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ORIGINAL ARTICLE

Decoy Receptor 3 as a Biomarker for Diagnosis of Bacterial Sepsis

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ABSTRACT

Background: *Sepsis is a leading cause of morbidity and mortality that has a global burden. Early recognition of sepsis and differentiating it from similar conditions is crucial.* ***Objective:*** *In the present study we aimed to measure the serum level of decoy receptor 3 (DcR3) in sepsis patients to study its role as a promising biomarker for bacterial sepsis.* ***Methodology:*** *The present study included 30 patients, divided into a sepsis group (n=15) and a systemic inflammatory response syndrome (SIRS) group (n=15), and 15 healthy controls. Sepsis patients were identified by positive blood culture or positive 16S ribosomal DNA (rDNA) polymerase chain reaction (PCR) results. SIRS patients were identified by negative blood culture or negative 16S rDNA PCR results. Serum DcR3 level was measured by quantitative enzyme-linked immunosorbent assay (ELISA). Receiver-operating characteristic (ROC) curve analysis was performed for DcR3 and C-reactive protein (CRP) alone and in combination.* ***Results:*** *The serum DcR3 level was significantly higher in sepsis than SIRS patients and healthy controls (5.21 ± 2.28 ng/mL, 1.96 ± 0.90 ng/mL, and 0.95 ± 0.79 ng/mL, respectively). The ROC area under the curve (AUC) of DcR3 for sepsis versus SIRS was 0.920 at a cut-off >2.4 ng/mL, with 93.33% sensitivity and 86.67% specificity. The AUC of combined positive DcR3 and positive CRP for sepsis versus SIRS was 0.967 with 93.33% sensitivity and 100% specificity.* ***Conclusion:*** *DcR3, alone or in combination with CRP, is a promising biomarker for distinguishing sepsis from SIRS patients and may efficiently guide physicians to identifying sepsis patients, for whom the further usage of new diagnostics can be cost-effective.*

INTRODUCTION

Sepsis is a dysregulated host response to infection that leads to life-threatening organ dysfunction[1]. The global incidence was estimated to be 19.4 million cases per year leading to 5.3 million deaths with a mortality rate of 26%[2]. Sepsis was recognized by the WHO in 2017 as a global health priority[3].

Early diagnosis and management of sepsis are crucial as every hour of delay leads to a 5-10% increase in mortality rates[4]. It is hard to differentiate between bacterial sepsis and the non-infectious causes of systemic inflammatory response syndrome (SIRS) like trauma, ischemia, pancreatitis, and burns, yet early differentiation between them is crucial as the early administration of proper antimicrobial treatment remains lifesaving for sepsis patients[5,6]. Also, a delayed or incorrect diagnosis prolongs the exposure to empirical antibiotic therapy, increases mortality rates, prolongs the length of stay, wastes health resources, and increases antimicrobial resistance[7].

Identification of the causative pathogen through blood cultures is time-consuming and has low positivity rates[8]. New technologies to rapidly detect the pathogen are emerging including the use of molecular diagnostics but are still too costly to be routinely performed[9]. Biomarkers, mainly from the blood, can increase early in the inflammatory process and some give different levels in bacterial sepsis from non-infectious inflammation[10].

Decoy receptor 3 (DcR3), a member of the tumor necrosis factor receptor superfamily (TNFRSF), is secreted as a soluble receptor that binds competitively and blocks three pro-apoptotic ligands: Fas ligand (FasL), LIGHT, and TL1A[11]. The upregulation of DcR3 is probably to maintain homeostasis in conditions where cell damage and apoptosis are increased[12]. DcR3 expression is selectively induced by bacterial antigens, as lipopolysaccharides and lipoteichoic acid, and their receptors TLR 2 and TLR 4, through the NF-κB pathway, but was not induced by TLR 7 which responds to single-stranded RNA common in viral genomes[13]. DcR3 serum level is very low in most normal individuals[14], and can be moderately elevated in different malignancies, inflammatory, and autoimmune diseases[11].

The aim of this study was to measure the serum level of DcR3 in sepsis patients and to study its role as a promising biomarker for diagnosis of bacterial sepsis.

