

Original Article in Economics and COVID-19

# Risk of hospitalization of diagnosed COVID-19 cases during the pandemic: A time-series analysis to unveil short- and long-run dynamics

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## **Abstract**

**Introduction:** The dynamics of the COVID-19 pandemic alternated periods of high incidence (waves) with others of low incidence, making it difficult to separate short- and long-run relationship between the number of COVID-19 cases diagnosed and the demand for hospital beds. The aim of this study was to model the risk of hospitalization of diagnosed cases during all the periods of the COVID-19 pandemic.

**Methods:** Time series techniques were applied to evaluate the short- and long-run relationship between daily number of COVID-19 cases diagnosed and daily number hospital admissions. Drawing on daily Spanish data from 11 May 2020 to 20 March 2022, an error correction model that introduces a short-run mechanism was applied to adjust transitory disequilibrium in the long term. The impact of vaccination on the need for in-patient care were assessed. To examine changes during different life stages, the same analysis was performed by age group.

**Results:** Dynamics between the number of positive cases and demand for hospital beds tended to the equilibrium in the long run, with 9% of any deviation being corrected after one period. Individuals aged between 50 and 69 benefited most from the mass vaccination policy, while vaccination proved to be less effective for people aged over 80.

**Discussion:** Models discriminating between the short- and long-run dynamics provide health planners with a valuable demand forecasting tool which should be useful for developing both structural programs and emergency interventions.

**Take-home message:** The number of diagnosed COVID-19 cases and daily hospitalizations trended toward long-term equilibrium, with transitory disequilibriums corrected in less than a month. Our dynamic modeling approach that distinguishes between long- and short-run dynamics is a valuable instrument to planning hospital resources in epidemics with high-incidence waves.

**Key words:** COVID-19; economics; health facility planning; hospital bed capacity; pandemic; vaccines.

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## INTRODUCTION

The SARS-CoV-2 pandemic marked a turning point in health planning worldwide. The limited capacity of healthcare and hospital resources and the unforeseen levels of demand resulted in situations bordering on collapse at the most critical moments, forcing healthcare services to increase the availability of hospital beds without their being able to implement correct processes of planning [1,2]. In response to these unprecedented circumstances, the scientific literature has hastened to provide health planners with methods for predicting hospital demand [3]. Other authors have studied how the hospital care required by patients with COVID-19 impacted the number of admissions for other pathologies [4,5].

The dynamics of the COVID-19 pandemic alternated periods of high incidence with others of low incidence [6], making it difficult to separate short- and long-run relationship between the number of cases diagnosed and the demand for hospital beds. Given that the number of diagnosed cases of COVID-19 and the number of hospital admissions exhibit a common stochastic trend, then an Error Correction Model (ECM) may be applied to describe the dynamic behaviour of these two time-series. The ECM model links the long-run equilibrium between the positive cases and hospital admissions jointly with the short-run adjustment mechanism that describes how the relationship reacts to stochastic fluctuations. Some studies have used ECM to measure the impact of the spread of SARS-CoV-2 on the healthcare system [7-9]. Nguyen et al. [10] drew on data from the metropolitan area of Charlotte (United States) to estimate a vector ECM for studying the relationship between the daily infection incidence and the aggregate number of hospital beds occupied by SARS-CoV-2 patients, while Mills [11] explored the changing relationship between infections, hospital admissions and deaths using data from England.

The aim of this article is to determine the short-long relationship between the number of COVID-19 cases detected in Spain and the number of hospital admissions due to the virus. An ECM is applied to estimate the long-term equilibrium between the number of diagnosed cases and the number of hospital admissions jointly with the short-run adjustment mechanism to stochastic fluctuations in the incidence of the disease. We evaluate the potential impact on the long-relationship of the vaccination policy to acquire immunity from SARS-CoV-2, and the effect of the population immunity to protect from risk of hospitalization with the presence of a new SARS-CoV-2 (Omicron) variant [12]. Finally, the analysis is carried out by different age groups to examine whether there are any differences of note in the relationship between the incidence of the disease during different life stages.

