Continuing Medical Education

Determinants of Perioperative Outcome in Frail Older Patients

Anna Mende, Ann-Kathrin Riegel, Lili Plümer, Cynthia Olotu, Alwin E. Goetz, Rainer Kiefmann

Summary

**Background:** Older patients are undergoing surgery in increasing numbers. Frailty is a key risk factor associated with higher rates of complications and mortality, longer hospital stays, and functional impairment.

**Methods:** This review is based on pertinent publications retrieved by a selective search in PubMed, including guidelines from Germany and abroad.

**Results:** Many studies have been published on the assessment of frailty and its consequences, but the scientific investigation of this topic and the clinical utility of the findings are made more difficult by the lack of a uniform definition and of uniform instruments for assessment. Some definitions of frailty include only physical aspects, while others encompass cognitive, emotional, and social factors as well. Despite this variability, the assessment of frailty enables better estimation of the perioperative risk so that the patient can be optimally prepared for the operation. Especially for frail elderly patients, an interdisciplinary approach is called for over the entire perioperative treatment period.

**Conclusion:** In the future, the definition of frailty will need to be standardized so that this parameter can be properly assessed and investigated in comparative studies.

Cite this as:
Learning goals
After reading this article, readers should be:
● Familiar with the most common definitions of frailty;
● Able to outline the perioperative risks and complications associated with frailty; and
● Familiar with the options for intervention and treatment in the perioperative setting in a patient with frailty syndrome.

Definition of and approaches to frailty
Most readers will be able to associate the word “frailty” with a particular image of an older person or indeed with one of their own patients. However, defining the term precisely is difficult. As an overall concept—the literature shows consensus here—“frailty” denotes restricted physiological reserves and an increased vulnerability to stress factors (3). A hospital stay or a surgical procedure can act as a stress factor of this kind. On the other hand, so far there is no agreement as to a standardized method of assessing frailty—which is a requirement if at-risk patients are to be identified and preventive and therapeutic measures put in place. The differing approaches to defining frailty also complicate attempts to study the topic scientifically, and make comparisons between studies harder.

Many different instruments exist for the assessment of frailty. They vary greatly as to the domains they examine. Some focus explicitly on physical function, while others also include cognitive, psychological, and/or social elements. The time required for the assessment and the way it is administered vary accordingly. In the next section we present a selection of these assessment instruments.

Fried phenotype
The oldest definition, and one of the most widely used, is the phenotype developed by Fried et al. (4). This definition was developed using data from the Cardiovascular Health Study, which included over 5300 participants. The Fried phenotype focuses primarily on physical or functional abilities. Five criteria are assessed: unintentional weight loss, exhaustion, muscular weakness, slow walking speed, and low physical activity. This is followed by assignment to one of three categories: robust, pre-frail, and frail (Table 1).

Canadian Study of Health and Aging Frailty Index and Frailty Scale
In addition to the physical state of health, Rockwood et al. also regarded the patient’s cognitive and psychological status as important. As part of the Canadian Study of Health and Aging (CSHA), the somewhat elaborate Frailty Index and the Frailty Scale were developed (5). The CSHA Frailty Index scores a total of 70 possible deficits or clinical signs and symptoms. The variables range from physical disease to psychological and cognitive problems to limitations in the ability to manage activities of everyday life. The CSHA Frailty Index is well-suited to be used in clinical studies except that it does take a lot of time. To increase its practicality for clinical use, the Frailty Scale was developed and validated using the CSHA Frailty Index and other established methods of measurement. The Frailty Scale is based on the idea that the examiner assesses the patient subjectively using a seven-point scale. It is helpful if the examiner is used to interacting with older patients. Both the CSHA Frailty Index and the CSHA Frailty Scale were presented by Rockwood et al. in a single publication (5). A German version of the CSHA Frailty Scale is available at www.prima-eds.eu (6).

Edmonton Frail Scale
The Edmonton Frail Scale, developed by Rolfson et al., claims to be easily usable by medical personnel with no special training in geriatrics. A total of ten domains are examined: cognitive function, mobility, functional independence, medication use, nutrition, social support, continence, burden of illness, mood, general health status, and quality of life (7).

