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REVIEW

Frailty In Patients Undergoing Vascular Surgery: A Narrative Review Of Current Evidence

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Abstract: Frailty is presumably associated with an elevated risk of postoperative mortality and adverse outcome in vascular surgery patients. The aim of our review was to identify possible methods for risk assessment and prehabilitation in order to improve recovery and postoperative outcome. The literature search was performed via PubMed, Embase, OvidSP, and the Cochrane Library. We collected papers published in peer-reviewed journals between 2001 and 2018. The selection criterion was the relationship between vascular surgery, frailty and postoperative outcome or mortality. A total number of 52 publications were included. Frailty increases the risk of non-home discharge independently of presence or absence of postoperative complications and it is related to a higher 30-day mortality and major morbidity. The modified Frailty Index showed significant association with elevated risk for post-interventional stroke, myocardial infarction, prolonged in-hospital stays and higher readmission rates. When adjusted for comorbidity and surgery type, frailty seems to impact medium-term survival (within 2 years). Preoperative physical exercising, avoidance of hypalbuminemia, psychological and cognitive training, maintenance of muscle strength, adequate perioperative nutrition, and management of smoking behaviours are leading to a reduced length of stay and a decreased incidence of readmission rate, thus improving the effectiveness of early rehabilitation. Pre-frailty is a dynamically changing state of the patient, capable of deteriorating or improving over time. With goal-directed preoperative interventions, the decline can be prevented.

Keywords: preoperative risk assessment, postoperative outcome, patient management, prehabilitation

Background

Thanks to the continuous development of surgical and anaesthetic techniques, patient-related factors have become another important focus of interest in the preoperative risk assessment. The introduction and use of physiological and surgical risk assessment systems, like the American Society of Anaesthesiology classification (ASA)[1] and the Vascular POSSUM system (Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity),[2,3] led to an easier decision-making process compared to the previous decades. The POSSUM scoring system predicts the risk for operative morbidity and mortality for patients undergoing surgery. It is divided into two parts: the first includes physiological variables from the preoperative period; the second contains data registered during the intra- and postoperative periods. The model includes 12 variables examining the clinical symptoms of each patient and the results of medical examinations, as well as laboratory and hematologic findings and electrocardiographic examinations. The

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POSSUM in summary analyses the outcome and complications of morbidity.[2,4] For vascular procedures, V-POSSUM equations (Physiology and operative, and physiology only) were developed by the Vascular Surgical Society of Great Britain and Ireland (VSSGBI). The scoring method is based on the operative outcome of this special patient population.[5]

Despite these well-developed stratification systems, the clinical experience shows that there must be other, presumably functional, social and psychological features influencing the postoperative outcome that have not been evaluated by the routinely used physiological prognostic systems. Behavioural maladaptation evolves in two different ways. First, it is due to irreversible individual and internal factors, like age-related physiological and psychological changes (deconditioning, loss of physiological capacity and reserve), disease burden or mental-health limitations. Second, it is due to the effect of the external influencers, like the environmental support (family and social networks), having a large extent in the development of frailty syndrome.[6] This latter is considered the most variable and improvable of the causative effects.

A good example for simultaneous application of physiological and psychological characteristics is the DSM-V criteria (Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association),[7] which primarily used to categorize mental disorders but it is also considering the physical health condition of the patients. The system is based on the principle that psychological and physical states should always be analysed together. The DSM-IV contains five different axes: axis I and axis II are including mental and psychiatric disorders, axis III is including the general medical condition, axis IV is containing psychosocial and environmental factors contributing to the disorder and axis V stands for the Global Assessment of Functioning.[7] The diagnosis of psychiatric disorders is multifactorial and the physical functioning itself can be either the cause or the consequence of these diseases. Considering this, the separate analysis of psychological and physiological vulnerabilities in the daily clinical routine may be misleading, especially when facing a patient with frailty syndrome. Several systematic reviews and meta-analyses are available regarding the assessment and the perioperative management of frail individuals,[8–10] but none of them is limited to vascular surgery patients.

The aim of our review was to summarize the current evidence in the literature regarding the impact of frailty on the outcome following vascular surgery and to collect the possibilities of risk assessment and prehabilitation in order to improve recovery and postoperative outcome.

Methods

We proceeded with a literature review to identify papers examining the impact of frailty on the postoperative outcome in the field of vascular surgeries. The research was performed via the Internet (PubMed; Embase; OvidSP and the Cochrane Library were used). The literature research process is presented in Figure 1. Major selection criteria were: the relationship between vascular surgery and postoperative outcome or mortality; the impacts of preoperative interventions or risk assessment tools and postoperative outcome or recovery. We included articles reporting data of patients undergoing elective vascular interventions of the following types: endovascular and open repair of abdominal aortic aneurysms; endovascular repair of thoracic aortic aneurysms; thoracic aortic dissections and thoracoabdominal aneurysms; open surgical reconstructions; balloon angioplasty or stenting in all vascular areas; bypass surgeries for peripheral artery diseases of the limbs; carotid endarterectomy and carotid artery stenting; surgical reconstructions for deep vein occlusions. Risk levels for vascular procedures were defined according to the occurrence of cardiac events defined by the European Society of Cardiology and Anesthesiology (ESC/ESA) 2014 Guidelines: low-risk – cardiac complication rate <1% (superficial venous interventions, carotid artery stenting); intermediate risk – cardiac complication rate 1–5% (carotid endarterectomies, peripheral arterial angioplasty, endovascular aneurysm repair) and high risk – cardiac complication rate >5% (aortic and major vascular surgery, open lower limb revascularization or thromboembolectomy).[11] We defined a time-interval between January 1st 2001 and December 30th 2018 and we evaluated publications fulfilling all the following criteria: (a) was published in a peer-reviewed journal in English between, 2018; (b) dealt with adult patients undergoing vascular surgery and reported outcome results in relationship with frailty (including cognitive dysfunction and quality-of-life); and (c) reported a statistically significant reduction or increase in short-, or long-term complication or mortality. Most important keywords were searched in relation to: frailty; frailty-syndrome; vascular surgery; mortality; short-term and long-term outcome; postoperative outcome; risk assessment; prehabilitation; perioperative management. Major complications described in the studies were: pulmonary (need for long-term mechanical ventilation, acute respiratory failure or acute respiratory distress

