Research Article

Xinhui Wu, Zhenjie Hu, Hufang Yuan, Lei Chen, Yong Li*, Congcong Zhao

Fluid resuscitation and markers of glycocalyx degradation in severe sepsis

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Abstract: Background: The aim of this study was to determine the relationship between fluid resuscitation and glycocalyx degradation in severe sepsis.

Methodology: 15 post-thoracotomy patients with severe sepsis and 11 patients in recovery after open chest surgery (controls) were enrolled.

Results: Plasma syndecan-1 concentrations were significantly higher in the sepsis group than that in control group, and were correlated with fluid balance in the sepsis group (P=0.026). Survival was not related to trends in plasma syndecan-1 concentrations (ascending/descending) in the sepsis group (P = 0.409). Fluid balance at 24 h was significantly higher in sepsis patients who died than in those who survived (P = 0.010). Acute Physiology and Chronic Health Evaluation II scores, Sequential Organ Failure Assessment scores, duration of mechanical ventilation, and length of intensive care unit stay did not differ with the trend of plasma syndecan-1 concentrations. Compared with plasma syndecan-1 concentrations, lactate clearance at a cutoff of 0.40% had a higher diagnostic value.

Conclusions: In patients with severe sepsis, the glycocalyx plays an important role in liquid distribution in different phases. With time, it changes as well. At present, lactate clearance has greater diagnostic value than plasma syndecan-1 concentrations in severe sepsis. A better indicator of endothelial glycocalyx is therefore required.

***Corresponding author: Yong Li,** Departments of Gastrointestinal Surgery, the Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, Hebei, China. Tel.: +86-311-86095367; Fax: +86-311-86077634; E-mail: liyongsjz@yeah.net
Xinhui Wu, Zhenjie Hu, Lei Chen, Congcong Zhao, Departments of ICU, the Fourth Hospital of Hebei Medical University, Shijiazhuang Hebei, China
Hufang Yuan,Departments of Gastrointestinal Surgery, the Fourth Hospital of Hebei Medical University, Shijiazhuang Hebei, China

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1 Introduction

Severe sepsis is a major healthcare problem in intensive care units (ICUs), affecting millions of people worldwide each year. Sepsis was the third largest cause of death in the USA in 2009, just behind cardiovascular disease and malignant tumors [1]. Fluid resuscitation is a key component in the early management of severe sepsis and septic shock, especially in patients with systemic inflammatory response syndrome and vascular leakage. The timing of fluid resuscitation is also very important. Recently, the Protocolized Care for Early Septic Shock (ProCESS) trial, the Trial of Early, Goal-Directed Resuscitation for Septic Shock (ProMISe), and the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial all failed to demonstrate any outcome benefit of early goal-directed therapy (EGDT) [2-4]. Kelm et al. reported that clinical evidence of persistent fluid overload was common in patients with severe sepsis and septic shock treated with EGDT; moreover, fluid overload was associated with the increased use of medical interventions and with in-hospital mortality [5].

The main pathological changes in severe sepsis and septic shock are altered oxygen distribution and microvascular dysfunction linked to tissue edema. Under these conditions, the development of vascular leakage is a sign of ensuing interstitial edema, arterial hypotension, and hypovolemia. Although EGDT is of considerable benefit in severe sepsis and septic shock, it is mostly aimed at improving macrohemodynamics [6]. Mounting evidence shows that the microcirculation also contributes greatly to the pathophysiology of critical illnesses [7].

The endothelial glycocalyx, a glycoprotein-polysaccharide, associated with various glycosaminoglycans, plays an important role in the maintenance not of only intravascular volume, but also vascular permeability [8, 9]. The plasma levels of glycocalyx markers increase in patients with sepsis, indicating significant flaking of the endothelial glycocalyx [10]. This glycocalyx degradation

affects vascular permeability. However, few experimental studies have investigated the dynamic relationship between glycocalyx shedding and fluid resuscitation. The present study, therefore, aimed to determine the relationship between fluid resuscitation and glycocalyx degradation in patients with severe sepsis. Specifically, we determined whether glycocalyx shedding had any prognostic value or necessitated changes in fluid resuscitation strategies in severe sepsis.

