic state of decreased reserves, and delirium is usually an acute condition.³⁹ A previously reported systematic review concluded that frailty is a significant predisposing factor for delirium, possibly because it contributes to the susceptibility for adverse outcomes.³³ The occurrence of delirium might be a sign of underlying frailty; however, the occurrence of delirium can also make a patient more susceptible to frailty. Therefore, both the reported data and the findings from our study have shown an interaction between delirium and frailty; however, which is the cause and which the effect remains unknown.

Our finding that the age of frail and nonfrail patients did not differ significantly further supports the idea that frailty is independent of age. During the past years, chronologic age or the occurrence of comorbidities have formed the basis of most surgical risk prediction tools.⁴⁰ However, these two characteristics do not highlight the patients' physical and physiologic reserves at surgical intervention. Because the absence or presence of the frailty syndrome can provide information about these reserves, the implementation of a standard preoperative frailty assessment is needed. This is especially applicable for vascular surgery patients, because most will be elderly patients with numerous chronic conditions and disabilities. The knowledge of a patient's preoperative frailty state could, therefore, be helpful for shared decisionmaking, because it gives more information about the procedural benefits and risks and the possibility that a particular vascular intervention can be fatal.⁴¹ Future frailty research in the field of vascular surgery should focus more on the therapeutic possibilities for frail patients. Individualized multicomponent therapies could be created to treat frailty, and existing frailty should be reduced to improve postoperative outcomes and, hopefully, survival.¹ The Comprehensive Geriatric Assessment is a diagnostic and therapeutic process that determines the physiologic and functional capability of a frail patient



| Fig 2. Probability of survival after elective vascular surgery, |
|---|
| excluding major limb amputation, stratified by frailty sta- |
| tus according to the Kaplan-Meier method. |

to create an individualized treatment plan.^{42,43} It has been shown that performing a Comprehensive Geriatric Assessment increases survival and decreases the length of hospital stay. Another method of optimizing frail surgical patients might be to implement prehabilitation using preoperative exercise therapy and nutritional interventions.^{44,45} Surgery could result in frail elderly patients functioning under their minimum level of capacity, the so-called critical zone, leading to an increased time for recovery and an increased risk of adverse outcomes.⁴⁶ The physiologic reserves of frail patients could be increased by implementing prehabilitation preoperatively, preventing these patients from reaching the critical zone and, therefore, decreasing the risk of adverse outcomes such as mortality. Cognitive frailty in terms of cognitive impairment could also possibly be improved by cognitive training or a combination of physical, nutritional, and cognitive interventions.⁴⁵ However, to the best of our knowledge, no studies have investigated the implementation and effectiveness of prehabilitation on a large scale in surgical practice.

The present study had some limitations. First, we used the GFI as an assessment tool to determine preoperative frailty. The GFI is a validated tool for vascular surgery patients. The questionnaire only requires 5 minutes to complete, yet covers all the domains of functioning. Because of the limited time required for completion, it is very suitable for usage in the busy outpatient setting. Despite these advantages, it remains a self-report questionnaire that contains patient-reported outcomes. Because of individual interpretation, patients could give an over- or underestimation of

| Table IV. | Multivariate Cox regression analysis comparing | g |
|-------------|--|---|
| frail and r | onfrail patients for 5-year mortality | |

| Variable | HR | 95% Cl | <i>P</i> value |
|--------------------------------|------|-------------|----------------|
| All patients | | | |
| Frail, model 1 | 2.09 | 1.572-2.771 | <.001 |
| Frail, model 2ª | 1.68 | 1.231-2.286 | .001 |
| Frail, model 3 ^b | 1.53 | 1.110-2.113 | .010 |
| Major limb amputation excluded | | | |
| Frail, model 1 | 1.82 | 1.302-2.542 | <.001 |
| Frail, model 2ª | 1.75 | 1.220-2.512 | .002 |
| Frail, model 3 ^b | 1.75 | 1.212-2.523 | .003 |

CI, Confidence interval; HR, hazard ratio.

Boldface P values represent statistical significance.

