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Derivation and validation of the CERES score for the prediction of late intubation in Covid-19

Predicting the risk of intubation in Covid-19 with the CERES score

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Abstract (199 words)

Background

Predictive scores assessing the risk of respiratory failure in Covid-19 mostly focused on the prediction of early intubation. A combined assessment of clinical parameters and biomarkers of endotheliopathy could allow to predict late worsening of acute respiratory failure (ARF) subsequently warranting intubation in Covid-19.

Methods

Retrospective single-center derivation (N = 92 subjects) and validation cohorts (N = 59 subjects), including severe Covid-19 patients with non-invasive respiratory support for at least 48h following ICU admission. We used stepwise regression to construct the Covid endothelial and respiratory failure (CERES) score in a derivation cohort, and secondly assessed its accuracy for the prediction of late ARF worsening requiring intubation within 15 days following ICU admission in an independent validation cohort.

Results

Platelets, fraction of inspired oxygen (FiO₂) and endocan measured on ICU admission were identified as the top 3 predictive variables for late ARF worsening and subsequently included in the CERES score. The area under the ROC curve of the CERES score to predict late ARF worsening was respectively calculated in the derivation and validation cohorts at 0.834 and 0.780.

Conclusions

The CERES score seems to exhibit good performances to predict a worsening of the respiratory failure, leading to secondary intubation.

Keywords: Covid-19, late intubation, prediction, score, endothelial

Background

Covid-19 can be responsible of severe hypoxemia, which may warrant the use of invasive mechanical ventilation, occurring in more than 48 hours after ICU admission in half of the patients (1,2).

Noninvasive respiratory strategies such as continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO) have been proposed to avoid invasive mechanical ventilation in patients with COVID-19-related acute hypoxemic respiratory failure (3). Recent data report that more than of the half patients admitted in ICU for severe Covid-19 during the Omicron wave in the US exclusively underwent non-invasive strategies (4). However, it has been shown that delayed intubation is associated with increased mortality in critically ill patients on HFNO therapy (5), especially in the setting of Covid-19 pneumonia (6,7). This phenomenon likely results from intense spontaneous inspiratory efforts associated with high transpulmonary pressures, contributing to the development of patient self-induced lung injury (7). Therefore, the identification of patients at high risk of progression to respiratory failure requiring intubation seems to be of major interest for the management of severe Covid-19, as this subgroup of patients could benefit from early intubation.

Among the means to predict the risk of failure of non-invasive strategies in severe Covid-19, the ROX index, based on the clinical assessment of respiratory rate and pulse oxygen saturation, has been widely investigated. However, studies which evaluated this score mainly assessed its performances for the prediction of early intubation (8). Consequently, the search for tools to predict the late failure of non-invasive strategies in patients with severe Covid-19 remains of major interest.

Previous studies have focused on the profile of biomarkers of endotheliopathy in severe Covid-19. Among these, some markers were found to be associated with a poor outcome (9,10). Nevertheless, the prognostic values of these markers taken individually remain insufficient to determine with optimal accuracy the risk of progression to unfavorable respiratory outcome. Furthermore, no study to date has evaluated the value of phenotypic categorization based on the combined assessment of these markers.

Subsequently, the aim of our work was to derive and validate the Covid-related endotheliopathy and respiratory failure (CERES) score, based on routinely available clinical variables and endotheliopathy biomarkers for the prediction of late worsening of acute respiratory failure (ARF) subsequently requiring intubation in severe Covid-19.

Methods

Study design and patients

This study was conducted in a 74-bed mixed ICU (Department of Intensive Care Medicine, Critical Care Centre, CHU of Lille). We retrospectively included patients who underwent blood samplings between August, 7th 2020, and April 30th, 2021 in the setting of the PREDICT study (Clinicaltrial registration: NCT04327180) and who met the following criteria: age 18 or over, a positive SARS-CoV-2 real-time polymerase chain reaction, patients undergoing HFNO and / or non-invasive ventilation (NIV) and / or CPAP within the first 48 hours following ICU admission, treatment by intravenous corticosteroids at a dose regimen ranging from 6 to 20 mg/day of equivalent Dexamethasone on ICU admission. The exclusion criteria were a need for tracheal intubation within 48 hours following ICU admission, and a limitation of therapeutic effort on tracheal intubation. Patients with sufficient blood samples available to perform a complete assessment of all biomarkers explored in our study were included in the derivation cohort, while patients with insufficient blood samples available were included in the validation cohort.

