Enhanced recovery and Patient Blood Management in colorectal surgery: the Italian ColoRectal Anastomotic Leakage study group (iCral 4).

Titolo della sperimentazione: **Protocolli di guarigione potenziata e di gestione del sangue in chirurgia colorettale: gruppo di studio italiano sulla deiscenza anastomotica colorettale (iCral4).**

Tipologia dello studio: **Osservazionale prospettico, multicentrico, no profit**

Codice Protocollo, versione e data: **iCral4, versione 1.2 del 20/01/2022**

Registrazione: **NCT05227014; ClinicalTrials.gov – NIH – US National Library of Medicine**

Promotore della sperimentazione**: Italian ColoRectal Anastomotic Leakage (iCral) study group, c/o UOC Chirurgia Generale – Ospedale Sandro Pertini – ASL Roma 2**

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BACKGROUND

The ultimate goal of any surgery is to return the patient to his baseline functional status, if not an improved one, as rapidly as possible and with the least amount of intercurrent disability. Enhanced Recovery After Surgery (ERAS) is a multimodal and multifactorial approach to the optimization of perioperative management (1, 2). In order to modify and improve the response to surgery-induced trauma, the program relies on a series of evidence-based items related to pre-, intra- and post-operative care (3).

Preoperative anemia is a contraindication to elective surgery. Nonetheless, it is very common, affecting up to 39% of patients candidate to general surgery (4, 5), 34% to non-cardiac surgery (6), 33% to vascular surgery (7), 26% to cardiac surgery (8), and 24% to gynecological surgery (9). Logically, it is the strongest predictor of blood transfusions (five-fold) in the post-operative period (5) and it is associated to several risks and morbidity (10, 11), such as infections (two-fold) and kidney injury (four-fold), as well as a 22% longer hospital stay (4). More importantly, peri-operative anemia is now recognized as strongly and independently related to post-operative mortality (adjusted odd ratio 2.36), also besides blood transfusions (4, 5). Post-operative anemia regards up to 90% of patients after major surgery (6). The main recognized causes are: pre-operative anemia,

peri-operative blood loss, poor nutritional intake in the post-operative period, frequent blood sampling for laboratory tests, and increased hepcidin due to inflammatory response to surgery (6). These effects can last for a few weeks after major surgery and aggravate post-operative iron deficiency anemia (6). The immediate and most widely used treatment for post-operative anemia is blood transfusion. Blood transfusions carry several complications, culminating in a high incidence of morbidity and mortality (12-15). In particular, they are related to increased length of hospital stay and rate of discharge to an inpatient facility, worse surgical and medical outcomes, allergic reactions, transfusion-related acute lung injury, volemic overload, venous thromboembolism, graft versus host disease, immunosuppression, and post-operative infections. In addition, blood transfusions are responsible of an increased burden on the health care system (12-15). Two previous prospective studies of the Italian ColoRectal Anastomotic Leakage (iCral) study group (15, 16) identified intra- and post-operative blood transfusions as an independent factor with negative influence on all early outcomes after colorectal surgery (Tab. 1). In particular, they resulted as a major independent determinant of anastomotic leakage (Fig. 1).

	Odds Ratios			
Variable	Overall morbidity	Major morbidity	Mortality	Leakage
Perioperative transfusions	19.33	10.17	3.71	8.15
ASA class > II	1.57	---	---	---
Procedure length > 180’	---	1.11	---	---
Age > 70 years	---	---	1.16	---

Tab. 1: Odds ratios for early outcomes in more than 1,500 patients enrolled in iCral1 prospective study (15).

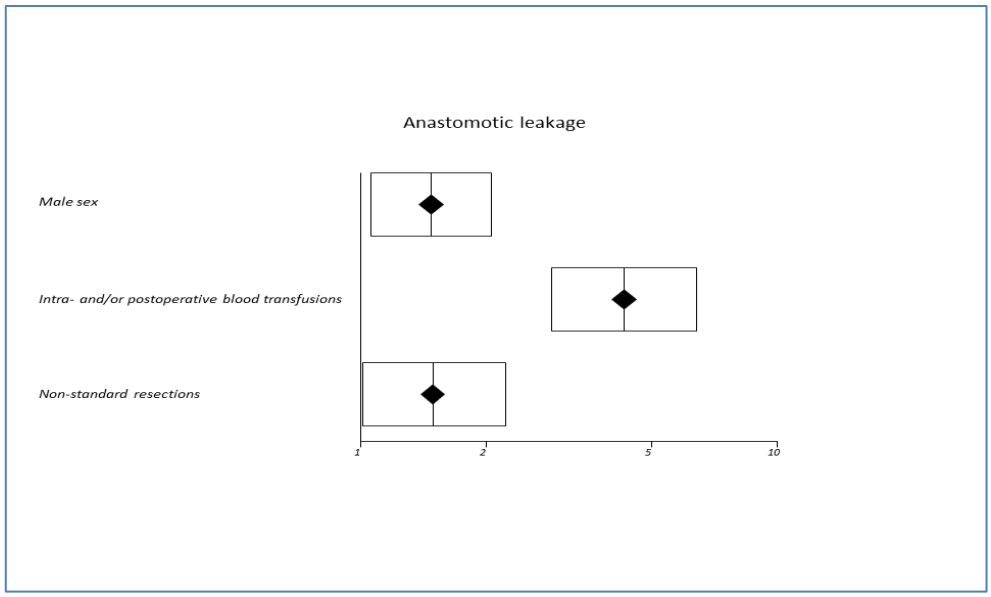

Fig. 1: Independent variables for anastomotic leakage in 3,830 patients enrolled in iCral2 prospective study (16).

The mechanisms by which blood transfusions worsen outcomes are still ill-defined. Erythrocyte transfusion results in transfusion-induced immunomodulation (TRIM) because of the infusion of cytokines, lipids, and other soluble bioactive substances, most likely because of allogenic leukocytes (17). Immunomodulation may lead to immune activation, resulting in transfusion-related lung injury or immune suppression, increasing susceptibility to infectious complications. Furthermore, erythrocyte storage leads to decreases in cellular deformability and increased adhesion to the vascular endothelium, resulting in impaired microvascular flow and decreased oxygen delivery: the transfusion of “older” (e.g. stored for > 35 days) packed red blood cells (PRBCs) was demonstrated to be significantly more detrimental than transfusion of “fresh” (e.g. stored for ≤ 35 days) PRBCs (18). Another mechanism of action could be mediated by enhancement of systemic inflammatory response (19). It remains difficult, if possible at all, to establish how much blood transfusion is a marker for “bad performers” (e.g. patients with severe blood loss and/or severe comorbidities) or how much it has a direct action on postoperative adverse events, but, as a wide

variability of perioperative transfusion practices in surgical units is still present (20), this topic deserves further clinical investigation.

In recent years, various strategies have been studied to reduce the use of blood transfusions to prevent transfusion-related adverse events, increase patient safety, and reduce costs. As a consequence, a new concept was born: the patient blood management (PBM). According to the World Health Organization (WHO), PBM is defined as the timely application of evidence-based medical and surgical concepts designed to maintain a patient's hemoglobin (Hb) concentration, optimize hemostasis and minimize blood loss in an effort to improve the outcomes. More in detail, PBM focuses on three pillars (21-27):

- optimizing red cell mass;
- minimizing blood loss and bleeding;
- optimizing tolerance of anemia.

The implementation of the three pillars of PBM leads to improved patient' outcomes by relying on his/her own blood rather than on that of a donor. PBM goes beyond the concept of appropriate use of blood products, because it precedes and strongly reduces the use of transfusions by correcting modifiable risk factors long before a transfusion may even be considered (21-27). Importantly, the PBM is transversal to diseases, procedures and disciplines. It is solely aimed at managing a patient's resource (i.e., his/her blood), shifting the attention from the blood component to the patient himself/herself.

