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BRIEF REPORT

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# Early plasma angiopoietin-2 is prognostic for ARDS and mortality among critically ill patients with sepsis

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## Abstract

Angiopoietin-2 (Ang-2) is associated with vascular endothelial injury and permeability in the acute respiratory distress syndrome (ARDS) and sepsis. Elevated circulating Ang-2 levels may identify critically ill patients with distinct pathobiology amenable to targeted therapy. We hypothesized that plasma Ang-2 measured shortly after hospitalization among patients with sepsis would be associated with the development of ARDS and poor clinical outcomes. To test this hypothesis, we measured plasma Ang-2 in a cohort of 757 patients with sepsis, including 267 with ARDS, enrolled in the emergency department or early in their ICU course before the COVID-19 pandemic. Multivariable models were used to test the association of Ang-2 with the development of ARDS and 30-day mortality. We found that early plasma Ang-2 in sepsis was associated with higher baseline severity of illness, the development of ARDS, and mortality risk. The association between Ang-2 and mortality was strongest among patients with ARDS and sepsis as compared to those with sepsis alone (OR 1.81 vs. 1.52 per log Ang-2 increase). These findings might inform models testing patient risk prediction and strengthen the evidence for Ang-2 as an appealing biomarker for patient selection for novel therapeutic agents to target vascular injury in sepsis and ARDS.

## Introduction

Biomarker-guided patient selection has the potential to match specific biologic therapies with the most relevant pathophysiology and therefore with the greatest potential for benefit in acute respiratory distress syndrome

(ARDS). The angiopoietin (Ang)-Tie pathway is a key regulator of vascular endothelial permeability that contributes to non-cardiogenic pulmonary edema in critically ill patients [1]. In ARDS and sepsis, antagonism of Tie2 signaling by soluble Ang-2 inhibitors disrupts endothelial cell tight junctions, leading to increased vascular permeability and inflammation (reviewed in [2]). Previous small prospective cohort studies of critically ill patients suggest an association between plasma Ang-2 and development of ARDS [3] and poor clinical outcomes in patients with sepsis, including those with respiratory failure [4, 5]. We hypothesized that higher plasma Ang-2 measured shortly after hospitalization

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(usually within 24 h) would be associated with worse clinical outcomes in a large cohort of critically ill patients with sepsis. More specifically, we hypothesized that early plasma Ang-2 would be associated with a higher incidence of developing ARDS and increased mortality after adjusting for relevant clinical and demographic features.

## Methods

We conducted a retrospective analysis of 758 prospectively enrolled septic patients admitted to the ICU from the emergency department in the EARLI (Early Assessment of Renal and Lung Injury study) cohort between October 2008 and August 2018 [3], 267 of whom developed ARDS according to the Berlin Definition within the first five days of ICU admission [6]. Sepsis was defined as meeting at least 2 SIRS criteria ( $>38.0^{\circ}\text{C}$  or hypothermia  $<36.0^{\circ}\text{C}$ , tachycardia  $>90$  beats/minute, tachypnea  $>20$  breaths/minute, leukocytosis  $>12 \times 10^9$  cells/L or leukopenia  $<4 \times 10^9$  cells/L) and confirmed positive microbiological culture or clinically diagnosed sepsis adjudicated by a research physician. The study was approved by the Institutional Review Board of the University of California, San Francisco. Procedures for informed consent have been previously described [3].

Plasma Ang-2 levels were measured using a Luminex™ multiplexed bead-based assay or ELISA (R&D™). Baseline (first available) Ang-2 values were used in all analyses, using  $\log_e$ -transformed values in analyses using Ang-2 as a continuous predictor variable. To assess the temporal relationship between elevated Ang-2 and ARDS development, we performed a subgroup analysis comparing Ang-2 levels between at-risk subjects who developed ARDS more than 24 h after plasma sampling ( $n=78$ ) to at-risk subjects who did not develop ARDS during our observation period ( $n=408$ ). This analysis excluded patients with ARDS identified within 24 h of ICU admission, for whom the timing of ARDS diagnosis was not clear, or for whom ARDS plasma was collected more than 24 h after enrollment.

Continuous variables are presented as median (IQR) and compared using Wilcoxon rank-sum tests. Categorical variables were compared using the Chi-square test. Adjusted logistic regression models (age and sex) were used to estimate the association between Ang-2 and 30-day mortality among all subjects. A separate analysis including an interaction term between log-transformed Ang-2 and ARDS was used to test whether ARDS mediated the association between Ang-2 and mortality. Adjustment for severity of illness scores was not included in these models as Ang-2 is on the same causal pathways as organ failures in our theoretical

causal model. A two-sided P value less than 0.05 was considered statistically significant. Statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R.

