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Comorbidities and Mortality in Patients With COVID-19 Aged 60 Years and Older in a University Hospital in Spain

Comorbilidades y mortalidad en pacientes con COVID-19 de 60 años o mayores en un hospital universitario en España

Dear Editor,

The prevalence of comorbidity in Europe is high with a large proportion of patients aged 60 years and older presenting multiple chronic diseases.[1] The management of patients with several comorbidities is challenging due to their frailty and increased risk of mortality. This management is more complex when patients acquire an acute infectious disease. Patients infected with SARS-CoV-2 have different levels of severity of the COVID-19.[2] Most of them do not need hospital admission. However, there is a large number of patients that will need advanced care. Just as the necessity of hospitalized care increases with age, so does the prevalence of comorbidities.

The presence of comorbidities in patients hospitalized with COVID-19 is common and may negatively affect their prognosis.[3–5] Previous studies have shown that pre-existing diabetes, cardiovascular or chronic kidney diseases can increase the risk of developing severe COVID-19[6] whereas the increase in mortality was mostly associated with cardiovascular diseases. These studies, however, have not addressed patients older than 59 years, with this group being of special interest due to its high prevalence of comorbidities. Therefore, our main objective is to analyze whether the type of comorbidities increased the risk of hospital mortality in patients with COVID-19 aged 60 years and older treated at the PSMAR (Parc de Salut Mar) university hospital in Barcelona, Spain.

We performed a retrospective evaluation of prospectively collected data from the PSMAR clinical records. This study was approved by the Ethics Committee of PSMAR in 2020. We included patients ≥60 years who had been hospitalized and discharged (alive or dead) from COVID-19 between 23rd February and 12th May of 2020 in the PSMAR. The PSMAR batches four health centres serving a population of approximately 350,000 inhabitants. Included patients had a diagnosis of COVID-19 from the Minimum Basic Data Set that collects the diagnosis leading to admission, and up to 10 comorbidities per patient. Diagnoses are coded according to the International Classification of Diseases 10th edition. We confirmed that patients had a positive result on polymerase chain reaction testing of a nasopharyngeal sample and/or a clinically/radiologically diagnosis of COVID-19. Patients were not followed after discharge but COVID-19 related early readmissions were considered as part of the COVID-19 course. Patients discharged alive directly from the emergency room were excluded.

We evaluated gender, age (60–74, 75–84, or ≥85 years), and the presence of the following comorbidities at the time of hospital admission: hypertension, heart failure, obesity, diabetes, chronic respiratory disease (chronic obstructive pulmonary disease or asthma), malignancy, chronic kidney disease (including kidney transplantation), and chronic liver disease. Mortality was recorded at hospital discharge.

After describing the clinical characteristics, we evaluated differences in the categories stratifying for those patients who died and those who did not using the Mann–Whitney's-*U* test or Chi-Square test. We used independent logistic regression models to estimate crude and adjusted odds ratios (aOR) of dying and its 95% confidence interval (95%CI) for each comorbidity adjusting by age and gender. All statistical tests were two-sided. *P* values less than .05 were considered statistically significant.

We included 834 COVID-19 patients aged 60 years and older. 53.5% were women, with an average age of 78.2 (SD = 9.8) years, and hospital mortality of 23.5%. The prevalence of patients with at least one comorbidity was 81.9%. Hypertension was the most frequent (64.6%), followed by chronic kidney disease (29.3%), diabetes (28.1%), chronic respiratory disease (17.1%), heart failure (11.9%), obesity (6.6%), malignancy (5.4%), and chronic liver disease (2.3%).

As expected, patients who died were older in average (84 vs. 77 years; *P*< .001). There was not significant difference in mortality by gender (maleOR = 0.89, 95%CI = 0.65–1.23). An increase in age increased the risk of dying. Adjusted by gender, the OR (95%CI)

