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Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Research Note

Assessing the impact of coronavirus disease 2019 on mortality: a population-based, matched case-control study

Adi Turjeman^{1, 2, *}, Eytan Wirtheim³, Itamar Poran^{2, 4}, Leonard Leibovici^{1, 2}¹ Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel² Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel³ Management, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel⁴ Intensive Care Unit, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel

ARTICLE INFO

Article history:

Received 19 May 2022

Received in revised form

11 August 2022

Accepted 18 August 2022

Available online xxx

Editor: L. Scudeller

Keywords:

COVID-19

Elderly

Mortality

Pandemic

Risk factors

ABSTRACT

Objectives: Estimating the isolated effect of coronavirus disease 2019 (COVID-19) on the risk of mortality is challenging. We aimed to determine whether COVID-19 was associated with high rates of mortality independently of age, sex and underlying disorders.

Methods: A population-based, matched, case-control study of adults insured by Clalit Health Services was performed. Cases were defined as patients who died of all causes between July and December 2020. Each case was matched in a ratio of 1:1 with a living control based on age, sex and co-morbidities. An unconditional logistic regression analysis was performed to identify independent risk factors for mortality.

Results: A total of 2874 patients who died were successfully matched with 2874 living controls. The prevalence of COVID-19 was higher among the patients who died than among the controls (13.5% [387/2874] vs. 4% [115/2874], respectively; OR, 3.73; 95% CI, 3.01–4.63; $p < 0.001$). A significantly increased odds of mortality was also observed in patients with COVID-19 without underlying diseases (OR, 3.67; 95% CI, 2.58–5.23) and in patients with COVID-19 and underlying diseases (OR, 3.77; 95% CI, 2.87–4.94). A multi-variate logistic analysis showed that COVID-19 (OR, 2.01; 95% CI, 1.07–3.77), low socio-economic status (OR, 1.36; 95% CI, 1.02–1.82), dementia (OR, 2.50; 95% CI, 2.10–3.01), smoking (OR, 1.35; 95% CI, 1.13–1.63) and an interaction variable of age >80 years and COVID-19 (OR, 2.27; 95% CI, 1.14–4.54) were independent risk factors for mortality, whereas influenza vaccination and high body mass index were associated with lower rates of mortality.

Conclusion: Testing positive for COVID-19 increased the risk of death three folds, regardless of underlying disorders. These results emphasize the effect of COVID-19 on mortality during the early period of the COVID-19 outbreak, when no vaccines or effective therapeutics were available. **Adi Turjeman, Clin Microbiol Infect 2022;■:1**

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Introduction

Since first detected in China, the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, has spread rapidly around the globe. The first case of COVID-19 was confirmed in Israel on 21 February 2020. WHO declared the COVID-19 outbreak a global pandemic on March 2020 [1].

Patients of older age and with pre-existing health conditions are at an increased risk of severe COVID-19 [2–4]. In a systematic review and meta-analysis of 42 studies and 423 117 patients, a statistically significant effect of older age, male sex, and chronic comorbidities on the fatal outcome of COVID-19 was found [4]. Given the fact that these risk factors also contribute to an increased risk of premature death, estimating the independent effect of COVID-19 on the risk of mortality is challenging. The association between COVID-19 and the risk of mortality among healthy and non-elderly people is controversial.

In this retrospective study, we aimed to determine whether COVID-19 was associated with high rates of mortality independently

* Corresponding author. Adi Turjeman, Research Authority, Rabin Medical Center, Beilinson Hospital, 39 Jabotinski Road, Petah-Tikva, 49100, Israel.

E-mail address: aditur88@gmail.com (A. Turjeman).

<https://doi.org/10.1016/j.cmi.2022.08.016>

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of age, sex and underlying disorders during the first wave of COVID-19 in Israel by comparing patients who died with their matched controls. In addition, we examined the interactions between COVID-19 and other risk factors for mortality. This case-control study was performed using the Clalit Health Services (CHS) database.

Methods

Setting and data source

A case-control study of patients insured by CHS was performed. CHS is the largest health-care delivery system in Israel, covering 53% of Israel's population. The study population included all insured members from the Dan-Petah-Tikva and Tel Aviv districts who were aged ≥ 22 years as of 1 January 2020 and had continuous membership in Clalit for at least 5 years before inclusion.

Cases and controls

The cases were all people who died of all causes between 1 July 2020 and 31 December 2020. Each case was matched in a ratio of 1:1 with a living control based on age (± 90 days), sex and underlying diseases: neoplasms (in three categories: no, acute leukaemia or other neoplasms), kidney diseases (in three categories: no, chronic kidney disease or haemodialysis), congestive heart failure, chronic obstructive pulmonary disease, ischemic heart disease and diabetes mellitus. These diseases were identified by the Israeli Ministry of Health as the leading causes of death in Israel in 2018 [5]. Each control was assigned an index date which was identical to that of his/her matched case, which was defined as the date of death.