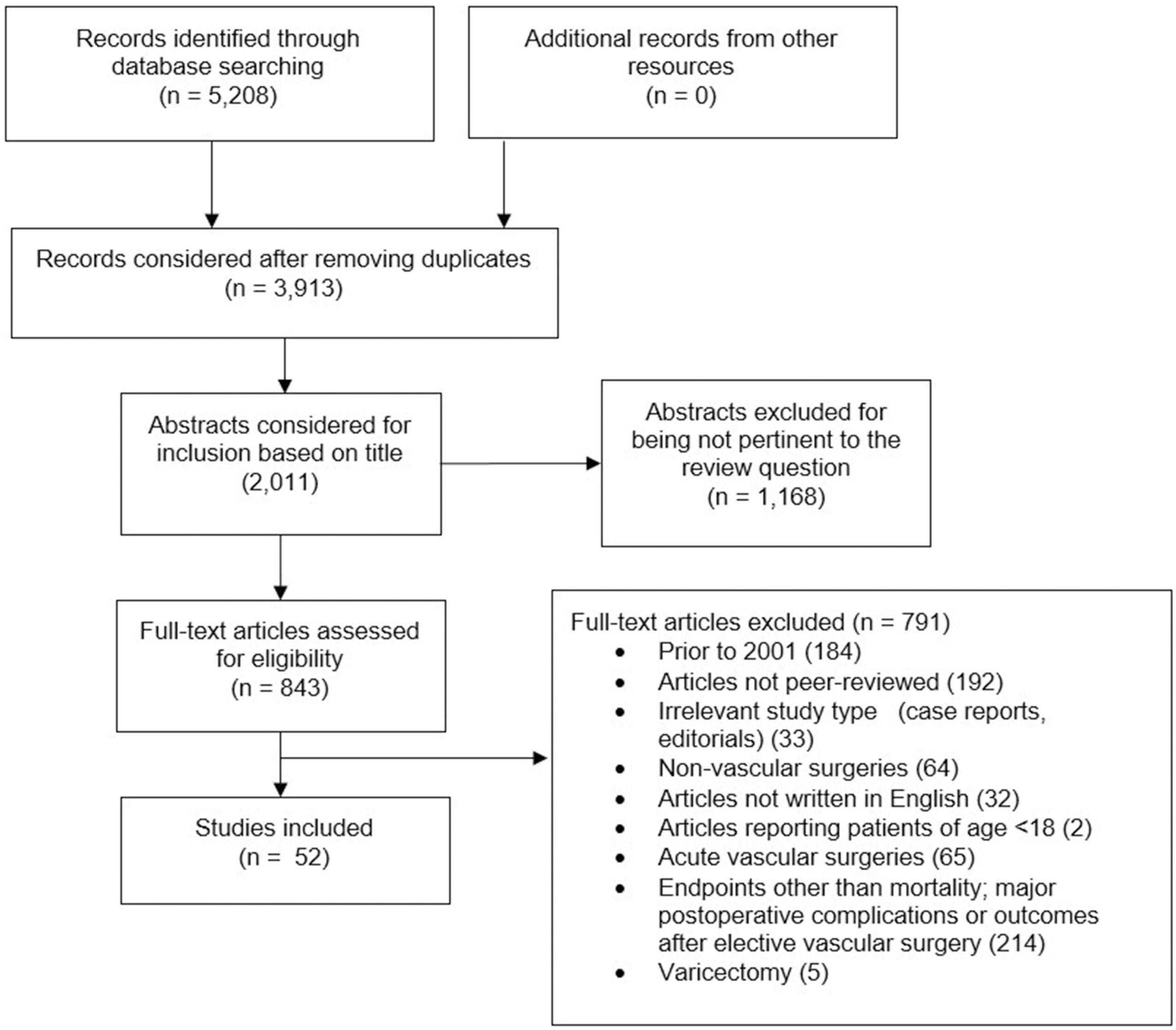

Figure 1 Flow chart of literature research process.
Note: PRISMA format used.[108]

syndrome (ARDS)); circulatory (acute heart failure, arrhythmias, need for inotropic support, peripheral circulatory failure); neurological (cerebrovascular events); infective complications; acute kidney injury (need for renal replacement therapy) and surgical complications (bleeding, reoperations due to graft failure or suture insufficiency).

Articles were excluded if the primary endpoint was other than postoperative outcome and/or mortality. We also excluded case-control and case report studies, papers reporting patients under 18 years of age and papers dealing with adult patients undergoing electrophysiological interventions (radiofrequency ablation – RFA, pacemaker implantation, etc.), varicectomy or cardiac surgery.

Results

A total number of 52 publications were included. We aimed to summarize the findings actually available about the perioperative management of frail patients in the field of vascular surgery.

Frailty

The proportion of elderly patients is high in vascular surgery, since atherosclerosis, the underlying cause of several vascular diseases, progresses with time. Factors such as comorbidities, functional reserve, dependence in daily activities and gait parameters are better predictors of surgical outcome than the age per se. Vascular surgeons and anesthesiologists face the challenge to evaluate the biological, rather than chronological, age of their patients' during preoperative risk assessment.[12,13]

The term of frailty was established by Vapuel in 1979.[14] Besides geriatric usage, it was rapidly adopted and integrated into the clinical decision-making process. The concept of frailty defines a multidimensional decline of the aging individual that results in an increased vulnerability.[15] There is a homeostenosis in frail patients, which means that they cannot maintain homeostasis required for even moderate-risk surgical situations.[16] In addition to this theoretical definition, efforts have been made to establish a more objective and measurable framework. Two different but not necessarily exclusive models have been created: the Phenotypic[17] and the Accumulating Deficits Model.[18]

The Phenotypic Model of Fried et al focuses on patient characteristic across five domains: unintentional weight loss, slow gait speed, self-reported exhaustion, impaired grip strength and low physical activity. Patients presenting three or more of these symptoms are considered "frail", those with 1 or 2 positive tests are defined as "pre-frails", while "stronger" individuals have the score of zero.[17]

The Canadian Study of Health and Aging defined frailty as the balance of deficits and assets: 70 different physical, mental, medical and functional problems are examined as part of the Comprehensive Geriatric Assessment. Frailty Index (FI) is calculated as the number of positive items divided by 70 (number of all items). If the FI is over 0.5, then "Frailty" is present.[18] This method evaluates accurately the frailty level of patients, but it is too time-consuming to use in clinical routine.

