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Elevated Syndecan-1 after Trauma and Risk of Sepsis: A Secondary Analysis of Patients from the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial

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Abstract

Background: Endotheliopathy of trauma is characterized by breakdown of the endothelial glycocalyx. Elevated biomarkers of endotheliopathy, such as serum syndecan-1 (Synd-1) ≥ 40 ng/mL, have been associated with increased need for transfusions, complications, and mortality. We hypothesized that severely injured trauma patients who exhibit elevated Synd-1 levels shortly after admission have an increased likelihood of developing sepsis.

Study Design: We analyzed a subset of PROPPR patients that survived at least 72 hours after hospital admission and determined elevated Synd-1 levels (≥ 40 ng/mL) 4 hours after hospital arrival. Sepsis was defined a priori as meeting systemic inflammatory response criteria and having a known or suspected infection. Univariate analysis was performed to identify variables associated with elevated Synd-1 levels and sepsis. Significant variables at a p-value <0.2 in the univariate analysis were chosen by purposeful selection and analyzed in a mixed effects multivariate logistic regression model to account for the 12 different study sites.

Results: We included 512 patients. Of these, 402 (79%) had elevated Synd-1 levels, and 180 (35%) developed sepsis. Median Synd-1 levels at 4 hours after admission were 70 ng/dL (IQR 36 – 157 ng/dL) in patients who did not develop sepsis, and 165 ng/dL (IQR 67 – 336 ng/dL) in those who did ($p < 0.001$). Adjusting for treatment arm and site, multivariable analyses revealed that

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Members of the PROPPR Study Group are listed in the Appendix.

elevated Synd-1 status, injury severity score (ISS), and total blood transfused were significantly associated with an increased likelihood of developing sepsis.

Conclusions: Elevated Synd-1 levels 4 hours after admission in severely injured adult trauma patients who survived the initial 72 hours after hospital admission is associated with subsequent sepsis.

Precis

In severely injured adult trauma patients, elevated syndecan-1 levels 4 hours after admission are associated with subsequent sepsis.

Introduction

Endotheliopathy of trauma is systemic injury to the vascular endothelium observed in severely injured trauma patients – particularly those with hemorrhagic shock – and leads to coagulopathy, inflammation, vascular leakage, and tissue edema and injury.[–] Endotheliopathy of trauma is characterized by a breakdown of the endothelial glycocalyx and is in part mediated by a heightened inflammatory response to injury through a surge in catecholamines.[,] The endothelial glycocalyx is composed of a network of proteoglycans and glycoproteins on the luminal side of the vascular endothelium. Damage to the glycocalyx leads to increased vascular permeability[,] and exposure of the underlying endothelium, which leads to alterations in coagulation and microcirculatory disturbances. Breakdown of the glycocalyx and vascular endothelial cell dysfunction attenuate the endothelium's control of vascular tone, blood fluidity, immunologic functions, and hydrostatic balance between intra- and extravascular spaces,[,–] culminating in microvascular disturbances and tissue edema, ultimately causing end-organ damage (Figure 1).[,,]

Syndecan-1 (Synd-1) is a proteoglycan found in the endothelial glycocalyx. It has been extensively studied as a biomarker of poor outcomes in several patient populations, including trauma and sepsis.[,,,] Elevated Synd-1 levels in these patient populations have been associated with increased transfusion requirement, complications, and mortality.[,,] A prospective observational study of 410 traumatically injured patients conducted at our institution defined Synd-1 levels ≥ 40 ng/mL to be associated with 30-day in-hospital mortality and higher transfusion requirements.

Given the endothelium's immunologic functions, endothelial injury incurred from trauma may predispose the already weakened endothelium to a second hit from infection. There have been no studies evaluating the relationship between patients with early elevated serum Synd-1 after trauma and their subsequent development of sepsis. We performed a secondary analysis of patients enrolled in the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) study, which was a randomized, controlled trial evaluating blood transfusion ratios in severely injured trauma patients across 12 level-1 trauma centers in North America.[] We hypothesized that PROPPR patients who exhibited elevated Synd-1 ≥ 40 ng/mL at 4 hours after hospital admission had an increased likelihood of developing sepsis.

