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Review Article

Frailty in Surgical Care: A Review

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ABSTRACT

Frailty is an important condition that affects treatment outcomes, especially in patients undergoing surgery. Currently, there is a world trend towards an aging society, increasing the number of frail patients. Physical, intellectual and social vulnerability is the leading cause in connection to falls, burden, disability, or permanent disability, resulting to a decrease in quality of life. In regards to caring for surgical patients, this translates to dealing with more elderly patients, and frailty is one of the key factors affecting further treatment outcomes. Thus, it becomes necessary to assess patients for vulnerability, prior to surgical intervention. Conducting preoperative vulnerability assessments can indicate the level of risk for adverse events after surgery and allow surgeons to tailor treatment options for the patient. In addition, it can aid in preventing or correcting their vulnerability, increasing the possibility of obtaining good surgical results and minimal complications. This is especially true when there is good cooperation between general physicians, senior physicians, anesthesiologists, and surgeons.

Keywords: frailty; surgical care

INTRODUCTION

The definition of frailty is being fragile or easily broken. Nevertheless, when this is applied in a medical context, it has a different meaning. Frailty syndrome is one of the more common symptoms in the elderly, transitioning from healthy to frail. Physical, intellectual and social vulnerability is associated to falls, burden, disability, or permanent disability resulting to a decrease in quality of life and complex care needs[1]. In the past, frailty was characterized by signs or symptoms such as the physical deterioration seen in elderly people as they age, and it is caused by age-related decline when the aging process continues naturally. Therefore, it is something that everyone has to face and can result to poor treatment results due to

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age-related deterioration. In fact, many studies have found that the incidence rate of vulnerability among the elderly varies according to individual, family, community, or social risk factors. It is important to find the associated risk factors so that prompt corrective action is undertaken[1,2]. Tarik's study[3] examined the relationship between the postoperative complications of arterial extremities bypass surgery and the modified frailty index (mFI), an assessment used to assess fragility of patients. Patients with an mFI greater than 0.54 had a 7.4% mortality at 30 days postoperatively and a 4% chance of myocardial ischemia. High frailty is also associated with a high mortality rate. In another study, Than et al[4]. examined the relationship between vulnerability and adverse outcomes at 30 days, postoperatively, in elderly patients undergoing gastroenterological surgery. Frail patients were seven times more likely to have adverse outcomes at 30 days, than non-frailty patients, due to respiratory failure, kidney failure and mortality. In addition, sepsis after surgery was found to be 8 times more common than non-frail patients.

The rapid increase in the elderly population, in current society, has increased the number of people that are over 60 years of age. Therefore, the incidence rate of frailty is also rapidly increasing. This condition will begin to show its characteristics as people get older, resulting in a rapidly increasing demand for health care[2]. This includes the care of surgical patients, with frailty becoming one of the key factors that can affect clinical outcomes.

Pathogenesis of frailty

The body's inappropriate stress response to physical activity leads to a loss of dynamic homeostasis. This assumes that a decrease in the response to inflammation or infection in the body, a loss of muscle strength (sarcopenia), and age-related changes in the endocrine system; such as decreased sex hormones, higher cortisol hormone or vitamin D deficiency, all can cause fragility. There are also other factors that affect vulnerability, such as genetics, environmental stress, chronic physical disease and others, as shown in Figure 1[5]. When the patient is