While a consensus has been reached on the elements of frailty and the five physical domains of Fried, supplemented by mental and cognitive domains, the clear operational definition and the most effective clinically applicable version is not yet established.[19] In the same time, the definition of "physical frailty" has been refined:

> A medical syndrome, with multiple causes and contributors that is characterized by diminished strength, endurance and reduced physiological function that increases an individual's vulnerability for developing increased dependency and/or death.[20]

There are several mechanisms that might be related to frailty such as inflammation, coagulation, oxidative stress and age-related modification of hormonal pathways. Altered function of the hypothalamic-pituitary-adrenal (HPA) or -testicular (HPT) as well as insulin-like growth factor (IGF-1) axes can result in impaired muscle and bone strength and mobility.[21]

Besides these theoretical approaches, clinicians are focusing on the incorporation of a simplified frailty assessment tool, which could be effectively integrated into the routine preoperative risk evaluation. Several scales and indices are available for more complex frailty assessment for clinicians.[22] The modified frailty index (mFI),[23] derived from the traditional FI – using at least 10 items of FI – was applied in the majority of studies assessing vascular surgical patients. Many papers reported higher postoperative mortality among frail patients following various vascular procedures using mFI[24–27] and further composite frailty instruments, for eg, Risk Analysis Index (RAI),[28] Addenbrooke's Vascular Frailty Score,[29] and others.[30,31] Not only mortality but postoperative adverse outcomes are also more frequent in frail individuals. Major complications,[25,27] longer hospital stay[29,32] and non-home discharge[29,33] following vascular surgery were associated with frailty. Higher mFI scores are associated with increased incidence of other postoperative complications, as acute myocardial infarction (MI), stroke, progressive renal failure and graft failure. Together with dialysis dependency, postoperative renal insufficiency, MI, postoperative acute renal failure and black race, an mFI score of 0.54–0.63, significantly increases the risk of mortality and complications after lower extremity revascularizations.[34]

Even a single marker of frailty can be a good predictor of adverse outcome following vascular surgery. In a large retrospective study analysing the data of 9782 functionally dependent and independent propensity-matched patient pairs derived from the American College of Surgeons National Surgical Quality Improvement Program database, functional dependency, as a marker of advanced frailty, was associated with 1.75-fold increased risk of death following vascular or general surgical procedures.[35] Lee et al found that core muscle size is a much more significant predictor of long-term mortality following open abdominal aortic aneurysm (AAA) repair than ASA scoring in itself.[36] The psoas muscle area is an independent predictor of all-cause mortality after open and endovascular AAA repairs.[37] The decline of gait parameters, used alone or as a part of a complex frailty assessment, is the leading symptom of peripheral arterial disease (PAD). Despite that frailty and PAD may interfere in gait performance, gait assessment was a sensitive and specific early predictor of pre-frailty,[38] and the gait initiation test can be effectively used in the evaluation of motor performance among PAD patients regardless of frailty.[39] The FI for critical limb ischemia (CLI) procedures is a risk factor for postoperative morbidity and in-hospital mortality with a hazard ratio of 3.21 and 6.32, respectively. Moreover, the CLI Frailty Index was significantly influencing the mortality rate 2 years after amputation-free survival (AFS). This finding can improve the prognostic prediction of outcome and could help clinicians in the selection of firstly applying treatment strategy.[40] Examining gender differences in a propensity score-matched analysis after lower limb endovascular interventions and a 1-year follow-up period, the following results were reported: women were at lower risk of mortality than men, despite that they underwent significantly more repeated revascularization procedures.[41] Frailty and self-efficacy are independent predictors for postoperative 6 mins walking-distance (6MWD) after elective open AAA surgery, which means that not only physical status, but also psychological factors can predict the effectiveness of postoperative rehabilitation and outcome. This suggests that attempts to improve self-efficacy preoperatively could improve rehabilitation after AAA surgery.[42] When adjusted for comorbidity and surgery type, frailty seems to impact medium-term survival (within 2 years) in vascular patients and the first clinical impressions in this patient cohort is an independent predictor of all-cause mortality and long-term postoperative death. This would help clinicians in a more precise definition of high-risk vascular surgery.[43]

Frailty was also made responsible for longer in-hospital stays and an increased rate of non-home discharge. The need for a higher level of care or nursing facility after hospitalization occurred with a higher incidence compared to non-frail patients.[44,45]

We have found one systematic review questioning the association between frailty and poorer postoperative outcome. The study focused on patients older than 75 years and reported several types of intervention, both acute and elective, including vascular surgeries.[46] The review presented 23 studies focusing mostly on the relationship between frailty and short-, and long-term mortality, postoperative complications and length of stay. Though they have found publications reporting non-significant results in some aspects, in all of the researches, frailty have been consistently related to adverse outcomes. In addition, the above-mentioned review, beyond excluding studies using single markers to determine frailty, was limited by including a very heterogeneous surgical patient population.[46]

Reports with the largest patient population and the clearest results about the effects of frailty in the field of vascular surgery are listed in Table 1.

