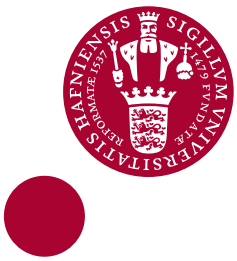

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Published in:
Danish Medical Journal

Publication date:
2021

Document version
Publisher's PDF, also known as Version of record

DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2021;68(3):A09200705

Prognostic factors of 90-day mortality in patients hospitalised with COVID-19

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Dan Med J 2021;68(3):A09200705

ABSTRACT

INTRODUCTION: Mortality due to COVID-19 is higher among elderly patients with comorbidities. Even so, prognostication in COVID-19 remains limited.

METHODS: We assessed 90-day mortality stratified by comorbidities, routine biochemical markers and oxygen need in a consecutive single-centre cohort from 2 March to 2 June 2020.

RESULTS: We included 263 hospitalised patients with laboratory-confirmed COVID-19. On admission, fitness for intensive care was determined in 254 patients including 98 (39%) with a do-not-resuscitate order. Ninety-day overall mortality was 29%, whereas intensive care unit (ICU) mortality was 35% (14/40). Alcohol abuse, liver disease and elevated urea were strongly associated with mortality in univariable analyses. In a mutually adjusted multivariable analysis, we found an independent incremental increase in 90-day mortality with each increasing age by decade (hazard ratio (HR) = 1.5; 95% confidence interval (CI): 1.2-1.9), Charlson Comorbidity Index (CCI) score (HR = 1.2; 95% CI: 1.0-1.4), number of abnormal blood tests (HR = 1.2; 95% CI: 1.1-1.3) and l/min. of supplemental oxygen (HR = 1.1; 95% CI: 1.1-1.2).

CONCLUSIONS: The overall mortality was similar to that of other hospitalised patients, whereas the ICU mortality was lower than expected. On admission, each additional age by decade, CCI score, number of abnormal blood tests and magnitude of supplemental oxygen were independently associated with increased mortality.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

The first known Danish case to become infected by novel coronavirus was recorded on 27 February 2020. Subsequently, the virus spread domestically as travellers returned from the national winter holidays [1]. On 11 March 2020, COVID-19 was declared a pandemic by the World Health Organization (WHO). With only 514 confirmed cases in Denmark, a prompt Danish nation-wide lockdown was established. The containment strategy employed by the Danish Government and the Danish Health Authorities during the lockdown focused on home isolation of COVID-19 cases with mild to moderate disease and without comorbidities, whereas patients with major comorbidities or severe COVID-19 requiring oxygen therapy were admitted to hospitals. As from April 2020, the lockdown was gradually lifted, which included partial reopening of day care, schools and small

businesses. As more widespread mitigation is being implemented, a second epidemic wave seems to be emerging.

Although young fit patients may develop severe and critical disease, epidemiological studies have shown a higher mortality among patients with comorbidities such as chronic pulmonary disease (CPD), diabetes, hypertension, coronary heart failure, stroke, cancer and older age. These features were more frequent among patients requiring intensive care (IC) and mechanical ventilation (MV) than among other patients [2, 3]. As such, 88% of New Yorkers had more than one comorbidity with a median Charlson Comorbidity Index (CCI) score of four, whereas the median number of comorbidities in hospitalised Danish patients was two, and 82% of fatal cases in Denmark had two or more comorbidities [1, 3, 4].

To investigate the prognostic impact of age, comorbidities, biochemical markers and severity of disease at the time of admission, we analysed data with complete follow-up on all patients hospitalised with COVID-19 from a single centre during of the first wave of the epidemic.

METHODS

Ethical considerations

The study was approved by the Danish Patient Safety Authority (registration no. 31-1521-304) and the Danish Data Protection Agency (record no. 2020-522-0236). According to Danish legislation, informed consent is not required for retrospective studies.

Inclusion and data collection

We included adult patients with laboratory-confirmed COVID-19 admitted to Herlev and Gentofte Hospital for at least 24 hours between 2 March and 2 June 2020. During this period, no patients received effective antiviral treatment. We retrospectively retrieved biochemical results and information on comorbidities and vital signs on admission from electronic patient records on Sundhedsplatformen. Last date of follow-up was 9 October 2020, and the median follow-up was 192 days (interquartile range (IQR): 176-200 days).