The recent and growing interest in PBM is principally driven by its notable impact on several outcomes (26). According to different studies PBM is able to reduce mortality up to 68%, reoperation up to 43%, readmissions up to 43%, composite morbidity up to 41%, infection rate up to 80%, average length of stay by 16 to 33%, transfusion from 10% to 95%, and costs from 10% to

84% (dependently from the healthcare system) (27). Consistently, from patient's safety and better outcomes, the PBM achieves the aim of costs saving and fast-track policies adoption, satisfying some key performance indicators. In this sense, there clearly appears to be an extraordinary similitude between ERAS and PBM programs: they are both multidisciplinary and multifactorial, both centered on the patient, embracing the entire perioperative period, both evidence-based, both offering measurable positive influence on early outcomes after surgery. Actually, most recent guidelines on ERAS programs in colorectal surgery (28, 29) include preoperative anemia management in their suggested items. Finally, although the available evidence strongly suggests that the adoption of ERAS and PBM programs may lead to a significant improvement of outcomes, there still are no studies investigating the effects of adherence to the two programs. Therefore, the Italian ColoRectal Anastomotic Leakage (iCral) study group decided to design this prospective study.

METHODS

Prospective enrollment from July 2022 to June 2023 in 100 Italian surgical centers. All patients undergoing elective or delayed urgency colorectal surgery with anastomosis will be included in a prospective database after written informed consent. A total of 5,000 patients is expected based on a mean of 50 cases per center.

Inclusion criteria

1. Patients submitted to laparoscopic/robotic/open/converted ileo-colo-rectal resection with anastomosis, including planned Hartmann's reversals.
2. American Society of Anesthesiologists' (ASA) class I, II, III or IV
3. Elective or delayed urgency (> 24 hours from admission) surgery
4. Patients' written acceptance to be included in the study.

Exclusion criteria

1. American Society of Anesthesiologists' (ASA) class V
2. Emergent surgery (≤ 24 hours from admission)
3. Pregnancy
4. Hyperthermic intraperitoneal chemotherapy for carcinomatosis.

Outcome measures

1. Preoperative risk factors for morbidity (age, gender, obesity, nutritional status, diabetes, cardiovascular disease, chronic liver disease, renal failure, inflammatory bowel disease, perioperative steroid therapy, ASA class, SARS-CoV-2 infection)
2. Operative parameters (approach, procedure, anastomotic technique, length of operation, pTNM stage)
3. Adherence to ERAS program items (Tab.2).
4. Adherence to PBM program items (Tab. 3)

Endpoints

<u>Primary</u>

1. Anastomotic leakage rate
2. Major morbidity rate *[any adverse event grade > II according to Clavien-Dindo (30, 31) and JCOG (32) classification]*
3. Postoperative hemoglobin values on postoperative day (POD) 4, at discharge (if different from POD4) and 6 to 8 weeks after surgery

<u>Secondary</u>

4. Overall morbidity *[any adverse event according to Clavien-Dindo (30, 31) and JCOG (32) classification]*

5. Number of transfused blood units
6. Overall length of postoperative hospital stay (including any readmission)
7. Difference between date of readiness for discharge (RFD, 33) and date of actual discharge
8. Readmission and reoperation rates
9. Patient-related outcomes measures (PROMs):
    a. Euro-QoL Group EQ-5D-5L (EQ-5D-5L, 34);
    b. MD Anderson Symptom Inventory for gastrointestinal surgery patients (MDASI-GI, 35);
    c. Functional Assessment of Cancer Therapy – Colorectal (FACT-C, 36)
10. Return to intended oncologic therapy (RIOT, 37)
11. Impact of anastomotic testing through air-leak test (ALT) and near-infrared fluorescence (NIR) narrow-band imaging (NBI) using indocyanine green (ICG) on anastomotic leakage rates

Recorded data and follow-up

Potential patient-specific and intraoperative risk factors will be recorded: gender, body mass index, nutritional status, frailty (38), surgical indication (cancer, polyps, chronic inflammatory bowel disease, diverticular disease), use of steroids, renal failure and dialysis, cardiovascular or respiratory disease, American Society of Anesthesiologist class, bowel preparation, type of approach, level of anastomosis and technique (mechanical or hand-sewn, intra- or extra-corporeal), operative time, presence of drainage. Any perioperative blood transfusion(s) will be recorded, together with the age of the blood product transfused. During the postoperative period, patients will be examined by the attending surgeon daily. Fever (central temperature > 38 °C), pulse, abdominal signs, bowel movements, volume and aspect of drainage (if present) will be recorded daily. The local attending

surgeon will make any decision for complementary exams and imaging according to his own criteria, the only exception being the creation of a proximal diverting stoma at operation, that mandates routine check of anastomotic integrity through an intraluminal contrast exam (standard x-rays or CT scan), MRI, or direct endoscopic evaluation three to six weeks after the operation. The rate of any adverse event will be calculated and graded according to Clavien-Dindo criteria (30, 31) and to Japan Clinical Oncology Group Postoperative Complications (JCOG-PC) extended criteria (32), including all anastomotic leaks, wound infection (according to the definitions of the Centers for Disease Control and Prevention and wound culture, 39), pneumonia (clinical symptoms, and physical and radiological examinations), central line infection (positive blood culture), urinary tract infection (positive urine culture with bacterial count). Patients will be followed-up in the outpatient clinic up to 8 weeks after discharge from the hospital. A long-term follow-up extended to 5 years after surgery is planned for patients operated for malignancy.

Anastomotic dehiscence (any deviation from the planned postoperative course related to the anastomosis, or presence of pus or enteric contents within the drains, presence of abdominal or pelvic collection in the area of the anastomosis on postoperative CT scan, leakage of contrast through the anastomosis during enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis) will be defined and graded according to international consensus guidelines (40, 41). Anastomotic testing will be performed intraoperatively with the air-leak test (ALT) and using ICG-NIR-NBI with a standard protocol *[ICG 25 mg diluted in 10 mL water (2.5 mg/mL); first bolus i.v. injection of 4 mL (10 mg) after vascular control and mesenteric division, just before proximal and/or distal bowel division; second bolus i.v. injection of 4 mL (10 mg) just before joining anastomotic stumps; third (optional) bolus i.v. injection of 2 mL (5 mg) after the anastomosis is completed; NIR-NBI observation within 120-180" after every ICG injection (direct, laparoscopic or endoscopic)].*

Anemia screening according to PBM program will be performed four to one weeks before the scheduled operation, and repeated routinely on POD 1 and on POD 4. If on POD 4 the patient is deemed non-anemic (Hb ≥ 120 g/L for women and ≥ 130 g/L for men, according to WHO criteria), the next anemia screening is scheduled at discharge (if different from POD 4) and 6 weeks after surgery, whereas, if anemic, the patient is treated and rescreened until necessary.

PROM questionnaires (34-36) will be administered to all enrolled patients four to one week before the planned operation, at discharge, and 6 to 8 weeks after the operation.

RIOT (37) rates will be recorded in all patients submitted to surgery for malignancy, according to national guidelines for colorectal cancer (42).

After anonymization, all data of each single case will be prospectively uploaded by local investigator(s) on a web-based database, protected by individual access credentials, and incorporated into a spreadsheet for data analysis. Any eventual discrepancy and/or mismatch will be checked, addressed and solved through strict cooperation between coordinating and local investigators.

