



RESEARCH ARTICLE

Limitations of care and comorbidities are associated with increased mortality in patients treated with non-invasive ventilation: A retrospective observational study in a single-center ICU. [version 1; peer review: 2 approved with reservations]

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Abstract



Background: Non-invasive ventilation (NIV) is a common treatment for acute respiratory failure in intensive care units (ICU). While there is increasing data on outcomes after NIV treatment, there are large variations in staffing and monitoring where NIV is provided, making results hard to generalize. The aim of this study was to characterize patients treated with NIV, describe outcomes, and identify factors associated with outcome in an ICU at a Swedish county hospital.

Methods: A single-centre retrospective observational study during 2018 of patients treated with NIV in a six-bed ICU at a Swedish county hospital. Patient characteristics, including comorbidities, details of ICU stay, simplified acute physiology score (SAPS-3), details of NIV treatment and 30-day mortality were collected, and the Charlson comorbidity index (CCI) was calculated. Primary outcomes were 30-day mortality and associated factors.


Results: 92 patients with mean age (71,3, SD 12,1) were treated with NIV during the study period. 42 (46%) were women. Median CCI was 3 (25th-75th percentiles 1.4)) and median SAPS-3 score was 66 (25th-75th percentiles 58). The 30-day mortality was 37% and in the univariate analysis, SAPS-3 score >66, Charlson comorbidity index, CCI>=3, pCO₂ <5.5 and limitation of care were factors associated with increased 30-day mortality. pH <7.35 and pO₂<8 at admission showed no associations with 30-day mortality.

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Conclusions: We found that patients treated with NIV in ICU were a diverse population where comorbidities and presence of limitations of care might be considered as better predictors of 30-day mortality, rather than physiological parameters.

Keywords

Critical Care, Noninvasive Ventilation, Mortality, Withholding treatment

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Introduction

Non-invasive ventilation (NIV), i.e. respiratory support through a non-invasive interface such as a facemask or nasal prongs, is an evolving therapy with a broad application in intensive care units (ICU)¹⁻³. NIV reduces the risks related to invasive mechanical ventilation in patients with acute respiratory failure in e.g. chronic obstructive pulmonary disease (COPD) and pneumonia⁴. Further, NIV improves survival after pulmonary oedema and respiratory failure of different aetiologies⁵⁻⁸.

A delayed start of NIV increases mortality⁹. Improper selection of patients and continuing treatment when NIV is not sufficient leads to unnecessary harm to the patients and delayed intubation and invasive mechanical ventilation, which is associated with increased mortality¹⁰.

The selection of patients who would benefit from an ICU-admission with NIV-treatment is often difficult, as the patients often present with a complex clinical picture¹¹. For decision support, there are several models that predict ICU outcome, such as the Simplified Acute Physiology Score (SAPS-3)¹² and the Acute Physiology and Chronic Health Evaluations (APACHE II)¹³. Further, the Charlson comorbidity index (CCI)¹⁴, a frequently used measure of comorbidity, is also able to predict mortality^{15,16}. Patients treated with NIV frequently have “do not intubate” (DNI) orders^{17,18}. It has been shown that the patients with DNI orders treated with NIV for acute respiratory failure who survive have similar life quality after three months compared to patients without limitations of care¹⁹.

The settings in which NIV is utilized differs between hospitals and countries where NIV is being increasingly used outside of the ICU^{4,20}. The outcome for patients treated with NIV in the acute care setting for specific diagnoses has been extensively studied⁷. However, there is limited knowledge of the outcomes in a mixed population receiving non-invasive ventilation at an ICU.

The aim of this study was to describe mortality after NIV at a Swedish county hospital and to identify factors associated with mortality.

Methods

Patient population and study design

A retrospective observational single-centre study conducted in a six-bed ICU at a county hospital (250-bed, Sundsvall, Sweden). Patients >18 years who received NIV in the ICU from January 2018 to December 2018 were included in the study. The study was approved by the Swedish Ethical Review Authority, Uppsala, Sweden (2019-04564, 2019-09-27) and patient consent was waived. The study protocol was performed in accordance with relevant guidelines and the study was registered in clinicaltrials.gov (NCT04115969).

