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Clotting

Evaluation of the carboxypeptidase U (CPU, TAFIa, CPB2) system in patients with SARS-CoV-2 infection

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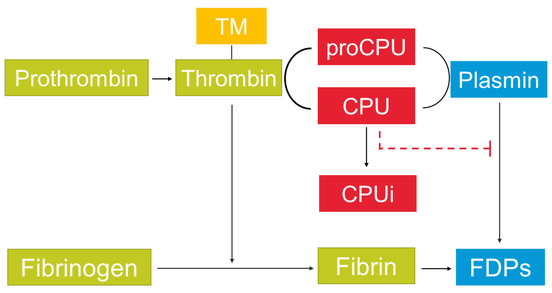
Early CPU generation with concomitant proCPU consumption during SARS-CoV-2 infection and **correlation** of **CPU+CPUi antigen levels** with **disease severity** and **duration of hospitalization**

BACKGROUND

- **Carboxypeptidase U**



  - Potent **antifibrinolytic enzyme**[1]
  - Present in the **circulation** as the **zymogen proCPU** (TAFI, proCPB2)
  - Activated by **plasmin** and **thrombin (-thrombomodulin)**[1]
  - Very **short half-life** (8-15 min) due to thermal inactivation (**CPUi**)[1]

- **COVID-19**
  - Viral lower **respiratory tract infection** caused by **SARS-CoV-2**[2]
  - Frequently **systemic thromboembolic complications** due to dysregulated hemostatic balance[2]

AIMS

- Explore the effect of SARS-CoV-2 infection on the CPU system
  - Influence on **proCPU levels**
  - Influence on **CPU and CPUi antigen levels**

METHODS

- **Study design**
  - **Hospitalized COVID-19 patients** (n = 56; 66% male; 58 ± 14 years)
    - Blood collection at inclusion (hospital admission) and every seven days until discharge
  - **Healthy controls** (n = 32; 63% male; 41 ± 15 years)
    - Blood collection at inclusion and four weeks later
- **Biochemical analyses**
  - **CPU+CPUi antigen levels** (Asserachrom TAFIa/ai ELISA - Stago)
  - **ProCPU determination** (in-house HPLC-assisted activity assay)[3]

RESULTS

- **Time course** of CPU-related parameters in SARS-CoV-2 infection
  - See right side ①
- Correlation **admission CPU+CPUi antigen levels**
  - See right side ②

CONCLUSION

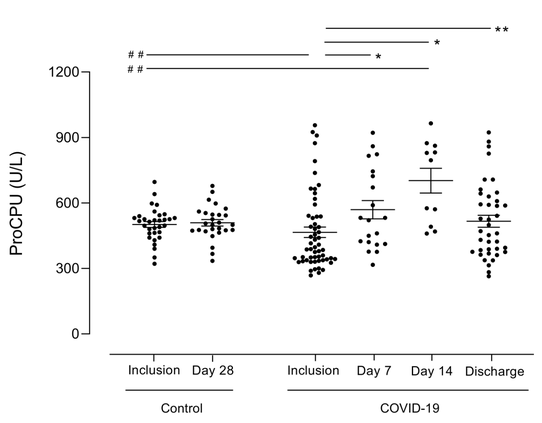
- The initial **CPU generation with simultaneous proCPU consumption** will (at least partly) **contribute to the hypofibrinolytic state** observed in COVID-19 patients and **enlarge their risk for thrombosis**.
- Given the **correlation of CPU+CPUi antigen levels** on admission with **disease severity** and the **duration of hospitalization**, this parameter may be a **potential biomarker with prognostic value** in SARS-CoV-2 infection.

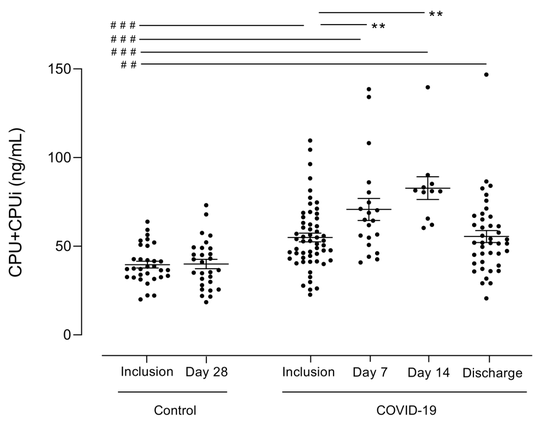
References

1. Claesen et al. Int J Mol Sci. 22(2), 883 (2021).
2. Yuki et al. Clin Immunol. 215 (2020).
3. Heylen. Anal Biochem. 396(1), 152 (2010).

