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An alternative strategy for COVID-pneumonitis: a retrospective analysis from a tertiary center in Belgium

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Abstract: At the start of the COVID-19 pandemic in Europe no clear guidelines on its treatment were available. While early intubation and the avoidance of steroids was proposed, an alternative strategy of non-invasive ventilation and steroid use in case of refractory hypoxemia after one week was implemented to decrease the burden on resources. This single center retrospective analysis assessed the feasibility and safety of such a strategy.

All patients admitted to the ICU with a confirmed COVID-19 pneumonitis from March to June 2020 were included in the analysis. Multivariable logistic regression was done to assess (1) the feasibility of ICU mortality prediction by the Charlson Comorbidity Index and the Clinical Frailty Score (2) the impact of invasive mechanical ventilation and steroid administration in ICU mortality.

97 patients were admitted to the ICU. Mean APACHE-III was 67 (16), with a predicted ICU mortality of 30%. Median P/F ratio was 91 (IQR 67-118) on admission. Only 37 (40%) patients were intubated and mechanically ventilated within their ICU stay. The ICU mortality rate was 20.6% (n=20). The multivariable logistic regression model for ICU mortality, using gender, Charlson Comorbidity Index and Clinical Frailty Score had an AUROC of 0.81, with an R^2 of 0.23. Thirty eight patients (39%) of 97 patients received steroids. Adding steroid administration to the multivariable model did not yield the latter as an independent factor of ICU-mortality (p=0.06). However, mechanical ventilation remained an independent risk factor for ICU-mortality (p=0.004) with an odds ratio of 9.9 (95%CI 1.8-53.6), after adjustment for baseline risk factors Charlson Comorbidity Index, Clinical Frailty Score and APACHE-III score.

This single center retrospective analysis demonstrated a safe alternative strategy using a non-invasive ventilation strategy and late administration of steroids. These findings need to be confirmed in multi-center prospective randomised controlled trials.

Keywords: COVID-19; SARS-CoV-2; critical care.

Introduction

In early spring, Belgium was struck hard by the COVID-19 pandemic, reporting one of the highest mortality rates in the world (1). Our hospital, *Ziekenhuis Oost-Limburg (ZOL),* is situated in the province of Limburg, which was the epicenter of the COVID crisis in Belgium, reporting the highest infection rate of all Belgian provinces (2). A total of 97 patients were admitted to the Intensive Care Unit because of respiratory failure due to COVID-19.

At the time of the outbreak, a number of publications stressed the need for early intubation and mechanical ventilation, citing the atypical nature of respiratory distress in COVD-19 patients (3-5), despite the high burden on ICU resources, potentially limiting the survival chances of other patients. In contrast, WHO advocated the use of non-invasive forms of respiratory support in their guidelines for the management of COVID-19

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Author contributions: TF, JB and WB conceived the study and drafted the manuscript. TF, MV and WB implemented the COVID-19 ICU management. XW, KE, LM and MV supervised patient recruitment and revised the manuscript for important intellectual content. NP and BG extracted the data from the electronic medical records and exported the data for statistical analysis. DM participated in the design of the study, performed the statistical analyses and drafted the manuscript. All authors read and approved the final manuscript. TF and JB contributed equally.

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patients, if adequate personal protective equipment (PPE) was available (6). Data confirming or refuting safety concerns regarding contamination risk for medical care givers via aerosol dispersal has been limited (7).

The use of highly dosed corticosteroids was surrounded by similar controversy. They might attenuate the "cytokine release syndrome" in the most severely affected patients. Others suggested the use of low dose oral or inhaled steroids (8) early in the disease course. The administration of steroids, in any dose, was not a routine practice during the European spring COVID pandemic. Hence, the feasibility and safety of a COVID protocol, in which postponing mechanical ventilation and the administration of highly dosed steroids in refractory hypoxemia were cornerstones, was unproven at the start of the European COVID outbreak.

Methods

This study is a single center retrospective analysis of our protocol, written in "tempore non suspecto". The study site was the ICU department of *Ziekenhuis Oost-Limburg*, one of the largest non-university teaching hospitals in Belgium. The ICU is a mixed medical-surgical unit, normally consisting of 36 beds. At the time of the COVID pandemic the ICU capacity was increased to 51 beds, of which 42 were dedicated to COVID patients. All patients admitted to the ICU, infected with COVID-19 and suffering from respiratory failure, were included.

Airway and Ventilation protocol

Patients were treated by high flow nasal cannula (HFNC) when possible. Non-invasive mask ventilation was not used for COVID-19 patients. However, the decision to intubate was not based on oxygenation or pO_2/fractional O_2 (P/F ratio) only, but on an integrated appraisal together with secondary organ dysfunction, such as confusion, hemodynamic instability and exhaustion. After intubation, patients underwent lung protective ventilation, as summarized in appendix 1.

