Nutritional support and inflammatory response:

A survival analysis in ICU patients

Universitat Oberta de Catalunya

María José Moreno Pavón

MU Bioinf. y Bioest.

Área del trabajo final: Estudios Clínicos y Epidemiológicos

Nombre Tutor/a de TF

Andrea Blasco Navarro

Juan Carlos López Delgado

Profesor/a responsable de la asignatura

Antonio Pita Lozano

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FICHA DEL TRABAJO FINAL

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Nombre del autor:	María José Moreno Pavón
Nombre del director/a:	Andrea Blasco Navarro Juan Carlos López Delgado
Nombre del PRA:	Antonio Pita Lozano
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Resumen del Trabajo

La inflamación sistémica es un factor clave en la aparición de complicaciones en pacientes ingresados en UCI. La proteína C reactive (PCR) es empleda frecuentemente como biomarcador inflamatorio, pero su relación con desenlaces clínicos aun requiere de mayor investigación. Este estudio evaluó PCR como predictor de complicaciones y su relación con el soporte nutricional.

Para ello, los pacientes adultos ingresados en UCI se dividieron según sus niveles de PCR al ingreso y al séptimo día (< 100 vs >100 mg/L). Se utilizaron modelos de regresión logística y de Cox para explorar predictores como el uso de fármacos vasoactivos (VDS), isquemia mesentérica (MI) y la reducción de PCR.

Los resultados mostraron que niveles elevados de PCR estuvieron asociados a EPOC y a puntaciones más altas en los índices SOFA y NUTRIC entre otros. Todos los casos de MI se dieron en pacientes con inflamación elevada. Entre los que recibieron una nutrición enteral (EN), una PCR elevada se asoció con menor ingesta calórica y mayor probabilidad de requerir VDS. El análisis de supervivencia mostró que los pacientes

traumáticos y aquellos que recibieron nutrición parenteral o combinada tuvieron menores probabilidades de reducir su PCR al séptimo día.

En conclusión, elevados niveles de PCR se asociaron a una mayor gravedad clínica e influyen en la tolerancia nutricional y desenlaces. Sin embargo, su capacidad predictiva es limitada de forma aislada, por lo que debe de usarse junto a otros marcadores clínicos para optimizar las decisiones nutricionales y terapéuticas.

Abstract

Systemic inflammation is a key factor in adverse outcomes in critically ill patients. C-reactive protein (CRP) is commonly used as an inflammatory biomarker, but its relationship with clinical outcomes requires further investigation. This study aimed to determine whether CRP can predict complications and how it relates to nutritional support.

For this purpose, Adult ICU patients were stratified based on their CRP levels at admission and day 7 (< 100 vs >100 mg/L). Logistic regression and Cox models were used to explore predictors of vasoactive drug support (VDS), mesenteric ischemia (MI) and CRP reduction over time.

The results indicated that elevated CRP levels were associated with COPD, higher SOFA and NUTRIC scores, among others. All mesenteric ischaemia cases occurred in patients exhibiting higher inflammation. In patients receiving EN, increased CRP was linked to lower caloric intake and a higher likelihood of requiring VDS. Time-to-event analysis revealed that trauma patients and those with PN or combined nutrition were less likely to reduce CRP by the seventh day.

In conclusion, elevated CRP levels are associated with greater clinical severity and influence nutritional tolerance and outcomes. However, its predictive accuracy remains limited when used alone, and CRP should be integrated with other clinical markers to better guide nutritional and therapeutic decisions.

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1. Introduction

1.1. Context and justification of the work

Most critically ill patients admitted to the Intensive Care Unit (ICU) require medical nutrition therapy (MNT) to meet their nutritional requirements of recommended energy and protein goals. MNT includes oral nutrition, enteral nutrition (EN), parenteral nutrition (PN), or any combination of these strategies. Current nutritional guidelines recommend early EN (24-48h after admission) for patients who cannot maintain sufficient oral intake. However, there is still debate about the optimal feeding route to follow in critically ill patients, since each day without nutrition increases the risk of death by approximately 15% in the first week of clinical evolution, as reflected in recent research and meta-analyses, but physicians are reluctant to give early PN (1,2).

EN is preferred over PN because it is considered more physiologic and provides nutritional and non-nutritional benefits, such as maintaining structural and functional gut integrity. The main problem with PN is its theoretical association with a higher risk of infectious complications due to hyperalimentation and hyperglycaemia. However, more contemporary studies have not seen this association between risk infection and PN. Thus, PN should be used as a first option when EN is contraindicated, even early, when the patient is at risk for malnutrition (3).

Additionally, recent research finding shows the importance of early EN in critically ill patients with a functional gastrointestinal tract to reduce bloodstream infections, improve recovery and reduce the ICU and hospital length of stays (4). Another study suggests that EN is even safe in mechanically ventilated, critically ill patients under vasoactive drug therapy. However, these patients must be under surveillance to detect intestinal ischemia warning signs and fed with EN only when the initial resuscitation/stabilisation stage is completed (5).

On the other hand, other studies suggest that early PN may be safe and does not necessarily lead to a higher complication rate. These findings indicate that critically ill patients may benefit from introducing EN as complementary nutrition or progressively transitioning from PN to EN (6) or that PN should be used as complementary nutrition of EN when the nutritional requirements cannot be achieved (1,7). A delay in the initiation of PN causes higher mortality rates (8).

C-reactive protein (CRP) is an acute-phase protein synthesised in the liver and regulated by inflammatory cytokines. It is produced during infections, chronic inflammatory illnesses, traumatic injuries (such as bone fracture or surgery), tissue ischemic injuries and cancers associated with tissue necrosis. It is considered an excellent biomarker of inflammation and infection; however, it is difficult to differentiate if the higher levels of CRP are caused by sepsis or systemic inflammatory response (SIR) from other causes (9,10). Kamarul Zaman et al. 2021 found that patients who developed diarrhoea had higher CRP (11) and Qu et al. 2020 results suggest that even inflammation without infection may still be associated with ICU mortality, showing that patients with lower CRP at ICU admission had a lower risk of ICU mortality.

This research analyses CRP levels and their evolution in patients admitted to the ICU. It will analyse the association between the degree of inflammation and the tolerance of MNT through CRP levels and macronutrient (i.e., mean caloric and protein) delivery, respectively, during the first week of ICU admission.

Therefore, the main goal of the present research is to obtain information that may help to evaluate the association of higher CRP levels with poor MNT tolerance and identify which factors and types of patients are related to a higher degree of inflammation.

1.2. Objectives

The main objectives of this research are:

- Determine whether CRP levels can predict the occurrence of clinical complications.
- Evaluate the influence of different nutritional support strategies on the probability of CRP reduction over time.

The secondary objectives of this research are:

- Describe the changes in CRP levels over time in critically ill patients.
- Determine how CRP concentrations and nutritional support are related to the occurrence of clinical complications.
- Compare the patient's clinical progression based on their inflammatory profile and the type of nutritional support received.

1.3. Sustainability, ethical, social, and diversity impact

This research could be enclosed in the following sustainable development goals:

- **SDG 3: Good health and Well-being.** This research analyses how the feeding routes influence the evolution of ICU patients. Hence, it will contribute to discovering better treatments and reducing complications. In other words, it will improve medical care and patient quality of life. In addition, evaluating how CRP levels and nutritional support influence patient recovery could lead to more effective strategies for managing critically ill patients, enhancing healthcare system resilience.
- **SDG 9: Industry, Innovation and Infrastructure**. This research will use statistical models and bioinformatics tools to analyse clinical data, contributing to innovation in biomedical science.

On the other hand, this project has some ethical, social and diversity impacts that must be taken into consideration:

- **Ethical impacts**: This research utilises clinical data that must comply with the General Data Protection Regulation (GDPR) and be anonymised to protect patients from potential discrimination based on their specific clinical conditions. In addition, if the research shows differences based on sex, it is important to identify if they come from biological differences or skewed data.
- **Social and diversity impacts**: Ensuring the research's discoveries are understandable to professionals, like doctors, is vital. Specifically, if these discoveries result in better treatments for clinically ill patients, they could potentially reduce ICU stays. Furthermore, as mentioned, skewed data must be avoided to prevent biased conclusions.

1.4. Approach and methodology

In this research, a statistical modelling approach is considered the most appropriate to achieve the objectives and provide a comprehensive understanding of the relationship among CRP levels, clinical complications, and nutritional support in ICU patients.

Although different approaches could be considered, such as descriptive analyses, this research will use a dataset from a multicentre prospective observational study conducted in various ICUs across Spain. Hence, a statistical modelling approach is well-suited to analyse associations.

This methodology will include:

- **Descriptive and comparative analysis**: A descriptive table will be created to compare clinical and demographic patient characteristics stratified by their CRP concentration. Statistical tests will be applied.
- **Regression model**: evaluate how different factors influence CRP levels. This step is critical to identify predictors and their impact on patient outcomes.
- **Survival Analysis (Cox model).** The duration of nutritional support will be modelled as a time-to-event variable. Thus, factors such as the type of nutritional support or complications will be tested to determine whether they influence the likelihood of CRP reduction.

All the patients included in this study are over 18 years old, have spent at least 72 hours in the ICU, and require nutritional support. Therefore, the first step will be an exploratory data analysis to exclude patients who do not meet these criteria. Additionally, selecting the relevant variables and addressing missing data will be necessary.

Exploratory data analyses and later statistical analyses will be performed on the software RStudio 2024.12.0+467 with R version 4.5.0.

The literature review will be conducted using Google Scholar and PubMed search engines. This literature will be managed with Mendeley, a free reference management software that can be integrated into word processors. This makes it particularly useful for sorting and keeping track of all materials used throughout the research.

1.5. Work planning

This section provides a calendar outlining the start and end dates of the different tasks. The master's degree final project requires approximately 22 hours per week to achieve the objectives; therefore, tasks and milestones have been defined accordingly.

As shown in the table below, milestones are highlighted in bold and coloured in blue. These milestones represent key events, the continuous assessment tests (PECs), which mark a transition between different project stages. Within these milestones, tasks are structured to facilitate meeting deadlines effectively.

Table 1: A list of milestones and tasks sorted by the date of each continuous assessment test must be completed

Tasks	Start	End
PEC 1: Project Definition	19/02/2025	05/03/2025
Literature review	19/02/2025	26/02/2025
Define the methodology to be followed	27/02/2025	28/02/2025
Risk-Mitigation strategies	01/03/2025	03/03/2025
Prepare the document for PEC1	04/03/2025	05/03/2025
PEC 2: State of the Art	06/03/2025	02/04/2025
Literature review	06/03/2025	13/03/2025
Start writing the report (state of the art)	14/03/2025	20/03/2025
Variable selection and flow chart of patient exclusion criteria	21/03/2025	27/03/2025
Prepare the document for PEC2	28/03/2025	02/04/2025
PEC3: Implementation	03/04/2025	07/05/2025
Data exploration	03/04/2025	10/04/2025
Statistical Analysis	10/04/2025	24/04/2025
Results Evaluation	25/04/2025	01/05/2025
Prepare the document for PEC3	02/05/2025	07/05/2025
PEC 4: Report and presentation	08/05/2025	04/06/2025
Final Report	08/05/2025	31/05/2025
Slide preparation and video recording	01/06/2025	04/06/2025
PEC 5: Public Defence		19/06/2025

In addition, a Gantt chart is provided:

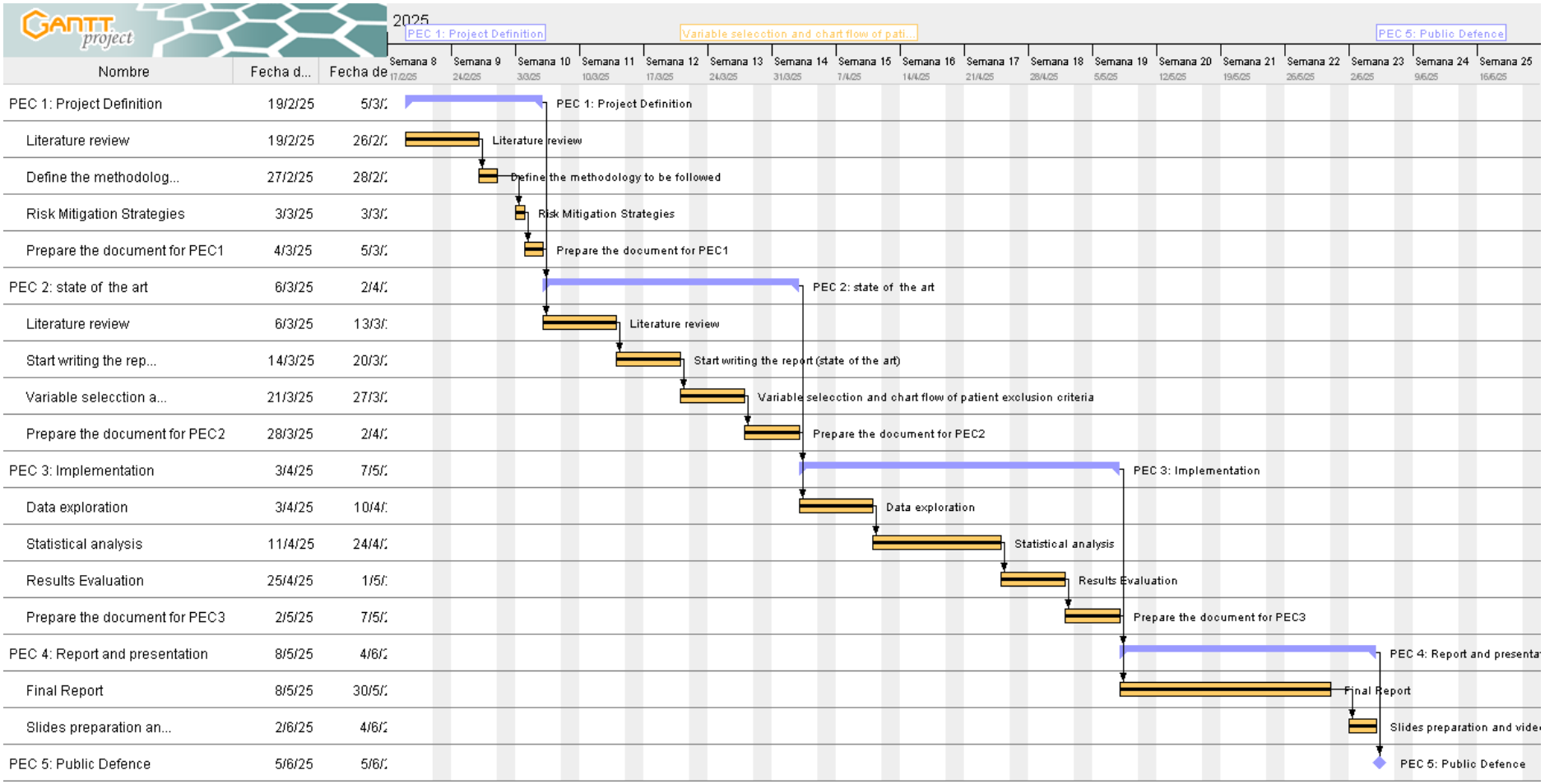


Figure 1: Gantt chart

Concerning the work plan, several potential risks must be identified and mitigated. The following points outline these risks and propose mitigation strategies:

- **Risks related to data:** This includes missing, skewed or poor-quality data, which may need additional time for cleaning and processing.
    - **Mitigation:** Exploratory data analysis must be done to identify these issues. Variable selection may be performed using Principal Component Analysis (PCA) and by consulting the supervisor to determine the key variables for this research.
- **Risk related to methodological and technical difficulties.** This includes possible problems with statistical models or violations of assumptions, which may require reformulating the study's approach. In addition, statistical analyses may be delayed due to failures in R or difficulties with some packages.
    - **Mitigation:** A literature review to identify methodologies used in previous research or models that are more effective in similar contexts. To avoid failures in R, GitHub can be used to control versions and avoid losing progress. Forums such as Stack Overflow and other resources can also be consulted in case of technical problems.
- **Risk related to planning and time**: This includes underestimating the time required to complete certain tasks or encountering unexpected issues that complicate the completion of the final report. The time for each task is limited, and a delay in any task may pause the report progress and, in the worst scenario, could prevent meeting deadlines.
    - **Mitigation**: Leave 10% of extra time between tasks to ensure they are completed as expected. Additionally, the final report must be started as soon as possible, as the different documents for the PECs are being made. This will help to maintain a clear and structured format throughout the process

1.6. Overview of obtained products

- The different PECs that will be committed during the research development process.
- Work planning: Gantt chart in PDF format.
- R Markdown file in.Rmd format the whole code and statistical analyses used during the project.

- Final master's degree project report in PDF. This document will include the objectives, methodology, state-of-the-art and results of the research
- Final master's degree project presentation in PowerPoint. A video presentation summarising the most important aspects of the project. This will include the slides and an audio recording.

1.7. Brief description of the other report chapters

- **State of the art**: This section aims to contextualise the research. For this reason, a literature review will be conducted on three lines: Biomarkers used in ICU, CRP as a Biomarker, Nutritional Support and Inflammatory Markers. Likewise, the methodology used in these studies will be evaluated.
- **Materials and methods:** Description of the study population, data processing and statistical analysis strategies applied.
- **Results:** Presentation of the statistical results and interpretation of it.
- **Conclusions:** Summary of the key findings and recommendations for future investigations.
- **Glossary:** initials and acronyms used during the research.
- **Bibliography:** A compilation of literature used.

