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The Effect of Nutrition Support on Nutrition and Clinical Outcomes in Critically Ill Patients

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DEDICATION

I dedicate this dissertation first to God almighty for making it all possible. Second, to my husband, who encouraged me to pursue my dreams and supported me all the way through. Third, to my family members for their ceaseless prayers. Fourth, my late mother-in-law Grace-Mary Aneni who was my inspiration to pursue my doctoral degree but unfortunately was unable to see me graduate. I know you are happier where you are now.....until we meet again. Finally, to my beautiful daughter Oluwataramisore Olufayo for being a bundle of joy!

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ABSTRACT

Objectives: This study examined the impacts of nutrition support on ICU patients with different nutrition risk, routine clinical laboratory measurements, and biomarkers of malnutrition and inflammation. The secondary purpose of this study was to evaluate whether malnutrition is associated with blood biomarkers of nutrition and inflammation in the ICU.

Design: A retrospective medical chart review.

Setting: Howard University Medical Intensive Care Unit, Washington DC.

Participants: A total of 60 patients admitted from Jan 2019 to Dec 2019 met the inclusionary criteria.

Primary and Secondary Outcome measures: mNUTRIC score and NRI were used to evaluate nutritional risk, and malnutrition were diagnosed using the GLIM criteria. Anthropometric measurements, clinical outcomes, routinely collected laboratory data, and the type of nutrition support were recorded from the day of ICU admission. Clinical outcomes, nutritional and inflammatory biomarkers, TLC, NRI, and NLCR, were compared between normal nutrition vs. malnourished and different BMI groups.

Results: Although the inflammatory markers WBC, NLCR, procalcitonin, absolute neutrophils, absolute lymphocytes were trending down, this was not significant. Hemoglobin, hematocrit, the total protein used as nutritional markers had decreased by day 14 with significant difference $p < 0.001$. TLC and NLCR were significantly lower in the group with malnutrition ($p < 0.01$). Logistic regression analysis showed that elevated NLCR, Neutrophils, and lower TLC, NRI, and Lymphocytes were independent factors in the prediction of malnutrition in ICU patients ($p < 0.01$). Malnutrition was found to correlate with TLC and BMI ($p < 0.05$) negatively.

Conclusion: The result demonstrated that malnutrition was associated with TLC, NLCR, NRI, Neutrophils, and Lymphocyte, making them useful biomarkers in diagnosing malnutrition. Malnutrition affects outcomes of ICU patients negatively. Nutrition support did not considerably improve nutritional status and immune function in malnourished patients in this study.

Abbreviations: MICU=Medical Intensive Care Unit, mNUTRIC= modified Nutrition Risk in Critically ill, NRI= Nutritional Risk Index, GLIM= Global Leadership Initiative on Malnutrition, BMI= Body Mass Index, TLC= Total Lymphocyte Count, NLCR: Neutrophil Lymphocyte Count Ratio, WBC= White Blood Cell.

Keywords: Malnutrition, Clinical outcomes, Nutrition support.

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LIST OF ABBREVIATIONS

ICU	Intensive Care Unit
mNUTRIC	Modified Nutrition Risk in Critically ill
NRI	Nutritional Risk Index
GLIM	Global Leadership Initiative on Malnutrition
BMI	Body Mass Index
TLC	Total Lymphocyte Count
NLCR	Neutrophil Lymphocyte Count Ratio
BMI	Body Mass Index
WBC	White Blood Cell
LOS	Length of Stay
A.S.P.E. N	The American Society for Parenteral and Enteral Nutrition
AND	Academy of Nutrition and Dietetics
EN	Enteral Nutrition
PN	Parenteral Nutrition
TPN	Total Parenteral Nutrition
SOFA	Sequential Organ Failure Assessment
APACHE II	Acute Physiological Assessment and Chronic Health Evaluation
NRI	Nutritional Risk Index
HUH	Howard University Hospital
LDH	Lactate dehydrogenase
TC	Total Cholesterol
HDL	High-Density Lipoprotein

NCHS	National Center for Health Statistics
GI	Gastrointestinal
ER	Estimated Energy Requirement
NRS-2002	Nutrition Risk Screening 2002
MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NST	Nutrition Screening Tool
MNA	Mini Nutritional Assessment
SGA	Subjective Global Assessment
PG-SGA	Patient Generated Subjective Global Assessment
RCLM	Routine Clinical Laboratory Measurements
PCT	Procalcitonin
CRP	C-Reactive Protein
IL-6	Interleukin 6
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
CASP	Critical Appraisal Skills Programme
EEN	Early Enteral Nutrition
DEN	Delayed Enteral Nutrition
SICU	Surgical Intensive Care Unit
MICU	Medical Intensive Care Unit
POD	Post-Operative Day
RCT	Randomized Control Trial
IgG	Immunoglobin G

RCT	Randomized Control Trial
hs-CRP	High Sensitive C-reactive Protein
NIHSS	The NIH Stroke Scale
VAP	Ventilator-associated pneumonia
TNF	Tumor necrosis factor
SPN	Supplemental Parenteral Nutrition
SNS	Specialized Nutrition Support
PICO	Population Intervention Comparators Outcomes
HIPAA	Health Insurance Portability and Accountability Act
Na	Sodium
K	Potassium
Cl	Chloride
CO_2	Carbon dioxide
BUN	Blood Urea Nitrogen
Ca	Calcium
Mg	Magnesium
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
RBC	Red Blood Cell
MCV	Mean Corpuscular Volume
LDL	Low Density Lipoprotein
CCI	Charlson Comorbidity Index

SEM	Standard Error Mean
NGT	Nasogastric Tube
OGT	Orogastric Tube
PEG	Percutaneous endoscopic gastrostomy
$\chi 2$	Chi-square
df	Degree of Freedom
OR	Odd Ratio
ROC	Receiver Operating Characteristics
CI	Confidence Interval

CHAPTER 1. INTRODUCTION

Statement of the Problem

Malnutrition is a common and critical problem that considerably impacts the clinical outcomes of hospitalized patients negatively, and there is a growing concern that malnutrition is both under-appreciated and under-diagnosed. The pathophysiology of malnutrition is related to disease or injury that could present as a result of either over-nutrition or undernutrition and acute or chronic inflammation. The prevalence of malnutrition in the United States ranges from 30% to 50%. However, only 7.1% of hospital stays involving malnutrition diagnosis have been documented (Weiss et al., 2013).

Malnutrition is defined as any nutrition imbalance. Malnutrition can also be described as a state resulting from lack of adequate oral intake or an impaired utilization of nutrients that leads to decreased fat-free mass leading to decreased physical and mental function and impaired clinical outcomes (Sobotka, 2012). "Malnutrition can result from starvation, disease, or advanced aging (e.g., >80 years), alone or in combination" (Pirlich et al., 2005). Malnutrition is not just undernutrition; it can also include micronutrient abnormalities, morbid obesity, cachexia, sarcopenia, and frailty (Jensen et al., 2010 and Cederholm 2017). Malnutrition may be caused by decreased energy intake or compromised assimilation of nutrients; it can also be caused by inflammation through associated anorexia and reduced food intake as well as altered metabolism with increased resting energy expenditure and increase muscle catabolism. Malnutrition is associated with unfavorable functional and clinical outcomes as a result of the modified body composition, which manifests as decreased muscle mass (Cederholm et al., 2019).

Malnutrition "may result from chronic starvation and conditions such as anorexia, but it may also be a consequence of acute and chronic inflammation/illness or injury" (White et al., 2012). Malnutrition is associated with many unpropitious clinical outcomes; it can result in higher infection rates, poor wound healing, a longer length of hospital stays (LOS), increased mortality and morbidity rates, higher frequency of hospital readmission, and increased costs (Corkins et al., 2014). Previous studies have shown that the use of appropriate nutrition screening, assessment, and early provision of nutrition care and interventions can improve outcomes in hospitalized patients (Tappenden et al., 2013; Borek et al., 2017; Sriram et al., 2017). Patients in the intensive care unit (ICU) are at high risk for malnutrition or are more likely than other patients to be malnourished. Furthermore, ICU patients are most likely ventilated, which may develop problems related to malnutrition which include increased risk of infection, impaired immune function, poor wound healing and extended hospital LOS (Ziegler, 2009; Singer et al., 2011; Philipson et al., 2013; Corkins et al., 2014).

The Joint Commission requires that every patient be screened with a validated nutritional screening tool within 24 hours of admission to an acute center. This screening is done to identify patients who are at risk of malnutrition or are malnourished in other to initiate early nutrition intervention. Despite the availability of malnutrition screening tools, malnutrition continues to be under-diagnosed and under-recognized (Duerken et al., 2015) [Table 3].

The underlying pathophysiologic mechanisms of malnutrition and their impacts on laboratory parameters are still incompletely understood despite its high occurrence amongst hospitalized patients, especially amongst patients in the ICU (Schutz 2015; Schutz et al., 2014). Screening, assessment, and diagnosis of malnutrition may require different parameters for varying patient populations such as hospitalized patients on the medical floor, patients in the ICU, patients

with renal disease, the elderly, and patients with frailty and sarcopenia, hence the need for use and compliance with biomarkers for malnutrition and inflammation. Inflammation has an enormous impact on the nutritional status of both acute and critically ill patients. Furthermore, dietary factors influence inflammatory response and outcomes (Felder, 2016). The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) has established systematized malnutrition parameters and features that reflect nutrition status versus inflammatory responses related to various diseases and conditions. However, malnutrition and inflammatory markers most useful in documentation need to be identified to support the characteristics proposed by A.S.P.E.N. A review by Zhang et al., (2017), confirmed that body mass index (BMI) and several blood biomarkers, including albumin, pre-albumin, hemoglobin, total cholesterol, and total protein, are functional biomarkers for supporting the diagnosis of malnutrition. The same study also confirmed that blood albumin and pre-albumin levels should be interpreted carefully in the healthcare settings, as they may be influenced by changes brought about by acute disease and the associated systemic inflammation.

Nutritional intervention may prevent malnutrition or improve outcomes in hospitalized patients, especially in critically ill patients (Tappenden et al., 2013). Moreover, nutritional support (oral nutrition support, enteral nutrition, and parenteral nutrition) can play an essential role in both the prevention and treatment of chronic critical illness. However, currently, limited data are available on this specific group of patients. Nutrition support is used in malnourished patients to improve nutrient intake (Borum, 2004), thereby maintaining or enhancing health and nutrition outcomes.

The use of inflammatory markers to diagnose malnutrition is emerging, and studies suggest that several blood biomarkers: C-reactive protein, procalcitonin, pro-adrenomedullin, albumin,

renal function markers, vitamin D25, corrected calcium, hemoglobin, and red blood cell distribution width correlates with poor nutritional status (Felder et al., 2016). However, there are not enough data showing the effects of nutrition support on most of these biomarkers, which of these blood biomarkers respond to nutrition treatment, and which biomarkers work better to identify the presence of malnutrition.

Purpose of the Study

The primary aim of this study was to assess the impacts of nutrition support (enteral nutrition, parenteral nutrition, or both) on patients with different nutrition risk, routine clinical laboratory measurements, and biomarkers of malnutrition and inflammation. The secondary aim was to study whether malnutrition is associated with blood biomarkers of nutrition and inflammation (NLCR, WBC, TLC, Neutrophils, Lymphocytes, Absolute neutrophils, Absolute lymphocytes, Albumin, Total Protein, Hemoglobin, Hematocrit).

Objectives

The objectives of the study are as follows:

1. Identify and compare the rate of malnutrition diagnoses in ICU patients at HUH with previously published data.
2. Examine the effects of nutrition support on selected malnutrition and inflammatory biomarkers (NLCR, WBC, TLC, Neutrophils, Lymphocytes, Absolute neutrophils, Absolute lymphocytes, Albumin, Total Protein, Hemoglobin, Hematocrit).
3. Compare the effects of nutrition support on clinical outcomes, different categories of nutritional risk, routine clinical laboratory measurements, and inflammatory biomarkers.
4. Evaluate the associations of malnutrition with mNUTRIC score, SOFA score, APACHE II, NRI, TLC, NLCR, WBC, Neutrophils, Absolute neutrophils, Absolute lymphocytes, Albumin, Hemoglobin, Hematocrit.

Hypotheses

The following hypotheses were tested:

1. The rate of malnutrition in the ICU at HUH will be the same or higher compared to previously published data.
2. Nutrition support will improve the following nutrition and inflammation biomarkers (NLCR, WBC, Neutrophils, Lymphocytes, Absolute neutrophils, Absolute lymphocytes, Albumin, Total Protein, Hemoglobin, Hematocrit).
3. Patients with high nutritional risk receiving nutrition support will have reduced hospital length of stay and improved clinical outcomes.
4. Malnutrition will be associated with mNUTRIC score, SOFA score, APACHE II, Charlson Comorbidity Index, NRI, TLC, NLCR, WBC, Neutrophils, Absolute neutrophils, Absolute lymphocytes, Albumin, Hemoglobin, Hematocrit.

Significance of the Study

Nutrition support is a vital component of the nutrition care plan for injured and critically ill patients. Critical illness or injury stimulates acute inflammatory responses that are associated with malnutrition. The presence of this inflammation may limit the efficacy of nutritional interventions, and related malnutrition may, in turn, weaken the clinical response to medical interventions. The importance of nutrition support in the hospital setting, especially in the ICU, cannot be overemphasized. Critical illness is popularly accompanied by a catabolic stress state in which patients exhibit systemic inflammatory responses associated with complications of increased infections, multiple-organ dysfunction, extended hospitalization, and increased mortality rate (Warren, McCarthy & Roberts, 2016).

Patients in the ICU are critically ill, and their nutritional status will be significantly affected by chronic and acute starvation, which leads to catabolic processes such as the depletion of

subcutaneous fat and muscle mass and in some cases multiple organ failure (Rahman et al., 2016; Heyland et al., 2011; Kalaiselvan, Renuka, and Arunkumar, 2017). Nutritional risk can be detected by analyzing a number of scoring systems, criteria, and tools, including Nutrition, Focused Physical Examination (NFPE), dietary intake, the severity of the disease, presence of inflammation, functional assessment, and anthropometric data (Kondrup 2014; Coltman et al., 2015). However, most of this assessment is not feasible for use in the ICU because most of the patients are sedated and ventilated. Weights of patients can be influenced by edema and fluid status, which makes it challenging to assess muscle and fat depletion. Furthermore, many of these nutritional assessment tools and criteria do not put into consideration inflammatory processes and hypermetabolic status in ICU patients (Chakravarty et al., 2013; Doig et al., 2008; Correia and Waitzberg, 2003).

The use of inflammatory markers to diagnose malnutrition is emerging, and previous studies have shown that several blood biomarkers correlate with poor nutritional status (Felder et al., 2016). However, there is sparse data showing the effect of nutrition support on these biomarkers. Combining patient's medical and dietary history with selected blood biomarkers may assist with prompt identification of patients at risk of malnutrition or with malnutrition, which will help promote timely and individualized and appropriate interventions and follow-up of responses to these interventions. Assessment of nutritional status should be fast and easy if using blood biomarkers that are routinely and frequently collected at the time of admission and while in-patient. Since many of these blood biomarkers are routinely assessed at admission, they can be obtained easily. Acute malnutrition has been linked with pronounced inflammatory response and alteration in biomarkers; however, studies are sparse on interventional trials to prove causality and on data

investigating whether the inflammatory status of patients impacts treatment response to nutritional support.

This study will help shed light on routine clinical laboratory measurements, selected inflammatory and malnutrition biomarkers that are affected by nutrition support. Also, this study will help to identify routinely collected biomarkers that can be used to diagnose malnutrition.

CHAPTER 2. LITERATURE REVIEW

Malnutrition

Malnutrition is any nutrition imbalance in the body. The pathophysiology of malnutrition connected with disease or injury could manifest as a result of either over-nutrition or undernutrition and acute or chronic inflammation (Jensen et al., 2010). Overweight or obese patients can also experience malnutrition in the presence of severe acute illness or when they encounter a major traumatic event (Cruz-Jentoft et al., 2010; Jensen et al., 2009). Malnutrition is described as a continuous nutritional reserve expenditure because of low energy and nutrients intake to support daily metabolic requirements or because there is an impairment in normal metabolisms, such as digestion and absorption (Thieme et al., 2013). Adults are generally considered to be malnourished if they lack sufficient calories, protein, or other nutrients needed to maintain and repair body tissues.

Malnutrition is characterized by inadequate nutrient intake, increased nutrients requirements, increased energy expenditure, impaired nutrient absorption, altered transport of nutrients, and altered nutrient utilization, which could eventually lead to a significant weight loss and other nutritional abnormalities. Nutritional uptake in adults is often compromised when there is chronic starvation without inflammation, chronic diseases, or even in conditions that inflict sustained inflammation of mild to a moderate degree and acute illness or injury with a marked systemic inflammatory response (Jensen et al., 2010). Individuals who are malnourished may also present with inflammatory, high metabolism, and catabolism. The acute phase inflammatory response leads to increased energy and protein requirements due to high energy expenditure and a negative nitrogen balance.

The definition of malnutrition varies in their terminology, and the criteria used to define this condition. Furthermore, in the past, were no set criteria for screening and diagnosing patients with malnutrition. This led to confusion and inconsistent practices among healthcare providers across the world. The recognition that inflammation plays a substantial role in the pathophysiology of malnutrition has not been fully established, adding to several misdiagnoses and a general under-recognition of the importance of malnutrition.

Concerns brought forth by the Centers for Medicare and Medicaid Services, and a desire to promote a national standard for consistent diagnosis prompted The Academy of Nutrition and Dietetics (Academy) and A.S.P.E.N. to develop an etiology-based methodology that incorporates the inflammatory process into the characterization of malnutrition in adults in the clinical setting (White et al., 2012). These organizations have adopted patient-specific definitions based on etiologies, including the social and environmental circumstances, chronic illnesses, and acute diseases for the diagnosis of malnutrition in adults in the clinical setting, a step towards recognizing the interaction and importance of inflammation on nutritional status see [Figure 1]. In the past, there was inconsistency in the definitions of malnutrition, leading to confusion and an absence of consensus on the meaning of the condition. The International Guideline Committee was constituted to agree on the definition of malnutrition for adults in the clinical setting. Three terms were developed by the Committee to describe malnutrition: starvation-related malnutrition, chronic disease-related malnutrition, and acute disease or injury-related malnutrition (Jensen et al., 2010). See [Figure 1].

Malnutrition related to starvation: should be used when there is a long period of starvation without inflammation. Examples of this type of malnutrition included medical conditions like anorexia nervosa. Malnutrition related to chronic disease: should be used when the presence of a

chronic mild to moderate degree of inflammation is detected. Example of this type of malnutrition includes single or multiple organ failure, certain types of cancer, rheumatoid arthritis, or sarcopenic obesity. Malnutrition related to acute disease or injury: should be used when acute inflammation of a severe degree is present. Examples of this type of malnutrition include severe infection, burns, trauma, or head injury.

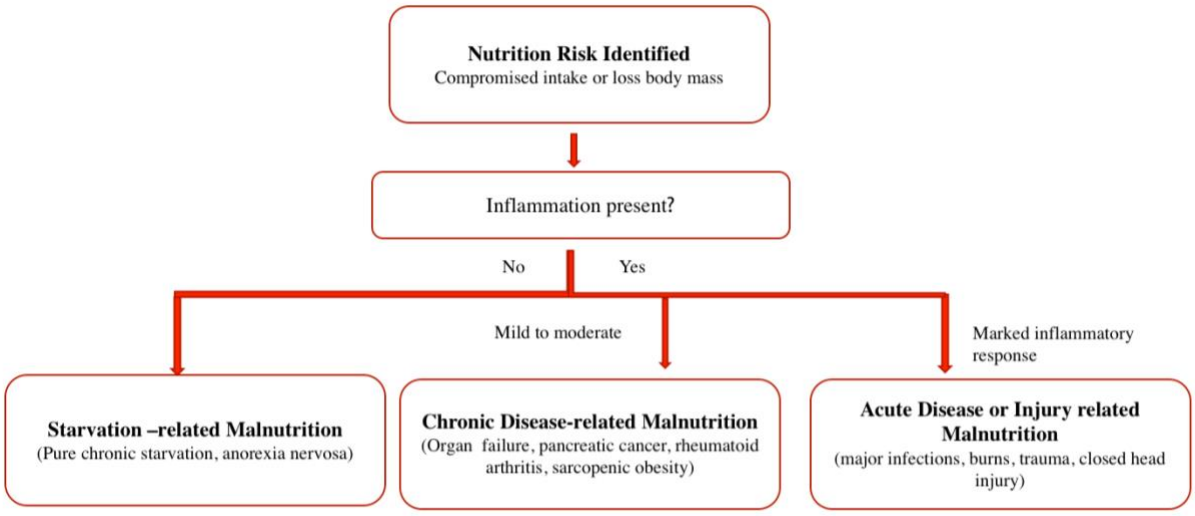

Figure 1 Etiology-based malnutrition definitions

Source: Tappenden et al., 2013.

The National Center for Health Statistics (NCHS) defines "chronic disease" as the disease that occurs for three months or longer. The academy of nutrition and dietetics and A.S.P.E.N. proposes malnutrition definitions that put into consideration the duration and severity of an inflammatory response in classifying a disease as acute or chronic (Jensen et al., 2010). There is a possibility of patients being diagnosed with one or more of these states and changing from one state to another

It is becoming a great concern regardless of the state of malnutrition, be it acute or chronic, eventually progresses with further loss of muscle mass.

Standardized markers and criteria that reflect nutrition status versus inflammatory response correlated to various diseases and conditions have been proposed by A.S.P.E.N. (Appendix A). The components recommended for diagnosis include are listed in [Table 1].

Table 1: The Characteristics Recommended for Diagnosis of Malnutrition

1. Inadequate energy intake as measured by nutrients consumed or administered compared with estimated energy requirements
2. Unintentional weight loss as measured by a percentage of weight loss from baseline regardless of the body mass index
3. Muscle mass depletion observed at temples, clavicles, shoulders, interosseous muscles, scapula, thigh and calf muscles using a scale ranging from mild to severe
4. Subcutaneous fat depletion observed especially from orbital and triceps areas, and/or fat overlying the ribs using a scale ranging from mild to severe
5. Localized or generalized fluid accumulation in extremities, vulvar/scrotum, and/or ascites that can mask weight loss and
6. Diminished functional status as measured by hand-grip.

Source: White, Guenter, and Jensen, 2012.

Early recognition of malnutrition is imperative using appropriate nutritional screening tools. The identification of two or more of the characteristics mentioned above is suggested for the diagnosis of adult malnutrition because no one parameter is definitive. Patients should be assessed regardless of the type of setting (acute, chronic, or transitional care settings) to ensure stability and improvements in patients' nutritional status. Patients deteriorate quickly regardless of the type of malnutrition they present with either starvation or chronic disease-related malnutrition, warranting close follow-up, and care.

A two-step approach was proposed by the Global leadership initiative on Malnutrition (GLIM) for the diagnosis of malnutrition. The first step of diagnosing a patient with malnutrition involves assessing to identify patients at nutritional risk using a validated screening. The second

step consists of an assessment for diagnosis and grading the severity of malnutrition. There are five criteria to be used for malnutrition diagnosis, three of which are phenotypic: "unintentional weight loss, low BMI, and loss of muscle mass and two etiologic: reduced food intake assimilation and inflammation or disease burden" (Cederholm et al., 2019).

Table 2: GLIM Criteria for the Diagnosis of Malnutrition

Phenotypic Criteria			**Etiologic Criteria**	
Weight loss (%) >5% within the past 6 months, or > 10% beyond 6 months	Low body mass index (kg/m2) <20 if <70 years or <22 if >70 years Asia: <18.5 if <70 years or <20 if >70 years	Reduced muscle mass Reduced by validated body composition measuring techniques	Reduced food intake or assimilation <50% of EER >1 week, or any reduction for >2 weeks, or any chronic GI condition that negatively impacts food assimilation or absorption	Inflammation Acute disease/injury or chronic disease-related.

GI = gastro-intestinal, EER = estimated energy requirements
Source: Cederholm et al., 2019.

Disease burden and inflammation have become widely accepted etiologic criteria in existing screen and assessment tools. Although severe inflammation may be easy to distinguish, clinical judgment is incumbent to recognize that of a mild degree. Laboratory markers of inflammation can act as supportive measures see [Table 5].

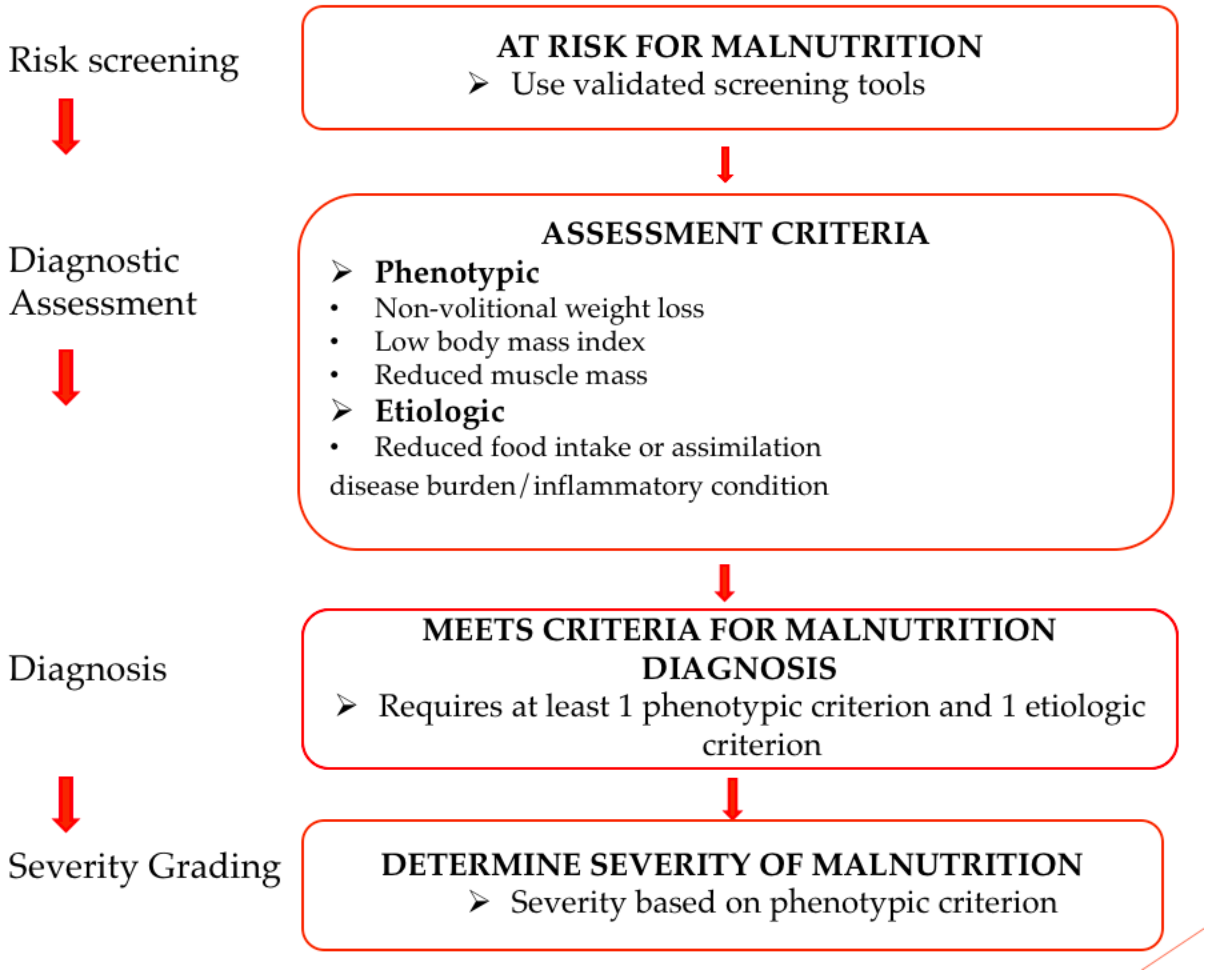

Figure 2: GLIM diagnostic proposal for screening, assessment, diagnosis, and grading of malnutrition

Source: Cederholm et al., 2019.

