Tidsskriftet Tidsskrift for Den norske legeforening

Does a history of cardiovascular disease or cancer affect mortality after SARS-CoV-2 infection?

ORIGINAL ARTICLE

RUNE KVÅLE

E-mail: rune.kvale@fhi.no
Department of Health Registry Research and Development
Norwegian Institute of Public Health, Bergen
and
Department of Oncology and Medical Physics,
Haukeland University Hospital
He has contributed to the concept and design, to data analysis and interpretation, to the literature search and to drafting and revision of the manuscript, and has approved the submitted version.
Rune Kvåle, PhD, senior consultant and specialist in oncology.
The author has completed the ICMJE form and declares no conflicts of interest.

KAARE HARALD BØNAA

Department of Cardiology,
St Olav's Hospital, Trondheim University Hospital
and
Department of Circulation and Medical Imaging,
NTNU
He has contributed with ideas for analyses, and has participated in data interpretation and in the drafting and revision of the manuscript, and has approved the submitted version.
Professor Kaare Harald Bønaa, PhD, specialist in internal medicine and in cardiology. He is a consultant in interventional cardiology and has research experience in epidemiology and randomised multicentre trials.
The author has completed the ICMJE form and declares no conflicts of interest.

RACHEL FORSTER

Department of Health Registry Research and Development,
Norwegian Institute of Public Health, Bergen
She has contributed to the study design and literature search, and to the drafting and revision of the manuscript, and has approved the submitted version.
Rachel Forster, PhD, specialises in the epidemiology of chronic diseases, including cardiovascular disease.
The author has completed the ICMJE form and declares no conflicts of interest.

KIRSTEN GRAVNINGEN

Department of Infection Control and Preparedness, Norwegian Institute of Public Health, Oslo
She has contributed to the interpretation of results, to the literature search, to the drafting and revision of the manuscript, and has approved the submitted version.
Kirsten Gravningen, PhD, senior consultant and specialist in medical microbiology.
The author has completed the ICMJE form and declares no conflicts of interest.

PÉTUR BENEDIKT JÚLÍUSSON

Department of Health Registry Research and Development,
Norwegian Institute of Public Health, Bergen
and
Children and Youth Clinic,
Haukeland University Hospital and
Department of Clinical Science,
University of Bergen
He has contributed to the interpretation of results, to the drafting and revision of the manuscript, and has approved the submitted version.
Professor Pétur Benedikt Júlíusson, PhD, senior consultant and head of department. He is a specialist in paediatrics.
The author has completed the ICMJE form and declares no conflicts of interest.

TOR ÅGE MYKLEBUST

Registry Department,
Cancer Registry of Norway, Oslo
and
Department of Research and Innovation, Møre og Romsdal Hospital Trust, Ålesund

He has contributed to the study design, data analysis and interpretation, to the drafting and revision of the manuscript, and has approved the submitted version.
Tor Åge Myklebust, PhD, researcher and statistician. He conducts registry-based research, with a primary focus on cancer epidemiology and survival analyses.
The author has completed the ICMJE form and declares no conflicts of interest.

BACKGROUND
Cardiovascular disease and cancer have been described as possible risk factors for COVID-19 mortality. The purpose of this study was to investigate whether a history of cardiovascular disease or cancer affects the risk of dying after a COVID-19 diagnosis in Norway.

MATERIAL AND METHOD
Data were compiled from the Norwegian Surveillance System for Communicable Diseases, the Norwegian Cardiovascular Disease Registry and the Cancer Registry of Norway. Univariable and multivariable regression models were used to calculate both relative and absolute risk.

RESULTS
In the first half of 2020, 8 809 people tested positive for SARS-CoV-2 and 260 COVID-19-associated deaths were registered. Increasing age, male sex (relative risk (RR): 1.5; confidence interval (CI): 1.2–2.0), prior stroke (RR: 1.5; CI: 1.0–2.1) and cancer with distant metastasis at the time of diagnosis (RR: 3.0; CI: 1.1–8.2) were independent risk factors for death after a diagnosis of COVID-19. After adjusting for age and sex, myocardial infarction, atrial fibrillation, heart failure, hypertension, and non-metastatic cancer were no longer statistically significant risk factors for death.

INTERPRETATION
The leading risk factor for death among individuals who tested positive for SARS-CoV-2 was age. Male sex, and a previous diagnosis of stroke or cancer with distant metastasis were also associated with an increased risk of death after a COVID-19 diagnosis.