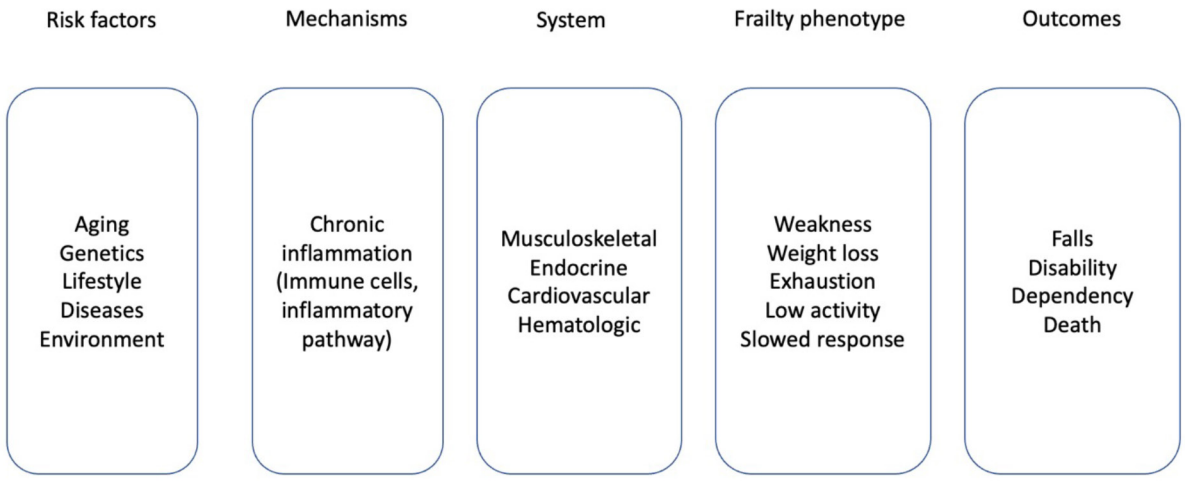

Figure 1 Pathogenesis of the frailty syndrome: current understanding of the potential underlying mechanisms and hypothetical modal pathways leading to frailty[5]

already fragile, if this is diagnosed and treated early then it can be reversed but if not then the patient can become permanently disabled. Screening and early diagnosis of this condition is critical in identifying groups focusing on prevention in regards to elderly people at risk or to provide care for vulnerable elderly patients before they become disabled[6-8].

In regards to the above figure, the factors that cause vulnerability can be divided into 2 parts: factors or causes that depend on each patient, i.e., increasing age, genetics, lifestyle, and diseases, including the environment together with factors or mechanisms that promote greater vulnerability, which can be divided as follows[4,5].

1. Chronic inflammation and immune activation

Fragility is directly related to the immune system when an infection or inflammation in the body influences the occurrence of fragility.

1.1 Molecules of chronic inflammation and immune system activation

Cell culture studies in rats, as well as studies in the elderly, investigated the relationship between increased interleukin 6 (IL-6) and vulnerability. In addition, other inflammatory molecules, C-reactive protein, or tumor necrosis factor alpha were found to have higher values in the elderly, especially those with frailty. An increase in neopterin was also associated with vulnerability, where neopterin is a consequence of the breakdown of macromolecules from guanosine triphosphate (GTP), one of the monocyte and macrophage immune mediators. Therefore, immunostimulation is an important process in the development of chronic inflammation in regards to the pathogenesis of fragility.

1.2 Cellular components of the immune system and the mechanism of vulnerability

An increase in white blood cells is an important parameter, in regards to indications of inflammatory conditions in the body, which may show a bacterial infection. Several studies have looked at the association of leukopenia with frailty. The specific leukocytes are neutrophils and monocytes, however, further elucidation of the cause or process of inflammatory and immune activation in fragile states remains to be studied. In addition, chronic cytomegalovirus (CMV) infection is associated with an increase in cluster of differentiation 8 (CD8) T-cells and neopterin in the elderly, which is associated with greater vulnerability. The effects of inflammatory molecules such as IL-6 directly contribute to the development of fragility and can lead to somatic features such as a decrease in muscle mass, reduced strength of organs or slower movements, etc. Chronic inflammation can result to fragility through the functions of other systems such as the musculoskeletal system, endocrine system, anemia, cardiovascular system, and malnutrition. Chronic inflammation on the body may be indirectly tested by testing the concentration of red blood cells, the level of insulin-like growth factor (IGF-1), serum albumin, or certain vitamins. This is inversely proportional to the increase in the substance or molecule of the inflammatory variables that can result to vulnerability.

2. Musculoskeletal system

Frailty has two important characteristics: weakness and slower movements and the presence of low muscle mass, sarcopenia, which is an important aspect of the pathophysiology of frailty. It can occur rapidly in regards to people over the age of 50 and is more commonly found together with chronic disease. It can manifest via age-related changes in motor neurons of muscle fibers causing more muscle atrophy together with malnutrition, reduction of the production of growth hormone and sex hormones, causing chronic inflammation which can affect the condition of lean muscle mass. It can also be detrimental to bone strength as well, so frailty is directly related to osteoporosis.