Prevalence of Malnutrition

Malnutrition is prevalent in United States hospitals, in skilled nursing facilities, in assisted living, and even in some patients with chronic medical conditions living at home. Malnutrition is quite common in hospitalized patients yet, remains underdiagnosed, especially in the frail and elderly population. Only 7.1% of the hospitalized population is diagnosed with malnutrition (Weiss et al., 2013). However, it is estimated that 30% to 50% of the hospitalized population are malnourished depending on the settings and the criteria used to define it (Jensen et al., 2009;

Kirkland et al., 2013; Malone and Hamilton, 2013; Corkin et al., 2014 Mulasi et al., 2016). Due to its high prevalence amongst hospitalized patients, malnutrition can be considered the most common disease condition in the hospital.

The implication of improper recognition or missed diagnosis of malnutrition could lead to significant financial burdens, see [Appendix H] (Goates, Braunshweig, and Arensberg, 2016). The economic burden of malnutrition has been estimated to be around $157 billion in the United States (Snider et al., 2014), and hospital stays involving malnutrition accounted for $49 billion (Barrett, Bailey and Owen, 2016). Additionally, malnutrition contributed to a longer LOS by an average of 11 days and was found to have higher rates of readmission or to require ongoing services such as home health care following discharge (Weiss et al., 2013).

Consequences of Malnutrition

There are severe consequences of malnutrition. If left untreated, exacerbate morbidities and lead to higher infection rates, increased mortality rates, a longer hospital LOS, increased readmission rates, and increased costs (NAIT and A.S.P.E.N Public Policy Committee and Board of Directors, 2010).

The Relationship between Inflammation and Malnutrition

Inflammation is a risk factor for malnutrition. Acute and chronic inflammation is integral to determine the etiology of malnutrition (Jensen et al., 2009). Therefore, A.S.P.E.N and the Academy method attempt to evaluate the presence and severity of the inflammatory process and how inflammation contributes to a patient's malnutrition (White et al., 2012). The onset of an inflammatory process begins with an insult to the body from trauma, pathogen, or other disease-causing agents. The developed inflammatory response increases cytokine production, which subsequently signals hepatocytes to suppress the production of negative acute-phase proteins (e.g. albumin, pre-albumin, and transferrin) in favor of freeing amino acids for the production of

positive acute-phase proteins (e.g. C-reactive protein and ferritin) (Gabay and Kushner, 1999). During pro-inflammatory states, hepatic transport proteins, such as albumin and pre-albumin reduces. Of note, these two acute phase proteins are poor indicators of nutritional status. The down-regulation of negative acute-phase proteins allows for more amino acids to be used for producing positive acute-phase proteins, which will help mitigate the consequences of infection and modify the immune response. Inflammation is often accompanied by anorexia, further compromising nutrition status. Some disorders and interventions may precipitate malnutrition because they adversely affect the body's ability to ingest or absorb nutrients or because they impose diet restrictions or other limitations.

Critical illness or injury, for example burns and cancer, promote an acute inflammatory response that leads to the breakdown of muscle mass, which may add to the morbidity of malnourished patients in severe cases (Hill, 1997). The inflammatory state in most diseases is chronic with the severity being impacted by the progression and severity of the disease, at which point tenacity of inflammation would result in severe muscle wasting associated with functional impairment; this would be termed "disease-related malnutrition" (Jensen et al., 2010). Disease-related malnutrition is, in part, attributed to reduced nutrient intake in addition to the presence of acute inflammation. It is essential to "recognize the presence or absence of a systemic inflammatory response because the inflammatory component has both diagnostic and therapeutic implications" (Jensen et al., 2009).

According to the Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient, "enteral nutrition should be initiated within the first 24-48 hours in the critically ill patient who is unable to maintain volitional intake" (McClave, 2016). Nutrition Interventions may not be as effective due to the presence of inflammation, and if

malnutrition is associated with this, it may compromise the clinical response to medical therapy. It is important to clarify the type of inflammation present in any degree, be it mild, moderate or severe, or transient or sustained. The priority for nutrition intervention, while medical treatment is provided, is to provide adequate and the appropriate nutrients to support the essential organs in the presence of a severe degree of inflammation. To achieve a positive response to nutrition intervention inpatient with malnutrition-related to chronic disease, successful treatment of underlying disease is of utmost importance.

The etiology-based classification of malnutrition developed by A.S.P.E.N/AND includes the understanding of how pro-inflammatory states affect malnutrition and seek to identify an etiology on a case-by-case basis as a framework for determining malnutrition. The first etiology, social/environmental/behavioral circumstances are when there is pure starvation, and inflammation is absent. Acute illness or injury and chronic illness incorporate different degrees of inflammation. Acute illness or injury involves inflammation that is short-lived and of much higher intensity. Chronic disease describes inflammation of a long-term condition with a mild to moderate severity (White et al., 2012; Jensen et al., 2010). Table 2 presents examples of medical conditions and their associated malnutrition etiolog

Table 3: The inflammatory States Associated with Various Medical/Surgical Diagnoses

Malnutrition Etiology	Associated Inflammatory Condition	Common Medical/Surgical Diagnosis
Acute illness/injury (short duration)	A heightened, intense inflammatory response	Critical illness; significant infection/sepsis; adult respiratory distress syndrome; systemic inflammatory response syndrome; severe burns; major abdominal surgery; multi-trauma; closed head injury; severe acute pancreatitis; postoperative ileus
Chronic illness (>3-month duration)	Mild to a moderate inflammatory response	Cardiovascular disease; congestive heart failure; cystic fibrosis; inflammatory bowel disease; celiac disease; chronic pancreatitis; rheumatoid arthritis; solid tumors; hematologic malignancies; cerebrovascular accident; neuromuscular disease; dementia; organ failure/transplant of the kidney, liver, heart, lung, or gut; periodontal disease; pressure wounds; chronic obstructive pulmonary disease; HIV; lupus; small bowel obstruction; prolonged ileus
Social/behavior/environmental circumstances	No inflammatory response	Starvation; anorexia nervosa; compromised food intake in the setting of financial disparity; dementia; alcohol/drug abuse; pain; small bowel obstruction

Source: Jensen et al., 2010; Malone and Hamilton, 2013

Malnutrition Screening and Assessment

The assessment of the nutritional status in hospitalized patients is a continuing process that starts with the administration of feeding either oral or through nutrition support, and this is not finished until the patient is discharged from the hospital setting. The continuing process of nutrition assessment begins with an identification of nutritional risk. Still, it goes on to determine energy and protein needs and goals, evaluate tolerance and monitor the adequacy of nutrition therapy delivery (Hurt, 2016). Critically ill patients are more predisposed to be at risk for poor nutritional status, and they also tend to develop malnutrition throughout their acute illness. The use of validated screening tools has to lead to increased meal intake (Yordy, Roberts, & Taggart, 2017). It has also led to the improvement of nutritional care and a lower prevalence of malnutrition (Eglseer, Halfens, & Lohrmann, 2017). Many screening and assessment tools and procedures fail to appreciate the role of the inflammatory response on acute phase proteins that are frequently used

as the primary indicator of nutritional status (Jensen et al., 2010; Soeters & Schols, Annemie, 2009).

A variety of nutrition screening tools exist, but not all have been appropriate for use in acute care or medical-surgical adult patient populations. This is because of the different criteria and cut-offs used and might not have been designed for purpose or populations. Table 4 lists screening and assessment tools with established reliability and validity. Nutrition assessment based on the tools listed below could be a complicated process because they frequently involve an assessment of adequate nutritional intake, unintentional weight loss, signs, and symptoms of nutrient deficiency or excess. The main challenge with this is that the assessments can be subjective per personal experience altering the information needed for accurate diagnosis of malnutrition. A lot of these tools listed have been validated for use in a different setting, but only the Nutritional Risk Screening 2002 (NRS-2002) and Nutrition Risk in Critically ill (NUTRIC) tools are recommended for use in critically ill adult patients because of their ability to account for nutrition status with the severity of disease (McClave et al., 2016).

Biomarkers of Malnutrition and Inflammation

Health practitioners have sought a fast, easily obtained laboratory values usually involving serum biochemical, measured as part of the routine blood test to identify patients at risk of being malnourished (Zhang et al., 2017). The advantage of using blood diagnostics ensures instantaneous nutrition assessment and quick intervention for patients who are at risk of malnutrition or malnourished. Albumin and pre-albumin are protein markers once used to diagnose malnutrition during hospital admissions (Taylor et al., 2016; Davis et al., 2012). However, studies have revealed that negative acute-phase proteins are affected "by many other factors such as inflammation, infection, liver damage, and fluid status" (Bharadwaj et al., 2016). Hence albumin and pre-albumin are no longer recommended for malnutrition diagnosis by A.S.P.E.N. and AND;

instead, they propose that malnutrition is diagnosed if least two of the characteristics listed in Table 1 are met. “These acute-phase proteins appear to reflect better the severity of the inflammatory response rather than poor nutrition status” (Jensen et al., 2009; Jensen et al., 2010).

Routine Clinical Laboratory Measurements

Routine Clinical Laboratory Measurements (RCLMs) had been indicated to be a prediction of mortality in older adults (Van Houwelingen et al., 2013). The level of serum albumin and cholesterol are predictors of hospital mortality, infections, and prolonged LOS (Delgado et al., 2002). Serum cholesterol, albumin, creatine, hemoglobin, and lymphocyte counts correlate with morbidity and mortality and are markers of malnutrition (Kubota et al., 2012). A study by Chen et al., 2015 showed significant associations between nutrition risk and RCLMs and adverse outcomes; their study demonstrated that ‘at risk’ not only correlates with increased incidences of abnormalities of nutritional markers but also closely associates with abnormalities of other biomarkers of RCLMs. Another study showed that malnourished patients had significantly lower serum albumin, total cholesterol, total lymphocyte count, hemoglobin, and hematocrit than well-nourished patients (Lee et al., 2013). Furthermore, it has been found that that malnutrition was significantly associated with some RCLMs such as albumin, prealbumin, protein, renal function markers, corrected calcium, high-density lipoprotein, cholesterol, triglycerides, hemoglobin, and red blood cells (Felder et al., 2016; Miao et al., 2018; Zhou et al., 2015; Demir 2015).

Table 4: Malnutrition Screening and Assessment Tools

Instrument	Anthropometry and diet-related	Severity of illness	Other (Physical, Psychological Variables or Symptoms)
SCREENING TOOLS			
Malnutrition Screening Tool (MST) Ferguson et al., 1999	Appetite, unintentional weight loss		
Malnutrition Universal Screening Tool (MUST) Elia, 2003	BMI, change in weight	Presence of acute disease	
Nutrition Screening Tool (NST) Skipper et al., 2012	Appetite, BMI, unintentional weight loss		
Nutrition Risk Screening 2002 (NRS-2002) Kondrup et al., 2003	Weight loss, BMI, food intake	Diagnosis (severity)	
NUTRITION ASSESSMENT TOOLS			
Mini Nutritional Assessment (MNA) Guigoz, 2006	Weight data, height, mid-arm, circumference, calf circumference, diet history, appetite, feeding mode	Albumin, pre-albumin, cholesterol, lymphocyte count	Self-perception of nutrition and health status
Subjective Global Assessment (SGA) Detsky et al., 2008	Weight history, diet history	Primary diagnosis, stress level	Physical symptoms (subcutaneous fat, muscle wasting, ankle edema, sacral edema, ascites), functional capacity, gastrointestinal symptoms

Blood biochemical tests could still be used to support the presence of inflammation and further contribute to the identification of the etiologic basis of the diagnosis of malnutrition. A review published by Zhang et al., (2017) found that BMI and numerous blood biochemical markers, including albumin, pre-albumin, hemoglobin, total cholesterol, and total protein, are useful in diagnosing malnutrition in adults, even in the presence of chronic inflammation.

Inflammatory Biomarkers

A patient's medical diagnosis alone should not be used to determine the malnutrition etiology, parameters for evidence of inflammation should be considered. There are currently

inconsistent views on the interpretation of malnutrition biomarkers, and there is research in progress on the effect of nutritional biomarkers during a concurrent inflammation. The underlying pathophysiologic mechanism and the impact on laboratory findings of malnutrition in hospital settings are still completely misunderstood (Schutz et al., 2014). Inflammation in both acute and chronically ill patients is thought to have a significant impact on nutritional status. Additionally, dietary factors have an effect on the response to inflammation and clinical outcomes (Felder et al., 2016). Some studies have evaluated the impact of inflammation on malnutrition. A study by Felder et al., 2016 showed that malnutrition was significantly associated with the inflammatory markers procalcitonin and albumin. The levels of the negative acute-phase proteins are typically reduced during inflammation with a simultaneous rise in the positive acute-phase proteins such as C-reactive protein (Shenkin, 2006; Myron et al., 2007). Table 5 lists malnutrition and inflammatory markers that can assist in evaluating patients for the presence and severity of inflammation. This table is not all-inclusive; although laboratory markers are beneficial for evaluation inflammation, they should be used in addition to other assessment data, such as medical history, nutrition-focused physical examination, and functional assessment, to diagnose malnutrition. Hence inflammatory markers should be considered within a broader scope of the patient's medical situation.

Neutrophil lymphocyte count ratio (NLCR) is a prognostic indicator for patients with various diseases. It has been established to be associated with mortality and morbidity, and it is a cost-effective inflammation marker (Kolaczkowska and Kubes 2013; Oncel et al., 2015; Horne et al., 2005; Karakas et al., 2016). NLCR can be used as an indicator of systemic inflammation has been shown to correlate positively with mortality and poor prognosis in various clinical conditions and most especially in critically ill patients (Kaya et al., 2019; Zahorec, 2001). It can be derived from the complete blood count parameters, absolute neutrophils, and absolute lymphocyte, which

are performed routinely in hospitals. When an injury occurs, neutrophils and lymphocytes are the first inflammatory markers and act as the first line of defense against foreign invaders. Their main job is to activate significant cell types involved in acute and chronic inflammation. NLCR is determined by dividing the absolute neutrophil count by the absolute lymphocyte count; the figured derived from this is used to indicate the presence of inflammation. Some studies have suggested that NLCR may also be related to nutritional status, especially in the elderly population (Min et al., 2018; Zhang et al., 2018; Zhao et al., 2018). NLCR has been used to determine the prognosis of cancer, community pneumonia, sepsis coronary artery disease, and Alzheimer's disease (Lee et al., 2018; Bhat et al., 2013; Chen et al., 2015; and Proctor et al., 2012). Furthermore, clinical studies have shown that NLCR is not just an inflammatory biomarker. It is also a prognostic predictor disease such as cancer of the lungs, liver, & ovarian and non-malignant conditions such as cardiovascular diseases such as acute ischemic stroke& chronic heart failure (Min et al., 2018; Yin et al., 2015; Zhang et al., 2018; Zhao et al., 2018; Tan et al., 2015; Yu et al., 2018; Yan et al., 2017; Kaya et al., 2019). Data from these studies suggest that NLCR may also be related to the nutritional status of patient and nutritional status be associated with mortality and prognosis. (Favaro-Moreira, 2016; Alvarez-Hernandez, 2012, Diekmann, 2013, Correia, 2003; Rasheed and Woods, 2013). No universal value for cut-off is currently available. Forget et al., 2017 identified the average NLCR values in the non-geriatric population in good health to be between 0.78 and 3.53, and Lee et al. (2018) found the mean value for NLCR across all ages to be 1.65. A review by Pirozzolo et al. (2019), consisting of 6457 patients, found the cut-off value ranges from 1.7 to 5. So far, there are insufficient data on the association between NLCR and nutritional status.

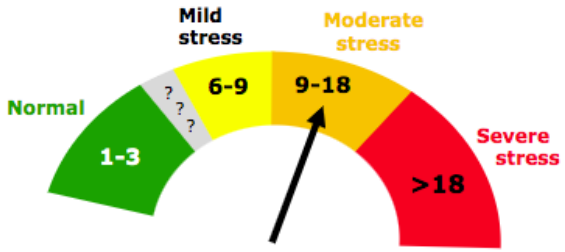

Figure 3: NLCR optimal cutoff value

Source: https://emcrit.org/pulmcrit/nlr/

Procalcitonin

Procalcitonin (PCT) is a biomarker that detects a bacterial infection. Serum levels of PCT would typically decrease following the administration of the appropriate antibiotics. PCT has a half-life of 20 to 24 hours; hence a decrease by up to 50% should be observed with the proper host immune response and antibiotic therapy (Lippi and Sanchis-Gomar, 2017). PCT is elevated in patients with trauma, burns, cancer, cardiogenic shock, cirrhosis, chronic kidney disease, and in patients on peritoneal dialysis (Hatzistilianou, 2010; Grace and Turner, 2014). The prognostic value of PCT has shown clinical significance by providing clinicians with a positive correlation between disease severity and elevated PCT serum levels, especially in patients that have sepsis (Cleland and Eranki, 2019).

Table 5: Laboratory Test Traditionally Used to Detect Malnutrition and Inflammation

Malnutrition	Inflammation
Albumin	C-reactive protein
Pre-albumin	White blood cell count
Transferrin	Cytokines (interleukins, interferons, tumor necrosis
Retinol-binding protein	factor)
Total protein	Fibrinogen
Lipids (cholesterol, HDL, and Leptin)	Sedimentation rates
	Lipoprotein(a)
	Arginine depletion

Source: White et al., 2012 and Malone and Hamilton 2013.

The Nutrition Risk in Critically Ill (NUTRIC) Score

NUTRIC score is a validated tool that is designed for critically ill patients, and it can be used to identify critically ill patients in the ICU that would be most likely to benefit from nutritional support. It is the first validated nutritional risk assessment tool designed explicitly for critically ill patients and was published by Heyland et al., (2011). The obtained score from the NUTRIC tool seeks to recognize critically ill patients that will gain from aggressive protein-energy administration during ICU admission, thereby reducing mortality rates and days on ventilation. The NUTRIC-score consists of variables such as age, APACHE II score, SOFA score, number of comorbidities, days from hospital admission to ICU admission, serum interleukin 6 (IL-6) level. In most cases, the IL-6 is not routinely measured, leading to the development of a modified NUTRIC score (mNUTRIC), which was validated by Rahman et al. (2016). The mNUTRIC form includes all the variables from the original form, except for IL-6. The mNUTRIC has a maximum score of 9; the scores 0 to 4 are classified as low nutritional risk, while 5 to 9 are classified as a high nutritional risk.

Table 6: mNUTRIC score interpretation

NUTRIC Score	Risk Level	28-day mortality
0	**Low risk**	~1%
1		~2%
2		~3%
3		~8%
4		~11%
5	**High risk**	~20%
6		~30%
7		~45%
8		~58%
9		~70%
10		~80%

The Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) Score

Knaus et al. 1985 designed the APACHE II score as a mortality prediction tool. This tool is not intended to guide the medical management of patients during their stay in the ICU. It is a severity-of-disease classification system, and it generates a point score ranging from 0 to 71 based on twelve physiologic variables, age, and underlying health conditions. Higher scores correspond to more disease severity and a higher risk of mortality. The twelve routine physiological measurements are as follows: "AaDO2 or PaO2 (depending on FiO2), temperature, mean arterial pressure, pH arterial, heart rate, respiratory rate, sodium (serum), potassium (serum), creatinine, hematocrit, white blood cell count, and Glasgow Coma Scale" (Knaus et al. 1985). The APACHE II score is usually calculated on the first day of ICU admission to help determine the patient's mortality risk for hospitalization and utilized in addition to information about past health histories such as surgery history, severe organ insufficiency, immunocompromised state, and baseline demographic.

Table 7: APACHE II approximated in-hospital mortality rates

APACHE II Score	Nonoperative	Postoperative
0-4	4%	1%
5-9	8%	3%
10-14	15%	7%
15-19	25%	12%
20-24	40%	30%
25-29	55%	35%
30-34	73%	73%
>34	85%	88%

Sequential Organ Failure Assessment (SOFA) Score

The SOFA score is a morbidity severity score and mortality estimation tool, which numerically quantifies the number and severity of failed organs. The SOFA score allows for the calculation of both the number and the severity of organ dysfunction in six organ systems: respiratory, coagulatory, liver, cardiovascular, renal, and neurologic (Vincent et al., 1998). The SOFA score can measure individual or aggregate organ dysfunction (Vincent et al., 1996). The SOFA scoring system is helpful in the prediction of clinical outcomes of critically ill patients.

Table 8: SOFA approximated in-hospital mortality rates

SOFA Score	Mortality if the initial score	Mortality if the highest score
0-1	0%	0%
2-3	6%	2%
4-5	20%	7%
6-7	22%	18%
8-9	33%	26%
10-11	50%	46%
12-14	95%	80%
>14	95%	90%

Systematic Review

Description of the Evidence

Literature Search

This comprehensive systematic review was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Data Sources and Search Strategy

A search was conducted on PubMed, Cochrane, Medline, CINAHL, EBSCO databases. Manual screening of the bibliographic references of selected studies was done to find possibly additional eligible studies. The search term used was "oral nutrition support," 'enteral nutrition," "parenteral nutrition," "disease-related malnutrition," "nutrition support and malnutrition," "malnutrition and inflammatory biomarkers," "nutrition support and clinical nutrition outcomes."

Inclusion and Exclusion Criteria

Studies were included in the systematic review if they met the following characteristics:

1. Type of study: Clinical study, clinical trials, multi-center observational study, prospective study, retrospective study, and randomized control trial with the publication date, not more than five years were included.
2. Population: Critically ill and hospitalized patients, > 18 years of age.
3. Intervention: Enteral nutrition vs parenteral nutrition; enteral nutrition+ parenteral nutrition; enteral or parenteral nutrition vs oral diet
4. Trial outcomes: The studies reported relevant clinical outcomes. Where available, data regarding mortality rate, including ICU, hospital LOS, duration of mechanical ventilation, infection rates, nutritional, biochemical, metabolic, and immunological outcomes, were extracted.

Studies were excluded if it was done in a nursing home, pediatrics, pregnant women, patients of home nutrition support, and outpatients.

Data Extraction

Titles and abstract resulting from the search strategy were evaluated. Data were extracted to a matrix table that consisted of following characteristics: names of authors, year of publication, study location, method and design used in the study, participants (types of participants, number of participants, age, attrition rate, and gender), prescribed nutrition support, study duration, and study findings. See Table 9.

Quality Assessment

The included studies were assessed for quality using the Critical Appraisal Skills Programme (CASP) appraisal tools. The tool is designed to help with the process of critically appraising articles in many types of research. CASP tool contains eleven criteria evaluating the purpose of the study, sources of bias, sampling, participation rate, study power, the methods used in collecting data, and confounding variables. The requirements were rated yes, no, or can't tell. An overall rating for the study as "positive "or "neutral" was provided.

Results

Study Characteristics

Twenty-five studies met the inclusion criteria for this systematic review on the effect of nutrition support on nutrition and clinical outcomes. The body of evidence consisted of eleven randomized control trials (RCTs) (Kim et al., 2015; Ding et al., 2015; Liu et al., 2015; Zheng et al., 2015; Li et al., 2015; Wang et al., 2015; Baker et al., 2015; Ostadrahimi et al., 2016; Barneveld et al., 2016; Zhang et al., 2016; Wischmeyer et al., 2017), six retrospective studies (Chen et al., 2014; Yin et al., 2014; Yao et al., 2015; Lu et al., 2016; Sun et al., 2017; Terzi et al., 2017), three

prospective studies (Shankar et al., 2015; Declercq et al., 2015; Lopez et al., 2017), one multicenter cohort study Reignier et al., (2015), one prospective randomized intervention trial Kruger et al., (2016), one retrospective and prospective study Finlay et al., (2017), and one prospective randomized pilot trial Ridley et al., (2018).

The studies were carried out between 2007 and 2016. Eleven studies were carried out in China, one in Japan, South Korea, India, New Zealand, Canada, United States, United Kingdom, Iran, Netherlands, Germany, Spain, two in Belgium, Australia, and three in France. The sample sizes ranged from 30 to 3032.

Table 9: Characteristics of studies included in the systematic review

	Study	Study design	Population/ Sample Size Age and Gender	Prescribed NS	Study duration	Health outcomes
1	Chen et al. (2014) China	Retrospective study	P= Patients who received total gastrectomy n= 74 Age= 61.0 Attrition rate= 2.7% Gender= Female (48.6%)	EEN vs TPN	May 2011 to May 2013	There was a statistically significant difference in the time to first defecation and time to first "soft diet" intake ($p<.05$). In addition, the hospitalization time of the group EEN was shorter than the group TPN. The incidence of complications was 22% in the EEN and 20% in the TPN group. There was no significant difference in complications between the EEN and TPN groups. Serum albumin, total protein, and PG-SGA reduced in both groups in the early stage of post-operation, after which the EEN group increased gradually by 3-5 days. The TPN Group increased 7-9 days later. There was a significant reduction in the body weight of patients in the TPN group when compared to the EEN group on POD day 21 ($p <.05$).
2	Yin et al. (2014) China	Retrospective cohort study	P= Patients with abdominal trauma n= 88 Age= 39 Attrition rate= Gender= Female (20.4%)	Early vs. delayed EN feeding	January 2007 to December 2012	There were no significant differences in feeding intolerance between the early-initiation group and the delayed-initiation group ($p>.05$) The patients in the early-initiation group had significantly reduced infectious

						complications and shorter length of stay in ICU and hospital (p<.05) than the patients in the delayed-initiation group.
3	Takesue et al. (2015) Japan	Prospective randomized trial	P= Pt who underwent thoracospic Esophagectomy n= 47 Age= 62.2 Attrition rate= 6% Gender= Female (21.2%)	EN or TPN	March 2012 to June 2014	Weight loss post-operation was significantly prevented in the EN group (p=.020). No differences in pre-albumin levels at POD 10 were observed between the two groups (p .257). No differences were observed in total bilirubin and CRP levels, and duration of ICU (p=.327) and postoperative hospital stay (p=.058).
4	Kim et al. (2015) South Korea	Pilot randomized control trial	P= Living donor liver transplant n= 36 Age= 54 Attrition rate=0% Gender= Female (8.3%)	EN	January 2013 to October 2013	The incidence of bacterial infection was statistically significantly lower in the EN group than in the control group (p=043). The incidence of bile duct complications in the EN group was lower than in the control group (p=.041). Multivariate analysis showed that early enteral feeding was closely associated with bacterial infections (OR, .178; p=.041). There was no statistically significant difference in nutritional status between both groups.
5	Ding et al. (2015) China	Randomized control trial	P= Gastric cancer patients n= 106 Age= 58.5 Attrition rate= N/A Gender= Female (33.9%)	Preoperative EN vs. Postoperative EN	January 2010 to December 2011	Prealbumin and IgG levels of the experimental group were significantly higher than those of the control group on POD 10 (p<.05). There was a statistically significant reduction in the IL-6 level of the experimental when compared to the control group (p< .05).
6	Shankar et al. (2015) India	Prospective observational study	P= Critically ill patients n= 308 Age= 55.59 Attrition rate= N/A Gender= female 36.4%	EN initiated within the first 6 hours vs. EN initiated after 6 hours	January 2012 to December 2012	There were no significant differences in percentages of calories and proteins delivered on day three between patients in both groups (p<0.05). There was no statistically significant difference in the number of patients that achieved the target calories and protein on day 3 in both groups (p=.5). There were no

						significant differences in the ICU LOS between the groups. 77.1% of patients were discharged in the group in whom EN was initiated within 6 hours, and 67.6% of patients were discharged in the group where EN was delayed. There was no significant difference in mortality rate between groups. There was no statistically significant difference in the incidence of EN interruptions between the two groups (p=.087).
	7	Liu et al. (2015) China	Randomized control trial	P= Patients after gastric cancer surgery n= 272 Age= 67.7 Attrition rate= N/A Gender= Female (33.8%)	EEN or EPN	January 2006 to December 2013	On POD 7, the body weight, transferrin, albumin, pre-albumin for both groups were significantly reduced compared with the levels on preoperative day 1 (p<.01). A significant decrease was observed in transferrin and pre-albumin in the PN group compared with the EEN group (p< .01). There was no significant difference in body weight and albumin between the two groups (p>.05). The HS-CRP level of both groups was significantly higher than on preoperative day 1; the PN group had significantly higher HS-CRP levels than the EEN group (p< .01). The anal exhaust time, length of hospital stays, and nutritional support cost were significantly lower in the EEN group than in the PN group (p< 0.01). There was no statistically significant difference in the incidence of complications between the two groups (p> 0.05).
	8	Zheng et al. (2015) China	Randomized control trial	P= Acute stroke and dysphagia n= 146 Age= 71.5 Attrition rate= N/A	EEN Vs. family managed nutrition	July 2011 to December 2013	The infection rate in the treatment group was significantly lower than that in the control group (chi-squared 5.265; p= .022. The nasogastric nutrition group had an improved nutritional status, reduced

			Gender= Female (41.8%)			nosocomial infection, and reduced mortality rates after 21 days compared with patients that their nutrition was managed by their families. The nasogastric nutrition group showed a lesser score on the NIHSS than the control group.
9	Reignier et al. (2015) France	Multicenter cohort study	P= Patients with invasive mechanical ventilation and shock n= 3032 Age= 66.3 Attrition rate= N/A Gender= Female (36.7%)	Early nutrition support (EN, PN & EN + PN) vs. delayed nutrition support	December 1996 to February 2013	Early nutrition was associated with lower day-28 mortality (p=.01] and day-7 mortality (p< .001) but not with lower day-7 to day-28 mortality (p=.98). Early nutrition increased VAP risk over the 28 days (p=.046) and until day 7 (p< .001) but decreased VAP risk from days 7 to 28 (p< .001).
10	Li et al. (2015) China	Randomized control trial	P= Gastric cancer surgery patients n= 300 Age= 60 Attrition rate= N/A Gender= Female (48.7%)	EEN	July 2010 to May 2014	The postoperative fever duration anal exhaust time and length of hospitalization differed significantly (p< .05). At POD 3 and 7, the CD3+, CD4+, natural killer cell, albumin, and pre-albumin levels and CD4+/CD8+ ratio were significantly higher in the experimental group than the control group (p < .05). CD8+ cell counts were statistically significantly lower in the experimental group than the control group (p< .05).
11	Wang et al. (2015) China	Randomized control trial	P= Gastric cancer surgery patients n= 200 Age= 55 Attrition rate= N/A Gender= Female (35%)	EN was starting one week before surgery (study group) and EN starting early after surgery	June 2010 to June 2012	The albumin and pre-albumin levels of the patients in both groups decreased one day after the operation (p<. 05). The levels increased by the end of the study (p<. 05). The pre-albumin level of the study group was higher than that of the control group at ten days after the operation (p<. 05). The IgG level of the experimental group was statistically

				(control group).		significantly higher than that of the control group at ten days after surgery (p<. 05). On POD 10, the inflammatory reaction indicators of the study group were lower than those of the control group (p<. 05).
12	Yao et al. (2015) China	Retrospective cohort study	P= Patients undergoing hepatectomy for hepatocellular carcinoma n= 79 Age= 54 Attrition rate=N/A Gender= Female (20.3%)	preoperative EN vs. postoperative EN	February 2010 to December 2014	The preoperative EN group had a significantly short postoperative hospital LOS, less exogenous albumin infusion, earliest first exhaust time, and first defecation time (p<.05). No significant differences were observed in the incidence of complications (32.6% versus 52.8%, p<.070), infectious complications (7.0% versus 8.3%, p= .1), and major complications (14.0% vs. 11.1%, p=.969).
13	Baker et al. (2015) Australia	Randomized control trial	P= Patient with suspected advanced epithelial ovarian cancer n= 109 Age= 63 Attrition rate=N/A Gender= N/A	EN vs. oral diet	2009 to 2013	There was no statistically significant difference in the quality of life between both groups at any time point. There was a trend towards improved nutritional status in patients who received EN, but the differences were not statistically significant.
14	Declercq et al. (2015) Belgium	prospective interventional non-randomized trial	P= Radical cystectomy patients n= 94 Age= 66 Attrition rate= Gender= female (30.9%)	PN vs. Oral diet	March 2011 to March 2013	There was a statistically significant reduction in median length of stay, which was associated with the oral nutrition protocol [18 days (IQR 15–22) in the control group vs. 14 days (IQR 13–18) in the interventional group (p< .001)].
15	Ostadrahimi et al. (2016) Iran	Double blind randomized control trial	P= Burn patients, 20-70% TBSA n= 30 Attrition rate= 26.8% Age= 33.14 Gender= Female (26.7%)	EN	March 2013 to December 2013	The result of the study showed that SOFA score and hospital LOS decreased significantly in the group that used nutrition support (p<.05) when compared to those that did not. This resulted in improved immunity and better wound healing, causing a decrease in the infection rate.