Methods

We performed a retrospective cohort study using patients enrolled in the PROPPR trial to determine if there is a relationship between patients with elevated serum Synd-1 ≥ 40 ng/mL at 4 hours after admission and subsequent development of sepsis during hospitalization. PROPPR patients were severely injured adult trauma patients who received pre-hospital blood or any blood product within 1 hour of hospital arrival who were predicted to require additional massive transfusions. They were randomized to receive transfusion ratios of 1: 1: 1 versus 1: 1: 2 of plasma to platelets to red blood cells. The earliest documented case of sepsis in the PROPPR trial occurred at 72 hours into hospitalization. Patients were excluded who died within 72 hours of hospitalization and who had missing Synd-1 data. Serum Synd-1 data were collected during the course of the PROPPR trial, and levels were quantified using an enzyme-linked immunosorbent assay (Diaclone SAS, Besancon, France; lower limit of detection: 4.49 mg/mL). Synd-1 levels were determined at 4 hours after admission. The time point of 4 hours was chosen because approximately 75% of PROPPR patients had finished receiving massive transfusion protocols at 4 hours [median time to completion of massive transfusion protocols in PROPPR patients was 171 minutes (IQR 120 −255 minutes)], and at least half of the patients were documented to be stabilized in the intensive care unit (ICU) at this time point. Therefore, blood samples taken at 4 hours were thought to be more uniform in that patients were at a similar point in their care in comparison to at other time points during the PROPPR study. Baseline patient variables including demographics, injury characteristics, initial vital signs and laboratory values, blood transfusions, operative procedures, and outcomes were collected. Sepsis was defined a priori as meeting systemic inflammatory response criteria and having a known or suspected infection. This older definition of sepsis was used because the PROPPR trial was conducted prior to establishment of the new Sepsis-3 definition. Complications were defined according to the PROPPR study, and outlined in section 12.3 of the PROPPR manual of operations. Urinary tract infections were defined as fever > 38.5 C, white blood cell (WBC) count > 10,000 or < 3,000 per cubic millimeter, urinary urgency, dysuria, or suprapubic tenderness, and have urinary culture confirmation of > 10^5 organisms per mL of urine within a 2-day period. Line infections must have a single positive blood culture from a peripheral vein, and fever > 38.5 C or WBC count > 10,000 or < 3,000 per cubic millimeter, or systolic blood pressure < 90 mmHg or 25% drop in systolic blood pressure, and microbiological evidence of catheter infection such as positive semi-quantitative culture in which the same organism is isolated from the catheter and peripheral blood, positive quantitative culture in white the same organism is isolated from the catheter and peripheral blood, simultaneous quantitative blood cultures with a ≥ 5:1 ratio of bacteria (central venous catheter to peripheral catheter), or differential period of central venous catheter culture versus peripheral blood culture positivity of > 2 hours. Surgical site infections are must occur within 30 days after the operation and infection involves the skin or subcutaneous tissues (superficial), fascial and muscle layers (deep), or any part of organs or spaces which was manipulated during the operation (organ/space), and also has purulent drainage, organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision, clinical or radiologic symptoms of infection, or diagnosis of a surgical site infection by a surgeon or attending physician. Ventilator-associated pneumonia must occur in patients who have been

on the ventilator for > 48 hours, and have radiologic evidence of infiltrate that persists for at least 24 hours, fever of > 38.5 C or < 35.0 C, WBC count > 12,000 or < 4,000 per cubic millimeter, quantitative microbiologic cultures via bronchoalveolar lavage yielding ≥ 10^4 colony-forming units (CFUs) or protected specimen brush > 10^3 CFUs, or abscess formation with bronchial and alveolar neutrophilia or quantitative culture of lung parenchyma showing ≥ 10^4 CFUs/gram tissue.

