Age and Multimorbidity Predict Death among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension

Original Article

Age and Multimorbidity Predict Death Among COVID-19 Patients

Results of the SARS-RAS Study of the Italian Society of Hypertension

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Abstract—Several factors have been proposed to explain the high death rate of the coronavirus disease 2019 (COVID-19) outbreak, including hypertension and hypertension-related treatment with Renin Angiotensin System inhibitors. Also, age and multimorbidity might be confounders. No sufficient data are available to demonstrate their independent role. We designed a cross-sectional, observational, multicenter, nationwide survey in Italy to verify whether renin-angiotensin system inhibitors are related to COVID-19 severe outcomes. We analyzed information from Italian patients diagnosed with COVID-19, admitted in 26 hospitals. One thousand five hundred ninety-one charts (male, 64.1%; 66±0.4 years) were recorded. At least 1 preexisting condition was observed in 73.4% of patients, with hypertension being the most represented (54.9%). One hundred eighty-eight deaths were recorded (11.8%; mean age, 79.6±0.9 years). In nonsurvivors, older age, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, coronary artery diseases, and heart failure were more represented than in survivors. The Charlson Comorbidity Index was significantly higher in nonsurvivors compared with survivors (4.3±0.15 versus 2.6±0.05; $P<0.001$). ACE (angiotensin-converting enzyme) inhibitors, diuretics, and β-blockers were more frequently used in nonsurvivors than in survivors. After correction by multivariate analysis, only age ($P=0.0001$), diabetes mellitus ($P=0.004$), chronic obstructive pulmonary disease ($P=0.011$), and chronic kidney disease ($P=0.004$) but not hypertension predicted mortality. Charlson Comorbidity Index, which cumulates age and comorbidities, predicts mortality with an exponential increase in the odds ratio by each point of score. In the COVID-19 outbreak, mortality is predicted by age and the presence of comorbidities. Our data do not support a significant interference of hypertension and antihypertensive therapy on COVID-19 lethality.

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Key Words: COVID-19 ■ hypertension ■ Italy ■ multimorbidity ■ odds ratio

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is claiming a high toll of victims. The clinical manifestation of this new coronavirus is referred to as coronavirus disease 2019 (COVID-19), and as of April 10, 2020, over 1 470 000 (source: World Health Organization website) cases are reported throughout the planet. The SARS-CoV-2 has features that were only, in part, observed during the previous outbreaks of CoV-1 in 2002 and the CoV-2 in 2013, which caused the severe acute respiratory syndrome and the Middle East Respiratory Syndrome epidemics, respectively.[1] In comparison to those outbreaks, COVID-19 has a fatality rate of 2.3%, which is lower than SARS (9.5%) and MERS (34.4%).[2] Nevertheless, the high reproductive number (R0) of COVID-19 (2–2.5), although still controversial, might be enough to favor the spreading of the disease around the world. The result is that the perceived case fatality rate is higher than the actual case fatality rate. Whatever the case, the absolute death toll of COVID-19 insofar is incredibly high, counting worldwide 87 987 people as of April 10th (source: World Health Organization website).

Why are so many people dying for such a condition? Interestingly, there are reports from China and Italy that associate COVID-19–related deaths to hypertension and cardiovascular disease.[3–7] Hypertension is widely distributed within the population of Western societies, and one-third of the general population is expected to be affected by this condition.[8]

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Prevalence increases with age so that above 65 years of age, >70% of the population is hypertensive.[9] This is relevant to COVID-19–related deaths because in Italy, and particularly in Lombardy, the death toll has been the highest reported especially in the population over 65 years of age, with a median of 79 years.[6] Therefore, it cannot be excluded that the observed association between hypertension and death for COVID-19 reflects the older age of patients dying. Interestingly, this hypothesis is furthermore supported by the mounting evidence that more comorbidities can be associated with death in COVID-19. In a recent meta-analysis of reports published in the first trimester of 2020, it has been shown that chronic conditions such as hypertension, cardiovascular diseases, diabetes mellitus, smoking, chronic obstructive respiratory disease (COPD), malignancy, and chronic kidney disease (CKD) were the most prevalent underlying causes among hospitalized patients with COVID-19.[4,10] The evidence that in COVID-19 comorbidities lead to death, independently from age, is still missing.