16	Barneveld et al. (2016) Netherlands	Randomized control trial	P= Locally advanced or recurrent rectal carcinoma requiring major rectal surgery n= 123 Age= 64 Attrition rate= 4.9% Gender= Female (31.6%)	EN or PN	January 2009 to October 2011	The occurrence of anastomotic leakage was associated with early parenteral feeding (p=.012), a more prolonged hospital admission (p< .001), and more infectious complications (p< .001).
17	Lu et al. (2016) China	Retrospective	P= Patients that had a pancreaticoduodenectomy patients n= 347 Age= 58 Attrition rate= 2% Gender= Female (41.8%)	EN+PN vs TPN	February 2009 to January 2013	Patients with EEN + PN following PD had a higher incidence of delayed gastric emptying (16.1% vs. 6.7%, p=.016), pulmonary infection (10.3% vs. 3.6%, p=.024), and probably intraperitoneal infection (18.4% vs. 10.3%, p=.059), which might account for their longer nasogastric tube retention time (9 d vs. 5 d, P .006), postoperative hospital stay (25 d vs. 20 d, p= .055) and higher hospitalization expenses (USD10397 vs. USD8663.9, p=.008), compared to those with TPN.
18	Kruger et al. (2016) Germany	Prospective randomized intervention trial	P= Patients with biliopancreatic tumors n= 100 Age= 64.9 Attrition rate= 18% Gender= Female (43%)	PN	June 2012 to February 2014	Within three months prior to hospital admission, patients had a median self-reported loss of 4.0 kg. On multivariate analysis, the nutritional intervention increased body weight by 1.7 kg (p =.027), particularly in patients with malignant lesions 2.7 kg (p< .01).
19	Zhang et al. (2016) China	Randomized control trial	P= patients with burn-induced invasive fungal infection n= 120 Age= 45.34 Attrition rate= Gender= Female (45%)	EEN vs. PN	August 2011 to December 2013	The levels of serum albumin, total protein, and transferrin of the enteral nutrition group were significantly higher than that of the PN group (p <.05). In comparison, the levels of serum endotoxin and D-lactic acid of the form group were significantly lower (p <.05). The levels of IL-6 and TNF-α were decreased considerably in the EN group after treatment when compared with the PN group (p <.05). The mean healing

						time in the EN group was significantly shorter than that of the PN group (p <.05).
20	Wischmeyer et al. (2017) Canada, Uthe S, Belgium, and, France	Multicenter randomized control pilot trial	P= Mechanically ventilated patients n= 125 Age= 55.4% Attrition rate= N/A Gender= Female (52%)	EN or EN + SPN	June 2011 to January 2015	No statistically significant difference in the rate of infection and mortality rate in both groups. However, SPN + PN significantly increased calorie/protein delivery over the first ICU week by 30%.
21	Lopez et al. (2017) Spain	Prospective study	P= Hospitalized patients with NRS score >3 n= 145 Age= 65.2 Attrition rate= N/A Gender= Female (34.5%)	EN	September 2013 to June 2014	The LOS of patients who received early specialized nutrition support (SNS) was lower than those who did not (p=.001). There was a lower incidence of total complication and mortality in the patient who received early SNS, but there was no statistically significant difference.
22	Sun et al. (2017) China	Retrospective observational study	P= Surgical Septic patient n= 109 Age= 71 Attrition rate= 1.8% Gender= Female (41.2%)	EEN vs DEN vs TPN	February 2014 to December 2015	The Th1, Th17 percentages, and Th1/Th2, Th17/Treg ratios of the EEN group were significantly lower than those of the DEN or TPN group on the 14th day after admission (p<.05). Compared with TPN, DEN might tend to decrease the Th1 and Th17 percentages. EEN could improve the disease severity and clinical outcomes of septic patients; however, no difference in 28-day mortality was found between EEN and DEN groups.
23	Terzi et al. (2017) France	Observational retrospective cohort study	P= Patients receiving noninvasive ventilation n= 1075 Age= 68.9 Attrition rate= N/A Gender= Female (38.9%)	EN vs. PN vs. oral nutrition vs. no nutrition	2000 and 2015	EN versus no nutrition was associated with higher 28-day mortality (adjusted HR, 2.3; 95% CI, 1.2–4.4) and invasive mechanical ventilation needs (adjusted HR, 2.1; 95% CI, 1.1–4.2), as well as with fewer ventilator-free days by day 28 (adjusted relative risk, 0.7; 95% CI, 0.5–0.9).

24	Finlay et al. (2017) United Kingdom	Retrospective and prospective study	P= combined pancreas and kidney transplant candidates n= 59 Age= 39 Attrition rate= N/A Gender= Female (59.3%)	Nutritional assessment and EEN	October 2007 to Dec 2013	Patients who received EEN were less frequently in pre-dialysis status 41.4% vs. 26.7%, p .001; and had higher incidence of BMI <22.5 kg/m_2 (63.3% vs. 48.3%, p<.005). The need for PN within those that received EEN was statistically significantly lower (7.1% vs. 20.7%, p < .005).
25	Ridley et al. (2018) Australia and New Zealand	A prospective randomized pilot trial	P= Critically ill adults n= 100 Age= 59 Attrition rate= 1% Gender= Female (29%)	Supplemental PN + EN vs. Standard ICU care practices	February 2014 to January 2016	The intervention group received significantly higher energy and protein from EN and/or PN than the group than received the usual care (p<.0001). The use of antibiotics, ICU LOS, hospital LOS, mortality rate, and functional outcomes were similar between the two groups.

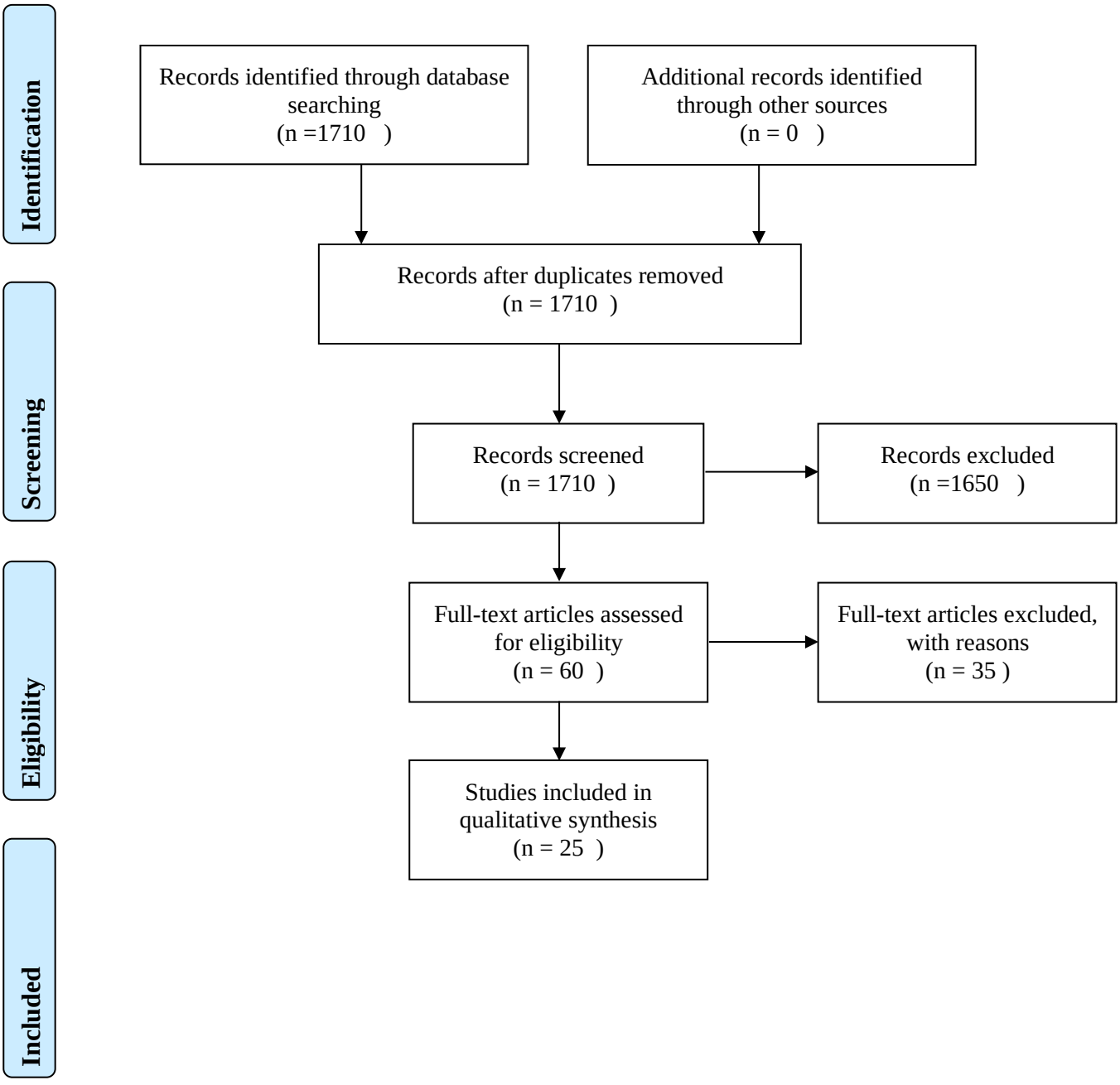

Figure 4: Flow diagram of the search and review process

Population

The baseline health status in these studies included participants who are critically ill (Ridley et al., 2018; Shankar et al., 2015), on mechanical ventilation (Reignier et al., 2015; Wischmeyer et al., 2017; Terzi et al., 2017) patients with abdominal trauma(Yin et al., 2014), patients that had an organ transplant (Kim et al., 2015; Finlay et al., 2017), patients who have cancer and underwent surgery (Chen et al., 2014; Takesue et al., 2015; Ding et al., 2015; Liu et al., 2015; Li et al., 2015; Wang et al., 2015; Yao et al., 2015; Declercq et al., 2015; Baker et al., 2015; Barneveld et al., 2016; Lu et al., 2016; Kruger et al., 2016; Sun et al., 2017), burns patients (Ostadrahimi et al., 2016; Zhang et al., 2016) and patients who had stroke status post dysphagia (Zheng et al., 2015). The mean age of the twenty-five studies ranged between 33 to 71.5 years. Female participation in the twenty-five studies was between 8.3% and 100%. Race nor ethnicity was not reported in the studies included in this systematic review.

Effects of Nutrition Support on LOS

Eleven studies were identified to have investigated the effects of nutrition support on hospital/ICU LOS. EN significantly decreased the LOS of ICU and hospital stay in six studies: (Yin et al., 2014, Ostadrahimi et al., 2016, Lopez et al., 2017, Liu et al. 2015, Li et al., 2015, Yao et al., 2015). One study (Barneveld et al., 2016) found that PN infusion was associated with a more extended hospital LOS, and one study Declercq et al. (2015) found that the control group had a shorter LOS vs. the experimental group. However, three studies (Takesue et al., 2015; Shanker et al., 2015; Ridley et al., 2018) found no significant difference in the effect of EN and PN infusion on LOS.

Table 10: PICO Chart

Population	Critically ill, organ transplant, surgery, burns and stroke s/p dysphagia adult male and female patient between ages of 18 -80 years
Intervention	enteral nutrition, parenteral nutrition, early enteral nutrition, supplemental parenteral nutrition, preoperative enteral nutrition
Comparators	Regular diet, no feeding, parenteral nutrition delayed enteral nutrition, postoperative enteral nutrition
Outcomes	**Intermediate Biomarkers/Physiological Effects** SOFA Tumor necrosis factor Pre-albumin Albumin Total protein Total bilirubin C-reactive protein Transferrin T-helper cells Interleukin-6 Immunoglobulin-G Change in body weight
	Health Outcomes/Clinical outcomes Infection rate Immunological outcomes Length of hospital stay Length of ICU stay Mortality rate Nutritional status

Effects of Nutrition support on Inflammatory Biomarkers

Six studies (Ding et al., 2015, Liu et al., 2015, Wang et al., 2015, Takesue et al., 2015, Zhang et al., 2016, Sun et al., 2017) identified from the literature search investigated the effects of EN or PN on inflammatory biomarkers such as IL-6, T-lymphocytes, T-helper cells, CRP and TNF α. They all found a significant reduction in these biomarkers when EN or/and PN was administered except for one study Takesue et al. (2015) that found no significant differences. Ding et al. (2015) found that the IL-6 level of the preoperative EN group was lower when compared to the postoperative EN group.

Effects of Nutrition support on Malnutrition Biomarkers

Seven studies (Chen et al., 2014, Ding et al., 2015, Liu et al., 2015, Li et al., 2015, Wang et al., 2015, Zhang et al., 2016, Takesue et al., 2015) identified from the literature investigating the effects of EN or PN on malnutrition biomarkers: albumin, pre-albumin, total protein, and transferrin. Chen et al. (2014) found that serum albumin, total protein in both the EN and TPN group increased gradually; however, these parameters increased faster in the EN group. Zhang et al. (2016) also found that the levels of albumin, total protein, and transferrin of the EN group were statistically significantly higher than those of the PN group. Takesue et al., (2015) found no significant difference in pre-albumin levels in both the EN and TPN group (Ding et al.,2015 and Wang et al., 2015) found that albumin and pre-albumin of the preoperative EN group were higher when compared to the postoperative EN group. Liu et al. (2015) saw a significant decrease in transferrin and pre-albumin in both the EN and PN groups and no significant difference in albumin in both groups. Li et al. (2015) found that albumin and pre-albumin were significantly higher with EEN administration.

Effects of Nutrition support on Mechanical Ventilated Patients

Two studies (Reignier et al., 2015 and Terzi et al., 2017) were identified from the literature to have investigated the effects of EN or PN or no nutrition or delayed nutrition support on patients receiving invasive mechanical ventilation and noninvasive ventilation. Early nutrition support was found to be associated with lower 28-day mortality, according to Reignier et al. (2015). On the contrary, Terzi et al. (2017) found that enteral nutrition vs. no nutrition was associated with higher 28-day mortality.

Effects of Nutrition support on Infections

Ten studies (Yin et al., 2014, Kim et al., 2015, Zheng et al., 2015, Li et al., 2015, Yao et al., 2015, Ostadrahimi et al., 2016, Barneveld et al., 2016, Wischmeyer et al., 2017, Sun et al., 2017 and Ridley et al., 2018) were identified to have investigated the effects of EN or/and PN on infections. They all found that the incidence of infection was significantly lower in the EN group except for (Yao et al., 2015, Wischmeyer et al., 2017 and Ridley et al., 2018) that found no significant differences in infection rates in either EN or PN group. On the contrary, Barneveld et al. (2016) found that higher infection rates were associated with only PN feedings.

Effects of Nutrition support on Mortality rates

Six studies (Reignier et al., 2015, Lopez et al., 2017, Terzi et al., 2017, Wischmeyer et al., 2017, Sun et al., 2017 and Ridley et al., 2018) were identified to have investigated the effects of EN or/and PN on mortality rate. Reignier et al. (2015) and Lopez et al. (2017) found that EN administration was associated with a lower mortality rate. (Wischmeyer et al., 2017, Sun et al., 2017 and Ridley et al., 2018) found no significant difference in mortality rate. Terzi et al. (2017) found that EN was associated with a higher mortality rate.

Conclusion

In this comprehensive systematic review, we found that the initiation time of nutrition support affects the clinical outcomes of patients. Overall, EN, as compared to PN, significantly reduced the rate of infectious complications, ICU & hospital LOS, and mortality rate. Besides, EN significantly reduced biomarkers of inflammation CRP, IL-6, T-lymphocytes, T-helper cells TNF α. The findings of the effect of EN/PN on biomarkers of malnutrition, such as serum albumin, total protein, and prealbumin, was conflicting. Some studies found a significant increase in albumin, total protein, and transferrin with EN administration, while other studies found no

significant difference in these biomarkers. In fact, some studies found no significant improvement in albumin and prealbumin with EN and PN administration. In contrast, some found a substantial decrease in transferrin and prealbumin with both EN and PN administration. Early EN infusion was found to be associated with lower 28-day mortality in ventilated patients. On the contrary, a study documented higher 28-day mortality with enteral nutrition versus no nutrition in ventilated patients.

CHAPTERS 3. METHODOLOGY

A retrospective chart review (RCR) was used to achieve the objectives of this study with a convenience sample of critically ill patients from Howard University Hospital Medical Intensive Care Unit (MICU). RCR uses pre-recorded, patient-centered data to answer one or more research questions (Worster and Haines, 2004). The data used exist in many forms: electronic databases results from diagnostic tests and documentation from healthcare providers. This methodology is widely used in many healthcare-based disciplines, and valuable information may be gathered from study results to initiate subsequent prospective studies.

Ethics and Approval

A letter of support was obtained from the chief medical officer (Appendix B), and the Institutional Review Board at Howard University approved the study (Appendix C). Because this was a retrospective study of data from the electronic medical record, the IRB gave a waiver for individual consent. The medical chart record of patients admitted from January 2019 to December 2019 was reviewed. Identifiable, private, or sensitive information of the participants was not obtained for this research. Datasets were stripped of all personal identifiers, which mitigates privacy risk. De-identification was achieved following the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. The "Safe Harbor Section 164.514(b)(2) was used to achieve de-identification following the HIPAA Privacy Rule. The eighteen types of identifiers (names, zip codes, all elements of dates, telephone numbers, vehicle identifies and serial numbers, fax numbers, device identifiers, email addresses, web universal resource locators, social security numbers, internet protocol addresses, medical record numbers, biometric identifiers, health plan beneficiary numbers, full-face photographs and any comparable images, account numbers, any unique identifying numbers, and certificates/license numbers) were removed. Each

participant was assigned a unique identification number. All data obtained were recorded on a password protected excel sheet. The master-list was saved on a laptop that is password protected. The computer was locked in a cabinet that could only be assessed by the principal investigator and student investigator. The following information was, however, recorded: date of admission, date of discharge, and age in years.

Setting

This research was a retrospective study conducted in the Medical Intensive Care Unit (MICU) at Howard University Hospital, Washington, DC.

Patients

Eligible patients were critically ill adults admitted to the MICU for at least three days, were older than 18 years of age, who were receiving who were administered enteral nutrition (EN) or parenteral nutrition (PN), or both for at least 72 hours. All critically ill patients with acute or chronic etiologies and those unable to self-feed were included in the study. Patients were excluded if their information was unavailable through electronic medical records, who had a prior history of EN or PN before ICU admission, who were admitted to the ICU for >60 days, and, with code status, do not resuscitate/intubate and have been placed on comfort care.

Data Collection

Patient Characteristics: Patient's baseline demographics information including (age and gender), body mass index, comorbidities, adequacy of nutritional support, time to initiation of nutrition support, nutrition support duration, mortality outcome, ICU admission diagnosis, length of stay (LOS) in the ICU, duration on mechanical ventilation, was obtained from patients' medical record. Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score (Appendix D) and Sequential Organ Failure Assessment (SOFA) score (Appendix E) were used to assess disease severity. Modified Nutrition Risk in Critically ill (mNUTRIC) score (Appendix F) was

used to assess patients' nutritional status. The patient was considered to be at low nutrition risk if they had mNUTRIC score less than or equal to four and high risk if they had mNUTRIC score greater than or equal to five. The Nutritional Risk Index (NRI) and Total Lymphocyte Count were also used to assess patients' nutritional status. NRI was calculated as [(1.519 × serum albumin, g/dL) + [41.7 × weight (kg)/ideal body weight (IBW; kg)]. Typically, NRI ≥ 100 indicates no evidence of malnourishment, 97.5 to 100 indicates mild, 83.5 to 97.5 moderate, and < 83.5 severe risks of malnourishment-related complications. TLC was calculated by multiplying lymphocyte count with the total white blood count. TLC was classified as >1500 cells/m^3, considered to be normal, 1200 to 1500 cells/m^3 indicates a mild degree of depletion, 800-1199 cells/m^3 indicates a moderate degree of depletion while <800 cells/m^3 indicates a severe degree of depletion. NLCR, WBC, transferrin, ferritin, procalcitonin, LDH, albumin was used to assess inflammatory or infection process. Hemoglobin, hematocrit, total protein, creatinine, glucose, total cholesterol, and HDL were used to assess nutritional markers. Data were recorded from the first day of ICU admission.

Routine Clinical Laboratory and Inflammation Markers: Markers such has a low level of serum total cholesterol, albumin, creatinine, hemoglobin, or total lymphocyte count are markers of malnutrition and inflammation. These markers in addition to sodium (Na), potassium (K), chloride (Cl), carbon dioxide (CO_2), glucose, blood urea nitrogen (BUN), calcium (Ca), magnesium (Mg), total protein, anion gap, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, phosphorus procalcitonin, lactic acid dehydrogenase, lactic acid and ferritin, transferrin, white blood cells (WBC), red blood cell (RBC), hematocrit, mean corpuscular volume (MCV), neutrophils, lymphocytes, absolute neutrophils, absolute lymphocytes, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein

(HDL) were recorded. The normal ranges for these markers are found in (Appendix G). NLCR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Energy and Protein Adequacy: Actual calories and protein needs were also collected. The daily caloric requirement was calculated using 25-30 kcal/kg. In the case of the patient with a BMI range of 30-50, 11-14 kcal/kg actual body weight was used, and 22-25 kcal/kg ideal body weight for patients with BMI >50. The protein demands of ICU patients were calculated as 1.2-1.5 g/kg/day for patients with normal BMI and renal function, and 0.8 g/kg/day for patients with renal impairment not on dialysis or on continuous renal replacement therapy. For BMI 30-40, 1.5-2.0 g/kg of IBW and 2.0-2.5 g/kg of IBW for BMI above 40 kg/m2 was used. For comparison of nutritional adequacy, the upper end of the caloric range was used for patients with a BMI of less than 25 kg/m2, and the lower end was used for BMI 25-29.9 kg/m2. The upper end of the caloric range was used for patients that were overweight but had comorbidities such as chronic obstructive pulmonary disease (COPD) or multiple wounds and were on hemodialysis.

Malnutrition Screening and Diagnosis: Malnutrition screening was performed using the GLIM criteria for diagnosing malnutrition (Cederholm, 2019). According to the recent consensus proposed by GLIM, the diagnosis of malnutrition is achieved in two steps. First, the patients were assessed for nutritional risk using two validated screening tools, mNUTRIC score, and Nutritional Risk Index (NRI). After meeting the criteria for being at risk of malnutrition by these validated tools, which is mandatory, those who are identified were then screened for diagnosis malnutrition. The diagnosis was performed by combining at least one phenotypic criterion, a low BMI (<20 kg/m2 if <70 years old or <22 kg/m2 if ≥70 years old), and one etiologic criterion (presence of inflammation).

Groups

Patients were divided into the following:

1. Two groups: normal nutritional status and malnourished.
2. Two groups: low nutrition risk and high nutrition risk
3. Two groups: early enteral nutrition initiation (EEN) and delayed enteral nutrition (DEN)
4. Three groups: BMI <22 kg/m2, BMI 22-30 kg/m2, BMI >30 kg/m2
5. Two groups: adequate calories and inadequate calories
6. Two groups: adequate protein and inadequate protein

Then the clinical characteristics, laboratory parameters, and clinical outcomes were compared.

Endpoint

Clinical characteristics of patients were recorded at baseline (ICU day 1) except for laboratory parameters there were recorded on day 1, 3, 7, and 14.

1. Primary endpoints: of this study were changes in RCLM and inflammatory biomarkers (NLCR, albumin, procalcitonin, WBC, Neutrophils, lymphocytes) with nutrition support infusion and a comparison of the clinical outcomes of the groups listed above.
2. Secondary endpoints: of this study was the:
    i. Correlation of Malnutrition, TLC, NLCR, mNUTRIC scores, NRI, and ICU LOS with selected characteristics.
    ii. Association of Malnutrition with mNUTRIC score, SOFA score, APACHE II, NRI, Charlson Comorbidity Index, TLC, NLCR, WBC, neutrophils, lymphocytes, Absolute neutrophils, Absolute lymphocytes, albumin, creatinine, hemoglobin, hematocrit.

Statistical Analysis

Percentages, mean, standard deviation, and median, were used to describe patient characteristics. Before data analysis, the data was cleaned for missing information and outliers. Continuous variables were expressed as mean values ± SEM. Chi-square, odds ratio t-test, and one-way ANOVA were used to describe the differences between different groups. Levene's homogeneity test ascertained the equality of sample variances. One-way ANOVA tests were used to compare the three BMI groups, and Tukey post hoc analysis was performed. Pearson correlation analysis was carried out to show the correlation between TLC, NLCR, mNUTRIC scores, NRI, and ICU LOS with selected characteristics. A binomial logistic regression model was implemented to determine selected laboratory parameters and other covariates associated with malnutrition and malnutrition risk; calculation of odds ratio was done to assess the strength of association. Statistical significance of estimated coefficients was assessed though the t-test. The level of significance for all tests was set at $p < 0.05$. Data collected were analyzed with the Statistical Package for the Social Sciences (SPSS) software, version 23.0 for the Apple MAC computer (IBM SPSS Inc, Chicago, Illinois).

