The Egyptian Journal of Bronchology

RESEARCH Open Access

The diagnostic role of C2PAC index in cases of sepsis-induced coagulopathy (SIC)

Mohamed Shaaban Mousa[1*], Salwa Hassan Ahmed[2], Fatma Abdel Wahab Abdel Maksoud[3], Soliman Belal Soliman[4] and Ahmed A. Tantawy[1]

Abstract

Background To study the potential role of the C2PAC index (a ratio of soluble type C lectin-like receptor 2 level sCLEC-2 and platelet count) in sepsis-induced coagulopathy with the possibility of using this index as an early predictor in sepsis and sepsis-induced coagulopathy.

Methods Our case–control study included a total of 86 participants divided into 2 groups: group I is the case group consisting of 56 patients of sepsis or septic shock and group II (control group) of 30 healthy persons: sex and age-matched healthy individuals. All patients were subjected to assessment of C lectin domain family 2 receptor (sCLEC2), by enzyme-linked immunosorbent assay ELIZA kit, then C2PAC index (a ratio of soluble type C lectin-like receptor 2 level sCLEC-2 and platelet count) was calculated using the platelet count.

Results Our study demonstrated that sCLEC-2 levels and C2PAC in group I were higher than in group II (p value < 0.001), and Klebsiella was the most common organism detected in ICU septic patients; detected in 25 patients (44.6%), there is a statistical significance (p value 0.045) between sCLEC2 levels and streptococcal infections. It was detected also that the SIC group was 17 patients (30.4%) and the sepsis without coagulopathy group was 39 patients (69.6%). Compared with the sepsis without coagulopathy group, the SIC group was significantly older and had a significantly higher SOFA score, sCLEC-2 levels, and C2PAC index. Lastly, the strong potentiality of using C2PAC as a diagnostic and prognostic marker for sepsis-induced coagulopathy with high statistical significance < 0.001.

Conclusions C2PAC index can be validated as an accurate marker of sepsis-induced coagulopathy with higher sensitivity when using the C2PAC index (82.4%) than using sCLEC-2 (58.8%) and both have the same specificity (89.7%). The C2PAC index is a useful predictor of SIC progression.

Keywords C lectin, Coagulopathy, C2PAC index, DIC, sCLEC-2, SIC

Introduction

Sepsis is potentiated by a dysregulated and abnormal reaction of the host to infection, leading to multiple organ damage with a high possibility of irreversible disabilities or maybe death. During sepsis, tissue injury results from the associated unlimited activation and interaction of the complement, coagulation, and inflammatory mediators as well as platelet dysfunction [1].

Platelets are the maestro in sepsis cascade by their dual responses (hemostasis and immune), what is called a "thrombosis-related signature and occurs as a

*Correspondence:
Mohamed Shaaban Mousa
Mohamed_shaaban190@yahoo.com
[1] Department of Pulmonary Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt
[2] Department of Internal Medicine and Clinical Hematology, Faculty of Medicine, Cairo University, Cairo, Egypt
[3] Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt
[4] Department of Critical Care Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

result of the interaction of neutrophils, monocytes, and dendritic cells, with the consequence of fibrin deposition and platelet activation and finally thrombosis [2].

The literature review detected a phenomenon named "immuno-thrombosis." This has been hypothesized that under certain circumstances, thrombosis is a defensive process of innate immunity in which platelets play a vital role. Therefore, to correlate the severity of sepsis, it may be crucial to detect the status of platelet activation rather than monitoring the changes in the platelet count [3]. Soluble C-type lectin-like receptor 2 (sCLEC-2) also known as CLEC1B has been investigated as a biomarker of thrombotic events and it is expressed on platelets' membranes [4]. Recent research demonstrated the elevation of sCLEC-2 in acute coronary syndrome, acute ischemic stroke, and acute brain infarction [5–8].

Disseminated intravascular coagulation (DIC) is a condition of persistent activation of coagulation with subsequent depletion of platelets and coagulation factors [9]. The incidence of coagulopathy in sepsis is around 30% [10]; hence, there is a term called sepsis-induced coagulopathy (SIC) [11]. sCLEC-2 was observed as a platelet activator marker and to be elevated in thrombotic events and in SIC [2].

The philosophy of using the C2PAC index is that it may be more reliable and accurate than calculating sCLEC-2 levels alone which will be affected by decreased platelet counts in many conditions like sepsis and DIC [2].

We hypothesized that the C2PAC index is an important predictor that might reflect early progression to SIC as it reflects the phase of platelets activation before the reduction of platelet count and development of coagulopathy so we conducted this case–control study to evaluate the role of the C2PAC index (a ratio of soluble type C lectin-like receptor 2 level sCLEC-2 and platelet count) in sepsis-induced coagulopathy (SIC).

Patients and methods

The current study included a total of 86 participants divided into 2 groups. This case–control study was divided into two groups.

Group I: 56 patients (presented with sepsis or septic shock).

Group II: 30 control groups of healthy volunteers matched for age and sex.

Study location

This case–control study was carried out in intensive care units of pulmonology, critical care, and internal medicine departments of Kasr Al Ainy University Hospital.

Inclusion criteria

1. Adult patients with age more than 18 years.
2. Both sexes (male and female).
3. Diagnosed with sepsis by sepsis-3 criteria, 2016 [12], and updated by sepsis guidelines protocol, 2021, regarding changes of some definitions and criteria for sepsis such as weak recommendation for using serum lactate and delayed capillary refill time and strong recommendation against using quick SOFA score [13], so in our study, we did not depend on serum lactate and capillary refill time and we used SOFA score instead of quick SOFA.

Diagnosis of sepsis can be established after the presence of infection, which can be proven or suspected, and 2 or more of the following criteria:

- Hypotension (systolic blood pressure < 90 mm Hg or fallen by > 40 from baseline, mean arterial pressure < 70 mm Hg).
- Fever > 38.3 °C.
- Hypothermia < 36 °C.
- Tachycardia (HR > 90/min).
- Tachypnea.
- Altered mental status.
- White blood cell count > 12,000 or less than 4000, or with > 10% "bands" (immature forms).
- Arterial hypoxemia ($paO_2/FiO_2 < 300$).
- Acute drop in urine output (< 0.5 ml/kg/h for at least 2 h despite fluid resuscitation or about 35 ml/h for a 70 kg person).
- Creatinine increase > 0.5 mg/dL.
- INR > 1.5 or aPTT > 60 s.
- Thrombocytopenia (platelet count < 100,000).
- High bilirubin (total bilirubin > 4 mg/dL).

