Age is the Main Determinant of COVID-19 Related in-Hospital Mortality with Minimal Impact of Pre-Existing Comorbidities: A Retrospective Cohort Study.

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Abstract

Background: Age and comorbidities increase COVID-19 related in-hospital mortality risk, but the extent by which comorbidities mediate the impact of age remains unknown.

Methods: In this multicenter retrospective cohort study of 45 Dutch hospitals, 4,806 proven COVID-19 patients hospitalized in Dutch hospitals (between February and July 2020) from the CAPACITY-COVID registry were included (age 69 [58-77] years, 64% men). The primary outcome was defined as a combination of in-hospital mortality or discharge with palliative care. Logistic regression analysis was performed to analyze the associations between sex, age, and comorbidities with in-hospital mortality. The effect of comorbidities on the relation of age with in-hospital mortality was evaluated using mediation analysis.

Results: In-hospital COVID-19 related mortality occurred in 1,108 (23%) patients, 836 (76%) were aged ≥ 70 years (70+). Both age 70+ and female sex were univariably associated with outcome (odds ratio [OR] 4.68, 95% confidence interval [4.02-5.45], OR 0.68 [0.59-0.79], respectively; both $p < 0.001$). All comorbidities were univariably associated with outcome ($p < 0.001$), and all but dyslipidemia remained significant after adjustment for age 70+ and sex. The impact of comorbidities was attenuated after age-spline adjustment, only leaving female sex, diabetes mellitus (DM), chronic kidney disease (CKD), and chronic pulmonary obstructive disease (COPD) significantly associated (female OR 0.65 [0.55-0.75], DM OR 1.47 [1.26-1.72], CKD OR 1.61 [1.32-1.97], COPD OR 1.30 [1.07-1.59]). Pre-existing comorbidities in older patients negligibly (<6% in all comorbidities) mediated the association between higher age and outcome.

Conclusions: Age is the main determinant of COVID-19 related in-hospital mortality, with negligible mediation effect of pre-existing comorbidities.

Trial registration: CAPACITY-COVID (NCT04325412).

Background

COVID-19 is a pandemic infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-19), which already accounts for over 4.1 million deaths worldwide (1). COVID-19 related mortality is particularly high in the elderly (2-6). Consequently, in the Netherlands, 90% of the deceased patients is 70 years or older (7).

Pre-existing comorbidities such as hypertension, diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and history of cardiac diseases are also associated with an increased risk of COVID-19 related (in-hospital) mortality (8-12). However, these comorbidities are also known to be more prevalent in the elderly (8, 9, 13). It remains unknown to which extent the higher in-hospital mortality rate is mediated by the higher prevalence of these comorbidities in the elderly.

The aim of this study was to explore to which extent existing comorbidities mediate the increased risk of COVID-19 related in-hospital mortality relative to age in a registry of 4,806 Dutch COVID-19 patients.

Methods

Study design and population

CAPACITY-COVID (NCT04325412) is an international patient registry established to investigate the role of cardiovascular disease in the COVID-19 pandemic (14, 15). The details of this registry have been outlined in detail previously (14). In short, adult patients (≥ 18 years) with (highly suspected) COVID-19 admitted to one of the participating hospitals were included in this registry (14). Forty-five Dutch hospitals contributed to the registry. For the current analysis, consecutive patients from all participating Dutch hospitals with proven COVID-19 infection based on at least one positive PCR for SARS-CoV-2 and/or a chest CT scan strongly suggestive for SARS-CoV-2 infection, hospitalized between January and July 2020 (first COVID-19 wave in the Netherlands), were included (16). In-hospital mortality was defined as a combination of in-hospital mortality or discharge with palliative care. The study was performed according to the Helsinki declaration and local ethics approval was obtained in all participating hospitals. Consent (when required by local ethical committees of all participating centers (METC, Medisch Ethische Toetsingscommissie) was obtained by either opt-in or opt-out approaches, following local regulations.

