

# El anticoagulante lúpico, el factor Von Willebrand y la interleucina-6 como predictores fiables de la necesidad de ventilación mecánica en la COVID-19

## *Lupus Anticoagulant, Von Willerbrand Factor and Interleukin-6 as a reliable predictor of the need for mechanical ventilation in Covid-19*

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### ABSTRACT

**Background:** Coronavirus disease 2019 is characterized by causing thromboembolic events due to a procoagulant state. The possible relationship between lupus anticoagulant and patient's procoagulant state is controversial and no study has specifically evaluated the impact of lupus anticoagulant on noninvasive mechanical ventilation.

**Objectives:** The aim of our study was to analyze the association between lupus anticoagulant and the need for noninvasive mechanical ventilation in 44 consecutive patients hospitalized for Severe acute respiratory syndrome Coronavirus 2 pneumonia.

**Methods:** This was a prospective, multicenter, observational study conducted between January 1 and March 31, 2022, which included a total of 44 consecutive patients, >18 years old and admitted for Severe acute respiratory syndrome Coronavirus 2 pneumonia. The following characteristics were determined: age, gender, blood group and Rh factor, plasma levels of Interleukin-6, Von Willerbrand Factor, lupus anticoagulant at admission, presence of venous thromboembolic disease, need for noninvasive mechanical ventilation, and intensive care unit admission. The relationship between the need for noninvasive mechanical ventilation and the levels of Von Willerbrand Factor and lupus anticoagulant was performed by T-student and its cutoff point was defined by ROC curve. Multivariate analysis was performed to establish worse prognosis factors. SPSS 27.0 statistical software was used, and an alpha error of 0.05 was established.

**Results:** 44 patients hospitalized with Severe acute respiratory syndrome Coronavirus 2 pneumonia (56.8% male, 68.5±17.9 years). 88.6% showed elevated Von Willerbrand Factor. Lupus anticoagulant levels were higher in patients requiring mechanical ventilation versus oxygen therapy (1.32±0.27 vs 1.12±0.17, p=0.011). The cutoff point for lupus anticoagulant levels that were associated with mechanical ventilation was 0.792 AUC (p=0.01). The predictors of noninvasive mechanical ventilation in the multivariate analysis were intensive care unit admission (p=0.02).

**Conclusions:** Plasma levels of Von Willerbrand Factor, lupus anticoagulant and Interleukin-6 can be a very useful prognostic tool for assessing the need for hospital admission to the critical care unit and the need for noninvasive mechanical ventilation. It would be interesting to include these determinations as routine assessments in patients with severe pneumonia.

**Keywords:** Severe acute respiratory syndrome; SARS-CoV-2; pneumonia; lupus anticoagulant; noninvasive mechanical ventilation.

### RESUMEN

**Antecedentes:** La enfermedad por coronavirus 2019 se caracteriza por provocar eventos tromboembólicos debido a un estado procoagulante. La posible relación entre el anticoagulante lúpico y el estado procoagulante del paciente es controvertida y ningún estudio ha evaluado específicamente el impacto del anticoagulante lúpico en la ventilación mecánica no invasiva.

**Objetivos:** El objetivo de nuestro estudio fue analizar la asociación entre el anticoagulante lúpico y la necesidad de ventilación mecánica no invasiva en 44 pacientes consecutivos hospitalizados por neumonía grave por síndrome respiratorio agudo severo coronavirus 2.

**Métodos:** Se trata de un estudio prospectivo, multicéntrico y observacional realizado entre el 1 de enero y el 31 de marzo de 2022, en el que participaron un total de 44 pacientes consecutivos, mayores de 18 años y hospitalizados por neumonía grave por coronavirus 2 del síndrome respiratorio agudo. Se determinaron las siguientes características: edad, sexo, grupo sanguíneo y factor Rh, niveles plasmáticos de interleucina-6, factor Von Willebrand, anticoagulante lúpico al ingreso, presencia de enfermedad tromboembólica venosa, necesidad de ventilación mecánica no invasiva e ingreso en la unidad de cuidados intensivos. La relación entre la necesidad de ventilación mecánica no invasiva y los niveles de factor von Willebrand y anticoagulante lúpico se realizó mediante la prueba T de Student y su punto de corte se definió mediante la curva ROC. Se realizó un análisis multivariante para establecer los factores de peor pronóstico. Se utilizó el software estadístico SPSS 27.0 y se estableció un error alfa de 0,05.