^aAdjusted for age, sex, history of smoking, Charlson Comorbidity Index, American Society of Anesthesiologists score, type of intervention, and postoperative complications. ^bAdjusted for age, sex, history of smoking, Charlson Comorbidity Index,

^bAdjusted for age, sex, history of smoking, Charlson Comorbidity Index, American Society of Anesthesiologists score, type of intervention, postoperative complications, and a history of delirium.

the actual problems that exist. Second, the distribution of the type of intervention differed between frail and nonfrail patients. In the frail group, more patients had undergone major limb amputation. However, after performing extra analyses with exclusion of the patients who had undergone major limb amputation, the effect of frailty on 5-year mortality persisted. Third, if a patient was frail in our study, a geriatrician was consulted. The long-term mortality rates of frail patients in our study might have been even more striking without this consultation. Fourth, we only included elective vascular interventions in the present study. Acute interventions were not included, making it impossible to determine the effect of frailty on the long-term mortality in a patient population with a generally greater mortality rate after surgery. Finally, our hospital is a tertiary referral teaching hospital. The patient population and, subsequently, our outcomes might be different from those in a general hospital.

CONCLUSIONS

Preoperative frailty is associated with significantly shortened long-term survival after elective vascular surgery. Even after adjusting for covariates such as age and comorbidities, the risk of 5-year mortality remained almost twice as high for frail patients. These results highlight the importance of implementing a standard, preoperative frailty assessment tool in vascular surgery to optimize the preoperative risk prediction and potentially intervene in causal domains of frailty. Prehabilitation, with attention on physical, nutritional, and cognitive improvement, has the potential to modify these domains and quicken recovery or prevent further deterioration.

AUTHOR CONTRIBUTIONS

Conception and design: LB, MM, LV, BL, CZ, RP Analysis and interpretation: LB, MM, LV, BL, CZ, RP Data collection: LB, LV, RP

Writing the article: LB, MM, LV, RP

Critical revision of the article: LB, MM, LV, BL, CZ, RP

Final approval of the article: LB, MM, LV, BL, CZ, RP

Statistical analysis: LB, MM, RP

Obtained funding: Not applicable

Overall responsibility: RP

REFERENCES

- Drudi LM, Ades M, Landry T, Gill HL, Grenon SM, Steinmetz OK, et al. Scoping review of frailty in vascular surgery. J Vasc Surg 2019;69: 1989-98.
- 2. Villacampa-Fernández P, Navarro-Pardo E, Tarín JJ, Cano A. Frailty and multimorbidity: two related yet different concepts. Maturitas 2017:95:31-5.
- Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:146-56.
- Partridge JSL, Fuller M, Harari D, Taylor PR, Martin FC, Dhesi JK. Frailty and poor functional status are common in arterial vascular surgical patients and affect postoperative outcomes. Int J Surg 2015;18:57-63.
- McRae PJ, Walker PJ, Peel NM, Hobson D, Parsonson F, Donovan P, et al. Frailty and geriatric syndromes in vascular surgical ward patients. Ann Vasc Surg 2016;35:9-18.
- 6. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. Eur J Intern Med 2016;31:3-10.
- 7. Baitar A, Van Fraeyenhove F, Vandebroek A, De Droogh E, Galdermans D, Mebis J, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. J Geriatr Oncol 2013;4:32-8.
- Wang J, Zou Y, Zhao J, Schneider DB, Yang Y, Ma Y, et al. The impact of frailty on outcomes of elderly patients after major vascular surgery: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2018;56:591-602.
- 9. Brahmbhatt R, Brewster LP, Shafii S, Rajani RR, Veeraswamy R, Salam A, et al. Gender and frailty predict poor outcomes in infrainguinal vascular surgery. J Surg Res 2016;201:156-65.
- Wahl TS, Graham LA, Hawn MT, Richman J, Hollis RH, Jones CE, et al. Association of the modified frailty index with 30-day surgical readmission. JAMA Surg 2017;152:749.
- Arya S, Kim SI, Duwayri Y, Brewster LP, Veeraswamy R, Salam A, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic aneurysm repair independent of age and comorbidities. J Vasc Surg 2015;61:324-31.
- Ambler GK, Brooks DE, Al Zuhir N, Ali A, Gohel MS, Hayes PD, et al. Effect of frailty on short- and mid-term outcomes in vascular surgical patients. Br J Surg 2015;102:638-45.
- Ehlert BA, Najafian A, Orion KC, Malas MB, Black JH, Abularrage CJ. Validation of a modified frailty index to predict mortality in vascular surgery patients. J Vasc Surg 2016;63:1595-601.
- Barbey SM, Scali ST, Kubilis P, Beck AW, Goodney P, Giles KA, et al. Interaction between frailty and sex on mortality after elective abdominal aortic aneurysm repair. J Vasc Surg 2019;70:1831-43.
- Tran DTT, Tu JV, Dupuis J, Bader Eddeen A, Sun LY. Association of frailty and long-term survival in patients undergoing coronary artery bypass grafting. J Am Heart Assoc 2018;7:e009882.
- Wang M-C, Li T-C, Li C-I, Liu C-S, Lin W-Y, Lin C-H, et al. Frailty, transition in frailty status and all-cause mortality in older adults of a Taichung community-based population. BMC Geriatr 2019;19:26.
- Lee Y, Kim J, Chon D, Lee K-E, Kim J-H, Myeong S, et al. The effects of frailty and cognitive impairment on 3-year mortality in older adults. Maturitas 2018;107:50-5.
- Beggs T, Sepehri A, Szwajcer A, Tangri N, Arora RC. Frailty and perioperative outcomes: a narrative review. Can J Anaesth 2015;62: 143-57.
- 19. Newton DH, Kim C, Lee N, Wolfe L, Pfeifer J, Amendola M. Sarcopenia predicts poor long-term survival in patients undergoing endovascular aortic aneurysm repair. J Vasc Surg 2018;67:453-9.
- 20. Visser L, Banning LBD, El Moumni M, Zeebregts CJ, Pol RA. The effect of frailty on outcome after vascular surgery. Eur J Vasc Endovasc Surg 2019;58:762-9.