Statistical analysis

Included patients were dichotomized by serum Synd-1 level (< 40 or ≥ 40 ng/mL) at 4 hours after hospital admission. A Synd-1 level ≥ 40 ng/mL (area under the ROC curve = 0.71, 95% CI 0.58 – 0.84) was the defined cutoff for elevated Synd-1 status based on a prior study using Synd-1 as a quantitative marker of poor outcomes. Univariate analyses using Chi Squared and Wilcoxon Rank Sum tests for categorical and continuous variables, respectively, were performed to identify variables associated with developing sepsis. Significant variables at a p-value <0.2 in the univariate analysis were chosen by purposeful selection and analyzed in a mixed effects multivariable logistic regression model to account for random effects from the 12 different study centers. A p-value < 0.05 in the multivariable analysis was considered statistically significant. All statistical analyses were performed using Stata (14.0, College Station, Texas).

Results

The PROPPR trial enrolled 680 patients, of which 152 patients died within 72 hours of admission and 16 additional patients did not have Synd-1 data available. Of the 512 patients that were included in the final analysis, 402 (79%) patients had elevated Synd-1 levels, and 180 (35%) patients developed sepsis. Of the 402 patients with elevated Synd-1, 165 (41%) developed sepsis, while of the 110 patients with lower Synd-1 levels, 15 (14%) developed sepsis (Figure 2).

Patients with elevated Synd-1 were significantly younger, had higher injury severity scores (ISS), and had significantly less penetrating injuries. Patients with elevated Synd-1 also had greater base deficit on admission, and received more total blood products [red blood cells (RBCs), plasma, and platelets] on admission. Patients in both Synd-1 groups did not significantly differ in need for operative interventions, initial systolic blood pressure, or time to sepsis development (Table 1). Median time to sepsis development was 8 days in patients with syndecan-1 < 40 ng/mL and 6 days in patients with syndecan-1 ≥ 40 ng/mL (Figure 3). Similarly, patients who developed sepsis had significantly higher Injury Severity Scores (ISS), suffered less penetrating injuries, underwent more operating room procedures, received more total blood products (RBCs, plasma, and platelets), had fewer ICU-free days and hospital-free days, and had higher in-hospital mortality. At 4 hours after admission, Synd-1 levels were significantly higher in patients who did versus did not develop sepsis (165 ng/dL versus 70 ng/dL, p < 0.001). There were no significant differences in ICU admission rates between the two groups (Table 2).

The most frequently occurring complication were infections (urinary tract, wound, or line-associated), followed by acute kidney injury (AKI). Patients with elevated Synd-1 had

significantly higher rates of SIRS, infections, AKI, acute lung injury, acute respiratory distress syndrome, and re-bleeding after initial hemostasis. There were no significant differences in length of intensive-care unit (ICU) stay or days requiring ventilator support. Discharge disposition of patients were also significantly different, in that a high proportion of patients with lower Synd-1 were discharged home, while a higher proportion of patients with elevated Synd-1 died (Table 3).

After adjusting for treatment site and treatment arm, elevated Synd-1 status, higher ISS, and increasing transfusion requirements were significantly associated with development of sepsis on multivariable analysis. Even after adjusting for injury severity, elevated Synd-1 status remained strongly associated with sepsis development. Patients with elevated Synd-1 at 4 hours after arrival to the hospital had three times higher odds of developing sepsis during their hospitalization, which is 2–3 folds higher odds of sepsis development compared to higher ISS and greater transfusion volumes (Table 4).

Discussion

This secondary analysis of a randomized trial evaluated severely injured adult trauma patients with and without elevated serum Synd-1 levels 4 hours after hospital admission who went on to develop sepsis. After adjusting for ISS and transfusion requirements, elevated Synd-1 status was independently associated with the development of sepsis during hospitalization. This is the first study to report the finding that elevated Synd-1 after trauma is positively associated with subsequent development of sepsis. Naumann et al recently showed that elevated Synd-1 occurs within minutes of injury, and that persistently abnormal Synd-1 levels at 4 – 12 hours after injury were associated with the development of multi-organ failure. However, the proportion of multi-organ failure attributable to sepsis was not reported.