Medical treatment for COVID-19

Antiviral therapy

Treatment regimens were based on the Belgian interim guidelines published on the Sciensano website (https://www.sciensano.be/en). Hydroxychloroquine (Plaquenil®) 400 mg was initiated at admission to ICU, then 400 mg 12h later, followed by 200 mg b.i.d. for 5 days. Azithromycine, given to patients admitted to the non-ICU pulmonary department, was stopped. In case of hydroxychloroquine use, daily ECG follow-up was instigated to monitor QTc-interval and magnesium was given IV 3 x 1 g per day, unless contra-indicated. If hydroxychloroquine was contraindicated lopinavir/ritonavir 400/100 mg (= 2 tablets Kaletra of 200/50 mg) was prescribed twice daily for 14 day. Though remdesivir was available in compassionate use early in the peak, this became unavailable later on.

Corticosteroids

Steroid therapy was initiated according to the surviving sepsis campaign guidelines (9) and the Canadian guidelines (10), underpinned by the recent retrospective study by Wu et al. (11). Steroid therapy was considered if, after 7 days, there were indications for Hemophagocytic Syndrome (12) or high P/F ratios without signs of recovery, though earlier implementation was allowed at the treating intensivist's discretion. Whenever steroid therapy was started, patients received methylprednisolone for a total of ten days.

On the first two days a bolus of 250 mg methylprednisolone was given. To prevent a re-bound effect the dose was tapered in the eight following days to 0.25 mg/kg once a day.

Antibiotic therapy

On admission, ceftriaxone 2 g 1x/d was empirically started for 5 days. In case of beta-lactam allergy, moxifloxacine 500 mg was used once daily. Surveillance cultures guided further antibiotic therapy.

Low molecular weight heparin (LMWH)

Because of the documented high risk of thrombosis, all patients prophylactically received intermediary dosed LMWH (approximately 1 mg/kg enoxaparin), guided by regular anti-Xa measurements. Twice weekly screening for deep vein thrombosis was performed using ultrasonography in all patients and if necessary LMWH therapy was increased to therapeutic values.

Capacity and Staffing

A total of 17 consultants, fully trained as intensivists, are members of the critical care group,.

In the normal setting, the ICU has a capacity of 36 beds. The ICU is staffed by intensivists, 24 hours per day, 7 days per week. During the pandemic, capacity was increased to a maximum of 51 ICU beds. The normal operating theatre activity was scaled down and the post-surgery recovery room was reassigned to the ICU. Because other activities were scaled down, it was possible to deploy the wider intensivist group on ICU to meet heightened demand. At peak pandemic 5 intensivists worked during the day shift on the expanded ICU and during out-of-hours' shifts 3 intensivists remained in house. A similar upscaling of nursing staff was implemented.

COVID ICU admission criteria and therapeutic limitations

A guideline was developed to help clinicians when deciding on ICU admission and treatment restriction concerning intensive care. It was based on the Charlson Comorbidity Index (CCI) (13) and the Clinical Frailty Score (CFS) (14). In every patient offered for admission to ICU, treatment options were actively considered. Any restriction in treatment was discussed among 3 consultants, of whom at least one was an intensivist and the referring specialist. The motivation for limiting treatment was always documented, as were particular limitations in patients admitted to the ICU (so called DNR code).

Statistical analysis

Categorical data were represented as numbers and percentages. The distribution of continuous data was analyzed and represented as either mean +/- SD or median and IQR. Outcome (ICU mortality) was assessed with three models. These multivariable analyses were adjusted for the following risk factors: Charlson Comorbidity Index (CCI) (continuous variable), Clinical Frailty Score (CFS) (categorical value). Model 1 included gender, CCI and CFS. Model 2 included gender, age and CFS; Model 3 included gender, CCI, CFS and APACHE-III score; Model 4 gender, CCI, CFS, APACHE-III score with steroid administration; Model 5: gender, CCI, CFS, APACHE III score with mechanical ventilation. Hence, for the comparison between patients, receiving steroids or not, and non-invasive mechanical ventilation on admission versus mechanical ventilation, further adjustment was done for severity of illness by the Acute Physiology and Chronic Health Evaluation score III (APACHE-III). All model variables were selected *a priori* on the basis of evidence from the literature. No data imputation was done as for all variables the missings were less than 15%. We assessed the performance of the models with the variance (R^2) and the area under the receiver operating characteristic (AUROC). Calibration of the model was tested by a goodness of fit test. The misclassification rate calculated and we estimated the fit of the model with the Akaike Information Criterion (AIC).