Statistical analyses

Variables are displayed as numbers (percentage), mean $\pm$ standard deviation (SD) or median and inter quartile ranges [IQR], as appropriate. Normality was assessed visually using Q-Q plots. Comparisons between groups were performed using chi-square tests for categorical data and for continuous variables by independent sample T-test or Mann Whitney-U test depending on normality of the distribution. Unadjusted binary logistic regression analysis was performed to analyze the associations between sex, age 60+, age 70+, a reported medical history of comorbidities (hypertension, DM, dyslipidemia, CKD, COPD, and a medical history of cardiac disease) and the comorbidity count (a sum of the presence of the before mentioned comorbidities categorized as 0 co-morbidities, 1-2 co-morbidities, and >2 co-morbidities) with in-hospital mortality. Definitions of pre-existing comorbidities as specified in the case report form are provided in the Supplemental Methods; **Additional file 1**). Subsequently, adjusted binary logistic regression analysis – with adjustment for age 70+ and sex – was performed to associate comorbidities and the comorbidity count with in-hospital mortality. Additionally, given the non-linear relationship between age and in-hospital mortality, age-restricted cubic spline adjusted logistic regression models were constructed for sex and the comorbidities(17).

R mediation package 4.5.0 was used to perform a mediation analysis (18). The mediation analysis tests whether a clinical variable (in this case age 70+) affects outcome through a mediator variable (in this case the co-morbidities) and to which extent. This divides the total effect of the model into a direct effect, called the average direct effect (ADE), and an indirect effect, called the average causal mediation effect (ACME). The proportion of ADE and ACME and the 95% confidence intervals (using 1000x bootstrapping)

were calculated and visualized for each comorbidity studied. Statistical analyses were conducted in R, and figures were made using the packages ggplot2, forest plot (19-21). Statistical significance was defined as a P value <0.05.

Results

Patient characteristics

In total, 4,806 patients fulfilled the inclusion criteria and were included in this study. Clinical characteristics stratified by age <70 and ≥ 70 years are outlined in Table 1. The median age was 69 [58-77] years, and approximately two-third were men (63%, N=3,051). All pre-existing comorbidities were more prevalent in the elderly (aged ≥ 70 years, all $p < 0.001$). Male patients more often had dyslipidemia (46% vs 39%), a history of cardiac disease (39% vs 30%, especially coronary artery disease and arrhythmias) and presence of two or more comorbidities (39% vs 33%, Additional file 2).

Table 1
Clinical characteristics of patients aged <70 and aged ≥70 (70+) years.

	<70 (N=2,504)	70+ (N=2,302)	Total (N=4,806)	P-value
Clinical Presentation				
Age, years	58 [51-64]	77 [73-82]	69 [58-77]	<0.001
Female	910 (36%)	845 (37%)	1755 (37%)	0.793
BMI, kg/m ²	27.9 [25.1-31.2]	26.7 [24.0-30.1]	27.3 [24.5-30.8]	< 0.001
Temperature, °C	37.9 ±1.1	37.7 ±1.1	37.8 ±1.1	< 0.001
Heart rate, bpm	91 [80-103]	86 [75-99]	89 [77-101]	< 0.001
Systolic BP, mmHg	133 ±21	136 ±24	135 ±23	< 0.001
Diastolic BP, mmHg	78 ±14	75 ±15	77 ±15	< 0.001
Breathing rate, rpm	22 [18–26]	21 [18–26]	22 [18–26]	0.620
Oxygen saturation, So2%	95 [92-97]	95 [92-96]	95 [92-97]	< 0.001
Medical History, n (%)				
Hypertension	1036 (41%)	1720 (75%)	2756 (57%)	< 0.001
Diabetes Mellitus	512 (20%)	701 (31%)	1213 (25%)	< 0.001
Dyslipidemia	764 (31%)	1303 (57%)	2067 (43%)	< 0.001
Chronic Kidney Disease	127 (5%)	392 (17%)	519 (11%)	< 0.001
COPD	206 (8%)	373 (16%)	579 (12%)	< 0.001
Cardiac disease	488 (20%)	1218 (53%)	1706 (36%)	< 0.001
Arrhyth./Conduc.	160 (6%)	612 (27%)	772 (16%)	< 0.001
Heart Failure	46 (2%)	228 (10%)	274 (6%)	< 0.001
Coronary Artery Disease	249 (10%)	574 (25%)	823 (17%)	< 0.001
Valvular Heart Disease	50 (2%)	201 (9%)	251 (5%)	< 0.001
Comorbidity count				< 0.001
0 comorbidities	1073 (43%)	250 (11%)	1323 (28%)	
1-2 comorbidities	896 (36%)	842 (37%)	1738 (36%)	

Arrhyth = arrhythmias; BMI = body mass index; BP = blood pressure; Conduc = conduction disorders; COPD = chronic obstructive pulmonary disease.

	<70 (N=2,504)	70+ (N=2,302)	Total (N=4,806)	P-value
>2 comorbidities	535 (21%)	1210 (53%)	1745 (36%)	
Arrhyth = arrhythmias; BMI = body mass index; BP = blood pressure; Conduc = conduction disorders; COPD = chronic obstructive pulmonary disease.				