Septic shock is severe sepsis with sepsis-induced hypotension [systolic blood pressure < 90 mm Hg (or a drop of > 40 mm Hg from baseline) or mean arterial pressure < 70 mm Hg] that persists after adequate fluid resuscitation.

Exclusion criteria

1. Post-cardiopulmonary arrest, liver cirrhosis (Child–Pugh grade C or above), chronic hemodialysis, pregnancy, and continuing antibiotic use for a course started before admission.
2. Patients who lacked any of the biomarkers of coagulation and inflammation.

Methodology in details

This is a case–control study. Patients who met the above-mentioned criteria and agreed to take part in the study were requested to sign an informed consent prior to conducting the study. After an informed consent had been signed by all patients, the following parameters were collected:

1. Demographic data: age, gender, and occupation.
2. History and physical examination parameters: history of chronic diseases and history of present illness
3. Laboratory investigations:

- Routine labs for sepsis and coagulopathy screening

Platelet count, WBCs, PT, PC, INR, PTT, D-dimer level, FDPs, CRP, ABG, liver, and kidney functions.

- Calculation of P/F ratio from ABG (PaO_2/FIO_2).
- Calculation of SOFA score
- Cultures according to localizing symptoms
- Specific test: plasma CLEC-2 (C-type lectin-like receptor 2) also named CLEC1B as a synonym will be measured using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer (Bioassay Technology Laboratory, Zhejiang, China), using STAT-FAX Eliza reader, results are converted to pg/ml.
- Calculation of the ratio between soluble type C lectin-like receptor 2 (sCLEC-2) levels and platelet counts for all participants to identify the C2PAC index.

Furthermore, written informed consent was obtained from all participants clarifying the purpose of the study conforming to the Helsinki Declarations (1964).

Our study had been approved by the committee of ethics of the Faculty of Medicine before we started under IRB number: N-37–2022.

Sample size

According to previous literature, the anticipated mean of the C2PAC index in controls is 87.2 (± 38.9), while in cases is 286 (± 205). By using the G*Power sample size calculator at 0.01 alpha errors, with and power of 0.99, the effect size will be 1.35, and the minimum sample in each group is 29 [2].

Statistical analysis

Data were coded and interpreted by the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, and minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test [14]. For comparing categorical data, chi-square (χ^2) test was performed. Fisher's exact test was used instead when the expected frequency is less than 5 [15]. Correlations between quantitative variables were done using the Spearman correlation coefficient [16]. ROC curve was constructed with the area under curve analysis performed to detect the best cutoff value of PLT, C lectin level, and C lectin/plt ratio for detection of SIC. *P* values less than 0.05 were considered as statistically significant.

Results

Our study included a total of (86) participants classified into 2 groups; Group I of 56 patients diagnosed with sepsis or septic shock and group II of 30 age- and sex-matched healthy individuals. As regards group I, it consisted of 31 males (55.4%) and 25 females (44.6%). Twenty-five cases (44.6%) were diabetic, and 27 cases (48.2%) were hypertensive. Smoking history was observed in 15 cases (26.8%). In the current study, pneumonia in 31 patients (55.4%) was the commonest diagnosis followed by urinary tract infection (UTI) in 16 patients (28.6%). Klebsiella 25 patients (44.6%) was the commonest organism detected in this study. In our study, patients who were diagnosed with sepsis were 40 (71.4%) while those who were diagnosed with septic shock were 16 (28.6%). All the descriptive data is illustrated in Table 1.

The age of sepsis patients ranged from 18 to 89 years with a mean of 59.6 ± 16.2. It was detected that platelet counts were 188.93 ± 128.36, sCLEC-2 level was 607.41 ± 457.37, and C2PAC index was 6.06 ± 7.06. All clinical and laboratory data of group I was illustrated in Table 2.

In the current study, a comparison between group I and group II showed that the sCLEC-2 level and C2PAC index were statistically significant (p value < 0.001) higher in group I (sepsis patients) as shown in Table 3.

In our study, we correlated C lectin level (sCLEC-2) with clinical data including comorbidities, and it showed a statistical significance of C lectin level value as regards altered mental status, septic shock, patients on vasopressors, patients with positive FDPs, and in streptococcal infections with p values < 0.001, 0.002, 0.006, 0.001, and 0.045, respectively; however, no statistical changes in relation with other cultures, different comorbidities, and various diagnoses as shown in Table 4.

Our research correlated C lectin/platelet ratio (C2PAC index) with clinical data and showed the highly statistical significance of the C2PAC index with p value < 0.001 in correlation to patients with altered mental status, septic shock, on vasopressors, and positive FDPs; however,

Table 1 Descriptive data of cases group (group I)

		Cases	
		Count	%
Sex	**M**	31	55.4%
	F	25	44.6%
Smoking history	**Yes**	15	26.8%
	No	41	73.2%
DM	**Yes**	25	44.6%
	No	31	55.4%
HTN	**Yes**	27	48.2%
	No	29	51.8%
Cardiac diseases	**Yes**	22	39.3%
	No	34	60.7%
Renal impairment	**Yes**	13	23.2%
	No	43	76.8%
Cancer	**Yes**	3	5.4%
	No	53	94.6%
Cerebrovascular accidents	**Yes**	7	12.5%
	No	49	87.5%
Mental state	**Conscious**	39	69.6%
	Altered	17	30.4%
Sepsis versus septic shock	**Sepsis**	40	71.4%
	septic shock	16	28.6%
Vasopressor	**Yes**	17	30.4%
	No	39	69.6%
FDPs	**Positive**	15	26.8%
	Negative	41	73.2%
Site of infection	**Wound infection, UTI**	1	1.8%
	Wound infection	7	12.5%
	UTI, pneumonia	5	8.9%
	UTI	10	17.9%
	Puerperal sepsis	1	1.8%
	Pneumonia, wound infection	3	5.4%
	Pneumonia	23	41.1%
	Infective endocarditis	2	3.6%
	Empyema	4	7.1%
Pneumonia	**Yes**	31	55.4%
	No	25	44.6%
UTI	**Yes**	16	28.6%
	No	40	71.4%
Wound	**Yes**	12	21.4%
	No	44	78.6%
Endocarditis	**Yes**	2	3.6%
	No	54	96.4%
Empyema	**Yes**	4	7.1%
	No	52	92.9%
Klebsiella	**Yes**	25	44.6%
	No	31	55.4%
Pseudomonas	**Yes**	13	23.2%
	No	43	76.8%
Acinetobacter	**Yes**	11	19.6%
	No	45	80.4%
MRSA	**Yes**	6	10.7%
	No	50	89.3%
E. coli	**Yes**	10	17.9%
	No	46	82.1%
Strept	**Yes**	5	8.9%
	No	51	91.1%
No growth	**Yes**	3	5.4%
	No	53	94.6%
SIC likely or not likely	**Yes**	17	30.4%
	No	39	69.6%

there was no statistical significance between C2PAC and streptococcal infections, different comorbidities, cultures, and various diagnoses as shown in Table 5.

