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Circulating levels of ACE2 zinc-metalloprotease and zinc/albumin ratio as potential biomarkers for a precision medicine approach to COVID-19

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Abstract

Background and Purpose: Highly mutable influenza is successfully countered based on individual susceptibility and similar precision-like medicine approach should be effective against SARS-COV-2. Among predictive markers to bring precision medicine to COVID-19, circulating ACE2 has potential features being upregulated in both severe COVID-19 and predisposing comorbidities. Spike SARS-CoVs were shown to induce ADAM17-mediated shedding of enzymatic active ACE2, thus accounting for its increased activity that has also been suggested to induce positive feedback loops leading to COVID-19-like manifestations. For this reason, pre-existing ACE2 activity and inhibition of ACE2/ADAM17 zinc-metalloproteases through zinc chelating agents have been proposed to predict COVID-19 outcome before infection and to protect from COVID-19, respectively. Since most diagnostic laboratories are not equipped for enzymatic activity determination, other potential predictive markers of disease progression exploitable by diagnostic laboratories were explored. Experimental approach: Concentrations of circulating ACE2 protein and activity, albumin and zinc were investigated in healthy, diabetic (COVID-19-susceptible) and SARS-CoV-2-negative COVID-19 individuals. Key Results: ACE2 both protein levels and activity significantly increased in COVID-19 and diabetic patients. Abnormal high levels of ACE2 characterised a subgroup (16-19%) of diabetics, while COVID-19 patients were characterised by significantly higher zinc/albumin ratios, pointing to a relative increase of albumin-unbound zinc species, such as ACE2-bound and free zinc ones. Conclusions & Implications: Data on circulating ACE2 levels are in line with the hypothesis that they can drive susceptibility to COVID-19 and elevated zinc/albumin ratios support the therapeutic use of zinc chelating inhibitors of ACE2/ADAM17 zinc-metalloproteases in a targeted therapy for COVID-19.

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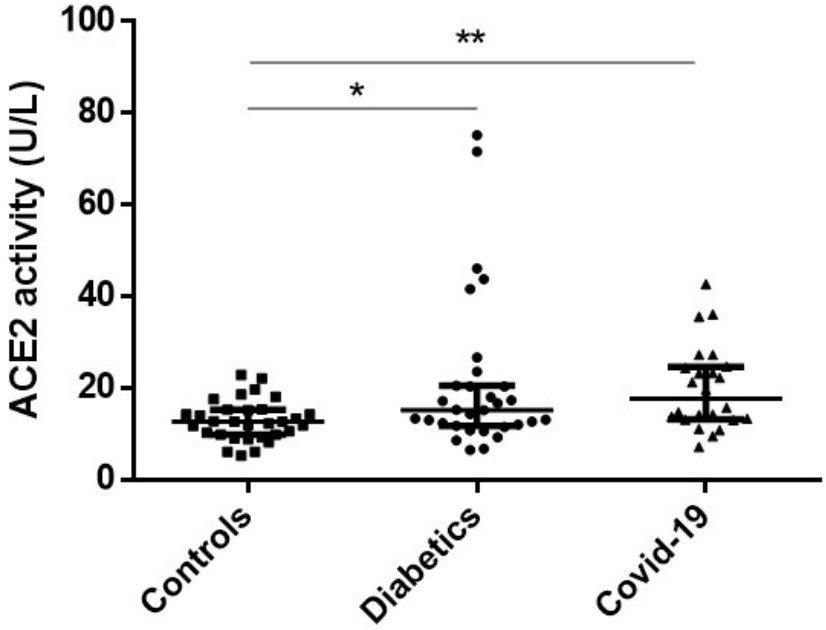

