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# Nutritional assessment and the role of preexisting inflammation with a bearing on COVID-19

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## Introduction

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A large number of premorbid conditions have been defined as risk factors for developing severe disease and organ failure when infected with COVID-19. Preexisting comorbidity is clearly associated with increased severity of pneumonia and risk to develop respiratory failure and subsequently multiorgan failure and death. However, all these different diseases, physical findings, and results of imaging and laboratory investigations do not allow to adequately assess risk associated with COVID-19. The question is how to weigh differently each potential risk indicator. In nutritional and metabolic scientific societies, the “malnourished” state has been defined as a **“a subacute or chronic state of nutrition in which a combination of varying degrees of over- or undernutrition and inflammatory activity, has led to a change in body composition and diminished**

**function”** and therefore in essence is a risk analysis to maintain adequate physical, immunological, and cognitive function [1]. It took at least 10 years to adopt identical elements in the definition and especially the European Society of Clinical Nutrition and Metabolism found it hard to include aspects of disease, specifically inflammatory activity. Only in 2017 consensus was reached and published simultaneously in European and American nutrition journals: **“Malnutrition is a subacute or chronic state in which a combination of negative energy balance and varying degrees of inflammatory activity has led to changed body composition, diminished function, and adverse outcomes”** [2, 3]. Although this means that there is consensus in the European (ESPEN), American (ASPEN), Latin-American (FELAMPE), and Asiatic (PENSA) nutrition and metabolic scientific societies regarding this definition, unfortunately the definition has not been operationalized when it

was first proposed [1]. This means that in different ethnicity or countries, the risk of malnutrition on outcome cannot be adequately determined or predicted. This is not only important to assess the risk of death when turning ill but also to assess how well a patient will recover from surgical or medical treatment, or what the odds are not to live long and function well (e.g., Karnowski index) [4, 5].

This is unfortunate because at present we are dealing with a large number of publications mentioning age, different diseases, gender, diabetes, and plasma parameters as risk factors for not doing well when affected by COVID-19 without allowing us to acquire a more accurate estimation of risk. Although it is clear that pre-existing under- or over-nutrition influences outcome, pre-existing chronic disease and an unhealthy lifestyle are usually taken as individual indices rather than assessing inflammatory activity and the influence on immune function and the adequacy of the host response. In this chapter, we will consider these factors in more detail and try to recommend a risk assessment (=nutritional assessment) based on previous nutritional intake, body composition, and degree of inflammation, in relation to infection with the COVID-19 virus. We will point out that these elements can be partly found in the publications but not in a concerted fashion. However, previous nutritional intake and aspects of undernutrition have rarely been mentioned.

### The virulence of the invading microorganism

In principle, a similar although not identical chain of events occurs in infected states as after trauma, and the body overcomes the majority of infectious insults successfully. However, chronic disease states, malnutrition and lifestyle (smoking, overeating, alcohol, drugs) can weaken the natural defenses of the body, allowing microorganisms to proliferate and cause

harm. In this situation, a number of different bacterial species are able to increase their numbers and to become pathogenic. They can detect these numbers themselves (quorum sensing) and when abundant, upregulate gene expression increasing their activity and thereby their virulence. Both Gram-positive and Gram-negative bacteria have been found to do this. Examples are *Pseudomonas aeruginosa*, *Salmonella* sp., *Escherichia coli*, *Acinetobacter* sp., *Staphylococcus aureus*, *Vibrio cholerae*, *Bacillus cereus*, and others [6, 7].

Viruses and parasites are not known to act in a similar way as bacteria but are more aggressive in conditions where the organism is weakened by malnutrition or, e.g., by other chronic infections. This has been extensively described for human immunodeficiency virus. Some bacterial sp. or viruses are so virulent that even in healthy individuals, they can cause infections. They overcome the natural defenses of the body "by changing metabolism of the host to their advantage." Much work has been done in patients suffering from *Pseudomonas aeruginosa* infections [8]. This is a complex area and beyond the scope of this chapter. However, these mechanisms explain why infection is more hazardous than clean trauma, in that microorganisms can change and compromise our natural defenses. After clean trauma, recovery is more successful and predictable, provided the individual is in good condition and damage control adequately achieved. This implies the removal of crushed or devascularized tissues.