2. State of the art

2.1. ICU's Biomarkers.

In the ICU, Biomarkers complement clinical judgement and interpretation of other diagnostic or prognostic tests. Figure 1 summarises the types of markers and what they are used for.(12)

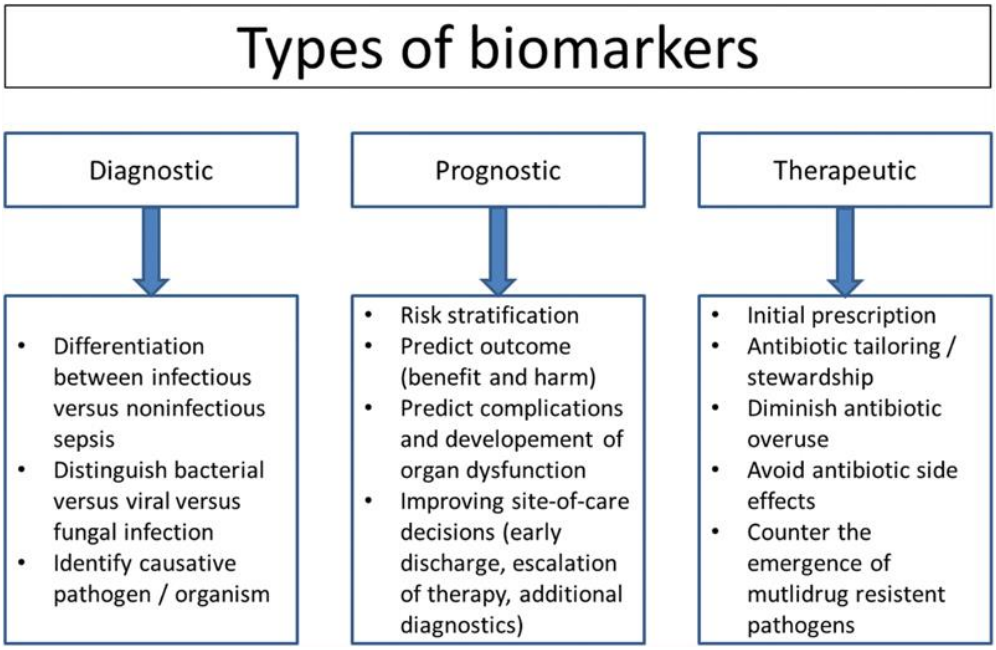


Figure 2: Types of biomarkers and their potential use. Picture from Heilmann et al. 2019 (12)

This research is focused on CRP as a prognostic biomarker, however other biomarkers included within this category are:

- **Albumin**. The most abundant protein circulating in plasma. Because its synthesis in the liver only occurs when the body is sustained properly, it has been highlighted by its capability to show overall health and nutritional status in patients. Hypoalbuminemia is not only associated with a poor nutritional status and inflammation but also with higher mortality rates in patients with cardiovascular diseases, acute respiratory distress syndrome, acute stroke, and chronic kidney disease (13,14).
- **CRP/albumin ratio**. A novel biomarker that combines the reactions of CRP and albumin to systemic inflammatory responses and dystrophy. Several studies have

associated elevated levels of CRP/albumin ratio with higher mortality in critically ill patients, making it a reliable marker for clinical monitoring (15–17).

- **Interleukin (IL)**. A type of cytokine produced by many body cells. There are 40 different interleukins; among them, IL-6 is a great predictor of mortality in critically ill patients (18,19) showing a significant reduction in survivors since day one and becoming more pronounced two or three days after ICU admission. Weidhase et al. 2019 concluded that IL-6 is better than Procalcitonin or CRP in predicting the treatment success of non-surgical sepsis within the first 48-72h (20).
- **Lactate.** Since its discovery in 1843, lactate has been used as a prognostic marker of outcomes in critically ill patients. In fact, it is used as a predictor of prognostic and mortality rates in cardiovascular, respiratory, or chronic liver diseases and sepsis(21).
- **Procalcitonin (PCT).** Biomarker widely used in critically ill patients to diagnose clinically significant infections and sepsis(22). Its levels rise during bacterial but not viral infections or non-infectious inflammatory reactions (18). Along with lactate, it is a good mortality predictor in surgical patients (23).

2.2. CRP as a Biomarker.

C-reactive protein (CRP) is a pentameric protein synthesised by the liver and induced by the IL-6 action on the gene responsible for its transcription during the acute phase of an inflammatory/infectious process. Its name comes from the fact that it was first identified as a substance in the serum of patients with acute inflammation. CRP levels have been associated with severe conditions such as severe sepsis, heart failure, cerebral disease, and other inflammatory conditions (24).

It has been described as a prognostic factor for poor outcomes in patients with community-acquired pneumonia (CAP) as well as a predictor of COVID-19's severity, where CRP levels above 100mg/L were associated with a severe form of the disease (25) and was a strong predictor of needing invasive mechanical ventilation (IMV) (26). In fact, Chalmers et al. 2008 suggested that patients whose CRP levels were higher than 100mg/L required IMV (27).

During an infection, the failed CRP reduction below 50 mg/L between the first and fourth day after admission is a sign of uncontrolled infection or the development of another(28). In addition, A reduction lower than 25% concerning its levels 24-48h before ICU

discharge is associated with higher in-hospital mortality, ICU readmission, post-ICU Length of Stay (LOS), and later hospital discharge (29)

There is no doubt that CRP is a useful marker of systemic inflammation, despite it does not discriminate infections from other inflammatory processes. Hence, some studies do not find statistical differences between survivors and non-survivors (23,30,31) or find that it has a modest or null prediction power in terms of mortality, hospital discharge or readmission (32,33)

The levels of CRP are reported in either mg/dL or mg/L. These levels can be stratified as follows:

- **<3 mg/L**: Normal
- **3 to 10 mg/L**: Normal or minor elevation (seen in patients with obesity, pregnancy, depression, diabetes, common cold, sedentary lifestyle, cigarette smoking, and genetic polymorphisms).
- **10 to 100.0 mg/L**: Moderate elevation (Systematic inflammation such as autoimmune diseases, malignancies, myocardial infarction, pancreatitis or bronchitis inter alia).
- **More than 100 mg/L**: Great elevation (found in acute bacterial infections, viral infections and major trauma)
- **More than 500 mg/l**: Severe elevation (related to acute bacterial infections, about 90%)(24,30)

The next section will describe how higher body systemic inflammation could influence how patients are able to tolerate MNT.

2.3. Inflammatory Parameters and Nutrition Therapy.

In critically ill patients, malnutrition is not only caused by inadequate nutritional intake, but it is often disease-related and associated with complex pathophysiological mechanisms that may negatively affect gastrointestinal function. Pro-inflammatory cytokines such as IL-6, IL-1β and tumour necrosis factor α are involved in these mechanisms and could affect central nervous system brain circuits which control food intake, causing delayed gastric emptying and increased skeletal muscle catabolism (34).

Every type of patient population has a different reaction to MNT, as nutritional and metabolic needs differ. Depending on the severity of the disease, the presence of previous malnutrition or the disease itself. Nevertheless, patients with a degree of

inflammation may have a prolonged catabolic status, although a prompt nutrition delivery is performed, a known strategy that may serve to attenuate such a catabolic process. In fact, high degrees of inflammation are the main reason for nonresponse to nutritional therapy in acutely malnourished ICU and surgical patients (34).

Elevated baseline CRP levels (higher than 100mg/L) are associated with a low treatment response to nutritional therapy in terms of patient survival. However, in patients with moderate or low baseline inflammation, there was a significant reduction in the 30-day mortality, with appropriate MNT in hospitalised patients with cancer (35), whereas those patients with increased CRP concentrations did not show any influence of nutritional therapy. Hence, inflammation is suggested as an important driver in addition to diagnosis (34).

An explanation for this nonresponse is that the high frequency of refeeding syndrome and the use of PN in patients with a high degree of inflammation may compromise their nutritional status, which can result in increased complication rates and potentially lead to worse outcomes (i.e. aspiration pneumonia, feeding tube dislocation, diarrhea, abdominal hypertension, intestinal ischemia, catheter infection, liver steatosis, hyperglycaemia or dyslipidaemia). In addition, continuous MNT such as PN or EN may suppress muscle protein synthesis and blunt the anabolic response by preventing the pulsatile increase in circulating amino acids, such as leucine, necessary to trigger effective muscle protein synthesis. Consequently, this may exacerbate the imbalance between protein degradation and synthesis, thereby contributing to muscle wasting and impaired recovery in critically ill patients (34,36,37).

On the other hand, nutritional support has also been reported to decrease complication rates in critically ill, undernourished patients (34). In patients with severe acute pancreatitis, an early EN reduced the CRP concentrations at 5, 9 and 14 days after their intervention, indicating that the inflammatory response is better managed(38). In addition, Li et al. 2015 found that CRP levels increased 6-8h after inflammation, making it a marker of surgical stress, and this stress was reduced in elderly patients with gastric cancer who received early EN instead of PN (39).

2.4. Methodology Approach

Logistic regression, also known as the logistic model or logit model, studies the relationship between one or more independent continuous variables and a dichotomous

(binary) dependent variable. It estimates the probability of an outcome occurring by fitting the input data to a logistic curve. The regression coefficients represent the predictive power of each variable in the model.

In this study, logistic regression was employed to evaluate the association between selected independent variables and a binary clinical outcome. This method has been extensively used in other research to identify mortality or clinical complications in critically ill patients.

In addition, survival analysis (especially, the Cox proportional hazards model) was used to analyse whether patients reduced their inflammation levels by the seventh day. Like logistic regression, this statistical method is commonly used in research where the main event of interest is often death.

Table 2 provides examples of studies that have employed similar statistical approaches

Table 2 : Sources for Methodological Approach

Author	Analysis	Population	Objective
Al-Subaie et al. 2010. (33)	Logistic regression model	Medical-surgical ICU patients	Assess the utility of CRP concentrations as a predictor of short-term hospital outcomes
Reny et al. 2002. (28)	Logistic regression model	ICU patients	To evaluate the diagnostic and prognostic values of CRP dosage in critically ill patients
Merker et al. 2020 (35)	Logistic regression and survival analysis	ICU patients with nutritional support	Assess whether patients' baseline inflammatory status is associated with the effect of MNT on 30-day mortality
Park et al. 2018 (16)	Logistic regression model and Cox proportional hazard regression	Pediatric ICU patients or patients with chronic hepatitis or liver cirrhosis	Identify associations between the CRP/albumin ratio and 28-day mortality, and predict its accuracy in predicting mortality

Oh et al. 2018 (40)	Multivariate Cox regression	ICU patients	Evaluate the prognostic value of the CRP/albumin ratio in predicting the 30-day mortality rate
Kieler et al. 2022 (41)	Logistic regression and Cox proportional hazard regression	Palliative patients	Identify clinical factors associated with the outcome of patients on PN
Lopez-Delgado et al. 2015 (42)	Logistic regression and Cox proportional hazard regression	Surgical ICU patients	Determine whether postoperative serial arterial lactate measurement after cardiac surgery could predict patients' outcomes
Zhang et al. 2021 (43)	Logistic regression and Cox proportional hazard regression	Patients with an acute myocardial infarction diagnosis	Explore the prognostic value of high-sensitivity CRP in patients with acute myocardial infarction
José et al. 2019 (44)	Cox proportional hazard regression	ICU patients with exclusive EN	Assess whether the caloric and protein deficits, the diagnosis and the NUTRIC score were risk factors associated with the survival time

3. Materials and methods

3.1. Study Design and Setting

This research is an ENPIC (Evaluation of Nutritional Practices in the Critical Care, ClinicalTrials.gov Identifier: NCT03634943) secondary analysis, a multicentre prospective observational study conducted at 38 ICUs across Spain between April and July 2018. Comité d'Etica i Assajos Clínics de Hospital Universitari de Bellvitge (Barcelona, Spain) approved the study protocol, and all patients or their representatives provided written informed consent.

An observational design meant that there was no attempt to influence general ICU care or the nutritional approach. In addition, nearly all participants were members of the Spanish Society of Intensive Care Medicine and the Nutrition and Metabolism Working Group. Thus, to determine the eligibility of the different hospitals, they were asked to provide information about their hospital and ICU characteristics, their nutrition practices and the adherence of the ICU team to general aspects related to nutrition (8).

3.2. Data collection

In a centralised database, all data extracted from the medical records of the patients were stored for further analysis (REDCap® electronic data at the Hospital Arnau de Vilanova, Lleida, Spain). These data were cleaned from August to November 2018. Before reviewing and closing the database, data queries were sent back to investigators for information verification.

The data collected includes: demographics; diagnoses and comorbidities; nutritional assessment, using the Subjective Global Assessment (SGA) and modified Nutrition Risk in the Critically Ill (mNUTRIC) scores (without the IL-6 component); and the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Simplified Acute Physiology Score (SAPS) II, and the Sequential Organ Failure Assessment (SOFA) score on ICU admission. Additionally, details of nutritional support therapy were included, such as: initiation of nutritional therapy, the mean energy and protein intakes until ICU discharge or for a maximum of 14 days, and EN-related complications during their ICU stay (i.e., residual gastric volume, diarrhoea, vomiting, aspiration, and mesenteric ischemia). Non-nutritional calories (such as dextrose infusion and propofol) and enteral protein supplementation were included to calculate the mean energy and protein intake.

Lastly, patients' outcomes were recorded during their stay in the ICU. These include details of hemodynamic support, renal replacement therapies (RRT), mechanical ventilation (MV), respiratory tract infection (RTI), and catheter-related infection (CTI). ICU and hospital mortality were followed up for 28 days (8).

3.3. Study population

Adult patients over 18 who required artificial nutritional therapy for at least 7 days were included. Individuals with incomplete baseline data, missing nutritional status assessments (APACHE II, SOFA, NUTRIC_Score…), or absent CRP measurements at admission, days 3 and 7 were excluded from the study. These criteria of exclusion are represented in a flow chart in **Figure 3**.

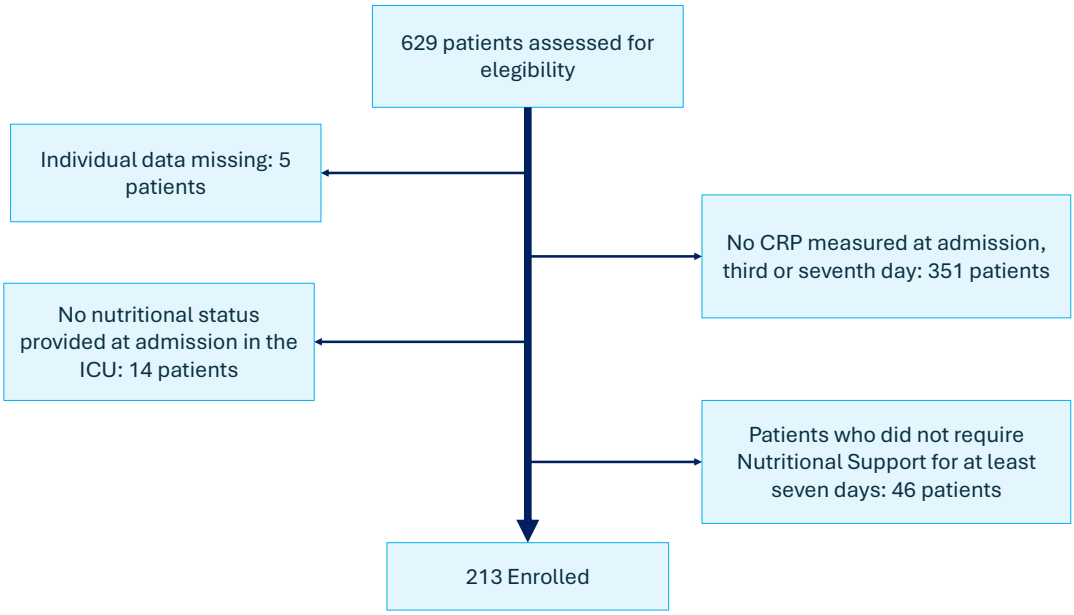


Figure 3: Illustration of exclusion criteria as utilised to select the final 213 patients

The dataset ENPIC is composed of 629 patients and 250 variables. After selecting the variables of interest and excluding the patients who did not meet the inclusion criteria, the final dataset contains 54 variables (10 were created using the available information) and 213 observations.

The patients are divided into two groups based on their CRP concentrations:

- Low to Moderate CRP levels: CRP ≤ 100 mg/L
- High to Severe CRP level: CRP > 100 mg/L

A cutoff of 100 mg/L is used, as it has been associated with a low response to nutritional therapy treatment (35).

3.4. Statistical methods

Before describing the methodology employed in this research, a brief overview of the theoretical background of these analyses is provided.

3.4.1. Theoretical Background

3.4.1.1 Logistic regression

Logistic regression, also known as the logistic model or logit model, studies the relationship between one or more independent continuous variables and a dichotomous (binary) dependent variable. It estimates the probability of an outcome occurring by fitting the input data to a logistic curve. The regression coefficients represent the predictive power of each variable in the model.

There are two types of models: binary logistic regression, used when the dependent variable is dichotomous and multivariate logistic regression, used when the dependent variable consists of more than two (45).

Logistic regression is usually used to evaluate the association of biomarkers with binary outcomes. The biomarkers can be included as continuous or categorical covariates. However, some of the biomarkers are skewed. Although logistic regression does not require the independent variables to be normally distributed, log-transformation of skewed biomarkers can improve model performance and interpretability. After log-transformation, variables approximate a normal distribution, allowing for more reliable estimation of odds ratios (OR). Grund et al. 2010 use a log-transformation of highly sensitive C-reactive protein (hsCRP)(46).