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METHODOLOGY

This case-control study was performed in the Intensive Care Units (ICUs) at Ain Shams University Hospital, Egypt, over a period from October 2018 to March 2019. The present study included 30 patients and 15 healthy individuals as a control group; the patients were divided into two groups as follows:

The sepsis group: included 15 patients who were identified by positive blood culture or positive 16S rDNA PCR results, in addition to the presence of at least two of the four SIRS criteria described in the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus classification (ACCP/SCCM, 1992): (1) body temperature of > 38 °C or < 36 °C, (2) heart rate (> 90 beats per min), (3) respiratory rate (>20 breaths per minute or an arterial CO2 pressure of < 32 mm Hg), (4) white blood cell (WBC) counts of > 12,000 cells/µl or <4,000 cells/µl or > 10% immature forms.

The SIRS group: included 15 patients that were identified by negative blood culture or negative 16S rDNA PCR results, in addition to the presence of at least two of the four SIRS criteria mentioned above.

***Exclusion criteria*:** patients were excluded from the study if they showed evidence of other comorbidities or an immunocompromised state.

For all patients, a 10 mL venous blood sample was drawn and used for doing the following tests: (1) blood culture, (2) detection of 16S rDNA gene by conventional PCR, (3) quantitative measurement of human DcR3 by ELISA. For the conventional PCR test the blood sample was stored in EDTA tubes under − 80 ℃ until used for detection of 16S rDNA gene, and for the ELISA test the blood sample was centrifuged then the serum was stored under − 80 ℃ until used for quantitative measurement of human DcR3 by ELISA. The total leukocytic count (TLC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) results were also studied.

For the healthy control group, a 2mL venous blood sample was drawn and centrifuged, and the serum was stored under – 80℃ until used for the quantitative measurement of human DcR3 by ELISA.

Blood culture

Blood cultures were done using adult bottles (Salix®, USA) which were inoculated and incubated at 37 ℃ for up to 7 days during which subcultures were done and the resulting organisms' colonies were identified by Gram stain and biochemical reactions according to Collee et al., 1996[15].

Conventional PCR of the bacterial 16S rDNA

DNA extraction from the blood samples was done using Ultraclean® Microbial DNA Isolation Kit (MO BIO, Qiagen, USA). Amplification of the 16S rDNA was done using the forward primer: TCC TAC GGG AGG CAG CAG T, and the reverse primer: GGA CTA CCA GGG TAT CTA ATC CTG TT (Invitrogen, Thermo Fisher Scientific, UK)[16], and GoTaq® colorless master mix (Promega, USA). Then the gel electrophoresis was done using agarose gel (2%), ethidium bromide, and a 100 bp DNA ladder (Promega, USA) and the band would have appeared at 250 base pairs.

Quantitative ELISA

Human DcR3 was quantitatively measured in the serum using ELISA kit (Bioassay Technology Laboratory, Shanghai, China, Cat. No. E4615Hu, Lot No. E1811002). This kit employs a sandwich ELISA using 96- wells plate which has been pre-coated with human DCR3 antibody. The procedure was done according to the manufacturer's instructions. Standards as well as samples were added to the wells. And then biotinylated human DCR3 Antibody was added and binds to DCR3 in the sample. Then Streptavidin-HRP was added and binds to the Biotinylated DCR3 antibody. After incubation, unbound Streptavidin-HRP was washed away during a washing step. Substrate solution was then added, and color developed in proportion to the amount of human DCR3. The reaction is terminated by addition of acidic stop solution and the optical density (OD) was measured at 450 nm by spectrophotometer.

Statistical analysis

Statistical procedures were carried out using the Statistical Package for Social Science **(SPSS 20).** For descriptive statistics, the mean and Standard Deviation (expressed as mean ± SD) were calculated for numerical data, while the frequency and percentage were calculated for non-numerical data. For analytical statistics, we used Student t-test to assess the statistical significance of the difference between the means of two study groups, ANOVA test to assess the statistical significance of the difference between the means of more than two study groups, and Post Hoc test for comparisons of all possible pairs of groups' means. To assess the strength of association between two quantitative variables we used correlation analysis, Pearson's method. ROC curve analysis was done to evaluate the sensitivity and specificity and to determine the optimal cut-off.

RESULTS

Demographic and laboratory data of the studied groups:

The present study included 3 groups; sepsis group of 15 patients (8 males, 53.3%; and 7 females, 46.7%; with mean age of 50.87 ± 17.80), SIRS group of 15 patients (9 females, 60%; and 6 males, 40%; with mean age of 55.53 ± 14.13), and control group of 15 healthy blood donors (9 males, 60%; 6 females, 40%; with mean age of 48.40 ± 16.90), and there was no statistically significant difference for the age and sex between the

three groups (p = 0.485, 0.537, respectively). Gram-negative bacteremia was more prevalent (9/15, 60%) in sepsis patients with *Klebsiella pneumoniae* as the most common isolate (4/15, 26%), while Gram-positive bacteremia was (6/15, 40%) with *Staphylococcus aureus* as the most common isolate (4/15, 26%) (Figure1, 2).