Frailty Index

A simplified frailty index is easily obtainable from patient general characteristics. The index counts deficits in health available in standard clinical data. The fraction of deficits that are present and those which are not gives us the exact index. Numerous calculation procedures have been created, but usually, the standard cut-off points are set at levels 0 (excellent health condition); 0.25 (very good); 0.5 (good); 0.75 (poor or fair) and 1 (very poor).[47] Understanding why and how frailty is influencing the postoperative outcome is not easy. Intentions to modify frailty risk factors are not yet entirely integrated into the daily routine. The increase of frailty index (FI) level causes a rise in the occurrence of postoperative wound infections and the odds ratio for mortality in vascular patients.[26,48,49] Complications and death also showed a higher incidence in female frail patients, especially following infrainguinal vascular surgery.[27,29] Patients older than 60, with a recognized risk of frailty and functional or cognitive impairment, are predicted to a longer hospital stay and to poorer outcome.[32] Therefore, it is necessary to identify and possibly modify the frailty index of these patients. Unfortunately, we did not find studies examining the influence of preoperative therapeutic interventions applied in order to reduce frailty symptoms.

Modifiable Factors

Our research showed that several elements of frailty seem to be modifiable risk factors, where therapeutic interventions are available and can be applied by involving professionals and experts (psychologist, psychiatrist, social workers, etc.). These interventions might effectively reduce the vulnerability of patients, keeping in mind that the short- or long-term negative outcomes are not negligible. Modifiable factors have several effects on short-, mid- and long-term outcomes. Short-term outcomes, as 30-day mortality, 30-days hospital readmission rate, postoperative major cardiac events, ischaemic complications, new onset arrhythmias, need for inotropic support and heart failure, pulmonary complications (severe pneumonia, need for mechanical ventilation longer than 48 hrs, unplanned tracheal re-intubation or occurrence of pulmonary embolism) and surgical site infections can be influenced by a 4–6 weeks of preoperative cardiopulmonary exercise training. Mid-term outcomes, like rehabilitation times, graft failure or limb amputation incidences, are dependent on preoperative glycaemic statuses, smoking behaviours and protein

Table 1 Publications Reporting The Effects Of Frailty On Patients Undergoing Vascular Procedures

Reference	Study Population	Measure Of Frailty	Results
Jeon-Slaughter H. et al (2017)[41]	1084 patients' propensity matched data who underwent 1702 endovascular procedures (449 men and 449 women).	Frailty hazard ratios	Women are at a lower risk of mortality than men; however, they underwent significantly more frequent repeat 12-month revascularization procedures.
Morisaki K. et al (2017)[40]	Retrospective, 266 patients undergoing infrapopliteal revascularization. Primary end-point: 2-year amputation-free survival (AFS).	CLI Frailty Index compared with mFI	The CLI Frailty Index is a risk factor for 2-year AFS after revascularization.
Ali TZ et al (2017) revascularizations[34]	Retrospective, 4704 patients (64% men and 36% women) undergoing infrainguinal arterial bypass surgery.	mFI	Patients with mFI score of 0.54–0.63 were at significantly higher risk of mortality and postoperative complications, beside black race, dialysis dependency, renal insufficiency, MI and acute renal failure.
Hayashi K. et al (2017)[42]	70 patients undergoing open AAA surgery.	HADS-A, 6MWD, SEPA	Preoperative self-efficacy predicted postoperative 6MWD after AAA surgery, which could predict and improve the effectiveness of postoperative rehabilitation.
O'Neill B.R. et al (2016)[43]	Retrospective review and follow-up of 392 patients (Male/Female 317/75) undergoing vascular surgery.	Complex, unspecified	The hazard ratio for mortality for frail vs not-frail was 2.14 (95% CI 1.51–3.05). The time to 20% mortality: 16 months in the frail group; 33 months in the not-frail group.
Drudi et al (2016)[37]	Retrospective, 149 patients (84% male, 16% female) undergoing endovascular or open AAA repair.	Psoas muscle area at L4	In a Cox-regression analysis adjusted for age, sex, revised cardiac risk index and surgical approach), PMA showed significant association with postoperative all-cause mortality (mean follow-up: 22.4 months).
Ehlert et al (2016)[25]	Retrospective, data derived from ACS NSQIP, 72,106 patients (approximately 70% male in the differently examined groups) undergoing carotid revascularization, AAA repair and lower extremity revascularization for PAD.	mFI	mFI showed better discrimination regarding mortality than LCRI and ASA. Regarding class IV complications, similar findings were reported after OAR and EVAR. There were no significant differences in the discrimination of mortality in the endovascular cohort or major complications after open or endovascular PAD or carotid endarterectomy.
Srinivasan et al (2016)[30]	Retrospective, single centre, 184 patients (85% male) treated for rAAA (108 underwent an open repair).	Complex, unspecified	A multivariate logistic regression model 12-month mortality using Katz score, Charlson score, number of admission medicines, visual and hearing impairment, haemoglobin level, and statin use as predictors reached an AUC of 0.84.
van Netten JJ et al (2016)[49]	Retrospective, data derived from ACS NSQIP, 9244 patients underwent above- or below-knee amputation.	Complex, unspecified	An additive risk index of 11 components (age, congestive heart failure, COPD, steroid use, major cardiac surgery, functional dependency, dyspnea, dialysis, impaired sensorium, preoperative sepsis) for 30-day mortality had a c-index of 0.74, clinical intervention should be taken over a score of 5.

(*Continued*)

Table 1 (Continued).

