

## Could urinary ACE2 protein level help identify individuals susceptible to SARS-CoV-2 infection and complication?

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Globally, SARS-CoV-2 has infected 3,113,447 people and killed 216,930 as of April 29, 2020. Identifying populations vulnerable to infection and their disease progression is critical to mitigating the negative impacts on healthcare systems. Recent studies have shown that angiotensin converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2 to enter human cells (Zhou et al., 2020), raising the possibility that a higher ACE2 expression level could facilitate SARS-CoV-2 infection.

We collected large amounts of urine proteome data using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) (Leng et al., 2017; Gao, 2019). ACE2 was detected and quantified in 80.1% of the human urine samples from 1,925 adults that had undergone routine physical examinations (Table S1 in Supporting Information) and 14.1% of the samples among 284 healthy young children (3.1–6.3 years old) (Table S1 in Supporting Information). The urine ACE2 protein levels showed significant differences based on sex and age, with the lowest expression seen

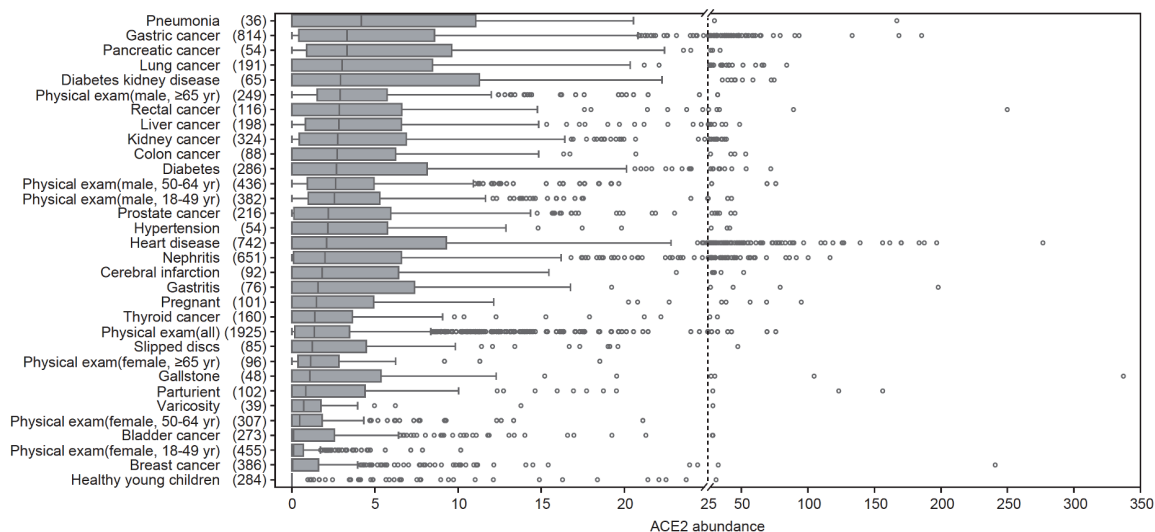
in young children (Figure 1; Table S1 in Supporting Information). These results are consistent with the observation from the epidemiological data of COVID-19, i.e., a lower risk of infection for children and a higher risk of death for men (Guan et al., 2020; Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention, 2020).

We derived a reference range interval (RI, 2.5%–97.5%)<sup>2</sup> for ACE2 levels detected in the 1,541 individuals from the routine physical exam. The RI varied from 0.072 to 15.63, suggesting a wide range of variation in the population. Thirty-nine individuals were detected with ACE2 levels above the 97.5% of the RI, and 32 of the 39 (82.1%) people had abnormal test results in the physical exam, including blood pressure, uric acid, fasting plasma glucose, and triglyceride (Table S1 in Supporting Information).

We analyzed urinary ACE2 in our database from 4,982 patients diagnosed with 22 types of diseases (Table S1 in Supporting Information). ACE2 levels in patients with pneumonia, cancer (including gastric, pancreatic, lung, rectal, liver, kidney, colon, and prostate), diabetes, hypertension, heart disease, and nephritis were significantly higher,

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**Figure 1** Urinary ACE2 levels in 22 types of diseases, six types of physical exam, individuals, healthy young children, and pregnant/parturient women. The boxplot displays the distribution of urinary ACE2 expression in each group. The number in the brackets corresponds to the number of urine samples in each group.

whereas patients who suffer from slipped discs, gallstone, varicosity, bladder cancer and breast cancers had similar levels to those of healthy people (Figure 1).

In a longitudinal study for health monitoring (July 2017–present) of a cohort of 80 people between 11 and 83 years of age (Table S2 in Supporting Information), multiple urine samples had been collected from each individual, with the median collection frequency as 11 (range 3 to 58) (Table S2 in Supporting Information). The RI of ACE2 was 0.21 to 17.36 in male samples and 0.05 to 7.65 in female samples. The coefficient of variation of ACE2 was smaller than 2 in 75 of the 80 (93.8%) individuals, indicating that low intra-personal variations over a period of time make ACE2 a suitable biomarker. We noticed that two of the five pregnant women (PHU00063, PHU00064) exhibited continuously high levels of ACE2 (Figure S1A in Supporting Information). To validate the finding, we examined the data from 203 pregnant or parturient women (18–40 years old, Table S2 in Supporting Information). The mean value of ACE2 in these women was 10 times higher than that obtained from the non-pregnant, non-parturient participants of the physical exam, which is statistically significant (Kruskal-Wallis test  $P$ -value:  $2.36 \times 10^{-11}$ , Figure S1B in Supporting Information), and 32% of them (65 of 203) exceeded the RI for young female adults (18–49 years old,  $n=455$ ).

Our data showed that ACE2 is detectable by mass spectrometry-based proteomics and is associated with a variety of

physiological and pathological conditions. This study raises the possibility that urinary ACE2 level might be used as a biomarker to predict the risk for SARS-CoV-2 infection and its associated complications. Future studies are required to investigate these possibilities.

**Compliance and ethics** The author(s) declare that they have no conflict of interest.

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## SUPPORTING INFORMATION

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