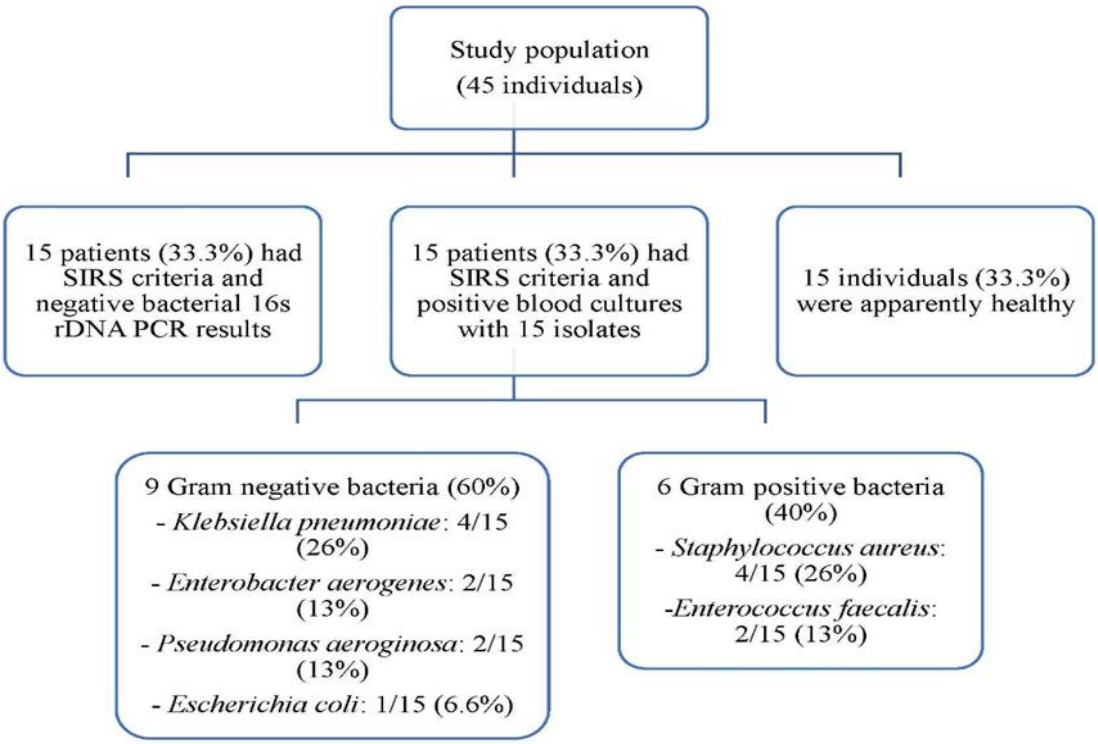

Fig. 1: Flow chart of the study groups including details of the isolated pathogens.

Fig. 2: Gel electrophoresis of the 16S rDNA PCR of the SIRS patients showing negative results.

Comparison of TLC, ESR, and CRP between sepsis and SIRS groups:

The mean TLC was higher in sepsis than SIRS but showed no statistically significant difference between the sepsis and the SIRS groups (p = 0.401), while the ESR and CRP were significantly higher in sepsis than SIRS (p = 0.013, 0.002, respectively) (Table 1).

Table 1: TLC, ESR, and CRP in sepsis and SIRS groups:

	Sepsis		SIRS		t-test	
	Mean	**SD**	**Mean**	**SD**	***P***	**Sig.**
TLC (n× 10^3/µL)	18.1	5.49	16.47	4.99	0.401	NS
ESR (mm/hr)	97.73	30.83	68.73	28.68	0.013	S
CRP (mg/L)	180.00	73.29	100.87	55.28	0.002	S

Sig. = significance, NS = non-significant, S = significant

Serum DcR3 levels in sepsis, SIRS, and healthy control groups:

The mean DcR3 level was significantly higher in sepsis (5.21 ± 2.28 ng/mL) than SIRS (1.96 ± 0.90 ng/mL) and healthy control (0.95 ± 0.79 ng/mL). DcR3 concentration between sepsis and SIRS showed a 2.6-fold difference which was statistically significant (p < 0.05). Also, DcR3 concentration between sepsis and healthy control showed a 5.5-fold difference which was statistically significant (p < 0.05) (Table 2, figure 3).