The underlying mechanism of how elevated Synd-1 could predispose patients to sepsis warrants further research. Elevated Synd-1 has been suggested to be indicative of breakdown of the glycocalyx and subsequent activation of the endothelium. Hemorrhagic shock and extended surgical interventions have been associated with imbalance of the innate immune response, such as by causing disturbances in the coagulation cascade and down-regulation of Human Leukocyte Antigen–antigen D Related (HLA-DR) on macrophages. The endothelium serves as an adhesive surface to guide immune cell migration between intra- and extravascular spaces, and it switches from an anti-adhesive to a pro-adhesive phenotype during trauma. Given the important role of the vascular endothelium in innate immunity, we postulated that endothelial injury, denoted by elevated serum Synd-1, incurred from the inciting trauma may have led to impairment of the endothelium’s ability to carry out its immunologic roles, thus predisposing patients to infections. Furthermore, glucosaminoglycans – such as Synd-1 – shed from the endothelium has been shown to inhibit antimicrobial peptides found in plasma. Any subsequent infection may then deliver a second insult to the already impaired endothelium, which could accelerate and amplify the ensuing coagulopathy, endothelial leakage, tissue edema, and organ dysfunction that make sepsis more clinically apparent.

Endotheliopathy observed in patients with sepsis may share similar pathophysiology as the purported endotheliopathy of trauma. Septic shock triggers activation of the sympathoadrenal system and causes release of catecholamines, leading to breakdown of the endothelial glycocalyx.[7–9] Through a parallel chain of events as those observed in endotheliopathy of trauma, sepsis leads to coagulopathy and endothelial leakage, which causes microvascular disturbances and tissue edema, ultimately resulting in end-organ dysfunction. Synd-1 has been well-described as a biomarker of sepsis-induced endotheliopathy, and increased serum levels appear to correlate with increased morbidity and mortality, such as higher Sequential Organ Failure Assessment scores and progression to disseminated intravascular coagulopathy.[7–9]

Synd-1 has been used as a quantitative index of endotheliopathy of trauma, and it has the potential to be a quantitative index for sepsis-induced endotheliopathy as well. Endotheliopathy of trauma persisted to have a strong association with the development of sepsis even after controlling for injury severity in the model. Therefore Synd-1 elevation is unlikely to be solely a surrogate marker of injury severity. Several other studies have made the association between Synd-1 elevation and increased morbidity and mortality after controlling for severity of injury.[7,9] Although Synd-1 is not a clinical assay that can be performed on every trauma patient, it may serve as a surrogate marker of response in research studies evaluating potential interventions that mitigate glycocalyx damage associated with the endotheliopathy of trauma. Alternatively, Synd-1 might be useful for stratifying patients at higher risk for sepsis for enrollment into trials evaluating promising interventions or preventive strategies.

Interventions that mitigate endotheliopathy are promising for treating septic shock. A recent animal study demonstrated that septic rats resuscitated with plasma versus crystalloid had a significantly attenuated rise in serum Synd-1. Plasma-resuscitated rats also had significantly improved 48-hour survival and reduced pulmonary wet-to-dry weight ratios, which is a reflection of less pulmonary edema. The benefits from plasma resuscitation observed in this animal model of septic shock may potentially be translatable to humans. Therefore, clinical trials are needed to determine if plasma resuscitation in patients with septic shock confers a similar benefit. Finally, it is unknown whether any early interventions to correct elevated Syn-1 levels in patients (such as plasma, factor concentrate, and tranexamic acid), can reduce their risk of subsequent inhospital sepsis.

There are several limitations to this study. First, this is a secondary analysis of the PROPPR study in which sepsis was not the primary outcome. However, the outcome of sepsis was predefined and actively collected during the duration of the study. Second, Synd-1 is not only derived from breakdown of the glycocalyx and may reflect other responses to traumatic injury. However, elevated Synd-1 has been shown to be correlated with adverse clinical outcomes, such as coagulopathy, tissue edema, and kidney injury. Third, the cut-off for Synd-1 was established based on our institutional data and laboratory kits, which may not be generalizable to other institutions. Therefore, these findings need to be replicated at other institutions. Lastly, the patient population to whom these results should be applied needs to be better defined. Patients enrolled in PROPPR were severely injured patients treated at

level-1 trauma centers in major metropolitan areas. Further studies are necessary to validate the findings in broader populations.

