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Endothelial glycocalyx shedding in patients with burns

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ABSTRACT

Shedding of syndecan-1 from the endothelial glycocalyx layer (EGL), referred to as endotheliopathy of trauma (EoT), is associated with poorer outcomes. This study aims to determine if EoT is also present in the burn population. We enrolled 458 burn and non-burn trauma patients at a Level 1 trauma center and defined EoT by a syndecan-1 level of ≥40 ng/mL. Sixty-eight of the enrolled patients had burns with a median TBSA of 19%, with 27.9% also suffering inhalational injury (II). Mortality was similar between the burn and non-burn group, also for patients with EoT. The incidence of II was significantly greater in the EoT+ burn group compared to the EoT− group ($p = 0.038$). Patients with II received significantly larger amounts of i.v. fluids ($p = 0.001$). The incidence of EoT was significantly different between the II-groups, as was mortality ($p_{EoT} = 0.038$, $p_{mortality} < 0.001$).

EoT is attributed to the shock rather than the mechanism of trauma and may in burns be associated to II rather than TBSA. Patients with burns and II had worse outcomes and higher mortality compared to patients with burns alone. Burn injury induces EGL shedding similar to that in non-burn patients with EoT, and results in similar higher rate of mortality.

Abbrevations: II, Inhalational injury; EGL, Endothelial glycocalyx layer; sTM, soluble thrombomodulin; EoT, Endotheliopathy of Trauma; ISS, Injury Severity Score.

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1. Introduction

Annually, 80,000 people in the USA are hospitalized for burns, of which 6500 patients (8%) expire [1]. Age, presence of inhalational injury (II), and burn size are commonly used as unmodifiable factors of mortality due to burns. Early post-burn, a hyper-inflammatory state occurs. It markedly increases metabolism, activates the endothelium and damages the endothelial glycocalyx layer (EGL) [2]. The EGL is a luminal mesh produced by endothelial cells as an integral part of the vascular wall. The EGL consists of glycoproteins and proteoglycans including syndecan-1 and soluble thrombomodulin (sTM). EGL acts as a barrier to macromolecules and blood cells [3–5], as a mechanotransducer of sheer stress [6] and contains a large non-circulating component of the plasma volume.

During hyper-inflammation associated with trauma, a surge in catecholamine levels causes the glycocalyx to be disrupted, shedding syndecan-1 and sTM [2]. Increases in syndecan-1 concentrations are proportional to the degree of EGL damage [7,8]. The pathophysiological event of endothelial activation and disruption of the EGL is characterized as the endotheliopathy of trauma (EoT) in an effort to describe the trigger of downstream systemic effects [9]. EoT defined by a syndecans-1 level of ≥40 ng/mL is associated with increased morbidity and mortality in trauma patients [10].

As the disruption of the EGL denudes the endothelium, fluids and colloids leak into the interstitium, causing edema and hypoalbuminemia, both common findings in burn patients [11,12]. Low intravascular colloid osmotic pressure also relates to increased endothelial shedding of syndecan-1 [7,10,13]. That syndecan-1 may also shed from the endothelial barrier in burns has been demonstrated in animal studies [14]. Thus, we hypothesize a similar response in patients.

Initial fluid resuscitation strategies for burns aims to restore intravascular volume with aggressive infusion of crystalloids to avoid hypovolemia and organ failure. Patients receive large amounts of fluids, often vastly exceeding those prescribed by the Modified Parkland or Modified Brooke Formula [15,16]. The increase in capillary permeability begins early post-burn and intensifies over the course of 24 h, and a relevant percentage of the resuscitation fluid and plasma proteins will leak into the interstitium causing tissue edema [17–19]. Large amounts of crystalloids may also hemodilute the patients. There is a delicate balance between over and under resuscitation of patients with burns, as both result in an increase in mortality [20].

We propose to investigate whether EoT is present in the burn population and contrast the findings with those observed in patients with traumatic injuries. Furthermore, we will investigate how the shedding of EGL and endothelial injury affect fluid resuscitation requirements and outcomes in burn patients.