Table 2: Serum DcR3 levels in sepsis, SIRS, and healthy control:

	Sepsis		SIRS		Control		ANOVA	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P***	**Sig.**
DcR3-Decoy receptor 3 (ng/mL)	5.21	2.28	1.96	0.90	0.95	0.79	< 0.001*	S

*Post Hoc test: SIRS vs sepsis (S: p < 0.05), SIRS vs control (NS: p > 0.05) and sepsis vs control (S: p < 0.05).

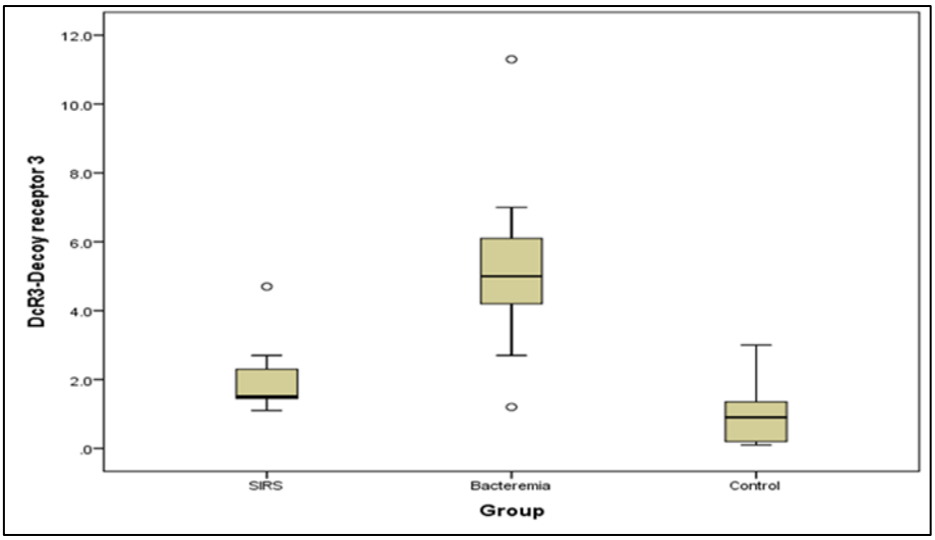

Fig. 3: Comparison between sepsis, SIRS, and healthy control regarding serum level of DcR3.

The relationship between the serum level of DcR3 and the type of bacterial infection:

Serum DcR3 was significantly higher in bacteremia caused by Gram-negative bacteria than bacteremia caused by Gram-positive bacteria ($p = 0.034$) (Table 3).

Table 3: The relationship between the serum level of DcR3 and the type of bacterial infection:

Type of the bacterial infection	DcR3-Decoy receptor 3 (ng/mL) Mean ± SD	t-test	
		P	Sig.
Gram negative (n=9)	6.200 ± 2.2074	0.034	S
Gram positive (n=6)	3.733 ± 1.5384		

Correlation between DcR3 serum level and TLC, ESR, and CRP in sepsis and SIRS groups:

Serum DcR3 showed a moderate positive correlation with ESR and CRP, and a weak positive correlation with TLC (Table 4, Figure 4).

Table 4: Correlation between DcR3 level and the levels of TLC, ESR, and CRP in sepsis and SIRS groups:

			TLC	ESR	CRP
DcR3	**SIRS**	*r*	0.333	-0.134	0.168
		p	0.226	0.635	0.549
	Sepsis	*r*	0.299	0.299	0.167
		p	0.278	0.278	0.551
	Cases (Sepsis + SIRS)	*r*	0.315	0.423	0.470
		p	0.090	0.020	0.009

