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SERUM ANGIOPOIETIN-2 AND SYNDECAN-1 AS PREDICTORS OF MULTI-ORGAN DYSFUNCTION IN SEPSIS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Endothelial injury may contribute to progression of organ dysfunction in sepsis. This study evaluated Angiopoietin-2 and Syndecan-1 as predictors of subsequent multi-organ dysfunction syndrome (MODS).

Methods: In this prospective observational study, 200 adults with sepsis were enrolled within 24 hours of recognition. Patients with established MODS at baseline were excluded. Serum Angiopoietin-2 and Syndecan-1 were measured at enrollment, and participants were followed for development of MODS within 7 days. Logistic regression and ROC analyses were performed.

Results: MODS developed in 73 patients (36.5%). Median Angiopoietin-2 and Syndecan-1 concentrations were significantly higher in the MODS group. Baseline SOFA, lactate, Angiopoietin-2, and Syndecan-1 remained independently associated with MODS. Angiopoietin-2 and Syndecan-1 showed AUCs of 0.766 and 0.784, respectively, while the combined clinical-biomarker model achieved an AUC of 0.859.

Conclusion: Angiopoietin-2 and Syndecan-1 improved early prediction of MODS beyond conventional clinical severity measures.

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INTRODUCTION

Sepsis is a complex clinical syndrome, which is caused by an infection and leads to an inappropriate host response with the potential to develop into acute organ dysfunction, circulatory failure and death. The contemporary definition of Sepsis-3 emphasizes organ dysfunction, and changes in the Sequential Organ Failure Assessment (SOFA) score are used to measure physiological deterioration [1]. The SOFA framework is a scoring system that assesses respiratory, coagulation, hepatic, cardiovascular, neurological and renal function and is widely used for longitudinal evaluation of critically ill patients [2]. Although clinically useful, traditional severity scores are largely based on organ injury once it is measurable, and there is interest in finding biomarkers that can detect patients who are at risk of developing subsequent multi-organ dysfunction at an earlier stage.

Increasingly, endothelial injury is recognized as an important component of organ failure associated with sepsis. Systemic inflammation leads to disruption of the integrity of the vascular barrier, changes in microvascular perfusion, increased interactions between leukocytes and endothelial cells, and tissue edema and decreased oxygen delivery. In particular, endothelial mediators such as Angiopoietin-2 (Ang-2) have biological relevance as they modify the signaling through the endothelial Tie2 receptor and promote vascular destabilization in inflammatory stress. In an initial clinical and experimental study, Parikh et al. showed that circulating Ang-2 was significantly elevated in sepsis and that elevated Ang-2 activity was associated with decreased endothelial barrier integrity and pulmonary vascular leak [3].

This association between Ang-2 and poor sepsis courses has been supported by subsequent studies. In independent patient cohorts, David et al. observed that early circulating Ang-2 levels were associated with severity of illness and that Ang-2 levels rose in nonsurvivors; higher values also preceded the development of shock and death [4]. Fisher et al. also showed associations between increased Ang-2, fluid accumulation, increased organ dysfunction and mortality in septic shock patients [5]. Together, these observations indicate that Ang-2 may offer insights into endothelial activation and vascular instability prior to the onset of the full clinical picture of developing organ injury, as defined by traditional markers.

One of the other manifestations of endothelial damage is disruption of the endothelial glycocalyx, which plays a role

in the control of vascular permeability, anticoagulant activity and microcirculatory homeostasis. Syndecan-1 is one of the transmembrane proteoglycans of this glycocalyx, which is released into the circulation during glycocalyx degradation. In clinical studies of sepsis, increased levels of Syndecan-1 have been correlated with increased severity and organ-specific complications. Syndecan-1 has been reported by Smart et al. to be linked with respiratory failure in patients with pneumonia-related sepsis [6]. In patients with sepsis-induced hypoperfusion presenting to the emergency department, Saoraya et al. demonstrated a correlation between baseline Syndecan-1 levels and SOFA score and showed that higher levels of Syndecan-1 were associated with increased subsequent fluid requirements, septic shock, vasopressor intensity, renal replacement therapy and mortality [7].

