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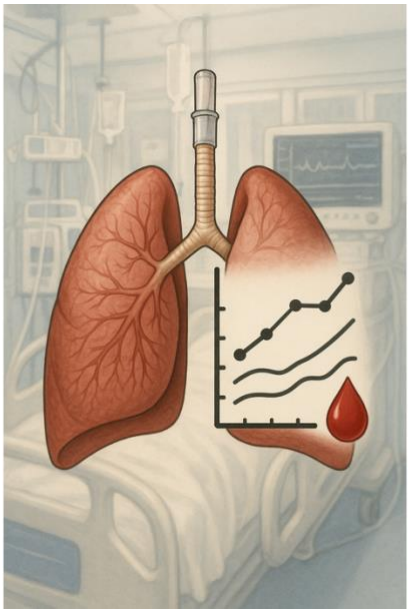

The impact of different types of respiratory failure on death in the ICU, in a Portuguese population with COVID-19

SUSANA ISABEL DE LOUSA CABRAL
(Licenciada em Enfermagem)

Dissertação para obtenção do grau de Mestre em Engenharia Biomédica

Orientadores:
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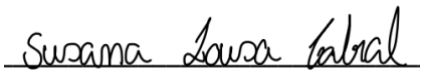
Statement of integrity

I declare that this dissertation / project work / internship report is the result of my personal and independent research. Its content is original, and all sources listed in the bibliographic references were consulted and are duly mentioned in the text. I further declare that all scientific and technical references relevant to the development of the work are duly cited and included in the bibliographic references.

The author



Lisbon, 30 de setembro de 2025

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O impacto dos diferentes tipos de falência respiratória na mortalidade na UCI, numa população portuguesa com COVID-19

Resumo

Introdução: A pandemia de COVID-19, causada pelo SARS-CoV-2, representou um dos maiores desafios do século XXI. A rápida disseminação resultou em manifestações clínicas de formas ligeiras a críticas. A identificação precoce de pacientes de alto risco foi essencial para otimizar tratamento e recursos. A gasimetria arterial teve papel central ao fornecer informações sobre oxigenação, ventilação e equilíbrio ácido-base, permitindo avaliação precoce da gravidade da doença.

Objetivos: Avaliar o valor preditivo dos parâmetros gasimétricos (PaO_2, $PaCO_2$, pH e lactato) para os desfechos clínicos adversos (mortalidade, necessidade de ventilação mecânica invasiva (VMI) e de oxigenação por membrana extracorporal (ECMO)) e a sua relação com a duração do internamento na unidade de cuidados intensivos (UCI) e dos suportes invasivos.

Métodos: Estudo observacional e retrospetivo que analisou 794 pacientes com COVID-19 internados na UCI da Unidade Local de Saúde de São José entre outubro de 2020 e janeiro de 2022. Foram analisados os parâmetros gasimétricos do dia de admissão e variáveis demográficas e clínicas, recorrendo a testes paramétricos e não paramétricos. Modelos lineares generalizados (GLM) com distribuição binomial negativa identificaram fatores associados à duração do internamento na UCI e dos suportes invasivos.

Resultados: Os não sobreviventes apresentaram pH e PaO_2 mais baixos e lactato mais elevado, indicando maior gravidade respiratória e metabólica. A necessidade de VMI e ECMO associou-se a pH reduzido e $PaCO_2$ elevada. Os pacientes com comorbilidades apresentaram maior mortalidade na UCI e houve diferenças significativas entre vagas pandémicas. Os GLM mostraram que $PaCO_2$ máxima, sexo masculino, ausência de doença pulmonar e ausência de vacinação prolongaram o internamento e a duração dos suportes invasivos, enquanto o lactato máximo e a ausência de obesidade se associaram a durações mais curtas.

Conclusão: A avaliação precoce da gasimetria arterial confirmou o valor destes parâmetros como ferramenta preditiva de risco, reforçando a sua utilidade na construção de modelos prognósticos e em abordagens personalizadas em cuidados intensivos.

Palavras-chave: ARDS; Desfechos UCI; COVID-19; parâmetros gasimétricos; desequilíbrios ácido-base.

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The impact of different types of respiratory failure on death in the ICU, in a Portuguese population with COVID-19

Abstract

Background: The COVID-19 pandemic, caused by SARS-CoV-2, was one of the major challenges of the 21st century. It rapidly spread worldwide, ranging from mild to critical forms. Early identification of high-risk patients was essential to optimize treatment and resources. Arterial blood gas (ABG) analysis provided information on oxygenation, ventilation, and acid-base balance, for early disease severity assessment at intensive care unit (ICU) admission.

Purpose: To assess the predictive value of ABG parameters (PaO_2, $PaCO_2$, pH, and lactate) for adverse clinical outcomes (ICU death, need for invasive mechanical ventilation (IMV), and extracorporeal membrane oxygenation (ECMO)) and their association with the duration of ICU stay and invasive supports.

Methods: Observational and retrospective study including 794 COVID-19 patients admitted to the ICU of *Unidade Local de Saúde de São José* between October 2020 and January 2022. ABG parameters from admission day, along with demographic and clinical variables, were analyzed using parametric and non-parametric tests. Generalized linear models (GLM) with a negative binomial distribution identified factors influencing the duration of ICU stay and invasive supports.

Results: Non-survivors had lower pH and PaO_2 and higher lactate levels, indicating more severe respiratory and metabolic impairment. IMV and ECMO needs were associated with lower pH and higher $PaCO_2$. Patients with comorbidities had higher ICU mortality, and significant difference was found across pandemic waves. The GLMs showed that maximum $PaCO_2$, being male, not having chronic lung disease and being unvaccinated prolonged ICU stay and support duration, while maximum lactate and non-obese were associated with shorter durations.

Conclusion: Early ABG assessment demonstrated the utility of these parameters as a predictive tool for risk stratification in critically ill COVID-19 patients, supporting their integration into prognostic models and personalized approaches to ICU management.

Keywords: ARDS; ICU Outcomes; COVID-19; arterial blood gas parameters; acid-basic disorders.

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List of Symbols and acronyms

2019-nCoV	2019 novel Coronavirus
ABG	Arterial Blood Gas
ACE2	Angiotensin-Converting Enzyme 2
AI	Artificial Intelligence
AIC	Akaike Information Criterion
ARDS	Acute Respiratory Distress Syndrome
BE	Base Excess
BPH	Benign Prostatic Hyperplasia
CHF	Congestive Heart Failure
cmH_2O	Centimeters of water
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
COVID-19-ARDS	COVID-19-related ARDS
CO_2	Carbon Dioxide
DM	Diabetes Mellitus
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
ICU-D	Intensive Care Unit Death
FiO_2	Fraction of Inspired Oxygen
GFR	Glomerular Filtration Rate
GLM	Generalized Linear Modelling
HCO_3^-	Bicarbonate
HTN	Hypertension
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
IQR	Interquartile Range
kPa	Kilopascals
MAE	Mean Absolute Error
mEq/L	Milliequivalents per liter
mRNA	Messenger Ribonucleic Acid
mmol/L	Millimoles per Liter
O_2	Oxygen
$PaCO_2$	Arterial Partial Pressure of Carbon Dioxide
PaO_2	Arterial partial Pressure of Oxygen

PaO_2/FiO_2	Ratio between PaO_2 e FiO_2
PEEP	Positive End Expiratory Pressure
PHEIC	Public Health Emergency of International Concern
PREMO	Predictive Models of COVID-19 Outcomes for Higher Risk Patients Towards a Precision Medicine
RAAS	Renin-Angiotensin-Aldosterone System
RNA	Ribonucleic Acid
RMSE	Root Mean Square Error
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SaO_2	Arterial Oxygen Saturation
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SpO_2	Peripheral Oxygen Saturation
SOFA	Sequential Organ Failure Assessment
VOC	Variant of Concern
WHO	World Health Organization

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1 Objectives and Structure of the Work

This chapter contextualizes the dissertation, defines the research question and objectives, proposes a solution, and describes the document structure.

1.1. Contextualization and Framework

The Coronavirus Disease 2019 (COVID-19) first appeared in Wuhan, China, in December 2019, as a pneumonia of unknown cause. Within weeks, the infection had spread beyond Hubei province and across all continents, evolving into a global pandemic. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for COVID-19, proved highly transmissible, causing manifestations from mild respiratory symptoms to severe pneumonia and multiorgan failure. The speed of transmission and unpredictable clinical course made COVID-19 one of the greatest challenges to modern healthcare systems [1], [2].

In hospitals across the world, record admissions spiked, causing system overload and shortfalls of beds and staff, especially in intensive care units (ICU). In this period, early stratification was important to identify patients likely to decompensate. The inability to rapidly identify which patients would require intensive care, and in particular invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) further stretched ICU capacity during pandemic peaks [3].

From the start of the pandemic, systematic assessment of clinical and laboratory parameters at admission was mandatory to understand disease progression and optimize resource allocation. Previous studies showed that comorbidities, sex, and arterial blood gas (ABG) parameters, affect clinical outcomes in critically ill COVID-19 patients. Findings suggest early and standardized assessment of these indicators to support triage decisions and enhance prognostic accuracy [4], [5].

The integration of such variables into predictive models emerged as an approach to improve clinical decision support. These models allow for more accurate prognostic estimation, standardize admission criteria, reduce subjectivity, and promote consistency in critical care management. When adapted and validated in specific clinical contexts, they can serve as tools for professional training and preparedness for future health emergencies [6], [7].

This dissertation is part of a broader project, PREMO (Predictive Models of COVID-19 Outcomes for Higher Risk Patients Towards a Precision Medicine), which aims to develop predictive models for identify prognostic factors in critically ill COVID-19 patients [19]. This involves patients with COVID-19 admitted to the ICU of the *Unidade Local de Saúde de São José*, and this work examines the associations between ABG parameters such as PaO_2 (arterial partial pressure of oxygen), $PaCO_2$ (arterial partial pressure of carbon dioxide), pH and lactate, and the most common outcomes for patients in an ICU which are: intensive care unit death (ICU-D), IMV need, and ECMO support. Furthermore, it incorporates predictive modelling to explore which factors most strongly influence ICU stay, IMV, and ECMO duration, thereby contributing to the identification of determinants of prolonged critical care and the development of evidence-based strategies for personalized ICU management.

1.2. Research Question

Which arterial blood gas parameters have the strongest predictive value for clinical outcomes (death, need for ECMO, and need for IMV) in critically ill COVID-19 patients admitted to an ICU in Portugal?

1.3. Specific Objectives

- To use a previously constructed database containing clinical, demographic and ABG data of COVID-19 ICU patients for statistical analysis and interpretation of results;
- To characterize the clinical, demographic and ABG profiles of the study sample using descriptive and inferential statistical methods, comparing patient groups according to clinical outcomes;
- To analyze variations in ABG parameters across outcomes;
- To examine the association between ABG parameters and comorbidities, assessing how underlying chronic conditions influence ABG profiles;

- To analyze ABG parameters and determine their variations across different COVID-19 waves;
- To compare ABG parameters and clinical outcomes according to vaccination status (vaccinated vs. unvaccinated) and vaccination periods (pre- and post-vaccination);
- To determine which ABG parameters have the greatest predictive power for the outcomes presented;
- To analyze the association between hospital length of stay, duration of invasive supports (IMV and ECMO), and clinical outcomes;
- To construct and evaluate predictive models with generalized linear models (GLM) to identify variables associated with the duration of ICU stay, IMV, and ECMO support.

1.4. Proposed Solution

This dissertation consists of an observational and retrospective study, analyzing demographic, clinical, and ABG data from critically ill COVID-19 patients admitted to the ICU of the *Unidade Local de Saúde de São José*. To achieve these objectives, descriptive, exploratory, and inferential statistical methods were applied to characterize the sample, compare groups, and assess associations.

Additionally, consistent with the PREMO project objectives, GLMs were developed to identify which demographic, clinical, and ABG variables most influence the duration of ICU stay and invasive supports (IMV and ECMO).

1.5. Document Organization

This dissertation is divided into six chapters.

- Chapter 1 contextualizes the topic, defines the research question and objectives, and proposes a solution;
- Chapter 2 reviews the literature regarding COVID-19 pandemic and SARS-CoV-2, ABG analysis, clinical outcomes, and precision medicine;
- Chapter 3 describes the methodological procedures, including the study sample, variables, and statistical methods such as the GLMs;

- Chapter 4 presents the results in three sections: (1) global characterization and variable associations; (2) temporal analyses; (3) GLMs for ICU stay, IMV, and ECMO duration ;
- Chapter 5 reviews the results in relation to literature, with emphasis on clinical implications, and presenting strengths and limitations;
- Chapter 6 summarizes the main conclusions and future directions of research.

2 Literature Review

This chapter summarizes the COVID-19 pandemic, SARS-CoV-2 characteristics, transmission modes, clinical manifestations and healthcare impact. It explores the mechanisms of respiratory failure, focusing on COVID-19-related acute respiratory distress syndrome (COVID-19-ARDS). Reviews systemic complications, the importance of ABG analysis in the management of critically ill patients, and the main clinical outcomes in the ICU. Finally, it synthesizes the main findings of published studies related to this dissertation and presents precision medicine.

2.1. COVID-19 Pandemic

SARS-CoV-2 was first identified in December 2019, in Wuhan, China, after pneumonia cases linked to the Huanan seafood market [1], [8]. In January 2020, the World Health Organization (WHO) identified the virus as a member of the coronavirus family and initially named it 2019-nCoV (2019 novel coronavirus). Later, the International Committee of Taxonomy of Viruses designated it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it causes as COVID-19 (Coronavirus Disease 2019) [1].

By the end of January 2020, SARS-CoV-2 had been detected in various countries, confirming its human-to-human transmissibility. On 30 January 2020, the WHO declared a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations, the highest global health alert, to determine measures to contain the virus. Despite strict containment measures, such as quarantines in Wuhan, the virus spread across Asia, Europe, and North America. On 11 March 2020, COVID-19 was officially declared a global pandemic, the first coronavirus pandemic in modern history [8], [9].

The rapid global spread placed unprecedented demands on healthcare systems, straining hospital capacity and resources. In Portugal, national guidelines were updated to protect healthcare professionals and improve patient management. The clinical protocols prioritized the early identification of high-risk patients, defining ICU admission criteria, and rational resource allocation. The use of personal protective equipment, restricted visits and improved ventilation, helped prevent in-hospital infection. Intensive care protocols were regularly updated with new evidence. Early ICU transfer suspicion allowed timely triage and effective critical care management [10].

2.1.1. Viral Evolution of SARS-CoV-2

SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) virus. Its spike glycoprotein binds to the angiotensin-converting enzyme 2 (ACE2) receptor on respiratory epithelial cells, facilitating membrane fusion and the release of viral RNA into the host cell. Other tissues also express ACE2 receptors, contributing to the virus's systemic tropism [1], [11].

Mutations of the spike protein, particularly on the receptor-binding domain, increase viral affinity for ACE2, enhancing infectivity, transmissibility, and, in some cases, immune evasion. From these mutations, several variants of concern (VOCs) emerged globally, leading to subsequent pandemic waves [12].

Throughout the pandemic, six waves were identified in Portugal, each associated with predominant variants that influenced transmissibility and disease severity. The 1st wave (March to June 2020) involved the ancestral Wuhan strain, followed by Alpha (early 2021), Delta (mid 2021) and later Omicron (late 2021 to early 2022). Progressive vaccination coverage and accumulated population immunity led to milder disease, shorter ICU stays, and reduced mortality during the final waves. Consistent with these patterns, there was a reduction in age at admission, lower need for invasive organ support, and improved survival across later waves [13].

2.1.2. Transmission and Symptoms

SARS-CoV-2 spreads mainly through droplets and aerosols released when an infected person breathes, speaks, or coughs. Transmission is also possible indirectly, through contaminated surfaces, though less common. The risk of infection increases in closed or poorly ventilated environments, which reinforces the importance of proper

ventilation, use of high-efficiency respirators, and physical distancing, in accordance with WHO guidance issued during the emergency phase [14], [15].

Symptomatology of COVID-19 depends on the host immune response. Some patients remain asymptomatic, others present with mild disease including fever, dry cough, fatigue, myalgia (muscle and joint pain), sore throat, headache, and anosmia (loss of smell). Because of the expression of ACE2 receptors in the intestinal epithelial cells, viral replication and inflammation in the intestinal tract cause gastrointestinal symptoms such as nausea, vomiting, and diarrhea, which are more frequent in children and immunocompromised patients [16], [17].

Older adults and those with cardiovascular disease, diabetes mellitus (DM), obesity, chronic obstructive pulmonary disease (COPD) or immunosuppressive conditions, are at higher risk of severe disease. These conditions cause inflammation, endothelial dysfunction, and affect the immune response, exacerbating viral injury and worsening clinical outcomes [4], [5].

In some patients, the disease progresses or relapses, which is referred to as “long COVID", or post-acute sequelae of SARS-CoV-2 infection. This is characterized by persistent or new onset symptoms beyond the acute phase, lasting for more than four weeks after the initial infection. Common manifestations include fatigue, dyspnea, myalgia, tachycardia and cognitive impairment such as forgetfulness and confusion. Although these symptoms may persist after virological recovery, there is currently no specific treatment for “long COVID”. Management remains mainly supportive, focusing on rehabilitation and symptomatic relief [18].

2.1.3. Vaccine Development

After the identification of the virus, an international collaboration, involving research institutions, pharmaceutical industry and health authorities worked on the vaccine design, testing, and emergency approval, to reduce transmission, disease severity, and pressure on healthcare systems [15], [16], [19].

The SARS-CoV-2 vaccines use different platforms, including traditional inactivated virus, viral vector, and novel mRNA (messenger RNA) technologies. In large scale Phase III trials, these strategies had efficacy rates of 62% to 95%. Initially, the Pfizer-BioNTech and Moderna (mRNA based), and AstraZeneca/Oxford and Janssen (viral-vector-based) vaccines were approved for emergency use [15], [16].

Between December 2020 and May 2021, the WHO included these vaccines in its Emergency Use Listing, allowing rapid global distribution during the health crisis [15].

In Portugal, the vaccination campaign began in December 2020 with Pfizer-BioNTech vaccine, followed by Moderna, AstraZeneca, and Janssen. Older adults, healthcare workers, and high-risk groups had priority. By mid 2021, vaccination was widely available to the population, and over 70% of citizens were fully vaccinated, achieving one of the highest coverage rates in Europe [13].

2.2. Respiratory Failure in COVID-19

Respiratory failure is a severe clinical condition in which the respiratory system is unable to maintain adequate gas exchange, resulting in insufficient oxygenation and/or carbon dioxide (CO_2) retention. This disrupts cellular metabolism and compromises organ function. It can be caused by abnormalities in the lungs, airways, respiratory muscles, or central control of breathing. If not rapidly corrected, it can lead to tissue hypoxia, CO_2 retention, and multiorgan failure [20].

2.2.1. Types of Respiratory Failure

Respiratory failure is classified according to whether the primary disturbance is in oxygenation or ventilation [20].

Type I (hypoxemic) respiratory failure is defined by a PaO_2 below 60 mmHg with normal or low $PaCO_2$ (normocapnia or hypocapnia). It results from impaired gas exchange caused by ventilation-perfusion mismatch, intrapulmonary shunt, or diffusion limitation, as observed in conditions such as pneumonia, pulmonary embolism, cardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS) [21].