3. Endocrine system

Sex hormones and IGF-1 affect the occurrence of disorders of the musculoskeletal system in the body. Estrogen decreases in women entering menopause, and a decrease in progesterone in older men can cause muscle mass and muscle strength to decrease. Hormonal changes (dehydroepiandrosterone sulfate and IGF-1) are the intermediates used in the production of growth hormone, which is found in less frail patients than the general population, especially in men.

4. Complex multifactorial etiology

A study by Blaum et al[9]. found a significant association between obesity and vulnerability in women aged 70-79, finding that obese individuals were more vulnerable. In regards to the above pathogenesis, it is either due to the patient's own internal factors or external factors that can determine whether it is an infection or inflammation in the body or a general weakness in connection to the musculoskeletal system. Furthermore, hormonal changes in the body ultimately can lead to weakness, fatigue, weight loss, physical response, slowing of thinking and mind leading to an increase in the rate of falls, disabilities, and dependence needs; ultimately leading to death.

Frailty measurement tools

The next important sequence is finding or screening which populations or patients are associated with vulnerabilities. The elderly are very vulnerable, but this does not mean that other populations do not have vulnerabilities. Therefore, specific efforts to identify any patient undergoing surgery with fragile conditions and efforts to prevent or correct these should be made in order to achieve a favorable outcome.

In general, the easiest preoperative assessment of patients is the eyeball test but it was found to be insufficiently accurate[10]. Several studies have attempted to find a more acceptable vulnerability testing tool. More than 70 vulnerability testing tools have been studied[11,12]. Some of the preferred tools are those that are highly sensitive and easy to use[13]. Here are some examples of tools that are commonly used today.

1. Single item tools

The quick and easy measurement tools assessed by using either values or testing, include the grip strength, and the time up and go test, which is used to test walking ability or fall risk[7] by measuring the time from the standing position to walking for a distance of 3 meters and then turning back to the normal position[14].

Another example is the direct measurement of lean muscle mass (sarcopenia) in order to assess frailty. The Asian Working Group for Sarcopenia (AWGS) 2019[15] consensus defined sarcopenia as "age-related loss of muscle mass, plus low muscle strength, and/or low physical performance" and specified cutoffs for each diagnostic component. (low muscle strength is defined as handgrip strength <28 kg for men and <18 kg for women; criteria for low physical performance are 6-m walk <1.0 m/s, Short Physical Performance Battery score ≤9, or 5-time hair stand test ≥12 seconds, dual-energy X-ray absorptiometry, <7.0 kg/m^2 in men and <5.4 kg/m^2 in women; and bioimpedance, <7.0 kg/m^2 in men and <5.7 kg/m^2 in women. In addition, the AWGS 2019 proposed separate algorithms for community vs hospital settings, which both begin by screening either calf circumference (<34 cm in men, <33 cm in women), to facilitate earlier identification of people at risk for sarcopenia. Some guidelines recommend using the body mass index adjusted muscle mass instead of the height-adjusted muscle in order define sarcopenia; however, more evidence is needed before changing current recommendations. The psoas muscle has been commonly assessed at the third lumbar level using cross-sectional computed tomography. Using the Hounsfield unit (HU) at -29 to +150 HU, the location of the amplitude of the scale was measured. Maximum muscle mass is predictive of sequelae after surgery[15-17].

Clinical applications

A study by Robinson et al[18]. studied the relationship between preoperative time up and go and postoperative adverse outcomes in patients over 65 years of age undergoing cardiac and intestinal surgery. More than 15 seconds was associated with more than one systemic postoperative complication and with repeat hospital stays, within 30 days, than those who tested less than 15 seconds.

2. Frailty phenotype

It is a tool that has been used in many research studies. A study by Fried et al[8]. proposed a frailty phenotype model in 2001 based on the 'Cardiovascular Health Study' to determine the risk factors for mortality in the elderly. The Hopkins Frailty Score was created based on the principle of Fried's frailty phenotype and was assessed in surgical patients[19,20] as shown in Table 1[24].