2 Methods

2.1 Ethics

This study was approved by the ethics committees of the Fourth Hospital of Hebei Medical University (2014MEC001). Written informed consent was obtained from all study subjects or their next of kin prior to enrolment. This trial has been registered at ClinicalTrials.gov (number: ChiCTR-OCS-14004681).

2.2 Patients

We enrolled 15 adult patients who underwent thoracotomy at the Fourth Hospital of Hebei Medical University between January 2014 and May 2014 and were admitted to the ICU due to severe sepsis. In addition, we randomly enrolled 11 patients who had undergone open chest surgery and recovered, as a control group. Severe sepsis was diagnosed if the following were observed on two consecutive measurements in a patient with a suspected infection: any two criteria for systemic inflammatory response syndrome (temperature, >38.3°C or <35.6°C; heart rate, >90 beats/min; respiratory rate, >20 breaths/min; or white blood cell count, $>12.0\times10^3$/μL or $<4.0\times10^3$ /μL) and sepsis-induced organ dysfunction or tissue hypoperfusion (systolic blood pressure, ≤90 mmHg; mean arterial pressure, ≤70 mmHg; or a fall of systolic blood pressure >40 mmHg from the baseline; or serum lactate level, ≥4 mmol/L regardless of the blood pressure) [11]. All enrolled patients had no history of diabetes and coronary artery disease. All sepsis patients received EGDT according to the 2012 recommendations of the Surviving Sepsis Campaign and subsequent organ-support therapy. No sepsis patient received hydrocortisone in this process.

2.3 Blood collection

The concentration of syndecan-1, a marker of the integrity of the endothelial glycocalyx, was determined with a commercial enzyme-linked immunosorbent assay kit. (Human syndecan-1/CD138 (SDC-1) ELISA Kit, Cusabio, Wuhan, China).

In the sepsis group, blood was collected into heparinized capillary tubes at baseline (upon ICU admission) and 3, 6, 24, and 48 h after ICU admission. Blood samples were also drawn from the 11 patients in the control group as these operations were finished at the same time. Each blood sample was centrifuged to obtain 100 μL plasma at18°C for 10 min (1000 g), which was stored at -80°C immediately until analysis. Blood syndecan-1 concentrations were determined at each of the above time points; blood lactate levels were analyzed at the baseline and at 6 h after admission to determine lactate clearance. Lactate clearance (percent) was defined using the following formula: lactate at the baseline (0 h) minus lactate at 6 h, divided by lactate at the baseline, then multiplied by 100.

2.4 Data collection

In the severe sepsis group, we determined fluid balance (fluid balance was defined as the difference between the input and output recorded over 3, 6, 24, and 48 h) at four time points: at 3, 6, 24, and 48 h after admission. We also collected data on the duration of ventilator treatment, length of ICU stay, in-ICU mortality rate, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) score on day 1 of treatment.

2.5 Statistical analysis

Data were analyzed with SPSS (version 16.0) (IBM, USA). *P* values of <0.05 were considered statistically significant. Measurement data were expressed as mean ± standard deviation; count data were expressed as percentages (n, %). Between-group differences in measurement data were assessed using the *t* test, chi-squared test or the rank sum test. Pearson correlation was used to analyze the relationship between plasma syndecan-1 concentrations and fluid balance. The diagnostic and prognostic value of average plasma concentrations of syndecan-1 and lactate clearance was determined. The optimal cutoff points of syndecan-1 concentrations and lactate clearance for diagnosing

septic shock were determined using receiver operating characteristic (ROC) curve analysis.