All P-values were 2-sided and considered significant when < 0.05. All analyses were performed with JMPsoftware version 15.0.0 (SAS Institute, Cary, NC, USA).

Table 1

Patient characteristics

Age, y, mean (SD)	67 (12)
Gender, male, n (%)	62 (64%)
BMI, median (IQR)	29.4 (26.8-33.4)
APACHE-III points, mean (SD)	67 (16)
GCS, mean (SD)	14.8 (0.5)
Charlson comorbidity index, median (IQR)	4 (2.5-6)
Diabetes mellitus, n (%)	29 (30.2%)
Chronic kidney disease at any stage, n (%)	20 (20.8%)
Hypertension, n (%)	47 (48.4%)
Employed as healthcare worker, n (%)	3 (3.1%)
Pre-ICU origin, n (%)	
General COVID ward	56 (58%)
Emergency department	35 (36%)
Other hospitals	6 (6%)

RESULTS

Study population

A total of 97 were admitted to the ICU because of COVID-19 related respiratory failure, in the period from 13-03-2020 to 20-06-2020 (Table 1).

Mean APACHE-III was 67 (16), indicating a mean predicted APACHE-IV mortality of 30% (15), using the APACHE-IV diagnostic code 172 (viral pneumonia). Forty nine patients (51%) had a CFS of at least 3 (Fig. 1). Eight patients (8%) had a CFS of more than 6. A treatment restriction for intubation (i.e. maximal respiratory support without intubation and mechanical ventilation, no CPR, otherwise standard treatment) was implemented on admission for 13 patients (13%). Median P/F ratio was 91 (67-

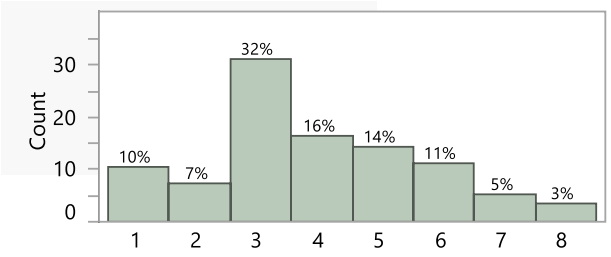

Fig. 1. — Rockwood clinical frailty score.

118) on admission. Only 28 (28.9%) patients were intubated and mechanically ventilated within 24h from ICU admission. 11 (11%) patients, initially treated by HFNC were intubated during their stay on ICU, resulting in a total of 39 of 97 (40%) patients intubated and mechanically ventilated at any time during their ICU-stay. Sixty (61%) patients were treated by hydroxychloroquine and only 2 (2%) were treated by lopinavir/ritonavir. Thirty eight patients (39%) of 97 patients received steroids.

A total of 20 patients died on ICU (20.6%). Median length of stay on ICU was 8 days (4-20) and 17 days (11-28) for index hospital stay. Four patients were placed on veno-venous-ECMO, of whom all survived. Four nurses contracted COVID infection, presumably while working in the COVID-ICU.

Comorbidity and Frailty in COVID-19 patients

The multivariable logistic regression model for ICU survival, using gender, CCI and CFS had an AUROC of 0.81, with an R^2 of 0.23, AIC of 99 and a goodness of fit with p=0.59 (Table 2, Model 1). The misclassification rate was 16.5%. In this model the CCI was the only independent factor associated with ICU non-survival (p=0.002), with an odds ratio of 1.43 (95%CI 1.16-1.85) per CCI unit.

In the multivariable logistic regression model for ICU survival, using gender, age and CFS, age was the only independent factor associated with ICU survival (p=0.0016) (Table 2, Model 2). The model had a AUROC of 0.83, with an R^2 of 0.27, AIC of 97 and a goodness of fit with p=0.96. The misclassification rate was 19.6%. The odds ratio of age per year added for ICU mortality was 1.12 (95%CI 1.05-1.21) in the latter multivariable model.

The multivariable model (Model 3) with gender, CCI, CFS and APACHE-III score had an AUROC of 0.85, R^2 of 0.29, AIC of 95 and a goodness of fit with p=0.92. The APACHE-III was here the only independent factor associated with ICU non-survival (p=0.02).

Steroid administration (Table 2, Model 4) was not an independent factor of ICU survival, when added to this model (p=0.13), with the APACHE-III score remaining as the only independent factor (p=0.03). In a multivariable model (Table 2, Model 5) with gender, CCI, CFS, APACHE-III score and mechanical ventilation at any time during ICU-stay, the independent factors, associated with ICU mortality were invasive ventilation (p=0.004), CCI (p=0.01) and APACHE-III score (p=0.04). The odds ratio of invasive ventilation for ICU non-survival was 9.9 (95%CI 1.8-53.6).

