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Transmission, start of symptom and morbidity among Danish COVID-19 patients admitted to hospital

Christian N. Meyer[1, 2]

1) Department of Internal Medicine, Zealand University Hospital, Roskilde, 2) Department of Clinical Medicine, University of Copenhagen, Denmark

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ABSTRACT

INTRODUCTION: We explored transmission of the coronavirus disease 2019 (COVID-19) in severely ill patients and analysed the relationship between co-morbidity and mortality or the need for intensive care unit (ICU) care.

METHODS: Clinical data, treatment and outcome were analysed in this retrospective study of 101 consecutive patients with COVID-19 admitted to a regional Danish hospital from 2 March 2020, based on data from electronic medical records.

RESULTS: The mean age was 71.8 years, 33% were never smokers and 82% had one or more predefined chronic diseases. In-hospital mortality was 30%, and 20% of the patients were offered ICU care. In ICU patients, we found a male preponderance (88% versus 44%, p = 0.006), but death (50% versus 25%, p = 0.053) and other pre-defined co-morbidities did not differ significantly from non-ICU patients. The source of infection was unknown in 74% of patients, related to endemic travel in 10%, hospital acquired in 6% and related to close acquaintances in 11%. COVID-19-related symptoms were initially observed from February 21 (week 8 and week 9) in the first three patients who had no known source of infection. We found that 7% of cases had an increased risk of in-hospital transmission, based on a 7-16 days delay in coronavirus testing.

CONCLUSIONS: The frequency of co-morbidity in hospital-admitted COVID-19 patients and the correlation to death and ICU attendance were analysed. In all, 74% of the infection cases were of unknown source during the first weeks of the epidemic, which points to considerable community transmission and possibly pre- or asymptomatic transmission, also several weeks before 21 February 2020.

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Following the outbreak of the epidemic, occurrence of the contagious viral pneumonia in China in December 2019 and identification of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as the cause of this new human coronavirus disease 2019 (COVID-19), several new epidemic centres evolved in South Korea, Iran, and – in late February – in Northern Italy. This was soon followed by rapidly evolving epidemics in other European countries, including Denmark, where the first COVID-19 patient was identified on 27 February 2020. The mode of transmission is primarily by droplets and direct and indirect contact, and the condition is characterised by a moderately high contagiousness with a basic reproductive number (R0) of 2-3.5 in the beginning of the epidemic before social distancing interventions were in place [1]. A pre-symptomatic but infectious period of 1-3 days has been described and also a substantial proportion of asymptomatic infected and infectious persons has been found, both of which contributed to the high transmission rate, thus increasing the spread of disease [2-5]. Several different and changing strategies have been chosen by different governments to control the disease in the community and to limit its impact on society and on hospital and intensive care unit (ICU) capacity and strain.

The clinical picture in the first published cohorts of COVID-19 patients is described as

respiratory disease, pneumonia, influenza-like disease, sepsis or – to a lesser degree – gastrointestinal disease [6-8]. The most severely ill patients are in need of hospital care and ICU attendance for treatment and supportive care for prolonged periods of time compared with usual bacterial or other viral pneumonia [9]. As only a small percentage of the all COVID-19 patients need treatment in hospital, hospital admission numbers may be seen as the tip of the iceberg.

The aim of our study was to describe a Danish population of hospital-admitted COVID-19 patients focussing on the start-point of symptoms, transmission routes, predefined underlying chronic disease and co-morbidity, and we planned to analyse the relationship between these co-morbidities and death or the need for ICU support.

METHODS

Patients

All adult patients admitted to Zealand University Hospital, Roskilde, Denmark, and diagnosed with COVID-19 were included retrospectively, beginning from 2 March 2020 (week 10).

Clinical data

From the electronic medical records, data were collected regarding age, sex, co-morbidity, recent travel, medication, tobacco and alcohol use, residence, home nursing, symptoms, possible infectious transmission, vital parameters, diagnostics, treatment, length of hospital stay (LOS), ICU stay and mortality.

Definitions

Co-morbidities used in the validated pneumonia severity algorithms (CURB-65, PSI, SMARTCOP etc.) were included. Tobacco user status was divided into never smoker, former smoker or present smoker. Severely ill patients were defined by need of hospital admission caused by COVID-19 symptoms.

Hospital-acquired status and increased risk of in-hospital transmission status was based on the start of COVID-19 symptoms, the length of prior hospital admission before the occurrence of COVID-19 symptoms and an expected virus incubation period of 2-12 days that was related to the date of positive SARS-CoV-2 sampling.

Age was divided into five groups to better uphold patient anonymity in the transmission results.