CHAPTER 4. RESULTS

A retrospective analysis of medical chart review was undertaken at a single center. Patients older than 19 years old and were admitted to the medical intensive care until from January 2019 to December 2019 and were on either enteral nutrition parenteral nutrition for at least three days were included in this study. Table 11 summarizes the main characteristics of the patients that were included in the study. The sample was composed of 60 patients, 32 (53%) being female, at the average age of the patients was 69.8±1.58 years old. We assessed comorbidity using the Charlson Comorbidity Index. Our study population had an important presence of comorbidities, with a mean of Charlson index score of 5.7 ± 0.36. The majority of patients had a medical history including hypertension (83%), diabetes (55%), chronic kidney disease (33%), chronic artery disease (23%), hyperlipidemia (22%), chronic obstructive pulmonary disease (20%), dementia (18%), cancer (17%), stroke (15%) and hepatitis (10%) [Figure 4]. The main ICU diagnosis were classified into 8 categories: respiratory (52%), sepsis (53%), gastrointestinal (1.7%), neurological (58.3%), trauma (3%), metabolic (6.7%), cardiovascular (23%), pneumonia (22%). [Figure 5]. Twenty percent of the patients had 3-5 days ICU LOS, 11.7% of the patient had 6-9 ICU LOS, while 68.3% of the patient had >10 days ICU LOS. Mortality in the ICU was 55%. See Table 13 for the average RCLM and inflammatory biomarkers for days 1, 3,7, and 14.

Table 11: Baseline Characteristics of Study Participants

Characteristics	Value
Age (years)	69.8±1.58
Sex	32 (53%) female
BMI (kg/m2)	
<22	19(32%)
22 to <30	23(38%)
≥30	18(30%)
Number of comorbidities n (%)	
0	2(3%)
1-5	37(62%)
>5	21(35%)
Charlson Comorbidity Index	5.7±0.36
Ventilation Use n (%); days	38(63%); 8.18±1.3
Medical History n (%)	
Hypertension	50(83%)
Diabetes	33(55%)
Cancer	10(17%)
Hyperlipidemia	13(22%)
Dementia	11(18%)
Stroke	9(15%)
CAD	14(23%)
Chronic kidney disease	20(33%)
COPD	12(20%)
Hepatitis	6(10%)
ICU Diagnosis	
Respiratory	31(52%)
Sepsis	31(52%)
Gastrointestinal	1(1.7%)
Neurological	35(58.3%)
Trauma	2(3%)
Metabolic	4(6.7%)
Cardiovascular	14(23%)
Pneumonia	12(22%)
APACHE II score n (%)	
<15	4 (6.7%)
15 to < 20	10 (16.7%)
20 to < 28	25 (41.7%)
> 28	21(35%)
SOFA score n (%)	
<6	16(26.7%)
6 to 10	33(55%)
> 10	11(18.3%)

mNUTRIC Score n (%)	
Low risk	17(28%)
High risk	43(72%)
Nutrition Risk Index n (%)	
No risk	0
Mild	0
Moderate	5(8.3%)
Severe	55 (91.7%)
Malnourished n (%)	18(30%)

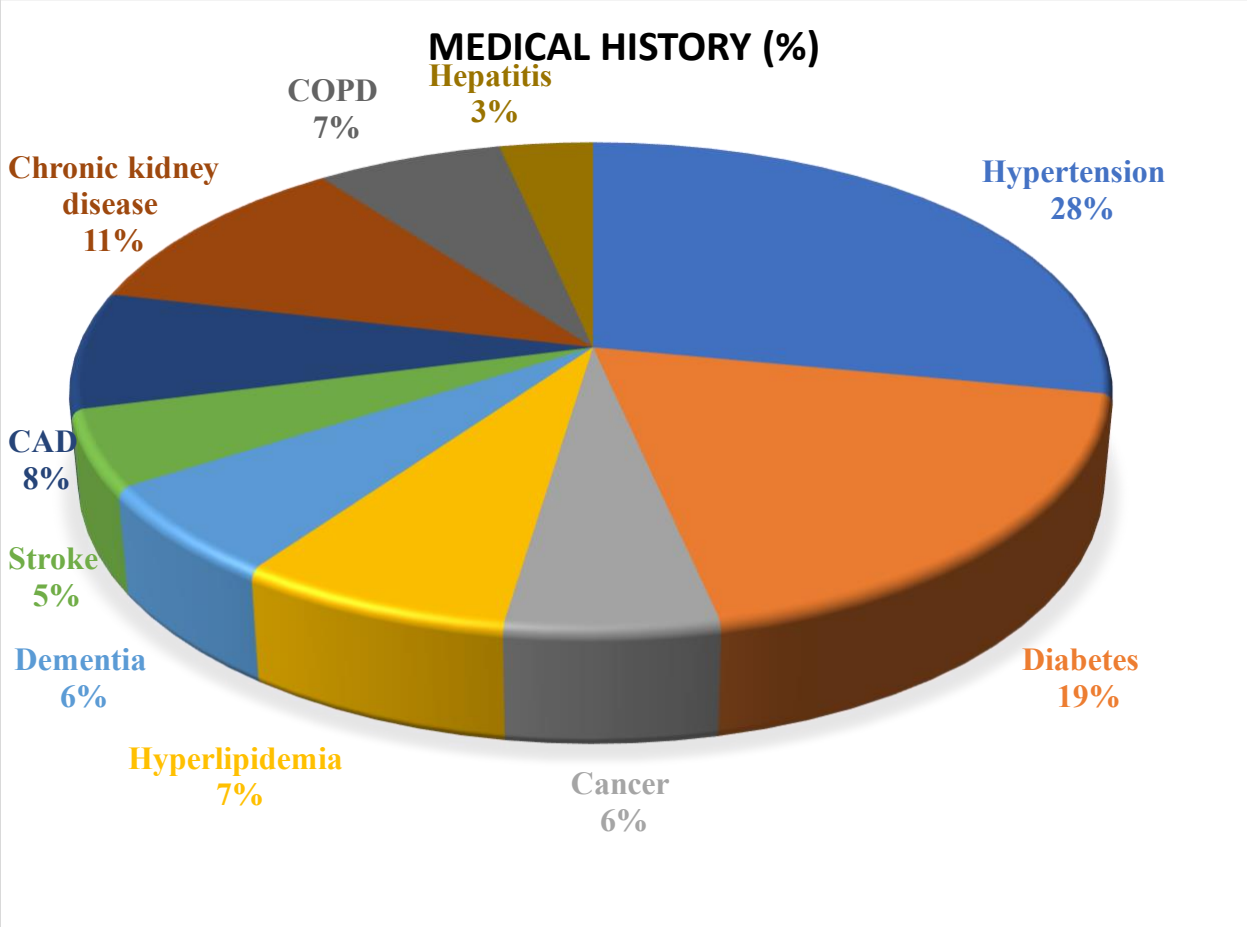

Figure 5: Chart showing percentages of past medical history.

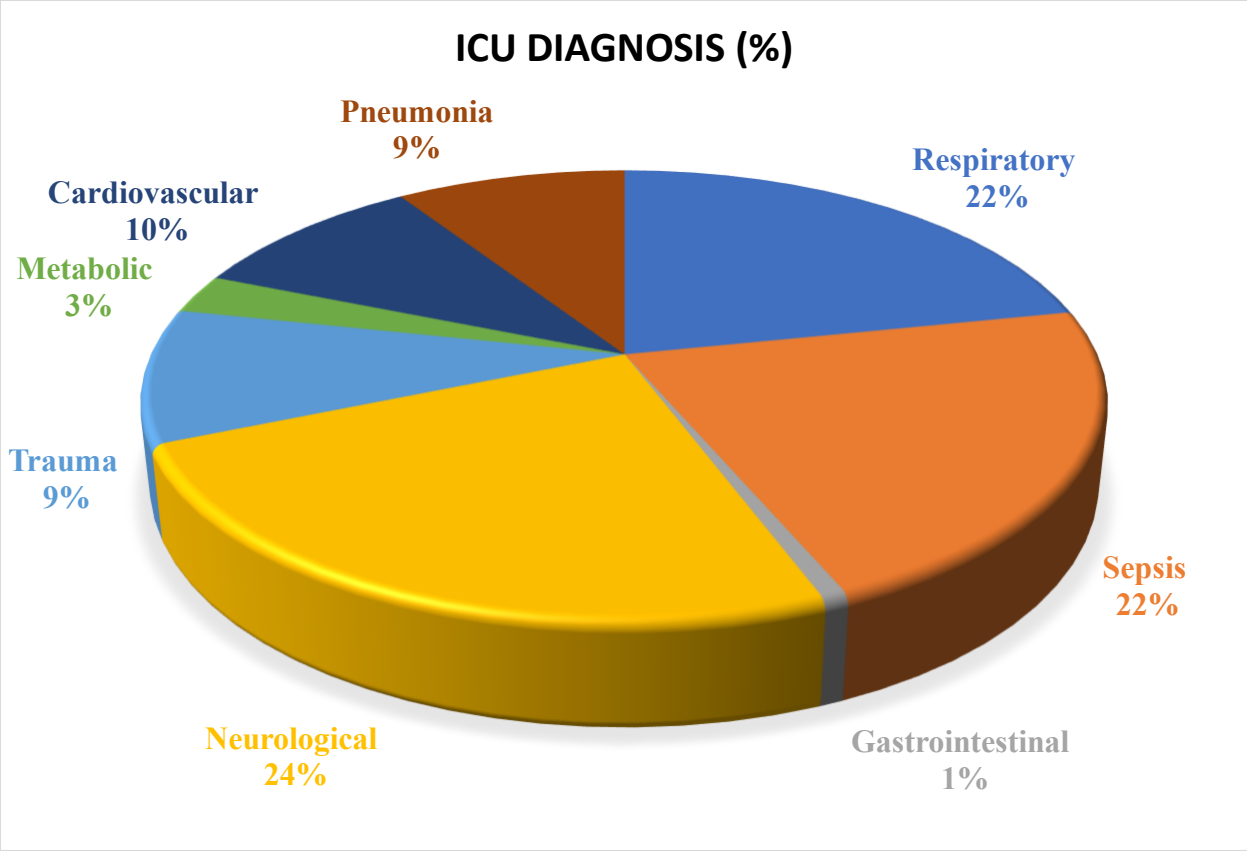

Figure 6: Chart showing the main ICU diagnosis.

Management and Clinical Outcomes

Of the 60 patients, 32(53%) received early enteral nutrition feeding within 24-48 hours (Table 12). The remaining 28(47%) patients who received enteral feeding after 48 hours of ICU admission were allocated to the delayed-initiation group. The majority of the patients admitted to the ICU received nutrition support via enteral nutrition, except for 2(3%) patients that were on supplemental parenteral nutrition (PN). Eighty percent of the patients received EN through a nasogastric tube (NGT), 20% received through an orogastric tube (OGT), and 22% of the patient got a PEG tube placed before discharge. Of the 60 patients, only 47(78%) received a dietitian's consult from the medical doctor or nurse.

Table 12: Management and Clinical Outcomes

Variable	Value
Time of initiation of enteral feeding (days)	
EEN*	32(53%)
DEN	28(47%)
Dietitian Consult	47(78%)
Route of enteral feeding n (%)	
NGT	48 (80%)
OGT	12 (20%)
PEG	13 (22%)
Supplemental PN, n (%)	2 (3%)
Energy Protein Intake	
Prescribed Calories	1734.7±31.9
Calculated Calories	1820.7±48.2
Prescribed Protein	85.2±2.0
Calculated Protein	113.4±3.28
ICU LOS (days)	
3-5	12(20%)
6- 9	7(11.7%)
≥ 10	41(68.3%)
ICU Mortality n (%)	33(55%)

*According to the Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient, enteral nutrition should be initiated within the first 24-48 hours in the critically ill patient who is unable to maintain volitional intake (McClave, 2016).

Comparison of changes in RCLM and Inflammatory Biomarkers

A one-way ANOVA was conducted to compare the means of RCLM and inflammatory markers between days 1, 3, 7, and 14 [Table 13]. The data is presented as a mean ± standard error mean. Hemoglobin, hematocrit, total protein, creatinine, glucose, total cholesterol, and HDL were used to assess nutritional markers while NLCR, WBC, neutrophils, lymphocyte, absolute neutrophils, absolute lymphocytes, and albumin was used to evaluate inflammatory or infection process. TLC was used to determine nutritional status. There was a significant decrease in total protein, albumin, hemoglobin, and hematocrit by day 14 ($p < 0.001$). Blood glucose was trending

down, but this was not statistically significant. By day 14, the mean TLC had reduced by more than half but with no statistical significance. WBC, NLCR, procalcitonin, absolute neutrophils, absolute lymphocytes were trending down but with no statistically significant difference in the mean comparison between days 1, 3, 7, and 14.

Table 13: Routine Clinical Laboratory Measurements and Inflammatory Biomarkers

Indicator	Day 1	Day 3	Day 7	Day 14
Sodium (mEq/L)	141.9±1.1	143.3±1.2	144.4±0.8	142.3±01.2
Potassium (mEq/L)	4.2±0.1	4.2±0.1	4.2±0.1	4.2±0.2
Chloride (mEq/L)	108.8±1.9	110.5±1.54	110.8±1.1	107.9±1.42
Carbon dioxide (mEq/L)	23.6±0.7	22.9±0.7	25.3±0.6	25±1.2
Glucose (mg/dL)	186.3±13.5	165.2±9.1	153.5±6.8	153±11.6
Blood urea nitrogen (mg/dL)	41.5±3.6	41.6±3.18	46.9±3.3	49.1±6.6
Creatinine (mg/dL)	2.5±0.3	2.8±0.3	3.0±0.3	2.3±0.3
Calcium (mg/dL)	8.2±1	7.8±14	8.1±0.1	8.0±0.2
Magnesium (mg/dL)	2.0±0.1	2.1±0.0	2.2±0.0	2.2±0.1
Total Protein (g/dL)	5.7±0.13	5.0±0.1	5.1±0.1	5.2±0.2**
Anion gap (mEq/L)	15.6±0.8	14.6±0.7	13.1±0.5	13.2±1.0
Albumin (g/dL)	2.7±0.1	2.3±0.1	2.4±0.0	2.1±0.1***
ALP (IU/L)	109.8±8.4	138.1±32	202.2±49.7	212.1±46.7
ALT (IU/L)	101.8±38	99.0±19	60.9±10.9	34.5±5.7
AST (IU/L)	212.9±92	233.7±65	102.7±31.7	48±6.5
Total Bilirubin (mg/dL)	1.5±0.39	1.8±0.43	1.4±0.5	1.2±0.4
Phosphorus (mg/dL)	4.1±0.22	4.2±0.3	4.2±0.2	4.4±0.4
Procalcitonin (ng/mL)	46.2±21.8	111.2±32.9	1.8±.7	1.1±0.2
Lactic acid (mm/L)	3.9±0.4	4.4±0.7	2.9±0.6	0.91±0.1
WBC	15.9±2.4	15.6±1.9	14.1±1.0	12.5±1.3
RBC	3.34±0.1	3.1±0.1	2.9±0.0	2.8±0.1***
Hemoglobin (g/dL)	9.6±0.3	9.0±0.2	8.2±0.2	7.9±0.2***
Hematocrit (%)	31.1±0.9	28.6±0.7	26.7±0.6	25.8±0.5***
MCV (fL)	93.5±1.1	92.9±1.1	92.7±1.2	93.5±1.7
Neutrophils (%)	77.6±1.9	79.5±1.6	76.3±1.8	76.4±2.52
Lymphocytes (%)	12.1±1.8	10.2±1.4	9.9±0.8	12.1±1.8
Absolute neutrophils	11.4±0.9	11.6±0.9	9.8±0.9	9.85±1.1
Absolute Lymphocytes	3.44±2.06	2.49±1.4	1.3±0.1	1.22±0.2
TLC (cells/m3)	3431.3±2063	2515±1419	1212±121.3	1226±163
NLCR	17.7±3.3	31.7±14.4	16.3±2.6	13.4±2.8

Total Cholesterol (mg/dL)	112.8±6.3
Triglycerides (mg/dL)	89.1±5.1
LDL (mg/dL)	57.2±4.7
HDL (mg/dL)	34.6±2.7
LDH (IU/L)	699.5±99
Ferritin (ng/mL)	773±148.9
Transferrin (mg/dL)	133.5±9.11

**P<0.01; ***P<0.001; LDH= lactic acid dehydrogenase; TLC= Total lymphocyte count; WBC= White blood cells; RBC= Red blood cells; MCV= Mean corpuscular volume; NLCR= Neutrophil lymphocyte count ratio; LDL= Low density lipoprotein; HDL= High density lipoprotein

Comparison of clinical outcomes of patients with different nutrition risks based on the mNUTRIC scale.

All patients were assessed for nutrition risk, as suggested by the GLIM criteria for diagnosing malnutrition. First, patients were assessed for malnutrition risk. Table 14 shows a comparative assessment of patients with different nutritional risks based on their mNUTRIC scores. NRI was also used to assess nutritional risk. An overall of 72% of the patients were at nutritional risk at admission using the mNUTRIC score, and 91.7% were found to be at nutritional risk using the NRI score. The mean value of the NRI analyzed in all the ICU patients was 54±2.2. In terms of outcomes using the mNUTRIC scores, there was no significant difference in ICU LOS (15.8±2.9 vs. 16±1.6, p = .96), days on ventilation (4.3±1.8 vs. 5.7±1.2, p = .53), duration on nutrition support (9.5±1.7 vs. 12.9±1.4, p = .16) between both low nutrition risk group and high nutrition risk group. However, patients with high nutrition risk had a higher infection rate of 28(65%) and mortality rate 26(60%) than the low nutrition risk group. There was a significant difference between both groups in glucose (146.7±12.1 vs. 202±17.7 p = .01), BUN (29.9±5.6 vs. 46±4.3, p = .04), ALP (147.3±23 vs. 97.9±8.4, p = .03), ALT (189.9±114.9 vs. 73.9±38.7, p = .03), AST (466.5±367 vs. 126±54.9, p = .003), total bilirubin (2.1±1.5 vs. 1.3±0.3, p = .05), phosphorus (3.1±0.3 vs .4.5±0.3, p = .02), hemoglobin (10±0.6 vs. 9.4±0.3, p = .05), MCV (90±2.03 vs. 94.9±1.3, p = .05, LDH (311.4±76.9 vs. 807.4±197.7, p = .01) and HDL (51.5±12.3 vs. 30.6±3.9,

p = .04). There was no significant difference in any other biochemical biomarkers, as shown in Table 14. There was no significant difference between the low nutrition risk group and the high nutrition risk group by day 14.

Table 14: Clinical outcomes between nutritional risk groups

Outcomes	Low nutrition risk group	High nutrition risk group
ICU LOS	15.8±2.9	16±1.6
Days on Ventilation	4.3±1.8	5.7±1.2
Duration on Nutrition support	9.5±1.7	12.9±1.4
Infection rate	47%	65%
Mortality rate	35%	60%

Indicators	Day 1		Day 3		Day 7		Day 14	
	Low nutrition risk group	High nutrition risk group	Low nutrition risk group	High nutrition risk group	Low nutrition risk group	High nutrition risk group	Low nutrition risk group	High nutrition risk group
Sodium (mEq/L)	139±1.6	143±1.3	142.9±2.8	143.5±1.3	145.5±2.6	144±0.9	142±2.7	142±1.4
Potassium (mEq/L)	4.1±0.2	4.3±0.1	4.0±0.1	4.3±1.3	4.1±0.1	4.2±0.1	3.9±0.1	4.3±0.2
Chloride (mEq/L)	109.5±5.8	108.4±1.5	109.5±3.5	110.9±1.7	108.4±3.2	111.5±1.3	105.7±2.8	108.6±1.7
Carbon dioxide (mEq/L)	25.4±1.1	22.9±0.9	24.5±1.1	22.2±0.8	27.2±1.2	24.6±0.7	27.3±1.3	24.6±1.5
Glucose (mg/dL)	146.7±12.1	202±17.7*	154.3±15.5	169.6±11.2	136.5±17.1	159±8.6	151.7±27.9	153.7±27.9
Blood Urea Nitrogen (mg/dL)	29.9±5.6	46±4.3*	30.3±5.4	46±3.7*	46.7±7.6	47.1±4.6	35.4±13	53.7±7.5
Creatinine (mg/dL)	1.8±0.5	2.9±0.3	2.1±0.4	3.1±0.3*	3.6±0.9	2.8±0.4	1.5±0.6	2.5±0.4
Calcium	8.4±0.2	8.2±0.2	8.1±0.2	7.6±0.2*	8.6±0.2	7.9±0.2*	8.3±0.3	7.9±0.2
Magnesium (mg/dL)	2.04±0.1	2.01±0.1	2.0±0.1	2.1±0.1	2.4±0.1	2.1±0.1*	2.2±0.1	2.2±0.1
Total Protein (g/dL)	5.9±0.3	5.7±0.2	5.2±0.2	4.9±0.2	5.5±0.3	5.0±0.2	5.1±0.6	5.2±0.26
Anion gap (mEq/L)	15.1±1.3	15.9±0.9	12.8±1.2	15.3±0.8	14.3±1.3	12.7±0.7	13.0±1.3	13.3±1.3
Albumin (g/dL)	3.04±0.2	2.6±0.1	2.6±0.1	2.2±0.1	2.9±0.4	2.3±0.1*	2.5±0.4	1.9±0.1
Alkaline Phosphatase (IU/L)	147.3±23	97.9±8.4*	133.7±21.6	139.9±61.9	188±65	205±96	166±44	222±72

Alanine Transaminase (IU/L)	189.9±114.9	73.9±38.7*	50.9±25	299.8±123*	85±38	55.8±19	28±14.9	35.8±8.5
Aspartate aminotransferase (IU/L)	466.5±367	126±54.9**	81.7±32	299.8±123*	102.2±36	102.7±61	51±18.5	47.3±9.6
Total Bilirubin (mg/dL)	2.1±1.5	1.3±0.3*	2.6±1.9	1.4±0.5	5.0±4.4	0.7±0.2*	0.6±0.2	1.3±0.6
Phosphorus (mg/dL)	3.1±0.3	4.5±0.3*	3.8±0.4	4.3±0.4	4.3±0.6	4.2±0.3	3.5±0.5	4.7±0.6
Procalcitonin (ng/mL)	0.9±0.2	57.1±34.7	19.8±16	156.8±96.9	2.5±2.2	1.5±0.5*	1.0±0	1.2±0.6
Lactic acid (mm/L)	2.04±0.4	4.4±0.6**	1.5±0.6	4.9±1.5*				
WBC	14.4±2.3	16.4±3.3	13.2±1.6	16.5±2.6	13.4±1.9	14.3±1.5	12.3±2.2	12.5±1.6
RBC	3.5±0.2	3.2±0.1	3.3±0.2	3.0±0.1	2.8±0.2	2.9±0.1	3.0±0.2	2.7±0.1
Hemoglobin (g/dL)	10±0.6	9.4±0.3*	9.4±0.5	8.8±0.2	7.9±0.3	8.3±0.3	8.1±0.2	7.9±0.2
Hematocrit (%)	31.6±1.9	30.8±1.1	29.9±1.4	28.10.8	25.9±1.2	26.9±0.9	26.3±0.8	25.6±0.6
MCV (fL)	90±2.03	94.9±1.3*	92.9±2.5	93±1.3	91.9±2.6	92.9±1.6	89.8±3.7	94.8±1.9
Neutrophils (%)	81.9±2.1	75.8±2.5	80.9±2.1	78.9±2.1	78.8±2.8	75.5±2.6	78.7±3.5	75.6±3.2
Lymphocytes (%)	9.6±1.8	13.1±2.4	9.4±1.6	10.5±1.9	11.4±2.4	9.4±1.1	10.5±3.2	12.5±2.2
Absolute neutrophils	12±2.0	11.1±0.9	10.9±1.5	11.9±1.1	10.9±1.9	11.3±1.2	10.1±2.2	9.8±1.3
Absolute Lymphocytes	1.2±0.2	4.3±2.9	1.0±0.2	3.1±1.9	1.2±0.2	1.3±0.2	0.9±0.2	1.3±0.2
TLC (cells/m3)	1154±200	1148.9±122.6	1046±151	1122±154	1272±226	1193±171.9	963.4±156	1313±209
NLCR	15.5±3.9	16.8±3.3	15.3±3.3	33.3±14.1	33.7±18.5	16.2±3.6	16.5±5.2	13±3.5
LDH (IU/L)	311.4±76.9	807.4±197.7*						
Ferritin (ng/mL)	301±119	891±242						
Transferrin (mg/dL)	152.5±16	132.5±10.6						
Total Cholesterol (mg/dL)	137±28	106.9±9.8						
Triglycerides (mg/dL)	73.8±9.8	92.7±9.2						
LDL (mg/dL)	62.3±17.4	55.9±8						
HDL (mg/dL)	51.5±12.3	30.6±3.9*						

*P<0.05; **P<0.01; LDH= lactic acid dehydrogenase; TLC= Total lymphocyte count; WBC= White blood cells; RBC= Red blood cells; MCV= Mean corpuscular volume; NLCR= Neutrophil lymphocyte count ratio; LDL= Low density lipoprotein; HDL= High density lipoprotein

Comparison of clinical outcomes between patient with normal nutrition and patient with malnutrition

30% of the ICU patients were found to be malnourished using the GLIM criteria for diagnosing malnutrition. The mean age of malnourished patients was 73.3±2.4 years. There was no significant difference in age between normal and malnourished patients (68.3± 1.9 vs. 73.3 ± 2.3, p = .153). No correlation was found between sex and nutritional status. Being a male or female is not a risk factor for being malnourished $\chi 2(1, N=60) = .051$, p = .82). The normal nutrition and malnourished group were similar in age, sex, APACHE II, SOFA and mNUTRIC score, ICU LOS, days on ventilation, and duration on nutrition support. However, the normal group had a higher NRI score (60.1±2.5 vs. 40.5±1.4, p = .01) and lower Charlson Comorbidity Index (5.3±0.4 vs. 6.8±0.8, p = .05) than the malnourished group (Table 15). At baseline, there was a significant difference in the laboratory biomarkers between the two in carbon dioxide (20.3±1.0 vs. 20.3±1.0 p = .002), BUN (35.5±3.2 vs. 55.4±8.6, p = .009), creatinine (2.3±0.3 vs. 3.3±0.6, p = .01), anion gap (14±0.7 vs. 19.4±1.7, p = .001), total bilirubin (1.0±0.2 vs. 2.6±1.3, p = .001), lactic acid (3.1±0.5 vs. 5.3±0.9, p = .03), MCV (92.1±1.4 vs. 97±1.6, p = .04), neutrophils (73.9±2.5 vs 85.9±1.9, p = .004), lymphocytes (14.7±2.4 vs. 5.9±1.2, p = .02), NLCR (10.5±1.8 vs 30.5±6.6, p = .001). On day 14, absolute lymphocyte (1.5±0.2 vs. 0.5±0.1, p = .006) and NLCR (9.4±2.0 vs. 25.7±7.6, p = .008) of both groups significantly decreased. There was a significant difference in TLC of both groups on day 1 (1380±121.8 vs. 639±134, p =.001); day 3 (1330.1±153 vs. 576±73.9, p = .002); day 7 (1505±176 vs. 626.8±138, p = .002); day 14 (1504±193 vs 531.8±98.6, p = .005). It was observed that glucose and total bilirubin in the normal nutrition group were trending down to normal when compared with the malnourished group, which remained high on day 14. BUN and ALP were trending high in both groups. Protein, albumin, and procalcitonin were trending

down in both groups but more obvious in the malnourished group. ALP, AST, absolute lymphocyte, NLCR, and TLC were observed to be trending down in both groups.

