

# Is Age the Most Important Risk Factor in COVID-19 Patients? The Relevance of Comorbidity Burden: A Retrospective Analysis of 10,551 Hospitalizations

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**Purpose:** To assess the contribution of age and comorbidity to the risk of critical illness in hospitalized COVID-19 patients using increasingly exhaustive tools for measuring comorbidity burden.

**Patients and Methods:** We assessed the effect of age and comorbidity burden in a retrospective, multicenter cohort of patients hospitalized due to COVID-19 in Catalonia (North-East Spain) between March 1, 2020, and January 31, 2022. Vaccinated individuals and those admitted within the first of the six COVID-19 epidemic waves were excluded from the primary analysis but were included in secondary analyses. The primary outcome was critical illness, defined as the need for invasive mechanical ventilation, transfer to the intensive care unit (ICU), or in-hospital death. Explanatory variables included age, sex, and four summary measures of comorbidity burden on admission extracted from three indices: the Charlson index (17 diagnostic group codes), the Elixhauser index and count (31 diagnostic group codes), and the Queraltx DxS index (3145 diagnostic group codes). All models were adjusted by wave and center. The proportion of the effect of age attributable to comorbidity burden was assessed using a causal mediation analysis.

**Results:** The primary analysis included 10,551 hospitalizations due to COVID-19; of them, 3632 (34.4%) experienced critical illness. The frequency of critical illness increased with age and comorbidity burden on admission, irrespective of the measure used. In multivariate analyses, the effect size of age decreased with the number of diagnoses considered to estimate comorbidity burden. When adjusting for the Queraltx DxS index, age showed a minimal contribution to critical illness; according to the causal mediation analysis, comorbidity burden on admission explained the 98.2% (95% CI 84.1–117.1%) of the observed effect of age on critical illness.

**Conclusion:** Comorbidity burden (when measured exhaustively) explains better than chronological age the increased risk of critical illness observed in patients hospitalized with COVID-19.

**Keywords:** COVID-19, comorbidities, comorbidity burden, risk assessment, hospitalized patients, case-mix tool

## Introduction

Since the beginning of the coronavirus disease (COVID-19) pandemic, age and the presence of comorbidities have both been pointed out as critical risk factors for developing severe illness.<sup>1</sup> Various authors have found that the influence of

age on severe outcomes decreased when adjusting for other factors, including but not limited to comorbidities.<sup>2-4</sup> Nevertheless, in most models such attenuation of the effect of age was only partial, and age was still acknowledged as the most important risk factor for severe illness.<sup>5-7</sup> In this context, age has been used as the main criterion for prioritizing vaccine allocation in many countries and driving many stratify-and-shield campaigns worldwide. However, using age as a risk proxy for prioritization of healthcare interventions risks ageism, with quantifiable adverse consequences in several settings, including COVID-19.<sup>8,9</sup>

While the effect of age can be easily measured in multivariate models, assessing the contribution of comorbidity burden has several challenges, which may bias the results. Most studies in the COVID-19 setting have assessed the presence or absence of a specific, relatively limited number of chronic conditions.<sup>5,6,10-13</sup> However, this approach addresses the effect of certain comorbidities rather than the effect of comorbidity burden as a whole. Alternatively, other authors have used summary measures of comorbidity burden, such number of chronic conditions (eg, stratified into categories from 0 to up to  $\geq 3$ ),<sup>6,14,15</sup> or summary indices such as the Charlson or Elixhauser.<sup>16-21</sup> These indices might underestimate comorbidity burden due to the limited number of diagnoses considered.<sup>22</sup>

Taking advantage of the systematic collection and integration of routine care data, we recently developed a set of comprehensive indices for risk assessment in hospitalized patients, which includes an index for measuring comorbidity burden of these patients: the Queralt index for comorbidities (Queralt DxS).<sup>23</sup> The index combines and weighs more than 3145 relevant acute and chronic diagnostic codes and provides a numerical index of comorbidity burden on admission. When used as adjustment factor in risk assessment of patients hospitalized with COVID-19, the Queralt DxS showed a remarkable contribution to explaining the risk of critical illness (ie, admission to intensive care unit or death) in individuals hospitalized with COVID-19.<sup>24</sup>

In this analysis, we investigated how the effect of chronological age on the risk of critical illness changes when comorbidity burden is measured using increasingly exhaustive tools: the Charlson index (17 diagnostic group codes), the Elixhauser index (31 diagnostic group codes), the count of diagnoses included in the Elixhauser index, and the Queralt DxS (3145 diagnostic group codes). We also aimed at evaluating the mediation role of comorbidity burden in the relationship between age and critical COVID-19 illness.

## Materials and Methods

### Study Design and Setting

This was a retrospective analysis of individuals hospitalized with COVID-19 as the primary diagnosis in the seven public hospitals of the Catalan Institute of Health, the leading healthcare provider in Catalonia (North-East Spain). The Catalan Institute of Health provides universal healthcare to nearly 70% of the Catalan population and accounts for 30% of the total acute hospitalizations in Catalonia.

We screened the database of the Catalan Institute of Health for all individuals admitted with COVID-19 as the primary diagnosis between March 1, 2020 and August 31, 2022. The database was locked on January 25, 2023. Patients derived from other hospitals or transferred to other hospitals on discharge were excluded from the record. For the primary diagnosis, we considered the following diagnosis codes of the international classification of diseases 10th version, clinical modification (ICD-10-CM): B97.29, B97.21, B34.2, J12.81, J12.89, and U07.1. The vaccination campaign in Catalonia started on December 27, 2020. [Figure S1](#) summarizes the prevalence of each variant of concern throughout the investigated period.

All data were handled according to the General Data Protection Regulation 2016/679 on data protection and privacy for all individuals within the European Union and the local regulatory framework regarding data protection. The study protocol was approved by the independent ethics committee of the Bellvitge Biomedical Research Institute (IDIBELL, Spain), which waived obtaining informed consent for the secondary use of data collected during routine care (ref. PR123/22).

