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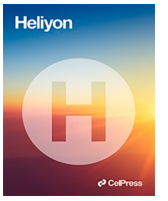

Predictive role of glycocalyx components and MMP-9 in cardiopulmonary bypass patients for ICU stay

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ABSTRACT

Background: Shedding of glycocalyx is relevant to worse prognosis in surgical patients, and elevated levels of serum matrix metalloproteinase-9 (MMP-9) are associated with this phenomenon. This study aimed to investigate the dynamic alterations of serum glycocalyx components and MMP-9 during cardiopulmonary bypass (CPB), and evaluate their predictive capacities for prolonged intensive care unit (ICU) stay, as well as their correlation with coagulation dysfunction.
Methods: This retrospective study analyzed serum levels of syndecan-1, heparan sulfate (HS), and MMP-9 at different time points during CPB, and assessed their association with prolonged ICU stay and coagulation dysfunction.
Results: Syndecan-1, HS, and MMP-9 exhibited divergent changes during CPB. Serum levels of syndecan-1 (AUC = 78.0 %) and MMP-9 (AUC = 78.4 %) were validated as reliable predictors for prolonged ICU stay, surpassing the predictive value of creatinine (AUC = 70.0 %). Syndecan-1 (rho = 0.566, $P < 0.01$ at T1 and rho = 0.526, $P < 0.01$ at T2) and HS (rho = 0.403, $P < 0.05$ at T4) exhibited correlations with activated partial thromboplastin time (APTT) ratio beyond the normal range.
Conclusions: Our findings advocate the potential efficacy of serum glycocalyx components and MMP-9 as early predictive indicators for extended ICU stay following cardiac surgery with CPB. Additionally, we observed a correlation between glycocalyx disruption during CPB and coagulation dysfunction. Further studies with expansive cohorts are warranted to consolidate our findings and explore the predictive potential of other glycocalyx components.

1. Introduction

Cardiopulmonary bypass (CPB) is indispensable for numerous cardiac surgeries, such as valve disease and coronary atherosclerotic cardiopathy [1]. Hemodynamic and respiratory monitoring and support in the intensive care unit (ICU) for a certain period, is a

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conventional post-CPB practice [2]. Patients undergoing cardiac surgery with CPB are susceptible to various pathological events, including microvascular dysfunction, capillary leak, and systemic inflammatory reaction [3]. These events may lead to adverse outcomes, such as coagulation dysfunction, thereby extending ICU stay [4]. Extended ICU stay is strongly associated with an unfavorable prognosis, including increased mortality and reduced survival rates [5]. Additionally, prolonged ICU stay can substantially escalate hospital costs for patients [6]. Therefore, it is crucial to identify early biomarkers for predicting extended ICU stay following CPB.

The glycocalyx, composed of glycoproteins, proteoglycans, and glycosaminoglycans [7], covers the luminal surface of vascular endothelial cells to regulate vascular permeability, signal transduction, immunity, and coagulation [8]. Its delicate nature renders it susceptible to disruption during CPB, precipitated by factors such as inflammation, ischemia, and hyperglycemia [9]. When the glycocalyx is damaged, its components, including syndecan-1 (a type of heparan sulfate proteoglycan), heparan sulfate (HS), and hyaluronic acid (HA), are released into the plasma, leading to increased serum levels [10]. Existing literature has corroborated the association of glycocalyx shedding with unfavorable prognosis [11,12]. For example, Huang et al. found that serum syndecan-1 levels correlated with systemic organ dysfunction in patients with influenza A (H1N1) [13], while Hatanaka et al. showed that serum syndecan-1 was relevant to organ failure in suspected sepsis patients [14]. Despite this, the comprehensive predictive values of different serum glycocalyx components during CPB for prolonged ICU stay and coagulation dysfunction have not been thoroughly investigated.

Matrix metalloproteinases (MMPs) comprise a family of zinc-containing proteolytic endopeptidases [15]. These enzymes play a pivotal role in the degradation of extracellular matrix (ECM) proteins, contributing to tissue remodeling [16]. MMP-9, a member of MMPs, is secreted by various cells, including vascular endothelial cells, smooth muscle cells, and microglial cells [17]. Its catalytic activity is directed towards gelatin [18]. MMP-9 participates in numerous pathophysiological processes, such as airway reconstruction and angiogenesis [19]. Notably, previous studies have demonstrated the capability of MMP-9 to damage the glycocalyx, particularly through the degradation of syndecan-1 [20]. Due to its multi-functionality, MMP-9 has been identified as a predictive marker for various diseases, such as osteosarcoma and ovarian cancer [21,22]. However, its predictive value for prolonged ICU stay after CPB remains unexplored.

