PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Acute Kidney Injury in COVID-19 patients in the Intensive Care Unit. Evaluation of risk factors and mortality in a national cohort.
AUTHORS	Aukland, Eirik; Klepstad, Pål; Aukland, Stein Magnus; Ghavidel, Fatemeh; Buanes, Eirik

VERSION 1 – REVIEW

REVIEWER	Moffitt, Richard Stony Brook University
REVIEW RETURNED	29-Dec-2021

GENERAL COMMENTS	This paper investigates the outcomes of 361 patients, representing 98% of Norwegian ICU stays. The strengths of this work are the completeness of the data and the relative lack of sampling bias in the study population as a result. A major weakness of the study, acknowledged by the authors, is the lack of Serum Creatinine data which would have allowed more nuanced temporal analysis. Furthermore, (1) a Simplified Acute Physiology Score II was used to define AKI in the ICU, and (2) the MDRD equation was used for estimating baseline creatinine was used for defining AKI upon hospital admission. These less definitive indicators may weaken the overall power of the study to draw clear associations. These limitations are unlikely to improve with revision, but they may be more clearly underlined in a revised discussion. As is, the study seems largely confirmatory of previous findings. In addition to these comments, I have the following concerns: Logistic regression and Kaplan-Meier analyses are used for associations with death. It may be more appropriate and powerful to use a Cox regression to model variables associated with survival times. There are some seemingly circular claims that need clarification. For example: “Patients with AKI at admission to ICU … had a higher SAPS II score (Table 2).” While SAPS score was used as a criteria for AKI. According to the methods, only significant univariate results were included in multivariable models, however CVD p = 0.089 was included in the multivariable analysis. Authors state “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.” However the intervals for AKI and CVD overlap, while the comparison of regression coefficients for a continuous variable like age to a categorical variable like AKI is inappropriate.

REVIEWER	Hultstrom, Michael University of Uppsala
REVIEW RETURNED	26-Jan-2022

GENERAL COMMENTS	Drs. Aukland and colleagues present a study of acute kidney injury in critically ill COVID-19 patients from Norway. The data is based on a national registry and includes almost all COVID-patients admitted to ICU in Norway. Interestingly, they report only AKI at ICU-admission based on SAPS-II not development of AKI during the ICU stay. Using this definition 32% out of 361 patients had AKI. They report 17% mortality at 30 days, and 22% mortality at 90 days. Age and circulatory fainlure and AKI were predictors of death. Cancer was a predictor of death only at 30 days. The study is interesting as a national report for Norway but has little generalisability and has several weaknesses. The definition of AKI includes only admission, which only covers a limited part of the time-points when AKI may develop. It also does not conform to current AKI definitions. However, they state AKI as defined by RIFLE-criteria in some places. It is not clear when this was calculated and for which patients. Acute circulatory failure makes no mention of vasopressor or inotrope use, which would be commonly used to define circulatory failure in ICU. Acute respiratory failure is also very lightly described and does not conform to ARDS criteria. In table 2 the authors state severe ARF and severe ACF but this is not defined as opposed to ARF/ACF. Logistic regression was performed on 337 patients without missing data, no imputation was performed. This is reasonable given the small population.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Discussion:

1. *The strengths of this work are the completeness of the data and the relative lack of sampling bias in the study population as a result. A major weakness of the study, acknowledged by the authors, is the lack of Serum Creatinine data which would have allowed more nuanced temporal analysis. Furthermore, (1) a Simplified Acute Physiology Score II was used to define AKI in the ICU, and (2) the MDRD equation was used for estimating baseline creatinine was used for defining AKI upon hospital admission. These less definitive indicators may weaken the overall power of the study to draw clear associations. These limitations are unlikely to improve with revision, but they may be more clearly underlined in a revised discussion. As is, the study seems largely confirmatory of previous findings."*

We agree that these limitations may be more clearly underlined and have revised the discussion accordingly:

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. ~~This limitation mandates that the results be interpreted with caution.~~ 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.

Methods/Results/Discussion

1. *Logistic regression and Kaplan-Meier analyses are used for associations with death. It may be more appropriate and powerful to use a Cox regression to model variables associated with survival times.*

We thank the reviewer for bringing this to our attention. As suggested by the reviewer, we have performed univariable and multivariable Cox regression analysis to assess risk factors associated with both 30- and 90-days mortality in addition to the logistic regression.

We have commented the results of the Cox regression analysis in the Results and Discussion-section of the manuscript. Tables with results from the Cox regression analyses are also included as supplementary files (S2 and S3).

Consequently, the manuscript contains the following changes:

Methods; Statistics:

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.

Results:

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:

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].

1. *There are some seemingly circular claims that need clarification. For example: "Patients with AKI at admission to ICU … had a higher SAPS II score (Table 2)." While SAPS score was used as a criteria for AKI.*

Thank you for bringing this to our attention. We agree and have removed this circular claim accordingly:

Patients with AKI at admission to ICU were more likely to have reduced GCS.~~, and they had a higher SAPS II score~~ (Table 2).

1. *According to the methods, only significant univariate results were included in multivariable models, however CVD p = 0.089 was included in the multivariable analysis.*

We apologize for the lack of clarity in the text. Variables which were found to be associated with AKI at ICU admission (p <0.1) in the univariable analysis were included in the multivariable logistic regression model. However, in the final multivariable analysis, p <0.05 was considered significant. We have clarified the methods section accordingly:

~~The variables which were found to be associated with AKI at ICU admission (p-value <0.1) were included in multivariable logistic regression model~~. 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.