Data and variables

Data were extracted from CHS using Clalit's data-sharing platform powered by MDClone (<https://www.mdclone.com>). The following data were extracted: age, sex, ethnicity, socio-economic status (SES), body mass index (BMI), smoking status, diagnoses of underlying diseases, history of influenza vaccinations and laboratory data for the diagnosis of COVID-19. Details regarding SES were obtained from the Israel Central Bureau of Statistics at the level of small residential areas. This measurement accounts for social and economic levels in four areas: demographics, education, standard of living and employment. The diagnoses of underlying diseases were identified according to the International Classification of Diseases, 10th Revision, Clinical Modification codes (Table S1). Data on mortality were obtained from the Israeli Interior Ministry's population registry, in which all deaths in Israel are reported by law. The data on mortality included deaths caused by all reasons.

Statistical analysis

Categorical variables were expressed as frequencies (percentages), and continuous variables were expressed as mean \pm standard deviation or as median and interquartile range (25%–75%), as appropriate based on their distribution.

The differences between the cases and controls were assessed using the Chi-square test for categorical variables and the *t* test or Mann-Whitney *U* test for continuous variables. A two-sided *p* value of <0.05 was considered to be indicating significance. We also performed stratified analyses to identify significant interactions between COVID-19 and other risk factors.

All variables and interactions which were significantly associated with death were included in a multi-variate analysis using generalized linear models. We used a logistic regression model (unconditional) to identify independent risk factors for mortality. The

goodness of fit of the multi-variate logistic model was assessed using the Akaike information criterion. The associations between the risk factors and death are presented as ORs with their 95% CIs, calculated using the Wald method. Because the proportion of missing data was low (3.1%, 176/5748), no imputation method was used. The statistical analyses were performed using IBM SPSS Statistics, version 26.

Ethical considerations

This study was approved by the Rabin Medical Center Institutional Review Board. The requirement for informed consent was waived.

Results

A total of 603 526 individuals aged ≥ 22 years were continuous members of CHS for a period of at least 5 years before 2020, of whom 3048 died between 1 July 2020 and 31 December 2020. We managed to successfully match 2874 cases (94% of the total) with 2874 controls based on age, sex and underlying diseases.

The demographic and clinical characteristics of the cases and controls are presented in Table 1. The median age of the cohort was 85 (interquartile range, 74–90) years, and 47% (2702/5748) were men. A significantly higher proportion of the cases had dementia, were from a lower SES, had lower BMI, were less likely to receive influenza vaccination in 2019 and were more likely to be current smokers compared with their matched controls.

The rate of COVID-19 was significantly higher among the patients who died than among the control subjects (13.5% [387/2874]

Table 1
Demographic and clinical characteristics of cases and controls^a

Variable	Dead (cases) N = 2874 (%)	Alive (controls) N = 2874 (%)	<i>p</i> value
Age, median (IQR), y ^b	85 (74–91)	85 (74–90)	NA
Sex, male ^b	1351 (47.0)	1351 (47.0)	NA
Ethnicity			0.34
Jews	2687 (98.0) N = 2741	2719 (98.4) N = 2764	
Arabs	54 (2.0) N = 2741	45 (1.6) N = 2764	
Low socio-economic status	130 (4.6) N = 2814	88 (3.1) N = 2821	0.004
BMI, median (IQR)	25.7 (22.7–29.7)	27.1 (24.0–30.5)	<0.001
Smoking status – current smoker	331 (11.7) N = 2838	259 (9.1) N = 2854	0.001
Neoplasms ^b			NA
No	2410 (83.9)	2410 (83.9)	
Acute leukaemia	1 (0.0)	1 (0.0)	
Other neoplasms	463 (16.1)	463 (16.1)	
Kidney diseases ^b			NA
No	2443 (85.0)	2442 (85.0)	
Chronic kidney disease	403 (14.0)	403 (14.0)	
Haemodialysis	28 (1.0)	28 (1.0)	
COPD ^b	209 (7.3)	209 (7.3)	NA
Ischaemic heart disease ^b	437 (15.2)	437 (15.2)	NA
Congestive heart failure ^b	365 (12.7)	365 (12.7)	NA
Diabetes mellitus ^b	1261 (43.9)	1261 (43.9)	NA
Cerebrovascular disease	315 (11.0)	286 (10.0)	0.211
Peripheral vascular disease	72 (2.5)	61 (2.1)	0.335
Dementia	427 (14.9)	193 (6.7)	<0.001
Obesity	148 (5.1)	180 (6.3)	0.069
HIV	8 (0.3)	3 (0.1)	0.131
Influenza vaccination in 2019	1773 (61.7)	1900 (66.1)	<0.001
COVID-19	387 (13.5)	115 (4.0)	<0.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HIV, human immuno-deficiency virus; IQR, interquartile range; NA, not applicable.

