

# Negative effects of iodine-based contrast agent on renal function in patients with moderate reduced renal function hospitalized for Covid-19

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## Research Article

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# Abstract

**Background** Kidney disease and renal failure are associated with hospital deaths in patients with Covid-19. We aimed to test if contrast enhancement (CE) affects short-term renal function in hospitalized Covid-19 patients.

**Methods** Plasma creatinine (P-creatinine) was measured on the day of computed tomography (CT) and 24 h, 48 h, and 4–10 days after CT. CE (n = 142) and non-CE (n = 24) groups were subdivided, based on estimated glomerular filtration rates (eGFR), > 60 and  $\geq 30$ –60 ml/min/1.73 m<sup>2</sup>. Contrast-induced acute renal failure (CI-AKI) was defined as  $\geq 27$   $\mu$ mol/L increase or a > 50% rise in P-creatinine from CT or initiation of renal replacement therapy (RRT) during follow-up. Patients with RRT were studied separately. We evaluated factors associated with a > 50% rise in P-creatinine.

**Results** Median P-creatinine at 24–48 h and days 4–10 post-CT in patients with eGFR > 60 and eGFR  $\geq 30$ –60 in CE and non-CE groups did not differ from basal values. CI-AKI was observed at 48 h and at 4–10 days post-CE in 24% and 36% (n = 5/14) of patients with eGFR  $\geq 30$ –60. Corresponding figures in the eGFR > 60 CE CT group were 5%, (p < 0.037 and p < 0.001, Pearson  $\chi^2$  test respectively). In the former group, four of the five patients died within 30 days. Odds ratio analysis showed that CI-AKI was associated with an eGFR  $\leq 60$  at CE and 30-day mortality both at 48 h and 4–10 days.

**Conclusion** Patients with Covid-19 and eGFR  $\geq 30$ –60 had a high frequency of CK-AKI at 48 h and at 4–10 days after CE, which was associated with increased 30-day mortality. For patients with eGFR  $\geq 30$ –60, we recommend strict indications are practiced for CE CT. CE had a modest effect in patients with eGFR > 60.

## Introduction

Iodine-based contrast agents for intravascular use may have a negative effect on kidney function, particularly in previously compromised kidneys (1). Contrast-induced acute kidney injury (CI-AKI) has been defined as an increase in plasma (P)-creatinine measured 2-3 days after computed tomography (CT) (2). A previous definition used a P-creatinine increase of 44  $\mu$ mol/L or above as diagnostic (3). A recent guideline recommends a lower limit (2). Patient related factors are known to affect the risk; most importantly kidney function, which is usually expressed as, estimated glomerular filtration rate (eGFR). A value <60 ml/min/1,73m<sup>2</sup> has been used to define a somewhat higher risk. eGFR <30 ml/min x 1.73 m<sup>2</sup> indicates severe renal failure and is considered a risk factor for CI-AKI (1, 2). The incidence of CI-AKI was shown to range from 0 to 24%, with the highest risk in diabetic nephropathy (4). Other background factors of importance are kidney surgery, proteinuria and hypertension (2). It is also well known that severity of present disease increases the risk substantially (5).

Thromboembolic diseases, including pulmonary embolism (PE), are seen with a high frequency in Covid-19 (6, 7). The primary method for confirming pulmonary embolism is CT angiography (8). Suspected PE was the dominating indication for CT angiography in our study. CI-AKI was defined as an increase in P-

creatinine  $\geq 27$   $\mu\text{mol/L}$  or  $>50\%$  rise in P-creatinine above the value on the day of CT (2). Kidney disease and renal failure were associated with hospital death in Covid-19 (4). This raised the question of whether patients with Covid-19 might be more susceptible to the harmful effects of iodinated contrast material (9). This possibility could influence risk assessments whether a CT angiogram is performed in Covid-19. We hypothesized that, in patients with Covid-19, the administration of contrast enhancement (CE) would increase P-creatinine and reduce eGFR to a greater extent than a non-CE approach in patients with a moderate renal impairment and  $\text{eGFR} \leq 60$   $\text{ml/min} \times 1.73 \text{ m}^2$ .

