First Wave of COVID-19 Hospital Admissions in Denmark: A Nationwide Population-Based Cohort Study

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated disease coronavirus disease 2019 (COVID-19), is a worldwide emergency. Demographic, clinical and laboratory factors associated with mortality in Danish patients hospitalised with COVID-19 is limited.

Methods: National health registries were used to identify all hospitalized patients with a COVID-19 diagnosis. We obtained demographics, Charlson Comorbidity Index (CCI), and laboratory results on admission and explored prognostic factors for death using multivariate Cox proportional hazard regression and competing risk survival analysis.

Results: Among 2,431 hospitalised patients with COVID-19 between February 27th and July 8th (median age 69 years [IQR 53–80], 54.1% males), 359 (14.8%) needed admission to an intensive care unit (ICU) and 455 (18.7%) died within 30 days of follow-up. The seven-day cumulative incidence of ICU admission was lower for females (7.9%) than for males (16.7%), ($p < 0.001$). Age, high CCI, elevated C-reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH), urea, creatinine, lymphopenia, neutrophilia, and thrombocytopenia within 24-hours of admission were independently associated with death within the first week in the multivariate analysis. Conditional upon surviving the first week, male sex, age, high CCI, elevated CRP, LDH, creatinine, urea and neutrophil count were associated with death within 30 days. Males presented with more pronounced laboratory abnormalities on admission.

Conclusions: Advanced age, male sex, comorbidity, higher levels of systemic inflammation and cell-turnover were prognostic factors for mortality. Age was the strongest predictor for death, moderate to high level of comorbidity were associated with a nearly two-fold increase in mortality. Mortality was significantly higher for males after surviving the first week.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global emergency. The first case in Denmark was diagnosed on February 27th, 2020, and during the first month, the number of laboratory-confirmed cases rose to more than 3,000; 500 patients were hospitalised, of which 30% required admission to an intensive care unit (ICU) and 5% died [1]. Starting on March 13th, Denmark introduced comprehensive lockdown measures, as one of the first European countries, and four weeks later the country gradually reopened. By early July, the daily incidence of new COVID-19 cases was below 0.35 per 100.000 marking the end of the first wave of the epidemic in Denmark [1].

Despite variations reported across countries, emerging evidence consistently indicates that older men with multiple comorbidities have poorer COVID-19-related outcomes [2–4]. To date, studies from Denmark focusing on the overall epidemiological characteristics during the early phase of the epidemic (until May 2020) [5, 6] and the association with several cardiovascular outcomes have been made publicly available [7]. From these early reports, COVID-19 related mortality in Denmark have been described to vary between

9.3–16.6% and rates of ICU admission between 12.9–17.8% depending on the specific groups of patients studied [5, 7].

Differences in laboratory markers of newly admitted COVID-19 cases and their association to severe outcomes have been reported from previous studies [4, 8, 17, 9–16], but remain unexplored in Denmark and other Scandinavian populations. We present a complete nationwide observational study with comprehensive clinical and laboratory parameters during the first 5 months of the COVID-19 epidemic in Denmark. Furthermore, we explored the effect of clinically relevant prognostic factors in mortality in our population.

Methods

Study design, setting and participants

All residents of Denmark have free access to health care. Using the Danish National Patient Register (DNPR), which contains detailed information on all hospital contacts nationwide, we identified all individuals in the entire population of 5.8 million [18] who had received a COVID-19 diagnosis [19]. Diagnoses in DNPR are coded according to the International Classification of Diseases 10th revision (ICD-10). All hospital contacts between January 1st and July 8th with an ICD-10 diagnosis code of *COVID-19 severe acute respiratory syndrome* (B972A) and/or *COVID-19 infection unspecified sites* (B342A) regardless of duration were considered eligible for inclusion. Patients without a unique personal registration number (PNR) in Denmark were excluded.

We defined a hospital admission as any hospital contact that lasted more than 12 hours or a shorter contact which resulted in transfer to ICU and/or death. Several hospital contacts within 24 hours were considered as one event. When admissions were less than one hour apart, the patient was considered to be hospitalised the period in between as well, thus counting towards the 12-hour hospital stay. The start of the first hospital admission to which the first COVID-19 diagnosis could be linked and which was not more than 14 days before or 30 days after the date of first COVID-19 diagnosis, was defined as the index date and was used to determine baseline characteristics as well as the start of follow-up (77.2% were admitted on the day of diagnosis).