## Variables and Data Sources

The study outcome was a composite outcome of critical illness, which included the need for invasive mechanical ventilation, transfer to the intensive care unit (ICU), or in-hospital death (any of them) as described elsewhere.<sup>13</sup> Information about admission to ICU and death are systematically collected in the electronic health records of Catalan Institute of Health hospitals, whereas the need for invasive mechanical ventilation was determined by the following codes of hospital procedures: 5A09357, 5A09457, 5A09557, 5A1935Z, 5A1945Z, 5A1955Z, 09HN7BZ, 09HN8BZ, 0BH13EZ, 0BH17EZ, 0BH18EZ, 0CHY7BZ.

Primary explanatory variables included age, sex, and measures of the comorbidity burden present on admission. The comorbidities present on admission were retrieved from a common electronic health record shared by all hospitals of the Catalan Institute of Health. We used four summary measures of comorbidity burden: the Charlson index,<sup>25</sup> the Elixhauser count (ie, number of diagnoses among the 31 codes considered in the Elixhauser index) and index,<sup>26</sup> and the Queralt index for secondary diagnoses present on admission (Queralt DxS).<sup>23</sup> The ICD-10 coding for the Charlson and Elixhauser scores was based on work by Quan et al.<sup>27</sup> Weights for the Charlson score are based on the original formulation by Charlson et al in 1987,<sup>25</sup> while weights for the Elixhauser score were based on work by Moore et al.<sup>28</sup> The Queralt DxS is part of a set of three indices for measuring the clinical complexity of hospitalized patients. It provides a numerical value from the weighted sum of secondary diagnoses present on admission from a list of 3145 diagnostic code groups.<sup>23</sup> The weights of the version used in this analysis (version 6.3) were estimated from health data collected in hospitalizations reported between 2018 and 2019 in the Catalan Institute of Health and were, therefore, not specific to COVID-19 patients.

Adjusting variables included the wave in which the admission occurred, the hospital, and the vaccination status for COVID-19 (the last used only in the secondary analyses presented in the [Supplementary File](#)). The vaccination status was retrieved from the K2 platform database, held by the Catalan Department of Health and used as a source of information for issuing COVID-19 certificates. The K2 database includes information on COVID-19 diagnoses from the primary and hospital care setting (both public and private) and vaccination information. Vaccination categories, used in the secondary analysis only, were defined as follows: partial vaccination (ie, one dose of a 2-dose regimen of an RNA-based vaccine), complete vaccination (ie, either two doses of an RNA vaccine or one dose of a single-dose regimen vaccine), and booster (ie, an additional dose to the complete vaccination regimen).

## Analysis

We defined two analysis datasets. The primary analysis dataset, presented in tables and figures in the main text, excluded vaccinated individuals and those admitted during the first wave of the COVID-19 outbreak in Catalonia (from March 1 to June 23, 2020). The reason for excluding these individuals was the high risk of bias. The first outbreak in Spain severely overwhelmed hospital resources and occurred very early in the pandemic, with limited knowledge on the management of COVID-19 in the hospital setting.<sup>13,29</sup> These two factors were expected to affect the mortality rate and factors influencing it. Likewise, vaccination significantly limits the progression toward severe illness and may challenge result interpretation. The secondary dataset, presented in the [Supplementary File](#), included the entire retrospective cohort, irrespective of the time of admission and vaccination status. In the secondary analysis, patients were stratified according to the wave in which they were admitted to facilitate results interpretation regarding the severity of the wave, the availability of vaccines, or the prevalence of different variants of concern ([Figure S1](#)).

For description purposes, age and the summary measures of comorbidity were categorized. Age was split into the following groups: 0–39, 40–49, 50–59, 60–69, 70–79, and  $\geq 80$ ). The indices of comorbidity were categorized into three risk levels of comorbidity burden that yield homogeneously sized high-risk groups: the Charlson index scores were grouped into low health risk (score 0), moderate (1–2), and high ( $\geq 3$ ); the Elixhauser and Queralt DxS indices were grouped into low (below the 50th percentile), moderate (50th – 85th), and high ( $>85$ th percentile); the Elixhauser count was grouped into low (0–1), moderate (2–3), and high ( $\geq 4$ ). The definition of the cut-off percentiles for the Elixhauser and Queralt DxS indices sought homoscedasticity with age (ie, 15% of the study sample was allocated in the upper age group).

The association between explanatory variables (age, sex, and comorbidity burden) and the study outcome (development of critical illness) was investigated using multiple logistic regression models for each measure of the comorbidity burden: Charlson index, Elixhauser index, Elixhauser count, and Queralt DxS index. Age was introduced as a categorical variable to ease the interpretation of the resulting model, although the same models with age as a continuous variable plus an additional quadratic term were built to confirm the equivalent performance of the model. In addition, while acknowledging potential clustering of patient characteristics by hospital,<sup>29</sup> all models were further adjusted by considering the random effects of hospitals in which admission occurred. First, we built separate models for age, sex, and each measure of the comorbidity burden; then, we built multivariate models including age, sex, and one comorbidity measure; finally, we built the same models accounting for interactions between age and the comorbidity measures. The same methodology was applied to secondary analyses in which each wave was analyzed separately, with models adjusted for hospital and vaccination status.

Finally, we used a causal mediation analysis<sup>30</sup> to investigate the hypothesis that comorbidity burden, would fully mediate the association between age (exposure factor or treatment variable) and critical illness (outcome). In this analysis, age and the comorbidity indices were used as continuous variables. The control and treatment age groups, required for the mediation analysis, were established based on the 50 and 75 years cutoffs. The average causal mediation effect of comorbidity (mediator), the average direct effect of age, and the total effect were estimated, and the 95% CI obtained using bootstrap from 2000 simulations, considered adequate for this type of analysis. The contribution of the comorbidity-mediating pathway was assessed using the proportion of the average causal mediation effect over the total effect. All analyses were performed using R 4.1.2.<sup>31</sup> The causal mediation analysis was conducted using the library mediation by Tingley et al,<sup>32</sup> the linear and mixed model adjustments were conducted using the lme4 library,<sup>33</sup> and the analyses of the ROC and precision-recall curves were done using the pROC<sup>34</sup> and PRROC<sup>35</sup> libraries, respectively. The Charlson and Elixhauser indices were computed using the Comorbidity library by Gasparini,<sup>36</sup> whereas the Queralt DxS was estimated using the updated version of the index R function (version 6.3; the software can be accessed from <https://ics.gencat.cat/ca/assistencia/coneixement-assistencial/sistema-de-Queralt/>).