## Results

Demographic characteristics of all septic patients and of those with sepsis and ARDS are presented in Table 1. At day 30, 25% of patients with sepsis in the overall cohort had died as compared with 39% of patients with both sepsis and ARDS. Baseline plasma Ang-2 was significantly associated with 30-day mortality in adjusted logistic regression models. In models adjusting for age and sex, a one unit change in log plasma Ang-2 was associated with 1.52-fold increase in the odds of death (95% CI 1.28–1.80) in the full cohort (of septic patients ( $n=757$ ) and a 1.81-fold increase (95% CI 1.37–2.40) in the patients with both sepsis and ARDS ( $n=267$ ) (Table 2). In a separate

**Table 1** Clinical and demographic data for the full cohort of septic patients and the nested cohorts of patients with sepsis and Berlin ARDS

Characteristic	Sepsis cohort ( $n=757$ )	Berlin ARDS Cohort ( $n=267$ )
Age, years (mean $\pm$ SD)	65 $\pm$ 16	66 $\pm$ 16
Male ( $n$ , %)	421, 56%	155, 58%
Female ( $n$ , %)	336, 44%	112, 42%
Caucasian ( $n$ , %)	374, 49%	132, 49%
African-American ( $n$ , %)	99, 13%	39, 15%
Asian ( $n$ , %)	191, 25%	64, 24%
Pacific Islander ( $n$ , %)	9, 1%	2, 1%
Native American ( $n$ , %)	5, 1%	1, 0%
Other ( $n$ , %)	79, 11%	29, 11%
Hispanic Ethnicity ( $n$ , %)	95, 13%	29, 11%
Sepsis ( $n$ , %)		
Pulmonary	361, 48%	169, 64%
Non-pulmonary	303, 40%	58, 22%
Both	62, 8%	26, 10%
Unclear	23, 3%	12, 5%
Lung injury risk factor ( $n$ , %)		
Direct lung injury risk factor	450, 59%	210, 79%
Indirect lung injury risk factor	307, 41%	57, 21%
None	0 (0%)	0 (0%)
Vasopressors on study day 1 ( $n$ , %)	435, 58%	186, 70%
APACHE III Score (mean $\pm$ SD)	98 $\pm$ 39	118 $\pm$ 39
PaO <sub>2</sub> /FiO <sub>2</sub> (median, IQR) on day 1	173 (103, 273)	136 (71, 206)
Ventilator free days by 28 days	25 (3, 28)	18 (0, 25)

Hospital mortality: Death at hospital discharge. 60d mortality is inclusive of 30d mortality

Patient survival is defined as surviving past day 60 after study enrollment. Patients who died after day 60 are still included for calculating length of stay

**Table 2** Higher Ang-2 is associated with mortality and ARDS in septic patients

	Odds ratio (95%CI)	
Sepsis cohort (n = 757)		
Death <sup>1</sup>	1.52 (1.28, 1.80)	< 0.001
ARDS <sup>2</sup>	1.32 (1.13, 1.53)	< 0.001
ARDS + Sepsis (n = 267)		
Death <sup>3</sup>	1.81 (1.37, 2.40)	< 0.001

<sup>1</sup> Death: 30-day hospital mortality. Final model was determined using a priori predictors for ARDS-related mortality. The final adjusted model includes: log(Ang-2) (shown above), age (odds ratio: 1.03; 95% CI 1.02–1.04;  $p < 0.001$ ), and male sex (odds ratio: 1.06; 95% CI 0.78–1.45;  $p = 0.72$ )

<sup>2</sup> ARDS: ARDS by Berlin Definition within first 5 days. Final model was determined using a priori predictors for ARDS-related mortality. The final adjusted model includes: log(Ang-2) (shown above), age (odds ratio: 1.01; 95% CI 1.00–1.01;  $p = 0.27$ ), and male sex (odds ratio: 1.26; 95% CI 0.94–1.69;  $p = 0.12$ )

<sup>3</sup> Same methodologies as full cohort. The final model includes: log(Ang-2) (shown above), age (odds ratio:), male sex (odds ratio: 1.27; 95% CI 0.74–2.17;  $p = 0.39$ )

logistic regression model of 30-day mortality including an interaction term between Ang-2 and ARDS, there was not a statistically significant interaction ( $p = 0.071$ ).