Data collection

Out of the 547 ICU-admissions during 2018, eligible patients were identified in the local ICU-registry. If a patient had more than one ICU-admission during 2018, only the first admission was included. Data sources were medical records, laboratory

records, the local ICU-registry and ICU-charts. Variables collected were patient characteristics, admission status (diagnosis, laboratory findings and risk-scoring), details of ventilatory support, arterial blood-gases, limitation-of-care decisions, and 30-day mortality. Further, overall 30-day mortality and the number of patients with limitations of care was retrieved for all patients admitted to the ICU during 2018.

ICU-scoring

The SAPS-3 and APACHE-II-scores were retrieved from the local ICU-registry. The scores were validated for each patient by a review of the records.

Comorbidities

Charlson comorbidity index (CCI) was used to quantify comorbidities and the CCI was calculated with weighting (according to the original study), with a maximum score of 33¹⁴.

Statistical analysis

All variables were registered in an anonymized spreadsheet (Excel, version 1902; Microsoft Excel, RRID:SCR_016137). A free alternative software is Google sheets). Data are presented as numbers (rates), mean (standard deviation, SD) or medians (25th-75th percentiles) as appropriate.

The dichotomisation of continuous variables was based on deviations from the normal values (pH<7.35, pO₂<8 kPa, pCO₂>5.5 kPa), clinically relevant cut-off points (CCI≥3, RLS (Reaction level scale) >3) or if no data for the decision was available, the median value (SAPS-3).

Univariate analysis was performed using the Chi-2 test to analyse factors associated with 30-day mortality and presented as unadjusted odds-ratios with a corresponding 95% confidence interval. P-values lower than 0.05 were considered statistically significant.

The statistical analyses were performed using SPSS version 25.0 (IBM SPSS Statistics, RRID:SCR_019096). An open-source alternative software is R, which can perform equivalent functions (R Project for Statistical Computing, RRID:SCR_001905).

Results

Patient characteristics

The inclusion of patients is presented in Figure 1. 92 patients were treated with NIV during the study period. The mean age was 71 years (SD 12) and 42 (46%) patients were females. Reason for admission to the ICU included respiratory (n=82; 87%) and/or cardiac causes (n=36; 38%). 30 patients (32%) were admitted from the emergency department, 56 (60%) from a hospital ward, 6 (6%) from the operating theatre and 2 (2%) from other ICUs. Further patient characteristics are presented in Table 1.

Comorbidity

The main comorbidities were chronic heart failure (n=44; 48%), chronic obstructive pulmonary disease (COPD) (n=42; 46%), diabetes mellitus (n=35; 38%), previous myocardial infarction