## Results

### Study Population

Between March 1, 2020 and August 31, 2022, 19,662 individuals were admitted to the hospitals of the Catalan Institute of Health with COVID-19 as the main diagnosis (Figure 1). Of them, 10,551 were non-vaccinated individuals admitted after the first wave (ie, from June 23, 2020 on) and were, therefore, included in the primary analysis: 3632 (34%) with critical illness and 6919 (66%) without critical illness. The second wave contributed the largest number of admissions to this analysis.

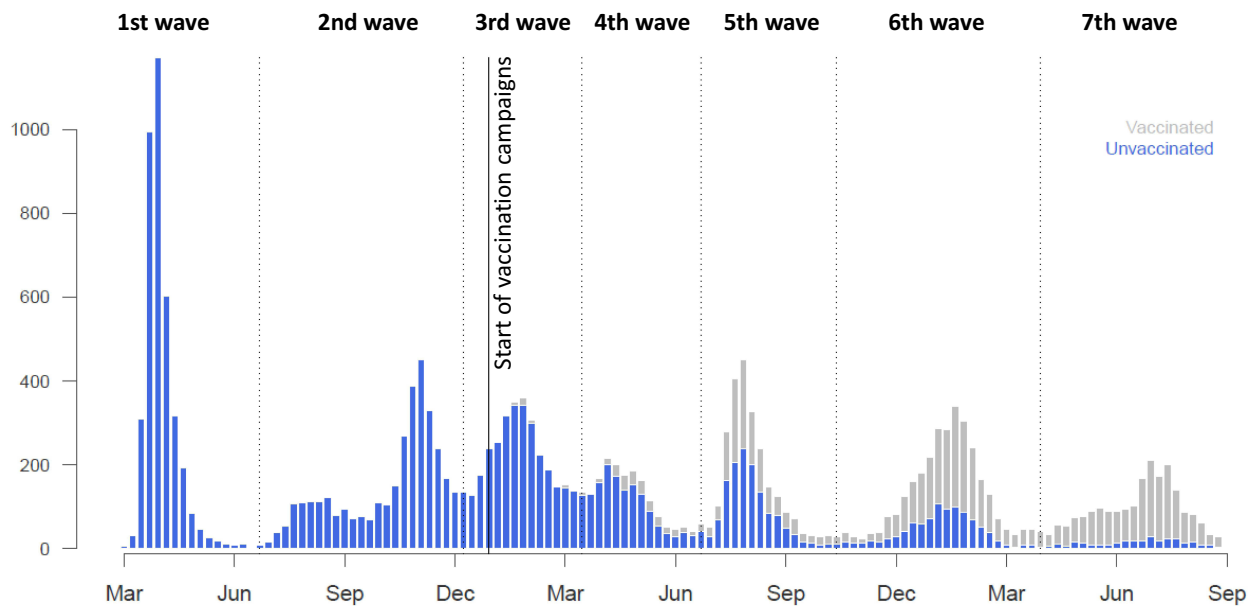
Table 1 summarizes the main demographic, epidemiological, and clinical characteristics of the study population of the primary analysis. The characteristics according to COVID-19 wave are listed in Tables S1–S7. The proportion of patients with critical illness increased with age and comorbidity burden, irrespective of the type of measure used. The same trends were observed when age and comorbidity burden were described as continuous variables. The greatest differences in the proportion of critical illness according to comorbidity were observed for the Queralt DxS.

### Estimated Risk and Critical Illness

The distribution of the study population across the Queralt DxS risk groups showed a higher proportion of individuals at high and moderate risk among patients who experienced critical illness (Figure 2). The distribution according to the successive waves showed a similar trend (Figures S2–S8).

### Risk Factors for Critical Illness

According to the baseline model, adjusted by age, sex, hospital, and wave, the risk of critical illness increased progressively with age and was higher in men (Figure 3). When adjusting also for summary indices of comorbidity, the effect size of sex remained relatively stable, whereas that of age progressively decreased with the exhaustivity of the



**Figure 1** Absolute number of weekly admissions throughout the period. Individuals in the no vaccine group had not received any dose of any type of vaccine against COVID-19. Vertical dotted lines indicate the start/end of each COVID-19 wave in our area.

comorbidity measure. Moreover, the risk of critical illness increased linearly with age and comorbidity burden, irrespective of the index used. The reduction of the effect size of age was the highest when comorbidity burden was summarized using the Queralt DxS (ie, the comorbidity measure that considers the highest number of possible diagnostic groups). We observed the same trend in all waves, including those occurred after the beginning of the nationwide vaccination campaign, except the first one, in which the effect of age was significant in group ages above 60 years after adjusting for the Queralt DxS ([Tables S8–S14](#)).

## Performance of Prediction Models for Critical Illness

[Table 2](#) summarizes the BIC, AUROC, and precision-recall estimates for models in three series of models: (1) Models including only sex, age, or a summary measure of the comorbidity burden (adjusted by hospital and wave), (2) Multivariate models including age, sex, and a comorbidity measure (also adjusted by hospital and wave), and (3) The corresponding models accounting for interactions between age and the comorbidity measures. In all model series, the performance increased with the number of diagnoses considered for the comorbidity burden estimate, with models using the Charlson index showing the poorest performance and models using the Queralt DxS the highest. According to the analysis with the entire cohort stratified by waves, models using the Queralt DxS for adjusting for the comorbidity burden had the highest performance in all waves ([Tables S15–S21](#)).