Ethics and dissemination

The study will be conducted according to the Helsinki declaration and to the Guideline for good clinical practice E6(R2) principles. This study protocol received the scientific patronage of the Associazione Chirurghi Ospedalieri Italiani (ACOI), Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva (SIAARTI) and Società Italiana di Emaferesi e Manipolazione cellulare (SIdEM); it was registered at ClinicalTrials.gov (NCT05227014) and will be submitted to the coordinating center ethics committee (Comitato Etico “Lazio 2”) for approval. Thereafter, all the participating centers will obtain authorization to participate from their local institutional review board. The results of the study are intended to be presented at national and international medical

congresses on corresponding fields of interest (colorectal surgery, abdominal surgery, transfusion medicine). Written publications of the results are planned within medical and surgical journals. The authorship for written publications is confirmed to all participating investigators in the case of substantive contributions to the design, conduct, data analysis, collection and interpretation. Anonymized participant-level datasets will be available after study completion upon reasonable request by contacting the principal investigator.

Statistical Analysis

Quantitative values will be expressed as mean ± standard deviation (SD), median and range; categorical data with percentage frequencies. For categorical data, analysis will include the use of cross tabulation, chi squared or Fisher's exact test where indicated. Continues or discrete variables will be analyzed using Student's two-sided t test (allowing for heterogeneity of variances) or with a non-parametric test (Mann-Whitney U test or Kruskal-Wallis test as indicated). Joint and conditional multivariate association between all variables shown to be significant on univariate analysis will be assessed using binary logistic or multiple linear regression. The odds ratio (OR) will be presented followed by 95% confidence interval (95% CI). For all statistical tests the significant level is fixed at $p < .05$. Statistical analyses will be carried out using STATA software (Stata Corp. College Station, Texas, USA).

Sample size assessment

In iCral2 prospective study (16), anastomotic leakage rates were 15.2%, or 37 out of 256 patients receiving intra- and/or postoperative blood transfusions, versus 3.4%, or 122 out of 3,574 patients not receiving any transfusion. Assuming that adherence to a PBM program could lead to at least 50% reduction of perioperative blood transfusions (43, 44), considering alpha at 0.04, beta at 0.95, the required sample size is n=2,025 (81 cases with perioperative transfusions and 1944 without), according to the following scheme: *Independent cohort study; Probability of event: control group = 0.034; experimental group = 0.152; Controls per case subject = 24; Alpha = 0.04; Power = 0.95; for corrected chi-square and Fisher's exact tests: N = 81 case subjects and 1,944 controls*

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Marco Catarci, MD, FACS; iCral study group coordinator; Chief investigator

Acronyms

- ACD: Anemia of chronic disease
- ALT: Air leak test
- ASA: American Society of Anesthesiologists
- AUC: Anemia of unknown cause
- CKD: Chronic kidney disease
- CRP: C-reactive protein;
- EQ-5D-5L: Euro-QoL Group EQ-5D-5L
- ERAS: Enhanced Recovery after Surgery
- FACT-C: Functional Assessment of Cancer Therapy – Colorectal
- FCM: Ferric carboxymaltose
- FID: functional iron deficiency
- Ft: Ferritin
- Hb: Hemoglobin
- ICG: indocyanine green
- ID: iron deficiency
- IDA: Iron deficiency anemia
- JCOG: Japan Clinical Oncology Group
- JCOG-PC: Japan Clinical Oncology Group - Postoperative Complications
- MCH: Mean corpuscular hemoglobin
- MCV: Mean corpuscular volume
- MDASI-GI: MD Anderson Symptom Inventory for gastrointestinal surgery patients
- MNA-SF: mini nutritional assessment – short form
- MRI: magnetic resonance imaging
- NBI: narrow-band imaging
- NIR: near-infrared
- PBM: patient blood management
- PNI: prognostic nutritional index
- PROs: patient-reported outcomes
- PROMs: patient-reported outcomes measures
- RFD: readyness for discharge
- RIOT: return to intended oncologic therapy
- TID: total iron deficiency
- TSAT: Transferrin saturation

Tab. 2: Definition of adherence to ERAS program items (28, 29).

	ITEM	Adherence criteria
Preoperative	Nutritional status screening	Patient submitted to nutritional screening through Mini Nutritional Assessment Short Form (MNA-SF) and Prognostic Nutritional Index (PNI)
	Nutritional Prehabilitation	All patients showing MNA-SF ≤ 11 (malnourished or suspect for malnutrition) and BMI > 30 (obesity) receive specific nutritional consultation
	Physical Prehabilitation	Patient receives a standard protocol of physical activity to be accomplished in the preoperative period; frail and limited motility patients are submitted to specific geriatrician/physiatrist consultation and personalized activity program
	Psychologic Prehabilitation	Patient and his familiars/caregivers are screened regarding any psychologic concern; in case of anxiety/depression upon diagnosis and related procedure, psychologic consultation is warranted
	Counseling	Patient and his familiars/caregivers receive full information and suggestions regarding perioperative program from surgeon, anesthesiologist and case-manager
	Preoperative Immunonutrition	Patient is administered Impact Oral ™ (Nestlè Health Science, Italy) 330 ml per os, three briks per day during 5 days preceding surgery or two bricks per day during 7 days preceding surgery
	Management of anemia	Please refer to the PBM section (Tab. 3)
	Antithrombotic prophylaxis	Patient receives graduate compression stockings and/or pneumatic compression device, together with prophylaxis with low molecular weight heparin during the perioperative period, to be extended up to 28 days after surgery in case of malignancy
	Antibiotic prophylaxis	Patient is administered i.v. antibiotic 30 to 60 minutes before incision, according to local protocols
	No bowel preparation	No routine bowel preparation is used, except in case of anticipated need for covering stoma
	Oral carbohydrates load	Carbohydrates rich beverage (12.5% maltrodextrins, PreOp™, Nutricia Italy) is given preoperatively (800 ml on the evening before surgery and 400 ml 2 to 3 hours before surgery)
	Preoperative fasting	Preoperative fasting is limited to two hours for clear liquids (water, coffee, tea) and to 6 hours for milk and solid food
Intraoperative	No premedication	No long- or medium-action sedatives. Short and ultra-short acting sedatives (e.g. Lorazepam, Midazolam, Methohexital, Dexmedetomidine, Ketamine) are allowed before performing spinal, epidural or loco-regional anesthesia
	PONV prophylaxis	Postoperative nausea/vomiting prophylaxis is administered according to individual risk assessment (Apfel score) through a multimodal approach
	Normothermia	Body temperature is monitored during surgery, utilizing fluid warmers and/or thermic blankets as necessary
	Standard anesthetic protocol	General anesthesia through short-acting anesthetics, cerebral activity monitoring to enhance recovery and to reduce postoperative delirium, anesthesia level monitoring and complete reversal of neuromuscular blockade
	Intraoperative fluid management	Restrictive fluid therapy (defined as maintenance fluids at <2 ml/kg/h) or goal-oriented fluid therapy (stroke volume)
	Multimodal analgesia	Use of more than two drugs or analgesia strategies (TAP-block or spinal anesthesia for minimally invasive surgery; thoracic epidural anesthesia for open surgery) in order to reduce the use of opiates
	Minimally invasive surgery	Patient submitted to laparoscopic, robotic or video-assisted surgery (conversions to open surgery included on a intention-to-treat basis)
Postoperative	No major opiates	Patient receives no major opiates in the postoperative period
	No nasogastric tube	Nasogastric tube, if used, is removed at the end of surgery
	No drain	No drain is placed in the abdominal cavity (pelvic drain allowed for pelvic surgery with low colorectal anastomosis)
	Bladdder catheter	Urinary catheter removed on POD 1 (up to POD 2 in case of pelvic surgery)
	Early mobilization	Patient receives passive mobilization on POD 0, active mobilization on POD 1
	Early oral feeding	Patient receives liquid oral diet starting 6 hours after surgery and semisolid diet starting on POD 1
	Pre-discharge check	Patient is checked just before discharge at home concerning adequate oral intake, bowel function, adequate pain control, active mobilization, no clinical/serological evidence of any postoperative complication, full agreement to go home
	Audit	All data regarding patients included in the program are reviewed by the local investigator(s) before uploading into the database; any adverse event is reviewed and discussed

Tab. 3: Definition of adherence to PBM program items (45-57).