This correlation between glycocalyx shedding and organ dysfunction seems to be organ-system independent. Suzuki et al. demonstrated that higher serum levels of Syndecan-1 were correlated with later changes in renal, hepatic and coagulation parameters and were also correlated with mortality in critically ill patients [8]. These results suggest that circulating Syndecan-1 could be a marker of generalized endothelial glycocalyx damage and not just localized vascular damage. Ang-2 and Syndecan-1 are two distinct aspects of endothelial disease: endothelial activation and barrier destabilization, and glycocalyx degradation, respectively, and might therefore be used together to give a more comprehensive picture of vascular injury during sepsis.

The incremental benefit of measuring both biomarkers to predict the development of multi-organ dysfunction, however, is not fully known when patients with pre-existing multi-organ dysfunction on presentation are excluded. It may be possible to distinguish the predictive role of these biomarkers from their association with organ failure that is already present by evaluating these biomarkers before subsequent deterioration. The present prospective observational study thus evaluated baseline serum Angiopoietin-2 and Syndecan-1 levels as predictors of multi-organ dysfunction occurring within 7 days in adults with sepsis and evaluated the incremental value of adding these endothelial markers to the clinical markers (SOFA score and lactate) for early risk discrimination.

METHODS

Study design and participants

This is a prospective observational cohort study of 200 adults with sepsis conducted between July and December 2026 at JIMSH. Patients were recruited within 24 hours of sepsis recognition and followed up prospectively for clinical outcomes. Eligible participants were ≥18 years of age, with suspected or confirmed infection and infection-related acute organ dysfunction that met the Sepsis-3 criteria, with adequate data to calculate baseline SOFA scores, and with baseline serum biomarker samples available.

Patients were excluded if they had multi-organ dysfunction (defined as ≥2 organ systems) at enrollment, **pregnancy**, major trauma/burns, major immediate postoperative endothelial injury, active intensive chemotherapy, advanced chronic liver failure, maintenance dialysis, severe chronic respiratory failure requiring long-term ventilation, systemic vasculitis or other major endothelial disorders, cardiac arrest prior to enrollment, anticipated death or comfort-only treatment within 24 hours, or if baseline biomarker or outcome data were unavailable.

Baseline assessment and biomarkers

Demographic data, comorbidities, source of infection, acquisition setting, microbiological results, vital signs, organ support requirements and routine laboratory parameters were documented at enrollment. The mean arterial pressure was determined by adding one-third of the pulse pressure to the diastolic blood pressure. Baseline investigations comprised complete blood count, renal and liver function tests, INR, C-reactive protein, procalcitonin, lactate, PaO_2, FiO_2 and PaO_2/FiO_2 ratio.

The severity of illness was evaluated by the Sequential Organ Failure Assessment (SOFA) score based on respiratory, coagulation, hepatic, cardiovascular, neurological and renal parameters. Respiratory rate, systolic blood pressure, and Glasgow Coma Scale were also used to calculate qSOFA. To evaluate biomarkers as predictors of subsequent, rather than established, multi-organ dysfunction, patients with baseline dysfunction of ≥2 organ systems were excluded.

Serum Angiopoietin-2 and Syndecan-1 levels were obtained within 24 hours of sepsis recognition. Biomarker samples were taken before determination of the subsequent MODS outcome.

Outcomes

The main outcome was the development of multi-organ dysfunction within 7 days. The definition of MODS was concurrent dysfunction of at least two of six organ systems (respiratory, coagulation, hepatic, cardiovascular, neurological, renal) as defined by the SOFA organ-component criteria during follow-up. Maximum SOFA during the first 7 days and the change from baseline SOFA were recorded.

Secondary outcomes were septic shock, mechanical ventilation, requirement for vasopressors, acute kidney injury, renal replacement therapy, acute respiratory distress syndrome, hepatic dysfunction, disseminated intravascular coagulation, admission to the intensive care unit, length of stay in the intensive care unit and hospital, and mortality at 28 days.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median [interquartile range] and categorical variables as n (%). Independent-samples t test or Mann-Whitney U test was used for continuous variables and chi-square or Fisher exact test for categorical variables to compare the patients with MODS with those without MODS.