## Mediation Analysis

According to the causal mediation analysis, the proportion of mediation by comorbidity burden over the total effect of age on the risk of critical illness increased with the exhaustivity of the comorbidity measure used ([Figure 4](#)). Using the Charlson index (ie, the comorbidity measure with the smallest effect size in our multivariate analysis), the proportion of the effect that was mediated was remarkably lower than the direct effect of age. In contrast, the reverse was true when comorbidity burden was measured using the Queralt DxS. In the latter analysis, the direct effect of age was no longer significant ([Figure 4](#)). The proportion of mediation effects was highest for the Queralt DxS index in all waves of the COVID-19 outbreak in Catalonia, with values ranging from 0.68 (95% CI 0.59–0.79) (first wave) to 1.30 (95% CI 0.64–5.29) (seventh wave) ([Figure 5](#) and [Tables S22–S28](#)).

**Table I** Demographic, Clinical, and Epidemiological Characteristics of Individuals Included in the Primary Analysis

	No Critical Illness (N=6919)	Critical Illness (N=3632)	Total (N=10,551)	P*
Age, mean (SD)	57.6 (19.6)	62.9 (17.6)	59.4 (19.1)	<0.001
Age group, n (%)				
0–39	1095 (75.4)	357 (24.6)	1452 (100.0)	<0.001
40–49	1060 (72.2)	409 (27.8)	1469 (100.0)	
50–59	1360 (66.8)	675 (33.2)	2035 (100.0)	
60–69	1418 (64.1)	793 (35.9)	2211 (100.0)	
70–79	1145 (60.3)	755 (39.7)	1900 (100.0)	
≥ 80	841 (56.7)	643 (43.3)	1484 (100.0)	
Sex, n (%)				
Men	3989 (62.7)	2372 (37.3)	6361 (100.0)	<0.001
Women	2930 (69.9)	1260 (30.1)	4190 (100.0)	
Hospital, n (%)				
Arnau de Vilanova	1353 (72.2)	522 (27.8)	1875 (100.0)	<0.001
Joan XXIII	741 (74.2)	257 (25.8)	998 (100.0)	
Verge de la Cinta	385 (72.9)	143 (27.1)	528 (100.0)	
Dr Trueta	571 (53.4)	499 (46.6)	1070 (100.0)	
Bellvitge	949 (62.2)	576 (37.8)	1525 (100.0)	
Germans Trias	1080 (55.8)	854 (44.2)	1934 (100.0)	
Vall Hebron	1840 (70.2)	781 (29.8)	2621 (100.0)	
Wave, n (%)				
2nd wave	2460 (70.0)	1055 (30.0)	3515 (100.0)	<0.001
3rd wave	1945 (64.0)	1095 (36.0)	3040 (100.0)	
4th wave	886 (62.0)	543 (38.0)	1429 (100.0)	
5th wave	826 (62.2)	503 (37.8)	1329 (100.0)	
6th wave	567 (59.7)	382 (40.3)	949 (100.0)	
7th wave	235 (81.3)	54 (18.7)	289 (100.0)	
Charlson index, mean (SD)	0.9 (1.4)	1.2 (1.7)	1.0 (1.6)	<0.001
Charlson risk, n (%)				
Low	3985 (69.6)	1740 (30.4)	5725 (100.0)	<0.001
Moderate	2182 (62.5)	1309 (37.5)	3491 (100.0)	
High	752 (56.3)	583 (43.7)	1335 (100.0)	
Elixhauser index, mean (SD)	1.5 (6.3)	3.8 (8.6)	2.3 (7.2)	<0.001

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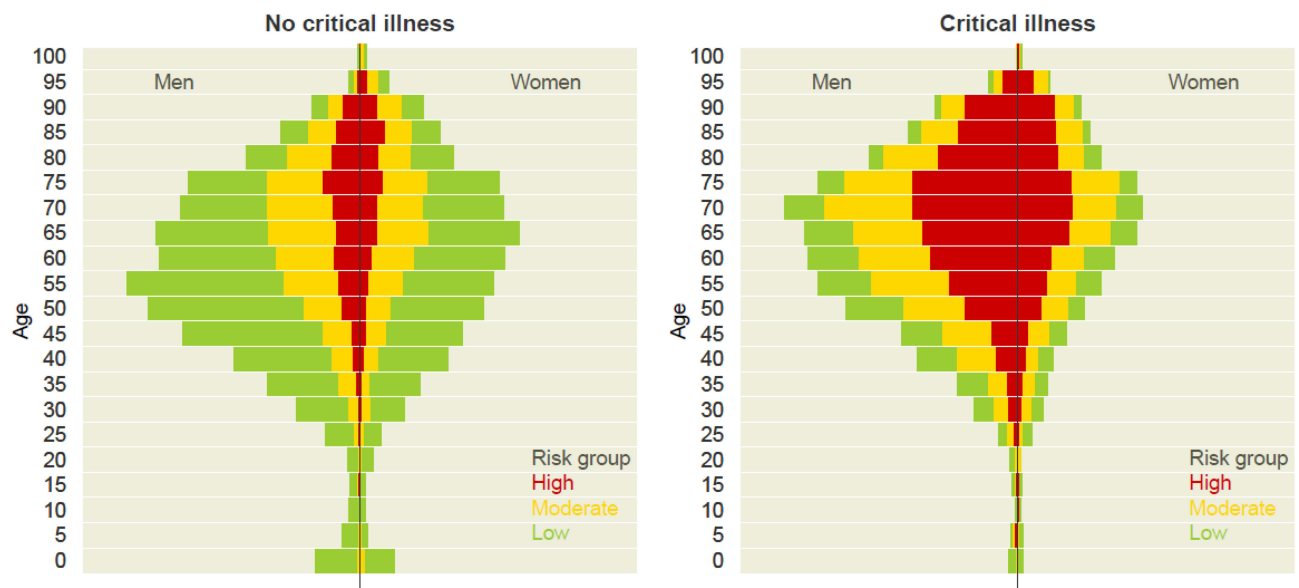
**Table I** (Continued).