3 Results

3.1 Demographic data

The average age was 65.47 ± 10.20 in the severe sepsis group and 62.91 ± 8.84 in control group. There was no significant difference between the ages of trial and control groups as compared by Student's *t*-test (t = 0.667, *P* = 0.511). The ratio of male to female was 11/4 in the trial group and 8/3 in control group, which verified that there was no statistically significant difference between the two groups by a chi-squared test (*X2 = 0.001, P = 0.973*). The demographic data are presented in Table 1.

3.2 Plasma syndecan-1 concentrations and fluid balance in the severe sepsis and control groups

The mean plasma syndecan-1 concentration was significantly higher in the severe sepsis group (107.34 ± 84.79 ng/ml) than in the control group (31.63 ± 19.93 ng/ml; Student's *t*-test, *t* = 2.889, *P* = 0.008). The changes in plasma syndecan-1 concentration and fluid balance over time are shown in Table 2. Pearson correlation analysis revealed that in the sepsis group, plasma syndecan-1 concentrations at the baseline and at 3, 6, 24, and 48 h were highly correlated with fluid balance at 3, 6, 24, and 48 h (*P* = 0.026, *r* = 0.974).

3.3 Prognostic value of plasma syndecan-1 concentrations

We divided the patients into an ICU survival group (n=11) and an ICU death group (n=4): see Table 3. The chi-squared test showed no significant relationship between ICU survival (survival vs. death) and the trend of plasma syndecan-1 concentrations (ascending vs. descending) in the sepsis group *(χ2 = 0.682, P = 0.409)*.

Normality tests revealed that the duration of mechanical ventilation and length of ICU stay were normally distributed, and were therefore assessed using the Student's *t*-test. In contrast, the SOFA and APACHE II scores were non-normally distributed; they were assessed using the rank sum test (Table 4). The duration of mechanical ventilation, length of ICU stay, SOFA scores, and APACHE II scores did not differ between those with ascending and descending plasma syndecan-1 concentrations.

Table 1: Demographics of severe sepsis patients and controls

	Age (years)	Gender (males/females)
Severe sepsis	65.47 + 10.20	11/4
Controls	62.91 + 8.84	8/3
t/ X^2	0.667	0.001
P value	0.511	0.973

3.4 Relationship of fluid balance with ICU survival

Before comparing fluid balance at 3, 6, 24, and 48 h between the ICU survival and death groups, we performed a normality test. The fluid balance data at 6 h were normally distributed and were assessed using the Student's *t*-test. The fluid balance data at the other time points were not normally distributed, and were therefore assessed using the rank sum test. Fluid balance at 24 h was significantly higher in the ICU death group than in the ICU survival group (Z = -2.481, *P* = 0.010), but no differences in fluid balance were detected at any of the other time points (Table 5).

3.5 Diagnostic value of plasma syndecan-1 concentrations and lactate clearance

The area under the ROC curve of the average syndecan-1 concentration was 0.364 (standard error, 0.141; 95% CI, 0.087, 0.641). At a cutoff plasma syndecan-1 concentration of 182.737 ng/ml, the sensitivity was 0.273, specificity was 0, and accuracy was 0.273. Thus, the accuracy of septic shock diagnoses based on plasma syndecan-1 concentrations was low. The area under the ROC curve of lactate clearance was 0.591 (standard error, 0.220; confidence interval, 0.160, 1.022). At a cutoff peak lactate clearance time of 0.40%, the sensitivity was 1, specificity was 0.5, and accuracy was 0.5. Thus, the accuracy of septic shock diagnoses based on lactate clearance was intermediate, showing that the diagnostic value of lactate clearance was higher than that of plasma syndecan-1 concentrations (Figure 1).