Univariable logistic regression was initially used to examine associations with 7-day MODS. Prespecified predictors were age, diabetes, infection source, baseline SOFA, lactate, platelet count, Angiopoietin-2, Syndecan-1, and PaO_2/FiO_2 ratio. Angiopoietin-2 was modelled per 1000 pg/mL increase, Syndecan-1 per 50 ng/mL increase, lactate per 1 mmol/L increase, and SOFA per 1-point increase. A multivariable logistic regression model was then developed with baseline SOFA, lactate, Angiopoietin-2, and Syndecan-1. Adjusted odds ratios with 95% confidence intervals were presented.

Predictive discrimination was assessed using receiver operating characteristic curves and area under the curve (AUC) for Angiopoietin-2, Syndecan-1, baseline SOFA, the clinical model, the dual-biomarker model, and the combined

clinical-biomarker model. Exploratory cut-offs were identified using the Youden index and reported with sensitivity and specificity. Model calibration was assessed using the Hosmer-Lemeshow test and overall predictive accuracy using the Brier score. Multicollinearity was evaluated before final model interpretation. All tests were two-sided, with $p<0.05$ considered statistically significant.

RESULTS

Participant characteristics and infection profile

A total of 200 adults with sepsis were included, of whom 73 (36.5%) developed multi-organ dysfunction within 7 days and 127 (63.5%) did not. The mean age was 55.5 ± 13.9 years, and 125 (62.5%) patients were male. Respiratory infection was the most frequent source, followed by urinary and intra-abdominal infection. Baseline demographic and comorbidity profiles were broadly similar between groups, whereas baseline SOFA, lactate, and mechanical ventilation at enrollment differed according to subsequent MODS status (Table 01).

Table 01: Baseline characteristics according to subsequent multi-organ dysfunction

Characteristic	Category	Overall (N=200)	No MODS (n=127)	MODS (n=73)	Test statistic	p-value
Age, years		55.5 ± 13.9	55.3 ± 13.6	55.9 ± 14.4	t=0.30	0.765
BMI, kg/m²		24.8 ± 4.1	24.4 ± 4.3	25.4 ± 3.6	t=1.68	0.095
Sex	Male	125 (62.5%)	84 (66.1%)	41 (56.2%)	χ^2=1.97	0.161
Infection source	Respiratory	70 (35.0%)	42 (33.1%)	28 (38.4%)	χ^2=13.88	0.031
	Urinary	48 (24.0%)	35 (27.6%)	13 (17.8%)		
	Intra-abdominal	34 (17.0%)	22 (17.3%)	12 (16.4%)		
	Skin/soft tissue	14 (7.0%)	11 (8.7%)	3 (4.1%)		
	Bloodstream	15 (7.5%)	9 (7.1%)	6 (8.2%)		
	CNS	11 (5.5%)	2 (1.6%)	9 (12.3%)		
	Other	8 (4.0%)	6 (4.7%)	2 (2.7%)		
Diabetes mellitus	Yes	53 (26.5%)	39 (30.7%)	14 (19.2%)	χ^2=3.16	0.075
Hypertension	Yes	56 (28.0%)	33 (26.0%)	23 (31.5%)	χ^2=0.70	0.402
Chronic kidney disease	Yes	28 (14.0%)	20 (15.7%)	8 (11.0%)	χ^2=0.88	0.347
Chronic liver disease	Yes	10 (5.0%)	7 (5.5%)	3 (4.1%)	Fisher exact	0.749
COPD	Yes	21 (10.5%)	15 (11.8%)	6 (8.2%)	χ^2=0.64	0.425
Ischemic heart disease	Yes	22 (11.0%)	16 (12.6%)	6 (8.2%)	χ^2=0.91	0.341
Immunosuppression	Yes	13 (6.5%)	10 (7.9%)	3 (4.1%)	Fisher exact	0.381
Baseline SOFA		3 [3–4]	3 [2–4]	4 [3–5]	U=6810.5	<0.001
Lactate, mmol/L		1.92 [1.34–2.81]	1.59 [1.27–2.18]	2.55 [1.88–3.52]	U=6772.5	<0.001
Vasopressor at enrollment	Yes	43 (21.5%)	23 (18.1%)	20 (27.4%)	χ^2=2.37	0.124
Mechanical ventilation at enrollment	Yes	7 (3.5%)	1 (0.8%)	6 (8.2%)	Fisher exact	0.010

Values are mean ± SD, median [IQR], or n (%), as appropriate. MODS, multi-organ dysfunction syndrome; SOFA, Sequential Organ Failure Assessment; BMI, body mass index; CNS, central nervous system. The infection-source statistic represents the overall comparison across source categories.