**Resultados:** 44 pacientes hospitalizados con neumonía por coronavirus 2 del síndrome respiratorio agudo grave (56,8 % hombres, 68,5 ± 17,9 años). El 88,6 % presentó niveles elevados del factor Von Willebrand. Los niveles de anticoagulante lúpico fueron más elevados en los pacientes que requirieron ventilación mecánica frente a los que recibieron oxigenoterapia (1,32±0,27 frente a 1,12±0,17, p=0,011). El punto de corte para los niveles de anticoagulante lúpico asociados a la ventilación mecánica fue de 0,792 AUC (p=0,01). Los predictores de ventilación mecánica no invasiva en el análisis multivariante fueron el ingreso en la unidad de cuidados intensivos (p=0,02).

**Conclusiones:** Los niveles plasmáticos del factor Von Willebrand, el anticoagulante lúpico y la interleucina-6 pueden ser una herramienta pronóstica muy útil para evaluar la necesidad de ingreso hospitalario en la unidad de cuidados intensivos y la necesidad de ventilación mecánica no invasiva. Sería interesante incluir estas determinaciones como evaluaciones rutinarias en pacientes con neumonía grave.

**Palabras clave:** Síndrome respiratorio agudo grave; SARS-CoV-2; neumonía; anticoagulante lúpico; ventilación mecánica no invasiva.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is characterized by triggering thromboembolic events due to a procoagulant state. There is sufficient evidence that SARS-CoV-2 is a proinflammatory and prothrombogenic virus with a high mutagenic profile, which produces active infection of variable duration in various organs and systems (lung, digestive system, central nervous system, skin...)<sup>1</sup>. The first complete necropsy studies performed show multiple and severe vascular involvement in the lungs, heart (myocarditis, vasculitis, and myocardial cell necrosis), liver with focal necrosis and neutrophilic infiltrates, and the same in the kidney, with microthrombi and fibrotic foci in the renal interstitium. Also, in the brain there is cerebral hyperemia and edema with glial degeneration<sup>2</sup>. The degree of endothelitis is almost imperceptible in light microscopy but sufficiently relevant to produce the well-known symptoms in the various organs and systems. Since the onset of the disease, patients have been observed to be at increased risk of venous, arterial, and microvascular thromboembolic disease, associated with the development of a hypercoagulable state.<sup>3</sup>

Emerging evidence prove that the ongoing pandemic of coronavirus disease 2019 (COVID-19) is strictly linked to coagulopathy even if pneumonia appears as the major clinical manifestation. The cumulative incidence of venous thromboembolism was 27% (95% CI 10%-47%), 4% (95% CI 1%-12%) for arterial thrombosis and 29% (95% CI 12-49%) for arterial thrombosis<sup>4</sup>, so that a relative significant number of studies have been performed to explore thrombotic risk in COVID-19 patients. Cytokine storm, mediated by pro-inflammatory interleukins, tumor necrosis factor  $\alpha$  and elevated acute phase reactants, is primarily responsible for COVID-19-associated hypercoagulopathy. Also, comorbidities, promoting endothelial dysfunction, contribute to a higher thromboembolic risk. Many of the mechanisms by which this prothrombotic state occurs are unknown, although it has been related to the overexpression of procoagulant factors and the generation of a proinflammatory state, endothelial activation and dysfunction that increases interleukin 6 (IL-6) levels, vWF and lupus anticoagulant (LA) all generating microvascular inflammatory thrombosis and producing the dreaded thrombotic episodes associated with the disease and its sequelae in different vascular territories.<sup>3,5,6</sup>

A high prevalence of antiphospholipid antibodies (aPL) has been reported in COVID-19 patients, however, the association of the same with thrombotic events in COVID-19 is very heterogeneous and thrombosis occurs later in patients with the presence of aPL, which is probably an additional prothrombotic factor<sup>7</sup>.