Previous investigations have explored the alterations in these markers during CPB [23,24]. For instance, Bol et al. conducted a study assessing syndecan-1, HS, and HA at four time points: after anesthesia induction, after CPB initiation, after CPB cessation, and 2 h post-surgery [25]. These studies demonstrated an increase in serum levels of glycocalyx biomarkers and MMP-9 during CPB, with subsequent recovery after the operation [24,26]. However, the primary focus of these studies was on the changes in biomarker levels during CPB, rather than their predictive values at different time points during CPB for poor prognosis. Consequently, there is a distinct need for research endeavors that specifically investigate the predictive values of these markers during CPB, aiming to pinpoint a time point that robustly predicts prognosis and facilitates optimal treatment timing.

Here, we embarked on a retrospective study encompassing patients who underwent cardiac surgery with CPB at our institution. Our hypothesis centered on the potential of serum components of the glycocalyx and matrix metalloproteinase-9 (MMP-9) during CPB as predictive indicators for the length of ICU stay. Moreover, we postulated a correlation between serum glycocalyx components and coagulation dysfunction. The primary objectives were to investigate the dynamic changes in various glycocalyx components during CPB and to identify early biomarkers that could effectively predict prolonged ICU stay after CPB. Additionally, we sought to evaluate the association between glycocalyx biomarkers and coagulation dysfunction.

2. Methods

2.1. Study design

This single-center, retrospective study encompassed 70 patients at the First Affiliated Hospital of Wenzhou Medical University between June 2018 and August 2019. Ethical approval for the study was obtained from the institutional ethical committee of the First Affiliated Hospital of Wenzhou Medical University (approval no. KY2022-R149) on September 29, 2022. This study was registered on chictr.org.cn (ChiCTR2200066155).

2.2. Patients

Inclusion criteria for the study were: (1) individuals aged 18–80 years without gender preference; (2) ASA grade II-IV; (3) patients undergoing cardiac surgery with CPB. Exclusion criteria included: (1) patients with significantly abnormal blood biochemical indices before surgery; (2) preoperative use of immunomodulators, hormones, or other anti-systemic inflammatory drugs.

2.3. Data collection

Biochemistry and coagulation data, along with the length of ICU stay, and other patient demographics were retrieved from the hospital's electronic medical records. Data of serum HS, syndecan-1, and MMP-9 were obtained from our team's database, with all patients providing informed consent before blood collection. Postoperative biochemistry and coagulation data were collected 24 h post-operation. Serum HS, syndecan-1, and MMP-9 data were collected at the following time points: before anesthesia induction (T0), after aortic opening (T1), at the time of closing the breastbone (T2), 1-h post-operation (T3), and 24 h post-operation (T4). The reported statistics were presented as ratios relative to the values at T0.

2.4. Statistical analyses

Statistical analyses were conducted using SPSS version 26 (IBM Inc., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages, non-normally distributed continuous variables as medians and inter-quartile range, and normally distributed continuous variables as mean and standard deviation. Differences in demography, biochemistry markers, coagulation function, syndecan-1, HS, and MMP-9 between the two groups, divided by the length of ICU stay, were analyzed by Independent-Sample *t*-test for normally distributed continuous variables, or Mann-Whitney *U* test for non-normally distributed continuous variables and categorical variables. The predictive performance of different glycocalyx biomarkers for the length of ICU stay was assessed through a receiver-operating characteristics (ROC) curve, providing area under the curve (AUC), sensitivity, and specificity. The association between different glycocalyx biomarkers and coagulation dysfunction was assessed by Pearson's correlation for normally distributed continuous variables or Spearman's rank correlation for non-normally distributed continuous variables. P-value <0.05 was considered statistically significant.

Table 1
Characteristics of patients with different length of ICU stay (<72 h and ≥72 h).