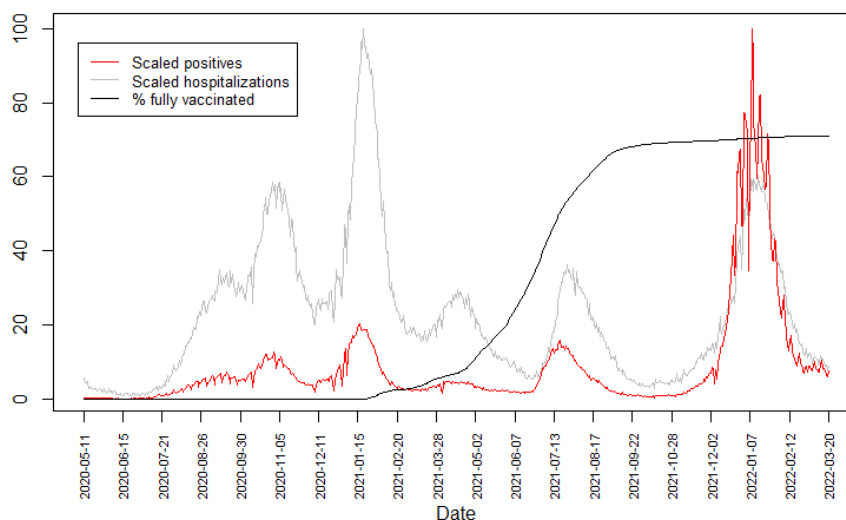
## METHODS

### *Time-series data*

Two free-access datasets from official organizations are used in this study. The daily number of detected cases and hospital admissions are obtained from Spain's National Epidemiology Centre (<https://cnecovid.isciii.es>). Positive cases are registered by date of diagnosis and hospitalizations by date of admission. Information is disaggregated by age intervals. The vaccination program was initiated in Spain on 27 December 2020. The percentage of the population fully vaccinated against COVID-19 is obtained from the weekly reporting data of the number of doses administered by age groups provided by the European Centre for Disease Prevention and Control (<https://opendata.ecdc.europa.eu/>). Our series covers the time period from 11 May 2020 to 20 March 2022.

Our preliminary analysis of the series revealed that the number of positive cases and hospital admissions presented a multiplicative weekly seasonality with cases being underreported at weekends. A log transformation was applied to both time series and the seasonal effect was adjusted using the Loess method [13]. Weekly vaccination information was converted to a daily time series assuming that the same number of doses was administered daily throughout the week. Figure 1 plots the positive cases, hospital admissions and the percentage of population fully vaccinated against COVID-19. For comparison purposes, positive cases and hospital admissions are shown on a 0-100 scale in Figure 1.

**Figure 1.** Time series\* for COVID-19 detected positives, hospital admissions and percentage of population fully vaccinated in Spain for the period from 11 May 2020 to 20 March 2022.



Note: \* For comparison purposes, positive cases and hospital admissions were transformed on a standardized scale from 0 to 100.

**Short- and long-run relationships**

The ECM model can link the long-run equilibrium between two time-series jointly with the short-run adjustment mechanism that describes how the relationship reacts to stochastic fluctuations. The long-run equilibrium relationship between positive cases and number of hospitalizations is represented by the cointegration equation as follows:

$$y_t = b_0 + b_1x_t + b_2x_t I_{immun} + b_3z_t + ect_t \tag{1}$$

where  $y_t$  corresponds to the logarithm of new hospital admissions on day  $t$  and  $x_t$  is the logarithm of the number of daily positive COVID-19 cases and  $t=1, \dots, T$ , where  $T=679$ , given that this is the number of days in the period under study. The constant term is  $b_0$  and  $z_t$  indicates the percentage of fully vaccinated population at time  $t$ . To analyse the effect of the population immunity to protect from risk of hospitalization with the presence of the Omicron variant, the dummy variable  $I_{immun}$  takes a value of 1 if  $t$  occurs on or after 29 November 2021 ( $t \geq 112$ ), the earliest date from which the Omicron variant was detected in Spain, and zero otherwise. Population immunity occurs when a large portion of individuals has acquired immunity because they have recovered from the disease or have been vaccinated against the disease. When the Omicron variant appeared in Spain, almost 70% of the total population was fully vaccinated, and this percentage rose to more than 90% of population over 50 years of age. Therefore, it is reasonable to assume that, at that time, there was population immunity against previous variants of SARS-CoV-2. Finally, the error correction term ( $ect$ ) captures the regression residuals.