2. Methods

2.1. Setting and patients

This single-center prospective observational study was carried out at the Dunn Burn Center in the Memorial Hermann Hospital at Texas Medical Center. This is an American Burn Association verified center and a Level 1 trauma center. Approval was obtained from The University of Texas Health Science Center at Houston Institutional Review Board (IRB) (Universal Study, HSC-GEN-12-0059).

During the study period from July 2011 to July 2017, 604 adult trauma patients at the highest level of trauma team activation met the criteria for screening for inclusion.

IRB approval was obtained for delayed consent. Consent was obtained 24–72 h post arrival to hospital, either from the patient or a legally authorized representative. If consent could not be obtained, patients were excluded, and any data or blood samples from the patient were destroyed. Patients under 16 years of age, pregnant women, prisoners, those enrolled in other studies or those from whom we were not able to collect an initial blood draw were excluded from the study. Non-trauma medical admissions, patients that expired within 24 h of hospital arrival, had missing syndecans-1 data, and received fluid resuscitation for <24 h were excluded.

This study contributes additional analysis of data published on trauma patients previously reported by Gonzalez et al. and Johansson et al. that excluded patients with burn injuries [10,21]. Patients suffering from EoT i.e. syndecan-1 level ≥40 ng/mL were defined as EoT+, whereas patients with syndecan-1 below 40 ng/mL were defined as EoT− [13].

2.2. Data collection

Pre-hospital fluid and blood product transfusion data as well as 24 h total fluid requirements, 24 h blood product transfusion data, and outcome data were retrospectively collected from medical records. Burn patients were resuscitated using the Modified Brooke Formula (2 mL/kg/total body surface area (TBSA)). Fluid resuscitation was initiated using Ringer's Lactate solution, transfusing the first half of the estimated 24-h fluid volume within 8 h post-arrival while fluid resuscitation after 8 h was titrated to a urine output of 30–50 mL/h. Blood products were used at the discretion of the attending physician. The attending surgeon assessed burn size in TBSA and severity within 48 h of injury. II was defined as a history of burn in an enclosed space or suspected smoke inhalation along with evidence of airway or lung injury confirmed by bronchoscopy.

2.3. Blood samples

At arrival to the emergency department, trained staff drew an admission blood sample into 3.2% citrate and EDTA Vacutainer tubes that were inverted to ensure efficient anticoagulation. Blood samples were then centrifuged and plasma aliquots were marked and frozen at −80 °C in 2 mL screw-cap microcentrifuge tubes for later analysis.

2.4. Enzyme-linked immunosorbent assay (ELISA)

Syndecan-1 and sTM were measured with ELISA. Trained laboratory personnel measured biomarker levels in admission aliquots with commercially available immunoassays. According to the manufacturer's instructions, syndecan-1 was measured using Diaclone SAS (lower limit of detection