	No Critical Illness (N=6919)	Critical Illness (N=3632)	Total (N=10,551)	P*
Elixhauser risk, n (%)				
Low	4670 (71.3)	1881 (28.7)	6551 (100.0)	<0.001
Moderate	1382 (60.8)	892 (39.2)	2274 (100.0)	
High	867 (50.2)	859 (49.8)	1726 (100.0)	
Elixhauser measure, mean (SD)	1.7 (1.6)	2.4 (1.7)	1.9 (1.7)	<0.001
Elix. measure risk, n (%)				
Low	3711 (74.1)	1294 (25.9)	5005 (100.0)	<0.001
Moderate	2259 (60.7)	1464 (39.3)	3723 (100.0)	
High	949 (52.1)	874 (47.9)	1823 (100.0)	
Queralt DxS index, mean (SD)	18.4 (11.2)	31.1 (16.5)	22.8 (14.6)	<0.001
Queralt DxS risk, n (%)				
Low	4244 (83.3)	852 (16.7)	5096 (100.0)	<0.001
Moderate	1808 (58.3)	1293 (41.7)	3101 (100.0)	
High	867 (36.8)	1487 (63.2)	2354 (100.0)	

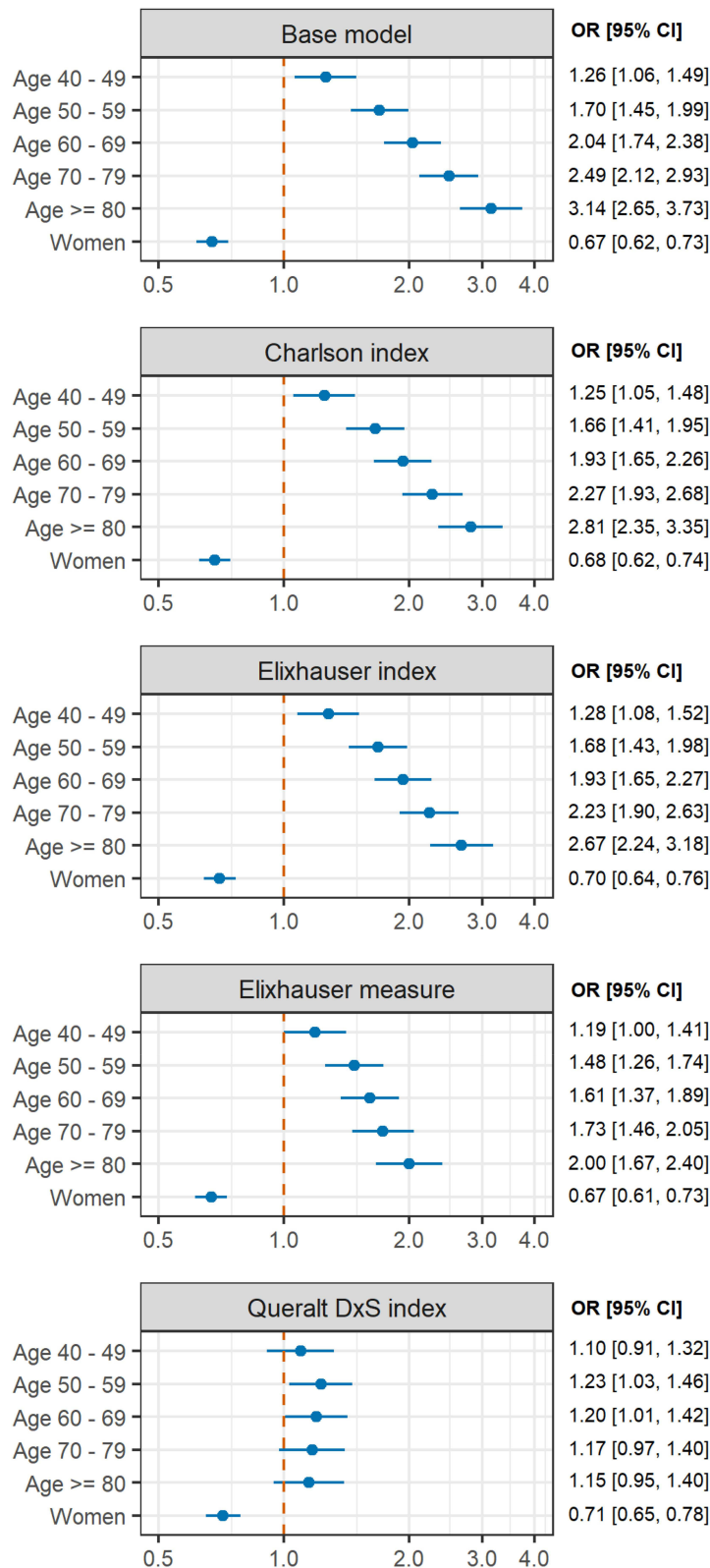
**Notes:** \*Continuous variables were compared using the ANOVA test and categorical variables with the Pearson's Chi-squared test.  
**Abbreviation:** SD, standard deviation.

## Discussion

In this retrospective analysis of 19,662 hospitalizations due to COVID-19, we found that the contribution of comorbidity burden to critical illness increases with the number of diagnoses considered for its measurement. When measured using a comprehensive index such as the Queralt DxS, which considers more than 3000 possible diagnosis groups, the



**Figure 2** Distribution of Queralt DxS-based risk groups, by age and sex, among individuals who did not and did develop critical illness. Primary analysis population (N=10,551).



**Figure 3** Effect of age and sex on critical illness using multiple logistic regressions (adjusted by wave). The baseline model included only age, sex, and hospital, whereas the other models were built by adjusting the baseline model for each of the multimorbidity measures: the Charlson index, the Elixhauser index, the unweighted count of Elixhauser diagnoses, and the Queralt DxS.