Characteristics	Total (N = 70)	Length of ICU stay		*p-value*
		<72 h (N = 13)	≥72 h (N = 57)	
Age (years)	57 (11)	54 (13)	60 (51–66)	0.232[b]
Gender				0.972[b]
Female	32 (45.7 %)	6 (46.2 %)	26 (45.6 %)	
Male	38 (54.3 %)	7 (53.8 %)	31 (54.4 %)	
BMI (kg/cm^2)	23.0 (3.0)	23.5 (2.9)	22.9 (3.0)	0.571[a]
ASA status				0.142[b]
II	15 (21.4 %)	2 (15.4 %)	13 (22.8 %)	
III	45 (64.3 %)	7 (53.8 %)	38 (66.7 %)	
IV	10 (14.3 %)	4 (30.8 %)	6 (10.5 %)	
Type of surgery				0.128[b]
CABG	9 (12.9 %)	0 (0 %)	9 (15.8 %)	
Valve replacement	61 (87.1 %)	13 (100 %)	48 (84.2 %)	
Preoperative biochemistry				
Creatinine (umol/l)	71.5 (61.0–83.0)	65.3 (11.4)	74.0 (15.4)	0.062[a]
ALT (U/L)	21.0 (13.0–32.5)	23.0 (17.0–41.5)	21.0 (13.0–31.5)	0.423[b]
AST (U/L)	25.0 (19.8–33.5)	29.7 (11.0)	24.0 (20.0–31.0)	0.487[b]
Albumin (g/L)	38.9 (4.0)	38.4 (5.3)	39.0 (3.6)	0.731[a]
Aortic occlusion time (min)	115.4 (33.1)	105.9 (24.3)	117.6 (34.6)	0.255[a]
CPB time (min)	152.32 (36.52)	144.54 (32.32)	154.12 (37.46)	0.398[a]
Intraoperative transfusion				0.622[b]
Yes	8 (11.4 %)	2 (15.4 %)	6 (10.5 %)	
No	62 (88.6 %)	11 (84.6 %)	51 (89.5 %)	
Mechanical ventilation time (h)	15.0 (13.8–20.0)	16.1 (8.0)	15.0 (14.0–20.0)	0.958[b]
Length of ICU stay (day)	4.9 (1.9)	2.8 (1.8–2.9)	5.8 (4.0–6.0)	0.000[b]
Postoperative coagulation				
Plt (10^9/L)	118 (100–154)	137 (41)	116 (99–154)	0.446[b]
FIB (g/L)	3.2 (2.7–3.9)	3.3 (3.0–3.8)	3.1 (2.6–3.9)	0.290[b]
APTT ratio	1.2 (1.1–1.3)	1.3 (0.2)	1.2 (1.1–1.3)	0.071[b]
PT (s)	16.2 (15.4–17.1)	16.3 (1.2)	16.2 (15.4–17.2)	0.874[b]
INR	1.3 (1.2–1.4)	1.3 (0.1)	1.3 (1.2–1.4)	0.797[b]
Postoperative biochemistry				
Creatinine (umol/l)	80.5 (65.0–102.5)	71.5 (14.2)	84.0 (65.5–108.5)	0.025[b]
ALT (U/L)	20.0 (14.8–35.5)	19.0 (11.0–37.5)	21.0 (15.0–35.0)	0.287[b]
AST (U/L)	67.0 (48.8–95.3)	76.0 (61.0–80.5)	65.0 (47.5–96.0)	0.672[b]
Albumin (g/L)	29.7 (3.2)	28.4 (27.3–35.9)	29.4 (2.9)	0.452[b]
lactate	2.3 (1.9–3.0)	2.3 (0.7)	2.3 (1.9–3.1)	0.515[b]
TnI	5.2 (2.6–10.4)	6.0 (2.9–20.7)	4.9 (2.1–10.4)	0.345[b]
SOFA score	5 (4–6)	4 (3–6)	5 (4–6)	0.217[b]

Data are presented as mean (standard deviation) for normally distributed continuous variables, medians (IQR) for non-normally distributed continuous variables, or n (%) for categorical variables.
Abbreviations: BMI, Body Mass Index; ASA: American Society of Anesthesiologists; CABG: Coronary artery bypass grafting; ALT: alanine transaminase; AST: glutamic oxalacetic transaminase; CPB: cardiopulmonary bypass; Plt: platelet; FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time: INR: international normalized ratio; TnI: Troponin I; SOFA: Sequential organ failure assessment. a: the difference between the two groups was analyzed by Independent-Sample *t*-test; b: the difference between the two groups was analyzed by the Mann-Whitney *U* test.

3. Results

3.1. Characteristics of patients

We enrolled 70 patients who underwent cardiac surgery with CPB in our study. Table 1 displayed the basic characteristics of the patients. This study consisted of 32 females (45.7 %) and 38 males (54.3 %), with an average age of 57 years. Previous references have established a strong association between prolonged ICU stay (larger than 72 h) and heightened severity of illness, as well as increased hospital mortality [27,28]. Therefore, we divided the patients into two groups: length of ICU stay <72 h group and length of ICU stay ≥72 h group. No significant differences were observed between the groups regarding preoperative biochemistry and postoperative coagulation. However, postoperative creatinine level, a recognized predictor for the length of ICU stay [28,29], exhibited a significant difference between the two groups ($P < 0.05$).