Type II (hypercapnic) respiratory failure occurs when $PaCO_2$ is higher than 45 mmHg, usually with hypoxemia. It results from inadequate alveolar ventilation, leading to CO_2 retention and secondary hypoxemia. Causes include COPD, decreased ventilatory drive, neuromuscular disorders, or structural thoracic abnormalities [21].

In critically ill patients, these mechanisms can coexist simultaneously, leading to mixed respiratory failure, reflecting the complex pathophysiology of severe respiratory compromise [21].

2.2.2. Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is a severe condition characterized by acute and diffuse lung inflammation, with non-cardiogenic pulmonary edema, severe hypoxemia, and respiratory failure. It results from inflammatory injury to the alveolar-capillary membrane, which increases vascular permeability and allows fluid to leak from the capillaries into the interstitial and alveolar spaces. The resulting exudate impairs gas exchange, decreases lung compliance, and leads to alveolar collapse, often requiring mechanical ventilation [22].

The Berlin Definition of ARDS, introduced in 2012 by the European Society of Intensive Care Medicine, established standardized diagnostic and severity criteria to improve consistency and prognostic accuracy. ARDS typically develops within one week of a known clinical insult or new/worsening respiratory symptoms. Imaging should show bilateral opacities unexplained by cardiac failure or fluid overload [22], [23].

Hypoxemia of ARDS is defined by the ratio PaO_2/FiO_2, measured under a minimum positive end-expiratory pressure (PEEP) of 5 cmH_2O. This ratio shows the O_2 transfer efficiency from alveoli to arterial blood, with lower values indicating gas exchange impairment. PEEP is the positive pressure applied at the end of expiration during mechanical ventilation, which prevents the collapse of the alveoli and allows standardized oxygenation assessment. ARDS severity classifications are mild (PaO_2/FiO_2 200-300 mmHg), moderate (PaO_2/FiO_2 100-200 mmHg) and severe (PaO_2/FiO_2 less than 100 mmHg) [22], [23].

2.2.3. COVID-19 and Respiratory Failure

COVID-19-related ARDS is characterized by heterogeneous lung compliance and gas exchange patterns, which requires caution in generalization and supports individualized ventilatory strategies [24], [25], [26].

The clinical and pathophysiological differences between COVID-19-ARDS and classical ARDS are also noted. Although both meet the Berlin Definition criteria, COVID-19-ARDS demonstrates more heterogeneity of lung mechanics and gas exchange patterns [2], [27].

Early on, patients have severe hypoxemia with preserved lung compliance, suggesting vascular dysregulation rather than extensive alveolar collapse. Endothelial

inflammation, pulmonary microvascular thrombosis, and impaired hypoxic vasoconstriction are mechanisms that led to areas of well-ventilated but poorly perfused lung tissue, in an atypical ventilation-perfusion mismatch for ARDS [2].

As the disease progresses, some patients develop a more classical ARDS phenotype, with decreased compliance, increased lung weight, and radiological consolidation as a result of cytopathic injury, cytokine-mediated inflammation, and mechanical ventilation-induced stress. The coexistence of vascular and alveolar injury complicates ventilatory management and prognostic stratification [25], [27].

Consequently, COVID-19-related respiratory failure presents a unique clinical challenge, requiring tailored ventilatory and monitoring strategies in the intensive care setting [2].

2.3. Systemic Complications

Although primarily affecting the lungs, COVID-19 is a systemic disease. The widespread expression of ACE2 receptors across multiple organs, together with the intense inflammatory and thrombotic response triggered by SARS-CoV-2, accounts for the multiorgan involvement in severe cases [11], [25]

In severe COVID-19, cardiovascular complications are common. The entry of the virus through ACE2 receptors on endothelial and myocardial cells leads to endothelial dysfunction, microvascular damage, and a prothrombotic state. Cytokine-mediated inflammation, hypoxemia, and autonomic imbalance, increase cardiac electrical instability, resulting in arrhythmias, such as atrial fibrillation, ventricular tachycardia, and bradyarrhythmias. In severe cases, these alterations cause right ventricular dysfunction and acute heart failure, especially with IMV or ECMO. This occurs because positive pressure ventilation and ECMO increase right ventricular afterload and myocardial stress. Because of the risk of malignant arrhythmias and cardiac events, continuous electrocardiogram (ECG) monitoring is required [11], [25], [28].

Renal impairment is frequent and may result from several mechanisms such as hypoperfusion secondary to shock or hypoxia, cytokine-induced tubular injury, and microthrombi formation in glomerular capillaries. Direct viral injury may also occur, since ACE2 receptors are abundantly expressed in renal tubular and glomerular cells. Acute kidney injury is independently associated with increased mortality and often occurs with multiorgan dysfunction [4], [16].

Hepatic involvement could be due to direct viral injury, since ACE2 receptors are also expressed in specific hepatic cells, systemic hypoxia, or drug-induced hepatotoxicity from antivirals and antibiotics [11]. Systemic inflammation and endothelial dysfunction induce a hypercoagulable state, resulting in thrombotic complications, manifested by deep vein thrombosis, pulmonary embolism, or disseminated intravascular coagulation [16].

Patients with severe COVID-19 often present with endocrine and metabolic dysfunctions. These are associated with systemic inflammatory response, and this especially occurs in patients with HTN, DM, dyslipidemia or obesity, since they already have a basal inflammation and endothelial dysfunction due to the conditions. Hyperglycemia induces oxidative stress and cytokine production, that aggravate endothelial injury and increase the risk of thrombosis and acute kidney failure [13].

Systemic involvement in severe COVID-19 reflects the interaction of inflammation, endothelial injury, and multiorgan dysfunction. Comprehensive management must therefore include cardiac rhythm surveillance, renal and hepatic function monitoring, and coagulation assessment to anticipate decompensation [13], [29].

2.4. Arterial Blood Gas Analysis

Analysis of the arterial blood gas (ABG) measures gas exchange and acid-base status to determine respiratory and metabolic function. Samples are drawn from the radial artery, but may be drawn from femoral or brachial arteries. Unlike venous blood, which represents tissue O_2 consumption, arterial samples represent the lungs' capacity to oxygenate blood and eliminate CO_2, making ABG analysis a direct and reliable tool in critical care [30].

ABG parameters include PaO_2, $PaCO_2$, pH, bicarbonate (HCO_3^-), and base excess (BE), and describe respiratory and metabolic components of acid-base regulation [31].

COVID-19 affects gas exchange, making ABG analysis essential for diagnosis and monitoring. ABG patterns among critically ill patients are consistent, with metabolic alkalosis being the most common disturbance in survivors, whereas non-survivors as a result of disease progression and multiorgan failure, most often present with metabolic or respiratory acidosis [32], [33]. These findings show that acid-base disturbances in COVID-19 are complex and dynamic, influenced by pulmonary dysfunction, renal injury, systemic inflammation, and therapeutic intervention. Regular and serial ABG

measurements permit early detection of deterioration and guide adjustment of O_2 therapy and mechanical ventilation. ABG interpretation reflects pulmonary and systemic failure, and allows individualized management of critically ill patients [34], [35], [36].

2.4.1. PaO_2

PaO_2 is the arterial partial pressure of O_2, and is related to both the amount of O_2 dissolved in arterial blood and the transfer efficiency of O_2 from alveoli to the systemic circulation. Healthy adults at sea level have normal values between 75 and 100 mmHg. Values below this range represent hypoxemia, meaning that arterial oxygenation is not sufficient to meet O_2 demands, but values above (hyperoxemia) may occur with supplemental O_2 therapy. PaO_2 is therefore one of the most important parameters to characterize respiratory failure [31].

Hypoxemia can vary in severity. It is called mild when PaO_2 is between 60 and 79 mmHg, moderate when between 40 and 59 mmHg, and severe when below 40 mmHg. Each step down reflects worsening alveolar gas transfer and increased risk of tissue hypoxia [21].

SARS-CoV-2 targets alveolar and endothelial cells expressing ACE2 receptors, triggering an inflammatory response that increases capillary permeability, and promotes fluid leakage into the alveoli. This process reduces the surface area for gas exchange and lowers PaO_2. In COVID-19, hypoxemia is common due to diffuse alveolar and endothelial injury, which causes alveolar inflammation, interstitial edema, and microvascular injury. These alterations impair O_2 diffusion and disrupt ventilation-perfusion balance [31], [34].

2.4.2. $PaCO_2$

Arterial partial pressure of CO_2 ($PaCO_2$) is the CO_2 content in arterial blood and directly measures alveolar ventilation efficiency. At sea level, $PaCO_2$ of healthy adults ranges between 35 and 45 mmHg. If below, it indicated hypocapnia, and if above, hypercapnia. Both situations help understand how the patient is ventilating [31], [36].

Hypocapnia occurs due to hyperventilation, which is the excessive alveolar ventilation and leads to excessive elimination of CO_2 and consequently elevated blood pH (respiratory alkalosis). It happens frequently in the early stages of COVID-19 as patients increase respiratory rate to compensate hypoxemia. Still, persistent hypocapnia

may constrict blood vessels, reducing O_2 supply to tissues, and increasing hypoxia [31], [37].

Hypercapnia results from inadequate alveolar ventilation and CO_2 retention, resulting in respiratory acidosis. In the case of COVID-19, this occurs in late or severe stages due to alveolar collapse, inflammation, or diffusion impairment. It is typical of patients with prolonged mechanical ventilation or ARDS, and is a marker of ventilatory failure and gas exchange impairment [34], [36], [37].

2.4.3. pH

Arterial pH reflects the acid-base balance determined by the blood concentration of hydrogen ions, which is essential for maintaining cellular homeostasis. pH should be between 7.35 and 7.45 in a healthy adult, and even slight deviations may impair cardiovascular, respiratory and neurological function [31], [36].

Acidemia is when pH below is 7.35 and alkalemia when above 7.45. They both can disrupt enzyme activity, O2 transport, and metabolic efficiency, making pH an important respiratory and metabolic status indicator [33], [34].

Acidemia might result from respiratory acidosis due to CO2 retention through hypoventilation, and/or metabolic acidosis due to accumulation of non-volatile acid or impairment of renal excretion of hydrogen ions. These are typical patterns of severe COVID-19, associated with tissue hypoxia and renal dysfunction. Alkalemia may be respiratory, caused by hyperventilation or metabolic, caused by electrolyte imbalance and HCO_3^- retention [31], [34], [38].

2.4.4. Lactate

Lactate is a major biomarker of tissue oxygenation and cellular metabolism, with extensive use in critically ill patients. It rises when O_2 delivery does not meet metabolic demand, causing anaerobic metabolism and lactic acid accumulation. Elevated lactate levels at ICU admission correlate with higher risk of complications and mortality. Monitoring lactate variations is essential for assessing treatment response and detecting early clinical deterioration [39].

A normal lactate level is below 2 mmol/L. Rising or persistently high values reflect ongoing hypoperfusion and cellular stress, while declining values reflect better O_2 delivery and therapeutic response [39].

Respiratory failure and microvascular dysfunction prevent O_2 delivery to tissues in severe COVID-19 and cause tissue hypoxia. This, along with systemic inflammation and enhanced metabolic demand, causes elevated lactate levels (hyperlactatemia). The “cytokine storm” further promotes anaerobic metabolism and metabolic acidosis [40].

2.4.5. Bicarbonate

Bicarbonate (HCO_3^-) is the principal extracellular buffer in maintaining acid-base balance. Normal concentrations range from 22 to 26 mEq/L. Because HCO_3^- integrates the metabolic and respiratory components of acid-base regulation, its variations help distinguish between primary metabolic disturbances and compensatory renal responses [31], [41].

High HCO_3^- levels may represent metabolic alkalosis or renal compensation for chronic CO_2 retention. ACE2 downregulation may disturb the renin-angiotensin-aldosterone system (RAAS), and promote aldosterone activity and renal hydrogen excretion, to induce metabolic alkalosis [33], [36], [42].

A reduction in HCO_3^- indicates metabolic acidosis. This decrease may be due to increased acid production (such as a rise in lactate) or decreased renal acid excretion as a result of kidney injury, often seen in severe COVID-19 [33], [43].

HCO_3^- interpretation must be integrated with pH and $PaCO_2$ values to identify whether the disturbance is primary or compensatory. Both high and low HCO_3^- levels have been associated with clinical deterioration, emphasizing the value of dynamic monitoring [40], [44].

2.4.6. Base Excess

Base excess (BE) is a metabolic component of acid-base balance. It is the amount of acid or base required to bring blood pH to the normal physiological range (7.35 - 7.45) under standard conditions. A negative value indicates metabolic acidosis, while positive value indicates alkalosis [34].

BE helps distinguish between respiratory and metabolic disorders in critically ill patients may guide treatment decisions. Commonly seen in renal failure or severe sepsis, the negative BE, characteristic of metabolic acidosis, may be caused by lactic acid production from tissue hypoxia and anaerobic metabolism. This alteration is associated with multiorgan failure and increased mortality. Conversely, a positive BE, indicative of metabolic alkalosis, often occurs in patients with dehydration, electrolyte imbalance, or hyperventilation, common features in severe COVID-19 [45].

Although HCO_3^- and BE describe metabolic acid-base components, they measure different aspects. HCO_3^- reflects the immediate buffering status, whereas BE represents the overall deviation of the extracellular buffer system from normal equilibrium. Together, they provide a comprehensive assessment of metabolic acid-base disturbances .[34], [44], [45]

2.5. Clinical Outcomes in the ICU

The COVID-19 pandemic placed unprecedented pressure on healthcare systems worldwide. Resource prioritization was needed to address increased hospitalization and ICU demand. Predictive assessment of clinical outcomes such as mortality, the need for IMV, or ECMO, became mandatory for therapeutic planning and resource allocation optimization. Early identification of high-risk patients allows targeted interventions to improve outcomes [46].

According to Marini and Gattinoni [46], mortality among ICU COVID-19 patients was high, ranging from 53% to 88% among those requiring IMV. This illustrates how early prognostic evaluation can guide timely interventions. Lung-protective ventilation and other evidence based ventilatory strategies have decreased IMV related injury and improved survival in ARDS patients [26], [47].

Care for severe COVID-19 involves ongoing clinical and laboratory monitoring, accurate risk stratification and multidisciplinary management. Personalized therapy and prognostic evaluation remain essential to optimize outcome in critically ill patients [48].

2.5.1. Need for Invasive Mechanical Ventilation

In patients with COVID-19-ARDS, invasive mechanical ventilation (IMV) is often required. Recognizing ventilatory failure is important because prompt start of support enhances oxygenation and avoids hypoxemia and organ injury [49].

Respiratory indicators like respiratory rate, oxygen saturation (SpO_2) and ABG parameters (pH, PaO_2, and $PaCO_2$) have to be continuously monitored for respiratory efficiency assessment and ventilatory adjustments. Persistent hypoxemia or hypercapnia on ABG evaluation can indicate the need for IMV. Serial measurements also guide treatment response and ventilator optimization [49], [50], [51].

IMV aims to reduce breathing work while maintaining adequate gas exchange. Efficacious synchronization between patient and ventilator reduces respiratory effort and avoids complications like asynchrony or hypercapnia. Hence, combining clinical assessment with continuous ventilatory data and ABG monitoring enables individualized ventilatory strategies, early detection of deterioration, and improved patient outcomes [52].

2.5.2. Need for Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is an advanced type of life support therapy during severe ARDS, when conventional ventilation is no longer sufficient for oxygenation or CO_2 elimination [53]. The procedure pumps blood from the body through an extracorporeal surface exchange circuit, in which gas exchange occurs across a semipermeable membrane, returning to systemic circulation for temporary pulmonary support [48], [53].

Since ECMO is a high-risk, resource-intensive procedure which requires a trained multidisciplinary team, it should only be performed in clinically selected cases. ABG analysis is central to this decision, as deterioration of gas exchange parameters, such as declining pH, rising $PaCO_2$, and persistently low PaO_2 or PaO_2/FiO_2 ratio despite optimal ventilation, suggest refractory respiratory failure and ECMO initiation is supported. Accurate patient selection is essential to minimize serious complications, such as bleeding, infection, and organ failure [47], [54].

Prognosis depends on multiple factors, including age, comorbidities, and duration of prior mechanical ventilation. Outcomes worsen in patients older than 65 years, with prolonged IMV (longer than 7 days), due to increased risk of ventilator-induced injury and multiorgan failure [55]. The Sequential Organ Failure Assessment (SOFA) score is essential for evaluating organ dysfunction and mortality risk, supporting rational ECMO indication. When appropriately selected, ECMO provides temporary gas exchange support, allowing pulmonary recovery while balancing procedural risks through standardized protocols and individualized management [46], [48].

2.5.3. Mortality

The mortality of critically ill COVID-19 patients reflects the association with advanced age, comorbidities such as DM, HTN and cardiovascular disease, severe hypoxemia, prolonged mechanical ventilation, and multiorgan dysfunction, all associated with ventilator-induced lung injury and systemic inflammation [46], [48].

Precise prediction of mortality risk permits tailored clinical strategies. Early recognition of high-risk patients allows for timely aggressive interventions, whereas recognition of limited recovery potential guides appropriate palliative decisions. Prognostic assessment based on oxygenation indices, acid-base parameters, and organ function scores supports evidence-based ICU management and resource prioritization [46], [48].

Transparent communication with patients' families is also essential in critical care. Discussing prognosis based on objective mortality risk fosters shared decision-making and prepares families for potential outcomes [46].

2.6. Synthesis of studies on Arterial Blood Gas as a predictive tool

The COVID-19 pandemic posed significant challenges for the clinical management of critically ill patients, making early identification essential for identifying those at higher risk of mortality and need for advanced ventilatory support. In this context, ABG analysis has been widely used as a tool to assess the severity of respiratory failure and patients' metabolic response. The parameters analyzed include PaO_2, $PaCO_2$, arterial pH, HCO_3^-, lactate, and BE, which can indicate respiratory and metabolic disturbances associated with patient prognosis [31], [39], [56].

The main objective of the present study is to determine which ABG parameters have the greatest predictive power for the clinical outcomes of mortality, need for ECMO, or IMV in patients admitted to an ICU in Portugal. To address this question, twelve scientific articles evaluating the relationship between ABG parameters and clinical outcomes in critically ill COVID-19 patients were analyzed.

Sembai *et al.* (2023) defined ABG profiles in patients with severe COVID-19 admitted to an ICU, and related them to clinical outcomes (recovery, improvement, or death). The

study included 41 patients, 29 (70.7%) recovered or improved, and 12 (29.3%) died. Of all ABG patterns identified, respiratory alkalosis was the most common acid-base disturbance, present in 24.4% of patients (n = 10). Metabolic alkalosis was the second (22.0%; n = 9). Less frequent disturbances included respiratory acidosis (12.2%), and partially compensated respiratory acidosis (9.8%). Regarding the relationship between ABG profile and clinical outcome, the data showed that metabolic alkalosis was the most frequent profile among patients with favorable evolution, present in 27.5% of the recovery or improvement cases. Conversely, respiratory alkalosis was observed in 33.3% of patients who died. In spite of these trends, the authors found no statistically significant association between the acid-base disturbances and clinical outcomes ($p > 0.05$ for all categories). This small sample size may have limited significant differences [37].