## Methods

This retrospective study was approved by the Ethical Review authority, (Dnr 2020-01882), and informed consent was waived. From March 19 to May 31, 2020, we included all patients with a PCR test positive for SARS-CoV-2 that were referred to thoracic or abdominal CT at our hospital.

### Measurements

We collected P-creatinine measured on the day of before CT and 24 h, 48 h, and 4-10 days after CT, when available. P-creatinine (anticoagulated with Li-heparin) was analyzed with an enzymatic photometric method (Cobas®, Roche Diagnostics, GmbH, Mannheim, Germany). The reference values were  $<100$   $\mu\text{mol/L}$  for men and  $<90$   $\mu\text{mol/L}$  for women. Pre-Covid-19 levels of P-creatinine were retrieved from patient records up to two years before the current hospitalization.

eGFR was calculated according to the chronic kidney disease epidemiology collaboration (CKD-EPI) formula (2). An  $\text{eGFR} \geq 90$   $\text{ml/min} \times 1.73 \text{ m}^2$  was taken as normal, values below  $\text{eGFR} 60$  indicated moderate reduced renal function and values below 30 indicated severe renal failure (2). CI-AKI was defined as an increase in P-creatinine  $\geq 27$   $\mu\text{mol/L}$  or  $>50\%$  rise in P-creatinine above the value on the day of CT (2).

CT was performed with a 256-slice multi-detector Revolution CT (GE Healthcare). The CE (Omnipaque 350 mg/ml) was applied at a flow rate of 5 ml/s.

We collected data on patient age, sex, weight, height, body mass index (BMI), anti-thrombotic treatment, co-morbidities, C-reactive protein (CRP; reference value  $<5.0$  mg/l) measured at the time of the CT scan, the contrast dose, intensive care unit (ICU) stay and 30-day mortality. CRP was determined with an immuno-turbidimetric analysis (Cobas®, Roche Diagnostics, GmbH, Mannheim, Germany).

### Study groups

The patient selection process is shown in Figure 1.

During the study period, 166 patients met the inclusion criteria. Among these, seven patients were included twice, because they underwent CT scans with and without CE. No patient underwent a repeated CE CT scan or a repeated non-CE CT scan.

Patients were divided into subgroups depending on renal function. The subgroups were defined as an eGFR >60 ml/min x 1.73 m<sup>2</sup> (eGFR>60) or an eGFR ≤60 ml/min x 1.73 m<sup>2</sup> (eGFR≤60). Patients on RRT at CT (n=20) were analyzed separately.

## Statistics

Anthropometric and laboratory data are presented as median and interquartile range (IQR, Table 1). Student t-test, analysis of variance (ANOVA), and Pearson's  $\chi^2$  -test were used for comparisons of categorical variables. Logistic regression analyses were used to calculate the odds ratio (OR) and 95% confidence interval (CI) (Table 2). We performed odds ratio analyses to investigate associations between P-creatinine 48 h after CT and P-creatinine 4-10 days after CT. A *P*-value <0.05 was considered significant. All statistical analyses were performed with Statistical Stat Soft, version 10.

## Results

### Patients with eGFR >60 ml/min x 1.73 m<sup>2</sup> without existing RRT examined with CE

The median P-creatinine levels at CT were 61 and 65 µmol/L in 110 patients with CE CT and in 8 patients with non-CE CT, respectively. The median P-creatinine values changed minimally at follow up (Table 1a). However in the CE CT group, five of 97 patients studied at 48 h and four of 78 patients studied at 4-10 days showed an increase in P-creatinine above definition for CI-AKI (Table 1a, Fig 2a).

At 48 h, the P-creatinine in three out of four of these patients was already above definition for CI-AKI. Two of these patients had RRT on day 7. In three of the four patients with a >50% increase in P-creatinine after 4-10 days, the median pre-Covid-19 P-creatinine level was 83 (IQR: 65-104) µmol/l.

Six patients died before the 4-10-day follow-up. Of these patients, one had a 200% rise in P-creatinine at 48 h, not seen in the other five patients.