Ethics statement

This research was examined and approved by the Institutional Review Board of Saint-Louis Hospital, Paris, France (Comité de Protection des Personnes Ile de France IV, approval number: 2020/30). Written informed consent was obtained from all the patients or their relatives.

Data collection

Patient demographic and clinical characteristics, severity scores, and comorbidities were recorded at baseline for all patients. Microbiological tests performed within 48h of admission were also recorded. Relevant tests included blood and sputum cultures, bronchoalveolar lavage fluids, multiplex PCRs on sputum, and urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae*. Further, data about clinical outcomes during the stay in ICU were obtained for all patients.

Laboratory testing

Blood was collected at ICU admission for each patient on 0.109 mol/L trisodium citrate tube (BD Vacutainer, BD Diagnostics, Sparks, MD). All analyses were performed on platelet-poor plasma obtained after a double centrifugation at 2500g for 15 minutes at room temperature.

The following biomarkers were measured in the derivation cohort: tissue factor pathway inhibitor (TFPI) was measured with Asserachrom total TFPI (Diagnostica Stago, Asnières sur Seine, France) and plasminogen activator inhibitor-1 (PAI-1) with Asserachrom PAI-1 (Diagnostica Stago); Angiopoietin 2 and vascular endothelial growth factor (VEGF) were measured using the Quantikine ELISA Kits (Biotechne, Rennes, France); Syndecan-1 was measured using the CD138 ELISA Kit (Diaclone, Besançon, France); Soluble urokinase plasminogen activator receptor (SUPAR) was measured using the suPARnostic® ELISA Kit (Virogates, Birkerød, Denmark).

The following biomarkers were measured in the derivation and validation cohorts: Prothrombin time and fibrinogen were measured on an STA R Max analyzer (Diagnostica Stago) using STA Neoplastin (Diagnostica Stago) and LiquidFib (Diagnostica Stago); D-dimers

levels were measured in $\mu\text{g}/\text{mL}$ fibrinogen equivalent units using an immunoturbidimetric latex-particle assay (Liatest DDI-Plus, Diagnostica Stago) on the STA R Max analyzer (Diagnostica Stago); Von Willebrand factor antigen (VWF:Ag) was measured using an immunoturbidimetric assay (LIAPHEN VWF:Ag, HYPHEN BioMed, Andresy, France), both on a CS 2400 analyzer (Sysmex, Kobe, Japan); Endocan was measured using the JDIYEK[®] ELISA Kit (Biothelis, Lille, France); Other laboratory blood tests including a complete blood count, CRP, procalcitonin, liver transaminases, bilirubin and creatinine were measured by standard methods as part of patient's care in the Biology and Pathology Center of Lille University Hospital.

Definitions

Criteria from the WHO ordinal scale for clinical improvement (**Supplementary Material 1**) were used for the definition of respiratory failure.

Accordingly, late ARF worsening was defined in our study as a progression on the WHO ordinal scale score from 5 to ≥ 6 , corresponding to patients who underwent invasive mechanical ventilation or who did not survive on the day of outcome assessment at D15, beyond 48h following ICU admission.

Objectives

The primary aim of this study was to derive and validate a predictive score based on routinely available clinical variables and endotheliopathy biomarkers for the prediction of late ARF worsening in severe Covid-19.

Variables

The end-point variable of our prediction model was the occurrence of late ARF worsening defined as a progression on WHO scale score from 5 at admission to ≥ 6 within 15 days following ICU admission (D15). The follow-up period was limited to 15 days to minimize the contribution of long-term ICU complications unspecific to COVID-19 as confounding events in outcome assessment.

We included the following exposure variables in our prediction model: age, gender, diabetes, chronic respiratory failure, chronic obstructive pulmonary disease (COPD), chronic heart failure, cirrhosis Child B or C, end stage kidney disease, immunosuppression, pulmonary embolism on ICU admission, body mass index (BMI), BMI > 30, simplified acute physiology score 2 (SAPS 2), sequential organ failure assessment (SOFA), computed tomography (CT)-scan extension, fraction of inspired oxygen (FiO₂), VWF:Ag, Angiopoietin 2, VEGF, syndecan-1, endocan, suPAR, PAI-1, TFPI, CRP, PCT, LDH, ALAT, ASAT, total bilirubin, creatinine, ferritin, TQ ratio, fibrinogen, D-dimers, hemoglobin, leucocytes, neutrophiles, lymphocytes, and platelets.