Statistics

Clinical data were analysed, and the t-test was used for analysing continuous data when normally distributed. $\chi 2$-test (two-sided) Fisher's exact test or the likelihood ratio test was

used for categorical data. Multivariate analysis of outcome including all hypothesised factors from the recent COVID-19 literature was not planned because a low absolute number of the outcome parameter (30 deaths) limited the number of independent variables in such analyses. The level of significance was set to $p < 0.05$.

Trial registration: The Ethics Committee of Region Zealand was contacted, and they informed that the study did not need their approval as no intervention was performed and biological material was not collected. Permission for data handling was granted by The Danish Data Protection Agency, Region Zealand (REG-070-2020).

RESULTS

Among the first 101 severely ill patients (defined as patients in need of hospital admission) who were diagnosed with COVID-19, the mean age was 71.8 years (range: 21-93 years), 12 patients were nursing-home residents, 11 patients received home nursing and 52 patients (51%) were male. Two patients were healthcare workers (HCW); one nursing-home nurse and one surgeon. At admission, 51 patients (50.5%) needed oxygen therapy. The in-hospital mortality was 30% and co-morbidity was found in 82% of all patients, Table 1. The mean BMI was 26.6. Never smokers accounted for 33 patients, active smokers ten and previous smokers 40 (18 with missing data). The mean LOS was 13.0 days (range: 1-60 days), with a longer mean LOS for ICU patients than for non-ICU patients, 22.8 days versus 10.6 days, respectively, $p < 0.01$. ICU support was offered to 20 patients (20%), 18 were intubated and ventilator treated, and the proportion of early intubation initiated within 24 hours of hospital admission was 6/20 patients (30%). The ICU patients had a higher male ratio (80% versus 44%, $p < 0.01$), a longer LOS (22.8 versus 10.6 days, $p < 0.01$) and a tendency towards a higher mortality (50% versus 25%, $p = 0.053$), but no significant difference in age (68.4 versus 72.6, $p = 0.23$), tobacco use ($p = 0.63$), BMI ($p = 0.22$), or other co-morbidity compared with non-ICU patients. Further details are shown in Table 1 (four patients had asthma and chronic obstructive pulmonary disease (COPD) simultaneously, so-called ACOS; five patients had ischemic heart disease and heart failure simultaneously).

TABLE 1 / Chronic disease (co-morbidity) and initial biochemistry among 101 patients with coronavirus disease 2019 admitted to hospital, related to intensive care unit usage or mortality status.

	No ICU vs ICU				Alive vs dead			
	no ICU (n = 81)	ICU (n = 20)	p-value	total (N = 101)	alive (n = 71)	dead (n = 30)	p-value	total (N = 101)
Male, n (%)	36 (44)	16 (80)	< 0.01	52	32 (45)	20 (67)	0.045	52
Age, yrs, mean	72.6	68.4	0.12	71.8	69.4	77.4	< 0.01	71.8
LOS, days, mean	10.6	22.8	< 0.01	12.9	12.6	13.9	0.64	12.9
BMI, kg/m^2, mean	26.2	27.9	0.22	26.6	26.5	26.8	0.85	26.6
No co-morbidity, n (%)	13 (16)	5 (25)	0.34	18	15 (21)	3 (10)	0.16	18
Chronic disease, n (%)								
Malignancy < 5 yrs	5 (6)	2 (10)	0.30	7	5 (7)	2 (7)	0.97	7
Asthma	12 (15)	3 (15)	1.00	15	12 (17)	3 (10)	0.54	15
COPD	13 (16)	0	0.48	13	7 (10)	8 (27)	0.07	15
Pulmonary fibrosis	3 (4)	1 (5)	1.00	4	1 (1)	2 (7)	0.21	3
Arterial hypertension	42 (52)	12 (60)	0.67	54	36 (51)	18 (60)	0.51	54
Ischaemic heart disease	11 (14)	4 (20)	0.57	15	11 (15)	3 (10)	0.38	14
Heart failure	8 (10)	2 (10)	0.64	10	6 (8)	4 (13)	0.06	10
Liver disease	1 (1)	0	0.80	1	0	1 (3)	0.30	1
Renal disease	5 (6)	0	0.58	5	3 (4)	2 (7)	0.63	5
Diabetes	9 (11)	5 (25)	0.15	14	8 (11)	6 (20)	0.34	14
Rheumatic disease	7 (9)	1 (5)	0.64	8	5 (7)	1 (3)	0.64	6
Immunodeficiency, acquired	1 (1)	1 (5)	0.36	2	2 (3)	0	1.00	2
Cerebrovascular disease	14 (17)	1 (5)	0.25	15	6 (8)	6 (20)	0.10	12
Biochemistry								
CRP concentration, mgl/l, mean	77	161	0.003	94	87	110	0.21	94
Eosinophil concentration, × 10^9/l, mean	0.007	0.010	0.74	0.90	0.003	0.2	0.07	0.90
Lymphocyte concentration, × 10^9/l, mean	0.90	0.91	0.96	0.01	1.0	0.8	0.11	0.01
LDH concentration, U/l, mean	308	457	< 0.001	338	323	372	0.10	338
Glucose concentration, mmol/l, mean	6.7	8.6	0.17	7.1	6.9	7.6	0.41	7.1

COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ICU = intensive-care unit; LDH = lactate dehydrogenase; LOS = length of hospital stay.