Baseline biomarkers and laboratory findings

Both endothelial biomarkers were higher among patients who subsequently developed MODS. Median Angiopoietin-2 was 6303 [4726-13344] pg/mL in the MODS group versus 3654 [2282-5710] pg/mL in those without MODS, while Syndecan-1 was 146.9 [103.5-202.2] versus 73.6 [49.5-112.0] ng/mL, respectively (both $p<0.001$). Lactate and procalcitonin were also higher among patients who developed MODS, whereas CRP, platelet count, creatinine, and PaO2/FiO2 did not differ significantly (Table 2).

Table 02: Baseline biomarkers and major laboratory parameters according to MODS status

Variable	No MODS	MODS	Difference (MODS−No MODS)	95% CI	Test statistic	p-value
Angiopoietin-2, pg/mL	3654 [2282–5710]	6303 [4726–13344]	2649	1562–5331	U=7106.0	<0.001
Syndecan-1, ng/mL	73.6 [49.5–112.0]	146.9 [103.5–202.2]	73.3	41.0–103.0	U=7267.5	<0.001
Lactate, mmol/L	1.59 [1.27–2.18]	2.55 [1.88–3.52]	0.96	0.57–1.45	U=6772.5	<0.001

CRP, mg/L	114.4 [77.2–171.5]	103.6 [74.0–160.0]	-10.8	-31.5–17.5	U=4335.5	0.447
Procalcitonin, ng/mL	2.63 [1.44–5.07]	4.21 [1.97–9.45]	1.58	0.05–3.22	U=5667.0	0.009
Platelets, $\times 10^9$/L	215.0 ± 75.5	202.1 ± 71.0	-12.9	-34.0–8.2	t=-1.21	0.228
Creatinine, mg/dL	1.06 [0.81–2.09]	1.26 [0.92–1.78]	0.20	0.00–0.49	U=5163.5	0.181
Total bilirubin, mg/dL	0.84 [0.64–1.09]	1.03 [0.68–1.53]	0.19	0.04–0.44	U=5440.0	0.041
PaO_2/FiO_2 ratio	423.9 [266.9–466.7]	405.8 [255.1–449.0]	-18.1	-73.0–7.1	U=4004.0	0.109

Values are mean ± SD or median [IQR]. Differences are MODS minus no MODS. CI, confidence interval; CRP, C-reactive protein; PaO2/FiO2, arterial oxygen partial pressure to inspired oxygen fraction ratio.

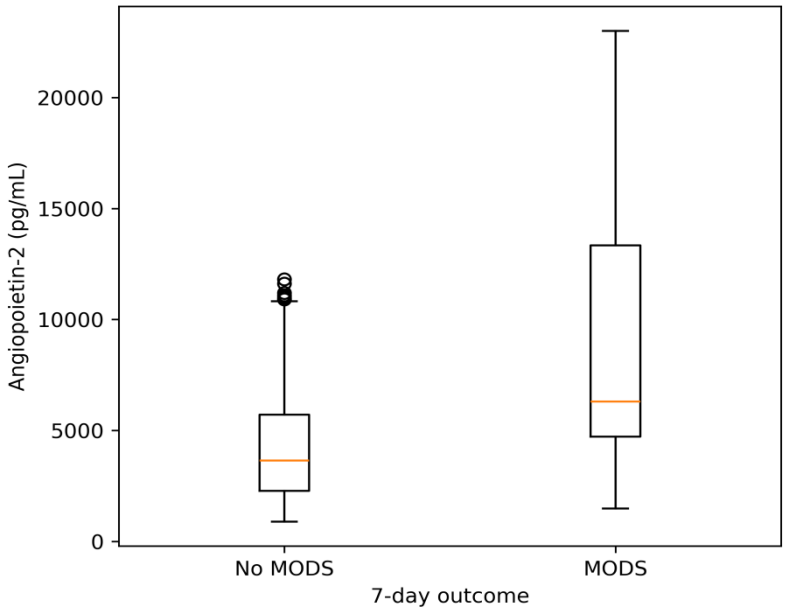

Figure 01: Baseline Angiopoietin-2 concentrations according to subsequent 7-day multi-organ dysfunction status. Boxes represent the interquartile range, central lines the median, and whiskers the distribution beyond the quartiles.

