Trends in COVID-19 Patient Characteristics and Mortality Throughout the Pandemic: Insights from a Portuguese Single-Centre Study

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***Abstract*—**As SARS-CoV-2 continues to circulate globally and new variants emerge, it remains relevant to gather data on the affected patients' clinical characteristics and outcomes to understand how individual factors and public health measures affect prognosis. Thus, we analyzed data of 870 ICU patients admitted for COVID-19 across two distinct phases of the pandemic: before and after the introduction of immunization. Experimental results showed that vaccination significantly impacted patient demographics after the third wave, and that waves number two and three, dominated by the *EU1* and *Alpha* variants, had higher mortality. Older age, the need for invasive mechanical ventilation, and hematologic cancer were significantly associated with an increased risk of death in the adjusted multivariable model (AUC: 0.778, 95% CI 0.746-0.810, p<0.001). As the pandemic progressed, while some public health interventions influenced the observed trends, individual patient characteristics had a more substantial impact on their outcome.

***Keywords*—**COVID-19 Waves, COVID-19 Vaccination, Intensive Care Unit, Mortality

I. Introduction

Since the beginning of the pandemic, numerous studies have gathered comprehensive data on the profiles of COVID-19 patients from diverse populations worldwide [1]-[5]. Analyzing patient characteristics and their types of comorbidities, alongside research on the effects of specific supportive measures and treatments, has led to a better understanding of the possible prognoses of high-risk COVID-19 patients. This advancement led to improved patient assessment and application of targeted therapies, which helped alleviate the severity of outcomes, specifically in the Intensive Care Unit (ICU) [6], [7].

Portugal has experienced six waves of the pandemic, with the most significant variants being *20A* and *B*, *EU1*, *Alpha V1*, *Delta* and *Omicron*, respectively. The introduction of immunization in late December 2020 (third wave), and other public health measures, played a crucial role in reducing the transmissibility of the virus. Significant measures included widespread testing, mask mandates, social distancing protocols and the implementation of total/partial lockdowns. Despite the extensive efforts to analyze and monitor the various viral variants throughout the country [8], there remains a notable gap when it comes to analyses relating the identified variants and ICU patients' outcomes. Understanding how ICU patients are affected by different variants is critical, as identifying trends in patient characteristics, risk factors, and mortality can improve the management of high-risk patients in critical care settings, as well as aid in preparing for future waves of infection.

Using a population of 870 ICU patients admitted for COVID-19, our goal was to analyze the key differences between two periods: before (the first three waves of the pandemic) and after (the last three waves) the onset of immunization. Furthermore, we also aimed to identify individual risk factors for mortality in the ICU and to determine the relative impact of these individual factors compared to public health measures, particularly immunization, on patients' outcome in the ICU.

II. Methodology

A. Study Design and Participants

A retrospective observational study was conducted on patients from the ICUs of *Unidade Local de Saúde São José* (ULSSJ), Lisbon, during the pandemic, focusing on those admitted due to SARS-CoV-2 infection and/or COVID-19-related acute respiratory distress syndrome (ARDS).

This study is part of the *Predictive Models of COVID-19 Outcomes for Higher Risk Patients Towards Precision Medicine* (PREMO) project, approved by the ULSSJ Ethics Committee (May 20, 2020; Ref. No. 1043/2021). Informed consent for data collection was obtained from each patient or their family members prior to participation and all data was anonymized. Patient data was sourced from the hospital's

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electronic health record system.

In a first approach, data was collected for all patients admitted to the ICU between March 2020 and the end of August 2022 with positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test results. Patients whose admission motive was not SARS-CoV-2 infection and/or COVID-19-related ARDS were then excluded, as well as underage patients and those having missing data on their ICU outcomes. As a result, the study included a population of 870 patients.

B. Immunization Periods and COVID-19 Waves

Waves (**Table I**) were defined based on hospital directives, and data gathered from The National Institute of Health Doutor Ricardo Jorge, I.P. (INSA) [8]. This data also allowed for inquiries into which SARS-CoV-2 variants were most prominent during each wave. Patients were grouped by wave according to their dates of disease onset. Since immunization began in late December 2020, *i.e.*, wave three, and no patients were vaccinated at that time, the period after immunization was considered to begin following this wave.