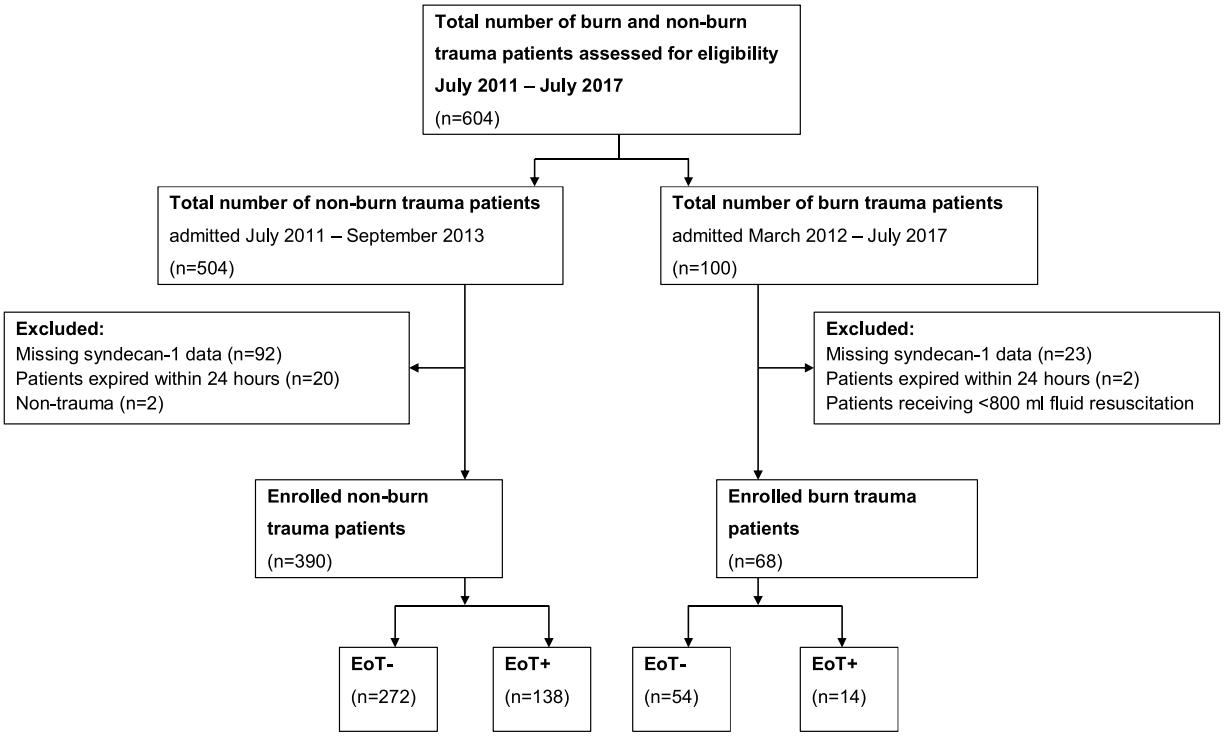

Fig. 1 – CONSORT flow diagram showing non-burn and burn trauma patient selection process and enrollment in the study. EoT: Endotheliopathy of Trauma.

4.94 ng/mL) and sTM was measured using Nordic Biosite (lower limit of detection 0.31 ng/mL).

Adrenaline and noradrenaline levels were only measured in burn patients using 2-CAT ELISA Labor Diagnostica Nord (lower limit of detection 10 pg/mL (adrenaline; normal reference, <100 pg/mL) and 50 pg/mL (noradrenaline; normal reference <600 pg/mL), respectively.

2.5. *Statistical analysis*

Data is presented with medians, upper and lower quartiles for continuous numerical variables. Patients were dichotomized into groups based on the presence of thermal injury. Burn subjects were compared to non-burn trauma patients. After assessing variables for normal distribution evaluating by Kolmogorov-Smirnov and Shapiro-Wilk tests; the Mann-Whitney-U-test was chosen as best suited for comparison of groups within numerical variables. Categorical data is presented as frequencies and is compared using the Chi-square test and Fisher's exact test where appropriate. Statistical analysis was performed using IBM SPSS Statistics version 24.0.

3. Results

The full study population consists of both burn trauma patients and non-burn trauma patients (n = 458): Burn patients with available syndecan-1 data that survived past 24 h and received fluid resuscitation during the first 24 h were included (n = 68). Trauma patients with available syndecan-1 data that survived past 24 h were also included (n = 390). A total of 146 patients were excluded due to missing syndecan-1 data (n = 115), death within 24 h (n = 22) and non-trauma medical admission (n = 2). Burn patients not receiving fluid resuscitation during the first 24 h of admission were also excluded from the study (n = 7). One burn patient had missing data on II status, and 24 burn patients had missing data on adrenaline and noradrenaline. (Fig. 1).

The sixty-eight burn patients included in this study were predominantly male (82.4%) with a median injury severity score (ISS) of 9 (Table 1). Patients had a median TBSA burn of 19% with 27.9% of the patient population suffering II. Of the burn population, 7.4% had additional minor non-burn trauma. None of these minor traumas were traumatic brain injuries. At arrival to the ED, patients with burns were slightly hypertensive with median systolic pressure at 140 mmHg and acidotic with a median pH of 7.33 and a median base excess of -2 (Table 1). Burn patients had median admission hemoglobin levels at 15.4 g/L and median platelet counts at 254×10^9/L. 30-day mortality amongst burn patients was 11.8%. Further details on demography, admission physiology and biomarkers, transfusions and outcomes can be found in Table 1.