All COVID-19 diagnoses were based on a positive polymerase chain reaction (PCR) test for SARS-CoV-2 on respiratory specimens collected by naso- or oropharyngeal swab, sputum expectoration, or tracheal suction.

Data Sources And Collection

The Danish Civil Registration system (CRS) assigns all residents a unique PNR which enables accurate linkage between the Danish national registries [20, 21]. We extracted information from the following specific registries: 1) The CRS [21], which comprise date of birth, sex, vital status, date of death,

emigration, area of residence; 2) The DNPR [22], which includes dates of admission and discharge, admitting departments, and all primary and secondary discharge diagnoses and procedure codes from hospital contacts; 3) Register of Laboratory Results for Research (RLRR) [20], which contains nationwide laboratory information (except Midtjylland Region, population 1.3 million) using Nomenclature for Property and Unit (NPU) codes (13). Subsequent analyses were performed on pseudo anonymized data.

Variables And Outcomes

The primary outcomes were death within 7 and 30 days from the index date. Need for ICU admission (including admission to an ICU ward or the codes for use of invasive mechanical ventilation (IMV), dialysis, inotropic/vasopressor therapy and extracorporeal membrane oxygenation (ECMO) [23]), were used as secondary outcomes (Supplementary Table S1). Age, sex, underlying medical conditions, and laboratory parameters were included in the analysis. We calculated the Charlson comorbidity index modified by Quan (CCI Quan) at time of admission, by retrieving ICD-10 coded hospital discharge diagnoses from the previous 10 years, and categorized patients with low (0), moderate (1–2) or high (> 2) levels of comorbidity [24].

Laboratory parameters were collected from admitted patients within 24 hours of the index date. If a measurement was repeated within 24 hours, we used an average. Patients were followed from index date until the date of death, completion of 30 days of follow-up, or July 8th, 2020, whichever first.

Statistical analysis

Baseline characteristics are presented as medians with interquartile range (IQR) for continuous variables, and numbers and percentages for categorical variables. All-cause 30-day mortality stratified by sex, age intervals, and CCI were investigated with Kaplan-Meier (KM) analyses. Prognostic factors for the primary outcomes were evaluated in a univariate and multivariate Cox proportional hazard regression and presented as unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CI). Covariates included age, sex, CCI and laboratory parameters (when available). Interaction between covariates where examined. Cumulative incidence rates of ICU admission were analysed with competing risk survival analysis (Aalen Johansen estimator with death as a competing event) using Grays test for statistical significance. Laboratory parameters underwent additional univariate analysis for differences between subgroups, using t-test for statistical significance. The analyses were stratified by sex, and primary and secondary outcomes.

Statistical significance level was set at 0.05. All tests of significance were two-sided. Statistical analyses were performed using Stata (Stata Corporation LP, Texas, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Ethics Approval

The study was approved by the Danish Health and Medicines Authority (ID: 31-1521-263) and by the Danish Data Protection Agency (P-2020-375). The study was conducted according to the STROBE statement [25].

Results

Patients

We identified 4,981 hospital contacts with a diagnosis of COVID-19, of these 2,465 were hospitalised, and 2,431 met our inclusion criteria. The median age of hospitalised patients was 69 years (IQR 53–80), the median length-of-stay was 5.5 days (IQR 2.2–11.1) and 54.1% were male. On admission, 60.7% had a registered comorbidity within the past 10 years. The most common comorbidities were hypertension (n = 412, 16.9%), immunosuppression and cancer (n = 459, 18.9%), and diabetes (n = 315, 13.0%). In total, 1,440 (59.2%) of hospitalised patients had a CCI Quan of zero (Table 1).

Table 1
Baseline characteristics of admitted COVID-19 diagnosed patients.