Main findings

In addition to increasing age and male sex, a history of stroke or cancer with distant metastasis at the time of diagnosis is associated with an increased risk of death after a COVID-19 diagnosis.

Cardiovascular disease and cancer have been described as possible risk factors for serious illness and death as a result of COVID-19 (1, 2). In addition to comorbidities, previously published studies have shown that increasing age and male sex are also associated with a greater mortality risk (3–6). Many studies have examined the impact of comorbidity on risk of death by studying hospitalised patients or patients followed up after having been identified in general practice. These studies thus include selected patient groups and have been performed in countries with health registries of varying quality. With the exception of a recently published study from Denmark (6), few other studies have used population-based data to investigate risk factors for mortality.

An overview of the case fatality rate in different age groups and in association with different risk factors among individuals who died after testing positive for SARS-CoV-2 in Norway, was recently published in the *Journal of the Norwegian Medical Association* (7). However, this previously published study did not examine the impact of prior disease history on risk of death. Our aim was therefore to use national health registry data to investigate whether a history of cardiovascular disease or cancer affected the risk of dying after testing positive for SARS-CoV-2 in the first half of 2020.

Material and method

Data sources

Data were obtained from the Norwegian Surveillance System for Communicable Diseases (MSIS), the Norwegian Cardiovascular Disease Registry and the Cancer Registry of Norway. Information from MSIS was linked to data from the Norwegian Cardiovascular Disease Registry and the Cancer Registry of Norway with the aid of a common project-specific serial number for the three registries. Only group-level data were retrieved and analysed.

From MSIS, we identified all individuals who had tested positive for SARS-CoV-2 via a polymerase chain reaction test during the first half of 2020 (extraction performed 30 June 2020). We then received information about all COVID-19-associated deaths within this group (updated 4 December 2020).

Deaths after a diagnosis of COVID-19 that have been reported to MSIS or to the Norwegian Cause of Death Registry, as well as all deaths within the first 30 days after a positive SARS-CoV-2 test, are registered as being COVID-19-associated. COVID-19-associated deaths therefore include those in which the person dies *of* COVID-19 as well as some cases where a person dies *with* COVID-19. However, a review of data in the Cause of Death Registry found COVID-19 to be the underlying cause of death for more than 91 % of the COVID-19-associated deaths reported (8).

The Norwegian Cardiovascular Disease Registry consists of a core registry and eight associated quality registries. The core registry contains information retrieved from the Norwegian Patient Registry on outpatient consultations and hospital stays for patients with cardiovascular disease, information on deaths

from the Norwegian Cause of Death Registry, as well as administrative data from the Norwegian Population Register. Prior cardiovascular disease (stroke, myocardial infarction, atrial fibrillation, heart failure and hypertension listed as a principal or secondary diagnosis during a hospital stay) and information on other comorbidities among individuals who tested positive were retrieved from the core registry for the period 2012–19 (Table 1). The core registry contains information about other diseases only if they were noted during the hospital stay/episode for which there was a cardiovascular diagnosis, therefore information about conditions other than cardiovascular disease is incomplete.

Table 1

Data sources and disease definitions used in the study.

Data sources (time period)	Disease	Inclusion criteria
Norwegian Surveillance System for Communicable Diseases (1st and 2nd quarters 2020)	COVID-19	Positive test for SARS-CoV-2
Cancer Registry of Norway (2010–19)	Cancer	All cancers except non-melanoma skin cancer
Norwegian Cardiovascular Disease Registry[1] (2012–19)	**Cardiovascular disease**	
	Acute stroke	I61, I63, I64
	Acute myocardial infarction	I21–I22
	Atrial fibrillation	I48
	Heart failure	I11.0, I13.0, I13.2, I50.0, I50.1, I50.9
	Hypertension	I10–I15
	Other comorbidities2	
	Asthma	J45, J46
	Dementia3	F00–F03, G30, G31.0 G31.2, G31.8
	Diabetes type 1	E10
	Diabetes type 2	E11
	Chronic obstructive pulmonary disease (COPD)	J43, J44
	Obesity4	E66
	Chronic kidney disease	N18.3–N18.5

[1]All principal or secondary diagnoses (ICD-10 codes)

[2]Diagnoses registered in addition to a cardiovascular diagnosis in the Norwegian Cardiovascular Disease Registry1

[3]The Norwegian Cardiovascular Disease Registry contains all individuals with a registered diagnosis of vascular dementia (F01)

[4]Body mass index ≥ 30 kg/m^2

From the Cancer Registry, we received data on all cancers (except non-melanoma skin cancer) with information on stage (localised or regional disease, distant metastasis) for the period 2010–19. For patients with cancer, we also had access to information about cardiovascular disease and any other comorbidities from the Norwegian Cardiovascular Disease Registry.

