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Long title:

Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort.

Short title: Acute Kidney Injury in ICU-treated COVID-19 patients.

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ABSTRACT

Objectives: Acute kidney injury (AKI) is a frequent complication among critical ill patients with COVID-19, but the actual incidence is unknown as AKI-incidence varies from 25 to 89% in intensive care unit (ICU) populations. We aimed to describe the prevalence and risk factors of AKI in COVID-19 patients admitted to ICU in Norway.

Design: Nation-wide observational study with data sampled from the Norwegian Intensive Care and Pandemic Registry (NIPaR) for the period between March 10th until December 31st, 2020.

Setting: ICU patients with COVID-19 in Norway. NIPaR collects data on intensive care stays covering more than 90% of Norwegian ICU and 98% of ICU stays.

Participants: Adult COVID-19 patients admitted to Norwegian ICU were included in the study. Patients with Chronic Kidney Disease (CKD) were excluded in order to avoid bias from CKD on the incidence of AKI.

Primary and secondary outcome measures: Primary outcome was AKI at ICU admission as defined by renal SAPS-II score in NIPaR. Secondary outcome measures included survival at 30 and 90 days after admission to hospital.

Results: A total number of 361 COVID-19 patients were included in the analysis. AKI was present in 32.0% of the patients at ICU admission. The risk for AKI at ICU admission was related to acute circulatory failure at admission to hospital. Survival for the study population at 30 and 90 days was 82.5% and 77.6%, respectively. Cancer was a predictor of 30-day mortality. Age, acute circulatory failure at hospital admission and AKI at ICU admission were predictors of both 30- and 90-day mortality.

Conclusions: A high number of COVID-19 patients had AKI at ICU admission. The study indicates that AKI at ICU admission was related to acute circulatory failure at hospital admission. Age, acute circulatory failure at hospital admission and AKI at ICU admission were associated with mortality.

ARTICLE SUMMARY

Strength and limitations of this study

- The study investigates a national registry cohort of ICU treated COVID-19 patients.
- The study provides prevalence, risk factors and outcome for COVID-19 patients with AKI in the ICU.
- AKI in the ICU was defined according to renal SAPS II score and does not fully comply with the RIFLE or KDIGO criteria due to the lack of creatinine-based measures of kidney function in the registry.

INTRODUCTION

COVID-19, an infectious disease caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has quickly developed into a pandemic since the early outbreak in Wuhan, China, in December 2019 [1].

Several studies report Acute Kidney Injury (AKI) among hospitalized COVID-19 patients while less data is obtained exclusively in Intensive Care Unit (ICU) patients [2-10]. To our knowledge, previous studies are not based upon all ICU admissions within a large population. Furthermore, there is a call from the consensus report on COVID-19 associated AKI published by the 25th Acute Dialysis Quality Initiative (ADQI) Workgroup that studies should "incorporate the information about the proportion of different comorbidities in patients with and without AKI, including potential risk factors for the development of AKI" [11].

National registries in Norway provide opportunities to perform nationwide registry studies in order to answer calls such as the one from the ADQI workgroup. The strength of such registry-based studies is that they are based on larger patient cohorts which make results more robust and generalizable. The drawback is that registry data set seldom are a direct fit for the research in question, making adaptations and extrapolations necessary.

This study is based on data available from the Norwegian Intensive Care and Pandemic Registry (NIPaR). NIPaR is a government funded national health registry constituted of two parts; the Norwegian Intensive Care Registry established in 1998, and the Norwegian Pandemic Registry established in March 2020 [12]. Registration is mandatory, and data is entered by hospital staff. For patients with COVID-19 in the ICU we report the prevalence of AKI, factors associated with AKI and the association between AKI and mortality.

METHODS

The Norwegian Intensive Care and Pandemic Registry (NIPaR) contains two patient populations. NIPaR collects data on intensive care stays in pre-defined ICU, covering more than 90% of Norwegian ICU and 98% of ICU stays [13]. Qualification criteria for ICU and intensive care patients are defined by NIPaR [14]. The Norwegian Pandemic Registry includes patients admitted to hospital in Norway with a positive PCR test for SARS-CoV-2 during the previous 3 months, and includes 99% of pandemic patients admitted to hospital [13]. Both registry parts employ automatic and manual validation to ensure data quality.

The study group included COVID-19 patients above the age of 18 years admitted to ICU in the period between March 10th, 2020 (the initial outbreak of SARS-CoV-2 in Norway), until December 31st, 2020. Patients with Chronic Kidney Disease (CKD), defined as previously diagnosed kidney disease upon hospital admission, were excluded in order to avoid bias from CKD on the effects of AKI.

Data collection at hospital admission included age, gender, height, weight, comorbidities, pregnancy, regular medication of Angiotensin-Converting Enzyme-inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB), smoking, S-Creatinine (SCr), organ complications at hospital admission (Acute Kidney Injury [AKI], Acute Respiratory Failure [ARF], Acute Circulatory Failure [ACF] recorded at the discretion of the attending physician).

Data collection from the ICU stay included primary reason for referral to ICU, clinical scoring systems in the ICU (Glasgow Coma Scale [GCS], SAPSII-score), length of stay (LOS), mechanical ventilation, Renal Replacement Therapy (RRT) (Intermittent [IRRT] and Continuous [CRRT]), and survival (ICU first 24 hours, in-hospital at ICU and at 30 and 90 days after admission to hospital).

Definitions

Due to lack of variables, it was not possible to employ creatinine values to define AKI in the ICU. The only available marker for renal function in the Norwegian Intensive Care Registry is contained within the Simplified Acute Physiology Score (SAPS II) [15]. As a result, renal Simplified Acute Physiology Score II (rSAPSII) is the sole marker for AKI during ICU stay in this study. AKI in the ICU was defined as rSAPSII score of ≥4 (Urine Output/24 h <1000

ml and/or Blood Urea Nitrogen >10 mmol/L). SAPS II is based on observations within the first 24 hours in the ICU.

AKI at admission to hospital was defined according to RIFLE-criteria. A serum creatinine increase of >1.5x baseline was available as a separate variable (RIFLE Risk-category). For missing data, AKI at hospital admission was based on serum creatinine at hospital admission and the MDRD equation for estimating baseline creatinine. An estimated Glomerular Filtration Rate (GFR) of 75 ml/min/1.73m2 was used to calculate baseline creatinine [16]. Data on ethnicity was not available for input in the equation.

Acute Circulatory Failure (ACF) was defined as acute deterioration in the patient circulation at admission to hospital as compared to normal state, resulting in circulatory symptoms in high, moderate or light exertion or in rest. This includes cardiac arrythmia, symptoms of heart failure and/or cardiac ischemia.

Acute Respiratory Failure (ARF) at admission to hospital was defined as acute deterioration of respiratory function at admission to hospital as compared to normal state, resulting in respiratory symptoms in high, moderate or light exertion or in rest.

Comorbidities are defined as pre-existing diagnoses upon admission to hospital. Comorbidities included Chronic Pulmonary Disease (CPD), Asthma, Diabetes Mellitus (DM) type 1 or 2, Chronic Kidney Disease (CKD), Cardiovascular Disease (CVD) including Hypertension, Liver disease, Chronic Neurological Disease (CND), Cancer, and Immunocompromised condition (including HIV and immunosuppressive therapy).

The primary outcome was the development of AKI at admission to ICU, while secondary outcomes included survival at 30 and 90 days after admission to hospital.

Statistics

Statistical analysis was performed using IBM SPSS Statistics ® (version 26) and R version 4.0.4. If not stated otherwise, continuous variables are presented as median and/or mean if data is normally distributed, and categorical variables are presented as the number (n) of patients (valid % of the study population). Shapiro-Wilk test of normality was performed for continuous variables. Patient characteristics for patients with or without AKI was compared

using Student's t-test for continuous variables and Fisher exact test for categorical variables. *p*-value <0.05 was considered statistically significant.

Univariate logistic regression analysis was performed to examine the predictors for AKI at ICU-admission (as defined by rSAPSII-score ≥4). Independent variables included age, gender, comorbidities, smoking-status, medication with ACEi or ARB, ACF and ARF at admission to hospital. AKI at admission to hospital was not included as an independent variable in the analysis due to discrepancy in AKI-definition. The variables which were found to be associated with AKI at ICU admission (*p*-value <0.1) were included in multivariable logistic regression model. Multicollinearity was evaluated using the variance inflation factor (VIF). *p*-value <0.05 was considered statistically significant.

Univariate and multivariable logistic regression analysis as described was also performed to assess risk factors associated with 30- and 90-days mortality and the role of AKI at ICU-admission for predicting survival. Independent variables in univariate logistic regression analysis included comorbidities, age, gender, smoking-status, medication with ACEi or ARB, ACF and ARF at admission to hospital, and AKI at ICU-admission. Multicollinearity was evaluated using the VIF. *p*-value <0.05 was considered statistically significant.

Kaplan-Meier survival analyses for the time to death was performed to compare the group with AKI at ICU-admission versus the group with no AKI. The comparison was done using log-rank test. Level of significance was considered *p*-value <0.05. Days from ICU-admission to death (event) or May 15th, 2021 (censoring), considered the time of analysis.

Ethics

The study was approved by Regional Committees for Medical and Health Research Ethics West (approval number 169604). Informed consent was waived based on information to participants in NIPaR about the registry and their right to withdraw from NIPaR.

RESULTS

A total of 394 adult patients were admitted to ICU with COVID-19 in the study period. Thirty-three of the patients were excluded due to CKD, resulting in a study population of 361 ICU-patients, 100 females and 261 males. Median age was 63.6 [IQR; 53.5-72.5] years and median BMI was 27.7 [24.8-32.0] kg/m^2. Current smokers constituted 2.5% of the patients. None of the female patients were pregnant. Median length of stay (LOS) at the ICU was 11.6 [5.7-19.5] days. Mechanical ventilation was initiated in 81.2% of the patients.

Comorbidity was reported in 68.1% of the study population, and 29.1% had two or more comorbidities. Regular medication of Angiotensin Converting Enzyme-inhibitor (ACEi) and/or Angiotensin II Receptor Blocker (ARB) was used by 23.4% of the study population (Table 1).

Table 1: Patient characteristics by AKI-status at ICU admission.

Patient demographics	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
Age in years, median [IQR]	63.6 [53.5-72.5]	-	65.6 [58.4-73.6]	61.6 [52.0-72.3]	**0.003**
Male	261 (72.3%)	-	86 (75.4%)	172 (71.1%)	0.233
Female	100 (27.7%)	-	28 (24.6%)	70 (28.9%)	0.233
BMI, median [IQR]	27.7 [24.8-32.0]	141	27.3 [23.0-30.6]	28.3 [25.1-32.4]	0.132
BMI ≥30	83 (37.7%)	141	21 (31.8%)	61 (40.4%)	0.147
Current smoker	9 (2.5%)	-	3 (2.6%)	6 (2.5%)	0.592
Comorbidity/ies	246 (68.1%)	-	81 (71.1%)	161 (66.5%)	0.233
1	141 (39.1%)	-	44 (38.6%)	94 (38.8%)	0.530
≥2	105 (29.1%)	-	37 (32.5%)	67 (27.7%)	0.212
CVD	158 (43.8%)	-	58 (50.9%)	98 (40.5%)	**0.042**
DM	74 (20.5%)	-	23 (20.2%)	50 (20.7%)	0.518
Asthma	55 (15.2%)	-	15 (13.2%)	39 (16.1%)	0.288
CPD	37 (10.2%)	-	14 (12.3%)	23 (9.5%)	0.266
Immunocompromised	20 (5.5%)	-	5 (4.4%)	14 (5.8%)	0.394
Cancer	17 (4.7%)	-	6 (5.3%)	11 (4.5%)	0.476
CND	12 (3.3%)	-	5 (4.4%)	7 (2.9%)	0.329
Liver disease	3 (0.8%)	-	1 (0.9%)	2 (0.8%)	0.687
ACEi/ARB	83 (23.4%)	7	34 (30.6%)	47 (19.7%)	**0.019**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, IQR = Interquartile Range, BMI = Body Mass Index, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, CND = Chronic Neurological Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker.

Patients with AKI at admission to the ICU were older than patients with no AKI. They also had more cardiovascular disease (CVD) and used more often ACEi or ARB (Table 1). Patients with AKI at admission to ICU were more likely to have reduced GCS, and they had a higher SAPS II score (Table 2).

Table 2: Laboratory findings and organ complications by AKI-status at ICU admission.

Variables at admission to hospital	All patients (N = 361)	Missing data (No of patients)	AKI (n= 114)	No AKI (n= 242)	*p*-value (AKI vs No AKI)
SCr in µmol/l, median [IQR]	85.0 [70.3-104.0]	1	98.0 [73.5-128.0]	80.5 [69.5-96.0]	**<0.000**
Estimated baseline SCr, median [IQR]	92.5 [76.0-95.6]	-	92.5 [85.0-94.5]	92.7 [75.3-96.1]	0.826
AKI at hospital-admission	105 (29.1%)	4	62 (54.4%)	42 (17.4%)	**<0.000**
Severe ARF	319 (88,6%)	1	103 (91,2%)	212 (87.2%)	0.213
Severe ACF	124 (35,4%)	11	49 (45,0%)	74 (31.4%)	**0.010**
Variables at ICU					
GCS					
14-15	323 (89.5%)	-	89 (78.1%)	229 (94.6%)	**<0.000**
≤13	38 (10.5%)	-	25 (21.9%)	13 (5.4%)	**<0.000**
SAPS II score, median [IQR]	34.0 [26.0-42.0]	-	43.0 [37.0-50.0]	31.0 [24.0-36.0]	**<0.000**
BUN in mmol/L		5			
<10	275 (77.2%)	-	33 (28.9%)	242 (100.0%)	**<0.000**
10-29,9	79 (21.9%)	-	79 (69.3%)		
≥30	2 (0.6%)	-	2 (1.8%)		
UO in ml per 24 hours					
>1000	307 (85.0%)	-	60 (52.6%)	242 (100.0%)	**<0.000**
500-999	35 (9.7%)	-	35 (30.7%)		
<500	19 (5.3%)	-	19 (16.7%)		
AKI at ICU admission	114 (32.0%)	5			

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, SCr = Serum-Creatinine, IQR = Interquartile Range, ARF = Acute Respiratory Failure, ACF = Acute Circulatory Failure, GCS = Glasgow Coma Scale, SAPS II = Simplified Acute Physiology Score II, BUN = Blood Urea Nitrogen, UO = Urine Output.

The distribution of organ failure at admission to hospital were 88.6%, 35.4% and 29.1% for Acute Respiratory Failure (ARF), Acute Circulatory Failure (ACF), and AKI (as defined by RIFLE-criteria), respectively. ACF at hospital admission was significantly more prevalent in patients who suffered AKI at ICU admission (*p*-value <0.05).

A total of 114 (32.0%) patients had AKI in the ICU. From these, 79 (69.3%) and 2 (1.8%) had BUN =10-29.9 mmol/L and ≥30 mmol/L, respectively. Urine Output (UO) of 500-999 ml/24 hours and <500 ml/24 hours were presented by 30.7% and 16.7%. More than half of the patients who had AKI at ICU-admission also had AKI at admission to hospital.

Renal Replacement Therapy (RRT) was required in 8.0% (n = 29) of the total patient group during the ICU-stay (Table 3). Continuous RRT (CRRT) was initiated in 28 patients, and intermittent RRT (IRRT) was initiated in 7 patients. Median time with CRRT was 9.0 [5.0-14.0] days and 6.5 [5.0-7.5] days with IRRT.

Table 3: Treatment and patient outcome by AKI-status at ICU admission.