Plasma samples were collected within 24 h of ICU admission for greater than 96% of patients, and within 48 h of for all patients for whom the timing of sample collection was recorded. Median (IQR) Ang-2 levels were higher among 78 sepsis patients in whom plasma was sampled more than 24 h prior to meeting Berlin ARDS diagnostic criteria compared to a group of 408 at-risk sepsis patients who did not develop ARDS during the first 5 days of hospitalization [7577 pg/ml (4216–16,699 pg/ml) vs. 6032 pg/ml (3009–11,821 pg/ml),  $p = 0.02$ ].

Among all patients with sepsis, median Ang-2 levels were higher in patients requiring vasopressors on ICU Day 1 compared with patients who did not. Patients who required vasopressors on day 1 in ICU had Ang-2 median levels of 8426 (3763–16,000) compared to 5000 (2587–9334) for those patients who did not require vasopressors ( $p < 0.0001$ ). In addition, patients in the highest quartile of Ang-2 compared to the lower three quartiles required a greater number of vasopressors ( $p < 0.0001$ ), suggesting that baseline plasma Ang-2 may enrich for vasoplegia and shock.

## Discussion

To our knowledge, these findings represent the largest biomarker study of early measurements of plasma Ang-2 in a cohort of critically ill patients with physician-adjudicated ARDS and sepsis. Prior reports have found an association between Ang-2 and both organ

failure and mortality in patients with respiratory failure [5] and an association between Ang-2 and the development of acute lung injury in smaller cohorts [3]. We present a novel finding with time-ordering data in critically ill patients with sepsis, demonstrating that higher plasma Ang-2 levels are associated with increased risk of developing ARDS, thereby strengthening the evidence for the importance of Ang-2 in the pathobiology of ARDS among critically ill patients with sepsis. The robust association between Ang-2 and 30-day mortality in patients with early sepsis, which is enhanced among a subgroup of patients with early sepsis who also have ARDS, suggests a conserved pathobiology role among heterogeneous critically ill patients. Our data support the potential role for measuring circulating Ang-2 to guide the delivery of therapeutic targets that target endothelial injury and may improve clinical outcomes in critical ill patients with sepsis, particularly those who are at risk of developing ARDS.

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## Author contributions

CSC, KD, CMH, KDL, MAM, KMR, KMS, and HZ contributed to study design, analysis and interpretation of data, and drafting and critical revision of manuscript. YC, AL, PS, KDW, and NW contributed to analysis and interpretation of data and critical revision of manuscript. DFC and DC contributed to study design, interpretation of data, and revision of manuscript. AG contributed to analysis and interpretation of data and revision of manuscript. AJ and KNK contributed to study design and analysis and interpretation of data. HC, SBK, SK, and MP contributed to study design and revision of manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of California, San Francisco. Subjects or a designated surrogate provided informed consent for study participation unless the subject died before their surrogate could be approached for informed consent or the subject was too ill to provide consent and a surrogate could not be identified within 28 days. In these cases, the IRB approved a waiver of consent.

### Consent for publication

Not applicable.

### Competing interests

YC, KD, ADG, AJ, KNK, SK, AL, KMS, KDW, NW, and HZ declare that they have no competing interests. DC, HC, DFC, AG, SBK, MP, and CMR were employed by Genentech and owned Roche stock at the time of the study. CSC declares grants and personal fees from Roche/Genentech, grants and personal fees from Bayer, personal fees from Gen1e Life Sciences, personal fees from Vasomune, grants from Quantum Leap Healthcare Collaborative, personal fees from Janssen, personal fees from Cellenkos, and personal fees from NGM Bio.

CMH received consultancy fees from Spring Discovery. KDL declares consultancy agreements with AM Pharma, Biomerieux, BOA Medical, Neumora, and Seastar Medical; stock in Amgen; serving on the Editorial Boards of American Journal of Kidney Diseases, American Journal of Respiratory and Critical Care Medicine, and CJASN; advisory or leadership roles for the American Thoracic Society and NKF Scientific Advisory Board; and other interests or relationships with UpToDate. MAM declares a research grant paid to UCSF from Genentech-Roche and consulting income from Johnson & Johnson, Novartis, Pliant Therapeutics, Quantum Health, and Gilead. PS declares Personal fees from Astra-Zeneca.

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