Discussion

The COVID-19 pandemic has put extreme strain on all services in healthcare, in particular ICU and emergency departments. This retrospective single center analysis indicated that a respiratory strategy, primarily using HFNC in the treatment of COVID-19 pneumonitis patients, is at least a safe alternative to early intubation and mechanical ventilation, provided the ample availability and correct use of PPE.

In our center only 29% of patients were intubated immediately on arrival on the ICU, while

Table 2

Multivariable models

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
Odds ratios non-survivor versus survivor					
Gender (male vs female)	2.16 (0.60-7.77)	2.36 (0.66-8.50)	2.38 (0.63-8.98)	3.12 (0.75-13.07)	3.33 (0.76-14.54)
Age (per year added)		1.12 (1.05-1.21)			
CCI (per unit added)	1.43 (1.14-1.80)		1.22 (0.93-1.61)	1.29 (0.97-1.72)	1.42 (1.00-2.00)
Frailty (across all categories)	NS	NS		NS	NS
APACHE-III (per unit added)			1.06 (1.01-1.11)	1.05 (1.00-1.08)	1.07 (1.01-1.13)
Steroid use (yes vs no)				2.98 (0.72-12.30)	
Mechanical ventilation (yes vs no)					7.13 (1.36-37.42)

50% patients met the criteria for severe ARDS on admission. This strategy appeared safe as only a further 11% needed intubation. Moreover, after thorough correction for baseline risk factors, need for mechanical ventilation remained a strong predictor of ICU non-survival. Evidence for specific thresholds for intubation and mechanical ventilation is sparse (15), though in the pre-COVID ARDS population there are indications that delaying intubation may increase mortality (16). The Chinese Society of Anesthesiology Task Force on Airway Management (17) recommended a P/ F ratio below 150 mm Hg as a threshold for intubation in COVID-19 patients. Ninety percent of our patients would have met this threshold for intubation. Adequate staffing of fully trained intensivists and nursing staff 24 hours a day, may have facilitated a wait-and-see strategy based on respiratory support using HFNC. This was not always possible in many other overstretched and understaffed ICU's, overwhelmed by a pandemic of historic proportions.

From our single center study we can conclude that the late administration of steroids in patients with refractory hypoxia did not worsen outcome. At the time it was feared that the administration of steroids would increase the incidence of bacterial surinfections and impair outcome. Therefore we opted for selective steroid administration in the most severely ill COVID patient population. The recent RECOVERY trial conveyed the potential benefit of early administration of steroids in a COVID population, not always requiring ICU admission (18) This drug's benefit seemed to be limited to those with acute hypoxemic respiratory failure (intubated, or patients requiring oxygen). Hence, it remains unclear whether a strategy of early administration of steroids, selectively in patients with severe COVID-19 ARDS would be the most optimal.

Last but not least, survival of COVID-pneumonitis mostly depends on pre-existing comorbidities, such as age, hypertension, diabetes (19). Likewise, frailty may also be a good predictor of poor outcome in COVID-19 patients (20). Here we demonstrated that the combination of the Charlson Comorbidity Index and the Rockwood Clinical frailty Score may be a reliable indicator for ICU mortality. They are also readily available, as they were always assessed at initial presentation at the hospital, mostly in the emergency department. Age and the burden of comorbidities were also the strongest predictors of ICU-mortality in other cohorts (21, 22). However, we could not confirm clinical frailty as an independent predictor of ICU mortality (23).

There are several limitations in our study. First, it is a single center retrospective analysis, which limits the generalizability of our findings. However, the fact that patients with ARDS on were receiving HFNC ventilation as well as mechanical ventilation is valuable in the assessment of the impact of mode of ventilation in COVID-19 outcome. Second, the cohort was too small for reliable definition of predictors of COVID-19 outcome. Large, multi-center patient cohorts, with proper case-mix adjustments, will be required to accurately develop, train and validate models prediction models. Third, bacterial surinfections may have been masked by the prophylactic/empirical administration of ceftriaxone during the first five days of ICU stay. However, the steroids were only administered after 1 week of refractory hypoxemia. Finally, the time horizon of this retrospective analysis was ICU-stay as a few patients were still hospitalized. Hence, the long term impact of our treatment choices could not be assessed.

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Appendix 1. — Lung protective invasive ventilation

Driving pressure <12-15 cm H2O,

Tidal volume van 5-7 ml/kg IBW. Pplat 25-27 cmH2O, RR for a pH >7.2 (permissive hypercapnia).

Optimal PEEP was titrated per patient based on defining optimal lung compliance.

Recruitment manoeuvres were limited to a minimum.

Prone ventilation considered in case of Severe ARDS defined as:

– 2x ABGW P/F ratio <150 mmHg

– PEEP according to high PEEP table in appendix 1

– $FiO_2 \geq 60\%$