### Patients with eGFR ≥30-60 ml/min x 1.73 m<sup>2</sup> without existing RRT examined with CE

In the CT CE group the median P-creatinine was 130 µmol/l (n=17 patients; Table 1a). This value remained unchanged at 24-48 h, and at 4-10 days after CE exposure for the whole group (Table 1a). However, at 48 h, the incidence of a P-creatinine rise above definition for CI-AKI was observed in 24% vs 5% in the CE CT eGFR>60 group (p=0.037, Table 1a). Five out of 14 patients that remained at follow-up days 4-10 showed a >50% P-creatinine increase, including initiation of RRT in two cases (Fig 2a, Table 1a). This incidence was higher than the figures observed in the CE CT eGFR>60 group (36% vs 5%, p<0.001, Table 1a) and also compared with the eGFR<60 group not receiving CE (36% vs 0%, p=0.043,  $\chi^2$ -test). These five patients had initial P-creatinine values of 121, 124, 129, 130, and 182 µmol/L (Fig 2a), and median pre-Covid P-creatinine of 97 (IQR: 82-106) µmol/L. Three of these patients had a pre-Covid eGFR <60 ml/min x 1.73 m<sup>2</sup>. These five patients did not seem to differ in pre-Covid P-creatinine compared with other patients in the CE CT ≥30-60 group (Table 1b). Four of these five patients died within 30 days

of the CE CT (Fig 2b) and in total, 30-day mortality was 53% in the whole group. Two of these patients died before follow up at 4-10 days. Of the two patients that died before follow-up, one showed a rise in P-creatinine above definition for CI-AKI at 24 h.

A higher pre-Covid-19 prevalence of renal disease and hypertension was seen in the  $eGFR \geq 30-60$  CE CT group compared with the  $eGFR > 60$  CE CT group (Table 1a). None of CE CT patients with  $eGFR \leq 60$  had an  $eGFR < 30$  ml/min x  $1.73$  m<sup>2</sup>.

### **Patients with $eGFR \leq 60$ ml/min x $1.73$ m<sup>2</sup> without existing RRT examined without CE**

In the non-CE CT group, among the 11 patients with  $eGFR \leq 60$ , the initial median P-creatinine level was 163  $\mu$ mol/l, which was significantly higher than the levels observed in the other groups. In this group, the median P-creatinine level fell progressively during follow-up (Table 1a). At 4-10 days after CT, none of nine patients showed a 50% increase in P-creatinine. 30-day mortality was 18 % compared with 53% in the  $eGFR \geq 30-60$  CE CT group ( $p=0.07$ ,  $\chi^2$ - test). Two of non-CE CT patients with  $eGFR \leq 60$  had an  $eGFR < 30$  ml/min x  $1.73$  m<sup>2</sup>.

In the non-CE CT group, no patient received RRT after CT during the study period.\

### **Patients with existing RRT examined with CE**

This group ( $n=15$ ) received higher doses of contrast agent than the doses given to patients that were not taking RRT (median doses: 110 ml, 95%CI: 60-129 vs. 60 ml, 95%CI: 60-70;  $p<0.001$ ). The median P-creatinine levels in this group declined from 161 at baseline to 127  $\mu$ mol/L at 48 h; then it rose to 188  $\mu$ mol/L at 4-10 days after CE exposure (not significantly different from baseline; Table 1c).

After 4-10 days, we observed a  $>50\%$  increase in P-creatinine in five out of remaining 14 patients in the RRT with CE CT group and only one out of 21 patients in the non-RRT non-CE CT group (36% vs. 5%;  $p=0.017$ ; Table 1b). Among the 24 patients that received a CT without CE during the study period, five were taking RRT at the time of the CT (5 patients included in Table 1c).

### **Odds ratio analysis**

Odds ratio analysis indicated that a  $>50\%$  rise in P-creatinine after 48 h and after 4-10 days was associated with  $eGFR \leq 60$  and CE at CT, with 30-day mortality and with RRT at CT (Table 2).