Reference	Study Population	Measure Of Frailty	Results
Arya et al (2016)[33]	Retrospective, data derived from ACS NSQIP, 15,843 home-dwelling patients underwent elective vascular surgery.	mFI	Frailty significantly increased the risk of non-home discharge even in presence or absence of complications.
Scarborough et al (2015)[35]	Retrospective, data derived from ACS NSQIP, patients undergoing complex general or vascular operation 9782 functionally dependent (51% female) and independent (72% female) propensity-matched patient pairs.	Dependence in activities of daily living	Dependent patients faced with significantly increased risk of 30-day postoperative mortality, major morbidity, failure to rescue and reoperation-procedure-specific analyses showed similar results regarding mortality and morbidity following endovascular and open AAA repair, carotid endarterectomy, infrainguinal bypass graft surgery.
Arya et al (2015)[24]	Retrospective, data derived from ACS NSQIP, 23,207 patients (approximately 70% female in each group) undergoing endovascular or open AAA repair.	mFI	Frailty was independently associated with 30-day postoperative mortality, morbidity and failure to rescue rate after EVAR and OAR.
Brahmbhatt et al (2015)[27]	Retrospective, data derived from ACS NSQIP, 24,645 patients undergoing infrainguinal vascular surgery. The analysis focused on the variation of mFI scores across gender differences.	mFI	Women were frailer. Female gender and higher mFI showed significant association with 30-day postoperative mortality and major morbidity. The interaction of frailty and female gender showed the highest impact on adjusted 30 day postoperative mortality and morbidity.
Melin et al (2015)[28]	Retrospective, data derived from ACS NSQIP, 44,832 patients undergoing carotid endarterectomy.	Frailty RAI	Frailty RAI, as continuous variable, showed significant association with mortality, stroke, MI and LOS. High-risk patients (RAI >10) faced with increased risk of stroke and death.
Ambler et al (2015)[29]	Prospective, single centre, 413 patients aged over 65 years with a LOS >2 days admitted to a tertiary vascular unit.	AVFS	AVFS was good predictor of 12 months postoperative mortality, prolonged LOS, discharge to care institutions, and showed significant association with readmission rates.
Partridge et al (2015)[32]	Prospective, observational, 125 patients (68.8% male), aged over 60 years, undergoing elective and emergency arterial vascular procedures.	EFS, functional status and MoCA	EFS ≥ 6.5 was predictive for extended LOS (12 days or above) (c-index 0.66). With the addition of MoCA<24 to the model, c-index reached 0.70).

Abbreviations: AAA, abdominal aortic aneurism; ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; AUC, area under curve; ASA, American Society of Anesthesiologists; AVFS, Addenbrooke's Vascular Frailty Score; CLI, Critical Limb Ischaemia; COPD, chronic obstructive pulmonary disease; EFS, Edmonton Frailty Scale; EVAR, endovascular aneurysm repair; LCRI, Lee Cardiac Risk Index; LGNRI, Low Geriatric Nutritional Risk Index; LOS, length of hospital stay; mFI, modified Frailty Index; MI, myocardial infarction; MoCA, Montreal Cognitive Assessment; OAR, open aneurysm repair; PAD, peripheral artery disease; PMA, psoas muscle area; rAAA, ruptured abdominal aortic aneurism; RAI, Risk Analysis Index; RVU, relative value units.

levels. Long-term complications as 3-year survival can be effectively improved by exercise training and modification of smoking behaviours. These preoperative interventions are detailed in the relevant sections of this review.

Randomized trials exist for potential therapeutic strategies, such as physical exercising,[50,51] nutritional preparation[52] or psychological intervention. The Frailty Intervention Trial[53] examined the effect of a multidisciplinary interventional method compared to the usual care of frail patients in a randomized controlled patient population. The study, however, reported data of hospitalization of any cause and not data of patients undergoing surgical procedures.

Unfortunately, we have found only a few publications reporting data on frail patients who underwent any therapeutic intervention preoperatively, even if the individual was diagnosed with frailty syndrome or mild cognitive impairment due to natural aging, dementia of any cause or due to organic dysfunction. The aim of the applied interventions in order to reduce frailty index could decrease the adverse outcomes in patients whose vulnerability or frailty syndrome seems to be irreversible. Successful therapies have positive effects not only on elderly patients themselves but also on their families and the whole society.[54]

Discussion

This review highlights some significant key points about the effects of frailty on the postoperative outcome after vascular surgeries. Based on the findings, it is clear that preoperative risk stratification should include simultaneous functional and psychosocial screening. The use of frailty evaluation systems could be a good predictor for postoperative adverse outcome in vascular surgery. Frailty increases the sensitivity of the clinically applied physiological scoring scales, like the V-POSSUM system. A multidisciplinary approach would be required to identify patients at high risk and start their preconditioning in order to improve the short-, mid- and long-term outcomes. It is well accepted that during preoperative management of vascular patients, we have to face some limitations. With this in mind, our review aims to highlight the possibilities of preoperative interventions in a larger view. The implementation of the different prehabilitation strategies varies institutionally and it is strongly dependent on technical supplies and human resources.

Cardiopulmonary Exercise Testing (CPET) In Vascular Disease

Cardiopulmonary exercise testing (CPET) is a standard method in the preoperative assessment of patients undergoing major surgery. It includes the measurement of the anaerobic threshold (AT); the maximum oxygen consumption (VO2 peak); the total time on the Duke Treadmill test and the ventilator equivalents for oxygen and carbon dioxide consumption (VE/VO2 and VE/VCO2, respectively).[55] The peak of VO2 stands for the maximum rate of oxygen consumption measured during incremental exercise[56] and it can be expressed by the ratio of ventilatory equivalent and carbon dioxide consumption (VE/VCO2). The peak of VO2 is an important marker for cardiovascular disease; however, it is often underused in clinical practice.[57]

According to the actual literature, the Duke treadmill score has a very good prognostic value in examining physical performance. Studies state that imaging is not even required if the patient reaches a value, superior to 10 metabolic equivalents (MET) on physical examination and there is no reason for stress testing before noncardiac surgeries in those patients who achieve 4 METs without symptoms.[58] However, there are findings reporting that an objective exercise testing between 4 and 6 METs is associated with low cardiovascular risk[59] and the measurement of mixed venous oxygen tension (PVO2) might only be used during the identification of patients at risk of developing postoperative complications. Parameters of the treadmill should not be used separately and without clinical assessment tools.[60]