N	Item	Adherence criteria
1	Patient Blood Management expert group	Hospital should have an agreed protocol between surgical, anaesthetic and transfusion teams for Patient Blood Management
2	Preoperative anemia screening	Each patient is submitted to evaluation of Hb levels, hematocrit, erythrocyte indices, full blood cells counts (including reticulocytes) body iron store (serum ferritin), iron availability (transferrin, transferrin saturation) and level of inflammation (C-reactive protein) within three to four weeks before surgery. Patient is declared anemic if Hb <120 g/L (females) or <130 g/L (males), according to the WHO criteria. Should anemia not be explained by initial work-up, further testing should include vitamin B12 and folic acid, haptoglobin, lactate dehydrogenase, and serum creatinine. The goal of preoperative anemia management should be the normalization of the Hb levels, in accordance with World Health Organization criteria.
3	Preoperative anemia management	The preoperative management of anemia varies according to its etiology. Please refer to **Figg.2-4** below.
4	Preoperative correction of iron-deficiency	Iron Deficiency Anemia (IDA) and Functional Iron Deficiency (FID) with Iron Deficiency (ID) are the most frequent types of anemia in candidates to major abdominal surgery. Iron supplementation is of paramount importance in this context, and should be administered upon the estimated total iron deficiency taking into account the amount of iron needed to restore normal Hb levels and to replenish iron stores. Anticipation of estimated iron loss due to ongoing chronic bleeding and perioperative blood loss should be also taken into account. Iron supplementation, with or without an erythropoiesis stimulating agent (ESA), should be administered preferably two to four weeks prior the scheduled procedure. Intravenous iron if oral iron is not tolerated or if surgery <4–6 weeks is preferable. Where possible, it should be administered using a single high-dose iron preparation for the repletion of iron stores.
5	Extended diagnostic of anemia for other etiology	If preoperative anemia does not fall into IDA, FID and/or ID, an hematology specialist should be involved into consultation
6	Timing of surgery	Elective surgery should be postponed until preoperative anemia has been classified and treated, whenever possible
7	Hemorragic risk screening	A careful personal and familiar medical history is recommended, aimed at detecting any bleeding risk, information on current drug therapy or on the intake of over-the-counter or herbal products, because it is considered more indicative of the risk of perioperative bleeding compared to the isolated evaluation of coagulation test results of preoperative screening. Should any history of perioperative bleeding be present, consultation with an expert in hemostasis and thrombosis is warranted. Antiplatelet and anticoagulant drugs should be withheld before surgery according to the following points.
7bis	Aminosalycilic Acid (ASA)	• If administered in primary prevention, ASA should be suspended 7 days before elective surgery, • If it is assumed in secondary prevention (in a patient with a previous cardiovascular episode), ASA should be continued also in the peri-operative period at a dosage of 100 mg / day.
7ter	Antiplatelet drugs	Clopidogrel and Plasugrel should be suspended 5 to 7 days before the operation, while Ticagrelor should be suspended 5 days before the procedure. Ticlopidine should be suspended 10 days before the procedure.
7quater	Acute/chronic coronary syndrome	Patients with acute coronary syndrome or previously submitted to coronary angioplasty (with stent implantation) benefit of the combination of ASA with another antiplatelet drug (thienopyridine or ticagrelor), also if this increases the risk of bleeding complications. Any decision concerning the continuation of treatment with antiplatelet agents in the peri-operative period should be the result of a multidisciplinary evaluation involving a cardiology specialist.
7penta	Anti-Vitamin K (AVK) drugs	• In patients with low / medium thromboembolic risk, it is suggested to discontinue therapy with AVK 5 days prior to elective surgery and to set up the bridging therapy [administering prophylactic low molecular weight heparin (LMWH)] according to the following scheme: last dose of the drug 5 days before surgery (-5); first subcutaneous dose of LMWH for once a day, starting on day - 4, if being treated with acenocoumarol, starting from day - 3 if, on the other hand, being treated with warfarin. • In patients at high thromboembolic risk (with AF and CHADS2 score> 2; with recurrent VTE treated for less than 3 months; with mechanical valve replacements) bridging therapy is recommended (administering LMWH in therapeutic dosage) according to the following scheme: last dose of the drug per day - 5; first dose LMWH twice daily starting on day - 4, if being treated with acenocoumarol, starting on day - 3, if being treated with warfarin. Last dose of LMWH at least 12 to 24 hours before surgery.
7esa	New Oral Anticoagulants (NOAs)	NOAs should be withheld 48 hours prior to elective surgery in patients with normal renal function (creatinine clearance, CCr ≥ 80 mL / minute). No bridging with LMWH is required. In case of impaired renal function, intervals remain the same for Apixaban and Rivaroxaban, while the intervals for Dabigatran should be as it follows: CCr 50-80 mL/minute: 72 hours; 30-50 mL/minute: 96 hours.

7epta	Coagulation disorders	Therapy for patients with disorders of haemostasis, either congenital or associated with systemic, metabolic or endocrine diseases, should be established through consultation with an expert in hemostasis and thrombosis
8	Reduction of surgery-related blood loss	• Minimally invasive surgery with ultrasonic or advanced bipolar instruments whenever possible • Free use of topic hemostatic adjuncts on raw surfaces (i.e. fibrin glue, thrombin matrix gel, hemostatic patch) • Intraoperative autologous blood collection and retransfusion (cell salvage) if expected blood loss > 500 mL through radiation/filtering of washed blood using leukocyte depletion filters for oncological procedures
9	Postoperative anemia screening	All patients submitted to major surgery (defined as blood loss > 500 ml or lasting > 2 h) and who had pre-operative anemia or moderate-to-severe blood loss during surgery must be screened for anemia after surgery. During recovery from uncomplicated major surgery, haemoglobin concentrations should be monitored, either by standard laboratory or point-of-care testing, on a regular daily basis, at least until the fourth postoperative day, to detect anemia (haemoglobin < 130 g/L for men, < 120 g/L for women). Postoperatively, iron deficiency should be defined by ferritin concentration < 100 µg/L, ferritin < 100–300 µg/L and transferrin saturation < 20%, or reticulocyte haemoglobin content < 28 pg. High blood loss during surgery may also indicate the need for iron replacement in anemic patients.
10	Limitation of iatrogenic blood loss	• Reduced size of blood collection tubes • Reduced sampling for blood cultures in daily routine (limit to established indications) • Closed in-line flush devices (arterial pressure transducer systems, central venous blood collection)
11	Postoperative anemia management	In the postoperative period, when the administration of iron is necessary, early intravenous (i.v.) iron therapy is recommended, after considering contraindications. Where possible, it should be administered using a single high-dose iron preparation for the repletion of iron stores. Refer to **Fig. 5** below
12	Restrictive transfusion thresholds	Policies and procedures for ordering, dispensing, and transfusing blood components need to comply with available national and local guidelines. If patient blood management measures did not prevent the development of severe postoperative anemia, the adoption of a restrictive transfusion threshold (hemoglobin level: 70 g/L in patients without cardiovascular comorbidities, 80 g/L in patients with cardiovascular comorbidities) is recommended in most adult, clinically stable hospitalized patients.
13	“One unit at the time” policy	Whenever needed in a stable, non-bleeding patient, transfuse only one red blood cell unit at the time, with post-transfusion re-assessment of further needs. One blood unit is an independent clinical decision. Consider i.v. iron supplementation after transfusion, using post-transfusion hemoglobin as actual hemoglobin for total iron deficiency calculation.
14	Use of erythropoiesis-stimulating agents	For patients with severe postoperative anemia and inflammation-induced blunted erythropoiesis (C-reactive protein > 5 mg/L), or those declining blood transfusion, we suggest considering additional treatment with an erythropoiesis-stimulating agent (ESA). Until more safety data in cancer patients are available, ESAs should be only used in the approved indications and following the recommendations of international guidelines.