Comparing the burn patients vs. non-burn trauma patients ISS was significantly lower in the burn population ($p < 0.001$) (Table 1). With regards to admission physiology and biochemistry, the burn patients had significantly higher systolic blood pressure, heart rate, platelet count, and hemoglobin levels compared to non-burn patients (Table 1). There was a trend towards EoT+ incidence being lower in the burn patients compared to the non-burn patients ($p = 0.063$). Syndecan-1 levels and sTM levels were similar in the two patients groups.

Table 1 – Patient demography, severity of injury, admission physiology and biochemistry, plasma biomarkers, fluid resuscitation, transfusion and outcome data with subgroup comparisons in 458 burn and non-burn trauma patients admitted to a Level 1 Trauma Center.

	Units	Burn trauma	Non-burn trauma	P-value
Demographics				
n	Patients	68	390	
Age	Years	46 (31, 54)	40 (28, 55)	0.954
Sex	Male (n %)	82.4 (56)	77.4 (302)	0.238
Injury type and severity				
ISS	Scale	9 (4, 16)	17 (9, 26)	**<0.001**
Traumatic brain injury	%	0 (0)	27.7 (108)	**0.001**
GCS	Scale	14.5 (3.0, 15.0)	12.5 (3.0, 15.0)	0.417
Transfer	%	8.8 (6)	41.3 (161)	**<0.001**
Admission physiology and biochemistry				
Systolic blood pressure	mmHg	140 (123, 158)	125 (108, 142)	**<0.001**
Heart rate	bpm	100 (83, 114)	92 (78, 109)	**0.036**
Base excess	mEq/L	−2 (-6, 0)	−3 (-5, 1)	0.791
pH	Scale	7.33 (7.27, 7.37)	7.32 (7.25, 7.37)	0.567
Platelet count	10^9/L	254 (193, 305)	223 (185, 272)	**0.024**
Hemoglobin	g/dL	15.4 (13.8, 16.1)	13.1 (11.9, 14.5)	**<0.001**
Plasma biomarkers				
Syndecan-1	ng/mL	23 (15, 35)	25 (13, 58)	0.338
EoT+	%	20.6 (14)	31.8 (124)	0.063
sTM	ng/mL	5.26 (4.02, 6.20)	5.13 (3.81, 7.07)	0.925
Fluid resuscitation				
i.v. Fluid resuscitation at 24 h	ml	5430 (3482, 9518)	1600 (0, 3767)	**<0.001**
Outcome	%			
Hospital-free days	Days	44 (28, 51)	55 (45, 59)	**<0.001**
ICU-free days	Days	58 (48, 60)	59 (55, 60)	**0.036**
Ventilator-free days	Days	59 (53, 60)	59 (57, 60)	0.126
Mortality at 30 days	%	11.8 (8)	12.6 (49)	0.854

Table includes data of 410 patients from the sample populations previously presented by Johansson et al. and Gonzalez et al. [10,21].
EoT+: Endotheliopathy of Trauma, defined by a syndecan-1 level of >40 ng/mL.
P-values < 0.05 are shown in bold.

Table 2 – Comparison of patient demography, severity of injury, admission physiology and biochemistry, plasma biomarkers, fluid resuscitation, transfusion and outcome data for 138 EoT + burn and non-burn trauma patients.

	Units	EoT+ Burn trauma	EoT+ Non-burn trauma	P-value
Demographics				
n	Patients	14	124	
Age	Years	32 (28, 49)	40 (28, 55)	0.058
Sex	Male (n %)	92.9 (13)	77.4 (96)	0.179
Injury type and severity				
ISS	Scale	9 (4, 25)	19 (19, 29)	0.052
TBI	%	–	24.2 (30)	–
GCS	Scale	7 (3, 15)	12 (3, 15)	0.398
Transfer	%	0.0 (0)	34.7 (43)	**0.005**
Admission physiology and biochemistry				
Systolic blood pressure	mmHg	137 (122, 155)	120 (92, 140)	**0.010**
Heart rate	bpm	103 (77, 123)	92 (79, 109)	0.494
Base excess	mEq/L	−9 (−5, 1)	−3 (−6, 1)	0.418
pH	Scale	7.33 (7.17, 7.36)	7.31 (7.23, 7.37)	0.858

