# Autoantibodies against the cardiovascular protective BPIFB4 in hospitalized patients with COVID-19

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**Funding Acknowledgement:** Type of funding sources: Public grant(s) – National budget only. Main funding source(s): Cariplo Foundation (n.2016-0874) to AAP and CV; Ministry of Health (RF-2016-02364864) to AAP and CV

**Background/Introduction:** The bactericidal/permeability-increasing fold-containing family-B-member-4 (BPIFB4) serves as a biomarker of healthy aging [1,2] and displays prognostic relevance in vascular pathology [3–5]. We recently described a drop in plasma BPIFB4 level in patients with severe COVID-19 compared to low-grade disease patients [6].

**Purpose:** As COVID-19 is associated with autoimmune features, we developed the methods for determination of Anti-BPIFB4 IgG (autoAbs) and then characterized their neutralizing activity in COVID-19 patients.

**Methods:** A sandwich ELISA-based colorimetric assay followed by immunoblot analysis detected the presence of autoAbs against BPIFB4 in 60 hospitalized COVID-19 patients and in 30 healthy volunteers. Compared to the healthy controls, the optical density (OD) level of autoAbs in COVID-19 showed considerable variability distributing over a range between 0.13 and 0.85. We thus divided the patients into two groups, one with OD $>$0,29 and the other one with a OD $>$0,29, where 0,29 represents the OD mean value of autoAbs against BPIFB4 in physiological conditions.

**Results:** Since patients with higher OD are mainly those who spend in average a higher number of days in hospital, we stratified the patients according to the Length of Stay (LoS) in hospital (Figure 1), and found a trend towards a positive correlation between AutoAbs OD level and length of hospitalization within COVID-19 patients.

When present, autoAbs exclusively target the WT-BPIFB4 autoantigens and neglect the recognition of the Longevity-associated-variant-(LAV) of the BPIFB4 gene known for its therapeutic efficacy in cardiomyopathy, atherosclerosis (4), diabetes (6) and platelets' reactivity.

As expected, the pre-treatment of human PrP with the recombinant rhLAV-BPIFB4 reduces platelets' aggregation in response to ADP and collagen in COVID-19 patients in vitro.

On the other hand, at functional level, the well established LAV-BPIFB4-regulated M2 macrophage polarization (4,7), is neutralized in presence of anti-BPIFB4 autoAbs-enriched plasma.

**Conclusion:** We conclude that a significant proportion of hospitalized COVID-19 patients displays BPIFB4-AutoAbs which are positively correlated with the Length of Stay (LoS) in hospital. In future, it will be of utmost importance to clarify if the 4 missense SNPs which distinguish LAV-BPIFB4 gene from its WT-counterpart, are instrumental to prevent the self-tolerance brake-down and the potential development of specific antibodies against endogenous cardiovascular protectors.

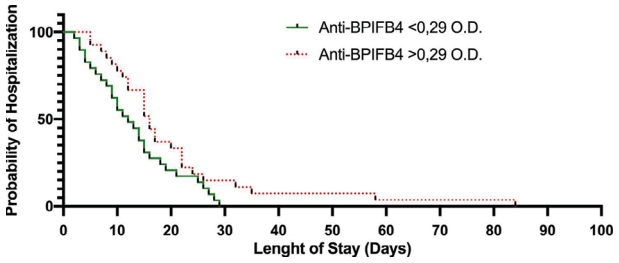


Figure 1