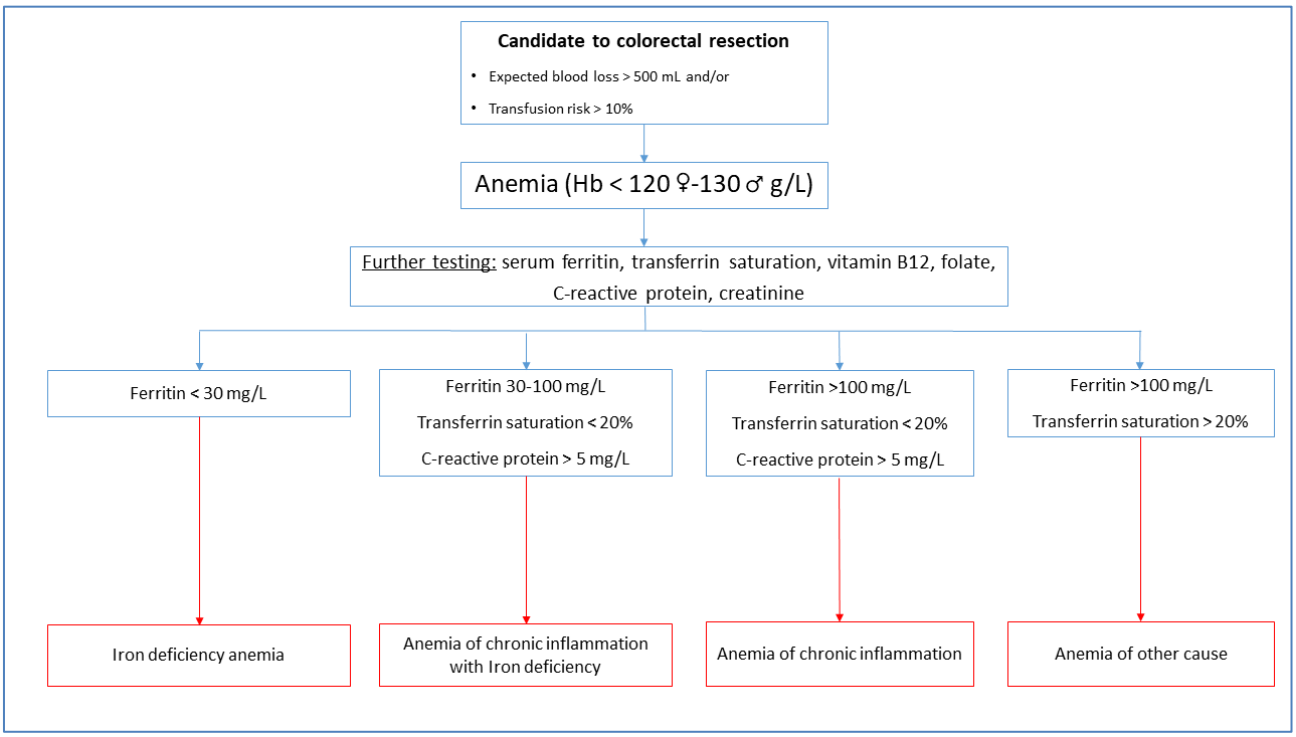


Fig. 2: Algorithm for preoperative anemia diagnosis [modified from Muñoz et al (45)].

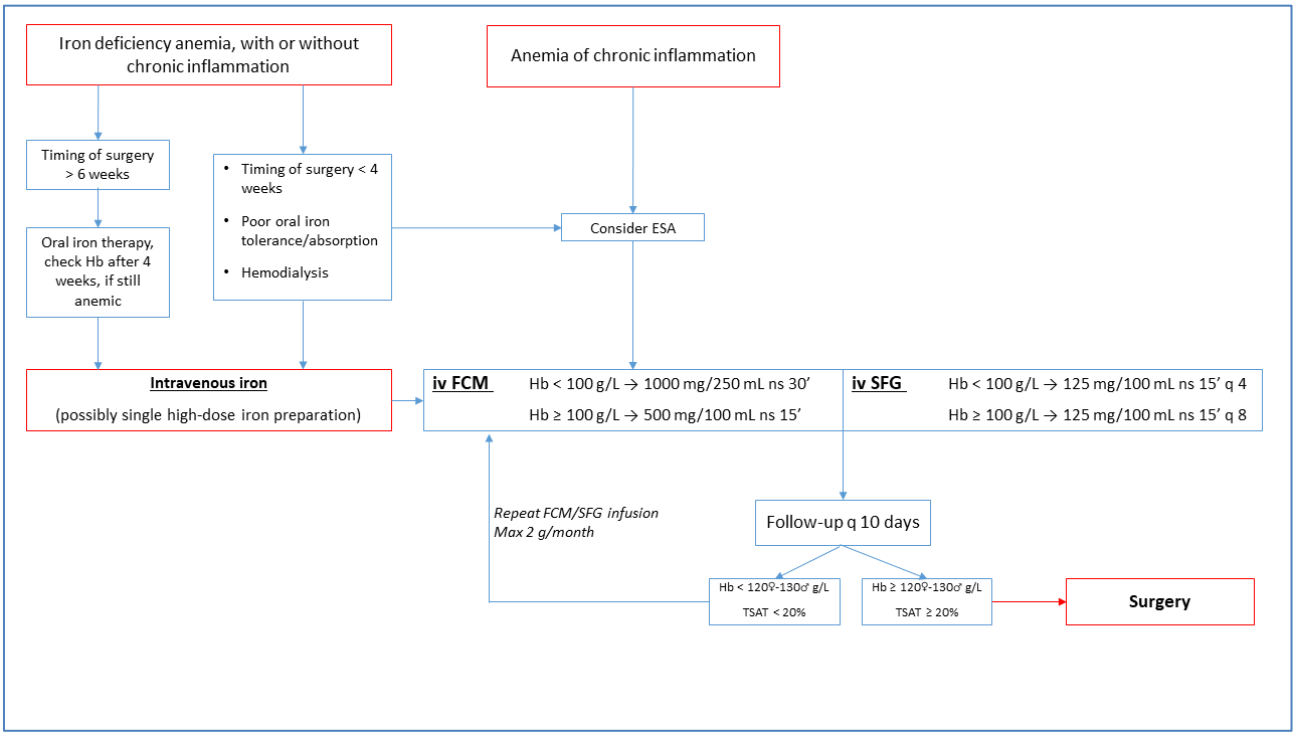


Fig.3: Management of preoperative anemia [modified from Munting et al (46)]; ESA: erythropoiesis stimulating agent (e.g. recombinant human erythropoietin - 40,000 IU, considering nephrologist referral for patients with chronic kidney disease); FCM: ferric carboxymaltose; Hb: haemoglobin; iv: intravenous; ns: normal saline; SCF: sodium ferrogluconate; TSAT: transferrin saturation.