**Abbreviations:** CI, confidence interval; OR, odds ratio.



**Table 2** Performance of the Models for Explaining Critical Illness. The Baseline Model Included Age, Sex, Wave, and the Hospital in Which Admission Occurred

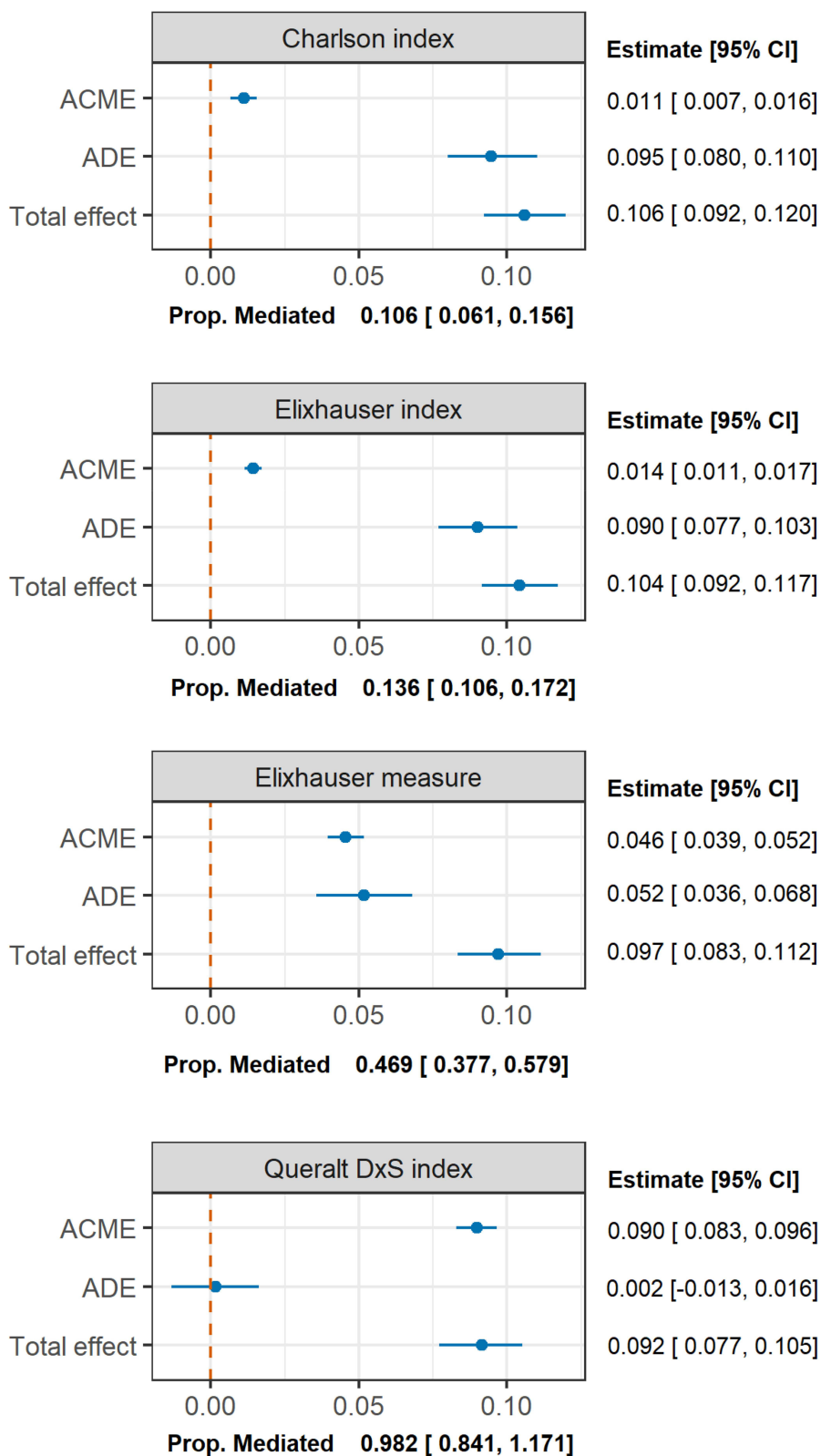
	BIC	AUROC		AUPRC	
		Estimate	95% CI	Estimate	95% CI
Age	13,155	0.642	0.631–0.653	0.465	0.450–0.479
Sex	13,287	0.617	0.605–0.628	0.449	0.435–0.465
Charlson	13,247	0.627	0.615–0.637	0.450	0.437–0.467
Elixhauser (index)	13,138	0.637	0.625–0.648	0.476	0.461–0.487
Elixhauser (count)	12,981	0.660	0.649–0.671	0.479	0.458–0.496
Queralto DxS	11,273	0.784	0.775–0.793	0.649	0.633–0.663
BL model (age and sex)	13,082	0.652	0.641–0.662	0.477	0.461–0.495
BL + Charlson	13,064	0.655	0.644–0.667	0.478	0.463–0.493
BL + Elixhauser (index)	12,976	0.663	0.652–0.673	0.497	0.483–0.518
BL + Elixhauser (count)	12,890	0.674	0.663–0.685	0.493	0.477–0.507
BL + Queralto DxS	11,273	0.787	0.778–0.796	0.653	0.639–0.667
BL + Charlson + int.	13,106	0.656	0.645–0.667	0.478	0.460–0.493
BL + Elixhauser (index) + int.	12,985	0.668	0.657–0.679	0.503	0.488–0.519
BL + Elixhauser (count) + int.	12,889	0.677	0.667–0.688	0.499	0.482–0.511
BL + Queralto DxS + int.	11,274	0.788	0.780–0.797	0.655	0.639–0.670

**Notes:** The point estimate cells are colored based on a gradient that ranges from red (poorer performance, corresponding to lower values for the AUROC and AUPRC, and higher values for the BIC) to green (better performance, corresponding to higher values for the AUROC and AUPRC, and lower values for the BIC).