Statistical methods

Unadjusted and adjusted relative risks were estimated for the age groups < 60, 60–69, 70–79, 80–84, 85–89 and ≥ 90, as well as for the various diseases included, using univariable and multivariable Poisson regression analyses. All analyses were performed in STATA (version 15.0). In the multivariable analyses, estimates from two different regression models were used.

In model 1 the data were adjusted for age and sex; the model included age group, sex, cardiovascular disease and cancer. Model 2 adjusted for age, sex, cardiovascular disease, cancer and any information available on other comorbidities (asthma, dementia, diabetes, obesity, COPD, chronic kidney disease). In this model, we also estimated relative risks after excluding individuals over the age of 84, in whom the probability of misclassifying the cause of death is higher owing to an increased likelihood of multimorbidity and greater all-cause mortality.

To supplement the estimated relative risks with absolute risks, we calculated probability of death based on a multivariable logistic regression analysis with the same covariates as in model 2.

Ethics

Statistical analysis was tailored to accommodate the regulations applicable to the registries. We had no access to national identity numbers or other personally identifiable information, and were supplied only with data aggregated into predefined groups.

Results

During the first half of 2020, 8 809 people in Norway were confirmed to have been infected with SARS-CoV-2, and within this group, there were 260 COVID-19-associated deaths. In all, 7 705 (87 %) of the positive tests and 34 (13 %) of the deaths were in people below the age of 70. Of those who tested positive for SARS-CoV-2 in this period, the percentage that died (case fatality rate) was 3.0 %; this varied from 0.2 % for individuals under the age of 60 to 57.6 % for

those aged 90 and above (Table 2). Hypertension was the most common previously registered cardiovascular disease, both among those who tested positive for SARS-CoV-2 (645 (7.3 %)) and among those who died (95 (36.5 %)). A total of 372 (4.2 %) individuals who tested positive for SARS-CoV-2, and 36 (13.9 %) who died, had a previous diagnosis of cancer.

Table 2

Patient characteristics and case fatality rate (percentage of deaths among those diagnosed) for individuals who tested positive for SARS-CoV-2 in the first half of 2020. Results are numbers (%) unless otherwise specified.

	Patients with positive tests	Deaths	Case fatality rate
Total	8 809 (100)	260 (100)	3.0
Age			
< 60 years	6 787 (77.0)	12 (4.6)	0.2
60–69 years	918 (10.4)	22 (8.5)	2.4
70–79 years	603 (6.8)	59 (22.7)	9.8
80–84 years	221 (2.5)	43 (16.5)	19.5
85–89 years	155 (1.8)	52 (20.0)	33.6
≥ 90 years	125 (1.4)	72 (27.7)	57.6
Sex			
Women	4 444 (50.5)	121 (46.5)	2.7
Men	4 365 (49.5)	139 (53.5)	3.2
Cardiovascular disease			
Prior stroke	125 (1.4)	34 (13.1)	27.2
Prior myocardial infarction	109 (1.2)	16 (6.2)	14.7
Atrial fibrillation	300 (3.4)	59 (22.7)	19.7
Heart failure	155 (1.8)	29 (11.2)	18.7
Hypertension	645 (7.3)	95 (36.5)	14.7
Cancer			
Total	372 (4.2)	36 (13.9)	9.7
Localised/regional disease	284 (3.2)	25 (9.6)	8.8
Metastatic1 disease	18 (0.2)	4 (1.5)	22.2
Stage unknown	70 (0.8)	7 (2.7)	10.0
Other comorbidities2			
Asthma	40 (0.5)	5 (1.9)	12.5
Dementia	73 (0.8)	38 (14.6)	52.1

	Patients with positive tests	Deaths	Case fatality rate
Diabetes type I	11 (0.1)	2 (0.8)	18.2
Diabetes type II	155 (1.8)	33 (12.7)	21.3
Obesity	39 (0.4)	3 (1.2)	7.7
COPD	55 (0.6)	14 (5.4)	25.5
Chronic kidney disease	57 (0.7)	18 (6.9)	31.6
One or more of the above	1 214 (13.8)	162 (62.3)	13.3