### Anecdotal reports of COVID-19

#### **Infections in Wuhan**

A multivariate analysis of 208 patients in China led to four factors predicting the severity of COVID-19 and mortality risk. Incorporating four factors into a nomogram achieved good concordance indexes of 0.86 (95% CI 0.81–0.91)

and included comorbidity, older age, lymphopenia, and higher LDH dehydrogenase. It was claimed that using this score improves the therapeutic effect and provides more accurate and reasonable “resolutions” on medical resources [9].

Older age and lymphopenia were confirmed as important risk factors in one study [10], whereas in another study, patients were retrospectively analyzed and the neutrophil/lymphocyte ratio proved to be an independent risk factor of in-hospital mortality, most significantly for males [11]. Older age, hypertension, and high LDH should lead to early intervention. Especially male patients with cardiac infarction, hyperglycemia, and high-dose corticosteroid use had a high mortality risk [12].

In 663 patients, male sex, a severe COVID-19 condition, expectoration, muscle ache, and hypoalbuminemia were independent risk factors negatively influencing recovery from disease [13].

In a large Chinese metaanalysis, risk factors to develop a severe form of COVID-19 were assessed. Out of the initial 1075 studies, 21 were consistent with inclusion requirements, including clinical symptoms, complications, outcome, and the most relevant comorbidities. Careful analysis of the data was performed [14]. The incidence of fever, cough, fatigue, and dyspnea symptoms was 85.6%, 65.7%, 42.4%, and 21.4%, respectively. The prevalence of diabetes was 7.7%, hypertension 15.6%, cardiovascular disease 4.7%, and of malignancy was 1.2%. The pooled estimate of adult respiratory distress syndrome (ARDS) risk was 9.4%, while acute cardiac injury with acute kidney injury (AKI) and shock occurred in 2.1% and 4.7% of cases, respectively. The risks of severe disease and mortality in the total patient cohort ranged from 12.6% to 23.5% and from 2.0% to 4.4%, with pooled estimates at 18.0% and 3.2%, respectively. The critical disease developed in 44.5% of diabetes patients and in 41.7% of patients with hypertension [14].

These findings were confirmed in a study addressing only severely ill patients in the hospital. Mortality rate was considered in patients with diabetes. Again, men did far worse than women [15]. Several reasons have been mentioned including the role of ACE2 inhibitors (see further), which not only play a role in the regulation of blood pressure but also in the immune response [16].

Aminotransferases (specifically aspartic acid aminotransferase) were found to correlate with mortality risk [17]. The authors attribute this to liver damage, but it is more likely that this reflects anaplerotic activation of the TCA cycle (see Chapter 6).

A multivariate regression analysis study in Wuhan revealed that risk factors for untoward outcome included age above 65 years, smoking, critical disease status, diabetes, hs-Troponin, and leukocytosis [18]. Similar findings have been reported in another Chinese study, emphasizing the risk of different types of comorbidity [19]. Hs-CRP and diabetes (specifically when on insulin therapy) were found to be risk factors [20]. In another study, low cholesterol levels correlated with more disease severity more [21].

## Studies in Europe

The occurrence of COVID-19 in Europe was reported a few months later. The most severely ill patients, requiring ICU admission when developing ARDS, needed long-term artificial ventilation and suffered high short-term mortality. Older age and preadmission hypertension were significant mortality risks [22]. Importantly, mortality and COVID-19 spread differed significantly between European countries. The (Finnish) study indicated the importance of timely restrictions and cooperation between people [23].

In 79 pregnant women, suffering from SARS, Middle East respiratory syndrome (MERS) or COVID-19, overt pneumonia, the rate of

miscarriage was 39.1%, the rate of preterm birth <37 weeks was 24.3%, premature rupture of membranes 20.7%, preeclampsia 16.2%, and fetal growth retardation 11.7%. Perinatal death amounted to 11.1%. All these rates were significantly higher than in healthy pregnancies [24]. Similar as in other studies, vertical transmission of the COVID-19 virus was not found to occur and was also found in other studies.

## Studies in the United States

Age  $\geq 85$  years was associated with ICU admittance and mortality while age  $\leq 19$  years was not nationally reported in the United States [25]. Only a minority of aged people was found to survive. In patients admitted to the ICU in the United States during 6 weeks between Feb 12 and March 28 (1.069 patients), the following comorbidities were found [25]: one or more conditions 33.5%, DM 16%, chronic lung disease 9%, cardiovascular disease 12%, compromised immunocompetence 4%, chronic renal disease 5%, and other chronic diseases 3.5%. The question remains to which extent different types and severity of comorbidity contribute to mortality.