Conclusion

Elevated Synd-1 plasma levels in severely injured adult trauma patients is associated with subsequent sepsis. Interventions that modulate serum Synd-1 as a surrogate marker for treatment response warrant further investigation as they may improve outcomes in hemorrhagic and septic shock populations.

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Appendix

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Abbreviations

ISS	injury severity score
ROC	receiver operating characteristic
IQR	interquartile range
CI	confidence interval
Synd-1	syndecan-1

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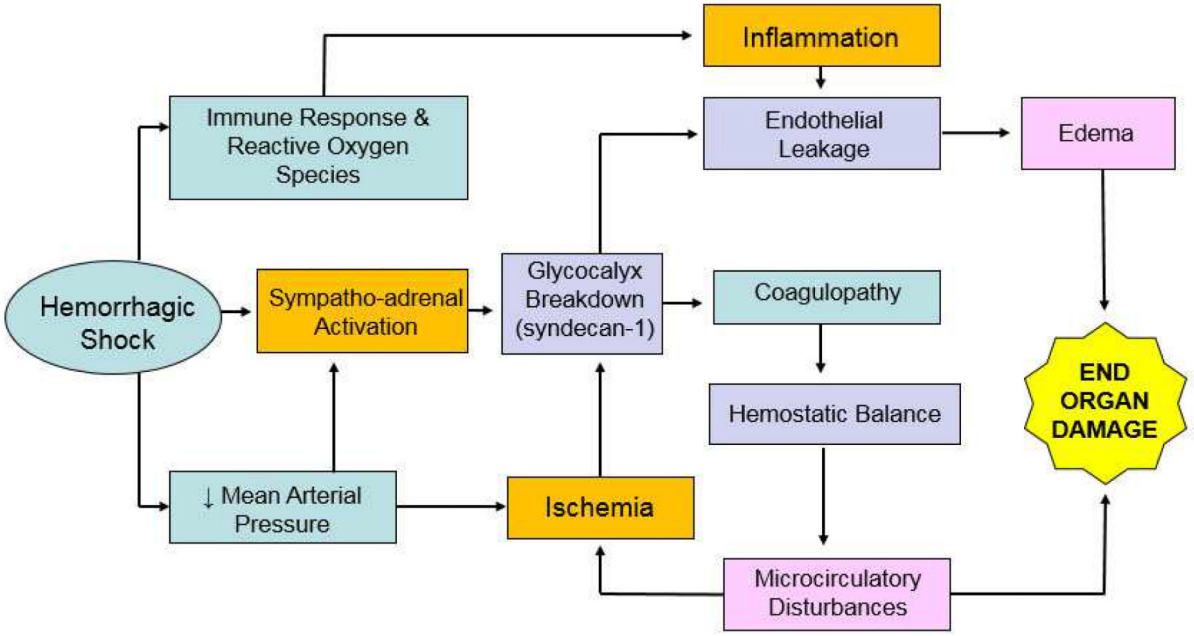

Figure 1.

Simplified conceptual model of how hemorrhagic shock leads to sympathoadrenal activation, inflammation, and ischemia, which affects the endothelial glycocalyx, endothelial permeability, and hemostatic balance, resulting in edema and microcirculatory disturbances that cause organ dysfunction.