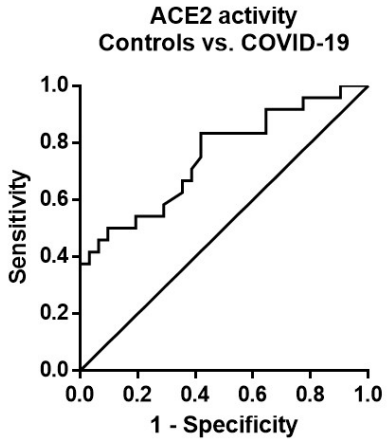

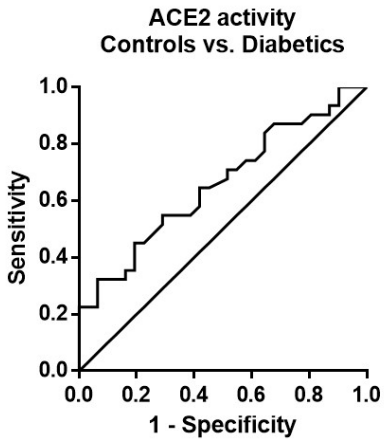

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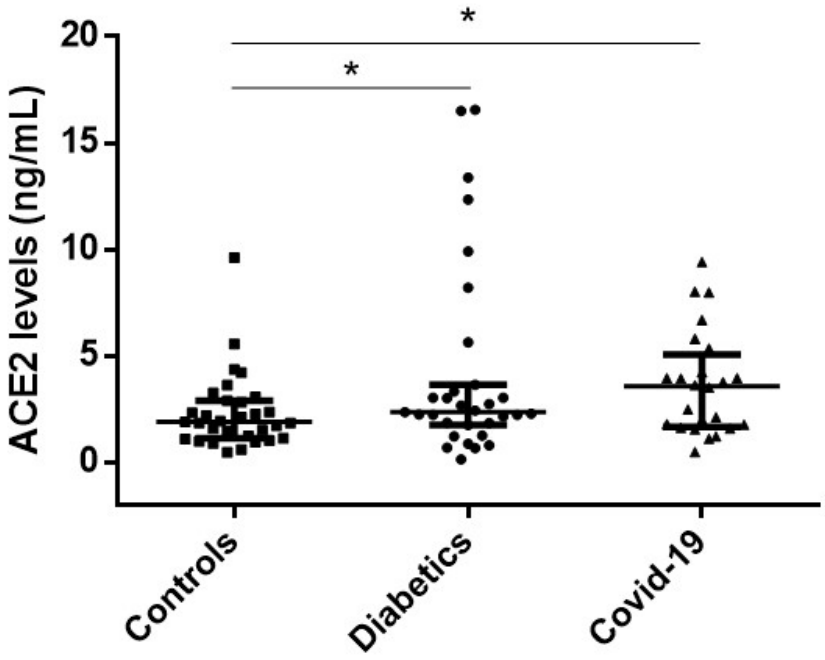