Statistical analysis

The primary endpoint was 90-day mortality according to age by decade, CCI score, number of abnormal blood tests and COVID-19 severity estimated using univariable and multivariable Cox regression. Patients were followed from the day of admission to death or 90 days of follow-up, whichever occurred first. We used WHO International Classification of Diseases, tenth version (ICD-10) diagnoses prior to admission to calculate CCI scores, as described elsewhere [5], whereas other comorbidities were defined as detailed in **Table S1**. Biochemical results on admission were considered abnormal according to local laboratory normal ranges, except for C-reactive protein (CRP); as CRP was expected to be elevated in all infected patients, we used a cut-off of 100 mg/l, which has previously been established as optimal for patients in the intensive care unit (ICU) [6]. Glycosylated haemoglobin (HbA_{1c}) was collected up to three months prior to admission. COVID-19 was considered mild to moderate, severe or critical in patients receiving 0-5, 6-10, and > 10 l/min. of supplemental oxygen, respectively [7], whereas CCI score and number of abnormal blood tests were stratified into tertiles. Variables with more than 10% missing values were excluded. Multivariable Cox regression analysis was performed to mutually adjust for age by decade, comorbidities, number of abnormal blood tests and COVID-19 severity. Statistical analyses were performed in R version 3.6.0.

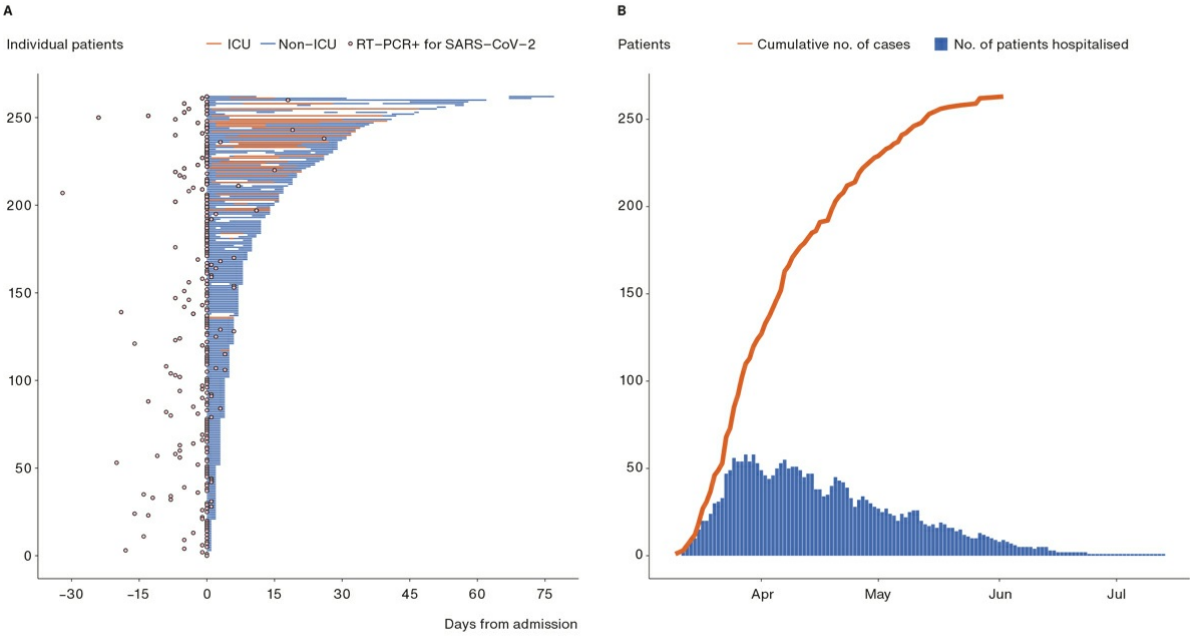
Trial registration: not relevant.