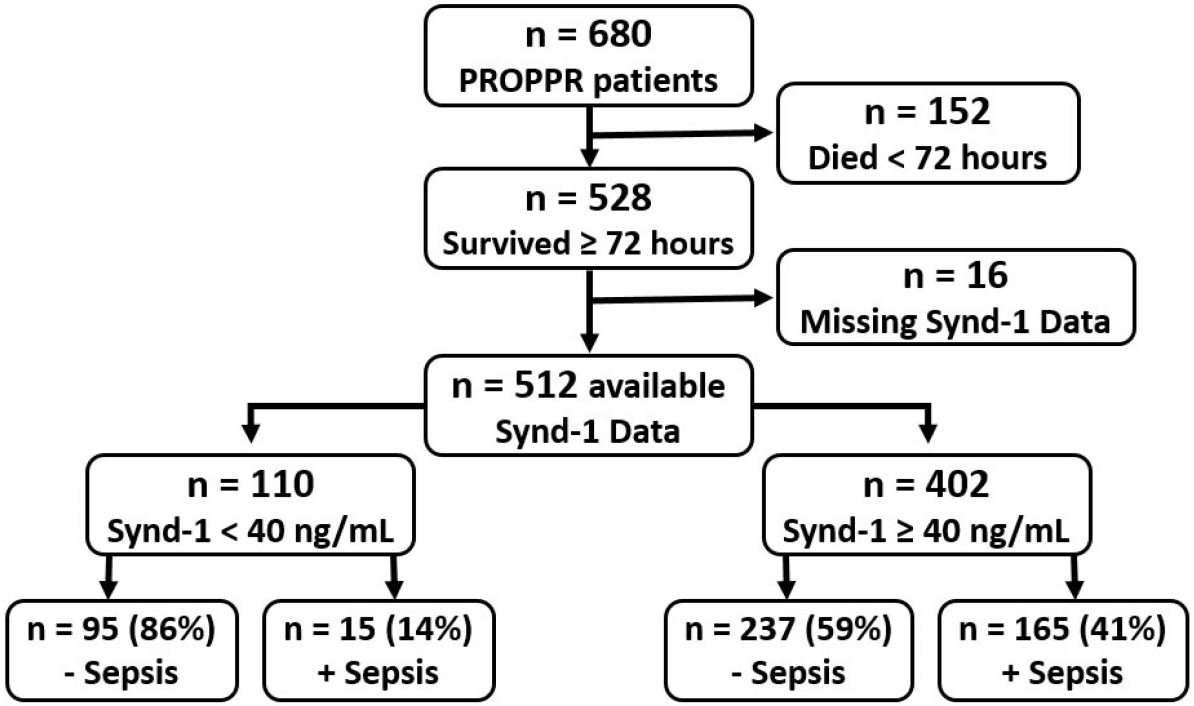

Figure 2.
Flow diagram of patient selection. PROPPR, Pragmatic, Randomized Optimal Platelet and Plasma Ratios Trial