## **Discussion**

We hypothesized that the administration of iodine-based CE to patients with Covid-19 would affect P-creatinine and renal function. In the present study, in all subgroups of renal function, small changes were seen in median values 24-48 hours after CE exposure. However, our findings indicated that in 24-36% of patients with moderate renal failure and an  $eGFR$  of 30-60 ml/min x  $1.73$  m<sup>2</sup> at the time of the CT, CE had a negative effect on renal function. These figures were significantly higher than the 5% observed in

patients with eGFR >60 and CE. Not surprisingly mortality was higher in CE patients with eGFR of 30-60 compared with those with eGFR above 60 (53% vs 11%). More patients with eGFR between 30-60 given CE developed CK-AKI compared to those not receiving CE (24-36% vs 0%). Patients in the non-CE CT group with eGFR ≤60 had high CRP and significantly higher median P-creatinine at CT scan compared with the eGFR ≥30-60 CE CT group. Despite this, 30-day mortality showed a tendency to be lower in the non-CE CT group. This indicates that CI-AKI identified a vulnerable group of Covid-19 patients.

The findings related to RRT are difficult to interpret without detailed knowledge of the RRT-intensity or diuresis. Not surprisingly, renal failure after CE CT was associated with an ICU stay and with 30-day mortality, but only slightly with age.

Barrios-Lopez et al reported, before the Covid-19 era, that the incidence of CK-AKI was only 1% in patients with chronic renal disease and eGFR 30-60 ml/min x 1.73 m<sup>2</sup> (10). The peak P-creatinine level is typically observed within 2 to 5 days after a contrast medium injection (10).

The risk factors associated with acute kidney injury after an iodinated contrast injection include advanced age, hypovolemia and dehydration, type 2 diabetes, and previously impaired kidney function (11). Chronic kidney disease was proposed to be the strongest risk factor associated with developing a contrast-associated acute kidney injury (12). Moreover, critically ill patients are at increased risk of CK-AKI. In 2011, Hoste et al reported that one out of six patients in the ICU developed CK-AKI (5). However, in a recent large meta-analysis with a control group, acute kidney injury was not associated with the administration of iodinated contrast material (13).

Deep vein thrombosis was found in 40% of autopsies in 80 cases with Covid-19 in Germany (14). Covid-19 was associated with an increased risk of thrombosis in both the micro- and macrovasculature (15). Acute kidney injury is a complication associated with severe Covid-19 infections (16). Microthrombosis might be involved in the decline of kidney function in patients with Covid-19. Furthermore, renal tubule cells may be targeted in Covid-19, because these cells express receptors for Sars-CoV-2 (17). In experimental studies, contrast agents reduced renal blood flow and induced oxygen free radicals, a scenario that leads to apoptosis of renal tubular cells (18) and reduced GFR.

Our patients with eGFR of 30-60 at the time of CE CT had higher CRP levels and a higher incidence of chronic renal disease before CT, compared to patients with eGFR >60 at the time of CE CT. Severely ill patients with Covid-19 that have moderate renal dysfunction might be more prone to the effects of iodinated contrast agents, due to the combination of the previous kidney disease and the SARS CoV-2 effect on tubular cells. Severe renal failure is a contra-indication for contrast agent injections; this is the main reason for the high P-creatinine levels found in the non-CE CT group.

Our study had some limitations. First, we evaluated relatively small numbers of patients in most of our study groups. Second, we lacked follow-up P-creatinine values at 4-10 days in 28% of patients in the eGFR >60 CE CT group. The reasons for this loss included death before follow-up (n=6), missing follow-up P-creatinine levels, and, hospital discharge.

Four out of 127 patients in the CE CT group initiated RRT during the study period. Among the patients that were taking RRT at the time of the CT scan, normal contrast doses did not cause obvious negative effects, compared to other patients with  $eGFR \leq 60 \text{ ml/min} \times 1.73 \text{ m}^2$ . However RRT at CE CT was associated with a  $>50\%$  rise in P-creatinine at 4-10 days and caution before CE CT for this group of patients seems appropriate.

To minimize the risks for CK-AKI we recommend that strict indications are practiced for CE CT in patients with an  $eGFR \geq 30-60 \text{ ml/min} \times 1.73 \text{ m}^2$ . Perhaps iodinated contrast agent should not be administered to Covid-19 patients with  $eGFR$  below 60 protected by full-dose thromboembolic treatment. If considered necessary CE CTs should be performed with a low kV setting and the lowest possible dose of a low- or iso-osmolality contrast agent (19). In addition, an infusion of isotonic saline, started hours before exposure to contrast agents, has been proposed for protection against CK-AKI (20).