^a Data are presented as number (%) unless otherwise indicated.

^b Matching criteria.

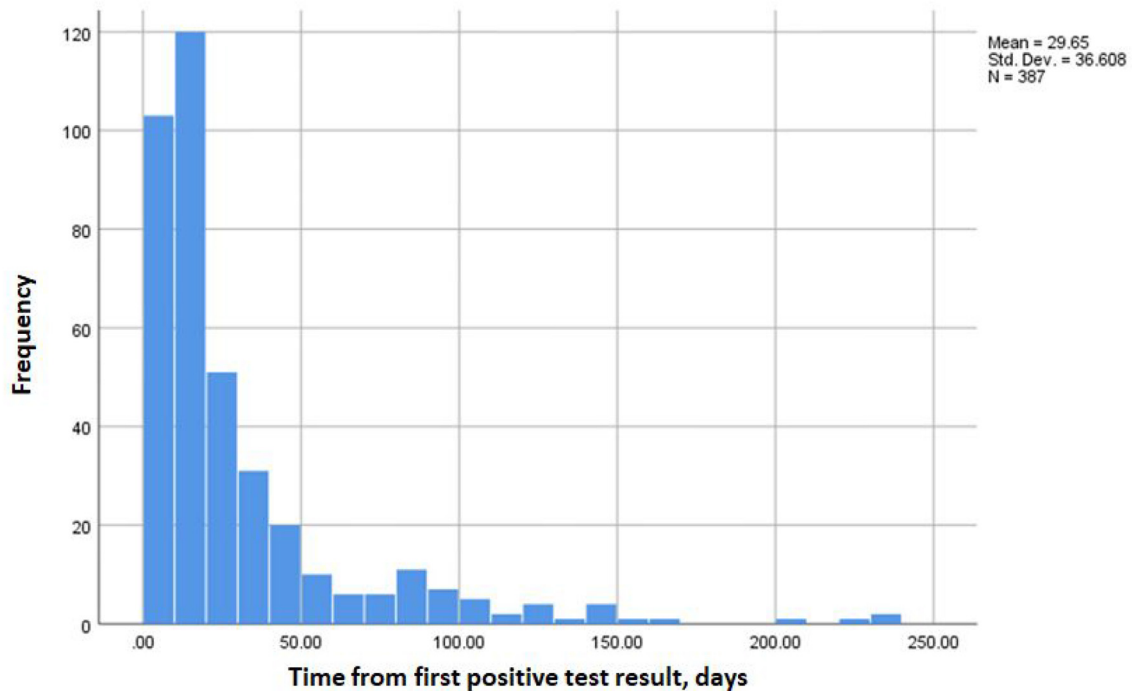


Fig. 1. Time between the first positive coronavirus disease 2019 test result and death. Std. Dev., standard deviation.

vs. 4% [115/2874], respectively; $p < 0.001$) (Table 1). Among 387 patients with COVID-19 who died, 278 (72%) died within 30 days of a positive COVID-19 test result (Fig. 1). In a uni-variate analysis, a 3.73-fold increase in the odds of mortality was observed in the patients with COVID-19 (OR, 3.73; 95% CI, 3.01–4.63) (Table 2). Significantly increased odds of mortality were also observed in patients with COVID-19 without underlying diseases (OR, 3.67; 95% CI, 2.58–5.23) and in patients with COVID-19 and underlying diseases (OR, 3.77; 95% CI, 2.87–4.94) (Table 2).

The multi-variate analysis showed that COVID-19 (OR, 2.01; 95% CI, 1.07–3.77), low SES (OR, 1.36; 95% CI, 1.02–1.82), dementia (OR, 2.50; 95% CI, 2.10–3.01), current smoking (OR, 1.35; 95% CI, 1.13–1.63) and an interaction variable of age >80 years and COVID-19 (OR, 2.27; 95% CI, 1.14–4.54) were independent risk factors for mortality, whereas influenza vaccination in 2019 (OR, 0.80; 95% CI, 0.72–0.90) and higher BMI (OR per BMI increment of 1 kg/m², 0.96; 95% CI, 0.95–0.97) were associated with lower rates of mortality (Table 3).