Development of multi-organ dysfunction and clinical outcomes

Patients who developed MODS had a substantially greater maximum SOFA score during the first 7 days and more frequently developed septic shock, required mechanical ventilation, developed acute kidney injury, and underwent renal replacement therapy. ICU and hospital stays were longer in the MODS group. Twenty-eight-day mortality was 7 (9.6%) among patients with MODS compared with 3 (2.4%) among those without MODS (Fisher exact p=0.039) (Table 03).

Table 03: Clinical outcomes according to 7-day MODS status

Outcome	Category	No MODS (n=127)	MODS (n=73)	Test statistic	p-value
Septic shock	Yes	23 (18.1%)	31 (42.5%)	χ^2=13.95	<0.001
Mechanical ventilation	Yes	1 (0.8%)	21 (28.8%)	Fisher exact	<0.001
Acute kidney injury	Yes	36 (28.3%)	33 (45.2%)	χ^2=5.83	0.016
Renal replacement therapy	Yes	0 (0.0%)	10 (13.7%)	Fisher exact	<0.001
Maximum SOFA, first 7 days		3 [3–4]	8 [6–11]	U=9017.5	<0.001
ICU length of stay, days		0 [0–4]	9 [7–10]	U=8587.0	<0.001
Hospital length of stay, days		12 [9–16]	20 [18–23]	U=8346.5	<0.001
28-day mortality	Yes	3 (2.4%)	7 (9.6%)	Fisher exact	0.039

Values are median [IQR] or n (%). SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit. Fisher exact testing was used where expected cell counts were small.

Univariable predictors of multi-organ dysfunction

Higher baseline SOFA, lactate, Angiopoietin-2, and Syndecan-1 were associated with subsequent MODS on univariable analysis. Infection source showed an overall association, driven principally by the CNS subgroup, whereas age, platelet count, and PaO2/FiO2 were not significantly associated with the primary outcome (Table 4).

Table 04: Univariable logistic regression for multi-organ dysfunction within 7 days

Predictor	Crude OR	95% CI	Test statistic	p-value
Age, per 10-year increase	1.03	0.84–1.27	Wald χ^2=0.09	0.761
Diabetes mellitus, Yes vs No	0.54	0.27–1.07	Wald χ^2=3.11	0.078

Infection source (global)	—	—	LR χ^2=13.89	0.031
Infection source: Urinary vs Respiratory	0.56	0.25–1.24	Wald χ^2=2.07	0.150
Infection source: Intra-abdominal vs Respiratory	0.82	0.35–1.92	Wald χ^2=0.21	0.644
Infection source: Skin/soft tissue vs Respiratory	0.41	0.10–1.60	Wald χ^2=1.65	0.199
Infection source: Bloodstream vs Respiratory	1.00	0.32–3.12	Wald χ^2=0.00	1.000
Infection source: CNS vs Respiratory	6.75	1.36–33.60	Wald χ^2=5.44	0.020
Infection source: Other vs Respiratory	0.50	0.09–2.66	Wald χ^2=0.66	0.416
Baseline SOFA, per 1-point increase	2.54	1.84–3.50	Wald χ^2=32.05	<0.001
Lactate, per 1 mmol/L increase	2.37	1.70–3.31	Wald χ^2=25.63	<0.001
Platelet count, per 50×10^9/L decrease	1.13	0.93–1.37	Wald χ^2=1.41	0.234
PaO_2/FiO_2, per 50-unit decrease	1.10	0.96–1.26	Wald χ^2=1.81	0.179
Angiopoietin-2, per 1000 pg/mL increase	1.30	1.18–1.43	Wald χ^2=30.17	<0.001
Syndecan-1, per 50 ng/mL increase	2.25	1.70–2.99	Wald χ^2=31.63	<0.001

OR, odds ratio; CI, confidence interval. Respiratory infection was the reference category for source-specific comparisons. Scaling of continuous variables is shown in the predictor labels.