If the residuals in (1) are stationary, the variables are cointegrated [14]. An ECM can then be specified to analyse the short-run adjustment mechanism and the long-run equilibrium between these variables as follows [15,16]:

$$\Delta y_t = c + \sum_{i=1}^k \psi_i \Delta y_{t-i} + \sum_{j=0}^q w_j \Delta x_{t-j} + \gamma \cdot ect_{t-1} + \varepsilon_t \tag{2}$$

In our case, the first difference of log hospital admissions ( $\Delta y_t = y_t - y_{t-1}$ ) is regressed on the lagged error correction term from (1),  $k$ -lagged values of the same variable and current and  $q$ -lagged values of the log hospital admissions, all in differences. The optimal numbers for  $k$  and  $q$  are determined when estimating the model. Coefficients  $\psi_i$  and  $w_j$  measure short-run reactions of the dependent variable with its previous changes and with changes in the explanatory variables, respectively. The intercept included in the regression is  $c$ , while  $\gamma$  corresponds to the error correction rate that indicates the speed of adjustment in the short term when there is a disequilibrium in the long term, i.e.,  $ect_{t-1} \neq 0$  [17]. Finally,  $\varepsilon_t$  is the error term which is normally distributed with zero mean and variance  $\sigma_\varepsilon^2$ ,  $\varepsilon_t \sim N(0, \sigma_\varepsilon^2)$ . A generalized autoregressive conditional heteroscedasticity (GARCH) [18] model specification is used to deal with the presence of heteroscedasticity. A GARCH(1,1) is proposed here to model the variance as  $\sigma_t^2 = \alpha_0 + \alpha_1 \varepsilon_{t-1}^2 + \alpha_2 \sigma_{t-1}^2$ . To conclude, it should be borne in mind that an autoregressive distributed lag model specification could be obtained from (2) by rearranging the variables [19].

**RESULTS**

The statistical analysis was conducted using R statistical software, version 4.1.1. [20,21]. The first step in this analysis involved examining the order of integration of the series, which is usually made using the augmented Dickey-Fuller (ADF) test [14]. The values of the ADF test statistics for the logarithm of hospital admissions  $y_t$  and the logarithm of positive cases  $x_t$  were -0.031 and 0.453, respectively. As a result, the null hypothesis, which states the presence of a unit root, was not rejected at a significance level of 5%. However, the null hypothesis was rejected when  $\Delta x_t$  and  $\Delta y_t$  were analysed, indicating that the first difference of the time series were stationary (ADF( $\Delta y_t$ )=-23.094 and ADF( $\Delta x_t$ )=-23.660). Therefore, both variables  $x_t$  and  $y_t$  are integrated of order one.

**Log-run equilibrium**

The cointegration equation expressed in (1) is estimated using fully modified least squares [22]. Table 1 reports the coefficient estimates and the ADF test performed on the cointegration residuals. The results show that the residuals are integrated of order zero (stationary), thus cointegration exists.

**Table 1.** Estimation of the cointegrating equation (long-run relationship) between time series of positive COVID-19 cases and hospital admissions, and ADF test on residuals.

Coefficient	Description	Estimate	95% Conf. Int.
$b_0$	Intercept	-1.228**	[-1.796, -0.660]
$b_1$	Positive cases (log)	0.855**	[0.789, 0.920]
$b_2$	Population immunity	-0.076**	[-0.102, -0.049]
$b_3$	% vaccinated population	-0.008**	[-0.011, -0.006]
ADF	ADF test on $ect$	-5.413**	

Note: \*\* p-value < 0.01.