3.2. Dynamics of serum glycocalyx component levels at different time points during CPB

To investigate the variations in different glycocalyx components during CPB, we analyzed the serum syndecan-1 and HS concentrations at different time points during CPB, as depicted in Fig. 1a and b, respectively. Both syndecan-1 and HS levels showed an increase after aortic opening (T1). Syndecan-1 levels continued to rise until the breastbone was closed (T2) and slightly decreased 1 h after the operation (T3). Twenty-four hours after surgery (T4), syndecan-1 levels (median= 1.385) significantly decreased but remained higher than T0 (median= 1.0). Conversely, HS serum concentrations remained relatively stable from T1 to T3 before significantly decreasing at T4, with the median level at T4 (median=1.014) nearly equal to T0 (median= 1.0). These findings suggest that glycocalyx disruption occurs during CPB, and different glycocalyx components exhibit distinct variations during the process.

3.3. Predictive value of serum glycocalyx components for the length of ICU stay

Employing the length of ICU stay as an indicator of postoperative patient severity [30], our study examined the correlation between serum glycocalyx component levels and patient outcomes after CPB surgery. The Mann-Whitney *U* test revealed significant difference between the groups for syndecan-1 at T4 ($P < 0.05$) (Fig. 2a). While no significant difference was observed between the groups for HS at any time point (Fig. 2b). Notably, there was no observed association between syndecan-1, HS and intra-operative events (Table 2). In the ROC analysis for the prediction of the length of ICU stay after surgery with CPB, the AUC was 78.0 % for serum syndecan-1 at T4, surpassing the predictive value of postoperative creatine, which was 70.0 % (Table 3 and Fig. 2c). Additionally, syndecan-1 demonstrated an optimum specificity of 84.6 % and an optimum sensitivity of 75.4 %, outperforming postoperative creatinine with a specificity of 76.9 % and sensitivity of 63.2 %. These results indicated that syndecan-1 hold promise as a novel predictor for the length of ICU stay, outperforming the known marker.

3.4. Association between MMP-9 and glycocalyx components

In our study, we identified no significant correlations between HS and MMP-9 at the same time points (Fig. 3a). However, MMP-9 at T2 demonstrated a significant correlation with syndecan-1 at T2 (rho = 0.633, $P < 0.01$) (Fig. 3b and c). MMP-9 at T3 exhibited significant correlations with syndecan-1 at T3 (rho = 0.348, $P < 0.01$) (Fig. 3b and d). These findings underscored the close association between glycocalyx disruption during CPB and MMP-9.

3.5. Predictive value of serum MMP-9 for the length of ICU stay

Having established the correlation between MMP-9 and glycocalyx, we posited that an increase in serum MMP-9 level might be associated with prolonged ICU stay. Initially, we investigated the changes in MMP-9 during CPB. MMP-9 levels increased from T1 to T3

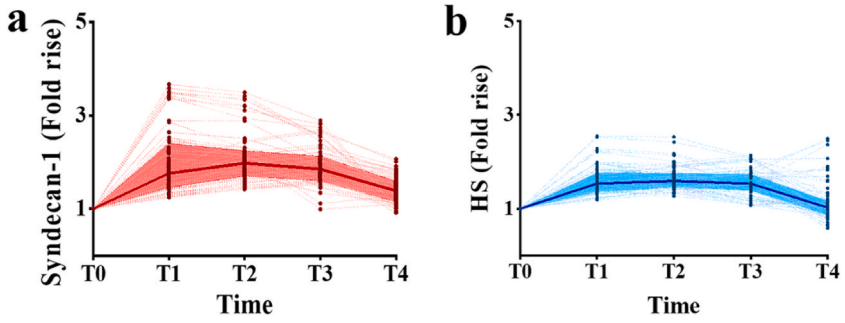

Fig. 1. Fold rise of serum syndecan-1 (a), HS (b) compared to T0 at different time points during CPB. The bold lines indicate the median values and the filled-in areas indicate interquartile ranges.