Treatment	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
LOS in ICU, median [IQR]	11.6 [5.7-19.5]	-	13.5 [5.9-25.6]	10.9 [5.7-19.0]	0.125
Mechanical ventilation[a]	293 (81.2%)	-	99 (86.8%)	192 (79.3%)	0.057
RRT	29 (8.0%)	-	16 (14.0%)	13 (5.4%)	**0.006**
CRRT	28 (7.8%)	-	15 (13.2%)	13 (5.4%)	**0.012**
Median days [IQR]	9.0 [5.0-14.0]	-	8.0 [5.0-12.0]	11.5 [5.5-16.3]	0.863
IRRT	7 (1.9%)	-	6 (5.3%)	0 (0.0%)	**0.001**
Median days [IQR]	6.5 [5.0-7.5]	-	6.5 [5.0-7.5]	-	-
Outcome					
Survival first 24 hours in ICU	358 (99.2%)	-	111 (97.4%)	242 (100.0%)	**0.032**
Survival at hospital discharge	295 (81.7%)	-	80 (70.2%)	210 (86.8%)	**<0.000**
Survival at 30 days	298 (82.5%)	-	77 (67.5%)	217 (89.7%)	**<0.000**
Survival at 90 days	280 (77.6%)	-	70 (61.4%)	206 (85.1%)	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, LOS = Length of stay, IQR = Interquartile Range, RRT = Renal Replacement Therapy, CRRT = Continuous Renal Replacement Therapy, IRRT = Intermittent Renal Replacement Therapy.

Survival for the total study population at 30 and 90 days was 82.5% and 77.6%, respectively. Survival at 30 and 90 days in patients with AKI at ICU admission were 67.5% and 61.4%, respectively, which was significantly lower compared to 89.7% and 85.1% in patients with no AKI.

A total of 337 patients with no missing data were included in three logistic regression analyses to assess risk factors for AKI at ICU admission and risk factors associated with mortality.

In the first multivariate model only ACF was significantly associated with the development of AKI at ICU-admission (OR 1.19; 95% CI: 1.05–1.35) (Table 4). Multicollinearity was evaluated using the variance inflation factor (VIF). VIF ranged from 1.02 (ACF) to 1.51 (CVD). The area under the curve (AUC) was 0.64 (95% CI: 0.57–0.70).

Table 4: Odds for AKI at ICU admission.

Univariate logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.50	0.11 - 1.58	0.281			
Liver disease	1.11	0.05 - 11.67	0.935			
Cancer	0.80	0.22 - 2.39	0.701			
CND	1.27	0.33 - 4.31	0.705			
Current smoker	1.11	0.23 - 4.29	0.886			
Gender	0.88	0.52 - 1.46	0.619			
Age	1.02	1.01 - 1.04	**0.013**	1.02	1.00 - 1.04	0.121
CVD	1.50	0.94 - 2.38	0.089	1.00	0.56 - 1.78	0.996
DM	0.95	0.52 - 1.69	0.867			
Asthma	0.79	0.39 - 1.49	0.474			
CPD	1.17	0.54 - 2.42	0.673			
ACEi/ARB	1.77	1.04 – 3.00	**0.033**	1.52	0.82 - 2.83	0.187
ACF	1.21	1.07 - 1.37	**0.002**	1.19	1.05 - 1.35	**0.006**
ARF	1.08	0.85 - 1.42	0.561			
(Intercept)				0.09	0.03 - 0.31	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure.

In the second multivariate model, risk factors associated with 30-day mortality were Cancer, Age, AKI at ICU-admission and ACF (Table 5). VIF ranged from 1.03 (ACF) to 1.47 (CVD). The AUC was 0.87 (95% CI 0.83–0.92).

Table 5: Odds for survival at 30 days.

Univariate logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.29	0.02 - 1.47	0.235			
Liver disease	2.28	0.11 - 24.21	0.503			
Cancer	3.24	1.05 - 9.35	**0.032**	4.39	1.17 - 15.90	**0.024**
CND	0.44	0.02 - 2.38	0.442			
Current smoker	1.30	0.19 - 5.55	0.746			
Gender	1.54	0.85 - 2.75	0.149			
Age	1.08	1.05 - 1.11	**<0.000**	1.07	1.04 - 1.11	**<0.000**
CVD	2.33	1.33 - 4.15	**0.004**	0.93	0.40 - 2.11	0.857
DM	1.14	0.56 - 2.20	0.707			
Asthma	1.09	0.49 - 2.25	0.818			
CPD	4.17	1.97 - 8.73	**<0.000**	2.50	0.98 - 6.43	0.055
ACEi/ARB	2.02	1.09 - 3.66	**0.023**	1.24	0.53 - 2.89	0.625
ACF	1.78	1.50 - 2.14	**<0.000**	1.70	1.41 - 2.09	**<0.000**
ARF	1.18	0.87 - 1.79	0.349			
AKI at ICU admission	4.32	2.44 - 7.78	**<0.000**	3.78	1.90 - 7.67	**<0.000**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

In the third model, age, AKI at ICU-admission and ACF were associated with 90-day mortality (Table S1). VIF in this model ranged from 1.02 (ACF) to 1.46 (CVD). The AUC was 0.87 (95% CI 0.82–0.91).

The results of Kaplan-Meier survival analysis stratified by AKI-status at admission to ICU showed that patients with AKI had significantly lower survival than patients without AKI (log-rank *p*-value <0.001) (Fig 1). The difference in survival was constrained to the first 50 days.

<Figure 1>

DISCUSSION

We performed a nationwide study of 361 adult patients with COVID-19 admitted to ICU. Prevalence of AKI at ICU admission was 32.0%. Acute Circulatory Failure (ACF) at hospital admission predicted AKI at ICU admission. Age, Cancer, ACF, and AKI at ICU admission were risk factors for mortality at 30 days.

The COVID-19 pandemic in Norway, with its population of 5.4 million people [17], has been relatively well contained. During the study period a total 50145 cases of SARS-CoV-2 were reported, of which 2185 were admitted to hospital and 394 to the ICU [18]. As in other countries, patients with COVID-19 in Norwegian ICU tend to be younger and more likely male compared with the general ICU-population [14]. Most patients in the study population were overweight, and a large proportion were obese, which is markedly different than in the general Norwegian population [19]. Comorbidities such as CVD, DM and Asthma, were also more prevalent in the study population than in the general Norwegian population [20].

The definition of AKI at ICU admission in our study does not fully comply with the AKI staging criteria due to the lack of creatinine-based measures of kidney function in the Norwegian Intensive Care Registry [21]. The SAPS II criteria for reduced urine output are similar to the staging criteria from the AKI network consensus, corresponding to AKI stage 2 and 3 (Table S2). BUN may increase by factors unrelated to kidney function, for instance due to steroid use which is regularly prescribed to COVID-19 patients in the ICU [22]. This would lead to an overestimate of AKI at ICU admission in our study, given standard enteral nutrition practices in Norwegian ICU. Creatinine is also influenced by several factors unrelated to kidney function but was chosen over BUN as the preferred biochemical parameter in the consensus process leading up to AKI definitions due to its widespread use [21 23].

While not fully in line with current AKI definitions, the combination of urine output and BUN should provide an estimate of AKI sufficiently similar to that of creatinine and urine output to be relevant in a registry study. The significant difference in s-creatinine at admission to hospital between patients with and without AKI at ICU admission in our material supports this assumption. Prevalence of AKI at ICU admission in our study is also similar to previous findings in the general ICU population. Bagshaw et al. report that on the

day of ICU-admission, 36% of the general ICU-population suffer AKI as defined by RIFLE-criteria, 16.3% in the Risk group and 19.9% in the Injury and Failure groups combined [24]. A narrative review in COVID-19 found 23% prevalence of AKI in the ICU [25]. In our study, 30.2% (n = 114) of COVID-19 patients admitted to ICU had AKI (Table 2).

Due to the lack of granularity in our data there are findings in our material that warrant further investigation. In our study group, 40.4% (n = 42) of the patients with AKI at admission to hospital did not present AKI at ICU admission. It is likely that different AKI criteria applied at hospital admission and ICU admission affects this difference. However, we cannot rule out, for instance, that patients with mild pre-renal AKI at admission were clinically stabilized to normal kidney function in a hospital ward prior to ICU admission due to respiratory failure. This would not contradict the impression that many COVID-19 patients in the ICU have single organ respiratory dysfunction [26]. On the other hand, 5.4% (n=13) of patients with no AKI at ICU admission received RRT during their ICU stay (Table 3). We would expect some patients with long ICU stays do develop AKI during their ICU stays, but we cannot rule out losing cases of AKI at ICU admission due to lack of creatinine values in the ICU. In order to establish the timeline of AKI in COVID-19 patients in ICU, studies with higher granularity data including serial urine output and creatinine measurements are needed.

In the regression model for AKI at ICU admission, only ACF at admission to hospital was found to be significantly associated. ACF is an uncommonly reported parameter at admission to hospital, and thus often not included in analysis for prediction of AKI. Although we biologically would expect collinearity between ACF and AKI at ICU admission, this was contradicted by low VIF in the statistical analysis. The results suggests that AKI at ICU admission is more closely associated to circulatory status than any other factors in critically ill COVID-19 patients.

In the regression model on survival, the factors Age, Cancer, ACF and AKI at ICU admission were significantly associated with increased risk of death during first 30 days. Age, ACF, and AKI at ICU admission were significantly associated with increased risk of death during first 90 days. AKI at ICU admission contributed considerably more to the regression model than both age and CVD, which are previously well-recognized risk factors for severe disease progression and mortality in COVID-19 [27]. The finding puts AKI at ICU admission up as a strong and clinically important marker of survival in critically ill COVID-19 patients, more

so than age and CVD. While cancer also had a high contribution to the model, only 17 patients with cancer are included in the study, which reduces the clinical impact of this finding. Chronic Pulmonary Disease (CPD) also contributes to the model but is only borderline significant. This is a risk factor in a larger group of the study population, 37 in total, and as such may be a more clinically relevant risk factor than cancer.

More than one out of three patients with AKI diagnosed first 24 hours of ICU-stay were deceased after 30-90 days. The Kaplan-Meier analysis illustrates that the mortality is predominantly in the short term within 50 days, in essence predominantly during the acute phase of illness. The finding supports that AKI at ICU-admission is a clinically important marker for poor outcome in COVID-19 (Figure 1). Low VIF in both regression models means that the effects of collinearity in the models are low. This puts further emphasis on AKI at ICU admission as an important prognostic factor for mortality in COVID-19.

We recognize several strengths and limitations in this study. The study is a national cohort containing complete data of all Norwegian COVID-19 patients (N = 394) admitted to ICU in the study period. Furthermore, because of the mandatory obligation by the Norwegian authorities to deliver data, the number of missing data was negligible. ICU admission criteria and treatment traditions are also similar in Norwegian ICUs which renders that data are comparable across centers. Furthermore, during the COVID-19 pandemic in Norway patients were not denied ICU care due to capacity concerns, thereby reducing selection bias due to triage decisions.

While national data increases generalizability, a limitation in this study is that the Norwegian Intensive Care and Pandemic Registry (NIPaR) does not contain creatinine-based measures for AKI. This limitation mandates that the results be interpreted with caution. We also lack data regarding the timeline of AKI in COVID-19. While the statistical analyses are rigorous, we nevertheless recommend that the results are treated as a basis for further investigation.

CONCLUSION

In this national cohort of COVID-19 patients admitted to ICUs in Norway 32.0% (n = 114) developed Acute Kidney Injury (AKI) during first 24 hours of ICU-admission. The majority presented clinical and/or biochemical signs of AKI at admission to hospital. The study indicates that Acute Circulatory Failure (ACF) at hospital admission was the most important risk factor for AKI at admission to ICU, and that age, cancer, ACF and AKI at ICU-admission were associated with mortality at 30 days after hospital admission.

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ABREVIATIONS

ACEi = Angiotensin-Converting Enzyme-inhibitor

ACF = Acute Circulatory Failure

ADQI = Acute Dialysis Quality Initiative

AKI = Acute Kidney Injury

ARB = Angiotensin II Receptor Blocker

ARF = Acute Respiratory Failure

BMI = Body Mass Index

BUN = Blood Urea Nitrogen

CKD = Chronic Kidney Disease

CND = Chronic Neurological Disease

COVID-19 = Corona Virus Disease-19

CPD = Chronic Pulmonary Disease

CRRT = Continuous Renal Replacement Therapy

CVD = Cardiovascular Disease

DM = Diabetes Mellitus

GFR = Glomerular Filtration Rate

GCS = Glasgow Coma Scale

ICU = Intensive Care Unit

IRRT = Intermittent Renal Replacement Therapy

KDIGO = The Kidney Disease: Improving Global Outcomes

NIPaR = Norwegian Intensive Care and Pandemic Registry

RIFLE = Risk, Injury, Failure, Loss of kidney function and End-stage renal disease

RRT = Renal Replacement Therapy

rSAPS II = renal Simplified Acute Physiology Score II

SAPS II = Simplified Acute Physiology Score II

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2

SCr = Serum-Creatinine

UO = Urine Output

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COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

DATA SHARING STATEMENT

Data cannot be shared publicly because of GDPR restrictions. Data are available from Norwegian Intensive Care and Pandemic Registry (NIPaR) upon application containing necessary approvals

AUTHOR CONTRIBUTIONS

All authors contributed to the study design. EAA and EAB collected data; EAA and FZG analyzed the data; All authors contributed to interpretation of results and in writing the paper.

EXCLUSIVE LICENSE STATEMENT

PATIENT CONSENT FORM

Not applicable.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

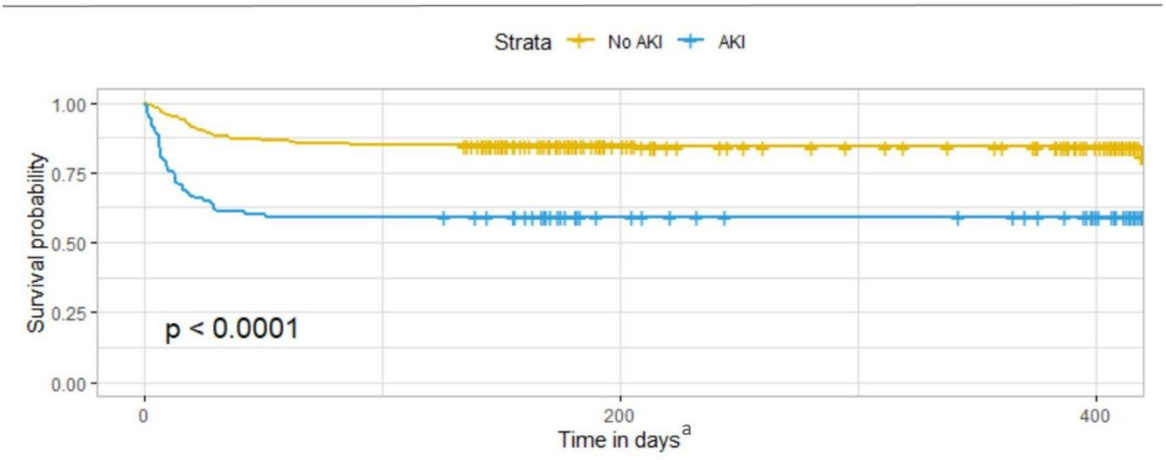
SUPPORTING INFORMATION

1. Figure(s)

Figure 1: Kaplan-Meier Survival analysis stratified by AKI-status at ICU admission.

Legends: Time in days from ICU admission. AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Figure 1: Kaplan-Meier survival analysis stratified by AKI-status at admission to ICU.



AKI = Acute Kidney Injury, ICU = Intensive Care Unit, [a]Time in days from ICU-admission,

2. Supplementary material

S1 Table (Supplementary table)**: Odds for survival at 90 days**. *Legends:* OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S1: Odds for survival at 90 days.

