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The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects



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ABSTRACT

Keywords:
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Objectives: Initial data on COVID-19 infection has pointed out a special vulnerability of older adults.

Design: We performed a meta-analysis with available national reports on May 7, 2020 from China, Italy, Spain, United Kingdom, and New York State. Analyses were performed by a random effects model, and sensitivity analyses were performed for the identification of potential sources of heterogeneity.

Setting and participants: COVID-19–positive patients reported in literature and national reports.

Measures: All-cause mortality by age.

Results: A total of 611,1583 subjects were analyzed and 141,745 (23.2%) were aged ≥ 80 years. The percentage of octogenarians was different in the 5 registries, the lowest being in China (3.2%) and the highest in the United Kingdom and New York State. The overall mortality rate was 12.10% and it varied widely between countries, the lowest being in China (3.1%) and the highest in the United Kingdom (20.8%) and New York State (20.99%). Mortality was $<1.1\%$ in patients aged <50 years and it increased exponentially after that age in the 5 national registries. As expected, the highest mortality rate was observed in patients aged ≥ 80 years. All age groups had significantly higher mortality compared with the immediately younger age group. The largest increase in mortality risk was observed in patients aged 60 to 69 years compared with those aged 50 to 59 years (odds ratio 3.13, 95% confidence interval 2.61–3.76). **Conclusions and Implications:** This meta-analysis with more than half million of COVID-19 patients from different countries highlights the determinant effect of age on mortality with the relevant thresholds on age >50 years and, especially, >60 years. Older adult patients should be prioritized in the implementation of preventive measures.

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In December 2019, in South China, a new type of acute respiratory infection caused by a novel type of coronavirus (SARS-COV-2) was discovered, known as coronavirus infectious disease–19 (COVID-19).

As soon as by the end of February 2020, it had become a pandemic and a public health emergency worldwide.¹ Clinical severity of the infection ranges from asymptomatic or mildly symptomatic patients to critical situation with bilateral pneumonia leading to multiorgan failure² and, therefore, it is essential to identify prognostic factors related to more severe forms of the disease and mortality.

Initial data have pointed out a special vulnerability of older adults. Case series have identified age as an independent prognostic factor for mortality.³ Also, national registries have shown a high mortality rate

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Table 1
Clinical Features of the National Reports

	China	Italy	Spain	New York State	United Kingdom	Total
N	44,672	214,103	220,375	2634	129,799	611,583
Age, y, mean	79.5	61	61	63	62	64.9
Fatality, n (%)	1023 (2.29)	27,955 (13.06)	17,489 (7.94)	553 (20.99)	27,008 (20.81)	74,028 (12.10)
Sex, male	22,981	99,667	96,297	3437	60,104	132,682
Hypertension	2683		23,962	1366		
Diabetes	1102		19,850	757		
Age groups						
Age <29	4584	16,007	13,795	131	12,081	46,598
Fatality	8 (0.2)	12 (0.1)	28 (0.2)	4 (0.3)	67 (0.6)	119 (0.3)
Age 30-39	7600	16,189	20,755	211	13,193	57,948
Fatality	18 (0.2)	54 (0.3)	57 (0.3)	8 (3.8)	134 (1.0)	271 (0.5)
Age 40-49	8571	27,553	32,208	432	15,712	84,476
Fatality	38 (0.4)	246 (0.9)	186 (0.6)	22 (5.1)	454 (2.9)	946 (1.1)
Age 50-59	10,008	38,299	39,355	515	19,436	107,613
Fatality	130 (1.3)	993 (2.6)	569 (1.4)	53 (10.2)	1518 (7.8)	3263 (3.0)
Age 60-69	8583	29,252	32,175	533	14,815	85,358
Fatality	309 (3.6)	2976 (10.2)	1543 (4.8)	84 (15.7)	3161 (21.3)	8073 (9.5)
Age 70-79	3918	31,627	30,844	451	18,273	85,113
Fatality	312 (8.0)	7849 (24.8)	4325 (14.02)	145 (32.2)	6765 (37.0)	19,396 (22.8)
Age >80	1408	55,020	50,504	441	34,372	141,745
Fatality	208 (14.8)	15,825 (28.8)	10,781 (21.3)	237 (53.7)	14,907 (43.4)	41,958 (29.6)

among patients older than 80 years.^{4–6} Therefore, older adults seem to have a higher proportion of severe cases of COVID-19 and fatal outcome. The present study aims to analyze the available data of mortality in the older adult population compared with its younger counterparts.