1. *"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." However, the intervals for AKI and CVD overlap, while the comparison of regression coefficients for a continuous variable like age to a categorical variable like AKI is inappropriate.*

We thank the reviewer for bringing the implications of our wording to our attention. We have revised the sentence in order to avoid inappropriate assumptions.

~~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~~. 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.

Reviewer 2:

Methods

1. *The definition of AKI includes only admission, which only covers a limited part of the time-points when AKI may develop. It also does not conform to current AKI definitions. However, they state AKI as defined by RIFLE-criteria in some places. It is not clear when this was calculated and for which patients.*

Thank you for bringing this to our attention. We agree that this point should have been addressed in more detail, and have clarified the definitions section accordingly:

> While AKI at ICU-admission was defined according to renal SAPSII score, AKI at admission to hospital was defined according to RIFLE-criteria. For missing data, AKI at hospital admission was based on serum creatinine at hospital admission and the MDRD equation for estimating baseline creatinine.

1. *Acute circulatory failure makes no mention of vasopressor or inotrope use, which would be commonly used to define circulatory failure in ICU.*

Thank you for bringing this to our attention. The definition of Acute Circulatory Failure (ACF) at admission to hospital does not include vasopressor or inotrope use. In the revised manuscript this is now clearly stated:

> Acute Circulatory Failure (ACF) at admission to hospital 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, regardless of vasopressor or inotrope treatment. Severe ACF was defined as circulatory symptoms in rest.

Limitations in the data set prohibited us from including vasopressor use in the ICU in our analyses. The available variable was not confined to the first 24 hours of ICU-admission, and we could not differentiate between vasopressor use secondary to sedation and vasopressor use due to circulatory failure.
Some ICUs register SOFA-score, which includes vasopressor use. Unfortunately, SOFA-score is not a mandatory data point. Inclusion of data from a subset of ICU in the analyses would introduce bias, and as a result we chose to refrain from this. We have added this in the limitations section:

> We also lack data regarding the timeline of AKI in COVID-19, and the use of vasopressor in the ICU.

1. *Acute respiratory failure is also very lightly described and does not conform to ARDS criteria.*

We agree that the definition of Acute Respiratory Failure (ARF) warrants further description. In the revised version we expand the definition of ARF, and its relation to Acute Respiratory Distress Syndrome (ARDS):

> 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.

We agree that it would have been interesting to examine the role of ARDS in predicting AKI at ICU-admission. However, the registry does not contain data for this condition alone, but ARDS is included in the broadly defined and less precise term "Acute Respiratory Failure".

1. *In table 2 the authors state severe ARF and severe ACF but this is not defined as opposed to ARF/ACF.*

Thank you for bringing this to our attention. We agree that the definition of severe ARF and ACF is deficient in the Methods section and have added the following explanatory sentences, also included in the reply to comments 2 and 3 from this reviewer above:

> Severe ACF was defined as circulatory symptoms in rest.
>
> Severe ARF was defined as respiratory symptoms in rest.

VERSION 2 – REVIEW

REVIEWER	Moffitt, Richard Stony Brook University
REVIEW RETURNED	18-Apr-2022

GENERAL COMMENTS	The authors have addressed my concerns. My only remaining suggestion is to be more explicit about how the Cox regression was performed for "30- and 90-days mortality". For example, were all data censored after 30 or 90 days?

REVIEWER	Hultstrom, Michael University of Uppsala

REVIEW RETURNED	10-Apr-2022

GENERAL COMMENTS	The authors have answered my questions. My remaining caveat is the use of non-standard definitions for AKI and circulatory and respiratory failure for a critical care study. This makes difficult to compare the results with previous literature and limits clinical usefulness.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Methods/results

1. *My only remaining suggestion is to be more explicit about how the Cox regression was performed for "30- and 90-days mortality". For example, were all data censored after 30 or 90 days?*

We thank the reviewer for bringing this to our attention. As suggested by the reviewer, we have revised the methods and results section accordingly.

~~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. p-value <0.05 was considered statistically significant.

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.

Reviewer: 2

1. *The authors have answered my questions. My remaining caveat is the use of non-standard definitions for AKI and circulatory and respiratory failure for a critical care study. This makes difficult to compare the results with previous literature and limits clinical usefulness.*

We agree that this is an important limitation of our study and that the reader must keep this in mind, when interpreting the results. Thus, we have attempted to emphasize this limitation throughout the manuscript; in the Article Summary, in the Methods and in the Discussion. The study was a national registry study, which has its limitations when it comes to both the number and complexity of (statistical) variables that are available. Consequently, 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. But as emphasized in the Discussion, the combination of urine output and BUN in renal SAPSII should provide an estimate of AKI sufficiently to be relevant.

Regarding the definitions on acute circulatory failure (ACF) and acute respiratory failure (ARF), the same applies – we are limited to the variables available in the national registry. However, we consider the variables and corresponding results relevant, and have stated them as precisely as we were able to, based on the data and information available in the national registry.

Regardless of these limitations which mandates that the results to be interpreted with caution, we consider the results to be rigorous and that they should be treated as a basis for further investigation.

VERSION 3 – REVIEW

REVIEWER	Moffitt, Richard Stony Brook University
REVIEW RETURNED	20-May-2022

GENERAL COMMENTS	I have no further suggestions.

REVIEWER	Hultstrom, Michael University of Uppsala
REVIEW RETURNED	06-May-2022

GENERAL COMMENTS	No further comments.