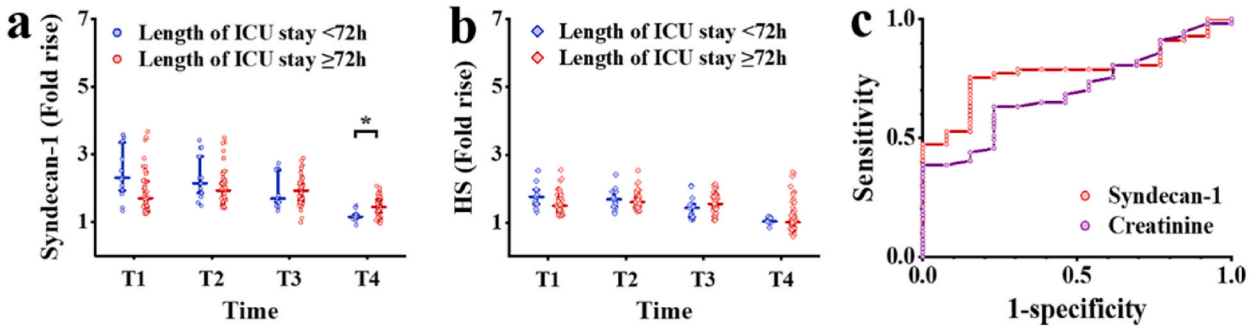

Fig. 2. Circulating biomarkers of glycocalyx can predict the length of ICU stay. (a) Serum syndecan-1 level in the length of ICU stay <72 h and ≥72 h group. (b) Serum HS level in the length of ICU stay <72 h and ≥72 h group. The lines indicate the medians and interquartile ranges in a and b. *P < 0.05. (c) Receiver-operating characteristics (ROC) curves for predicting the length of ICU stay are shown concerning the following variables: syndecan-1 on T4, and postoperative creatine.

Table 2
Correlation between glycocalyx components, MMP-9 and intra-operative events.

	Aortic occlusion time		CPB time	
	CC	*p-value*	CC	*p-value*
Syndecan-1 T1	−0.160[b]	0.186	0.030[b]	0.809
Syndecan-1 T2	−0.163[b]	0.178	0.024[b]	0.846
Syndecan-1 T3	−0.019[a]	0.878	0.012[a]	0.924
Syndecan-1 T4	0.117[b]	0.336	−0.074[b]	0.544
HS T1	−0.095[b]	0.433	−0.047[b]	0.699
HS T2	−0.014[b]	0.909	−0.024[b]	0.842
HS T3	−0.007[a]	0.956	−0.145[a]	0.236
HS T4	0.152[b]	0.209	0.058[b]	0.636
MMP-9 T1	0.132[b]	0.276	−0.014[b]	0.909
MMP-9 T2	−0.083[b]	0.495	0.109[b]	0.371
MMP-9 T3	−0.085[b]	0.486	0.097[b]	0.430
MMP-9 T4	−0.120[b]	0.321	0.073[b]	0.550

Abbreviations: CPB: cardiopulmonary bypass; CC: correlation coefficient; HS: heparan sulfate; MMP: matrix metalloproteinase. a: the Pearson correlation coefficient; b: the Spearman correlation coefficient.

Table 3
The predictive ability of glycocalyx biomarker and MMP-9 for the length of ICU stay.

	Syndecan-1	MMP-9	Creatinine
Sensitivity	75.4 %	68.4 %	63.2 %
Specificity	84.6 %	84.6 %	76.9 %
AUC	78.0 %	78.4 %	70.0 %

and slightly decreased at T4. However, the median level at T4 (median= 2.011) remained higher than T0 (median= 1.0) (Fig. 4a). Subsequently, a significant difference between the two groups for MMP-9 at T1 ($P < 0.01$) was identified (Fig. 4b), with no observed correlation between MMP-9 and intra-operative events (Table 2). In the ROC analysis predicting the length of ICU stay after CPB surgery, the AUC was 78.4 % for serum MMP-9 at T1 (Table 3 and Fig. 4c). Additionally, MMP-9 demonstrated an optimal specificity of 84.6 % and an optimal sensitivity of 68.4 %. These results indicated that MMP-9 also holds potential as a novel predictor for prolonged ICU stay, outperforming the known marker.

3.6. Serum glycocalyx components are associated with coagulation disorders

To investigate the correlation between glycocalyx components and coagulation disorders, we categorized each coagulation factor into two groups: the normal group and the outside the normal range group (Table 4). Subsequently, we analyzed the correlation between glycocalyx components and coagulation factors in the group outside the normal range. Significant correlations were identified between the APTT ratio outside the normal range and syndecan-1 at T1 (rho = 0.566, $P < 0.01$) and T2 (rho = 0.526, $P < 0.01$) (Fig. 5a and b). Additionally, the APTT ratio outside the normal range showed a significant correlation with HS at T4 (rho = 0.403, $P < 0.05$) (Fig. 5c and d). These findings demonstrated that glycocalyx disruption during CPB was closely associated with postoperative coagulation disorders.