Immunosuppression included solid organ transplantation, haematopoietic stem cell transplantation in the last 6 months, corticosteroid therapy at a dosage higher than or equivalent to prednisone 1 mg/kg/day for more than 3 months, uncontrolled human immunodeficiency virus infection (<200 CD4/mm³), active solid malign tumor or hematologic malignancy in the last 6 months. FiO₂ was defined as the highest FiO₂ value recorded at any time within 48 hours following ICU admission. CT-scan extension was defined as the lung parenchymal extension of pneumonia on CT-scan performed on the day of admission in the ICU.

Statistical analysis

Categorical variables were expressed as numbers (percentages) and compared using Chi-square test or Fisher's exact test, as appropriate. Normality of distribution of continuous variables was checked graphically and by using the Shapiro–Wilk test. Normally distributed continuous variables were presented as means (SD), and compared using Student's t-test.

We performed missing value imputation for continuous variables in the derivation cohort using the predictive mean matching method with the *mice* function in R (*mice* R package) (11). No missing data were reported for outcomes variables, neither for categorical variables at the exception of pulmonary embolism on CT-scan on ICU admission (respectively missing for 31/92 and 22/59 subjects in the derivation and validation cohorts) and predominant findings on CT-scan (respectively missing for 20/92 and 12/59 subjects in the derivation and validation cohorts). Counts of missing data for continuous variables are shown in **Supplementary material 2**. Variables with missing data exceeding 30% of total count were excluded from the analysis.

We used univariate and multivariate logistic regression in the derivation dataset to estimate the coefficients of each potential predictor of late ARF worsening on D15. We selected the predictor variables that contribute the most to the model using the stepwise regression method. We therefore fitted the final model as the one with the smallest Akaike information criterion, allowing to maximize the predictive performance, while limiting model complexity. We assessed the predictive performance of the model in the derivation and validation cohorts by calculating its area under receiver operating characteristics (AUROC) to predict late ARF worsening at D15. Sensitivity and specificity were calculated for different scores. We finally computed Kaplan-Meier curves for late ARF worsening at D15

between groups with predefined CERES values and compared the probability of late ARF worsening between groups using the log-rang test.

All statistical tests were two-tailed, and p values < 0.05 were considered statistically significant. The statistical analyses were performed using R version 4.1.2 (R foundation for statistical computing, Vienna, Austria).

Results

Patient characteristics

Characteristics of the patients included in our study are shown in **Table 1**. The derivation cohort included 92 patients, of which 29 met the criteria for late ARF worsening on D15. The validation cohort included 59 patients, of which 14 met the criteria for late ARF worsening on D15.

In the derivation cohort, subjects with late ARF worsening on D15 were older (mean (SD): 69 (8) years in the late ARF worsening group vs 63 (13) years in the no late ARF worsening group, $p = 0.02$), had higher FiO₂ values (mean (SD): 88 (16) in the late ARF worsening group vs 77 (20) in the no late ARF worsening group, $p = 0.01$), higher mortality in ICU ($N = 22$ (76%) in the late ARF worsening group vs 1 (2%) in the no late ARF worsening group, $p < 10^{-3}$) and longer ICU stay (mean (SD): 21 (15) days in the late ARF worsening group vs 9.5 (12) days in the no late ARF worsening group, $p < 10^{-3}$).

In the validation cohort, subjects with late ARF worsening had a higher frequency of COPD ($N = 6$ (43%) in the late ARF worsening group vs 5 (11%) in the no late ARF worsening group, $p = 0.01$), higher FiO₂ values (mean (SD): 84 (16) in the late ARF worsening group vs 70 (20) in the no late ARF worsening group, $p = 0.01$), higher mortality in ICU ($N = 11$ (79%) in the late ARF worsening group vs 1 (2%) in the no late ARF worsening group, $p < 10^{-3}$) and longer ICU stay (mean (SD): 27 (17) days in the late ARF worsening group vs 8 (5) days in the no late ARF worsening group, $p < 10^{-3}$).

Biomarkers on ICU admission

Results of biomarkers levels assessed on ICU admission are shown in **Table 2**.