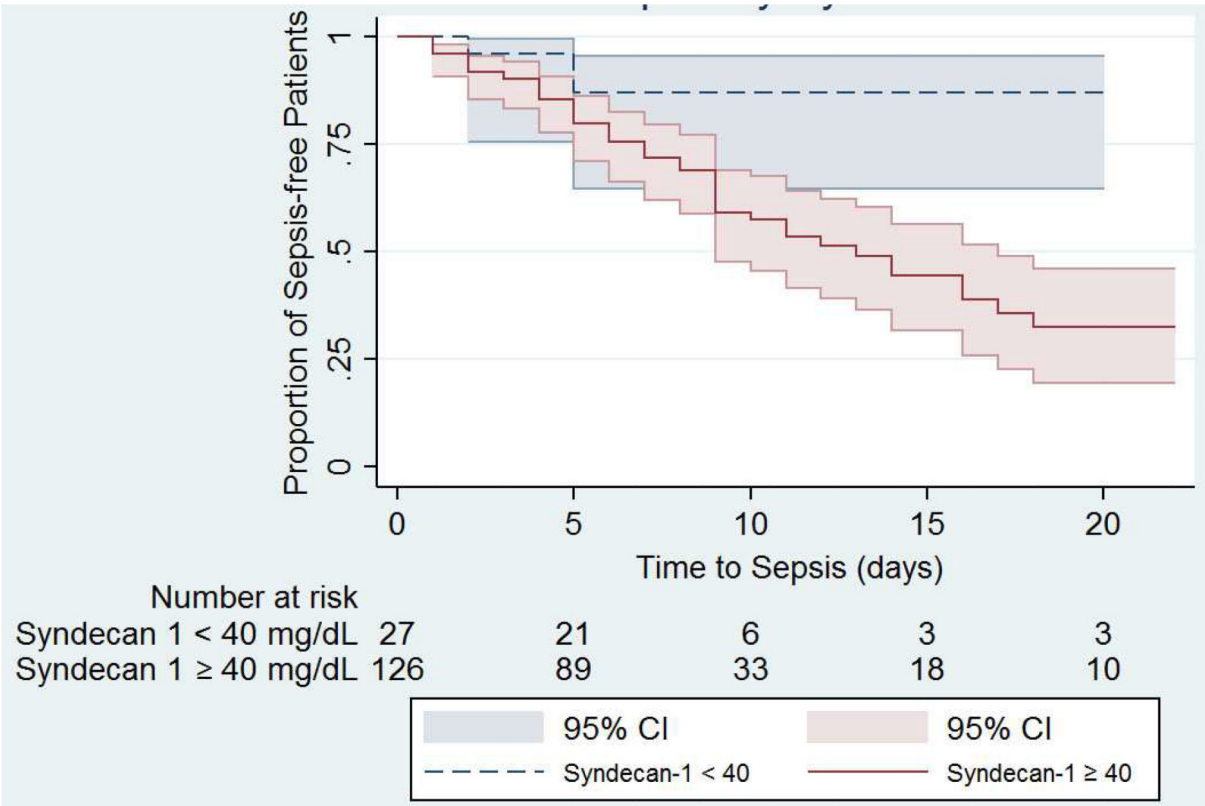

Figure 3.

Days to sepsis development in patients with low (< 40 ng/mL) vs high (≥ 40 ng/mL) syndecan-1 levels at 4 hours after admission. The median time to sepsis development was 8 days and 6 days (p = 0.4) in low and high syndecan-1 groups, respectively. The number of patients at risk was derived based on “time to sepsis” data available for 153 patients. Time to sepsis data was missing for 27 patients. The solid and dotted lines represent proportion of patients who are sepsis free out of the total 153 sepsis patients. The majority of patients in both syndecan-1 groups developed sepsis within the first 10 days of admission, and there is substantial overlap of the 95% confidence intervals suggesting that there is no significant differences in time to sepsis between the two groups.

Table 1:

Patient Characteristics by Synd-1 Status Upon Admission

Variable	Synd-1 < 40 ng/mL (n = 110)	Synd-1 ≥ 40 ng/mL (n = 402)	p Value
Age, y, median (IQR)	40 (30 – 51)	32 (24 – 47)	0.002
Injury Severity Score, median (IQR)	19 (10 – 26)	26 (17 – 38)	<0.001
Penetrating injury, n (%)	72 (65)	189 (47)	0.001
OR procedure, n (%)	102 (93)	387 (96)	0.11
1st SBP, mmHg, median (IQR)	100 (78 – 124)	104 (82 – 127)	0.24
1st hemoglobin, g/dL, median (IQR)	12 (10 – 13)	12 (10 – 13)	0.49
1st WBC count, 1000/uL, median (IQR)	11 (8 – 16)	13 (9 – 17)	0.23
1st base deficit, mmol/L, median (IQR)	6 (9 – 2)	8 (12 – 4)	0.002
Total units of blood product, median (IQR)	13 (8 – 19)	26 (14 – 44)	<0.001
Units of RBCs, median (IQR)	6 (3 – 8)	9 (6 – 16)	<0.001
Units of plasma, median (IQR)	3 (1 – 5)	7 (3 – 12)	<0.001
Units of platelets, median (IQR)	6 (0 – 6)	6 (6 – 18)	<0.001
Time to ICU admission, minutes, median (IQR)	231 (160 – 347)	242 (183 – 350)	0.12
Sepsis, n (%)	15 (14)	165 (41)	<0.001
Time to sepsis, d, median (IQR)	8 (5 – 9)	6 (4 – 10)	0.4