The European Society of Anaesthesiology recommends the use of the Edmonton Frail Scale (2), but a limitation for its clinical use in Germany could be the lack to date of a validated German translation of this instrument.

Oldest description of frailty
The Fried phenotype is the oldest description of frailty and focuses on physical functions.

Other aids to assessment
Often additional aids are needed to reach an assessment of a patient’s frailty. These include tests to evaluate cognitive function. Depending on the approach taken, it is up to the examiner to select an appropriate instrument.
# Table 2

**LUCAS Function Index (U. Dapp et al. [8])**

<table>
<thead>
<tr>
<th>Marker question</th>
<th>Answer</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FRAIL risk 1</strong> Have you lost 5 kg or more over the past 6 months without trying to do so?</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td><strong>FRAIL risk 2</strong> Over the past 6 months, has the way you walk 1 km on foot changed for physical or health reasons?</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td><strong>FRAIL risk 3</strong> Over the past 12 months, has the way you walk up 10 steps changed for physical or health reasons?</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td><strong>FRAIL risk 4</strong> Over the past 12 months, has the way you get on or off a bus or train changed for physical or health reasons?</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td><strong>FRAIL risk 5</strong> On how many days during the past week were you out walking, outside of the home, for any reason?</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1–2 days/week</td>
<td>1</td>
</tr>
<tr>
<td><strong>FRAIL risk 6</strong> Have you had a fall at any time during the past 12 months?</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Subtotal, FRAIL markers (0–6)

| FIT resource 1 Do you ride a bicycle? | No, I never learned | 0 |
|                                     | No, I've stopped doing so                     |   |
|                                     | Yes, sometimes                                | 1 |
|                                     | Yes, regularly at least once a week            |   |

| FIT resource 2 On how many days during the past week were you out walking, outside of the home, for any reason? | None | 0 |
|                                                                 | 1–2 days/week                                  | 1 |
|                                                                 | 3–4 days/week                                  |   |
|                                                                 | 5–7 days/week                                  |   |
| FIT resource 3 Do you regularly take part at least once a week in moderate sport or exercise? | No | 0 |
|                                                                 | Yes: Strength training, e.g., aquarobics, using strength training equipment, TheraBand exercises | 1 |
|                                                                 | Yes: Balance training, e.g., cycling, tai chi, dance |   |
|                                                                 | Yes: Endurance training, e.g., walking in the grounds, going for walks, jogging, swimming |   |
| FIT resource 4 Do you regularly take part at least once a week in strenuous sport or exercise? | No | 0 |
|                                                                 | Yes: Strength training, e.g., circuit training on strength training equipment, bench presses | 1 |
|                                                                 | Yes: Balance training, e.g., competitive ballroom dancing |   |
|                                                                 | Yes: Endurance training, e.g., competitive circuit training on weight training apparatus, spinning |   |
| FIT resource 5 Do you do any voluntary work/volunteering at present? | No | 0 |
|                                                                 | Yes, part time                                 | 1 |
|                                                                 | Yes, full time                                 |   |
| FIT resource 6 Do you limit certain activities because you are afraid you will fall? | No | 0 |
|                                                                 | Yes                                          | 1 |

Subtotal, FIT markers (0–6)

<table>
<thead>
<tr>
<th>Classification as FIT, Pre-FRAIL, or FRAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 FRAIL markers</td>
</tr>
<tr>
<td>3–6 FRAIL markers</td>
</tr>
<tr>
<td>Pre-FRAIL</td>
</tr>
<tr>
<td>FIT</td>
</tr>
<tr>
<td>Pre-FRAIL</td>
</tr>
</tbody>
</table>