In the current study, the correlation coefficient of platelet counts, sCLEC2 levels, and C2PAC index in relation to MAP, D dimer, and SOFA score showed the following: MAP was positively correlated to platelet counts r 0.450 and p value 0.001, however negatively correlated to CLEC-2 levels and C2PAC index r (−0.286, −0.444) with p value (0.45, 0.001), respectively. D dimer was negatively correlated to platelet count r −0.373, p value 0.005, while positively correlated to CLEC-2 levels and C2PAC index r (0.406, 0.496) p value (0.002, < 0.001), respectively. SOFA score was negatively correlated to platelet count r −0.553, p value < 0.001, while positively correlated to CLEC-2 levels and C2PAC index r (0.392, 0.589) p value (0.003, < 0.001), respectively, as shown in Table 6. There was a positive correlation between the C2PAC index and SOFA score as shown in Fig. 1.

Comparison between sepsis-induced coagulopathy and sepsis without coagulopathy presented that there was a statistical significance difference regarding SBP (p value > 0.001) being lower in SIC, DBP (p value > 0.001) being lower in SIC, HR (p value 0.033) being higher in SIC, and MAP (p value > 0.001) being lower in SIC. It revealed also statistical significance in APTT, INR, and D dimer (p value > 0.001) being higher in SIC, PLT count, PC, and P/F ratio (p value > 0.001) being lower in SIC. Also, ALT, AST, T.bil, D.bil, sCLEC2 level, and C2PAC index and SOFA score showed a statistical significance difference being higher in SIC as shown in Table 7.

sCLEC-2 level and C2PAC index can be used for diagnosis of sepsis-induced coagulopathy with higher sensitivity when using the C2PAC index (82.4%) than using

Table 2 Clinical and laboratory data of sepsis patients (group I)

	Cases				
	Mean	**Standard deviation**	**Median**	**Minimum**	**Maximum**
Age	59.66	16.22	62.00	17.00	89.00
Sepsis onset (day)	5.14	2.18	5.00	1.00	10.00
SBP	108.30	19.19	110.00	80.00	160.00
DBP	68.04	13.81	70.00	50.00	100.00
HR (heartbeats/minute)	101.66	19.79	102.50	30.00	150.00
RR (respiratory rate/minute)	25.21	5.13	25	14.00	38.00
Temp (°C)	37.57	0.704	37.5	36.2	39.50
UOP (mL/24 h)	1881.43	865.17	1800.00	350.00	4200.00
MAP	81.01	15.58	81.65	60.00	120.00
PTT (s), *N* (35–45)	44.64	6.01	43.00	38.00	58.00
INR	1.47	0.38	1.40	1.00	2.50
D dimer (ug/mL)	1.86	2.96	0.65	0.30	16.00
TLC ($\times 10^3$/uL)	14.30	7.66	12.25	2.10	37.20
Hb (g/dL)	9.20	1.62	8.65	6.30	13.20
PLT ($\times 10^3$/uL)	188.93	128.36	155.00	22.00	651.00
CRP (mg/L)	168.73	112.47	130.00	39.00	589.00
PC (%)	63.75	13.41	65.00	27.00	85.00
ALT (U/L)	73.55	146.73	40.50	3.00	1069.00
AST (U/L)	77.13	110.06	56.00	7.00	765.00
Bilirubin T (mg/dL)	1.28	1.41	0.90	0.20	8.30
Bilirubin D (mg/dL)	0.54	0.81	0.30	0.08	4.70
Creatinine (mg/dL)	1.92	1.228	1.5	0.40	5.5
Urea (mg/dL)	85.70	66.51	63.50	21.00	400.00
P/F ratio	285.11	122.29	283.00	72.00	547.00
SOFA score	6.43	4.28	5.00	2.00	17.00
C lectin level (pg/ml)	607.41	457.37	433.80	36.70	2277.00
C lectin/plt ratio	6.06	7.06	2.60	0.10	29.06

Table 3 Comparison between cases and control groups

	Cases					**Control**					***P* value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	
TLC ($\times 10^3$/uL)	14.30	7.66	12.25	2.10	37.20	6.90	2.32	6.83	3.94	14.26	< 0.001
Hb (g/dL)	9.20	1.62	8.65	6.30	13.20	12.98	1.81	12.60	9.30	18.50	< 0.001
PLT ($\times 10^3$/uL)	188.93	128.36	155.00	22.00	651.00	278.37	84.50	263.50	150.00	452.00	< 0.001
sCLEC-2 level (pg/ml)	607.41	457.37	433.80	36.70	2277.00	261.61	481.67	81.05	1.00	1883.00	< 0.001
C2PAC index	6.06	7.06	2.60	0.10	29.06	1.06	2.00	0.33	0.00	8.54	< 0.001

sCLEC-2 (58.8%) and both have the same specificity (89.7%) as shown in Table 8.

ROC curve analysis for both sensitivity and specificity of both C lectin level, C lectin/Plt ratio (C2PAC index), and platelets count revealed the following: for C lectin level, at cutoff < 845, the area under the curve (AUC) was 0.765 with 58% sensitivity and 89.7% specificity (p value > 0.001), for C lectin/Plt ratio at cutoff < 5.02, the area under the curve (AUC) was 0.938, with 82.4% sensitivity and 89.7% specificity (p value > 0.001), while for platelets count > 135, the area under the curve (AUC) was 0.956, and 94% sensitivity and 87.2% specificity (p value > 0.001) as shown in Figs. 2 and 3.