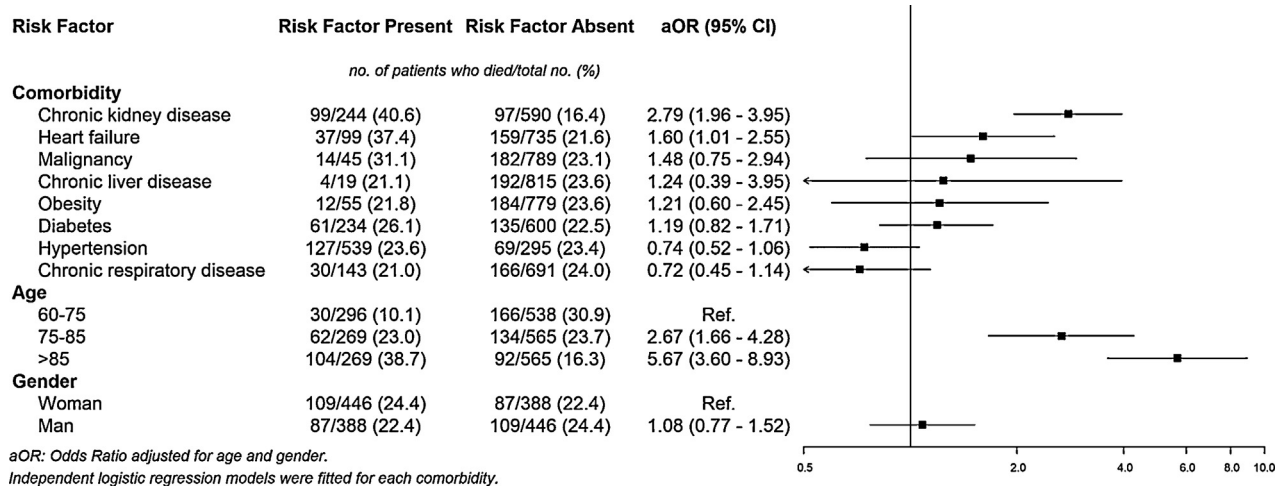

Fig. 1. Comorbidity, age, and gender as risk factors of hospital mortality in patients aged 60 years and older with COVID-19 attended at the university hospital Pac de Salut Mar, Barcelona, Spain.

were: <75 years = Reference; 75–85 years = 2.67 (1.66–4.28); and >85 years = 5.67 (3.60–8.93). Adjusted by age and gender, the aOR for hospital mortality was 2.79 (CI95% = 1.96–3.95) and 1.60 (CI95% = 1.01–2.55) for patients with chronic kidney disease and heart failure, respectively. Patients with malignancy (aOR = 1.48, CI95% = 0.75–2.94), chronic liver disease (aOR = 1.24, CI95% = 0.39–3.95), obesity (aOR = 1.21, CI95% = 0.60–2.45), and diabetes (aOR = 1.19, CI95% = 0.82–1.71) also presented higher aORs for dying than those without, although these results were not statistically significant. The presence of hypertension and chronic respiratory disease was not associated with hospital mortality (Fig. 1).

In our population of COVID-19 hospitalized patients aged 60 years and older, the presence of pre-existing comorbidities such as heart failure and chronic kidney disease was associated with an increased risk of hospital mortality. We also confirmed that COVID-19-related mortality increased with age. Conversely, we were not able to confirm the association of malignancy, chronic liver disease, obesity, or diabetes with in-hospital mortality but a potential increase in risk was observed. Unexpectedly, the odds ratios for dying of patients with hypertension or chronic respiratory disease were lower than one.

In agreement with previous international studies,[6,7] we found that patients with heart failure and chronic kidney disease were more likely to die for COVID-19 than patients without these conditions. It has been suggested that both the direct SARS-CoV-2 infection and the immunologic human response could destabilize pre-existing myocardial and kidney illnesses. Complications, such as acute cardiac[8] or kidney[9] injuries may, therefore, most frequently occur in patients with these underlying comorbidities leading to an increased risk of death.

The main limitations of this study derive from the modest number of included patients and the information available from the clinical records. Also, we could not address the effect of inpatient treatment or procedures performed during hospitalization. Finally, our analyses were not extended beyond discharge but mortality after this is likely to be small.

In conclusion, in a population of COVID-19 patients aged 60 years and older, the presence of comorbidities such as heart failure and chronic kidney disease is associated with an increased risk of hospital mortality. The mechanisms that underlie the development of severe COVID-19 in patients with pre-existing comorbidities are still poorly understood and warrant further investigation.

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Pulmonary Embolism in Patients With Covid-19 Pneumonia: The Utility of D-dimer

Embolia pulmonar en pacientes con neumonia por covid-19: utilidad del dímero-d

Dear Editor,

D-dimer levels are increased in pulmonary embolism (PE) but also in many other conditions including inflammation, cancer, pregnancy, trauma, and sepsis.[1] D-dimer is a useful rule-out test for avoiding imaging in several clinical settings.[2] In fact, in patients with low or intermediate clinical probability, D-dimer has negative predictive value to exclude deep vein thrombosis or PE without further testing in the outpatient setting.[3] Nevertheless, its usefulness in hospitalized patients with suspected thromboembolism is less well established. Only few studies have evaluated the predictive value of quantification of D-dimers in hospitalized patients with PE,[4] and there are no studies addressing this topic in patients with COVID-19. Thus, in the context of the COVID pandemic, in which seriously ill patients have respiratory symptoms, it is even more convenient to find an adequate value of D-dimer that can help when requesting imaging studies, such as computed tomography pulmonary angiography (CTPA).