Note: The question, “Do you ride a bicycle?”, (FIT resource 1) may be replaced if appropriate (due to local physical geography or general absence of bicycling locally) by the question: “Can you walk 500 m by yourself unaided?”. However, the bicycling question has higher sensitivity in terms of identifying the first signs of frailty.
LUCAS Functional Index
In the Longitudinal Urban Cohort Age Study (LUCAS) in Hamburg, a functional index (LUCAS-FI) was developed (Table 2). The LUCAS-FI was conceived for use in general practitioners’ offices for patients not in need of care (≥ 60 years old); it uses a self-assessment questionnaire with 12 questions evaluating both the risks and the resources of the participant. The six questions relating to risk are based mainly on the Fried criteria, with the addition of the criterion “instability,” referring to the risk of fall in older patients. The questions about resources relate to physical and social activities and cognitive flexibility. On the basis of their pattern of risk and resource factors, patients are classified as “fit,” “pre-frail,” or “frail” (8).

Fried phenotype
Questions are asked about five criteria: unintended weight loss, exhaustion, weakness, slow walking speed, and low physical activity.

Edmonton Frail Scale
Ten domains are tested: cognitive function, mobility, functional independence, medication consumption, nutrition, social support, continence, burden of illness, mood, general state of health, and quality of life.

TABLE 3
Selected instruments for frailty assessment

<table>
<thead>
<tr>
<th>Frailty definition/assessment instrument</th>
<th>Categories</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Fried phenotype (4)                    | Five criteria:  
– Unintended weight loss  
– Exhaustion  
– Weakness  
– Slow walking speed  
– Low physical activity | Focuses primarily on the physical domain |
| CSHA Frailty Index (5)                  | Seventy items  
– Physical function  
– Cognition  
– Psychiatric illness  
– Ability to perform activities of daily life | Time-consuming |
| CSHA Frailty Scale (5)                  | Subjective assessment by the examiner  
Seven levels | |
| Edmonton Frail Scale (7)               | Ten domains  
– Cognition: Clock-drawing task  
– General state of health  
– Quality of life  
– Functional independence  
– Social support  
– Medication history  
– Nutrition  
– Mood  
– Continence  
– Mobility test: Timed Up and Go test | |
| LUCAS Functional Index (8)             | Questionnaire for the patient to fill out, consisting of 12 marker questions  
– Resources and risks  
– Classification into FIT/pre-FRAIL/FRAIL | |
| MAGIC (9)                              | Nine domains  
– Ability to perform activities of daily life  
– Vision  
– Hearing  
– Falls  
– Urinary incontinence  
– Depression  
– Social environment  
– Immunization status  
– Orientation test of cognitive function (clock test) | Two screening questions before the assessment:  
“Do you feel full of energy?”  
“Do you find it difficult to walk 400 m?”  
If the questions uncover any matter of concern, the MAGIC Assessment tool is used.  
Other optional contents:  
– Chronic pain  
– Vertigo  
– Mobility  
– Unintended weight loss  
– Medication check |
**Manageable Geriatric Assessment**

The guideline adopted by the German College of General Practitioners and Family Physicians (DEGAM, Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin), “Geriatric Assessment in General Practice” (9), recommends that patients aged 70 or older should first be screened using two preliminary questions relating to mobility and energy. This should allow the identification of frail or pre-frail patients who would benefit from further examination and possible interventions. If the screening questions reveal anything of concern, the Manageable Geriatric Assessment (MAGIC) is then used to investigate nine domains including performance in everyday activities and cognition. The screening questions and the internet URL of the MAGIC worksheet are given in the guideline itself.

**Frailty screening, assessment instruments**

Depending on the definition used, different assessment instruments are employed to assess patients for frailty. To assess mobility, often the grip strength test, the timed Up and Go test (e1), or the Sit to Stand test (e2) are required. The grip strength test requires a dynamometer, but the other two tests can be carried out in almost any environment – the only equipment required is a chair with (Up and Go test) or without arms (Sit to Stand test) and a stopwatch. However, these tests can be difficult to carry out especially in trauma patients. Table 3 shows a selection of frailty screening instruments.

Examples of tests of cognitive function are the MiniCog test (e3), the clock-drawing test (e4), the DemTect test (10), and the Mini-Mental State test (e5). While some frailty assessment instruments (e.g., Edmonton Frail Scale) stipulate a particular test for cognitive assessment, others leave evaluation of this point more open, formulating the characteristic simply as “cognitive impairment.”