Table 4 Correlation between sCLEC-2 level in relation to comorbidities, diagnoses, and organisms in cultures

		sCLEC-2 level					*P* value
		Mean	SD	Median	Minimum	Maximum	
Sex	**M**	594.78	392.24	468.30	36.70	1883.00	0.458
	F	623.08	535.36	419.20	45.90	2277.00	
Smoking history	**Yes**	673.22	488.93	500.00	200.00	1883.00	0.395
	No	583.34	449.16	419.20	36.70	2277.00	
DM	**Yes**	581.30	497.98	396.60	53.30	2277.00	0.299
	No	628.47	429.06	500.00	36.70	1883.00	
HTN	**Yes**	664.62	512.90	468.30	53.30	2277.00	0.342
	No	554.15	400.66	412.00	36.70	1883.00	
Cardiac diseases	**Yes**	669.88	545.61	431.90	45.90	2277.00	0.700
	No	566.99	393.59	447.05	36.70	1883.00	
Renal impairment	**Yes**	508.94	377.57	380.70	53.30	1600.00	0.443
	No	637.19	478.84	468.30	36.70	2277.00	
Cancer	**Yes**	500.60	442.59	525.90	45.90	930.00	1
	No	613.46	461.54	423.00	36.70	2277.00	
Cerebrovascular accidents	**Yes**	491.54	240.85	412.00	342.30	1028.00	0.716
	No	623.97	479.79	463.20	36.70	2277.00	
Mental state	**Conscious**	470.74	388.80	394.90	36.70	2277.00	< 0.001
	Altered	920.95	458.34	930.00	376.70	1883.00	
Sepsis versus septic shock	**Sepsis**	494.61	396.31	395.75	36.70	2277.00	0.002
	Septic shock	889.42	489.78	910.00	328.80	1883.00	
Vasopressor	**Yes**	856.27	493.53	890.00	325.90	1883.00	0.006
	No	498.94	400.54	396.60	36.70	2277.00	
FDPs	**Positive**	985.50	571.84	930.00	328.80	2277.00	0.001
	Negative	469.09	316.17	404.50	36.70	1600.00	
Pneumonia	**Yes**	590.15	348.60	468.30	53.30	1600.00	0.415
	No	628.82	571.50	419.20	36.70	2277.00	
UTI	**Yes**	608.80	545.02	421.10	53.30	2277.00	0.793
	No	606.86	425.15	453.90	36.70	1883.00	
Wound	**Yes**	586.55	394.89	453.90	36.70	1500.00	0.873
	No	613.10	476.99	421.10	45.90	2277.00	
Endocarditis	**Yes**	688.30	486.07	688.30	344.60	1032.00	0.878
	No	604.42	460.83	433.80	36.70	2277.00	
Empyema	**Yes**	657.23	838.65	350.00	45.90	1883.00	0.612
	No	603.58	428.96	433.80	36.70	2277.00	
Klebsiella	**Yes**	602.24	419.86	468.30	45.90	1883.00	0.735
	No	611.59	492.38	412.00	36.70	2277.00	
Pseudomonas	**Yes**	556.75	317.02	444.60	375.70	1500.00	0.473
	No	622.73	494.15	423.00	36.70	2277.00	
Acinetobacter	**Yes**	630.62	390.52	477.90	320.30	1600.00	0.536
	No	601.74	476.08	412.00	36.70	2277.00	
MRSA	**Yes**	583.07	371.38	635.35	53.30	930.00	1
	No	610.34	469.73	433.80	36.70	2277.00	
E. coli	**Yes**	670.44	636.68	384.15	305.00	2277.00	0.708
	No	593.71	416.56	453.90	36.70	1883.00	
Strept	**Yes**	293.00	174.65	342.30	45.90	500.00	0.045
	No	638.24	465.63	463.20	36.70	2277.00	
No growth	**Yes**	488.43	503.96	396.60	36.70	1032.00	0.680
	No	614.15	458.93	444.60	45.90	2277.00	

Table 5 Correlation between C2PAC index in relation to comorbidities, diagnoses, and organisms in cultures

		C2PAC index					*P* value
		Mean	SD	Median	Minimum	Maximum	
Sex	**M**	5.91	6.91	2.60	0.10	29.06	0.967
	F	6.24	7.38	2.55	0.21	27.14	
Smoking history	**Yes**	8.58	8.60	3.33	1.10	29.06	0.071
	No	5.14	6.28	2.53	0.10	27.14	
DM	**Yes**	4.80	5.55	2.53	0.24	21.43	0.504
	No	7.08	8.02	3.06	0.10	29.06	
HTN	**Yes**	5.76	6.14	2.55	0.25	21.43	0.980
	No	6.34	7.92	2.60	0.10	29.06	
Cardiac	**Yes**	8.46	9.12	3.28	0.21	29.06	0.119
	No	4.51	4.88	2.39	0.10	20.92	
Renal impairment	**Yes**	6.16	8.42	2.59	0.25	29.06	0.634
	No	6.03	6.71	2.60	0.10	27.14	
Cancer	**Yes**	14.49	14.43	14.21	0.21	29.06	0.486
	No	5.58	6.36	2.59	0.10	27.14	
Cerebrovascular accidents	**Yes**	3.37	2.78	2.34	0.57	7.34	0.496
	No	6.45	7.41	2.60	0.10	29.06	
Mental state	**Conscious**	3.50	3.97	2.19	0.10	15.81	< 0.001
	Altered	11.93	9.03	11.87	1.13	29.06	
Sepsis versus septic shock	**Sepsis**	3.13	3.46	2.15	0.10	15.81	< 0.001
	Septic shock	13.38	8.47	12.63	1.13	29.06	
Vasopressor	**Yes**	12.67	8.71	12.03	1.13	29.06	< 0.001
	No	3.18	3.49	2.19	0.10	15.81	
FDPs	**Positive**	14.60	7.85	14.95	3.29	29.06	< 0.001
	Negative	2.94	3.11	2.02	0.10	14.21	
Pneumonia	**Yes**	5.46	5.95	3.27	0.25	27.14	0.378
	No	6.80	8.30	1.85	0.10	29.06	
UTI	**Yes**	5.41	5.72	2.32	0.24	16.38	0.663
	No	6.32	7.58	3.17	0.10	29.06	
Wound	**Yes**	7.58	9.51	2.81	0.10	29.06	0.936
	No	5.65	6.31	2.60	0.21	27.14	
Endocarditis	**Yes**	7.89	7.55	7.89	2.55	13.23	0.494
	No	5.99	7.11	2.60	0.10	29.06	
Empyema	**Yes**	6.39	9.78	2.22	0.21	20.92	0.612
	No	6.04	6.94	2.60	0.10	29.06	
Klebsiella	**Yes**	6.09	6.98	3.33	0.21	27.14	0.352
	No	6.04	7.24	2.02	0.10	29.06	
Pseudomonas	**Yes**	6.47	8.63	3.27	1.13	29.06	0.567
	No	5.94	6.63	2.55	0.10	27.14	
Acinetobacter	**Yes**	4.04	4.04	2.44	0.73	12.03	0.628
	No	6.55	7.57	3.06	0.10	29.06	
MRSA	**Yes**	7.77	11.13	2.81	0.24	29.06	0.747
	No	5.86	6.55	2.60	0.10	27.14	
E. coli	**Yes**	6.65	6.08	3.20	0.57	15.81	0.358
	No	5.93	7.31	2.49	0.10	29.06	
Strept	**Yes**	1.67	1.20	1.39	0.21	3.33	0.091
	No	6.49	7.25	3.06	0.10	29.06	
No growth	**Yes**	5.12	7.09	2.02	0.10	13.23	0.580
	No	6.11	7.12	2.60	0.21	29.06	