	Admitted	Admitted to ICU	30-day follow-up	
Variable	**Total**		**Survivors**	**Non-survivors**
N (%)	2431	359 (14.8%)	1976 (81.3%)	455 (18.7%)
Age in years, Median (IQR, 25% – 75%)	69 (53–80)	69 (59–75)	64 (49–77)	81 (74-86.5)
Sex (%)				
Female	1116 (45.9%)	106 (29.5%)	(47.5%)	178 (39.1%)
Male	1315 (54.1%)	253 (70.5%)	1038 (52.5%)	277 (60.9%)
Age in age groups, year (%)				
0–4	10 (0.4%)	-	10 (0.5%)	-
5–17	13 (0.5%)	-	13 (0.7%)	-
18–39	230 (9.5%)	20 (5.6%)	229 (11.6%)	1 (0.2%)
40–49	243 (10%)	23 (6.4%)	243 (12.3%)	-
50–64	543 (22.34%)	92 (25.63%)	521 (26.37%)	22 (4.84%)
65–84	1072 (44.1%)	212 (59.05%)	790 (39.98%)	282 (61.98%)
85+	320 (13.16%)	12 (3.34%)	170 (8.6%)	150 (32.97%)
Admissions and duration				

Groups with less than five patients are presented as < 5.

* Values expressed as total number (fraction) and medians [25 percentile-75 percentile] as appropriate. Chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables.

**Readmission is defined as a hospital contact at least 24 hours after a previous hospital contact and a duration of 12 hours or more

*** Any hospital contacts in the past 10 years

	Admitted	Admitted to ICU	30-day follow-up	
Median duration of hospitalizations > 12 hours in days (IQR)	5.47 (2.2-11.11)	19.38 (10.42–29.05)	5.19 (1.6-10.55)	7.02 (3.35–11.48)
Patients needing				
ICU admission	359 (14.8%)	359 (100%)	252 (12.8%)	107 (23.5%)
Mechanical respirator use	240 (9.9%)	240 (66.9%)	167 (8.5%)	73 (16%)
ECMO	18 (0.7%)	18 (5%)	13 (0.7%)	5 (1.1%)
Dialysis	78 (3.2%)	78 (21.7%)	48 (2.4%)	30 (6.6%)
Inotropic/Vasopressor use	210 (8.6%)	210 (58.5%)	143 (7.2%)	67 (14.7%)
Comorbidities* **				
Any comorbidities	1475 (60.7%)	225 (62.7%)	1086 (55.0%)	389 (85.5%)
Cardiovascular disease				
Myocardial infarct	122 (5%)	22 (6.1%)	83 (4.2%)	39 (8.6%)
Hypertension	412 (16.9%)	55 (15.3%)	294 (14.9%)	118 (25.9%)
Congestive heart failure	175 (7.2%)	19 (5.3%)	114 (5.8%)	61 (13.4%)
Peripheral vascular disease	144 (5.9%)	30 (8.4%)	93 (4.7%)	51 (11.2%)
Cerebrovascular diseases	259 (10.7%)	28 (7.8%)	176 (8.9%)	83 (18.2%)
Chronic respiratory disease	298 (12.3%)	45 (12.5%)	219 (11.1%)	79 (17.4%)
Asthma	122 (5%)	20 (5.6%)	108 (5.5%)	14 (3.1%)
COPD	216 (8.9%)	36 (10%)	143 (7.2%)	73 (16%)

Groups with less than five patients are presented as < 5.

* Values expressed as total number (fraction) and medians [25 percentile-75 percentile] as appropriate. Chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables.

**Readmission is defined as a hospital contact at least 24 hours after a previous hospital contact and a duration of 12 hours or more

*** Any hospital contacts in the past 10 years

	Admitted	Admitted to ICU	30-day follow-up	
Immunosuppression	459 (18.9%)	84 (23.4%)	327 (16.5%)	132 (29%)
Of which cancer	324 (13.3%)	64 (17.8%)	234 (11.8%)	90 (19.8%)
Kidney disease	130 (5.3%)	22 (6.1%)	79 (4%)	51 (11.2%)
Rheumatologic disease/Connective tissue disease	104 (4.3%)	17 (4.7%)	78 (3.9%)	26 (5.7%)
Liver disease	51 (2.1%)	10 (2.8%)	43 (2.2%)	81.8%)
Metabolic disease				
Diabetes	315 (13%)	55 (15.3%)	225 (11.4%)	90 (19.8%)
Obesity	135 (5.6%)	23 (6.4%)	112 (5.7%)	23 (5.1%)
Neurological disease	271 (11.1%)	38 (10.6%)	206 (10.4%)	65 (14.3%)
Comorbidity level (CCI Quan)				
0 (reference)	1440 (59.2%)	201 (56%)	1281 (64.8%)	159 (34.9%)
1 to 2	703 (28.9%)	118 (32.9%)	512 (25.9%)	191 (42%)
>2	287 (11.8%)	40 (11.1%)	182 (9.2%)	105 (23.1%)
Groups with less than five patients are presented as < 5.				
* Values expressed as total number (fraction) and medians [25 percentile-75 percentile] as appropriate. Chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables.				
**Readmission is defined as a hospital contact at least 24 hours after a previous hospital contact and a duration of 12 hours or more				
*** Any hospital contacts in the past 10 years				