RESULTS

Patients and materials

In total, 263 patients were included. COVID-19 was diagnosed on pharyngeal swabs and tracheal sputum in 237 (90.1%) and 26 (9.9%) patients, respectively. Most patients (154 or 58.6%) were diagnosed on the day of admission, 77 patients (29.2%) had been diagnosed prior to admission (median of five days (IQR: 2-8 days)), whereas 32 (12.2%) patients were diagnosed after a median of 2.5 days from admission (IQR: 1-6 days; **Figure 1**A). Up to 16 new patients were admitted daily with a peak of 58 patients hospitalised in one day (Figure 1B). Within 90 days from admission, 38 patients (14%) were readmitted to our institution.

FIGURE 1 Swimmer plot showing the diagnosis and clinical course in 263 patients admitted between 2 March and 2 June 2020. Most patients were diagnosed on the day of admission, and 40 patients were transferred to the intensive care unit. Reverse-transcriptase-polymerase-chain-reaction (**A**). Cumulative incidence of COVID-19 at our institution. We admitted up to 16 patients daily with a peak of 58 patients hospitalised in late March (**B**).



ICU = intensive care unit; RT-PCR = reverse-transcriptase-polymerase-chain-reaction.

Clinical characteristics

Baseline characteristics are summarised in **Table 1**. The median age was 72 years (IQR: 60.5-81 days) and 54.8% were male. The most frequent comorbidities included hypertension (32.3%), CPD (22.1%), diabetes with or without complications (19.8%), any cancer (15.2%), atrial fibrillation (14.1%), cerebrovascular disease (14.1%) and dementia (11.4%). The median CCI score was 1 (IQR: 0-2): 92 (35.0%), 73 (27.8%), 46 (17.5%) and 52 (19.8%) patients scored 0, 1, 2 and > 2, respectively. Furthermore, most patients were lymphopenic with elevated levels of blood glucose, fibrin D-dimer, ferritin, CRP, and lactate and dehydrogenase (LDH), whereas albumin levels were mostly decreased (**Table S2**). Several abnormal biochemical markers significantly co-occurred, whereas for comorbidities only diabetes and renal disease co-occurred (**Supplementary data**). On admission, 120 patients (45.6%) required supplemental oxygen: 236 patients (89.7%), 14 (5.3%), and 13 patients (4.9%) required ≤ 5, 6-10 and > 10 l/min. of supplemental oxygen, respectively (Table 1).

TABLE 1 Baseline characteristics (N = 263).

	n (%)	Median (IQR)
Demographics		
Age, yrs		72.0 (60.5-81.0)
Males	144 (54.8)	