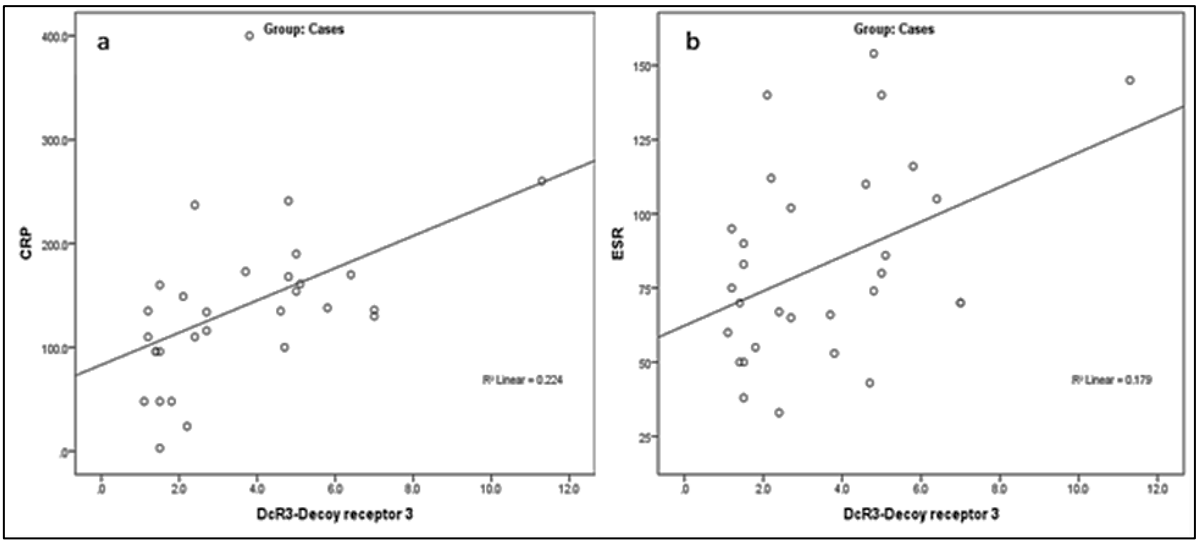

Fig. 4: Correlation between DcR3 serum level and TLC, ESR, and CRP in sepsis and SIRS group. a) DcR3 and CRP levels. b) DcR3 and ESR levels.

The discriminative ability of serum DcR3 for predicting sepsis patients:

By ROC curve analysis, serum DcR3 had excellent diagnostic accuracy in distinguishing sepsis patients from healthy controls with an AUC of 0.969 at a cut-off >1.5 ng/mL with 93.33% sensitivity and 93.33% specificity. Also, DcR3 had excellent diagnostic accuracy in distinguishing sepsis from SIRS patients with an AUC of 0.920 at a cut-off >2.4 ng/mL, with 93.33% sensitivity and 86.67% specificity. Our results revealed that DcR3 had good diagnostic accuracy in distinguishing SIRS patients from healthy controls with an AUC of 0.849 at a cut-off >1.3 ng/mL, with 86.7% sensitivity and 73.3% specificity (Table 5, Figure 5).

Table 5: The discriminative ability of serum DcR3 level in predicting sepsis from SIRS patients and healthy controls:

Diagnosis	AUC	95% CI	*P*	Sig.	Cut-off point (ng/mL)	Sensitivity (%)	Specificity (%)	+PV (%)	-PV (%)
Sepsis versus control	0.969	0.831-0.999	0.0001	S	>1.5	93.33	93.33	93.3	93.3
Sepsis versus SIRS	0.920	0.761-0.987	0.0001	S	>2.4	93.33	86.67	87.5	92.9
SIRS versus control	0.849	0.671-0.953	0.0001	S	>1.3	86.7	73.3	76.5	84.6

+PV = positive predictive value, -PV = negative predictive value.

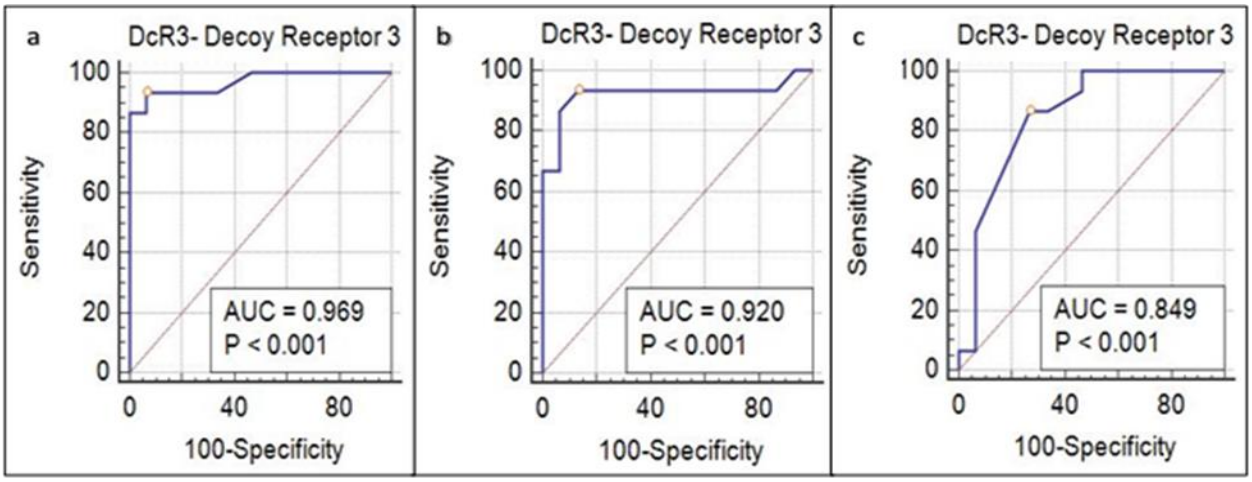

Fig. 5: ROC curves of serum DcR3. a) sepsis patients versus healthy controls. b) sepsis versus SIRS patients. c) SIRS patients versus healthy controls.