- The World Medical Association. WMA Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Available at: https://www.wma.net/policies-post/wma-declarationof-helsinki-ethical-principles-for-medical-research-involving-humansubjects/. Accessed April 5, 2020.
- 22. Peters LL, Boter H, Burgerhof JGM, Slaets JPJ, Buskens E. Construct validity of the Groningen Frailty Indicator established in a large sample of home-dwelling elderly persons: evidence of stability across age and gender. Exp Gerontol 2015;69:129-41.
- Bielderman A, van der Schans CP, van Lieshout M-RJ, de Greef MH, Boersma F, Krijnen WP, et al. Multidimensional structure of the Groningen Frailty Indicator in community-dwelling older people. BMC Geriatr 2013;13:86.
- 24. Pol RA, van Leeuwen BL, Visser L, Izaks GJ, van den Dungen JJAM, Tielliu IFJ, et al. Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: a prospective cohort study. Eur J Vasc Endovasc Surg 2011;42:824-30.
- Steverink N, Slaets J, Schuurmans H, Van Lis M. Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator). Gerontologist 2001;41:236-7.
- 26. Schopmeyer L, El Moumni M, Nieuwenhuijs-Moeke GJ, Berger SP, Bakker SJL, Pol RA. Frailty has a significant influence on postoperative complications after kidney transplantation—a prospective study on short-term outcomes. Transpl Int 2019;32:66-74.
- Drudi LM, Ades M, Mancini R, Boudrias C, Obrand DI, Steinmetz OK, et al. Frailty assessment in older adults undergoing interventions for peripheral arterial disease. J Vasc Surg 2019;70:1594-602.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
- 29. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. BMC Cancer 2004;4:94.
- Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1-7.
- Clavien P-A, Vetter D, Staiger RD, Slankamenac K, Mehra T, Graf R, et al. The comprehensive complication index (CCI®): added value and clinical perspectives 3 years "down the line. Ann Surg 2017;265: 1045-50.
- Personal Records Database (BRP). Personal data. Available at: https:// www.government.nl/topics/personal-data/personal-records-databasebrp. Accessed January 16, 2020.
- Persico I, Cesari M, Morandi A, Haas J, Mazzola P, Zambon A, et al. Frailty and delirium in older adults: a systematic review and metaanalysis of the literature. J Am Geriatr Soc 2018;66:2022-30.
- Houghton JSM, Nickinson ATO, Morton AJ, Nduwayo S, Pepper CJ, Rayt HS, et al. Frailty factors and outcomes in vascular surgery patients: a systematic review and meta-analysis. Ann Surg 2020;272: 266-76.
- Ghaffarian AA, Foss WT, Donald G, Kraiss LW, Sarfati M, Griffin CL, et al. Prognostic implications of diagnosing frailty and sarcopenia in vascular surgery practice. J Vasc Surg 2019;70:892-900.
- **36.** Takeji Y, Yamaji K, Tomoi Y, Okazaki J, Tanaka K, Nagae A, et al. Impact of frailty on clinical outcomes in patients with critical limb ischemia. Circ Cardiovasc Interv 2018;11:e006778.
- Monaro S, West S, Gullick J. Patient outcomes following lower leg major amputations for peripheral arterial disease: a series review. J Vasc Nurs 2017;35:49-56.
- Panayi AC, Orkaby AR, Sakthivel D, Endo Y, Varon D, Roh D, et al. Impact of frailty on outcomes in surgical patients: a systematic review and meta-analysis. Am J Surg 2019;218:393-400.
- Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911-22.
- Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr 2002;2:1-8.
- van de Pol MHJ, Fluit CRMG, Lagro J, Slaats Y, Olde Rikkert MGM, Lagro-Janssen ALM. Shared decision making with frail older patients: proposed teaching framework and practice recommendations. Gerontol Geriatr Educ 2017;38:482-95.
- 42. Harari D, Hopper A, Dhesi J, Babic-Illman G, Lockwood L, Martin F. Proactive care of older people undergoing surgery ("POPS"): designing, embedding, evaluating and funding a comprehensive