Charlson comorbidities		
Myocardial infarction	6 (2.3)	
Coronary heart failure	15 (5.7)	
Peripheral artery disease	12 (4.6)	
Cerebrovascular disease	37 (14.1)	
Dementia	30 (11.4)	
Chronic pulmonary disease	58 (22.1)	
Rheumatologic disease	5 (1.9)	
Peptic ulcer disease	3 (1.1)	
Mild liver disease	5 (1.9)	
Moderate to severe liver disease	2 (0.8)	
Diabetes without chronic complications	34 (12.9)	
Diabetes with chronic complications	21 (8.0)	
Hemiplegia or paraplegia	0	
Renal disease	13 (4.9)	
Any malignancy including leukaemia and lymphoma	40 (15.2)	
Metastatic solid tumour	6 (2.3)	
AIDS/HIV	0	
Charlson Comorbidity Index score		1 (0-2)
Other comorbidities		
Atrial fibrillation	37 (14.1)	
Alcohol abuse	12 (4.6)	
Psychiatrics	18 (6.8)	
Asthma	24 (9.1)	
Hypertension	85 (32.3)	
Obesity: BMI > 25 kg/m^2	93 (62.0)	
Missing	113	
Medication		
ARB or ACEI	74(28.1)	
Anticoagulant therapy[a]	64 (24.3)	
Blood workup		
Haemoglobin concentration, g/dl		8.2 (7.5-8.9)
WBC, × 10^3/µl		6.7 (5.1-9.4)
ALC, × 10^3/µl		0.8 (0.6-1.2)
Missing	2	
ANC, × 10^3/µl		5.3 (3.6-7.5)
Missing	2	
ALC/ANC ratio		0.2 (0.1-0.2)
Missing	2	
Platelet concentration, × 10^3/µl		218.0 (167.5-286.5)
Fibrin D-dimer concentration, mg/l		1.0 (0.6-2.2)
Missing	128	
INR		1.0 (1.0-1.1)
Missing	8	
Ferritin concentration, µg/l		561.0 (186.0-1,090.0)
Missing	116	
CRP concentration, mg/l		69.0 (34.0-134.5)
Albumin concentration, g/l		33.0 (29.0-36.0)
Missing	5	
Na^+ concentration, mmol/l		138.0 (135.0-141.0)
K^+ concentration, mmol/l		3.7 (3.4-4.0)
Creatinine concentration, µmol/l		77.0 (63.0-99.5)
Urea concentration, mmol/l		6.6 (4.7-9.9)
Missing	11	
ALT concentration, U/L		30.0 (19.0-50.5)
Missing	8	
Amylase concentration, U/l		57.0 (42.0-81.0)
Missing	14	
ALP concentration, U/l		74.0 (59.0-101.0)
Missing	4	
Bilirubin concentration, µmol/l		9.0 (7.0-13.0)
Missing	4	
LDH concentration, U/l		292.0 (220.5-386.5)
Missing	8	
Blood glucose concentration, mmol/l		6.7 (5.9-8.3)
Missing	8	
HbA_{1c} concentration, mmol/mol		37.0 (34.0-45.0)
Missing	82	
Vital signs		
Systolic BP, mmHg		130.0 (115.0-144.0)
Missing	3	
Diastolic BP, mmHg		74.0 (65.0-81.0)
Missing	3	
Pulse, beats/min.		87.0 (78.0-101.0)
Missing	2	
Temperature, °C		37.7 (36.9-38.4)
Missing	6	
Respiratory rate, /min.		20.0 (18.0-24.0)
Missing	2	
O_2 saturation, %		96.0 (94.0-97.0)
Supplemental O_2, l/min.		0.0 (0.0-3.0)
Patient fitness		
Do-not-resuscitate	98 (38.6)	
Missing	9	