IQR, interquartile range; OR, operating room; SBP, systolic blood pressure; WBC, white blood cell; ICU, intensive care unit

Table 2:

Patient Characteristics by Sepsis

Variable	No sepsis (n = 332)	Sepsis (n = 180)	p Value
Age, y, median (IQR)	33 (25–47)	36 (24–51)	0.4
Injury Severity Score, median (IQR)	22 (14–33)	32 (22–41)	<0.001
Penetrating injury, n (%)	184 (55)	77 (43)	0.006
OR procedure, n (%)	312 (94)	177 (98)	0.01
Units of blood product, median (IQR)	17 (10–29)	33 (19–53)	<0.001
RBC, units, median (IQR)	7 (4–11)	12 (8–20)	<0.001
Plasma, units, median (IQR)	4 (2–7)	9 (5–15)	<0.001
Platelets, units, median (IQR)	6 (0–12)	12 (6–18)	<0.001
ICU admission, n (%)	324 (98)	178 (99)	0.5
Synd-1, ng/mL, median (IQR)	70 (36–157)	165 (67 – 336)	<0.001
Synd-1 ≥ 40 ng/mL, n (%)	237 (71)	165 (92)	<0.001
ICU-free days, median (IQR)	25 (20–27)	10 (0–18)	<0.001
Hospital-free days, median (IQR)	15 (5 – 22)	0 (0–5)	<0.001
Deaths, n (%)	18 (5)	20 (11)	0.014

IQR, interquartile range; OR, operating room; RBC, red blood cell; ICU, intensive care unit

Table 3:

Patient complications and outcomes by Synd-1 status

Variable	Synd-1 < 40 ng/mL (n = 110)	Synd-1 ≥ 40 ng/mL (n = 402)	p Value
Complication, n (%)			
UTI, wound, or line infection (n = 190)	26 (24)	164 (41)	0.001
AKI (n = 136)	12 (11)	124 (31)	<0.001
Ventilator-associated pneumonia (n = 109)	5 (5)	104 (26)	<0.001
Acute lung injury (n = 87)	7 (6)	80 (20)	0.001
Transfusion-related complication (n = 84)	16 (15)	68 (17)	0.7
ARDS (n = 82)	9 (8)	73 (18)	0.01
DVT (n = 46)	8 (7)	38 (9)	0.5
Multi-organ failure (n = 28)	3 (3)	25 (6)	0.2
Symptomatic PE (n = 26)	5 (5)	21 (5)	0.8
Re-bleed after hemostasis (n = 22)	0 (0)	22 (5)	0.007
Rhabdomyolysis (n = 17)	0 (0)	17 (4)	0.03
Stroke (n = 17)	3 (3)	14 (3)	1
ICU-free days, median (IQR)	8 (4–12)	7 (2–12)	0.3
Ventilator-free days, median (IQR)	10 (6–16)	10 (5–17)	0.7
Discharge disposition [*], n (%)			
Home	58 (62)	146 (54)	0.003
Rehabilitation center	11 (12)	33 (12)	
Skilled nursing facility	7 (7)	17 (6)	
Long-term acute care facility	0 (0)	15 (6)	
Other [§]	15 (16)	23 (9)	
Morgue	3 (3)	34 (13)	

[*] Due to missing data, discharge disposition was only available for 362 patients (Synd-1 < 40 ng/mL = 94, Synd-1 ≥ 40 ng/mL = 268)

[§] Other = Assisted Living, Psychiatric Facility, Acute Care Hospital, Jail

UTI, urinary tract infection; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; PE, pulmonary embolus; ICU, intensive care unit; IQR, interquartile range

Table 4:

Multivariable Analysis of Factors Associated with Sepsis

Variable	odds ratio	95% confidence interval	p Value
Synd-1 ≥ 40 ng/mL	2.94	1.53 – 5.66	0.001
Injury Severity Score	1.03	1.01 – 1.05	0.001
Total blood transfused	1.02	1.01 – 1.03	<0.001
Treatment arm	0.87	0.57 – 1.34	0.53