Original Article

Determinants of healing among patients with COVID-19: the results of the SARS-RAS study of the Italian Society of Hypertension

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Objective: The burst of COVID-19 epidemics in Italy prompted the Italian Society of Hypertension to start an observational study to explore the characteristics of the hospitalized victims of the disease. The current analysis aimed to investigate the predictors of healing among Italian COVID-19 patients. We also assessed the effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers on the outcome.

Methods: We designed a cross-sectional, observational, multicenter, nationwide survey in Italy to explore the demographic and clinical characteristics of patients with confirmed COVID-19 infection. We analyzed information from 2446 charts of Italian patients admitted for certified COVID-19 in 27 hospitals. Healing from COVID-19 infection, defined as two consecutive negative swabs, was reported in 544 patients (22.2%), 95% of them were hospitalized.

Results: Age and Charlson Comorbidity Index were significantly lower in healing compared with nonhealing patients (63 ± 15 vs. 69 ± 15 and 2 ± 2 vs. 3 ± 2, both $P < 0.05$). In multivariable regression model, predictors of healing were younger age (OR: 0.99; 95% CI 0.98–0.99, $P = 0.0001$), absence of chronic kidney disease (OR: 0.35; 95% CI 0.17–0.70, $P = 0.003$) or heart failure (OR: 0.44; 95% CI, 0.28–0.70, $P = 0.001$). In the subgroup of patients suffering from hypertension and/or heart failure ($n = 1498$), no differences were observed in the use of ACE inhibitors and angiotensin receptor blockers.

Conclusion: Our study demonstrated that younger age and absence of comorbidities play a major role in determining healing in patients with COVID-19. No effects of ACE inhibitors and angiotensin receptor blockers on the outcome was reported.

Keywords: chronic conditions, coronavirus disease 2019, multimorbidity, outcomes, recovery

Abbreviations: ACE-2, angiotensin-converting enzyme 2 receptor; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

At the beginning of 2020, an unexpected novel nosographic entity outbreak, named COVID-19 caused by a new coronavirus, made headlines all over the world for its furious spreading and the number of victims requiring hospitalization. The number of COVID-19 patients has reached more than 17 million affected people and more than 650 000 deaths to date. The rampage of the disease came along with a disoriented clinical response because of the lack of knowledge. Collection of data

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regarding the clinical manifestation of the disease and reports regarding the worse outcome are increasing dramatically, so that the number of publications about COVID-19 has raised from January to date to more than 33 000 (source: PubMed, 20 July 2020). In the last few months, we have gained knowledge regarding the determinants of the worse outcomes of the disease. It has become clear that age and multimorbidity are the major causes of more severe clinical manifestation of COVID-19 [1,2]. In particular, recent finding from Italy have highlighted the importance of age, sex and comorbidity as the main determinants of severe/lethal COVID-19 disease [3,4] whereas registry data demonstrated that prior use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) among patients with hypertension was not significantly associated with COVID-19 diagnosis, severity or mortality [5]. Less investigated are the determinants of the recovery from the disease. The healed patient is the one who resolves the symptoms of COVID-19 infection and who is negative in two consecutive swabs, carried out 24 h apart, for the search for SARS-CoV-2. At the date, almost 11 million patients recovered from COVID-19 worldwide. Despite several reports have identified predictors of death and ICU admission in COVID-19 patients [6,7], no information is available on predictors of healing. It has been proposed that ACEi and ARBs might protect patients from more severe disease [8–10]. The Italian Society of Hypertension started a cross-sectional observational study named SARS-RAS, collecting data from COVID-19 centers nationwide in Italy [9]. The collaboration generated a database that we interrogated to verify the determinants of recovery from COVID-19. We also tested the hypothesis that ACEI/ARBs could foster recovery, in a subanalysis conducted in COVID-19 patients affected by hypertension or heart failure.

METHODS

Study population

The SARS-RAS study is a cross-sectional, multicenter, observational one conducted in 27 hospitals and centers in Italy. The centers were in 13 regions, and the contribution of each reflected the geographical distribution of the disease, most of the patients being in Northern regions, especially Lombardy. The patients' cohort included 2460 patients aged 18–101 years with confirmed COVID-19, according to WHO's interim guidance [11]. The observation period started on 9 March 2020 and ended on 18 June 2020. The study is performed under 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 anonymization (https://gdpr-info.eu). The SARS-RAS study is registered in Clinicaltrials.gov at the accession number NCT04331574.