(continued on next page)

Table 2 (continued)

	Units	EoT+ Burn trauma	EoT+ Non-burn trauma	P-value
Plasma biomarkers				
Syndecan-1	ng/mL	76 (62, 107)	103 (60, 202)	0.154
sTM	ng/mL	6.20 (5.27, 10.56)	6.62 (5.12, 9.26)	0.772
Fluid resuscitation				
i.v. Fluid resuscitation at 24 h	mL	5340 (2899, 16,435)	3300 (700, 5810)	**0.023**
Outcome	%			
Hospital-free days	Days	47 (33, 50)	53 (42, 58)	0.064
ICU-free days	Days	57 (47, 60)	58 (51, 60)	0.625
Ventilator-free days	Days	58 (48 60)	59 (56, 60)	0.261
Mortality at 30 days	%	21.4 (3)	16.9 (21)	0.711

Table includes data of 410 patients from the sample populations previously presented by Johansson et al. and Gonzalez et al. [10,21].
EoT+: Endotheliopathy of Trauma, defined by a syndecan-1 level of >40 ng/mL.
P-values < 0.05 are shown in bold.

Table 3 – Comparison of patient demography, severity of injury, admission physiology and biochemistry, plasma biomarkers, fluid resuscitation, transfusion and outcome data for 68 burn patients.

	Unit	EoT+ burns	EoT- burns	P-value
Demographics				
n	Patients	14	54	
Age	Years	32 (28, 49)	47 (33, 55)	0.062
Sex	male %	92.9 (13)	81.5 (44)	0.437
Injury severity				
ISS	Scale	9 (4, 25)	9 (4, 16)	0.602
TBSA	%	17 (3, 58)	19 (1, 32)	0.808
II	%	50.0 (7)	22.2 (12)	**0.038**
GCS	Scale	7 (3, 15)	15 (3, 15)	0.123
Fluid resuscitation				
All iv. fluids received at 24 h post arrival	mL	5340 (2873, 16,794)	4732 (3397, 9435)	0.705
Fluid requirements for first 24 h estimated by MBF	mL	2950 (579, 8189)	1363 (1745, 5705)	0.750
Fluids exceeding estimated prediction by MBF	mL	4064 (1011, 6914)	2297 (413, 4086)	0.243
Net fluid balance at 24 h post arrival	mL	4021 (1609, 15,234)	3402 (1517, 8230)	0.590
Admission physiology and biochemistry				
Systolic blood pressure	mmHg	137 (122, 155)	140 (126, 160)	0.946
Heart rate	bpm	103 (77, 123)	100 (86, 111)	0.953
Base excess	mEq/L	−5 (−9, 1)	−2 (−5, 0)	0.370
pH	Scale	7.33 (7.17, 7.36)	7.33 (7.27, 7.37)	0.269
Plasma biomarkers				
Syndecan-1	ng/mL	76 (62, 107)	21 (12, 25)	
sTM	ng/mL	6.2 (5.3, 10.6)	4.8 (3.8, 5.9)	**0.012**
Adrenaline	pg/mL	531 (256, 1246)	259 (86, 477)	0.062
Noradrenaline	pg/mL	1387 (532, 1814)	1022 (435, 1367)	0.300
Outcome				
Hospital-free days	Days	47 (33, 50)	42 (25, 51)	0.682
ICU-free days	Days	57 (47, 60)	58 (40, 60)	0.804
Ventilator-free days	Days	58 (48, 60)	59 (54, 60)	0.313
Mortality at 30 days	%	21.4 (3)	9.3 (5)	0.347

EoT+: Endotheliopathy of Trauma, defined by a syndecan-1 level of >40 ng/mL.
MBF: Modified Brooke Formula.
P-values < 0.05 are shown in bold.