Table 6 Correlation of platelet counts, sCLEC2 level, and C2PAC index in relation to clinical data, laboratory investigations, and SOFA score

		PLT	sCLEC-2 level	C2PAC index
Age	**Correlation coefficient**	0.082	−0.054	−0.061
	***P* value**	0.550	0.693	0.657
	N	56	56	56
Sepsis onset (day)	**Correlation coefficient**	0.002	−0.018	−0.036
	***P* value**	0.988	0.897	0.791
	N	56	56	56
Systolic blood pressure (SBP)	**Correlation coefficient**	0.484	−0.311	−0.483
	***P* value**	< 0.001	0.020	< 0.001
	N	56	56	56
Diastolic blood pressure (DBP)	**Correlation coefficient**	0.403	−0.224	−0.391
	***P* value**	0.002	0.097	0.003
	N	56	56	56
Heart rate (HR)	**Correlation coefficient**	−0.204	0.470	0.354
	***P* value**	0.131	< 0.001	0.007
	N	56	56	56
Respiratory rate (RR)	**Correlation coefficient**	0.047	0.051	−0.060
	***P* value**	0.731	0.710	0.662
	N	56	56	56
Temperature	**Correlation coefficient**	−0.100	−0.013	0.081
	***P* value**	0.464	0.923	0.553
	N	56	56	56
Urine output	**Correlation coefficient**	0.384	−0.134	−0.357
	***P* value**	0.003	0.325	0.007
	N	56	56	56
Mean arterial pressure (MAP)	**Correlation coefficient**	0.450	−0.268	−0.444
	***P* value**	0.001	0.045	0.001
	N	56	56	56
PTT, *N* (35–45)	**Correlation coefficient**	−0.483	0.318	0.507
	***P* value**	< 0.001	0.017	< 0.001
	N	56	56	56
INR	**Correlation coefficient**	−0.432	0.270	0.432
	***P* value**	0.001	0.044	0.001
	N	56	56	56
D-dimer	**Correlation coefficient**	−0.373	0.406	0.469
	***P* value**	0.005	0.002	< 0.001
	N	56	56	56
TLC	**Correlation coefficient**	0.236	−0.175	−0.255
	***P* value**	0.080	0.196	0.058
	N	56	56	56
Hb	**Correlation coefficient**	0.131	−0.010	−0.067
	***P* value**	0.335	0.944	0.622
	N	56	56	56
CRP	**Correlation coefficient**	−0.052	0.104	0.100
	***P* value**	0.703	0.444	0.464
	N	56	56	56
PC	**Correlation coefficient**	0.321	−0.209	−0.332
	***P* value**	0.016	0.122	0.012
	N	56	56	56

Table 6 (continued)

		PLT	sCLEC-2 level	C2PAC index
ALT	**Correlation coefficient**	−0.201	0.158	0.221
	***P* value**	0.138	0.244	0.102
	N	56	56	56
AST	**Correlation coefficient**	−0.115	0.108	0.162
	***P* value**	0.398	0.428	0.233
	N	56	56	56
Bilirubin T	**Correlation coefficient**	−0.071	0.001	0.030
	***P* value**	0.601	0.994	0.827
	N	56	56	56
Bilirubin D	**Correlation coefficient**	−0.211	0.038	0.138
	***P* value**	0.118	0.779	0.312
	N	56	56	56
Creatinine	**Correlation coefficient**	−0.057	−0.151	0.010
	***P* value**	0.678	0.266	0.945
	N	56	56	56
Urea	**Correlation coefficient**	−0.049	−0.081	0.006
	***P* value**	0.719	0.554	0.965
	N	56	56	56
P/F ratio	**Correlation coefficient**	0.298	−0.325	−0.358
	***P* value**	0.026	0.015	0.007
	N	56	56	56
SOFA score	**Correlation coefficient**	−0.553	0.392	0.589
	***P* value**	< 0.001	0.003	< 0.001
	N	56	56	56

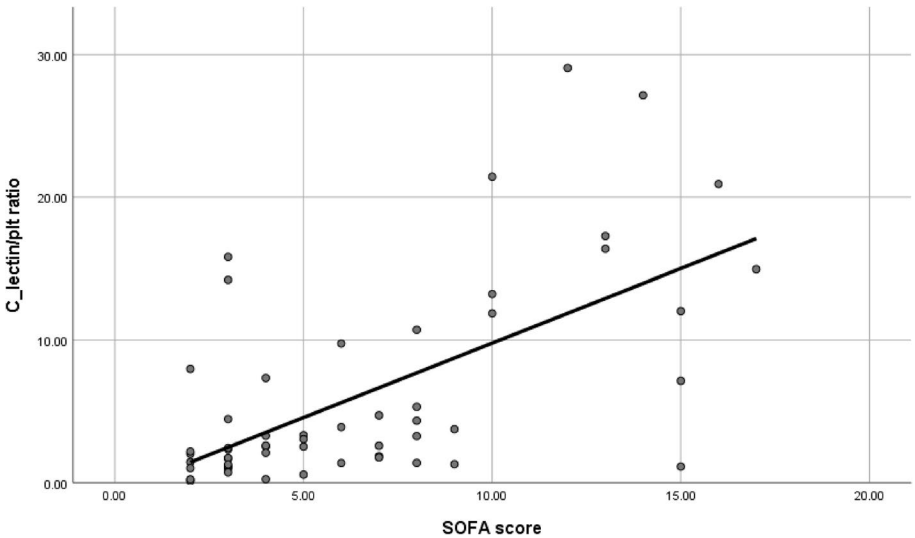

Fig. 1 Spearman correlation between C2PAC index and SOFA score

Discussion

Sepsis and septic shock are fatal conditions that must be diagnosed early without delay for early administration of the proper antimicrobial agents [13].