Gupta *et al*. (2021) in a retrospective analysis, evaluated ABG parameters and alveolar-arterial oxygen gradient (A-a gradient), as independent predictors of 28 day mortality in COVID-19 pneumonia, with non-invasive ventilation. In this study, 165 admissions for acute COVID-19 pneumonia were followed, 20.6% died and 79.4% survived. Results showed statistical differences in ABG parameters between survivors and non-survivors. Lower PaO_2 in non-survivors was associated with higher mortality risk. $PaCO_2$ had significant differences, it was higher in survivors, indicating that very low arterial CO_2 values were associated with higher mortality, possibly due to hyperventilation and respiratory exhaustion. The cut-offs that predict 28 day mortality, for the cohort of this study were, $PaO_2 \leq 54$ mmHg, $PaCO_2 > 24.9$ mmHg, pH ≤ 7.47, and A-a gradient ≤ 430.4 mmHg. Non-survivors had significantly lower PaO_2 and $PaCO_2$ values, consistent with hypoxemia and hyperventilation. The mortality predictor with the best discriminative capacity was A-a gradient ($p < 0.001$) [42].

Iriani *et al.* (2024) performed a retrospective study on 152 ICU admitted patients with COVID-19, to assess clinical severity and clinical outcome (survival vs. death). Of the cases analyzed, 54% of patients didn't survive. Survivors and non-survivors differed statistically. Acid-base variations were associated with worse prognosis and lower pH in non-survivors (median = 7.41 vs. 7.44). Additionally, non-survivors had lower PaO_2 (median = 48.8 vs. 73.5 mmHg), indicating hypoxemia. This group also showed more severe metabolic acidosis, with a lower HCO_3^- value (median = 22.6 vs. 25.6 mmol/L). SpO_2, measured by oximetry, was significantly lower in non-survivors (median = 83.7 vs. 95.6%) [57].

Lakhani *et al.* (2021) analyzed acid-base disturbances in 80 critically ill COVID-19 patients admitted to the ICU, from ABGs on days 1, 5, and 10 of admission. The major

finding was mixed acid-base disorders, which was present in 66.3% of admissions. It was respiratory alkalosis combined with metabolic acidosis the most frequent ABG disturbance, followed by respiratory alkalosis with metabolic alkalosis. The opposite pattern was found in non-survivors, suggesting an association with unfavorable prognosis due to combined respiratory failure and metabolic decompensation. Mixed acid-base disorders, whether involving alkalosis and acidosis, were observed in both survivors and non-survivors and showed no clear discriminatory value for outcome. The overall mortality rate was 40%, and the presence of mixed disturbances may reflect early multiorgan involvement. Sequential ABG monitoring was valuable for assessing disease progression in severe COVID-19 [52].

Bezuidenhout *et al.* (2021) analyzed the association of admission ABG profiles with clinical outcomes, of 56 patients admitted to the ICU with confirmed COVID-19. Of the 56 patients, 31 survived and 25 died. For pH, the differences were statistically significant, higher values for survivors (median = 7.48) than non-survivors (median = 7.46). Almost all patients presented with alkalemia (pH > 7.45) (64.3%) and of these 74.2% survived. PaO_2 of survivors was higher (median = 59.3 mmHg) than non-survivors (median = 48.8 mmHg). The study results indicate that improved oxygenation status on admission is related to better outcome. There was a tendency for higher HCO_3^- in survivors compared to non-survivors (median = 28.0 vs. 26.3 mmol/L), although this was not statistically significant (p = 0.059). Admission pH and PaO_2 may relate to survival in critically ill COVID-19 patients [39].

Note: In the article by Bezuidenhout *et al.* (2021), original PaO_2 values were given in kilopascals (kPa). The values were converted to millimeters of mercury (mmHg) by using the formula 1 kPa ≈ 7.5 mmHg, for standardization and comparison with the other studies presented in this dissertation.

The retrospective study by Ilczak *et al.* (2022) analyzed a cohort of 200 COVID-19 patients hospitalized from October 2020 to March 2021 to determine if ABG at triage was useful in predicting length of stay and in-hospital mortality. The authors found that the need for O_2 therapy on admission was a significant risk factor for prolonged hospitalization, and that lower pH values were associated with longer hospital stay, both statistically significant. Patients requiring O_2, with a mean pH of 7.36, had a mean length of stay 39.7% greater than the reference group (patients not requiring oxygen and pH of 7.44). Additionally, 87.0% of patients had PaO_2 < 70 mmHg, suggesting high prevalence of hypoxemia at admission. While absolute PaO_2 values did not directly influence the length of stay, admission SaO_2 was a significant predictor of mortality, with a 1.0%

increase in SaO_2 being associated with an 8.0% reduction in the risk of death. The results reinforce ABG's role as a useful and accessible tool for initial risk stratification in hospital settings, particularly in resource limited environments [58].

The observational study by Amrita and Singh (2022) evaluated 170 ABG samples from 17 patients with severe COVID-19 admitted to the ICU, to determine the prognostic value of ABG parameters. pH was significantly negatively associated with $PaCO_2$, whereas pH was positively associated with HCO_3^-, indicating that rising $PaCO_2$ corresponds to acidosis, whereas rising HCO_3^- corresponds to alkalosis. Most had mixed acid-base imbalances, 53.0% mixed disorders, 41.0% respiratory alkalosis and 6.0% respiratory acidosis. These findings underscore the physiopathological complexity of severe COVID-19 and suggest that ABG analysis may play an important role in assessing clinical severity upon ICU admission [59].

In the retrospective study by Mondal *et al.* (2021), ABG patterns in 314 ICU patients were characterized and correlated with disease severity. In 58.3% of patients, the most frequent acid-base disturbance was alkalosis ($p > 7.45$), with a rare incidence of acidosis (6.0%). As evidenced by the prevalence of hypocapnia and $PaCO_2$ < 35.0 mmHg in 55.4% of patients, respiratory alkalosis was observed. The majority (45.9%) had hypoxemia (PaO_2 < 75 mmHg) and 45.9%, had elevated HCO_3^- (> 26 mmol/L), suggesting metabolic alkalosis. Only 15.9% had low values of HCO_3^- (< 22 mmol/L). Statistical analysis revealed significant correlations between $PaCO_2$ and pH, and between $PaCO_2$ and HCO_3^-, indicating a relationship between respiratory and metabolic mechanisms regulating acid-base balance [36].

The retrospective study by Sanghani *et al.* (2022) analyzed 267 patients with moderate to severe COVID-19, to characterize ABG profiles at admission and their relationship with comorbidities. There was a high prevalence of acid-base disturbances on the first day of hospitalization. 54.3% of the patients had alkalosis, while 18.7% had acidosis. The most common pattern was primary respiratory alkalosis with secondary metabolic acidosis (25.1%). It was followed by primary respiratory alkalosis with secondary metabolic alkalosis (20.2%). 55.8% had hypocapnia, suggestive of respiratory alkalosis, and 25.8% had hypoxemia. There were significant associations between pH, $PaCO_2$ and presence of comorbidities. Patients with comorbidities exhibited the most common acid-base imbalance of isolated or combined respiratory alkalosis. There were also significant correlations among ABG parameters, with negative correlation between pH and $PaCO_2$, and positive correlation between pH and HCO_3^-, pH and BE, showing the interdependence of respiratory and metabolic components in acid-base regulation.

The data point to ABG's utility as an early assessment and monitoring tool in severe COVID-19, particularly in the presence of comorbidities [60].

Silva *et al.* (2022) conducted an integrative review to assess the importance of ABG in the follow-up of severe COVID-19 cases. Over 11 scientific articles, the authors concluded that ABG is essential for monitoring respiratory function and acid-base balance in critically ill patients, and for precise assessment of metabolic and respiratory disturbances associated with the disease. Among the main findings, hypoxemia was the most consistent parameter used to predict advanced ventilatory support need and mortality. Additionally, metabolic and respiratory acidosis was often reported as an indicator of adverse clinical outcome, indicating the utility of ABG for early detection of respiratory failure. The authors also emphasize that systematic ABG use in intensive care settings supports therapeutic decision-making, for mechanical ventilation and O_2 administration. This real time monitoring enables more targeted interventions, potentially improving prognosis and reducing in-hospital mortality due to severe COVID-19 [55].

In a study by Karuna *et al.* (2021), 97 patients with COVID-19, were analyzed. According to the clinical outcome they were divided into three groups, hospitalized, recovered, and dead. Non-survivors had significant changes in ABG, hematological and biochemical parameters, relevant to infection severity. Non-survivors had lower pH mean values than survivors (mean = 7.24 vs. 7.39), indicating that worse evolution had more intense acidemia. Non-survivors had a higher $PaCO_2$ (48.6 mmHg) than hospitalized (42.6 mmHg) and recovered (30.8 mmHg), indicating a tendency to hypercapnia with ventilatory dysfunction in death. Conversely, the mean PaO_2 value of non-survivors was 43.1 mmHg, lower than recovered (mean = 63.7 mmHg) and hospitalized (mean = 46.2 mmHg), thus indicating serious arterial oxygenation damage. According to these, there is an association between altered ABG parameters, and acidemia, hypoxemia, hypercapnia, and mortality, which supports the clinical utility of ABG in prognostic stratification of critically ill COVID-19 patients [61].

Ali *et al.* (2021) compared acid-base disturbances with clinical outcomes in 32 critically ill COVID-19 patients admitted to the ICU. There were 26 survivors and 6 non-survivors. Non-survivors had lower pH (mean = 7.23 vs. 7.42), suggesting that non-survivors were more acidotic. This group also had HCO_3^- levels slightly higher than in survivors (mean = 26.6 vs. 25.3 mmol/L), but not statistically significant. The non-survivors had a lower PaO_2 which was not statistically significant (mean = 78.1 vs. 85.5 mmHg), possibly due to greater hypoxemia. There was no significant difference in $PaCO_2$, although values were higher in non-survivors (42.1 vs 39.7 mmHg). Respiratory

acidosis was the most common acid-base profile, seen in 66.6% of patients. Metabolic acidosis was identified in 33.3%. Among survivors, metabolic alkalosis (21.9%) was the most frequent change, indicating better prognosis. They suggest that acid-base disturbances, particularly respiratory and metabolic acidosis, may be associated with higher clinical severity and mortality risk [33].

Analysis of the selected studies revealed a significant association between ABG parameters and clinical outcomes in patients with COVID-19 admitted to the ICU. Hypoxemia emerged as the parameter most uniformly related to disease severity, need for IMV and mortality. This association was particularly evident in the studies by Gupta *et al.* (2021), Iriani *et al.* (2024), Karuna *et al.* (2021), and Silva *et al.* (2022), which identified reduced PaO_2 as a strong predictor of adverse outcomes, underscoring arterial oxygenation as an important indicator of clinical status [39], [42], [55], [57].

Regarding acid-base balance, acidosis, both metabolic and respiratory, were associated with worse prognosis. Studies by Gupta *et al.* (2021), Lakhani *et al.* (2021), Karuna *et al.* (2021), and Ali *et al.* (2021) reported significantly lower pH and higher $PaCO_2$ values among non-survivors, suggesting that acid-base disturbances reflect respiratory failure and systemic decompensation [33], [42], [52], [61]. Similarly, lower HCO_3^- concentration, indicative of metabolic acidosis, was also identified as marker of clinical decompensation, as shown by Iriani *et al*. (2024) and Ilczak *et al.* (2022) [57], [58].

Metabolic alkalosis in early stages of disease has been associated with a more favorable prognosis. Lakhani *et al.* (2021), Bezuidenhout *et al.* (2021), and Ali *et al.* (2021) observed a higher alkalosis prevalence in survivors, which may be a physiological compensatory response to initial respiratory disease [33], [39], [52]. However, this association was not universal Sembai *et al.* (2023) found no statistically significant association, perhaps because of influencing factors such as comorbidities, length of hospital stay and differences in therapeutic management [37].

In the early phase of infection, compensatory hyperventilation and reduced $PaCO_2$ values have been described by Mondal *et al.* (2021) and Sanghani *et al.* (2022), reflecting an adaptive mechanism to hypoxia. Nevertheless, the persistence of this pattern may lead to ventilatory fatigue, acidosis, and progressive clinical deterioration [36], [60].

Overall, the literature shows worse outcomes with low PaO_2, low pH, and elevated $PaCO_2$ [31], [32], [39], [42], [44], [57]. Conversely, higher pH and HCO_3^- values (metabolic alkalosis) were associated with better prognosis [33], [39], [52]. All these findings reinforce the role of ABG as a valuable predictive tool for risk stratification, continuous monitoring, and therapeutic decision-making in critically ill COVID-19 patients [42], [57], [58].

2.7. COVID-19 and Precision Medicine

According to Akhoon [6], precision medicine represents a paradigm shift, away from “one-size-fits-all” model to an individualized approach to prevention, diagnosis, and treatment. It seeks to provide “the right treatment, at the right time, to the right person”, by integrating information on each individual’s genetics, environment, and lifestyle. The concept emerged from major advances in molecular and genomic sciences, such as proteomics, metabolomics, and genomics, that allow a better understanding of biological variability in patients. Utilizing this variability, precision medicine aims to maximize therapeutic efficacy with minimal side effects [6].

The relevance of the principles of precision medicine for understanding disease mechanisms and guiding clinical interventions increased considerably during the COVID-19 pandemic. SARS-CoV-2 infection revealed inter-individual variability in clinical manifestations not explained by age or comorbidities alone. That extends to vaccine response and immune profiling too. Genetic and environmental factors affect antibody production and immune memory formation after vaccination. Understanding such determinants may help identify subgroups of lower vaccine efficacy and guide alternative dosing regimens or booster strategies [7].

This study follows the principles of precision medicine, identifying predictive markers of clinical outcomes in critically ill COVID-19 patients based on ABG parameters and other clinical and demographic variables. By examining these variables, this dissertation supports individualized risk profiles for early clinical decision-making and tailored interventions in the intensive care setting. This reflects the goal of precision medicine to translate physiological and biochemical variability into individualized and evidence-based strategies to improve prognosis and resource allocation in severe respiratory failure [6], [7].

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3 Methodology

3.1. Study population, Sample and Data Organization

Patients admitted to the ICU of *Unidade Local de Saúde de São José* with a COVID-19 diagnosis confirmed by RT-PCR test (reverse transcription polymerase chain reaction), between March 2020 and August 2022, were included in this study population. Only patients aged over 18 years with full clinical record and ABG data were eligible. Using these criteria, the final study sample included 794 patients.

This study included within the PREMO project, as previously mentioned, was approved by the institution's Ethics Committee and was developed in accordance with legal and ethical standards.

For the analysis, a validated Microsoft Excel database belonging to the PREMO project was used, with patient information including clinical and demographic data and ABG results. Missing or implausible values were excluded prior to analysis. All data were extracted from electronic hospital records.

3.2. Clinical and demographic data

Demographic variables included sex, age, and country of origin (Portugal or not). Temporal variables included ICU admission and discharge dates, COVID-19 diagnosis date, and the lengths of hospitalization, ICU stay and IMV and ECMO duration were determined. The ABG sampling date was always verified to ensure it coincided with the first day of ICU admission.

For patients who died, the discharge date coincided with the death date. This information was reflected in the variables ‘ICU Death’ and ‘Hospital Death’. In this analysis, the variable ‘ICU Death’ was used instead of ‘Hospital Death’, as it more directly

reflects the outcome within the ICU. Since all variables analyzed correspond to data collected during the ICU stay, this outcome ensures consistency between clinical parameters and the corresponding prognostic result. Accordingly, this variable will be referred to throughout the text as 'ICU-D'.

For the temporal context of the pandemic, patients were categorized into COVID-19 waves, based on criteria from a previous PREMO study: 1st wave: 10 March – 22 August 2020; 2nd wave: 23 August – 19 December 2020; 3rd wave: 20 December 2020 – 31 May 2021; 4th wave: 01 June – 31 October 2021; 5th wave: 01 November – 31 March 2022; and 6th wave: 01 April – 08 August 2022 [13].

Using this criterion throughout the study, patient assignment to each wave was based on the earliest date of RT-PCR diagnosis and symptom onset.

Vaccination status (vaccinated or unvaccinated) was determined at admission to the ICU. The cut-off date was defined as 31 December 2020, to mark the start of national vaccine rollout.

Respiratory support included IMV and/or ECMO, depending on disease severity. Durations were calculated in days.

The variable 'Reason for Admission' was included in the database and categorized as: COVID-19 and/or ARDS diagnosis, emergency surgery, ischemic heart disease, stroke, septic shock, arrhythmia, Guillain-Barré syndrome, renal failure, and 'Other' for reasons not covered by the previous categories.

Comorbidities previously assessed by healthcare professionals were recorded. The comorbidities considered were: hypertension (HTN), ischemic heart disease, congestive heart failure (CHF), diabetes mellitus (DM), chronic pulmonary disease (chronic obstructive pulmonary disease (COPD)/asthma/pulmonary emphysema), pulmonary hypertension, renal insufficiency, benign prostatic hyperplasia (BPH), dyslipidemia, hyperuricemia, solid tumor, hematologic malignancy, depression, amyloidosis, multiple sclerosis, obesity, hypothyroidism, acquired immunodeficiency syndrome (AIDS), dysrhythmia, chronic liver disease, stroke, transplant, autoimmune disease, Parkinson's disease, epilepsy, or schizophrenia.

3.3. Arterial Blood Gas parameters

Regarding ABG results, each variable was measured repeatedly during the first 24 hours of ICU admission to assess early disease progression and detect variations. For this reason, the maximum and minimum values for the variables under study were included in the database.

3.4. Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics software, (v30.0.0.0) (IBM Corp., Armonk, NY, USA), which ensured the rigorous application of the selected statistical tests and systematic organization of the results obtained [62].

The statistical approach constituted the core of the study, including descriptive, exploratory, and inferential analyses adapted to the nature of the data in line with the study hypotheses, to identify associations and predictive patterns between ABG parameters and clinical outcomes, as well as assessing their variation across vaccination periods and pandemic waves. It also encompassed the analysis of ICU length of stay, duration of IMV and ECMO support, and the development of GLMs to assess outcome determinants.

Initially, the variables in the database were organized according to their type and the clinical range restrictions given by the clinical specialist Dr. Luís Bento. Categorical variables included sex, country of origin (Portugal or not), vaccination status, need for IMV and ECMO, presence of IMV or ECMO at the time of ABG sampling, presence of comorbidities (specified through binary variables), Hospital death and ICU death, pandemic wave code, and reason for admission (with nine categories coded from 1 to 9). Numerical variables were subdivided into continuous and discrete. Continuous variables included age and maximum and minimum values of ABG parameters. Discrete variables included, for example, the number of days between ICU admission and ABG sampling date.

For continuous variables, normality tests, Kolmogorov-Smirnov and Shapiro-Wilk tests were applied. In most cases, continuous variables were not normally distributed. Variables were summarized as median and IQR [P_{25}-P_{75}]. Age was the only exception, because it followed a normal distribution, and was reported as mean and standard deviation (SD). Categorical variables were described as absolute and relative frequencies.

Based on the variable type and its distribution, different statistical tests were applied. For comparisons between two independent groups, such as survivors versus non-survivors or patients with versus without IMV or ECMO, the Pearson chi-square test was used for categorical variables. When more than 20% of the expected cell counts were below five, the Fisher-Freeman-Halton test was applied to ensure the robustness of the results. For continuous variables with non-normal distributions, non-parametric methods were used, specifically the Mann-Whitney U test for comparisons between two independent groups. When comparisons involved more than two groups, such as the analysis of ABG parameters across the six pandemic waves, the non-parametric Kruskal-Wallis test was employed.