In a follow-up report, findings were similar, but men appeared to be more vulnerable than women. This has also been found and discussed in a very recent study and has been attributed to a number of potential factors: underlying cardiovascular risk factors, high-risk behavior, immune response, and biological differences between men and women [26]. In the same article, the suggestion is raised that the expression of angiotensin-converting enzyme 2 receptor (ACE2) inhibitors may be different between men and women. Not only does this have an impact on cardiac functioning but these receptors also play a role in primarily reacting to infection. ACE2 plays an antiinflammatory role which may be enforced in women because located on the X chromosome [27]. Interestingly, the use of ACE-inhibitors has been questioned in view of potential acute heart failure occurring in

critical illness where maximal cardiac pump capacity is required. Recommendations are diverse. A middle road has been advocated in an editorial in the BMJ, in which it is recommended to discontinue ACE inhibitor use as a “precautionary principle,” deferring long-term cardiovascular benefit to reduce a theoretical short-term risk from continuing treatment while being infected and at risk to develop respiratory and cardiac failure [28]. At this moment, consensus has not yet been reached.

## Objective measurements to detect malnourished patients

In 1985, we selected patients who, on the basis of clinical criteria only, were considered to be malnourished and, therefore, at risk of not doing well after major surgery, and we evaluated a combination of objective parameters and compared these with a younger healthy control group about to undergo minor surgery [29]. The history taking included daily food intake, weight loss, anorexia, vomiting, diarrhea, alcohol, drugs, chronic illness, living alone, and old age. Acute stress and infectious states were excluded. Healthy patients scheduled to undergo minor surgery acted as a control group (varicectomy and herniorrhaphy). Physical examination included edema, muscle wasting, subcutaneous fat, anemia, loss of hair, and bad nails. The correct allocation ratio of every variable (CAR) was computed to allocate the patient correctly in the malnourished or in the well-nourished group (Table 1).

From these initial findings, we learned that plasma solutes and cells such as Hb, Alb, PALB, and TLC, body composition parameters such as PIW and MAMC, and immunological parameters such as DCH were highly significantly associated with the malnourished state. We proposed to utilize the combination of ALB, PALB, PIW, and TLC as a nutritional index to assess malnutrition. In practice, it did not receive much support, but we learned that

plasma proteins were important indicators of malnutrition risk and that these proteins decreased in and were indicative of the inflammatory state. Since then, a multitude of publications have confirmed that the presence of inflammatory activity as indicated by low albumin levels was a strong predictor and risk factor for untoward outcome in disease, trauma, and longevity [30] (see [Chapter 11](#)). Importantly, the study also revealed that plasma hemoglobin and lymphocyte levels were decreased in the group of patients considered to be malnourished on clinical grounds.

### Nutritional assessment includes assessment of risk

On the basis of the findings reported above we started to consider the elements mentioned in [Table 2](#) as a reflection of malnutrition but grounded on studies in cohorts with patients suffering from abdominal catastrophe also as risk factors for the bad outcome (see [Chapter 22](#)). Consequently, both inflammatory activity (from infectious and noninfectious causes) and undernutrition were evaluated before undertaking surgery for estimation of the degree of malnourishment.

Until 2009, the definition of malnutrition exclusively relied on sufficient in- and uptake of nutrients. However, the findings mentioned in [Tables 1 and 2](#) led us to the consideration that following this definition the true functional state of a patient could not correctly be assessed and that inflammatory activity (alb, PALB, total lymphocytes) and function should also be taken into account. In doing so, the nutritional assessment would become a risk analysis with respect to outcome after stressful events. In 2009, we therefore proposed a definition of malnutrition, which includes **a combination of undernutrition and inflammation**.

It took 10 years before the definition was embraced by major European, American, and

Asiatic nutritional societies [3, 31]. However still today, the definition has not yet been operationalized. This is unfortunate because it would have helped greatly in assessing the risk of patients suffering from COVID-19. Importantly, the proposed approach does not require to look for a large number of disease states, because it defines the functional effects of these harmful morbidities. It should be realized that CVD is rarely a primary factor, but generally the consequence of a final common pathway initiated by other morbidities leading to MetS.

### Operationalization of the definition of malnutrition

In 2008, we have proposed to operationalize the definition of malnutrition by assessing the elements included in the definition of malnutrition. We also suggested performing a dietary history, although we considered the result less reliable than the other measures proposed and because a reliable history is not always possible in critically ill patients. We therefore proposed measures that can be accurately obtained. Below we list three categories of measurements that can be reliably obtained. Of every category, relevant measures should be obtained. Here we will not discuss, which ones would be most suitable.