Like other coronaviruses, also the SARS-CoV-2 interacts with the ACE (angiotensin-converting enzyme) 2[11,12]—a carboxyl peptidase enzyme that participates to the cleavage of angiotensin II and leads to angiotensin II 1–7 generation. Thus, ACE2 activity has been considered as the determinant SARS-CoV-2 infection.[13,14] Due to the supposed ability of ACE inhibitors and angiotensin receptor blockers (ARBs) to promote ACE2 expression,[15,16] it has been suggested that all drugs that interact with the Renin Angiotensin System (RAS) might modulate the expression of ACE2[13] and detrimentally influence COVID-19 prognosis.[14,17–20] To date, there are no epidemiological data in support of this hypothesis.[21,22] Also, ACE2 has been claimed to markedly protect the lung against acute inflammatory injury.[23,24] Thus, the ability of RAS inhibitors to promote ACE2 expression, if present, has been also suggested to be protective against SARS-CoV-2 infection.[25,26] This controversial issue has never been investigated prospectively in the clinical scenario. A recent retrospective analysis of a Chinese cohort indicates that in hospitalized COVID-19 patients with hypertension, the inpatient use of ACE inhibitor/ARB was associated with a lower risk of septic shock, leading to reduced all-cause mortality. Yet, these data need further validation in geographically diverse, cohort studies, given also the low number of patients on RAS inhibitors (n=188).[27]

We designed a cross-sectional, multicenter, observational study involving 26 hospitals approached through the Italian Society of Hypertension network in 13 regions of Italy to achieve a nationally representative population sample. The study is based on an online questionnaire to be filled in with data collected from the hospital charts of COVID-19 patients. In this study, we explored the influence of hypertension, as well as treatment and comorbidities on death or survival of patients admitted to the hospital with a certified diagnosis of COVID-19.

Methods

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The Phase IV Observational Study to Associate Hypertension and Hypertension Treatment to COVID-19 (SARS-RAS) study is a cross-sectional, multicenter, observational one conducted in 26 hospitals and centers in Italy. The centers were located in 13 regions in Italy, and the contribution of the centers reflected the geographic distribution of the disease, most of the patients being located in Northern regions, especially Lombardy, compared with Southern regions. The patients' cohort included 1761 patients aged 18 to 101 years with confirmed COVID-19, according to the World Health Organization interim guidance.[28] The observation period started on March 9 and ended on April 9, 2020. The study is performed following the article 89 of the General Data Protection and Regulation, which allows the processing of personal data for archiving purposes in the public interest, scientific or historical research purposes, or statistical purposes, provided that technical and organizational measures are in place to ensure the principle of data minimization (https://gdpr-info.eu). The SARS-RAS study is registered in https://www.clinicaltrials.gov at the accession number NCT04331574.

Procedures

An online questionnaire was distributed among the centers to collect reviewed epidemiological, clinical, and outcomes data from hospital emergency rooms and regular and intensive care wards. Each center designated ≥1 physicians who were instructed to the acquisition and review of the requested information. Patients were pseudonymized by assigning a deidentified identification code. The questionnaire collected information regarding the center and the age, sex, nationality (Italian or other), and city of origin of the patient. From the anamnesis, we collected whether the patient had a known diagnosis of hypertension with prescribed antihypertensive drugs, coronary artery disease (history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft), heart failure (HF; based on clinical history) diabetes mellitus (with prescribed antidiabetic drugs), CKD (based on anamnestic estimated glomerular filtration rate below 60 mL/min per kg), chronic obstructive pulmonary disease (based on the presence of signs and symptoms according to Global Initiative for Chronic Obstructive Lung Disease 2019), obesity (body mass index, >30 kg/m^2), history of blood and solid tumors, liver disease, and other comorbidities; pharmacological treatment as regards the use of RAS inhibitors (ACE inhibitors, ARBs) and other antihypertensives; and the degree of the severity of COVID-19.[29] The electronic data were transmitted with the modern cryptography systems over the web and stored in a locked, password-protected computer. All collected records were then quality checked by an author (G.I.) and an investigator (C.M.).

COVID-19 diagnosis was confirmed in all patients by RT-PCR performed on throat swab samples,[5] in each center by the designated institutions.