Burn patients received significantly more fluids ($p < 0.001$), but were less likely to be transfused blood products or require a massive transfusion compared to non-burn patients.

Burn patients had significantly less hospital-free ($p < 0.001$) and ICU-free days ($p = 0.036$) compared to non-burn patients. Mortality was similar between burn and non-burn patients (11.8% vs. 12.6%, $p = 0.854$).

For patients who suffered from EoT+, the comparisons between burn and non-burn trauma patients were repeated with similar findings as described above (Table 2).

When investigating the burn population EoT+ vs. EoT− burn patients had no significant difference in ISS or TBSA (Table 3). The incidence of II was significantly greater in EoT+ group vs. the EoT− group ($p = 0.038$). No significant differences in fluid administration were found (Table 3). The EoT+ group had significantly higher sTM levels ($p = 0.012$). However, no significant differences in adrenaline and noradrenaline levels were found between groups. EoT+ burn patients experienced a non-significant two-fold increase in mortality rate compared to the EoT− group (21.4% vs. 9.3%, $p = 0.347$) (Table 3).

Burn patients were dichotomized by the presence of II; TBSA, EoT+, and ISS were significantly higher in the II group vs. the non-II group ($p_{TBSA} = 0.050$, $p_{EoT+} = 0.038$ and $p_{ISS} < 0.001$). GCS was significantly lower in the II group vs. the non-II group ($p = 0.023$). At arrival to the emergency department, II patients had significantly more negative base excesses ($p = 0.012$) and significantly lower pH ($p = 0.006$) (Table 4). The II burns had received significantly higher amounts of IV fluids at 24 h post arrival to the hospital ($p = 0.001$). Amounts of fluid resuscitation in excess to the estimated prescribed was significantly larger in the II group when compared to the non-II group ($p = 0.001$) (Table 4).

II burn patients had significantly less ICU-free days and ventilator-free days compared to the non-II burn patients ($p_{ICU\text{-}free} = 0.001$ and $p_{ventilator\text{-}free} < 0.001$). 30-day mortality was significantly higher in the II burns in the non-II burns ($p < 0.001$) (Table 4).

Table 4 – Comparison of patient demography, severity of injury, admission physiology and biochemistry, plasma biomarkers, fluid resuscitation, transfusion and outcome data for 68 burn patients dichotomized by II.

	Unit	II burns	Non-II burns	P-value
Demographics				
n		19	48	
Age	Years	49 (29, 57)	45 (32, 52)	0.796
Sex	Male (n %)	78.9 (15)	85.4 (41)	0.492
Injury severity				
ISS	Scale	17 (10, 25)	9 (4, 16)	**<0.001**
TBSA	%	32 (10, 60)	15 (8, 29)	**0.050**
GCS	Scale	3 (3, 15)	15 (4, 15)	**0.023**
Fluid resuscitation				
All iv. fluids received at 24 h post arrival	mL	9461 (6043, 17,741)	4115 (3215, 7544)	**0.001**
Fluid requirements for first 24 h estimated by MBF	mL	5120 (1664, 9408)	2909 (1490, 4800)	0.083
Fluids exceeding estimated prediction by MBF	mL	4139 (2338, 7664)	1865 (21, 3961)	**0.001**
Net fluid balance at 24 h post arrival	mL	8476 (4348, 15,475)	2821 (1304, 6426)	**0.001**
Admission physiology and biochemistry				
Systolic blood pressure	mmHg	149 (126, 160)	140 (123, 158)	0.733
Heart rate	bpm	120 (79, 145)	97 (86, 109)	0.082
Base excess	mEq/L	−5 (−8,−2)	−2 (−4, 1)	**0.012**
pH	Scale	7.31 (7.26, 7.33)	7.35 (7.31, 7.38)	**0.006**
Plasma biomarkers				
Syndecan-1	ng/mL	34 (17, 48)	23 (13, 28)	0.128
EoT+	%	36.8 (7)	12.5 (6)	**0.038**
sTM	ng/mL	4.6 (3.7,5.5)	5.6 (4.2,6.8)	0.171
Adrenaline	pg/mL	289 (136, 878)	256 (86, 531)	0.540
Noradrenaline	pg/mL	1266 (1022, 1789)	800 (406, 1387)	0.090
Outcome				
Hospital-free days	Days	43 (25, 56)	46 (28, 51)	0.738
ICU-free days	Days	49 (38, 57)	59 (51, 60)	**0.001**
Ventilator-free days	Days	56 (42, 58)	60 (57, 60)	**<0.001**
Mortality at 30 days	%	36.8 (7)	2.1 (1)	**<0.001**