#### **Anthropometry (measurement of body composition)**

- Height
- Body mass index (BMI) (kg/m<sup>2</sup>)
- Percentage ideal body weight (PIW)
- Mid-arm muscle circumference (MAMC)
- Triceps skin fold (TSF)
- Bioelectrical impedance analysis (BIA), bioimpedance spectroscopy (BIS)
- Sophisticated measures (see text)

TABLE 1 Correct allocation ratios for different plasma and function parameters.

Var	Not malnourished			Malnourished			
	Mean	± (sem)	Mean	± (sem)	MDSQD	P-value	CAR <sup>a</sup>
HB	9.11	(0.133)	7.36	(0.192)	2.70	0.000	85
PALB	0.30	(0.013)	0.18	(0.009)	3.35	0.000	85
ALB	39.5	(0.47)	31.0	(0.90)	3.30	0.000	84
DCH <sup>b</sup>	0.06	(0.042)	0.64	(0.075)	2.15	0.000	77
TLC	2.25	(0.135)	1.41	(0.086)	1.58	0.000	73
TIBC	57.2	(2.09)	43.7	(1.78)	1.34	0.000	73
PIW	109.2	(2.44)	90.5	(2.29)	1.65	0.000	72
APH	84.8	(2.35)	105.5	(4.89)	0.67	0.000	72
MAMC	25.7	(0.48)	22.5	(0.54)	1.03	0.000	68
CA	2.28	(0.018)	2.19	(0.021)	0.49	0.005	66
UC	11.4	(0.68)	35.2	(5.23)	0.87	0.137	66
CR	82.4	(3.07)	75.4	(3.59)	0.11	0.065	64
AL	400.8	(13.49)	371.5	(19.99)	0.07	0.078	64
LA	1.44	(0.102)	1.60	(0.078)	0.08	0.121	57
CHI	91.3	(5.88)	83.7	(3.71)	0.07	0.240	56
UR	5.07	(0.242)	5.60	(0.288)	0.10	0.398	56
UU	314.2	(17.7)	351.6	(18.3)	0.11	0.318	54
FPW	21	(2.1)	22	(1.6)	0.02	0.535	52

HB (hemoglobin), PALB (prealbumin), Alb (albumin), DCH (delayed cutaneous hypersensitivity), TLC (total lymphocytes), TIBC (total iron binding capacity), PIW (percentage ideal body weight), APH (alkaline phosphatase), MAMC (mid-arm muscle circumference) and CA (plasma calcium) differed highly significantly between the malnourished and the well-nourished groups with CARs (correct allocation rates) amounted to between 85% and 68%.

<sup>a</sup> CARs are always given as percentages.

<sup>b</sup> DCH is a binary variable, mean stands for proportion of positive reactions and the Mann-Whitney is equivalent to the chi-square test.

Based on de Jong PC, Wesdorp RI, Volovics A, Roufflard M, Greep JM, Soeters PB. The value of objective measurements to select patients who are malnourished. *Clin Nutr* 1985;4(2):61–6.

### Measurement of inflammatory activity

Albumin levels  
Hemoglobin  
High-sensitive-C-reactive protein (hs-CRP)  
Cytokines (IL-6)  
Leukocyte differentiation  
(polymorphonuclear neutrophils; PMNL,  
lymphocytes; TLC)

### Measurement of function (is in fact a composite measure of the first two measures)

Muscle function (handgrip strength a.o.)  
Immune function (DCH)  
Immune challenge (lymphopenia)  
Cognitive function (MMSE a.o.)

TABLE 2 A combination of these factors performed better.

Variables	MDSQD	CAR
ALB, PALB, PIW, TLC	6.70	93
ALB, PALB, HB, TLC	6.86	92
ALB, PALB, PIW, DCH	6.11	89

A subset of ALB, PALB, (PIW or HB), TLC scored CARs of 93% and 92%, and ALB, PALB, PIW, and DCH scored 89%.

\*All *P*-values for Hotelling's test were smaller than 0.001.

Based on de Jong PC, Wesdorp RJ, Volovics A, Roufflart M, Greep JM, Soeters PB. The value of objective measurements to select patients who are malnourished. *Clin Nutr* 1985;4(2):61–6.