In the derivation cohort, patients with late ARF worsening had higher levels of endocan (mean (SD): 9.13 (15.34) ng/ml in the late ARF worsening group vs 3.39 (3.08) ng/ml in the no late ARF worsening group, $p < 10^{-2}$), suPAR (mean (SD): 7.52 (4.01) ng/ml in the late ARF worsening group vs 6.22 (2.21) ng/ml in the no late ARF worsening group, $p = 0.048$), PCT (mean (SD): 6.45 (21.88) ng/ml in the late ARF worsening group vs 0.57 (0.74) ng/ml in the no late ARF worsening group, $p = 0.03$), D-dimers (mean (SD): 6.85 (15.53) $\mu\text{g/ml}$ in the late ARF worsening group vs 2.13 (3.39) $\mu\text{g/ml}$ in the no late ARF worsening group, $p = 0.02$), and lower platelets levels (mean (SD): 200 (65) G/l in the late ARF worsening group vs 274 (109) G/l in the no late ARF worsening group, $p < 10^{-2}$).

In the validation cohort, patients from the late ARF worsening group had lower fibrinogen levels (mean (SD): 6.05 (1.62) g/l in the late ARF worsening group vs 7.06 (1.65) g/l in the no late ARF worsening group, $p = 0.049$) and fewer leucocytes (mean (SD): 5.57 (2.28) G/l in the late ARF worsening group vs 7.84 (3.89) G/l in the no late ARF worsening group, $p = 0.04$).

Derivation and validation of the CERES score

According to the stepwise regression performed in our derivation cohort, platelets level was identified as the variable exhibiting the strongest association with late ARF worsening on D15 (per additional G/l, OR (95% CI): 0.99 (0.98 – 0.99)), followed by FiO₂ (per additional %, OR (95% CI): 1.05 (1.02 – 1.09)) and endocan (per additional ng/ml, OR (95% CI): 1.13 (1.04 – 1.31)) (**Figure 1**).

We then computed the AUROC to predict late ARF on D15 for: 1) the CERES score, calculated as $- 1.04 * \text{platelets (G/l)} + 5.12 * \text{FiO}_2 (\%) + 10.4 * \text{endocan (ng/ml)}$, 2) the top 2

predicting variables-based model, calculated as: $- 1.09 * \text{platelets (G/l)} + 4.11 * \text{FiO}_2 (\%)$, 3) platelets, identified as the top-predicting variable in our model. The AUROC for prediction of late ARF worsening on D15 in the derivation and validation cohorts was calculated respectively at 0.834 ($p < 10^{-3}$) and 0.780 ($p < 10^{-2}$) for the CERES score, 0.796 ($p < 10^{-3}$) and 0.769 ($p < 10^{-2}$) for the top 2 predicting variables-based model, and 0.719 ($p < 10^{-3}$) and 0.666 ($p = 0.06$) for platelets (**Figure 2A**). According to the Youden index, best cut-offs for the detection of late ARF worsening on D15 were found respectively for CERES values ≥ 216 in the derivation cohort (sensitivity = 0.9, specificity = 0.7) and 232 in the validation cohort (sensitivity = 0.71, specificity = 0.73). A CERES value ≥ 140 showed the best sensitivity to predict late ARF worsening on D15, observed respectively at 1 and 0.93 in the derivation and validation cohorts, while specificity was found at 0.48 and 0.44, respectively. Further, the best specificity for the prediction of late ARF worsening on D15 was observed for a CERES value ≥ 333 , being then respectively found at 0.9 and 0.93 in the derivation and validation cohorts, while sensitivity was measured at 0.45 and 0.5 with this cut-off (**Figure 2B**). Survival analysis revealed in the derivation and validations cohorts a higher probability of late ARF on D15 in case of CERES ≥ 140 vs CERES < 140 ($p < 10^{-3}$ in both cohorts) (**Figure 3**), and in case of CERES ≥ 333 vs CERES < 333 ($p < 10^{-3}$ and $p = 0.012$, respectively) (**Figure 4**).

Discussion

Non-invasive techniques remain frequently used as respiratory support for patients admitted to the ICU for Covid-19 (3,4). Nevertheless, the risk of failure of non-invasive methods remains high (4), being then associated with an increased severity of Covid-induced lung injury in case of late intubation, and consequently, with a poor prognosis for patients (6,7).