The severity of the disease was classified according to the Chinese Center for Disease Control[29] into 3 groups: asymptomatic or with light symptoms (patients who could be confined in isolation at home), moderate symptoms to be treated in the regular ward (patients requiring specific treatment and oxygen support in non invasive ventilation), and severe intensity (patients requiring intensive care and invasive ventilation).

We collected also the outcomes (hospital dismission or exitus). All patients for whom the course of the disease was in an active state were classified as such.[28]

For each patient, we calculated the Charlson Comorbidity Index (CCI) based on the available data.[30]

Statistical Analysis

Descriptive analyses of the variables were expressed as mean and standard errors or frequencies expressed in absolute numbers and percentages. Age was grouped for statistical purposes in decades starting from 20 years. To facilitate grouping, 3 patients aged <20 years were included in the 20- to 30-year decade. Patients over 80 years of age were considered cumulatively in the >80-year group. Continuous variables were analyzed by ANOVA; categorical data were compared using the χ^2 test or the Kruskal-Wallis test as appropriate. Regression analyses, odds ratio, and confidence intervals were tested on the

variables of interest grouped by outcomes in survivors and nonsurvivors; multivariable regression analyses were performed on the significant and clinically relevant continuous and categorical variables.

Results

Demographics and Characteristics

We collected 1761 questionnaires; after quality check, 170 were discharged for incompleteness, and 1591 patients were included in the study (Table 1). The average age was 66.5±0.4 years, and 65% were men; patients were prevalent of Italian nationality (94%). Patients presented with several comorbidities including hypertension, diabetes mellitus, COPD, coronary artery disease, HF, obesity, valvular disease, CKD, and history of tumors (see Table 1 for the most frequent comorbidities). The large majority of patients were hospitalized in the regular wards (1245 patients, 78% of the population), while 235 (15%) were in intensive care and 111 (7%) stayed at home. The largest part (72.7%) of patients were in the active phase of the disease, 11.2% of patients were dead, and 16.9% had been dismissed from the hospital.

As expected, the number of comorbidities increases by age (Figure 1A). Accordingly, also the prevalence of hypertension among the COVID-19 population gets higher by age (Figure 1B). To verify whether the prevalence of hypertensives among COVID-19 is indeed higher than that observed in the general population, we used previously published data from the Italian records in the occasion of the World Hypertension Day of the years 2010 to 2018 as a comparison.[31,32] As illustrated in Figure 1B, there is a comparable prevalence of hypertensives in these 2 population samples.

Given the high number of patients in our population being treated for cardiovascular conditions, we verified the use of cardiovascular agents among the whole population (Table 2) with various drug classes more represented in survivors than in nonsurvivors.

Survivors Versus Nonsurvivors

The death count in our population is consistent with that reported by the Italian Health Superior Institute (n=188); the fraction of nonsurvivors in our studied population is 11.8%, reflecting the contributions of the share of patients that from the emergency room were sent home or admitted to the hospital regular and intensive care wards. When grouping our population by survivors/nonsurvivors, we observed that age and the presence of other concomitant conditions such as hypertension, COPD, diabetes mellitus, coronary artery disease, CKD, and HF were all increased in the nonsurvivors' group (Table 1). Similarly, also cardiovascular therapy appears to stratify differently between nonsurvivors and survivors, since ACE inhibitors, diuretics, and β-blockers but not calcium blockers and ARBs are more often observed among nonsurvivors (Table 2).

All these differences in comorbidities might be the effect of older age (Figure 1A). Therefore, we corrected in a multivariable logistic regression all the variables that were statistically associated in the univariate analysis to the worst outcome. After correction, only age, CKD, COPD, and diabetes mellitus maintained their significant impact on the nonsurvivors (Table 3). The corrected odds ratio in nonsurvivors of these variables is described in Figure 2A. Interestingly, no effects of treatment with ACE inhibitors or other antihypertensive drugs resulted significant after this correction. Therefore, age and comorbidities represent the 2 major factors leading to death among COVID-19 patients.

To further assess the role of comorbidities, we grouped our population by the CCI. This index takes into account age and coexisting conditions, in an algorithm used to predict 10-year mortality. Indeed, as indicated in Figure 2B, the percentage of deaths increases with the Charlson Index; this index was a logarithmic multiplier when the risk of death was assessed by increasing by one point the score, starting from the score of 2 (Figure 2C).