	Univariate logistic regression			**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.21	0.01 - 1.07	0.135			
Liver disease	1.67	0.08 - 17.65	0.678			
Cancer	2.32	0.75 - 6.64	0.123			
CND	0.32	0.02 - 1.73	0.285			
Current smoker	0.95	0.14 - 4.02	0.947			
Gender	1.15	0.66 - 1.99	0.611			
Age	1.08	1.06 - 1.11	**<0.000**	1.08	1.04 - 1.11	**<0.000**
CVD	2.25	1.35 - 3.79	**0.002**	0.72	0.33 - 1.53	0.396
DM	0.97	0.50 - 1.81	0.928			
Asthma	0.76	0.35 - 1.54	0.468			
CPD	3.26	1.57 - 6.71	**0.001**	2.03	0.79 - 5.23	0.139
ACEi/ARB	2.54	1.45 - 4.45	**0.001**	1.94	0.88 - 4.32	0.102
ACF	1.78	1.53 - 2.10	**<0.000**	1.72	1.46 - 2.06	**<0.000**
ARF	1.31	0.96 – 2.00	0.133			
AKI at ICU-admission	3.90	2.31 - 6.67	**<0.000**	3.14	1.66 - 6.00	**0.001**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

S2 Table (Supplementary table): **Comparison of AKI definitions and staging criteria**.

Legends: AKI = Acute Kidney Injury, KDIGO = Kidney Disease, RIFLE =, SAPS II =, SCr = Serum Creatinine, GFR = Glomerular Filtration Rate, UO = Urine Output, BUN = Blood Urea Nitrogen, RRT = Renal Replacement Therapy, h = hours.

Table S2: Comparison of AKI definitions and staging criteria

KDIGO		RIFLE			Renal SAPS II		
Stage	**SCr[a]**	**Class**	**SCr or GFR**	**UO[b]**	**Score**	**UO/24 h**	**BUN**
					0	>1000 ml	<10 mmol/L
1	1.5-1.9x baseline or >26.5 µmol/L increase	**Risk**	SCr increase 1.5x baseline or eGFR decrease ≥25%	<0.5ml/kg/h for 6 h			
2	2.0-2.9x baseline	**Injury**	SCr increase 2.0x baseline or eGFR decrease ≥50%	<0.5 ml/kg/h for 12 h (<840 ml/24 h[c])	**4**	500-999 ml	
					6		10-29.9 mmol/L
3	≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) increase or initiation of RRT	**Failure**	SCr increase ≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) or GFR decrease ≥75%	<0.3 ml/kg/h for 24 h (<504 ml/24 h[c]) or anuria for 12 hours.	**10**		>30 mmol/L
					11	<500 ml	

[a]SCr-increase within 48 hours.

[b]UO criteria are shared by KDIGO and RIFLE.

[c]Standardized for a patient with a weight of 70 kg.

AKI = Acute Kidney Injury, KDIGO: Kidney Disease: Improving Global Outcomes, RIFLE: Risk, Injury, Failure, Loss, End-stage kidney disease, SAPS II = Simplified Acute Physiology Score II, SCr = Serum Creatinine, GFR = Glomerular Filtration Rate, UO = Urine Output, BUN = Blood Urea Nitrogen, RRT = Renal Replacement Therapy, h = hours.

Table 1: Patient characteristics by AKI-status at ICU-admission.

Patient demographics	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
Age in years, median [IQR]	63.6 [53.5-72.5]	-	65.6 [58.4-73.6]	61.6 [52.0-72.3]	**0.003**
Height in cm, median [IQR]	174.0 [166.0-180.0]	138	175.0 [169.0-180.0]	173.0 [165.0-180.0]	0.258
Weight in kg, median [IQR]	85.0 [75.0-95.1]	90	83.0 [70.0-96.3]	85.2 [75.0-95.0]	0.418
BMI (CI), median [IQR]	27.7 [24.8-32.0]	141	27.3 [23.0-30.6]	28.3 [25.1-32.4]	0.132
	No of patients (%)				
BMI ≥30	83 (37.7%)	141	21 (31.8%)	61 (40.4%)	0.147
Male	261 (72.3%)	-	86 (75.4%)	172 (71.1%)	0.233
Female	100 (27.7%)	-	28 (24.6%)	70 (28.9%)	0.233
Current smoker	9 (2.5%)	-	3 (2.6%)	6 (2.5%)	0.592
Comorbidity/ies	246 (68.1%)	-	81 (71.1%)	161 (66.5%)	0.233
1	141 (39.1%)	-	44 (38.6%)	94 (38.8%)	0.530
≥2	105 (29.1%)	-	37 (32.5%)	67 (27.7%)	0.212
CVD	158 (43.8%)	-	58 (50.9%)	98 (40.5%)	**0.042**
DM	74 (20.5%)	-	23 (20.2%)	50 (20.7%)	0.518
Asthma	55 (15.2%)	-	15 (13.2%)	39 (16.1%)	0.288
CPD	37 (10.2%)	-	14 (12.3%)	23 (9.5%)	0.266
Immunocompromised	20 (5.5%)	-	5 (4.4%)	14 (5.8%)	0.394
Cancer	17 (4.7%)	-	6 (5.3%)	11 (4.5%)	0.476
CND	12 (3.3%)	-	5 (4.4%)	7 (2.9%)	0.329
Liver disease	3 (0.8%)	-	1 (0.9%)	2 (0.8%)	0.687
ACEi/ARB	83 (23.4%)	7	34 (30.6%)	47 (19.7%)	**0.019**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, IQR = Interquartile Range, BMI = Body Mass Index, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, CND = Chronic Neurological Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker.

Table 1: Patient characteristics by AKI-status at ICU admission.

109x97mm (300 x 300 DPI)

Table 2: Laboratory findings and organ complications by AKI-status at ICU-admission.

Variables at admission to hospital	All patients (N = 361)	Missing data (No of patients)	AKI (n= 114)	No AKI (n= 242)	*p*-value (AKI vs No AKI)
SCr in µmol/l, median [IQR]	85.0 [70.3-104.0]	1	98.0 [73.5-128.0]	80.5 [69.5-96.0]	**<0.000**
Estimated baseline SCr, median [IQR]	92.5 [76.0-95.6]	-	92.5 [85.0-94.5]	92.7 [75.3-96.1]	0.826
AKI at hospital-admission	105 (29.1%)	4	62 (54.4%)	42 (17.4%)	**<0.000**
Severe ARF	319 (88,6%)	1	103 (91,2%)	212 (87.2%)	0.213
Severe ACF	124 (35,4%)	11	49 (45,0%)	74 (31.4%)	**0.010**
Variables at ICU					
GCS					
14-15	323 (89.5%)	-	89 (78.1%)	229 (94.6%)	**<0.000**
≤13	38 (10.5%)	-	25 (21.9%)	13 (5.4%)	**<0.000**
SAPS II score, median [IQR]	34.0 [26.0-42.0]	-	43.0 [37.0-50.0]	31.0 [24.0-36.0]	**<0.000**
BUN in mmol/L		5			
<10	275 (77.2%)	-	33 (28.9%)	242 (100.0%)	**<0.000**
10-29,9	79 (21.9%)	-	79 (69.3%)		
≥30	2 (0.6%)	-	2 (1.8%)		
UO in ml per 24 hours					
>1000	307 (85.0%)	-	60 (52.6%)	242 (100.0%)	**<0.000**
500-999	35 (9.7%)	-	35 (30.7%)		
<500	19 (5.3%)	-	19 (16.7%)		
AKI at ICU-admission	114 (32.0%)	5			

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, SCr = Serum-Creatinine, IQR = Interquartile Range, ARF = Acute Respiratory Failure, ACF = Acute Circulatory Failure, GCS = Glasgow Coma Scale, SAPS II = Simplified Acute Physiology Score II, BUN = Blood Urea Nitrogen, UO = Urine Output.

Table 2: Laboratory findings and organ complications by AKI-status at ICU admission.

122x99mm (300 x 300 DPI)

Table 3: Treatment and patient outcome by AKI-status at ICU-admission.					
Treatment	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
LOS in ICU, median [IQR]	11.6 [5.7-19.5]	-	13.5 [5.9-25.6]	10.9 [5.7-19.0]	0.125
Mechanical ventilation[a]	293 (81.2%)	-	99 (86.8%)	192 (79.3%)	0.057
RRT	29 (8.0%)	-	16 (14.0%)	13 (5.4%)	**0.006**
CRRT	28 (7.8%)	-	15 (13.2%)	13 (5.4%)	**0.012**
Median days [IQR]	9.0 [5.0-14.0]	-	8.0 [5.0-12.0]	11.5 [5.5-16.3]	0.863
IRRT	7 (1.9%)	-	6 (5.3%)	0 (0.0%)	**0.001**
Median days [IQR]	6.5 [5.0-7.5]	-	6.5 [5.0-7.5]	-	-
Outcome					
Survival first 24 hours in ICU	358 (99.2%)	-	111 (97.4%)	242 (100.0%)	**0.032**
Survival at hospital discharge	295 (81.7%)	-	80 (70.2%)	210 (86.8%)	**<0.000**
Survival at 30 days	298 (82.5%)	-	77 (67.5%)	217 (89.7%)	**<0.000**
Survival at 90 days	280 (77.6%)	-	70 (61.4%)	206 (85.1%)	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, LOS = Length of stay, IQR = Interquartile Range, RRT = Renal Replacement Therapy, CRRT = Continuous Renal Replacement Therapy, IRRT = Intermittent Renal Replacement Therapy.

Table 3: Treatment and patient outcome by AKI-status at ICU admission.

163x97mm (300 x 300 DPI)

Table 4: Odds for AKI at ICU-admission.						
Univariate logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.50	0.11 - 1.58	0.281			
Liver disease	1.11	0.05 - 11.67	0.935			
Cancer	0.80	0.22 - 2.39	0.701			
CND	1.27	0.33 - 4.31	0.705			
Current smoker	1.11	0.23 - 4.29	0.886			
Gender	0.88	0.52 - 1.46	0.619			
Age	1.02	1.01 - 1.04	**0.013**	1.02	1.00 - 1.04	0.121
CVD	1.50	0.94 - 2.38	0.089	1.00	0.56 - 1.78	0.996
DM	0.95	0.52 - 1.69	0.867			
Asthma	0.79	0.39 - 1.49	0.474			
CPD	1.17	0.54 - 2.42	0.673			
ACEi/ARB	1.77	1.04 – 3.00	**0.033**	1.52	0.82 - 2.83	0.187
ACF	1.21	1.07 - 1.37	**0.002**	1.19	1.05 - 1.35	**0.006**
ARF	1.08	0.85 - 1.42	0.561			
(Intercept)				0.09	0.03 - 0.31	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure.

Table 4: Odds for AKI at ICU-admission.

135x98mm (300 x 300 DPI)

Table 5: Odds for survival at 30 days.

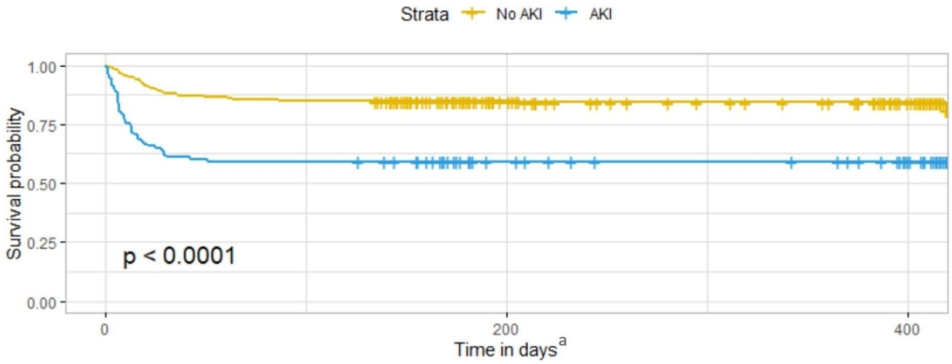
Univariate logistic regression				Multivariable logistic regression		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.29	0.02 - 1.47	0.235			
Liver disease	2.28	0.11 - 24.21	0.503			
Cancer	3.24	1.05 - 9.35	**0.032**	4.39	1.17 - 15.90	**0.024**
CND	0.44	0.02 - 2.38	0.442			
Current smoker	1.30	0.19 - 5.55	0.746			
Gender	1.54	0.85 - 2.75	0.149			
Age	1.08	1.05 - 1.11	**<0.000**	1.07	1.04 - 1.11	**<0.000**
CVD	2.33	1.33 - 4.15	**0.004**	0.93	0.40 - 2.11	0.857
DM	1.14	0.56 - 2.20	0.707			
Asthma	1.09	0.49 - 2.25	0.818			
CPD	4.17	1.97 - 8.73	**<0.000**	2.50	0.98 - 6.43	0.055
ACEi/ARB	2.02	1.09 - 3.66	**0.023**	1.24	0.53 - 2.89	0.625
ACF	1.78	1.50 - 2.14	**<0.000**	1.70	1.41 - 2.09	**<0.000**
ARF	1.18	0.87 - 1.79	0.349			
AKI at ICU-admission	4.32	2.44 - 7.78	**<0.000**	3.78	1.90 - 7.67	**<0.000**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table 5: Odds for survival at 30 days.

140x106mm (300 x 300 DPI)

Figure 1: Kaplan-Meier survival analysis stratified by AKI-status at admission to ICU.



AKI = Acute Kidney Injury, ICU = Intensive Care Unit, [a]Time in days from ICU-admission,

Figure 1: Kaplan-Meier Survival analysis stratified by AKI-status at ICU admission.

156x82mm (300 x 300 DPI)

Table S1: Odds for survival at 90 days.

Univariate logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.21	0.01 - 1.07	0.135			
Liver disease	1.67	0.08 - 17.65	0.678			
Cancer	2.32	0.75 - 6.64	0.123			
CND	0.32	0.02 - 1.73	0.285			
Current smoker	0.95	0.14 - 4.02	0.947			
Gender	1.15	0.66 - 1.99	0.611			
Age	1.08	1.06 - 1.11	**<0.000**	1.08	1.04 - 1.11	**<0.000**
CVD	2.25	1.35 - 3.79	**0.002**	0.72	0.33 - 1.53	0.396
DM	0.97	0.50 - 1.81	0.928			
Asthma	0.76	0.35 - 1.54	0.468			
CPD	3.26	1.57 - 6.71	**0.001**	2.03	0.79 - 5.23	0.139
ACEi/ARB	2.54	1.45 - 4.45	**0.001**	1.94	0.88 - 4.32	0.102
ACF	1.78	1.53 - 2.10	**<0.000**	1.72	1.46 - 2.06	**<0.000**
ARF	1.31	0.96 – 2.00	0.133			
AKI at ICU-admission	3.90	2.31 - 6.67	**<0.000**	3.14	1.66 - 6.00	**0.001**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

(Supplementary) Table S1: Odds for survival at 90 days.

129x98mm (300 x 300 DPI)

Table S2: Comparison of AKI definitions and staging criteria

KDIGO		RIFLE			Renal SAPS II		
Stage	**SCr[a]**	**Class**	**SCr or GFR**	**UO[b]**	**Score**	**UO/24 h**	**BUN**
					0	>1000 ml	<10 mmol/L
1	1.5-1.9x baseline or >26.5 µmol/L increase	**Risk**	SCr increase 1.5x baseline or eGFR decrease ≥25%	<0.5ml/kg/h for 6 h			
2	2.0-2.9x baseline	**Injury**	SCr increase 2.0x baseline or eGFR decrease ≥50%	<0.5 ml/kg/h for 12 h (<840 ml/24 h[c])	**4**	500-999 ml	
					6		10-29.9 mmol/L
3	≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) increase or initiation of RRT	**Failure**	SCr increase ≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) or GFR decrease ≥75%	<0.3 ml/kg/h for 24 h (<504 ml/24 h[c]) or anuria for 12 hours.	**10**		>30 mmol/L
					11	<500 ml	

[a]SCr-increase within 48 hours.

[b]UO criteria are shared by KDIGO and RIFLE.

