Uppsala ICU COVID-19 Research
Uppsala ICU COVID Projects

ICU admission because of severe disease ~10 days after infection

Pre-ICU

ICU discharge

Follow-up at 3-6 months after ICU discharge

Follow-up at 1 year after ICU discharge

Convalescence

PRONMED – COVID-19

FUP-COVID

Uppsala COVID-19 ICU Biobank

Clinical data CRF
Uppsala ICU COVID Collaboration

Complement and Coagulation Group
Department of Immunology, Genetics, and Pathology
Uppsala University

Neuro-COVID
Department of Neuroscience
Uppsala University

COVID-19 Host Genetics Initiative
The Genetic Predisposition to Severe Covid-19

Karolinska Institutet

McGill University

Zoonosis Science Center
Department of Medical Sciences
Uppsala University

Kidney Research Group
Department of Medical Cell Biology
Uppsala University

Virology
Department of Medical Sciences

Clinical Chemistry
Department of Medical Sciences
Uppsala University

Vascular Biology Group
Department of Immunology, Genetics, and Pathology
Uppsala University

Radiology
Department of Surgical Sciences
Uppsala University

Global Burden of Disease Study
Institute for Health Metrics and Evaluation, Seattle, WA

ScriLifeLab Biomarkers
Uppsala University

Clinical Physiology
Department of Medical Sciences
Uppsala University

Thermo Fisher Scientific
Immunodiagnostics

Zoonosis Science Center
Department of Medical Sciences
Uppsala University

Department of Women's and Children's Health
Uppsala University

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Guest Professor

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Solveig Helgadottir
MD PhD

Oskar Eriksson
MD PhD

Elham Rostami
MD PhD Assoc Prof

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Assoc Prof

Sarah Wulf Hanson
PhD

Kristina Nilsson Ekdahl
Professor

Sara Bülow Anderberg
MD

Andrei Malinovischi
Professor

Emil Ekbom
MD

Frank Flachskampf
Professor

Anders Forsberg
MD PhD Assoc Prof

Lena Moberg
MSc

Forskningsingegör

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Uppsala University

Oskar Nensén
MD

Fredrik Palm
Professor

McGill University

Karolinska Institutet

ScriLifeLab

European Commission
Horizon 2020 European Union funding for Research & Innovation

SciLifeLab

Knut och Alice Wallenberg Stiftelse

Svenska Läkaresällskapet

njurfonden

Vetenskapsrådet


3. **Evolution of NETosis markers and DAMPs have prognostic value in critically ill COVID-19 patients.** Gerry A.F. Nicolaes, Joram Huckriede, Sara Bülow Anderberg, Albert Morales, Femke de Vries, Michael Hultström, Anders Bergqvist, José T. Ortiz, Jan Willem Sels, Kanin Wichapong, Miklos Lipcsey, Marcel van de Poll, Anders Larsson, Tomas Luther, Chris Reutelingsperger, Pablo García de Frutos, Robert Frithiof. Preprint, DOI: 10.21203/rs.3.rs-52432/v1.


<table>
<thead>
<tr>
<th>Poster winner</th>
<th>SLS COVID-19 State of the Art</th>
</tr>
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</table>
Inadequate prophylactic effect of low-molecular weight heparin in critically ill COVID-19 patients


Department of Surgical Sciences, Anesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden.

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Department of Medical Cell Biology, Integrative Physiology, Uppsala University, Uppsala, Sweden.

Keywords: Hypercoagulation, anticoagulation, COVID-19, Thromboelastography (TEG), Low molecular weight heparins (LMHW).

Introduction

Intensive care unit (ICU) patients with COVID-19 have been reported to have hypercoagulability with high Maximum Amplitude (MA) on Thromboelastography (TEG). However, data is limited on the effect of LMWH in these patients.

Purpose

The aim was to characterize coagulation abnormalities and the effect of LMWH on thromboprophylaxis in critically ill COVID-19 patients.