Table 15: Clinical outcomes between patients with normal nutrition and malnourished group

	Patients with Normal Nutrition	Patients with Malnutrition
Characteristics		
Age	68.3±1.9	73.3±2.4
Sex(female)	53.30%	46.70%
APACHE II	24.3±0.9	24.9±1.6
SOFA	6.8±0.4	8.3±0.8
mNutric Score	5.2±0.2	5.8±0.4
NRI	60.1±2.5	40.5±1.4*
Charlson Comorbidity Index	5.3±0.4	6.8±0.8*
Outcomes		
ICU LOS	16.6±1.8	14.4±2.1
Days on ventilation	5±1.2	5.8±1.9
Duration on NS	12.4±1.4	10.9±1.9

	Day 1		Day 3		Day 7		Day 14	
	Normal nutrition	Malnutrition	Normal nutrition	Malnutrition	Normal nutrition	Malnutrition	Normal nutrition	Malnutrition
Indicators								
Sodium (mEq/L)	141.7±1.04	142.7±2.7	142.8±1.4	144.7±2.4	145.1±1.3	143±1.2	143.1±1.5	140.3±1.9
Potassium (mEq/L)	4.2±0.1	4.5±0.2	4.2±0.1	4.1±0.2	4.1±0.1	4.3±0.1	4.1±0.1	4.5±0.5
Chloride (mEq/L)	109±2±2.5	107.7±2.9	110±1.8	111±3.0	111.6±1.7	109.2±1.6	108.6±1.7	106±2.6
Carbon dioxide (mEq/L)	25±0.8	20.3±1.0**	23.3±0.8	22.1±1.2	25.2±0.8	25.3±0.9	25.9±1.3	23.7±2.6
Glucose (mg/dL)	181.5±14.7	197.6±29.6	164.4±10.5	167.2±18.5	150.5±10	159.5±12	139.8±10.9	186±27.7
Blood urea nitrogen (mg/dL)	35.5±3.2	55.4±8.6**	39.1±3.1	47.7±7.7*	44.4±5.2	52.2±5.3	42.1±7.6	66.8±11.2
Creatinine (mg/dL)	2.3±0.3	3.3±0.6*	2.9±0.3	2.7±0.4	3.0±0.5	3.0±0.6		
Calcium	8.2±0.2	8.4±0.2	7.8±0.2	7.6±0.2	8.1±1.2	7.9±0.3	8.0±0.2	8.2±0.4
Magnesium (mg/dL)	1.99±0.7	2.1±0.1	2.0±0.1	2.1±0.1	2.2±0.1	2.3±0.9	2.1±0.9	2.4±0.1

Total Protein (g/dL)	5.8±0.2	5.4±0.3	5.1±0.2	4.8±0.2	5.3±0.3	4.7±0.2	5.3±0.2	4.5±0.4
Anion gap (mEq/L)	14±0.7	19.4±1.7***	14.4±0.8	15±1.3	13.2±0.7	13.0±1.2	12.5±0.8	14.9±2.9
Albumin (g/dL)	2.7±0.1	2.8±0.2	2.3±0.1	2.5±0.2	2.3±0.1	2.5±0.2	2.1±0.1	1.9±0.1
ALP (IU/L)	110±10.9	107±15	99.3±11.8	215.4±128*	140±27	298±203.7*	165.6±20.9	324±204**
ALT (IU/L)	106.7±54	90.13±47	74±29	149±50.9	57.2±22.7	66.6±29.5	31.1±10	42.8±5.7
AST (IU/L)	232.5±134	166.3±81	160±86.5	381±197	58.8±17.9	170.9±129*	47±9.7	50.4±17.7
Total Bilirubin (mg/dL)	1.0±0.2	2.6±1.3***	1.4±0.5	2.6±1.7	0.8±0.2	2.5±2*	0.9±0.2	2.1±1.7
Phosphorus (mg/dL)	4.1±0.3	4.3±0.6	4.2±0.4	4.2±0.4	4.3±0.4	4.1±0.4	3.8±0.3	6.7±1.4**
Procalcitonin (ng/mL)	56.7±0.3	27.5±2.1	154.2±123	62±27	2.1±0.9	1±0.5		
Lactic acid (mm/L)	3.1±0.5	5.3±0.9*	5.1±1.8	3.1±1.4				
WBC	17.4±3.4	12.3±1.3	17.4±2.6	11.3±1.6	15.8±1.6	10.7±0.9*	13.0±1.6	11.1±1.8
RBC	3.3±0.1	3.3±0.2	3.1±0.1	2.9±0.1	2.9±0.1	2.7±0.1	2.9±0.1	2.6±0.1
Hemoglobin (g/dL)	9.4±0.3	10.1±0.5	8.9±0.3	9.0±0.3	8.3±0.3	8.1±0.2	8.0±0.1	7.9±0.4
Hematocrit (%)	30.6±1.1	32.1±1.7	28.8±0.9	28.3±1.7	27.2±1.0	25.7±0.8	26.1±0.5	25.1±1.2
MCV (fL)	92.1±1.4	97±1.6*	92±1.5	95±1.7	91.6±1.6	94.9±2.5	92±1.8	97.3±3.5
Neutrophils (%)	73.9±2.5	85.9±1.9**	77.3±2.1	84.8±1.6*	75±1.8	78.7±5.1	72.7±2.97	85.7±2.9*
Lymphocytes (%)	14.7±2.4	5.9±1.2*	11.6±1.9	6.9±1.2	11.4±1.3	6.7±1.6*	14.3±2.3	6.2±1.8*
Absolute neutrophils	11.1±0.9	11.9±2.9	12.4±1.0	9.9±1.7	12.3±1.4	9.1±0.9	9.9±1.4	9.6±1.8
Absolute Lymphocytes	4.6±2.9	0.7±0.13	3.3±2	0.6±0.1	1.6±0.2	0.6±0.1**	1.5±0.2	0.5±0.1**
TLC (cells/m3)	1380±121.8	639±134***	1330±153	576±73.9**	1505±176	626.8±138**	1504±193	531.8±98.6**
NLCR	10.5±1.8	30.5±6.6***	15.07±2.4	59.2±33*	17.1±6.9	27.3±7.5	9.4±2.02	25.7±7.6**
LDH (IU/L)	796.4±227	517±176.6						
Ferritin (ng/mL)	717±228	1009±516						
Transferrin (mg/dL)	141.1±11.8	125±12.8						
Total Cholesterol (mg/dL)	118.2±12	98.1±14						
Triglycerides (mg/dL)	92.4±10.1	80±9.2						
LDL (mg/dL)	62.6±8.6	42.6±11.8						
HDL (mg/dL)	34.3±5.5	35.4±4.1						

*P<0.05; **P<0.01; ***P<0.001; NRI= Nutritional Risk Index; LDH= lactic acid dehydrogenase; TLC= Total lymphocyte count; WBC= White blood cells; RBC= Red blood cells; MCV= Mean corpuscular volume; NLCR= Neutrophil lymphocyte count ratio; LDL= Low density lipoprotein; HDL= High density lipoprotein; NS= Nutrition Support.

Comparison between the clinical outcomes of the early enteral nutrition group and delayed enteral nutrition group

There was no significant difference in BMI, mNUTRIC score, ICU LOS and days on ventilation support between the EEN and DEN group. There was however, a significant difference in APACHE II scores (26.4±1.1 vs. 22.1±1.1, p = .009), SOFA score (7.6±0.5 vs. 6.8±0.4, p = .02) and duration on nutrition support (10.6±1.3 vs. 13.6±1.9, p = .02) between the two group (Table 16). On day 1 of ICU admission, there were significant differences in potassium (4.6±0.2 vs. 3.8±0.1, p = .001), albumin (2.9±0.1 vs. 2.5±0.1, p = .03), ALT (64.5±25 vs. 152.1±88, p = 0.02), AST (121.6±44 vs. 335.9±221, p = .02), RBC (3.6±0.1 vs. 3.1±0.1, p = .01) hemoglobin (10.4±0.4 vs. 8.6±0.4, p = .02), hematocrit (33.5±1.2 vs. 27.7±1.2, p = .01), lymphocytes (13.2±3.0 vs. 10.7±1.2, p = .02), and HDL (42.7±6.6 vs. 26.5±4.1, p = .04) between the two groups. On day 14, there were significant differences in BUN (59.5±11 vs. 38.6±6.1, p = .02), creatinine (2.7±0.6 vs. 1.9±0.3, p = .008), calcium (8.4±0.2 vs. 7.7±0.2, p = .03), magnesium (2.4±0.1 vs. 2.0±0.1, p = .01), MCV (97±2.3 vs. 90.1±2.1, p = .03), neutrophils (81.8±2.7 vs. 71.1±3.9, p = .03), absolute lymphocytes (0.8±0.1 vs. 1.6±0.2, p = .007), TLC (809±123.5 vs. 1642±261, p = .008) NLCR (20.4±5 vs. 7.7±1.9, p = .02) between both groups. There was a trend of decrease in total bilirubin, procalcitonin, lactic acid, WBC, RBC, hemoglobin and hematocrit but with no significant difference between both groups. Total protein and albumin remained low with a decrease in albumin by day 14 when compared to day 1. Sodium, potassium, chloride, carbon dioxide, and magnesium remained within normal limit.

Table 16: Comparison between the clinical outcomes of the early enteral nutrition group and delayed enteral nutrition group

	EEN group	DEN group
Characteristics		
BMI	25.6±1.4	27.5±1.4
mNutric score	5.6±0.3	5.1±0.3
APACHE II	26.4±1.1	22.1±1.1**
SOFA score	7.6±0.5	6.8±0.4*
Outcomes		
ICU LOS	13.9±1.9	18.6±1.9
Days on Ventilation	5.3±1.2	5.2±1.7
Duration on Nutrition Support	10.6±1.3	13.6±1.9*

Indicators

	Day 1		Day 3		Day 7		Day 14	
	EEN group	**DEN group**	**EEN group**	**DEN group**	**EEN group**	**DEN group**	**EEN group**	**DEN group**
Sodium (mEq/L)	140.9±1.3	143±1.8	143.4±1.6	143.3±1.8	143.9±1.4	144.9±1.2	140.4±1.8	144±1.5
Potassium (mEq/L)	4.6±0.2	3.8±0.1***	4.3±0.1	4.1±0.1	4.1±0.1	4.2±0.1	4.4±0.3	4.1±0.1
Chloride (mEq/L)	108.9±2.9	108.5±2.2	111.2±2.2	109.5±2.2	110.5±1.9	111±1.6	105.8±1.9	109.9±1.9
Carbon dioxide (mEq/L)	23±0.9	24.4±1.1	22.5±0.9	23.4±0.9	25.2±0.9	25.2±0.9	23.9±1.6	26.7±1.7
Glucose (mg/dL)	202.4±19	165.4±17.9	171±13	157.4±12.4	153.2±11.4	153.9±10.7	164.5±17	141±14.7
Blood Urea Nitrogen (mg/dL)	41±4.5	42±5.9	39.1±4.1	44.9±4.9	46.7±5.6	47.3±5.5	59.5±11	38.6±6.1*
Creatinine (mg/dL)	2.6±0.4	2.5±0.4	2.6±0.3	3.1±0.4	2.9±0.5	3.2±0.6	2.7±0.6	1.9±0.3**
Calcium	8.3±0.2	8.1±0.2	7.7±0.2	7.9±0.2	7.9±0.2	8.2±0.2	8.4±0.2	7.7±0.2*
Magnesium (mg/dL)	2.1±0.1	1.9±0.1	2.1±0.1	2.1±0.1	2.3±0.1	2.1±0.1	2.4±0.1	2.0±0.1*
Total Protein (g/dL)	5.8±0.2	5.6±0.2	4.8±0.9	5.2±0.2	4.9±0.3	5.2±0.2	5.1±0.2	5.3±0.5
Anion gap (mEq/L)	16.5±1.1	14.4±0.9	14.3±0.9	14.9±1.1	13.3±0.8	12.9±0.9	15.0±1.7	11.4±0.9
Albumin (g/dL)	2.9±0.1	2.5±0.1*	2.3±0.1	2.3±0.1	2.4±0.1	2.3±0.1	2.2±0.2	1.9±0.1
Alkaline Phosphatase (IU/L)	104.3±10.7	117.2±15	159.6±70.9	104.9±16.7	269±166	140.5±31	235±102.2	179±24.7
Alanine Transaminase (IU/L)	64.5±25	152.1±88*	124.1±36.5	60.4±33.9*	86.5±31.8	37±15.4*	44.1±10.8	20.9±6.7

Aspartate aminotransferase (IU/L)	121.6±44	335.9±221*	330.9±140.6	84.1±30.2*	157.8±105.8	52.1±15.7	52.1±13	42.1±8.6
Total Bilirubin (mg/dL)	1.4±0.4	1.6±0.8	1.4±0.5	2.4±1.5	0.9±0.3	1.9±1.5	1.6±0.9	0.6±0.1
Phosphorus (mg/dL)	4.1±0.4	4.0±0.3	3.7±0.4	4.7±0.4	3.9±0.3	4.6±1.5	4.8±0.7	3.9±0.4
Procalcitonin (ng/mL)	70.5±45.7	7.9±3.3	173.9±106.7	17±13.7	1.63±2.5	2.1±1.6		
Lactic acid (mm/L)	3.9±0.7	3.8±0.7	4.1±1.6	4.8±2.3	3.4±2.5	0.7±0.0		
WBC	18.2±4.2	12.9±1.1	15.8±3.1	15.3±1.63	13.6±1.8	14.7±1.6	12.2±1.9	12.7±1.8
RBC	3.6±0.1	3.1±0.1*	3.2±0.1	2.9±0.1	3.0±0.1	2.7±0.1	2.7±0.1	2.9±0.1
Hemoglobin (g/dL)	10.4±0.4	8.6±0.4*	9.3±0.3	8.6±0.3	8.8±0.4	7.6±0.1*	7.9±0.2	8.1±0.2
Hematocrit (%)	33.5±1.2	27.7±1.2*	29.7±1.0	27.2±0.8	28.4±1.2	24.7±0.5*	25.5±0.7	26±0.7
MCV (fL)	95.2±1.5	91.5±1.7	94.2±1.6	91.3±1.7	94.4±1.9	90.7±1.9	97±2.3	90.1±2.1*
Neutrophils (%)	77.8±2.1	77.2±1.7	79±2.6	80.2±1.6	75.3±3.2	77.3±2.4	81.8±2.7	71.1±3.9*
Lymphocytes (%)	13.2±3.0	10.7±1.2*	11.3±1.2	8.7±1.0	9.2±1.4	10.6±1.5	8.9±1.9	15.2±2.9
Absolute neutrophils	11.7±1.2	10.9±1.3	11.3±1.2	12.0±1.3	10.9±1.5	11.6±1.4	10.3±1.7	9.4±1.5
Absolute Lymphocytes	5.1±3.6	1.3±0.1	3.4±2.5	1.2±0.1	1.2±0.2	1.3±0.2	0.8±0.1	1.6±0.2*
TLC (cells/m3)	1063.9±145	1257±147	998.8±150.3	1229±186.5	1042±155	1407±239	809±123.5	1642±261**
NLCR	18.3±3.5	14.0±3.8	38.4±17.8	15±2.7	18.3±5.0	22.9±9.8	20.5±5	7.7±1.9*
LDH (IU/L)	868.5±232	590±219						
Ferritin (ng/mL)	613.9±224.9	956.5±359.2						
Transferrin (mg/dL)	145.3±13.8	126.1±11.3						
Total Cholesterol (mg/dL)	119.8±14.4	105±12.9						
Triglycerides (mg/dL)	82.9±7	95.2±13.9						
LDL (mg/dL)	58.9±10.2	55.5±10.5						
HDL (mg/dL)	42.7±6.6	26.5±4.1*						

*P<0.05; **P<0.01; ***P<0.001; LDH= lactic acid dehydrogenase; TLC= Total lymphocyte count; WBC= White blood cells; RBC= Red blood cells; MCV= Mean corpuscular volume; NLCR= Neutrophil lymphocyte count ratio; LDL= Low density lipoprotein; HDL= High density lipoprotein.

Caloric Balance and Clinical outcomes

The mean caloric balance is presented in Table 17. Seventy-eight percent of the patients met the estimated caloric requirement, while the proportion of patients that met the estimated protein requirement was only 40%.

Table 17: Energy Protein Intake

Calorie prescribed	**Mean**	**Median**
Kcal	1734.7±31.9	1782
Protein (g)	85.2±2.0	80
Calorie estimated	**Mean**	**Median**
Kcal	1820.7±48.2	1825
Protein (g)	113.4±3.28	114
Calorie balance	**Mean**	**Median**
Kcal	86±16.3	43
Protein (g)	28.2±1.20	34

The group of patients with inadequate calories had a higher duration on nutrition support when compared to the group of patients with adequate calories. Still, the difference was not significant (13±3.1 vs. 11.6±1.5, p = .63). There was a significant difference in the NRI (48.9±3.1 vs. 55.4±2.6, p = .04), and procalcitonin (113.7±110.8 vs. 23.7±9.4, p = .002) between the inadequate and the adequate calories group. On day 7, there was a significant difference between the two groups in total protein (5.9±0.5 vs. 4.9±0.2, p = .03), and absolute lymphocyte (2.0±0.6 vs. 1.1±0.1, p = .01). There was a trend of decrease in albumin in both groups with a significant difference on day 14 (1.9±0.1 vs. 2.2±0.1, p = .03). See [Table 18]

Table 18: Caloric intake and clinical outcomes

	Inadequate	Adequate						
Outcomes								
ICU LOS	15.8±3.4	16±1.5						
Duration on Nutrition Support	13±3.1	11.6±1.5						
NRI	48.9±3.1	55.4±2.6*						
	Day 1		**Day 3**		**Day 7**		**Day 14**	
	Inadequate	**Adequate**	**Inadequate**	**Adequate**	**Inadequate**	**Adequate**	**Inadequate**	**Adequate**
Indicators								
Total Protein (g/dL)	5.8±0.3	5.7±0.2	5.5±0.5	4.9±0.1	5.9±0.5	4.9±0.2*	5.5±0.6	5.0±0.2
Albumin (g/dL)	2.4±0.2	2.9±0.1	2.3±0.2	2.3±0.1	2.3±0.1	2.4±0.1	1.9±0.1	2.2±0.1*
Total Bilirubin (mg/dL)	0.9±0.2	1.7±0.5	0.7±0.1	2.2±0.8	0.6±0.1	1.7±1.0	1.1±0.6	1.2±0.7
Lactic acid (mm/L)	3.1±1.1	4.0±0.6	1.7±0.5	4.9±1.5*				
WBC	13.2±1.8	16.7±3.1	15.7±2.1	15.6±2.4	17.4±2.8	13.3±1.3	13.3±3.2	12.2±1.4
RBC	3.5±0.3	3.3±0.1	3.3±0.2	3.0±0.1	3.2±0.2	2.8±0.1	2.9±0.2	12.2±1.4
Hemoglobin (g/dL)	9.3±0.7	9.7±0.3	9.2±0.4	8.9±0.3	8.4±0.5	8.2±0.3	7.7±0.3	7.9±0.2
Hematocrit (%)	30±2.1	31.3±1.0	29.2±1.3	28.4±0.8	27.7±1.4	26.4±0.8	25.7±0.9	25.8±0.6
Neutrophils (%)	79.6±2.9	77±2.3	80.9±2.7	79.1±1.9	74.7±4.2	76.7±2.4	71±8.7	77.9±2.2
Lymphocytes (%)	9.5±1.5	12.7±2.2	8.9±1.8	10.6±1.8	9.7±2.8	9.9±1.1	14.9±6.4	11.3±1.6
Absolute neutrophils	10.8±1.7	11.5±1.0	12.4±1.7	11.5±1.0	13.4±2.4	10.7±1.1	10.5±3.1	9.7±1.2
Absolute Lymphocytes	1.1±0.2	4.1±2.6	1.2±0.2	2.9±1.8	2.0±0.6	1.1±0.1*	1.3±0.3	1.2±0.2
TLC (mm3)	1119±176	1159±124.4	1272±323	1051±121.1	1528±514	1133±121	1263±260	1216±197
NCLR	14.8±5	16.9±3.1	19.7±5.7	30±12.9	12.1±3.9	22.6±6.5	11±4.1	14.8±3.5

*P<0.05; **P<0.01; ***P<0.001; TLC= Total lymphocyte count; WBC= White blood cells; RBC= Red blood cells; NCLR= Neutrophil count lymphocyte ratio

Table 19: Protein intake and clinical outcomes

	Inadequate	Adequate						
Outcomes								
ICU LOS	17±1.8	14.5±2.1						
Duration on Nutrition Support	13.5±1.6	9.5±1.3*						
NRI	59±2.7	45.9±1.8**						
	Day 1		**Day 3**		**Day 7**		**Day 14**	
	Inadequate	**Adequate**	**Inadequate**	**Adequate**	**Inadequate**	**Adequate**	**Inadequate**	**Adequate**
Indicators								
Total Protein (g/dL)	5.9±0.2	5.3±0.2	5.3±0.2	4.7±0.2*	5.2±0.2	5.0±0.3	5.4±0.3	4.9±0.3
Albumin (g/dL)	2.6±0.1	2.8±0.2	2.3±0.1	2.4±0.1	2.3±0.1	2.5±0.2*	2.0±0.1	2.2±0.2
Total Bilirubin (mg/dL)	1.4±0.4	1.7±0.9	1.1±0.5	2.8±1.4	0.8±0.2	2.4±2.0	1.4±0.8	0.9±0.5
Lactic acid (mm/L)	3.1±0.6	4.9±0.7	4.0±1.6	5.0±2.3	0.9±0.1	5.8±5.0		
WBC	18.2±3.9	12.4±1.2	17.6±3.0	12.6±1.4	15.1±1.8	12.5±1.2*	12.1±1.8	13.1±1.7
RBC	3.3±0.1	3.5±0.2	3.0±0.1	3.2±0.1	2.8±0.1	2.9±0.2	2.9±0.1	2.6±0.1
Hemoglobin (g/dL)	9.1±0.3	10.3±0.5*	8.6±0.2	9.6±0.4*	7.9±0.2	8.9±0.6*	8.0±0.1	7.8±0.3
Hematocrit (%)	29.8±1.1	32.9±1.6	27.8±0.8	29.8±1.3	25.8±0.5	28.1±1.7	26.3±0.5	24.9±1.0
Neutrophils (%)	77.7±2.3	77.4±3.4	78.1±2.2	81.7±2.4	75.1±1.7	78.1±4.6	71.6±3.2	85±2.4*
Lymphocytes (%)	11.8±2.3	12.4±2.9	11.6±2.1	8.2±2.4	11.5±1.3	7.3±1.6*	15.2±2.4	6.3±1.5*
Absolute neutrophils	11.9±1.1	10.6±1.4	12.3±1.1	10.7±1.4	11.7±1.3	10.5±1.1*	9.1±1.5	11.3±1.6
Absolute Lymphocytes	4.7±3.4	1.6±0.6	3.6±2.4	0.8±0.2	1.5±0.21	0.8±0.2*	1.5±0.2	0.7±0.2*
TLC (mm3)	1238±119.3	1015±188	1264±147	861±186*	1448±185	824±179*	1469±212.9	753±174*
NCLR	12.6±2.1	22.3±7.5	13.5±2.4	50±24	16.9±7.4	26.4±6.7*	7.6±1.6	25.6±6.2*

*P<0.05; **P<0.01; ***P<0.001; TLC= Total lymphocyte count; WBC= White blood cells; RBC= Red blood cells; NCLR= Neutrophil count lymphocyte ratio.

The group of patients with inadequate protein had a significantly higher duration on nutrition support (13.5±1.6 vs. 9.5±1.3, p = .008) and higher ICU LOS (17±1.8 vs. 14.5±2.1, p = .37) but with no significant difference when compared to the adequate protein group. On day 1, there was no significant difference between both groups, except for hemoglobin (9.1±0.3 vs. 10.3±0.5, p = .04). There was a trend of a decrease in total protein, albumin procalcitonin, WBC, hemoglobin, and hematocrit. On day 14, there was a significant difference between both groups in the markers of inflammation neutrophils (71.6±3.2 vs. 85±2.4, p = .008), lymphocytes (15.2±2.4 vs. 6.3±1.5, p = .01), absolute lymphocyte (1.5±0.2 vs. 0.7±0.2, p =.02), TLC (1489±212.9 vs. 753±174, p = 0.02) and NLCR (7.6±1.6 vs. 25.6±6.2, p = .001) with the inadequate protein group having more favorable outcomes than the adequate protein group. (See Table 19). This study found that patients that received inadequate protein had more favorable outcomes in TLC and NLCR when compared with patients that got adequate protein.

Comparison of clinical outcomes between three BMI groups

Patients were divided into three groups: group A with BMI <22 kg/m2 (n=19); group B with BMI of 22 to <30 kg/m2 (n= 23); and group C with BMI > 30 kg/m2 (n=18). One-way ANOVA was used to compare the clinical outcomes between the three BMI group. [Table 20]. There was a significant difference in APACHE II [F (2, 57) = 3.606, p = .034] with the statistical difference between group B and C, p = .02; and NRI [F (2, 52) = 71.20, p <.0001] with the statistical difference between the three groups, p <.01. There was no statistical difference in ICU LOS, SOFA scores, Charlson Comorbidity scores, days on ventilation, duration of nutrition support, infection rate and mortality rate.

We found statistically significant differences in the following biochemical laboratory markers on day 1:

- Carbon dioxide [F (2, 57) = 6.92, p = .002] with the statistical difference between group A and B, p = .02.
- Anion gap [F (2, 57) = 6.92, p = .002] with the statistical difference between groups A and B, p = .005 and A and C, p = .007.
- Lactic acid [F (2, 33) = 3.35, p = .04] with the statistical difference between group A and C, p = .04.
- MCV [F (2, 57) = 3.09, p = .05] with the statistical difference between group A and C, p =.05.
- Neutrophil [F (2, 57) = 3.64, p = .03] with the statistical difference between group A and C, p = .05.
- TLC [F (2, 55) = 6.6, p = .003] with the statistical difference between groups A and B, p = .02 and A and C, p = .003.
- NLCR [F (2, 57) = 6.14, p = .004] with the statistical difference between groups A and B, p = .008, and A and C, p = .01.

We found statistically significant difference in the following biochemical laboratory markers on day 3:

- RBC [F (2, 57) = 3.66, p = .03] with the statistical difference between group B and C, p = .03.
- Hemoglobin [F (2, 57) = 4.76, p = .01] with the statistical difference between group B and C, p = .009.
- Hematocrit [F (2, 57) = 3.60, p = .03] with the statistical difference between group B and C, p = .02.

- TLC [F (2, 56) = 5.94, p = .005] with the statistical difference between groups A and B, p = .005, and A and C, p = .03.

We found statistically significant difference in the following biochemical laboratory markers on day 7:

- Chloride [F (2,42) = 4.96, p = .01] with the statistical difference between groups A and B, p = .03, and B and C, p = .01.
- Total protein [F (2, 19) = 6.5, p = .007] with the statistical difference between groups A and B, p = .01, and B and C, p = .01.
- Procalcitonin [F (2, 6) = 7.39, p = .02] with the statistical difference between group B and C, p = .02.
- Absolute lymphocyte [F (2,42) = 6.19, p = .003] with the statistical difference between group A and B, p = .002.
- TLC [F (2, 42) = 6.20, p = .004] with the statistical difference between groups A and B, p = .009, and A and C, p = .01.

We found statistically significant difference in the following biochemical laboratory markers on day 14:

- MCV [F (2, 25) = 3.25, p = .05] with the statistical difference between group A and C, p = .04.
- Neutrophils [F (2,25) = 3.52, p = .04] with the statistical difference between group A and B, p = .04.
- Lymphocyte [F (2, 25) = 3.18, p = .05] with the statistical difference between group A and B, p = .05.

- Absolute lymphocyte [F (2, 25) = 6.74, p = .005] with the statistical difference between groups A and B, p = .005, and A and C, p = .03.
- TLC [F (2, 25) = 6.45, p = .005] with the statistical difference between groups A and B, p = .005, and A and C, p = .03.
- NLR [F (2, 25) = 6.32, p = .006] with the statistical difference between groups A and B, p = .01, and A and C, p = .01.