ACEI = angiotensin converting enzyme inhibitor; ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARB = angiotensin-receptor blocker; BP = blood pressure; CRP = C-reactive protein; HbA1c = glycosylated haemoglobin; INR = international normalised ratio; IQR = interquartile range; LDH = lactate dehydrogenase; WBC = white blood count.
a) Included apixaban, clopidogrel, dabigatran, and warfarin.

Indications for intensive care

On admission, the patients' fitness for IC was determined by the treating physician in 254/263 (97%) cases. A do-not-resuscitate (DNR) order was given in 98 patients (39%), whereas no restrictions were ordered in 156 (61%). Fitness for IC was reassessed in 23 patients who were given a DNR order later during their admission.

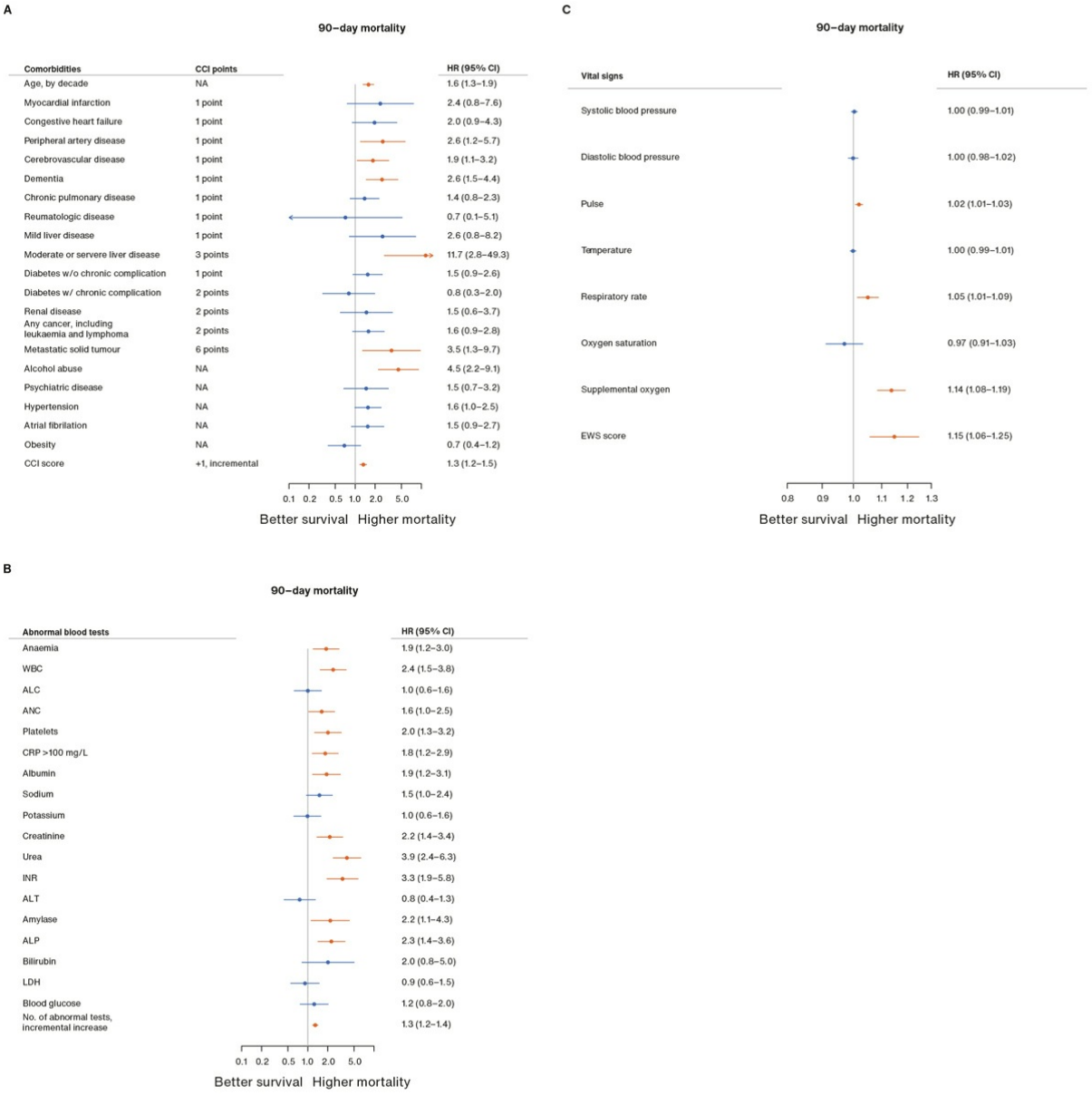
Clinical outcomes

Patients were admitted for a median of seven days (IQR: 3-25 days). The 30-day and 90-day overall mortality rates were 25.1% and 28.9%, respectively. Among 40/263 patients requiring IC (15.2%), 14/40 died (35%) and 26/40 were discharged alive (65%). Excluding the 40 patients requiring IC, 54 of 98 patients with a DNR order had died (55.1%), whereas only eight of 116 patients initially considered fit for resuscitation and MV had died (7.1%) (**Supplementary data** https://ugeskriftet.dk/files/a09200705_-_supplementary.pdf).

In univariable analyses of the association of individual comorbidities and blood results with 90-day mortality, we

found a significantly higher mortality in elderly patients with known peripheral artery disease, cerebrovascular disease, dementia, moderate to severe liver disease, metastatic cancer and alcohol abuse (**Figure 2**A). Due to considerable missing data on fibrin D-dimer, ferritin and HbA_{1c} (Table 1), we excluded these patients from further analysis. We next demonstrated a significantly higher mortality in patients with abnormal haemoglobin, white blood count, absolute neutrophil count, platelets, CRP, sodium, creatinine, urea, international normalised ratio, amylase and alkaline phosphatase (Figure 2B). For vital signs, an increased pulse, respiratory rate, need of supplemental oxygen and early warning system score at time of admission were associated with higher mortality (Figure 2C).

FIGURE 2 Univariable analyses of the association between comorbidities (**A**), abnormal blood tests and vital signs (**C**) on overall mortality (**B**). Red colour indicates p < 0.05.