To evaluate the association between patient ABG parameters and the three clinical outcomes: length of stay in the ICU, duration of IMV, and duration of ECMO, given the count nature of these outcomes, the generalized linear models (GLMs) with a Poisson distribution and a log link function were applied. Each outcome was modeled separately using the following GLM specification:

- Dependent variables:
    - ICU length of stay: number of days in the ICU;
    - IMV duration: number of days on invasive mechanical ventilation;
    - ECMO duration: number of days on ECMO support;
- Independent variables:
    - ABG indicators measured at ICU admission, including:
        - Arterial pH;
        - Arterial partial pressure of oxygen (PaO_2);
        - Arterial partial pressure of carbon dioxide ($PaCO_2$);
        - Lactate levels;
    - The demographic and clinical patient characteristics (comorbidities).

The GLM was implemented with a logarithmic link function to model the natural log of the expected count as a linear function of the predictors.

The general model form was:

$$\log(E[Y_i]) = \beta_0 + \beta_1 \cdot pH_i + \beta_2 \cdot PaO_{2i} + \beta_3 \cdot PaCO_{2\,i} + \beta_4 \cdot HCO_3^-{}_i + \beta_5 \cdot Lactate_{\,i} + \varepsilon_i$$

Where (Yi) represents one of the three outcomes for patient (i).

To assess model performance, the following model fit indicators were used:

- Deviance and Pearson Chi-Square statistics;
- Akaike information criterion (AIC);
- Log-likelihood.

For overdispersion assessment, the ratio of Pearson Chi-Square to degrees of freedom was examined. If overdispersion was detected, a negative binomial model was considered as an alternative. To analyze the prediction accuracy, the predicted values and residuals were saved for each model, as well as the root mean square error (RMSE) and mean absolute error (MAE). Residual plots were visually inspected to detect non-random patterns or outliers. For Influence Diagnostics the Cook's Distance was calculated to identify influential observations that could disproportionately affect model estimates. Likelihood Ratio Tests were used to assess the contribution of each predictor to the model. The parameter estimates were reported with 95% confidence intervals and *p-values*.

All statistical analyses were two-sided, with a significance level of $p < 0.05$, and all procedures complied with the assumptions required for test validity.

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4 Results

This chapter presents the descriptive, exploratory and inferential analyses performed in this study, to address the objectives.

The results are structured into three main sections. The first provides a characterization of the study sample, including demographic and clinical variables and their association with the outcomes and ABG parameters. The second explores how ABG parameters and clinical outcomes change over time, throughout the vaccination periods and COVID-19 waves. Finally, the third analyzes the duration of ICU stay and advanced life supports (IMV and ECMO), identifying factors associated with the duration of care.

Whenever possible, both descriptive and inferential statistics are presented, with emphasis on statistically significant results ($p < 0.05$). Depending on the data type, tables include absolute and relative frequencies, as well as medians accompanied by the 25^{th} and 75^{th} percentiles (P_{25} – P_{75}). These percentiles are reported to illustrate the distribution of the data but are discussed only when relevant to the interpretation of the results.

4.1. Analysis of the Total Sample

4.1.1. Global Characterization

4.1.1.1. Clinical and Demographic Profile

Table 4.1 presents the patients profile, with context on age, sex, comorbidities, and ICU admission reasons.

The sample had 794 patients, mostly male (68.5%; n = 544 vs. 31.5%; n = 250). The mean age was 60 ± 15.8 years. The majority (81.6%; n = 648) had at least one comorbidity, and the most frequent conditions were HTN (52.3%), DM (31.1%), dyslipidemia (22.8%), and obesity (21.7%). The most common ICU admission reason was COVID-19 and/or ARDS (87.5%; n = 695), followed by emergency surgery (3.7%) and acute kidney failure (2.6%).

Table 4.1. - Demographic and Clinical Characteristics of the Study Sample.

Category	Variable	Value
Study sample	**Total ICU admissions**	794
Sex	**Male**	68.5% (n=544)
	Female	31.5% (n=250)
Age	**Mean ± SD**	60 ± 15.8 years
Comorbidities (≥ 1)	**Presence of at least 1 comorbidity**	81.6% (n=648)
	Hypertension	52.3% (n=415)
	Diabetes mellitus	31.1% (n=247)
	Dyslipidemia	22.8% (n=181)
	Obesity	21.7% (n=172)
	Respiratory diseases	12.6% (n=100)
	Ischemic heart disease	8.9% (n=71)
	Renal insufficiency	8.3% (n=66)
	Cardiac arrhythmias	6.3% (n=50)
	Solid tumor	6.2% (n=49)
	Hypothyroidism	4.7% (n=37)
	Hematologic malignancy	4.5% (n=36)
	Autoimmune disease	4.2% (n=33)
	Stroke	3.9% (n=31)
	Benign prostatic hyperplasia	3.8% (n=30)
	Hyperuricemia	3.4% (n=27)
	Congestive heart failure	2.6% (n=21)
	Pulmonary hypertension	0.1% (n=1)
ICU admission reason	**COVID-19 and/or ARDS**	87.5% (n=695)
	Emergency surgery	3.7% (n=29)
	Kidney failure	2.6% (n=21)
	Stroke	1.6% (n=13)
	Others	1.4% (n=11)
	Guillain-Barré syndrome	1.0% (n=8)
	Septic shock	0.9% (n=7)
	Heart rate changes	0.9% (n=7)
	Myocardial infarction	0.4% (n=3)

4.1.1.2. Clinical Outcomes by Admission Reason

Table 4.2 demonstrates the association of ICU admission reasons with clinical outcomes.

In the cohort (n = 794), 28.6% died in the ICU (n = 227), 69.9% needed IMV (n = 555), and 8.6% needed ECMO (n = 68). Most admissions (87.5%) were due to COVID-19 and/or ARDS. Of the patients admitted for COVID-19 and/or ARDS, 31.2% died in the ICU, 79.9% required IMV and 9.8% had ECMO. Patients who were admitted because of COVID-19 and/or ARDS had the highest ICU-D (31.2%), followed by septic shock (19.0%) and renal failure (14.3%). But renal failure and septic shock had small number of cases (n = 3 and n = 4, respectively), and percentages of these groups should be considered cautiously, as small groups may exaggerate differences.

Table 4.2. – Clinical Outcomes by Admission Reason.

Clinical Outcomes	ICU-D (28.6%; n=227)	IMV (69.9%; n=555)	ECMO (8.6%; n=68)
COVID-19 and/or ARDS (n=695)	31.2% (n=217)	79.9% (n=555)	9.8% (n=68)
Emergency surgery (n=29)	3.4% (n=1)	0.0% (n=0)	0.0% (n=0)
Myocardial infarction (n=3)	0.0% (n=0)	0.0% (n=0)	0.0% (n=0)
Stroke (n=13)	7.7% (n=1)	0.0% (n=0)	0.0% (n=0)
Septic shock (n=7)	19.0% (n=4)	0.0% (n=0)	0.0% (n=0)
Heart rate changes (n=7)	0.0% (n=0)	0.0% (n=0)	0.0% (n=0)
Guillain-Barré syndrome (n=8)	0.0% (n=0)	0.0% (n=0)	0.0% (n=0)
Kidney failure (n=21)	14.3% (n=3)	0.0% (n=0)	0.0% (n=0)
Other (n=11)	9.1% (n=1)	0.0% (n=0)	0.0% (n=0)

Table 4.3 aims to evaluate whether the admission reason, specifically COVID-19 and/or ARDS compared with all other admission reasons, is associated with the clinical outcomes.

For admitted COVID-19 and/or ARDS patients, 31.2% (n = 217) died in the ICU, 79.9% (n = 555) required IMV, and 9.8% (n = 68) required ECMO. Those admitted for another cause had 10.1% ICU-D (n = 10), with no IMV or ECMO. ICU-D showed statistical difference ($p < 0.001$), as it was the only outcome with sufficient cell counts to have validity of the test. For IMV and ECMO, no *p-value* was reported because all events occurred in the COVID and/or ARDS group.

Table 4.3 differs from Table 4.2, in that in 4.2 the distribution of all specific admission reasons is examined in relation to the clinical outcomes and is given an insight into their

associations. Table 4.3 compares specifically COVID-19 and/or ARDS admissions with all other causes together, to determine whether admission due to COVID-19 and/or ARDS was associated with the observed outcomes.

Table 4.3. – Clinical Outcomes by COVID-19 and/or ARDS.

Clinical Outcomes	ICU-D (28.6%; n=227)	IMV (69.9%; n=555)	ECMO (8.6%; n=68)
COVID-19 and/or ARDS (n=695)	31.2% (n=217)	79.9% (n=555)	9.8% (n=68)
Other admission reasons (n=99)	10.1% (n=10)	0.0% (n=0)	0.0% (n=0)
p-value*	< 0.001		

* *p-value* obtained using Pearson's Chi-square test

4.1.1.3. IMV and ECMO Relationship

Table 4.4 shows the relationship between IMV need and ECMO support.

Of the 794 patients included, 555 (69.9%) were on IMV, while 68 (8.6%) were on ECMO support. All patients who were on ECMO were also on IMV, as evident from the absence of cases under the category "ECMO Yes / IMV No". However, among the patients who received IMV, only a small proportion (12.3%) were also on ECMO.

These results showed that there is a strong relationship between IMV and ECMO, given that ECMO support occurred exclusively in patients who were also on IMV.

Table 4.4. - Relationship between IMV and ECMO.

Support		ECMO		
		No	Yes	Total (n)
IMV	No	100% (n=239)	0% (n=0)	239
	Yes	87.5% (n=487)	12.3% (n=68)	555
Total (n)		726	68	794

4.1.1.4. Sex-Based Differences

Table 4.5 and Figure 4.1 present the comparison of prevalence and distribution of comorbidities and clinical outcomes by sex. This analysis evaluates whether there are significant differences between men and women regarding the presence of specific comorbidities and about clinical outcomes.

The following comparisons are based on the first two columns of Table 4.5, that correspond to the proportions tested for statistical significance. The percentage of patients that had at least one comorbidity was significantly higher in women (90.0%) in comparison to men (77.8%) ($p < 0.001$), suggesting that women had a more comorbid clinical profile.

Some comorbidities had statistically significant sex-based differences. Women more often presented with DM (38.4% vs. 27.8%, $p = 0.003$), obesity (30.4% vs. 17.6%, $p < 0.001$), hypothyroidism (8.8% vs. 2.8%, $p < 0.001$), autoimmune diseases (6.8% vs. 2.2%, $p = 0.004$) and depression (3.2% vs. 0.9%, $p = 0.031$). Men had a greater frequency of hyperuricemia (4.8% vs. 0.4%, $p = 0.002$) and respiratory diseases (14.5% vs. 8.4%, $p = 0.016$).

Regarding clinical outcomes, the need for IMV was higher in men (72.6% vs. 64.0%, $p = 0.014$). ICU-D and ECMO were not significantly different between sexes ($p = 0.355$; $p = 0.352$, respectively).

Table 4.5 has four main columns divided into two sets for men and women. The first two columns (“Men” and “Women”) present the absolute and relative frequencies of each comorbidity and clinical outcome within each sex, allowing direct comparison of prevalence rates between male and female patients. In the columns to the right (“Case distribution (% Men)” and “Case distribution (% Women)”), for each variable, the proportion of total cases contributed by each sex, is shown, that is, how the total number of patients with a given condition or outcome is distributed between men and women. This allows a more detailed interpretation. It distinguishes whether one sex is more commonly affected by one comorbidity (prevalence) or whether that sex accounts for a larger proportion of the total cases (distribution across the cohort).

To take the obesity row as an example, 30.4% of women (n = 96) and 17.6% of men (n = 76) were obese. In relative terms, women were more prevalent than men. Despite a bigger percentage of cases in women, men still made up most of the cases of obesity (55.8% of total obese patients), probably because men were a larger proportion of the cohort (68.5%).

To summarize, the burden of comorbidity was higher in women, particularly for DM, obesity, hypothyroidism, autoimmune diseases and depression. Men presented more frequently with hyperuricemia and respiratory diseases and were more likely to require IMV.

Table 4.5. – Comorbidities and Clinical Outcomes by Sex.

Sex	Men (68.5%; n=544)	Women (31.5%; n=250)	*p-value* *	Case distribution (% Men)	Case distribution (% Women)
Presence of ≥ 1 comorbidity	77.8% (n=423)	90.0% (n=225)	< 0.001	65.3%	34.7%
Hypertension	50.2% (n=273)	56.8% (n=142)	0.083	65.8%	34.2%
Diabetes mellitus	27.8% (n=151)	38.4% (n=96)	0.003	61.1%	38.9%
Dyslipidemia	23.7% (n=129)	20.8% (n=52)	0.363	71.3%	28.7%
Hyperuricemia	4.8% (n=26)	0.4% (n=1)	0.002	96.3%	3.7%
Obesity	17.6% (n=96)	30.4% (n=76)	< 0.001	55.8%	44.2%
Ischemic heart disease	9.6% (n=52)	7.6% (n=19)	0.369	73.2%	26.8%
CHF	2.8% (n=15)	2.4% (n=6)	0.771	71.4%	28.6%
Heart rate changes	6.8% (n=37)	5.2% (n=13)	0.388	74.0%	26.0%
Hypothyroidism	2.8% (n=15)	8.8% (n=22)	< 0.001	40.5%	59.5%
Depression	0.9% (n=5)	3.2% (n=8)	0.031[A]	38.5%	61.5%
Respiratory diseases	14.5% (n=79)	8.4% (n=19)	0.016	79.0%	21.0%
Autoimmune diseases	2.2% (n=12)	6.8% (n=17)	0.004	41.4%	58.6%
Hematologic malignancy	5.3% (n=29)	2.8% (n=7)	0.111	80.6%	19.4%
Solid tumor	6.4% (n=35)	5.6% (n=14)	0.650	71.4%	28.6%
Chronic liver failure	2.9% (n=16)	1.6% (n=4)	0.263	80.0%	20.0%
ICU-D	29.6% (n=161)	26.4% (n=66)	0.355	70.9%	29.1%
ECMO	9.2% (n=34)	7.2% (n=16)	0.352	73.5%	26.5%
IMV	72.6% (n=377)	64.0% (n=167)	0.014	71.2%	28.8%

* *p-value* obtained using Pearson's Chi-square test

[A] *p-value* obtained using Fisher-Freeman-Halton exact test

Figures 4.1.1 and 4.1.2 show the distribution of comorbidities and outcomes by patients' sex.

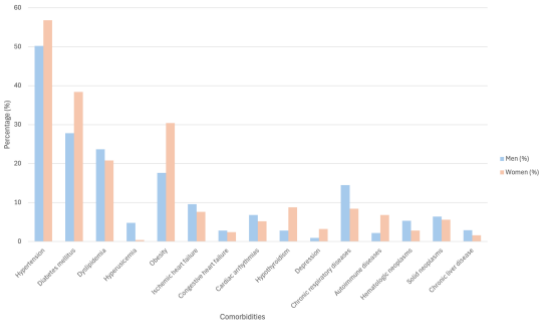

Figure 4.1.1 - Comorbidities by Sex

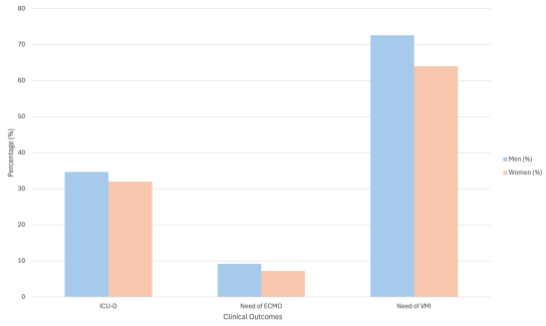

Figure 4.1.2 - Clinical outcomes by sex

4.1.1.5. Vaccination Status and Clinical Outcomes

Table 4.6 and Figure 4.2 present the association between the status of vaccination against COVID-19 (vaccinated or unvaccinated) with clinical outcomes. This evaluates whether vaccination was associated with clinical outcomes.

As an example, in the “IMV Yes" row, of the 555 patients that were on IMV, 468 were unvaccinated and only 87 were vaccinated. Unvaccinated patients had a higher prevalence of ICU-D (29.9% vs. 23.7%), but not significant (p = 0.111). This group also presented a higher and significant prevalence of IMV need (74.9% vs. 51.5%, p < 0.001), suggesting a lower need for IMV in vaccinated patients. ECMO support was also more prevalent in unvaccinated patients (9.3% vs. 5.9%), but this was not significantly different (p = 0.166).

The rows labeled “No” for each outcome represent patients who did not experience the corresponding adverse event, representing those who survived their ICU stay (ICU-D “No”), did not require IMV (IMV “No”), or did not need ECMO (ECMO “No”). Higher percentages in these “No” rows correspond to better clinical outcomes, reflecting survival and lower disease severity.

Across all outcomes, a consistent trend was observed in which vaccinated patients showed lower proportions of adverse clinical events (ICU-D, IMV and ECMO) and higher proportions of favorable outcomes (survival without advanced support). Although statistical significance was only reached for the need for IMV.

Table 4.6. – Clinical Outcomes by Vaccination Status.

Vaccination Status		Unvaccinated	Vaccinated	*p-value* *
ICU-D	**Yes (n=227)**	29.9% (n=187)	23.7% (n=40)	0.111
	No (n=567)	70.1% (n=438)	76.3% (n=129)	
IMV	**Yes (n=555)**	74.9% (n=468)	51.5% (n=87)	< 0.001
	No (n=239)	25.1% (n=157)	48.5% (n=82)	
ECMO	**Yes (n=68)**	9.3% (n=58)	5.9% (n=10)	0.166
	No (n=726)	90.7% (n=567)	94.1% (n=159)	

* *p-value* obtained using Pearson’s Chi-square test

Figure 4.2 is the visual representation of the distribution of clinical outcomes according to vaccination status.

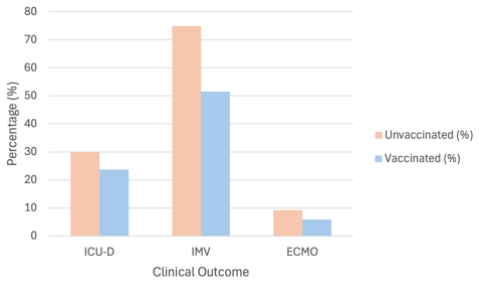

Figure 4.2. – Clinical outcomes by vaccination status.

4.1.1.6. Lengths of Stay and Duration of Supports

Table 4.7 and Figure 4.3 present the association between the number of ICU stay days, duration of IMV and ECMO, and the clinical outcomes. The purpose is to establish if differences in the outcomes were related to the duration of ICU stay and use of respiratory and circulatory support.