In conclusion, we demonstrated that hospitalized Covid-19 patients with moderate renal impairment and an  $eGFR$  of  $30-60 \text{ ml/min} \times 1.73 \text{ m}^2$ , showed an increased risk of worsened renal impairment after an iodine-based contrast injection. We observed a  $>50\%$  rise in P-creatinine or RRT initiation at 4-10 days after CE CT in 36% of patients with  $eGFR$  between 30-60, compared to 5% of patients with  $eGFR$  above 60. This report could aid in risk assessments before ordering a CE CT in patients with Covid-19. Larger studies are needed to confirm our observations.

## Declarations

**Ethics approval:** The authors hereby confirm that all methods were carried out in accordance with relevant guidelines and regulations. The Swedish Ethical Review Authority, Uppsala, Sweden, approved the waiver for informed consent for this retrospective study, application number 2020-01882.

**Consent for publication:** Not applicable

**Availability of data and material:** figshare.com

**Competing interests:** The authors declare no conflicts related to the submitted work

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**Authors contribution:** AK, MB, and SN were involved in the concept and design of the study. AK and CT performed the analysis of the data. AK, CT, AMS, MB, FS, MS och SN all contributed in the interpretation of the data. The first draft was written by AK and all co-authors were engaged in revising the final version of the manuscript. All co-authors also did a final approval of the version to be published.

**Consent to participate:** Not applicable

**Availability of data and material:** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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## Tables

**Table 1. Demographics, laboratory data, and outcome in patients with Covid-19, grouped by eGFR<sup>7</sup> >60 or ≤60 ml/min x 1.73 m<sup>2</sup> and CT with or without CE**

(a) Patients without RRT at CT	1. eGFR $\geq$ 30-60 CE (n=17)	2. eGFR>60 CE (n=110)	3. eGFR $\leq$ 60 non-CE (n=11)	4. eGFR>60 non-CE (n=8)	p-value*
<b>DEMOGRAPHICS</b>					
Men/women (n)	14/3	77/33	7/4	6/2	0.65
Age (years)	65 (61-76)	58 (49-64)	59 (51-68)	64 (50-70)	0.029
Weight (kg)	75 (72-87)	80 (72-93)	74 (61-87)	79 (64-90)	0.53
BMI (kg/m <sup>2</sup> )	25 (23-30)	28 (24-31)	25 (21-29)	25 (21-27)	0.19
<b>Thromboembolic treatment</b>					
before CT exam (%) (n=no/yes), n=144	76 (n=4/n=13)	76 (n=26/n=84)	89 (n=1/n=8)	88 (n=1/n=7)	0.75
<b>CO-MORBIDITIES</b>					
Renal disease (%) (n=no/yes), n=144	25 (4/12)	0 (0/109)	55 (6/5)	13 (1/7)	<0.001
Hypertension (%) (n=no/yes), n=141	60 (9/6)	36 (38/68)	64 (7/4)	13 (1/7)	0.037
Heart failure (%) (n=no/yes), n=144	13 (2/14)	5 (5/104)	18 (2/9)	13 (1/7)	0.24
Type 2 diabetes (%) (n=no/yes), n=143	24 (4/12)	20 (22/86)	18 (2/9)	25 (2/6)	0.96
<b>LABORATORY DATA</b>					
P-creatinine at CT, n=146	130 (121-153)	61 (48-76)	163 (132-201)	65 (45-80)	1 vs 3 <0.001/ 2 vs 4 0.85
creatinine 24 h after CT exam, n=127	130 (118-186)	61 (49-74)	136 (105-151)	63 (43-89)	1 vs 3 0.97/ 2 vs 4 0.97
creatinine 48 h after CT exam, n=128	130 (111-192)	62 (50-73)	123 (112-159)	69 (54-74)	1 vs 3 0.46/ 2 vs 4 ns 0.95
creatinine 4-10 days after CT exam, n=110	129 (77-197) (n=14)	62 (48-75) (n=78)	85 (70-124) (n=9)	64 (53-79) (n=9)	1 vs 3 0.09/ 2 vs 4 0.59
creatinine rise >26.5 $\mu$ mol/L or >50% 48 h after CT exam (%) (n=yes/n=no), n=128	24 (n=3/n=14)	5 (n=5/n=92)	20 (n=2/n=8)	0 (n=5)	0.037 †
creatinine rise >50% at 4-10 days after CT exam or RRT initiated, (%) (n=yes/n=no), n=110	36 (n=5/n=9)	5 (n=4/n=75)	0 (n=9)	0 (n=8)	<0.001 †
CRP at CT scan (mg/l), n=126	186 (71-292)	71 (26-163)	186 (74-257)	96 (42-197)	0.005, 1 vs 2 p<0.01, 1 vs 4 p<0.05
Total contrast dose (ml), n=111	60 (50-100) (n=15)	60 (60-70) (n=96)	n.a.	n.a.	0.96
Contrast dose (ml/kg), n=98	0.80 (0.69-1.22)	0.76 (0.65-0.94)	n.a.	n.a.	0.58
<b>OUTCOME DATA</b>					
Support at CT exam (%) (n=yes/n=no), n=144	56 (n=9/n=7)	23 (n=25/n=84)	18 (n=2/n=9)	0 (n=0/n=8)	<0.01 †
30-day mortality (%), n=146	53 (n=9/n=8)	11 (n=12/n=98)	18 (n=2/n=9)	13 (n=1/n=7)	<0.001 †