An OR measures the association between an exposure and an outcome. ORs are used to compare and determine which exposure (i.e. health characteristics or comorbidities) is a risk factor for a particular outcome (i.e. death or disease). The results can be:

- OR=1 Exposure does not affect odds of outcome
- OR>1 Exposure associated with higher odds of outcome
- OR<1 Exposure associated with lower odds of outcome(47)

It is usually used to compare several biomarkers measured on different scales because the ORs describe the increased odds of the event per 1 standard deviation (SD) of biomarkers. As an alternative, some researchers report ORs per 1 interquartile range (IQR); this approach is preferred if there are outliers.(46)

On the other hand, some investigators prefer to categorise the biomarker and report ORs that compare the odds of the event in each category. These categories may be clinically relevant thresholds or may be broken into quartiles, tertiles or quintiles. It is preferred when the relationship between the risk and the biomarker is nonlinear to prevent giving incorrect OR estimates. Additionally, it is an alternative to analyse highly skewed biomarkers without transforming(46).

Firth's penalised logistic regression

Logistic regression is commonly used to obtain the adjusted odds ratio, allowing scientists to conduct inference and applications in public health and policy. Maximum likelihood (ML) is used in logistic regressions for this purpose. However, these estimations may become unreliable when the dataset is small, there are rare exposures or outcomes, or substantial underlying effects, particularly when all these issues arise together.

Analysing further these issues, small datasets may produce wide confidence intervals and unreliable hypothesis tests. On the other hand, in case of rare events, traditional logistic regression underestimates the probabilities associated with it, exhibiting the model a bias toward zero and causing important impacts in decision-making processes and policy recommendations.

In this scenario, Firth's logistic regression approach resolved the limitations stated above. In fact, this method has gained recognition as a powerful tool in scenarios where a complete separation within the data prevents traditional ML logistic regression from converging, thanks to its penalty term introduced into the standard ML function to generate parameter estimates and standard errors for the logistic regression model resulting a in improved accuracy and reliability of the results. Although the sample size approaches an infinite number of observations, the penalty term tends to converge towards zero, making it ideal to address small sample bias or rare health outcomes or adverse events. In summary, Firth's penalised logistic regression provides more accurate parameter estimates in small or sparse datasets, particularly when standard logistic regression fails due to data separation. (48).

Model evaluation

Regardless of the specific logistic regression model used, to evaluate the model, the following steps must be taken:

1. **Evaluation of the overall model.** Involves comparing the predicted model to a null model (with no independent variable) fitted to the input data. The model will only be a better fit if it demonstrates an improvement over the empty model.
2. **Predictive accuracy and discrimination of the model**. Assessed from the sensitivity and specificity of the model by using a confusion matrix.
3. **Statistical significance of regression coefficients of independent variables.** Wald statistic, the odds ratio (OR) and the likelihood ratio test might be used to determine if the variable has a significant predictive value.
4. **Validation of the model**. Does the model fit with another subset of the population? In this case, the model can be used in a different dataset (external validation) or, in opposite, the model is tested using a similar subset of the population, if not the same (internal validation).
    a. **Split-sample technique**. Splitting the dataset randomly into training and validation sets. The main disadvantage is the dataset's reduction, which may produce different results. Cross-validation mimics this method. It is a resampling technique where development and testing are done in rounds.
    b. **Bootstrap validation**. Used in logistic regression modelled in smaller samples, where the whole dataset is resampled several times with replacement, with statistics being generated on each resampling, and these statistics are merged in a specific way (45).

Evaluation of biomarkers as prognostic markers

- **ROC curves**

ROC curves describe how the model discriminates correctly between "cases" (Patients with the outcome of interest) and "non-cases" (Patients without the outcome). The ROC curve plots the sensitivity of the predictive model rule against one minus the specificity (46).

On the other hand, the area under the curve (AUC) is a measure used to summarise the overall model's performance. A higher value indicates better model performance, as it

signifies greater discrimination between the two groups. **Table 3** provides a guide for the interpretation of the AUC value (49).

Table 3: Guide to interpret the AUC values. Adapted from Elkahwagy et al. 2024 (45)

AUC of ROC	Interpretation
0.50-0.60	No value diagnostic biomarker
0.60-0.70	Poor diagnostic biomarker
0.70-0.80	Acceptable diagnostic biomarker
0.80-0.90	Good diagnostic biomarker
0.90-1.00	Excellent diagnostic biomarker

3.4.1.2 Survival Analysis

The survival analysis is a time-to-event examination where the length of time until the occurrence of an event of interest is studied. This event must be clinically relevant, well-defined, unambiguous and preferably easy to observe. Hence, in many survival analyses, time to death is the event of interest(50).

The variable time records two different things:

- The survival time in patients who are “successful” in reaching the event.
- The time from the start of the observation until the point of censoring (51).

Sometimes, individuals present incomplete survival time. That is called **censoring**. For example, censoring occurs when some patients have not experienced the event by the end of the data collection, a patient is lost to follow-up during the study period (inability to show up for a clinic visit due to a deterioration in their health) or withdraws from the study because of death (In the case that death is not the event of interest) (50).

There are 3 major types of censoring:

- **Right censoring**: The most common. It is due to the incomplete survival time on the right side of the follow-up period. As stated above, the patient may experience the event after the study period or withdraw from the study. Both patients require censoring because the exact survival time is not known.
- **Left censoring:** The event has already occurred when observation begins.
- **Interval-censored:** The event occurs between two observations.

A related concept that is sometimes confused with censoring is **truncation**. It differs from censoring because no information is provided about the patient whose event is not in this interval (They are excluded from observation). However, censoring gives partial information about each subject(52,53).

As in censoring, two types of truncations can be differentiated:

- **Left truncation.** The patients who have already experienced the event are omitted. For example, in a study of risk factors for delays in the diagnosis of colorectal cancer, a left truncation would be to exclude all the patients who have already been diagnosed with colorectal cancer (the event).
- **Right truncation.** The entire study population has already experienced the event. Following the last example, a right truncation would be to use the data from a cancer registry where all the patients already have a cancer diagnosis. In this case, the data is missing the people who have not been diagnosed yet.

It is important to prevent truncation to avoid length-biased data(54). Even though these subjects cannot be excluded from the dataset, the sample size may be reduced (55).

Survival and hazard

The survival data is described and modelled by two related probabilities: survival and hazard.

If T is a continuous random variable with probability density function f(t) and cumulative distribution function $F(t) = Pr\{T < t\}$, giving the probability that the event has taken place by time t.

The **survival function**, S(t), is the probability of surviving at least to time t. The plot of S(t) against t is called the **survival curve**.

$$S(t) = Pr\{T \geq t\} = 1 - F(t) = \int_t^{\infty} f(x)dx,$$

On the other hand, the **hazard function** h(t) represents the conditional probability of experiencing the event at time t, given survival up to that time. There is no simple way to estimate h(t), but **the cumulative hazard** H(t) is commonly employed. The cumulative hazard is the integral of the hazard or the area under the hazard function between times 0 and t. It can be calculated as follows:

$$H(t) = -\log[s(t)]$$

The easiest way to interpret H(t) is as the total risk accumulated over time. H(t) is also an intermediate to estimate h(t) whose formula is:

$$h(t) = -\frac{d}{dt}[\log S(t)]$$

The formula above shows a clear relationship between s(t) and h(t)(56).

Non-parametric estimation

Kaplan-Meier estimator

The Kaplan-Meier estimator allows for the robust estimation of survival probability over time, even when dealing with varying follow-up times and patient dropouts.

There are three assumptions in this analysis:

- The subjects censored have the same survival prospects as those who continue to be followed.
- The survival probabilities are the same for individuals who started the study at an early stage as those who started later.
- The event occurs at a specific time.

If the event of interest is death, the survival probability at any time is calculated as it follows:

$$S_t = \frac{Number\ of\ subjects\ living\ at\ the\ start - Number\ of\ subjects\ died}{Number\ of\ subjects\ living\ at\ the\ start}$$

The survival curve is plotted as a step function: the surviving proportion remains unchanged between events, even if there are some censored observations. Survival curves can be compared. For instance, **Figure 4** represents the survival patterns for individuals on a standard therapy with a newer therapy.

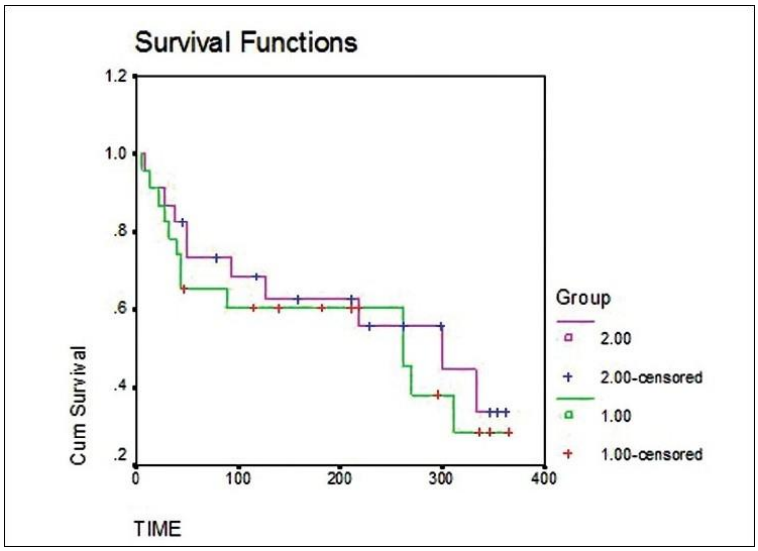


Figure 4: Survival curves of a group of patients receiving two different therapies for HIV infection. The horizontal axis shows the time to the event

An important issue of the Kaplan-Meier method is that it can only study the effect of one factor at a time and cannot be used for multivariate analysis. In these cases, regression analyses such as the Cox proportional hazard models should be used instead (57).

Log-Rank test

The log-rank test assesses for significant differences between the populations in the probability of an event (here, the death) at any time. The null hypothesis is that there is no difference in survival among groups. The analysis is based on the times of events (most of the time, deaths). It follows the same assumptions as the Kaplan-Meier survival curve (58).

The log-rank test can effectively compare the survival between two groups. However, it presents important limitations:

- The log-rank test can only assess the effect of one variable at a time on prognosis
- Can be used to detect the impact of a categorical confounder by looking at survival curves, but it does not allow the evaluation of the simultaneous influence of multiple potential confounders
- The results only show if there is a significant difference between groups because it does not provide the hazard rate or hazard ratio. In other words, it cannot quantify this difference(59).

Cox Proportional Hazards Model

The Cox Proportional Hazards model (CPH) is a frequently employed semiparametric model for analysing survival data. It allows for studying the effects of several continuous and categorical variables on survival, while accounting for possible confounders and providing an estimate of the hazard ratio and its confidence interval. This model can be described as follows: (59,60)

$$h(t) = h0(t)e^{(b1X1+b2X2+\cdots+bpXp)}$$

where:

- h is the hazard at the time
- h0(t) represents the baseline hazard when the predictor X1, X2…Xp is equal to 0.
- B is a parameter to be estimated that represents the effect of the covariate on the outcome.

The exponential function ensures that the hazard ratio is always positive. The covariates have an additive effect on the log hazard ratio (the natural logarithm of the hazard ratio) (53).

This model relies on certain assumptions:

- **The proportional hazards assumption**: the hazard ratio must remain constant throughout the study.
- **The survival time** of a patient does not depend on the survival time of another. In other words, the survival times must be independent.
- **Censoring is uninformative**; therefore, if the patients fail to follow up with the appointment, they have the same risk of suffering the event even if they are censored in the study.

Once these assumptions are met, the results of this model are consistent. Furthermore, the coefficients obtained in the CPH model can be used to model and predict the expected survival of patients with specific values of covariates that are included in the model (59).

3.4.2. Statistical Analysis

This analysis used the R statistical program via the R Studio interface, version 2024.12.1+563. For descriptive analysis, where demographic and clinical data between groups are compared, continuous variables were expressed as medians and SD, and frequencies were expressed as percentages and counts. Variables' normality distribution was evaluated with the Kolmogorov-Smirnov test. Mann-Whitney U test or two-sample t-test (Student's t-test) was used to compare the two groups depending on data distribution; chi-squared (X^2) test was used to evaluate the categorical variables in the univariate analysis.

Variables demonstrating statistical significance ($p<0.05$) were considered for inclusion in subsequent multivariate models, and those with a p-value < 0.2 were included as candidate covariates in the multivariate model to reduce the risk of omitting relevant predictors due to confounding.

To determine CRP evolution over time, repeated measures of variance (ANOVA) or the Friedman test were used. Post-hoc test will be performed if statistically significant differences are found.

Logistic regression analysis, odds ratios (ORs) and 95% confidence intervals (CIs) have been performed on the statistically significant outcome variables to evaluate CRP's ability to predict poor outcomes. If the model demonstrated significance, its ROC and AUC were calculated to assess the predictive accuracy of CRP.

Finally, a survival analysis has been conducted using an adjusted multiple Cox regression analysis to evaluate CRP levels based on the nutritional support received. As Servia-Goixart et al. 2022 did, variables were included in the initial model if they had a P-value <0.2 and were considered suitable based on careful consideration of confounding(8).

4. Results

This section presents the primary findings derived from the data analyses. These results are shown through charts, tables and descriptive summaries to enhance their interpretation.

This study started evaluating the distribution of CRP variables, which were found to be right-skewed. This pattern is expected, as normal CRP concentrations commonly remain close to 0 mg/L. This observation is supported by **Figure 5**, where CRP levels increase their skewness throughout the days, suggesting that most patients reached near-normal levels by the seventh day.

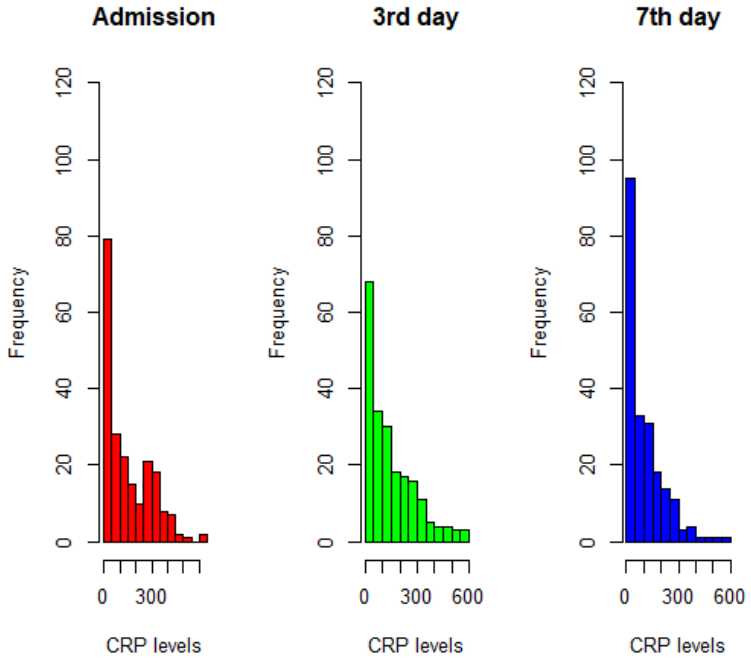


Figure 5: Distribution of CRP levels on three different days: admission (red), day 3 (green), and day 7 (blue).

Subsequently, the presence of outliers is assessed. As shown in **Figure 6**, the analysis revealed some outliers on the third and seventh days. These outliers were retained in the analysis as they potentially represent patients with complications or complex clinical conditions. However, there is a clear trend in the reduction of inflammation among the majority of patients

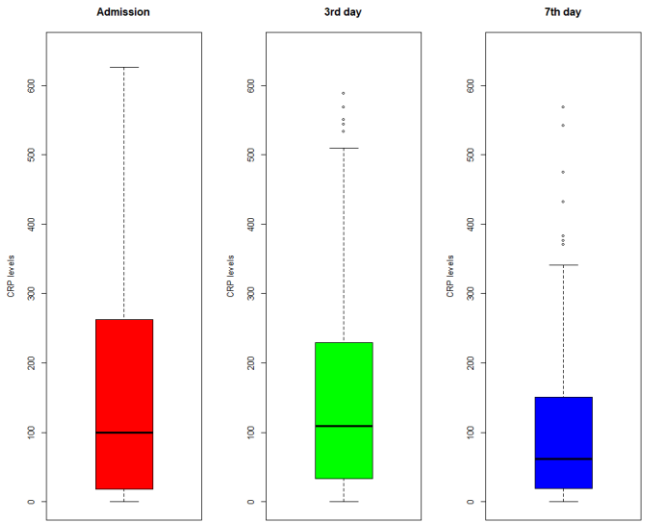


Figure 6: Boxplot of CRP values on admission, day 3, and day 7.

Then, the Kolmogorov-Smirnov test was used to assess these variables' normal distribution. This test confirmed that none of the CRP measurements followed a normal distribution (**Figure 7**).

Normal distribution test

Test	CRP1	CRP3	CRP7
Kolmogorov-Smirnov	3.44029e-13	2.30893e-11	6.617501e-17

Figure 7: Kolmogorov-Smirnov test results.

To assess statistical differences between the repeated measures of CRP (CRP1, CRP3, CRP7), the Friedman test was applied. This analysis revealed a statistically significant result ($p<0.001$), indicating overall differences across the time points. Post-hoc pairwise comparisons indicated significant reductions in CRP levels between CRP1 and CRP7 ($p = 0.046$), and between CRP3 and CRP7 ($p =0.001$). No significant changes were observed between CRP1 and CRP3 ($p = 1.000$). Consequently, the subsequent analysis will focus on the changes between admission and the seventh day.

In addition, **Figure 8** illustrates the mean CRP levels stratified by type of nutritional support received. Patients receiving EN had lower inflammation levels when they were admitted to the ICU compared to the other groups. Those treated with EN or combined EN-PN experienced a rise in CRP levels on day 3, followed by a decrease. In contrast,

patients receiving PN or PN-EN started with higher CRP levels, but their concentrations decreased significantly. By the seventh day, only patients fed with EN or PN-EN had CRP levels lower than 100 mg/L.