The psychological domain is complex. Depression is a significant factor. According to a study from the Robert Koch Institute, about 7% of 60- to 69-year-olds and 6% of 70- to 79-year-olds in Germany have symptoms of depression (11). Options for assessing for the presence of a depressive syndrome are the Patient Health Questionnaire (PHQ) (e6), the Geriatric Depression Scale (GDS) (12), and the Hospital Anxiety and Depression Scale (HADS) (e7).

When it comes to evaluating the social situation of very elderly patients, the Nikolaus questionnaire can be used. This instrument is based on 27 questions aimed at obtaining information about interpersonal interactions, the patient’s home environment, and the patient’s financial situation (13).

It must be pointed out here that this article presents only a selection of possible assessment instruments. Although there is still no generally accepted definition of frailty, and therefore no standardized instrument for assessing it, even just assessing its individual elements does appear to be worthwhile. For example, grip strength results correlate with the risk of falling (frequency of falls increased as grip strength decreased in the study by Reis et al.; p<0.05) and with increased mortality (pooled hazard ratio [HR] 1.79 in the meta-analysis by Rijk et al. in the context of the baseline assessment; a HR of 0.96 was calculated for every kilogram of greater grip strength at baseline, indicating a reduction in mortality) (14, 15). Similarly, it has been shown that moderate to severe depression is associated with increased mortality after heart surgery (HR 2.4; 95% confidence interval [CI]: [1.4; 4.0]; p = 0.001) compared to mortality in the patient group without depression (16). That said, a multimodal assessment such as is provided by the Fried definition or the Edmonton Frail Scale is to be preferred if possible to individual assessment of separate components (according to the European Society of Anaesthesiology guideline) (2).

**Clinical significance of preoperative frailty screening**

Although there are different approaches to defining frailty, the goal is the same in all cases: to determine a predictive value relating to the perioperative risk for the individual patient. The point is to identify at-risk patients as early as possible so that individualized management decisions can be made. Data on the prevalence of frailty are of limited usefulness because of differences between the measuring methods that produce them. However, the literature indicates that between 26% and 56% of older patients undergoing surgery are to be regarded as frail (17). It is therefore imperative to understand the consequences of frailty syndrome.

A review article by Lin et al. included 23 studies investigating the relationship between frailty and postoperative outcome. A significant association was shown between frailty and increased 30-day, 90-day, and 1-year mortality; the occurrence of postoperative complications; and increased duration of hospital stay (18). The findings are exemplified by the very large study (N = 12 979) by Neuman et al. in older patients (>80 years old). In this study, frailty was the strongest predictor of 90-day mortality (odds ratio [OR]: 10.4;
Increased postoperative mortality and complications
Frailty is common and of clinical significance. It is associated with increased mortality and complication rates and with longer hospital stays.

But the significance of frailty is more than just medical. Frailty syndrome also has significant economic consequences. In one study of 235 patients undergoing heart surgery, additional treatment costs of over US$ 20,000 per case ([US$ 12,418; US$ 30,073]; \( p < 0.001 \)) were incurred for patients diagnosed as frail. In seven cases the total costs amounted to over US$ 100,000—all of these patients, without exception, were frail (21).

Implications of a frailty assessment
The identification of frailty should impact clinical actions. Throughout the perioperative management process, a variety of interventions exist that can help to optimize postoperative outcome.

Prehabilitation
The time while the patient is waiting for surgery can be put to good use by a “prehabilitation” program aimed at improving his or her functional status. The idea behind prehabilitation is for the patient to follow an individually tailored program of physical exercise during the preoperative period. In 2017, the Deutsches Ärzteblatt published an article on this subject, “Getting fit for surgery” (22). The aim is to improve the patient’s physical condition and thus to lay a better foundation for surgery and the regenerative processes that follow. Published results on the benefits of prehabilitation do not yet give a clear picture. Great differences exist between studies in terms of patient groups, the interventions used, and the variations in the amount of time available preoperatively, making clarity harder to achieve. Preoperative nutritional supplementation is often included in a multimodal prehabilitation concept (23). In the study by Minnella et al., a multimodal approach to prehabilitation led to improved physical condition at 8 weeks after surgery, as measured by 6-minute walking test results, compared to a control group. The control group was given the same rehabilitation program as the treatment group but only after surgery (17.0 ± 84.0 m versus –8.8 ± 74.0 m change from baseline 6-minute walking test before surgery, \( p = 0.047 \)). The multimodal prehabilitation program consisted of physical exercises, nutritional supplementation, and anxiety management strategies (24).