The discriminative ability of CRP alone and in combination with DcR3 in predicting sepsis from SIRS patients:

The ROC curve analysis for CRP alone had an AUC of 0.867 at a cut-off >116 mg/L, with 93.33% sensitivity and 73.33% specificity. The performance of CRP in combination with DcR3 revealed that a combination in which at least one of the biomarkers was positive showed an AUC of 0.767 with 93.33% sensitivity and 60% specificity. Moreover, the combination in which both biomarkers were positive showed an AUC of 0.967 with 93.33% sensitivity and 100% specificity (Table 6 and Figure 6).

Table 6: Performance of CRP alone and in combination with DcR3 for discriminating sepsis from SIRS patients:

	AUC	95% CI	*P*	Sig.	Cut-off point	Sensitivity (%)	Specificity (%)	+PV (%)	-PV (%)
CRP	0.867	0.693-0.962	0.0001	S	>116mg/L	93.33	73.33	77.8	91.7
At least one is positive	0.767	0.577-0.901	0.0003	S	-	93.33	60	70	90
When both are positive	0.967	0.828-0.999	0.0001	S	-	93.33	100	100	93.7

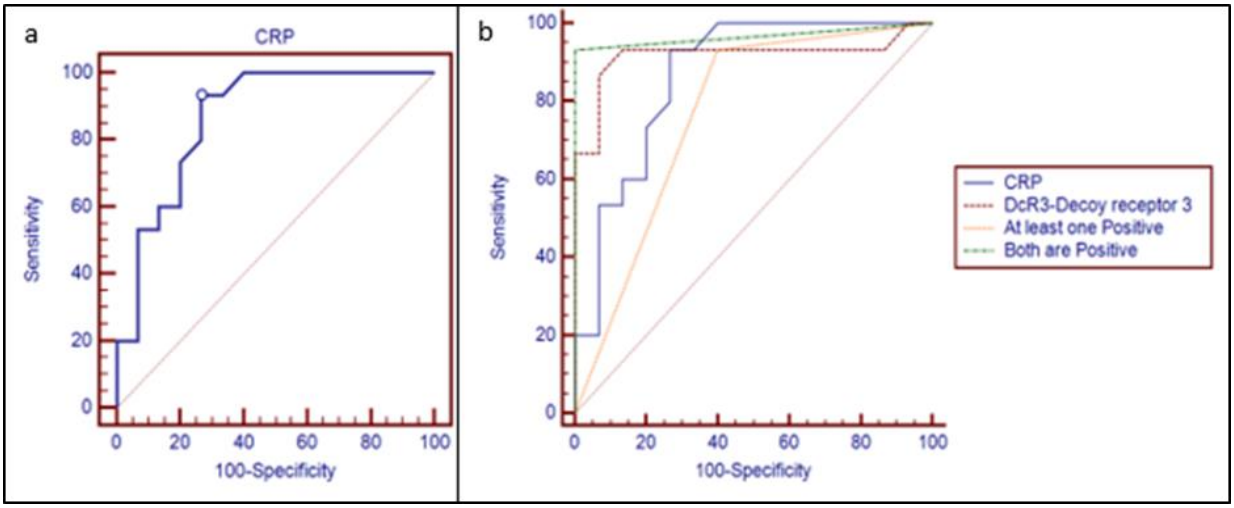

Fig. 6: ROC curve analyses for: a) CRP in sepsis versus SIRS patients. b) The combined DcR3 and CRP in sepsis versus SIRS patients.

DISCUSSION

Early diagnosis of sepsis remains problematic as clinically it resembles non-infectious SIRS[10]. The microbiological diagnosis has low sensitivity and consumes a lot of time[7]. Biomarkers can rise early in the inflammatory response and some are promising candidates for early differentiation between sepsis and non-infectious SIRS[17]. The present study aimed to measure the serum level of DcR3 in sepsis patients to study its role as a promising biomarker for diagnosis of bacterial sepsis.