(b) Patients without RRT at CT and eGFR $\geq$ 30-60 CE	1. P-creatinine rise >50% at 4-10 days after CT exam and/or RRT initiated (n= 5)	2. P-creatinine rise <50% at 4-10 days after CT exam (n=9)	p-value*
DEMOGRAPHICS			
Age	68 (65-76)	64 (54-70)	0.55
Weight	72 (64-75)	76 (79-86)	0.21
LABORATORY DATA			
Pre-Covid P-creatinine	97 (82-106)	97 (77-114)	0.95
P-creatinine at CT	129 (124-130)	143 (118-155)	0.49
P-creatinine at 24 h	143 (126-196)	123 (116-139)	0.31
P-creatinine at 48 h	163 (138-196)	108 (103-126)	0.13
P-creatinine at 4-10 days	207 (197-237)	88 (68-118)	<0.001
CRP in mg/l	295 (274-331)	136 (59-221)	0.06
OUTCOME			
30-day mortality (%) (n=yes/no)	80 (4/1)	33 (3/6)	0.09 †

(c) Patients with existing RRT at CE CT vs. the entire non-CE CT group	1. CE CT and RRT (n=15)	3. Non-CE CT (n=24, including 19 without and 5 with RRT)	p-value*
<b>DEMOGRAPHICS</b>			
Men/women (n)	13/2	18/6	0.37
Age (years)	59 (55-64)	62 (48-67)	0.65
Weight (kg)	85 (70-100)	76 (68-90)	0.16
BMI (kg/m <sup>2</sup> )	28 (24-32)	25 (23-27)	0.08
Thromboembolic treatment 24 h before CT exam (%) (n=no/yes), n=37	87 (n=2/n=13)	86 (n=3/n=19)	0.98
<b>CO-MORBIDITIES</b>			
Renal disease (%) (n=no/yes)	7 (1/14)	30 (7/17)	0.08
Hypertension (%) (n=no/yes)	36 (5/9)	43 (10/13)	0.64
Heart failure (%) (n=no/yes)	0 (0/15)	13 (3/20)	0.14
Type 2 diabetes (%) (n=no/yes)	13 (2/13)	26 (6/17)	0.35
<b>LABORATORY DATA</b>			
P-creatinine, n=39	161 (130-232)	129 (80-187)	0.68
P-creatinine 24 h after CT exam, n=34	151 (132-219)	108 (86-151)	0.47
P-creatinine 48 h after CT exam, n=33	127 (105-175)	117(74-159)	0.69
P-creatinine 4-10 days after CT exam, n=33	188 (67-358) (n=14)	82 (62-131) (n=21)	0.12
P-creatinine rise 26.5 µmol/L or >50% 48 h after CT exam (%) (n=yes/n=no), n=33	29 (n=4/n=10)	11 (n=2/17)	0.18 †
P-creatinine rise >50% 4-10 days after CT (%) (n=yes/n=no), n=33	36 (n=5/n=9)	5 (n=1/20)	0.017 †
CRP at CT scan (mg/l)	101 (54-190)	127 (74-204)	0.70
Total contrast dose (ml), n=14	110 (60-129)	n.a.	
Contrast dose (ml/kg), n=11	1.10 (0.69-1.43)	n.a.	
<b>OUTCOME DATA</b>			
ICU support at CT exam (%) (n=yes/n=no), n=39	100 (n=15/n=0)	25 (n=6/n=18)	<0.001 †
30-day mortality (%) (n=yes/n=no), n=39	40 (n=6/n=9)	21 (n=5/n=19)	0.20 †