For prehabilitation to be carried out efficiently in future, organizational structures must be set up to allow this to happen. Preadmission or day clinics might be possible ways of doing this. However, exercises can also be carried out at home (Figure).
Correcting malnutrition
Malnutrition is often a problem among the older population. In acute hospitals, 35% to 56% of older patients admitted as inpatients show signs of malnutrition; in geriatrics departments, the figure can be as high as 60% (25). A variety of questionnaires are available for use as screening instruments. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends using the Mini Nutritional Assessment (MNA) tool (26, 27). As part of Nutrition Day, a worldwide survey of the nutritional situation in hospitals and care homes, inadequate food intake was identified as an independent risk factor for hospital mortality (food intake during the previous week lower than “normal” showed increased mortality with HR between 1.54 and 2.01, \( p<0.01 \); BMI below 18.5 kg/m²; HR 1.46 ([1.12; 1.91], \( p<0.01 \)) (28).

In addition, during the preoperative preparation period, minimal fasting times are of importance. The relevant guideline here is that of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI, Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin): solid food may be taken up to 6 hours before surgery and clear fluids up to 2 hours before surgery (29). The Enhanced Recovery After Surgery (ERAS) program incorporates a perioperative nutritional strategy that accords with the ESPEN guideline (30). This program also stipulates ensuring the rapid supply of adequate nutrition postoperatively by means of enteral or parenteral nutrition if oral intake is not high enough.

Prevention of delirium
Postoperative delirium (POD) is associated with increased mortality (reported odds ratios lie between 1.5 and 6.66 [31–34]) and with a longer hospital stay. Frailty is regarded as a predisposing factor for the development of POD. The guideline of the European Society of Anaesthesiology (ESA) gives an overview of recognized risk factors, from which it derives recommendations for the prevention and treatment of POD (35). Indiscriminate administration of benzodiazepines for premedication should be avoided—a recommendation also adopted in the DGAI’s “Smart decision making” (“Klug entscheiden”) initiative (36). In connection with delirium prevention, the use of EEG to monitor the depth of anesthesia and avoid deep anesthesia is advised, since, especially in older patients with their altered metabolism, drug effects can vary greatly. Appropriate postoperative pain management is also important. In addition, standardized early and repeated screening for delirium is essential (35). However, it should be mentioned here that at present there are no reliable data to show that improving frailty status before surgery does in fact lower the rate of POD.

Intraoperative management
Particular care needs to be taken with frail patients in the intraoperative situation. Special attention should be paid to altered pharmacokinetics and pharmacodynamics caused by these patients’ reduced physiological reserves (37). Short-acting substances that are eliminated organ-independently are advantageous for managing anesthesia. Neuromuscular monitoring allows the effect of muscle relaxants to be tested if necessary in order to rule out any residual effect before extubation (38). Although to date no universally agreed recommendation has been reached on particular intraoperative treatment methods in relation to frail patients, identifying frailty does help surgeons to make decisions for or against the use of such methods.