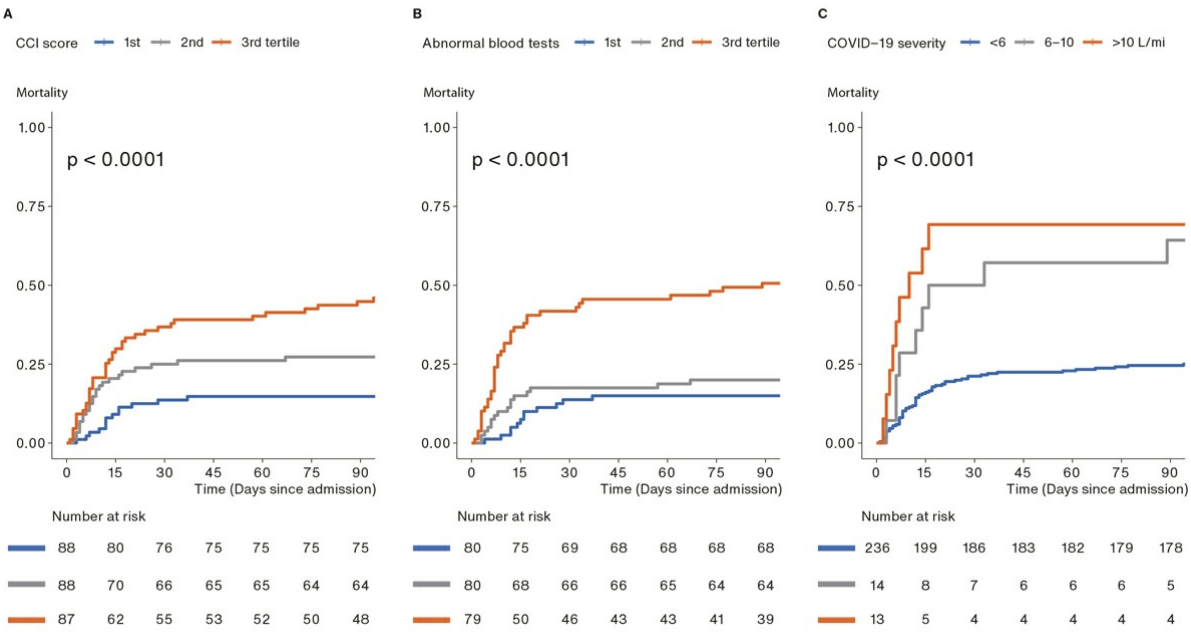


ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; CCI = Charlson Comorbidity Index; CI = confidence interval; CRP = C-reactive protein; EWS = Early Warning Score; HR = hazard ratio; INR = international normalised ratio; LDH = lactate dehydrogenase; WBC = white blood count. Red colour: p < 0.05.

Assessing 90-day mortality, we found that an increasing CCI score was associated with a higher mortality; and

patients in the first, second and third CCI score tertile had a 90-day mortality of 15%, 27% and 45%, respectively (**Figure 3**A). Furthermore, we demonstrated that an increasing number of abnormal blood tests was associated with a gradually higher 90-day mortality of 15%, 20% and 51% for patients in the first, second and third tertile, respectively (Figure 3B). Moreover, an increasing need for supplemental oxygen at the time of admission was associated with a gradually higher mortality; the 90-day mortality was 24%, 64% and 69% for patients requiring ≤ 5 versus 6-10 versus > 10 l/min. of supplemental oxygen, respectively (Figure 3C). Finally, age by decade (hazard ratio (HR) = 1.5; 95% confidence interval (CI): 1.2-1.9), CCI score (HR = 1.2; 95% CI: 1.0-1.4), number of abnormal blood tests (HR = 1.2; 95% CI: 1.1-1.3) and number of l/min. of supplemental oxygen at time of admission (HR = 1.1; 95% CI: 1.1-1.2) were independently associated with an adverse mortality in a mutually adjusted multivariable Cox analysis (**Supplementary data**).

FIGURE 3 Ninety-day mortality stratified by the Charlson Comorbidity Index (CCI) score (**A**), number of abnormal blood tests (**B**) and COVID-19 severity as defined by the magnitude of supplemental oxygen required on admission (**C**).



DISCUSSION

We here describe a cohort of patients with COVID-19 who were hospitalised during the first wave of the coronavirus pandemic at one the hospitals in the Copenhagen University Hospital cooperation with more than six months of follow-up. At the end of the inclusion period (2 June 2020), the cohort comprised 263 patients corresponding to 10.4% of the total number of hospitalised patients with COVID-19 in Denmark [1, 8]. The 90-day overall mortality and ICU mortality were 29% and 35%, respectively. We found that several individual comorbidities and abnormal blood tests as well as age had a negative impact on 90-day mortality. We further demonstrate that age by decade, CCI score, number of abnormal blood tests and supplemental oxygen need were independently associated with adverse 90-day mortality (Figure 3).