Laboratory parameters

Laboratory parameters within 24 hours of admission were available from 1,999 patients (82%). Stratified univariate analyses of laboratory parameters at the time of hospitalisation revealed significant sex differences in levels of C-reactive protein (CRP), ferritin, lymphocyte and platelet counts, lactate dehydrogenase (LDH), creatinine, urea, and blood glucose. Males presented with more pronounced laboratory abnormalities on admission, compared to females, but differences were less pronounced in

the subgroups of patients who later required ICU admission or those who died (Table 2). Patients who died, had more marked derangement of all the above test results (Table 3).

Mortality

During follow-up, 455 (18.7%) hospitalised patients died, 277 (60.9%) were males. The 30-day mortality among patients admitted to ICU was 107 (29.8%) (Table 1). The 30-day KM survival rate was 81.2% (95% CI: 79.7–82.8). This was lower for males than for females (78.9% [95% CI: 76.7–81.1%] and 84.0% [95% CI: 81.9–86.2%] respectively, $p < 0.01$). Patients with higher CCI index had lower 30-day survival rates with 63.3% (95% CI: 58.0–69.2%) for those with a CCI > 2 and 88.9% (CI: 87.3–90.6%) for CCI of zero. The effect of the level of CCI was more pronounced in patients of older age (Fig. 1).

ICU admission

Among all 2,431 hospitalised patients, 359 (14.8%) were admitted to the ICU (median age 69 years [IQR 59–75], 70.5% male), 240 (66.9%) required IMV, 78 (21.7%) dialysis, 210 (58.5%) vasopressors and 18 (5%) ECMO (Table 1). The cumulative incidence rate of ICU admission during the first week after hospitalisation was 12.6% (95% CI: 11.3–13.9%), the risk was lower for females than males (7.9% vs. 16.7%, $p < 0.001$) and for patients aged 85 and older compared to those under 85 (5.4% vs. 15.1%, $p < 0.001$). There was no difference on CCI with 12.7% (95% CI: 11.0–14.4%), 13.7% (95% CI: 11.1–16.2%) and, 9.7% (95% CI: 6.3–13.1%) for CCI zero, 1–2 and > 2 respectively ($p = 0.601$). The cumulative incidence of ICU admission only increased slightly after the first 7 days of follow-up.

Prognostic factors for death

In the multivariate analyses (Fig. 2A and B), the strongest risk factor for death within both days 1–7 and 8–30 was age. Conditional upon surviving the first week, the underlying comorbidity level, increasing age and male sex were all associated with death during day 8–30. All explored baseline laboratory parameters at admission were associated with death within the first 7 days except alanine transaminase, whereas elevated CRP, neutrophil count, LDH, Creatinine and urea were associated with death within 30-days given survival of the first week.

Discussion

In this nationwide study of COVID-19 patients, 2,431 individuals, of which 60.7% had a registered comorbidity within the past 10 years, were hospitalised. ICU admission was required in 14.8% individuals. Advanced age, high levels of systemic inflammation (CRP, ferritin, D-dimer), high cell turnover (LDH), azotaemia (urea, creatinine), and haemato-lymphoid reaction (lymphopenia, neutrophilia, thrombocytopenia) were associated with death within the first week of admission. Conditional upon surviving the first week, male sex, age, comorbidity, elevated CRP, LDH, creatinine, urea and neutrophilia were associated with death within 8–30 days. Patients who later required ICU admission had higher markers of inflammation, cell-turnover and metabolic dysregulation.