Interdisciplinary collaboration
Frailty is a complex concept and the disease processes associated with it are likewise complex. Managing frail patients appropriately requires a variety of approaches deriving from surgical, anesthesiological, geriatric, general medical, nutritional, physiotherapeutic, and pharmacological considerations. Ideally, the assessment of frailty and implementation of preventive measures will start in the primary care physician’s office, but at any rate no later than during the period of preoperative diagnosis and treatment at the hospital. If frail patients are to be cared for in a properly targeted manner, the most important thing is collaboration between the medical disciplines. In a randomized, controlled study of just under 400 patients undergoing treatment for hip fracture, Prestmo et al. showed that, after 12 months, patients being cared for in a special “orthogeriatric” ward had significantly better results for mobility (Short Physical Performance Battery scores 5.3 versus 4.61, \( p<0.05 \)), activities of daily living (Barthel Index 16.46 versus 15.33, \( p<0.001 \); Nottingham Extended ADL Scale 35.20 versus 28.81, \( p = 0.001 \)), and quality of life (EuroQol-5D-3L 0.52 versus 0.45, \( p<0.05 \)) than those in ordinary wards (39). Close collaboration should therefore play an important role in treatment.

Summary
Identifying frailty syndrome in a patient creates an opportunity during routine clinical practice to identify at-risk patients before surgery. Because there is currently no agreed definition of frailty, it is difficult to
Interdisciplinary collaboration
Interdisciplinary collaboration is essential for appropriate care of frail patients.

Summary
Further scientific study is needed to develop a standardized concept of frailty and thus enable appropriate decisions to be made in the management of the individual patient.

References


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► Supplementary material
For eReferences please refer to:
www.aerzteblatt-international.de/ref0519

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**Question 1**
Which patients should be described as frail?

a) Those who are aged 65 or older  
b) Those living in a care home  
c) Those with reduced physiological reserves and increased vulnerability to stress factors  
d) Those with more than five diagnosed conditions  
e) Those who have experienced great misfortune during their life

**Question 2**
Which of the following criteria does the Fried phenotype take into account when classifying patients according to the Frailty Index?

a) Unintended weight loss  
b) Anemia  
c) Cognitive impairment  
d) Social isolation  
e) Incontinence

**Question 3**
Which frailty assessment instrument takes into account both patients’ risks and their resources?

a) Fried phenotype  
b) CSHA Frailty Index  
c) CSHA Frailty Scale  
d) Edmonton Frail Scale  
e) LUCAS Functional Index

**Question 4**
Which of the following abilities is taken into account in the Edmonton Frail Scale?

a) Communication  
b) Leadership quality  
c) Creativity  
d) Continence  
e) Rhetoric

**Question 5**
Which instrument is recommended by the ESPEN guideline for assessment of malnutrition in the older population?

a) Nutrition and Ability 2005 (NA2005)  
b) Mini Nutritional Assessment (MNA)  
c) Nutrition Short Screening (NSS)  
d) Vitamin and Nutritional Screening (VNS)  
e) Canadian Nutrition Self-Assessment (CNSA)

**Question 6**
According to the German Society of Anaesthesiology and Intensive Care Medicine (DGAI, Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin), what are the current preoperative fasting times to be adhered to by adults?

a) 10 hours for solid food and 4 hours for clear fluids  
b) 6 hours for solid food and 4 hours for clear fluids  
c) 4 hours for solid food and 4 hours for clear fluids  
d) 6 hours for solid food and 2 hours for clear fluids  
e) 10 hours for solid food and 2 hours for clear fluids

**Question 7**
How high is the incidence of malnutrition among older patients in acute hospitals?

a) 0.05% to 2%  
b) 5% to 10%  
c) 15% to 25%  
d) 35% to 56%  
e) 60% to 70%

**Question 8**
What is the aim of prehabilitation?

a) Early planning of rehabilitation  
b) Accustomizing the patient to the hospital stay  
c) Optimizing physical fitness before surgery  
d) Reducing the depression rate  
e) Pharmacological therapy

**Question 9**
According to studies, for which of the following conditions is frailty a risk factor?

a) Postoperative delirium  
b) Breast cancer  
c) Schizophrenia  
d) Tuberous sclerosis  
e) APC resistance

**Question 10**
What action should follow when a patient is identified as frail?

a) Cancel surgery  
b) Create an interdisciplinary management plan  
c) Carry out surgery as soon as possible  
d) Plan for a postoperative stay in intensive care  
e) Motivate the patient to lose weight

► Participation is possible only via the Internet: cme.aerzteblatt.de
Supplementary material to:

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