Frailty phenotype can be tested in 10–15 minutes[12]. It is used by most researchers because it is simple and can be used in many population[21–23]. A stopwatch must be used in conjunction with such an instrument for physical vulnerability testing without considering the social and mental aspects[12,25].

Clinical application

A study by Sikder et al[22]. found an association between frailty phenotype and greater than 6 months postoperative recovery in patients older than 65 years who had abdominal surgery using the frailty phenotype. In the frail group and the pre-frail group, the length of hospital stays, postoperative complications, the rate of re-hospitalization and its return to the emergency room was higher compared to the robust group. In addition, a study by Tan Y et al[23]. examined how frailty affects the incidence of adverse outcomes after intestinal surgery in patients over 75 years of age using a frailty phenotype of 3 points or higher.

3. Deficit accumulation model or frailty index

A 2001 study by Mitnitski et al[26]. and a 2004 study by Rockwood et al[27]. presented the accumulation of deficit model as part of the Canadian Study on Health and Aging (CSHA). This assessment represents the analysis of different variables of many factors leading to weakness or vulnerability. Frailty index (FI) is an accepted tool. It consists of many variables such as physiology, work, social and core knowledge, congenital disease, etc[12,27] as shown in Figure 2.

The deficit accumulation model of frailty was adapted into a 36-factor assessment with scores of 0 and 1 but there are many variables making the frailty index difficult to implement, so it has been modified to make it easier to use, with a reduction to 16 variables in 2012. It was later on adjusted to 11 variables, and in 2015 reduced to 5

Table 1 Frailty phenotype tool and interpretation[24]

Domains of Frailty	Measure		Score
Shrinking (weight loss)	10-pound or more unintentional weight loss in the past year		1
Weakness	Grip strength in the lowest 20% based on body mass index and gender		1
Exhaustion	Self-reported exhaustion		1
Slow gait speed	Time to walk 15 feet at normal speed in lowest 20% based in height and gender		1
Low activity	Kilocalories expenditure per week in the lowest 20%		1
Scoring	0–1 robust	2–3 pre-frail	4–5 frail

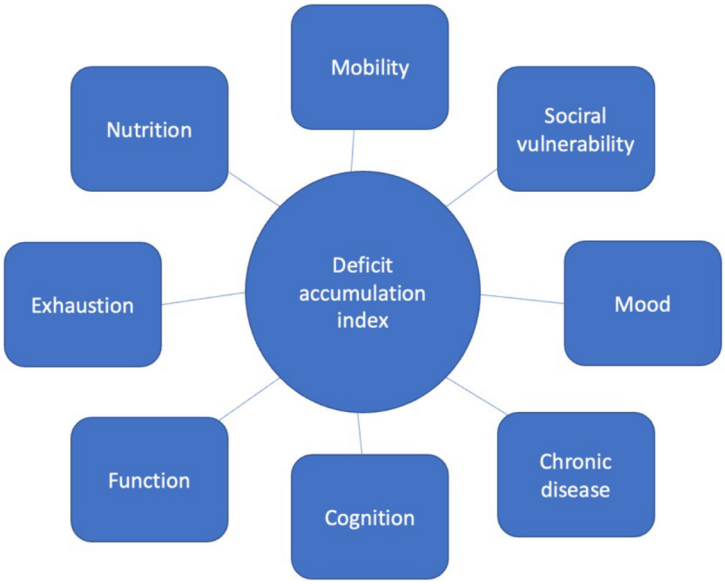

Figure 2 The deficit accumulation model of frailty[24]

Table 2 Five-item modified frailty index (mFI-5)[29]

Comorbid factors			Score
Congestive heart failure (within 30 days of surgery)			1
Diabetes mellitus (insulin dependent or noninsulin dependent)			1
Chronic obstructive pulmonary disease or pneumonia			1
Dependent functional health status (total or partial) at time of surgery			1
Hypertension requiring medication			1
Score	Group 1: mFI-5=0	Group 2: mFI-5=1	Group 3: mFI-5≥2

mFI-5 = five-item modified frailty index

variables, known as the modified frailty index (mFI). It was discovered that the mFI had the same reliability compared to the frailty index and it was more readily usable[28]. The mFI-5 assessment scale, as shown in Table 2, has been divided into three groups: 0, 1, and greater than 2 points. A study by Sagal and Wilson concluded that an mFI score that is greater than or equal to 2 increased the likelihood of high incidence of complications post-surgery[29].