The value  $e^{b_0}$  corresponds to the proportion of corrected positive cases,  $e^{(b_1+b_2 I_{immun})x_t+b_3 z_t}$ , estimated as being admitted to hospital. Thus, 29.3% of the corrected number of positive cases is estimated as being admitted to hospital. The long-run coefficient of the (log) number of positive cases is greater than 0, meaning that an increase in the number of COVID-19 cases diagnosed implies an increase in the number of hospitalizations. The coefficient associated with the population immunity presents a significant negative sign, suggesting that after 29 November 2021 an increase in the number of positive cases is associated with a smaller increase in the number of patients requiring hospitalization. Here, we find that the number of positive cases in the original scale ( $e^{x_t}$ ) has to be raised to a power and later multiplied by 0.293 to compute the number of hospitalizations. The power value ranged from 0.885 before 29 November 2021 to 0.779 (=0.855-0.076) after this date. The fact that both values are lower than one means that any increase in the number of positive cases generates a lower increase in the number of hospitalizations, with this reduction being greater as of November

29. Additionally, the long-run coefficient for the percentage of fully vaccinated is negative, which indicates that the greater the number of people with full vaccination status, the fewer the number of people that have to be hospitalized. Specifically, a 1% increase in the fully vaccinated population reduced the risk of hospitalization approximately by 0.8% (i.e.,  $e^{-0.008} - 1$ ).

**Error correction model estimation**

The estimated coefficients of the ECM corrected for heteroscedasticity through a GARCH(1,1) specification are shown in Table 2. The selection of the order ( $k,q$ ) was based on the Bayesian information criterion (BIC) [23]. The model specification with the lowest BIC had 11 lags on the difference of log hospital admissions and 1 lag on the difference of log positive cases.

**Table 2.** Error correction model (short-run relationship) between time series of positive COVID-19 cases and hospital admissions (in log scale).

Coefficient	Description	Estimate	95% Conf. Int.
$c$	Intercept	-0.003	[-0.011, 0.006]
$\psi_1$	1-lagged hospitalization difference	-0.591**	[-0.674, -0.509]
$\psi_2$	2-lagged hospitalization difference	-0.298**	[-0.394, -0.202]
$\psi_3$	3-lagged hospitalization difference	-0.074	[-0.171, 0.022]
$\psi_4$	4-lagged hospitalization difference	0.009	[-0.084, 0.102]
$\psi_5$	5-lagged hospitalization difference	0.115*	[0.026, 0.204]
$\psi_6$	6-lagged hospitalization difference	0.160**	[0.071, 0.248]
$\psi_7$	7-lagged hospitalization difference	0.349**	[0.263, 0.435]
$\psi_8$	8-lagged hospitalization difference	0.232**	[0.140, 0.324]
$\psi_9$	9-lagged hospitalization difference	0.183**	[0.089, 0.276]
$\psi_{10}$	10-lagged hospitalization difference	0.179**	[0.087, 0.270]
$\psi_{11}$	11-lagged hospitalizations difference	0.105**	[0.029, 0.180]
$w_0$	Difference of positive cases	0.304**	[0.267, 0.341]
$w_1$	1-lagged difference of positive cases	-0.047**	[-0.082, -0.012]
<i>Error correction</i>			
$\gamma$	Error correction term	-0.088**	[-0.109, -0.066]
<i>Variance equation</i>			
$\alpha_0$	Variance equation intercept	1.6·10 <sup>-4</sup> **	[3.8·10 <sup>-5</sup> , 2.8·10 <sup>-4</sup> ]
$\alpha_1$	Variance equation error term	0.110**	[0.065, 0.155]
$\alpha_2$	Variance equation variance term	0.866**	[0.820, 0.913]
AIC	AIC of the ECM	-2.169	
BIC	BIC of the ECM	-2.049	
HC	HQ of the ECM	-2.123	
R <sup>2</sup>	ECM coefficient of determination	0.425	

Note: \*\* p-value < 0.01; \* p-value < 0.05.