The main purpose of this study was to develop a score to early identify, at admission, patients at high risk of late failure of the non-invasive respiratory management strategy in severe Covid-19. We hereby report the results from derivation and validation of the CERES score, based on the assessment of 3 variables: platelets, FiO₂ and endocan, to predict the risk of late respiratory failure requiring intubation in critically ill Covid patients.

Our findings regarding the factors associated with poor outcomes in Covid-19 are consistent with previously published data from the literature. Indeed, the association between thrombocytopenia and severity of illness in Covid-19 has been consistently reported early in the pandemics (12). This association may result from the endothelial injury with endothelial cell membrane disruption occurring in severe Covid-19 (9,13). On the other hand, a positive correlation has been reported between the severity of Covid-19 and circulating levels of endocan (10,14), an endothelial-cell borne biomarker secreted in the deep lung under inflammatory conditions (15). Furthermore, FiO₂ has been widely used as a key component of predictive models for Covid-19-related outcomes, such as the ROX index (8,16–19). Nonetheless, this clinical score has been mostly described as a good predictor of an imminent need for intubation, mostly occurring within less than 24h (8), contrasting with

the setting of our study, which explored the accuracy of the CERES score to predict the need for invasive mechanical ventilation beyond 48h.

Two distinct clinical applications may be derived from our results. First, we found that a CERES value ≥ 140 has a very high sensitivity for the detection of patients who will eventually require invasive respiratory support. Accordingly, the non-invasive strategy was successful in nearly all patients with a CERES score < 140 . Based on our results, we could therefore propose to maintain non-invasive strategies in patients with a CERES score < 140 . This latter point seems of major importance, as growing evidence supports the hypothesis that delayed intubation and late failure of non-invasive strategies are associated with an increase in mortality and worse pulmonary sequelae (7,20). In the same view, a CERES score ≥ 333 , which detected the further need for invasive support with a high specificity, could be used to propose earlier intubation in patients with the highest risk of failure of non-invasive strategies.

Our study has several limitations. Firstly, some variables were collected retrospectively, thus resulting in missing data for several exposition factors analyzed in our prediction model. However, counts of missing data remained limited for most variables, allowing to perform data imputation to conduct our analysis. Secondly, the sample sizes of our cohorts remained limited, thus questioning the extrapolability of our findings. Nevertheless, the results observed in our derivation cohort were almost completely reproduced in our validation cohort, especially regarding sensitivities and specificities associated with CERES values at 140 and 333, thus strengthening the reliability of our findings. Thirdly, we found higher PCT values in subjects with late ARF worsening in the derivation cohort, raising the question of a higher frequency of bacterial coinfections in these patients. However, both groups had

similar rates of microbiological confirmation. In addition, PCT values were not found different between groups in the validation cohort, with little influence on the performances of the CERES score which appeared to be preserved in this cohort. Fourthly, nearly half patients from our study had a CERES score in the “grey zone”. Indeed, CERES values between the highly sensitive and specific boundaries, respectively set at 140 and 330, concerned 45/92 subjects in the derivation cohort and 28/59 subjects in the validation cohort. Subsequently, our model seems too inaccurate to be used in the decision process of whether to perform intubation or not in those patients. Conversely, the CERES score may be used to guide the decision of intubation in more than half patients, thus appearing as a helpful means to accurately identify the most appropriate strategy in terms of respiratory support. Finally, subjects included in our study were recruited in a time frame when the original strain and the alpha variant of Covid-19 accounted for most cases of the disease. Further prospective investigations in larger cohorts are warranted to confirm our results.

Conclusions

In patients with severe Covid-19 undergoing non-invasive respiratory support, CERES values < 140 and ≥ 333 appear as accurate predictors of late ARF worsening with subsequent need for intubation. Accordingly, our results suggest that these cut-offs could be used, at ICU admission, to drive the decision of intubation in these patients.

Declarations

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

Conceptualization, A.G, A.D, A.T, S.S and J.P.; Methodology, A.G and J.P.; Validation, A.D, S.S. and J.P.; Formal Analysis, A.G and J.P.; Investigation, B.G, A.D, E.P. and C.B.; Resources, A.D, A.T. and S.S.; Data Curation, A.G.; Writing – Original Draft Preparation, A.G and B.G; Writing – Review & Editing, J.P.; Supervision, A.D, S.S and J.P.; Funding Acquisition, A.G. and A.T.