Antiphospholipid antibodies abnormally target phospholipid proteins, and the presence of these antibodies is central to the diagnosis of the antiphospholipid syndrome<sup>8,9</sup>. However, these antibodies can also arise transiently in patients with critical illness and various infections. The presence of these antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy<sup>10</sup>. In fact, the possible relationship between LA and the patient's procoagulant status is controversial and no study has specifically evaluated the impact of LA on NIMV.

The aim of our study was to analyze the association between lupus anticoagulant, von Willebrand factor and interleukin-6 and the need for

noninvasive mechanical ventilation in 44 consecutive patients hospitalized for severe SARS-CoV-2 pneumonia.

## MATERIALS AND METHODS

### Design

This is a prospective, multicenter, observational study conducted between January 1 and March 31, 2022, in which the Internal Medicine Services of the Public Hospital of Monforte de Lemos, the Complejo Hospitalario Universitario de Ourense and the Complejo Hospitalario Universitario de Santiago de Compostela located in northwestern Spain participated. A total of 44 consecutive patients who met the inclusion criteria of being over 18 years of age and having a hospitalization for severe infection secondary to SARS-CoV-2 were included.

### Variables

A patient with COVID-19 was defined as a patient with a positive PCR determination for SARS-CoV-2 virus. The following variables were analyzed at the time of hospital admission: age, gender, blood group and Rh, IL-6 values, presence of venous thromboembolic disease, need for NIMV, admission to the intensive care unit, IL-6 values, vWF and circulating LA levels. Non-invasive mechanical ventilation (NIMV) is defined as a respiratory support approach that provides assistance to the patient without the need for invasive intervention, such as the insertion of an endotracheal tube into the trachea. Instead, NIMV utilizes non-invasive interfaces, such as facial or nasal masks, to administer airflow and aid in ventilation. Severe illness due to SARS-CoV2 pneumonia was defined as that requiring mechanical ventilation.

The analytical parameters were determined by an analytical study at the time of admission. A 20 mL blood sample was obtained from an antecubital vein and analyzed at the time of blood collection. The determination of vWF was performed by the multimeric analysis technique. It consists of diluting the plasma samples in a loading buffer according to the amount of vWF antigen, they are subjected to non-reducing electrophoresis in the presence of the denaturing agent sodium dodecylsulfate (SDS, Sigma-Aldrich S.A., Madrid, Spain), on 1% low resolution gels (Agarose Seakem HGT (P), Iberlabo S.A., Madrid, Spain) and 2% high resolution gels (Agarose Type VII, Sigma-Aldrich S.A., Madrid, Spain). The proteins are then transferred by electrical transfer (Hoeffer TE65, Amersham Bioscience, Piscataway, USA) to a polyvinylidene vinylidene fluoride (PVDF) immobilon membrane (Millipore Corporation, Bedford, MA, USA), pretreated with methanol and distilled water.

Visualization of the multimers is achieved by incubating the membrane first with a rabbit anti-human vWF antibody (Ac) (Dako, Glostrup, Denmark), then with a goat anti-IgG rabbit Ac (Dako, Glostrup, Denmark) and finally with a goat anti-IgG Ac containing alkaline phosphatase (Sigma-Aldrich S.A., Madrid, Spain), which develops color using a histological stain for this enzyme and chromogenic substrates (Fast Blue RR SALT, Sigma). Normal vWF range is 45% to 150% in our laboratory (IU/dL). LA was determined by the diluted Russell's viper venom test (screening and confirmatory). In the screening test a ratio was established between the clotting time of the sample and the reference time obtained with normal plasmas. If this ratio was higher than 1.2 the screening was considered positive. In the confirmatory test a ratio was established in a similar way, but the test result was given by the normalized ratio (NR): ratio screen/ratio confirm. If this NR

was higher than 1.2 the lupus anticoagulant was considered positive. Thromboembolic disease was studied by means of three variables: symptomatology, venous echo-Doppler study of the lower extremities and computed tomography angiography study when there was a high clinical suspicion of pulmonary embolism.

### Ethical issues

The investigators declare that the development of the project was carried out respecting the Standards of Good Clinical Practice, the fundamental ethical principles established in the Declaration of Helsinki and the Oviedo Convention, as well as the requirements established in Spanish legislation on research. All participants gave their informed consent, and the study has been conducted under the auspices of the "Registry SEMI-COVID.19" approved by the CEIC of Andalusia (SPAIN) on March 27, 2020.