Table 20: Comparison of clinical outcomes between three BMI groups

	Group A	Group B	Group C	p values
Characteristics				
APACHE II	24.95±1.6	22.04±1.1	27.17±6.3$_{b}$*	0.03
SOFA	8.2±0.7	6.3±0.5	7.6±0.5	0.06
mNUTRIC score	5.6±0.4	4.8±0.3	5.8±0.3	0.08
NRI	40.8±1.5	50±1.6 $_{a}$***	75.2±2.9 $_{a,b}$***	<0.0001
Charlson Comorbidity Index	6.4±0.8	5.4±0.6	5.4±0.4	0.49
Outcomes				
Days on ventilation (days)	5.4±1.8	3.6±1.0	6.9±2.2	0.37
Duration on Nutrition Support (days)	11.2±1.7	11.1±1.9	13.8±1.1	0.55
Infection (%)	74%	78%	100%	0.55
Mortality (%)	47%	61%	56%	0.69
ICU LOS (days)	16.69±2.6	14.22±2.1	17.28±2.6	0.60
Day 1				
Indicators				
	Group A	**Group B**	**Group C**	
Sodium (mEq/L)	142±2.6	142±1	141.5±1.9	0.96
Potassium (mEq/L)	4.4±0.2	4.1±0.1	4.3±0.2	0.65
Chloride (mEq/L)	106.4±2.9	111.9±4	107.2±2.2	0.43
Carbon dioxide (mEq/L)	20.8±1.1	25.3±1.2$_{a}$*	24.4±1.3	0.02
Glucose (mg/dL)	198±27	187±23	172±17	0.77
Blood Urea Nitrogen (mg/dL)	52.58±8.4	33.5±4.1	40±5.3	0.80
Creatinine (mg/dL)	3.2±0.6	1.9±0.3	2.8±0.4	0.119
Calcium	8.5±0.2	8.3±0.3	7.9±0.2	0.38
Magnesium (mg/dL)	2.09±0.1	2.04±0.1	1.9±0.1	0.53
Total Protein (g/dL)	5.5±0.3	5.8±0.2	5.8±0.3	0.61
Anion gap (mEq/L)	19.5±1.5	13.9±0.8 $_{a}$**	13.8±1.4 $_{a}$**	0.002
Albumin (g/dL)	2.8±0.2	2.6±0.1	2.7±0.2	0.69
Alkaline Phosphatase (IU/L)	107.7±15.3	121.2±15	94.5±13.1	0.47
Alanine Transaminase (IU/L)	48.7±25	60±29	222±133	0.18
Aspartate aminotransferase (IU/L)	108.9±57	103±46	491±336	0.21

Total Bilirubin (mg/dL)	2.6±1.3	0.9±0.1	1.3±0.5	0.20
Phosphorus (mg/dL)	4.2±0.6	4.1±0.4	3.9±0.4	0.94
Procalcitonin (ng/mL)	29.8±13.7	75±71	24.5±19.8	0.71
Lactic acid (mm/L)	5.4±0.9	3.4±0.7	2.6±0.8 a*	0.04
WBC	12.3±1.2	12.4±1.7	24.2±7.5	0.08
RBC	3.24±0.2	3.6±0.2	3.2±0.1	0.23
Hemoglobin (g/dL)	9.8±0.5	10.1±0.5	8.7±0.4	0.11
Hematocrit (%)	31.4±1.6	32.6±1.7	28.6±1.3	0.18
MCV (fL)	97.3±1.5	92.6±1.9	90.7±2.1 a*	0.05
Neutrophils (%)	84.8±1.9	74.6±3.2	73.7±4.1 a*	0.03
Lymphocytes (%)	6.3±1.2	14.9±2.9	14.4±4.3	0.09
Absolute neutrophils	11.7±1.7	9.2±1.4	13.6±1.3	0.10
Absolute Lymphocytes	0.7±0.1	1.9±0.6	8.3±6.8	0.29
TLC (cells/m3)	671±125	1294±177 a**	1499±178 a**	0.003
NLCR	28.8±6.4	10.8±2.9 a**	10.6±1.9 a*	0.004
LDH (IU/L)	548.3±200	966.2±409	609.5±222	0.56
Ferritin (ng/mL)	1009±519	1136±569	574±242	0.51
Transferrin (mg/dL)	122.6±14	127±12.5	155.3±17.6	0.32
Total Cholesterol (mg/dL)	98±14	124.85±15.4	103.7±18	0.46
Triglycerides (mg/dL)	80±9.3	90.5±8	96.7±28.5	0.75
LDL (mg/dL)	42.6±11.8	67.6±10.4	51.7±16	0.32
HDL (mg/dL)	35.4±4.1	36.7±7.8	29.3±4.9	0.78

Day 3

	Group A	**Group B**	**Group C**	
Sodium (mEq/L)	143±2.6	145±3	141±1.3	0.37
Potassium (mEq/L)	4.1±0.2	4±0.1	4.5±0.2	0.11
Chloride (mEq/L)	109.9±3.1	113.4±2.7	107.5±1.8	0.29
Carbon dioxide (mEq/L)	21.9±1.1	24.1±1.1	22.3±1.3	0.35
Glucose (mg/dL)	166.6±17.6	164.3±15.9	165±14	0.99
Blood Urea Nitrogen (mg/dL)	46.4±7.4	36.5±3.7	43.2±5.3	0.41
Creatinine (mg/dL)	2.7±0.4	2.3±0.4	3.6±0.5	0.08
Calcium	7.7±0.2	8±0.3	7.4±0.2	0.17
Magnesium (mg/dL)	2.1±0.1	2.1±0.1	1.9±0.1	0.24
Total Protein (g/dL)	4.8±0.2	5.1±0.3	5.0±0.2	0.56
Anion gap (mEq/L)	15.6±1.2	12.9±0.9	15.6±1.4	0.15
Albumin (g/dL)	2.5±0.2	2.2±0.1	2.3±0.2	0.57

Alkaline Phosphatase (IU/L)	224±128	99±14.9	90±12.4	0.38
Alanine Transaminase (IU/L)	126.6±50.5	56±24.9	120±59.7	0.47
Aspartate aminotransferase (IU/L)	368.7±199	94.8±45	252.8±184	0.43
Total Bilirubin (mg/dL)	2.7±1.7	1.3±0.5	1.5±0.9	0.67
Phosphorus (mg/dL)	4.2±0.4	3.7±0.5	4.9±0.5	0.26
Procalcitonin (ng/mL)	62±27.3	206±198	67.7±66	0.63
Lactic acid (mm/L)	3.1±1.4	3.6±1.9	6.8±3.4	0.47
WBC	11.4±1.5	14±1.6	22.1±5.6	0.06
RBC	2.9±0.1	3.4±0.2	2.9±0.1 $_{b*}$	0.03
Hemoglobin (g/dL)	9.1±0.3	9.6±0.4	8.0±0.2 $_{b**}$	0.01
Hematocrit (%)	28.4±0.9	30.6±1.4	26.3±0.8 $_{b*}$	0.03
MCV (fL)	95.3±1.7	92.2±1.9	91.6±2.5	0.39
Neutrophils (%)	84.7±1.5	76.4±2.5	77.9±3.9	0.08
Lymphocytes (%)	6.6±1.0	11.4±1.9	12.4±3.9	0.22
Absolute neutrophils	10.0±1.6	10.4±1.2	14.9±1.7	0.04
Absolute Lymphocytes	0.5±0.1	1.4±0.2	6.0±4.7	0.26
TLC (cells/m3)	564±71.9	1418±246 $_{a**}$	1269±158 $_{a*}$	0.005
NLCR	58.3±31.2	14.7±3.7	13.9±2.9	0.13

Day 7

	Group A	**Group B**	**Group C**	
Sodium (mEq/L)	142.8±1.2	147.5±1.9	142.9±1.5	0.06
Potassium (mEq/L)	4.2±0.1	3.9±0.1	4.4±0.2	0.08
Chloride (mEq/L)	108.6±1.7	116±2.6 $_{a*}$	107.7±1.7 $_{b*}$	0.01
Carbon dioxide (mEq/L)	25.5±0.9	24.4±1.5	25.9±0.6	0.61
Glucose (mg/dL)	155.6±11	143±12.3	161±17	0.64
Blood Urea Nitrogen (mg/dL)	50.6±5.2	42.47±8.2	47.6±6.9	0.69
Creatinine (mg/dL)	2.9±0.6	2.3±0.5	3.9±0.8	0.17
Calcium	8.1±0.3	8.2±0.3	7.9±0.1	0.82
Magnesium (mg/dL)	2.2±0.1	2.1±0.1	2.1±0.1	0.65
Total Protein (g/dL)	4.8±0.2	6.0±0.3 $_{a**}$	4.8±0.2 $_{b*}$	0.007
Anion gap (mEq/L)	13.1±1.1	12.8±1.09	13.5±1.1	0.9
Albumin (g/dL)	2.5±0.2	2.3±0.1	2.3±0.1	0.8
Alkaline Phosphatase (IU/L)	298±203	167.4±52	113.4±19	0.63
Alanine Transaminase (IU/L)	66.6±29	46.9±23.7	67.6±40	0.88
Aspartate aminotransferase (IU/L)	170.9±129	56±23.4	61.4±28.8	0.58
Total Bilirubin (mg/dL)	2.5±2	0.6±0.1	0.9±0.5	0.58
Phosphorus (mg/dL)	3.9±0.4	4.1±.5	4.6±0.5	0.6

Procalcitonin (ng/mL)	1.0±0.5	0.4±0.1	4.3±1.4 b*	0.02
Lactic acid (mm/L)	0.8±0.0	4.1±3.3	1.2±0.0	0.84
WBC	10.5±0.9	15.9±1.9	16.3±2.9	0.88
RBC	2.7±0.1	3.1±0.2	2.8±0.1	0.07
Hemoglobin (g/dL)	8.1±0.2	8.9±0.6	7.8±0.2	0.17
Hematocrit (%)	25.7±0.7	28.7±1.9	25.7±0.6	0.15
MCV (fL)	95.4±2.4	92±2.6	90.4±2.1	0.31
Neutrophils (%)	78.9±4.8	74.2±2.8	75.4±2.3	0.63
Lymphocytes (%)	6.7±1.5	11.5±2.0	11.8±1.6	0.07
Absolute neutrophils	8.9±0.8	12.1±1.7	12.8±2.4	0.23
Absolute Lymphocytes	0.6±0.1	1.9±0.4 a**	1.4±0.2	0.003
TLC (cells/m3)	615±130	1561±323 a**	1521±147 a**	0.004
NLCR	26.6±7.1	11.1±3.0	23.6±14.7	0.45

Day 14

	Group A	Group B	Group C	
Sodium (mEq/L)	139.8±1.8	145.80±1.8	140±2.2	0.07
Potassium (mEq/L)	4.5±0.4	4.2±0.2	4.1±0.1	0.54
Chloride (mEq/L)	105.7±2.3	111.6±2.3	105.9±2.5	0.14
Carbon dioxide (mEq/L)	23.7±2.3	25.9±2.4	26.3±0.9	0.62
Glucose (mg/dL)	179.6±25	149±13	130±19	0.23
Blood Urea Nitrogen (mg/dL)	60.78±11.5	47.30±12.70	39.4±9.4	0.43
Creatinine (mg/dL)	2.7±0.7	1.8±0.5	2.4±0.6	0.47
Calcium	8.3±0.3	7.8±0.3	8.0±0.2	0.52
Magnesium (mg/dL)	2.3±0.1	2.2±0.2	2.1±0.1	0.28
Total Protein (g/dL)	4.8±0.4	5.4±0.5	5.2±0.3	0.59
Anion gap (mEq/L)	14.9±2.6	12.4±1.6	12.6±0.6	0.58
Albumin (g/dL)	2.2±0.3	1.9±0.1	2.2±0.1	0.48
Alkaline Phosphatase (IU/L)	289±170	191.6±36	152.8±28	0.64
Alanine Transaminase (IU/L)	38.50±6.3	27.6±9.1	36.3±19.5	0.84
Aspartate aminotransferase (IU/L)	47.5±14.7	50.8±14	46±16	0.97
Total Bilirubin (mg/dL)	1.8±1.4	1.1±0.6	0.7±0.1	0.69
Phosphorus (mg/dL)	5.8±1.4	3.2±0.3	4.6±0.5	0.07
Procalcitonin (ng/mL)	-	1.4±0.7	0.5±0.4	0.41
Lactic acid (mm/L)				
WBC	10.9±1.6	14.1±2.8	12.2±1.9	0.59
RBC	2.6±0.2	2.8±0.1	2.9±0.1	0.08

Hemoglobin (g/dL)	7.8±0.4	8.1±0.2	7.9±0.2	0.66
Hematocrit (%)	24.8±1.1	26.5±0.7	26.1±0.7	0.36
MCV (fL)	98±3.2	94.3±2.4	88.2±7.5 a*	0.05
Neutrophils (%)	85.2±2.6	70.8±5.1 a*	73.9±3.6	0.04
Lymphocytes (%)	6.0±1.6	16.0±3.9	13.6±2.6	0.05
Absolute neutrophils	9.4±1.6	10.7±2.4	9.4±1.8	0.86
Absolute Lymphocytes	0.5±0.1	1.7±0.3 a**	1.4±0.2 a*	0.005
TLC (cells/m^3)	523.8±87	1679±312 a**	1425±233 a*	0.005
NLCR	26.7±6.8	8.2±2.6 a*	7.8±1.9 a*	0.006

*P<0.05; **P<0.01; ***P<0.001; a There was statistically significant difference from Group A; b There was a statistically significant difference from group B. Data were shown as mean ± SEM; Group A=BMI <22 kg/m^2; Group B= BMI 22 to <30 kg/m^2; Group C= BMI >/=30 kg/m^2 LDH= lactic acid dehydrogenase; TLC= Total lymphocyte count; WBC= White blood cells; RBC= Red blood cells; MCV= Mean corpuscular volume; NLCR= Neutrophil lymphocyte count ratio; LDL= Low density lipoprotein; HDL= High density lipoprotein.

Pearson Correlation Analysis

Table 21 shows the Pearson correlation analysis of the mNUTRIC score tool with APACHE II, SOFA score, NRI, infection, and death. APACHE II and SOFA scores correlated with mNUTRIC scores ($p < .0001$), while NRI, infection, and mortality showed no correlation with mNUTRIC score.

Table 22 shows the Pearson correlation analysis of ICU LOS with BMI, mNUTRIC score, NRI, malnutrition, and nutrition support initiation time. No correlation was found between ICU LOS and the selected parameter. However, a positive correlation was found between ICU LOS and nutrition support initiation time $\chi 2(2, N=60) = 2.99$, $p = .05$.

Table 23 shows the Pearson correlation analysis of NRI with APACHE II, SOFA, mNutric score, infection, and mortality. No correlation was found.

Table 24 shows the Pearson correlation coefficient TLC with BMI, nutrition support initiation time, ICU LOS, mNUTRIC score, NRI, malnutrition, APACHE, and SOFA scores. There was a positive correlation with BMI $\chi 2(6, N=60) = 13.4$, $p = .036$. and a negative correlation with malnutrition $\chi 2(2, N=60) = 13.7$, $p = .001$. All other variables showed no correlation with TLC.

The Pearson correlation coefficient of malnutrition with selected clinical characteristics is shown in Table 25. There was a significant a negative correlation between malnutrition and BMI $\chi 2(2, N=60) = 46.9$, $P < .0001$ and TLC $\chi 2(2, N=60) = 13.7$, $p < .001$.

The Pearson correlation coefficient of NLCR with selected clinical characteristics is shown in Table 26. There was a significant a negative correlation between NLCR and TLC $\chi 2(2, N=60) = 21.8$, $p < .0001$.

Table 21: Pearson correlation analysis of mNUTRIC score with selected clinical characteristics

	Pearson Chi-Square	df	p-value
APACHE II score	43.4	3	<0.0001
SOFA score	22	2	<0.0001
NRI	1.7	1	0.192
Infection	1.66	2	0.436
Death	1.83	1	0.176

APACHE II: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, NRI: Nutritional Risk Index.

Table 22: Pearson correlation analysis of ICU LOS with selected clinical characteristics

	Pearson Chi-Square	df	p-value
BMI	2.99	6	0.809
mNUTRIC score	0.84	2	0.655
NRI	0.27	2	0.873
Malnutrition	0.81	2	0.667
Nutrition support initiation time	5.87	2	0.05

BMI: Body Mass Index, mNutric Score: modified Nutrition Risk in Critically ill score, NRI: Nutritional Risk Index.

Table 23: Pearson correlation analysis s of NRI with selected clinical characteristics

	Pearson Chi-Square	df	p-value
APACHE II score	4.25	3	0.236
SOFA score	2.28	2	0.318
mNUTRIC score	1.7	1	0.192
Infection	2.04	2	0.359
Mortality	0.59	1	0.439

APACHE II: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, mNutric Score: Nutrition Risk in Critically ill score.

Table 24: Pearson correlation analysis of TLC with selected clinical characteristics

	Pearson Chi-Square	df	p-value
BMI	13.4	6	0.036
Nutrition support initiation time	3.46	2	0.177
ICU LOS	0.71	4	0.949
mNUTRIC score	0.57	2	0.749
NRI	0.61	2	0.736
Malnutrition	13.7	2	0.001
APACHE II score	3.81	6	0.700
SOFA II score	2.5	4	0.644

BMI: Body Mass Index, APACHE II: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, mNutric Score: modified Nutrition Risk in Critically ill score, NRI: Nutritional Risk Index, ICU LOS: intensive unit care length of stay.

Logistic Regression Analysis

To determine if APACHE II score, SOFA score, mNUTRIC scores, Charlson comorbidity index, WBC, hemoglobin, hematocrit, neutrophils, lymphocytes, absolute neutrophils, absolute lymphocytes, NLCR, TLC, and NRI are reliable for the prediction of malnutrition, we performed a binomial logistic regression analysis as shown in [Table 27]. The logistic regression model was statistically significant, $\chi 2(1) = 28.436$, $p < .0001$. The model explained 40.4% and 56.9% of the variance as determined by Cox and Snell R_2, Nagelkerke R_2 models, respectively. 85.5% of cases were classified correctly by the model. Sensitivity was 76.5%, specificity was 89.5%. An association was found in NRI (OR -.213, p = .001); NLCR (OR .119, p = 002); TLC (OR -.002, p = .003); Neutrophils (OR .125, p = .004) and Lymphocyte (OR -.188, p = .009) with malnutrition. The area under the receiver operating characteristics (ROC) curve is as shown in Figures 6-10 below. All markers from ROC analysis allowed for an excellent level of discrimination as good predictive markers.

Table 25: Pearson correlation coefficients of malnutrition with selected clinical characteristics

	Pearson Chi-Square	df	p-value
BMI	46.92	2	<0.0001
NRI	2.46	1	0.117
APACHE II score	0.098	3	0.992
SOFA score	2.851	2	0.240
mNUTRIC score	0.004	1	0.950
Infection	0.056	2	0.972
TLC	13.75	2	0.001
ICU LOS	0.811	2	0.667
Nutrition support initiation time	1.047	1	0.306
Charlson Comorbidity Index	0.932	1	0.334
Death	1.158	1	0.282
Albumin	1.468	2	0.480
Duration on nutrition support	0.148	2	0.929
NLCR	1.688	1	0.194

BMI: Body Mass Index, APACHE II: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, mNutric Score: modified Nutrition Risk in Critically ill score, NRI: Nutritional Risk Index, ICU LOS: intensive unit care length of stay, TLC: Total Lymphocyte Count, NLCR: Neutrophil Lymphocyte Count Ratio.

Table 26: Pearson correlation coefficients of NLCR with selected clinical characteristics

	Pearson Chi-Square	df	p-value
NRI	1.535	1	0.215
APACHE II Score	1.594	3	0.661
SOFA Score	0.226	2	0.893
Charlson Comorbidity Index	0.254	1	0.614
mNUTRIC score	1.37	1	0.242
Infection	1.632	2	0.442
Death	0.525	1	0.469
Albumin	1.391	2	0.499
TLC	21.8	2	0.0001
ICU LOS	0.305	2	0.858
Nutrition support initiation time	0.054	1	0.817
Duration on nutrition support	0.097	2	0.953

APACHE II: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, mNutric Score: modified Nutrition Risk in Critically ill score, NRI: Nutritional Risk Index, ICU LOS: intensive unit care length of stay, TLC: Total Lymphocyte Count, NLCR: Neutrophil Lymphocyte Count Ratio.

Table 27: A logistic regression model of nutrition and inflammatory biomarkers and other covariates associated with malnutrition

	B	SE of ß	p-value	OR
APACHE II	0.016	0.045	0.722	1.016
SOFA	0.199	0.11	0.071	1.221
mNUTRIC	0.246	0.195	0.206	1.279
NRI	-0.213	0.066	0.001	0.808
Charlson Comorbidity Index	0.199	0.106	0.062	1.22
NLCR	0.119	0.039	0.002	1.126
TLC	-0.002	0.001	0.003	0.998
Creatinine	0.236	0.138	0.086	1.266
Albumin	0.315	0.406	0.437	1.37
Hemoglobin	0.131	0.127	0.304	1.14
Hematocrit	0.029	0.039	0.466	1.029
WBC	-0.046	0.047	0.332	0.955
Neutrophils	0.125	0.043	0.004	1.133
Lymphocytes	-0.188	0.072	0.009	0.829
Absolute neutrophils	0.02	0.041	0.627	1.02

APACHE II: The Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, mNutric Score: modified Nutrition Risk in Critically ill score, NRI: Nutritional Risk Index, TLC: Total Lymphocyte Count, NLCR: Neutrophil Lymphocyte Count Ratio, WBC: White Blood Cells.

NRI

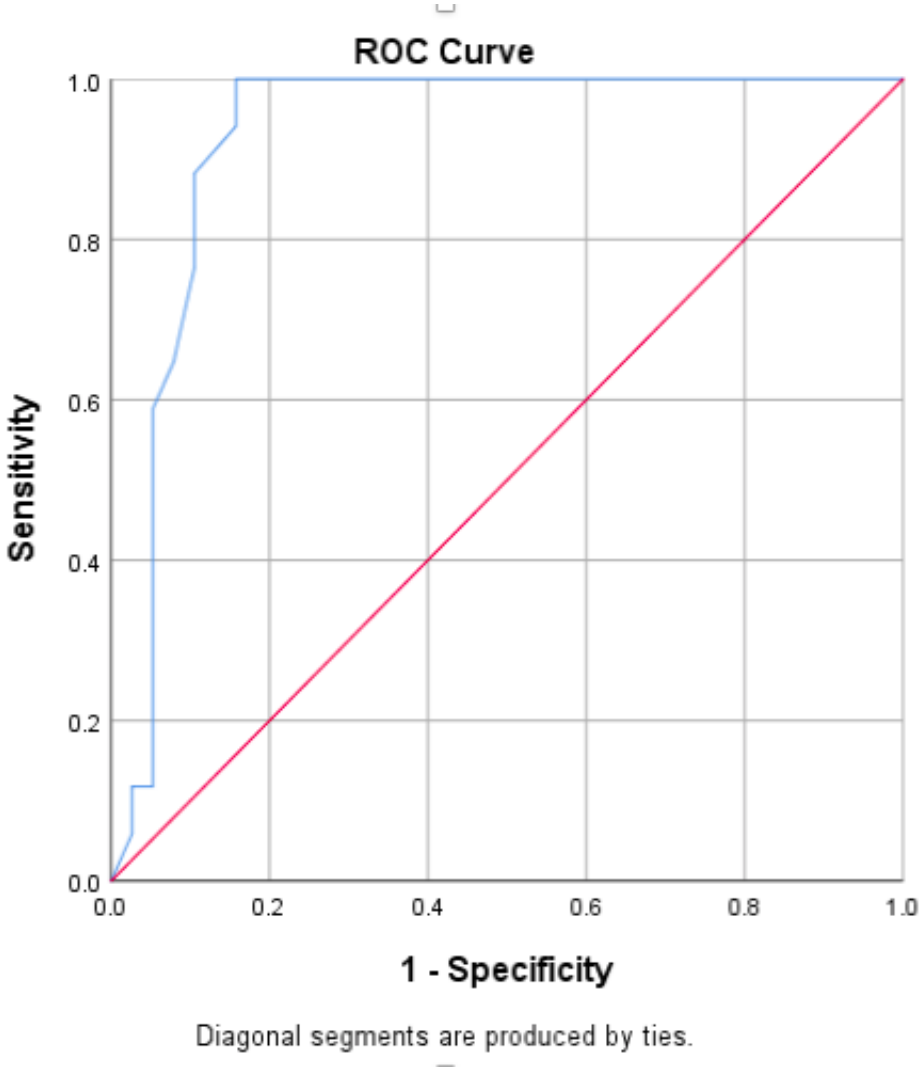

Figure 7: ROC curves based on a model showing the power of NRI to predict patients with malnutrition.

The area under the curve was 0.929 (P <.0001, 95% CI: .0857-1.000). ROC, receiver operating characteristics; NRI, nutritional risk index.

NLCR

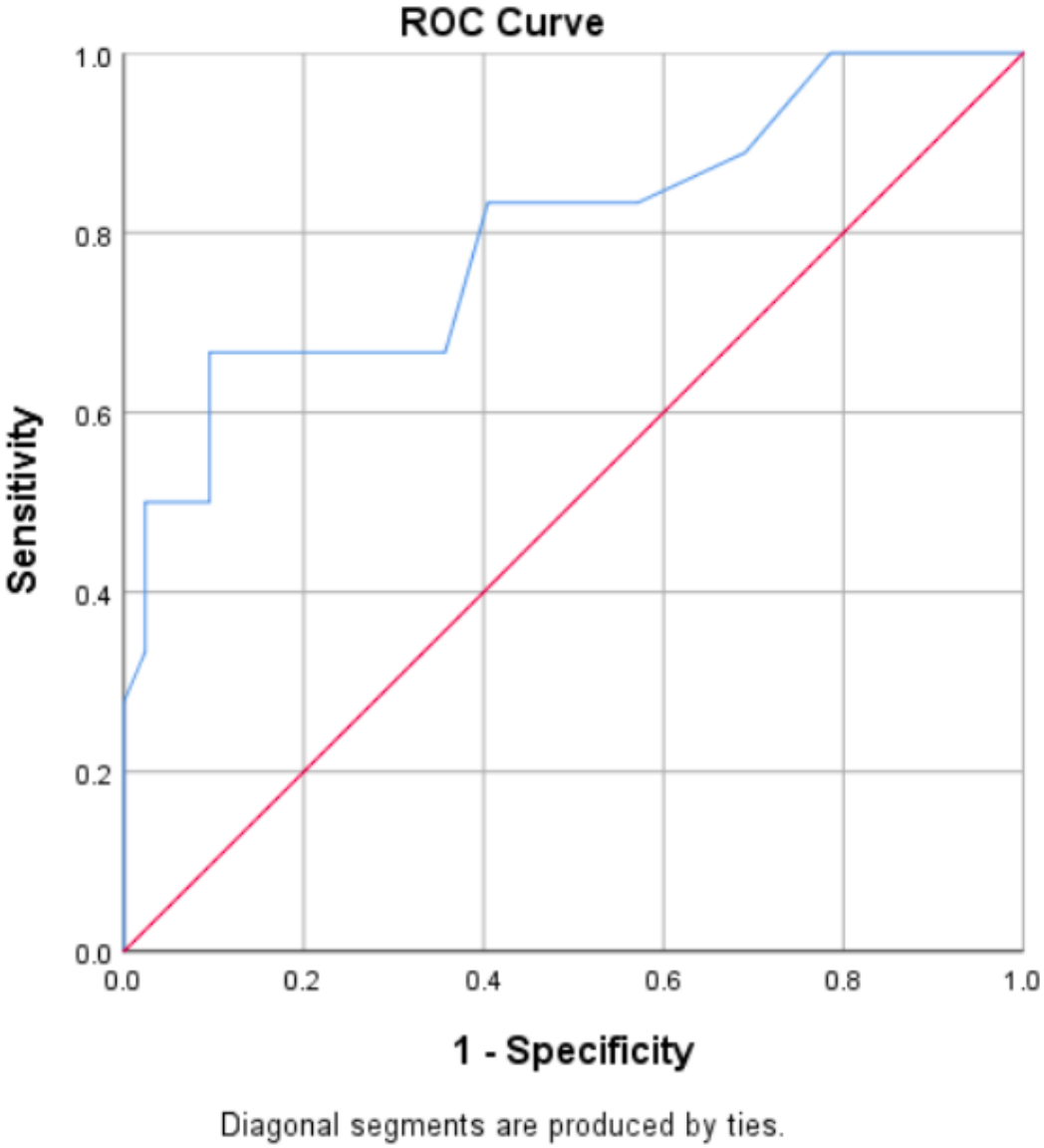

Figure 8: ROC curves based on a model showing the power of NLCR to predict patients with malnutrition.

The area under the curve was 0.799 (P <.0001, 95% CI: .667-.931). ROC, receiver operating characteristics; NLCR, neutrophil-to-lymphocyte count ratio.