The present study included a total of (86) divided into 2 groups; group I: 56 patients diagnosed with sepsis

Table 7 Comparison between sepsis-induced coagulopathy and sepsis without coagulopathy as regards vital signs and laboratory investigations

	Sepsis induced coagulopathy (*N* = 17 patients)					Sepsis without coagulopathy (*N* = 39 patients)					*P* value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age	59.00	18.08	65.00	17.00	80.00	59.95	15.59	60.00	20.00	89.00	0.844
Sepsis onset (day)	5.12	2.03	5.00	1.00	10.00	5.15	2.27	5.00	1.00	10.00	0.921
SBP	94.71	18.75	90.00	80.00	150.00	114.23	16.32	110.00	80.00	160.00	< 0.001
DBP	57.65	12.00	50.00	50.00	90.00	72.56	12.08	70.00	50.00	100.00	< 0.001
HR	106.71	19.22	110.00	50.00	130.00	99.46	19.87	98.00	30.00	150.00	0.033
RR	33.71	24.28	24.00	14.00	99.00	26.67	14.05	25.00	3.00	105.00	0.655
Temperature	37.25	2.62	37.80	27.50	39.50	37.49	0.63	37.20	36.50	39.00	0.145
Urine output	1597.06	848.06	1400.00	350.00	2800.00	2005.38	853.59	2100.00	600.00	4200.00	0.097
MAP	68.61	14.38	63.30	60.00	110.00	86.42	12.86	83.30	60.00	120.00	< 0.001
aPTT, *N* (35–45)	51.12	5.89	53.00	40.00	58.00	41.82	3.28	40.00	38.00	50.00	< 0.001
INR	1.89	0.32	1.80	1.50	2.50	1.29	0.23	1.30	1.00	2.00	< 0.001
D-dimer	4.56	4.20	4.00	0.30	16.00	0.68	0.74	0.50	0.30	5.00	< 0.001
TLC	14.96	6.64	14.30	7.00	30.00	14.01	8.12	11.90	2.10	37.20	0.407
Hb	8.94	1.55	8.60	6.30	12.20	9.31	1.65	8.70	7.10	13.20	0.438
PLT	82.65	39.12	83.00	22.00	144.00	235.26	126.29	210.00	37.00	651.00	< 0.001
CRP	174.95	124.19	130.00	69.20	589.00	166.01	108.59	137.00	39.00	540.00	0.708
PC	50.76	9.91	53.00	27.00	65.00	69.41	10.52	70.00	35.00	85.00	< 0.001
ALT	148.88	251.71	87.00	3.00	1069.00	40.72	28.93	35.00	6.00	122.00	0.006
AST	132.18	181.00	81.00	13.00	765.00	53.13	42.34	48.00	7.00	243.00	0.023
Bilirubin T	2.14	2.15	1.20	0.30	8.30	0.91	0.69	0.70	0.20	3.80	0.010
Bilirubin D	1.01	1.22	0.50	0.09	4.70	0.34	0.44	0.24	0.08	2.70	0.001
Creatinine	2.18	1.31	2.10	0.80	5.29	2.15	1.93	1.50	0.40	9.50	0.427
Urea	91.24	56.48	65.00	21.00	191.00	83.28	70.99	54.00	21.00	400.00	0.273
P/F ratio	238.71	110.96	250.00	82.00	423.00	305.33	122.79	300.00	72.00	547.00	0.039
SOFA score	10.47	4.43	10.00	3.00	17.00	4.67	2.78	4.00	2.00	15.00	< 0.001
sCLEC-2 level	958.76	592.33	930.00	328.80	2277.00	454.26	275.20	404.50	36.70	1300.00	0.002
C2PAC index	13.71	7.95	13.23	2.55	29.06	2.73	2.83	1.85	0.10	14.21	< 0.001

Table 8 Sensitivity and specificity of C lectin level, C lectin/plt ratio, and platelets in sepsis-induced coagulopathy

	Area under the curve	*P* value	Asymptotic 95% confidence interval		Cutoff	Sensitivity %	Specificity %
			Lower bound	Upper bound			
C lectin level (sCLEC-2)	0.765	< 0.001	0.623	0.907	> 845	58.8	89.7
C lectin/plt ratio (C2PAC index)	0.938	< 0.001	0.878	0.998	> 5.02	82.4	89.7
PLT	0.956	< 0.001	0.906	1.006	< 135.5	94.1	87.2

or septic shock and group II: 30 age and sex-matched healthy individuals. In the current study, males diagnosed with sepsis were more than females, 31 males (55.4%) and 25 females (44.6%).

Several studies have reported sex-based differences in sepsis and septic shock patients, and all these studies show a higher risk of sepsis in men which may be due to male sex hormones (androgens), as they were shown to be suppressive on cell-mediated immune responses. In contrast, female sex hormones exhibited protective effects [17].

There is a statistical significance (p value 0.045) between sCLEC2 level and streptococcal infections. This may be explained by the innate immune system

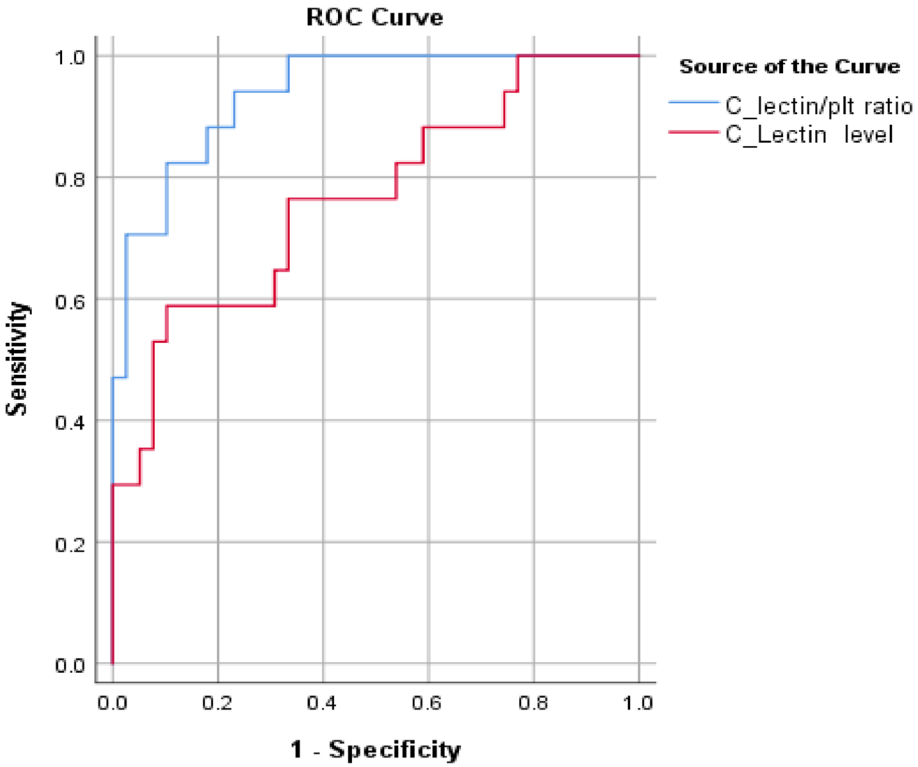

Fig. 2 ROC curve in correlation to C lectin level and C lectin/Plt ratio (C2PAC index)

employs C-type lectin receptors (CLRs) to recognize carbohydrate structures on pathogens and self-antigens. The macrophage-inducible C-type lectin (Mincle) is a FcRγ-coupled CLR that was shown to bind to mycobacterial cord factor. Several studies detected that Mincle can recognize *S. pneumonia* but is not required for the anti-pneumococcal innate immune response [18].