Our findings are in line with the previously reported effects of age, male sex, and level of comorbidities on both mortality and the need for ICU admission [2, 4, 8, 17, 26]. In contrast to previous reports [2, 3, 16], a remarkably high proportion (nearly two thirds of patients) had low levels of comorbidity previous the COVID-19 admission. Having a moderate to high level of comorbidity was associated with a nearly two-fold increase in mortality. Males and females had similar mortality rates during the first week of admission, but likelihood for death significantly diverged towards an increased fatality rate among males after surviving the first week for all analysed strata. The reasons behind these differences in early and late mortality are not clear for us, but probably multifactorial. Residual confounding is a possibility we acknowledge.

In line with previous findings, patients who were at highest risk of ICU admission were males with higher CRP, LDH and blood glucose among others, indicating higher levels of inflammation, cell-turnover and metabolic dysregulation [4, 8, 15, 27]. Sex differences in laboratory parameters were markedly less pronounced in the subgroup of patients who presented with more severe outcomes, including ICU admission and death. Differences in the degree of inflammatory response between males and females could be a field for future research.

Abnormal coagulation parameters on admission, including D-dimer, were associated with a higher risk of death but not ICU admission (Table 3) as shown in other studies [8, 17]. This could be related to a low number of events among patients where the test was taken.

Study Strengths And Limitations

Since Danish health care registries are independently recorded and complete [20–22], the risk of selection bias and loss to follow-up was minimal. However, we acknowledge potential differences in referral patterns during the epidemic. Moreover, during the early-stage of the epidemic, treatment of COVID-19 was merely symptomatic. By early April 2020, a few pharmacological interventions were available mostly within the frame of clinical trials [28], which, alongside with improved clinical management, could have had an impact on our outcome estimates over time. In comparison to previous studies from Denmark [5–7] we found a higher mortality. However, we report outcomes in a selected group of patients namely those in need of hospitalisation and therefore presenting with a more severe clinical course.

The diagnosis of COVID-19 and several other variables have not yet undergone full internal validation to date. In our survival analysis, loss to follow-up in relation to the primary outcome (mortality) could cause informative censoring. However, as borders were closed during most of the study period, we consider this problem minimal. Also, we did not have access to vital parameters (blood pressure, oxygen saturation etc.) through the data sources.

Studies of diseases and conditions that may develop rapidly with fatal outcome can be susceptible to Neyman bias, which arises when a gap in time occurs between exposure and selection of study participants [29]. E.g. if a sizable number of individuals arrived at the hospital but died before COVID-19 testing was in place, this bias may apply. We addressed this bias by using the first admission date to the

hospital as the start of follow-up rather than the date of diagnosis. This first admission was identified by iteratively looking back for any hospital contacts within 24 hours previously.

Regarding missing data, we argue that laboratory parameters are missing in a systematic, non-random fashion as blood samples were taken only when a healthcare worker deemed it appropriate based on a clinical judgment. The adjusted hazard ratios should thus be interpreted as prognostic factors for a highly selected population for which laboratory parameters were relevant for clinical reasons [30]. Laboratory parameters were missing from the western region of Denmark, but 82% of the study population had blood samples taken within 24 hours of admission. However, the majority of cases have been seen in the capital region [1].

The laboratory cut-off parameters for the multivariate analysis were arbitrary selected by the investigators. This could perhaps have resulted in an underestimation of the association between some laboratory parameters and outcomes. We have therefore included detailed stratified description of the results in Tables 2 and 3, and the multivariate analysis should be interpreted in this context.

Finally, the generalizability of our results to other settings would be limited due to organizational and capacity differences between health systems in different countries, particularly regarding the definitions of ICU admissions.

Conclusion

Among hospitalised patients during the first wave of COVID-19 in Denmark, advanced age, male sex, chronic comorbidities, and selected clinical and laboratory parameters were all associated with higher risk of severe COVID-19 related outcomes. Males presented with more pronounced laboratory abnormalities at hospital admission. Males and females had comparable mortality during the first week of admission, but the likelihood for death was significantly higher for males after the first week. ICU admitted patients had higher markers of inflammation, cell-turnover, and metabolic dysregulation. Identification of such factors can be used for planning strategies targeting specific high-risk individuals.

Declarations

Acknowledgments

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Author contributions

JGH, ZBH planned, conceived and coordinated the study. RE, MvW, JGH, analysed the data. JGH, ZBH prepared the first draft of the manuscript. JGH, RE, MvW, have full access to the data. All authors contributed to interpretation of results, edited and approved the final version and the manuscript.