Patients who died had a higher age (77.4 versus 69.4, $p < 0.01$) than patients who did not, but co-morbidity, biochemical results or LOS (12.6 versus 13.9 days) did not correlate significantly with death, though a trend was seen towards correlation with COPD (27% versus 10%, $p = 0.07$), heart failure (13% versus 8%, $p = 0.06$) and cerebrovascular disease ($p = 0.10$), see Table 1. Thus, neither BMI ($p = 0.85$), tobacco user status ($p = 0.33$), arterial hypertension ($p = 0.51$), nursing home attendance ($p = 0.11$), nor any other pre-defined co-morbidity (all $p > 0.20$) correlated with death by univariate analysis.

COVID-19 symptoms among these hospital-admitted Danish patients began 21 February (one 64-year-old patient in week 8; two patients aged 68 and 71 years, in week 9) among elderly patients with no travel history. The initial symptoms in the first week of March (week 10) occurred among two nursing-home residents (aged 84 and 91 years), three patients with daily home-nursing needs (aged 74-93 years), six endemic travelling patients (aged 56-75 years) and in nine patients with unknown transmission route (age median = 65 years, range: 46-80 years). In a total of ten patients, transmission of SARS-CoV-2 presumably occurred during travel to or contact to persons from endemic regions (three Austrian ski-sports

resort, two Northern Italy, one Spain, one Canary Islands, one Dublin, one London/Manchester, one US cruise ship), Table 2. Known close contact with family, friend or co-worker developing COVID-19 disease was found in 11 cases; but in 74 cases, the person serving as the infectious source remained unknown, see Table 2. The number of days from COVID-19 compatible symptoms to hospital admission had negative values in several patients in the first two weeks of the epidemic, meaning that symptoms started many days (up to 23) after hospital admission, Table 2. Based on the virus incubation period and the length of prior hospital admission before the occurrence of COVID-19 symptoms, six cases were hospital acquired when including the HCW (a surgeon) at work. In addition, further in-hospital transmission could have occurred among seven patients who had a 7-16-day delay in their coronavirus diagnosis, see Table 3.

TABLE 2 / Transmission data, pre-admission nursing needs, co-morbidity, and days until diagnosis in patients with coronavirus disease 2019, by week of hospital admission.

	Week 10 (n = 3)	Week 11 (n = 20)	Week 12 (n = 42)	Week 13 (n = 22)	Week 14 (n = 11)	Week 15 (n = 3)	All (N = 101)
Transmission, n							
Unknown	1	15	33	15	7	3	74
Travel, endemic country	1	4	3	2	0	0	10
Hospital acquired[a]	1	1	2	2	0	0	6
Family/friend/work	0	0	4	3	4	0	11
Pre-admission nursing, n							
Nursing home resident	0	4	1	4	3	0	12
Daily home nursing	1	4	4	2	0	0	11
Co-morbidity, n							
No co-morbidity	0	3	8	2	5	0	18
Co-morbidities, mean	1.3	1.8	1.6	1.5	1.1	2	1.6
Time until diagnosis, days							
From symptoms to admission, mean (min.-max.)	-4 (-23-7)	6.3 (-12-20)	7.6 (1-14)	7.0 (-1-22)	7.1 (1-22)	13.3 (5-21)	7.0 (-23-22)
From admission to diagnosis, mean (min.-max.)	11.7 (2-23)	1.5 (-8-16)	-0.3 (-8-5)	0.5 (-9-2)	-0.9 (-10-1)	-2.3 (-14-7)	0.4 (-14-23)

a) Including a consultant with contact to a later coronavirus disease 2019-positive patient.

TABLE 3 / Hospital-acquired cases of coronavirus disease 2019 and late diagnosed cases with increased in-hospital transmission risk.