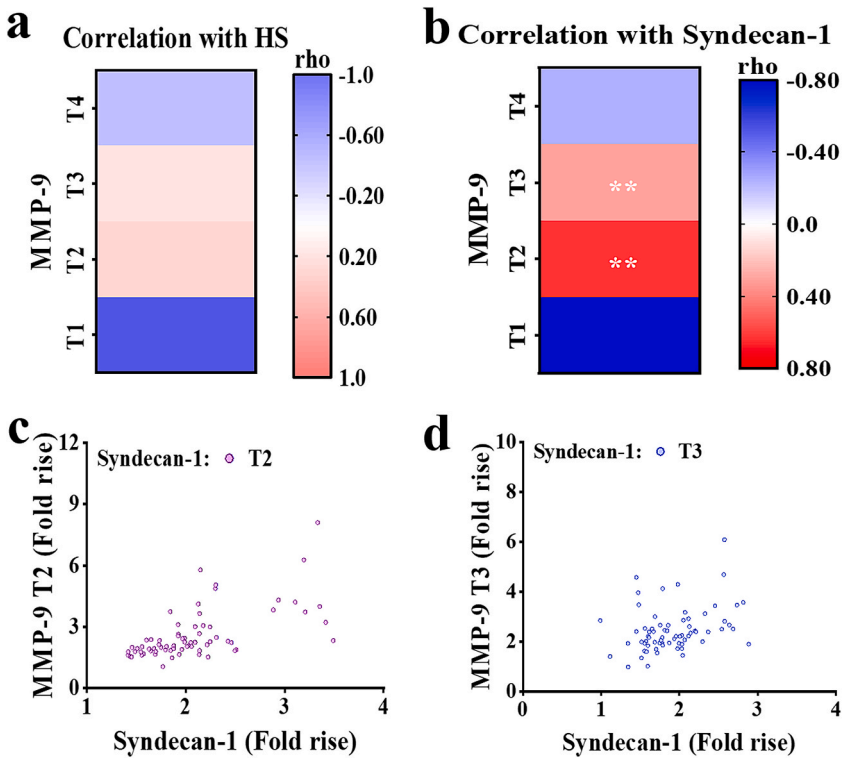

Fig. 3. Correlation between serum glycocalyx components and MMP-9 at different time points during CPB. (a) Correlation between serum HS and MMP-9 at the same time points. (b), (c), (d) Correlation between serum syndecan-1 and MMP-9 at the same time points. The intensities of the correlation are color-coded according to Spearman's rho values in (a) and (b). **P < 0.01.

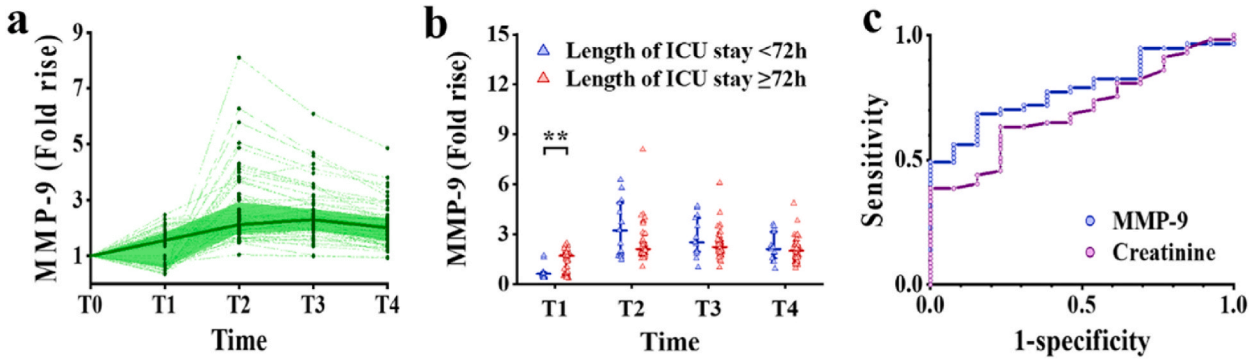

Fig. 4. Predictive value of serum MMP-9 for the length of ICU stay. (a) Fold rise of serum MMP-9 compared to T0 at different time points. The bold lines indicate the median values and the filled-in areas indicate interquartile ranges. (b) Serum MMP-9 level in the length of ICU stay <72 h and ≥72 h group. The lines indicate the medians and interquartile ranges. **P < 0.01. (c) Receiver-operating characteristics (ROC) curves for predicting the length of ICU stay are shown concerning the following variables: MMP-9 on T1, and postoperative creatine.

4. Discussion

In this study, our primary objectives were to investigate the dynamic changes in serum components of glycocalyx during CPB, assess the potential of serum levels of glycocalyx components and MMP-9 as early predictors for prolonged ICU stay, and evaluate the relationship between glycocalyx components and coagulation dysfunction. Our observations revealed distinct dynamic changes in syndecan-1, HS, and MMP-9 during CPB. Additionally, significant differences in the levels of syndecan-1 and MMP-9 were observed between the two groups, categorized based on the length of ICU stay. Furthermore, we demonstrated that both syndecan-1 and MMP-9 served as reliable predictors for prolonged ICU stay, surpassing the predictive value of the established marker, postoperative creatinine. Besides, we found an association between glycocalyx shedding during CPB and postoperative coagulation dysfunction. Our results suggest that early prevention of glycocalyx disruption during CPB could potentially reduce the length of ICU stay and mitigate

Table 4
Characteristics of coagulation factors.