TABLE I
IMMUNIZATION PERIODS AND COVID-19 WAVES

Period	Wave	Start Date *	End Date *	Included Patients (n)
Before Immunization	One	2020-03-10	2020-08-22	125
	Two	2020-08-23	2020-12-19	176
	Three	2020-12-20	2021-05-31	280
After Immunization	Four	2021-06-01	2021-10-31	147
	Five	2021-11-01	2022-03-30	92
	Six	2022-04-01	2022-08-08	50

*Considered date format: YYYY-MM-DD.

C. Variables

The demographic variables considered in the study included age (in years) and sex (male or female). Information on patients' SARS-CoV-2 vaccination status was obtained at the time of ICU admission; however, details regarding the number of vaccine doses administered were not available. The vaccination program in Portugal started in late December 2020 and accelerated in early 2021. Consequently, vaccinated patients only appear after wave four in this study. Regarding comorbidities, the following were considered: arterial hypertension, chronic kidney disease, chronic lung disease, diabetes, dyslipidemia, hematologic cancer, coronary heart disease, solid cancer, and stroke.

Respiratory support included invasive mechanical ventilation (IMV) and extracorporeal membrane oxygenation (ECMO), at least one time during the patients' admission.

The most commonly reported medications in COVID-19-related research were categorized, including antibiotics, anticoagulants, antivirals, corticosteroids, immune modulators, and cardiovascular drugs, specifically Angiotensin-Converting Enzyme (ACE) inhibitors. However, indication on whether these medications were administered solely during ICU admission or if patients were already taking them routinely was not available, nor was information regarding the duration of their administration. Consequently, these variables were excluded from the logistic regression analysis.

D. Statistical Analysis

Categorical data were presented as absolute frequencies and percentages. For continuous variables, normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, as applicable. As continuous variables exhibited deviations from normality and asymmetric distributions, they were reported as medians with the respective interquartile ranges (IQRs). Comparisons between independent groups for nominal variables were conducted using chi-squared or Fisher's exact tests. The Mann Whitney U and Kruskal-Wallis One-Way ANOVA test, with significance values adjusted using the Bonferroni correction for pairwise comparisons, were used for continuous variables, as appropriate.

To determine individual risk factors associated with mortality in the ICU, an univariable logistic regression analysis was initially conducted. For the multivariable logistic regression model, variables that had a p-value of less than 0.25 in the univariable analysis were included. The multivariable models were developed using a forward stepwise selection approach, with the final models selected based on achieving the highest area under the receiver operating characteristic (ROC) curve (AUC). Adjusted odds ratios ($a\widehat{OR}$) and their corresponding 95% confidence intervals (95% CI) were presented for the variables included in the multivariable model.

Descriptive and inferential statistics were generated using IBM SPSS Statistics software, version 26 (IBM Corp., New York, United States), as well as the boxplot and ROC analysis images. All other plots were created using Microsoft Excel, version 2021 (Microsoft Corp., Redmond, Washington, United States). Statistical significance was set for two-sided *p* values of less than 0.05.

III. RESULTS AND DISCUSSION

Demographics and other characteristics, including the immunization status of the patients, as well as the most common comorbidities, were analyzed and compared across the six waves and the two periods (**Table II**). The waves with the highest percentages of admissions were three (32%), two (20%), and four (17%), while the lowest percentage of admissions occurred in wave six (6%).

Patients median age was significantly lower after immunization, with those from wave three being significantly younger than those in waves one (p=0.028) and six (p=0.011). Interestingly, patients in wave four were significantly younger than those in all other waves (p-values <0.001). A contributing factor was the significantly younger age of unvaccinated patients in this wave (p<0.001), with a median of 43 years (IQR: 33-61) compared to 59 years (IQR: 46-69) for vaccinated patients (**Fig.1**). This difference may be attributed to Portugal's initial immunization strategy, which prioritized older segments of the population [9], leaving younger individuals at a higher risk of infection. Following this stage, the median age of infected patients increased, with no significant age difference between vaccinated and unvaccinated groups, likely because the immunization program became more effective in mid-wave four. Hence, the prevalence of vaccinated patients significantly increased from wave four to wave six, rising from 38% to 70%.