[c]Standardized for a patient with a weight of 70 kg.

AKI = Acute Kidney Injury, KDIGO: Kidney Disease: Improving Global Outcomes, RIFLE: Risk, Injury, Failure, Loss, End-stage kidney disease, SAPS II = Simplified Acute Physiology Score II, SCr = Serum Creatinine, GFR = Glomerular Filtration Rate, UO = Urine Output, BUN = Blood Urea Nitrogen, RRT = Renal Replacement Therapy, h = hours.

(Supplementary) Table S2: Comparison of AKI definitions and staging criteria.

194x125mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

For article:

"Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort."

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	(4-)5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-11

			(b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	
Outcome data		15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion				
Key results	18		Summarise key results with reference to study objectives	14
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-16
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21		Discuss the generalisability (external validity) of the study results	16
Other information				
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort.

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Long title:

Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort.

Short title: Acute Kidney Injury in ICU-treated COVID-19 patients.

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ABSTRACT

Objectives: Acute kidney injury (AKI) is a frequent complication among critical ill patients with COVID-19, but the actual incidence is unknown as AKI-incidence varies from 25 to 89% in intensive care unit (ICU) populations. We aimed to describe the prevalence and risk factors of AKI in COVID-19 patients admitted to ICU in Norway.

Design: Nation-wide observational study with data sampled from the Norwegian Intensive Care and Pandemic Registry (NIPaR) for the period between March 10th until December 31st, 2020.

Setting: ICU patients with COVID-19 in Norway. NIPaR collects data on intensive care stays covering more than 90% of Norwegian ICU and 98% of ICU stays.

Participants: Adult COVID-19 patients admitted to Norwegian ICU were included in the study. Patients with Chronic Kidney Disease (CKD) were excluded in order to avoid bias from CKD on the incidence of AKI.

Primary and secondary outcome measures: Primary outcome was AKI at ICU admission as defined by renal SAPS-II score in NIPaR. Secondary outcome measures included survival at 30 and 90 days after admission to hospital.

Results: A total number of 361 COVID-19 patients were included in the analysis. AKI was present in 32.0% of the patients at ICU admission. The risk for AKI at ICU admission was related to acute circulatory failure at admission to hospital. Survival for the study population at 30 and 90 days was 82.5% and 77.6%, respectively. Cancer was a predictor of 30-day mortality. Age, acute circulatory failure at hospital admission and AKI at ICU admission were predictors of both 30- and 90-day mortality.

Conclusions: A high number of COVID-19 patients had AKI at ICU admission. The study indicates that AKI at ICU admission was related to acute circulatory failure at hospital admission. Age, acute circulatory failure at hospital admission and AKI at ICU admission were associated with mortality.

ARTICLE SUMMARY

Strength and limitations of this study

- The study is a national cohort of Norwegian COVID-19 patients admitted to ICUs in the study period.
- The study has few missing data, and the inclusion rate is high.
- The health system functioned within capacity during the study period, which renders that results are less likely to be biased due to capacity strains.
- AKI in the ICU was defined according to renal SAPS II score and does not fully comply with the RIFLE or KDIGO criteria due to the lack of creatinine-based measures of kidney function in the registry.
- While the study provides complete data on AKI at ICU-admission, it does not present the ICU trajectory of AKI in COVID-19 patients.

INTRODUCTION

COVID-19, an infectious disease caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has quickly developed into a pandemic since the early outbreak in Wuhan, China, in December 2019 [1].

Several studies report Acute Kidney Injury (AKI) among hospitalized COVID-19 patients while less data is obtained exclusively in Intensive Care Unit (ICU) patients [2-10]. To our knowledge, previous studies are not based upon all ICU admissions within a large population. Furthermore, there is a call from the consensus report on COVID-19 associated AKI published by the 25th Acute Dialysis Quality Initiative (ADQI) Workgroup that studies should "incorporate the information about the proportion of different comorbidities in patients with and without AKI, including potential risk factors for the development of AKI" [11].

National registries in Norway provide opportunities to perform nationwide registry studies in order to answer calls such as the one from the ADQI workgroup. The strength of such registry-based studies is that they are based on larger patient cohorts which make results more robust and generalizable. The drawback is that registry data set seldom are a direct fit for the research in question, making adaptations and extrapolations necessary.

This study is based on data available from the Norwegian Intensive Care and Pandemic Registry (NIPaR). NIPaR is a government funded national health registry constituted of two parts; the Norwegian Intensive Care Registry established in 1998, and the Norwegian Pandemic Registry established in March 2020 [12]. Registration is mandatory, and data is entered by hospital staff. For patients with COVID-19 in the ICU we report the prevalence of AKI, factors associated with AKI and the association between AKI and mortality.

METHODS

The Norwegian Intensive Care and Pandemic Registry (NIPaR) contains two patient populations. NIPaR collects data on intensive care stays in pre-defined ICU, covering more than 90% of Norwegian ICU and 98% of ICU stays [13]. Qualification criteria for ICU and intensive care patients are defined by NIPaR [14]. The Norwegian Pandemic Registry includes patients admitted to hospital in Norway with a positive PCR test for SARS-CoV-2 during the previous 3 months, and includes 99% of pandemic patients admitted to hospital [13]. Both registry parts employ automatic and manual validation to ensure data quality.

The study group included COVID-19 patients above the age of 18 years admitted to ICU in the period between March 10th, 2020 (the initial outbreak of SARS-CoV-2 in Norway), until December 31st, 2020. Patients with Chronic Kidney Disease (CKD), defined as previously diagnosed kidney disease upon hospital admission, were excluded in order to avoid bias from CKD on the effects of AKI.

Data collection at hospital admission included age, gender, height, weight, comorbidities, pregnancy, regular medication of Angiotensin-Converting Enzyme-inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB), smoking, S-Creatinine (SCr), organ complications at hospital admission (Acute Kidney Injury [AKI], Acute Respiratory Failure [ARF], Acute Circulatory Failure [ACF] recorded at the discretion of the attending physician).

Data collection from the ICU stay included primary reason for referral to ICU, clinical scoring systems in the ICU (Glasgow Coma Scale [GCS], SAPSII-score), length of stay (LOS), mechanical ventilation, Renal Replacement Therapy (RRT) (Intermittent [IRRT] and Continuous [CRRT]), and survival (ICU first 24 hours, in-hospital at ICU and at 30 and 90 days after admission to hospital).

Definitions

Due to lack of variables, it was not possible to employ creatinine values to define AKI in the ICU. The only available marker for renal function in the Norwegian Intensive Care Registry is contained within the Simplified Acute Physiology Score (SAPS II) [15]. As a result, renal Simplified Acute Physiology Score II (rSAPSII) is the sole marker for AKI during ICU stay in this study. AKI in the ICU was defined as rSAPSII score of ≥4 (Urine Output/24 h <1000

ml and/or Blood Urea Nitrogen >10 mmol/L). SAPS II is based on observations within the first 24 hours in the ICU.

While AKI at ICU-admission was defined according to rSAPSII score, AKI at admission to hospital was defined according to RIFLE-criteria. A serum creatinine increase of >1.5x baseline was available as a separate variable (RIFLE Risk-category). For missing data, AKI at hospital admission was based on serum creatinine at hospital admission and the MDRD equation for estimating baseline creatinine. An estimated Glomerular Filtration Rate (GFR) of 75 ml/min/1.73m2 was used to calculate baseline creatinine [16]. Data on ethnicity was not available for input in the equation.

Acute Circulatory Failure (ACF) at admission to hospital was defined as acute deterioration in the patient circulation as compared to normal state, resulting in circulatory symptoms in high, moderate or light exertion or in rest. This includes cardiac arrythmia, symptoms of heart failure and/or cardiac ischemia, regardless of vasopressor or inotrope treatment. Severe ACF was defined as circulatory symptoms in rest.

Acute Respiratory Failure (ARF) at admission to hospital was defined as acute deterioration of respiratory function at admission to hospital as compared to normal state, resulting in respiratory symptoms in high, moderate or light exertion or in rest. This includes all conditions which can cause acute deterioration of respiratory function, including bacterial, viral, or cryptogenic pneumoniae, acute respiratory distress syndrome (ARDS), pneumothorax, pleural fluid, and bronchiolitis. Severe ARF was defined as respiratory symptoms in rest.

Comorbidities are defined as pre-existing diagnoses upon admission to hospital. Comorbidities included Chronic Pulmonary Disease (CPD), Asthma, Diabetes Mellitus (DM) type 1 or 2, Chronic Kidney Disease (CKD), Cardiovascular Disease (CVD) including Hypertension, Liver disease, Chronic Neurological Disease (CND), Cancer, and Immunocompromised condition (including HIV and immunosuppressive therapy).

The primary outcome was the development of AKI at admission to ICU, while secondary outcomes included survival at 30 and 90 days after admission to hospital.

Statistics

Statistical analysis was performed using IBM SPSS Statistics ® (version 26) and R version 4.0.4. If not stated otherwise, continuous variables are presented as median and/or mean if data is normally distributed, and categorical variables are presented as the number (n) of patients (valid % of the study population). Shapiro-Wilk test of normality was performed for continuous variables. Patient characteristics for patients with or without AKI was compared using Student's t-test for continuous variables and Fisher exact test for categorical variables. A *p*-value <0.05 was considered statistically significant

Univariable logistic regression analysis was performed to examine the predictors for AKI at ICU-admission (as defined by rSAPSII-score ≥4). Independent variables included age, gender, comorbidities, smoking-status, medication with ACEi or ARB, ACF and ARF at admission to hospital. AKI at admission to hospital was not included as an independent variable in the analysis due to discrepancy in AKI-definition. Variables with a p-value <0.1 in the univariable regression were included in the multivariable regression, where a p-value <0.05 was considered as statistically significant. Multicollinearity was evaluated using the variance inflation factor (VIF).

Both univariable and multivariable logistic regression analysis as described, and univariable and multivariable Cox regression analysis, was performed to assess risk factors associated with 30- and 90-days mortality and the role of AKI at ICU-admission for predicting survival. Independent variables in univariable logistic regression analysis included comorbidities, age, gender, smoking-status, medication with ACEi or ARB, ACF and ARF at admission to hospital, and AKI at ICU-admission. Multicollinearity was evaluated using the VIF.

Kaplan-Meier survival analyses for the time to death was performed to compare the group with AKI at ICU-admission versus the group with no AKI. The comparison was done using log-rank test. Level of significance was considered *p*-value <0.05. Days from ICU-admission to death (event) or May 15th, 2021 (censoring), considered the time of analysis.

Ethics

The study was approved by Regional Committees for Medical and Health Research Ethics West (approval number 169604). Informed consent was waived based on information to participants in NIPaR about the registry and their right to withdraw from NIPaR.

RESULTS

A total of 394 adult patients were admitted to ICU with COVID-19 in the study period. Thirty-three of the patients were excluded due to CKD, resulting in a study population of 361 ICU-patients, 100 females and 261 males. From these, 105 (29.1%) had AKI at hospital admission. Median age was 63.6 [IQR; 53.5-72.5] years and median BMI was 27.7 [24.8-32.0] kg/m^2. Current smokers constituted 2.5% of the patients. None of the female patients were pregnant. Median length of stay (LOS) at the ICU was 11.6 [5.7-19.5] days. Mechanical ventilation was initiated in 81.2% of the patients.

Comorbidity was reported in 68.1% of the study population, and 29.1% had two or more comorbidities. Regular medication of Angiotensin Converting Enzyme-inhibitor (ACEi) and/or Angiotensin II Receptor Blocker (ARB) was used by 23.4% of the study population (Table 1).

Table 1: Patient characteristics by AKI-status at ICU admission.

Patient demographics	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
Age in years, median [IQR]	63.6 [53.5-72.5]	-	65.6 [58.4-73.6]	61.6 [52.0-72.3]	**0.003**
Male	261 (72.3%)	-	86 (75.4%)	172 (71.1%)	0.233
Female	100 (27.7%)	-	28 (24.6%)	70 (28.9%)	0.233
BMI, median [IQR]	27.7 [24.8-32.0]	141	27.3 [23.0-30.6]	28.3 [25.1-32.4]	0.132
BMI ≥30	83 (37.7%)	141	21 (31.8%)	61 (40.4%)	0.147
Current smoker	9 (2.5%)	-	3 (2.6%)	6 (2.5%)	0.592
Comorbidity/ies	246 (68.1%)	-	81 (71.1%)	161 (66.5%)	0.233
1	141 (39.1%)	-	44 (38.6%)	94 (38.8%)	0.530
≥2	105 (29.1%)	-	37 (32.5%)	67 (27.7%)	0.212
CVD	158 (43.8%)	-	58 (50.9%)	98 (40.5%)	**0.042**
DM	74 (20.5%)	-	23 (20.2%)	50 (20.7%)	0.518
Asthma	55 (15.2%)	-	15 (13.2%)	39 (16.1%)	0.288
CPD	37 (10.2%)	-	14 (12.3%)	23 (9.5%)	0.266
Immunocompromised	20 (5.5%)	-	5 (4.4%)	14 (5.8%)	0.394
Cancer	17 (4.7%)	-	6 (5.3%)	11 (4.5%)	0.476
CND	12 (3.3%)	-	5 (4.4%)	7 (2.9%)	0.329
Liver disease	3 (0.8%)	-	1 (0.9%)	2 (0.8%)	0.687
ACEi/ARB	83 (23.4%)	7	34 (30.6%)	47 (19.7%)	**0.019**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, IQR = Interquartile Range, BMI = Body Mass Index, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, CND = Chronic Neurological Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker.

Patients with AKI at admission to the ICU were older than patients with no AKI. They also had more cardiovascular disease (CVD) and more often used ACEi or ARB (Table 1). Patients with AKI at admission to ICU were more likely to have reduced GCS (Table 2).

Table 2: Laboratory findings and organ complications by AKI-status at ICU admission.

Variables at admission to hospital	All patients (N = 361)	Missing data (No of patients)	AKI (n= 114)	No AKI (n= 242)	*p*-value (AKI vs No AKI)
SCr in µmol/l, median [IQR]	85.0 [70.3-104.0]	1	98.0 [73.5-128.0]	80.5 [69.5-96.0]	**<0.000**
Estimated baseline SCr, median [IQR]	92.5 [76.0-95.6]	-	92.5 [85.0-94.5]	92.7 [75.3-96.1]	0.826
AKI at hospital-admission	105 (29.1%)	4	62 (54.4%)	42 (17.4%)	**<0.000**
Severe ARF	319 (88,6%)	1	103 (91,2%)	212 (87.2%)	0.213
Severe ACF	124 (35,4%)	11	49 (45,0%)	74 (31.4%)	**0.010**
Variables at ICU					
GCS					
14-15	323 (89.5%)	-	89 (78.1%)	229 (94.6%)	**<0.000**
≤13	38 (10.5%)	-	25 (21.9%)	13 (5.4%)	**<0.000**
SAPS II score, median [IQR]	34.0 [26.0-42.0]	-	43.0 [37.0-50.0]	31.0 [24.0-36.0]	**<0.000**
BUN in mmol/L		5			
<10	275 (77.2%)	-	33 (28.9%)	242 (100.0%)	**<0.000**
10-29,9	79 (21.9%)	-	79 (69.3%)		
≥30	2 (0.6%)	-	2 (1.8%)		
UO in ml per 24 hours					
>1000	307 (85.0%)	-	60 (52.6%)	242 (100.0%)	**<0.000**
500-999	35 (9.7%)	-	35 (30.7%)		
<500	19 (5.3%)	-	19 (16.7%)		
AKI at ICU admission	114 (32.0%)	5			

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, SCr = Serum-Creatinine, IQR = Interquartile Range, ARF = Acute Respiratory Failure, ACF = Acute Circulatory Failure, GCS = Glasgow Coma Scale, SAPS II = Simplified Acute Physiology Score II, BUN = Blood Urea Nitrogen, UO = Urine Output.