Patients who required IMV had significantly longer ICU stay (median = 11 days [P_{25}-P_{75}: 6-18] vs. 3 days [P_{25}-P_{75}: 2-6], $p < 0.001$). Likewise, patients on ECMO had longer ICU stay (median = 22 days [P_{25}-P_{75}: 12-39] vs. 7 days [P_{25}-P_{75}: 4-13], $p < 0.001$). Wider IQRs across groups reflect greater variability in ICU stay among patients with advanced support. ICU-D did not significantly affect ICU stay duration (median = 9 vs. 8 days; $p = 0.500$). There was no significant difference in IMV duration among survivors and non-survivors (median = 8 vs. 9 days; $p = 0.747$). However, IMV need was longer in ECMO patients (median = 19 days [P_{25}-P_{75}: 9-41] vs. 8 days [P_{25}-P_{75}: 4-13]; $p < 0.001$). Median ECMO duration was comparable in survivors and non-survivors (median = 12 vs. 14 days; $p = 0.828$).

Some cells were not applicable, because some comparisons were not possible (for example, IMV duration in patients never ventilated). Overall, it shows that the longer length of ICU stay as well as higher medians and wider percentiles of patients requiring IMV and ECMO reflects greater clinical complexity and heterogeneity. In addition, the duration of support and care was not statistically related to survival outcome.

Table 4.7. – Duration of Care and Clinical Outcomes.

Clinical Outcome		ICU-D		IMV		ECMO	
		Yes	No	Yes	No	Yes	No
No. of ICU stay days	Median [P_{25}-P_{75}]	8 [4-16]	8 [4-15]	11 [6-18]	3 [2-6]	22 [12-39]	7 [4-13]
	*p-value**	0.500		< 0.001		< 0.001	
No. of days with IMV	Median [P_{25}-P_{75}]	9 [4-16]	8 [4-16]	-	-	19 [9-41]	8 [4-13]
	*p-value**	0.747		-		< 0.001	
No. of days with ECMO	Median [P_{25}-P_{75}]	14 [5-29]	12 [5-28]	-	-	-	-
	*p-value**	0.828		-		-	

* *p-value* obtained using the Mann-Whitney U test

Figure 4.3 is the visual representation of hospitalization, IMV and ECMO duration according to clinical outcomes.

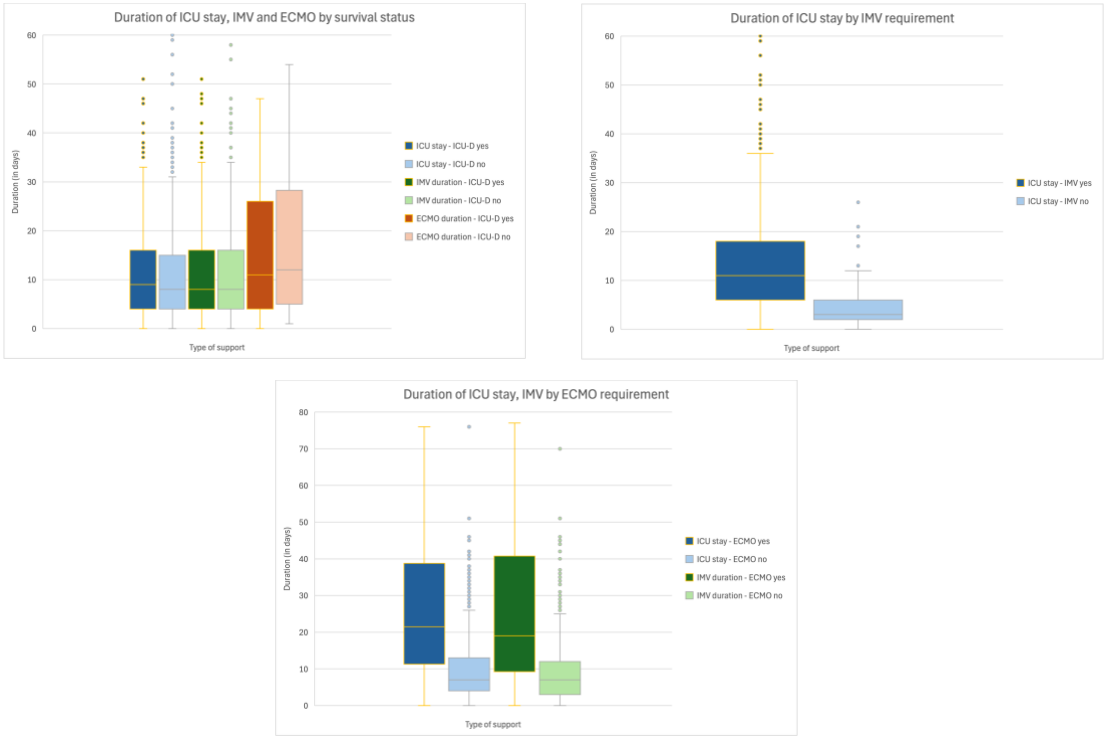

Figure 4.3. – Duration of ICU stay, IMV and ECMO.

The ICU cohort was composed of mostly men, with a mean age of 60 years old, and had a high prevalence of chronic conditions, including HTN, DM, and obesity. ICU-D was significantly associated with admission reason including COVID-19 and/or ARDS. Women had greater metabolic and endocrine comorbidities, while men had more

respiratory disease and were more likely to require IMV. Vaccination appeared to reduce IMV requirement, and longer ICU stay or support durations reflected disease complexity rather than mortality.

4.1.2. Arterial Blood Gas Analysis

4.1.2.1. Association with Clinical Outcomes

Figure 4.4

Table 4.8 and compare ABG parameters between patients across the different clinical outcomes. This analysis identifies ABG trends related to each outcome and seeks patterns that define disease severity in critically ill patients.

Results showed a pattern, in which deterioration of ABG parameters is associated with increased clinical severity. Lower maximum and minimum pH values, corresponding to greater acidemia and higher maximum $PaCO_2$ values in non-survivors, suggested reduced alveolar ventilation efficiency. Also increased maximum lactate in non-survivors suggested impaired tissue perfusion and metabolic stress. PaO_2 values remained relatively stable across groups suggesting that oxygenation alone did not discriminate clinical severity.

Table 4.8. – ABG Parameters by Clinical Outcomes.

ABG Parameters		pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
ICU-D Median [P_{25}-P_{75}]	**Yes**	7.43 [7.37-7.48]	7.36 [7.28-7.42]	83.3 [62.1-109.3]	85.7 [73.6-74.4]	44.0 [36.6-52.1]	36.9 [31.9-42.4]	1.5 [1.1-2.1]	1.1 [0.8-1.5]
	No	7.45 [7.41-7.49]	7.41 [7.34-7.45]	101.0 [68.4-113.0]	85.7 [75.2-95.7]	40.2 [36.1-46.5]	35.7 [32.1-39.3]	1.3 [0.9-1.8]	0.9 [0.7-1.2]
ECMO Median [P_{25}-P_{75}]	**Yes**	7.46 [7.38-7.49]	7.37 [7.29-7.42]	97.1 [66.1-112.0]	85.7 [74.2-95.5]	53.4 [42.5-61.8]	41.7 [31.5-51.3]	1.4 [1.0-1.9]	1.0 [0.7-1.6]
	No	7.45 [7.40-7.48]	7.40 [7.32-7.45]	101.1 [63.7-114.0]	85.9 [77.9-94.6]	40.3 [35.8-46.9]	35.8 [31.9-39.6]	1.3 [1.0-1.8]	0.9 [0.7-1.2]
IMV Median [P_{25}-P_{75}]	**Yes**	7.44 [7.39-7.48]	7.37 [7.30-7.43]	89.0 [70.7-110.0]	85.4 [73.6-96.2]	43.6 [38.6-51.1]	36.9 [32.8-41.7]	1.3 [1.0-1.9]	0.9 [0.7-1.3]
	No	7.46 [7.42-7.49]	7.44 [7.39-7.46]	101.0 [63.7-114.0]	85.7 [75.0-94.7]	36.9 [33.2-40.7]	34.2 [30.2-37.5]	1.3 [0.8-1.9]	1.0 [0.7-1.3]

Figure 4.4 represents ABG parameters according to clinical outcomes.

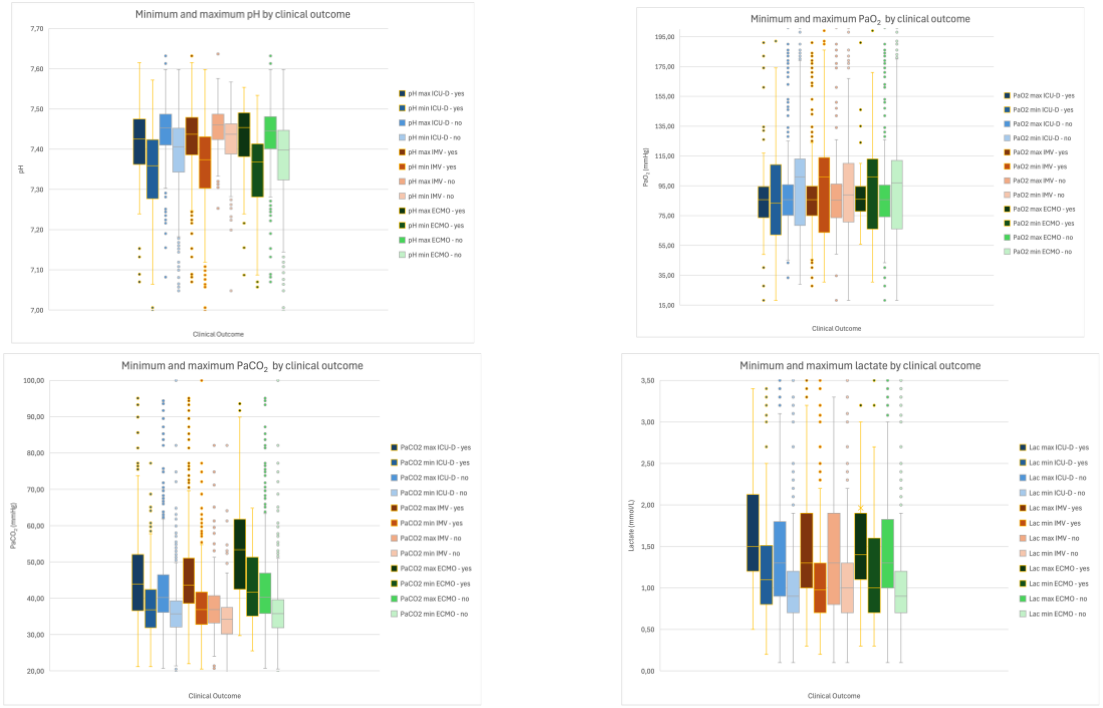

Figure 4.4. – ABG parameters by clinical outcomes.

4.1.2.1.1. ICU Mortality

Table 4.9 compares ABG parameters between survivors and non-survivors to assess association between these variables and ICU-D.

Both maximum and minimum pH were significantly lower in non-survivors than in survivors (maximum pH: 7.43 vs. 7.45, $p < 0.001$; minimum pH: 7.36 vs. 7.41, $p < 0.001$), suggesting a more acidotic state in non-survivors.

Non-survivors had lower maximum PaO_2 levels than survivors (median = 83.3 vs. 101.0 mmHg, $p = 0.025$). But minimum PaO_2 was not different between groups (median = 85.7 mmHg, $p = 0.189$), corresponding to lower oxygenation on admission day in non-survivors. Maximum and minimum $PaCO_2$ were higher in non-survivors than in survivors (maximum: median = 44.0 vs. 40.2 mmHg, $p < 0.001$; minimum: median = 36.9 vs. 35.7 mmHg, $p = 0.014$), showing that CO_2 retention was elevated in non-survivors.

For maximum and minimum lactate medians in non-survivors, similar statistically significant results were obtained (maximum: 1.5 vs. 1.3 mmol/L, $p < 0.001$; minimum: 1.1 vs. 0.9 mmol/L, $p < 0.001$), indicating that increased lactate was associated with worse outcomes.

In summary, pH, maximum PaO_2, $PaCO_2$ and lactate were significantly different in survivors compared to non-survivors, indicating worse acid-base balance, ventilation and perfusion in non-survivors.

Table 4.9. – ABG Parameters by ICU-D.

ABG Parameters		pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
UCI-D Median [P_{25}-P_{75}]	**Yes**	7.43 [7.37-7.48]	7.36 [7.28-7.42]	83.3 [62.1-109.3]	85.7 [73.6-94.4]	44.0 [36.6-52.1]	36.9 [31.9-42.4]	1.5 [1.1-2.1]	1.1 [0.8-1.5]
	No	7.45 [7.41-7.49]	7.41 [7.34-7.45]	101.0 [68.4-113.0]	85.7 [75.2-95.7]	40.2 [36.1-46.5]	35.7 [32.1-39.3]	1.3 [0.9-1.8]	0.9 [0.7-1.2]
***p-value* ***		< 0.001	< 0.001	0.025	0.189	< 0.001	0.014	< 0.001	< 0.001

* *p-value* obtained using the Mann-Whitney U test

4.1.2.1.2. IMV Requirement

Table 4.10 identifies ABG parameters associated with IMV need in patients who required and did not require IMV.

Maximum and minimum pH medians were significantly lower in ventilated patients (maximum pH: 7.44 vs. 7.46, $p < 0.001$; minimum pH: 7.37 vs. 7.44, $p < 0.001$). This suggests that IMV patients had greater metabolic and/or respiratory disruption.

Maximum and minimum PaO_2 were lower but not significantly different in ventilated patients ($p = 0.785$ for both). Maximum $PaCO_2$ did not differ significantly between groups ($p = 0.753$). However, minimum $PaCO_2$ levels in ventilated patients were significantly higher (median = 36.9 vs. 34.2 mmHg, $p < 0.001$). This reflects higher CO_2 retention and lower ventilatory efficiency in IMV patients.

Maximum lactate levels were similar between groups (1.3 mmol/L, $p = 0.467$), and minimum lactate was slightly lower in IMV patients (0.9 vs. 1.0 mmol/L), but not statistically different ($p = 0.088$). This suggests lactate was not significantly associated to IMV need.

In all patients, pH and minimum $PaCO_2$ differed significantly between IMV and non-IMV patients, suggesting that acidemia and higher CO_2 retention were the main invasive ventilatory support need markers.

Table 4.10. – ABG Parameters by IMV Need.

ABG Parameters		pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
IMV Median [P_{25}-P_{75}]	**Yes**	7.44 [7.39-7.48]	7.37 [7.30-7.43]	89.0 [70.7-110.0]	85.4 [73.6-96.2]	43.6 [38.6-51.1]	36.9 [32.8-41.7]	1.3 [1.0-1.9]	0.9 [0.7-1.3]
	No	7.46 [7.42-7.49]	7.44 [7.39-7.46]	101.0 [63.7-114.0]	85.7 [75.0-94.7]	36.9 [33.2-40.7]	34.2 [30.2-37.5]	1.3 [0.8-1.9]	1.0 [0.7-1.3]
***p-value* ***		< 0.001	< 0.001	0.785	0.785	0.753	< 0.001	0.467	0.088

* *p-value* obtained using the Mann-Whitney U test

4.1.2.1.3. ECMO Requirement

In Table 4.11, ABG parameters between ECMO and non-ECMO patients are analyzed to identify ABG variables associated with ECMO need.

Non-ECMO patients had slightly, but significantly, lower maximum pH than patients with ECMO (median = 7.45 vs. 7.46, p = 0.005). The minimum differed pH between groups, not significantly (p = 0.975). This difference in the maximum pH was small and not likely to be clinically relevant although statistically significant.

Maximum and minimum levels of PaO_2, although slightly lower in ECMO patients, did not differ significantly (p = 0.557 for both). Maximum $PaCO_2$ was higher in ECMO patients but not significantly (p = 0.666). Minimum $PaCO_2$ was higher in ECMO patients (median = 41.7 vs. 35.8 mmHg, p < 0.001). This reflects higher CO_2 retention and reduced ventilatory efficiency in ECMO patients.

In ECMO patients the median maximum and minimum lactate were slightly higher than in non-ECMO patients (maximum: 1.4 vs. 1.3 mmol/L; minimum: 1.0 vs. 0.9 mmol/L), however neither difference was statistically significant (p = 0.086; p = 0.089, respectively). This suggests that lactate is not associated with ECMO need, despite a higher lactate values in ECMO patients.

Results indicate that maximum pH and minimum $PaCO_2$ differed significantly between ECMO and non-ECMO patients, but the clinical value of the difference in maximum pH seems limited.

Table 4.11. – ABG Parameters by ECMO Need.

ABG Parameters		pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
ECMO Median [P_{25}-P_{75}]	**Yes**	7.46 [7.38-7.49]	7.37 [7.29-7.42]	97.1 [66.1-112.0]	85.7 [74.2-95.5]	53.4 [42.5-61.8]	41.7 [31.5-51.3]	1.4 [1.1-1.9]	1.0 [0.7-1.6]
	No	7.45 [7.40-7.48]	7.40 [7.32-7.48]	101.1 [63.7-114.0]	85.9 [77.9-94.6]	40.3 [35.8-46.9]	35.8 [31.9-39.6]	1.3 [1.0-1.8]	0.9 [0.7-1.2]
***p-value* ***		0.005	0.975	0.557	0.557	0.666	< 0.001	0.086	0.089

* *p-value* obtained using the Mann-Whitney U test

4.1.2.2. Influence of Comorbidities

Table 4.12 compares ABG parameters in patients with and without at least one comorbidity to assess if comorbidity was associated with significant ABG parameters changes.

Patients with comorbidities presented lower maximum and minimum pH values (maximum: median = 7.44 vs. 7.45; minimum: median = 7.37 vs. 7.41). These were statistically significant ($p = 0.028$; $p = 0.016$) and indicate an increased tendency towards acidemia in comorbidity patients.

No significant differences were observed in PaO_2, $PaCO_2$ or lactate values between the two groups. PaO_2 and $PaCO_2$ values remained stable between groups, indicating similar ventilation and oxygenation.

With comorbidities, lactate levels were slightly increased but not statistically significant (maximum: $p = 0.061$; minimum: $p = 0.210$).

When specific comorbidities were analyzed, HTN was associated with lower minimum pH and minimum PaO_2 values, DM with lower minimum pH and higher minimum $PaCO_2$, and CHF with higher maximum lactate levels. The remaining comorbidities showed no differences.

Overall results showed that comorbidities were associated with lower pH values indicating higher acid-base imbalance, whereas PaO_2, $PaCO_2$ and lactate were comparable between patients with and without comorbidities.

Table 4.12. – ABG Parameters by Comorbidity Status.

ABG Parameters	pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
With ≥ 1 comorbidity (n=648)								
Median [P_{25}-P_{75}]	7.44 [7.39-7.48]	7.37 [7.30-7.43]	90.8 [70.0-110.0]	85.6 [75.0-95.0]	40.0 [35.0-46.0]	35.7 [31.7-40.6]	1.3 [1.0-1.9]	0.9 [0.7-1.2]
Without comorbidities (n=146)								
Median [P_{25}-P_{75}]	7.45 [7.41-7.49]	7.41 [7.35-7.46]	94.1 [71.0-112.0]	85.7 [74.0-96.0]	39.3 [34.0-45.0]	35.5 [31.8-39.5]	1.2 [1.0-1.8]	0.9 [0.7-1.3]
***p-value* ***	0.028	0.016	0.464	0.358	0.693	0.328	0.061	0.210

* *p-value* obtained using the Mann-Whitney U test

4.1.2.3. Influence of Vaccination

Table 4.13 compares ABG parameters between vaccinated and unvaccinated patients, to identify differences related to vaccination status.