Cardiorespiratory fitness testing in patients with diagnosed abdominal aortic aneurism (AAA) may be problematic, but should not be automatically excluded from the preoperative screening tools. Randomized trials showed that supervised exercise testing in patients scheduled for AAA repair can also be improving and could effectively direct the clinical decision-making process regarding the type of operation or the postoperative allocation.[55,61,62] During exercise testing of AAA patients, a moderately higher rate of blood pressure fluctuation was observed compared to age-matched controls and no serious event occurred during the examination.[63] The research group stated that CPET can be safely and routinely used during the preoperative risk stratification process.[63] It is potentially useful in AAA patients in the prediction of postoperative complications and the length of critical care and hospital stay.[61] The test is also declared to be an independent predictor of a 30-day outcome, 30-day mortality and 3-year survival.[62,64] Some evaluations did not reach the same conclusion: CPE testing combined with a simple co-morbidity screening showed reduced mid-term survival in patients undergoing successful AAA repair[63] and test results were associated neither with 30-day mortality nor with the length of the hospital stay.[65] These latter publications, however, are in accordance regarding the prediction of postoperative complications like cardiac events (myocardial infarction, ischemic complications, new onset arrhythmia, need for inotropic support for at least 12 hrs, congestive heart failure) or pulmonary complications (pneumonia, need for mechanical ventilation longer than 48 hrs, unplanned tracheal re-intubation, pulmonary embolism).[63,65] In certain centres, CPET is routinely used in the decision-making process regarding the type of the operation (endovascular or open repair surgery); however, retrospective data confirm that the utilization of preoperative CPET is useful mostly in the prediction of complications and the reduction of health care utilization.[58] It seems that CPET can help in the differentiation of the existing pathology, no matter if it is cardiovascular or respiratory.[62]

Based on examinations, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines concluded that the routine use of CPET in noncardiac interventions, including vascular surgery patients, may be more beneficial than its risks (evidence level B, IIb).[66] Modalities for stress testing are different; therefore, we have to minimize the risks of the examination itself. Exercise electrocardiography is a widely available tool for testing. However, in vascular patients, its usage is limited: patients suffering from claudication, limb ischemia, peripheral vascular diseases and poor functional capacity are unable to reach ischemic thresholds. In addition, this testing type provides few information about cardiac function examinable with other imaging modalities, like echocardiography, myocardium scintigraphy or cardiac magnetic resonance imaging (MRI).[67] Stress echocardiography may be preferred in patients awaiting for carotid endarterectomies, peripheral vascular interventions or patients with known bronchospastic lung diseases. Additional information about cardiac functions are provided; however, because of dobutamine usage, this type of testing should be avoided in patients with known arrhythmias and symptomatic or large aortic aneurysms (55 millimeters or larger).[66,68] Myocardial perfusion imaging is an effective alternative of the above-mentioned modalities for testing intermediate or high-risk vascular patients. It is the most suitable for patients with known left or right ventricular dysfunction and it is designed to identify flow-limiting stenosis. It should be avoided in patients with known lung disease, as dipyridamole can induce bronchospasm; and in severe carotid stenosis because of its hypotensive effect. Long testing times, ionizing radiation and technetium usage with a very low hepatic clearance represent the most severe disadvantages of this technique.[67,69] In addition, this imaging form reveals ischaemia only in the most unsupplied myocardial territories and it cannot detect subclinical atherosclerosis.

The above-described findings give facility to clinicians in the routine use of CPE testing in vascular surgery patients. Where clinical doubt exists regarding a candidate's suitability or the postoperative outcomes, exercise testing can be safely applied if the modality for testing is well chosen.

Nutrition

Outcomes associated with malnutrition in vascular surgery candidates are still unclear. Patients awaiting vascular surgery are frequently in poor nutritional condition, consisting as part of the frailty-syndrome. Malnutrition is associated with a longer hospital stay, muscle weakness, fatigue, depression, immunological dysfunction, slower wound healing and longer need for rehabilitation.[70,71] In vascular patients, serious wound infection could lead to the contamination of the vascular graft, causing severe bleeding, loss of the limb or even death.[72] It is known that a 10-day preoperative nutritional supplementation, with physiotherapy and cognitive training in frail patients undergoing abdominal interventions, significantly reduces the length of postoperative hospital stay and the need for prolonged rehabilitation.[73]

Even postoperative morbidity and mortality can be significantly reduced by the use of any form (enteral or parenteral) of preoperative alimentation, especially by improving the immune competence of the patient.[72,74] It is also well accepted that metabolic complications can be effectively reduced by the preference of an early started enteral nutrition instead of parenteral. The avoidance of nasogastric tube is recommended in order to the fast return of normal bowel function and the reduction of pulmonary complications.[75] In case of bowel dysfunction, metoclopramide and erythromycin have to be chosen as a first-line therapy.[75]

After lower extremity bypass surgeries, a higher morbidity and mortality was observed in patients with preoperative hypalbuminemia.[76] This finding was confirmed also in candidates for juxtarenal and thoracoabdominal aortic aneurysm repairs, independently of the type of the surgery (open vs. endovascular abdominal aortic aneurysm repair).[76,77] Patients with severe hypalbuminemia (albumin levels lower than 2.4 g/dl) have increased 30-day mortality, which can be reduced by a controlled preoperative nutritional intake.[76,78] Based on findings, a guiding list was created to help the preoperative clinical assessment of vascular patients. In this population, the preoperative mechanical bowel preparation should be ignored; early removal or avoidance of nasogastric tube is preferred; metoclopramide and erythromycin have to be chosen as first-line prokinetics; enteral feeding can be started in the first 24–48 hrs postoperatively and glucose levels should not exceed 11.9 mmol/L (215 mg/dl).[79] In order to avoid dehydration, consequent pain and nausea, preoperative fasting is not recommended. Clear carbohydrate fluids applied before the operation (at least two hours before) can decrease postoperative stress levels and anxiety.[80] Oral protein supplementation and short-term continuous supervised physical exercise training (six weeks at least) are the most improving interventions in frail patients undergoing surgery.[81] In candidates for elective AAA repair surgery, the physical training significantly with protein supplementation reduces postoperative cardiorespiratory events, renal complications and the length of hospital stay.[82] Equal results were reported after a 4-week long preoperative high-intensity (HIT) interval training in AAA repair awaiting patients.[83]