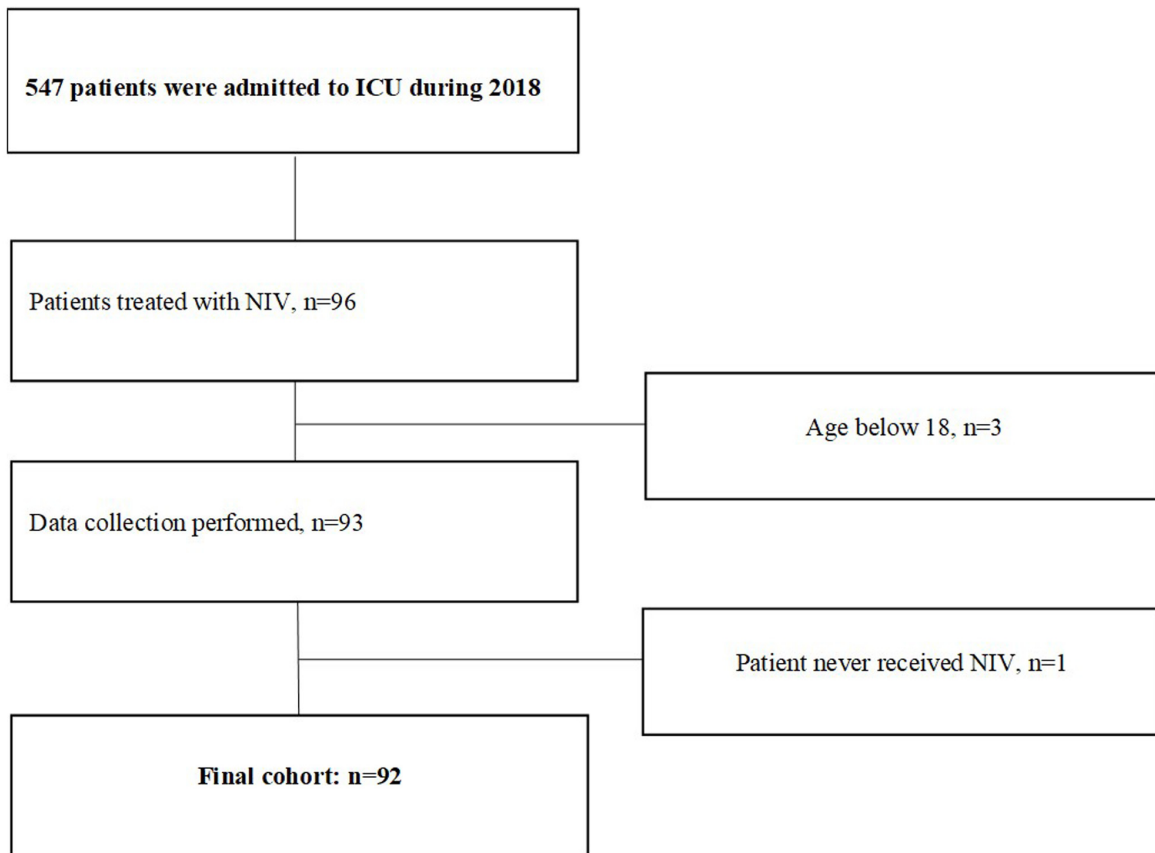


Figure 1. Screening and inclusion of patients.

(n=27; 29%), and cerebrovascular disease (n=15; 16%). 11 patients (12%) had a CCI of 0, 33 patients (35%) a CCI of 1 or 2, and 50 patients (54%) a CCI \geq 3.

Characteristics of ICU stay

The median time spent in the ICU was 1.8 (0.8–5.0) days and the median duration of NIV-treatment was 17 (6–34) hours. 24 patients (26%) were also treated with invasive ventilation during the ICU stay. A total of 38 patients (41%) had limitations of care. 34 (36%) with ‘no intubation’ and 37 (39%) ‘no CPR’. Further details of the ICU stay are presented in [Table 2](#).

Outcome and predictors of 30-day mortality

The 30-day mortality in the study cohort was 37% (n=34). In the univariate analysis, SAPS-3 score >66 , CCI ≥ 3 , pCO₂ <5.5 kPa and limitations of care were factors associated with an increased 30-day mortality, see [Table 3](#).

Characteristics of the ICU

30-day mortality for all patients admitted to the ICU during the study period was 21% (n=547). Further, 12% of all patients had limitations of care.

Discussion

Our retrospective study included all patients treated with NIV at a county hospital ICU during one year. We found that one third of these patients had died within 30 days, and the mortality was almost double compared to all patients admitted to the ICU. Further, 30-day mortality was associated with the presence of co-morbidities and limitations of care.

A recent meta-analysis evaluating noninvasive ventilation and survival in acute care settings showed a hospital mortality of 11%⁷, a much lower mortality than in our cohort. However, there were great variabilities in the studies included in the meta-analysis, regarding the severity and type of conditions treated. A French study evaluating outcome after acute respiratory failure in 14 different ICUs showed a hospital mortality of 30% in patients treated with NIV, which is comparable to our results⁴. The high mortality in our cohort might also be explained by advanced age, severity of disease, and a high number of patients with limitations of care.