Table 2: Changes in plasma syndecan-1 concentrations and fluid balance over time (n=15)

	Minimum	Maximum	Mean	SD
Fluid balance (mL)				
3 h	-250.0	2235.0	1015.800	841.54
6 h	365	3655	1335.80	972.68
24 h	5	2612	1104.60	849.24
48 h	542	3507	1616.27	1113.06
Syndecan-1 (ng/ml)				
Baseline	11.1	187.55	82.2047	53.45
3 h	2.57	399.50	105.6213	92.68
6 h	3.4	238.1	94.243	71.35
24 h	2.37	462.32	116.99	121.22
48h	1.4	616.1	137.64	182.36

Notes: SD, standard deviation.

Table 3: Relationship of two different trends of plasma syndecan-1 concentrations (ascending vs. descending) with ICU survival

Syndecan-1	Prognosis		χ2	P
	Survived	Died		
Descending	8 (80%)	2 (20%)	0.682	0.409
Ascending	3 (60.0%)	2 (40%)		

Table 4: Comparison of APACHE II scores, SOFA scores, duration of mechanical ventilation, and length of ICU stay between patients with ascending and descending plasma syndecan-1 concentrations

Trend	Sample size	APACHEII score	SOFA score	Duration of MV (hours)	Length of stay in ICU (hours)
Descending	10	16.6 ± 6.36	6.00 ± 2.98	196.5 ± 125.5	294.0 ± 185.8
Ascending	5	19.6 ± 12.8	5.60 ± 3.72	197.0 ± 110.0	249.2 ± 143.1
t		-0.123	-0.189	-0.008	0.471
P value		0.953	0.859	0.994	0.646

Table 5: Comparison of fluid balance between the ICU survival (n=11) and death (n=4) groups

Fluid balance (mL)	3 h	6 h	24 h	48 h
ICU survival group	792 ± 692	1110 ± 507	760 ± 679	1241 ± 778
ICU death group	1630 ± 1010	1957 ± 1690	2052 ± 442	1753 ± 1215
t	-1.845	-0.261	-2.481	-0.719
P value	0.088	0.851	0.010*	0.489

Notes: *$P < 0.05$ indicates significant difference.

4 Discussion

In our study, plasma syndecan-1 concentrations were significantly higher in patients with severe sepsis and septic shock than in the control patients. Our finding corroborates the previously reported result that plasma syndecan-1 levels are increased in septic shock [10]. Syndecan-1 is an important marker of damage to the glycocalyx, and

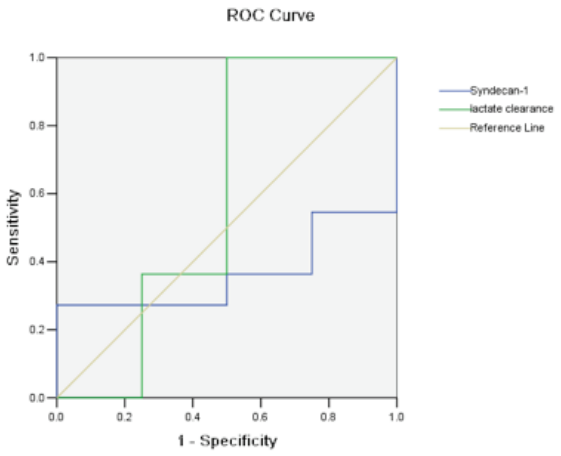

Figure 1: Comparison of diagnostic value of plasma syndecan-1 concentrations and lactate clearance

plasma syndecan-1 levels increase significantly in the setting of glycocalyx degradation. Rapid loss of glycocalyx function has been directly and indirectly evidenced during vascular endothelial injury, which is the first step in inflammatory response [12].

In this study, Pearson correlation analysis revealed that the plasma syndecan-1 concentrations at the baseline and at 3, 6, 24, and 48 h were highly correlated with the fluid balance at 3, 6, 24, and 48 h in the sepsis group. Due to the underlying pathophysiology, fluid management is particularly difficult in patients with severe sepsis and septic shock. The ProMISe, ProCESS, and ARISE trials have demonstrated that EGDT does not improve the outcomes of patients with severe sepsis and septic shock [2-4]. It appears that although we emphasize the importance of the amount of fluid used for resuscitation, we have failed to recognize the differences in the fluid needs of patients at different time points and the inter-individual differences in fluid resuscitation.

