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In-hospital and long-term all-cause mortality in 75 years and older hospitalized patients with and without COVID-19

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Backgrounds and purpose. In-hospital older patients have a high mortality and a higher risk of severe COVID-19 outcomes. However, it is unclear whether COVID-19 infection further increases the already-high mortality risk. This study aimed to assess whether COVID-19 could impact in-hospital and post-discharge mortality in older individuals.
Methods. We compared in-hospital and up to 240 days after hospital discharge all-cause mortality in hospitalized 75 years and older patients with and without COVID-19. One-to-one propensity score allocated study participants into two balanced groups (n = 69 for both). Notably, this study was carried out in 2020, when COVID-19 vaccination was not available yet.
Results. COVID-19 patients died more frequently within 30 days of hospital admission than non-COVID patients (36.2 *vs* 18.8%, respectively; p = 0.018). In contrast, the 240-day post-discharge mortality rate did not differ between groups (42.0 *vs* 47.8%, respectively; p = 0.304). After controlling for clinical covariates, we found that 30-day all cause-mortality was significantly and independently associated with COVID-19 infection (HR = 2.284, 95% CI = 1.068-4.883, p = 0.033) whereas 240-day all-cause mortality was not significantly associated with the infection (HR = 1.525, 95% CI = 0.869-2.678, p = 0.141).
Conclusions. Our results confirm that COVID-19 significantly increases the mortality risk of patients aged 75 or older during hospitalization. However, we found no substantial difference in post-discharge mortality risk between COVID-19 and non-COVID-19 patients. We suggest that continued monitoring of COVID-19 patients after discharge remains crucial to understand the breadth and severity of the long-term effects of SARS-CoV-2 infection, particularly as currently the number of COVID-19 unvaccinated individuals is still high.

Key words: aging, COVID-19, in hospital mortality, frailty, multimorbidity

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INTRODUCTION

One of the potentially harmful challenges that old and frail patients may face in the latter part of their life is hospitalization. Moreover, hospitalization is associated with an irreversible decline in functional status, cognitive performance, and quality of life [1]. Because of these challenges associated

with hospitalization, in-hospital mortality increases with increasing patient age. For example, in England, mortality among hospitalized patients aged 75-84 is 10% for males and 8.8% for females, whereas in-hospital mortality for people over 85 years old increases to 17.5% for males and 15.9% for females [2].

The health care landscape for older individuals was further complicated by the COVID-19 pandemic. Although hypertension, obesity, and diabetes are the most common non-communicable diseases among individuals with confirmed COVID-19 cases [3,4], age remains the key determinant of severe disease and death from COVID-19. Specifically, older adults are more susceptible to severe COVID-19 outcomes because of chronic inflammation and other age-related declines in immune function [5]. In the United States, 80% of COVID-19-related deaths occurred in patients aged > 65 years [6], and older adults were more likely to develop COVID-19-induced acute respiratory distress syndrome and end-stage multiple organ failure [7]. However, public health responses have varied since the start of the pandemic and the scenario has slightly changed between the first and last pandemic waves [8]. In fact, as COVID-19 vaccinations as well as new effective therapeutic options became available the hospitalizations declined, resulting in reduced mortality rate and several regional and country-level differences in the use of non-pharmaceutical interventions, with corresponding effects on the circulation of respiratory viruses in the community.

However, although patients aged 75 or older have a high mortality risk during hospitalization and a higher risk of severe COVID-19 outcomes, it is unclear whether SARS-CoV-2 infection further increases the already-high mortality risk in old, hospitalized patients. To address this question, we conducted a retrospective study of older patients with and without COVID-19 who were admitted to the hospital for acute diseases or relapse of a chronic disease. We matched COVID-positive and COVID-negative patients to ensure patients were similar with respect to age, sex, BMI, and level of frailty, and we then determined all-cause mortality during hospitalization and up to 240 days after hospital discharge for patients with and without COVID-19 during the first and successive waves in Italy prior to the availability of vaccines.

METHODS

We conducted a retrospective study of patients aged 75 years and older who were admitted at the Tor Vergata University Hospital (Rome) between February and December 2020 for either acute disease or relapse of a chronic disease.

After being admitted to the emergency room, patients underwent nasopharyngeal swabs for SARS-CoV-2 real-time reverse transcription-polymerase chain reaction testing (Allpex™ 2019-nCOV Assay).