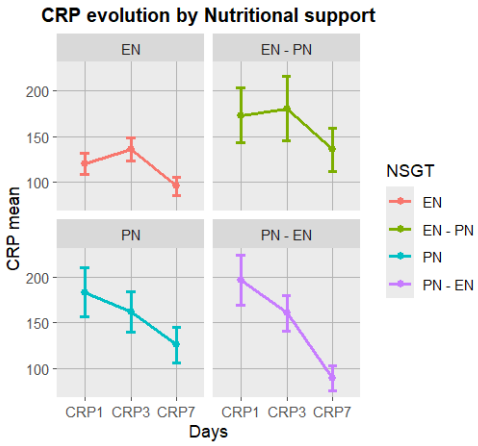
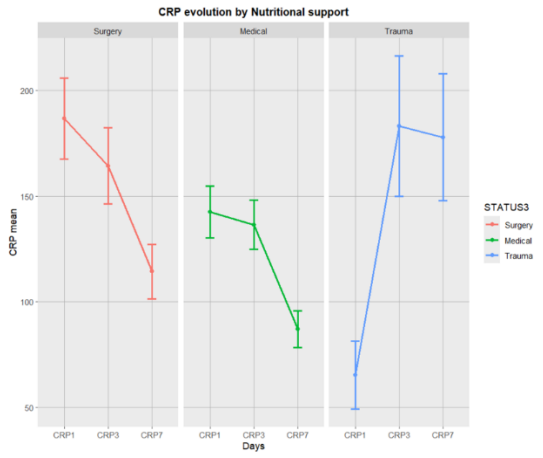


Figure 8: Mean CRP levels by type of nutritional support over time.

On the other hand, **Figure 9** shows CRP evolution based on the type of patient. Surgical patients were more likely to present increased concentrations of CRP at admission (mean: 186.8 mg/L), followed by a reduction in the subsequent days. Medical patients followed a similar pattern. However, Trauma patients followed a different trajectory. They were admitted to the ICU with a mean CRP concentration of 65.30 mg/L, but then, an increase was recorded, reaching its peak on the third day with 177.92 mg/L. On the seventh day, trauma patients remained significantly elevated compared to patients in the other groups.



STATUS3	n	meanCRP 1	meanCRP 3	meanCRP 7
Surgery	49	186.80	164.30	114.23
Medical	144	142.56	136.48	86.97
Trauma	20	65.30	183.18	177.92

Figure 9: Mean CRP concentration based on type of patient: surgery (Red), medical (green), trauma (Blue).

As a final step, bivariate correlations were computed between clinical, nutritional, and outcomes-related variables (**Figure 10**). Given that CRP did not follow a normal distribution, Spearman's rank correlation coefficient was used. The correlation analysis revealed relevant patterns:

- **Inflammatory markers (CRP):** CRP variables correlated, which is expected because CRP variables measure different days. In addition, CRP levels were positively correlated with several clinical severity indicators, such as SOFA, requirement of IMV, vasoactive drug support (VDS) and RTT.
- **Duration of medical nutrition therapy (NSDays):** a strong correlation was found between the days the patients were with nutritional support with ICU length of stay (r = 0.78), and with days of IMV (r = 0.73), suggesting that longer duration of MNT is associated with more severe illness. NSDays also showed a moderate correlation with the mean caloric and protein intake during the second week (r = 0.53, r = 0.49, respectively) and LOS (r = 0.60).
- **Early enteral nutrition (EN_48h):** This variable was negatively associated with the type of nutritional support received (r = -0.74). On the other hand, early EN was significantly negatively correlated with the time until the start of MNT (r = -0.38), which is expected as these variables refer especially to those patients who started EN within the first 48h. In addition, a negative correlation was observed between EN_48h and CRP levels at admission and on the seventh day, as well as with the nutritional assessment score and ICU mortality. These findings suggest that patients may benefit from early enteral nutrition in terms of reducing inflammation and improving prognosis.
- **Mean caloric intake during the first week:** It showed a negative correlation with the length of ICU stays (r = - 0.39) and LOS (r = -0.25). This indicates that a higher early caloric intake may be associated with shorter LOS.
- **ICU length of stay**: The length of stay in the ICU was associated with the duration of IMV (r = 0.73), MNT (r = 0.78), and overall LOS (r = 0.59). Moreover, there was a positive correlation between the mean of proteins and caloric intake in the second week (r = 0.58, r = 0.6), contrary to the first week, where the caloric intake was negatively associated (r = -0.39).
- **28-day mortality:** Outcome significantly associated with death in ICU (r = 0.74), age (r = 0.24), development of Mesenteric Ischemia (MI) (r = 0.21) and the nutritional assessment based on SGA (r = 0.23). On the contrary, there was a negative

correlation with LOS (r = -0.47), length of stay in ICU (r = -0.23) and NSDays (r =-0.21), likely reflecting early deaths in some patients.

- **Nutritional risk:** Patients at nutritional risk showed positive correlations with severity scores such as SAPSII (r = 0.4), SOFA (r =0.37) and APACHE II (r = 0.56), as well as comorbidities such as diabetes (r =0.26) or hypertension (r = 0.23). Furthermore, it was slightly associated with a 28-day mortality (r = 0.16) and had negative correlations with the mean of protein and calorie intake during the second week (r = -0.17 and r = -0.14, respectively)

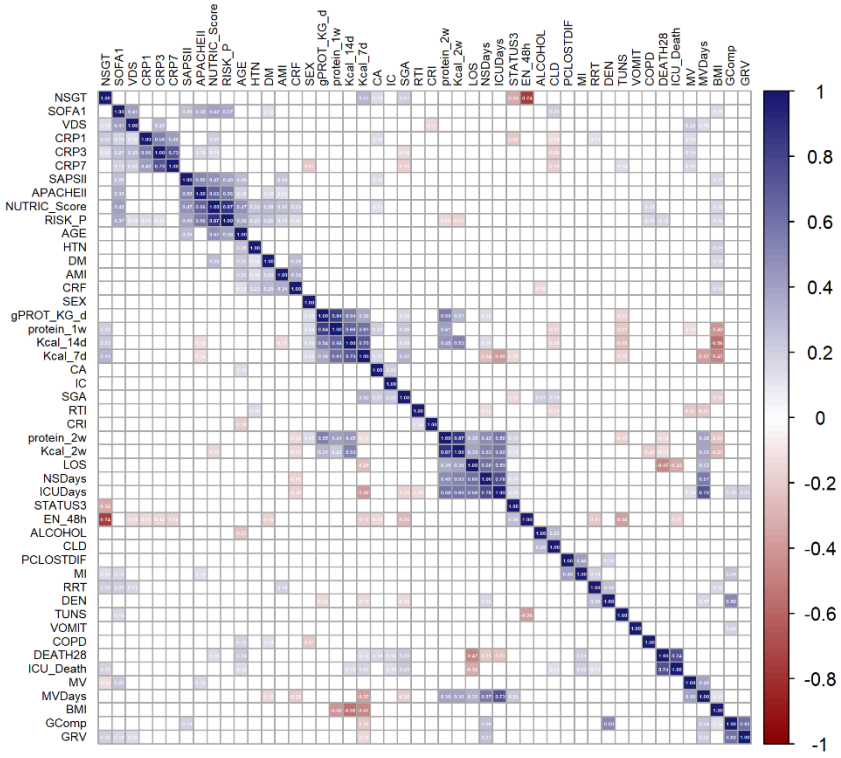


Figure 10: Correlation matrix

4.1. Demographic and Clinical Features

4.1.1. Demographics and Clinical Features of the Overall Patient Population.

As shown in **Table 4**, patients with CRP > 100mg/L were older than those with lower CRP levels at admission. However, these differences were not statistically significant (p = 0.2). Chronic obstructive pulmonary disease (COPD) was significantly more frequent in patients with CRP above 100 mg/L (24%, p = 0.017). Nevertheless, Chronic liver Disease (CLD) was often found in patients classified within <100mg/L (10% vs 2.8%, p

= 0.028). Among all types of patients included in the study, the surgical ones are prone to have elevated CRP concentrations (31%, p=0.005). Furthermore, these patients had increased severity scores, with significantly high APACHE II, SOFA, and NUTRIC scores (p =0.030, p = 0.002, and p = 0.006, respectively).

133 patients received EN as their nutritional support, 105 commencing EN within 48h of admission. In both, a higher proportion of patients exhibited significantly low CRP levels (73%, p=0.02;56%, p=0.047). On the other hand, most patients who were admitted with increased CRP levels required vasoactive drug support (VDS) (p=0.045) or developed Mesenteric ischemia (MI), finding that the only six patients who suffered from this complication were the ones who had higher CRP concentrations (p=0.014).

By the seventh day, some clinical and nutritional characteristics remained associated with increased levels of CRP. Specifically, males appeared to be disproportionately represented among individuals with higher CRP concentrations. While 144 out of 213 patients were male, their proportion was marginally significant in the >100mg/L group (p 0.051). Trauma patients presented a significant increase in the patients classified in the > 100 mg/L group (p = 0.004). Contrary, CLD was more prevalent in the <100 mg/L group (p = 0.010).

As a severity score, only the SOFA score remained significantly elevated in the >100 mg/L group (p=0.020). The same happened with NS's initiation time (p = 0.044). Most enteral patients (N =133) were categorised within <100 mg/L (69%, p=0.020) and received early EN (56%, p=0.013). Contrarily, parenteral or EN-PN patients were classified mostly within >100mg/L (18%, p = 0.048; 14%, p = 0.030, respectively). Regarding outcomes, support needs and complications, there were significant differences among the patients who developed MI (most within >100mg/L, 5.9%, p = 0.038) and required VSD. Principally, most patients classified with higher CRP levels on the seventh day (N = 85) required VDS (92%, p = 0.009).

Table 4: Outcomes based on the difference of CRP blood levels between ICU admission and the seventh day. * During the administration or at least the first 14 days of nutritional support. Significant p-values are written in bold.

Characteristic	CRP on admission				CRP on the seventh day		
	Overall N = 213[1]	**<100** N = 107[1]	**>100** N = 106[1]	**p-value**[2]	**<100** N = 128[1]	**>100** N = 85[1]	**p-value**[2]
Demographic characteristics and comorbidities							
Mean age (years)	62.16 (±15.32)	60.29 (± 16.83)	64.05 (± 13.45)	0.2	62.30 (± 15.37)	61.94 (± 15.34)	0.8
Sex (male)	144 (68%)	72 (67%)	72 (68%)	>0.9	80 (63%)	64 (75%)	0.051
BMI (Kg*m-2)	28.40 (± 5.91)	28.24 (± 6.16)	28.56 (± 5.67)	0.5	28.59 (± 6.00)	28.12 (± 5.80)	0.7
Alcohol	28 (13%)	15 (14%)	13 (12%)	0.7	16 (13%)	12 (14%)	0.7
Diabetes	58 (27%)	26 (24%)	32 (30%)	0.3	32 (25%)	26 (31%)	0.4
Hypertension	105 (49%)	52 (49%)	53 (50%)	0.8	64 (50%)	41 (48%)	0.8
COPD	37 (17%)	12 (11%)	25 (24%)	**0.017**	23 (18%)	14 (16%)	0.8
AMI	36 (17%)	19 (18%)	17 (16%)	0.7	20 (16%)	16 (19%)	0.5
Chronic Liver Disease	14 (6.6%)	11 (10%)	3 (2.8%)	**0.028**	13 (10%)	1 (1.2%)	**0.010**
Chronic Renal Failure	28 (13%)	13 (12%)	15 (14%)	0.7	18 (14%)	10 (12%)	0.6
Immunosuppression	30 (14%)	16 (15%)	14 (13%)	0.7	21 (16%)	9 (11%)	0.2
Neoplasia	41 (19%)	16 (15%)	25 (24%)	0.11	26 (20%)	15 (18%)	0.6
Type of patient							
Surgery	49 (23%)	16 (15%)	33 (31%)	**0.005**	26 (20%)	23 (27%)	0.3
Medical	144 (68%)	78 (73%)	66 (62%)	0.10	96 (75%)	48 (56%)	**0.005**
Trauma	20 (9.4%)	13 (12%)	7 (6.6%)	0.2	6 (4.7%)	14 (16%)	**0.004**
Prognosis ICU scores & scores for evaluating nutritional status on admission							
APACHEII	21.04 (± 7.98)	19.66 (± 7.05)	22.42 (± 8.63)	**0.030**	20.21 (± 7.49)	22.28 (± 8.55)	0.094

Characteristic	CRP on admission				CRP on the seventh day		
	Overall N = 213[1]	**<100** N = 107[1]	**>100** N = 106[1]	**p-value**[2]	**<100** N = 128[1]	**>100** N = 85[1]	**p-value**[2]
SAPSII	52.23 (± 16.59)	50.62 (± 15.18)	53.86 (± 17.83)	0.2	50.91 (± 15.39)	54.21 (± 18.16)	0.3
SOFA (on admission)	7.75 (± 3.26)	7.11 (± 3.02)	8.40 (± 3.38)	**0.002**	7.35 (± 3.22)	8.35 (± 3.25)	**0.020**
Patient with malnutrition (SGA)	95 (45%)	50 (47%)	45 (42%)	0.5	64 (50%)	31 (36%)	0.052
NUTRIC_Score	4.53 (± 2.10)	4.12 (± 2.03)	4.93 (± 2.10)	**0.006**	4.45 (± 1.98)	4.65 (± 2.28)	0.5
Patient at risk (Based on Nutric Score)	109 (51%)	48 (45%)	61 (58%)	0.064	62 (48%)	47 (55%)	0.3
Characteristics of Nutritional Support							
Time of initiation of NS (h)	35.32 (± 29.32)	36.79 (± 32.93)	33.84 (± 25.23)	>0.9	32.61 (± 27.90)	39.41 (± 31.07)	**0.044**
Early EN (<48h)	105 (49%)	60 (56%)	45 (42%)	**0.047**	72 (56%)	33 (39%)	**0.013**
EN	133 (62%)	78 (73%)	55 (52%)	**0.002**	88 (69%)	45 (53%)	**0.020**
PN	26 (12%)	10 (9.3%)	16 (15%)	0.2	11 (8.6%)	15 (18%)	**0.048**
EN_PN	19 (8.9%)	6 (5.6%)	13 (12%)	0.088	7 (5.5%)	12 (14%)	**0.030**
PN_EN	35 (16%)	13 (12%)	22 (21%)	0.090	22 (17%)	13 (15%)	0.7
Mean Kcal/Kg/day* (Total)	18.12 (± 5.78)	18.12 (± 5.59)	18.11 (± 6.00)	0.9	18.55 (± 5.59)	17.46 (± 6.03)	0.2
Mean g protein/Kg/day (Total)	1.06 (± 0.35)	1.06 (± 0.33)	1.06 (± 0.37)	>0.9	1.09 (± 0.33)	1.03 (± 0.38)	0.2
Mean Kcal/Kg/day (1º week)	10.25 (± 4.48)	10.09 (± 4.04)	10.41 (± 4.90)	>0.9	10.53 (± 4.42)	9.82 (± 4.55)	0.2
Mean g protein/Kg/day (1º week)	0.90 (± 0.35)	0.92 (± 0.35)	0.89 (± 0.36)	0.5	0.93 (± 0.34)	0.86 (± 0.37)	0.2

Characteristic	CRP on admission				CRP on the seventh day		
	Overall N = 213[1]	**<100** N = 107[1]	**>100** N = 106[1]	**p-value**[2]	**<100** N = 128[1]	**>100** N = 85[1]	**p-value**[2]
Mean Kcal/Kg/day (2º week)	14.62 (± 8.49)	14.98 (± 8.08)	14.26 (± 8.91)	0.4	14.91 (± 8.06)	14.20 (± 9.13)	0.4
Mean g protein/Kg/day (1º week)	0.79 (± 0.47)	0.80 (± 0.44)	0.78 (± 0.51)	0.6	0.78 (± 0.44)	0.79 (± 0.52)	>0.9
EN-related complications							
Any complication	71 (33%)	35 (33%)	36 (34%)	0.8	44 (34%)	27 (32%)	0.7
GRV	34 (16%)	17 (16%)	17 (16%)	>0.9	20 (16%)	14 (16%)	0.9
Diarrhea	24 (11%)	12 (11%)	12 (11%)	>0.9	17 (13%)	7 (8.2%)	0.3
Vomiting	4 (1.9%)	3 (2.8%)	1 (0.9%)	0.6	4 (3.1%)	0 (0%)	0.2
Aspiration	0 (0%)	0 (0%)	0 (0%)	>0.9	0 (0%)	0 (0%)	>0.9
Mesenteric ischemia	6 (2.8%)	0 (0%)	6 (5.7%)	**0.014**	1 (0.8%)	5 (5.9%)	**0.038**
Outcomes							
Mechanical ventilation	201 (94%)	98 (92%)	103 (97%)	0.077	118 (92%)	83 (98%)	0.13
Days on mechanical ventilation	18.20 (± 17.25)	17.90 (± 18.14)	18.51 (± 16.38)	0.8	18.06 (± 17.25)	18.41 (± 17.34)	0.7
Vasoactive drug support	178 (84%)	84 (79%)	94 (89%)	**0.045**	100 (78%)	78 (92%)	**0.009**
RRT needs	47 (22%)	19 (18%)	28 (26%)	0.13	29 (23%)	18 (21%)	0.8
Respiratory tract infection	49 (23%)	23 (21%)	26 (25%)	0.6	28 (22%)	21 (25%)	0.6
Catheter-related infection	10 (4.7%)	6 (5.6%)	4 (3.8%)	0.7	8 (6.3%)	2 (2.4%)	0.3
Mean ICU stay (days)	26.08 (± 18.65)	26.87 (± 19.63)	25.28 (± 17.67)	0.4	26.58 (± 18.49)	25.33 (± 18.98)	0.6
Mean hospital stay (days)	45.46 (± 33.08)	46.35 (± 33.82)	44.58 (± 32.46)	0.9	46.08 (± 31.99)	44.54 (± 34.84)	0.4

Characteristic	CRP on admission				CRP on the seventh day		
	Overall N = 213[1]	**<100** N = 107[1]	**>100** N = 106[1]	**p-value**[2]	**<100** N = 128[1]	**>100** N = 85[1]	**p-value**[2]
ICU mortality	57 (27%)	29 (27%)	28 (26%)	>0.9	36 (28%)	21 (25%)	0.6
28-days mortality	61 (29%)	30 (28%)	31 (29%)	0.8	36 (28%)	25 (29%)	0.8

[1]Mean (± SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

4.1.2. Characteristics of Patients Receiving Enteral Nutrition

Significant differences were found in patients who received EN on admission and day 7, so another table with only these 133 patients was built. As shown in **Table 5**, 78 patients had their CRP levels below 100 mg/L, while 55 patients had values above this threshold. Notably, a significantly higher proportion of patients with elevated CRP levels had COPD (24% vs 10%, p = 0.037) within higher CRP concentrations. Furthermore, those patients showed worse SOFA and NUTRIC scores (p = 0.022; p = 0.012, respectively), and a greater proportion were considered at risk (p = 0.038). Although the APACHE II score was also higher in this group, the difference did not reach statistical significance (p = 0.054).