Multivariable prediction

In the parsimonious adjusted model, baseline SOFA, lactate, Angiopoietin-2, and Syndecan-1 each remained independently associated with 7-day MODS (Table 05). The model was significant overall (likelihood-ratio χ^2=90.81, df=4; p<0.001), with an AUC of 0.859 (95% CI 0.801-0.912), a Brier score of 0.139, and acceptable calibration (Hosmer-Lemeshow χ^2=6.15; p=0.630).

Table 05: Parsimonious multivariable logistic regression for 7-day multi-organ dysfunction

Predictor	Adjusted OR	95% CI	Test statistic	p-value
Baseline SOFA, per 1-point increase	1.73	1.17–2.56	Wald χ^2=7.54	0.006
Lactate, per 1 mmol/L increase	1.58	1.08–2.31	Wald χ^2=5.59	0.018
Angiopoietin-2, per 1000 pg/mL increase	1.18	1.07–1.31	Wald χ^2=10.85	<0.001
Syndecan-1, per 50 ng/mL increase	1.62	1.16–2.27	Wald χ^2=7.83	0.005

aOR, adjusted odds ratio; CI, confidence interval. Model likelihood-ratio χ^2=90.81 (df=4), p<0.001; AUC=0.859; Brier score=0.139; Hosmer-Lemeshow χ^2=6.15, p=0.630.

ROC analysis

Angiopoietin-2 and Syndecan-1 demonstrated moderate discrimination for subsequent MODS, with AUCs of 0.766 and 0.784, respectively. The clinical model yielded an AUC of 0.789, the dual-biomarker model 0.826, and the combined clinical-biomarker model the greatest discrimination (AUC 0.859). Exploratory Youden cut-offs and corresponding sensitivity and specificity estimates are presented in Table 06 and Figure 02.

Table 06: Receiver operating characteristic analysis for 7-day multi-organ dysfunction

Predictor/model	AUC	95% CI	Exploratory Youden cut-off	Sensitivity	Specificity
Angiopoietin-2	0.766	0.701–0.832	4508 pg/mL	0.822	0.583
Syndecan-1	0.784	0.718–0.846	108.9 ng/mL	0.740	0.732
Baseline SOFA	0.735	0.667–0.799	5.0	0.384	0.976
Clinical model	0.789	0.712–0.853	0.302 predicted probability	0.753	0.724
Dual-biomarker model	0.826	0.765–0.879	0.322 predicted probability	0.795	0.764
Combined model	0.859	0.799–0.912	0.456 predicted probability	0.699	0.882

AUC, area under the receiver operating characteristic curve; CI, confidence interval. Cut-offs were derived using the Youden index and are exploratory.

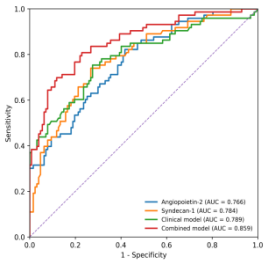

Figure 02: Receiver operating characteristic curves for Angiopoietin-2, Syndecan-1, the clinical model, and the combined clinical-biomarker model for discrimination of multi-organ dysfunction within 7 days.

DISCUSSION

In this prospective cohort, 36.5% of patients went on to develop multi-organ dysfunction within 7 days. The baseline Angiopoietin-2 and Syndecan-1 levels were significantly elevated in patients who went on to develop MODS and both remained independently associated with MODS even after adjusting for SOFA and lactate. Moderate individual discrimination was seen with Angiopoietin-2 and Syndecan-1, and the dual-biomarker and combined clinical-biomarker models were better, with the latter having an AUC of 0.859. The results indicate that endothelial activation and glycocalyx injury are complementary prognostic markers to conventional severity assessment.

The correlation between Angiopoietin-2 and subsequent deterioration is in line with previous research that showed the Ang/Tie2 pathway to be associated with the severity of sepsis. Kümpers et al. reported Angiopoietin-2 levels that increased with each stage of non-septic illness, sepsis and septic shock, with significant correlations with SOFA, APACHE II and impaired oxygenation; higher levels of Angiopoietin-2 were also correlated with poorer 30-day survival [9]. In a multicentre study of severe sepsis, Ricciuto et al. also observed significantly higher serial Angiopoietin-2 levels in nonsurvivors and a c-index of ~0.80 for fatal outcome with a biomarker panel of endothelial markers [10]. Lymperopoulou et al. also demonstrated that Angiopoietin-2 was higher in patients with more failing organs and in those with metabolic acidosis, coagulopathy and fatal outcomes [11]. Our results confirm these observations and demonstrate that Angiopoietin-2 was predictive of newly developed MODS in patients who did not have established multi-organ dysfunction at enrollment.