In the current study, the C2PAC index showed a statistically significant difference (p value < 0.001) between group I (6.06 ± 7.06) and group II (1.06 ± 2.00) being lower in group II (healthy volunteers). Hiroyasu Ishikura also obtained the same results that The C2PAC index is significantly lower in the healthy volunteers than in septic patients [2].

Platelets play a pivotal role in sepsis starting with coagulation activation at the infection site and thrombus formation and this is recognized as an immune-thrombosis mechanism. When these reactions spread to the whole body, depletion of platelets occurs followed by DIC [19, 20].

Platelet count showed a statistically significant difference (p value < 0.001) between group I (188 ± 128) and group II (278 ± 84) being lower in group I (septic patients). sCLEC-2 level showed a statistically significant difference (p value < 0.001) between group I (607 ± 457) and group II (261 ± 481) being higher in group I (septic patients).

Hiroyasu Ishikura detected the same results that the septic patients had a significantly lower platelet count and significantly higher sCLEC-2 level on ICU admission compared with the healthy volunteers (P < 0.01) [2].

Regarding the comparison between sepsis-induced coagulopathy (SIC) and sepsis without coagulopathy in the current study, the C2PAC index and platelets showed a statistically significant difference (p value < 0.001). The C2PAC index is higher in SIC, but platelets are lower in SIC. sCLEC-2 level was significantly higher in SIC than sepsis without coagulopathy (p value < 0.002) but not as high as the C2PAC index and platelets; however, Hiroyasu Ishikura detected that the sCLEC-2 level did not significantly differ between the two groups [2].

In this study, it was detected that the SIC group was 17 patients (30.4%) and the sepsis without coagulopathy group was 39 patients (69.6%). Compared with the non-SIC group, the SIC group was significantly older and had a significantly higher SOFA score, C lectin levels, and C2PAC index. This proposed that The C2PAC index is a useful predictor of SIC progression and diagnosis in septic patients.

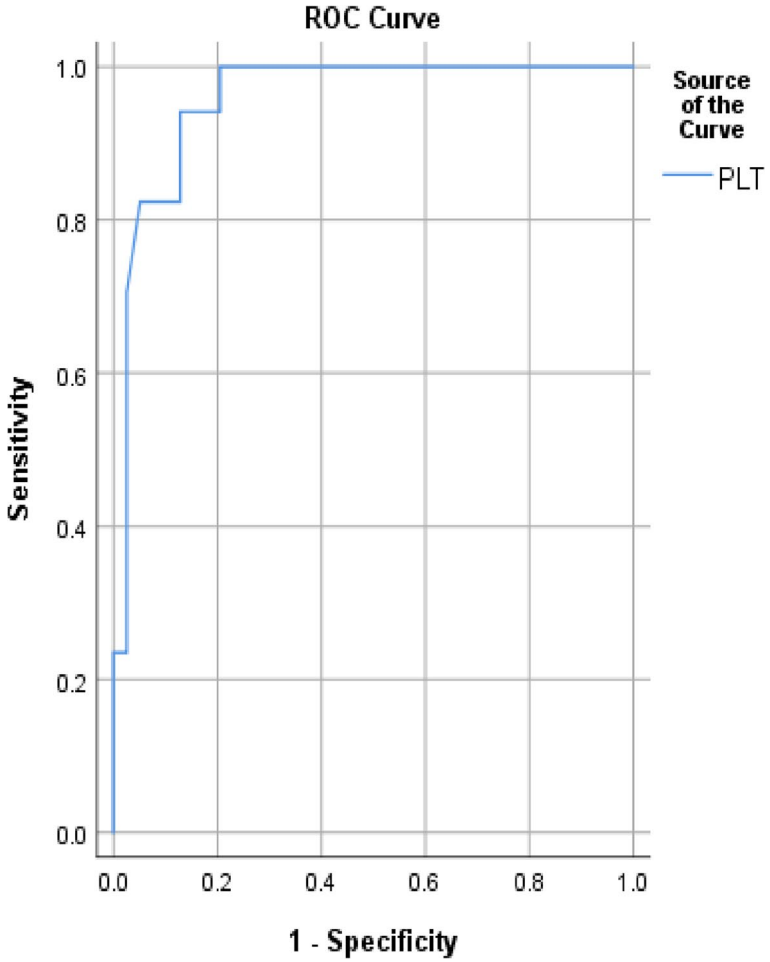

Fig. 3 ROC curve in correlation to platelets' count

Hiroyasu Ishikura obtained different results regarding the number of patients diagnosed with SIC in a study conducted on 70 patients in which the non-SIC group and SIC group were 26 and 44 patients, respectively. However, they obtained the same results regarding the comparison between SIC and non-SIC, compared with the non-SID group, the SID group was significantly older and had a significantly higher SOFA score [2].

In the current study, it was detected that the C2PAC index at cutoff < 5.02, the area under the curve (AUC) was 0.938 with 82.4% sensitivity and 89.7% specificity (p value > 0.001). Our results had a higher C2PAC index cutoff compared to Ishikura et al. that concluded the C2PAC index at cutoff 1.4 was possible to diagnose SIC with (AUC 0.805, sensitivity of 75.0% and specificity of 76.9%) on a study conducted on 70 Japanese septic patients [2]. The difference in the C2PAC index cutoff between these two studies could be explained by the different ethnicities. The second explanation could be due to more reduction in the platelets count in the SIC group in our study (82.65 ± 39.12) compared to Ishikura et al. study in which the platelet count in the SIC group was 134 ± 87 which may reflect higher C2PAC index in the current study.

Also, the difference in the C2PAC index may be explained by the difference in sepsis severity guided by SOFA score; however, this was not detected between these two studies in which the SOFA score in the current study was 10.47 ± 4.43, while in Ishikura et al.'s study, it was (10.1 ± 3.7) [2].