### Ad. Anthropometry (measurement of body composition)

Bodyweight, height, and calculated body mass index (BMI) are basic measures that should always be obtained but should be controlled for substantial shortening of the thoracolumbar spine. Anthropometric techniques were applied to measure body compartments including fat-free mass (FFM), fat mass (FM), skin folds, and mid-arm muscle circumference (MAMC) have not been validated very well. Nevertheless, these measures are necessary in view of the low costs of the equipment and the relative ease of the measurement. Percent ideal bodyweight (PIW) would also be a valuable measure, but normal values are only available for a largely Caucasian US population based on morbidity prevalence in different weight categories.

BIA/BIS (bioelectric impedance analysis/bioimpedance spectroscopy) has been promoted but is only valid in healthy subjects, not suffering from inflammatory activity [32, 33]. Similarly, computer tomography (CT) and dual excitation absorption tomography (DEXA)-derived estimates of the size of body compartments (specifically muscle mass) suffer from increased water content of these tissues in inflammatory states. In Chapter 11, we suggested that plasma albumin levels might allow for the assessment of the degree of

overhydration and consequently be used to correct for increased fluid content, thereby providing a more accurate estimate of the solid content of the tissues. Such a hypothesis could be supported by assessing tissue solids by high-tech total body potassium counting with  $K^+$  [34] or assessing total body nitrogen levels by neutron activation analysis [35]. These analytic techniques require advanced technology and are unsuitable for daily practice but may deliver precise data of total body nitrogen as a measure of total body protein and lesser amounts of smaller nitrogen-containing molecules. This is crucial in individuals with severe malnutrition, especially when subject to severe inflammatory activity. In this situation, the organism is severely overhydrated, which leads to a decrease of the ratio between intracellular/extracellular water (ICW/ECW) due to an increase in ECW (see earlier Chapter 11; [36–39]). This interferes with the correct assessment of cellular mass and particularly tissue solids, which would furnish a correct measure of the most essential part of body composition (cell mass and tissue solids) in potentially malnourished individuals but also in obese, traumatized, or infected individuals. Despite these limitations, carefully executed BIA/BIS measurements may yield trends that are valuable indications of changes in body compartments in the individual patient although the absolute values may be subject to systematic error, which should be taken into account in ill patients.

### Ad. The measurement of inflammatory activity

In the past century, plasma albumin and prealbumin values have been confirmed to decrease in inflammatory states and therefore to be an indicator of inflammation rather than an indicator of being well-nourished or not. Prealbumin has a far shorter half-life (2 days)



than albumin and is more sensitive to short-term changes like being postabsorptive or postprandial. Decreased concentrations of plasma albumin definitely are a risk factor for infectious complications or healing failure after (surgical) trauma [40–48] (see [Chapter 11](#)). Inflammatory activity leads to catabolism of body cell mass, which will shrink when the inflammatory cause takes weeks or longer to heal. In acute trauma or disease, a very rapid decrease of plasma albumin levels develops, while body cell mass will start to shrink in the course of dealing with damage. Body cell mass (specifically muscle mass) contributes to dealing with this event and will shrink depending on how long it takes for the organism to deal with damage or infection. The longer it takes to eradicate this primary cause, the more fat-free (muscle) mass will be lost, and during this COVID-19 era, we witness on TV when well-known individuals having barely survived their stay on the respirator in intensive care, are leaving the hospital in a wheelchair.

Specifically, muscle is active in healing, because delivering amino acids for the immune response and dealing with harm, but also acting as a modifier of the substrate mix that is produced (e.g., producing glutamine, alanine, serine, and glycine in larger amounts than present in muscle protein). In addition, also the other composing amino acids of muscle protein are released. After effectively dealing with the primary cause, the pro-oxidative phase will change into an antiinflammatory phase in which inflammation changes to promote the rebuilding of wounds or other damaged tissue, and slowly rebuilding body cell mass while in this stage nutritional support becomes effective and leads to anabolism.

The decrease of inflammatory activity leads to a negative fluid balance and an increase in plasma albumin levels and other plasma solutes (see [Chapter 11](#)). Consequently, albumin levels (and fluid balance) are reliable indicators of whether inflammation improves or worsens,

signifying that the patient's conditions improve or deteriorates [49, 50]. Classic studies show that this improvement is associated with the normalization of plasma and intracellular electrolyte concentrations. Only after 3 months, values of these solutes have completely normalized, reflecting normalization of membrane integrity and potential [51, 52]. This goes hand in hand with changes in intracellular and extracellular fluid composition [39, 53] and consequently with the distribution volume of albumin (intravascular and extravascular). An increased extravascular volume after trauma and in renal disease explains to a large extent the decrease of plasma albumin, which distributes in this volume and exchanges with the intravascular albumin pool [49, 50] (see [Chapter 11](#)). Changes in synthesis may not explain the decrease in plasma concentrations because in intensive care patients, in patients with liver failure, and in several other patient groups fractional synthesis rates in plasma are normal or increased [54–59]. Still, the significance of this finding is somewhat uncertain, because total synthesis is difficult to measure and in addition, when albumin is oxidized or has acted as a scavenger, it is more rapidly broken down. It is therefore possible that despite increases in distribution volume, pool sizes are diminished in acute and chronic disease states.