Clinical application

A study by Choe et al[30]. assessed how preoperative frailty affects adverse outcomes after gastric cancer surgery using the Study of Osteoporotic Fractures (SOF), which is an easy to use tool. In the event of a score of 2-3, it was found that vulnerable patients were more likely to be hospitalized within 1 year of gastric bypass surgery compared to normal. A further study by Vermillion et al[31]. found that a high mFI score was associated with

adverse outcomes after gastrointestinal cancer surgery in regards to elderly patients. The mFI instrument used in this study used 11 variables which were accounted for as a proportion of the full score. Therefore, the score ranges from 0 to 1, with mFI scores greater than 0.27 considered to be fragile; and it was found that as many as 36.8% of complications occurred in this category. Nevertheless, those with an mFI score of less than or equal to 0.27 were very unlikely to experience either minor or severe complications. Another study by Mogal et al[32]. looked at vulnerability and complications after pancreatic and duodenal surgery. In pancreaticoduodenectomy, patients with an mFI score that is greater than 0.27 were 40.8% more likely to develop serious complications than those with an mFI score that is less than 0.27, who had a 27.7 percent likelihood of developing complications after surgery. Another study by Choi and Orouji et al[33,34]. used a 50-variable mFI to assess vulnerability and postoperative complications.

4. Comprehensive geriatric assessment (CGA)

It is a vulnerability assessment form using physical characteristics, psychological and social characteristics to assess physiology age and proficiency[35,36]. There are several advantages which are related to this approach. First, it specifically demonstrates a wider range of patient problems, including co-morbidities, potential polypharmacy, and quality of life, as well as physical and cognitive functioning, that might not always be considered during a disease-oriented medical assessment. Second, it allows for more specific, individualized care planning for the patient, resulting in better quality of care[36]. However, this assessment has some limitations. There is a lack of standardization in the assessment and care approach. This tool has developed a range of validated and standardized setting-specific instruments for older patients but further research is needed. There are two quick and easy screening tools: Geriatric-8 (G-8) and Vulnerable Elder Survey-13 (VES-13)[37].

4.1 Geriatric-8 (G-8)

It is a tool developed from the Mini-Nutritional Assessment-Short Form Questionnaire especially in cancer patients. A systematic review study was conducted to screen the vulnerability of older adults with cancer. Compared to other instruments, the G-8 was the most sensitive but had low specificity. The sensitivity was greater than 80% using the cut-off point score 14 as shown in Table 3[38]. Modified G-8 can increase specificity by adding 14 variables from the original, increasing specificity from 57.7 to 79% at intersections greater than 6[39].

4.2 Vulnerable elders survey-13 (VES-13)

This is an assessment of risk factors for decreased physical function in the elderly. Comprising 13 key variables, this assessment had more specificity versus sensitivity; therefore, it is less useful in screening for vulnerabilities. The sensitivity rate was 39-88% and the specificity rate was 62-100%[40]. It was found that when VES-13 was used in combination with G-8, the sensitivity and specificity, in connection to vulnerability, were both increased[39].

Clinical application

A study by Giannotti et al[41]. aimed to determine the accuracy of a 40-item mFI versus CGA in predicting mortality at 1 year, and the functional status after intestinal surgery in regards to elderly patients by using the G-8 instrument model, with frailty patients who had a score that was greater than 3. In this study, CGA was not able to predict long-term mortality, possibly because of the small sample size in the study. The 40-item mFI tool found that in regards to vulnerable patients with mFI greater than or equal to 0.25, the mFI was highly accurate in predicting mortality at 1 year; but in regards to functional conditions the CGA was not, making it inferior to mFI in regards to predicting such conditions.