Methods

We performed a systematic search [using PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar], without language restriction, for papers using the Medical Subject Headings terms “Coronavirus,” “Covid-19,” “Mortality,” “Clinical outcomes” and “Clinical course” up to May 7, 2020. We also

searched for national reports in the official health services’ website of all European Countries. Primary outcome was all-cause death. As a result, of the 17 studies that reported clinical features of patients who died vs survivors, most were hospital registries,^{3,7–9} 4 were national reports (from China,⁴ Italy,⁵ and Spain,⁶ and United Kingdom¹⁰), and 1 was a publication from Northwell Health, the largest academic health system in New York State.¹¹ Hospital registries did not include age distribution and, therefore, could not be included. Older adult patients were defined as those aged 80 years or older.

We performed a meta-analysis in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.¹² Clinical features and mortality rates were available in all studies. Relative

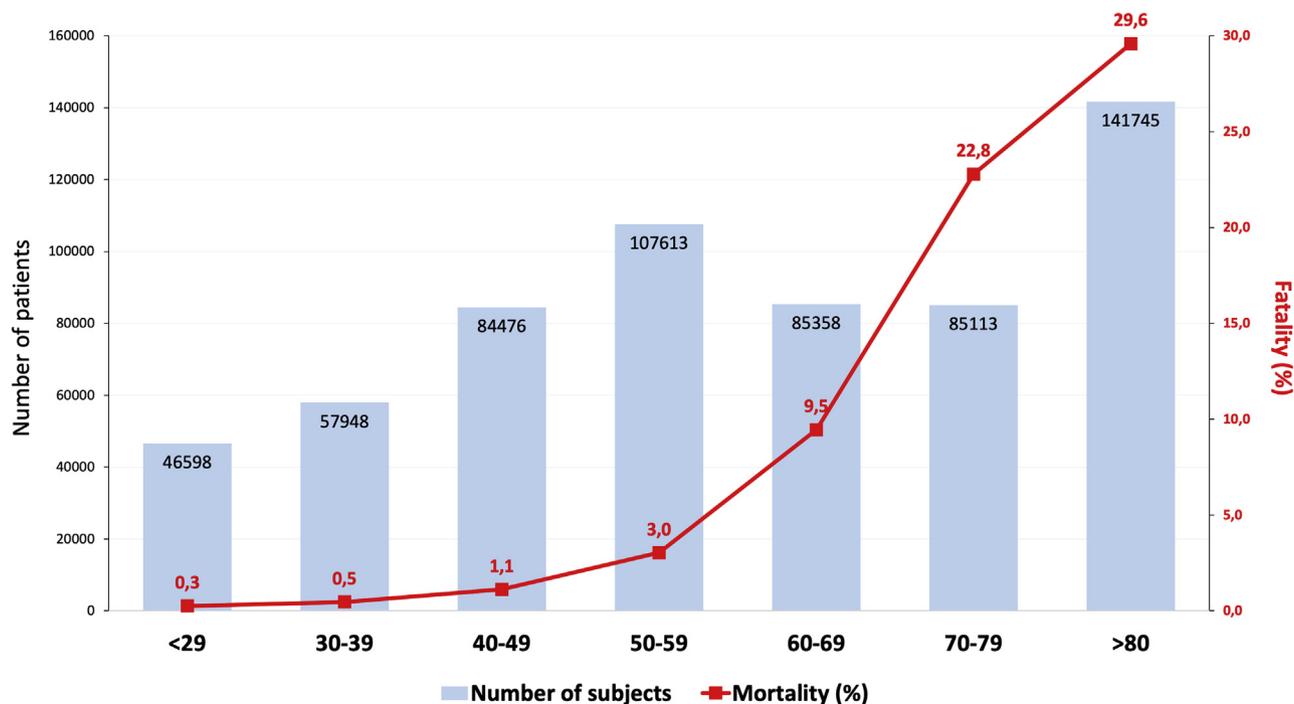


Fig. 1. Histogram of patients according to age groups and crude mortality rates.