The current study proposed that C2PAC was more accurate and impressive than using platelets' counts alone with higher specificity (89.7% versus 87.2%, respectively). C2PAC index was more sensitive than sCLEC-2 levels (82.4% versus 58%, respectively) in the detection of SIC, and this matched with the same results of Ishikura et al. [2].

Limitation to this study

Our study is a single-center experience on small numbers of patients with only one reading of sCLEC-2 level in

each patient due to funding limitations. We need multiple centers of research with multiple readings of sCLEC-2 levels for each patient during the progress of either sepsis or sepsis-induced coagulopathy to detect also the prognostic value and validity to be used as an early predictor test. Some limitations of the present study should be noted. It was a small single-center observational study, making it difficult to generalize the findings globally.

Conclusion

This study concluded that sCLEC-2 and C2PAC index (a ratio of sCLEC-2 levels and platelet count) could be used as diagnostic markers of sepsis. However, it is more precise to use the C2PAC index and could be validated as a predictor of sepsis-induced coagulopathy with both high sensitivity and specificity (82.4%, 89.7%, respectively) rather than using sCLEC-2 alone (sensitivity 58.8%).

Abbreviations

ABG	Arterial blood gases
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the curve
C2PAC	A ratio of soluble type C lectin-like receptor 2 (sCLEC-2) level and platelet count
CRP	C-reactive protein
D.Bil	Direct bilirubin
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DIC	Disseminated intravascular coagulation
ELISA	Enzyme-linked immunosorbent assay
FDPs	Fibrinogen degradation products
Hb	Hemoglobin
HR	Heart rate
HTN	Hypertension
INR	International normalized ratio
MAP	Mean arterial pressure
PC	Prothrombin concentration
P/F ratio	The ratio between the partial pressure of oxygen in ABG to the fraction of inspired oxygen
Pg	Pico gram
PLT	Platelets
PT	Prothrombin time
PTT	Partial thromboplastin time
SBP	Systolic blood pressure
sCLEC-2	Soluble type C lectin-like receptor 2
SIC	Sepsis-induced coagulopathy
ROC analysis	Receiver-operating characteristic analysis
SOFA score	Sequential organ failure assessment score
RR	Respiratory rate
T. Bil	Total bilirubin
TLC	Total leucocytic count
UOP	Urine output
UTI	Urinary tract infection

Acknowledgements
Not applicable.

Authors' contributions
All authors shared in the collection of data, analysis of results, and writing the manuscript.

Funding
No.

Availability of data and materials
With the corresponding author upon request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained before starting research under number N-37–2022.

Consent for publication
Not applicable as neither personal images nor personal data of the participants were included in the manuscript.

Competing interests
The authors declare that they have no competing interests.

Received: 1 September 2023 Accepted: 12 October 2023
Published online: 18 October 2023

References

1. Assinger A, Schrottmaier WC, Salzmann M, Rayes J (2019) Platelets in sepsis: an update on experimental models and clinical data. Front Immunol 10:1687
2. Ishikura H, Irie Y, Kawamura M, Hoshino K, Nakamura Y, Mizunuma M et al (2022) Early recognition of sepsis-induced coagulopathy using the C2PAC index: a ratio of soluble type C lectin-like receptor 2 (sCLEC-2) level and platelet count. Platelets 33(6):935–944
3. Vardon-Bounes F, Ruiz S, Gratacap MP, Garcia C, Payrastre B, Minville V (2019) Platelets are critical key players in sepsis. Int J Mol Sci 20(14):3494
4. Kazama F, Nakamura J, Osada M, Inoue O, Oosawa M, Tamura S et al (2015) Measurement of soluble C-type lectin-like receptor 2 in human plasma. Platelets 26(8):711–719
5. Inoue O, Osada M, Nakamura J, Kazama F, Shirai T, Tsukiji N et al (2019) Soluble CLEC-2 is generated independently of ADAM10 and is increased in plasma in acute coronary syndrome: comparison with soluble GPVI. Int J Hematol 110(3):285–294
6. Fei M, Xiang L, Chai X, Jin J, You T, Zhao Y et al (2020) Plasma soluble C-type lectin-like receptor-2 is associated with the risk of coronary artery disease. Front Med 14(1):81–90
7. Zhang X, Zhang W, Wu X, Li H, Zhang C, Huang Z, et al (2018) Prognostic significance of plasma CLEC-2 (C-type lectin-like receptor 2) in patients with acute ischemic stroke. Stroke 7: STROKEAHA118022563
8. Nishigaki A, Ichikawa Y, Ezaki M, Yamamoto A, Suzuki K, Tachibana K et al (2021) Soluble C-type lectin-like receptor 2 elevation in patients with acute cerebral infarction. J Clin Med 10(15):3408
9. Levi M, Ten Cate H (1999) Disseminated intravascular coagulation. N Engl J Med 341(8):586–592
10. Iba T, Levy JH (2020) Sepsis-induced coagulopathy and disseminated intravascular coagulation. Anesthesiology 132(5):1238–1245
11. Saito S, Uchino S, Hayakawa M, Yamakawa K, Kudo D, Iizuka Y et al (2019) Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group: epidemiology of disseminated intravascular coagulation in sepsis and validation of scoring systems. J Crit Care 50:23–30
12. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315(8):801–810
13. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C et al (2021) Executive summary: surviving sepsis campaign: international guidelines for the management of sepsis and septic shock 2021. Crit Care Med 49(11):1974–1982
14. Chan YH (2003) Biostatistics102: quantitative data – parametric & non-parametric tests. Singapore Med J 44(8):391–396
15. Chan YH (2003) Biostatistics 103: qualitative data –tests of independence. Singapore Med J 44(10):498–503
16. Chan YH (2003) Biostatistics 104: correlational analysis. Singapore Med J 44(12):614–619

17. Lakbar I, Einav S, Lalevée N, Martin-Loeches I, Pastene B, Leone M (2023) Interactions between gender and sepsis—implications for the future. Microorganisms 11(3):746
18. Rabes A, Zimmermann S, Reppe K, Lang R, Seeberger PH, Suttorp N et al (2015) The C-type lectin receptor Mincle binds to Streptococcus pneumoniae but plays a limited role in the anti-pneumococcal innate immune response. PLoS ONE 10(2):e0117022
19. Parikh F (2016) Infections and thrombocytopenia. J Assoc Physicians India 64(2):11–12
20. Wang Y, Ouyang Y, Liu B, Ma X, Ding R (2018) Platelet activation and antiplatelet therapy in sepsis: a narrative review. Thromb Res 166:28–36

Publisher's Note