Smoking

The most common modifiable risk factor in patients with vascular disease is smoking. The level of nicotine dependence can be easily specified by the Fagerstrom test.[84] In addition to the well-known physiological risk factors (congestive heart failure, age, diabetes, chronic obstructive pulmonary disease, unused statin therapy, chronic renal failure), smoking is also independently associated with an increased risk of mortality following carotid endarterectomies.[85] After lower extremity bypasses, 30-days hospital readmission rate was increased by current smoking; besides dialysis-dependence, tissue loss, graft insufficiency and female gender. Consequently, the number of readmissions are linearly associated with long-term limb loss.[86] However, there are findings describing that the presence of smoking, metabolic syndrome or renal insufficiency are less important in risk prediction of postoperative infectious complications, compared to operating times, presence of preoperative open wound or inpatient operation.[87]

Even if smoking rates have decreased,[88] few of the vascular surgeons give assistance to their patients in the cessation procedure, even if patients themselves have the intention to quit, independently of the planned operation or the symptomatic status.[88] Those who have a history of more than 30 pack-year have more failed attempts to quit in their lives compared to episodic smokers or those who have a shorter pack-year history. A brief smoking cessation (3 months) with the help of vascular surgeon can increase patients' desire to quit. It is also important to make patients aware of the possible long-term consequences of nicotine dependence.[89] The VAPOR trial (Vascular Physician Offer and Report) designed a three-step smoking cessation intervention (advising to quit, replacing nicotine, telephone-followed quitline) and compared it to routine care. The trial reported a 40.3% 3-month cessation in the intervention group (23 patients of 57) after the physician's advice and the nicotine replacement therapy.[90]

Our review finding suggests that an exact preoperative screening regarding smoking behaviours of the patients and the intention to intervene is an effective way to reduce postoperative infectious complications and future hospital readmissions.

Management Of Glycemic Status

The relationship between high blood glucose levels and worsened postoperative outcomes (major amputation, graft occlusion, tissue loss, cardiovascular events, renal insufficiency) is well known. Poor glycaemic control is associated with an enforced progression of cardiovascular disease, an increased mortality and an elevated perioperative complication rate.[91] Mortality rate is doubled when glucose levels are above 140–150 mg/dl in the perioperative period. The goal of insulin therapy is to avoid surgical wound complications,[92] gastrointestinal function and inflammatory responses.[70] Every 40 mg/dl increase in glucose levels increases the risk for graft failure and infection by 30%, followed by a longer intensive care unit (ICU) stay.[93] Increased glucose tolerance, diagnosed by fasting glucose levels and OGTT (oral glucose tolerance test) resulted in a significantly higher risk for developing postoperative cardiovascular events (myocardial infarction, angina pectoris, transient ischemic attacks or cerebrovascular occlusions), compared to diabetic patients, showing non-significant risk-increase.[94]

After lower extremity revascularization, elevated haemoglobin A1c (HbA1c) levels are associated with increased risk for limb amputation and major adverse limb events. This tendency was also observed in patients having HbA1c levels higher than 7%, with no preoperative diagnosis of diabetes mellitus. These latter patients are at 50% higher risk for amputation or major adverse events than patients with normal glycolysed haemoglobin levels.[95,96] Even a short-term thigh glycaemic control has the potential to reduce amputation rates in patients with type 2 diabetes[97] and the risk for surgical site infections.[98] HbA1c can identify patients at higher long-term mortality risk before PAD revascularization, even if candidates have an unknown glycaemic status or undiagnosed diabetes mellitus.[99] The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) reported comparison of the risk prediction values of haemoglobin glycation index (HGI) and HbA1c levels. According to the trial, in patients with type 2 diabetes, the risk evaluating the value of either HbA1c and HGI cannot be clearly suggested, due to the discordant results.[100] It has also been shown that diabetic and non-diabetic patients with long-term elevated blood glucose levels are at an increased risk for abdominal aneurysm progression. During a 5-year ultrasound guided follow-up (subtrial of *Viborg Vascular* Randomized Screening Trail),[101] abdominal aortic aneurysms under 5 centimetres of diameter have shown significant progress in patients with higher HbA1c levels, compared to euglycaemic individuals.[101]

It is suitable for non-diabetic patients undergoing vascular surgery to be tested for glucose regulation dysfunctions before interventions. It seems that gylcolysed haemoglobin is a useful tool to predict the risk for infections, long-term risk for limb-loss and postoperative mortality.

Early Rehabilitation

In general surgery patients, fast-track recovery programs have been created, resulting in decreased patient morbidity and mortality after major surgeries.[102] Such programs have not been created specifically for vascular surgery patients; however, the protocols available can be adapted to this patient population as well. The most commonly used multimodal evidence-based fast-track program is described by the ERAS protocol (Enhanced Recovery After Surgery), which, besides the preoperative interventions, involves all the major postoperative principles.[79] The program is already standard in colorectal and general abdominal surgery. The major principles are: reduction in the use of nasogastric tubes and enforcement of early enteral nutrition; early removal of drains; use of patient-controlled and non-opioid analgesia; goal-directed fluid therapy; avoidance of urine catheters when possible and early mobilization.[79] An important element of early recovery is pain management. Patient-controlled epidural analgesia resulted in fewer cardiovascular and renal complications in the postoperative period, compared to systemic opioid usage, with no difference in mortality rates.[103]

The ERAS was used by randomized prospective and other studies,[62,102–104] involving vascular surgery candidates. After elective open infrarenal aneurysm repair surgery, patients managed with a fast-track recovery program (avoidance of long-term preoperative fasting and bowel preparation, early post-operative enteral nutrition, patient-controlled epidural analgesia (PCEA) early mobilization) showed significantly better outcomes compared to those receiving conservative treatments.[102] The need for postoperative-assisted ventilation, the incidence of all-cause complications and the time to reach full enteral nutrition were significantly decreased.[102]

Deriving from its multifactorial characteristic, this clinical syndrome needs multimodal intervention: physical exercising, maintenance of muscle strength, adequate perioperative nutrition, glycaemic control and management of smoking behaviours can lead to increased patient survival and a quality of life even in advanced ages. With exercise prehabilitation programs, the health-related quality-of-life of vascular surgery patients seems to be significantly improved after discharge.[105] The preoperative management algorithm of frail vascular surgery patients is presented in Figure 2.