The distribution of organ failure at admission to hospital were 88.6%, 35.4% and 29.1% for Acute Respiratory Failure (ARF), Acute Circulatory Failure (ACF), and AKI (as defined by RIFLE-criteria), respectively. ACF at hospital admission was significantly more prevalent in patients who suffered AKI at ICU admission (*p*-value <0.05).

A total of 114 (32.0%) patients had AKI in the ICU. From these, 79 (69.3%) and 2 (1.8%) had BUN =10-29.9 mmol/L and ≥30 mmol/L, respectively. Urine Output (UO) of 500-999 ml/24 hours and <500 ml/24 hours were presented by 30.7% and 16.7%. More than half of the patients who had AKI at ICU-admission also had AKI at admission to hospital.

Renal Replacement Therapy (RRT) was required in 8.0% (n = 29) of the total patient group during the ICU-stay (Table 3). Continuous RRT (CRRT) was initiated in 28 patients, and intermittent RRT (IRRT) was initiated in 7 patients. Median time with CRRT was 9.0 [5.0-14.0] days and 6.5 [5.0-7.5] days with IRRT.

Table 3: Treatment and patient outcome by AKI-status at ICU admission.

Treatment	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
LOS in ICU, median [IQR]	11.6 [5.7-19.5]	-	13.5 [5.9-25.6]	10.9 [5.7-19.0]	0.125
Mechanical ventilation[a]	293 (81.2%)	-	99 (86.8%)	192 (79.3%)	0.057
RRT	29 (8.0%)	-	16 (14.0%)	13 (5.4%)	**0.006**
CRRT	28 (7.8%)	-	15 (13.2%)	13 (5.4%)	**0.012**
Median days [IQR]	9.0 [5.0-14.0]	-	8.0 [5.0-12.0]	11.5 [5.5-16.3]	0.863
IRRT	7 (1.9%)	-	6 (5.3%)	0 (0.0%)	**0.001**
Median days [IQR]	6.5 [5.0-7.5]	-	6.5 [5.0-7.5]	-	-
Outcome					
Survival first 24 hours in ICU	358 (99.2%)	-	111 (97.4%)	242 (100.0%)	**0.032**
Survival at hospital discharge	295 (81.7%)	-	80 (70.2%)	210 (86.8%)	**<0.000**
Survival at 30 days	298 (82.5%)	-	77 (67.5%)	217 (89.7%)	**<0.000**
Survival at 90 days	280 (77.6%)	-	70 (61.4%)	206 (85.1%)	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, LOS = Length of stay, IQR = Interquartile Range, RRT = Renal Replacement Therapy, CRRT = Continuous Renal Replacement Therapy, IRRT = Intermittent Renal Replacement Therapy.

Survival for the total study population at 30 and 90 days was 82.5% and 77.6%, respectively. Survival at 30 and 90 days in patients with AKI at ICU admission were 67.5% and 61.4%, respectively, which was significantly lower compared to 89.7% and 85.1% in patients with no AKI.

A total of 337 patients with no missing data were included in three logistic regression analyses to assess risk factors for AKI at ICU admission and risk factors associated with mortality.

In the first multivariable model only ACF was significantly associated with the development of AKI at ICU-admission (OR 1.19; 95% CI: 1.05–1.35) (Table 4). Multicollinearity was evaluated using the variance inflation factor (VIF). VIF ranged from 1.02 (ACF) to 1.51 (CVD). The area under the curve (AUC) was 0.64 (95% CI: 0.57–0.70).

Table 4: Odds for AKI at ICU admission.

	Univariable logistic regression			Multivariable logistic regression		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.50	0.11 - 1.58	0.281			
Liver disease	1.11	0.05 - 11.67	0.935			
Cancer	0.80	0.22 - 2.39	0.701			
CND	1.27	0.33 - 4.31	0.705			
Current smoker	1.11	0.23 - 4.29	0.886			
Gender	0.88	0.52 - 1.46	0.619			
Age	1.02	1.01 - 1.04	**0.013**	1.02	1.00 - 1.04	0.121
CVD	1.50	0.94 - 2.38	**0.089**	1.00	0.56 - 1.78	0.996
DM	0.95	0.52 - 1.69	0.867			
Asthma	0.79	0.39 - 1.49	0.474			
CPD	1.17	0.54 - 2.42	0.673			
ACEi/ARB	1.77	1.04 – 3.00	**0.033**	1.52	0.82 - 2.83	0.187
ACF	1.21	1.07 - 1.37	**0.002**	1.19	1.05 - 1.35	**0.006**
ARF	1.08	0.85 - 1.42	0.561			
(Intercept)				0.09	0.03 - 0.31	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure.

In the second multivariable model, risk factors associated with 30-day mortality were Cancer, Age, AKI at ICU-admission and ACF (Table 5). VIF ranged from 1.03 (ACF) to 1.47 (CVD). The AUC was 0.87 (95% CI 0.83–0.92).

Table 5: Odds for survival at 30 days.

Univariable logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.29	0.02 - 1.47	0.235			
Liver disease	2.28	0.11 - 24.21	0.503			
Cancer	3.24	1.05 - 9.35	**0.032**	4.39	1.17 - 15.90	**0.024**
CND	0.44	0.02 - 2.38	0.442			
Current smoker	1.30	0.19 - 5.55	0.746			
Gender	1.54	0.85 - 2.75	0.149			
Age	1.08	1.05 - 1.11	**<0.000**	1.07	1.04 - 1.11	**<0.000**
CVD	2.33	1.33 - 4.15	**0.004**	0.93	0.40 - 2.11	0.857
DM	1.14	0.56 - 2.20	0.707			
Asthma	1.09	0.49 - 2.25	0.818			
CPD	4.17	1.97 - 8.73	**<0.000**	2.50	0.98 - 6.43	0.055
ACEi/ARB	2.02	1.09 - 3.66	**0.023**	1.24	0.53 - 2.89	0.625
ACF	1.78	1.50 - 2.14	**<0.000**	1.70	1.41 - 2.09	**<0.000**
ARF	1.18	0.87 - 1.79	0.349			
AKI at ICU admission	4.32	2.44 - 7.78	**<0.000**	3.78	1.90 - 7.67	**<0.000**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

In the third model, age, AKI at ICU-admission and ACF were associated with 90-day mortality (Table S1). VIF in this model ranged from 1.02 (ACF) to 1.46 (CVD). The AUC was 0.87 (95% CI 0.82–0.91).

The results of Kaplan-Meier survival analysis stratified by AKI-status at admission to ICU showed that patients with AKI had significantly lower survival than patients without AKI (log-rank *p*-value <0.001) (Fig 1). The difference in survival was constrained to the first 50 days.

<Figure 1>

A Cox regression analysis was performed as an additional approach. The results for survival at 30 days were in agreement with the results from logistic regression analysis. For survival at 90 days, the results were also in agreement, while CPD and regular medication of ACEi and/or ARB were additional significant predictors of mortality (Table S2 & S3).

DISCUSSION

We performed a nationwide study of 361 adult patients with COVID-19 admitted to ICU. Prevalence of AKI at ICU admission was 32.0%. Acute Circulatory Failure (ACF) at hospital admission predicted AKI at ICU admission. Age, Cancer, ACF, and AKI at ICU admission were risk factors for mortality at 30 days.

The COVID-19 pandemic in Norway, with its population of 5.4 million people [17], has been relatively well contained. During the study period a total 50145 cases of SARS-CoV-2 were reported, of which 2185 were admitted to hospital and 394 to the ICU [18]. As in other countries, patients with COVID-19 in Norwegian ICU tend to be younger and more likely male compared with the general ICU-population [14]. Most patients in the study population were overweight, and a large proportion were obese, which is markedly different than in the general Norwegian population [19]. Comorbidities such as CVD, DM and Asthma, were also more prevalent in the study population than in the general Norwegian population [20].

The definition of AKI at ICU admission in our study does not fully comply with the AKI staging criteria due to the lack of creatinine-based measures of kidney function in the Norwegian Intensive Care Registry [21]. The SAPS II criteria for reduced urine output are similar to the staging criteria from the AKI network consensus, corresponding to AKI stage 2 and 3 (Table S4). BUN may increase by factors unrelated to kidney function, for instance due to steroid use which is regularly prescribed to COVID-19 patients in the ICU [22]. This would lead to an overestimate of AKI at ICU admission in our study, given standard enteral nutrition practices in Norwegian ICU. Creatinine is also influenced by several factors unrelated to kidney function but was chosen over BUN as the preferred biochemical parameter in the consensus process leading up to AKI definitions due to its widespread use [21 23].

While not fully in line with current AKI definitions, the combination of urine output and BUN should provide an estimate of AKI sufficiently similar to that of creatinine and urine output to be relevant in a registry study. The significant difference in s-creatinine at admission to hospital between patients with and without AKI at ICU admission in our material supports this assumption. Prevalence of AKI at ICU admission in our study is also similar to previous findings in the general ICU population. Bagshaw et al. report that on the

day of ICU-admission, 36% of the general ICU-population suffer AKI as defined by RIFLE-criteria, 16.3% in the Risk group and 19.9% in the Injury and Failure groups combined [24]. A narrative review in COVID-19 found 23% prevalence of AKI in the ICU [25]. In our study, 30.2% (n = 114) of COVID-19 patients admitted to ICU had AKI (Table 2).

Due to the lack of granularity in our data there are findings in our material that warrant further investigation. In our study group, 40.4% (n = 42) of the patients with AKI at admission to hospital did not present AKI at ICU admission. It is likely that different AKI criteria applied at hospital admission and ICU admission affects this difference. However, we cannot rule out, for instance, that patients with mild pre-renal AKI at admission were clinically stabilized to normal kidney function in a hospital ward prior to ICU admission due to respiratory failure. This would not contradict the impression that many COVID-19 patients in the ICU have single organ respiratory dysfunction [26]. On the other hand, 5.4% (n=13) of patients with no AKI at ICU admission received RRT during their ICU stay (Table 3). We would expect some patients with long ICU stays do develop AKI during their ICU stays, but we cannot rule out losing cases of AKI at ICU admission due to lack of creatinine values in the ICU. In order to establish the timeline of AKI in COVID-19 patients in ICU, studies with higher granularity data including serial urine output and creatinine measurements are needed.

In the regression model for AKI at ICU admission, only ACF at admission to hospital was found to be significantly associated. ACF is an uncommonly reported parameter at admission to hospital, and thus often not included in analysis for prediction of AKI. Although we biologically would expect collinearity between ACF and AKI at ICU admission, this was contradicted by low VIF in the statistical analysis. The results suggests that AKI at ICU admission is more closely associated to circulatory status than any other factors in critically ill COVID-19 patients.

In the regression model on survival, the factors Age, Cancer, ACF and AKI at ICU admission were significantly associated with increased risk of death during first 30 days. Age, ACF, and AKI at ICU admission were significantly associated with increased risk of death during first 90 days. AKI at ICU admission contributed considerably to the regression model. The finding puts AKI at ICU admission up as a strong and clinically important marker for survival in critically ill COVID-19 patients. While cancer also had a high contribution to the model, only 17 patients with cancer are included in the study, which reduces the clinical impact of this

finding. Chronic Pulmonary Disease (CPD) also contributes to the model but is only borderline significant. However, in the supplementary Cox regression model CPD was found significantly associated with risk of death during both first 30 and 90 days. Additionally, CPD is a risk factor in a larger group of the study population, 37 in total, and as such may be a more clinically relevant risk factor than cancer. Furthermore, respiratory disease, in addition to age, CVD and diabetes, is a previously well-recognized risk factor for severe disease progression and mortality in COVID-19 [27].

More than one out of three patients with AKI diagnosed first 24 hours of ICU-stay were deceased after 30-90 days. The Kaplan-Meier analysis illustrates that the mortality is predominantly in the short term within 50 days, in essence predominantly during the acute phase of illness. The finding supports that AKI at ICU-admission is a clinically important marker for poor outcome in COVID-19 (Figure 1). Low VIF in both regression models means that the effects of collinearity in the models are low. This puts further emphasis on AKI at ICU admission as an important prognostic factor for mortality in COVID-19.

We recognize several strengths and limitations in this study. The study is a national cohort containing complete data of all Norwegian COVID-19 patients (N = 394) admitted to ICU in the study period. Furthermore, because of the mandatory obligation by the Norwegian authorities to deliver data, the number of missing data was negligible. ICU admission criteria and treatment traditions are also similar in Norwegian ICUs which renders that data are comparable across centers. Furthermore, during the COVID-19 pandemic in Norway patients were not denied ICU care due to capacity concerns, thereby reducing selection bias due to triage decisions.

While national data increases generalizability, a major limitation in this study is that the Norwegian Intensive Care and Pandemic Registry (NIPaR) does not contain creatinine-based measures for AKI. Although the combination of urine output and BUN in rSAPSII should provide an estimate of AKI sufficiently similar to that of urine output and creatinine to be relevant, these indicators mandates that the results be interpreted with caution and limit generalizability. We also lack data regarding the timeline of AKI in COVID-19, and the use of vasopressor in the ICU. While the statistical analyses are rigorous, we nevertheless recommend that the results are treated as a basis for further investigation.

CONCLUSION

In this national cohort of COVID-19 patients admitted to ICUs in Norway 32.0% (n = 114) developed Acute Kidney Injury (AKI) during first 24 hours of ICU-admission. The majority presented clinical and/or biochemical signs of AKI at admission to hospital. The study indicates that Acute Circulatory Failure (ACF) at hospital admission was the most important risk factor for AKI at admission to ICU, and that age, cancer, ACF and AKI at ICU-admission were associated with mortality at 30 days after hospital admission.

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ABREVIATIONS

ACEi = Angiotensin-Converting Enzyme-inhibitor

ACF = Acute Circulatory Failure

ADQI = Acute Dialysis Quality Initiative

AKI = Acute Kidney Injury

ARB = Angiotensin II Receptor Blocker

ARDS = Acute Respiratory Distress Syndrome

ARF = Acute Respiratory Failure

BMI = Body Mass Index

BUN = Blood Urea Nitrogen

CKD = Chronic Kidney Disease

CND = Chronic Neurological Disease

COVID-19 = Corona Virus Disease-19

CPD = Chronic Pulmonary Disease

CRRT = Continuous Renal Replacement Therapy

CVD = Cardiovascular Disease

DM = Diabetes Mellitus

GFR = Glomerular Filtration Rate

GCS = Glasgow Coma Scale

ICU = Intensive Care Unit

IRRT = Intermittent Renal Replacement Therapy

KDIGO = The Kidney Disease: Improving Global Outcomes

NIPaR = Norwegian Intensive Care and Pandemic Registry

RIFLE = Risk, Injury, Failure, Loss of kidney function and End-stage renal disease

RRT = Renal Replacement Therapy

rSAPS II = renal Simplified Acute Physiology Score II

SAPS II = Simplified Acute Physiology Score II

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2

SCr = Serum-Creatinine

UO = Urine Output

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COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

DATA SHARING STATEMENT

Data cannot be shared publicly because of GDPR restrictions. Data are available from Norwegian Intensive Care and Pandemic Registry (NIPaR) upon application containing necessary approvals

AUTHOR CONTRIBUTIONS

All authors contributed to the study design. EAA and EAB collected data; EAA and FZG analyzed the data; All authors contributed to interpretation of results and in writing the paper.