[1]At the time of diagnosis

[2]Diagnoses registered in addition to a cardiovascular diagnosis in the Norwegian Cardiovascular Disease Registry

A previous diagnosis of cancer was associated with a significantly increased risk of death in the unadjusted analyses, as were all of the cardiovascular diagnoses examined. Relative risk ranged from 3.3 for non-metastatic cancer to 10.5 for stroke (Table 3, univariable analyses). After adjusting for age, sex, and other comorbidities, patients with a history of stroke (RR: 1.5; CI: 1.0–2.1) or cancer with metastasis at the time of diagnosis (RR: 3.0; CI: 1.1–8.2) had a significantly increased risk of death.

Table 3

Risk of death following a COVID-19 diagnosis in the first half of 2020. Univariable and multivariable analyses (RR = relative risk, CI = confidence interval).

	Univariable analyses	Multivariable analyses		
		Model 1[2]	Model 2[3]	
			All age groups	Age < 85 years
Age	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)
< 60 years	Ref.	Ref.	Ref.	Ref.
60–69 years	13.6 (6.7–27.4)	13.3 (6.6–26.9)	13.1 (6.5–26.6)	12.5 (6.2–25.3)
70–79 years	55.3 (29.7–102.9)	54.5 (29.3–101.4)	51.0 (27.2–95.7)	45.1 (23.7–85.6)
80–84 years	110.0 (58.0–208.7)	114.3 (60.2–216.8)	105.4 (54.9–202.1)	81.3 (41.1–160.8)
85–90 years	189.7 (101.3–355.4)	193.4 (103.2–362.2)	178.4 (93.8–339.5)	–
≥ 90 years	325.8 (176.8–600.2)	345.8 (187.4–637.8)	306.4 (163.0–575.8)	–

	Univariable analyses	Multivariable analyses		
		Model 1[2]	Model 2[3]	
			All age groups	Age < 85 years
Male (ref. women)	1.2 (0.9–1.5)	1.5 (1.2–1.9)	1.5 (1.2–2.0)	1.7 (1.2–2.4)
Cardiovascular disease[1]				
Stroke	10.5 (7.3–15.0)	1.5 (1.1–2.2)	1.5 (1.0–2.1)	1.8 (0.9–3.3)
Myocardial infarction	5.2 (3.2–8.7)	0.9 (0.6–1.6)	0.8 (0.4–1.3)	0.7 (0.3–1.6)
Atrial fibrillation	8.3 (6.2–11.1)	1.3 (0.9–1.7)	1.2 (0.8–1.6)	1.2 (0.7–2.0)
Heart failure	7.0 (4.8–10.3)	1.2 (0.8–1.8)	0.9 (0.6–1.4)	0.9 (0.5–1.8)
Hypertension	7.3 (5.7–9.4)	1.2 (0.9–1.5)	0.9 (0.7–1.2)	0.7 (0.4–1.1)
Cancer[1]				
Localised/regional disease	3.3 (2.2–5.0)	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.7 (0.4–1.4)
Metastatic[1] disease	8.4 (3.1–22.5)	2.6 (1.0–7.1)	3.0 (1.1–8.2)	3.0 (0.9–9.8)
Stage unknown	3.8 (1.8–8.0)	1.1 (0.5–2.3)	1.1 (0.5–2.3)	1.6 (0.7–3.8)

[1]Reference: Individuals without the disease in question

[2]Model 1: Adjusted for age and sex

[3]Model 2: Adjusted for age, sex, cardiovascular disease, cancer, and any information on other comorbidities (asthma, dementia, diabetes, obesity, COPD, chronic kidney disease)

Male sex (RR: 1.5; CI: 1.2–2.0) was also associated with a significantly increased risk of death (Table 3, model 2). Atrial fibrillation was associated with a higher risk after adjusting for age, sex and other comorbidities, but the association was not statistically significant. Our analyses also revealed a significantly increased risk of death when dementia, chronic kidney disease and type 2 diabetes mellitus were registered in addition to cardiovascular disease (data not shown).

Excluding individuals over the age of 84 led to somewhat higher risk estimates for sex (RR: 1.7; CI: 1.2–2.4) and stroke (RR: 1.8; CI: 0.9–3.3), and somewhat lower estimates for the age groups 60–69, 70–79 and 80–84 years (Table 3, model 2 < 85 years). Including the other disease groups in the 'I' chapter of ICD-10 (diseases of the circulatory system) did not affect the results (data not shown).