The most common comorbidities were arterial hypertension (53%), diabetes (30%) and dyslipidemia (22%). When comparing periods, the three aforementioned comorbidities, along with chronic lung disease, were more prevalent in the first three waves. In contrast, conditions such as chronic kidney disease, cancer, coronary heart disease, and stroke were more frequent in the last three waves. This may be a consequence of the introduction of immunization, as the older population, with higher prevalence of comorbidities like diabetes and hypertension, was initially unvaccinated and therefore more vulnerable to severe outcomes (*e.g.*, hospitalization, ICU admission, and need for ventilatory or organ support) [10], [11]. This led to prioritizing these groups for vaccination, as both age and such underlying health conditions can worsen the impact of a SARS-CoV-2 infection or impair the body's ability to resolve it [10], [11]. The comparatively higher percentage of cancer patients further along in the pandemic could be attributed to shielding behaviors of this population. Following government-imposed public health measures, many cancer patients likely adopted extra precautions to reduce exposure during the most intense stages of the pandemic, potentially influencing infection rates and outcomes over time. Hospital visits were in fact minimized to avoid unnecessary risk, and cancer treatments and diagnoses were often delayed, as the benefits and risks of these procedures had to be carefully weighed in the context of the COVID-19 pandemic [11], [12].

TABLE II
CHARACTERISTICS AND COMORBIDITIES OF THE STUDY POPULATION

	Before Immunization			After Immunization			
Variables \ Waves	1 (n=125)	2 (n=176)	3 (n=280)	4 (n=147)	5 (n=92)	6 (n=50)	*p* value
Demography							
Age, years	67 (54-76)	66 (54-74)	61 (52-70)	49 (37-65)	62 (52-72)	68 (59-79)	**
Sex, male	100 (80%)	125 (71%)	182 (65%)	106 (72%)	64 (70%)	32 (64%)	-
Vaccination	-	-	-	56 (38%)	52 (57%)	35 (70%)	NA
Comorbidities							
Arterial hypertension	74 (59%)	107 (61%)	158 (56%)	52 (35%)	44 (48%)	27 (54%)	**
Chronic kidney disease	13 (10%)	11 (6%)	17 (6%)	7 (5%)	11 (12%)	7 (14%)	-
Chronic lung disease	14 (11%)	26 (15%)	38 (14%)	12 (8%)	10 (11%)	7 (14%)	-
Diabetes	40 (32%)	66 (38%)	89 (32%)	24 (16%)	28 (31%)	14 (28%)	**
Dyslipidemia	28 (22%)	47 (27%)	69 (25%)	24 (16%)	17 (19%)	10 (20%)	*
Hematologic cancer	5 (4%)	5 (3%)	7 (3%)	5 (3%)	10 (11%)	6 (12%)	*
Coronary heart disease	8 (6%)	6 (3%)	25 (9%)	7 (5%)	12 (13%)	5 (10%)	-
Solid Cancer	11 (9%)	6 (3%)	17 (6%)	4 (3%)	7 (8%)	5 (10%)	-
Stroke	3 (2%)	4 (2%)	10 (4%)	4 (3%)	7 (8%)	7 (14%)	*

p values from comparisons between the two immunization periods. p value ≥0.05 (-); *p* value <0.05 (*); *p* value <0.001 (**).

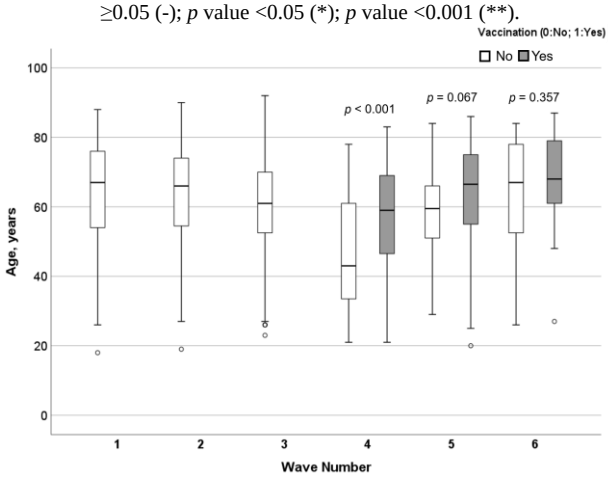

Fig. 1. Distribution of age (years) by wave, with comparisons between vaccinated and unvaccinated patients.

Concerning respiratory support techniques (**Table III**), IMV was utilized in over 74% of patients across all waves, with a higher frequency observed in the period before immunization. ECMO was primarily used in wave four, specifically in 16% of patients, while only 2% of patients required it in wave six. The most frequently administered medications included anticoagulants (used in over 84% of patients across all waves), corticosteroids (administered to more than 80% of patients in all waves), and antibiotics (given to over 78% of patients in all waves). This emphasizes the severity of patients' conditions as well as the presence of other underlying health issues.