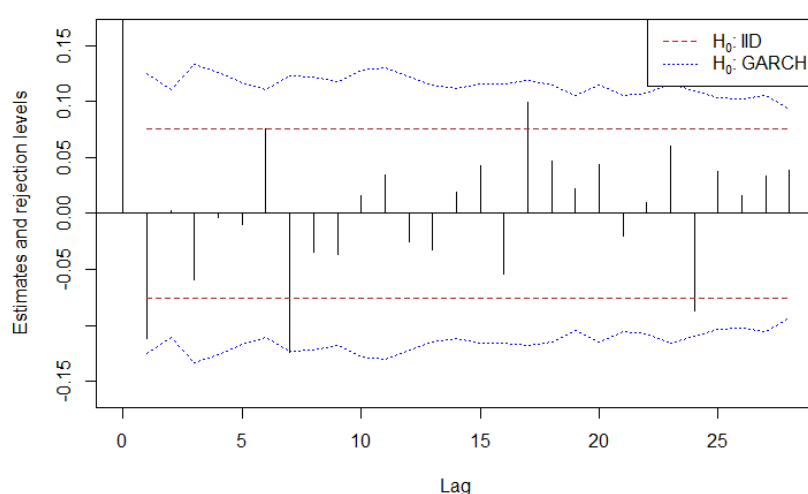
Table 2 shows that the coefficient associated with the error correction term is significant and takes a value between -1 and 0, which are the necessary conditions for stating that the dynamics between the analysed variables tend to equilibrium. Specifically, the estimated coefficient reflects the speed of adjustment in case of long-run disequilibrium. Its value suggests that, when a disequilibrium in the long-run relationship is observed, around 9% of any deviation (gap) dissipates after one period. That means, a gap in the long-run relationship between positives and hospitalizations is expected to be reduced by 50% in less than eight days.

**Model diagnostics**

To obtain both consistent and efficient estimates, the residuals in (2) should follow an uncorrelated white noise process. Figure 2 shows the partial autocorrelations of the model (2)

residuals. The rejection limits of the null hypothesis stating that the residuals follow a white noise process were computed under the independent and identically distributed (IID) and GARCH assumptions [24]. The partial autocorrelations were not-significant under the GARCH hypothesis, so the null hypothesis was not rejected. The assumption of normal conditional distribution of residuals was not rejected at the 5% significance level based on the adjusted Pearson goodness-of-fit test [25]. No serial dependence for the residuals of the mean process was found according to the Ljung-Box test. Finally, time-varying phenomena in the residuals of the variance process were not detected and leverage effects were not found [26]. Hence, it can be concluded that the dynamics of the variance process were correctly captured and there was no evidence of misspecification.

**Figure 2.** Partial autocorrelation function of residuals and rejection limits of white noise process under IID and GARCH hypotheses.



### Age groups

The ECM was further calibrated for four different age groups. The age intervals considered are 20–49, 50–69, 70–79 and 80 years or more. The results of the estimation of the ECM and the cointegration equation for each age group are shown in Table 3. The selected models now include two/three lags of the difference of (log) hospitalizations and zero/one lag of the difference of (log) positive cases.

**Table 3.** Error correction model for positive cases and hospital admissions (in log scale), and long-run coefficients by age groups.

Coeff.	Description	Estimates			
		20-49	50-69	70-79	80+
<i>Long-run coefficients</i>					
$b_0$	Intercept	-1.970**	-2.198**	-1.372**	-1.004**
$b_1$	Positive cases (log)	0.829**	1.005**	1.005**	0.998**
$b_2$	Population immunity	-0.114**	-0.146**	-0.133**	-0.117**
$b_3$	% vaccinated population	-0.005**	-0.005**	-0.004**	-0.001*
<i>Short-run coefficients</i>					
c	Intercept	-0.001	-	-	0.001
$\psi_1$	1-lagged hospitalization difference	-0.665**	-0.637**	-0.776**	-0.548**
$\psi_2$	2-lagged hospitalization difference	-0.316**	-0.266**	-0.433**	-0.234**
$\psi_3$	3-lagged hospitalization difference	-	-	-0.162**	-