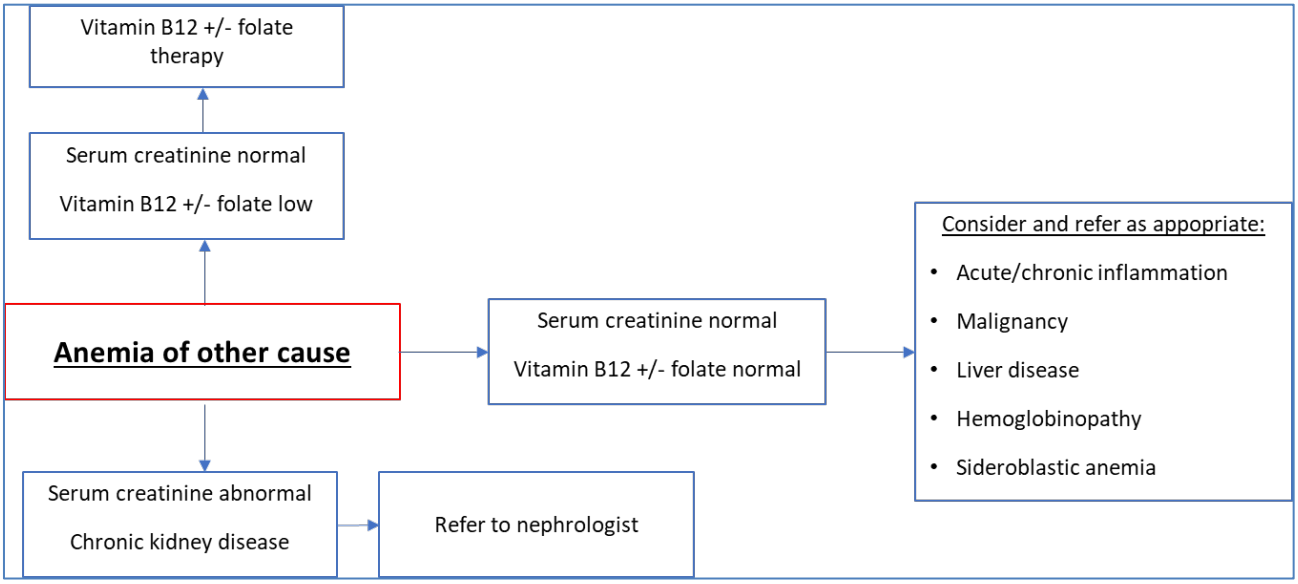


Fig.4: Preoperative management of anemia of other cause [modified from Munting et al (46)].

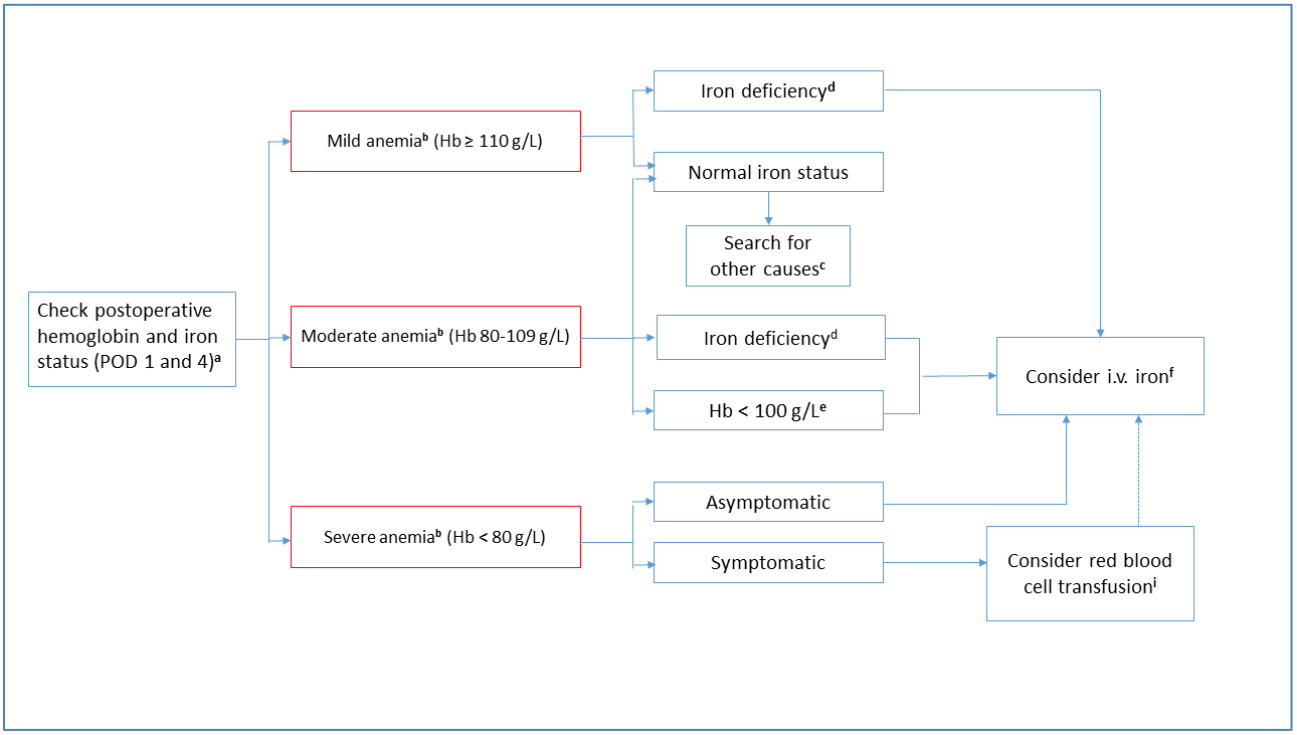


Fig. 5: Postoperative anemia management [modified from Muñoz et al (47)]. (a) Whenever possible, assess iron status within 24 h postoperatively, if it has not been already performed in the pre-operative assessment. Monitor hemoglobin for 4 days postoperatively. (b) According to WHO classification. (c) Appropriate treatment should be considered. (d) Postoperative ferritin < 100 µg/L, ferritin < 300 µg/L and transferrin saturation < 20% or reticulocyte hemoglobin content < 28 pg. (e) Due to pre-operative anemia or heavy surgical bleeding, irrespective of iron status. (f) Total iron deficiency = (target hemoglobin - actual hemoglobin) x weight (kg) x 0.24. Add another 10 mg/kg for replenishing iron stores, especially in patients with pre-operative iron deficiency. Consider adding recombinant human erythropoietin (40,000 IU) for patients with severe anemia or declining transfusion. (i) Transfuse one red blood cell unit at the time, with post-transfusion re-assessment of further needs. Consider i.v. iron supplementation after transfusion, using post-transfusion hemoglobin as actual hemoglobin for total iron deficiency calculation.

Appendix 1 **CLAVIEN-DINDO CLASSIFICATION (30, 31)**

Grade	**Definition**
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Grades	**Organ System**	**Examples**
Grade I	Cardiac	Atrial fibrillation converting after correction of K_-level
	Respiratory	Atelectasis requiring physiotherapy
	Neurological	Transient confusion not requiring therapy
	Gastrointestinal	Noninfectious diarrhea
	Renal	Transient elevation of serum creatinine
	Other	Wound infection treated by opening of the wound at the bedside
Grade II	Cardiac	Tachyarrhythmia requiring _-receptor antagonists for heart rate control
	Respiratory	Pneumonia treated with antibiotics on the ward
	Neurological	TIA requiring treatment with anticoagulants
	Gastrointestinal	Infectious diarrhea requiring antibiotics
	Renal	Urinary tract infection requiring antibiotics
	Other	Same for I followed by tx with antibiotics for phlegmonous infection
Grade IIIa	Cardiac	Bradyarrhythmia requiring pacemaker implantation in local anesthesia
	Neurological	See grade IV
	Gastrointestinal	Biloma after liver resection requiring percutaneous drainage
	Renal	Stenosis of the ureter after kidney transplantation treated by stenting
	Other	Closure of dehiscent noninfected wound in the OR under local anesthesia
Grade IIIb	Cardiac	Cardiac temponade after thoracic surgery requiring fenestration
	Respiratory	Bronchopleural fistulas after thoracic surgery requiring surgical closure
	Neurological	See grade IV
	Gastrointestinal	Anastomotic leakage after descendorectostomy requiring relaparotomy
	Renal	Stenosis of the ureter after kidney transplantation treated by surgery
	Other	Wound infection leading to eventration of small bowel
	Grade IVa Cardiac	Heart failure leading to low-output syndrome
	Respiratory	Lung failure requiring intubation
	Neurological	Ischemic stroke/brain hemorrhage
	Gastrointestinal	Necrotizing pancreatitis
	Renal	Renal insufficiency requiring dialysis
Grade IVb	Cardiac	Same as for IVa but in combination with renal failure
	Respiratory	Same as for IVa but in combination with renal failure
	Gastrointestinal	Same as for IVa but in combination with hemodynamic instability
	Neurological	Ischemic stroke/brain hemorrhage with respiratory failure
	Renal	Same as for IVa but in combination with hemodynamic instability

Suffix “d” Cardiac Cardiac insufficiency after myocardial infarction (IVa–d)
Respiratory Dyspnea after pneumonectomy for severe bleeding after chest tube placement (IIIb–d)
Gastrointestinal Residual fecal incontinence after abscess following descendorectostomy with surgical evacuation. (IIIb–d)
Neurological Stroke with sensorimotor hemisyndrome (IVa–d)
Renal Residual renal insufficiency after sepsis with multiorgan dysfunction (IVb–d)
Other Hoarseness after thyroid surgery (I–d)
TIA, transient ischemic attack; OR, operating room.