NIV was used in every fifth patient in our ICU, a higher amount number compared to a study of more than thirteen

Table 1. Patient characteristics at admission to ICU in patients undergoing non-invasive ventilation (n=92) with relation to 30-day mortality.

Variable	All patients (n=92)	Day 30 after admission to ICU		p-value
		Non-survivors (n=34)	Survivors (n=58)	
Age, years	75 (67–80)	77 (70–81)	72 (65–79)	0.15
Female gender, number of patients	42 (46%)	9 (26%)	33 (57%)	<0.005
BMI, kg/m ²	30 (26–35)	30 (26–33)	30 (25–35)	1.00
Missing values BMI, number of patients	10	3	7	
Charlson comorbidity index (CCI)				
· 0	11 (12%)	4 (12%)	7 (12%)	0.073
· 1–2	32 (35%)	7 (21%)	25 (43%)	
· ≥3	49 (53%)	23 (68%)	26 (45%)	
SAPS-3 score	66 (57–77)	75 (66–82)	62 (55–71)	<0.001
Reason for ICU admission, number of patients				N.A.
· Observation only	1 (1%)	0 (0%)	1 (2%)	
· Cardiac	35 (38%)	19 (56%)	16 (28%)	
· Liver	1 (1%)	0 (0%)	1 (2%)	
· Gastrointestinal	13 (14%)	8 (24%)	5 (9%)	
· Neuro	32 (35%)	15 (44%)	17 (29%)	
· Renal	24 (26%)	14 (41%)	10 (17%)	
· Respiratory	80 (87%)	32 (94%)	48 (83%)	
· Hematological	4 (4%)	4 (12%)	0 (0%)	
· Metabolic	36 (39%)	17 (50%)	19 (33%)	
· Trauma	2 (2%)	0 (0%)	2 (3%)	
· Other	4 (4%)	1 (3%)	3 (5%)	
Admitted from, number of patients				N.A.
· Emergency department	29 (32%)	4 (12%)	25 (43%)	
· Hospital ward	55 (60%)	28 (82%)	27 (47%)	
· Other ICU	2 (2%)	0 (0%)	2 (3%)	
· Operating theatre	6 (6%)	2 (6%)	4 (7%)	
Reaction Level Scale (RLS)	2 (1.3)	2 (1.4)	2 (1.3)	0.67
Missing values RLS, number of patients*	2	0	2	
pH	7.29 (7.21–7.35)	7.28 (7.21–7.33)	7.29 (7.23–7.35)	0.33
Missing values pH, number of patients	1	0	1	
pO₂/FIO₂ ratio, kPa	21.3 (15.4–28.7)	18.8 (13.8–25.6)	24.8 (16.6–32.3)	0.066
Missing values pO ₂ /FIO ₂ , number of patients	3	0	3	
pCO₂, kPa	7.3 (4.8–9.5)	7.0 (3.9–10)	7.4 (5.6–9.3)	0.440
Missing values pCO ₂ , number of patients	11	2	9	

Data are presented as numbers (%) or median (25th–75th percentile). The Mann-Whitney-U test and the Chi-2 test was used for continuous and categorical variables, respectively, to evaluate statistical differences between the groups. ICU=Intensive Care Unit, BMI=Body mass index, CCI=Charlson comorbidity index, *SAPS 3=Simplified Acute Physiology Score, RLS=Reaction Level Scale, N.A=not applicable

Table 2. Characteristics of ICU stay for patients undergoing non-invasive ventilation.