Maximum and minimum pH values were comparable in vaccinated and unvaccinated patients (p = 0.870; p = 0.580, respectively). This suggests that acid-base balance was not significantly different by vaccination status, suggesting that vaccination did not influence metabolic or respiratory acidemia.

Maximum PaO_2 was higher in vaccinated patients (median = 101.0 vs. 93.2 mmHg), but not statistically significant (p = 0.051). Minimum PaO_2 also differed significantly, with higher median in vaccinated patients (87.9 vs. 85.2 mmHg, p = 0.013). These results indicate that vaccinated patients had better oxygenation levels. Maximum $PaCO_2$ was significantly lower in vaccinated patients (39.9 vs. 40.7 mmHg, p = 0.008), while minimum $PaCO_2$ did not differ significantly between groups (p = 0.131). This suggests better ventilatory efficiency and lower CO_2 retention in vaccinated patients.

Maximum and minimum lactate levels were similar between groups, indicating that vaccination was not significantly associated to systemic perfusion or metabolic stress (maximum: p = 0.767; minimum: p = 0.850).

Vaccination status had no significant effect on pH or lactate levels but improved oxygenation with higher minimum PaO_2 and efficient ventilation with lower maximum $PaCO_2$.

Table 4.13. – ABG Parameters by Vaccination Status.

ABG Parameters	pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
Unvaccinated Median [P_{25}-P_{75}]	7.45 [7.40-7.48]	7.39 [7.32-7.45]	93.2 [65.1-114.0]	85.2 [73.8-94.7]	40.7 [35.6-47.1]	36.1 [32.2-40.7]	1.3 [1.0-1.8]	1.0 [0.8-1.2]
Vaccinated Median [P_{25}-P_{75}]	7.45 [7.39-7.49]	7.39 [7.32-7.45]	101.0 [71.3-110.5]	87.9 [77.5-97.5]	39.9 [35.0-46.4]	35.5 [31.5-39.4]	1.4 [1.0-1.9]	1.1 [0.8-1.3]
***p-value* ***	0.870	0.580	0.051	0.013	0.008	0.131	0.767	0.850

* *p-value* obtained using the Mann-Whitney U test

Figure 4.5 is the visual representation of ABG parameters according to vaccination status.

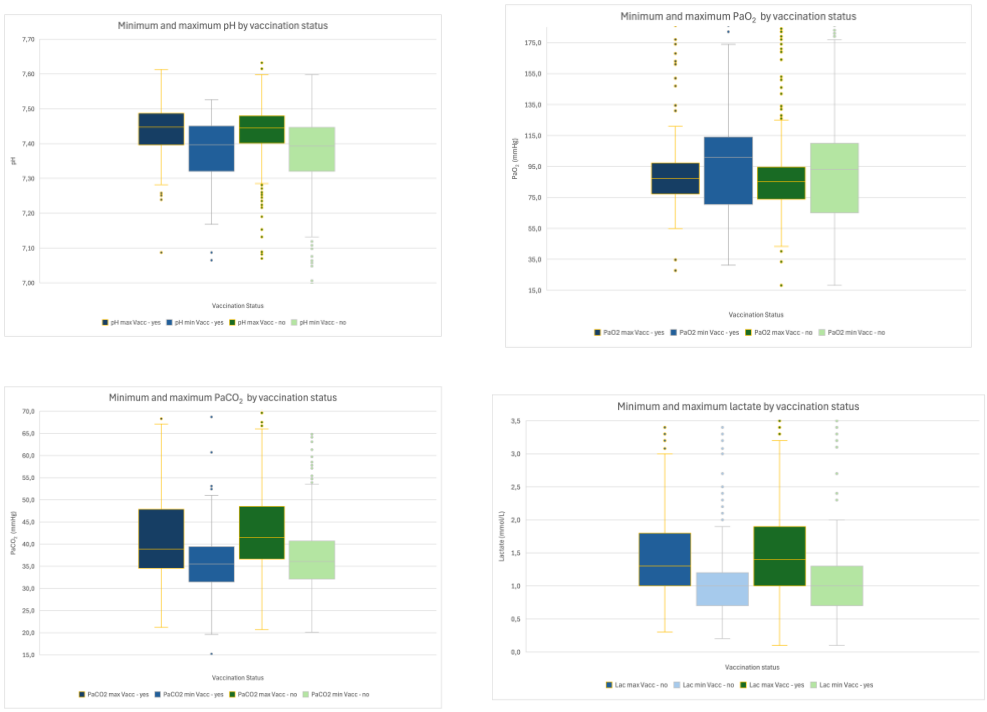

Figure 4.5. – ABG parameters by vaccination status.

4.2. Temporal Analysis: Vaccination Periods and COVID-19 Waves

To characterize the clinical course of ICU-admitted patients throughout the different phases of the pandemic, patients were analyzed according to their clinical outcomes and ABG parameters across two temporal axes, COVID-19 waves and vaccination period.

4.2.1. Comparison by Vaccination Period

4.2.1.1. Arterial Blood Gas Variation

Table 4.14 compares the ABG parameters of patients admitted before (pre-vaccination) and after (post-vaccination) the start of the vaccination campaign. The analysis assesses whether ABG changed parameters between the two periods.

Maximum and minimum pH values were similar between the two periods, with no significant difference (p = 0.668; p = 0.625, respectively). This indicates that the metabolic and respiratory disease severity associated with acidemia remained stable in the two periods.

Maximum PaO_2 was slightly higher in post-vaccination patients (median = 100.0 vs. 93.2 mmHg), and minimum PaO_2 was the same between groups (median = 87.5 mmHg), without statistical significance (p = 0.766). This finding suggests that arterial oxygenation levels did not differ statistically between periods. Post-vaccination minimum $PaCO_2$ was significantly higher (median = 36.5 vs. 35.1 mmHg, p = 0.007), but maximum $PaCO_2$ was not different statistically (p = 0.127). This indicates a small but significant increase in CO_2 retention in admitted patients after the vaccination campaign.

Maximum and minimum lactate were identical in both periods (p = 0.560; p = 0.935, respectively), suggesting no significant differences in tissue perfusion or metabolic stress.

Only minimum $PaCO_2$ differed significantly, which suggests general stability of ABG profile of critically ill patients over the pre- and post-vaccination periods.

Table 4.14. – ABG Parameters by Vaccination Period.

ABG Parameters	pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
Pre-vaccination Median [P_{25}-P_{75}]	7.44 [7.40-7.49]	7.39 [7.32-7.44]	93.2 [63.0-111.0]	85.7 [73.8-94.6]	40.4 [36.0-47.1]	35.1 [31.2-39.1]	1.3 [1.0-1.9]	0.9 [0.7-1.3]
Post-vaccination Median [P_{25}-P_{75}]	7.45 [7.39-7.48]	7.40 [7.32-7.45]	100.0 [68.3-113.0]	85.7 [75.1-95.9]	41.3 [36.4-49.2]	36.5 [32.3-41.1]	1.3 [1.0-1.8]	1.0 [0.7-1.3]
***p-value* ***	0.668	0.625	0.319	0.766	0.127	0.007	0.560	0.935

* *p-value* obtained using the Mann-Whitney U test

Figure 4.6 is the visual representation of ABG parameters according to vaccination period.

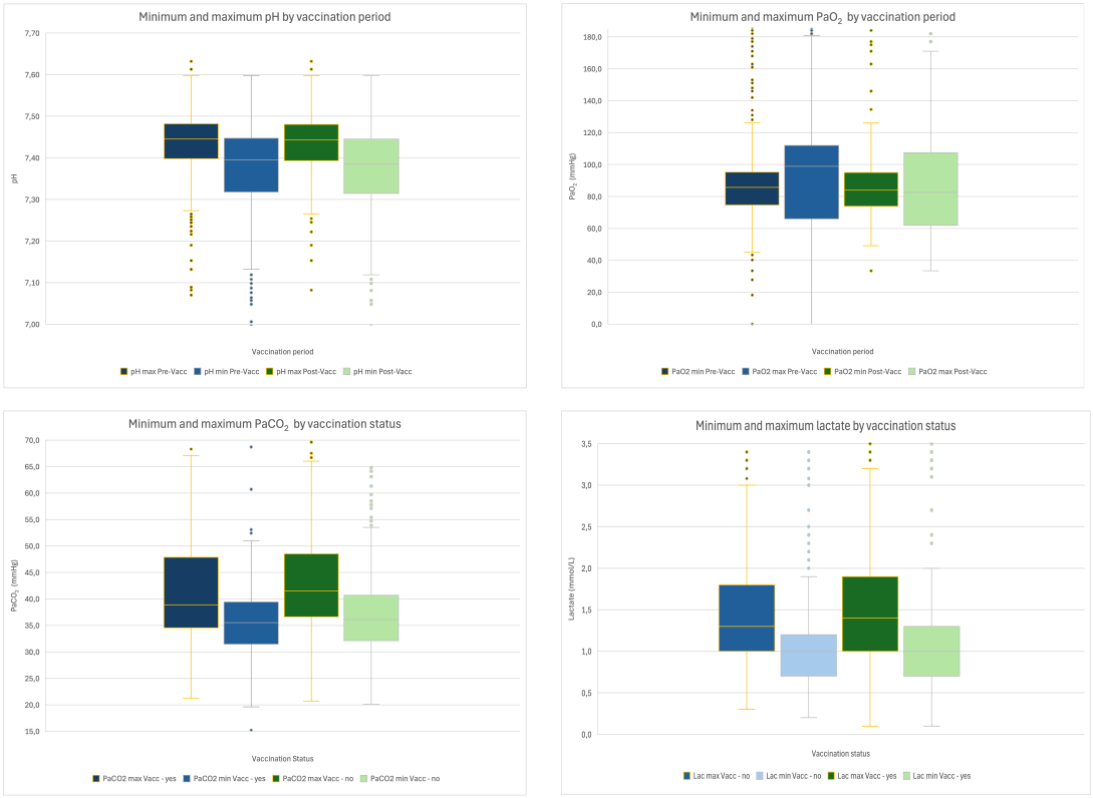

Figure 4.6. – ABG parameters by vaccination period.

4.2.1.2. Clinical Outcomes

Table 4.15 compares the distribution of clinical outcomes in admitted patients to the ICU before and after the start of the COVID-19 vaccination campaign, to determine whether vaccination was associated with changes in the clinical outcomes.

Of patients admitted before vaccination, 68.7% needed IMV compared with 72.4% after vaccination. This reflects a slightly higher IMV patients proportion in the post-vaccination period, but not statistically significant (p = 0.280). Similar for ICU-D, this was comparable between periods (27.8% vs. 30.3%; p = 0.464). ECMO support also was not significantly different (pre-vaccination: 9.0% vs. post-vaccination: 45.6%; p = 525), but not statistically significant (p = 0.525).

The rows labeled “No” in each outcome category represent patients who did not experience the corresponding adverse event, that is, those who survived the ICU admission (ICU-D “No”), did not require IMV (IMV “No”), or did not need ECMO (ECMO “No”). Higher proportions in these “No” rows reflect a more favorable clinical evolution.

Overall, the results demonstrate that ICU-D and need for IMV and ECMO did not differ significantly between pre- and post-vaccination periods. Although vaccination may have contributed to improved systemic immunity and clinical management, its effect was no statistically significant in this cohort.

Table 4.15. – Clinical Outcomes by Vaccination Period.

Vaccination Period		Pre-vaccination (n=533)	Post-vaccination (n=261)	*p-value* *
ICU-D	**Yes (n=227)**	27.8% (n=148)	30.3% (n=79)	0.464
	No (n=567)	72.2% (n=385)	69.7% (n=182)	
IMV	**Yes (n=555)**	68.7% (n=366)	72.4% (n=189)	0.280
	No (n=239)	31.3% (n=167)	27.6% (n=72)	
ECMO	**Yes (n=68)**	9.0% (n=48)	7.7% (n=20)	0.525
	No (n=726)	91.9% (n=485)	92.3% (n=241)	

* *p-value* obtained using the Pearson's Chi-square test

Figure 4.7 is the visual representation of clinical outcomes according to vaccination period.

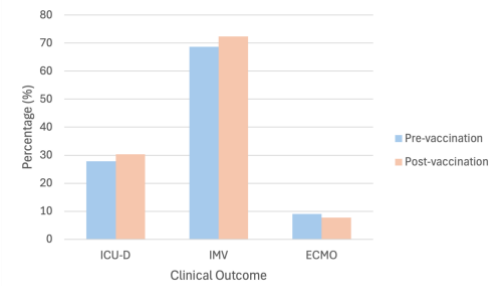

Figure 4.7. - Clinical outcomes by vaccination period

Analyzing ABG profiles by vaccination period revealed no significant changes among critically ill patients. Clinically, ICU-D, IMV, and ECMO rates decreased numerically but not significantly, suggesting a positive trend without significant physiological differences between phases.

4.2.2. Comparison by COVID-19 Wave

4.2.2.1. Arterial Blood Gas Variation

Table 4.16 analyzes the variation in ABG parameters across the COVID-19 waves, to assess whether there were significant differences between waves.

Almost all ABG parameters demonstrated significant variation across waves, suggesting temporal heterogeneity in acid-base balance, oxygenation, and ventilation patterns.

Both maximum pH (p = 0.048) and minimum pH (p = 0.003) differed statistically. Minimum pH had the lowest median values during the 1st (7.35) and 6th (7.36) waves and the highest during the 4th (7.39) and 5th (7.41) waves.

Maximum PaO_2 differed significantly ($p < 0.001$), with lower medians in 2nd and 3rd waves (90.1 and 91.5 mmHg, respectively), and higher in 5th and 6th waves (108.4 and 104.3 mmHg). Minimum PaO_2 did not differ statistically (p = 0.053). Both maximum and minimum $PaCO_2$ also varied significantly (p = 0.037; p = 0.026, respectively), with higher medians in the 6th wave (45.8 and 40.4 mmHg).

For lactate, maximum values did not differ significantly (p = 0.061), while minimum showed a small but significant variation (p = 0.049), with slightly higher medians in the 6th wave (1.08 mmol/L) compared with earlier phases (0.9-1.0 mmol/L).

Overall, these findings indicate temporal variability in ABG parameters across pandemic waves, reflecting dynamic changes in respiratory and metabolic profiles among critically ill patients throughout the course of the pandemic.

Table 4.16. – ABG Parameters by COVID-19 Wave.

ABG Parameters	pH max	pH min	PaO_2 max (mmHg)	PaO_2 min (mmHg)	$PaCO_2$ max (mmHg)	$PaCO_2$ min (mmHg)	Lactate max (mmol/L)	Lactate min (mmol/L)
1st wave Median [P_{25}-P_{75}]	7.44 [7.39-7.48]	7.35 [7.30-7.43]	103.0 [68.0-123.0]	103.0 [67.6-123.0]	44.2 [38.1-48.6]	36.3 [31.1-39.2]	1.3 [0.9-1.8]	0.9 [0.7-1.1]
2nd wave Median [P_{25}-P_{75}]	7.45 [7.40-7.49]	7.38 [7.32-7.44]	90.1 [76.2-98.6]	78.6 [61.7-107.0]	41.7 [36.3-48.6]	36.2 [31.9-40.1]	1.4 [1.0-2.1]	1.0 [0.8-1.4]
3rd wave Median [P_{25}-P_{75}]	7.44 [7.38-7.48]	7.37 [7.31-7.43]	91.5 [77.6-103.0]	88.8 [65.6-112.0]	45.3 [40.0-50.9]	38.2 [33.2-42.3]	1.3 [1.0-1.7]	1.0 [0.7-1.2]
4th wave Median [P_{25}-P_{75}]	7.46 [7.41-7.48]	7.39 [7.33-7.45]	103.9 [92.1-118.0]	102.0 [67.2-114.8]	43.9 [37.7-50.6]	37.1 [32.2-42.5]	1.4 [1.0-1.9]	0.95 [0.7-1.2]
5th wave Median [P_{25}-P_{75}]	7.45 [7.40-7.49]	7.41 [7.34-7.47]	108.4 [91.3-127.2]	100.0 [71.9-120.0]	43.3 [36.4-49.3]	37.7 [32.5-42.1]	1.4 [1.0-2.0]	0.9 [0.7-1.3]
6th wave Median [P_{25}-P_{75}]	7.43 [7.40-7.48]	7.36 [7.30-7.43]	104.3 [85.4-117.6]	101.0 [71.9-107.0]	45.8 [36.2-55.3]	40.4 [32.3-48.1]	1.4 [1.0-2.3]	1.08 [0.7-1.5]
***p-value* ***	0.048	0.003	< 0.001	0.053	0.037	0.026	0.061	0.049

* *p-value* obtained using the Kruskal-Wallis test

Figure 4.8 is the visual representation of ABG parameter variations across the six COVID-19 waves.

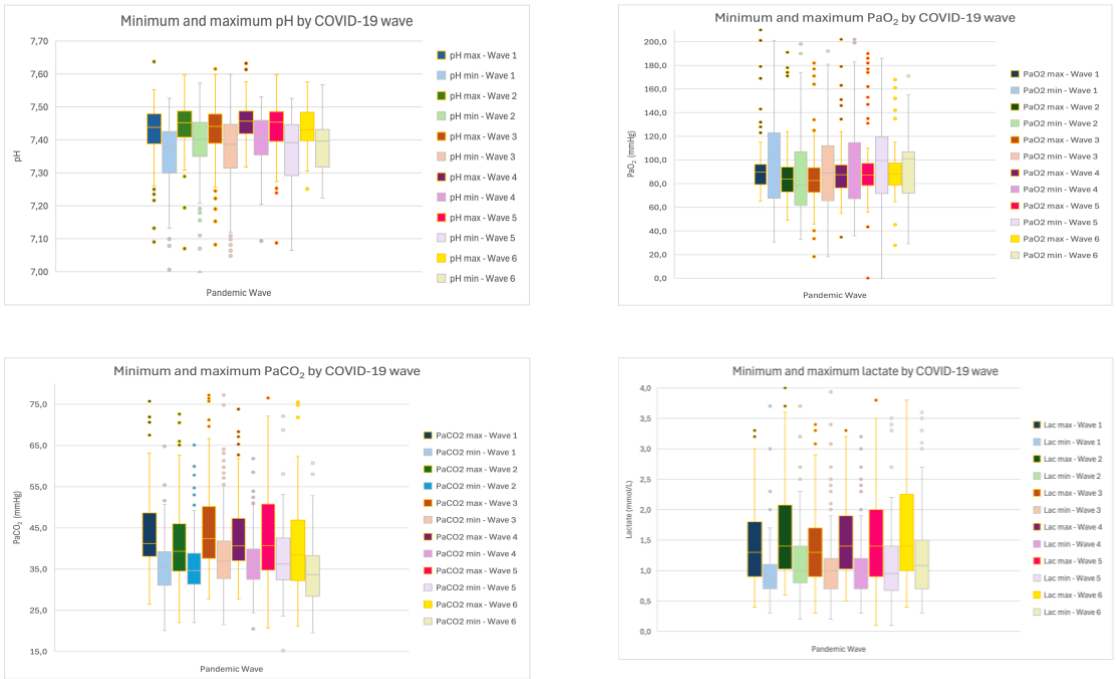

Figure 4.8. – ABG parameters by COVID-19 wave.