By the seventh day, most medical patients had lower CRP levels (84%, p = <0.001, while the opposite it is found in trauma patients (29%, p = < 0.001). None of the prognosis scores were significant, only SOFA was found nearly significant (p = 0.052), again suggesting a potential association between persistent inflammation and clinical severity.

In terms of nutritional support, patients categorised as <100 mg/L received higher mean caloric intake overall and during the first week, though these differences were not statistically significant (p = 0.088; p = 0.082, respectively). Likewise, gastrointestinal complications such as gastric residual volume (GRV) were more frequent in patients with CRP > 100 mg/L (18% vs 8%), but this difference was also not significant (p = 0.090).

To conclude, A higher proportion of patients with elevated CRP levels required VDS (93% vs 73%, p = 0.005), which might further highlight the association between persistent systemic inflammation and clinical instability.

Table 5: Outcomes based on the difference in CRP blood levels between ICU admission and the seventh day only in Enteral patients. * During the administration or at least the first 14 days of nutritional support. Significant p-values are written in bold

Characteristic	CRP on admission			CRP on the seventh day		
	<100 N = 78[1]	**>100** N = 55[1]	**p-value**[2]	**<100** N = 88[1]	**>100** N = 45[1]	**p-value**[2]
Demographic characteristics and comorbidities						
Mean age (years)	59.81 (± 17.34)	64.78 (± 14.04)	0.11	61.28 (± 16.28)	63.00 (± 16.12)	0.6
Sex (male)	51 (65%)	36 (65%)	>0.9	54 (61%)	33 (73%)	0.2
BMI (Kg*m-2)	28.53 (± 6.75)	29.58 (± 6.33)	0.3	29.01 (± 6.58)	28.87 (± 6.65)	>0.9
Alcohol	10 (13%)	4 (7.3%)	0.3	10 (11%)	4 (8.9%)	0.8
Diabetes	17 (22%)	14 (25%)	0.6	21 (24%)	10 (22%)	0.8
Hypertension	37 (47%)	30 (55%)	0.4	45 (51%)	22 (49%)	0.8
COPD	8 (10%)	13 (24%)	**0.037**	15 (17%)	6 (13%)	0.6
AMI	13 (17%)	7 (13%)	0.5	12 (14%)	8 (18%)	0.5
Chronic Liver Disease	10 (13%)	2 (3.6%)	0.12	11 (13%)	1 (2.2%)	0.059
Chronic Renal Failure	9 (12%)	10 (18%)	0.3	13 (15%)	6 (13%)	0.8
Immunosuppression	9 (12%)	7 (13%)	0.8	12 (14%)	4 (8.9%)	0.4
Neoplasia	11 (14%)	9 (16%)	0.7	15 (17%)	5 (11%)	0.4
Type of patient						
Surgery	10 (13%)	7 (13%)	>0.9	9 (10%)	8 (18%)	0.2
Medical	56 (72%)	42 (76%)	0.6	74 (84%)	24 (53%)	**<0.001**
Trauma	12 (15%)	6 (11%)	0.5	5 (5.7%)	13 (29%)	**<0.001**
Prognosis ICU scores & scores for evaluating nutritional status on admission						

Characteristic	CRP on admission			CRP on the seventh day		
	<100 N = 78[1]	**>100** N = 55[1]	**p-value**[2]	**<100** N = 88[1]	**>100** N = 45[1]	**p-value**[2]
APACHEII	19.97 (± 7.17)	23.27 (± 9.18)	0.054	21.09 (± 7.40)	21.82 (± 9.63)	>0.9
SAPSII	50.59 (± 15.06)	55.47 (± 19.50)	0.13	51.80 (± 15.29)	54.20 (± 20.38)	0.7
SOFA (on admission)	7.15 (± 2.71)	8.20 (± 3.02)	**0.022**	7.25 (± 2.88)	8.24 (± 2.80)	0.052
Patients with malnutrition (SGA)	32 (41%)	16 (29%)	0.2	36 (41%)	12 (27%)	0.11
NUTRIC_Score	4.00 (± 2.02)	4.91 (± 2.24)	**0.012**	4.39 (± 2.04)	4.36 (± 2.38)	>0.9
Patient at risk (Based on Nutric Score)	34 (44%)	34 (62%)	**0.038**	44 (50%)	24 (53%)	0.7
Characteristics of Nutritional Support						
Time of initiation of NS (h)	37.11 (± 31.67)	29.64 (± 20.39)	0.3	31.70 (± 24.74)	38.56 (± 32.62)	0.15
Early EN (<48h)	60 (77%)	45 (82%)	0.5	72 (82%)	33 (73%)	0.3
Mean Kcal/Kg/day* (Total)	17.27 (± 4.82)	16.88 (± 5.45)	0.6	17.70 (± 4.95)	15.96 (± 5.18)	0.088
Mean g protein/Kg/day (Total)	1.02 (± 0.32)	1.06 (± 0.37)	0.5	1.06 (± 0.33)	1.00 (± 0.35)	0.4
Mean Kcal/Kg/day (1º week)	9.06 (± 3.16)	9.45 (± 4.97)	0.7	9.60 (± 3.72)	8.48 (± 4.44)	0.082
Mean g protein/Kg/day (1º week)	0.86 (± 0.31)	0.83 (± 0.35)	0.5	0.87 (± 0.32)	0.80 (± 0.35)	0.3
Mean Kcal/Kg/day (2º week)	15.46 (± 7.23)	13.86 (± 7.90)	0.2	15.18 (± 7.45)	14.06 (± 7.70)	0.5
Mean g protein/Kg/day (1º week)	0.83 (± 0.41)	0.78 (± 0.47)	0.6	0.81 (± 0.43)	0.80 (± 0.45)	>0.9

Characteristic	CRP on admission			CRP on the seventh day		
	<100 N = 78[1]	**>100** N = 55[1]	**p-value**[2]	**<100** N = 88[1]	**>100** N = 45[1]	**p-value**[2]
EN-related complications						
Any complication	25 (32%)	16 (29%)	0.7	27 (31%)	14 (31%)	>0.9
GRV	11 (14%)	4 (7.3%)	0.2	7 (8.0%)	8 (18%)	0.090
Diarrhea	10 (13%)	5 (9.1%)	0.5	12 (14%)	3 (6.7%)	0.2
Vomiting	3 (3.8%)	1 (1.8%)	0.6	4 (4.5%)	0 (0%)	0.3
Aspiration	0 (0%)	0 (0%)	>0.9	0 (0%)	0 (0%)	>0.9
Mesenteric ischemia	0 (0%)	1 (1.8%)	0.4	1 (1.1%)	0 (0%)	>0.9
Outcomes						
Mechanical ventilation	74 (95%)	55 (100%)	0.14	85 (97%)	44 (98%)	>0.9
Days on mechanical ventilation	19.10 (± 18.43)	18.35 (± 15.24)	0.8	19.31 (± 17.79)	17.78 (± 15.89)	>0.9
Vasoactive drug support	58 (74%)	48 (87%)	0.068	64 (73%)	42 (93%)	**0.005**
RRT needs	10 (13%)	9 (16%)	0.6	15 (17%)	4 (8.9%)	0.2
Respiratory tract infection	14 (18%)	14 (25%)	0.3	16 (18%)	12 (27%)	0.3
Catheter-related infection	5 (6.4%)	2 (3.6%)	0.7	6 (6.8%)	1 (2.2%)	0.4
Mean ICU stay (days)	28.23 (± 20.44)	24.29 (± 17.26)	0.2	27.41 (± 19.34)	25.02 (± 19.10)	0.5
Mean hospital stay (days)	49.85 (± 35.38)	39.84 (± 23.98)	0.2	48.22 (± 32.88)	40.80 (± 28.22)	0.2
ICU mortality	15 (19%)	12 (22%)	0.7	20 (23%)	7 (16%)	0.3
28-days mortality	19 (24%)	16 (29%)	0.5	24 (27%)	11 (24%)	0.7

[1]Mean (± SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

This table, which was initially focused on patients exclusively receiving EN, was expanded to include a group of 17 patients who transitioned from EN to PN. **Table 6** shows the combined results.

In this extended dataset, CRP concentrations remained significantly associated with higher illness severity, as reflected by higher APACHE II (23.35 ± 8.84 vs 20.02 ± 7.02; p = 0.027) and SOFA scores (8.57 ± 3.14 vs 7.35 ± 2.77; p = 0.006), as well as higher NUTRIC scores (5.01 ± 2.24 vs 4.10 ± 2.05; p = 0.006). A greater proportion of patients in this group were at nutritional risk based on the NUTRIC score (63% vs 45%; p = 0.027).

CLD was more frequently observed among patients with CRP <100 mg/L (12% vs 2.9%; p = 0.038). MI was only reported in patients with elevated CRP (5.9%; p = 0.038). There was a non-significant trend toward increased use of VDS in the high CRP group (88% vs 76%; p = 0.057).

By the seventh day of nutritional support, patients with increased CRP continued to exhibit greater severity, as shown by higher SOFA scores (8.72 ± 2.96 vs 7.4 ± 2.92; p = 0.005) and more frequent use of vasoactive drugs (93% vs 75%; p = 0.005). Early EN was less common among patients with a persistently high CRP (58% vs 76%; p = 0.021).

Differences were also noted in patient type: patients with CRP < 100 mg/L were more frequently classified as medical (81% vs 60%; p = 0.004), while those with CRP > 100 mg/L were more frequently classified as trauma (23% vs 6.3%; p = 0.003).

Table 6: Outcomes based on the difference in CRP blood levels between ICU admission and the seventh day in patients receiving EN-PN and exclusively EN. * During the administration or at least the first 14 days of nutritional support. Significant p-values are written in bold

Characteristic	CRP on admission			CRP on the seventh day		
	<100 N = 84[1]	**>100** N = 68[1]	**p-value**[2]	**<100** N = 95[1]	**>100** N = 57[1]	**p-value**[2]
Demographic characteristics and comorbidities						
Mean age (years)	60.35 (± 16.94)	63.69 (± 14.45)	0.2	61.65 (± 16.07)	62.16 (± 15.78)	>0.9
Sex (male)	56 (67%)	45 (66%)	>0.9	59 (62%)	42 (74%)	0.14

Characteristic	CRP on admission			CRP on the seventh day		
	<100 N = 84[1]	**>100** N = 68[1]	**p-value**[2]	**<100** N = 95[1]	**>100** N = 57[1]	**p-value**[2]
BMI (Kg*m-2)	28.62 (± 6.55)	29.27 (± 6.12)	0.4	29.16 (± 6.39)	28.50 (± 6.30)	0.6
Alcohol	11 (13%)	5 (7.4%)	0.3	11 (12%)	5 (8.8%)	0.6
Diabetes	19 (23%)	20 (29%)	0.3	23 (24%)	16 (28%)	0.6
Hypertension	42 (50%)	35 (51%)	0.9	50 (53%)	27 (47%)	0.5
COPD	10 (12%)	16 (24%)	0.058	17 (18%)	9 (16%)	0.7
AMI	15 (18%)	10 (15%)	0.6	15 (16%)	10 (18%)	0.8
Chronic Liver Disease	10 (12%)	2 (2.9%)	**0.042**	11 (12%)	1 (1.8%)	**0.032**
Chronic Renal Failure	11 (13%)	10 (15%)	0.8	14 (15%)	7 (12%)	0.7
Immunosuppression	10 (12%)	10 (15%)	0.6	13 (14%)	7 (12%)	0.8
Neoplasia	11 (13%)	12 (18%)	0.4	15 (16%)	8 (14%)	0.8
Type of patient						
Surgery	11 (13%)	11 (16%)	0.6	12 (13%)	10 (18%)	0.4
Medical	61 (73%)	50 (74%)	0.9	77 (81%)	34 (60%)	**0.004**
Trauma	12 (14%)	7 (10%)	0.5	6 (6.3%)	13 (23%)	**0.003**
Prognosis ICU scores & scores for evaluating nutritional status on admission						
APACHEII	20.02 (± 7.02)	23.35 (± 8.84)	**0.027**	21.13 (± 7.21)	22.16 (± 9.28)	0.7
SAPSII	50.99 (± 14.81)	54.01 (± 18.78)	0.4	51.82 (± 15.13)	53.21 (± 19.17)	>0.9
SOFA (on admission)	7.35 (± 2.77)	8.57 (± 3.14)	**0.006**	7.40 (± 2.92)	8.72 (± 2.96)	**0.005**
Patient with malnutrition (SGA)	33 (39%)	22 (32%)	0.4	38 (40%)	17 (30%)	0.2
NUTRIC_Score	4.10 (± 2.05)	5.01 (± 2.24)	**0.006**	4.46 (± 2.04)	4.58 (± 2.41)	0.7
Patient at risk (Based on Nutric Score)	38 (45%)	43 (63%)	**0.027**	49 (52%)	32 (56%)	0.6

Characteristic	CRP on admission			CRP on the seventh day		
	<100 N = 84[1]	**>100** N = 68[1]	**p-value**[2]	**<100** N = 95[1]	**>100** N = 57[1]	**p-value**[2]
Characteristics of Nutritional Support						
Time of initiation of NS (h)	36.88 (± 30.62)	30.90 (± 21.42)	0.4	31.54 (± 24.23)	38.66 (± 30.73)	0.076
Early EN (<48h)	60 (71%)	45 (66%)	0.5	72 (76%)	33 (58%)	**0.021**
Mean Kcal/Kg/day* (Total)	17.24 (± 4.81)	16.84 (± 5.52)	0.4	17.57 (± 4.86)	16.21 (± 5.47)	0.13
Mean g protein/Kg/day (Total)	1.02 (± 0.31)	1.04 (± 0.36)	0.8	1.05 (± 0.32)	0.99 (± 0.34)	0.3
Mean Kcal/Kg/day (1º week)	9.05 (± 3.10)	9.29 (± 4.65)	0.6	9.44 (± 3.65)	8.68 (± 4.18)	0.2
Mean g protein/Kg/day (1º week)	0.85 (± 0.30)	0.82 (± 0.33)	0.4	0.87 (± 0.31)	0.80 (± 0.33)	0.3
Mean Kcal/Kg/day (2º week)	15.47 (± 7.23)	14.01 (± 7.84)	0.2	15.29 (± 7.24)	14.03 (± 7.97)	0.3
Mean g protein/Kg/day (1º week)	0.83 (± 0.41)	0.78 (± 0.46)	0.5	0.81 (± 0.42)	0.79 (± 0.46)	0.9
EN-related complications						
Any complication	30 (36%)	26 (38%)	0.7	33 (35%)	23 (40%)	0.5
GRV	14 (17%)	10 (15%)	0.7	11 (12%)	13 (23%)	0.066
Diarrhoa	12 (14%)	10 (15%)	>0.9	16 (17%)	6 (11%)	0.3
Vomiting	3 (3.6%)	1 (1.5%)	0.6	4 (4.2%)	0 (0%)	0.3
Aspiration	0 (0%)	0 (0%)	>0.9	0 (0%)	0 (0%)	>0.9
Mesenteric ischemia	0 (0%)	4 (5.9%)	**0.038**	1 (1.1%)	3 (5.3%)	0.15
Outcomes						
Mechanical ventilation	80 (95%)	68 (100%)	0.13	92 (97%)	56 (98%)	>0.9
Days on mechanical ventilation	19.52 (± 18.49)	21.32 (± 17.50)	0.6	20.33 (± 18.19)	20.33 (± 17.87)	0.7

Characteristic	CRP on admission			CRP on the seventh day		
	<100 N = 84[1]	**>100** N = 68[1]	**p-value**[2]	**<100** N = 95[1]	**>100** N = 57[1]	**p-value**[2]
Vasoactive drug support	64 (76%)	60 (88%)	0.057	71 (75%)	53 (93%)	**0.005**
RRT needs	14 (17%)	14 (21%)	0.5	22 (23%)	6 (11%)	0.052
Respiratory tract infection	15 (18%)	16 (24%)	0.4	17 (18%)	14 (25%)	0.3
Catheter-related infection	5 (6.0%)	2 (2.9%)	0.5	6 (6.3%)	1 (1.8%)	0.3
Mean ICU stay (days)	28.52 (± 20.55)	26.56 (± 18.74)	0.4	28.17 (± 19.41)	26.77 (± 20.36)	0.5
Mean hospital stay (days)	49.85 (± 34.85)	42.24 (± 26.61)	0.3	48.59 (± 32.19)	42.86 (± 30.44)	0.14
ICU mortality	18 (21%)	18 (26%)	0.5	23 (24%)	13 (23%)	0.8
28-days mortality	21 (25%)	21 (31%)	0.4	25 (26%)	17 (30%)	0.6

[1]Mean (± SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

4.2. Logistic regression

4.2.1. Univariate logistic regression

Firstly, CRP was evaluated as an independent variable without adjustment for covariates (**Table 7**). In this analysis, higher levels of CRP were significantly associated with the requirement for VDS on admission (OR: 3.20; IC 95%: 1.25-9.32; p = 0.021) and on the seventh day (OR: 3.03; IC 95%: 1.14-9.60; p = 0.038).