Our study reported that Gram-negative bacteremia was more prevalent (9/15,60%) with *Klebsiella pneumoniae* as the most common isolate (4/15, 26%), while the isolated Gram-positive bacteria were (6/15, 40%), and the most common was *Staphylococcus aureus* (4/15, 26%). Similarly, Lee et al.[18] reported that *Klebsiella pneumoniae* was the most commonly isolated Gram-negative bacteria (84/879, 9.6%), and *Staphylococcus aureus* was the most commonly isolated Gram-positive bacteria (182/879, 20.7%). However, Prakash et al.[19] found that *Escherichia coli* was the most commonly isolated Gram-negative bacteria (43/360, 11.9%), while the most commonly isolated Gram-positive bacteria was *Streptococcus* species (76/360, 21.1%).The variability in culture results can be explained by the different geographical locations, seasonal variations, epidemiological differences, and the different infection control policies[20].

The present study showed that mean TLC was higher in sepsis group than SIRS group, 18.1±5.49 n×10³/µL and 16.47 ± 4.99 n×10³/µL, respectively, yet that difference was not statistically significant. Similarly, Zhao et al.[8] reported that TLC was non-significantly higher in sepsis than SIRS patients, 18.40±3.52 n×10³/µL, and 16.62±4.58 n×10³/µL, respectively. But Anand et al.[21] found that the TLC was significantly higher in sepsis group, 20.6 n×10³/µL, than in SIRS group, 15.1 n×10³/µL.

Also, the present study revealed that ESR and CRP levels were significantly higher in sepsis than SIRS group with a mean CRP of 180 ± 73.29 mg/L and 100.87 ± 55.28 mg/L, respectively, and a mean ESR of 97.73 ± 30.83 mm/hr and 68.73 ± 28.68 mm/hr, respectively. These results agreed with Birlutiu and Birlutiu[22] who reported a significantly higher CRP and ESR levels in septic than non-septic patients with a mean CRP of 159.38 ± 108 mg/L and 85 ± 97 mg/L, respectively, and a mean ESR of 67 ± 32.84 mm/hr and 57 ± 39 mm/hr, respectively. However, Jekarl et al.[23] found that CRP and ESR were non-significantly higher in sepsis than non-sepsis patients with a mean CRP of 96.5 ± 66.5 mg/L and 78.5 ± 66.3 mg/L, respectively, and a mean ESR of 49.6 ± 25.8 mm/hr and 45.8 ± 25.1 mm/hr, respectively. These variations in TLC, CRP, and ESR levels can be explained by the different population characteristics and the different sample sizes.

DcR3 exerts, in addition to its decoy action, non-decoy immunomodulatory actions as the induction M2-like macrophages and the skewing of T helper response towards Th2 phenotype[24]. Other studies found that DcR3 serum level was elevated in rheumatoid arthritis[25], colorectal carcinoma[26], and renal cell carcinoma[27]. Yet its elevation in these various disorders was moderate unlike its drastic elevation in sepsis[13].

In the present study, the mean serum DcR3 levels in sepsis, SIRS, and healthy control groups were 5.21 ± 2.28 ng/mL, 1.96 ± 0.90 ng/mL, and 0.95 ± 0.79 ng/mL, respectively, with a 2.6-fold difference in DcR3 level between sepsis and SIRS groups, and the DcR3 level was significantly higher in sepsis than SIRS and healthy control groups. These results were in concordance with Hou et al.[11] who reported mean DcR3 levels of 6.11 ± 2.58 ng/ml, 2.62 ± 1.46 ng/ml, and 0.91 ± 0.56 ng/ml in sepsis patients, SIRS patients, and healthy controls,

respectively, with a 2.33-fold difference between sepsis and SIRS groups. Also, Ali et al.[28] reported that the mean DcR3 values for sepsis, SIRS, and control groups were 5.59 ± 4.79 ng/mL, 1.67 ± 0.66 ng/mL, and 0.541 ± 0.11 ng/mL, respectively, with a 3.35-fold difference between sepsis and SIRS groups. Contrarily, Kim et al.[13] found that the mean DcR3 values for sepsis, SIRS, and normal groups were 10.46 ± 1.46 ng/mL, 2.06 ± 0.33 ng/mL, and 0.43 ± 0.08 ng/mL respectively, with a 5.1-fold difference between sepsis and SIRS groups. That variation in DcR3 mean levels and fold differences of the different studies could be attributed to the use of different ELISA kits for each study, since all of them are research-only kits still in need for better standardization[29], or due to patient-related factors[11,] or sample sizes.