Conflicts of Interest

All authors declare no competing interest related to the submitted work. Dr. Kirk reports personal fees and non-financial support from Gilead, personal fees from Viiv, personal fees from Merck, personal fees from Janssen, outside the submitted work.

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Data Sharing

Data is available upon request from the Danish health data authority. None of the data will be shared by the authors.

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Tables

Due to technical limitations, table 2 & 3 is only available as a download in the Supplemental Files section.

Figures

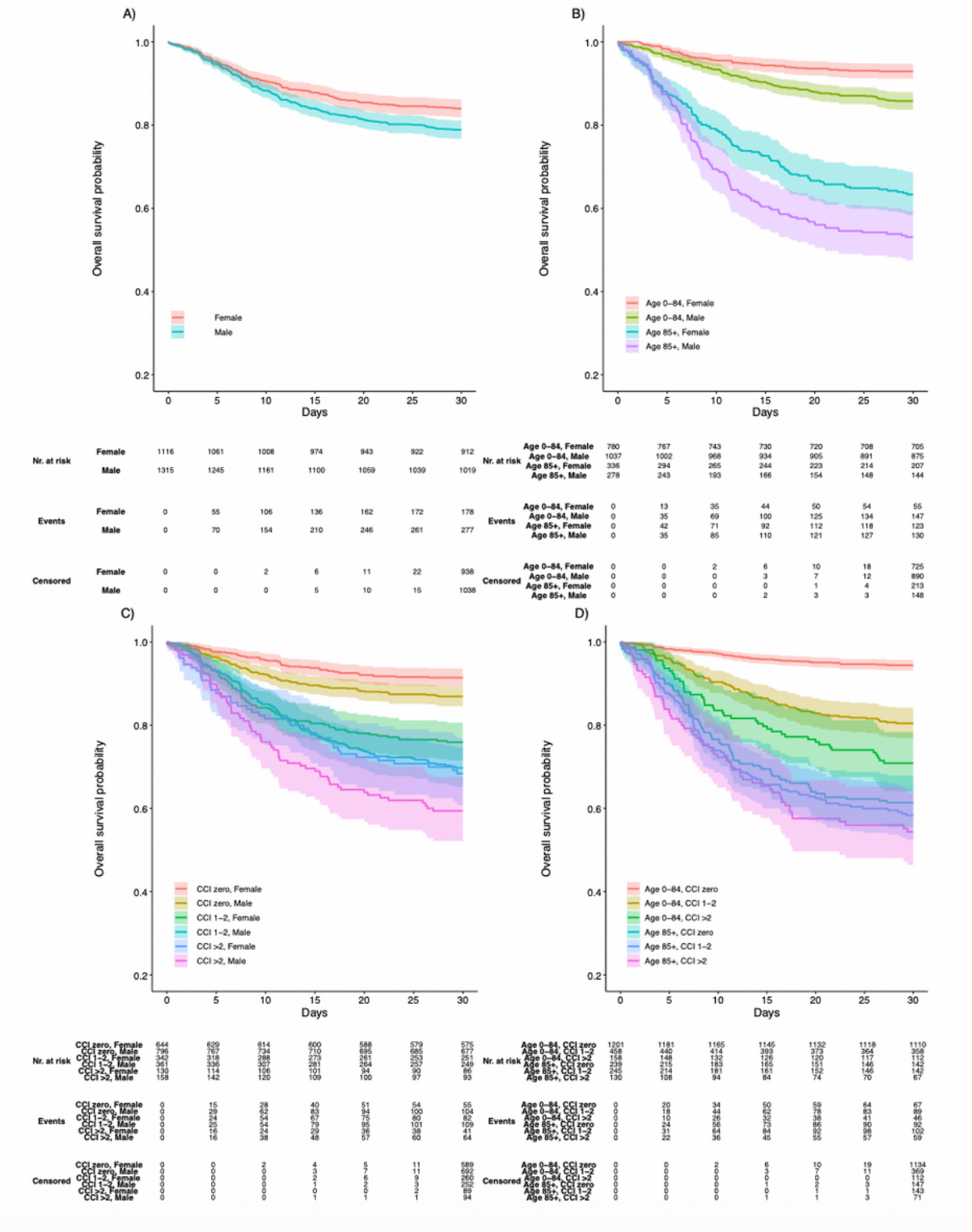

Figure 1

Kaplan-Meier curves illustrating 30-day survival. A) Sex. B) Sex and age. C) Charlson comorbidity index modified by Quan and sex. D) Charlson comorbidity index modified by Quan and age-group.