TABLE III
SUPPORTIVE MEASURES AND ADMINISTERED TREATMENTS DURING ICU ADMISSION

	Before Immunization			After Immunization			
Variables \ Waves	1 (n=125)	2 (n=176)	3 (n=280)	4 (n=147)	5 (n=92)	6 (n=50)	*p* value
Respiratory Support							
IMV	110 (88%)	131 (74%)	243 (87%)	109 (74%)	72 (78%)	37 (74%)	*
ECMO	14 (11%)	18 (10%)	21 (8%)	24 (16%)	11 (12%)	1 (2%)	-
Therapeutics							
ACE inhibitors	58 (47%)	70 (41%)	109 (40%)	39 (27%)	33 (38%)	15 (31%)	*
Antibiotics	103 (84%)	134 (78%)	239 87%)	112 (76%)	77 (88%)	41 (84%)	-
Anticoagulants	121 (98%)	168 (97%)	270 (98%)	145 (99%)	82 (93%)	41 (84%)	*
Antivirals	52 (42%)	92 (53%)	76 (28%)	33 (22%)	21 (24%)	9 (18%)	**
Corticosteroids	112 (91%)	161 (93%)	259 (94%)	142 (97%)	78 (89%)	39 (80%)	-
Other immune modulators	25 (20%)	9 (5%)	11 (4%)	3 (2%)	11 (13%)	5 (10%)	-

p values from comparisons between the two immunization periods. p value ≥0.05 (-); *p* value <0.05 (*); *p* value <0.001 (**).

Given that all patients were admitted to the ICU and their condition was either severe (requiring hospitalization and

oxygen therapy) or critical (requiring noninvasive or invasive mechanical ventilation), prophylactic anticoagulation is usually indicated. This is largely due to the increased risk of thromboinflammatory syndrome associated with COVID-19, which can lead to micro/macrovascular thrombosis [13]. Corticosteroids are primarily used in COVID-19 to manage the excessive inflammatory response/*Cytokine Storm* observed in critically ill patients. Dexamethasone, the first-line for patients needing oxygen therapy, has showed significant reductions in 28-day mortality in these cases [14], being the most commonly administered corticosteroid in this study, followed by Beclomethasone. The high percentage of antibiotic usage is likely related to the treatment and/or prevention of secondary bacterial infections, such as pneumonia, common in critically ill patients that require prolonged ICU stays and IMV. A percentage of the administered medications was most likely directed at other underlying diseases and comorbidities. However, detailed information on this topic was not available, yielding some uncertainty as to whether the high usage rates were solely related to COVID-19. Moreover, ACE inhibitors, anticoagulants, and antivirals were more frequently administered prior to immunization, likely due to the older age of the patients; however, this remains speculative.

Regarding patient outcomes, there were no significant differences in the time of ICU admission between waves ($p<0.05$) (**Fig.2**). Similarly, when comparing the periods before and after immunization, there were also no significant differences detected ($p<0.05$, data not shown). This pattern persisted even when comparing vaccinated and non-vaccinated patients across each of the last three waves (**Fig.2**).

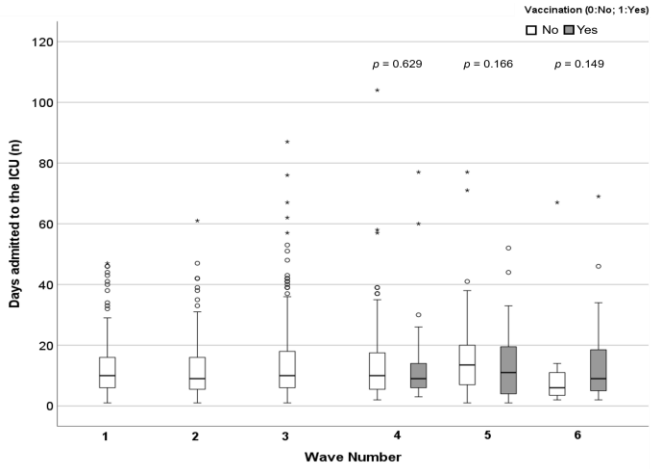

Fig. 2. Distribution of the number of days patients were admitted to the ICU, by wave, with comparisons between vaccinated and unvaccinated patients.