On the other hand, increased CRP levels on admission were associated with the development of Mesenteric Ischemia (MI) (OR: 10.18; IC 95%: 1.06-1358.55; p = 0.044). Nevertheless, the confidence interval was extremely wide, despite a Firth's penalised logistic regression being used. This limitation likely stems from the small number of events observed; only 6 out of 213 patients developed MI, and all of them had elevated CRP concentrations. To conclude, CRP measured on the seventh day was not significantly associated with MI, despite an elevated OR (OR: 3.8; IC 95%: 0.61-40; p = 0.155).

Table 7: Univariate logistic regression between CRP concentrations and clinical outcomes. OR = odds ratio, CI = confidence interval

Variables	OR (95% CI)
Vasoactive drug support	
NCRP1>100	3.20 (1.25-9.32, p=0.021)
NCRP7>100	3.03 (1.14-9.60, p=0.038)
Mesenteric Ischemia	
NCRP1>100	10.18(1.06-1358.55, p=0.044)
NCRP7>100	3.8(0.61-40, p=0.155)

The next step was to evaluate the predictive performance of CRP for these outcomes. As shown in **Table 8**, the only acceptable AUC value is CRP on admission as a predictor of MI (AUC = 0.74). However, it is noteworthy that CI was wide, again suggesting potential model uncertainty. Besides, its cutoff value represents that the model always predicts that the patient will develop MI when they have a 3% or higher percentage of development. Hence, the sensitivity value is 100, but its specificity was limited (48.4%).

In contrast, the AUC value of CRP7 as a predictor of VDS indicates that this is not a good predictor (AUC = 0.62). Similarly, CRP1 did not demonstrate significant predictive capability for VDS (AUC = 0.51).

Table 8: ROC analysis: performance of CRP1 and CRP7 as a predictor of VDS and MI. AUC: area under the curve, SD: Standard deviation, CI: confidence interval.

Variable	AUC	SD	CI_95	Cutoff	Sensitivity	Specificity
CRP1 as a predictor of VDS	0.51	0.09	(0.3-0.7)	0.84	55.6	45.5
CRP7 as a predictor of VDS	0.62	0.07	(0.5-0.8)	0.85	42.6	81.8
CRP1 as a predictor of MI	0.74	0.03	(0.7-0.8)	0.03	100.0	48.4

Logistic Regression Analysis in the Enteral Nutrition Cohort

In the subset of enteral-only patients, significant differences in the need for VDS were observed only on the seventh day. Therefore, CRP on day 7 was assessed as a potential predictor. The results suggest there is no statistical association (OR: 4.33; IC 95%: 1.12-28.76; p = 0.063), as shown in **Table 9**.

Table 9: Univariate logistic regression for CRP7 and VDS in enteral nutrition patients. OR = odds ratio, CI = confidence interval

Variables	OR (95% CI)
NCRP7>100	4.33 (1.12-28.76, p=0.063)

As statistical significance was not achieved, no further analysis of its predictive performance was carried out.

4.2.2. Multivariate logistic regression Analysis

Then, a multivariate analysis was conducted to explore the independent role of CRP along with other clinical and nutritional variables in predicting the need for VDS. These logistic regressions were fit using Firth's penalised logistic regression to reduce bias in small sample sizes. No multivariate analysis was performed for MI due to the very low number of cases (only 6 out of 213 individuals).

VDS multivariate model – CRP1

The full model included variables with $p < 0.2$ in univariate analyses: CRP on admission, COPD, age, type of patient, neoplasia, chronic liver disease, APACHE, SOFA, Nutric_score, SAPS, SGA, EN before 48h, type of nutritional support, mechanical ventilation, MI, patient at risk, RRT.

Four models were compared:

- Full model with all eligible variables
- Model with only significant predictors ($p < 0.05$)
- A reduced model that only includes significant coefficients from the full model.
- Stepwise model.

The stepwise model was the model selected and is presented in **Table 10**. CRP on admission was not retained in the final model, suggesting that it does not independently predict the requirement of VDS. Predictors such as SOFA were statistically significant ($p < 0.001$). Regarding the type of nutritional support, PN-EN was also a statistically significant predictor ($p = 0.005$). This latter variable exhibited a high OR and wide CI, suggesting possible model instability due to the limited number of cases within this group.

Table 10: Multivariate logistic regression for VDS prediction (admission predictors). OR = odds ratio, CI = confidence interval

Characteristic	OR	95% CI	p-value
CLD			
No	—	—	
Yes	0.22	0.03, 1.65	0.13
APACHEII	0.95	0.88, 1.02	0.14
SOFA1	1.60	1.30, 2.05	<0.001
SGA			
Good	—	—	
Bad	0.35	0.11, 1.03	0.057
NSGT			
EN	—	—	
EN - PN	0.85	0.14, 9.27	0.9
PN	2.06	0.54, 9.44	0.3
PN - EN	11.6	1.93, 142	0.005

Abbreviation: CI = Confidence Interval

No multicollinearity was found between variables (VIF < 2).

This multivariate model showed good discriminatory ability, with an AUC of 0.8 (**Figure 11**) (IC95%: 0.6-0.9; SD = 0.07). The optimal cutoff point of the model's predicted probability was 0.8, which results in a sensitivity of 70.4% and a specificity of 81.8%, as shown in **Table 11**. That reflects a good balance in discrimination. However, the negative predictive value was low (36%), which means there is a high rate of false negatives: when the model predicts that a patient will not require a VDS, it is frequently wrong.

The overall accuracy was 72.3%. The kappa index was 0.35, indicating fair agreement between the model's predictions and the actual observations. McNemar's test was significant (p = 0.002), suggesting a systematic bias in predicting negatives versus positives.

To summarise, the model is good at confirming VDS when it predicts it (PPV = 95%). However, further validations with more balanced populations or adjustments are necessary to improve the detection of patients who do not require VDS.

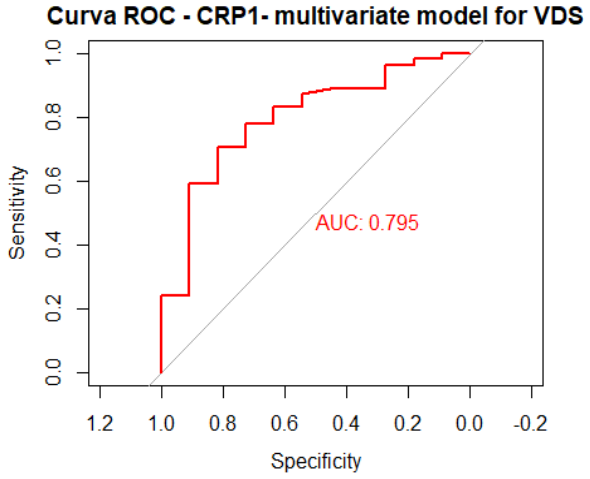


Figure 11: ROC curve to evaluate the multivariate model for VDS

Table 11: ROC analysis of the multivariate model for predicting VDS. AUC: area under the curve, SD: Standard deviation, CI: confidence interval.

Variable	AUC	SD	CI_95	Cutoff	Sensitivity	Specificity
CRP1- multivariate model for VDS	0.8	0.07	(0.6-0.9)	0.8	70.4	81.8

VDS multivariate model – CRP 7

The same process was applied to build the best multivariate logistic model using the variables collected on the seventh day. The following variables were included: CRP7, sex, type of patient, immunosuppression, CLD, APACHE, SOFA, SAPSII, SGA, Time until nutritional support, Enteral support before 48h, type of nutritional support, Mechanical ventilation, MI, vomit, mean kcal first week, mean kcal, mean protein first week and mean protein

The stepwise model was selected again (**Table 12**). In this case, the measurement of CRP on the seventh day was included in the model, even though this was not significant ($p = 0.2$), indicating that its independent effect was inconclusive. However, SOFA on admission was significantly associated with a higher risk of needing VDS (OR = 1.53; IC95%: 1.25-1.94; $p < 0.001$), indicating that for each value SOFA increases, the risk of needing VDS increases by 53%.

Interestingly, according to the SGA, patients with poor nutritional status had a lower probability of requiring VDS (OR= 0.35; IC95: 0.12-0.99; p = 0.048). Regarding the type of nutritional support, patients receiving PN-EN exhibited a significantly higher risk of needing VDS compared to those receiving EN (OR = 10.6; IC95%: 1.61-138; p = 0.011), although the wide CI suggest caution, likely due to the small number of patients in this category.

Additionally, the proteins administered during the first week showed a trend towards an increased risk of VDS. However, this variable did not reach statistical significance (OR = 4.25; IC95%: 0.86-23.7; p = 0.076).

Table 12: Multivariate logistic regression for VDS with significant variables on the seventh day. OR = odds ratio, CI = confidence interval

Characteristic	OR	95% CI	p-value
NCRP7			
<100	—	—	
>100	2.27	0.73, 8.05	0.2
SOFA1	1.53	1.25, 1.94	<0.001
SGA			
Good	—	—	
Bad	0.35	0.12, 0.99	0.048
NSGT			
EN	—	—	
EN - PN	2.12	0.25, 53.8	0.5
PN	1.99	0.51, 8.98	0.3
PN - EN	10.6	1.61, 138	0.011
MI			
No	—	—	
Yes	0.07	0.00, 1.64	0.094
protein_1w	4.25	0.86, 23.7	0.076

Abbreviation: CI = Confidence Interval

This multivariate model demonstrated good discriminatory ability, with an AUC of 0.8 (95% CI: 0.6-1), indicating that the model classified correctly patients with and without VDS in 80% of the cases (**Figure 12, Table 13**).

Its overall accuracy was 86.2% with a sensitivity of 88.9% and a specificity of 72.7%, suggesting a strong performance in detecting true positives, while it maintains an acceptable discrimination of true negatives. The fact that PPV was high (94.1%) indicates that most patients predicted to need VDS truly required it. However, the NPV was low (57.1%), suggesting a higher risk of false negatives. There is a moderate

agreement between the model's predictions and the actual observations, given the Kappa index (0.56), and the McNemar test did not reveal significant classification errors (p = 0.505)

To summarise, the model exhibits good performance in detecting patients requiring VDS. However, its practical utility could benefit from some improvements in the detection of negatives or from additional validations in more balanced samples. That means to try this model in populations where there is a higher prevalence of patients not requiring VDS, given that the current dataset is predominantly comprised of patients who need VDS.

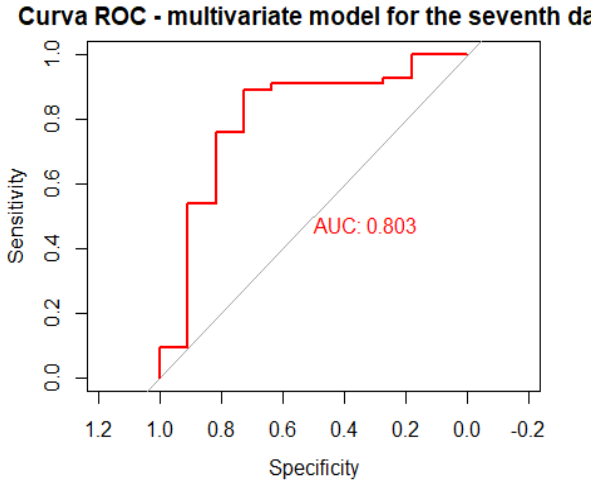


Figure 12: ROC curve to evaluate the multivariate model for VDS

Table 13: ROC analysis for multivariate model on day 7. AUC: area under the curve, SD: Standard deviation, CI: confidence interval.

Variable	AUC	SD	CI_95	Cutoff	Sensitivity	Specificity
Multivariate model for the seventh day	0.8	0.09	(0.6-1)	0.63	88.9	72.7

Multivariate logistic regression for enteral patients

In this case, the following variables were considered for inclusion: CRP7, sex, type of patient, CLD, SOFA, SGA, Time until nutritional support, EN before 48h, type of nutritional support, LOS, GRV, diarrhoea, RRT, caloric intake (first week and overall).

After applying the same selection process, the final stepwise model excluded CRP7, suggesting that CRP does not have an independent influence in predicting the need for VDS in this subgroup (**Table 14**).

Medical patients exhibited a trend towards a greater risk of requiring VDS compared to surgical patients, although this increase did not reach statistical significance (p = 15; OR = 3.62). Trauma patients had a significantly higher risk (OR = 36.2; 95% CI 1.48-7429; p = 0.025), but the extremely wide CI indicates considerable uncertainty, likely due to the very small number of patients in this group.

Finally, the SOFA score seems to be a strong and independent predictor of the event of needing VDS, where each additional point on the SOFA scale is associated with more than double the risk of the event (p <0.001; OR = 2.08; CI 1.51-3.20). The SGA variable suggested that the patients with poor nutritional status tended to have a lower probability of requiring VDS, however, this association was not significant (p = 0.12; OR = 0.32)

Table 14: Multivariate logistic regression for VDS with significant variables on the seventh day in patients receiving EN. OR = odds ratio, CI = confidence interval

Characteristic	OR	95% CI	p-value
STATUS3			
Surgery	—	—	
Medical	3.62	0.63, 20.6	0.15
Trauma	36.2	1.48, 7,429	**0.025**
SOFA1	2.08	1.51, 3.20	**<0.001**
SGA			
Good	—	—	
Bad	0.32	0.07, 1.32	0.12

Abbreviation: CI = Confidence Interval

This multivariate model presents a moderate discriminative ability (AUC = 0.74; 95% CI: 0.5-0.9; SD: 0.1) (**Figure 13**). With a cutoff of 0.52, the model reached a sensitivity of 84.4% and a specificity of 66.7% (**Table 15**), which reflects a good ability to correctly identify patients with VDS, even though there is a moderate false positive rate.

The overall accuracy was 80.5%, and the kappa coefficient (0.47) showed moderate agreement between the model's predictions and the observed values. Furthermore, the McNemar's test (p = 0.72) does not detect any systematic classification errors.

On the other hand, the PPV of the model was 90%, while the NPV was 54.5%, indicating some limitations in confidently ruling out VDS.

In summary, the model demonstrates good performance in detecting patients who require VDS but has limitations with negative cases. Consequently, this model may only be useful in contexts where maximising detection is preferred, even at the cost of accepting some false positives.

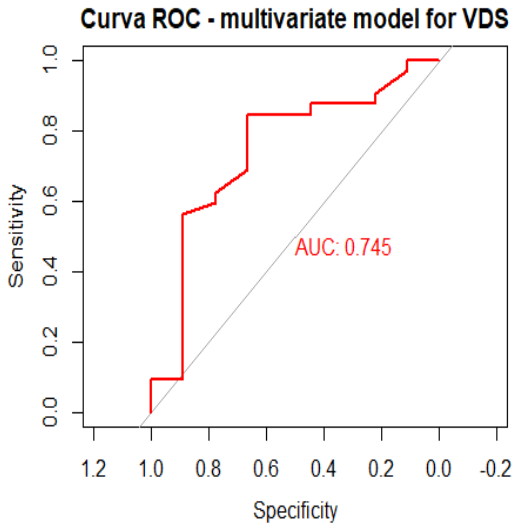


Figure 13: ROC curve to evaluate the multivariate model for VDS

Table 15: ROC analysis: performance of the multivariate model of significant variables on the seventh day for predicting VDS in enteral patients. AUC: area under the curve, SD: Standard deviation, CI: confidence interval.

Variable	AUC	SD	CI_95	Cutoff	Sensitivity	Specificity
Multivariate model for VDS	0.74	0.1	(0.5-0.9)	0.52	84.4	66.7

4.3. Survival analysis

A survival analysis was performed to determine which factors are associated with a reduction of CRP concentration by the seventh day in the ICU, specifically focusing on the type and duration of nutritional support received.

The follow-up time was defined as the number of days each patient remained on nutritional support, and the event of interest was the decrease in CRP concentration by day 7, considered a marker of inflammatory improvement. Patients who did not show this reduction during the observation period were censored.

This methodological approach allowed the evaluation of whether the type of nutritional support (enteral, parenteral, or combined nutrition) influences the time to inflammatory improvement and identifies other potential clinical or nutritional factors that might be associated with achieving this reduction in CRP levels.

4.3.1. Overall dataset

Hazard Box-Cox regression

As in multivariate logistic regression, an initial model with the variables with a p-value ≤ 0.2 was fitted. This was compared to a model including only significant variables ($p < 0.05$), a reduced model including only significant coefficients from the initial model (a reduced model), and a model chosen by a stepwise regression.