Variable	All patient (n=92)	Day 30 after admission to ICU		p-value
		Non-survivors (n=34)	Survivors (n=58)	
Time in ICU, Days	1.8 (0.8–5)	3.2 (1.2–5.4)	1.2 (0.8–3.8)	0.096
Limitation of care orders				
-‘Do-not-intubate’, number of patients	33 (36%)	19 (56%)	14 (24%)	0.0022
-No CPR, number of patients	36 (39%)	23 (68%)	13 (22%)	<0.001
Readmission within 72 hours, number of patients	6 (6.5%)	4 (12%)	2 (3%)	0.12
NIV treatment time, hours	17 (6–34)	21 (3–39)	15 (7–30)	0.82
IPAP cmH2O	10 (8–13)	10 (8–13)	10 (8–13)	0.66
Missing values, number of patients	9	4	5	
EPAP cmH2O	6 (5–6)	6 (5–7)	6 (5–6)	0.41
Missing values, number of patients	7	2	5	
Invasive ventilation, number of patients (%)	24 (26%)	11 (32%)	13 (22%)	0.29
Highflow oxygen, number of patients (%)	27 (29%)	11 (32%)	16 (28%)	0.63
pO2/FiO2 ratio at 1–2 hours after start of NIV	26 (18.9–30.7)	24.2 (14.8–29.8)	27 (19.8–30.9)	0.16
Missing values, number of patients	12	2	10	
pCO2 at 1–2 hours after start of NIV	7.08 (4.9–8.8)	6.6 (4.6–8.9)	7.38 (5.6–8.7)	0.27
Missing values, number of patients	13	3	10	
pH at 1–2 hours after start of NIV	7.32 (7.27–7.39)	7.30 (7.25–7.37)	7.33 (7.28–7.40)	0.094
Missing values, number of patients	12	2	10	

Data presented as number (%) or median (25th–75th percentiles). The Mann-Whitney-U test and the Chi-2 test was used for continuous and categorical variables, respectively, to evaluate statistical differences between the groups. ICU-Intensive Care unit; CPR-Cardiopulmonary resuscitation; NIV-Non-invasive ventilation; IPAP-Inspiratory positive airway pressure; EPAP Expiratory positive airway pressure

Table 3. Univariate analysis of factors associated with 30-day mortality in a cohort of patients (n=92) treated with non-invasive ventilation at an intensive care unit.

Variable	Number of patients	30-day mortality	Odds ratio (95% C.I.)	P-value
SAPS-3 score, ≥ 66 vs. 0–65	49/43	53% / 19%	4.95 (1.9–12.6)	<0.001
CCI score, ≥ 3 vs. 0–2	49/43	47% / 26%	2.57 (1.07–6.20)	0.034
pH at admission, <7.35 vs. ≥ 7.35	67/24	39% / 33%	1.27 (0.48–3.33)	0.63
pCO ₂ at admission (kPa), ≥ 5.5 vs. <5.5	56/25	32% / 56%	0.37 (0.14–0.97)	0.04
pO ₂ at admission (kPa), ≥ 8 vs. <8	68/21	40% / 33%	1.32 (0.48–3.61)	0.60
BMI (kg·m ⁻²), ≥ 35 vs. <35	18/64	28% / 41%	0.56 (0.19–1.73)	0.32
Age (years), ≥ 75 vs. <75	45/47	44% / 30%	1.89 (0.80–4.43)	0.15
RLS score, ≥ 3 vs. <3	30/62	37% / 37%	0.98 (0.40–2.41)	0.97
Limitation of care, yes vs. no	38/54	63% / 19%	7.54 (2.93–19.4)	<0.0001

SAPS 3, Simplified acute physiology score; CI, Confidence interval; CCI, Charlson comorbidity index; BMI, body mass index; RLS, Reaction level scale. For the univariate analysis, the Chi-2 test was used.

thousand ICU patients, where 4% received NIV²¹. This might reflect different practices of NIV globally, where NIV more often is used at wards and intermediary units outside the ICU compared to our study setting.

We found that a high SAPS3-score, a high Charlson Comorbidity Index (CCI), limitation of care and a low pCO₂ on admission were associated with an increased mortality. SAPS-3 is a validated score to predict ICU mortality, but when used for patients undergoing NIV in intermediate care units, the prediction accuracy could be lower, but by combining SAPS-3 with patient-risk factors, the mortality prediction can be improved²². This is in line with our results, as we found an association between mortality and co-morbidities.