TLC

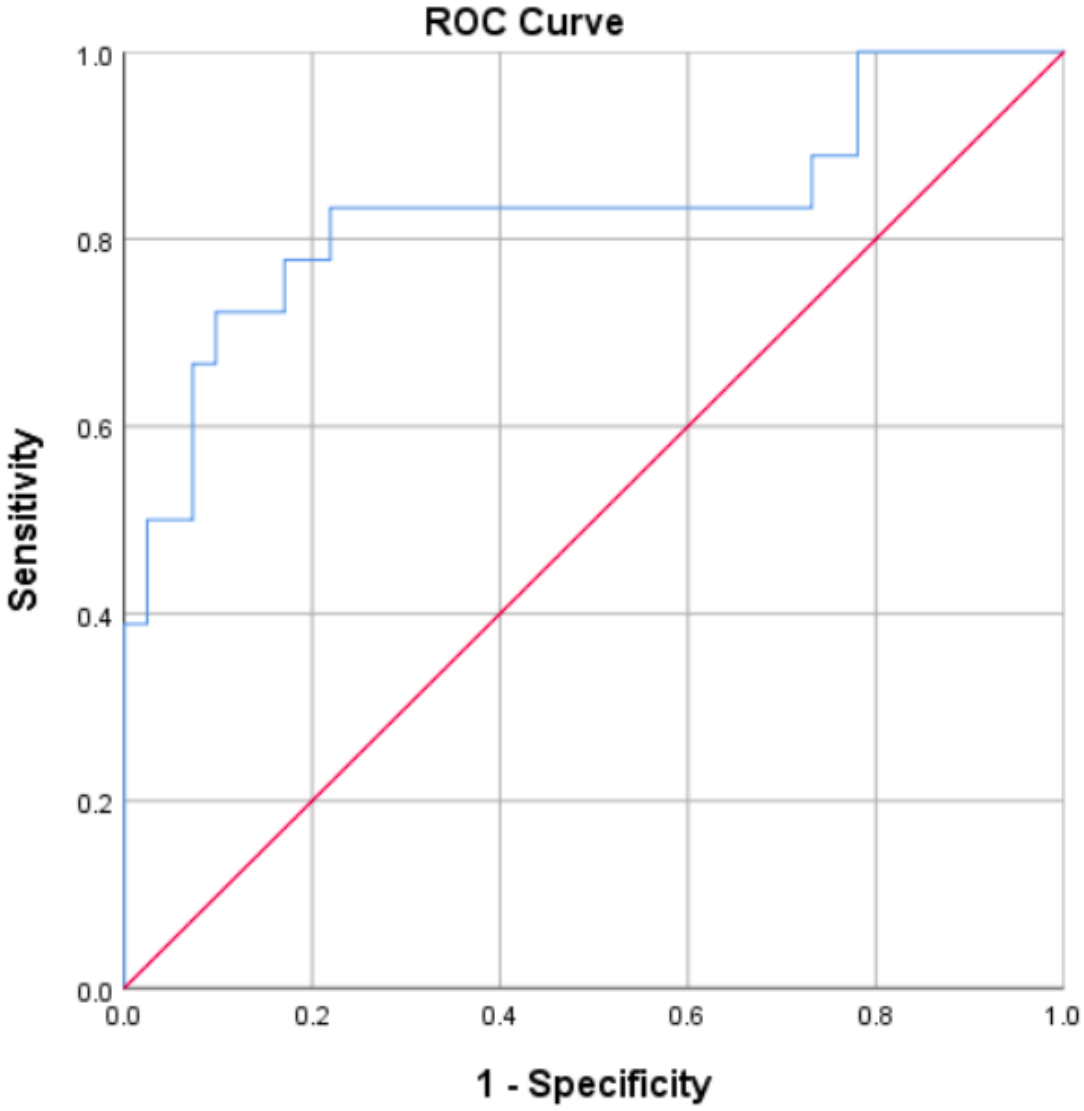

Figure 9: ROC curves based on a model showing the power of TLC to predict patients with malnutrition.

The area under the curve was 0.831 (P <.0001, 95% CI: .697-.964). ROC, receiver operating characteristics; TLC, total lymphocyte count.

Neutrophils

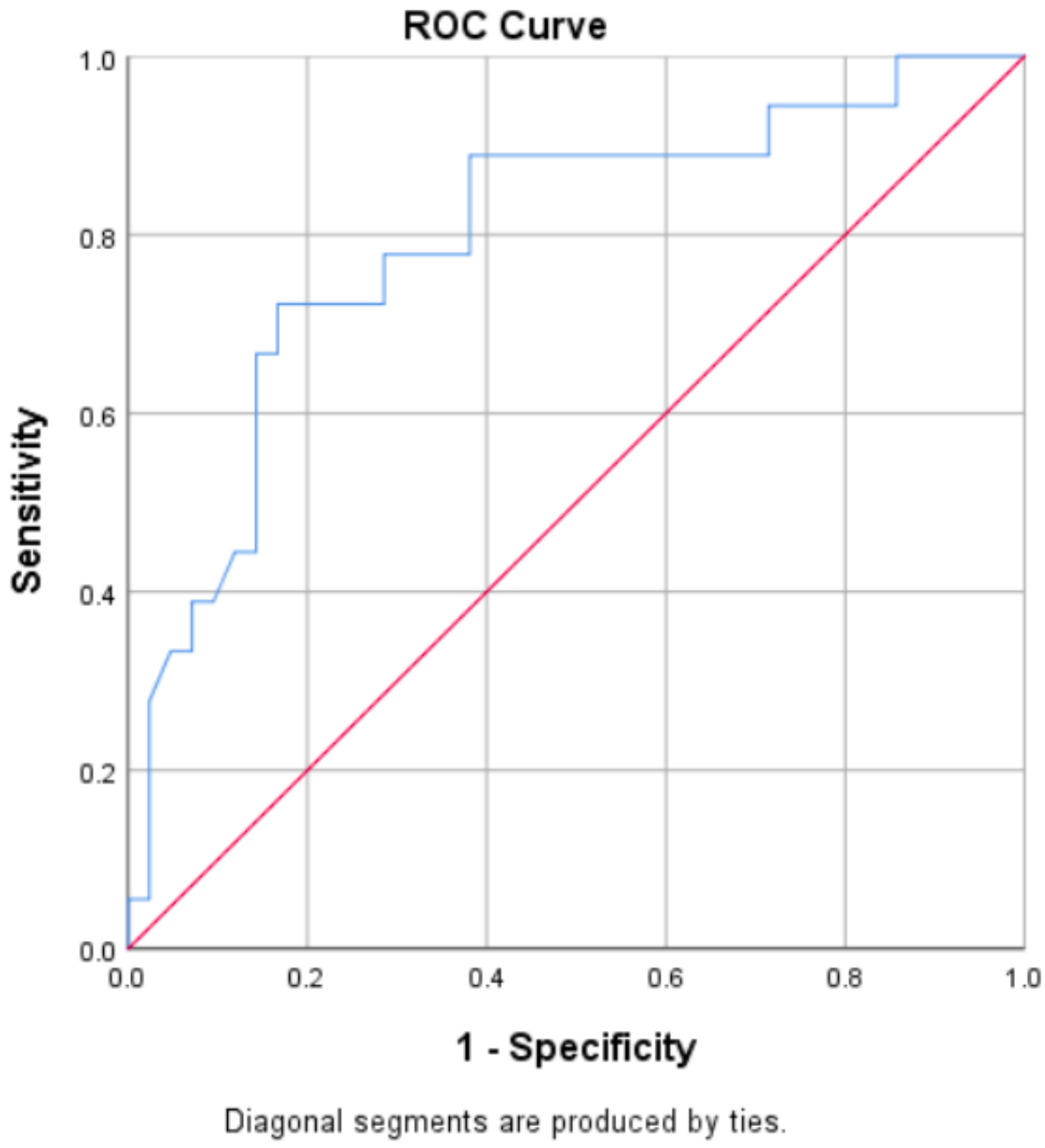

Figure 10: ROC curves based on a model showing the power of neutrophils to predict patients with malnutrition.

The area under the curve was 0.796 (P <.0001, 95% CI: .668-.925). ROC, receiver operating characteristics.

Lymphocyte

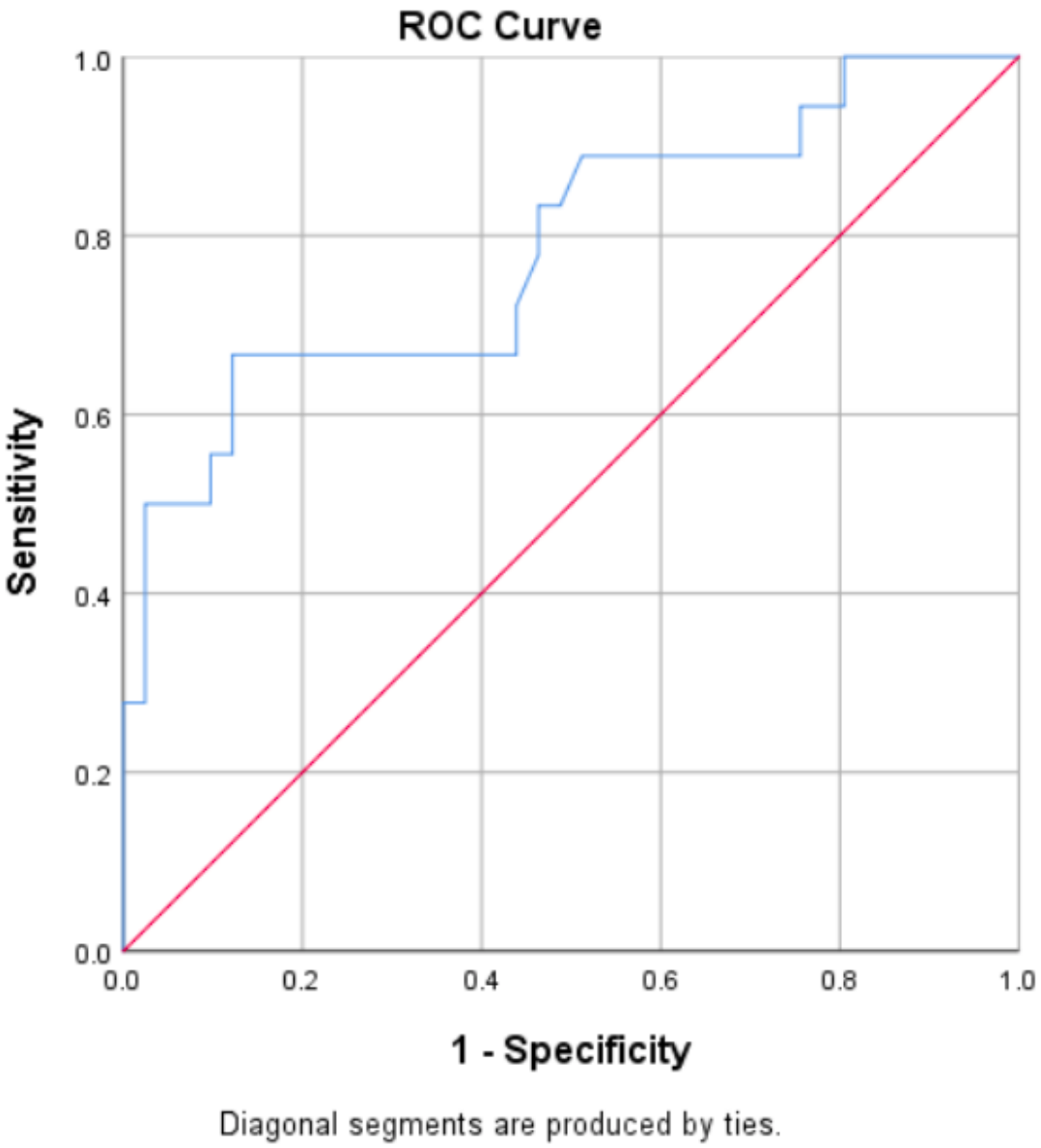

Figure 11: ROC curves based on a model showing the power of lymphocyte to predict patients with malnutrition.

The area under the curve was 0.786 (P <.001, 95% CI: .649-.922). ROC, receiver operating characteristics.

CHAPTER 5. DISCUSSION

A retrospective analysis of medical chart review was undertaken at a single center to assess malnutrition and malnutrition risk in the ICU. Also, to compare the clinical outcomes of patients on nutrition support between different groups. The groups compared are as follows: normal nutrition vs. malnourished; low nutrition risk vs. high nutrition risk; early enteral nutrition initiation vs. delayed enteral nutrition initiation; inadequate vs. adequate caloric and protein intake; and BMI <22 kg/m2 vs. BMI 22 to 30 kg/m2 vs. BMI >30 kg/m2. Patients older than 19 years' old who were admitted to the medical intensive care unit from January 2019 to December 2019 and were on either enteral nutrition or parenteral nutrition for at least three days were included in this investigation. The prevalence of malnutrition in the hospital setting has been widely documented, and this ranges from 30% to 50%, depending on the settings and criteria used to define it (Mulasi et al., 2016). The patients admitted to the ICU were critically ill. Critical illness with malnutrition in these patients results in several complications such as delayed wound healing, higher infection rate, altered gastrointestinal functioning, increased morbidity, and mortality and increase hospital LOS (Berbel et al., 2014; Ozbilgin et al., 2016; Alberda et al., 2019). Criteria, such as anthropometric measurements, BMI, blood laboratory markers, TLC, could be used alone or in combination to diagnose malnutrition.

In this study, the malnutrition diagnosis of the ICU patients was assessed using the GLIM working group criteria (Cederholm et al., 2019). This method and criteria were chosen because it was feasible for a retrospective chart review, and it can be used in the routine assessment of the nutritional status of patients. This study included 60 patients admitted to the MICU at HUH. We found that 30% of the patients were malnourished and the group with malnutrition had a mean age of 73.3±2.4 years. There was no significant difference in age between patients with normal

nutrition and malnourished patients (p = .153); neither was any correlation found between sex and nutritional status; hence gender has no association with nutritional status. The incidence of malnutrition in this study is consistent with that reported in another study conducted by Baker et al. (2011). We also compared the clinical characteristics and outcomes, and laboratory biomarkers of normal nutrition versus malnourished. We found that patients with normal nutrition had significantly higher NRI scores (60.1±2.5 vs. 40.5±1.4, p = .01) and TLC (1380±121.8 vs. 639±134, p <.0001) and a lower Charlson comorbidity index (5.3±0.4 vs. 6.8±0.8, p = .05). Malnourished patients had significantly higher neutrophils (73.9±2.5 vs. 85.9±1.9, p = .004), NLCR (10.5±1.8 vs. 30.5±6.6, p <.0001), and lower lymphocytes (14.7±2.4 vs. 5.9±1.2, p = .02). There was no significant difference in age, sex, APACHE II, SOFA scores, ICU LOS, days on ventilation, and duration on nutrition support. We found that TLC improved in patients with normal nutrition and decreased in malnourished patients by day 14 (1504±193 vs. 531.8±98.6, p = .005), while NLCR increased by day 14 in the malnourished group (9.4±2.02 vs. 25.7±7.6, p = .008). We also found that TLC strongly correlated with malnutrition $\chi 2(2, N=60) = 13.7$, p = .001. Furthermore, we performed a binomial logistic regression to find an association between malnutrition and nutrition and inflammatory markers. We found a strong association with NRI (p =.001), NLCR (p = .002) TLC p = 0.002), neutrophils (p = 0.004), and lymphocytes (p = 0.009), hence proved to be useful as predictors of malnutrition.

Nutritional screening has been proposed to be the first step to identify patients who are malnourished or at risk of malnutrition (Cederholm, 2019). The objective of nutritional screening is to identify those patients who are at high nutrition risk and who will benefit from nutritional treatment (Zhou et al., 2015). Nutritional screening and assessment tools with high sensitivity and specificity should be used. To evaluate the risk of malnutrition, we used mNUTRIC score, which

was explicitly designed to identify critically ill patients that will benefit from early and aggressive nutrition intervention, especially nutrition support (Heyland et al., 2011). In the present study, the diagnosis of nutritional status through mNUTRIC score found 72% of the ICU patients to be at high nutritional risk, which is higher than the 48.6% rate reported by Mendes et al. (2017) in ICU patients. In addition to the mNUTRIC score, we also used the nutritional risk index score, and easily calculated measure that incorporates albumin and body size. This study found all of the ICU patients to be at nutrition risk using the NRI with mean score of 54±2.2; 8.3% being moderate and 91.7% being severe. The mean value of the NRI score was lower than the value shown for the high nutrition risk group suggested in the previous research (Bouillanne et al., 2005). The higher percentage of high nutrition risk using NRI maybe because NRI factors in albumin while the mNUTRIC score does not. Patients in the high nutrition risk group had a higher infection rate of 65%. The mortality rate of the high nutrition risk group in this study was 60%, which is higher than those of other studies, such as (Atu ur-Rehman et al., 2018; Kalaiselvan et al., 2017). The high nutritional risk group also had a higher duration on nutrition support (9.5±1.7 vs. 12.9±1.4, p = .16) but with no statistically significant difference. Glucose, BUN, LDH were significantly higher, while hemoglobin and HDL were lower in the high nutrition risk group when compared with the low nutrition risk group ($p < 0.05$), see [Table 15].

This study assessed several parameters that can be used to evaluate the following: disease severity (APACHE II and SOFA scores); comorbidity burden (CCI); nutritional status (TLC, hemoglobin, hematocrit, total cholesterol, high-density lipoprotein, and total protein); and inflammation (NLCR, albumin, WBC, neutrophils, lymphocyte, absolute neutrophils, absolute lymphocytes, transferrin, ferritin, LDH, and procalcitonin).

Of the 60 patients in this study, 6.7% had an APACHE II score of <15, 16.7% had a score of 15 to <20, 41.7% had a score of 20 to <28, and 35% had a score of >28. This indicates that 41.7% of patients in the ICU had at least a 35% risk of mortality, while 35% of the patient in this study had at least a 63% risk of mortality. APACHE II and SOFA scores were not significantly different between the group with normal nutrition and malnutrition ($p > .05$). However, there was a significant difference in both parameters between the EEN and the DEN groups ($p < .05$). On the other hand, in the comparisons of the BMI groups, only APACHE II was significantly different amongst groups ($p < .05$) while the SOFA score was not. The Pearson correlation analysis done showed a strong correlation in mNUTRIC score with APACHE II and SOFA, ($p < .0001$). This is expected as both APACHE II and SOFA scores are used in the mNUTRIC score assessment.

When evaluating the effect of nutrition support of nutritional and inflammatory biomarkers, we found that of the patients in the ICU, only 78% and 40% met hundred percent of their estimated kcal and protein needs, respectively. There was a statistically significant decrease in the following parameters by day 14: total protein, albumin, RBC, hemoglobin, and hematocrit ($p < .05$). Glucose, lactic acid, bilirubin, WBC, absolute neutrophils, and NLCR were trending down but with no significant difference by day 14. There have been studies showing the positive effect on clinical outcomes with nutrition support especially among patient that are malnourished and patient with multiple illnesses (Schuetz et al., 2019; Gomes et al., 2019; Deutz et al., 2016; Merker et al., 2020). Some of the results from these studies yielded no significant results (Takesue et al., 2015; Yao et 2015; Ridley et al., 2018) while some yielded negative result (Terzi et al., 2017; Rice et al., 2012) hence nutrition intervention does not have the same impact in all patients. A simple explanation of this might be the presence of a very strong systemic inflammatory response. A randomized control trial by Merker et al. (2020) showed no beneficial effect of

nutrition support on patients with high inflammation. Our study is in line with these observations; the majority of the patient in this study was critically ill and had high inflammation as shown by the mean values of albumin, WBC, absolute neutrophils, NLCR, LDH, ferritin, and transferrin.

TLC is an inexpensive clinical marker that has been shown to assess nutritional status and 'an indicator of poor prognosis" (Omran and Morley, 2000; O'Daly et al., 2010). Also, Leandro-Merhi et al. (2017) found that TLC may be considered as a nutritional biomarker as it correlates to nutritional risk according to the Nutrition Risk Score-2002 in hospitalized older patients. In the same study, they found that patients who were malnourished had a significantly lower TLC mean than those that were not. When comparing the TLC in the different groups in this study, we found that TLC of the normal nutrition group was significantly higher than the malnourished group ($p = .0001$). This result is in agreement with previous studies (Rocha and Fortes, 2015; Wakahara et al., 2007; Fiacaforri et al., 1999); therefore, TLC can be considered a surrogate marker to diagnosing malnutrition. Caution should be taken when interpreting TLC as a nutritional biomarker in the clinical setting because cancer, Acquired Immunodeficiency Syndrome (AIDS), elderly age, and some medications can influence the values; hence these diseases should be considered as confounding variables. The TLC between BMI groups was also statistically significant [$F (2, 55) = 6.6$, $p = .003$] with the statistical difference between groups A and B, ($p = .02$) and A and C, ($p = .003$). This present study found that TLC had a positive correlation with BMI, which is consistent with what Rocha and Fortes, (2015) found, and a negative correlation with malnutrition. In binomial logistic regression, we found an association between malnutrition and TLC, which is in line with what Rocha and Fortes, (2015) and Leandro-Merhi et al. (2017) found. It was observed that TLC was improved by day 14 in the normal nutrition group with no changes in the malnourished group. The reverse was found in the low nutrition risk group, early

enteral nutrition group, adequate-protein group. There was an improvement in the TLC in the group with BMI groups B by day 14, but not in group A and C.

Biochemical markers are routinely checked in the clinical setting and can be used in addition to other screening tools to assess nutritional status. They can aid in the diagnosis of malnutrition by supporting the presence of an inflammation, which further contributes to the identification of the etiologic basis. Interpretation of blood biomarkers for the diagnosis of malnutrition should be used with caution as there are no validated recommendations on the optimal cutoffs and reference ranges for respective marker levels. The laboratory biomarkers will vary with age, sex, race, diet, and disease status (Blank et al., 2003). This study investigated biomarkers that can be used to evaluate both nutritional and inflammatory status in the clinical setting, see [Appendix G] for the laboratory values and reference ranges. Combining one or more of these biomarkers with anthropometric measures can help identify malnutrition (Lee et al., 2013; Chen et al., 2015; Felder et al., 2016; Merker et al., 2020; Miao et al., 2019; Zhou 2015; Demir et al., 2015).

Regarding variables studied, albumin, a negative acute-phase protein when low, can be an indication of inflammation, impairment of liver or renal function, and poor nutritional status. In several studies, low albumin correlated with longer hospitalization and increased mortality (Cabrerizo et al., 2015; Chiu et al., 2016). Albumin should be used with caution because it is reduced with systemic inflammatory diseases (Devoto et al., 2006; Lopez-Hellin et al., 2002) and it has low specificity in the diagnosis of malnutrition in hospitalized older adults (Covinsky et al., 2002) and it is an insensitive marker of nutritional status. In the present study, when assessing the effect of nutrition support on nutritional biomarkers, we found that albumin significantly decreased by day 14 ($p < .05$). Albumin was also significantly lower in the high nutrition risk group ($p = .01$)

when compared to the low nutrition risk group. Albumin has been categorized in previous studies as patients with <3.5 g/dL as having protein-energy malnutrition (Robinson, 2015) or as ">3.5 g/dl (nourished), 3.0 a 3.5 g/dl (mild malnutrition), 2.4 a 2.9 g/dl (moderate malnutrition), and <2.4 g/dl (severe malnutrition)" (Rocha and Fortes, 2015). However, it has been shown that it is not a suitable marker for diagnosing malnutrition. This study was unable to show a correlation or association between albumin and malnutrition, unlike previous studies (Rocha and Fortes, 2015; Robinson, 2015).

Clinical studies have shown that NLCR is an inflammatory biomarker, a prognostic predictor for many diseases and positively correlates with mortality (Min et al., 2018; Yin et al., 2015; Zhang et al., 2018; Zhao et al., 2018; Tan et al., 2015; Yu et al., 2018; Yan et al., 2017; Kaya et al., 2019). Data from these studies suggest that NLCR may also be associated with the nutritional status of patients. Many studies have suggested for "high risk" to range from 2.5 to 5; however, studies from western countries suggest higher cutoffs (Dirican et al., 2015; Templeton et al., 2014; Aliustaoglu et al., 2010). This study shows the mean NLCR of all patients was (17.7±3) and decreased by day 14 (13.4±2.8) with no significant difference. NLCR was significantly lower in patients with normal nutritional status than that of patients that were malnourished (10.5±1.8 vs. 30.5±6.6, p <.001). Our findings are in line with Kaya et al. (2019). By day 14, NLCR had reduced in both groups, but the group with normal nutritional status still had a significantly lower value when compared to the malnourished group (9.4±2.02 vs. 25.7±7.6, p = .008). There was also a significant difference between the BMI groups. The patients with BMI <22 kg/m2 had a higher NLCR than patients with BMI 22-30 kg/m2 and BMI >30 kg/m2, p = .004, with a slight decrease in all groups by day 14; however, the group with BMI < 22 still had a significantly higher NLCR value than the other groups. There was a negative correlation between NLCR and TLC (p <.0001).

We also found an association between malnutrition and NLCR, which is in line with what Kaya et al. (2019) found. Most of the patients in this study had very high NLCR, most likely due to critical and chronic illnesses such as malignancies, myocardial infarction, vascular diseases, and rheumatic diseases.

Hemoglobin has been found to decrease with progressive malnutrition (Zhou et al., 2015; Weng et al., 2016). The cut-off of hemoglobin for the diagnosis of malnutrition is <13 g/dL (Zhang et al., 2017). In this study, the mean hemoglobin for all patients on day 1 was 9.6±0.3 and significantly decreased by day 14 ($p < .05$). This study found no statistical difference in hemoglobin levels in normal nutrition and malnourished group neither was there any improvements in the levels by day 14. There was a significant difference between low nutrition risk and the high nutrition risk group (10±0.6 vs. 9.4±0.3, $p < .05$).

Previous studies suggest that there is a relationship between malnutrition and LOS (Jeejeebhoy et al., 2015; Lim et al., 2012). In this study, we found that there was no significant difference in ICU LOS during a comparison of normal nutrition vs. malnourished and low nutrition risk vs. high nutrition risk. We did, however, found that the DEN group had a high ICU LOS when compared to the EEN group (13.9±1.9 vs. 18.6±1.9, $p = .09$), but this was not statistically significant. The patients that received adequate protein had a lower ICU LOS when compared to the patients that did not but with no statistically significant difference (17±1.8 vs. 14.5±2.1, $p = .37$). This study found that ICU LOS correlated positively with nutrition support initiation time $\chi 2(2, N=60) = 2.99$, $p = .05$.

Despite the awareness of malnutrition and improvements in the assessments, only a few malnourished patients received appropriate nutrition support while hospitalized (Korfali et al., 2009; Sorensen et al., 2008). Nutrition support is necessary for patients that are critically ill who

have inadequate oral intake and are malnourished. In this study, there was no significant difference of interest between the group that received adequate calories and the group that did not. The group that had inadequate calories did have a higher duration on nutrition support, but this was not significant. When comparing the group with inadequate protein to the group with adequate protein, we found that the former had a significantly higher duration on nutrition support than the later (13.5±1.6 vs. 9.5±1.3, $p < .05$).

Early nutritional support either by enteral route or parenteral route, when feasible, could reduce complications associated with malnutrition or high malnutrition risk (Kondrup et al., 2003). Early enteral nutrition delivery has also been shown to be related to the modulation of stress and the systemic immune response, and reduction in the severity of disease (Krzak, Pleva, and Napolitano, 2011). In the present study, there was a significant difference in APACHE II and SOFA scores between both groups ($p < .05$). Inconsistent with the results of previous studies (Yin et al., 2015), the EEN group had a lower duration on nutrition support when compared with the DEN ($p < .05$). On day 14, the DEN group had significantly lower blood urea nitrogen, creatinine, calcium, magnesium, mean corpuscular volume, and NLCR ($p < .05$). On the other hand, TLC and absolute neutrophils were significantly lower in the EEN group when compared to the DEN.

Our study found strong associations between nutritional status and some biomarkers on inflammation and hematological function. Moreover, comparison within the malnutrition and BMI groups, patients at nutritional risk had more pronounced alterations of biomarker levels. Blood urea nitrogen, creatinine, lactic acid, total bilirubin, neutrophils, NLCR were significantly higher in the malnourished group when compared to the normal nutritional status group ($p < .05$). Meanwhile, TLC and lymphocyte were significantly lower in the malnourished group when compared to the normal nutrition group. Similarly, the <22 kg/m2 BMI group had significantly

lower TLC and higher NLCR than other groups. Further comparison of the low nutrition risk group to the higher nutrition risk group revealed that the later had significantly higher levels of glucose, blood urea nitrogen, lactic acid, LDH, and a significantly lower levels of HDL and hemoglobin. These findings support the hypothesis that the adverse outcomes often seen in malnourished patients are linked through abnormalities in their biomarkers.