The step model was selected as the final model (**Table 16**). Some variables were significantly associated as follows:

- **Type of patient**: Trauma patients had a lower probability of CRP reduction compared to surgical patients (HR = 0.37; 95% CI: 0.14-0.94; p = 0.036), which suggests a longer inflammatory process and a longer duration of nutritional support to achieve it. Nevertheless, no significant differences were observed between medical and surgical patients (HR = 0.91; 95% CI: 0.56-1.46; p = 0.7).
- **Patient with malnutrition**: Patients with poor nutritional status showed a higher rate of CRP reduction (HR = 1.54; 95% CI: 1.07-2.23; p = 0.012). This might be possible due to a more intensive nutritional intervention in this group.
- **Type of Nutritional Support**. A combination of EN-PN was associated with a lower rate of CRP reduction (HR = 0.36; 95% CI: 0.17-0.8; p = 0.012) compared with only enteral nutrition
- **Female Sex**: Females show a higher rate of reduction of CRP, but this tendency was only marginally significant (HR = 1.41; 95% CI: 0.98-2.04; p=0.064)

Table 16: Proportional hazard Boxcox regression: factors associated with time to CRP reduction on the seventh day within nutritional support. HR = Hazard ratio, CI = confidence interval

Characteristic	HR	95% CI	p-value
SEX			
M	—	—	
F	1.41	0.98, 2.04	0.064
STATUS3			
Surgery	—	—	
Medical	0.91	0.56, 1.46	0.7
Trauma	0.37	0.14, 0.94	**0.036**
SGA			
Good	—	—	
Bad	1.54	1.07, 2.23	**0.021**
NSGT			
EN	—	—	
EN - PN	0.36	0.17, 0.80	**0.012**
PN	0.90	0.46, 1.75	0.8
PN - EN	0.71	0.43, 1.16	0.2

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

No multicollinearity was detected (VIF < 2).

Since all variables were categorical, the linearity assumption was not applicable. However, the proportionality assumption was evaluated, as shown in **Figure 14**, by the Schoenfeld residuals test.

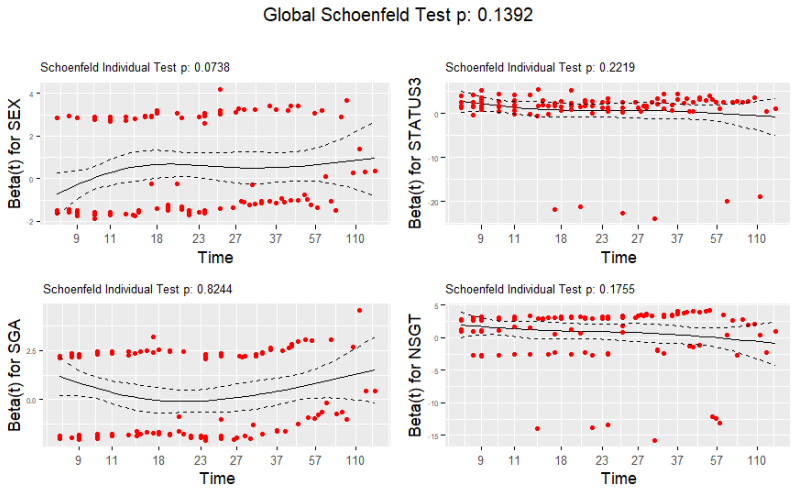


Figure 14: Schoenfeld residuals test

There are no significant violations because all the individual values were higher than 0.05. Furthermore, the global test is above 0.05 as well, indicating that all variables meet the proportionality assumption.

4.3.2. Enteral Nutrition Subgroup

Hazard Box-Cox regression

A similar procedure was applied to the subset of patients who received exclusive EN. The stepwise model was again selected. Significant findings (**Table 17**) include:

- **Type of patient**: trauma patients had a significantly lower probability of achieving a CRP reduction compared to surgical patients (HR: 0.15; CI: 0.05-0.53; p = 0.003), which suggests that inflammation persists longer in this group and requires more days of nutritional support. However, no significant differences were observed between medical and surgical patients (HR: 1.37; 95% CI: 0.67-2.79; p =0.4).
- **Nutritional status**: SGA showed that patients with poor nutritional status had a higher probability of CRP reduction than patients who presented good nourishment (HR: 1.57; 95% CI: 1.01- 2.46; p = 0.047).
- **Gastrointestinal complications**: Patients with an elevated GRV were associated with lower probabilities of decreasing CRP levels below 100mg/L (HR: 0.27; 95% CI: 0.12-0.62; p = 0.002). Having diarrhoea was also associated with a lower probability of achieving this reduction, but it was not significant (HR: 0.54; 95% CI: 0.27-1.08; p = 0.083).

- **RRT**: Patients who received renal replacement therapy showed a trend towards a higher probability of achieving it, even though it did not reach a statistical significance (HR: 1.67; 95% CI: 0.91-3.05; p = 0.095).
- **LOS**. Longer stays were significantly associated with a lower probability of early CRP reduction (HR: 0.97; 95% CI: 0.96-0.98; p < 0.001). These patients might be facing a severe or complicated clinical course.

Table 17: Proportional hazard Boxcox regression: factors associated with time to CRP reduction on the seventh day in enteral nutrition patients. HR = Hazard ratio, CI = confidence interval

Characteristic	HR	95% CI	p-value
STATUS3			
Surgery	—	—	
Medical	1.37	0.67, 2.79	0.4
Trauma	0.15	0.05, 0.53	**0.003**
SGA			
Good	—	—	
Bad	1.57	1.01, 2.46	**0.047**
GRV			
No	—	—	
Yes	0.27	0.12, 0.62	**0.002**
DEN			
No	—	—	
Yes	0.54	0.27, 1.08	0.083
RRT			
No	—	—	
Yes	1.67	0.91, 3.05	0.095
LOS	0.97	0.96, 0.98	**<0.001**

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

No multicollinearity was detected (VIF < 2).

The proportional hazards assumption was evaluated, as shown in **Figure 15**, by the Schoenfeld residuals test. There are no significant violations because all the individual values were higher than 0.05. Furthermore, the global test is above 0.05 as well, indicating that all variables meet it.

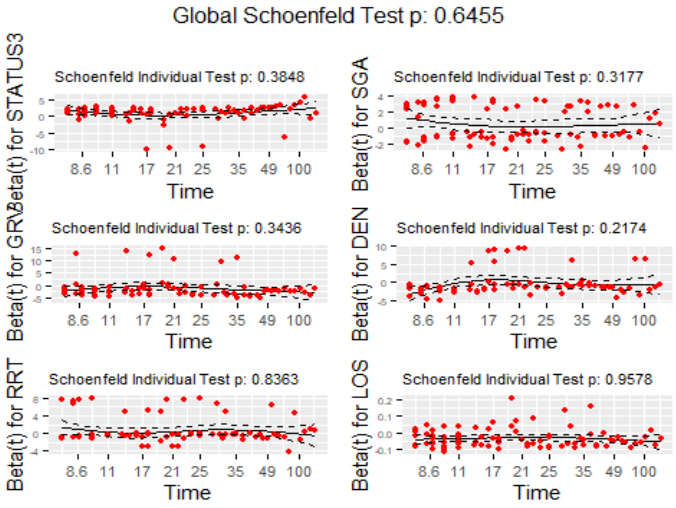


Figure 15: Schoenfeld residuals test

To assess the linearity assumption, Martingale residuals were used (**Figure 16**). The smoothed curve of the residuals remains close to zero across the range of values, which shows that there is no evidence of systematic patterns of deviation, and no clear evidence of violation of the linearity assumption was observed.

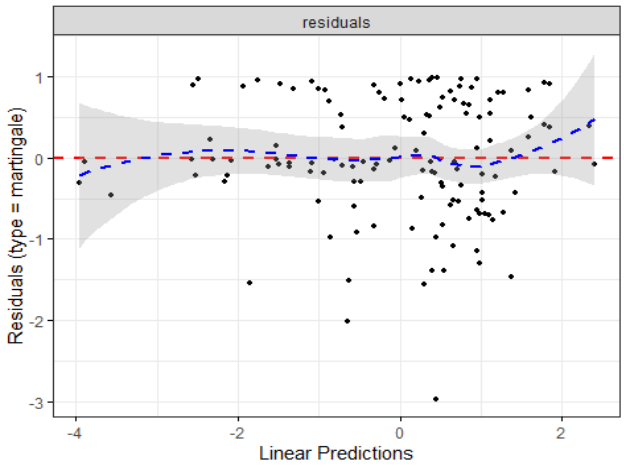


Figure 16: Martingale residuals to test the linearity assumption

5. Discussion.

5.1. CRP and Clinical Features in All ICU Patients

The higher proportion of COPD as a comorbidity among patients with elevated CRP levels at admission aligns with previous evidence indicating a state of persistent systemic inflammation in this population. A chronic inflammation in COPD has been linked to disease progression, morbidity, and mortality, which may explain the elevated CRP concentrations found in these patients (61).

On the other hand, a higher proportion of patients with CLD showed CRP concentrations below 100mg/L. At first glance, this may appear counterintuitive; however, in advanced stages of CLD, the liver undergoes structural changes (such as extensive fibrosis and a marked reduction in functional hepatocytes) that limit the hepatic synthesis of CRP, leading to a reduced inflammatory response(62). These findings remained even on the seventh day.

The trajectory of CRP concentrations also differs across the admission categories. Surgical patients showed higher CRP levels on ICU entry, likely reflecting an early postoperative inflammatory peak. Previous studies have observed a rise in their inflammation within 48-72 hours post-surgery(63). Hence, the earlier elevation exhibited in this study could be explained by a delay between surgery and ICU admission, reaching the peak when the first CRP measurement is taken. In contrast, trauma patients exhibited a delayed increase in CRP levels and showed a remaining elevated concentration on day 7.

Severity scores such as SOFA and APACHE were consistently higher in patients with CRP concentrations above 100 mg/L. Both variables showed a statistically significant correlation, however, they remained weak, suggesting that while inflammation is associated with illness severity, CRP alone may not reflect organ dysfunction. Previous studies have explored the value of combining CRP with severity scores to improve prognostic accuracy, specifically in infectious conditions (64–66). These low correlation coefficients suggest that CRP alone may not be a reliable marker of disease severity in heterogeneous ICU populations.

The observed association between high inflammatory status and increased NUTRIC scores underscores how inflammation contributes to nutritional risk in critically ill patients.

Elevated NUTRIC scores have been consistently associated with poor outcomes, highlighting the importance of starting early nutrition. Despite this, patients with increased levels of inflammation were less likely to receive early enteral nutrition (67). This delay was more pronounced by day 7 and often coincided with parental or combined nutritional strategies. These patterns likely reflect clinical complications that make enteral feeding more difficult. These clinical scenarios underline the complexity of nutritional decisions for patients with severe inflammation.

5.2. CRP and Clinical Features in Patients Receiving Enteral Nutrition

Among patients nourished with EN (whether exclusively or in combination with PN), several clinical and nutritional factors were associated with elevated CRP levels at admission and on the seventh day. No significant differences were found in baseline characteristics such as age, sex, or BMI. However, patients with an elevated CRP concentration at admission had a higher prevalence of COPD, as well as higher SOFA and NUTRIC scores, which suggests more severe clinical status and greater nutritional risk.

On the seventh day, a larger proportion of medical patients exhibited CRP levels below 100 mg/L, whereas the trauma patients demonstrated the opposite trend. Although there is no significant difference in calorie or protein intake between the groups, patients with higher CRP concentrations tended to receive fewer calories during the first week of EN. This may indicate reduced tolerance to EN or more frequent interruptions, possibly due to complications such as an increased GRV. Among this group, the most significant outcome associated with a CRP above 100 mg/l was the need for VDS.

No significant difference in mortality or LOS were found either in the full dataset or within the EN group alone. Thus, these findings suggest the need for further studies with larger samples or longer follow-up to confirm these associations.

These associations remained consistent even when including patients who later required parental support. The addition of these patients did not substantially alter the relationships observed between CRP levels, clinical severity, nutritional intake or outcomes. This may suggest that the link between systemic inflammation and nutritional markers is stable and not limited to patients receiving only EN.

5.3. CRP as a Predictor of Outcomes

The association between elevated CRP levels and adverse outcomes emphasise the potential role of inflammation in the clinical course of critically ill patients. Especially, the observation that all patients who developed MI had CRP concentrations above 100 mg/L underscores the possible utility of CRP as an early warning marker in this subgroup. However, given the very small number of cases in this cohort, this finding must be interpreted cautiously because even though Firth's penalised logistic regression was used, the resulting wide confidence intervals suggest considerable uncertainty, highlighting the need for further validation in larger datasets.

Although CRP levels (both at admission and on the seventh day) were associated with clinical severity indicators such as the use of VDS, their predictive accuracy was limited. In this study, even the models that achieved high sensitivity did so at the expense of reduced specificity, which limits their clinical applicability for confidently ruling out low-risk patients. These findings reinforce the idea that CRP should not be regarded as a stand-alone predictor, but rather as a complementary marker integrated into multivariate models.

PN-EN showed a consistent association with worse outcomes, such as increased need for VDS. Nevertheless, there was also a small number of patients in this subgroup. Therefore, this finding should be interpreted cautiously as it may be influenced by residual confounding or selection bias.

In conclusion, whereas CRP-based models may help with identifying patients at risk of these outcomes, they should be used in combination with other clinical variables and require further validation in more balanced populations, particularly with a higher proportion of individuals with a lower risk of complications. On the other hand, due to the small number of cases, MI could not be included in multivariate models, which limits to draw robust conclusions about its predictors.

5.4. Dynamics of inflammation: Time-to-event Analysis

The proportional hazard Cox regression identified several clinical and nutritional factors associated with a lower likelihood of achieving CRP concentrations below 100 mg/L by the seventh day. Female patients tended to reduce their inflammation earlier than males, although this was not statistically significant. Trauma patients had statistically significantly lower probabilities of reducing their inflammation levels by the seventh day.

As stated, trauma patients exhibited their peak on the third day, followed by only a slight reduction on the seventh day.

Besides, patients who received PN or EN-PN were less likely to reach CRP levels below 100mg/L compared to those receiving EN solely. This might reflect more severe inflammatory states and gastrointestinal complications, which difficult the use of EN exclusively. Similar results were obtained by Luo et al. 2020 who reported longer LOS in patients receiving combined nutritional support (68).

Unexpectedly, patients classified as malnourished according to SGA showed a higher probability of reducing their CRP levels by the seventh day. This finding contrasts with initial expectations, as a poorer baseline status would typically be associated with worse outcomes. This could reflect a greater therapeutic effort by the clinical team, focusing on these more vulnerable individuals. However, it is also possible that this association is influenced by confounding factors not included in the current analysis.

It is noteworthy that patients considered well-nourished tended to present with more pronounced inflammation at admission. This could suggest that the better outcomes observed in malnourished patients are not solely due to nutritional status, but also to lower systemic inflammation. This aligns with existing literature that suggests that patients with very high levels of CRP may not respond to nutritional support or treatment.(34,35).

Among patients fed exclusively by EN, similar trends were observed. In addition, GRV was associated with a lower probability of CRP reduction. Although GRV is considered a clinical marker of EN tolerance, some studies question its reliability, suggesting a weak correlation with actual indicators of intolerance, such as delayed gastric emptying or abdominal distension(69).

To conclude, the LOS was longer in patients who did not reduce their CRP levels by the seventh day, potentially indicating a more severe disease course in this group.

6. Conclusions

The main findings in this work are as follows:

- **CRP reflects clinical severity and inflammatory response at ICU admission**: higher CRP levels (> 100 mg/L) were associated with comorbidities such as COPD, increased SOFA and APACHE II scores, and the type of patient.
- **CRP levels influence and are influenced by the type and timing of nutritional support**: patients who received only enteral nutrition showed better inflammatory evolution. On the other hand, the patients who required PN or EN-PN had elevated CRP levels on the seventh day. Furthermore, these patients tended to receive nutritional support later.
- **CRP alone has limited predictive value for adverse outcomes**: CRP should be included in multivariate models alongside other clinical variables.
- **Time-to-event analysis reveals important patterns in inflammatory resolutions**: Patients with trauma who required EN-PN had a lower probability of reducing CRP levels.

6.1. Objective achievement

The study results confirm that all the contemplated objectives are successfully covered.

- **Logistic Regression and ROC analysis** were applied to determine if CRP on admission and the seventh day can predict the occurrence of complications (MI) or bad outcomes (VDS).
- **Proportional hazard Cox regression** was employed to evaluate how the nutritional support selected affected the inflammatory response. Patients fed via PN or EN-PN were less likely to reduce their CRP by the seventh day.
- **CRP evolution** was described based on the type of patient (surgical, medical, trauma), nutritional status and type of nutritional support.
- **Multivariate logistic regression** demonstrated that patients with elevated CRP were frequently fed via PN or EN-PN; this was associated with a greater requirement of VDS.
- **Descriptive tables** were used to compare the clinical evolution of the patients based on their inflammatory profile and the nutritional support they received, finding that the patients with highly inflamed profiles exhibited worse outcomes and response to nutrition therapy.

6.2. Critical Analysis

Throughout the development of this Master's Final Project, the work plan considered at the beginning was largely respected. However, the final stages, where the final report was drafted and refined, required more time than initially anticipated. Despite this delay, all required documents for the final continuous assessment (PEC) were submitted on schedule.

The methodology employed in this research was deemed suitable for addressing the project's objectives. One of the primary challenges was managing the limited size of the dataset when logistic regression was used. However, this issue, which fell within the anticipated methodological risks, was resolved through a new literature review that identified Firth's penalised logistic regression as an alternative statistical method.

On the other hand, this study has contributed to the generation of knowledge that may, in the long term, help with identifying new strategies to minimise complications associated with MNT in critically ill patients with elevated inflammation. Therefore, this research is considered to have had a positive impact on the Sustainable Development Goals described in the introduction sections.

Similarly, the patient's anonymity was preserved throughout the study, and the language used is considered accessible to professionals from various disciplines, concluding that no adverse ethical or social impact is considered to have arisen in this work.

6.3. Limitations and future perspectives

This study has several limitations that must be highlighted. Firstly, the retrospective and observational design restricts the ability to establish causal relationships between CRP concentrations and the clinical and nutritional factors examined. Though multivariate analyses were conducted to account for potential confounders, residual confounding cannot be excluded, including omitted variables from our dataset.