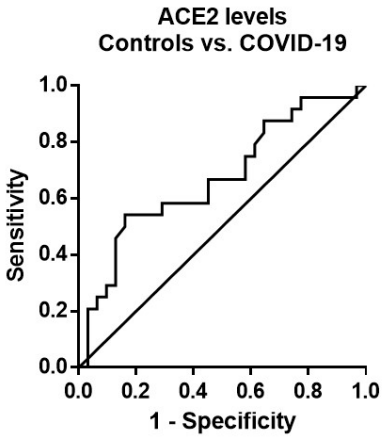

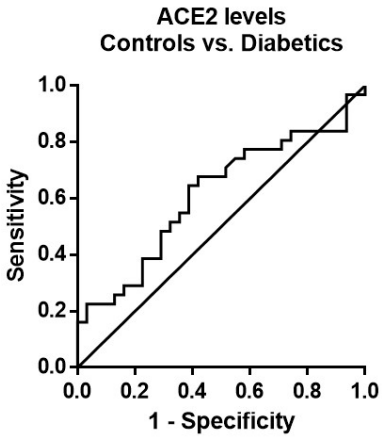

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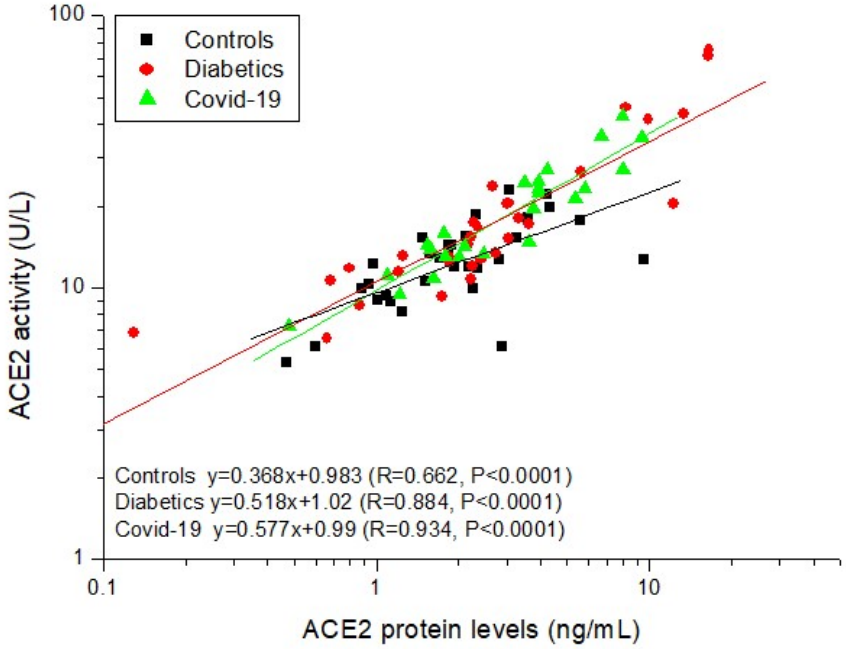

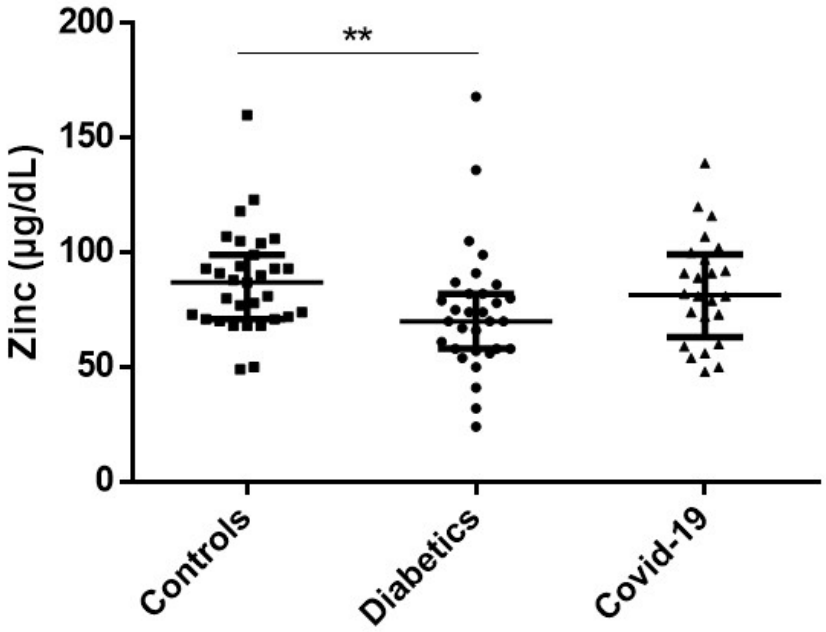

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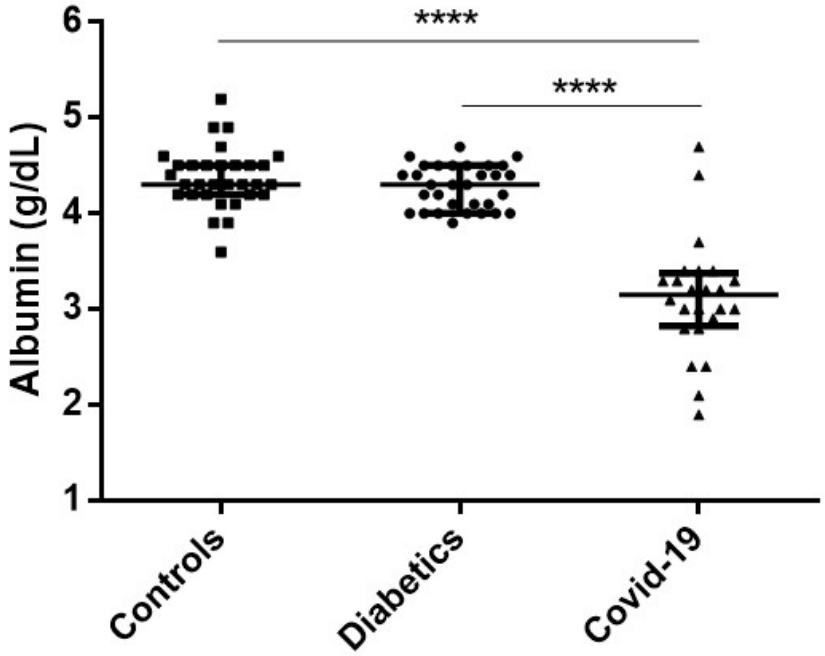