	Normal		Outside the normal range	
	N	Range	N	Medians (IQR)
Plt	32	125–350	38	−24.50 (−39.00–12.75)
PT	5	11.7–14.8	65	1.50 (0.75–2.40)
INR	4	0.85–1.15	66	0.16 (0.08–0.25)
FIB	57	2.0–4.0	13	0.56 (0.12–1.62)
APTT ratio	32	0.8–1.2	38	0.12 (0.06–0.19)

Abbreviations: Plt: platelet; PT: prothrombin time; INR: international normalized ratio; FIB: fibrinogen; APTT: activated partial thromboplastin time.

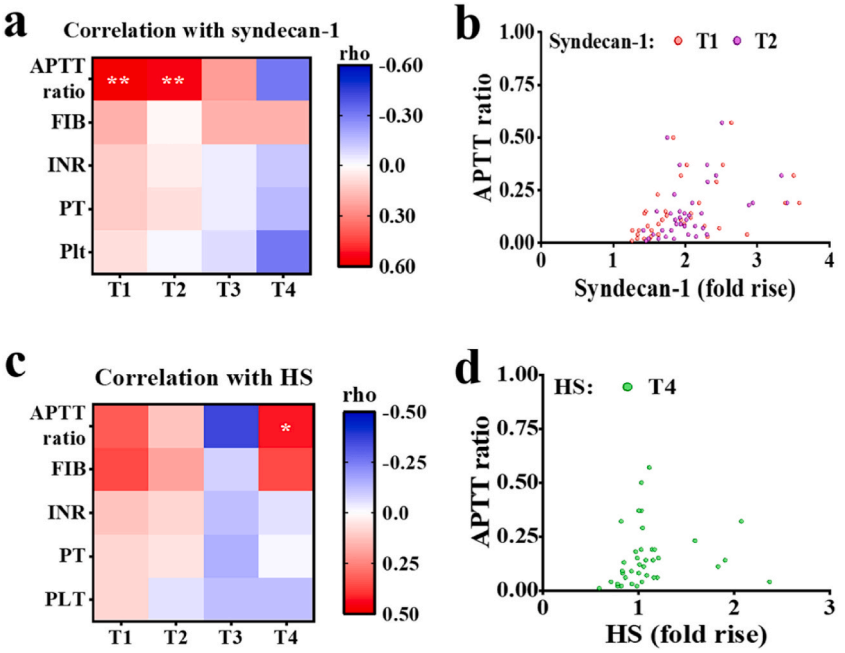

Fig. 5. Serum glycocalyx components are associated with coagulation disorders. (a)、(b) Relationships between serum syndecan-1 at different time points and coagulation function markers outside the normal range. (c)、(d) Relationships between serum HS at different time points and coagulation function markers outside the normal range. The intensities of the correlation are color-coded according to Spearman's rho values in (a) and (c). Plt: platelet; FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time: INR: international normalized ratio. *P < 0.05. **P < 0.01.

postoperative coagulation disorders. Therefore, our study proposes a novel early therapeutic target during CPB to enhance patient outcomes. To our knowledge, this is the first study to investigate the predictive values of serum glycocalyx components and MMP-9 at different time points during CPB, introducing new early predictive markers for the length of ICU stay.

Cardiopulmonary bypass (CPB) is an essential intervention for various cardiac diseases, but it triggers a series of pathological responses, including microvascular dysfunction, capillary leak, and systemic inflammatory reactions [3]. These pathological events are thought to be attributed to glycocalyx disruption [1]. Serum glycocalyx components serve as indicators to evaluate glycocalyx damage [31]. In our study, we observed that glycocalyx shedding from the surface of vascular endothelium resulted in increased serum levels of glycocalyx components (syndecan-1 and HS) during CPB. Ischemia-reperfusion, a recognized factor causing glycocalyx damage during CPB [32], aligns with our findings that both serum syndecan-1 and HS significantly increased after aortic opening (T1).

Increased glycocalyx disruption has been consistently associated with a poor prognosis [12,33]. Binding with plasma constituents, glycocalyx establishes a compact endothelial surface layer that serves as an interface between blood and endothelium [34]. The small protein-free zone beneath the glycocalyx is instrumental in constructing the oncotic pressure difference, a parameter closely linked to fluid homeostasis [35]. Consequently, disruption of the glycocalyx enhances vessel permeability, leading to interstitial edema in multiple organs, and contributing to further pathological deterioration [36]. Moreover, serum glycocalyx components can activate dendritic cells, stimulate the secretion of pro-inflammatory cytokines, and ultimately precipitate inflammatory reactions and even inflammatory disorders [37]. In addition, glycocalyx damage can decrease microvascular perfusion, contributing to microvascular dysfunction [38]. Microvascular perfusion is crucial for safeguarding the normal function of essential organs, and microvascular dysfunction during CPB is strongly correlated with postoperative tissue edema and organ dysfunction [39]. Any of these events-tissue

edema, inflammatory disorders, and organ dysfunction can contribute to a poor prognosis. Our study demonstrated that syndecan-1 can serve as a robust predictor for unsatisfactory prognosis, such as prolonged ICU stay, exhibiting superior predictive value compared to postoperative creatinine, a recognized marker for prolonged ICU stay.