Further, several studies identify CCI as a predictor of ICU mortality^{15,16,23}. A study of 347 patients outside an ICU undergoing NIV due to pneumonia concluded that in-hospital mortality was mainly associated with patients' co-morbidities and limitations of care, rather than the degree of acute respiratory failure²⁴. The evidence is conflicting however, as others have not found CCI to be a good predictor for short and medium-term outcomes in patients submitted for NIV due to acute respiratory failure²⁵. However, our data indicates that CCI might be considered as a predictor of mortality in NIV patients in an ICU setting.

pCO₂ on admission is not included in SAPS3 or APACHE II scoring systems. pCO₂ has been studied as a prognostic indicator for patients admitted with pneumonia, but no significant association has been found with mortality²⁶. We found that patients with a high pCO₂ had a lower mortality. This might either be explained by a suggested mortality benefit with NIV treatment in hypercapnic COPD patients⁶ or that patients with normal or low pCO₂ had conditions causing respiratory failure with a higher mortality.

41% of our patients had limitations of care, in contrast to all our ICU patients where only 12% had limitations of care. The observations are in line with a recent meta-analysis which concluded that 27% of patients with acute respiratory failure had a do-not-intubate order²⁷.

It is a difficult clinical task to identify patients that would benefit from NIV treatment, and several factors might influence the selection of patients admitted to an ICU²⁸. Since limitations of care are common among these patients, it is important to set clear goals with the NIV treatment²⁹. An older age, ARDS or pneumonia, or failure to improve after one hour of treatment is associated with higher risk of NIV failure in hypoxemic patients³⁰. Better prediction tools that can be used clinically, before the ICU admission, are needed³¹.

Except for details of comorbidities, pCO₂ and NIV-parameters, our data included the same variables that is sent to/included in the Swedish intensive care registry and this makes it possible to perform similar studies on a national level. However, variables are usually collected during the ICU-stay and many of

the variables are not known to the clinician when the decision to start NIV treatment is made. Therefore, a strength with the CCI is that it can be calculated at the time of admission to the ICU, in contrast to physiology-based scores that are dependent on laboratory and bedside clinical data. CCI as a predictor of outcome in the population treated with NIV in ICU has not previously been studied and our study indicates that it might be a usable tool.

Our study has limitations and strengths. Patients treated with NIV are a heterogeneous group and NIV was used in many different clinical conditions making it hard to generalize results and our single study setting further decreases external validity. However, even though our study was retrospective, our review of patient records added more variable than included in national intensive care registries. Further, we included almost all patients admitted to our ICU for one year. This is a strength as it reflects a general cohort of patients in the need of NIV treatment.

Conclusions

We conclude that patients treated with NIV in ICU are a diverse population where comorbidities and presence of limitations of care might be considered as better predictors of 30-day mortality, rather than physiological parameters.

List of abbreviations

APACHE II, Acute Physiology and Chronic Health Evaluations II

ARDS, Acute respiratory distress syndrome

CCI, Charlson's co-morbidity index

CI, Confidence Interval

COPD, Chronic obstructive pulmonary disease

CPR, Cardiopulmonary resuscitation

DNI, 'do-not-intubate'

ICU, Intensive care unit

NIV, Non-invasive ventilation

RLS, Reaction level scale

SAPS 3, Simplified Acute Physiology Score 3

SD, Standard deviation

Declarations

Ethical approval and consent to participate

The study was approved by the Swedish Ethical Review Authority (2019-04564, 2019-09-27) and patient consent was waived.

(Swedish Ethical Review Authority, Box 2110, 750 02 Uppsala, Sweden. registrator@etikprovningmyndigheten.se)

Consent for publication

Not applicable

Availability of data and materials

Data in the study could not be fully de-identified, and according to the General Data Protection Regulation (GDPR), they cannot be publicly shared. Further, the Ethical Review Authority only permitted us to publicly share data on a group level. However, the dataset generated and analysed during the current study are available from the corresponding author (jakob.wallden@umu.se) upon reasonable request. The dataset will be edited to comply with regulations to preserve privacy before being released for a limited use.