Values are presented as the median (interquartile range), the number (n), or in percent, as indicated. Statistics are based on: \*analysis of variance (ANOVA) with post-hoc Fisher's test or t-test, or †Pearson chi square test. BMI: body mass index; CE: contrast enhancement; CRP: C-reactive protein; CT: computed tomography; eGFR: estimated glomerular filtration rate (ml/min × 1.73 m<sup>2</sup>); ICU: intensive care unit; n.a.: not applicable; non-CE: CT without CE; P-creatinine: plasma creatinine in µmol/L; RRT: renal replacement therapy

**Table 2. Linear regression analysis of variables associated with a >25% rise in P-creatinine at 48 h or 4-10 days after CT**

Variable	Numbers at 48 h / N at 4-10 days after CT	Above or below median value	P-creatinine rise 26.5 $\mu\text{mol/L}$ or $>50\%$ at 48 h after CT, OR (95% CI)	p-value	P-creatinine rise 26.5 $\mu\text{mol/L}$ or $>50\%$ and/or RRT initiation at 4-10 days after CT, OR (95% CI)	p-value
P-creatinine ( $\mu\text{mol/L}$ ) at CT	114/93	$>67$	1.7 (0.4-6.7)	0.46	2.4 (0.6-11)	0.22
eGFR $\geq$ 30-60 and CE at CT	114/93		5.7 (1.3-24)	0.018	10.4 (2.3-47)	0.002
Dose/weight (ml/kg)	89/70	$>0.78$	0.68 (0.14-3.3)	0.63	0.9 (0.2-3.9)	0.86
Male sex	114/93		1.2 (0.2-6)	0.86	3.0 (0.3-26)	0.25
Age (years)	114/102	$>59$	2.2 (0.5-9.4)	0.27	4.7 (0.9-24)	0.042
Thromboembolic treatment	114/93		0.59 (0.1- 2.6)	0.49	0.95 (0.2-5)	0.96
ICU care	113/92		2.0 (0.5-8)	0.34	5.7 (1.2-27)	0.023
30-day mortality	114/93		12 (2.7-54)	$<0.001$	16 (3-79)	$<0.001$
RRT at CT	128/106		4.7 (1.2-18)	0.037	5.2 (1.4-19)	0.017