The questions is, how should the differences be understoon? We know that numerous alterations in the microcirculation occur in sepsis: microthrombi, capillary leakage, leukocyte rolling, and rouleaux phenomenon. In these changes, the endothelial malfunction and glycocalyx rupture probably play a central role [13]. Glycocalyx disruption can lead to the loss of barrier function, thereby increasing vascular permeability and leading to edema. The glycocalyx is present in a substantial volume of the intravascular space. Therefore, studies of blood volume should assess the protection and restoration of glycocalyx function [8]. Recent studies have shown that the glycocalyx plays a role in inflammatory processes and in immune reactions [14, 15], and mediates the release of vasoregulatory agents such as nitric oxide [16-18]. Another important biological property of the glycocalyx may be its ability to prevent contact between the circulating blood cells and the endothelial cells to prevent cell adhesion [19]. The glycocalyx has been suggested to play an important role in numerous physiological processes, including the regulation of vascular permeability, prevention of the marginalization of blood cells to the vessel wall, and the transmission of shear stress [20]. The glycocalyx, as an important vascular barrier, undergoes many structural and functional changes in sepsis and in ischemia/reperfusion injury. We should develop a method to adjust fluid resuscitation in septic shock based on the concentration of glycocalyx-degradation products in the plasma [21]. Steppan et al. [10] demonstrated that breakdown of the endothelial glycocalyx occurred in patients with sepsis as well as in those who undergo major abdominal surgery. This explains the third spacing of fluids after major abdominal surgery, resulting from the loss of the barrier function of the glycocalyx owing to its nonspecific breakdown. Given this finding, stabilization of the glycocalyx could be a new therapeutic target for patients with sepsis and those undergoing major surgery [10]. The prevention of intravascular hypervolemia may protect a significant part of the glycocalyx. Intravascular hypervolemia causes the release of atrial natriuretic peptide and rapidly induces the matrix metalloproteinase–mediated digestion of the endothelial glycocalyx [22]. Our study concluded that there is a close relationship between fluid resuscitation and glycocalyx degradation. This may explain that the 6-h bundle has been updated this year; however, the 3-h SSC bundle was not affected. There should be a repeat focused exam (after initial fluid resuscitation). Our study also concluded that fluid balance at 24 h was significantly higher in the ICU death group than in the ICU survival group, but no differences in fluid balance were detected at any of the other time points. However, more studies are needed to confirm the function of the glycocalyx and the relationship between this function and fluid resuscitation administered at different time points during severe sepsis. With the development of glycocalyx degradation during the course of severe sepsis, the fluid distribution and demand may change as well.

The recovery of macrohemodynamic stability is not necessarily associated with microhemodynamic improvement. In other words, good cardiac output may not achieve good oxygen delivery and oxygen diffusion. Therefore, blood pressure, cardiac index, and other macrohemodynamic variables should not be considered reliable markers of recovery from septic shock [6]. Marik et al. reported that EGDT should not be used in patients

with severe sepsis and septic shock [23]. Aggressive fluid resuscitation may have disastrous consequences in these patients by increasing tissue edema (pulmonary edema, cerebral edema, etc.) and prolonging ventilator treatment and ICU stay. Thus, factors other than fluid resuscitation that can improve tissue perfusion should be considered in these patients. Research has shown that only 50% of hemodynamically unstable patients benefit from fluid resuscitation [24]. Therefore, with the development of severe sepsis, the fluid responsiveness of patients should be repeatedly evaluated to avoid a condition of hypervolemia that increases the release of ANP and causes enhanced shedding of the endothelial glycocalyx [25].