The relative risk of death for those in the age groups 60–69, 70–79, 80–84, 85–89 and ≥ 90 was approximately 13, 50, 100, 180 and 300 times greater, respectively, than that of the reference group (positive test and age < 60 years) in analyses adjusted for sex, cardiovascular disease, cancer and other comorbidities (Table 3, model 2). The estimated absolute risk of death for individuals in whom no underlying conditions had been registered, increased from 0.17 % for those aged under 60, to 53.7 % for the group aged 90 and above (Table 4).

Table 4

Estimated absolute risk (%) of death after a COVID-19 diagnosis in the first half of 2020 for individuals with a history of stroke or cancer that was metastatic at diagnosis, versus individuals with no known history of cardiovascular disease, cancer or any other comorbidity examined in this study (women, men and both sexes combined).

	Both sexes[1]	Women/ Men[1]	Stroke[2]		Metastatic cancer[2]	
			Both sexes	Women/ Men	Both sexes	Women/ Men
< 60 years	0.17	0.12/0.22	0.31	0.22/0.40	0.78	0.56/1.00
60–69 years	2.1	1.5/2.7	3.8	2.8/4.9	8.9	6.6/11.3
70–79 years	7.8	5.8/10.0	13.3	10.0 /16.7	27.5	21.7/33.3
80–84 years	16.1	12.2/20.1	25.7	20.2/31.3	45.9	38.7/53.2
85–89 years	27.8	22.0/33.7	40.9	33.9/48.0	62.8	56.1/69.7
≥ 90 years	53.7	46.5/61.0	67.6	61.2/74.0	83.6	79.7/87.6
Total	2.5	2.0/3.1	3.8	3.1/4.6	6.8	5.7/8.0

[1]Assumes that none of the diseases included in the study are present (based on a multivariable logistic regression model with all covariates)

[2]Assumes that none of the other diseases included in the study are present (based on a multivariable logistic regression model with all covariates. For some groups the estimates are based on a limited number of cases and have therefore been extrapolated from a model)

For individuals with a known history of stroke, the estimated absolute risk of death was increased by 0.14 % in those aged under 60 and by 13.9 % in those aged 90 and above, relative to individuals with no such history. The estimated absolute risk of death for persons with metastatic cancer at diagnosis was increased by 0.61 % for those aged under 60 and by 29.9 % for those aged 90

and above, compared to those with non-metastatic disease. The absolute risk of death was 0.10 % higher for men versus women among those aged under 60, and 14.5 % higher for men versus women in those aged 90 and above (Table 4).

Discussion

In this linked registry analysis using data from the Norwegian Surveillance System for Communicable Diseases, the Norwegian Cardiovascular Disease Registry and the Cancer Registry of Norway on 8 809 individuals who tested positive for SARS-CoV-2, we found that increasing age, male sex, and a history of stroke or of cancer with distant metastasis at the time of diagnosis were all associated with an increased risk of death following a COVID-19 diagnosis. Individuals who died after a COVID-19 diagnosis were more likely than those who survived to have had a previous diagnosis of myocardial infarction, atrial fibrillation, heart failure, hypertension or non-metastatic cancer. However, after adjusting for age and sex in multivariable analyses, we found that these diseases were no longer statistically significant risk factors for mortality.

For individuals who had been hospitalised for stroke in the period 2012–19, the risk of dying after infection with SARS-CoV-2 was increased by 50 % after adjusting for age, sex and comorbidities. Our results confirm findings from several previous studies that have suggested an increased risk of death in patients with cerebrovascular disease (5, 9). A previous stroke may result in poorer functional status and a reduced likelihood of benefiting from intensive care. There has also been discussion as to whether individuals with a history of stroke may be at increased risk of vascular events as a result of COVID-19-induced coagulopathies, which may lead to serious complications and an increased risk of death (9).

With the exception of stroke, none of the other cardiovascular diseases included in our study were associated with a statistically significant increase in mortality risk. The results of previous studies have been somewhat mixed in terms of the risk of death in individuals with underlying cardiovascular disease (10). Our findings are in line with results from Denmark (6), where the risk of death was found to be lower in individuals with ischaemic heart disease (OR 0.7 (CI: 0.5–0.9)) or hypertension (OR 0.6 (CI: 0.5–0.8)) after adjusting for age, sex and the number of comorbidities.