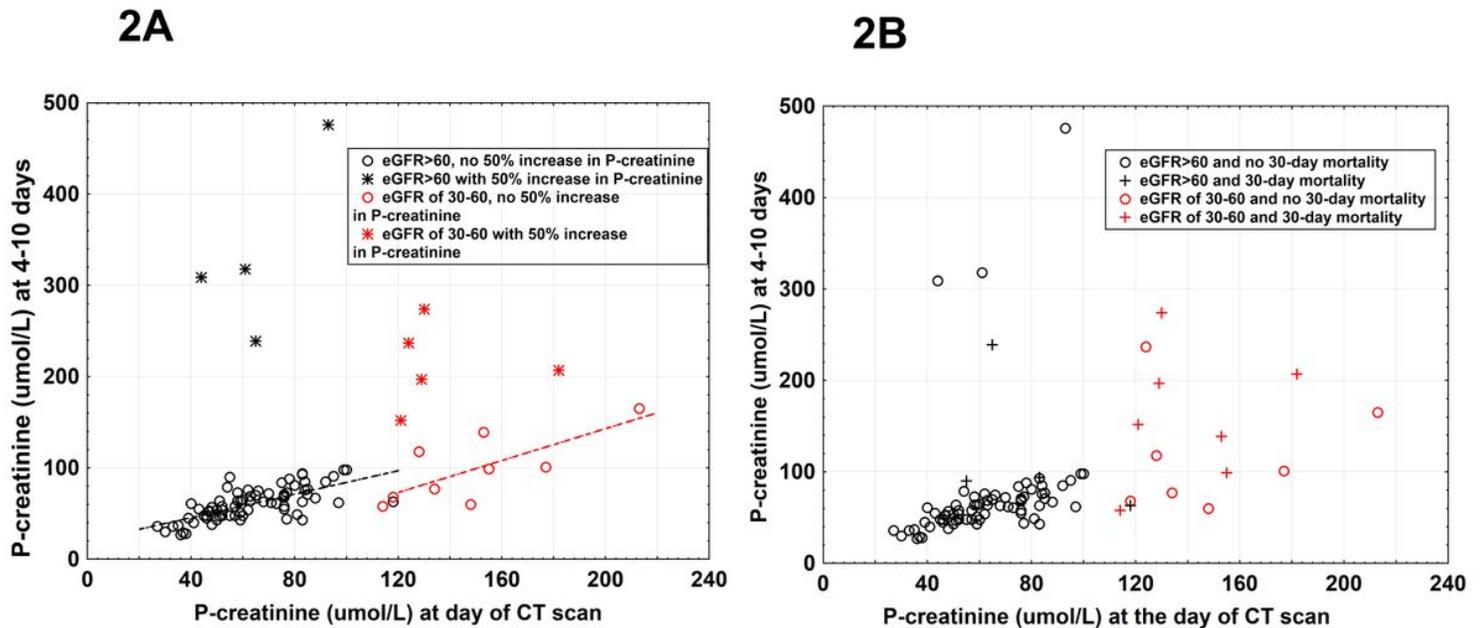
CE= contrast enhancement; CI: confidence interval; CT= computed tomography; eGFR: estimated glomerular filtration rate ( $\text{ml}/\text{min} \times 1.73 \text{ m}^2$ ); h=hours; ICU= intensive care unit; OR: odds ratio; P-creatinine=plasma creatinine; RRT= renal replacement therapy

## Figures



Figure 1

Flowchart shows the patient selection process. CE: contrast enhancement; CT: computed tomography; eGFR: estimated glomerular filtration rate



**Figure 2**

Outcomes, based on eGFR, in patients hospitalized with Covid-19 that underwent CE CT. P-creatinine values ( $\mu\text{mol/L}$ ) at the time of CT are plotted relative to P-creatinine values at 4-10 days after CT. Patients with renal replacement therapy (RRT) at the time of CT were excluded. (a) eGFR and a CE-induced rise in P-creatinine. Black unfilled circles or stars represent patients with an eGFR  $>60 \text{ ml/min} \times 1.73 \text{ m}^2$  ( $n=79$ ). Black stars indicate patients with a  $>50\%$  rise in P-creatinine at 4-10 days ( $n=4$ ). Black unfilled circles represent patients without a  $>50\%$  rise in P-creatinine or RRT initiation ( $n=75$ ). The dashed black line shows the correlation between P-creatinine at CT and P-creatinine at 4-10 days; ( $r=0.71, p<0.001$ ). Red unfilled circles or stars represent patients with an eGFR of 30-60  $\text{ml/min} \times 1.73 \text{ m}^2$  ( $n=14$ ). Red stars indicate patients with a  $>50\%$  rise in P-creatinine or an RRT initiation ( $n=5$ ). Red unfilled circles represent patients without a  $>50\%$  rise in P-creatinine or an RRT initiation ( $n=9$ ). The dashed red line shows the correlation between P-creatinine at CT and P-creatinine at 4-10 days ( $r=0.74, p=0.024$ ). (b) eGFR and 30-day mortality. Black unfilled circles and crosses represent patients with an eGFR  $>60 \text{ ml/min} \times 1.73 \text{ m}^2$ .

Black unfilled circles represent patients that did not die within 30 days after CT. Black crosses represent patients that died within 30 days after the CT. Red unfilled circles and crosses represent patients with an eGFR of 30-60 ml/min  $\times$  1.73 m<sup>2</sup>. Red unfilled circles represent patients that did not die within 30 days of the CT. Red crosses represent patients that died within 30 days after the CT. CE: contrast enhancement; CT: computed tomography; eGFR: estimated glomerular filtration rate; P-creatinine: plasma creatinine, RRT: renal replacement therapy.