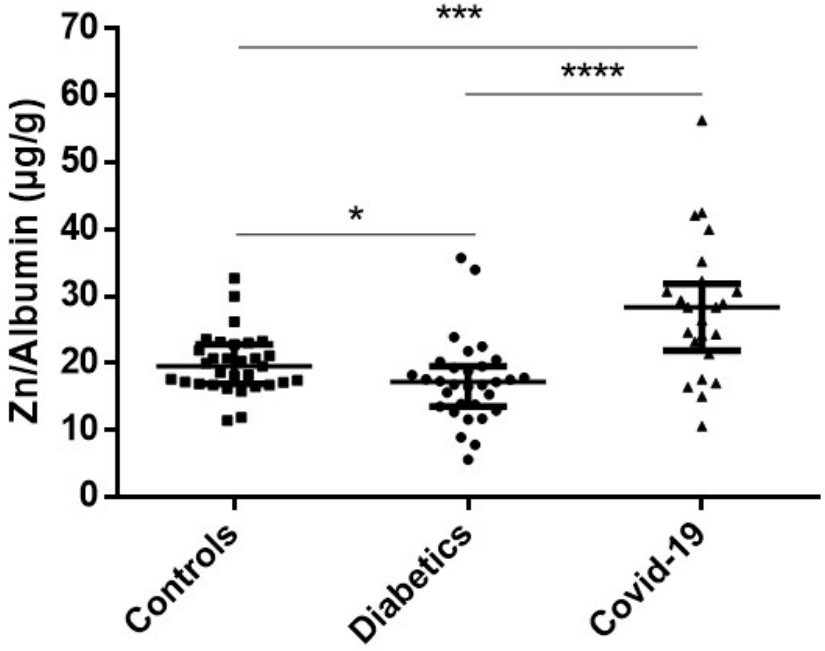

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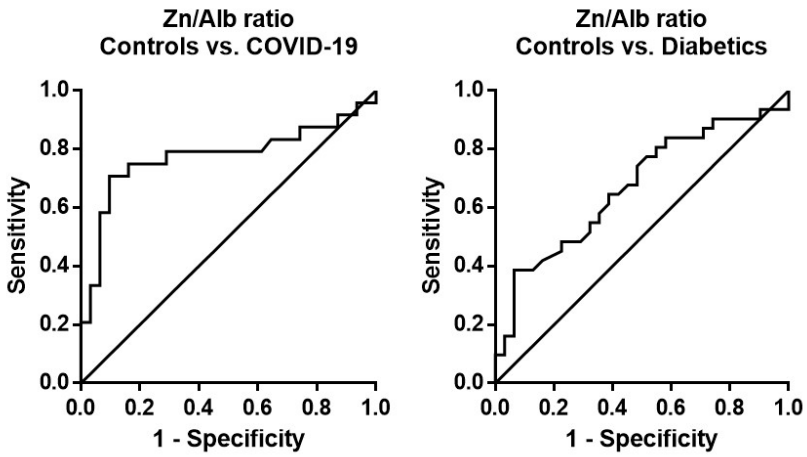