With regard to comorbidities, the patients in this cohort resembled those described in the United States and China [1-3], whereas patients were generally less co-morbid compared with Danish nation-wide data [1]. Similarly to other studies, we found that individual comorbidities also had a negative prognostic impact on 90-day mortality [1, 9, 10]. Notably, we found that alcohol abuse and dementia were associated with a higher

mortality compared with Danish nation-wide data [1]. We believe that these findings call for further actions as preventive measures among socially marginalised individuals are possible. When including age by decade, the median CCI score was similar to that reported in American data (4 versus 4) [3], and we demonstrated a gradually higher mortality with increasing CCI score in agreement with others [4, 11, 12]. Similarly, Danish nation-wide data have demonstrated a higher mortality for patients with an increasing number of comorbidities [1].

Like others [2, 3, 13-15], we found a high degree of lymphopenia as well as elevated CRP, LDH, ferritin and fibrin D-dimer. However, ferritin, fibrin D-dimer and HbA_{1c} were only available for approximately half of all patients as these tests were not part of the routine blood work-up in the beginning of the pandemic at our institution. Several biochemical markers were associated with a higher mortality. Interestingly, increasing age and elevated urea were strong individual prognosticators and are well-established predictors of outcome for pneumonia included in the CURB-65 score [16]. In agreement with the negative prognostic value of CRP > 100 mg/l in this study, higher cut-off values might have revealed similar associations for other acute-phase reactants [6]. By counting the number of abnormal blood tests, we demonstrated a gradually higher mortality for each additional abnormal blood test. Moreover, our study confirmed an association between COVID-19 severity defined by the demand for supplemental oxygen and higher mortality [7, 17].

Overall, the baseline age by decade, CCI score, number of abnormal blood tests and magnitude of supplemental oxygen were independently associated with adverse mortality. Including a smaller subset of comorbidities and blood tests without concurrence and with a stronger individual prognostic impact in larger studies is likely required to develop a prognostic tool to help refine the prognosis in patients with newly diagnosed COVID-19.

We found a 30-day overall mortality rate similar to rates reported by others (25% versus 21-28%) [1, 3, 13, 14]. After 90 days of follow-up, overall mortality had increased further (29%), and readmissions were common (14%). Although the proportion of patients requiring IC was similar to proportions reported in Chinese, American and Danish data (15% versus 13-15%) [1-3], the ICU mortality in the present study was considerably lower than in most other studies (35% versus 43-78%) [2, 3, 14, 18], but similar to nationwide Danish data (35% versus 37%) [19]. A recent meta-analysis reported a combined ICU mortality of 42% [20]. Deciding on fitness for IC and MV in 97% of patients in the present study, all patients considered fit for and requiring MV were also transferred to the ICU. For patients who remained in the medical ward (non-ICU), only 7% of those considered fit for IC had died at the end of follow-up, whereas 55% of the patients with an initial DNR order had died. This underscores the dismal clinical course of COVID-19 in frail patients who are considered medically unfit for IC. Even though the ICU mortality rate has fallen over time [20], we speculate whether a firm policy to consider a DNR order on admission might have yielded a lower ICU mortality as only the healthiest patients considered to benefit from IC and MV were admitted to the ICU. Since the first day of the Danish epidemic, we stressed the importance of assessing IC fitness in all patients, thereby easing triage and collaboration with the ICU as well as relieving patients of futile weeks in MV. We thus encourage consideration of IC fitness on admission in all patients with COVID-19.

CONCLUSIONS

We have described a cohort of the first 263 patients with COVID-19 at a Danish university hospital with an overall mortality similar to that reported by others but an ICU mortality that was lower than most. Consequently, we encourage assessment of IC fitness in all newly diagnosed patients. Furthermore, we found an independent association with higher mortality with each additional increase in age by decade, CCI score, each additional abnormal blood test and each additional litre per minute of supplemental oxygen.

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Accepted 11 January 2021

Conflicts of interest none. Disclosure forms provided by the authors are available with the full text of this article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2021;68(3):A09200705

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