4.2.2.2. Clinical Outcomes

Table 4.17 analyzes the clinical outcomes across the six COVID-19 waves, to understand how these outcomes varied across pandemic waves.

Statistically significant differences were observed in all outcomes (ICU-D: $p < 0.001$; IMV: $p < 0.001$; ECMO: $p = 0.012$). ICU-D ranged from 24.7% in the 3rd wave to 7.6% in the 5th wave. This pattern suggests decreasing ICU-D over the course of the pandemic. The need for IMV followed a similar trend, being more frequent in the 3rd wave (34.7%) and less in the 5th (6.7%) and 6th waves (9.7%). This reflects a gradual reduction in respiratory failure severity over time. Although less frequent, ECMO also showed significant variability between waves, reaching its highest proportion in the 4th wave (26.9%) and lowest in the 1st (6.0%).

These findings demonstrate that the clinical outcomes varied significantly between pandemic waves, with a trend toward improvement, reflected by lower ICU-D and decreased need for IMV and ECMO, in the later stages of the pandemic.

Table 4.17. – Clinical Outcomes by COVID-19 Wave.

COVID-19 Wave		1st wave	2nd wave	3rd wave	4th wave	5th wave	6th wave	*p-value* *
ICU-D	**Yes (n=208)**	12.5% (n=63)	23.1% (n=116)	24.7% (n=124)	17.5% (n=88)	7.6% (n=38)	14.5% (n=73)	< 0.001
	No (n=502)	5.3% (n=11)	31.3% (n=65)	40.9% (n=85)	5.8% (n=12)	5.8% (n=12)	11.1% (n=23)	
IMV	**Yes (n=525)**	11.8% (n=62)	23.2% (n=122)	34.7% (n=182)	13.9% (n=73)	6.7% (n=35)	9.7% (n=51)	< 0.001
	No (n=185)	6.5% (n=12)	31.9% (n=59)	14.6% (n=27)	14.6% (n=27)	8.1% (n=15)	24.3% (n=45)	
ECMO	**Yes (n=67)**	6.0% (n=4)	23.9% (n=16)	17.9% (n=12)	26.9% (n=18)	10.4% (n=7)	14.9% (n=10)	0.012
	No (n=643)	10.9% (n=70)	25.7% (n=165)	30.6% (n=197)	12.8% (n=82)	6.7% (n=43)	13.4% (n=86)	

* *p-value* obtained using the Pearson's Chi-square test

Figure 4.9 is the visual representation of clinical outcomes across the six COVID-19 waves.

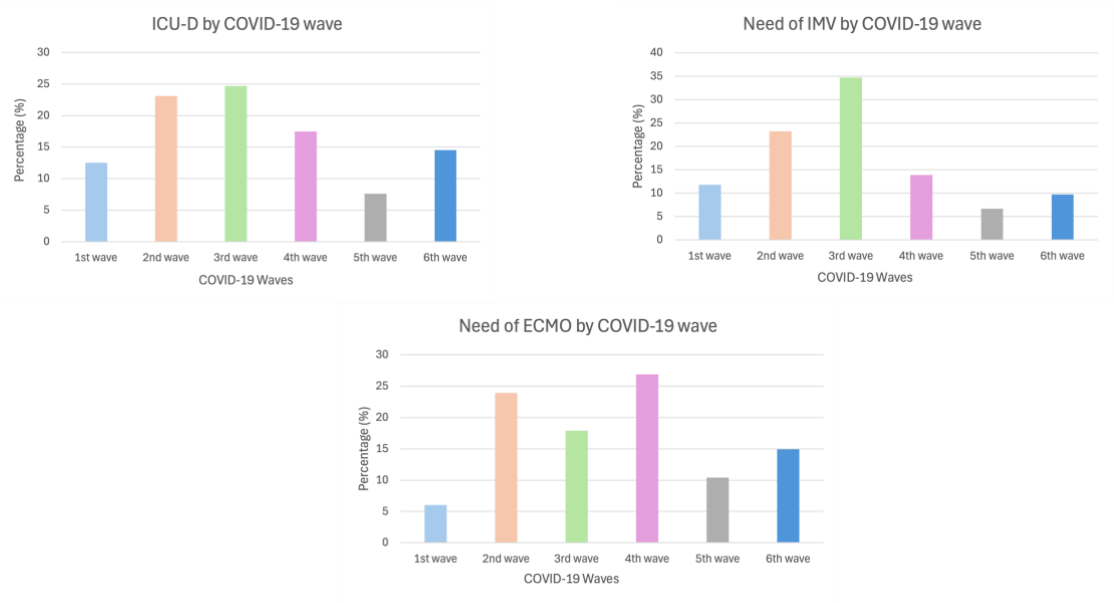

Figure 4.9. - Clinical outcomes by COVID-19 wave.

Throughout the COVID-19 waves, both physiological and clinical outcomes improved notably. Earlier waves showed more severe acidemia and hypoxemia, while later showed improved oxygenation, metabolic stability, and reduced ICU-D, need for IMV and ECMO.

4.3. Duration of Care and Associated Variables

To identify factors influencing the duration of ICU stay, IMV, and ECMO, GLMs were developed with a negative binomial distribution. Each GLM included relevant demographic, clinical, and ABG variables.

4.3.1. ICU Length of Stay

Table 4.18 presents the factors associated with ICU stay duration. Predictors were maximum lactate, maximum $PaCO_2$, vaccination status, and sex, and the dependent variable was the total number of ICU days.

The GLM identified four significant predictors of ICU length of stay. Maximum $PaCO_2$ was associated with longer ICU stays, so an increase of 1 mmHg in $PaCO_2$ corresponded to an approximately 1.7% increase in the mean number of ICU days. Maximum lactate was, however, negatively associated with ICU duration, and was associated with shorter ICU stays by 11.1%. Vaccination status was a protective factor, with unvaccinated patients hospitalized for about 32.8% longer than vaccinated patients. Male sex had a 19.1% longer ICU stay than females.

These results indicate that variation in ICU length of stay among critically ill COVID-19 patients is explained by respiratory and metabolic parameters, together with sex and vaccination status.

The GLM demonstrated good fit, as indicated by a low deviance value (608.07). The Pearson Chi-Square/df was below 1 (0.94), suggesting no evidence of overdispersion and confirming the adequacy of the negative binomial distribution.

Table 4.18. - Predictors of ICU stay duration according to the GLM

Variable	*p-value*	Exp(B)
Maximum Lactate (mmol/L)	< 0.001	0.889
Maximum $PaCO_2$ (mmHg)	< 0.001	1.017
Vaccination (0=No; 1=Yes) Reference category is to be vaccinated	0.002	1.328
Sex (0=Male; 1=Female) Reference category is to be female	0.021	1.191

4.3.2. IMV Duration

Table 4.19 presents the factors associated with the duration of IMV. The predictors included sex, presence of chronic pulmonary disease, maximum $PaCO_2$, maximum lactate, and vaccination status, and the dependent variable was the total number of IMV days.

The GLM identified five significant predictors of IMV duration. Maximum $PaCO_2$ is associated with longer IMV, so that a 1 mmHg increase in $PaCO_2$ is associated with an increase in mean number of days of IMV by about 3.1%. A similar effect was observed in patients without chronic pulmonary disease, who required 51.7% longer IMV periods than those with disease. Conversely, maximum lactate was negatively associated with IMV duration, resulting in about 11.3% shorter IMV duration. Vaccination status was a

significant factor, unvaccinated patients had IMV for approximately 64.5% longer than vaccinated patients. Men had longer IMV duration than women by 30.1%.

The model demonstrated that respiratory and metabolic variables, as well as sex, chronic respiratory disease, and vaccination status, influence the IMV duration in critically ill COVID-19 patients.

The GLM demonstrated an acceptable fit, as indicated by the deviance value (1473.78). The Pearson Chi-Square/df was 1.75, slightly above 1, suggesting mild overdispersion.

Table 4.19. - Predictors of IMV Duration according to the GLM

Variable	*p-value*	Exp(B)
Sex (0=Male; 1=Female) Reference category is to be female	0.014	1.301
Chronic Pulmonary Disease (0=No; 1=Yes) Reference category is to have chronic pulmonary disease	< 0.001	1.517
Maximum $PaCO_2$ (mmHg)	< 0.001	1.031
Vaccination (0=No; 1=Yes) Reference category is to be vaccinated	< 0.001	1.645
Maximum Lactate (mmol/L)	0.001	0.887

4.3.3. ECMO Duration

Table 4.20 presents the factors associated with the duration of ECMO. The predictors included sex, chronic pulmonary disease, obesity, maximum $PaCO_2$, maximum lactate, and vaccination status, and the dependent variable was the total number of ECMO days.

The GLM identified six significant predictors of ECMO duration. Maximum $PaCO_2$ values were associated with longer duration of ECMO support, indicating that each 1 mmHg increase in $PaCO_2$ corresponds to an approximate 3.0% rise in the mean number of ECMO days. Similarly, patients without chronic pulmonary disease required 54.4% longer ECMO duration, compared to those with disease. Non-obese patients were on ECMO for 23.6% shorter time, indicating that obese patients required longer periods on ECMO. Maximum lactate was negatively associated with ECMO duration, meaning shorter ECMO duration by 11.1%. Unvaccinated patients were on ECMO for approximately 61.6% longer than vaccinated patients. Men showed longer ECMO duration than women, by approximately 36.5%, in line with prior evidence of greater disease severity among men.

ECMO support duration is substantially determined by respiratory and metabolic variables, as well as sex, chronic respiratory disease, obesity, and vaccination status among critically ill COVID-19 patients.

The GLM demonstrated an acceptable fit, as indicated by the deviance value (1465.24). The Pearson Chi-Square/df was 1.73, slightly above 1, suggesting mild overdispersion.

Table 4.20. - Predictors of ECMO Duration according to the GLM

Variable	*p-value*	Exp(B)
Sex (0=Male; 1=Female) Reference category is to be female	0.002	1.365
Chronic Pulmonary Disease (0=No; 1=Yes) Reference category is to have chronic pulmonary disease	< 0.001	1.544
Obesity (0=No; 1=Yes) Reference category is to have obesity	0.015	0.764
Maximum $PaCO_2$ (mmHg)	< 0.001	1.030
Maximum Lactate (mmol/L)	0.001	0.889
Vaccination (0=No; 1=Yes) Reference category is to be vaccinated	< 0.001	1.616

In summary, respiratory and metabolic parameters, along with patient factors, were the main determinants of prolonged ICU stay, IMV, and ECMO duration, emphasizing the relationship between physiological and individual vulnerability in severe COVID-19.

5 Discussion

This chapter describes the main findings, while integrating statistical results, current evidence and clinical relevance of the findings. GLMs provide further insight into the determinants of prolonged critical care, supporting clinical decision-making. The contribution of this study is contextualized within the framework of precision medicine.

5.1. Characterization of the Study Sample

5.1.1. Demographic and Clinical Profile

The study cohort included 794 patients admitted to the ICU, predominantly male (68.5%) and with a mean age of 60 years. Furthermore, more than 80% of the population presented at least one comorbidity, most frequently HTN, DM, dyslipidemia and obesity, and the vast majority were admitted for COVID-19 and/or ARDS. These findings outline a clinically vulnerable population, with a considerable burden of cardiometabolic and chronic conditions.

This demographic and clinical profile is highly consistent with the patterns described in international and national studies of critically ill COVID-19 patients. Advanced age and male sex have repeatedly emerged as major risk factors for severe disease, higher ICU admission rates and increased mortality, reflecting both biological susceptibility and differential immune responses [9], [41], [56]. The male predominance observed in this cohort aligns with previous ICU series in which men also showed a higher need for IMV [25], [56].

The high prevalence of comorbidities in this sample also mirrors the Portuguese epidemiological landscape, particularly among older adults, in whom HTN, DM, dyslipidemia and obesity are highly prevalent [10], [13]. The presence of chronic respiratory diseases, although less frequent, is clinically relevant given that pre-existing

pulmonary pathology has been associated with increased vulnerability to COVID-19-related ARDS and more complex impairments in gas exchange [25], [63]. Similarly, the predominance of admissions due to COVID-19 and/or ARDS reflects the significant reconfiguration of ICU resources during the pandemic, consistent with national reports documenting the central role of respiratory failure in driving critical care utilization [10], [13].

Across the pandemic period, the ICU admission profile in Portugal gradually shifted from younger patients without major comorbidities to older, multimorbid individuals with reduced physiological reserve. This transition has been attributed to increasing population-level immunity, widespread vaccination, and changes in circulating viral variants, which collectively reduced the incidence of severe hypoxemic respiratory failure among low-risk groups. As documented in national datasets, post-vaccination ICU admissions were increasingly dominated by individuals with cardiometabolic or chronic respiratory disease, whose diminished ventilatory capacity predisposed to CO_2 retention and acid-base imbalance [4], [10], [13], [56]. This broader epidemiological context provides a coherent explanation for the clinical profile observed in the present cohort, where chronic disease burden and impaired ventilatory efficiency likely contributed to the severity of illness at ICU admission.

5.1.2. Admission Reason and Clinical Outcomes

In this cohort, admission reason showed a clear relation with clinical severity. Patients admitted for COVID-19 and/or ARDS represented the largest subgroup and exhibited the highest rates of ICU-D, IMV and ECMO use. Specifically, 31.2% of these patients died in the ICU, 79.9% required IMV, and all ECMO cases occurred within this group. In contrast, patients admitted for other causes had substantially lower ICU-D (10.1%) and no cases requiring IMV or ECMO. Although septic shock and acute kidney failure also showed relatively elevated mortality, these categories included very small numbers of patients, meaning that their percentages should be interpreted cautiously to avoid overestimating potential associations.

These findings highlight the central contribution of COVID-19-ARDS to ICU burden and adverse outcomes during the study period. The strong association between COVID-19 and/or ARDS admission and ICU-D aligns with multicenter evidence from early pandemic waves, in which COVID-19-ARDS contributed disproportionately to critical illness severity and death compared with other ICU admission etiologies [25], [56]. The pathophysiological mechanisms of COVID-19-ARDS, marked by diffuse alveolar,

capillary damage, endothelial dysfunction and extensive pulmonary microthrombosis, explain the high rates of IMV and the elevated mortality in this group. These processes contribute to refractory hypoxemia, decreased lung compliance and severe gas exchange impairment, ultimately driving the need for advanced respiratory support and contributing to the unfavorable outcomes reported in multiple international cohorts [24], [25].

ECMO use did not vary significantly by admission reason beyond COVID-19 and/or ARDS, which is consistent with its role as a selective rescue therapy reserved for a small subset of patients with refractory hypoxemia who meet strict eligibility criteria. Additionally, resource limitations and prioritization strategies during pandemic surges further constrained ECMO use, a pattern reported across several countries [35], [47].

5.1.3. Relationship Between IMV and ECMO

In this cohort, all patients who required ECMO were also on IMV, confirming that ECMO support occurred exclusively in ventilated patients. However, only a small proportion of those on IMV (12.3%) progressed to ECMO, illustrating that although IMV was common, escalation to ECMO remained selective and infrequent.

This pattern is fully aligned with established clinical practice. ECMO is indicated as a rescue therapy for refractory hypoxemia only after failure of optimized IMV strategies, including lung-protective ventilation, appropriate PEEP and prone positioning [25], [47]. Therefore, the absence of ECMO use in non-ventilated patients reflects expected therapeutic sequencing rather than a cohort-specific anomaly.

The low proportion of IMV patients who received ECMO also mirrors findings from other ICU cohorts during the COVID-19 pandemic. Strict eligibility criteria, such as age, reversibility of lung injury, absence of multiorgan failure and adequate physiological reserve, limit the number of patients considered suitable for ECMO. Moreover, constrained ECMO capacity in many centers during pandemic surges further restricted its use to highly selected cases [48], [51].

5.1.4. Sex-based Differences in Comorbidities and Outcomes

In this cohort, women presented a substantially higher prevalence of at least one comorbidity despite representing a smaller proportion of the sample. Conditions such as DM, obesity, hypothyroidism, autoimmune diseases and depression occurred more

frequently in women, while men showed higher rates of hyperuricemia and chronic respiratory diseases. Men were also more likely to require IMV, whereas no significant sex-based differences were observed for ICU-D or ECMO use.

These findings reflect known sex-based epidemiological patterns. Women have higher prevalence of several endocrine and autoimmune diseases, consistent with broader epidemiological data showing increased rates of metabolic and immunological disorders in female populations [64], [65]. Biological mechanisms may contribute to these differences, like estrogens enhance innate and adaptive immune responses, promoting more efficient viral clearance, while multiple immune-regulatory genes on the X chromosome amplify immune activation. Although advantageous during infection, this heightened immunological activity increases susceptibility to autoimmune and endocrine diseases, supporting the comorbidity patterns observed among women in this study [64].

Men, on the other hand, exhibited more hyperuricemia and chronic respiratory disease and had a higher likelihood of requiring IMV. This profile is compatible with biological and behavioral determinants frequently described in male populations. Men tend to demonstrate weaker innate immune responses and higher ACE2 expression, potentially facilitating viral entry, while lifestyle factors such as smoking and alcohol consumption contribute to chronic lung injury and reduced ventilatory reserve [41], [64]. These mechanisms may explain the greater vulnerability of men to respiratory deterioration and the higher IMV requirement observed both in this cohort and in other ICU series.

Although the comorbidity burden differed significantly between sexes, ICU-D and ECMO use did not, suggesting that once critical illness was established, outcomes tended to converge. Similar patterns have been reported in other studies of critically ill COVID-19 patients, where sex-based differences influenced disease susceptibility and progression but did not consistently translate into differences in ICU-level outcomes [13], [49].

5.1.5. Vaccination Status and Clinical Outcomes

In this cohort, vaccination status was associated with marked differences in clinical severity. Vaccinated patients showed a significantly lower need for IMV compared with unvaccinated individuals, while lower proportions of ICU-D and ECMO use were also observed in the vaccinated group, although these differences did not reach statistical significance. The overall distribution of outcomes indicated a consistent trend in which

vaccinated patients had fewer adverse clinical events and higher proportions of favorable results.

These findings align with the biological mechanisms through which COVID-19 vaccination reduces disease severity. Vaccines elicit robust humoral and cellular immune responses, decreasing viral replication, attenuating systemic inflammation and limiting pulmonary involvement. This immunological protection lowers the risk of progression to severe hypoxemic respiratory failure, which is reflected in the reduced need for IMV among vaccinated patients [13], [19], [66]. The absence of significant differences in ICU-D and ECMO use may be related to the smaller number of vaccinated individuals in this cohort, heterogeneity in variant circulation during the study period, and the presence of residual vulnerability among older or multimorbid vaccinated patients.

Evidence from national and international ICU cohorts has consistently shown that vaccination is associated with lower rates of respiratory support escalation and improved clinical trajectories in critically ill COVID-19 patients [13], [15]. The pattern observed in this study is therefore coherent with established literature, underscoring the protective effect of vaccination against progression to severe respiratory failure requiring IMV.

5.1.6. Duration of Hospitalization and Supports

Patients who required IMV had substantially longer ICU stays, and those treated with ECMO showed even more prolonged hospitalization. These extended admissions reflect the high clinical complexity of severe COVID-19, including persistent lung injury, susceptibility to secondary infections, and neuromuscular weakness associated with prolonged critical illness. ECMO cases, in particular, face additional challenges related to continuous anticoagulation, circuit-associated complications and the slower recovery of alveolar function inherent to severe ARDS [27], [47], [53].