Discussion

Our data represent the first analysis of death outcome in an Italian COVID-19 population through a cross-sectional, multicenter, observational, nationwide study; a previous publication in Chinese analyzed composite end points, which consisted of admission to the intensive care unit, invasive ventilation, or death.[33] The number of Italian centers that have

Table 1. Demographic Characteristics of the Study Population

Variable	Total Study Population (N=1591)	Nonsurvivors (n=188)	Survivors (n=1403)	*P* Value
Age, y	66.5±0.4	79.6±0.8	64.7±0.4	0.0001
Men, %	64.0	66.5	63.6	NS
Hypertension, %	54.9	72.9	52.5	0.0001
Obesity, %	6.4	6.4	6.4	NS
Diabetes mellitus, %	16.9	32.4	14.8	0.0001
COPD, %	7.7	14.9	6.7	0.0001
CKD, %	5.5	16.5	4.0	0.0001
Coronary artery disease, %	13.6	29.8	11.4	0.0001
HF, %	11.8	30.3	9.3	0.0001
Charlson Index	2.83±0.05	4.37±0.14	2.63±0.05	0.0001

P values for continuous variables (age and Charlson Index) were calculated by unpaired *t* test; for categorical variables, the χ^2 test was used. CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; and NS, nonsignificant.

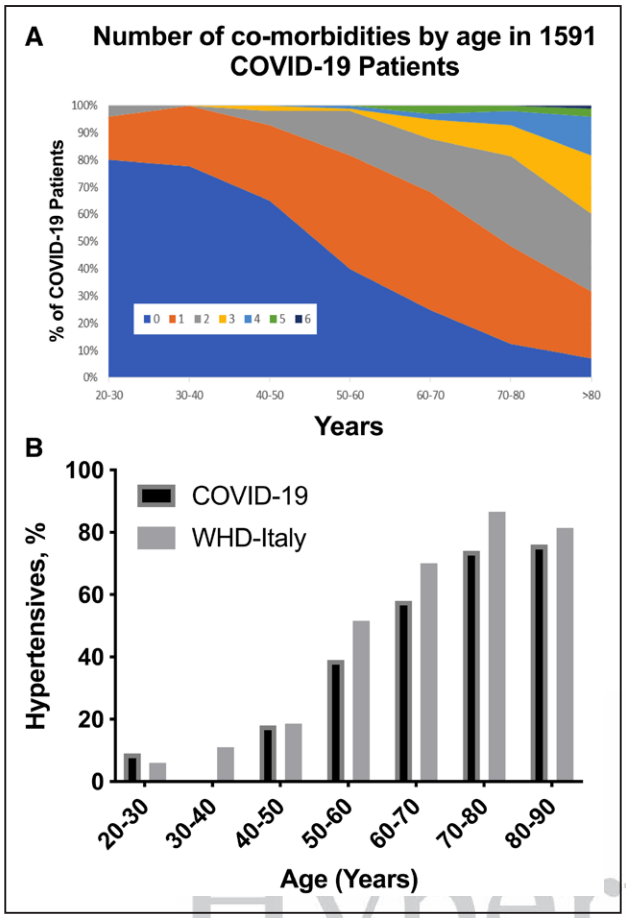

Figure 1. Comorbidities and hypertension prevalence among 1591 Italian COVID-19 Patients. **A**, One thousand five hundred ninety-one Italian coronavirus disease 2019 (COVID-19) patients were grouped by age decades to depict the fraction of them that at each decade of age group were affected by 0 to up to 6 comorbidities. To facilitate the representation, patients below 20 y of age were added to the 20- to 30-y group. 0, 1, 2, 3, 4, 5, and 6 represent the number of preexisting conditions. **B**, The prevalence of hypertension among the 1591 COVID-19 patients was stratified against the decades of age group and compared with the similar data collected in occasion for the Italian events of the World Hypertension Day (WHD-Italy) held from 2010 to 2018.

been involved, as well as the geographic distribution, is representative of the epidemiology of the disease in Italy.