Procedures

An online questionnaire was distributed among the centers to collect reviewed epidemiological, clinical and outcome data from hospital emergency rooms, regular and intensive care wards. Each center designated one or more physicians that were instructed to the acquisition and review of the requested information. Patients were pseudonymized by assigning a de-identified identification code. The questionnaire collected information regarding the center and the age, sex, nationality (Italian or other), and city of origin of the patients. From the anamnesis, we collected known diagnosis of hypertension with prescribed antihypertensive drugs, coronary artery disease (CAD) (history of myocardial infarction, percutaneous or transthoracic intervention), heart failure, diabetes (with prescribed antidiabetic drugs), chronic kidney disease [CKD, based on anamnestic estimated glomerular filtration rate (eGFR) below 60 ml/min per 1.73m^2], chronic obstructive pulmonary disease (COPD, based on the presence of signs and symptoms according to GOLD 2019), and obesity (BMI >30 kg/m^2). We also collected pharmacological regimens with renin–angiotensin system (RAS) inhibitors (ACEi, ARBs) and other antihypertensive drugs and the degree of the severity of COVID-19 [12]. The electronic data was 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 two authors (G.I. and C.M.).

COVID-19 diagnosis was confirmed in all patients by RT-PCR performed on nasopharyngeal or throat swab samples [13] in each center by the designated institutions. We also collected the outcomes (hospital discharges or death). All patients for which the course of the disease was in an active state, were classified as such [11]. Healing from COVID-19 infection was defined as two consecutive negative swabs [6].

Heart failure and hypertension status were double-checked and verified by the presence of appropriate therapy. All conditions were considered at the time of the COVID-19 diagnosis.

For each patient, we calculated the Charlson Co-Morbidity index based on the available data [14].

Statistical analysis

Descriptive analyses of the variables were expressed as mean and standard deviation (SD) or frequencies expressed in percentages. Continuous variables were analyzed by ANOVA; categorical data were compared using the χ^2-test as appropriate. Regression analyses, odds ratio, and confidence intervals were tested on the interest variables grouped by healing or nonhealing patients. Multivariable regression analyses were performed on the continuous and categorical variables that resulted significant at the univariate analysis, to assess the independent determinants of healing. P less than 0.05 was considered statistically significant.

RESULTS

We collected 2460 questionnaires. After quality checking (completeness and consistency of the responses), 2446 questionnaires were considered for analysis. Healing from COVID-19 infection was reported in 544 patients (22.2%), 95% of them were hospitalized. Patients who at the time of the questionnaire were already healed were younger and with fewer comorbidities as compared with nonhealing

TABLE 1. Demographic characteristics of the study population

	Total study population ($n = 2446$)	Healing ($n = 544$)	Nonhealing ($n = 1902$)	*P*
Age (years)	67.9 ± 15.6	63.4 ± 14.8	69.3 ± 15.5	0.0001
Women (%)	38.0	38.4	37.4	0.66
Hypertension (%)	58.8	48.0	62.0	0.0001
Obesity (%)	6.9	6.4	7.0	0.650
Diabetes (%)	18.0	13.6	19.3	0.002
COPD (%)	8.9	7.7	9.2	0.284
CKD (%)	5.8	1.7	7.0	0.0001
CAD (%)	14.2	7.7	16.1	0.0001
Heart failure (%)	12.1	4.2	14.4	0.0001
Charlson index	3.0 ± 2.0	2.3 ± 1.7	3.2 ± 2.0	0.0001

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease. *P* values for continuous variables (age and Charlson Index) were calculated by ANOVA; for categorical variables, the χ^2-test was used.

patients ($P < 0.01$, Table 1). Among different reported comorbidities, the prevalence of hypertension, diabetes, CKD, CAD, and heart failure was lower in healing compared with nonhealing patients (all $P < 0.001$, Table 1). The use of ACEi/ARBs was assessed in the subgroup of patients suffering from hypertension and/or heart failure ($n = 1498$). No differences were observed in the use of ACEi/ARBs, whereas only diuretics were less frequently prescribed among patients experiencing healing ($P < 0.05$, Table 2).

In the multivariable regression model, the independent predictors of healing were younger age and the absence of CKD and heart failure (Table 3).