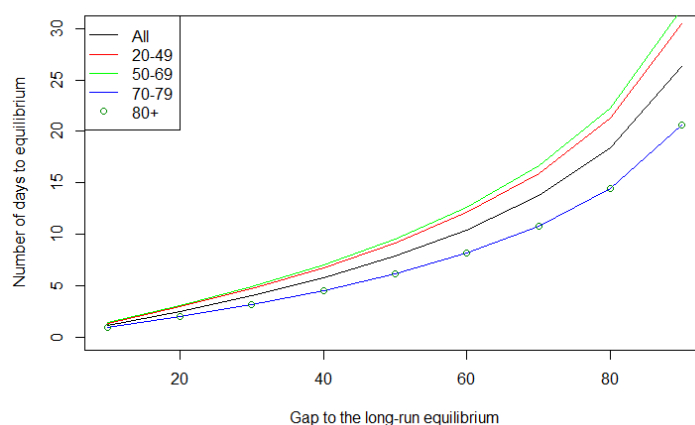
$w_0$	Difference of positive cases	0.301**	0.365**	0.410**	0.314**
$w_1$	1-lagged difference of positive cases	-	-	-	0.091**
<i>Error correction</i>					
$\gamma$	Error correction term	-0.076**	-0.072**	-0.112**	-0.112**
<i>Variance equation</i>					
$\alpha_0$	Variance equation intercept	4·10 <sup>-4</sup> *	5·10 <sup>-4</sup> **	4·10 <sup>-4</sup> *	2·10 <sup>-4</sup> *
$\alpha_1$	Variance equation error term	0.126**	0.110**	0.126**	0.121**
$\alpha_2$	Variance equation variance term	0.861**	0.866**	0.868**	0.878**
AIC	AIC of the ECM	-0.858	-1.126	-0.717	-1.008
BIC	BIC of the ECM	-0.804	-1.072	-0.656	-0.948
HQ	HQ of the ECM	-0.837	-1.105	-0.693	-0.985
R <sup>2</sup>	ECM coefficient of determination	0.436	0.409	0.478	0.290

Note: \*\* significance level at 1%; \* significance level at 5%.

A number of differences by age group in the long-run relationship and the speed of adjustment in the short-run are worth highlighting. For example, in the case of the long-run equilibrium coefficients, the intercept estimates present higher values for the older age groups. Thus, the value corresponding to the proportion of corrected positive cases estimated as being admitted to hospital,  $e^{b_0}$ , is higher for older ages. Additionally, the coefficients  $b_1$ , associated with the correction of positive cases, indicate that an increase in the number of cases is associated with an increase in the number of hospitalizations; however, this increment is smaller in the case of the youngest age group. This impact on the number of hospitalizations falls after 29 November 2021, as the coefficients  $b_2$ , associated with the population immunity, are significant and negative in all age groups, most notably in the 50–69 age group. It is also evident that the beneficial effects of an increase in the percentage of fully vaccinated  $b_3$  on falling numbers of hospitalizations holds for all ages, albeit that this effect decreases as people get older.

Additionally, all the error correction term coefficients are significant and negative. The number of days required to close the gap between current and equilibrium hospital admissions for the different group ages are shown in Figure 3. The number of days required to correct a long-run disequilibrium are computed using the approach devised by Galeotti et al. [27]. We find that adjustment to the long-run equilibrium is more rapid in the case of the two oldest age groups. For example, reducing the temporary gap by 50% requires 9.2 days for the 20-49 age group, 9.6 days for the 50-69 age groups, and 6.2 days for the two older age groups.

**Figure 3.** Speed of adjustment to equilibrium in days.



These results obtained after disaggregating by age should, however, be treated with some caution, given that residual autocorrelation that might affect the efficiency of estimates was detected [24]. In all likelihood, this effect is attributable to the low number of lagged regressors selected based on the best goodness-of-fit performance of the models.

## **DISCUSSION**

This article has examined the short-long relationship between the number of COVID-19 cases detected in Spain and the number of hospital admissions due to the virus. The long-run relationship followed a multiplicative model (additive after logarithmic transformations), in line with Santolino et al. [3] who linked hospital admissions and nine-period-lagged positive cases. The dynamics of the relationship between our time series proved to be stable and tended to long-run equilibrium. Alternative designs of the long-run equilibrium equation were investigated to capture other forms of relationship between the number of hospitalizations and the number of positives detected and the vaccination status, but a poorer performance was observed in terms of goodness-of-fit in all cases.

The behaviour of the pandemic indicators was not steady over time as periods of high incidence alternated with others of low incidence. We detected two distinct factors impacting the long-run equilibrium between the number of cases and the number of hospitalizations: that is, vaccination and population immunity with the presence of a new SARS-CoV-2 variant (Omicron). The effectiveness of COVID-19 vaccines has been extensively studied [28-32]. Previous studies have shown that vaccination reduces the risk of hospitalization [33,34]. Our research also shows that hospital pressure decreased as the vaccination program was progressively rolled out. The Omicron variant appeared in late 2021 and rapidly replaced Delta as the dominant variant globally due to increased immune evasion [35,36]. Some studies suggest that this variant presents a lower risk of hospitalization and death than earlier SARS-CoV-2 variants of the virus [36]. In the same line, we found evidence in this study that population immunity was effective to reduce the risk of hospitalization of detected positives after the appearance of this variant.