Materials and Methods

We conducted a prospective study in 31 consecutive adult intensive care unit (ICU) patients. TEG with and without heparinase and anti-factor Xa analysis were performed. Standard prophylactic dose of dalteparin (75 IU/kg subcutaneously) was given with heparinase to the sample eliminates the iatrogenic heparin effect in patients with COVID-19 but interpreting the results in relation to risk of thromboembolic disease, anti-factor Xa activity and TEG was variable and could not be reliably predicted. This study was approved by the National Ethical Review Agency.

Results

Out of 31 patients included in the study, 20 had elevated MA on TEG. The effect of LMWH on patients with COVID-19 indicates that standard prophylactic doses of LMWH may be insufficient in patients with COVID-19 and how they are affected by LMWH.

Fig. 1. The association between dalteparin dose and anti-factor Xa in the cohort with corresponding Spearman rank correlation coefficient.
Mannose-Binding Lectin is Associated with Thrombosis and Coagulopathy in Critically Ill COVID-19 Patients

Oskar Eriksson¹, Michael Hultström²,3, Barbro Persson¹, Miklos Lipcsey²,4
Kristina Nilsson Ekdahl¹,5 Bo Nilsson¹, Robert Frithiof²,4

Thrombosis and Haemostasis 2020
We investigated the antibody response to SARS-CoV-2 [1]. A robust generation and a dynamic pattern of IgA, IgG, and IgM have been observed in critically ill COVID-19 patients in the early stages of the disease [1]. Antibody responses to SARS-CoV-2 in critically ill COVID-19 patients have confirmed the development of a typical antibody response to an acute viral infection in COVID-19 patients [1]. The weak anti-SARS-CoV-2 antibody response is associated with mortality in a Swedish cohort of COVID-19 patients in critical care [1].

Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors (n=15)</th>
<th>Dead (n=4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length-of-stay in ICU, median (range)</td>
<td>10 (6–14) days</td>
<td>18 (11–38) days</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ferritin, median (range)</td>
<td>92 (67–116) g/L</td>
<td>49 (39–63) g/L</td>
<td>0.002</td>
</tr>
<tr>
<td>C-reactive protein, median (range)</td>
<td>15 (79) mg/L</td>
<td>57 (26–76) mg/L</td>
<td>0.05</td>
</tr>
<tr>
<td>Respiratory rate, median (range)</td>
<td>24 (18–30) min</td>
<td>21 (15–30) min</td>
<td>0.01</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>4 (21) %</td>
<td>6 (30) %</td>
<td>0.01</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
<td>18 (93) %</td>
<td>3 (21) %</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (83) %</td>
<td>10 (25) %</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The authors thank research nurses Joanna Wessbergh and Elin Söderman, and the following departments: Anesthesia and Intensive Care Medicine, Department of Surgery, Uppsala University, Uppsala, Sweden. Women's and Children's Health, Uppsala University, Uppsala, Sweden. Surgical Sciences, Uppsala University, Uppsala, Sweden.

The authors declare that they have no conflict of interest. Not applicable.

Ethics approval and consent to participate

The Swedish Ethical Review Authority (Dnr 2020-00677) and the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2020-0182) approved the study. Written informed consent from the patients or their legal representatives was obtained prior to inclusion in the study. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.

Open Access

Funding

The study was funded by Uppsala University. The presented data are part of a study approved by the National Ethical Review Board in Uppsala, Sweden (Dnr 2020-0182) and the Swedish Research Council to RF (2014-02569). MH (KAW 2020.0182), and the Swedish Research Council to RF (2014-02569). The authors thank research nurses Joanna Wessbergh and Elin Söderman, and the following departments: Anesthesia and Intensive Care Medicine, Department of Surgery, Uppsala University, Uppsala, Sweden. Women's and Children's Health, Uppsala University, Uppsala, Sweden. Surgical Sciences, Uppsala University, Uppsala, Sweden. The authors thank research nurses Joanna Wessbergh and Elin Söderman, and the following departments: Anesthesia and Intensive Care Medicine, Department of Surgery, Uppsala University, Uppsala, Sweden. Women's and Children's Health, Uppsala University, Uppsala, Sweden. Surgical Sciences, Uppsala University, Uppsala, Sweden.
Blood type and mortality