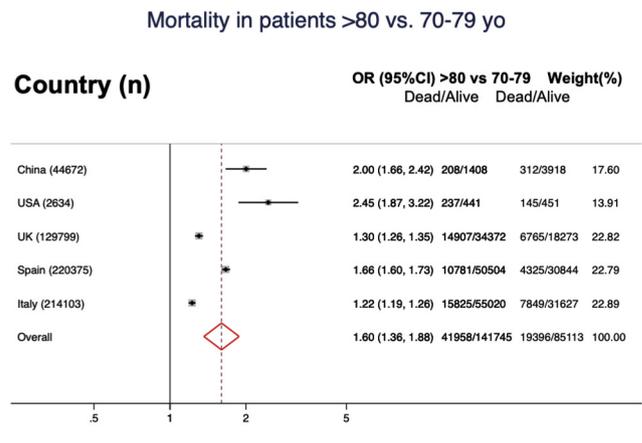
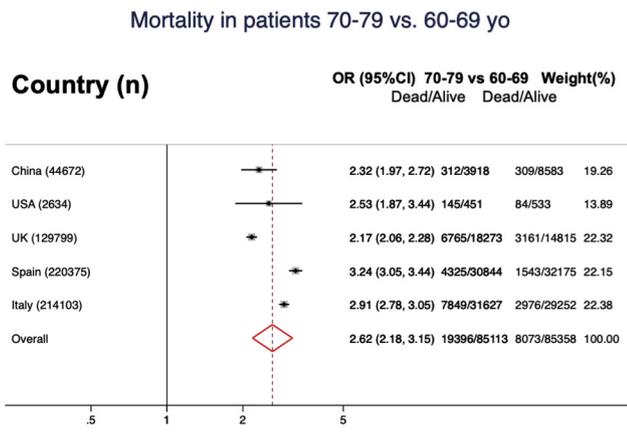
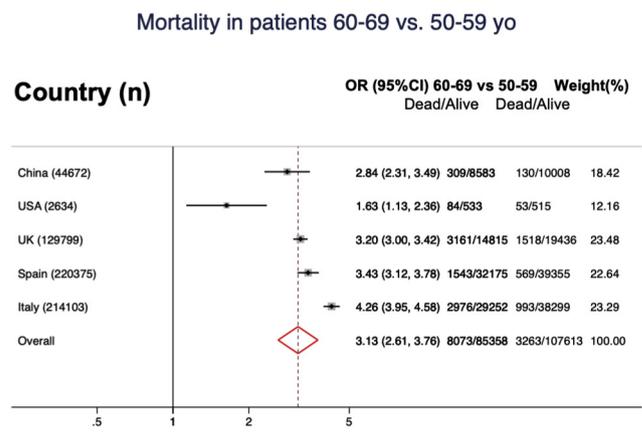
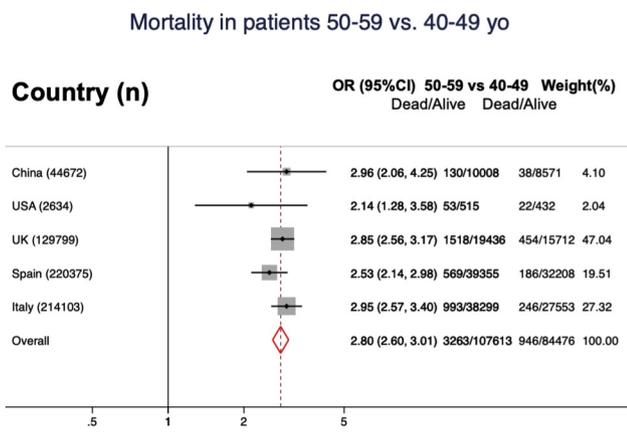
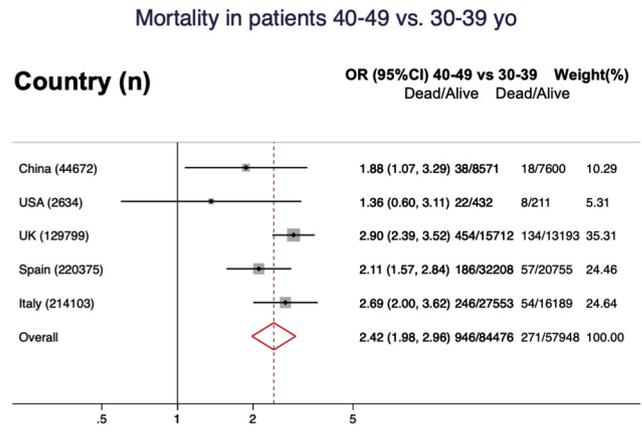
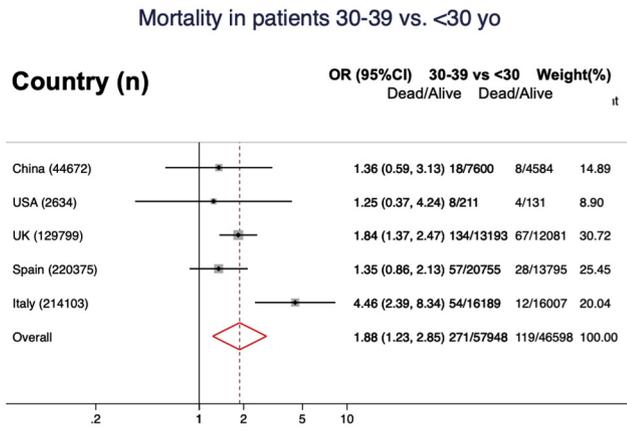