EXCLUSIVE LICENSE STATEMENT

PATIENT CONSENT FORM

Not applicable.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

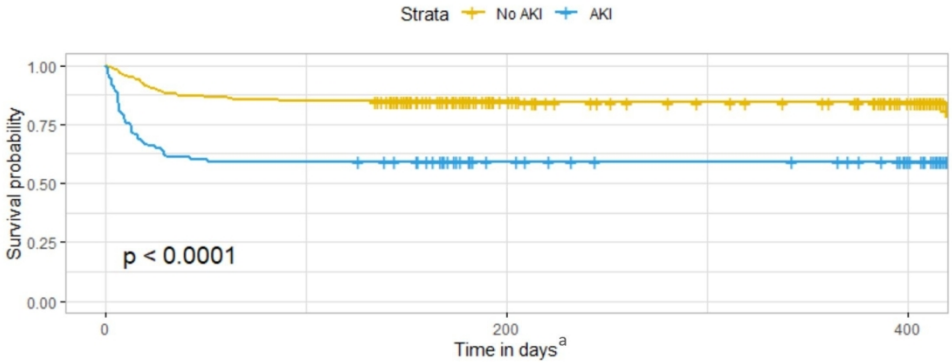
SUPPORTING INFORMATION

1. Figure(s)

Figure 1: Kaplan-Meier Survival analysis stratified by AKI-status at ICU admission.

Legends: Time in days from ICU admission. AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Figure 1: Kaplan-Meier survival analysis stratified by AKI-status at admission to ICU.



AKI = Acute Kidney Injury, ICU = Intensive Care Unit, [a]Time in days from ICU-admission,

Figure 1: Kaplan-Meier Survival analysis stratified by AKI-status at ICU admission.

156x82mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Table S1: Odds for survival at 90 days. *Legends:* OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S1: Odds for survival at 90 days.

Univariate logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.21	0.01 - 1.07	0.135			
Liver disease	1.67	0.08 - 17.65	0.678			
Cancer	2.32	0.75 - 6.64	0.123			
CND	0.32	0.02 - 1.73	0.285			
Current smoker	0.95	0.14 - 4.02	0.947			
Gender	1.15	0.66 - 1.99	0.611			
Age	1.08	1.06 - 1.11	**<0.000**	1.08	1.04 - 1.11	**<0.000**
CVD	2.25	1.35 - 3.79	**0.002**	0.72	0.33 - 1.53	0.396
DM	0.97	0.50 - 1.81	0.928			
Asthma	0.76	0.35 - 1.54	0.468			
CPD	3.26	1.57 - 6.71	**0.001**	2.03	0.79 - 5.23	0.139
ACEi/ARB	2.54	1.45 - 4.45	**0.001**	1.94	0.88 - 4.32	0.102
ACF	1.78	1.53 - 2.10	**<0.000**	1.72	1.46 - 2.06	**<0.000**
ARF	1.31	0.96 – 2.00	0.133			
AKI at ICU-admission	3.90	2.31 - 6.67	**<0.000**	3.14	1.66 - 6.00	**0.001**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S2: Hazard ratio for survival at 30 days. *Legends:* HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S2: Hazard ratio for survival at 30 days.

Univariable Cox regression				**Multivariable Cox regression**		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Immunocompromised	0.32	0.05 - 2.30	0.261			
Liver disease	0.85	0.33 - 17.00	0.398			
Cancer	0.97	1.10 - 6.20	**0.023**	2.65	1.11 - 6.36	**0.029**
CND	-0.73	0.07 - 3.50	0.468			
Current smoker	0.15	0.29 - 4.80	0.830			
Gender	0.41	0.90 - 2.60	0.121			
Age	0.07	1.00 - 1.10	**<0.000**	1.05	1.03 - 1.08	**<0.000**
CVD	0.77	1.30 - 3.60	**0.004**	0.96	0.52 - 1.76	0.886
DM	0.12	0.61 - 2.10	0.695			
Asthma	0.08	0.55 - 2.10	0.807			
CPD	1.30	2.00 - 6.40	**<0.000**	2.31	1.25 - 4.25	**0.008**
ACEi/ARB	0.63	1.10 - 3.20	**0.019**	1.37	0.75 - 2.50	0.311
ACF	0.52	1.40 - 2.00	**<0.000**	1.56	1.32 - 1.85	**<0.000**
ARF	0.15	0.83 - 1.60	0.379			
AKI at ICU admission	1.30	2.30 - 6.30	**<0.000**	2.92	1.74 - 4.90	**<0.000**

HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S3: Hazard ratio for survival at 90 days. *Legends:* HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S3: Hazard ratio for survival at 90 days.

Univariable Cox regression				**Multivariable Cox regression**		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Immunocompromised	0.24	0.03 - 1.70	0.160			
Liver disease	1.80	0.25 - 13.00	0.557			
Cancer	2.10	0.90 - 4.80	**0.086**	2.07	0.88 - 4.88	0.095
CND	0.37	0.05 - 2.60	0.317			
Current smoker	0.92	0.22 - 3.70	0.902			
Gender	1.20	0.74 - 1.90	0.472			
Age	1.10	1.00 - 1.10	**<0.000**	1.05	1.03 - 1.08	**<0.000**
CVD	2.10	1.30 - 3.20	**0.002**	0.85	0.50 - 1.46	0.558
DM	0.99	0.56 - 1.70	0.964			
Asthma	0.81	0.42 - 1.60	0.527			
CPD	2.90	1.70 - 5.10	**<0.000**	2.09	1.18 - 3.70	**0.012**
ACEi/ARB	2.20	1.40 - 3.50	**<0.000**	1.78	1.05 - 3.01	**0.032**
ACF	1.70	1.40 - 1.90	**<0.000**	1.56	1.35 - 1.80	**<0.000**
ARF	1.30	0.91 - 1.80	0.159			
AKI at ICU admission	3.40	2.20 - 5.30	**<0.000**	2.66	1.69 - 4.19	**<0.000**

HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S4: Comparison of AKI definitions and staging criteria. *Legends:* AKI = Acute Kidney Injury, KDIGO = Kidney Disease: Improving Global Outcomes, RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease, SAPS II = Simplified Acute Physiology Score II, SCr = Serum Creatinine, GFR = Glomerular Filtration Rate, UO = Urine Output, BUN = Blood Urea Nitrogen, RRT = Renal Replacement Therapy, h = hours.

Table S4: Comparison of AKI definitions and staging criteria.

KDIGO		RIFLE			Renal SAPS II		
Stage	**SCr[a]**	**Class**	**SCr or GFR**	**UO[b]**	**Score**	**UO/24 h**	**BUN**
					0	>1000 ml	<10 mmol/L
1	1.5-1.9x baseline or >26.5 µmol/L increase	**Risk**	SCr increase 1.5x baseline or eGFR decrease ≥25%	<0.5ml/kg/h for 6 h			
2	2.0-2.9x baseline	**Injury**	SCr increase 2.0x baseline or eGFR decrease ≥50%	<0.5 ml/kg/h for 12 h (<840 ml/24 h[c])	**4**	500-999 ml	
					6		10-29.9 mmol/L
3	≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) increase or initiation of RRT	**Failure**	SCr increase ≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) or GFR decrease ≥75%	<0.3 ml/kg/h for 24 h (<504 ml/24 h[c]) or anuria for 12 hours.	**10**		>30 mmol/L
					11	<500 ml	

[a]SCr-increase within 48 hours.

[b]UO criteria are shared by KDIGO and RIFLE.

[c]Standardized for a patient with a weight of 70 kg.

AKI = Acute Kidney Injury, KDIGO: Kidney Disease: Improving Global Outcomes, RIFLE: Risk, Injury, Failure, Loss, End-stage kidney disease, SAPS II = Simplified Acute Physiology Score II, SCr = Serum Creatinine, GFR = Glomerular Filtration Rate, UO = Urine Output, BUN = Blood Urea Nitrogen, RRT = Renal Replacement Therapy, h = hours.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

For article:

"Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort."

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	(4-)5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-11

			(b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	
Outcome data		15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion				
Key results	18		Summarise key results with reference to study objectives	14
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-16
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21		Discuss the generalisability (external validity) of the study results	16
Other information				
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort.

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Long title:

Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort.

Short title: Acute Kidney Injury in ICU-treated COVID-19 patients.

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ABSTRACT

Objectives: Acute kidney injury (AKI) is a frequent complication among critical ill patients with COVID-19, but the actual incidence is unknown as AKI-incidence varies from 25 to 89% in intensive care unit (ICU) populations. We aimed to describe the prevalence and risk factors of AKI in COVID-19 patients admitted to ICU in Norway.

Design: Nation-wide observational study with data sampled from the Norwegian Intensive Care and Pandemic Registry (NIPaR) for the period between March 10th until December 31st, 2020.

Setting: ICU patients with COVID-19 in Norway. NIPaR collects data on intensive care stays covering more than 90% of Norwegian ICU and 98% of ICU stays.

Participants: Adult COVID-19 patients admitted to Norwegian ICU were included in the study. Patients with Chronic Kidney Disease (CKD) were excluded in order to avoid bias from CKD on the incidence of AKI.

Primary and secondary outcome measures: Primary outcome was AKI at ICU admission as defined by renal SAPS-II score in NIPaR. Secondary outcome measures included survival at 30 and 90 days after admission to hospital.

Results: A total number of 361 COVID-19 patients were included in the analysis. AKI was present in 32.0% of the patients at ICU admission. The risk for AKI at ICU admission was related to acute circulatory failure at admission to hospital. Survival for the study population at 30 and 90 days was 82.5% and 77.6%, respectively. Cancer was a predictor of 30-day mortality. Age, acute circulatory failure at hospital admission and AKI at ICU admission were predictors of both 30- and 90-day mortality.

Conclusions: A high number of COVID-19 patients had AKI at ICU admission. The study indicates that AKI at ICU admission was related to acute circulatory failure at hospital admission. Age, acute circulatory failure at hospital admission and AKI at ICU admission were associated with mortality.

ARTICLE SUMMARY

Strength and limitations of this study

- The study is a national cohort of Norwegian COVID-19 patients admitted to ICUs in the study period.
- The study has few missing data, and the inclusion rate is high.
- The health system functioned within capacity during the study period, which renders that results are less likely to be biased due to capacity strains.
- AKI in the ICU was defined according to renal SAPS II score and does not fully comply with the RIFLE or KDIGO criteria due to the lack of creatinine-based measures of kidney function in the registry.
- While the study provides complete data on AKI at ICU-admission, it does not present the ICU trajectory of AKI in COVID-19 patients.

INTRODUCTION

COVID-19, an infectious disease caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has quickly developed into a pandemic since the early outbreak in Wuhan, China, in December 2019 [1].

Several studies report Acute Kidney Injury (AKI) among hospitalized COVID-19 patients while less data is obtained exclusively in Intensive Care Unit (ICU) patients [2-10]. To our knowledge, previous studies are not based upon all ICU admissions within a large population. Furthermore, there is a call from the consensus report on COVID-19 associated AKI published by the 25th Acute Dialysis Quality Initiative (ADQI) Workgroup that studies should "incorporate the information about the proportion of different comorbidities in patients with and without AKI, including potential risk factors for the development of AKI" [11].

National registries in Norway provide opportunities to perform nationwide registry studies in order to answer calls such as the one from the ADQI workgroup. The strength of such registry-based studies is that they are based on larger patient cohorts which make results more robust and generalizable. The drawback is that registry data set seldom are a direct fit for the research in question, making adaptations and extrapolations necessary.

This study is based on data available from the Norwegian Intensive Care and Pandemic Registry (NIPaR). NIPaR is a government funded national health registry constituted of two parts; the Norwegian Intensive Care Registry established in 1998, and the Norwegian Pandemic Registry established in March 2020 [12]. Registration is mandatory, and data is entered by hospital staff. For patients with COVID-19 in the ICU we report the prevalence of AKI, factors associated with AKI and the association between AKI and mortality.

METHODS

The Norwegian Intensive Care and Pandemic Registry (NIPaR) contains two patient populations. NIPaR collects data on intensive care stays in pre-defined ICU, covering more than 90% of Norwegian ICU and 98% of ICU stays [13]. Qualification criteria for ICU and intensive care patients are defined by NIPaR [14]. The Norwegian Pandemic Registry includes patients admitted to hospital in Norway with a positive PCR test for SARS-CoV-2 during the previous 3 months, and includes 99% of pandemic patients admitted to hospital [13]. Both registry parts employ automatic and manual validation to ensure data quality.

The study group included COVID-19 patients above the age of 18 years admitted to ICU in the period between March 10th, 2020 (the initial outbreak of SARS-CoV-2 in Norway), until December 31st, 2020. Patients with Chronic Kidney Disease (CKD), defined as previously diagnosed kidney disease upon hospital admission, were excluded in order to avoid bias from CKD on the effects of AKI.

Data collection at hospital admission included age, gender, height, weight, comorbidities, pregnancy, regular medication of Angiotensin-Converting Enzyme-inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB), smoking, S-Creatinine (SCr), organ complications at hospital admission (Acute Kidney Injury [AKI], Acute Respiratory Failure [ARF], Acute Circulatory Failure [ACF] recorded at the discretion of the attending physician).

Data collection from the ICU stay included primary reason for referral to ICU, clinical scoring systems in the ICU (Glasgow Coma Scale [GCS], SAPSII-score), length of stay (LOS), mechanical ventilation, Renal Replacement Therapy (RRT) (Intermittent [IRRT] and Continuous [CRRT]), and survival (ICU first 24 hours, in-hospital at ICU and at 30 and 90 days after admission to hospital).

Definitions

Due to lack of variables, it was not possible to employ creatinine values to define AKI in the ICU. The only available marker for renal function in the Norwegian Intensive Care Registry is contained within the Simplified Acute Physiology Score (SAPS II) [15]. As a result, renal Simplified Acute Physiology Score II (rSAPSII) is the sole marker for AKI during ICU stay in this study. AKI in the ICU was defined as rSAPSII score of ≥4 (Urine Output/24 h <1000

ml and/or Blood Urea Nitrogen >10 mmol/L). SAPS II is based on observations within the first 24 hours in the ICU.

While AKI at ICU-admission was defined according to rSAPSII score, AKI at admission to hospital was defined according to RIFLE-criteria. A serum creatinine increase of >1.5x baseline was available as a separate variable (RIFLE Risk-category). For missing data, AKI at hospital admission was based on serum creatinine at hospital admission and the MDRD equation for estimating baseline creatinine. An estimated Glomerular Filtration Rate (GFR) of 75 ml/min/1.73m2 was used to calculate baseline creatinine [16]. Data on ethnicity was not available for input in the equation.

Acute Circulatory Failure (ACF) at admission to hospital was defined as acute deterioration in the patient circulation as compared to normal state, resulting in circulatory symptoms in high, moderate or light exertion or in rest. This includes cardiac arrythmia, symptoms of heart failure and/or cardiac ischemia, regardless of vasopressor or inotrope treatment. Severe ACF was defined as circulatory symptoms in rest.

Acute Respiratory Failure (ARF) at admission to hospital was defined as acute deterioration of respiratory function at admission to hospital as compared to normal state, resulting in respiratory symptoms in high, moderate or light exertion or in rest. This includes all conditions which can cause acute deterioration of respiratory function, including bacterial, viral, or cryptogenic pneumoniae, acute respiratory distress syndrome (ARDS), pneumothorax, pleural fluid, and bronchiolitis. Severe ARF was defined as respiratory symptoms in rest.

Comorbidities are defined as pre-existing diagnoses upon admission to hospital. Comorbidities included Chronic Pulmonary Disease (CPD), Asthma, Diabetes Mellitus (DM) type 1 or 2, Chronic Kidney Disease (CKD), Cardiovascular Disease (CVD) including Hypertension, Liver disease, Chronic Neurological Disease (CND), Cancer, and Immunocompromised condition (including HIV and immunosuppressive therapy).

The primary outcome was the development of AKI at admission to ICU, while secondary outcomes included survival at 30 and 90 days after admission to hospital.