Limitations

During data research, we had to face some limitations. Comorbidities may vary by races and nationalities, while frailty as a well-defined syndrome lacks these discrepancies. Our review did not differentiate vascular procedure types (except varicectomies) and operations were considered more or less equivalent to each other. This makes the generalizability of our findings questionable. We also have no data about the ease of implementation of prehabilitation procedures, as it varies centre by centre and it is dependent on the human and financial resources of each institution. Therefore, the cost-effectiveness of the interventions in the field of vascular frail patients is very specific. Additionally, our review lacks detailed data about the quality of life of the patients after discharge, which could also be an important reflection to the effectiveness of prehabilitation programs applied in order to reduce negative influence of frailty syndrome on the outcome. Publication found in this latter field reports that the generalizability of the data is limited by the heterogeneity of the patient populations; thus, the creation of a statistical pool across trials was not possible.[105] Further evaluations are needed. Regarding cost-effectiveness and resource utilisation, we lack data in the field of vascular surgery frail patients, despite that several analyses are available in other surgery types. These studies reported increased post-operative resource utilisation across various metrics, but the improved cost-effectiveness seemed to be of low certainty due to the inconsistency among researches.[106,107]

Conclusion

Frailty has a great influence on postoperative outcomes in patients undergoing vascular surgery. The development of well-designed prehabilitation programs would

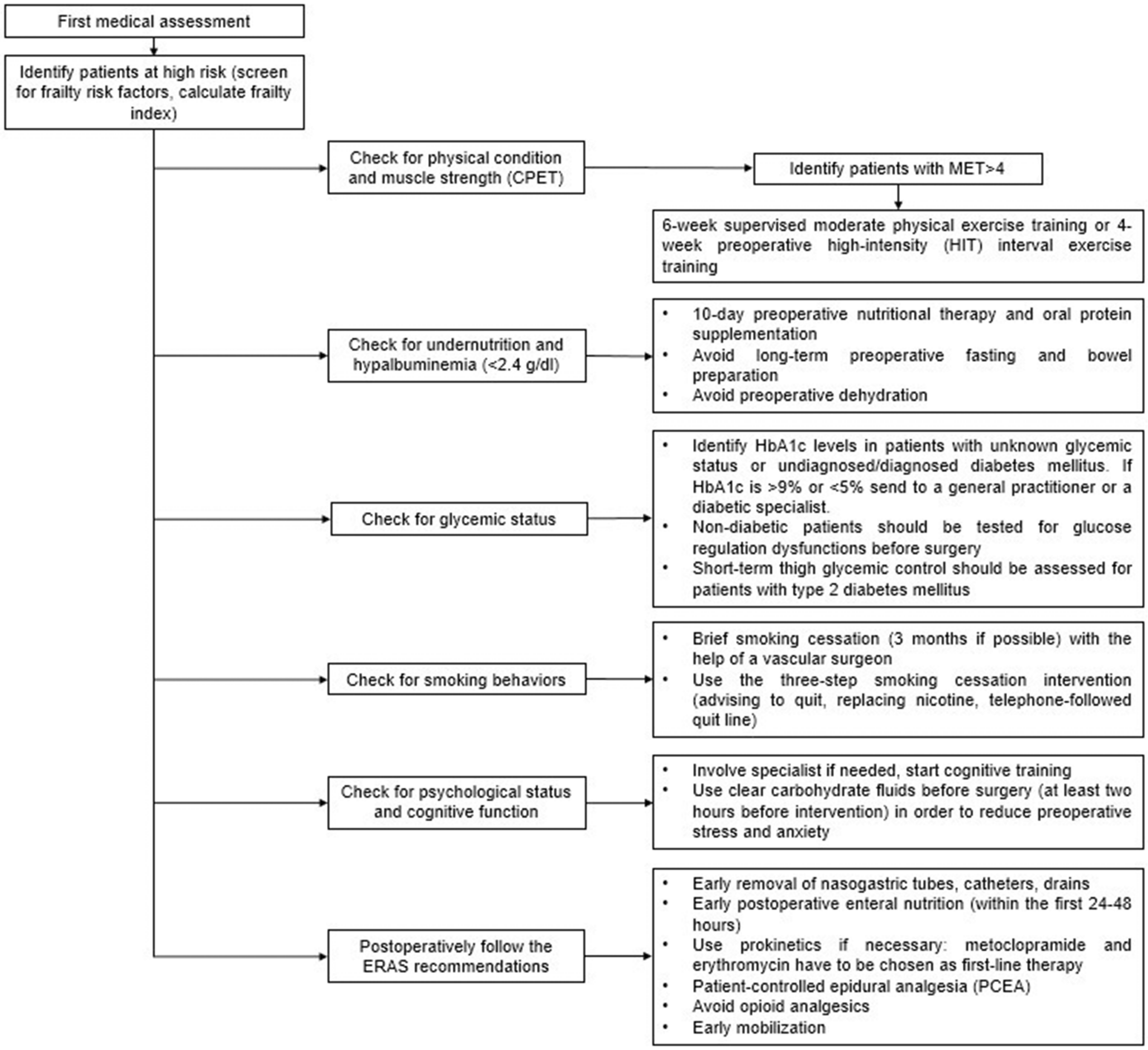

Figure 2 Preoperative screening and intervening algorithm of frail vascular patients.

help the achievement of a better outcome in this patient population. It is well accepted that surgery itself can cause postoperative frailty. It is desirable to understand prevention methods, because frailty syndrome can also occur as a consequence of complex and stressful vascular surgeries. Efforts are needed in order to reduce the length of stay, the number of readmissions and the time required for recovery. We have to understand that frailty is a dynamically changing state of the patient: pre-frail patients, with the worsening of their conditions, can anticipate in a complex and irreversible frailty-syndrome, but with goal-directed preoperative interventions, this deterioration can be prevented.

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