Patient no.	Age-group, yrs	Hospital acquired	Symptom date	Admission date	COVID-19 date	Hospital admissions
Hospital-acquired cases						
1	80-95	Very probably	15/3	16/3	17/3	8/3-13/3, 16/3-1/4
2	80-95	Very probably	18/3	3/3	26/3	3/3-25/3, 26/3-14/4
3	70-80	Very probably	23/3	9/3	25/3	9/3-30/3
4	80-95	Very probably	25/3	26/3	26/3	15/3-24/3, 26/3-9/4
5[a]	70-80	Possibly	25/3	26/3	26/3	10/3-20/3, 25/3-28/4
Late diagnosed cases						
6	80-95	Transmission risk	2/3	9/3	16/3	9/3-31/3
7	80-95	Transmission risk	2/3	6/3	16/3	6/3-23/3
8	80-95	Transmission risk	3/3	14/3	14/3	8/3-13/3, 14/3-20/3
9	80-95	Transmission risk	7/3	10/3	16/3	10/3-22/3
10[b]	70-80	Transmission risk	12/3	20/3	25/3	20/3-23/3, 25/3-30/3
11	80-95	Transmission risk	13/3	4/4	2/4	13/3-17/3, 4/4-9/4
12	80-95	Transmission risk	19/3	26/3	4/4	26/3-9/4

COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
a) Recent admission with epistaxis and dyspnoea and (possible true) negative SARS-CoV-2 swab on 13/3.
b) Prior possible false-negative SARS-CoV-2 swab on 21/3.

DISCUSSION

Our population of 101 consecutively hospital-admitted COVID-19 patients was older than the population in the first published Chinese cohorts (71.8 years versus 47-56 years) and had a higher mortality (30% versus 3.1%, 8%, 11% and 30%) and overall co-morbidity (82% versus 25%, 38% and 51%) [7, 10-12]. Compared with published Italian patients who also had a high mean age, co-morbidity and mortality seemed similar to our study [13, 14]. This may not be surprising as age has been proposed to be very closely associated with outcome [14]. The results showing a significant age correlation with outcome were also reproduced in our cohort by univariate analyses ($p = 0.009$). The limited number of included patient in our study may produce type 2 error regarding published correlations of other co-morbidities and outcomes [11, 15]. On the other hand, a well-known selection procedure or "selection bias" is usually performed in the ruling of whom may not or may benefit from, and therefore be offered, ICU admittance [13, 16]. This renders estimates in such sub-group comparisons less convincing in non-randomised descriptive studies. The hypothesis that

overweight or tobacco use may be risk factors for overall outcome could not be confirmed by our dataset. Recently published Danish single-centre studies describe early experiences in the ICU setting or in all departments at one hospital before all patients were discharged [17, 18]. These publications found similarity in mean age (71 years), co-morbidity (71%) and mortality (at least 24.6%) with our study. The slightly higher proportion of patients treated for hypertension in our study (53% versus 41.9%) cannot be explained by a difference in the very similar mean age or in a larger proportion of patients with diabetes (14% versus 26.3%), but may relate to other co-morbidities (cerebrovascular disease) or simply be due to a different patient case-mix [18].

The relatively small absolute number of outcome events in our study typically does not justify use of multivariate analysis modelling with more than 2-3 parameters and therefore was not planned.

Transmission among nursing-home residents was recently described in detail in separate states in the USA, and reports of transmission to HCW in China and in Italy, some of which had lethal outcomes, have been published [4, 14, 19, 20]. In our cohort, the two HCW both had a short and rather unremarkable hospital stay. To our surprise, several patients seem to have been infected during moderately long hospital-admissions with COVID-19-compatible symptoms occurring many days after their hospital admission (Table 3). Whether transmission occurred from HCWs, visiting family or from fellow patients remains unknown, but none of these patients had a COVID-19-affected family member or friend mentioned as a possible source in the electronic medical record. Among seven other patients admitted to hospital with COVID-19-compatible symptoms (Table 3), coronavirus infection was diagnosed with 7-16 days of delay, thus possibly increasing the spread of infection among HCW and other patients in the absence of both patient isolation and adequate use of personal protective equipment.

The starting point of the SARS-CoV-2 epidemic in Denmark is uncertain but has hitherto been estimated by the official authorities to the last week of February and to be related to skiers returning from holiday in Northern Italy and Austria. Taking into account that the early symptoms occurred around 21 February among our elderly hospital-admitted patients with no travel history or with no known infection source (no influenza-ridden or otherwise ill acquaintances), it seems reasonable to assume that transmission among persons with pre-symptomatic or common-cold-like mild disease had been occurring in the community several weeks earlier than hitherto expected. Additionally, as previously described, many asymptomatic but infected and infectious citizens may have contributed to considerable transmission for several weeks, thus up-sizing the evolving epidemic by causing a subsequent high number of hospital admissions.

Correspondence: *Christian N. Meyer.* E-mail: cnm@regionsjaelland.dk

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