Focusing on ICU mortality, an increasing trend by age group was observed, with patients over 80 years old showing the highest mortality rate at 57.8% (**Fig.3a**), given their greater risk of infection and severe disease. In fact, older age is recognized as a risk factor in COVID-19, since older patients often have more vulnerable immune systems, reduced ability to endure inflammation, and heightened production of pro-inflammatory cytokines, leading to poorer outcomes [10]. Additionally, the presence of underlying comorbidities contributes to disease severity not only by negatively affecting the patients' overall condition but, for example, by increasing ACE2 expression in some cases, which potentiates viral entry into host cells and disrupts the Renin-Angiotensin System, giving rise to further complications [10], [11]. Higher mortality rates were observed before immunization (34.3% vs. 22.8%). When analyzing mortality by wave, (**Fig.3b**), an increasing trend can be observed from waves one to three. Increased mortality during waves two and three, which was also reported in other studies [2], [5], can be attributed to several factors: the more transmissible and virulent variants that contributed to higher infection rates and disease severity (*i.e.*, Alpha variant); the strain placed on the healthcare facilities due to the significant surge in COVID-19 cases; delays in the implementation of immunization programs; and variability in public health measures across different countries and their compliance. The lowest percentage was observed in wave four, primarily due to the younger age of the patients, as previously mentioned.

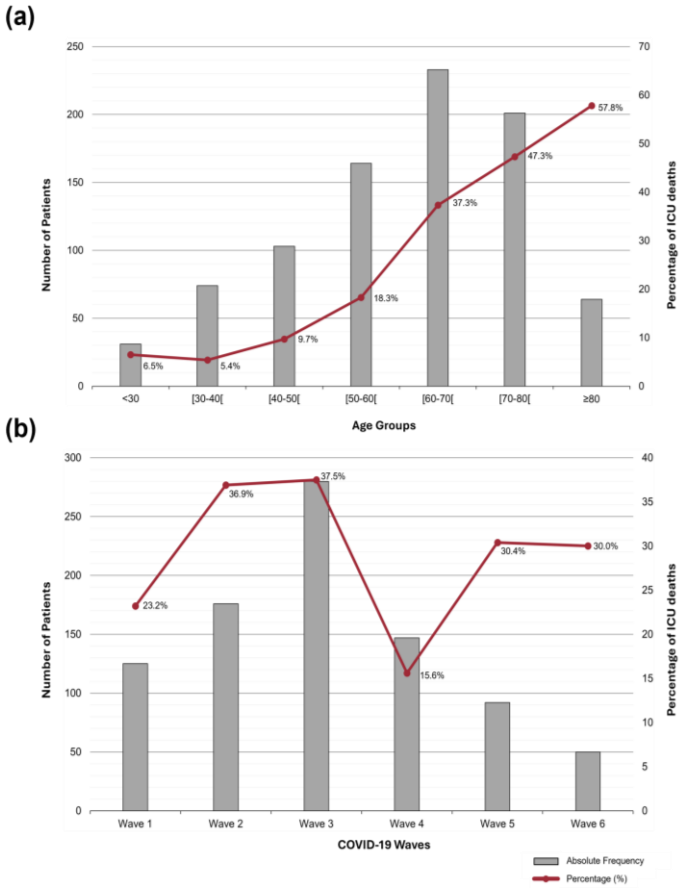

Fig. 3. Mortality in the ICU by age group (**a**) and COVID-19 Wave (**b**). Bars represent absolute frequencies, and trend lines (red) represent mortality percentages.

Through univariate logistic regression, individual factors associated with mortality in the ICU were identified (**Table IV**). Older age was significantly associated with increased mortality, besides several comorbidities and the need for IMV. Vaccination itself was not significant in the univariate analysis ($\widehat{OR}$ 0.831; 95%CI: 0.557-1.240; p=0.365). However, when assessing mortality risk across periods, a significant reduction

was observed after immunization ($\widehat{OR}$ 0.568; 95%CI: 0.411-0.785; p<0.001), likely reflecting its protective effect.