Table 3 G-8 Screening questionnaire[38]

Items	Possible answers	Score
Food intake in the last 3 months	0: severe reduction in food intake	
	1: moderate reduction in food intake	
	2: normal food intake	
Weight loss during the last 3 months	0: weight loss >3 kg	
	1: does not know	
	2: weight loss between 1 and 3 kg	
	3: no weight loss	
Mobility	0: bed/chair bound	
	1: able to get out of bed/chair but does not go out	
	2: goes out	
Neuropsychological problems	0: severe dementia or depression	
	1: mild dementia or depression	
	2: no psychological problems	
Body mass index (BMI) (kg/m^2)	0: BMI <19	
	1: BMI 19 to <21	
	2: BMI 21 to <23	
	3: BMI 23 or greater	
Takes more than 3 medications/day	0: yes	
	1: no	
Self-rated heath status	0: not as good	
	0.5: does not know	
	1: as good	
	2: better	
Age (year)	0: >85	
	1: 80-85	
	2: <80	

Total score (0-17): cut-off ≤14 indicating impairment

5. Clinical frailty scale/score (CFS)

Rockwood et al. From the Canadian Study of Heath and Aging[42]. developed the CFS tool with a range of scores from 1 (very fit) to 7 (complete dependent), with each score based on symptoms and ability to self-help. CFS is a quick and easy to use tool, without physical tests, such as time up and go or hand grip, or length of hospital stays; and the factors contributing to mortality can be predicted by assessing both physically social and mental health in the elderly. The cut-off value for fragility is greater than 5[43,44].

Clinical application

A study by Goeteyn et al[45]. found a higher incidence of fragility in patients undergoing emergency general surgery. The assessment of vulnerability using the CFS tool was a full score of 7, with patients with scores 1-4 classified as non-frail and scores 5-7 in the frail group. Vulnerability was also found to be statistically associated with 30-day and 90-day mortality. Another study by Parmar et al[46]. examined the incidence and association of vulnerability among older adults undergoing emergency laparoscopic surgery and postmortem mortality and found that emergency laparoscopic surgery had a 20 percent incidence of vulnerability regardless of age, and also that increased vulnerability increased mortality rates.

6. Edmonton frailty scale (EFS)

It is a nine-factor instrument with a total score of 17 and takes less than 5 minutes to assess. It is commonly used in the assessment of intraoperative vulnerability by the

British Geriatric Society[43,47]. Frailty has a score of 12–17, apparent vulnerability has a score of 6–11, and non-frailty has a score of less than or equal to 5.

Clinical application

Perna's study[48]. used EFS to assess vulnerability. The results found that EFS is a useful and useful tool for assessing vulnerability and its relationship with older adults, such as vulnerability, freedom, taking medicine, mood, mind, work and nutrition.

7. FRAIL scale

It is an assessment that can be done quickly and can be done alone. It is as accurate as the Fried frailty phenotype, and it consists of five questions: fatigue, resistance, ambulation, illness, and loss of weight, taking less than 5 minutes to complete. The assessment[49] is divided as such: 0 is robust, 1–2 is pre-frail and ≥3 is frail as in Table 4.

Clinical application

The Kojima et al[50]. studied the relationship between FRAIL score and mortality. A systematic review study found that it took less time to ask just five questions and found that vulnerable patients had a higher mortality rate than those without the vulnerabilities.