However, discrete and repeated changes in plasma albumin of, e.g., 5% can be reliably measured. The slow 3–6 months-long recovery of tissue integrity after trauma or inflammatory/infectious illness is mirrored by slowly increasing albumin levels, decreasing ECW, and increasing ICW/ECW ratio. In clinical practice, this has led us to adopt albumin levels not only as a measure of recent or chronic inflammatory activity but also as a measure reflecting whether patients have fully recovered and are sufficiently fit to recover well from renewed treatment, trauma, or disease [60, 61]. Per contra, when the primary cause (e.g., infection) is prolonged, inevitably and despite nutritional

support, more muscle protein will be lost and recovery of normal body composition and protein content may take months or longer. In very severe cases, barely surviving, severe damage may persist. Personal experience includes middle-aged patients who develop osteoporosis and fractures after a partial recovery, as well as the persisting loss of mental capacity.

C-reactive protein is often used as an indicator of inflammatory activity [46]. It rises rapidly after an insult but also decreases rapidly and is therefore not a very reliable indicator of whether the patient has recovered well from trauma or disease, which takes longer than the duration of the CRP elevation. The respective values of plasma CRP and albumin levels as predictors of in-hospital mortality have, as far as we know, only been compared in one study [46]. In this study, albumin proved to be a superior risk indicator compared to CRP. In several studies where albumin was not taken into account, CRP proved to be a significant risk indicator for mortality or disability [62, 63] (see for more information [Chapter 11](#)).

Hemoglobin may not be a true indicator of inflammatory activity but is always low in patients who are truly malnourished or subject to inflammatory activity. A low hemoglobin level in the absence of iron, folic acid, or vitamin B12 deficiency, and in the absence of hematological disease, almost without exception points to inflammation and/or low body cell mass [29]. Similar to the loss of muscle mass in the defense against trauma/infection, teleological reasoning may lead to the hypothesis that a previously healthy individual can still function at lower hemoglobin concentrations but preferentially stimulates and increases the synthesis of leukocytes in the bone marrow, for this purpose sparing substrate by decreasing the synthesis rate of erythrocytes.

Cytokines increase after trauma and the onset of disease, as well as during chronic illness in a rather characteristic way. Especially IL-6 has

been proven to be an important risk indicator for disability and longevity at the population level [62–64]. The interindividual variation of cytokines is large, however, precluding their use as inflammatory measures in the individual patient. Nor is their measurement available in most hospital settings.

Finally, lymphopenia has been found to be an indicator of inflammatory activity in our study. In the COVID-19 studies, lymphopenia was found to be a risk factor for mortality. The exact kinetics of leukocytes are not well defined. Lymphocytes are active in the defense against the virus, producing cytokines in turn stimulating transcription factors driving reparative metabolism. Possibly lymphopenia therefore implies that the organism is maximally challenged increasing lymphocyte nesting in many organs and reactive tissues producing cytokines and their utilization. This then may decrease their plasma numbers although their fluxes remain unknown, even more, because in inflammatory conditions the distribution space in plasma increases and may play a contributory role in decreasing their numbers. In contradistinction, PMNLs and their left shift increase in numbers and apparently can be synthesized in excess. In conclusion, the kinetics of white cells remain somewhat enigmatic.

#### **Ad. The measurement of function**

The most easily measurable function is muscle force. For this purpose, handgrip strength is often used, but other more sophisticated measures for muscle strength and endurance are available [65]. To reach consensus which measures are most reliable and reproducible, multicenter research is needed. Consensus reports are available regarding the measurement of muscle force in patients with cardiovascular or respiratory diseases [65]. The advantage of measures of muscle force is that the equipment to measure it is cheap and easy to purchase. Validation and

training of the technique are necessary, however.