### Statistical analysis

A descriptive analysis of the data was performed where continuous variables were expressed as mean and standard deviation and categorical variables as frequencies and percentages (%). The normal distribution of quantitative variables was tested using the Shapiro-Wilks test. In the case that the quantitative variables had normal distribution, the relationship between the need for NIMV and vWF and LA levels were analyzed by T-student and its cut-off point was defined by ROC curve. Multivariate analysis was performed to establish poor prognostic factors. A decision tree was performed to prognostically categorize patients. SPSS 27.0 statistical software was used, and an alpha error of 0.05 was established as a threshold for statistical significance.

## RESULTS

In our series of 44 patients hospitalized with severe SARS-CoV-2 pneumonia there were 25 males (56.8%). The mean age of the patients was 68.5 ( $\pm 17.9$ ) years. None of the patients studied developed venous thromboembolic disease. All patients received low-molecular-weight heparin at prophylactic doses as part of the treatment protocol in our hospital and in-hospital mortality was 11.36%.

At the time of admission, plasma vWF levels were determined, being in 39 patients (88.6%) higher than 200%. LA levels were determined, the mean values being  $1.32 \pm 0.27$  in patients who required NIMV versus  $1.12 \pm 0.17$  in those who only required conventional oxygen therapy ( $p=0.011$ ) (Figure 1).

In 21 patients (47.7%) the LA values were higher than 1.1 IU and 8 of these patients required NIMV. No patient with LA  $< 1.1$  required NIMV, being the difference statistically significant ( $p=0.003$ ) (Figure 2).

A ROC curve was performed to determine the optimal cut-off point for plasma LA levels with a discriminatory point to predict the need for NIMV. The estimated cut-off point was 1.11 with an AUB of 0.79 (0.64-0.93) (Figure 3).

Plasma IL-6 levels were analyzed. Patients with plasma IL-6 levels  $> 78$  pg/mL showed a higher probability of ICU admission ( $p=0.01$ ) (Figure 4).

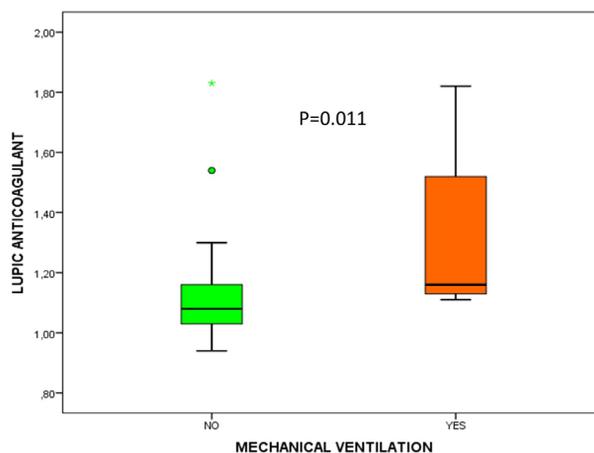


Figure 1. Box plot of lupus anticoagulant levels as a function of the need for noninvasive mechanical ventilation (NIMV).

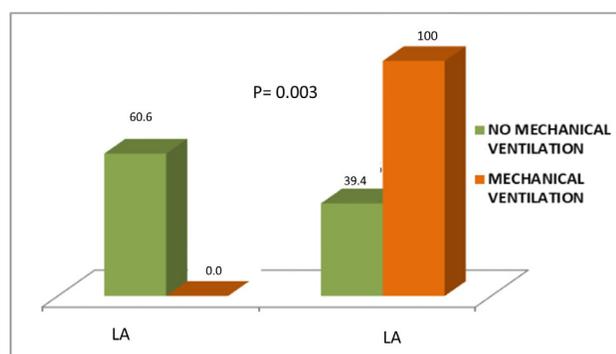


Figure 2. Cut-off point of lupus anticoagulant levels for prediction of noninvasive mechanical ventilation (NIMV).