Median duration of hospitalization stay till the study endpoint was 7 [4 - 15] days. In-hospital mortality (N=1,066) or palliative discharge (N=42) occurred in 1,108 (23%) patients, of which 836 (76%) were aged 70+ and 272 (24%) were aged <70 ($p<0.001$; Table 2). The observed and predicted association between age (splined adjusted) and in-hospital mortality are shown in Figure 1. Male sex and the individual comorbidities were more prevalent, and comorbidity count per patient was higher in the in-hospital mortality group ($p<0.001$, Table 2). In total, 1,312 (27%) patients were referred to the intensive care unit (ICU) during hospitalization, of which 446 were aged 70+ (34%) and 866 (66%) were aged <70 ($p<0.001$).

Table 2
Clinical characteristics of patients with and without event.

	No mortality or Palliative Care (N=3,698)	Mortality or Palliative Care (N=1,108)	Total (N=4,806)	P-value
Clinical Presentation				
Age, years	65 [56-74]	76 [70-82]	69 [58-77]	<0.001
Female	1423 (39%)	332 (30%)	1755 (37%)	<0.001
BMI, kgm ⁻²	27.5 [24.7-30.8]	26.8 [24.1-30.5]	27.3 [24.5-30.8]	0.010
Temperature, °C	37.8 ±1.1	37.8 ±1.1	37.8 ±1.1	0.454
Heart rate, bpm	89 [78-100]	90 [77-103]	89 [77-101]	0.087
systolic BP, mmHg	135 ±22	134 ±25	135 ±23	0.301
diastolic BP, mmHg	77 ±14	73 ±16	77 ±15	<0.001
Breathing rate, rpm	20 [17–25]	24 [19–28]	22 [18–26]	<0.001
Oxygen saturation, So2%	95 [93-97]	94 [91-96]	95 [92-97]	<0.001
Medical History				
Hypertension	1979 (54%)	777 (70%)	2756 (57%)	<0.001
Diabetes Mellitus	835 (23%)	378 (34%)	1213 (25%)	<0.001
Dyslipidemia	1479 (40%)	588 (53%)	2067 (43%)	<0.001
Chronic Kidney Disease	311 (8%)	208 (19%)	519 (11%)	<0.001
COPD	389 (11%)	190 (17%)	579 (12%)	<0.001
Cardiac disease	1170 (32%)	536 (48%)	1706 (36%)	<0.001
Arrhyth./Conduc.	509 (14%)	263 (24%)	772 (16%)	<0.001
Heart Failure	168 (5%)	106 (10%)	274 (6%)	<0.001
Coronary Artery Disease	540 (15%)	283 (26%)	823 (17%)	<0.001
Valvular Heart Disease	155 (4%)	96 (9%)	251 (5%)	<0.001

Arrhyth = arrhythmias; BMI = body mass index; BP = blood pressure; Conduc = conduction disorders; COPD = chronic obstructive pulmonary disease.

	No mortality or Palliative Care (N=3,698)	Mortality or Palliative Care (N=1,108)	Total (N=4,806)	P-value
Comorbidity count				<0.001
0 comorbidities	1164 (32%)	159 (14%)	1323 (28%)	
1-2 comorbidities	1354 (37%)	384 (35%)	1738 (36%)	
>2 comorbidities	1180 (32%)	565 (51%)	1745 (36%)	
Arrhyth = arrhythmias; BMI = body mass index; BP = blood pressure; Conduc = conduction disorders; COPD = chronic obstructive pulmonary disease.				

Univariable and multivariable associations and mediation effect of comorbidities and in-hospital mortality

Higher age (70+), male sex, and the individual comorbidities were all significantly associated with in-hospital mortality in univariable analysis (all $p < 0.001$; Figure 2A). Hypertension, DM, CKD, COPD and a history of cardiac disease remained significantly associated after adjustment for age 70+ and sex (hypertension odds ratio [OR] 1.29, 95% confidence interval [CI] 1.10-1.51, $p = 0.001$; DM OR 1.55 [1.33-1.81], $p < 0.001$; dyslipidemia OR 1.15 [1.00-1.34], $p = 0.053$; CKD OR 1.74 [1.43-2.13], $p < 0.001$; COPD OR 1.41 [1.15-1.72], $p < 0.001$; history of cardiac disease OR 1.22 [1.05-1.41], $p = 0.010$, Figure 2B). Additionally, given the non-linear relationship between age and in-hospital mortality, age-spline adjusted analysis was performed for the association of sex and all comorbidities with in-hospital mortality (Figure 2C). The effects were attenuated after age-spline adjustment, only leaving sex, DM, CKD, and COPD significantly associated with in-hospital mortality (female OR 0.65 [0.55-0.75], $p < 0.001$; DM OR 1.47 [1.26-1.72], $p < 0.001$; CKD OR 1.61 [1.32-1.97], $p < 0.001$; COPD OR 1.30 [1.07-1.59], $p = 0.010$, Figure 2C).