The present study reported that DcR3 was significantly higher in Gram-negative bacteremia than Gram-positive bacteremia. On the contrary, Gao et al.[12] found that DcR3 level was not correlated with the pathogen type. However, this result in our study might reflect an association between higher DcR3 level and higher severity of sepsis, commonly associated with Gram-negative bacteremia[30], and not necessarily a direct association between DcR3 level and pathogen type.

The present study showed a moderate positive correlation between DcR3 level and the levels of ESR and CRP, and a weak positive correlation between DcR3 and TLC. Similarly, Ali et al.[28] reported a significant correlation between DcR3 and both ESR and CRP, and a non-significant correlation between DcR3 and TLC.

The ROC curve analysis of the present study demonstrated that serum DcR3 had excellent diagnostic accuracy in distinguishing sepsis from SIRS patients at a cut-off >2.4 ng/mL, with 93.33% sensitivity and 86.67% specificity. Similarly Hou et al.[11] reported a DcR3 cut-off value of 2.85 ng/mL, with 95.8% sensitivity and 67.4% specificity. Also, Gao et al. [12] found that the optimal cut-off for DcR3 was 1.96 ng/mL with 90.77% sensitivity and 98.40% specificity. However, Zhao et al.[8] reported a lower cut-off, 1.69 ng/mL, with 91.2% sensitivity and 82.4% specificity. On the other hand, Kim et al.[13] found a higher cut-off, 3.24 ng/mL, with 96% sensitivity and 82.6% specificity.

Also, the present study showed that DcR3 had excellent diagnostic accuracy in discriminating sepsis patients from healthy controls at a cut-off >1.5 ng/mL, with 93.33% sensitivity and 93.33% specificity. This result was in concordance with Kim et al.[13] who reported a cut-off of 1.65 ng/mL with 100% sensitivity and 97.8% specificity. Conversely, Gao et al.[12] found a lower cut-off, 0.50 ng/mL, with 97.69% sensitivity and 98.04% specificity. That difference in DcR3 cut-off values could be attributed to the severity of cases included in different studies, as Gao et al.[12] reported that DcR3 level increased with severity and predicted the prognosis of sepsis.

CRP is an acute-phase protein of the pentraxin family that is synthesized mainly by hepatocytes after stimulation by interleukin-6 and other cytokines[31]. The normal concentration of CRP in healthy adults is below 10 mg/L and that level can be markedly increased during inflammation[32]. CRP concentration is used as a general indicator of inflammation and to monitor the patient's response to treatment[31].

In the present study, the optimal cut-off for CRP to distinguish sepsis from SIRS patients was >116 mg/L with 93.3% sensitivity and 73.3% specificity. Our results almost matched those found by Castelli et al.[33] who reported a cut-off value of 90 mg/L with 74% sensitivity and 85% specificity. However, Patil et al.[34] found 150 mg/L as a cut-off value with 69.6% sensitivity and 52.9% specificity. On the other hand, Jekarl et al.[23] reported a cut-off value of 51.16 mg/L with 66.5% sensitivity and 50.8% specificity. That heterogeneity in CRP results could be explained by the differences in patient populations and the different types of diagnostic kits used[35].

In the present study, ROC curve analysis of combined DcR3 and CRP for discriminating sepsis from SIRS patients showed that for a combination in which at least one of the biomarkers was positive the AUC was 0.767 with 93.33% sensitivity and 60% specificity. However, in the combination where both biomarkers were positive the AUC increased to be 0.967 with 93.33% sensitivity and 100% specificity. Other studies explored the possible benefit of using combinations of different biomarkers as Zhao et al.[8] who showed that a combination of DcR3, procalcitonin, and soluble urokinase type plasminogen activator receptor (suPAR) had the best performance to distinguish sepsis from SIRS patients, better than any of them alone or in a combination.

CONCLUSION

DcR3, alone or in combination with CRP, is a promising biomarker for distinguishing sepsis from SIRS patients and may efficiently guide physicians to identifying sepsis patients, for whom the further usage of new diagnostics can be cost-effective. Further large-scale studies in different populations are recommended to evaluate the role of DcR3 as a diagnostic and prognostic biomarker and to assess its role in therapeutic guidance.

Ethical considerations:

This study was approved by the Research Ethics Committee of Faculty of Medicine, Ain Shams University, with the approval number of FMASU M S 316 / 2020.

Conflicts of interest:
The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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