In our cohort, Syndecan-1 also had important prognostic value and was slightly more discriminatory than Angiopoietin-2 on an individual basis. Puskarich et al. reported that Syndecan-1 levels were higher in nonsurvivors and in patients who developed acute kidney injury, and that levels >240 ng/mL identified patients who were at increased risk of intubation during aggressive fluid resuscitation in a study of 175 patients with severe sepsis or septic shock [12]. Murphy et al. also showed that higher levels of Syndecan-1 were associated with hepatic, renal, coagulation, and circulatory failure, with levels being higher in patients who needed vasopressors, and with each log increase being independently associated with hospital mortality [13]. These findings are similar to the increased incidence of septic shock, mechanical ventilation, acute kidney injury, and renal replacement therapy observed in our study of patients who developed MODS.

The prospective ALBIOS biomarker substudy also reinforces the use of Syndecan-1 as a marker of progressive endothelial injury. In septic shock, Piotti et al. evaluated 375 patients and showed that Syndecan-1 was related to organ failure and independently associated with subsequent renal replacement therapy and incident coagulation failure; among the endothelial markers examined, it was also independently associated with 90-day mortality [14]. Similarly, Qian et al. found persistently elevated levels of Syndecan-1 in nonsurvivors, with a threshold of ≥121 ng/mL associated with poorer survival. Discrimination improved from an AUC of 0.706 for Syndecan-1 alone to 0.773 when combined with lactate [15]. The improvements seen in our combined model further support the notion that endothelial biomarkers provide additional information, not a substitute for existing clinical markers.

These findings are further supported by evidence from meta-analysis. In a meta-analysis of 11 studies with 2318 patients, Sun et al. reported that Syndecan-1 levels were significantly elevated in patients with adverse outcomes, mortality, septic shock and acute kidney injury, with standardized mean differences ranging from 0.48 to 0.81 [16]. This supports the biological plausibility of the use of Syndecan-1 as a marker of systemic endothelial glycocalyx injury rather than isolated organ damage.

An important finding of the present study is the incremental value of endothelial biomarkers in addition to SOFA and lactate. SOFA is a measure of clinically apparent organ dysfunction; lactate is a measure of perfusion and metabolic stress; Angiopoietin-2 is a measure of endothelial destabilization; and Syndecan-1 is a measure of glycocalyx shedding. Their independent associations and the improvement in clinical-model AUC from 0.789 to 0.859 indicate that they capture partly distinct aspects of sepsis progression. Patients who developed MODS had higher maximum SOFA scores, septic shock, mechanical ventilation, renal replacement therapy, longer ICU stay, and higher 28-day mortality, thus adding further clinical coherence to this model.

There are several strengths to the study: prospective enrollment within 24 hours of recognition of sepsis, exclusion of patients with established MODS, and baseline biomarker sampling prior to the primary outcome being established. Some limitations are the single-centre design, the modest sample size and the 73 MODS events, which limited the multivariable model complexity. Biomarkers were measured at baseline, but serial measurements may be helpful. Additionally, there is some variation in assays, which makes it difficult to compare absolute biomarker thresholds across studies, and the exploratory cut-offs need to be validated.

Overall, increased Angiopoietin-2 and Syndecan-1 were independently associated with subsequent multi-organ dysfunction and improved risk discrimination when added to SOFA and lactate. These results support further evaluation of combined endothelial-clinical prediction models in larger multicentre studies.

CONCLUSION

Angiopoietin-2 and Syndecan-1 were independently related to subsequent multi-organ dysfunction in sepsis. Their addition to SOFA and lactate enhanced risk discrimination, thus supporting a combined endothelial-clinical assessment for early prognostication.

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AUTHOR CONTRIBUTIOON

All Authors are Contributed Equally.

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