Uni- and multivariable (spline-adjusted) analysis of comorbidity count revealed a significant, univariable association with in-hospital mortality ($p < 0.001$; **Additional file 3**), which remained significant in the multivariable model with an attenuated effect. In the age-spline multivariable adjusted analysis, the association of the comorbidity count was not significant for a comorbidity count of 1-2 (OR 1.15 [0.9-1.4]) and attenuated for >2 comorbidity count (OR 1.4 [1.1-1.7]).

All individual comorbidities significantly mediated the association between age 70+ and in-hospital mortality (ACME; Figure 3). However, the proportion of this effect was below 6% for all comorbidities, and thereby the increased risk of in-hospital mortality in the elderly was explained mainly by the direct effect (ADE; Figure 3) of age 70+ within this analysis (Figure 3). Additionally, a mediation analysis was performed to quantify the mediation effect of a comorbidity count >2 on the association between age and in-hospital mortality. Although the proportion of this effect was higher than the comorbidities separately, it remained minimal (8%, $p < 0.001$, **Additional file 4**).

Age-spline plots showed a steep increase in the predicted risk of in-hospital mortality from 60 years and higher (Figure 1; stratified by sex and the individual comorbidities is shown in **Additional file 5**). Correspondingly, in-hospital mortality rates were significantly lower in patients <60 years when compared to the older patients (age<60 years, 6% (N=87) vs 30% (N=1,021), $p<0.001$; **Additional file 6**). All comorbidities also occurred less frequently present in this younger patient group (**Additional file 6**). None of the co-morbidities, except for history of cardiac disease, were significantly associated with in-hospital mortality in univariable analysis in patients <60 years (hypertension OR 1.31 [0.83-2.06], $p=0.240$; DM OR 1.38 [0.82-2.35], $p=0.228$; dyslipidemia OR 1.26 [0.76-2.10], $p=0.367$; CKD OR 2.33 [0.96-5.66], $p=0.062$; COPD OR 0.62 [0.19-2.00], $p=0.421$; history of cardiac disease OR 1.90 [1.10-3.27], $p=0.021$, **Additional file 7**). In the total patient population, age 60+ was significantly associated with in-hospital mortality (OR 6.35[5.05-7.98], $p<0.001$; **Additional file 7A**).

Discussion

This study reveals that higher age is the main determinant of COVID-19 related in-hospital mortality in the Netherlands. While pre-existing comorbidities (including hypertension, DM, dyslipidemia, CKD, COPD, and cardiac diseases) are more prevalent in the elderly, their contributing effect to COVID-19 related in-hospital mortality is minimal.

Over the last months, studies revealed multiple risk factors independently associated with COVID-19 related (in-hospital) mortality, including higher age, pre-existing co-morbidities, and male sex, which is in line with current findings (9, 10, 22-25). A recent study of 2,273 COVID-19 hospitalized Dutch patients showed that a mortality prediction model using ten clinical features including age, number of home medications, admission blood values urea nitrogen/LDH/albumin, oxygen saturation, blood gas pH and history of chronic cardiac disease, improved discrimination over age-based decision rules only (26). Nonetheless, no data regarding to which extent age and cardiovascular comorbidities contributed to the mortality risks were provided. We show that the contributing effect of pre-existing comorbidities was negligible relative to age.

In the Netherlands, the vast majority (90%) of deceased patients due to COVID-19 is over 70 years of age. The prevalence of comorbidities among hospitalized COVID-19 patients is particularly high, especially in the elderly (7, 8). The current study included 4,806 patients from 45 Dutch - both academic and local - hospitals, accounting for around 40% of all COVID-19 related hospitalizations between January 2020 and July 2020 in the Netherlands (7). Therefore, this population adequately represents the total hospitalized population during the first COVID-19 pandemic wave in the Netherlands. The higher prevalence of male COVID patients observed in the current registry and the increased mortality risk of males is in line with previous findings and likely due to a less effective viral control of the immune system in males (24, 27), together with the higher comorbidity rates in males compared to females (24, 28). The observed association of history of cardiac disease and in-hospital mortality in the young has been studied and discussed before by current consortium, which is mainly driven by the presence of coronary artery disease and severe (NYHA $\geq$ 3) heart failure (29).