Appendix 2 **Mini Nutritional Assessment Short Form (MNA-SF®) (58)**

A Presenta una perdita dell' appetito? Ha mangiato meno negli ultimi 3 mesi? (perdita d'appetito, problemi digestivi, difficoltà di masticazione o deglutizione)
0 = Grave riduzione dell'assunzione di cibo
1 = Moderata riduzione dell'assunzione di cibo
2 = Nessuna riduzione dell'assunzione di cibo

B Perdita di peso recente (<3 mesi)
0 = perdita di peso > 3 kg
1 = non sa
2 = perdita di peso tra 1 e 3 kg
3 = nessuna perdita di peso

C Motricità
0 = dal letto alla poltrona
1 = autonomo a domicilio
2 = esce di casa

D Nell' arco degli ultimi 3 mesi: malattie acute o stress psicologici?
0 = sì 2 = no

E Problemi neuropsicologici
0 = demenza o depressione grave
1 = demenza moderata
2 = nessun problema psicologico

F1 Indice di massa corporea (IMC) = peso in kg / (altezza in m)^2
0 = IMC <19
1 = 19 ≤ IMC < 21
2 = 21 ≤ IMC < 23
3 = IMC ≥ 23

SE L' IMC NON E' DISPONIBILE, SOSTITUIRE LA DOMANDA F1 CON LA DOMANDA F2.
NON RISPONDERE ALLA DOMANDA F2 SE LA DOMANDA F1 E GIA' STATA COMPLETATA

F2 Circonferenza del polpaccio (CP in cm)
0 = CP inferiore a 31
3 = CP 31 o superiore

Valutazione di screening (max.14 punti) **12-14** punti**:** stato nutrizionale normale; **8-11** punti**:** a rischio di malnutrizione; **0-7** punti**:** malnutrito.

Appendix 3 **Prognostic Nutritional Index (PNI) (59)**

PNI = Serum albumin (g/L) + (0.005 x total lymphocyte count/µL)
Valutazione di screening ≥50: stato nutrizionale normale; **45-50:** a rischio di malnutrizione; **<45:**malnutrito.

Appendix 4 Questionario sulla salute – Versione Italiana **Euro-QoL Group EQ-5D-5L™ (34)**

Data compilazione / / ; preop □; dimissione □; tardivo □

Sotto ciascun argomento, faccia una crocetta sulla casella (UNA SOLA) che descrive meglio la sua salute OGGI.

CAPACITÀ DI MOVIMENTO

Non ho difficoltà nel camminare	❑5
Ho lievi difficoltà nel camminare	❑4
Ho moderate difficoltà nel camminare	❑3
Ho gravi difficoltà nel camminare	❑2
Non sono in grado di camminare	❑1

CURA DELLA PERSONA

Non ho difficoltà nel lavarmi o vestirmi	❑5
Ho lievi difficoltà nel lavarmi o vestirmi	❑4
Ho moderate difficoltà nel lavarmi o vestirmi	❑3
Ho gravi difficoltà nel lavarmi o vestirmi	❑2
Non sono in grado di lavarmi o vestirmi	❑1

ATTIVITÀ ABITUALI (*per es. lavoro, studio, lavori domestici,attività familiari o di svago)*

Non ho difficoltà nello svolgimento delle attività abituali	❑5
Ho lievi difficoltà nello svolgimento delle attività abituali	❑4
Ho moderate difficoltà nello svolgimento delle attività abituali	❑3
Ho gravi difficoltà nello svolgimento delle attività abituali	❑2
Non sono in grado di svolgere le mie attività abituali	❑1

DOLORE O FASTIDIO

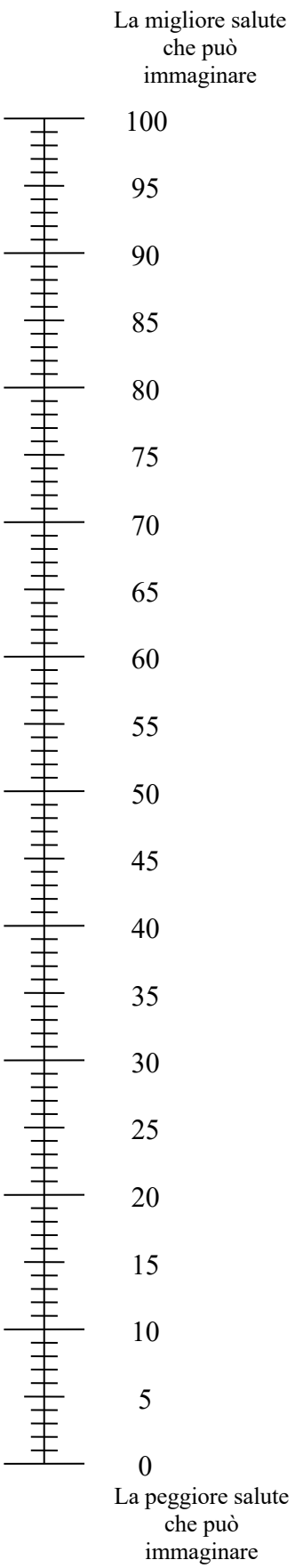
Non provo alcun dolore o fastidio	❑5
Provo lieve dolore o fastidio	❑4
Provo moderato dolore o fastidio	❑3
Provo grave dolore o fastidio	❑2
Provo estremo dolore o fastidio	❑1

ANSIA O DEPRESSIONE

Non sono ansioso/a o depresso/a	❑5
Sono lievemente ansioso/a o depresso/a	❑4
Sono moderatamente ansioso/a o depresso/a	❑3
Sono gravemente ansioso/a o depresso/a	❑2
Sono estremamente ansioso/a o depresso/a	❑1

- Vorremmo sapere quanto è buona o cattiva la sua salute OGGI.
- Questa è una scala numerata che va da 0 a 100.
- 100 rappresenta la migliore salute che può immaginare.
  0 rappresenta la peggiore salute che può immaginare.
- Segni una X sul punto della scala per indicare com'è la sua salute OGGI.
- Poi, scriva nella casella qui sotto il numero che ha segnato sulla scala numerata.

LA SUA SALUTE OGGI = ☐



Appendix 5 **MD Anderson Symptom Inventory for gastrointestinal surgery patients (MDASI-GI) (35)**

Data compilazione / / ; preop □; dimissione □; tardivo □

I Parte: Come sono I tuoi sintomi? Le chiediamo quanto ritiene che i suoi sintomi siano stati forti nelle ultime 24 ore. Per favore selezioni per ogni elemento un numero da 0 (sintomi assenti) a 10 (sintomi presenti al massimo).