From this analysis, that involved >15 hundred patients, several conclusions can be drawn. First of all, the suspected or perceived association of COVID-19 and hypertension[6,34] is not confirmed by our findings and probably reflects the older age of patients who do not survive. Indeed, the prevalence of hypertension among COVID-19 patients is comparable to that expected based on the data recorded in the general population during the World Hypertension Day in Italy from 2010 to 2018. As expected, also comorbidities increase by age.[35] Hypertension prevalence increases as well and so do other risk factors and chronic comorbidities, such as diabetes mellitus, CKD, and COPD.

Table 2. Cardiovascular Active Drugs in the Study Population

Variable	Total Study Population (N=1591)	Nonsurvivors (n=188)	Survivors (n=1403)	*P* Value
ACE inhibitors, %	21.9	33.5	20.3	0.001
ARBs, %	19.3	22.9	18.8	NS
β-Blockers, %	23.3	35.6	21.7	0.001
Ca antagonists, %	14.5	19.1	13.9	NS
Diuretics, %	21.7	43.6	18.8	0.001

P values for categorical variables were calculated by the χ^2 test. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; and NS, nonsignificant.

Table 3. Logistic Regression Analysis for Death in the Nonsurvivors' Group

	Model 1	
Variable	*P* Value	β
Age, y	0.0001	1.083
Sex (M/F)	NS	0.801
Hypertension, n/y	NS	0.944
Diabetes mellitus, n/y	0.004	1.756
COPD, n/y	0.011	1.925
CKD, n/y	0.004	2.197
Coronary artery disease, n/y	NS	1.382
HF, n/y	NS	1.219
ACE inhibitors, n/y	NS	1.474
β-Blockers, n/y	NS	0.905
Diuretics, n/y	NS	1.238

ACE indicates angiotensin-converting enzyme; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; F, female; HF, heart failure; M, male; and NS, nonsignificant.

The second conclusion that our data allow drawing is that, when grouping the population according to the outcome, diabetes mellitus, CKD, and COPD can predict death even after adjustment by age. Although HF does not reach significance in the multivariable analysis, it should be considered that it is likely that an underestimation of HF with preserved systolic function, which is most common in the elderly, may have contributed to this, and other studies will be required to better define this aspect.

A third conclusion is that ACE inhibitors and ARBs do not play a significant contribution in causing death in COVID-19 patients. The experimental evidence that RAS inhibitors might increase the level of expression of ACE2, the gate SARS-CoV-2 uses to enter and infect the host, has raised the hypothesis that these drugs could determine a worse outcome of the disease.[14] Our data show that ARBs do not associate with nonsurvivors and that ACE inhibitors lose their weak statistical significance when corrected by comorbidities and age. The eventual role of ACE inhibitors deserves further investigations in larger cohorts. On this note, it is challenging to dissect an independent role of ACE inhibitors, since they are the most widely used drugs in patients with relevant comorbidities (diabetes mellitus, CKD, HF, hypertension, and coronary artery disease).

Finally, the presence of multiple comorbidities contributes with an exponential fashion to mortality, independently from age. Age and comorbidities participate in the definition of the CCI, which predicts mortality over 10 years.[30] We used this index to verify whether it predicts short-term mortality in the settings of COVID-19. We found that the CCI score