Statistics

Statistical analysis was performed using IBM SPSS Statistics ® (version 26) and R version 4.0.4. If not stated otherwise, continuous variables are presented as median and/or mean if data is normally distributed, and categorical variables are presented as the number (n) of patients (valid % of the study population). Shapiro-Wilk test of normality was performed for continuous variables. Patient characteristics for patients with or without AKI was compared using Student's t-test for continuous variables and Fisher exact test for categorical variables. A *p*-value <0.05 was considered statistically significant

Univariable logistic regression analysis was performed to examine the predictors for AKI at ICU-admission (as defined by rSAPSII-score ≥4). Independent variables included age, gender, comorbidities, smoking-status, medication with ACEi or ARB, ACF and ARF at admission to hospital. AKI at admission to hospital was not included as an independent variable in the analysis due to discrepancy in AKI-definition. Variables with a p-value <0.1 in the univariable regression were included in the multivariable regression, where a p-value <0.05 was considered as statistically significant. Multicollinearity was evaluated using the variance inflation factor (VIF).

Univariable and multivariable logistic regression analysis as described, was performed to assess risk factors associated with 30- and 90-days mortality and the role of AKI at ICU-admission for predicting survival. Independent variables in univariable logistic regression analysis included comorbidities, age, gender, smoking-status, medication with ACEi or ARB, ACF and ARF at admission to hospital, and AKI at ICU-admission. Multicollinearity was evaluated using the VIF.

Univariable and multivariable Cox regression analysis was performed in a similar fashion, as an additional approach to assess 30- and 90-days mortality. The data was censored at 30 and 90 days.

Kaplan-Meier survival analyses for the time to death was performed to compare the group with AKI at ICU-admission versus the group with no AKI. The comparison was done using log-rank test. Level of significance was considered *p*-value <0.05. Days from ICU-admission to death (event) or May 15th, 2021 (censoring), considered the time of analysis.

Ethics

The study was approved by Regional Committees for Medical and Health Research Ethics West (approval number 169604). Informed consent was waived based on information to participants in NIPaR about the registry and their right to withdraw from NIPaR.

RESULTS

A total of 394 adult patients were admitted to ICU with COVID-19 in the study period. Thirty-three of the patients were excluded due to CKD, resulting in a study population of 361 ICU-patients, 100 females and 261 males. From these, 105 (29.1%) had AKI at hospital admission. Median age was 63.6 [IQR; 53.5-72.5] years and median BMI was 27.7 [24.8-32.0] kg/m^2. Current smokers constituted 2.5% of the patients. None of the female patients were pregnant. Median length of stay (LOS) at the ICU was 11.6 [5.7-19.5] days. Mechanical ventilation was initiated in 81.2% of the patients.

Comorbidity was reported in 68.1% of the study population, and 29.1% had two or more comorbidities. Regular medication of Angiotensin Converting Enzyme-inhibitor (ACEi) and/or Angiotensin II Receptor Blocker (ARB) was used by 23.4% of the study population (Table 1).

Table 1: Patient characteristics by AKI-status at ICU admission.

Patient demographics	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
Age in years, median [IQR]	63.6 [53.5-72.5]	-	65.6 [58.4-73.6]	61.6 [52.0-72.3]	**0.003**
Male	261 (72.3%)	-	86 (75.4%)	172 (71.1%)	0.233
Female	100 (27.7%)	-	28 (24.6%)	70 (28.9%)	0.233
BMI, median [IQR]	27.7 [24.8-32.0]	141	27.3 [23.0-30.6]	28.3 [25.1-32.4]	0.132
BMI ≥30	83 (37.7%)	141	21 (31.8%)	61 (40.4%)	0.147
Current smoker	9 (2.5%)	-	3 (2.6%)	6 (2.5%)	0.592
Comorbidity/ies	246 (68.1%)	-	81 (71.1%)	161 (66.5%)	0.233
1	141 (39.1%)	-	44 (38.6%)	94 (38.8%)	0.530
≥2	105 (29.1%)	-	37 (32.5%)	67 (27.7%)	0.212
CVD	158 (43.8%)	-	58 (50.9%)	98 (40.5%)	**0.042**
DM	74 (20.5%)	-	23 (20.2%)	50 (20.7%)	0.518
Asthma	55 (15.2%)	-	15 (13.2%)	39 (16.1%)	0.288
CPD	37 (10.2%)	-	14 (12.3%)	23 (9.5%)	0.266
Immunocompromised	20 (5.5%)	-	5 (4.4%)	14 (5.8%)	0.394
Cancer	17 (4.7%)	-	6 (5.3%)	11 (4.5%)	0.476
CND	12 (3.3%)	-	5 (4.4%)	7 (2.9%)	0.329
Liver disease	3 (0.8%)	-	1 (0.9%)	2 (0.8%)	0.687
ACEi/ARB	83 (23.4%)	7	34 (30.6%)	47 (19.7%)	**0.019**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, IQR = Interquartile Range, BMI = Body Mass Index, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, CND = Chronic Neurological Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker.

Patients with AKI at admission to the ICU were older than patients with no AKI. They also had more cardiovascular disease (CVD) and more often used ACEi or ARB (Table 1). Patients with AKI at admission to ICU were more likely to have reduced GCS (Table 2).

Table 2: Laboratory findings and organ complications by AKI-status at ICU admission.

Variables at admission to hospital	All patients (N = 361)	Missing data (No of patients)	AKI (n= 114)	No AKI (n= 242)	*p*-value (AKI vs No AKI)
SCr in µmol/l, median [IQR]	85.0 [70.3-104.0]	1	98.0 [73.5-128.0]	80.5 [69.5-96.0]	**<0.000**
Estimated baseline SCr, median [IQR]	92.5 [76.0-95.6]	-	92.5 [85.0-94.5]	92.7 [75.3-96.1]	0.826
AKI at hospital-admission	105 (29.1%)	4	62 (54.4%)	42 (17.4%)	**<0.000**
Severe ARF	319 (88,6%)	1	103 (91,2%)	212 (87.2%)	0.213
Severe ACF	124 (35,4%)	11	49 (45,0%)	74 (31.4%)	**0.010**
Variables at ICU					
GCS					
14-15	323 (89.5%)	-	89 (78.1%)	229 (94.6%)	**<0.000**
≤13	38 (10.5%)	-	25 (21.9%)	13 (5.4%)	**<0.000**
SAPS II score, median [IQR]	34.0 [26.0-42.0]	-	43.0 [37.0-50.0]	31.0 [24.0-36.0]	**<0.000**
BUN in mmol/L		5			
<10	275 (77.2%)	-	33 (28.9%)	242 (100.0%)	**<0.000**
10-29,9	79 (21.9%)	-	79 (69.3%)		
≥30	2 (0.6%)	-	2 (1.8%)		
UO in ml per 24 hours					
>1000	307 (85.0%)	-	60 (52.6%)	242 (100.0%)	**<0.000**
500-999	35 (9.7%)	-	35 (30.7%)		
<500	19 (5.3%)	-	19 (16.7%)		
AKI at ICU admission	114 (32.0%)	5			

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, SCr = Serum-Creatinine, IQR = Interquartile Range, ARF = Acute Respiratory Failure, ACF = Acute Circulatory Failure, GCS = Glasgow Coma Scale, SAPS II = Simplified Acute Physiology Score II, BUN = Blood Urea Nitrogen, UO = Urine Output.

The distribution of organ failure at admission to hospital were 88.6%, 35.4% and 29.1% for Acute Respiratory Failure (ARF), Acute Circulatory Failure (ACF), and AKI (as defined by RIFLE-criteria), respectively. ACF at hospital admission was significantly more prevalent in patients who suffered AKI at ICU admission (*p*-value <0.05).

A total of 114 (32.0%) patients had AKI in the ICU. From these, 79 (69.3%) and 2 (1.8%) had BUN =10-29.9 mmol/L and ≥30 mmol/L, respectively. Urine Output (UO) of 500-999 ml/24 hours and <500 ml/24 hours were presented by 30.7% and 16.7%. More than half of the patients who had AKI at ICU-admission also had AKI at admission to hospital.

Renal Replacement Therapy (RRT) was required in 8.0% (n = 29) of the total patient group during the ICU-stay (Table 3). Continuous RRT (CRRT) was initiated in 28 patients, and intermittent RRT (IRRT) was initiated in 7 patients. Median time with CRRT was 9.0 [5.0-14.0] days and 6.5 [5.0-7.5] days with IRRT.

Table 3: Treatment and patient outcome by AKI-status at ICU admission.

Treatment	All patients (N = 361)	Missing data (No of patients)	AKI (n = 114)	No AKI (n = 242)	*p*-value (AKI vs no AKI)
LOS in ICU, median [IQR]	11.6 [5.7-19.5]	-	13.5 [5.9-25.6]	10.9 [5.7-19.0]	0.125
Mechanical ventilation[a]	293 (81.2%)	-	99 (86.8%)	192 (79.3%)	0.057
RRT	29 (8.0%)	-	16 (14.0%)	13 (5.4%)	**0.006**
CRRT	28 (7.8%)	-	15 (13.2%)	13 (5.4%)	**0.012**
Median days [IQR]	9.0 [5.0-14.0]	-	8.0 [5.0-12.0]	11.5 [5.5-16.3]	0.863
IRRT	7 (1.9%)	-	6 (5.3%)	0 (0.0%)	**0.001**
Median days [IQR]	6.5 [5.0-7.5]	-	6.5 [5.0-7.5]	-	-
Outcome					
Survival first 24 hours in ICU	358 (99.2%)	-	111 (97.4%)	242 (100.0%)	**0.032**
Survival at hospital discharge	295 (81.7%)	-	80 (70.2%)	210 (86.8%)	**<0.000**
Survival at 30 days	298 (82.5%)	-	77 (67.5%)	217 (89.7%)	**<0.000**
Survival at 90 days	280 (77.6%)	-	70 (61.4%)	206 (85.1%)	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, LOS = Length of stay, IQR = Interquartile Range, RRT = Renal Replacement Therapy, CRRT = Continuous Renal Replacement Therapy, IRRT = Intermittent Renal Replacement Therapy.

Survival for the total study population at 30 and 90 days was 82.5% and 77.6%, respectively. Survival at 30 and 90 days in patients with AKI at ICU admission were 67.5% and 61.4%, respectively, which was significantly lower compared to 89.7% and 85.1% in patients with no AKI.

A total of 337 patients with no missing data were included in three logistic regression analyses to assess risk factors for AKI at ICU admission and risk factors associated with mortality.

In the first multivariable model only ACF was significantly associated with the development of AKI at ICU-admission (OR 1.19; 95% CI: 1.05–1.35) (Table 4). Multicollinearity was evaluated using the variance inflation factor (VIF). VIF ranged from 1.02 (ACF) to 1.51 (CVD). The area under the curve (AUC) was 0.64 (95% CI: 0.57–0.70).

Table 4: Odds for AKI at ICU admission.

	Univariable logistic regression			Multivariable logistic regression		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.50	0.11 - 1.58	0.281			
Liver disease	1.11	0.05 - 11.67	0.935			
Cancer	0.80	0.22 - 2.39	0.701			
CND	1.27	0.33 - 4.31	0.705			
Current smoker	1.11	0.23 - 4.29	0.886			
Gender	0.88	0.52 - 1.46	0.619			
Age	1.02	1.01 - 1.04	**0.013**	1.02	1.00 - 1.04	0.121
CVD	1.50	0.94 - 2.38	**0.089**	1.00	0.56 - 1.78	0.996
DM	0.95	0.52 - 1.69	0.867			
Asthma	0.79	0.39 - 1.49	0.474			
CPD	1.17	0.54 - 2.42	0.673			
ACEi/ARB	1.77	1.04 – 3.00	**0.033**	1.52	0.82 - 2.83	0.187
ACF	1.21	1.07 - 1.37	**0.002**	1.19	1.05 - 1.35	**0.006**
ARF	1.08	0.85 - 1.42	0.561			
(Intercept)				0.09	0.03 - 0.31	**<0.000**

AKI = Acute Kidney Injury, ICU = Intensive Care Unit, OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure.

In the second multivariable model, risk factors associated with 30-day mortality were Cancer, Age, AKI at ICU-admission and ACF (Table 5). VIF ranged from 1.03 (ACF) to 1.47 (CVD). The AUC was 0.87 (95% CI 0.83–0.92).

Table 5: Odds for survival at 30 days.

Univariable logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.29	0.02 - 1.47	0.235			
Liver disease	2.28	0.11 - 24.21	0.503			
Cancer	3.24	1.05 - 9.35	**0.032**	4.39	1.17 - 15.90	**0.024**
CND	0.44	0.02 - 2.38	0.442			
Current smoker	1.30	0.19 - 5.55	0.746			
Gender	1.54	0.85 - 2.75	0.149			
Age	1.08	1.05 - 1.11	**<0.000**	1.07	1.04 - 1.11	**<0.000**
CVD	2.33	1.33 - 4.15	**0.004**	0.93	0.40 - 2.11	0.857
DM	1.14	0.56 - 2.20	0.707			
Asthma	1.09	0.49 - 2.25	0.818			
CPD	4.17	1.97 - 8.73	**<0.000**	2.50	0.98 - 6.43	0.055
ACEi/ARB	2.02	1.09 - 3.66	**0.023**	1.24	0.53 - 2.89	0.625
ACF	1.78	1.50 - 2.14	**<0.000**	1.70	1.41 - 2.09	**<0.000**
ARF	1.18	0.87 - 1.79	0.349			
AKI at ICU admission	4.32	2.44 - 7.78	**<0.000**	3.78	1.90 - 7.67	**<0.000**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

In the third model, age, AKI at ICU-admission and ACF were associated with 90-day mortality (Table S1). VIF in this model ranged from 1.02 (ACF) to 1.46 (CVD). The AUC was 0.87 (95% CI 0.82–0.91).

The results of Kaplan-Meier survival analysis stratified by AKI-status at admission to ICU showed that patients with AKI had significantly lower survival than patients without AKI (log-rank *p*-value <0.001) (Fig 1). The difference in survival was constrained to the first 50 days.

<Figure 1>

The results from Cox regression analysis for survival at 30 days were in agreement with the results from logistic regression analysis. For survival at 90 days, the results were also in agreement, while CPD and regular medication of ACEi and/or ARB were additional significant predictors of mortality (Table S2 & S3).

DISCUSSION

We performed a nationwide study of 361 adult patients with COVID-19 admitted to ICU. Prevalence of AKI at ICU admission was 32.0%. Acute Circulatory Failure (ACF) at hospital admission predicted AKI at ICU admission. Age, Cancer, ACF, and AKI at ICU admission were risk factors for mortality at 30 days.

The COVID-19 pandemic in Norway, with its population of 5.4 million people [17], has been relatively well contained. During the study period a total 50145 cases of SARS-CoV-2 were reported, of which 2185 were admitted to hospital and 394 to the ICU [18]. As in other countries, patients with COVID-19 in Norwegian ICU tend to be younger and more likely male compared with the general ICU-population [14]. Most patients in the study population were overweight, and a large proportion were obese, which is markedly different than in the general Norwegian population [19]. Comorbidities such as CVD, DM and Asthma, were also more prevalent in the study population than in the general Norwegian population [20].

The definition of AKI at ICU admission in our study does not fully comply with the AKI staging criteria due to the lack of creatinine-based measures of kidney function in the Norwegian Intensive Care Registry [21]. The SAPS II criteria for reduced urine output are similar to the staging criteria from the AKI network consensus, corresponding to AKI stage 2 and 3 (Table S4). BUN may increase by factors unrelated to kidney function, for instance due to steroid use which is regularly prescribed to COVID-19 patients in the ICU [22]. This would lead to an overestimate of AKI at ICU admission in our study, given standard enteral nutrition practices in Norwegian ICU. Creatinine is also influenced by several factors unrelated to kidney function but was chosen over BUN as the preferred biochemical parameter in the consensus process leading up to AKI definitions due to its widespread use [21 23].