Participants selection

To be included in the study, patients needed to be at least 75 years old, to complete a standardized Comprehensive Geriatric Assessment (CGA) at hospital admission, which was then used to calculate the Frailty Index (FI) [9], Multidimensional Prognostic Index (MPI) [10], and Cumulative Illness Rating Scale-Geriatrics (CIRS-G) [11] and provide informed consent. Informed consent was obtained from all subjects and/or their legal guardian(s). Exclusion criteria were evaluated on the first day patients were admitted to the ward and included: (a) end-stage neoplastic disease, (b) end-stage chronic kidney disease (estimated glomerular filtration rate ≤ 15 ml min^{-1} [1.73 $m]^{-2}$, according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), (c) connective tissue or bowel inflammatory disease, (d) sepsis, and (e) need for mechanical ventilation during hospitalization.

The admitting physicians recorded routine medical and demographic data. Anthropometric data were collected at the time of admission. The BMI was calculated as the weight (in kilograms) divided by the square of the height (in meters). The average of three measurements was used to calculate systolic and diastolic blood pressure. During COVID-19 pandemic we routinely collected a 30 ml whole blood sample from each patient between 6:00 and 7:00 AM on the first day of ward admission, following an overnight fast, also determining the expression level of the cytokines IL-1β and TNF-α in all in-hospital patients. The blood sample was drawn also for determination of HbA1c, Albumin, serum creatinine, cholesterol, hemoglobin, white blood cells and reactive c protein.

Frailty tests

Frailty index (FI) is used to measure the health status of older individuals; it serves as a proxy measure of aging and vulnerability to poor outcomes. This index has defined as the proportion of deficits present in an individual out of the total number of age-related health variables considered. FI was calculated according to a standard procedure [9].

The MPI is an algorithm developed in older patients that is a good and well validated tool to deduce frailty in older patients in several different setting, including during hospitalization, as well as efficiently predicts 1-year mortality [10]. Briefly, the MPI was developed to include information from the eight domains of the CGA including medication use and cohabitation. The sum of the calculated scores from the eight domains is divided by

eight to obtain a final MPI risk score between 0= no risk and 1= higher risk of mortality. As previously reported [10], the MPI is expressed as three grades of risk: MPI-1, low risk (MPI value ≤ 0.33); MPI-2, moderate risk (MPI value between 0.34 and 0.66); and MPI-3, severe risk (MPI value > 0.66).

The CIRS-G is an index that addresses all relevant physiological systems rather than being based on specific diagnoses and consists of two parts: the CI and the severity index [11]. The advantage of this scale built for geriatrics patients is that it assesses the severity of diseases according to their impact of disability.

The main endpoints of interest in this study were (a) in-hospital mortality, which we defined as all-cause mortality within 30 days of hospital admission; and (b) all-cause mortality within eight months of hospital discharge. We recorded study outcomes during hospitalization. For patients who were discharged, survival status was determined after 240 days using certificates of death publicly accessible, medical records and/or records of contact with the participants, their next of kin, or other health care professionals such as caregivers or surrogates.

Statistical analysis

All quantitative data are expressed as mean±standard deviation, and all categorical variables are expressed as number (percentage) of participants. Data were tested for skewness via visual inspection of QeQ plots and each continuous variable was checked for normality by Shapiro-Wilk goodness of fit test.

We used a one-to-one propensity score to match individuals one-to-one between the two study groups (COVID-positive and COVID-negative participants). The propensity score was estimated using a logistic regression using age, sex, multimorbidity, and MPI score as predictors, applying a caliper of 0.015 to ensure that patients with similar propensity scores were appropriately matched.

Time-to-event (i.e., time to mortality) data were analysed with log-rank tests and univariate Cox models for categorical and continuous variables, respectively. All reported p-values are two-tailed, and the significance level was fixed at 5%. For the multivariate regression, we set the maximum number of predictors to four, according to a common heuristic rule of having approximately one predictor per 15 events. All analyses were performed using IBM SPSS Statistics 27.0 for Windows.