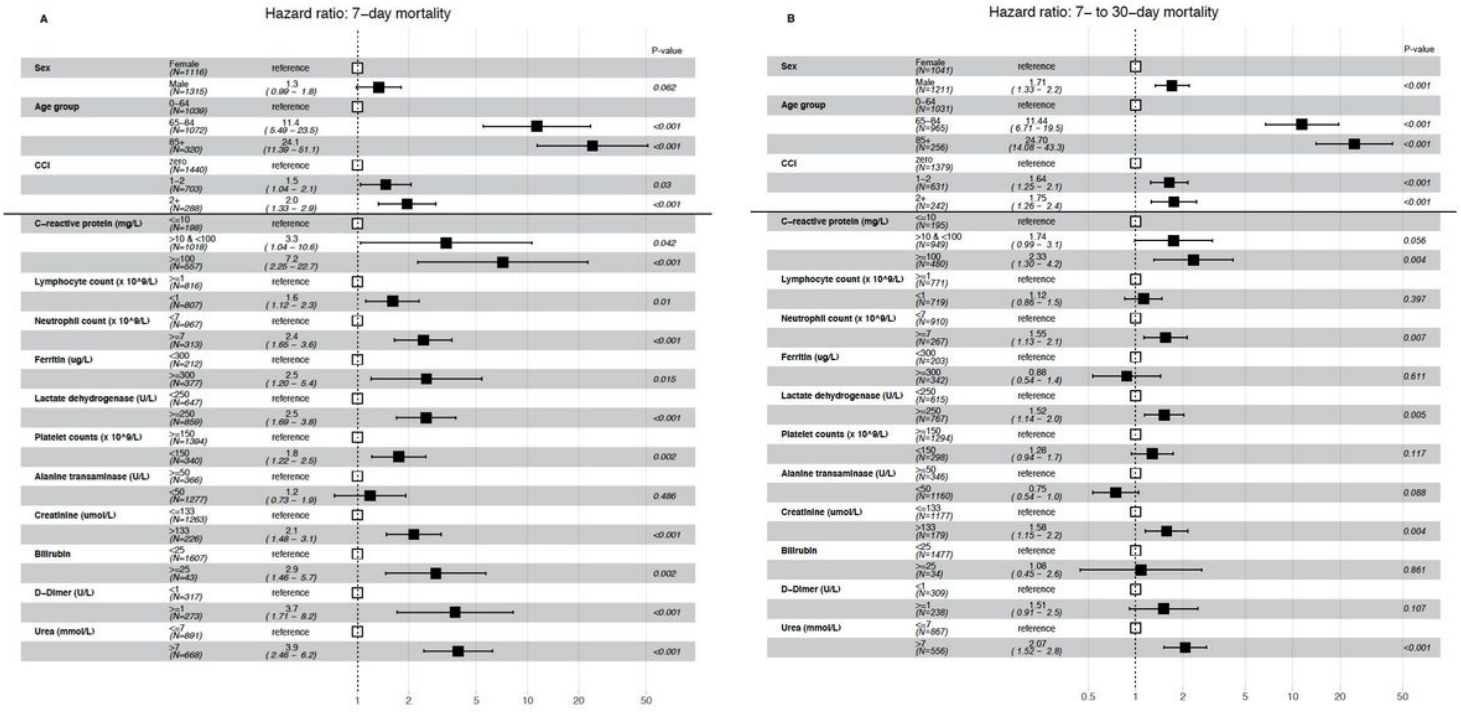

Figure 2

(A and B). Forest plot showing hazard ratios obtained by multivariate Cox regression analysis of prognostic factors of death in patients admitted with Covid-19. Patients who died during the first 7-days after admission were excluded from the analyses of 8 to 30-day mortality. Models were adjusted for sex, age-group, and Charlson Comorbidity Index (0, 1-2, >2). Laboratory measures were each adjusted individually. Where noted, the biometrics were entered on the log2 scale. Reference: normal value; CI: confidence interval; HR: hazard ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.docx
- Table3.docx
- SupplementaryTableS1.docx