1	Dolore	0	1	2	3	4	5	6	7	8	9	10
2	Stanchezza	0	1	2	3	4	5	6	7	8	9	10
3	Nausea	0	1	2	3	4	5	6	7	8	9	10
4	Sonno disturbato	0	1	2	3	4	5	6	7	8	9	10
5	Non sentirsi a proprio agio	0	1	2	3	4	5	6	7	8	9	10
6	Affanno	0	1	2	3	4	5	6	7	8	9	10
7	Non ricordare le cose	0	1	2	3	4	5	6	7	8	9	10
8	Mancanza di appetito	0	1	2	3	4	5	6	7	8	9	10
9	Sonnolenza	0	1	2	3	4	5	6	7	8	9	10
10	Secchezza delle fauci	0	1	2	3	4	5	6	7	8	9	10
11	Tristezza	0	1	2	3	4	5	6	7	8	9	10
12	Vomito	0	1	2	3	4	5	6	7	8	9	10
13	Formicolii	0	1	2	3	4	5	6	7	8	9	10
14	Stitichezza	0	1	2	3	4	5	6	7	8	9	10
15	Diarrea (feci liquide)	0	1	2	3	4	5	6	7	8	9	10
16	Difficoltà a deglutire	0	1	2	3	4	5	6	7	8	9	10
17	Alterazione del gusto	0	1	2	3	4	5	6	7	8	9	10
18	Sensazione di gonfiore	0	1	2	3	4	5	6	7	8	9	10

II Parte: Quanto i suoi sintomi hanno interferito con la sua vita? Quanto i suoi sintomi hanno interferito con i seguenti elementi nelle ultime 24 ore? Per favore selezioni per ogni elemento un numero da 0 (i sintomi non hanno interferito) a 10 (i sintomi hanno interferito completamente).

19	Attività quotidiana	0	1	2	3	4	5	6	7	8	9	10
20	Umore	0	1	2	3	4	5	6	7	8	9	10
21	Lavoro (anche domestico)	0	1	2	3	4	5	6	7	8	9	10
22	Rapporto con altre persone	0	1	2	3	4	5	6	7	8	9	10
23	Camminare	0	1	2	3	4	5	6	7	8	9	10
24	Godimento della vita	0	1	2	3	4	5	6	7	8	9	10

Appendix 6 **Functional Assessment of Cancer Therapy – Colorectal® FACT-C (36)**

Data compilazione / / ; preop □; dimissione □; tardivo □

Sotto abbiamo elencato delle affermazioni ritenute importanti da persone con la sua stessa malattia. ***La preghiamo di cerchiare o contrassegnare un solo numero per riga per indicare la sua risposta in riferimento agli ultimi 7 giorni.***

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BENESSERE FISICO		Per Niente	Un po	Abbastanza	Molto	Moltissimo
GP1	Mi manca l'energia	0	1	2	3	4
GP2	Ho nausea	0	1	2	3	4
GP3	Ho difficoltà ad occuparmi delle necessità della mia famiglia a causa delle mie condizioni fisiche	0	1	2	3	4
GP4	Ho dolori	0	1	2	3	4
GP5	Mi danno fastidio gli effetti collaterali della cura	0	1	2	3	4
GP6	Mi sento male	0	1	2	3	4
GP7	Sono costretto a trascorrere del tempo a letto	0	1	2	3	4

BENESSERE SOCIALE/FAMILIARE		Per Niente	Un po	Abbastanza	Molto	Moltissimo
GS1	Mi sento vicino ai miei amici	0	1	2	3	4
GS2	La mia famiglia mi sostiene moralmente	0	1	2	3	4
GS3	Ho appoggio morale dai miei amici	0	1	2	3	4
GS4	La mia famiglia ha accettato la mia malattia	0	1	2	3	4
GS5	Sono soddisfatto della comunicazione a proposito della malattia nella mia famiglia	0	1	2	3	4
GS6	Mi sento vicino al mio compagno/a	0	1	2	3	4
*Q1 * Se preferisce non rispondere alla domanda successiva barri la seguente casella* □						
GS7*	Sono sodisfatto della mia attività sessuale	0	1	2	3	4 %

BENESSERE EMOTIVO		Per Niente	Un po	Abbastanza	Molto	Moltissimo
GE1	Mi sento triste	0	1	2	3	4
GE2	Sono soddisfatto/a di come sto affrontando la mia malattia	0	1	2	3	4
GE3	Sto perdendo la speranza nella lotta contro la mia malattia	0	1	2	3	4
GE4	Sono nervoso	0	1	2	3	4
GE5	Mi preoccupo al pensiero della morte	0	1	2	3	4
GE6	Mi preoccupo che le mie condizioni possano peggiorare	0	1	2	3	4
BENESSERE FUNZIONALE		Per Niente	Un po	Abbastanza	Molto	Moltissimo
GF1	Sono in grado di lavorare (si intende anche il lavoro a casa)	0	1	2	3	4
GF2	Il mio lavoro (si intende anche il lavoro a casa) mi gratifica	0	1	2	3	4
GF3	Riesco a godermi la vita	0	1	2	3	4
GF4	Ho accettato la mia malattia	0	1	2	3	4
GF5	Dormo bene	0	1	2	3	4
GF6	Provo ancora piacere nel dedicarmi ad attività di tempo libero	0	1	2	3	4
GF7	Al momento, sono soddisfatto/a della qualità della mia vita	0	1	2	3	4

ULTERIORI PROBLEMI		Per Niente	Un po	Abbastanza	Molto	Moltissimo
C1	Ho gonfiore o crampi nella zona dello Stomaco	0	1	2	3	4
C2	Sto dimagrendo	0	1	2	3	4
C3	Riesco a controllare le mie funzioni Intestinali	0	1	2	3	4
		Per Niente	Un po	Abbastanza	Molto	Moltissimo
C4	Digerisco bene ciò che mangio	0	1	2	3	4
C5	Soffro di diarrea	0	1	2	3	4
C6	Il mio appetito è buono	0	1	2	3	4
C7	Sono soddisfatto/a del mio aspetto fisico	0	1	2	3	4
Q2	*Deve portare un sistema per pazienti che hanno subito stomia addominale?*					
	□ ***No (ignori le domande successive;***	□ ***SI (risponda alle domande successive)***				
C8	Mi imbarazza dover portare il sistema a seguito della stomia addominale	0	1	2	3	4
C9	Mi riesce difficile prendermi cura del sistema che devo usare per la stomia	0	1	2	3	4

Appendix 7 **Edmonton Frailty Scale (38)**

Data gg/mm/aaaa	0 punti	1 punto	2 punti
Metta le braccia ad indicare le 11:10 come sul quarante di un orologio	No errori □;	impreciso□;	errori □;
Nell'ultimo anno, quante volte è stato ricoverato in ospedale?	Mai □;	1-2 volte □;	> 2 volte □;
Indipendenza funzionale In generale, come descriverebbe la sua salute?	Buona □;	Discreta □;	Scarsa □;
Per quante attività ha bisogno di aiuto (cucinare, shopping, mobilità, telefonare, faccende domestiche, lavanderia, gestione del denaro, assumere la terapia)	0-1 □;	2-4 □;	> 4 □;
Quando ha bisogno di aiuto, può contare su qualcuno disponibile e in grado di risolvere il suo bisogno?	Sempre □;	Talvolta □;	Mai □;
Assumi 5 o più farmaci al giorno?	No □;	Si □;	
Recentemente hai perso peso tanto che i vestiti ti vanno larghi?	No □;	Si □;	
Ti senti spesso infelice o depresso?	No □;	Si □;	
Hai problemi nel controllo delle urine?	No □;	Si □;	
Seduto a riposo su una sedia; al VIA, si alzi e cammini con calma per 3 metri E, quindi, torni a sedersi rilassato (durata in secondi)	0-10s □;	11-20s □;	>20s □;

Punteggio (somma; 0-17): _____

Appendix 8 **Coordinating Investigators**

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