RESULTS

During the enrollment period, 175 patients admitted to our hospital were screened for eligibility. Eighteen patients were excluded: three were younger than 75 years old, four had end-stage chronic kidney disease, and clinical data was incomplete or missing for the remaining eleven. Our final clinical sample included 157 patients with a mean age of 83.4 ± 4.7 years (range, 75-95 years). However, the propensity score-matching procedure excluded an additional 19 patients, eleven from the COVID-negative group and eight from the COVID-positive group. Among the remaining 138 individuals, 69 COVID-negative participants were matched one-to-one to 69 COVID-positive participants. The distributions of propensity scores among COVID-negative and COVID-positive patients were perfectly aligned (p = 0.939). Demographic and clinical characteristics of the two groups are shown in Table I. Overall, 55.8% of patients were female, and the mean age was 83.5 ± 4.6 years. COVID-positive individuals had significantly lower HDL levels upon admission than COVID-negative patients (Table I, p = 0.002). However, the two groups had similar mean levels of total cholesterol, triglycerides, and glucose, as well as similar levels of comorbidity and similar needs for passive oxygen ventilation. Among the inflammatory markers we quantified, only TNF-alpha levels were significantly higher in COVID-negative individuals (p = 0.004).

We recorded 38 deaths during hospitalization and 62 deaths up to 240 days after discharge; the median follow-up period was 104 days. As a result, the overall in-hospital and eight-month mortality rates were 27.5% and 49.9%, respectively. The best multivariate Cox regression model predicting mortality included HDL cholesterol and TNF-alpha as covariates. As shown in Figure 1, in-hospital all-cause mortality was significantly and independently associated with COVID-19 infection (hazard ratio [HR] = 2.284, 95% confidence interval [CI] = 1.068-4.883, p = 0.033). In contrast, eight-month all-cause mortality was not significantly associated with COVID-19 infection (HR = 1.525, 95% CI = 0.869-2.678, p = 0.141).

DISCUSSION

We found that 75 years and older, hospitalized patients who tested positive for COVID-19 had a significantly higher likelihood of in-hospital all-cause mortality compared with COVID-negative patients matched for age, sex, frailty, and level of multimorbidity. Although, as commonly perceived, advancing age is the major mortality risk factor for diverse types of chronic and killer diseases, including cancer, cardiovascular disease, and dementia, lower respiratory infection mortality depends only in part on age [12]. Nevertheless, some studies examining mortality of hospitalized COVID-19 patients and mortality after

Table I. Baseline clinical and laboratory characteristics of patients divided according to COVID-19 testing. Data are shown as numbers or mean (± SD).

Parameters	Overall (n = 138)	COVID+old patients (n = 69)	COVID-old patients (n = 69)	p
Age (years)	83.5 ± 4.6	83.8 ± 4.8	83.1 ± 4.4	0.361
Sex (male/female)	61/77	29/40	32/37	0.607
BMI	24.6 ± 4.0	24.6 ± 3.5	24.6 ± 4.5	0.953
Systolic BP (mmHg)	134.7 ± 21.1	134.2 ± 20.4	135.3 ± 23.0	0.767
Diastolic BP (mmHg)	69.5 ± 11.9	70.9 ± 12.6	68.2 ± 11.1	0.188
Fasting glucose (mg/dl)	122.7 ± 59.5	123.3 ± 63.3	122.3 ± 55.7	0.924
HbA1c (mmol/mol)	44.7 ± 13.0	43.6 ± 9.7	45.7 ± 15.4	0.357
Albumin (mg/dl)	3.0 ± 0.6	2.9 ± 0.6	3.1 ± 0.5	0.144
Total cholesterol (mg/dl)	148.0 ± 42.3	146.8 ± 36.4	149.1 ± 48.3	0.758
HDL cholesterol (mg/dl)	31.7 ± 13.7	28.4 ± 10.3	35.0 ± 15.7	0.004
Tryglicerides (mg/dl)	110.6 ± 42.1	107.3 ± 49.4	110.5 ± 48.1	0.679
Creatinin (mg/dl)	1.4 ± 1.4	1.5 ± 1.9	1.2 ± 2.0	0.156
White blood cells (n/mm^3)	9.5 ± 6.4	7.9 ± 3.6	10.5 ± 6.6	0.207
Hgb (g/dl)	11.4 ± 2.0	11.5 ± 2.2	11.3 ± 1.8	0.525
Frailty Index (< 0.25 / ≥ 0.25)	25/103	16/53	19/50	0.557
MPI	0.55 ± 0.23	0.55 ± 0.23	0.57 ± 0.24	0.480
Passive oxygen ventilation (yes/no)	26/112	15/54	11/58	0.383
CVD (yes/no)	53/84	26/43	28/41	0.727
Previous cancer (yes/no)	18/120	11/58	7/62	0.311
Follow-up (days)	106.1 ± 79.6	79.0 ± 64.5	133.1 ± 84.5	< 0.001
Reactive C protein (mg/dl)	76.2 ± 149.3	74.3 ± 71.7	78.2 ± 189.3	0.880
TNF-α (ng/ml)	17.7 ± 15.3	13.7 ± 9.9	21.7 ± 18.5	0.002
IL6 (ng/ml)	31.2 ± 32.7	33.4 ± 28.4	28.9 ± 36.5	0.429
CIRS-G (total score)	12.38±2.67	11.56 ± 2.54	12.51 ± 2.98	0.551
Hospital stay (days)	19.5 ± 4.8	20.8 ± 3.2	18.3 ± 6.0	0.401
Death during hospitalization, n (%)	38 (27.5)	25 (36.2)	13 (18.8)	0.018
Death at 8 months, n (%)	62 (44.9)	33 (47.8)	29 (42.0)	0.304