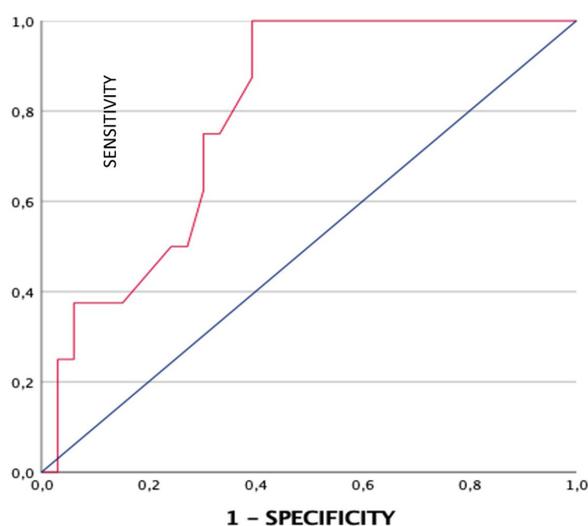
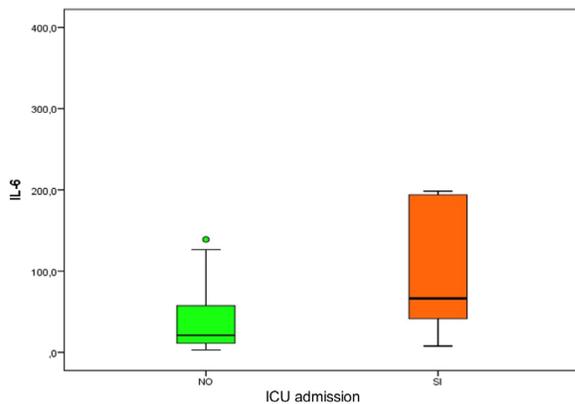


Figure 3. Determination of the cut-off point for lupus anticoagulant levels for prediction of noninvasive mechanical ventilation (NIMV).

Figure 4. Plasma levels of IL-6 as a function of the need for admission to the critical care unit.



There were no significant differences in clinical outcome according to blood group or Rh factor. A multivariate analysis was performed to determine the worst prognostic factors in relation to NIMV. The following covariables were included: age, gender, and admission to the ICU. Of these, only ICU admission was statistically significant in the multivariate analysis ( $p=0.02$ ) (OR 0.055 [0.009-0.35]). For NIMV risk, LA has a sensitivity of 1, specificity of 0.62 and a NPV (negative predictive value) of 1 being the most discriminative parameter with a positive likelihood ratio of 2.63. Although the NPV of vWF is 1 and that of IL-6 is 0.94, their specificities are much lower (0.11 and 0.48 respectively). A predictive analysis was performed by means of a decision tree in which the dependent variable was the need for mechanical or NIMV and the independent variables were plasma levels of LA, IL-6, age, blood group and Rh. CRT was introduced as a growth method, which allows the data to be divided into segments to make them as homogeneous as possible with respect to the dependent variable. In this classification the most important group of patients requiring NIMV were patients with plasma levels of LA  $>1.105$  and an age  $>57.5$  years (38.6% of the total). This method had a predictive capacity of 81.8%.

## DISCUSSION

Patients with elevated plasma levels of vWF and LA are more likely to be admitted to a critical care unit and receive NIMV, reflecting a situation of disseminated microthrombosis that aggravates the clinical situation of patients with severe SARS-CoV2 pneumonia.

It is currently accepted that this entity causes a chronic reactive endothelitis mediated by a chronic oxidative stress mechanism<sup>3</sup>. This situation triggers a release of vWF multimers<sup>4</sup> and generates hypercoagulability, despite the thrombopenia caused by SARS-CoV-2. An imbalance occurs that resolves in favor of prothrombotic situation, whereby thrombin and D-dimer levels are elevated. D-dimer levels have been shown to be a prognostic factor for disease severity, especially in the older population<sup>11</sup>. Sieiro-Santos *et al.* demonstrated that LA, in addition to vWF, fibrinogen, thrombin and Beta-2 glycoprotein (B2Gp), have an important influence on the development of thrombogenesis mediated by SARS-CoV-2.<sup>6,12,13</sup>

In our study, no patient developed venous thromboembolic disease, perhaps due to the correct prophylaxis with low-molecular-weight heparin from the time of admission.