While not fully in line with current AKI definitions, the combination of urine output and BUN should provide an estimate of AKI sufficiently similar to that of creatinine and urine output to be relevant in a registry study. The significant difference in s-creatinine at admission to hospital between patients with and without AKI at ICU admission in our material supports this assumption. Prevalence of AKI at ICU admission in our study is also similar to previous findings in the general ICU population. Bagshaw et al. report that on the

day of ICU-admission, 36% of the general ICU-population suffer AKI as defined by RIFLE-criteria, 16.3% in the Risk group and 19.9% in the Injury and Failure groups combined [24]. A narrative review in COVID-19 found 23% prevalence of AKI in the ICU [25]. In our study, 30.2% (n = 114) of COVID-19 patients admitted to ICU had AKI (Table 2).

Due to the lack of granularity in our data there are findings in our material that warrant further investigation. In our study group, 40.4% (n = 42) of the patients with AKI at admission to hospital did not present AKI at ICU admission. It is likely that different AKI criteria applied at hospital admission and ICU admission affects this difference. However, we cannot rule out, for instance, that patients with mild pre-renal AKI at admission were clinically stabilized to normal kidney function in a hospital ward prior to ICU admission due to respiratory failure. This would not contradict the impression that many COVID-19 patients in the ICU have single organ respiratory dysfunction [26]. On the other hand, 5.4% (n=13) of patients with no AKI at ICU admission received RRT during their ICU stay (Table 3). We would expect some patients with long ICU stays do develop AKI during their ICU stays, but we cannot rule out losing cases of AKI at ICU admission due to lack of creatinine values in the ICU. In order to establish the timeline of AKI in COVID-19 patients in ICU, studies with higher granularity data including serial urine output and creatinine measurements are needed.

In the regression model for AKI at ICU admission, only ACF at admission to hospital was found to be significantly associated. ACF is an uncommonly reported parameter at admission to hospital, and thus often not included in analysis for prediction of AKI. Although we biologically would expect collinearity between ACF and AKI at ICU admission, this was contradicted by low VIF in the statistical analysis. The results suggests that AKI at ICU admission is more closely associated to circulatory status than any other factors in critically ill COVID-19 patients.

In the regression model on survival, the factors Age, Cancer, ACF and AKI at ICU admission were significantly associated with increased risk of death during first 30 days. Age, ACF, and AKI at ICU admission were significantly associated with increased risk of death during first 90 days. AKI at ICU admission contributed considerably to the regression model. The finding puts AKI at ICU admission up as a strong and clinically important marker for survival in critically ill COVID-19 patients. While cancer also had a high contribution to the model, only 17 patients with cancer are included in the study, which reduces the clinical impact of this

finding. Chronic Pulmonary Disease (CPD) also contributes to the model but is only borderline significant. However, in the supplementary Cox regression model CPD was found significantly associated with risk of death during both first 30 and 90 days. Additionally, CPD is a risk factor in a larger group of the study population, 37 in total, and as such may be a more clinically relevant risk factor than cancer. Furthermore, respiratory disease, in addition to age, CVD and diabetes, is a previously well-recognized risk factor for severe disease progression and mortality in COVID-19 [27].

More than one out of three patients with AKI diagnosed first 24 hours of ICU-stay were deceased after 30-90 days. The Kaplan-Meier analysis illustrates that the mortality is predominantly in the short term within 50 days, in essence predominantly during the acute phase of illness. The finding supports that AKI at ICU-admission is a clinically important marker for poor outcome in COVID-19 (Figure 1). Low VIF in both regression models means that the effects of collinearity in the models are low. This puts further emphasis on AKI at ICU admission as an important prognostic factor for mortality in COVID-19.

We recognize several strengths and limitations in this study. The study is a national cohort containing complete data of all Norwegian COVID-19 patients (N = 394) admitted to ICU in the study period. Furthermore, because of the mandatory obligation by the Norwegian authorities to deliver data, the number of missing data was negligible. ICU admission criteria and treatment traditions are also similar in Norwegian ICUs which renders that data are comparable across centers. Furthermore, during the COVID-19 pandemic in Norway patients were not denied ICU care due to capacity concerns, thereby reducing selection bias due to triage decisions.

While national data increases generalizability, a major limitation in this study is that the Norwegian Intensive Care and Pandemic Registry (NIPaR) does not contain creatinine-based measures for AKI. Although the combination of urine output and BUN in rSAPSII should provide an estimate of AKI sufficiently similar to that of urine output and creatinine to be relevant, these indicators mandates that the results be interpreted with caution and limit generalizability. We also lack data regarding the timeline of AKI in COVID-19, and the use of vasopressor in the ICU. While the statistical analyses are rigorous, we nevertheless recommend that the results are treated as a basis for further investigation.

CONCLUSION

In this national cohort of COVID-19 patients admitted to ICUs in Norway 32.0% (n = 114) developed Acute Kidney Injury (AKI) during first 24 hours of ICU-admission. The majority presented clinical and/or biochemical signs of AKI at admission to hospital. The study indicates that Acute Circulatory Failure (ACF) at hospital admission was the most important risk factor for AKI at admission to ICU, and that age, cancer, ACF and AKI at ICU-admission were associated with mortality at 30 days after hospital admission.

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ABREVIATIONS

ACEi = Angiotensin-Converting Enzyme-inhibitor

ACF = Acute Circulatory Failure

ADQI = Acute Dialysis Quality Initiative

AKI = Acute Kidney Injury

ARB = Angiotensin II Receptor Blocker

ARDS = Acute Respiratory Distress Syndrome

ARF = Acute Respiratory Failure

BMI = Body Mass Index

BUN = Blood Urea Nitrogen

CKD = Chronic Kidney Disease

CND = Chronic Neurological Disease

COVID-19 = Corona Virus Disease-19

CPD = Chronic Pulmonary Disease

CRRT = Continuous Renal Replacement Therapy

CVD = Cardiovascular Disease

DM = Diabetes Mellitus

GFR = Glomerular Filtration Rate

GCS = Glasgow Coma Scale

ICU = Intensive Care Unit

IRRT = Intermittent Renal Replacement Therapy

KDIGO = The Kidney Disease: Improving Global Outcomes

NIPaR = Norwegian Intensive Care and Pandemic Registry

RIFLE = Risk, Injury, Failure, Loss of kidney function and End-stage renal disease

RRT = Renal Replacement Therapy

rSAPS II = renal Simplified Acute Physiology Score II

SAPS II = Simplified Acute Physiology Score II

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2

SCr = Serum-Creatinine

UO = Urine Output

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COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

DATA SHARING STATEMENT

Data cannot be shared publicly because of GDPR restrictions. Data are available from Norwegian Intensive Care and Pandemic Registry (NIPaR) upon application containing necessary approvals

AUTHOR CONTRIBUTIONS

Eirik Aasen Aukland (submitting author) conceptualized and designed the study, performed data cleaning and assisted with the data analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

Pål Klepstad and Stein Magnus Aukland conceptualized and designed the study, contributed to the interpretation of the results, and critically reviewed the manuscript.

Fatemeh Zamanzad Ghavidel conducted the data analyses and critically reviewed the manuscript.

Eirik Alnes Buanes conceptualized and designed the study, collected the data, contributed to the interpretation of the results, and critically reviewed the paper.

All authors approved the final version of the manuscript.

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Not applicable.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

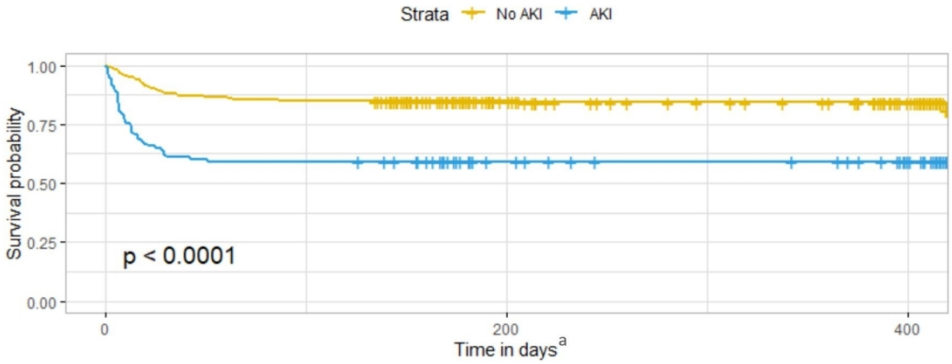
SUPPORTING INFORMATION

1. Figure(s)

Figure 1: Kaplan-Meier Survival analysis stratified by AKI-status at ICU admission.

Legends: Time in days from ICU admission. AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Figure 1: Kaplan-Meier survival analysis stratified by AKI-status at admission to ICU.



AKI = Acute Kidney Injury, ICU = Intensive Care Unit, [a]Time in days from ICU-admission,

Figure 1: Kaplan-Meier Survival analysis stratified by AKI-status at ICU admission.

156x82mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Table S1: Odds for survival at 90 days. *Legends:* OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S1: Odds for survival at 90 days.

Univariate logistic regression				**Multivariable logistic regression**		
Variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Immunocompromised	0.21	0.01 - 1.07	0.135			
Liver disease	1.67	0.08 - 17.65	0.678			
Cancer	2.32	0.75 - 6.64	0.123			
CND	0.32	0.02 - 1.73	0.285			
Current smoker	0.95	0.14 - 4.02	0.947			
Gender	1.15	0.66 - 1.99	0.611			
Age	1.08	1.06 - 1.11	**<0.000**	1.08	1.04 - 1.11	**<0.000**
CVD	2.25	1.35 - 3.79	**0.002**	0.72	0.33 - 1.53	0.396
DM	0.97	0.50 - 1.81	0.928			
Asthma	0.76	0.35 - 1.54	0.468			
CPD	3.26	1.57 - 6.71	**0.001**	2.03	0.79 - 5.23	0.139
ACEi/ARB	2.54	1.45 - 4.45	**0.001**	1.94	0.88 - 4.32	0.102
ACF	1.78	1.53 - 2.10	**<0.000**	1.72	1.46 - 2.06	**<0.000**
ARF	1.31	0.96 – 2.00	0.133			
AKI at ICU-admission	3.90	2.31 - 6.67	**<0.000**	3.14	1.66 - 6.00	**0.001**
(Intercept)				0.00	0.00 - 0.002	**<0.000**

OR = Odds Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S2: Hazard ratio for survival at 30 days. *Legends:* HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S2: Hazard ratio for survival at 30 days.

Univariable Cox regression				**Multivariable Cox regression**		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Immunocompromised	0.32	0.05 - 2.30	0.261			
Liver disease	0.85	0.33 - 17.00	0.398			
Cancer	0.97	1.10 - 6.20	**0.023**	2.65	1.11 - 6.36	**0.029**
CND	-0.73	0.07 - 3.50	0.468			
Current smoker	0.15	0.29 - 4.80	0.830			
Gender	0.41	0.90 - 2.60	0.121			
Age	0.07	1.00 - 1.10	**<0.000**	1.05	1.03 - 1.08	**<0.000**
CVD	0.77	1.30 - 3.60	**0.004**	0.96	0.52 - 1.76	0.886
DM	0.12	0.61 - 2.10	0.695			
Asthma	0.08	0.55 - 2.10	0.807			
CPD	1.30	2.00 - 6.40	**<0.000**	2.31	1.25 - 4.25	**0.008**
ACEi/ARB	0.63	1.10 - 3.20	**0.019**	1.37	0.75 - 2.50	0.311
ACF	0.52	1.40 - 2.00	**<0.000**	1.56	1.32 - 1.85	**<0.000**
ARF	0.15	0.83 - 1.60	0.379			
AKI at ICU admission	1.30	2.30 - 6.30	**<0.000**	2.92	1.74 - 4.90	**<0.000**

HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S3: Hazard ratio for survival at 90 days. *Legends:* HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S3: Hazard ratio for survival at 90 days.

Univariable Cox regression				**Multivariable Cox regression**		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Immunocompromised	0.24	0.03 - 1.70	0.160			
Liver disease	1.80	0.25 - 13.00	0.557			
Cancer	2.10	0.90 - 4.80	**0.086**	2.07	0.88 - 4.88	0.095
CND	0.37	0.05 - 2.60	0.317			
Current smoker	0.92	0.22 - 3.70	0.902			
Gender	1.20	0.74 - 1.90	0.472			
Age	1.10	1.00 - 1.10	**<0.000**	1.05	1.03 - 1.08	**<0.000**
CVD	2.10	1.30 - 3.20	**0.002**	0.85	0.50 - 1.46	0.558
DM	0.99	0.56 - 1.70	0.964			
Asthma	0.81	0.42 - 1.60	0.527			
CPD	2.90	1.70 - 5.10	**<0.000**	2.09	1.18 - 3.70	**0.012**
ACEi/ARB	2.20	1.40 - 3.50	**<0.000**	1.78	1.05 - 3.01	**0.032**
ACF	1.70	1.40 - 1.90	**<0.000**	1.56	1.35 - 1.80	**<0.000**
ARF	1.30	0.91 - 1.80	0.159			
AKI at ICU admission	3.40	2.20 - 5.30	**<0.000**	2.66	1.69 - 4.19	**<0.000**

HR = Hazard Ratio, CI = Confidence Interval, CND = Chronic Neurological Disease, CVD = Cardiovascular Disease, DM = Diabetes Mellitus, CPD = Chronic Pulmonary Disease, ACEi = Angiotensin-Converting Enzyme-inhibitor, ARB = Angiotensin II Receptor Blocker, ACF = Acute Circulatory Failure, ARF = Acute Respiratory Failure, AKI = Acute Kidney Injury, ICU = Intensive Care Unit.

Table S4: Comparison of AKI definitions and staging criteria. *Legends:* AKI = Acute Kidney Injury, KDIGO = Kidney Disease: Improving Global Outcomes, RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease, SAPS II = Simplified Acute Physiology Score II, SCr = Serum Creatinine, GFR = Glomerular Filtration Rate, UO = Urine Output, BUN = Blood Urea Nitrogen, RRT = Renal Replacement Therapy, h = hours.

Table S4: Comparison of AKI definitions and staging criteria.

KDIGO		RIFLE			Renal SAPS II		
Stage	**SCr[a]**	**Class**	**SCr or GFR**	**UO[b]**	**Score**	**UO/24 h**	**BUN**
					0	>1000 ml	<10 mmol/L
1	1.5-1.9x baseline or >26.5 µmol/L increase	**Risk**	SCr increase 1.5x baseline or eGFR decrease ≥25%	<0.5ml/kg/h for 6 h			
2	2.0-2.9x baseline	**Injury**	SCr increase 2.0x baseline or eGFR decrease ≥50%	<0.5 ml/kg/h for 12 h (<840 ml/24 h[c])	**4**	500-999 ml	
					6		10-29.9 mmol/L
3	≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) increase or initiation of RRT	**Failure**	SCr increase ≥3.0x baseline or ≥4 mg/dl (= 353.7 µmol/L) or GFR decrease ≥75%	<0.3 ml/kg/h for 24 h (<504 ml/24 h[c]) or anuria for 12 hours.	**10**		>30 mmol/L
					11	<500 ml	

[a]SCr-increase within 48 hours.

[b]UO criteria are shared by KDIGO and RIFLE.

[c]Standardized for a patient with a weight of 70 kg.

AKI = Acute Kidney Injury, KDIGO: Kidney Disease: Improving Global Outcomes, RIFLE: Risk, Injury, Failure, Loss, End-stage kidney disease, SAPS II = Simplified Acute Physiology Score II, SCr = Serum Creatinine, GFR = Glomerular Filtration Rate, UO = Urine Output, BUN = Blood Urea Nitrogen, RRT = Renal Replacement Therapy, h = hours.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

For article:

"Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort."

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	(4-)5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6-7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-11

			(b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	
Outcome data		15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion				
Key results	18		Summarise key results with reference to study objectives	14
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-16
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21		Discuss the generalisability (external validity) of the study results	16
Other information				
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.