Reply to Sun *et al.*

From the Authors:

We thank Sun and colleagues for their interest in our recent work published in the *Journal* (1). In short, we found lower circGSAP (circular RNA–γ-secretase–activating protein) levels were associated with increased occurrence and poorer outcomes in patients with idiopathic pulmonary arterial hypertension (IPAH), which means that circGSAP may be an emerging biomarker for the diagnosis and prognosis of IPAH. As commended by Sun and colleagues, this is an important field, and the impact of circular RNAs (circRNAs) on the diagnosis and treatment of IPAH has not yet been fully studied. Here, we answer comments raised by Sun and colleagues.

We agree with Sun and colleagues on their suggestion to list *P* values for comparisons of baseline information between healthy control subjects and patients with IPAH. Indeed, there was no significant difference in age, body mass index (BMI), and hazard ratio (HR) between the healthy control subjects and the patients with IPAH in the discovery group (age, $P = 0.790$; BMI, $P = 0.891$; HR, $P = 0.431$) or in the validation group (age, $P = 0.166$; BMI, $P = 0.112$; HR, $P = 0.183$). Although there was significant difference in sex between the healthy control subjects and the patients with IPAH in the validation group ($P = 0.023$), our results were accurate after adjusting for age, sex, and BMI in the multivariate regression analysis.

Sun and colleagues suggested building a model to predict IPAH through taking circGSAP and other renowned indicators into account. We acknowledged in our study that 6-minute-walk distance and NT-proBNP are reliable indicators for the prognosis of IPAH (1). It is believed that an optimal model can be built to predict the diagnosis and prognosis of patients with IPAH by including circGSAP, 6-minute-walk distance, NT-proBNP, or even other hemodynamic parameters. To highlight the impact of circGSAP on IPAH, only the receiver operating curve area of circGSAP was shown in our manuscript.

We cannot agree more with Sun and colleagues on their suggestion to expand the sample size by recruiting patients from multicenters. We have collected the plasma and peripheral blood mononuclear cells of patients with pulmonary hypertension (PH) due to other etiologies in our center to validate our findings from patients with IPAH. Furthermore, we have drafted a plan to run a multicentered prospective study to test the downregulation of circGSAP in PH.

Finally, Sun and colleagues suggested to summarize signaling pathways related to circGSAP for facilitating future research on potential mechanisms and therapeutic targets. It is known that circRNAs are covalently closed, abundant, and evolutionarily conserved. Many of them are involved in important biological functions by acting as microRNA sponges, binding to RNA-binding proteins, regulating mRNA transcription, expression, or translating into proteins (2–6). In our study, we found that circGSAP was an exonic circRNA and could serve as microRNA sponges to regulate mRNA in the development of IPAH (1). We are studying its downstream signaling pathways regarding the proliferation or apoptosis of endothelial cells of the pulmonary arteries both *in vivo* and *in vitro*. This work is near completion and our results will be presented in the next publication. It is also our hope to find novel therapeutic targets through elaborating the functional characteristics of circGSAP in the pathogenesis of PH. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Yuan-Yuan Sun, M.D.
Lan Wang, M.D.
Jin-Ming Liu, M.D.
Ping Yuan, M.D.*
Shanghai Pulmonary Hospital Affiliated to Tongji University
Shanghai, China

*Corresponding author (e-mail: pandyyuan@tongji.edu.cn).

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High Circulating Plasma Soluble Receptor for Advanced Glycation End-Products in Early COVID-19–associated Acute Respiratory Distress Syndrome: Pathophysiological Significance?

To the Editor:

I read with interest the article by Kapandji and colleagues (1) arguing in favor of the early intense lung alveolar epithelial injury as the

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