On the other hand, our group has already demonstrated that cytokine storm also amplifies platelet production, leading to increased formation of disseminated microthrombi in various vascular territories<sup>7</sup>. Helms *et al.* observed that 87.7% of 57 ICU patients had elevated LA and that this correlated with major thrombotic problems, mainly pulmonary thromboembolism<sup>16</sup>. Other authors found elevated LA in 20-50% of the sample but did not find significant differences either in the use of NIMV or in mortality<sup>17,18</sup> probably because the sample sizes were small. Devreese *et al.* state that the elevation of LA plasma levels is transient and should be studied in greater depth in view of the existing controversy<sup>19</sup>. What seems clear is that the thrombogenicity of SARS-CoV-2 directly influences the clinical deterioration of patients and that elevated LA levels could contribute to the selection of a subgroup of patients at greater risk of thrombosis and admission to the ICU<sup>20</sup>. Cases have recently been published following vaccination against COVID19.<sup>21</sup>

To confirm this finding, studies with a larger sample size and longer follow-up time should be performed. Our study has limitations. Although it is a multicenter study, the sample size is small, and this limits the generalizability of our conclusions. However, statistically significant differences are shown, which support the hypothesis of this work. Another limitation is the non-applicability of the results to pediatric patients, since one of the inclusion criteria was being older than 18 years, although, fortunately, children rarely require NIMV for severe COVID-19 pneumonia. The study only evaluated patients during their hospital stay, and no subsequent follow-up was performed to assess their short- to medium-term prognosis. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

In Conclusion, Plasma levels of von Willebrand factor, lupus anticoagulant and IL-6 can be a very useful prognostic tool for assessing the need for hospital admission to the critical care unit and the need for noninvasive mechanical ventilation. It would be interesting to include these determinations as routine assessments in patients with severe SARV-CoV2 pneumonia.

### FUNDING

No funding has been received for this project.

### INSTITUTIONAL REVIEW BOARD STATEMENT

The investigators declare that the development of the project was carried out respecting the Standards of Good Clinical Practice, the fundamental ethical principles established in the Declaration of Helsinki and the Oviedo Convention, as well as the requirements established in Spanish legislation on research.

### INFORMED CONSENT STATEMENT

All participants gave their informed consent, and the study has been conducted under the auspices of the "Registro SEMI-COVID.19" approved by the CEIC of Andalusia- SPAIN on March 27, 2020.

### CONFLICTS OF INTEREST

None declared.

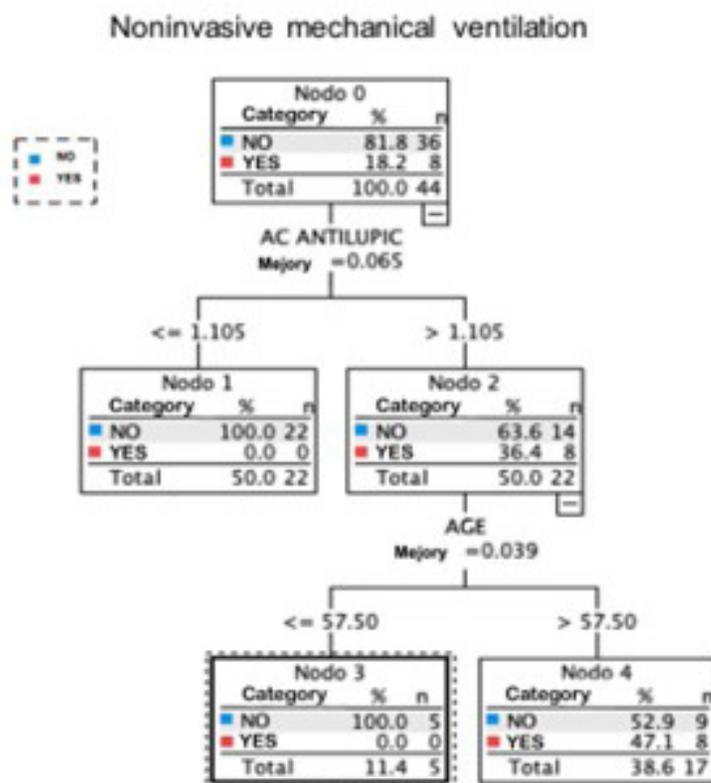


Figure 5. Decision tree for classification of patients who required noninvasive mechanical ventilation (NIMV) according to age, plasma levels of lupus anticoagulant, Rh and blood group.

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