Frailty management

The goal of vulnerability care and management is to prevent, mitigate or reduce the severity of vulnerability and prevent or mitigate adverse effects in vulnerable patients. The frailty management is multimodal approach that comprises of nutritional support, exercise, pharmaceutical components, pre/rehabilitation and preopeative and perioperative care. Exercise is a highly researched method that can be useful in the treatment of fragility. It affects many organs and systems especially the musculoskeletal system, endocrine and immune system by increasing muscle strength. In addition, proper nutrition is another important factor. However, there are probably less studies showing a clear benefit about this versus exercise. Studies on drugs and hormones such as testosterone have found evidence that that it could influence increasing muscle strength. A study on IGF-1 administration found that it increased bone and muscle strength in people diagnosed with IGF-1 deficiency. Another study found that vitamin D and angiotensin-converting enzyme Inhibitors are commonly used, and are safe drugs that could potentially be used to prevent and treat frailty. There were some studies to evaluate the relationship between sarcopenia and both exercise and nutrition found that hospital-based interventions, which included resistance exercise plus nutritional supplements including branched-chain amino acids, vitamin D, whey protein, and hydroxymethylbutyrate (HMB) enriched milk, can significantly increase physical function, muscle mass, and strength. In a 24-week study of women in Japan, those taking whey protein after resistance exercise had increased muscle mass, grip strength, and gait speed compared with those in either single intervention arm. Another study compared community-living men and women randomized to either 12 weeks of exercise, exercise plus HMB-enriched supplement, or a wait-listed control group; there was no effect on the primary outcome of gait speed, but both intervention groups had improved leg extension and 5-time chair stand performance, which persisted for 12 weeks after the intervention ended. Leg muscle mass and ASM only increased in the exercise plus nutritional supplementation group; however, the increase in

Table 4 FRAIL score[50]

F	Fatigue (Are you fatigued?)
R	Resistance (Can you climb 1 flight of stairs?)
A	Ambulation (Can you walk 1 block?)
I	Illnesses (Greater than 5 illnesses)
L	Loss of weight (greater that 5% in 1 year)

muscle mass had disappeared by 24 weeks. This evidence recommends that exercise plus nutritional support improved muscle function, mass and strength[15]. Nevertheless, more studies are still needed in the future[5]. The other factor of poor nutritional status in frailty patients is dysphagia especially in postoperative care period. A prospective observation study[51] reported that post-extubation dysphagia in critically ill surgical patients was associated with an increased risk of morbidities and mortalities as well as with pulmonary complications. In this study, the screening tool used is the water swallowing test, using oral water ingestion to detect swallowing-related aspiration and by confirming the diagnosis by fiberoptic endoscopic evaluation of swallowing. This tool will help the early detection of dysphagia and could improve outcomes in both frailty and non-frailty surgical patients. In addition, managing or taking care of physical matters has a bearing on the vulnerability of the elderly. Therefore, good cooperation of physicians, especially geriatric physicians, nurses, pharmacists, and physical therapists plays an important role in helping the elderly to be free from frailty[5]. Prehabilitation is a term referring to any intervention delivered in advance of surgery that improves function and decreases postoperative morbidity and mortality in surgical patients. However, evidence demonstrating the benefit of prehabilitation for patients with frailty is limited. Current guidelines recommend that inspiratory muscle training should be suggested in a prehabilitation program[52]. A recent randomized controlled trial by Boden et al[53]. demonstrated that a single 30-minute physiotherapy session within 6 weeks of surgery can reduce the rate of postoperative pulmonary complications. Besides, the frailty assessment should extend beyond its role in pre-operative risk stratification. The identification of frailty in a surgical patient should begin the initiation of a set of interventions that may reduce morbidity and enhance functional recovery after surgery; and include the Enhanced Recovery After Surgery (ERAS) pathway, an integrated clinical care delivery program recently shown to improve clinical and functional outcomes in older surgical patients. Furthermore, include prehabilitation programs that aim to improve physical function and optimize comorbidity, as well as geriatric interdisciplinary assessment and treatment models that have been demonstrated to improve the clinical outcomes of frail adults[54].

CONCLUSION

Frailty is an important condition that affects treatment outcomes, especially in patients undergoing surgery, as there is a trend towards an aging society, as most are fragile. This makes it necessary to assess patients for vulnerability, prior to treatment. Conducting a preoperative vulnerability assessment can show the risk of adverse events after surgery and allow surgeons to tailor treatment options for the patient. Currently, there is no optimum assessment of vulnerability. However, simply using one of the aforementioned assessments to look for vulnerabilities before surgery is beneficial for patients, as it may be possible to correct or prevent vulnerability. This could result to better results and less complications but it also depends on a good level of cooperation between general physicians, senior physician, anesthesiologists, and surgeons.

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