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Figure legends

Figure 1. Odds ratios for the prediction of late ARF worsening at D15 by multivariate logistic regression in the derivation cohort.

Results are shown as OR with 95% CI for the top 3 predictive variables, included in the CERES score. *ARF* Acute respiratory failure, *D15* Day 15 following ICU admission, *FiO2* Fraction of inspired oxygen, *OR* Odds ratio.

Figure 2. ROC curves for the prediction of late ARF worsening at D15 in the derivation and validation cohorts.

A) ROC curves were computerized in derivation and validation cohorts for the CERES score (black plain line), for the top 2 predictive variables-based model including platelets and *FiO2* (red dashed line) and for platelets (blue dotted line). B) Values of sensitivity and specificity for the CERES score. *ARF* Acute respiratory failure, *AUC* Area under the curve, *D15* Day 15 following ICU admission, *FiO2* Fraction of inspired oxygen, *Se* Sensitivity, *Sp* Specificity

Figure 3. Kaplan-Meier curves of late ARF worsening at D15 in the derivation and validation cohorts according to the high sensitivity CERES cut-off.

Probabilities of late worsening of ARF on D15 in subjects with CERES \geq 140 (yellow) vs subjects with CERES $<$ 140 (blue). Probabilities of survival measured in our cohorts are displayed by dashed lines. Colored areas represent 95% CI. *ARF* Acute respiratory failure, *D15* Day 15 following ICU admission.

Figure 4. Kaplan-Meier curves of late ARF worsening at D15 in the derivation and validation cohorts according to the high specificity CERES cut-off.

Probabilities of late worsening of ARF on D15 in subjects with CERES ≥ 333 (yellow) vs subjects with CERES < 333 (blue). Probabilities of survival measured in our cohorts are displayed by dashed lines. Colored areas represent 95% CI. *ARF* Acute respiratory failure, *D15* Day 15 following ICU admission.

Supplementary material

Supplementary material 1. Description of the WHO ordinal scale for clinical improvement.

RRT Renal replacement therapy, *ECMO* Extra-corporeal membrane oxygenation.

Supplementary material 2. Counts of missing data for continuous variables. Results are presented as number (%). *BMI* Body mass index, *CT* Computed tomography, *FiO2* fraction of inspired oxygen, *PAI-1* Plasminogen activator inhibitor-1, *SAPS 2* Simplified acute physiology score 2, *SOFA* Sequential organ failure assessment, *suPAR* Soluble urokinase plasminogen activator receptor, *TFPI* Tissue factor pathway inhibitor, *VEGF* Vascular endothelial growth factor, *VWF:Ag* Von Willebrand factor antigen.

Supplementary material 3. Univariate logistic regressions in the derivation cohort for continuous and categorical variables on ICU admission. Results are presented as OR with 95% CI for late worsening of acute respiratory failure within 15 days following ICU admission. *BMI* Body mass index, *COPD* Chronic obstructive pulmonary disease, *CT* Computed tomography, *FiO2* fraction of inspired oxygen, *ICU* Intensive care unit, *OR* Odds ratio, *PAI-1* Plasminogen activator inhibitor-1, *SAPS 2* Simplified acute physiology score 2, *SOFA* Sequential organ failure assessment, *suPAR* Soluble urokinase plasminogen activator receptor, *TFPI* Tissue factor pathway inhibitor, *VEGF* Vascular endothelial growth factor, *VWF:Ag* Von Willebrand factor antigen.

Supplementary material 4. Univariate logistic regressions in the validation cohort for continuous and categorical variables on ICU admission. Results are presented as OR with 95% CI for late worsening of acute respiratory failure within 15 days following ICU admission. *BMI* Body mass index, *COPD* Chronic obstructive pulmonary disease, *CT*

Computed tomography, *FiO2* fraction of inspired oxygen, *ICU* Intensive care unit, *PAI-1* Plasminogen activator inhibitor-1, *OR* Odds ratio, *SAPS 2* Simplified acute physiology score 2, *SOFA* Sequential organ failure assessment, *suPAR* Soluble urokinase plasminogen activator receptor, *TFPI* Tissue factor pathway inhibitor, *VEGF* Vascular endothelial growth factor, *VWF:Ag* Von Willebrand factor antigen.