Discussion

In this case-control study, we found that COVID-19 is an independent risk factor for mortality after controlling for age, sex and

Table 2
Association between coronavirus disease 2019 and mortality among patients with or without underlying disorders

Population	Dead	Alive	Or (95% CI)
All patients with COVID-19	387/2874 (13.5%)	115/2874 (4.0)	3.73 (3.01–4.63)
Patients with COVID-19 and underlying disorders	245/1859 (13.2%)	72/1859 (3.9%)	3.77 (2.87–4.94)
Patients with COVID-19 without underlying disorders	142/1015 (14.0%)	43/1015 (4.2%)	3.67 (2.58–5.23)

COVID-19, coronavirus disease 2019.

co-morbidities which were considered as potential risk factors for mortality. The odds of death for individuals who tested positive for COVID-19 were increased by more than three folds. This was even more prominent among individuals aged ≥ 80 years. An increased risk of mortality was also observed among people without underlying diseases and with COVID-19. Dementia, smoking and low SES were also independently associated with higher mortality rates, whereas receiving influenza vaccination in 2019 and high BMI were found to have a protective effect.

Several studies have tried to assess both the direct and indirect effects of COVID-19 on mortality. There are difficulties in evaluating the direct effect of COVID-19 on mortality because other frequent co-morbidities may affect this association. In this study, we used a

Table 3
Multivariable analysis for mortality^a

Risk factor	Multi-variate logistic regression analysis OR (95% CI)	p value
Age, y		
<65	Reference	Reference
65–80	1.04 (0.84–1.28)	0.75
>80	0.95 (0.78–1.16)	0.61
Low socio-economic status	1.36 (1.02–1.82)	0.036
BMI	0.96 (0.95–0.97)	<0.001
Dementia	2.50 (2.10 to –3.01)	<0.001
Influenza vaccine in 2019	0.80 (0.72–0.90)	<0.001
Smoking status - current smoker	1.35 (1.13–1.63)	0.001
COVID-19	2.01 (1.07–3.77)	0.029
Interaction of age between 65 and 80 y and COVID-19	2.00 (0.94–4.25)	0.073
Interaction of age >80 y and COVID-19	2.27 (1.14–4.54)	0.02

BMI, body mass index; COVID-19, coronavirus disease 2019.

^a Multi-variate analysis for mortality. Multi-variate analysis using generalised linear models. Goodness of fit- Akaike information criteria 6681.623, N = 5572, constant = 1.001.

matched case-control design, which allows us to eliminate potential confounding factors which may influence mortality (age, sex or co-morbidities).

Studies investigating the risk factors for COVID-19 severity and fatality were recently published [6]. Age is a well-known independent risk factor for increased morbidity and mortality [7]. We found that among patients with COVID-19, older age was the greatest risk factor for mortality. The plausible reasons for these results include age-related co-morbidities (not accounted for in the matching) and lower efficiency of the immune system [8].

Another known risk factor for mortality among patients with COVID-19 is dementia. Tahira et al. [9] found that all-cause dementia and Alzheimer disease were age-independent risk factors for COVID-19-related mortality. In our study, patients with dementia had a 2.5-fold increased risk of death.

Several studies have described a potential protective effect of influenza vaccination against COVID-19 [10,11]. In our study, we found that patients who received influenza vaccination in 2019 had lower mortality rates in 2020 than non-vaccinated patients. This can be explained by “well managed” or “healthy user” biases; patients who adhere to medical treatments or preventive therapies are more likely to have better health outcomes.

There are some conflicting results in the literature regarding the association between BMI and mortality. Although several studies have demonstrated that being underweight or overweight is associated with an increased risk of mortality [12–15], others have reported results similar to ours, i.e. being overweight is associated with a decreased risk of mortality [16,17]. Low SES has been associated with morbidity and premature mortality world-wide. In a large multi-cohort study with 1.7 million participants from the United States, Europe and Australia, low SES was associated with a 26% higher risk of mortality. The strongest association was found between current smoking and mortality [18]. In our study, both low SES and current smoking were independently associated with increased mortality.

Our study has limitations. The patients with COVID-19 were those who were infected with the wild-type virus. Our study provides an insight into the impact of COVID-19 on mortality at the beginning of the pandemic, when little was known about this novel virus and no vaccines were available. Residual confounding by other underlying disorders cannot be ruled out. We used OR as the measure of association between exposure and outcomes. However, if the outcome of interest is rare, OR is a good estimate of relative risk [19]. In our study, death occurred in 0.5% of the total population (3048/603 526).

In conclusion, we demonstrated that COVID-19 was independently associated with a 3.7-fold increased OR for mortality during the first wave of COVID-19 in Israel. People without underlying diseases and with COVID-19 were also at an increased risk of dying. The odds of dying were even higher in the older patient group (aged >80 years) with COVID-19. These results emphasize the effect of COVID-19 on mortality during the early period of the COVID-19 outbreak, when prevention efforts were focused on face masks, hand hygiene, social distancing and lock-down, and no vaccines or effective therapeutics were available.

Transparency declaration

The authors declare that they have no conflicts of interest.

Author contributions

All authors contributed to the study's conception and design. A.T. and L.L.: material preparation, data collection and analysis; A.T. and L.L.: writing of the first draft of the manuscript; and all authors

commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2022.08.016>.

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