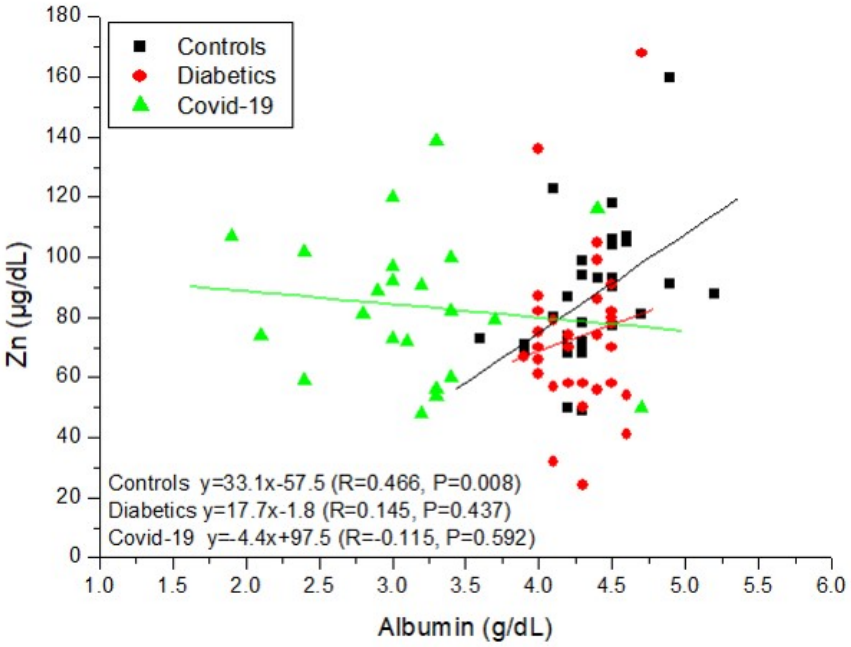

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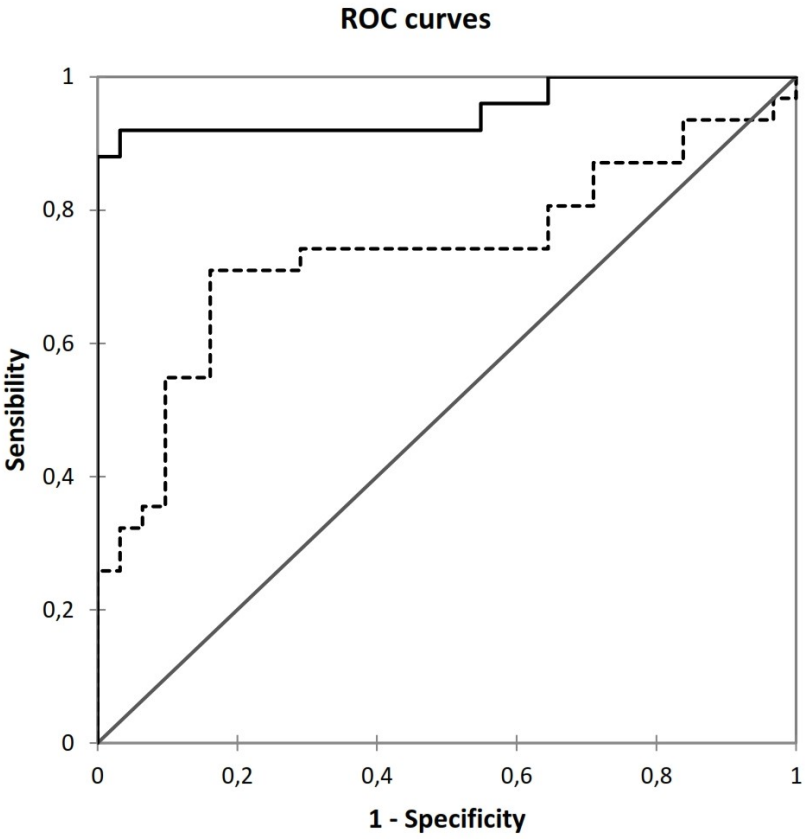

Table 1: Logistic regression analysis for controls vs. diabetics and controls vs. COVID-19s.

Variables	P(χ^2)	O.R. (95% C.I.)
Controls versus diabetics		
Intercept	0.997	
Zn (µg/dL)	0.065	0.978 (0.955-1.001)
ACE2 activity	0.046	1.109 (1.002-1.227)
Controls versus COVID-19s		
Intercept	< 0.0001	
Zn (µg/dL)	< 0.0001	0.793 (0.697-0.902)
Zn/Alb (*10^{-6})	0.001	2.575 (1.481-4.478)