Assessment of cognitive function has not been widely practiced in the nutritional and metabolic world. It is a second important element determining the quality of life and learning ability [66]. No consensus exists on which tests to use in clinical practice. The Mini-Mental State Examination (MMSE) is an example of a test which could be evaluated [67]. Interestingly in many, although not in all studies cognitive function correlated with physical fitness [68]. As it is unlikely that there is a direct causal relationship between the two, they probably share a common basis: a healthy organism implying normal body composition, no substantial inflammatory activity, and normal function.

Immune function is the third and final element determining together with muscle force and cognitive function, quality of life, and the ability to respond adequately to trauma and disease. Consensus as to how immune function must be assessed is badly needed. At present assessment depends more on diagnosing the presence of active inflammatory activity and its likely immunosuppressive effects (second hit) [69, 70] and on body composition than on any particular immunological measure, immunological parameters obtained in clinical practice (e.g., lymphocyte counts, delayed cutaneous hypersensitivity) are predominantly binary variables and do not furnish graded measures of immune function but rather yes or no answers.

### **Nutritional assessment should consist of assessing risk “not to do well.”**

Fortunately, there is now agreement that “malnutrition” is characterized by three crucial elements: undernutrition, inflammation, and diminished function, the latter being a composite measure of these two others. In principle, nutritional screening should come first, because it is important to know whether the patient is at

nutritional risk. In this regard, the loss of body weight is a crucial element. To arrive at the conclusion that body composition is abnormal, multicenter studies need to be performed in defined populations to establish normal values. These values should be validated with the best available gold standards.

The second component of nutritional assessment consists of establishing the presence of inflammatory activity. Here it is also necessary to establish normal values and cut-off points below which risk substantially increases. If body cell mass is normal and if there is no inflammatory activity, it is highly unlikely that function will be abnormal, provided the individual is cooperative.

The third component consists of function measures for which also agreement needs to be reached what equipment to use and what the cut-off values are for different populations. Muscle function has been chosen as the function parameter. Cognitive and immune functions are harder to assess reliably and there is no easy correlation with anatomic structures. In practice, it may be possible to construct a scale from 0 to 10, which reflects the severity of malnutrition (Table 3). The weight attributed to the standard deviations of the measures is an estimate and must be established in multicenter studies.

In Table 3, we have listed a hypothetical approach to nutritional assessment.

We suggest that the proposed nutritional assessment techniques may have general applicability and may not require disease-specific equations. In 2008, we have suggested adopting this approach. The nutrition societies have focused very much on screening, which is a laudable effort. However, the true assessment of malnutrition has received little attention and action. The reports on COVID-19 and the multitude of risk factors reported, prove that there is no concerted approach to assessing risk in critically ill patients. We suggest that such a project might benefit the medical world, the nutritional community, and individuals cared for.

TABLE 3 Hypothetical estimation of the severity of malnutrition and the weight of muscle mass, inflammation, and muscle function on outcome.

Undernutrition Sd below the mean of controls	Muscle mass	Inflammatory activity	Muscle function <sup>a</sup>	Total <sup>b</sup>
Less than 1 Sd below the mean	0	0	0	
More than 1 Sd below the mean	1	2	2	
More than 2 Sd below the mean	2	4	4	
More than 3 Sd below the mean	4	6	6	
Result				

Published in 2008 [1].

True weights of muscle mass, inflammation, and function **on outcome** should be assessed in homogeneous study cohorts in different countries, races, income levels, and others. Fields to focus on may be among others surgery, oncology, transplantation, hospices, nursing homes, and others.

Nutrient balance should be estimated whenever possible and will furnish an estimate of the contribution of undernutrition to malnutrition. In the hypothetical approach in this table actual measures are those that can be obtained in practice with some certainty. This by definition also furnishes an estimate of the risk of complications of disease and injury, or a prediction of longevity and disability in chronic disease and in the elderly. Scores above 2 may already indicate a substantially increased risk. Scores below 3 may indicate a minor risk that can only be demonstrated in large populations.

N.B.: Here it is proposed to use standard deviations of the mean of values in an appropriate control group as cut-off values to categorize the degree of abnormality of muscle mass, inflammation, and muscle function. The final proposal should be decided based on multicenter studies. The attribution of weight to the different measures on a scale of 0–4 for muscle mass and 0–6 for inflammation and muscle function is based on estimated guesses, and therefore should ultimately be determined based on studies in which deviations of control values are related to outcome (clinical, longevity, quality of life). In view of the fact that muscle mass and inflammatory activity are important determinants of muscle function, we propose to add only surplus points of muscle function when decreased muscle function is more standard deviations below the mean than the degree of inflammation. Consequently the highest total score (severest form of malnutrition) cannot exceed 10.