Blood type A associates with critical COVID-19 and death in a Swedish cohort

Michael Hultström1,2,*, Barbro Persson3, Oskar Eriksson3, Miklos Lipcey1, Robert Frithiof1,3 and Bo Nilsson1,3

Fig. 1 Distribution of blood types A/AB antigen and B/O antigen in the Swedish population (A/AB 47%, B/O 53%) compared to intensive care patients who survived (n = 45, A/AB 62%, B/O 38%) and who died (n = 19, A/AB 74%, B/O 26%) of COVID-19 at a tertiary care critical care facility in Sweden. Blood type A/AB is associated with an increased risk of death: hazard ratio (95% CI) = 3.16 (1.28–7.77)

Percentage (%)
High renin and high sodium

Hyperreninemia and low total body water may contribute to acute kidney injury in COVID-19 patients in intensive care

Michael Hultström, Magnus von Seth, and Robert Frithiof

Journal of Hypertension

Volume 38 • Number 8 • August 2020
COVID-19 patients in intensive care develop predominantly oliguric acute kidney injury

Tomas Luther\textsuperscript{1} \textsuperscript{E} | Sara Bülow-Anderberg\textsuperscript{1} \textsuperscript{E} | Anders Larsson\textsuperscript{2} \textsuperscript{E} | Sten Rubertsson\textsuperscript{1} | Miklos Lipcey\textsuperscript{1,3} \textsuperscript{E} | Robert Frithiof\textsuperscript{1} | Michael Hultström\textsuperscript{1,4} \textsuperscript{E}
Presence of SARS-CoV-2 in urine is rare and not associated with acute kidney injury in critically ill COVID-19 patients

Robert Frithiof1,2,†, Anders Bergqvist2,3,†, Josef D. Järhult1, Miklos Lipcsey1,5 and Michael Hultström1,6

Table 1  Patient characteristics and ICU treatment of 81 patients admitted to intensive care due to severe COVID-19 divided by findings of SARS-CoV-2 in urine or not. Values are represented as median (IQR) or n (%). Data for “SAPS3” and “Days between onset of symptoms and sampling” were missing for one and 4 patients, respectively, in the group negative for SARS-CoV-2 in urine. The p value originates from the Mann-Whitney U test for continuous parameters and the chi-square test for categorical parameters. Values are represented as median (IQR) or n (%); p < 0.05 is considered significant. AKI, acute kidney injury.

Virus in urine and AKI

Patients who died during the ICU stay had higher Simplified Acute Physiology Score 3 (SAPS3) on admission, length of stay in the ICU, the number of ICU-free days, and the number of renal replacement therapy-free days (Table 1). Only 5 (10%) of those patients had detectable SARS-CoV-2 RNA levels in the urine. This indicated a slow viral shedding that may have led to the underestimation of viral presence in urine. No significant differences in age, gender, days between onset of symptoms and sample collection, or days between peak AKI and sample collection were identified between patients with positive and negative SARS-CoV-2 in urine samples (Table 1).

Coes et al. Critical Care 2020, 24:587
https://doi.org/10.1186/s13054-020-03302-w
Plasma Cytokines and endpoints

Increased levels of plasma cytokines and correlations to organ failure and 30-day mortality in critically ill Covid-19 patients

Sara Bålow Ånderberg 1,2,3, Tomas Luther 3, Malin Berglund 3, Rolf Larsen 4, Sten Robertsson 4, Miklos Lipsey 1,3, Anders Lannoy 3, Robert Frichkö 4, Michael Hultstrosen 1,3

Cytokine
Available online 14 December 2020, 115389
In Press, Journal Pre-proof

Color Key
-4 0 4
Column Z-Score

Th1
Th2
NLRP3
Chemokines
Risk factors for ICU admission and death


Björn Ahlström, Robert Frithiof, Michael Hultström, Ing-Marie Larsson, Gunnar Strandberg, Miklos Lipscey.