geriatric assessment service for older elective surgical patients. Age Ageing 2007;36:190-6.

- Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. BMJ 2011;343: 1034.
- 44. Milder DA, Pillinger NL, Kam PCA. The role of prehabilitation in frail surgical patients: a systematic review. Acta Anaesthesiol Scand 2018;62:1356-66.
- 45. Ng TP, Feng L, Nyunt MSZ, Feng L, Niti M, Tan BY, et al. Nutritional, physical, cognitive, and combination interventions and frailty reversal

among older adults: a randomized controlled trial. Am J Med 2015;128: 1225-36.

 Hulzebos EHJ, van Meeteren NLU. Making the elderly fit for surgery. Br J Surg 2016;103:463.

Submitted May 26, 2020; accepted Oct 29, 2020.

Additional material for this article may be found online at www.jvascsurg.org.



| Type of intervention | Time (months) | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|------------------------------|--------------------|-----|------|------|------|------|------|------|------|
| Open aneurysm repair | Number at risk (n) | 103 | 85 | 79 | 70 | 64 | 43 | 23 | 9 |
| | Standard error (%) | 0% | 3.3% | 3.6% | 4.2% | 4.3% | 4.7% | 4.9% | 4.9% |
| Endovascular aneurysm repair | Number at risk (n) | 184 | 164 | 149 | 132 | 107 | 69 | 37 | 13 |
| | Standard error (%) | 0% | 2.2% | 2.7% | 3.1% | 3.4% | 3.5% | 3.7% | 3.7% |
| Peripheral bypass | Number at risk (n) | 128 | 122 | 112 | 95 | 79 | 52 | 27 | 9 |
| | Standard error (%) | 0% | 2.0% | 2.9% | 3.6% | 4.0% | 4.1% | 4.1% | 4.1% |
| Carotid | Number at risk (n) | 150 | 128 | 107 | 92 | 73 | 45 | 26 | 10 |
| | Standard error (%) | 0% | 1.0% | 1.9% | 3.3% | 3.8% | 4.5% | 4.5% | 4.5% |
| Major limb amputation | Number at risk (n) | 65 | 46 | 37 | 30 | 23 | 11 | 6 | 2 |
| | Standard error (%) | 0% | 5.7% | 6.2% | 6.3% | 6.2% | 5.8% | 5.8% | 5.8% |

Supplementary Fig 1 (online only). Probability of survival after elective vascular surgery stratified by frailty status according to Kaplan-Meier method.



Supplementary Fig 2 (online only). Graphs showing probability of survival after endovascular aneurysm repair **(A)**, open aneurysm repair **(B)**, peripheral bypass surgery **(C)**, carotid surgery **(D)**, and major limb amputation **(E)** stratified by frailty status using the Kaplan-Meier method.