MMP-9 plays a crucial role in degrading ECM proteins and participates in various pathological processes [16]. For example, Dobra et al. demonstrated that MMP-9 was positively correlated with aggressiveness, making it a potential prognostic marker for brain tumors [40]. Jia et al. showed that MMP-9 was positively relevant to aortic diameter and pseudolumen area, and independently correlated with mortality in patients with acute aortic dissection [41]. In our study, we noted a significant difference in the levels of MMP-9 between the two groups stratified by the length of ICU stay. We identified MMP-9 as a valuable prognostic marker for predicting the length of ICU stay. Previous studies showed that MMP-9 mediated the shedding of the glycocalyx, especially syndecan-1 [20]. Our result aligned with them that serum MMP-9 at T2 was associated with syndecan-1 at T2, and MMP-9 at T3 was associated with syndecan-1 at T3.

As a lining on the luminal surface of vascular endothelial cells, disruption of glycocalyx is implicated in the development of coagulation disorders [42]. Disruption of glycocalyx can damage the vascular barrier function, and increase the exposure of underlying adhesive proteins, thus enhancing the adhesion of platelets and leukocytes in the circulatory system [43,44]. Additionally, certain proteins that participate in the regulation of hemostasis have binding sites for HS, such as ATIII. After the shedding of the glycocalyx, the interactions between HS and these proteins are disrupted, leading to pro-coagulant conditions [45]. In our study, we observed that the elevation in serum levels of syndecan-1 and HS was associated with coagulation disorders. This aligned with previous studies indicating that increased syndecan-1 levels were relevant to persistent thrombocytopenia and disseminated intravascular coagulation scores in patients with suspected sepsis [46]. However, syndecan-1 was associated with the APTT ratio outside the normal range at T1 and T2, while HS was only associated with APTT outside the normal range at T4. This discrepancy may be attributed to our small sample size. Besides, some studies have suggested a connection between glycocalyx disruption and PT and platelet count in septic patients [47]. In our study, we did not observe a significant correlation between glycocalyx biomarkers and PT or platelet count, possibly due to hemodilution and blood loss during CPB. The presence of residual heparin during CPB may also contribute to the lack of a significant correlation between glycocalyx disruption and PT.

This study still has several limitations. Firstly, this retrospective study cannot fully control irrelevant variables. Secondly, the limited sample size in this single-center study cannot support multivariate analysis. Thirdly, data collection in this study was restricted to the first-day post-operation, thus failing to capture long-term outcomes for patients. Finally, this study focused on only two components of the glycocalyx, while other components like hyaluronic acid and chondroitin sulfate are also integral to glycocalyx. Hence, further observational studies with larger patient populations are warranted to comprehensively explore the predictive value of various glycocalyx components for patients undergoing cardiac surgery with CPB.

5. Conclusions

In our study, we observed distinct alterations in various glycocalyx components during CPB. Serum glycocalyx components and MMP-9 emerged as potential predictive markers for the length of ICU stay in patients who experience cardiac surgery with CPB. And the predictive capacities of syndecan-1 and MMP-9 surpassed those of the established marker-creatine, for predicting the length of ICU stay. Furthermore, our findings indicated a correlation between glycocalyx disruption during cardiac surgery with CPB and the occurrence of coagulation disorders.

Ethics statement

This study was reviewed and approved by the institutional ethical committee of the First Affiliated Hospital of Wenzhou Medical University, with the approval number: [KY2022-R149]. Data of serum HS, syndecan-1, and MMP-9 was obtained from our team's database, and all patients provided informed consent before blood collection.

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Data availability statement

Data associated with this study has not been deposited into a publicly available repository. And data of this study will be made available on request.

CRediT authorship contribution statement

Lina Lin: Writing - review & editing, Writing - original draft, Investigation, Formal analysis, Data curation. **Mengying Niu:** Investigation, Formal analysis. **Wei Gao:** Resources, Formal analysis, Data curation, Conceptualization. **Chundong Wang:** Resources, Data curation. **Qiaolin Wu:** Software, Data curation. **Fuquan Fang:** Resources, Data curation. **Yongan Wang:** Resources, Data curation. **Weijian Wang:** Writing - review & editing, Writing - original draft, Resources, Methodology, Formal analysis, Data curation,

Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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