<table>
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<th>Variable</th>
<th>OR</th>
<th>95 % CI</th>
<th>p-value</th>
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<td>Steroid use</td>
<td>1.41</td>
<td>1.10-1.81</td>
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<td>Severe oliguria within first 2 days after admission</td>
<td>1.50</td>
<td>1.04-2.15</td>
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<td>1.09</td>
<td>0.66-1.80</td>
<td>0.778</td>
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The ICU admission cohort with population controls

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Dear Editor,

Severe acute kidney injury associated with progression of chronic kidney disease after critical COVID-19

Michael Hultström1,2✉, Miklos Lipcsey1,3, Ewa Wallin1, Ing-Marie Larsson1, Anders Larsson4 and Robert Frithiof1

Data are expressed as mean ± standard deviation, unless otherwise stated. As we have previously reported, the association between severe kidney injury during critical care and CKD progression is left 60 patients analysed in the present study. Ten patients progressed to AKI stage 3, at the maximum creatinine (45%) and 19 (31%) did not develop AKI. The odds ratio of developing AKI was 4.9 [1.4–31], compared to those that did not with regards to basic CKD stage (AKI lasting for more than 7 weeks). Ten patients progressed to AKI stage 3 during their ICU stay. A mixed model ANOVA for the log-transformed creatinine concentration showed a significant difference in creatinine between stages (p = 3.0*10^-17) as well as time points (p = 1.4*10^-9), with a significant interaction (p = 2.3*10^-7). 

1Department of Clinical Sciences, Uppsala University Hospital, Uppsala University, Entrance 78, etg
2Department of Critical Care Medicine, Intensive Care Medicine, Department of Medical Cell Biology, Uppsala University, Sweden.
3Miklos Lipcsey, PhD, 4Anders Larsson, MD.

*Indicates significant difference compared to patients who did not develop AKI. Compared to baseline for the same stage, and †compared to hospital maximum for the same stage by TukeysHSD.

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**Table 1:** Demographics and CKD progression among patients with and without AKI progression.

<table>
<thead>
<tr>
<th>Category</th>
<th>All patients</th>
<th>No progression</th>
<th>CKD progression</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td><strong>Demographics</strong></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>60 ± 12</td>
<td>60 ± 13</td>
<td>59 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Women</td>
<td>17 (28%)</td>
<td>15 (30%)</td>
<td>2 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 6</td>
<td>30 ± 6</td>
<td>29 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Severe AKI (stage 3)</td>
<td>9 (15%)</td>
<td>5 (10%)</td>
<td>4 (40%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Acute kidney disease (y/n)</td>
<td>14 (23%)</td>
<td>5 (10%)</td>
<td>9 (90%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Dialysis in ICU (y/n)</td>
<td>6 (10%)</td>
<td>3 (6%)</td>
<td>3 (30%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Fig. 1: Progression of plasma creatinine in patients who developed AKI during intensive care. AKI (No AKI n = 27, Stage 1 n = 29, Stage 2 n = 6, Stage 3 n = 6) during their ICU stay. A mixed model ANOVA for the log-transformed creatinine concentration showed a significant difference in creatinine between stages (p = 3.0*10^-17) as well as time points (p = 1.4*10^-9), with a significant interaction (p = 2.3*10^-7). 

Many patients were more likely to progress to a higher CKD stage during critical care treatment in intensive care (ICU) compared to those that did not with regards to basic CKD stage (AKI lasting for more than 7 weeks). Ten patients progressed to AKI stage 3 during their ICU stay. A mixed model ANOVA for the log-transformed creatinine concentration showed a significant difference in creatinine between stages (p = 3.0*10^-17) as well as time points (p = 1.4*10^-9), with a significant interaction (p = 2.3*10^-7).