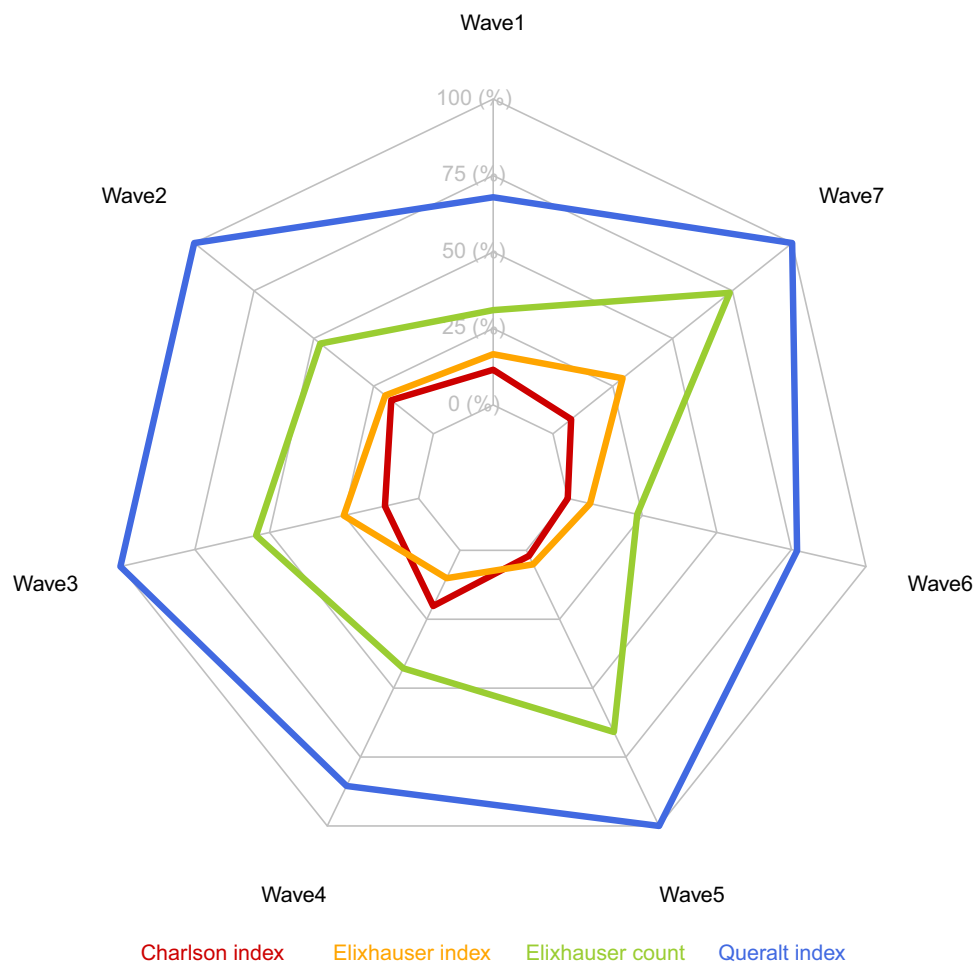
**Abbreviations:** AUPRC, area under the precision-recall curve; AUROC, area under the receiving operating characteristics curve; BIC, bayesian criteria; Int., models accounting for interactions between age and the comorbidity measure.

contribution of age to critical illness was remarkably reduced, with age groups 70–79 years and >80 years no longer associated with the odds of developing critical illness and comorbidity burden explaining a significant proportion of the effect of chronological age on this outcome.

The effect of comorbidities on COVID-19 outcomes has been extensively investigated, with some reports showing an age-dependent effect of comorbidities (and other risk factors for severe COVID-19) in hospitalized patients.<sup>37–39</sup> However, the vast majority of studies included in systematic reviews addressing the role of comorbidities in these patients measured the effect of individual comorbidities such as hypertension, diabetes or COPD, among others,<sup>40–44</sup> or stratifying patients based on the presence of one or multiple comorbidities.<sup>45</sup> In line with the general trend approaching the assessment of comorbidities in COVID-19, studies investigating the question of whether age is the most important factor in explaining COVID-19 outcomes have assessed the effect of comorbidities by considering the presence or absence of a pre-defined list of diagnoses. Semenzato et al concluded that age was the most important factor based on the individual hazards of an extensive list of 47 comorbidities.<sup>5</sup> However, the authors acknowledged that the sum of the number of comorbidities does not account for the different severity of each of them. Henkens et al followed a similar approach using a shorter list of comorbidities.<sup>6</sup> Additionally, the authors investigated the mediation effect of each comorbidity on the effect of age on in-hospital mortality and found that the direct effect of age was  $\geq 95\%$  in all diagnoses. However, when adjusting for the comorbidity burden, they used an unweighted count of diagnoses, stratified as 0, 1–2, and >2 comorbidities. These two approaches (ie, the risk estimate of each diagnosis independently and the



**Figure 4** Causal mediation analysis: role of comorbidity burden on the association between age and incidence of critical illness, with comorbidity burden assessed using the Charlson index, the Elixhauser index, the Elixhauser count, and the Queralt DxS index. The proportion mediated shows the contribution of the comorbidity-mediating pathway to critical illness, estimated as the proportion between the ACME and the total effect. The dotted line indicates the null value of the effect. **Abbreviations:** ACME, average causal mediation effect of comorbidity (mediator); ADE, average direct effect of age.



**Figure 5** Proportion of mediation of comorbidity over the total effect of age on the risk of critical illness according to wave. Each color corresponds to a measure of comorbidity burden. For display purposes, the mediation proportion is limited to a 0–100 scale (values higher than 100 are set to 100 and values lower than 0 are set to 0).

unweighted count of the number of diseases) lose sight of the actual disease burden and are likely to underestimate the effect of comorbidity burden as a whole, particularly in patients with relevant diagnoses simultaneously.