Reporting guidelines

Harvard dataverse: "STROBE checklist for 'Limitations of care and comorbidities are associated with increased mortality in patients treated with non-invasive ventilation: A retrospective observational study in a single-center ICU.'" <https://doi.org/10.7910/DVN/BMQDZO>

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

Author contributions

ES and JW are the main contributions to the concept and design of the study. ES is the main author working with the

review of patient charts, collection of data and analysis. ES drafted the manuscript, including the tables, with substantial revisions and feedback from JW and JT. All authors have read and approved the final version of the manuscript.

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? **Hans-Henrik Bülow** 

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This paper describes data of one year (2018) of treatment with non-invasive ventilation (NIV) in a single center ICU. The paper is well written with sufficient data to get an impression of the results and conclusions that the authors draw, but there are a number of reservations.

The first reviewer has pointed out the general problem with a single center retrospective study like this one, and I agree. I also agree with the first reviewer that it would be interesting to describe why so many patients had limitations.

There are 3 issues that, in my opinion, are lacking in this paper, before it can be indexed.

1. I do not understand why only the first admission during the data sampling period is included. COPD patients so ill that they need admittance to an ICU are generally in the last period of their disease before death – and their 2nd and any other following admissions is also part of the picture of non-invasive ventilation in an ICU.
2. Three patients below 18 years are not included in the dataset. As this is just a description of treatment already done in the ICU, I see no reservations with regard to ethics concerning treatment of children/adolescents – and data on NIV and children are not as well described as with adults – something might be learned here.
3. Unfortunately, the authors only note that 26% of the patients were also treated with invasive ventilation – but this information is of very little value as it is not noted if it was before or after NIV or perhaps both before and after? Different outcomes are often seen whether NIV has to be changed into invasive ventilation because of insufficient ventilation of the patient – or whether NIV is used as “a bridge” to spontaneous breathing after a course of invasive ventilation.

The authors have one interesting finding which I think they should elaborate on: Patients with a

pCO₂ below 5.5 had higher mortality than those with higher pCO₂s. Most likely these patients suffered from pneumonia (and not COPD) and pneumonia is very difficult to treat with NIV.

If these patients did not have limitations, they should probably have been changed to invasive ventilation earlier. If these patients had limitations in the form of “do-not-intubate”, then NIV was their last possibility for treatment, and it is not surprising that they died. These data are worth looking into.

The authors write in the discussion section: “Older age, ARDS, pneumonia or failure to improve after one hour of NIV treatment is associated with higher risk of NIV failure ---- better prediction tools are needed” I do not agree with this conclusion. I believe that with the reservations towards NIV that the authors do note, then we have the tools to predict fairly well if NIV treatment has a chance of being successful. But CCI may be an interesting tool to do further research on.

I am not too happy about the conclusion: “limitation of care is associated with higher mortality”.. e.g., the Ethicus-II study with data from 2016 from a number of European ICU’s has just shown, that an increase in number of limitations in 2016 did not lead to higher mortality compared to data from the same ICU’s in 1999. (Please see Reference 1).

With regard to references I would not refer to papers from acute care, as this is often a very different setting and different patient cases compared to the ICU setting.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: non-invasive ventilation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 24 September 2021

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John Botha

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This study has all the limitations of a single centre retrospective study. The conclusions that can be drawn are limited and unlikely to provide assistance to clinicians in critical care.

In this, centre NIV ventilation appears to be the default mode of ventilatory support for patients who will not have their level of care escalated. The mortality of patients in the study was over 30% and this indicates a cohort of patients that were critically ill. The study would be more informative if only patients destined for active care were included in the study.

I would suggest that the sample size be increased over time and that only patients that did not have limitations of care be included.

The hours of NIV in the non survivors was minimal suggesting they were pre terminal prior to the initiation of ventilation.

If the study were to be indexed in its current form the reasons as to why so many patients were NFR would strengthen the study.

I consider the study able to be indexed if these changes were made.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ventilation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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