Limitations

This study has limitations that need to be taken into consideration. First, this study was limited to a single ICU center, which might weaken its validity and general applicability. Moreover, the small sample size may limit the statistical robustness on a broader scale. Second, the retrospective study design can be considered a limitation. As this study was performed retrospectively, reviewing medical chart records, a nutrition-focused physical exam which could have aided in the diagnosis of malnutrition was impossible; it is, therefore, possible that missing observed criteria affected the rate of malnutrition diagnosis. Unaccounted malnutrition diagnosis may have had a significant impact on our findings. Third, our patient population had a strong racial African American predominance, which may be a confounding variable when these findings are extrapolated to other study populations composed of a different race. Fourth, it is important to note that clinical outcomes analyzed might have been influenced by a number of factors such as disease severity or diagnosis, the age which may also be a bias to the result obtained. Unfortunately, it was impossible to adjust for all possible cofounders, mainly due to the small sample size.

Recommendations

Malnutrition screening should be done at both ends of the BMI spectrum, especially in the ICU. This is difficult to achieve with the current validated screening tools for ICU patients as they only account for low BMI and not high BMIs. To the best of our knowledge, there are currently no validated screening tools that put into consideration high BMIs. This tool might need to be

adjusted to have validity. Using biomarkers of nutrition and inflammatory status identified in this study can be used to screen patients with high BMIs. Clinicians and responsible parties of the consensus guidelines for developing criteria for diagnosing malnutrition should mandate the use of at least one objective measure as a criterion in the diagnosis of malnutrition. The use of validated screening tools in the ICU should be mandated in other to misdiagnosis. Dietitians should not only be knowledgeable in criteria required for diagnosing malnutrition, but also, we need to be vast in interpreting and utilizing inflammatory biomarkers that can be useful in the diagnosis of malnutrition, as seen in this study. Remember, malnutrition is any nutrition imbalance, dietitians and other clinicians should be skilled and confident in interpreting laboratory makers and using the nutrition-focused physical exam to identify micronutrient deficiencies or excesses. Dietitians should also be proficient in identifying sarcopenic obesity in the elderly because as this might mask malnutrition. All healthcare professionals should be educated on nutrition screening. And Finally, we need to create awareness of the actual burden of malnutrition.

Future Research

1. Perform a multicenter study with a much larger sample size in other to strengthen the validity and applicability.
2. Create malnutrition screening tools that incorporate BMI at both ends of the spectrum and routinely collected markers of nutrition and inflammatory status such as TLC and NLCR.
3. Investigate other tools such as Controlling Nutrition Status (CONUT) score and a tool that combines Hemoglobin, Lymphocyte, Albumin, and Neutrophil (HLAN) for use in the ICU or critically ill patients. The Controlling Nutritional Status (CONUT) score is a screening tool to identify undernourished patients in the hospitalized population. The score is derived from the values of serum albumin, total cholesterol, and lymphocyte counts.

4. Finally, adjust current validated tools such as Nutrition Risk Score-2002 and Mini nutrition assessment screening tool to account for high BMIs and test for validity. MNA is commonly used for nutrition screening in the elderly, but it does not account for high BMI. This tool needs to be adjusted and validated in the acute setting, long term setting, as well as in the community.

Conclusion

Critically ill patients with normal nutritional status do not always have better outcomes because of confounding factors associated with their illnesses. Similarly, clinical outcomes and prognosis of the patient with poor nutritional status are even worse. There is rarely any complete method for determining the nutritional status of patients in the clinical setting despite the availability of several nutritional screening tools and measures. It is even more difficult to evaluate the nutritional status of patients in the ICU due to the severity of disease or systemic inflammation. Early diagnosis of malnutrition and identifying those at high nutritional risk is integral to implementing adequate and appropriate nutrition therapy to improve and maintain nutritional status and to avoid the progression of malnutrition and its complication. More importantly, it is important for the diagnosis of malnutrition to be fast, feasible, cost-effective, and accurate.

In conclusion, nutritional risk and malnutrition diagnosis will vary depending on the applied method. It was found that TLC correlated with BMI and malnutrition. Furthermore, we showed that NLCR, TLC, neutrophils, and lymphocyte were found to be associated with malnutrition; hence they can be useful nutritional markers for the evaluation of the nutritional status of patients in the ICU. Our results and that of previous studies indicate that these biomarkers can be considered low-cost and easy to obtain and can be used as part of the etiologic criteria to support the diagnosis of malnutrition using the GLIM criteria. This study was unable to find a significant improvement in nutrition support on laboratory biomarkers.

To the best of our knowledge, this is the first study evaluating the possible use of TLC, NRI, and NLCR as predictors of malnutrition in ICU patients.

Appendices

Appendix A: Academy/A.S.P.E.N. Clinical Characteristics that the RD can obtain and Document to Support a Diagnosis of Malnutrition.

Academy of Nutrition and Dietetics

Academy/A.S.P.E.N. Clinical Characteristics that the RD can obtain and Document to Support a Diagnosis of Malnutrition.

Clinical Characteristic	Malnutrition in the context of acute illness or injury				Malnutrition in the context of chronic illness				Malnutrition in the context of social or environmental circumstances			
	Non-severe (moderate) malnutrition		Severe malnutrition		Non-severe (moderate) malnutrition		Severe malnutrition		Non-severe (moderate) malnutrition		Severe malnutrition	
Energy intake[1] Malnutrition is the result of inadequate food and nutrient intake or assimilation, thus recent intake compared to estimated requirements is a primary criterion defining malnutrition. The RD obtains or reviews the food and nutrition history, estimates optimum energy needs, compares them with estimates of energy consumed and reports inadequate intake as a percentage of estimated energy requirements over time.	< 75% of estimated energy requirement for > 7 days		≤ 50% of estimated energy requirement for ≥ 5 days		< 75% of estimated energy requirement for ≥ 1 month		≤ 75% of estimated energy requirement for ≥ 1 month		< 75% of estimated energy requirement for ≥3 months		≤ 50% of estimated energy requirement for ≥ 1 month	
Interpretation of weight loss[2-5] The RD evaluates weight in light of other clinical findings including the presence of under- or over-hydration. The RD assesses weight change over time reported as a percentage of weight lost from baseline.	%	Time	%	Time	%	Time	%	Time	%	Time	%	Time
	1-2	1 week	>2	1 week	5	1 month	>5	1 month	>5	1 month	>5	1 month
	5	1 month	>5	1 month	7.5	3 months	> 7.5	3 months	> 7.5	3 months	> 7.5	3 months
	7.5	3 months	> 7.5	3 months	10	6 months	>10	6 months	> 10	6 months	>10	6 months
					20	1 year	> 20	1 year	>20	1 year	>20	1 year

Clinical characteristics that the RD can obtain and document to support a diagnosis of malnutrition – Page 1
Skipper A. Malnutrition Coding in Skipper A. Ed. Nutrition Care Manual, October, 2011 release.
Available at http://nutritioncaremanual.org/category.cfm?ncm_category_id=11. Accessed October 18, 2011.

Physical Findings[5,6] Malnutrition typically results in changes to the physical exam. The RD may perform a physical exam and document any one of the physical exam findings below as an indicator of malnutrition.						
Body Fat Loss of subcutaneous fat (e.g. orbital, triceps, fat overlying the ribs).	Mild	Moderate	Mild	Severe	Mild	Severe
Muscle Mass Muscle loss (for example wasting of the temples (temporalis muscle); clavicles (pectoralis & deltoids); shoulders (deltoids); interosseous muscles; scapula (latissimus dorsi, trapezious, deltoids); thigh (quadriceps) and calf (gastrocnemius)).	Mild	Moderate	Mild	Severe	Mild	Severe
Fluid Accumulation The RD evaluates generalized or localized fluid accumulation evident on exam (extremities; vulvar/scrotal edema or ascites). Weight loss is often masked by generalized fluid retention (edema) and weight gain may be observed	Mild	Moderate to severe	Mild	Severe	Mild	Severe

Clinical characteristics that the RD can obtain and document to support a diagnosis of malnutrition – Page 2
Skipper A. Malnutrition Coding in Skipper A. Ed. Nutrition Care Manual, October, 2011 release.
Available at http://nutritioncaremanual.org/category.cfm?ncm_category_id=11. Accessed October 18, 2011.

Reduced Grip Strength[7] Consult normative standards supplied by the manufacturer of the measurement device	N/A	Measurably reduced	N/A	Measurably reduced	N/A	Measurably Reduced

A minimum of two characteristics is recommended for diagnosis of either severe or non-severe malnutrition.

Notes:

Height and weight should be measured rather than estimated to determine BMI.

Usual weight should be obtained in order to determine the percentage and to interpret the significance of weight loss.

Basic indicators of nutritional status such as body weight, weight change, and appetite may substantively improve with refeeding in the absence of inflammation. Refeeding and/or nutrition support may stabilize but not significantly improve nutrition parameters in the presence of inflammation.

The National Center for Health Statistics defines "chronic" as a disease/condition lasting 3 months or longer[8].

Serum proteins such as albumin and prealbumin are not included as defining characteristics of malnutrition because recent evidence analysis shows that serum levels of these proteins do not change in response to changes in nutrient intake[9-12].

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This table was developed by Annalynn Skipper PhD, RD, FADA. The content was developed by an Academy workgroup composed of Jane White PhD, RD, FADA, LDN, Chair, Maree Ferguson MBA, PhD, RD, Sherri Jones MS, MBA, RD, LDN, Ainsley Malone, MS, RD, LD, CNSD, Louise Merriman, MS, RD, CDN, Terese Scollard MBA, RD, Annalynn Skipper PhD, RD, FADA, and Academy staff member Pam Michael, MBA, RD. Content was approved by an A.S.P.E.N. committee consisting of Gordon L. Jensen, MD, PhD, Co-Chair, Ainsley Malone, MS, RD, CNSD, Co-Chair, Rose Ann Dimaria, PhD, RN, CNSN, Christine M. Framson, RD, PHD, CSND, Nilesh Mehta, MD, DCH, Steve Plogsted PharmD, RPh, BCNSP, Annalynn Skipper, PhD, RD, FADA, Jennifer Wooley, MS, RD, CNSD, Jay Mirtallo, RPh, BCNSP Board Liaison, and A.S.P.E.N. staff member Peggi Guenter, PhD, CNSN. Subsequently, it was approved by the A.S.P.E.N. Board of Directors. The information in the table is current as of 9/30/2011. Changes in the defining characteristics may be made as new research is published.

Appendix B: Letter of support from the chief medical officer at Howard University Hospital.

HU
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202/865 6100
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April 16th, 2019

Celia Batista Almeida, PhD, MS, LN
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Dear Dr. Batista:

I am pleased to provide this letter of support on behalf of the Howard University Hospital for the project titled **"The Effect of Nutrition Support on Nutrition and Clinical Outcomes in Critically Ill Patients".**

It is our understanding that the purpose of this project is to assess the impacts of nutrition support on patient with high nutrition risk, routine clinical laboratory measurements, biomarkers of malnutrition and inflammation.

The objectives of the study are as follows:

1. Identify and compare the rate of malnutrition diagnoses in the ICU with previously published data.
2. Evaluate the associations among different categories of nutritional risk and clinical outcomes.
3. Examine the effects of nutrition support on different categories of nutrition risk and routine clinical laboratory measurements (hematological panel, electrolytes and renal profile, liver function test, fasting blood glucose, lipid profile).

4. Examine the effects of nutrition support on selected malnutrition and inflammatory biomarkers (Pre-albumin, albumin, serum creatinine, C-reactive protein, transferrin, lipids, total protein, hemoglobin, lymphocyte counts).

Methodology:

A retrospective chart review (RCR) will be used to achieve this study. Medical record of patients admitted to the Surgical Intensive Care Unit (SICU) and Medical Intensive Care Unit (MICU) over the period of six months will be reviewed. Participants are eligible if they were in the SICU or MICU for at least three days and who were administered enteral nutrition (EN) or Parenteral Nutrition (PN). Baseline demographic information, including age, gender, height, weight, body mass index, comorbidities, ICU admission diagnosis, length of stay (LOS) in the ICU, mechanical ventilation use, medical history, nutrition status, malnutrition biomarkers, inflammatory biomarkers, and routine clinical laboratory measurement will be collected. Assessment of patients will include the measurement of the Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) Score. A modified Nutrition Risk in Critically ill (NUTRIC) Score will be used to quantify the nutritional state of the patients; it will be calculated using data from the first 24 h after ICU admission. Other clinical outcomes such as routes of nutrition support, nutrition support initiation time and, hospital length of stay.

On behalf of the Howard University Hospital, I grant you permission to conduct a medical record review of medical records of ICU patients for the period from May 1st to September 1st, 2019. I wish you success in conducting your research. I look forward to our collaboration in this important work.

Sincerely,

Shelly R. McDonald-Pinkett, MD, FACP
Chief Medical Officer
2041 Georgia Ave, NW, Suite 2092
Washington, DC 20060
Smcdonald-pinkett@howard.edu

Appendix C: Institutional Review Board Approval

HOWARD UNIVERSITY

Office of Regulatory Research Compliance
Institutional Review Board

Date:	October 1, 2019
To:	Celia B. Almerdia, Ph.D Department of Nutritional Science
From:	Office of Regulatory Research Compliance
Title:	**IRB-19-CPNAH-12:** The Effect of Nutrition Support on Nutritional and Clinical Outcomes in Critically Ill Patients
Approval Date:	**September 30, 2019**
Expiration Date:	**September 29, 2020**
Action:	Expedited Review- *Chart Review*
Purpose:	Research/Data Analysis

The above-referenced submission was approved by expedited review on September 30, 2019. Approval for this chart review is through **September 29, 2020**. The IRB has granted **Oluwakemi Adeola** access to patient complete medical records and laboratory results without identifiers for the purposes of research/data analysis.

Please be reminded of the following:

1. Everyone approved to conduct the chart review is required to maintain HIPAA certification. Please contact Mustafa Hersi, J.D., Chief Compliance Officer, HUH for this information.
2. It is your responsibility to ensure that a continuing review report is submitted to the IRB in a timely manner. Should you anticipate renewing this protocol at the end of the approved time frame, please submit the B-1 Form **60 days prior to the expiration date** (Please note that this office will automatically terminate the project on the date stated above, unless reviewed and re-approved by the IRB.);
3. If you plan to close this protocol, a close-out report must be submitted to the IRB within 30 days after completion. Use a B-1 Form for this purpose as well; and
4. During the project period of this research, the IRB has the right to conduct a monitoring site visit and you will be given prior notice; and.
5. Any changes including changes in personnel, modifications to the protocol and advertising must be reviewed and approved by the IRB prior to initiation.
6. The HU IRB Federal Wide Assurance number is FWA00000891.

Please refer to the above-mentioned date and protocol number when making inquiries concerning this protocol.

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CC: IRB File
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Appendix D: Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score form

THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE			LOW ABNORMAL RANGE					
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE — rectal (°C)	≥41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥160	130-159	110-129		70-109		50-69		≤49
HEART RATE (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
OXYGENATION: A-aDO_2 or PaO_2 (mm Hg) a. $FiO_2 \geq 0.5$ record A-aDO_2	≥500	350-499	200-349		<200				
b. $FiO_2 < 0.5$ record only PaO_2					PO_2 > 70	PO_2 61-70		PO_2 55-60	PO_2 < 55
ARTERIAL pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
SERUM SODIUM (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
SERUM POTASSIUM (mMol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
SERUM CREATININE (mg/100 ml) (Double point score for **acute** renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
HEMATOCRIT (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GLASGOW COMA SCORE (GCS): Score = 15 minus actual GCS									
A Total ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points									
Serum HCO_3 (venous-mMol/L) [Not preferred, use if no ABGs]	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

B AGE POINTS:
Assign points to **age** as follows:

AGE(yrs)	Points
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

C CHRONIC HEALTH POINTS
If the patient has a history of **severe** organ system insufficiency or is immuno-compromised assign points as follows:
a. for nonoperative or emergency postoperative patients — 5 points
or
b. for elective postoperative patients — 2 points

DEFINITIONS
Organ Insufficiency or immuno-compromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II SCORE

Sum of A + B + C :

A APS points _____

B Age points _____

C Chronic Health points _____

Total APACHE II _____

Appendix E: Sequential Organ Failure Assessment (SOFA) score form

SOFA Score: What it is and How to Use it in Triage

January 5, 2017

What is the SOFA Score?

The Sequential Organ Failure Assessment (SOFA) score is a scoring system that assesses the performance of several organ systems in the body (neurologic, blood, liver, kidney, and blood pressure/hemodynamics) and assigns a score based on the data obtained in each category. The higher the SOFA score, the higher the likely mortality.

Why was the SOFA Score Developed?

The SOFA score was designed as a research tool so that groups of patients (e.g., those with sepsis, and infection in the bloodstream which can lead to shock and death) could be categorized based on their risk of death. SOFA is quite accurate when used in sepsis cases and when applied to groups of patients. For example, if 100 severely ill septic patients requiring intensive care unit (ICU) treatment have a SOFA score greater than 11, over 90% of them will die (Vincent et al., 1996). One benefit of SOFA is that it requires only six common points of data to calculate. Comparable predictive systems require much more data.

What are the Limitations of SOFA?

Because SOFA was designed to look at populations, and not individual patients, it cannot accurately predict which patients will survive when the mortality rate is high (i.e., if mortality is 90%, which 10 patients will survive) or which patients will die if the mortality rate is low. Some of the factors used in scoring can be difficult to assess depending on the care being provided (e.g., it is difficult to assess a level of coma when a patient is receiving sedatives) and some of the medications listed are no longer used routinely (e.g., low dose dopamine or dobutamine). Though SOFA was developed for sepsis research and has been validated in additional settings, there is concern that it does not accurately predict mortality when used for patients with isolated respiratory failure as demonstrated during the 2009 H1N1 pandemic.

Who is Using SOFA Now?

SOFA has been recommended (along with a less validated, more clinical tool called "quick SOFA" or qSOFA) for assessment of patients with sepsis by the new 2016 Sepsis Definitions Consensus Statement (Sepsis 3), though it is not usually used outside of larger, academic centers. While the clinical utility of SOFA in daily practice is unproven, many states have included SOFA in their crisis standards of care plans as an element of the triage framework for scarce resources.

What is the Advantage of Using SOFA for Triage?

SOFA creates a standardized, numeric score that is familiar to critical care physicians. Physicians can use it to compare patient status and the score has been shown to have a significant correlation with outcome. This makes it helpful for triage teams. Of the scoring systems available, SOFA achieves a good balance between easily available data and good prediction. When calculated daily it can also be used to establish trends in the individual patient's course.

What are Some Challenges with Using SOFA for Triage?

SOFA was developed to be used with populations and though it is good at determining overall mortality, the score cannot predict individual mortality well. Clinicians should not use the SOFA score in isolation to exclude a patient from receiving interventions. The predictive value of the score also depends on the disease state. Finally, SOFA is well-validated in adults, but not in children.

How Should the SOFA Score be Used in Triage?

It is best to use the SOFA score when comparing patients and deciding how to best allocate resources. Regardless of exact performance, a large difference in SOFA scores does certainly correlate with general prognosis, so a patient who scores a 2 is much more likely to survive than a patient who scores an 11, and may preferentially receive resources unless there are other medical conditions or factors that affect the prognosis. The new suggestions on critical care triage from the American College of Chest Physicians are consistent with this strategy, which is also reflected in the Minnesota Department of Health clinical cardset (Patient Care Strategies in Scarce Resource Situations) where SOFA is included among other considerations in a comparative framework.

> Let's say that a group of patients is being admitted to the ICU that are so sick that half will die despite ICU care. In this group a SOFA score of >11 will correlate well with a >90% chance of death and be potentially very helpful in making decisions. But, patients admitted to an ICU during an influenza pandemic would have a much better chance of living than that. So if we assume they have a 10% chance of dying then the SOFA score's accuracy would fall to the point where only *half* of those with a SOFA score >11 would die – meaning you might as well flip a coin than use the data for triage. These articles provide more discussion and specifics: "An observational cohort study of triage for critical care provision during pandemic influenza: 'clipboard physicians' or 'evidenced based medicine'?"; "A modified sequential organ failure assessment score for critical care triage"; and "MSOFA: An important step forward, but are we spending too much time on the SOFA?"

States that are developing, or have developed, triage frameworks should ensure that if SOFA is used, it is done so to compare patients competing for

the same resource, or to follow patients daily for trends (Ferreira, et al. 2001). SOFA is *not* used as a screening tool to determine who will receive care or interventions.

It is important to remember that SOFA is a single criteria, and other patient factors (e.g., underlying diseases and current response to treatment) should be taken into account when making triage decisions. Disease-specific predictive factors may also need to be accounted for and included in the triage decision-making. Assuring that the triage team members are experienced critical care providers that have access to the relevant patient information, guidance, and are part of a defined, structured process for triage whenever possible is critical to making fair, accountable, transparent decisions about resource allocation.

The SOFA Score*

***Organ System,* Measurement**	**SOFA Score**				
	0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

* Source: Vincent et al., 1996.
**Adrenergic agents administered for at least 1 hour (doses given are in mcg/kg/min).

For More Information

For annotated resources to assist with crisis standards of care planning, access ASPR TRACIE's Crisis Standards of Care Topic Collection.

Appendix F: Modified Nutrition Risk in Critically ill (mNUTRIC) score form.

Critical Care Nutrition
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NUTRIC Score[1]

The NUTRIC Score is designed to quantify the risk of critically ill patients developing adverse events that may be modified by aggressive nutrition therapy. The score, of 1-10, is based on 6 variables that are explained below in Table 1. The scoring system is shown in Tables 2 and 3.

Table 1: NUTRIC Score variables

Variable	Range	Points
Age	<50	0
	50 - <75	1
	≥75	2
APACHE II	<15	0
	15 - <20	1
	20-28	2
	≥28	3
SOFA	<6	0
	6 - <10	1
	≥10	2
Number of Co-morbidities	0-1	0
	≥2	1
Days from hospital to ICU admission	0 - <1	0
	≥1	1
IL-6	0 - <400	0
	≥ 400	1

Table 2: NUTRIC Score scoring system: if IL-6 available

Sum of points	Category	Explanation
6-10	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-5	Low Score	➢ These patients have a low malnutrition risk.

Table 3. NUTRIC Score scoring system: If no IL-6 available*

Sum of points	Category	Explanation
5-9	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-4	Low Score	➢ These patients have a low malnutrition risk.

*It is acceptable to not include IL-6 data when it is not routinely available; it was shown to contribute very little to the overall prediction of the NUTRIC score.[2]

[1] Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Critical Care. 2011;15(6):R268.
[2] Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool. Clin Nutr. 2015. [Epub ahead of print]

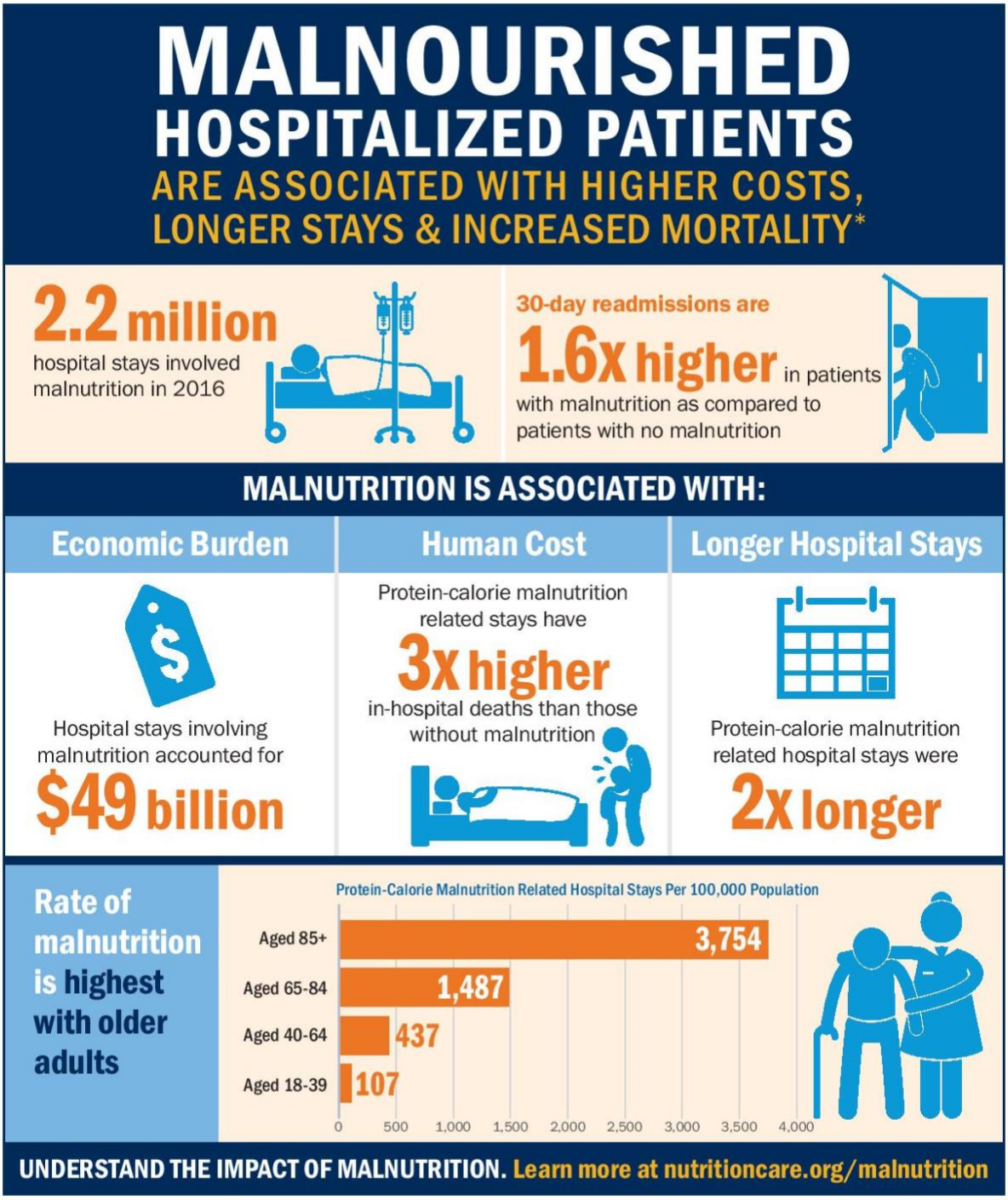
December 16th 2015

Appendix G: Normal Ranges of Blood Biomarkers

Normal Ranges of Blood Biomarkers

Blood Marker	Normal Ranges	SI Unit
Sodium	135-145	mEq/L
Potassium	3.5-5.1	mEq/L
Chloride	95-111	mEq/L
Carbon dioxide	22-32	mEq/L
Glucose	70-100	mg/dL
Blood Urea Nitrogen	7-25	mg/dL
Creatinine	0.6-1.2	mg/dL
Calcium	8.5-10.3	mg/dL
Magnesium	1.7-2.5	mg/dL
Total protein	6.2-8.3	g/dL
Anion gap	7-16	mEq/L
Albumin	3.2-5.5	g/dL
Alanine Phosphatase	30-130	IU/L
Alanine Transferase	0-55	IU/L
Aspartate Transaminase	0-50	IU/L
Total Bilirubin	0.2-1.2	mg/dL
Phosphorus	2.5-4.5	mg/dL
Procalcitonin	< 0.50	ng/mL
Lactic Acid	0.5-2.2	mm/L
Lactate Dehydrogenase	100-250	IU/L
Transferrin	180-362	mg/dL
White Blood Cells	(3.2-10.6) X $10E_9$	
Red Blood Cells	(4.6-6.07) X $10E_1$	
Hemoglobin	(14.6-17.8)	g/dL
Hematocrit	40.8-51.9	%
Mean Corpuscular Volume	77.8-94.0	fL
Neutrophil %	38-80	%
Lymphocyte %	11-49	%
Absolute neutrophil	(1.3-7.1) X $10E_9$	
Absolute lymphocyte	(0.9-3.2) X $10E_9$	
Ferritin	12 to 300	ng/mL

Appendix H: Malnutrition In Hospitalized Patients In The United States



* Barrett ML, Bailey MK, Owens PL. Non-maternal and Non-neonatal Inpatient Stays in the United States Involving Malnutrition, 2016. ONLINE. August 30, 2018. U.S. Agency for Healthcare Research and Quality. Available: www.hcup-us.ahrq.gov/reports.jsp

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