Alternatively, we measured the comorbidity burden using a very comprehensive index that considers more than 3000 possible diagnosis groups and weights them according to their impact on health outcomes.<sup>23</sup> This measure has shown a high capacity for explaining hospital outcomes in other settings. Our results regarding the explaining capacity of this variable for COVID-19 outcomes were consistent across various waves of the outbreak in our region and in different analysis approaches. This trend was weaker in patients admitted during the first wave, which were excluded from the primary analysis. The extreme demand for ICU beds during the first wave exceeded by far the ICU capacity in our region. In this context, along with the limited information on therapeutic options of hospitalized patients,<sup>46,47</sup> the criteria for ICU admission were unclear, and we cannot rule out an age bias in ICU transfers. This limitation was also noted by Henkens et al.<sup>6</sup> Furthermore, retrospective analyses of the clinical presentation and hospital outcomes throughout successive waves have highlighted the progressive consolidation of evidence-based practices in the management of COVID-19 patients in the hospital setting,<sup>13,29</sup> which may contribute to explaining the differences between waves. These two factors (ie, improvement in clinical knowledge and management of COVID-19 cases and reduction of hospital services burden), likely to contribute to reducing the frequency of critical illness, would align with the drop in AUPRC, which depends on the incidence of the measured outcome. Finally, during the first wave, quick decision-making in a context of overwhelmed systems and a very high number of cases might have resulted in suboptimal documentation of chronic comorbidities.

Besides age and the comorbidity burden, we included sex in our analyses based on its relevance in COVID-19 and health outcomes in general.<sup>48</sup> As expected, female sex was associated with lower risk of severe disease. Interestingly, although the inclusion of the comorbidity burden into the model reduced the size effect of sex, females remained as an important factor significantly reducing the risk of severe disease. This observation supports the hypothesis that male sex is independently associated with poorer COVID-19 outcomes, regardless of the presence of other risk factors.<sup>49</sup>

Our analysis is strengthened by the exhaustive data collection of a large number of diagnoses routinely reported in the hospital records in our region. Although we could not cover all hospitalizations occurred in Catalonia, the percentage of critically ill patients in our cohort was in line with population-based reports, which showed nearly 40% of critically ill cases among hospitalized patients in early waves,<sup>29,50</sup> suggesting representativeness of our figures. The exhaustive data collection allowed us to identify and consider in our models most (if not all) concomitant clinical conditions in patients admitted to the hospital because of COVID-19. It is noteworthy, however, that our model can only be applied in healthcare systems with a systematic and exhaustive collection of diagnostic information. On the other hand, the use of administrative databases of routine care data has some limitations that must be considered for result interpretation. First, although we selected only hospitalizations with COVID-19 as a main diagnosis, we cannot rule out that, in some cases, complications of other underlying conditions triggered ICU admission or death. Another important limitation associated with the retrospective design is the constraint of the analysis to the information recorded in the databases. Thus, aside from the diagnoses, other clinical conditions not recorded in these databases may play a role in the observed effect of age. These conditions include—but are not limited to—frailty (ie, physical deterioration, not considered a diagnosis per se), weight loss, mild cognitive decline (ie, not qualifying for dementia), the recent loss of a relative, or subclinical depression. These conditions are likely to impact mortality, regardless of the presence of comorbidities.<sup>51,52</sup> Therefore, they should also be considered to understand the effect of chronological age on COVID-19 outcomes completely. Another potential limitation in this regard is the lack of adjustment by baseline drug treatments; although the therapeutic burden is expected to reflect comorbidity burden, the type and number of drugs may differ between patients and impact in a different way on the risk of critical illness.<sup>53</sup> Nevertheless, the features captured by Queralt DxS were already able to explain almost the full effect of age on the odds of developing critical COVID-19 disease. Retrospective analyses based on data collected during routine care can be also affected by the quality of the data. Hence, although the tool considers all possible diagnoses, not all clinical conditions are reported and recorded with the same accuracy, and some conditions could be underestimated. Likewise, it is worth mentioning that we covered only deaths occurred in the hospital setting; while this was the case for most people, we cannot rule out a certain number of deaths occurred outside the hospital, particularly during the first wave. Finally, the factors influencing critical illness may change based on the emergence of new variants and progression of population vaccination campaigns; therefore, besides the main analysis, we conducted subanalyses for each wave, thus covering a broad period with different scenarios.

Our findings have various implications. First, in light of the prognostic importance of comorbidity burden as a whole, comprehensive and weighted metrics of this variable may increase the accuracy of risk estimate, as suggested by Semenzano et al.<sup>5</sup> This approach would reduce the risk of ageism (and the potential deleterious effects associated) in health planning and healthcare delivery, providing professionals with an autonomous risk score for these patients. It is worth mentioning that, unlike age, which is always available and accessible, not all healthcare organizations systematically collect all diagnoses in a central registry. However, in healthcare environments in which diagnoses are adequately and exhaustively reported in the electronic health records, the Queralt DxS, freely available, might be used to summarize the comorbidity burden in a single index used as an adjustment covariate for autonomous risk scores informing complexity on admission. The same adjustment can be used to develop predictive models using machine learning approaches, in which the summary of multiple comorbidities into a single weighted index may prevent overfitting. Finally, in healthcare systems that integrate primary and hospital care data,<sup>54</sup> comorbidity burden could be estimated in advance to anticipate resource prioritization. These models would allow identifying patients at higher risk of critical illness and creating stratification systems for prioritizing and allocating healthcare resources such as COVID-19 vaccines or anticipating the demand of hospital services.

Our findings highlight the importance of considering the comorbidity burden as a whole (rather than individual diagnoses) and in a comprehensive way for assessing the risk of critical illness in COVID-19 patients. This perspective encourages the digitalization of healthcare systems for the systematic collection and integration of healthcare data that

provides an accurate view of the clinical complexity of patients. Future steps in this pathway include the external validation of this tool and the inclusion of social care and functional information in these records.

## Conclusion

In summary, although age is often regarded as a key prognostic factor in people hospitalized with COVID-19, our study suggests that when measured exhaustively, comorbidity burden explains better than chronological age the higher risk of critical illness. Moving forward, greater attention to comorbidity burden rather than to chronological age may inform more accurate risk stratification, management, and preventive therapy allocation.

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## Disclosure

DM declares that he is the developer of the Queralt System, which is freely available. The other authors report no conflicts of interest in this work.

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