The duration of IMV and ECMO did not differ significantly between survivors and patients with ICU-D, indicating that once invasive support was initiated, the overall course of treatment proceeded in a broadly similar manner across outcome groups. This pattern is consistent with the considerable heterogeneity within both survivors and those with ICU-D, some individuals had short ICU stays despite adverse outcomes, while others, regardless of survival status, remained hospitalized for extended periods. Such variability within groups reduces the likelihood of detecting systematic differences in support duration, even when the underlying clinical trajectories are markedly heterogeneous.

These observations are aligned with prior evidence showing that prolonged IMV and ECMO courses primarily reflect the severity of underlying respiratory failure rather than inefficiency or delays in care [45], [53]. Support duration, therefore, appears to function more as a marker of illness burden than as a discriminator of survival.

5.2. Association Between Arterial Blood Gas Parameters and Clinical Outcomes

In this cohort, alterations in ABG parameters were closely associated with clinical outcomes, revealing how disturbances in ventilatory efficiency, acid-base homeostasis and systemic perfusion relate to disease severity. Across all analyses, pH, $PaCO_2$ and lactate showed the strongest associations with clinical deterioration, whereas PaO_2 demonstrated limited discriminatory power. These patterns are consistent with previous studies that identified gasometric abnormalities as early markers of severity in COVID-19-related critical illness [5], [54], [67].

5.2.1. Arterial Blood Gas and Clinical Outcomes

Patients with ICU-D presented significantly lower maximum and minimum pH values, higher $PaCO_2$ levels and higher maximum lactate, indicating more pronounced acidemia, reduced ventilatory efficiency and greater metabolic stress. Maximum PaO_2 was also significantly lower among patients with ICU-D, although minimum PaO_2 did not differ between groups. This suggests that while oxygenation capacity was impaired, isolated PaO_2 values were insufficient to differentiate survival trajectories. Because ABG sampling was performed under varying levels of oxygen supplementation, PaO_2 measurements may partly reflect treatment conditions rather than intrinsic oxygenation capacity [5], [39], [67]. Taken together, these findings indicate that ventilatory and metabolic dysfunctions were more closely associated with ICU-D than hypoxemia alone, aligning with evidence showing pH, $PaCO_2$ and lactate as robust predictors of deterioration in severe COVID-19 [32], [42], [67].

For IMV requirement, ventilated patients showed significantly lower pH and higher minimum $PaCO_2$, consistent with acidemia and hypercapnia as key drivers of IMV. PaO_2 and lactate did not differ significantly between IMV and non-IMV groups, reinforcing that IMV initiation was primarily related to ventilatory failure rather than impaired oxygenation or systemic hypoperfusion. These findings align with reports identifying pH and $PaCO_2$

as early indicators of respiratory fatigue and predictors of IMV need in critically ill COVID-19 patients .[5], [42]

Patients requiring ECMO demonstrated even more pronounced ventilatory impairment. Minimum $PaCO_2$ was substantially higher in ECMO patients, reflecting severe and refractory CO_2 retention. Maximum pH was slightly lower, though the difference was small and of limited clinical relevance. PaO_2 and lactate values did not differ significantly between ECMO and non-ECMO groups. These patterns correspond to the typical ECMO indication profile, in which escalation is triggered predominantly by refractory hypercapnia and severe ventilatory failure rather than by isolated hypoxemia or circulatory collapse [45], [47], [48], [53].

The results across all outcomes are consistent with prior evidence showing that worsening hypoxemia, acidemia and hypercapnia are associated with deteriorating prognosis, whereas higher pH levels correspond to more favorable trajectories [31]. Although several studies describe hypoxemia as a marker of severity in COVID-19, its predictive capacity in this cohort was limited, likely influenced by timing of ABG sampling and variability in oxygen therapy [39], [42].

Patients with at least one comorbidity had significantly lower pH values, suggesting greater acidemia and reduced metabolic compensation. This pattern may reflect the cumulative burden of chronic cardiometabolic and renal conditions, which are known to impair acid-base regulation and diminish physiological reserve [4], [31].

PaO_2, $PaCO_2$ and lactate values did not differ significantly between patients with and without comorbidities, indicating preserved oxygenation and ventilation across groups. However, the modest reduction in pH among comorbid patients suggests a subtle metabolic vulnerability, consistent with findings reported in studies of COVID-19-ARDS, where comorbid conditions contributed to physiological fragility without necessarily altering gas exchange parameters [31].

5.2.2. Arterial Blood Gas and Comorbidity Profile

Patients with at least one comorbidity presented significantly lower maximum and minimum pH values compared with those without comorbidities, reflecting a greater tendency toward acidemia. PaO_2, $PaCO_2$ and lactate did not differ significantly between groups, indicating that oxygenation and ventilation efficiency were largely preserved regardless of comorbidity status. When individual comorbidities were examined, HTN

was associated with lower minimum pH and lower minimum PaO_2, DM with lower minimum pH and higher minimum $PaCO_2$, and CHF with higher maximum lactate, whereas the remaining conditions showed no significant associations.

These findings suggest that comorbidities exerted their main influence through subtle disturbances in acid-base regulation rather than through overt changes in oxygenation or ventilation. The lower pH values in comorbid patients may reflect the cumulative metabolic burden of chronic diseases such as HTN, DM and renal dysfunction, which are known to impair compensatory mechanisms responsible for maintaining acid-base homeostasis [4], [31]. The associations with individual comorbidities further support this interpretation, reduced pH and altered $PaCO_2$ in patients with DM may indicate impaired ventilatory adaptation to metabolic acidosis, while the higher lactate observed in CHF likely reflects reduced perfusion reserve.

Although PaO_2 and $PaCO_2$ did not differ substantially between those with and without comorbidities, the modest decline in pH among comorbid patients points to reduced physiological reserve, aligning with reports that chronic cardiometabolic and renal diseases contribute to diminished buffer capacity and greater vulnerability to metabolic stress in COVID-19-ARDS [31]. The overall pattern indicates that comorbidities did not markedly alter gas exchange parameters but were linked to a subtle metabolic fragility that may influence clinical trajectories in critically ill patients.

5.2.3. Arterial Blood Gas and Vaccination Status

Vaccinated and unvaccinated patients showed similar pH and lactate values, indicating that vaccination did not substantially influence metabolic or respiratory acidemia. In contrast, differences in oxygenation and ventilatory efficiency were evident, vaccinated patients demonstrated higher PaO_2 values, particularly minimum PaO_2, and lower maximum $PaCO_2$. These findings suggest that vaccinated individuals maintained more effective oxygenation and experienced less CO_2 retention, reflecting better ventilatory performance.

These patterns are consistent with the biological mechanisms through which COVID-19 vaccination attenuates pulmonary inflammation and preserves alveolar function. By promoting earlier viral clearance and reducing inflammatory injury in the lung, vaccination contributes to improved gas exchange and a lower likelihood of progression to severe ventilatory impairment [13], [19], [66]. The absence of significant differences in pH and

lactate supports the notion that the protective effect of vaccination in this cohort was primarily respiratory rather than systemic.

Previous Portuguese ICU data have similarly shown that vaccinated patients had lower risk of escalation to advanced respiratory supports, despite presenting with comparable metabolic profiles [13]. This aligns with the present analysis, where the only clinical outcome significantly associated with vaccination status was the need for IMV. Vaccinated patients were substantially less likely to require IMV, indicating that preserved ventilatory efficiency, reflected in higher PaO_2 and lower $PaCO_2$, may contribute to delaying or avoiding progression to invasive support.

5.3. Temporal trends in Arterial Blood Gas Parameters and Clinical Outcomes

ABG and clinical patterns of ICU COVID-19 patients evolved. ABG parameters revealed temporal alterations, reflecting changes in respiratory parameters, patient demographics, and clinical practice. The middle waves showed the best acid-base and oxygenation profiles, paralleled by a decline in mortality, IMV, and ECMO rates. After vaccination rollout, physiological stability and outcome improvement became more consistent, consolidating the transition from the early high-severity phenotype to a more manageable clinical course.

According to these findings, the ongoing adaptation of critical-care practices and immunization helped mitigate disease severity while enhancing the respiratory and metabolic trajectories of critically ill COVID-19 patients .[13], [56], [66].

5.3.1. Arterial Blood Gas variation across pandemic waves and vaccination periods

Across the pre- and post-vaccination periods, ABG parameters remained largely stable. Maximum and minimum pH values showed no significant differences, indicating comparable acid-base status between the two phases. PaO_2 and lactate levels were also similar, suggesting preserved oxygenation and tissue perfusion irrespective of vaccination rollout [13], [66], [68]. The only parameter that differed significantly was minimum $PaCO_2$, which was slightly higher in the post-vaccination period. This small increase in CO_2 retention may reflect differences in patient characteristics, disease phenotype or ventilatory management rather than an effect attributable to vaccination

itself. The overall stability of ABG parameters suggests that the physiological profile of critically ill patients admitted before and after the vaccination campaign did not undergo major shifts at the time of ICU admission.

When ABG variation was examined across the six pandemic waves, a clearer temporal heterogeneity emerged. Both maximum and minimum pH values differed significantly between waves, with lower medians during the 1st and 6th waves and higher values during the 4th and 5th. These patterns suggest that acid-base disturbances were more pronounced in the earliest phase of the pandemic, dominated by unvaccinated patients with severe hypoxemic respiratory failure, and again in the late phase, when admissions increasingly involved older, multimorbid individuals with reduced physiological reserve [31], [32], [67]. The relative stability in the intermediate waves parallels periods of more standardized clinical practice and gradual improvements in disease management.

$PaCO_2$ values also demonstrated temporal variation, with both maximum and minimum levels reaching their highest medians in the 6th wave. This trend is compatible with the predominance of hypercapnic respiratory failure in later stages of the pandemic, a phenomenon attributed to prolonged disease trajectories, sequelae such as fibrotic lung, and the rising proportion of patients with chronic respiratory disease or diminished ventilatory drive [2], [24], [45]. In contrast, maximum PaO_2 values tended to increase across waves, particularly in the 5th and 6th, reflecting accumulated experience in ventilatory strategies, improvements in oxygenation techniques and increased familiarity with the respiratory management of COVID-19-ARDS.

Minimum lactate values showed small but statistically significant fluctuations, with slightly higher medians in the 6th wave. This may reflect marginally greater systemic stress or the higher comorbidity burden characteristic of late-pandemic ICU admissions [4], [31]. Unlike PaO_2 and $PaCO_2$, whose fluctuations align closely with respiratory pathophysiology, lactate variation appears to correspond more to the evolving clinical profile of patients rather than to pandemic timing itself.

5.3.2. Clinical outcomes variation across pandemic waves and vaccination periods

Across the pre- and post-vaccination periods, clinical outcomes remained stable. ICU-D, IMV and ECMO frequencies did not differ significantly between phases, indicating that the introduction of vaccination did not translate into immediate measurable changes

in outcomes among patients already requiring ICU admission. Although the proportion of IMV and ICU-D was slightly higher in the post-vaccination period, these differences were small and non-significant. This pattern suggests that once patients reached the threshold for critical care, their risk of requiring invasive support or experiencing ICU-D was similar regardless of vaccination period, and may reflect the selective admission of individuals with greater disease severity or comorbidity burden during later pandemic phases.

When outcomes were examined across the six COVID-19 waves, temporal heterogeneity became evident. ICU-D, IMV and ECMO showed statistically significant variation across waves, with the highest proportions occurring during the early phases, particularly the 3rd and 4th waves, and a progressive decline in subsequent waves. These trends reflect the evolving clinical landscape of the pandemic, with reduced respiratory failure severity and lower frequency of advanced support in later stages. Improvements in clinical practice, greater familiarity with COVID-19-ARDS management and broader vaccination coverage likely contributed to the reduction in IMV and ECMO need observed in the 5th and 6th waves.

These observations align with multicentric evidence describing a progressive improvement in ICU outcomes over the course of the pandemic, supported by better recognition of respiratory deterioration, refined ventilatory strategies and cumulative experience in the management of severe COVID-19 [2], [10], [13], [56]. The decreasing reliance on IMV and ECMO parallels international reports documenting the global attenuation of disease severity following mid-2021, coinciding with the widespread implementation of vaccination and the optimization of therapeutic protocols [13], [66].

5.4. Generalized Linear Models

The GLMs identified several variables associated with the duration of ICU stay and advanced respiratory support. Across all three models, higher maximum $PaCO_2$ values were consistently associated with longer ICU, IMV and ECMO durations, indicating that hypercapnia was a strong marker of sustained ventilatory impairment. Maximum lactate showed an inverse association with duration of care, correlating with shorter ICU and support periods. This pattern is likely influenced by the fact that patients with higher lactate tended to deteriorate more rapidly, leading to earlier progression to ICU-D and therefore shorter observed durations of support, a phenomenon previously described in studies of severe COVID-19 and COVID-19-ARDS [54].

Sex and vaccination status were also significant predictors across models. Men consistently required longer ICU stay, IMV and ECMO duration, which aligns with evidence showing more severe respiratory disease and slower recovery trajectories among male patients [13], [29], [69]. Similarly, unvaccinated patients had substantially longer durations of IMV and ECMO, reflecting greater disease severity and delayed physiological recovery in this group, consistent with studies demonstrating the protective effect of vaccination against severe COVID-19 [13]. Chronic pulmonary disease and obesity influenced support duration in wave-specific ways, patients without chronic respiratory disease required longer IMV and ECMO durations, while obesity was associated with prolonged ECMO use. These findings mirror the heterogeneity described in prior literature, where baseline respiratory mechanics and body habitus modulate the complexity and duration of advanced ventilatory support [53], [69].

The integration of respiratory variables ($PaCO_2$), systemic markers (lactate) and patient characteristics (sex, vaccination status, comorbidity profile) across the GLMs illustrates that the duration of ICU care and ventilatory support in severe COVID-19 arises from the interaction of multiple physiological and demographic factors rather than from a single dominant determinant. The consistency of these associations reinforces the clinical value of ABG parameters as dynamic indicators of disease progression and the need for sustained support. Within the scope of the PREMO project, these findings contribute to more refined approaches for early risk stratification and individualized critical care, strengthening the potential for models tailored to support decision-making and resource allocation in ICUs managing severe COVID-19.

All three GLMs demonstrated satisfactory performance. The GLM for ICU stay showed optimal adjustment with no evidence of overdispersion, while the IMV and ECMO models demonstrated mild overdispersion adequately addressed through the negative binomial distribution. The overall consistency of model fit supports the reliability of the associations identified between ABG parameters, demographic factors and the duration of critical care [62].

5.5. Integration with Precision Medicine

The results of this study support the principles of precision medicine applied to critical care, which advocate for individualized monitoring and dynamic tailoring of treatment to each patients' physiological profile. In this context, ABG analysis is an effective tool, which enables identification of specific ventilatory or metabolic patterns allowing adjustment of respiratory support, timing of escalation and resource use [7].

The enhancement of this methodology through the incorporation of temporal variables such as support duration demonstrates that combining ABG trends with time-dependent data can enhance prognostic accuracy and personalization.

5.6. Strengths and Limitations

The strengths of this study are its large sample size, the use of standardized data collection and assessment of important outcomes (ICU-D, IMV, and ECMO) across different pandemic phases. Integration of clinical, demographic, and ABG variables enabled detailed characterization of disease severity and its evolution over time, to provide a dynamic view of the pandemic's impact on ICU case mix and management. Vaccination status and comorbidity burden were added to improve the framework for contextualized analysis of outcome variability. Additionally, the application of GLMs strengthened the analytical approach by identifying independent predictors of longer ICU stay and invasive support.

However, some limitations must be acknowledged. The retrospective, single-center design limits causal inference and generalization to other settings. Missing parameters such as FiO_2, PaO_2/FiO_2 ratio, HCO_3^-, and BE restricted the assessment of ARDS severity and the evaluation of metabolic compensation. This limitation is particularly relevant because metabolic alkalosis is common among survivors, whereas metabolic or respiratory acidosis predominates in non-survivors, reflecting the interdependence between respiratory and metabolic mechanisms regulating acid-base balance in critically ill COVID-19 patients [33], [39], [52]. In addition, changes in treatment protocols and patient profiles across pandemic waves may have introduced unmeasured influencing factors. These constraints, also reported in comparable ICU studies, reduce inter-cohort comparability but do not compromise the strong and consistent associations observed between early ABG alterations and adverse outcomes [31], [57].

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6 Conclusions and Future Work

6.1. Conclusions

This study demonstrated that ABG parameters measured on the day of ICU admission hold substantial prognostic value for critically ill COVID-19 patients. The research question defined in Chapter 1 was fully addressed, and all specific objectives of the dissertation were achieved. Overall, the findings show that early disturbances in oxygenation, ventilation, and acid-base status are clinically meaningful markers of disease severity and adverse outcomes.

First, hypoxemia emerged as a significant predictor of ICU mortality, with lower PaO_2 values indicating more severe pulmonary injury and impaired gas exchange capacity. Second, lower pH and CO_2 retention proved to be markers of clinical complexity, reflecting the progression from isolated respiratory failure to combined ventilatory and metabolic compromise. Third, elevated lactate was confirmed as an indicator of systemic stress and poor prognosis, reinforcing its role as a global marker of severity in critical illness.

In addition to these physiological alterations, longer ICU stays and prolonged durations of invasive supports (IMV and ECMO) reflected the overall burden of disease severity, rather than differences in survival alone. The negative binomial GLM models further supported these conclusions by identifying maximum $PaCO_2$, maximum lactate, and individual patient factors as determinants of prolonged ICU admission and need for advanced supports, reinforcing the potential for individualized and risk-adjusted clinical decision-making.

Taken together, these findings demonstrate that ABG analysis is not merely a diagnostic tool, but a readily available, objective, and early prognostic instrument capable

of supporting risk stratification, anticipating clinical deterioration, and informing resource allocation in intensive care settings. In the context of pandemic pressures and constrained ICU capacity, this reinforces the relevance of ABG as a universal and high-impact tool for precision critical care.

6.2. Future Work

Continuation of the findings from this study, through several directions would be desirable in future work. First, multicenter validation should confirm the external validity of these results across Portuguese ICUs, so that the prognostic associations observed are comparable across clinical and epidemiological settings. A multicenter approach would also make these findings generalizable and allow benchmarking across institutions.

Second, additional ABG and respiratory parameters like FiO_2, the PaO_2/FiO_2 ratio, HCO_3^- and BE should be studied. These measures would allow assessment of COVID-19-ARDS severity and metabolic compensation mechanisms underlying respiratory failure in critically ill COVID-19 patients.

Third, ABG trends should be followed longitudinally after admission. ABG evolution over time could reveal patterns of ventilatory adaptation, treatment response, and early physiological signs of deterioration to refine dynamic prognostic assessment.

Finally, innovation in integrating ABG data into advanced analytical frameworks represents a promising direction. Validated ABG, clinical, biochemical, and demographic variables could enable artificial intelligence (AI) based models for real-time triage and optimal resource allocation. This multidimensional approach would facilitate clinical decision-making and healthcare readiness, and turn ABG analysis from a static diagnostic tool to a dynamic tool supporting personalized critical care [70].

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