As in our study, the Danish study found no significant increase in the risk of death in association with atrial fibrillation or heart failure, whereas a study from England found an increased risk in association with heart failure or ischaemic heart disease in both sexes, and in association with atrial fibrillation in women only (5). In our study, we were unable to detect sex differences within diagnostic subgroups as there were too few deaths in each group following stratification, and therefore high levels of uncertainty. The number of deaths in our study is relatively low, and thus we cannot exclude the possibility that the other cardiovascular diseases besides stroke are independent risk factors for death after COVID-19 (cf. wide confidence intervals, Table 3).

A recently published review on clinical characteristics of cancer patients with COVID-19 found that, after adjusting for age and other comorbidities, cancer was not an independent risk factor for death (11). This is consistent with findings from our study for all cancer stages combined (data not shown). However, we found a significantly increased risk of death in patients with cancer with distant metastasis at the time of diagnosis. Patients with metastatic disease at diagnosis have a poorer prognosis and functional status than patients without metastasis, and often receive more intensive chemotherapy than other cancer patients. This group may therefore be more likely to experience a severe COVID-19 disease course. Chemotherapy has previously been identified as a possible risk factor for death from COVID-19 (5). In our study, we did not have information about cancer type or the treatment that patients had received, and therefore could not draw any specific conclusions about which cancer patients had an increased risk of death after COVID-19. It would also be beneficial to repeat our analyses with a larger dataset, owing to the small size of the group of individuals with metastatic cancer at diagnosis. Any misclassification of stage or cause of death for these patients could potentially affect the results.

After adjusting for other risk factors for which information was available, our results show that the risk of death was significantly increased in those aged 60 and above compared to those in the age groups under 60. The estimated absolute risk of death for a person without any of the comorbidities included in our study was 0.17 % for those under 60, 2.1 % for those aged 60–69 years and 7.8 % for those aged 70–79 years. The results of our study are consistent with those from Denmark, where the case fatality rate in persons without comorbidities was less than 5 % for those aged under 80 (6).

We found that men had a 50 % (all age groups) to 70 % (< 85 years) increased risk of death relative to women after adjusting for age and other risk factors. This is consistent with the results of many previous studies (3, 4, 12, 13), and some have argued that this phenomenon may, in part, reflect sex differences in the immune response (14). Another possibility that has been considered is that the sex differences may reflect greater alcohol consumption among men than women, but studies that have attempted to correct for this difference have not found alcohol to be a confounding factor (13).

In Norway, the proportion of deaths among those diagnosed (case fatality rate) was 3.0 % in total over the study period. Reported case fatality rates vary greatly between different countries and patient populations. In studies from China, Denmark and Italy, the reported case fatality rates were 2.3 %, 5.2 % and 7.2 %, respectively (6, 15). The main reason for Italy's very high case fatality rate is the high proportion of elderly persons among those who tested positive. As well as differences related to treatment, differences in testing strategies and in how COVID-19-associated deaths are defined may also lead to differences between countries. The case fatality rate can also change significantly over time as a result of changes in testing practices, age composition and treatment. In Norway, low testing capacity in the first wave of the pandemic meant that many of those who were ill were not tested. From August onwards, the amount of testing increased significantly, and a larger proportion of infections were identified. In addition, the average age of those infected dropped. As a result of this, and probably also improvements in

treatment, the case fatality rate in Norway has decreased. A rough estimate based on the total number of infected individuals as per 8 November 2020 (25 520) and the number of deaths as per 8 December 2020 (361), yields a case fatality rate for Norway for the entire period from February to December of approximately 1.4 %.

A key strength of our study is that we have examined the risk of death for individuals who tested positive for SARS-CoV-2 across an entire national population. Most studies, with the exception of that by Reilev *et al.* in Denmark (6), have examined risk factors in selected patient groups and therefore cannot draw any firm conclusions about the general population risk of death from COVID-19 among those with underlying diseases (16). The individuals with positive test results in our study may also be a somewhat selected group, as the criteria used for testing during the study period may have meant that those with underlying diseases were more likely to be tested than those without such conditions. However, the results of a previous analysis on the same patient dataset in Norway found that there were small differences in the incidence of underlying diseases between people who had tested positive for COVID-19 and the general population (17). Future studies comparing the total mortality in a group with positive tests to that in a control group with negative tests will be needed to obtain further information on the impact of various risk factors on COVID-19 mortality.