hospitalization [13-15] reported that in patients with SARS-CoV-2-positive tests, overall mortality was much more elevated in patients older than 75 years (21%) than in those younger than 18 years (0.2%). Nonetheless, to our knowledge, this is the first report that analyses the impact of COVID-19 on mortality in hospitalized, older patients by comparing COVID-positive and COVID-negative patients who otherwise had the same clinical conditions in the same setting. In-hospital mortality naturally increases with patient age [16], independently of whether patients are infected with COVID-19. Moreover, hospitalized multimorbid patients are far sicker than the general population and therefore have a higher risk of death, independently of COVID-19 infection. The comparatively high (36%) in-hospital mortality rate among older patients with COVID-19 confirms that frailty is a key prognostic factor for a poor COVID-19 outcome. As a confirmation of this, a recent work reported that since the beginning of the COVID-19 pandemic the in-hospital mortality rate among 645 Asiatic children and young people (ages 0-17) was 2.5% [17].

It is conceivable that mortality is higher among 75 years and older patients with COVID-19 because the weaker immune system of older individuals allows for an uncontrolled viral progression [18]. This progression could play an important role in SARS-CoV-2 pathogenesis and poor recovery. However, in-hospital COVID-related mortality additionally depends on whether study participants were vaccinated against SARS-CoV-2 at the time of enrollment; Italy's vaccination campaign for frail and older individuals only started at the beginning of 2021, but all patients in this study were enrolled by the end of December 2020.

The novelty of our findings is that during the eight months after hospital discharge, all-cause mortality was no longer influenced by COVID-19 infection. This result is rather surprising, as some COVID-related pathological processes such as increased chronic inflammation and coagulopathy can still persist even when SARS-CoV-2 is no longer detectable [19]. Accordingly, some studies reported that the incidence of thrombosis, pulmonary embolism, and ischemic stroke are particularly high after COVID-19 patients are discharged from the hospital [20,21]. For example,