Fig. 2. Forest plots showing the pooled odds ratio (OR) with 95% confidence intervals of mortality for each age group.

risk reductions and percentage incidences were used. The study-specific standard errors for the estimated odds ratio were used to model the within-study variation. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic. Once heterogeneity was observed and assuming that the study effect sizes were different as well as that the collected

studies represented a random sample from a larger population, all the analyses were performed by a random effects model. Sensitivity analyses were performed for the identification of potential sources of heterogeneity between studies with meta-regression analyses and the Harbord test to assess the small-study effects.¹³ All analyses were performed using Stata, release 14.3 (StataCorp LP, College Station, TX).

Results

A total of 611,583 subjects were analyzed; the mean age was 61.3 years and 192,786 (31.5%) were male (Table 1). A total of 141,745 patients (23.2%) were ≥ 80 years old; the percentage of older adults was different in the 5 reports, the lowest being in China and the highest in the United Kingdom and New York State. The overall mortality rate was 12.10% and it varied widely between countries, the lowest being in China and the highest in the United Kingdom and New York State.

According to age, mortality was $< 1\%$ in patients aged < 50 years, and it increased exponentially after that age (Figure 1). As expected, the highest mortality rate was observed in patients aged ≥ 80 years. All age groups had significantly higher mortality compared to the immediately younger age group (Figure 2). The largest increase in mortality risk was observed in patients aged 60 to 69 years compared with 50 to 59 years. Patients aged > 80 years had 60% higher risk of death compared to patients with age 70 to 79 years but it was 6-fold higher (odds ratio: 6.25, 95% confidence interval 5.38–7.25; $P < .001$) if they were compared to all patients aged < 80 years.

Significant heterogeneity ($P < .001$) was observed. The funnel plot is presented in Figure 2. Meta-regression identified sample size ($P = .002$), countries ($P = .001$), and mean age ($P = .001$) as significant sources of heterogeneity; the small-effect study was also observed (Harbor test, $P = .013$).

Discussion

The meta-analysis of currently available national and regional reports of patients with COVID-19 infection highlights the effect of age on mortality. These results have important clinical implications such as on specific preventive measures and the clinical management of COVID-19 patients.

Since the start of the pandemic, age has been outlined as the key prognosis determinant in COVID-19 patients. Based on the early statistical data of China, the case-fatality rate (CRF) increases markedly from the age of 60, reaching 14.8% in those older than 80 years.¹⁴ Initial data from Italian patients also described that mortality increased significantly in septuagenarian patients and almost tripled in octogenarians.¹⁵ In a Chinese cohort study, age was identified as an independent predictor of mortality, with an odds ratio of 1.1 (95% confidence interval 1.03, 1.17) for each year.³ Our analysis of 611,583 patients shows a mortality increase related to age; this is evident in patients aged ≥ 60 years, increasing significantly in each decade of life. Therefore, the highest mortality occurs in the patients aged ≥ 80 years in whom it was 6 times higher than in younger patients.

These findings are consistent with a higher susceptibility to the infection and severe clinical manifestations observed in older adult patients.^{3,16} This fact could be influenced by both the physiological aging process and, especially, the greater prevalence in older adult patients of frailty and comorbidities that contribute to a decrease in functional reserve that reduces intrinsic capacity and resilience and hinders the fight against infections.¹⁷ In this line of thought, comorbidities such as cardiovascular disease, hypertension, and diabetes are highly prevalent in older adults and have been associated with worse outcomes in COVID-19.³ Many mechanisms underlying this worse prognosis in older adults with COVID-19 might explain our results that might lead to further research.¹⁸

Our study has several limitations, mainly derived from the data source. National reports might be designed and performed with different methodologies in each country. Population characteristics might also be quite different, especially between Europe and China.¹⁹ Specifically, in older adults the percentage of infected and dead in nursing homes and socio-sanitary centers is not published, therefore the real incidence and mortality of COVID-19 may be underestimated.

Future studies are necessary to analyze the factors that, beyond age, make this population especially susceptible and vulnerable to having a serious infection with complications and a higher mortality rate.

Conclusions and Implications

The meta-analysis of currently available data suggest a determinant effect of age on mortality of COVID-19 patients with a relevant threshold on age > 50 and especially > 60 . Nevertheless, more clinical and basic research is needed to elucidate the mechanism involved in the COVID-19 infection in older adults and to develop strategies to improve outcomes in these patients.

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