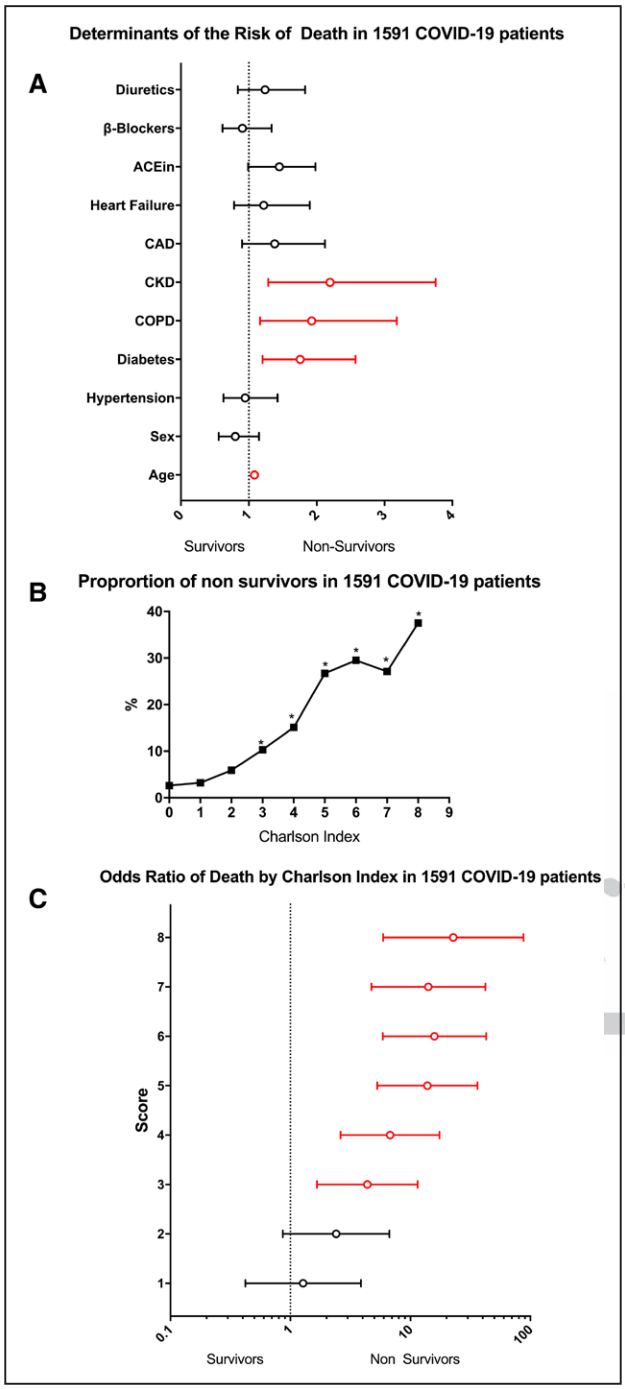

Figure 2. Risk of death among 1591 Italian COVID-19 patients. **A,** Forrest plot of the odds ratio and CIs calculated for each variable found to be independently associated with the nonsurvivors group. Logistic regression analysis was performed to predict survivor/nonsurvivor using age as a continuous variable and all other variables as categorical. In red are indicated those variables with a $P<0.05$. **B**, Association in the coronavirus disease 2019 (COVID-19) population between increasing CCI and the percentage of nonsurvivors. Data were analyzed by Kruskal-Wallis test. *$P<0.05$ vs 0. **C**, Forest plot of the odds ratio and CIs calculated for each score of the Charlson Index. In red are indicated scores with a $P<0.05$. ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; CKD, chronic kidney disease; and COPD, chronic obstructive pulmonary disease.

can exponentially predict nonsurvivors' patients. A high score could have an important meaning not only in predicting an unfavorable outcome in COVID-19 patients but also in better identifying people who may benefit from more intense measures of personal isolation, quarantine, and earlier preventive or treatment strategies.

Most recently, an article on >6000 COVID-19 patients from the Lombardy region authored by Mancia et al[36] has been released. The article of Mancia et al uses a completely different set of data, which is the Regione Lombardia administrative database for drug and treatment reimbursements; it is limited to the patients of the Lombardy region, whereas our work is a nationwide study. In their article, Mancia et al reported that cardiovascular conditions are more frequently observed among the COVID-19 patients and conclude that the use of ACE inhibitors and ARBs is more frequent among COVID-19 patients for being the most used drugs for cardiovascular conditions. Differently, in our analysis, we focused on death as an outcome: on this hard event, the major impact is that of age and comorbidities, so that the CCI, which contains both, becomes a critical instrument to identify those patients at higher risk of death. We believe this represents an added value that provides novelty to our work.

In conclusion, our study shows that age and comorbidities are the most important determinants of death among COVID-19 patients. Hypertension and antihypertensive therapy on COVID do not affect the outcome of COVID-19, consistent with recent literature.[37] The CCI might represent a powerful screening to apply for ad admission in hospital after COVID-19 diagnosis, for the identification of those patients who are at higher risk of death.

Perspectives

Understanding the clinical characteristics that anticipate the worse outcome in COVID-19 spread is key for the management and the appropriate use of the resources. CCI can be an easy-to-apply, powerful tool to predict the outcome at the time of diagnosis of COVID-19 patients.

APPENDIX

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