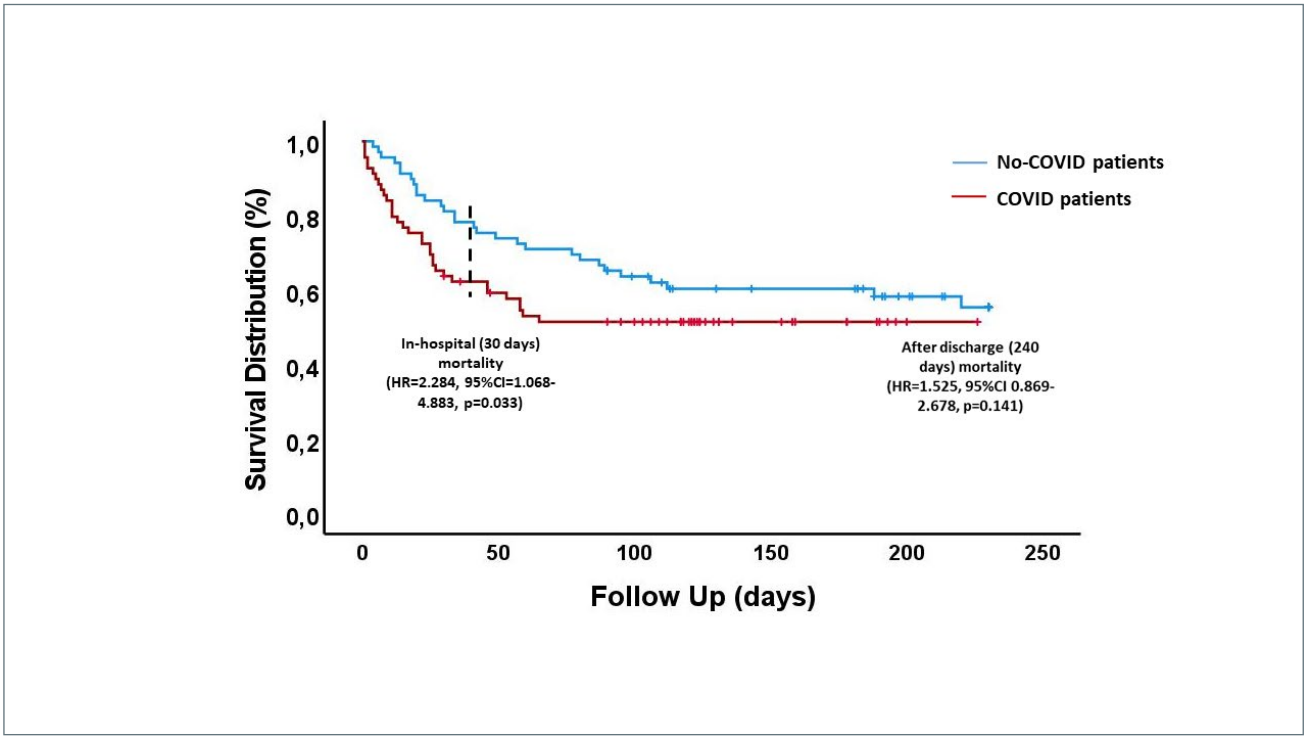

Figure 1. Survival curves showing all-cause mortality among older patients who tested positive (red) or negative (blue) for COVID-19.

one study on American veterans – who are, on average, older than the general population – reported that veterans with COVID-19 were more likely to develop serious pulmonary and extrapulmonary complications after hospital discharge and had a higher risk of death [22]. Therefore, we think that hospitalization itself may have imposed a form of biological selection. In other words, we suspect that 75 years and older COVID-19 patients who survive hospitalization are robust enough to achieve the same risk of post-discharge death as COVID-negative individuals who are otherwise very similar in terms of health status and clinical condition. Overall, our results suggest that there is no substantial difference in post-discharge mortality risk between old, frail, multimorbid patients with or without COVID-19. Moreover, although this study was performed before the beginning of the COVID-19 vaccination campaign, our findings are still relevant because of the relative high rate of unvaccinated individuals. In particular, in Italy has been estimated that about 5% of over 80 years old individuals did never receive any COVID-19 vaccine inoculation [23] whereas vaccination had an important impact in reducing mortality among frail older patients with COVID-19, even during hospitalization especially if affected by sarcopenia [24]. The main flaw of this study is the limited number of participants; however, we attempted to overcome this limitation by propensity score-matching the two study groups to ensure they were equivalent in terms of age and health status. A second limitation of this study is that some variables such as body composition and sarcopenia were not analyzed. Therefore, recommend future studies to confirm our hypothesis in a larger cohort with similar characteristics. In addition, it will be interesting to observe the effect of vaccination on the mortality of hospitalized COVID-19 patients.

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Conflict of interest statement

The authors declare no conflict of interest.

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Author contribution

SR, MF: acquisition of data; SR, AB: data analysis.All authors contributed to the study concept and design, interpretation of the data, and preparation of the manuscript.

Ethical consideration

This study was designed following the Declaration of Helsinki and the Guidelines for Good Clinical Practice,

and it was approved by the local independent Tor Vergata Foundation ethics committee (protocol number: 102/20).

The datasets analysed during the current study are not publicly available due to reasons established by independent Tor Vergata Foundation ethics committee but are available from the corresponding author on reasonable request.

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