COVID-19 hospitalization rates are known to be exponentially associated with age [37]. Our study showed that the percentage of individuals with a positive diagnosis requiring hospitalization was higher among people who were fifty years of age or older. Population immunity with the appearance of the Omicron variance was effective to protect from risk of hospitalization in all groups, but particularly among the late middle-aged. Sievers et al. [38], likewise, worked with different age groups and found the reduction of the hospitalization risk to be apparently greater in the early middle-aged. Finally, in line with other studies [39,40], our results showed that vaccination proved to be less effective for older people.

Our study has relevant implications for health planners. The different waves of the coronavirus have produced fluctuating and unpredictable levels of pressure on hospitals [41,42]. The dynamic model proposed here seeks to be a useful health planning tool that can forecast the amount of hospital resources required at any specific moment based on the prevailing incidence of the disease, the virulence of the dominant variant, and the proportion of the population with full vaccination status. Our methodology allows health planners to predict the expected number of hospitalizations based on the number of observed positives and the percentage of vaccinated population. Thus, health planners have a mechanism to help them determine the number of hospital beds needed at any point in time. By differentiating between long- and short-run effects, in case of deviations of the long-term relationship between positives and hospitalizations, health planners may know in advance the expected time required to return to the long-run equilibrium. Deviations of observed hospitalizations from expected hospitalizations can be positive (higher) or negative (lower). In both cases, health planners could forecast the variations in the hospital admissions during this transition period to long-term equilibrium.

Policy implications are derived from our study. We evaluate the impact of mass vaccination policy on reducing the long-term relationship between positives and hospitalizations for the total population and by age groups. By doing so, valuable information is provided to policymakers for the design of strategies of priority vaccination. Furthermore, the dynamic modelling approach followed



in this study may be extended in at least two ways. First, other health policies could be evaluated with this methodology in terms of their long- and short-term impact on the balance between coronavirus positives and hospitalizations. Second, our modelling approach is not limited to the coronavirus pandemic, and could easily be adapted to apply to future pandemics to anticipate the demand for hospital beds and to assess the long- and short-term impact of health policies on reducing hospital pressure. To summarise, our methodology furnishes healthcare decision-makers with a dual mechanism that facilitates their evaluations of the impact of (i) the structural health policies aimed at addressing the long-run relationship between positive cases and the demand for hospital beds, and (ii) emergency interventions with a short-run impact on the demand for hospital admissions.

This study is not exempt from limitations, not least the fact that access to reliable data is essential for developing an accurate, realistic model. As Hyafil and Moriña [43] stress, the number of tests performed has a direct effect on the number of positive cases detected, which suggests there are likely to have been undiagnosed cases not considered in this study. The degree of underreporting cases varies over time and between countries [44]. Additionally, here we have had to use weekly vaccination information to estimate daily rates of inoculation, as complete daily data on the number of individuals with full vaccination status were unavailable. Finally, risk factors, such as gender, were not analysed as they were not registered by the databases [45].

## CONCLUSION

The application of the error correction model introduces a short-run mechanism to adjust transitory disequilibrium in the long-run relationship between the number of COVID-19 cases diagnosed and the consequent demand for hospital beds. Results revealed that the dynamics between the number of positive cases and demand for hospital beds tended to the equilibrium in the long run, with 9% of any deviation being corrected after one period. The dynamic modelling approach proposed herein should represent a valuable instrument for planning hospital resources in any pathology that necessitates in-patient care, especially epidemics with waves of contagion. Based on the cases detected in primary care, it would be possible to predict the number of hospital admissions, thus allowing health planners to anticipate both the long- and short-run impact on hospital pressure created by any disease.

**Author Contributions:** Conceptualization: MA. and MS. Methodology: ME, MS. Software: ME. Validation: MA, MS. Formal analysis: ME, MS. Investigation: MA, MS. Resources: MA. Data curation: ME. Writing—original draft preparation: ME. Writing—review and editing: MA, MS. Visualization: MS. Supervision: MA. Project administration: MA. Funding acquisition: MS. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

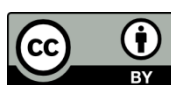
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