1 Time course of CPU-related parameters in COVID-19 patients

- **Whole study population**





Upon hospital admission, **proCPU levels** were **significantly lower** in COVID-19 patients **compared to healthy controls.**

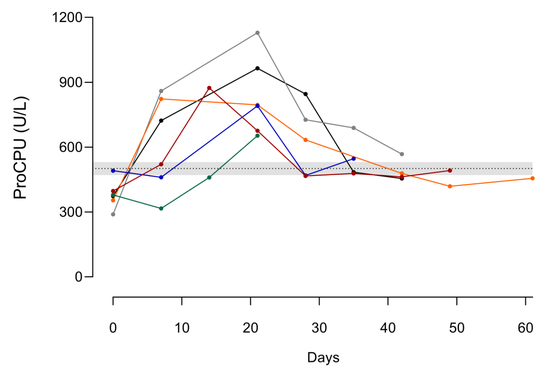
Following low **proCPU** levels at admission, a **pronounced elevation** of plasma proCPU levels was observed **up to day 14** in COVID-19 patients. **At day 14**, proCPU levels were **significantly higher** compared to controls. Hereafter, proCPU levels **declined**, with levels at **discharge** that were **comparable to** those of the **control population**.

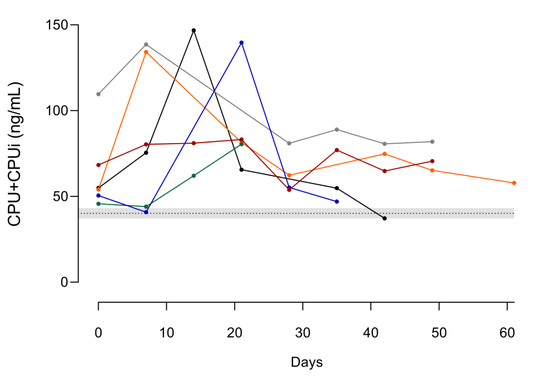
Admission CPU+CPUi antigen levels were **significantly higher** in COVID-19 patients.

CPU+CPUi antigen levels **progressively increased up to day 14**. This period was **followed by** a clear and **significant decrease** in CPU+CPUi antigen levels. **During the whole study period**, CPU+CPUi antigen levels were **higher** in COVID-19 patients **vs controls**, although not significant at all time points.

(Mann-Whitney test: * p < 0.05, ** p < 0.01, *** p < 0.001; Wilcoxon Matched-Pairs Signed Rank test: ## p < 0.01, ### p < 0.001)

- **ICU patients**



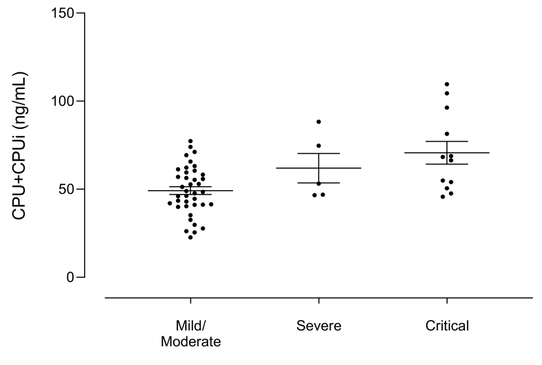


The **individual proCPU profiles of six ICU patients** (samples at ≥ 4 time points available), the pattern of **low admission proCPU levels** that **markedly increased during the first weeks** of hospitalization, followed by a **progressive decline until normalization** was also clearly visible.

The **individual CPU+CPUi antigen level profiles** showed **substantial inter-individual variability** in the **extent** of the CPU+CPUi antigen peak levels (65 – 150 ng/mL), as wel as for the **time** when these **peak levels** were reached (ranging between 7 and 42 days).

2 Correlations of CPU+CPUi antigen levels with clinical parameters

CPU+CPUi antigen levels on admission are **related to disease severity** (mild/ moderate, sever and critical): sicker patients present with higher CPU+CPUi antigen levels.



Baseline CPU+CPUi antigen levels were found to be positively **correlated with** the **duration of a patients hospital stay**.