Second, even if the sample size was adequate for most analyses, it was limited in certain subgroups, especially in patients who developed MI or received PN-EN. The small number of MI may have resulted in unstable estimates and prevented its inclusion in multivariate models.

Finally, in this research, CRP was the only inflammatory marker analysed, which may provide an incomplete picture of the inflammatory status. Other biomarkers might

complement the information provided by CRP, especially in the early identification of complications or outcomes.

7. Glossary

Initial	Meaning
AMI	Acute Myocardial Infarction
APACHE II	Acute Physiology and Chronic Health Evaluation II
CLD	Chronic Liver Disease
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CTI	Catheter-Related Infection
EN	Enteral Nutrition
hsCRP	Highly sensitive C-reactive Protein
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
IQR	Interquantile Range
MI	Mesenteric Ischemia
ML	Maximum Likelihood
MNT	Medical Nutrition Therapy
NPV	Negative Predictive Value
OR	Odds Ratio
OR	Odds Ratio
PN	Parenteral Nutrition
PPV	Positive Predictive Value
RRT	Renal Replacement Therapies
RTI	Respiratory Tract Infection
SAPS II	Simplified Acute Physiology Score II

SD	Standard Deviation
SGA	Subjective Global Assessment
SOFA	Sequential Organ Failure Assessment
VDS	Vasoactive Drug Support

8. Bibliography

1. Hill A, Heyland DK, Ortiz Reyes LA, Laaf E, Wendt S, Elke G, et al. Combination of enteral and parenteral nutrition in the acute phase of critical illness: An updated systematic review and meta-analysis. Journal of Parenteral and Enteral Nutrition. 2022 Feb 1;46(2):395–410.

2. Loss SH, Teichmann P do V, Pedroso de Paula T, Gross L de A, Costa VL, Lisboa BO, et al. Nutrition as a risk for mortality and functionality in critically ill older adults. Journal of Parenteral and Enteral Nutrition. 2022 Nov 1;46(8):1867–74.

3. Elke G, van Zanten ARH, Lemieux M, McCall M, Jeejeebhoy KN, Kott M, et al. Enteral versus parenteral nutrition in critically ill patients: An updated systematic review and meta-analysis of randomized controlled trials. Crit Care. 2016 Apr 29;20(1).

4. Baik SM, Kim M, Lee JG. Comparison of Early Enteral Nutrition Versus Early Parenteral Nutrition in Critically Ill Patients: A Systematic Review and Meta-Analysis. Vol. 17, Nutrients . Multidisciplinary Digital Publishing Institute (MDPI); 2025.

5. Flordelís Lasierra JL, Montejo González JC, López Delgado JC, Zárate Chug P, Martínez Lozano-Aranaga F, Lorencio Cárdenas C, et al. Enteral nutrition in critically ill patients under vasoactive drug therapy: The NUTRIVAD study. Journal of Parenteral and Enteral Nutrition. 2022 Aug 1;46(6):1420–30.

6. Lopez-Delgado JC, Grau-Carmona T, Mor-Marco E, Bordeje-Laguna ML, Portugal-Rodriguez E, Lorencio-Cardenas C, et al. Parenteral Nutrition: Current Use, Complications, and Nutrition Delivery in Critically Ill Patients. Nutrients. 2023 Nov 1;15(21).

7. Alsharif DJ, Alsharif FJ, Aljuraiban GS, Abulmeaty MMA. Effect of supplemental parenteral nutrition versus enteral nutrition alone on clinical outcomes in critically ill adult patients: A systematic review and meta-analysis of randomized controlled trials. Vol. 12, Nutrients. MDPI AG; 2020. p. 1–16.

8. Servia-Goixart L, Lopez-Delgado JC, Grau-Carmona T, Trujillano-Cabello J, Bordeje-Laguna ML, Mor-Marco E, et al. Evaluation of Nutritional Practices in

the Critical Care patient (The ENPIC study): Does nutrition really affect ICU mortality? Clin Nutr ESPEN. 2022 Feb 1;47:325–32.

9. Rahali FZ, Mimouni N, Boukhira A, Chellak S. The Clinical Utility of Standard and High-Sensitivity C-Reactive Protein: A Narrative Review. SN Compr Clin Med. 2024 Jun 5;6(1).

10. Qu R, Hu L, Ling Y, Hou Y, Fang H, Zhang H, et al. C-reactive protein concentration as a risk predictor of mortality in intensive care unit: a multicenter, prospective, observational study. BMC Anesthesiol. 2020 Dec 1;20(1).

11. Kamarul Zaman M, Syakilla Raja Noor Azman R, Pei Chien T, Shahnaz Hasan M, Puncak Alam B, Darul Ehsan S. Diarrhoea Risk Factors in Critically Ill Patients Receiving Enteral Nutrition. Vol. 17, Malaysian Journal of Medicine and Health Sciences. 2021.

12. Heilmann E, Gregoriano C, Schuetz P. Biomarkers of Infection: Are They Useful in the ICU? Semin Respir Crit Care Med. 2019;40(4):465–75.

13. Riviati N, Legiran, Indrajaya T, Saleh I, Ali Z, Irfannuddin, et al. Serum Albumin as Prognostic Marker for Older Adults in Hospital and Community Settings. Vol. 10, Gerontology and Geriatric Medicine. SAGE Publications Inc.; 2024.

14. Moman RN, Gupta N, Varacallo MA. StatPearls [Internet]. 2022 [cited 2025 Mar 24]. Physiology, Albumin. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459198/

15. Bai M, Wu Y, Ji Z, Wang S, Lin Z, Pan S, et al. Prognostic value of C-reactive protein/albumin ratio in neurocritically ill patients. Minerva Anestesiol. 2019 Dec 1;85(12):1299–307.

16. Park JE, Chung KS, Song JH, Kim SY, Kim EY, Jung JY, et al. The C-reactive protein/albumin ratio as a predictor of mortality in critically ill patients. J Clin Med. 2018 Oct 1;7(10).

17. Mousa DB, Moussa HH, Elgazzar MA, Hani BM, El-Hamid AMA. Predicting early mortality in critically ill patients: the role of the CRP/albumin ratio and its relationship with the APACHE II score. The Egyptian Journal of Bronchology [Internet]. 2025 Mar 10;19(1):23. Available from: https://ejb.springeropen.com/articles/10.1186/s43168-025-00379-1

18. Pettilä V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Med. 2002;28(9):1220–5.

19. Justiz Vaillant AA, Qurie A. StatPearls [Internet]. 2022 [cited 2025 Mar 13]. Interleukin. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499840/

20. Weidhase L, Wellhöfer D, Schulze G, Kaiser T, Drogies T, Wurst U, et al. Is Interleukin-6 a better predictor of successful antibiotic therapy than procalcitonin and C-reactive protein? A single center study in critically ill adults. BMC Infect Dis. 2019 Feb 13;19(1).

21. Li X, Yang Y, Zhang B, Lin X, Fu X, An Y, et al. Lactate metabolism in human health and disease. Signal Transduct Target Ther. 2022 Dec 1;7(1).

22. Cornelissen CG, Frechen DA, Schreiner K, Marx N, Krüger S. Inflammatory parameters and prediction of prognosis in infective endocarditis. BMC Infect Dis. 2013 Jun 15;13(1).

23. Suarez-De-La-Rica A, Maseda E, Anillo V, Tamayo E, Garcia-Bernedo CA, Ramasco F, et al. Biomarkers (procalcitonin, C reactive protein, and lactate) as predictors of mortality in surgical patients with complicated intra-abdominal infection. Surg Infect (Larchmt). 2015 Jun 1;16(3):346–51.

24. Rizo-Téllez SA, Sekheri M, Filep JG. C-reactive protein: a target for therapy to reduce inflammation. Front Immunol. 2023;14.

25. Bouayed MZ, Laaribi I, Chatar CEM, Benaini I, Bouazzaoui MA, Oujidi Y, et al. C-Reactive Protein (CRP): A poor prognostic biomarker in COVID-19. Front Immunol. 2022 Nov 14;13.

26. Fazal M. C-Reactive Protein a Promising Biomarker of COVID-19 Severity. The Korean Journal of Clinical Laboratory Science. 2021 Sep 30;53(3):201–7.

27. Chalmers JD, Singanayagam A, Hill AT. C-Reactive Protein Is an Independent Predictor of Severity in Community-acquired Pneumonia. American Journal of Medicine. 2008 Mar;121(3):219–25.

28. Reny JL, Vuagnat A, Ract C, Benoit MO, Safar M, Fagon JY. Diagnosis and follow-up of infections in intensive care patients: Value of C-reactive protein compared with other clinical and biological variables*. 2002;30(3).

29. Ranzani OT, Prada LF, Zampieri FG, Battaini LC, Pinaffi J V., Setogute YC, et al. Failure to reduce C-reactive protein levels more than 25% in the last 24 hours before intensive care unit discharge predicts higher in-hospital mortality: A cohort study. J Crit Care. 2012;27(5):525.e9-525.e15.

30. Nehring SM, Goyal A, Patel BC. StatPearls [Internet]. 2025 [cited 2025 Mar 7]. C Reactive Protein. [Updated 2023 Jul 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441843/

31. Tanriverdi H, Tor MM, Kart L, Altin R, Atalay F, Sumbsümbüloglu V. Prognostic value of serum procalcitonin and C-reactive protein levels in critically ill patients who developed ventilator-associated pneumonia. Ann Thorac Med. 2015 Apr 1;10(2):137–42.

32. Bogaty P, Boyer L, Simard S, Dauwe F, Dupuis R, Verret B, et al. Clinical Utility of C-Reactive Protein Measured at Admission, Hospital Discharge, and 1 Month Later to Predict Outcome in Patients With Acute Coronary Disease. The RISCA (Recurrence and Inflammation in the Acute Coronary Syndromes) Study. J Am Coll Cardiol. 2008 Jun 17;51(24):2339–46.

33. Al-Subaie N, Reynolds T, Myers A, Sunderland R, Rhodes A, Grounds RM, et al. C-reactive protein as a predictor of outcome after discharge from the intensive care: A prospective observational study. Br J Anaesth. 2010;105(3):318–25.

34. Stumpf F, Keller B, Gressies C, Schuetz P. Inflammation and Nutrition: Friend or Foe? Vol. 15, Nutrients. MDPI; 2023.

35. Merker M, Felder M, Gueissaz L, Bolliger R, Tribolet P, Kägi-Braun N, et al. Association of Baseline Inflammation With Effectiveness of Nutritional Support Among Patients With Disease-Related Malnutrition A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2020 Mar 10;3(3):E200663.

36. Marik PE. Nutritional Support among Medical Inpatients - Feed the Cold (and Malnourished) and Starve the Febrile. Vol. 2, JAMA Network Open. American Medical Association; 2019.

37. Schetz M, Casaer MP, den Berghe G Van. Does artificial nutrition improve outcome of critical illness? Crit Care. 2013;17(302).

38. Tang M, Yanhong H. The impact of early enteral nutrition care on plasma levels of albumin (ALB), C-reactive protein (CRP), and complications in patients with severe pancreatitis. Arch Clin Psychiatry. 2022;49(2):472–5.

39. Li B, Liu HY, Guo SH, Sun P, Gong FM, Jia BQ. Impact of early enteral and parenteral nutrition on prealbumin and high-sensitivity C-reactive protein after gastric surgery. Genetics and Molecular Research. 2015;14(2):7130–5.

40. Oh TK, Song IA, Lee JH. Clinical usefulness of C-reactive protein to albumin ratio in predicting 30-day mortality in critically ill patients: A retrospective analysis. Vol. 8, Scientific Reports. Nature Publishing Group; 2018 Dec.

41. Kieler M, Kössler P, Milovic M, Meyer E, Križanová K, Kum L, et al. C-reactive protein and white blood cell count are adverse prognostic markers for patients with advanced cancer on parenteral nutrition in a palliative care unit setting: A retrospective cohort study. Palliat Med. 2022 Mar 1;36(3):540–8.

42. Lopez-Delgado JC, Esteve F, Javierre C, Torrado H, Rodriguez-Castro D, Carrio ML, et al. Evaluation of Serial Arterial Lactate Levels as a Predictor of Hospital and Long-Term Mortality in Patients after Cardiac Surgery. J Cardiothorac Vasc Anesth. 2015 Dec 1;29(6):1441–53.

43. Zhang X, Wang S, Fang S, Yu B. Prognostic Role of High Sensitivity C-Reactive Protein in Patients With Acute Myocardial Infarction. Front Cardiovasc Med. 2021;8.

44. José IB, Leandro-Merhi VA, de Aquino JLB, Mendonça JA. The diagnosis and nutric score of critically ill patients in enteral nutrition are risk factors for the survival time in an intensive care unit? Nutr Hosp. 2019 Sep 1;36(5):1027–36.

45. Elkahwagy DMAS, Kiriacos CJ, Mansour M. Logistic regression and other statistical tools in diagnostic biomarker studies. Clinical and Translational Oncology. 2024 Sep 1;26(9):2172–80.

46. Grund B, Sabin C. Analysis of biomarker data: Logs, odds ratios, and receiver operating characteristic curves. Vol. 5, Current Opinion in HIV and AIDS. 2010. p. 473–9.

47. Szumilas M. Information Management for the Busy Practitioner Explaining Odds Ratios [Internet]. Vol. 19, Sun Life Financial Chair in Adolescent Mental Health. 2010 Aug. Available from: http://www.csm-oxford.org.uk/

48. Suhas S, Manjunatha N, Kumar CN, Benegal V, Rao GN, Varghese M, et al. Firth's penalized logistic regression: A superior approach for analysis of data from India's National Mental Health Survey, 2016. Indian J Psychiatry. 2023 Dec 1;65(12):1208–13.

49. Seshan VE, Gönen M, Begg CB. Comparing ROC curves derived from regression models. Stat Med. 2013 Apr 30;32(9):1483–93.

50. Schober P, Vetter TR. Survival analysis and interpretation of time-to-event data: The tortoise and the hare. Anesth Analg. 2018;127(3):792–8.

51. Turkson AJ, Ayiah-Mensah F, Nimoh V. Handling Censoring and Censored Data in Survival Analysis: A Standalone Systematic Literature Review. Vol. 2021, International Journal of Mathematics and Mathematical Sciences. Hindawi Limited; 2021.

52. Klein JP, Moeschberger ML. 3 Censoring and Truncation. Survival analysis: techniques for censored and truncated data. 2003. p. 63–90.

53. Kartsonaki C. Survival analysis.

54. Hosmer D, Lemeshow S, May S. Applied Survival Analysis: Regression Modeling of Time to Event Data. 2nd ed. Vol. 95, Journal of the American Statistical Association. Wiley-Interscience; 2008.

55. Goel M, Khanna P, Kishore J. Understanding survival analysis: Kaplan-Meier estimate. Int J Ayurveda Res. 2010;1(4):274.

56. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival Analysis Part I: Basic concepts and first analyses. Vol. 89, British Journal of Cancer. 2003. p. 232–8.

57. Jager KJ, Van Dijk PC, Zoccali C, Dekker FW. The analysis of survival data: The Kaplan-Meier method. Kidney Int. 2008 Sep;74(5):560–5.

58. Bland JM, Altman DG. Statistics Notes The logrank test.

59. Deo SV, Deo V, Sundaram V. Survival analysis—part 2: Cox proportional hazards model. Indian J Thorac Cardiovasc Surg. 2021 Mar 1;37(2):229–33.

60. Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. Vol. 48, Antimicrobial Agents and Chemotherapy. 2004. p. 2787–92.

61. Hassan A, Jabbar N. C-reactive Protein as a Predictor of Severity in Chronic Obstructive Pulmonary Disease: An Experience From a Tertiary Care Hospital. Cureus. 2022 Aug 21;

62. Pieri G, Agarwal B, Burroughs AK. C-reactive protein and bacterial infection in cirrhosis [Internet]. Vol. 27, Annals of Gastroenterology. 2014. Available from: www.annalsgastro.gr

63. Plat VD, Voeten DM, Daams F, van der Peet DL, Straatman J. C-reactive protein after major abdominal surgery in daily practice. Surgery (United States). 2021 Oct 1;170(4):1131–9.

64. C K, V T, P K, PH C. Correlation of C-reactive protein with clinical outcome in critically ill patients with sepsis. Journal of Medical and Scientific Research [Internet]. 2024 Jul 2;12(3):231–4. Available from: https://jmsronline.com/archive-article/C-reactive-protein-clinical-outcome-critically-ill-sepsis

65. Lin Y, Dong S, Yuan J, Yu D, Bei W, Chen R, et al. Accuracy and Prognosis Value of the Sequential Organ Failure Assessment Score Combined With C-Reactive Protein in Patients With Complicated Infective Endocarditis. Front Med (Lausanne). 2021 Mar 25;8.

66. Karande CB, Krishnan D, Manivannan P. PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN AND APACHE II SCORING SYSTEM. Journal of Pharmaceutical Negative Results ¦. 2023;14(02).

67. Moretti D, Bagilet DH, Buncuga M, Settecase CJ, Quaglino MB, Quintana R. Estudio de dos variantes de la puntuacion de riesgo nutricional 'NUTRIC' en pacientes criticos ventilados. Nutr Hosp. 2014;29(1):166–72.

68. Luo Y, Qian Y, Kantarçeken B. Effect of combined parenteral and enteral nutrition for patients with a critical illness: A meta-analysis of randomized controlled trials. Vol. 99, Medicine (United States). Lippincott Williams and Wilkins; 2020.

69. Ridley EJ, Davies AR. Practicalities of nutrition support in the intensive care unit: The usefulness of gastric residual volume and prokinetic agents with enteral nutrition. Vol. 27, Nutrition. 2011. p. 509–12.

9. Appendix