EoT+: Endotheliopathy of Trauma, defined by a syndecan-1 level of >40 ng/mL.
MBF: Modified Brooke Formula.
P-values < 0.05 are shown in bold.

4. Discussion

The main finding in this study is that EoT, defined as a syndecan-1 level ≥40 ng/mL, exists in the burn population, but it does not seem to be related to injury severity as measured by TBSA. Rather, II may cause EoT in burn patients in alignment with that glycocalyx is abundant in the lungs. The finding that II in burn trauma patients was associated with increases in syndecan-1 levels, fluid demands, and mortality confirms this.

The occurrence of EoT, including in burns, is attributed to the shock with high catecholamine levels, not the mechanical trauma itself. The finding of EoT in a burn trauma cohort having similar mortality rates as non-burn trauma patients supports this. The shock-induced effects on vascular permeability due to sympathoadrenal hyperactivation and systemic disruption of glycocalyx in patients with EoT contributes to extravasation of fluid and protein in the lung specifically. Low plasma oncotic pressure correlates well with glycocalyx degradation in trauma patients, confirming its consequent effect on vascular permeability [7]. Also, II further exacerbates vascular hyperpermeability in the lung vasculature [22–24].

The extravasation of fluids and protein in burn patients is combated with aggressive resuscitation treatment. Presence of EoT in burn patients is significantly associated with fluid resuscitation that is in excess of amounts prescribed, increasing the risk of edema and organ failure. Osuka et al. recently confirmed this association and also found that admission syndecan-1 was not associated to TBSA [25]. Conversely, their finding that glycocalyx shedding was enhanced by increased age was not reproduced in this study. As such, early measurement of syndecan-1 levels may be a useful tool in predicting patients at high risk of complications associated with edema due to iatrogenic fluid administration.

Volume resuscitation with plasma has been reported to improve endothelial barrier function in rodent models of hemorrhagic shock secondary to restoration of the glycocalyx [26]. In alignment with this, we recently reported that coagulation support with plasma reduced the levels of circulating syndecan-1 as a marker of EGL restoration in patients undergoing emergency surgery for a thoracic aortic dissection [27]. Consequently, initially focusing on volume restoration with plasma may also prove beneficial for the vascular integrity in burn patients [26,28].

In alignment with the findings discussed above, a plausible explanation for the high mortality in patients with burn may be attributed to vascular leakage with II, hypotension, and shock leading to organ failure and death [12]. This may be exasperated by excessive fluid administrated dictated by an inadequate renal response to volume resuscitation, as the administered fluid is moved to the extravascular space. Methodologies, such as the administration of beta-blockers to negate the catecholamine effects on the endothelium leading to EoT, appear to be required.

This study has several limitations. It is a single-center retrospective analysis of observational data with a limited number of patients included, and as such, no causality of the findings can be made. Furthermore, the patients were included over a seven-year period and clinical care may have changed during this time. Also, withdrawal-of-care bias may influence results secondary to the inclusion and exclusion criteria chosen given that one patient was excluded due to death within 24 h after admission to hospital [29]. A further limitation is that the endothelial biomarkers were only measured at arrival to the hospital and consequently, no data on the progression of EoT can be made.

5. Conclusion

This study confirms that severe burn injury induces EGL shedding similar to that seen in non-burn patients with EoT as defined by a syndecan-1 level ≥40 ng/mL. Furthermore, patients with burns and II had higher ISS, higher frequency of EoT, larger fluid demands and higher mortality compared to patients with burns alone. The presence of EoT in patients with burns or trauma results in a similar higher mortality rate.

Declaration of interest

The authors have no conflicts of interest to declare.

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