A retrospective study was performed to analyze the predictive value of D-dimer to assess CTPA for diagnosis of PE in patients with COVID-19 pneumonia during their hospitalization. The local Clinical Research Ethical approved the study.

All patients included in current study were COVID-19 positive according to present diagnostic criterion.[5] They had undergone CTPA scans due to suspected PE and underwent D-dimer tests according guidelines.[6] D-dimers were checked at least at the time of admission and prior to CTPA. D-dimer (local reference range: <500 mcg/L FEU), was measured by a commercial latex-enhanced immunoturbidimetric assay (Siemens AG SYSMEX CS-5100). CTPA examinations were obtained in a multidetector CT scanner (Discovery CT750 HD, GE Healthcare, Milwaukee, USA) by using a Dual-Energy CTPA protocol (Gemstone Spectral Imaging GSI). Highest observed values of D-dimer (of at least one assessment during hospitalization) before CTPA for each patient were used as diagnostic threshold and their sensitivity and specificity was estimated. Positive predictive (PPV)- and negative predictive (NPV)-values were calculated to evaluate the correct positive and correct negative test procedure results.[7] The calculations were made with SPSS/PC for Windows (version 25.0, SPSS Inc., Chicago, IL, USA) and MedCalc (version 9.3.9.0; MedCalc, Mariakerke, Belgium). *P* values of <.05 were considered statistically significant.

A total of 52 patients with a confirmed diagnosis of COVID-19 pneumonia and suspected PE were included. The main causes for CTPA assessment were clinical worsening (85%) and/or elevated D-dimer (15%). Only two patients had right ventricle dilatation at the time of PE diagnosis. Dyslipidaemia and obesity were more frequent in patients with PE, but there were no significant differences found between groups when analysing with other variables. Forty-nine patients received low weight molecular heparin (LWMH) as thromboprophylaxis at standard dose (40 mg/day, $n=25$) or intermediate dose (1 mg/kg/day, $n=18$) according D-dimer value ($\leq$2000 and >2000, respectively) or therapeutic LWMH (1 mg/kg/12 h, $n=6$) for medical conditions (atrial fibrillation and others). Three patients (2 with PE and 1 non-PE) did not receive thromboprophylaxis.

At the time of admission, D-dimer levels were not different among patients that developed PE [(median (P5–P75) 2350 (1070–10500) mcg/L] and those who did not [3030 (650–12415) mcg/L], ($P=.87$). We found significant differences in the highest values of D-dimer before performing CTPA only in patients with PE [14,240 (5140–31550) mcg/L, $P=.007$]. The mean changes from the baseline to the highest values before CTPA for patients with PE was 9406 (2917) mcg/L. In Table 1, we set out estimates of sensitivity, specificity, Positive Predicted Value (PPV), Negative Predicted Value (NPV), Positive Likelihood Ratio (LR+), and (LR−) values to predict the diagnosis of PE. D-dimer of 2000 mcg/L resulted in the best cut-off point of sensitivity for patients with PE: sensitivity, 1.00; PPV, 0.60; specificity, 0.44; and, NPV, 1.00; LR−, 0. Using this threshold there were zero negative false cases; however, there were 18 (35%) positive false cases. By contrast, D-dimer of 30,000 mcg/L or higher was the best threshold for the diagnosis of PE; sensitivity, 0.26; PPV, 0.75; specificity, 0.93; NPV, 0.61, and LR+, 3.78; but we found only 2 (3.8%) positive false cases at this cut-off. In addition, we found that a variation in D-dimer of 4000 mcg/L or more from admission to the highest value before CPTA was predictive of PE with a sensitivity, 0.48; PPV, 0.79; specificity, 0.90; NPV, 0.68; LR+ 4.62, and LR− 0.58. This magnitude showed only 3 positive false cases. Among the subjects included in the study, only 2 deaths were confirmed to be caused by severe respiratory syndrome, with no evidence of PE.

The current retrospective study identified that a D-dimer value of 2000 mcg/L was the best sensitivity cut-off point to rule out PE in patients with COVID-19 pneumonia. Besides, we recognized a D-dimer level of 30,000 mcg/L as the best value of specificity to predict PE. Also, an increase of D-dimer of 4000 mcg/L from admission