Our data on comorbidities other than cardiovascular disease and cancer are incomplete. The Norwegian Cardiovascular Disease Registry contains information only on diseases noted during the same hospital stay/episode as the cardiovascular diagnosis. It is reasonable to assume that those in hospital with multiple diagnoses and a comorbid cardiovascular diagnosis are the most severe cases. Knowing this allows us to adjust for patient morbidity in order to obtain better estimates for the other factors in the analysis models. The impact of comorbidities other than cardiovascular disease and cancer on mortality after a diagnosis of COVID-19 in Norway should be investigated in future studies with more comprehensive information about other diseases.

The leading risk factor for death among individuals who tested positive for SARS-CoV-2 in the first half of 2020 was age. Male sex, a history of stroke, and cancer with distant metastasis were also associated with an increased risk of death after a diagnosis of COVID-19. Further studies are needed to determine the impact of cancer type on mortality after a diagnosis of COVID-19 in Norway.

This article has been peer-reviewed.

LITERATURE

1. Kuderer NM, Choueiri TK, Shah DP et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020; 395: 1907–18. [PubMed][CrossRef]

2. Petrilli CM, Jones SA, Yang J et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease

2019 in New York City: prospective cohort study. BMJ 2020; 369: m1966. [PubMed][CrossRef]

3. Williamson EJ, Walker AJ, Bhaskaran K et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020; 584: 430–6. [PubMed][CrossRef]

4. Barron E, Bakhai C, Kar P et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020; 8: 813–22. [PubMed][CrossRef]

5. Clift AK, Coupland CAC, Keogh RH et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 2020; 371: m3731. [PubMed][CrossRef]

6. Reilev M, Kristensen KB, Pottegård A et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol 2020; 49: 1468–81. [PubMed][CrossRef]

7. Gulseth HL, Helland E, Johansen KI et al. Deaths after confirmed SARS-CoV-2 in Norway. Tidsskr Nor Legeforen 2020; 140. doi: 10.4045/tidsskr.20.0693. [PubMed][CrossRef]

8. Folkehelseinstituttet. Foreløpige tall for covid-19-assosierte dødsfall i Dødsårsaksregisteret. https://www.fhi.no/hn/helseregistre-og-registre/dodsarsaksregisteret/forelopige-tall-for-covid-19-assosierte-dodsfall-i-dodsarsaksregisteret/ Accessed 16.11.2020.

9. Tehrani S, Killander A, Åstrand P et al. Risk factors for death in adult COVID-19 patients: Frailty predicts fatal outcome in older patients. Int J Infect Dis 2021; 102: 415–21. [PubMed][CrossRef]

10. Himmels JPW, Borge TC, Brurberg KG et al. COVID-19 and risk factors for hospital admission, severe disease and death. A rapid review – 3rd update. Oslo: Folkehelseinstituttet, 2020. https://www.fhi.no/publ/2020/covid-19-og-risikofaktorer-for-sykehusinnleggelse-alvorlig-sykdom-og-dod/ Accessed 16.11.2020.

11. Zhang H, Han H, He T et al. Clinical characteristics and outcomes of COVID-19-infected cancer patients: A systematic review and meta-analysis J Natl Cancer Inst 2020; 112: djaa168. [PubMed][CrossRef]

12. Gupta S, Hayek SS, Wang W et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med 2020; 180: 1–12. [PubMed][CrossRef]

13. Kragholm K, Andersen MP, Gerds TA et al. Association between male sex and outcomes of Coronavirus Disease 2019 (Covid-19) - a Danish nationwide, register-based study. Clin Infect Dis 2020; 71: ciaa924. [PubMed][CrossRef]

14. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents 2020; 34: 339–43. [PubMed]

15. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020; 323: 1775–6. [PubMed][CrossRef]

16. Griffith GJ, Morris TT, Tudball MJ et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. Nat Commun 2020; 11: 5749. [PubMed][CrossRef]

17. Nystad W, Hjellvik V, Larsen IK et al. Underlying conditions in adults with COVID-19. Tidsskr Nor Legeforen 2020; 140. doi: 10.4045/tidsskr.20.0512. [PubMed][CrossRef]

Publisert: 29 December 2020. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.20.0956
Received 23.11.2020, first revision submitted 9.12.2020, accepted 11.12.2020.