There is a dynamic relationship between the microcirculation and macrohemodynamic status. The microcirculatory alterations in sepsis play an important role in the development of organ dysfunction and are not simply an indication of the severity of sepsis [26]. Several recent studies have provided convincing evidence that microvascular leakage is not merely a byproduct of sepsis, but rather is a major contributor to morbidity and mortality [27]. The above findings show that deterioration of the endothelial glycocalyx initiates a breakdown of the vascular barrier in sepsis.

Our study showed no significant relationship between ICU survival and the trend of plasma syndecan-1 concentrations in the sepsis group, possibly due to the small sample size. Perhaps for the same reason, the differences in the duration of mechanical ventilation and length of ICU stay between patients with ascending and descending plasma syndecan-1 concentrations were not statistically significant. Furthermore, the differences in SOFA scores and APACHE II scores between the ascending and descending groups were not statistically significant.

Johansson et al. have reported that high circulating levels of syndecan-1, a marker of endothelial glycocalyx degradation, were associated with inflammation, coagulopathy, and increased mortality in trauma patients [28]. De Backer et al. [29] found on multivariate analysis that the proportion of perfused small vessels and lactate levels were independent predictors of outcomes in early sepsis. They also concluded that microcirculatory alterations are stronger predictors of outcomes than are global hemodynamic variables [29]. In sepsis patients, microcirculatory disorder appears to be a major disturbance with prognostic significance: this condition possibly represents an early triggering event in the development of sepsis-induced multi-organ dysfunction syndrome. Many experimental studies have reported data on the structural and functional changes in the glycocalyx during various types of inflammatory conditions [8-10, 13]. These changes are suggested to promote inflammatory processes. We observed changes in the levels of a marker of glycocalyx degradation (syndecan-1) and in lactate clearance in patients with severe sepsis and found that lactate clearance was a better diagnostic indicator of severe sepsis. Although the glycocalyx plays an important role in the microcirculatory alterations in severe sepsis, the impact of many therapeutic interventions on the glycocalyx has not yet been determined. Thus, at present, the lactate clearance rate remains the bridge between macrohemodynamics and the microcirculation. Recently, some authors have reported that lactate levels may not necessarily indicate the need to deliberately increase calculated systemic oxygen delivery because these levels may not accurately represent oxygen deficiency [30].

We recognize that our study has some limitations. First, our sample size was small. The study had an observational design. Thus, the relationship between glycocalyx function and fluid therapy should be confirmed in a larger study with a more general patient population with severe sepsis. Second, whether different types of fluids are associated with different microvascular responses remains to be determined. Resuscitation with different types of fluids may have different effects on the endothelial glycocalyx. More prospective studies are needed to determine the influence of different resuscitation fluids.

To our knowledge, there is no good marker of glycocalyx function, so we cannot determine the best point at which we should intervene and protect this function. Although non-invasive side stream dark-field microscopy can monitor the sublingual glycocalyx, it has yet to be tested in clinical trials [31]. Future studies should address both the ideal combination of monitoring devices as well as the choice of resuscitation fluids to develop the best possible treatment strategy for specific clinical scenarios. A successful fluid management strategy needs to be incorporated into a multimodal interdisciplinary plan of care [32].

In conclusion, the plasma concentrations of syndecan-1, a marker of endothelial glycocalyx damage, were significantly higher in patients with severe sepsis than in the control patients. Thus, at present, lactate clearance has a higher diagnostic value than plasma syndecan-1 concentrations in severe sepsis. In addition, plasma syndecan-1 concentrations were correlated with fluid balance, indicating the link between fluid overload and glycocalyx damage. We consider that a better marker for determining the condition of the endothelial glycocalyx, which plays an important role in the regulation of fluid distribution, is required. Understanding the complex changes in the glycocalyx during sepsis is crucial for the adequate treat-

ment of patients and the development of new fluid resuscitation strategies that will improve clinical outcomes and avoid fluid overload. Further large-scale studies analyzing the degradation of the glycocalyx and the outcomes of patients with severe sepsis are required.

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