DISCUSSION

Our study is the first to demonstrate that younger age and absence of comorbidities are the main determinants of healing among patients hospitalized for COVID-19 infection. Different retrospective studies have identified potentially linked predictors of deaths and disease severity among patients with COVID-19, including age and cardiovascular comorbidities that still require confirmation [15]. The presence of hypertension and diabetes is reported to be associated with disease severity and mortality in different studies all over the world but its impact on mortality rate is likely to be confounded by age and comorbidities [16]. However, as demonstrated in our analysis, CKD and heart failure are the main factors influencing the possibility of healing from COVID-19. These conditions are associated with diuretics use, which in the univariate analysis significantly impact the possibility to heal, while lose significance in the multivariate regression model, probably because of the larger impact of CKD and heart failure. Patients with CKD are more susceptible to infections, and the acute deterioration of renal function because of COVID-19 infection can evolve in acute renal failure. This latter associates with worse prognosis and death, according to a study by Uribarri *et al.* [17] in a cohort of more than 700 patients. Heart failure has been reported to be associated with an increased hazard of mortality in patients with COVID-19 [18] and our findings, in line with current literature, support the role of heart failure as the main factor influencing the chance of healing. Hypertension is less prevalent in healing patients (relative reduction of −48%), although in the multivariate regression model its significant impact as a predictor of nonhealing is lost. The main reason could be related to the missing information on hypertension grade and duration, which are probably worse and longer in patients with heart failure and CKD (i.e. long-standing history of hypertension and related hypertension-mediated target organ damage).

Activation of RAS and the downregulation of ACE2 expression are partially responsible for lung injury after SARS-CoV infection; furthermore, serum level of angiotensin II demonstrated a positive linear correlation to viral load and lung injury [19]. Thus, the intake of ACEIs/ARBs might probably relieve the lung injury and decrease heart and renal damage resulting from the RAS activation. We analyzed the possible impact of ACEIs/ARB therapy as determinant of healing in COVID-19 patients. Our results did not show any protective effect of RAS-blocking therapy in COVID-19 patients, confirming previous findings [20,21]. Overall, our data support the concept that the rate of

TABLE 2. Use of antihypertensive drugs among hypertensive and heart failure patients

	Total study population ($n = 1498$)	Healing ($n = 266$)	Nonhealing ($n = 1232$)	*P*
ACE-inhibitors (%)	35.4	34.2	35.6	0.660
ARBs (%)	29.7	33.8	28.8	0.104
β-blockers (%)	35.1	32.7	35.6	0.365
Ca-antagonists (%)	13.7	17.3	12.9	0.06
Diuretics (%)	24.6	19.5	25.7	0.034

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor 1 blockers; β-adrenergic receptor blockers *P* values for categorical variables, were calculated by the χ^2-test.

TABLE 3. Multivariable logistic regression analysis for determinants of healing in the total study population

	Model		
	P	Beta	95% CI
Age (grouped by 5 years)	0.0001	0.95	0.90–0.99
Hypertension (n/y)	0.06	0.813	0.65–1.01
Diabetes (n/y)	0.560	0.920	0.69–1.22
CAD (n/y)	0.07	0.713	0.50–1.22
CKD (n/y)	0.003	0.350	0.17–0.70
Heart failure (n/y)	0.001	0.441	0.27–0.70
Diuretics (n/y)	0.129	0.78	0.56–1.08

CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease.

prescription of different cardiovascular drugs is mainly the expression of related comorbidities and does not affect the risk of more severe COVID-19 infection [22].

Our study has some limitations. First, only symptomatic patients with available medical charts were included, while patients with suspected disease, not confirmed by nasal or pharyngeal swabs, were excluded. Our analysis is mainly cross-sectional and not prospective; thus, our study does not allow to identify any direct cause–effect relationship. Data on adherence to therapy with RAS inhibitors prior to the admission and persistence of therapy during hospital admission was not available in our dataset. We did not collect the duration of the disease and cannot provide information on the outcomes of patients affected by COVID-19 at the time of the survey. Nevertheless, our study is powerful in generating hypotheses to be further demonstrated in larger prospective studies.

In conclusion, chance of healing from COVID-19 is strongly associated with young age and absence of comorbidities, mainly heart failure and CKD. The use of antihypertensive therapy with ACEIs/ARB does not affect the possibility of recovering from COVID-19 infection.

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Neither whole nor part of this work has been presented previously.

Conflicts of interest

There are no conflicts of interest.

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