It is important to notice that during the first wave of COVID-19, the median age of people referred to the ICU department decreased when the total number of patients referred to the ICU department increased (30). Younger (<70+) patients were more likely to be referred to the ICU department due to bed shortages. The lower percentage of mortality (75%) of patients 70+ in the current study is lower than the overall mortality rate in this age group in the Netherlands in 2020 (90%) (31). This likely results from fewer referrals of elderly patients to the hospitals (possibly even independent of the presence of comorbidities) due to the overwhelming stress on hospitals during the first COVID-19 wave. However, even in the group aged <60 years - in whom likely no or limited referral “restrictions” were present - the effect of pre-existing comorbidities on mortality was limited in the current study, indicating that age as such is likely the main driver of in-hospital mortality.

Our study revealed that pre-existing co-morbidities, highly prevalent in the elderly, contributed minimally to the larger in-hospital mortality rates when compared to age. Moreover, the contribution of the comorbidities to outcome in patients aged <60 years was limited to a history of cardiac disease without any significant association for DM, CKD, and COPD. As a result, the present study stresses the need for primary preventive efforts to protect the elderly (males) from an infection with SARS-CoV-19.

Limitations

Data concerning the patients' frailty and the reasons for not referring patients to the hospital or the ICU, were not collected within this registry. To which extent the lower hospital and ICU referral rate of the elderly and frailty contributed to the in-hospital mortality rate could therefore not be assessed and requires further research. Such research could help to understand better the association of higher age and in-hospital mortality beyond the comorbidities and might guide decision making on treatment, counselling and admission to high care facilities in the future.

Conclusion

Age is the main determinant of COVID-19 related in-hospital mortality, which is negligibly mediated by pre-existing comorbidities in the Netherlands.

Abbreviations

Average direct effect = ADE

Average causal mediation effect = ACME

Chronic kidney disease = CKD

Chronic obstructive pulmonary disease = COPD

Coronavirus 2 = SARS-CoV-19

Diabetes mellitus = DM

Intensive care unit = ICU

Declarations

Ethics approval and consent to participate

The study was performed according to the Helsinki declaration and local ethics approval was obtained in all participating hospitals. Consent (when required by local ethical committees) was obtained by either opt-in or opt-out approaches, following local regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

MH, AR and ML were in the lead for data collection. MH, AR and JV were in the lead for the conception and design of the study, the analysis and interpretation of the data. MvS and PW helped with the analysis and interpretation of data. MH and AR were also in the lead for drafting the article. JV, ML, MvS, BvH, RT, MJ, RtB, MHazebroek, IvdH, FA, FM and SH provided additive contribution to the conception, design and

interpretation of the data and critically revised the draft. All authors fulfil all three of the ICMJE guidelines for authorship: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

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CAPACITY-COVID collaborative consortium

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Figures

Figure 1

Predicted and observed in-hospital mortality (univariable age-restricted cubic spline adjusted). % Mortality predicted: The white line represents the predicted mortality rates at different ages, accompanied by 95% confidence intervals in blue. # Observed patients: The grey bars represent the number of patients observed within the different age categories. The light grey bars are the patients that were discharged without palliative care. The dark grey bars are the patients in which in-hospital mortality (or palliative discharge) occurred.

Figure 2

Associations of age and comorbidities with in-hospital mortality. A) Univariable association of age 70+, sex, and comorbidities with in-hospital mortality; B) Association of all comorbidities after adjustment for age 70+ and sex; C) Association of sex and all comorbidities after age spline adjustment. COPD= chronic obstructive pulmonary disease.

Figure 3

Mediation analysis with age ≥ 70 years as independent predictor, the individual comorbidities as mediator and in-hospital mortality as outcome. All comorbidities partly mediated the effect of age on in-hospital mortality (all p-values < 0.001). The mediation effect was 5% (95% CI 2-9%) for hypertension, 3% (95% CI 2-4%) for diabetes mellitus, 3% (95% CI 0.4-6%) for dyslipidemia, 5% (95% CI 3-7%) for chronic kidney disease, 2% (95% CI 1-3%) for COPD, and 5% (95% CI 2-9%) for history of cardiac disease. COPD= chronic obstructive pulmonary disease.

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