<sup>a</sup> Add only surplus points when function is more compromised than inflammation.

<sup>b</sup> Total ranges from 0 to 10.

Based on de Jong PC, Wesdorp RJ, Volovics A, Roufflart M, Greep JM, Soeters PB. The value of objective measurements to select patients who are malnourished. *Clin Nutr* 1985;4(2):61–6.

## Discussion

The essential message of this chapter is that “malnutrition” entails more than deficient nutritional intake and its sequelae. The purpose is to outline that “malnutrition” in our countries as well as in countries with endemic malnutrition almost always is caused by varying degrees of deficient nutritional intake in combination with the disease or other damaging inflammatory causes of differing severity. Together this combination leads to diminished functional capacities, including inadequately responding to renewed challenges like COVID-19. Most patients, being severely ill due to COVID-19 were not investigated before becoming ill. However, their

medical history generally included comorbidity or an unhealthy lifestyle. Chronic diseases (CVD, diabetes, COPD, obesity), medication, aging, gender, ACE inhibitors were mentioned which were considered as risk factors for severe forms of the disease. We simply interpret the findings to signify that due to the preexisting comorbidity, the organism must have been subject to a Th1 predominant inflammatory response (first hit), during which a second hit (COVID-19 infection) could not be adequately handled leading to persistence of the infection and the TH1 inflammatory state.

However, these considerations do not satisfactorily answer the question, why the organism cannot clear the virus despite an extremely

active inflammatory response with increased capillary permeability, high fluid requirements, low constitutional proteins (albumin, prealbumin), fever, muscle weakness, and large muscle losses, known to furnish a substrate mix suitable for host response, and other symptoms of severe illness. This strongly contrasts with young individuals with no comorbidity, who develop very mild signs of illness or not at all but nevertheless adequately clear the virus. What makes the difference? Along similar lines, the question poses itself whether aged individuals without comorbidity can clear the virus without becoming very ill, or is aging alone (and this seems to be the case) also intensifying the response to disease due to the damage caused by a long life of modest harm without comorbidity but due to being exposed to the stresses of daily life. The interesting and puzzling aspect is the enormous contrast between youngsters dealing adequately with the virus and the strongly weakened response in aged people. The question then is why there is this rapid decrease in functional capacity. Is it the decay of the last 4–7 years. In these last years of life, in addition to chronic disease or even without comorbidity, FFM shrinks to very low levels, not supplying sufficient amounts of building blocks (amino acids, cholesterol).

Another interesting question is why men have higher mortality than women? In anthropology circles, this has been ascribed to the “mother hypothesis,” which states that postmenopausal longevity evolved because it is advantageous for women to cease reproduction and concentrate their resources and energy in raising children already produced [71]. This theory does not address the question, how this is affected physiologically. A more pathophysiological explanation has been proposed, where women’s longevity has been ascribed to women having two X-chromosomes, one taking over defensive responses when the other fails. This supposes that the superior dealing by women

with stresses is genetically determined from the start.

An alternative explanation may be that in evolution not so much the genetic XX configurations but other genetic traits have determined differences between men and women. These traits should explain what actually happens in the body in stressed conditions. In evolution, we needed to overcome disease and trauma for at least 25 years (men) and 30 years (women) to allow donating our genes to the next generation and to safeguard their survival. The difference between men and women is telling that women had to survive illness and trauma more effectively and longer than men to allow their offspring to grow and their genes to survive. Men not necessarily needed to ensure continuity of children’s care, but needed to be strong to protect the family, to collect food, and to ascertain their position to mate, ensuring survival of their genetic traits but also modifying their genome differently compared to women. This may imply that the capacity to survive trauma or illness, was not important for the survival of their genome, because this could almost instantaneously be taken over by other males in the tribe. This happens in a large number of vertebrates in wildlife. Although this reasoning relies on wild guesses, apart from the physical procreative role, unquestionably the role of women and men differed and needed to be different, which must have influenced the survival of genes, coding for these different roles. The female genome appears to be better equipped to survive intercurrent trauma or illness than the male one, impacting longevity and the ability to overcome COVID-19 at higher ages. Lifestyle (smoking, alcohol, heavy labor) used to differ between men and women, but this difference is narrowing in recent decades. Nevertheless, the gap in longevity appears to widen, providing further support for the claim that the male genome is the weaker genome with respect to countering disease and life expectancy.

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