TABLE IV
UNIVARIATE LOGISTIC REGRESSION FOR COVID-19 MORTALITY IN THE ICU

Variables	Crude $\widehat{OR}$	95% CI	*p value*
Age, years	1.068	1.054-1.082	**<0.001**
Immunization Period	0.568	0.411-0.785	**<0.001**
Arterial hypertension	2.313	1.710-3.128	**<0.001**
Chronic kidney disease	1.886	1.134-3.139	**0.015**
Chronic lung disease	1.791	1.183-2.712	**0.006**
Diabetes	1.592	1.169-2.166	**0.003**
Dyslipidemia	1.790	1.285-2.496	**<0.001**
Hematologic cancer	2.662	1.384-5.120	**0.003**
Coronary heart disease	2.213	1.319-3.712	**0.003**
Solid Cancer	2.035	1.144-3.619	**0.016**
IMV	4.231	2.561-6.989	**<0.001**

Adjusted odds ratios estimates ($a\widehat{OR}$) and corresponding 95% confidence intervals (95% CI), were obtained for all the variables, and those with p values less than 0.250 were displayed and used in the multivariable model. For the variable "Immunization Period", the period before immunization was used as the reference category. For the remaining categorical variables, the absence of the characteristic was considered the reference category.

In the multivariable model, significant independent predictors of ICU mortality included older age, hematological cancer, and the need for IMV (**Table V**). While the variable "Immunization Period" lost significance in the adjusted model, it was retained for adjustment due to its relevance. The final multivariable model demonstrated good discriminatory performance, with an *AUC of 0.778 (95% CI 0.746–0.810, p<0.001).*

In comparison to a study involving 10,000 hospitalized COVID-19 patients during the pandemic [15], which reported a lower mortality risk during the Omicron-dominant period (OR=0.61; 95% CI: 0.45–0.82; p=0.0010), our study similarly observed reduced mortality in the period after immunization, including corresponding waves five and six. Notably, the mentioned study also found that vaccination was associated with a lower risk in the adjusted model (OR=0.47; 95% CI: 0.34–0.65; p<0.0001). This effect may be indirectly reflected in our model by adjusting for immunization periods.

Patients with hematological cancers had three times more risk of dying in the ICU, likely due to their compromised immune systems and ongoing immunosuppression. Increased risk results not only from the cancer itself but also from the effects of treatment, which heighten susceptibility to infections and complications [10]. As previously reported, patients with hematological malignancies are at a greater risk than those with solid cancers [16]. However, while several studies reached this conclusion, it still needs to be confirmed with larger cohorts.

Patients requiring IMV had over five times the odds of dying in the ICU compared to those who did not, emphasizing the connection between this intervention and greater disease severity. Similarly, another study with ICU patients reported an even greater risk of death for those requiring IMV (OR = 11; 95% CI: 6.1–19.9; p < 0.001), reinforcing the strong association between the need for IMV and ICU mortality [17]. This elevated risk may also be a result from complications related to prolonged IMV, such as secondary infection (*e.g.*, ventilator-acquired pneumonia), ventilator-induced lung injury, and complications related to organ support such as delirium [11].

TABLE V
MULTIVARIABLE LOGISTIC REGRESSION FOR INDEPENDENT FACTORS ASSOCIATED WITH COVID-19 MORTALITY IN THE ICU

Variables	a$\widehat{OR}$	95% CI	*p value*
Age, years	1.070	1.056-1.085	**<0.001**
Immunization Period	0.705	0.488-1.019	0.063
Hematologic Cancer	3.058	1.437-6.506	**0.004**
IMV	5.549	3.206-9.603	**<0.001**

Adjusted odds ratios estimates ($a\widehat{OR}$) and corresponding 95% confidence intervals (95% CI) were obtained for all the variables in the multivariable model. For the variable "Immunization Period", the period before immunization was used as the reference category. For the remaining categorical variables, the absence of the characteristic was considered the reference category.

IV. CONCLUSION

Through the analysis and comparison of two periods of the COVID-19 pandemic in Portugal, this preliminary research led to the conclusion that while immunization influenced the trends observed in the last three waves, individual patient characteristics and the severity of their disease had a more substantial impact on ICU outcomes. Hence, when conducting analyses on COVID-19 populations, it is important to make adjustments not only for patient characteristics but also consider the individual COVID-19 waves, as the variants and public health measures in place during each wave can significantly influence the results of multivariable models. In the future, we plan to conduct similar analyses with a larger population to gain a deeper understanding of the impact of the six COVID-19 waves, identify more robust predictors of patient outcomes, and incorporate additional data, including ICU blood analysis results.

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