The Accuracy of Delta Neutrophil Index as a Marker of Sepsis Severity Level Compare to Serum Amyloid A

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Abstract

Background. Early diagnosis of infection before its progression to become organ dysfunction or circulation failure has an important clinical effect and critical patient outcome. Diagnostic modality used as a gold standard on diagnosing sepsis condition still relies on microbial culture. Microbial culture needed a long duration to grow bacteria in high numbers be identified. The upcoming alternative diagnostic modality used as a marker of sepsis severity level was Delta Neutrophil Index (DNI) and Serum Amyloid A (SAA). There were no references to compare the accuracy of DNI and SAA as a marker of sepsis severity level.
Methods. The comparative study using cross sectional design was used in patients with sepsis and severe sepsis or septic shock. The subject of the study were patients that first came known to the Emergency Room or underwent treatment in the inpatient unit, ICU (Intensive Care Unit) or IMC (Intermediate Care) Sardjito's Hospital who fulfilled the inclusion and exclusion criteria from 1 August 2016 to 7 January 2017. The independent variable was DNI and the dependent variable was sepsis severity level. All of blood samples underwent DNI and SAA tests. Distributed data used the Kolmogorov-Smirnov test. DNI and SAA accuracy used sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio (LR) and receiver-operating characteristics (ROC) curve.
Results. The study consisted of 45 subjects. The mean age was 52.98 years. The mean of SAA was 54.39 ± 45.53 mg/L, while the mean of DNI in was 12.47 ± 8.79 %. Cut off point DNI 6.85% with value of sensitivity 93%, specificity 70%, positive predictive value (PPV) 79.31%, and negative predictive value (NPV) 87.5%, likelihood ratio for a positive test result (LR+) (PLR) 14.28 and like hood ratio for a negative test result (LR-) (NLR) 3.3. Cut off for SAA 54.93 mg/L with value of sensitivity 60%, specificity 56%, positive predictive value (PPV) 52%, negative predictive value (NPV) 64%, like hood ratio for a positive test result (LR+) (PLR) 1.36 and likelihood ratio for a negative test result (LR-) (NLR) 0.71.
Conclusions. The DNI has better diagnostic accuracy value as a marker of sepsis severity level than SAA value. Periodic DNI may serve as prognostic factor for sepsis.

Keywords. *Sepsis, sepsis severity level, Delta Neutrophil Index (DNI), Serum Amyloid A (SAA)*

Abstrak

Latar Belakang: *Diagnosis dini infeksi sebelum berkembang menjadi disfungsi organ atau kegagalan sirkulasi memiliki dampak penting pada klinis dan keluaran pasien sakit kritis. Standar emas dalam mendiagnosis sepsis sampai saat ini masih menggunakan kultur mikroba. Namun, dibutuhkan waktu yang lama untuk menumbuhkan kuman dalam jumlah yang dapat diidentifikasi. Adanya alternatif diagnostik baru sebagai penanda derajat keparahan sepsis yaitu delta neutrophil index (DNI) dan serum amiloid a (SAA). Sampai saat ini belum ada yang membandingkan antara akurasi DNI dan SAA sebagai penanda derajat keparahan sepsis.*

***Metode penelitian**. Penelitian ini menggunakan Uji perbandingan dengan pasien sepsis dan sepsis berat atau syok sepsis. Pengambilan data dilakukan dengan pasien yang pertama kali diketahui baik saat pertama periksa ke IGD, atau sedang dalam perawatan di ruang rawat inap, ICU, maupun IMC RSUP Dr. Sardjito yang memenuhi kriteria inklusi dan eksklusi. Variabel bebas DNI dan variabel tergantung derajat keparahan sepsis. Kemudian semua tabung sampel darah pasien sepsis dilakukan pemeriksaan DNI dan SAA. Untuk mengetahui sebaran data berdistribusi normal atau tidak digunakan analisa statistik uji normalitas Kolmogorov-Smirnov. Untuk melihat akurasi DNI dan SAA menggunakan sensitivitas, spesifisitas, positif predictive value, negative predictive value, likelihood ratio dan kurva receiver-operating characteristics.*
***Hasil.** Penelitian terdiri dari 45 subjek. Umur rata-rata subjek adalah 52,98 tahun. Rata-rata SAA dalam penelitian ini adalah 54,39 ± 45,53 mg/L, sedangkan rata-rata DNI adalah 12,47 ± 8,79 %. Cut off point DNI 6,85% dengan nilai sensitivitas 93%, Spesifisitas 70%, Nilai duga + (PPV) 79.31%, Nilai duga - (NPV) 87.5%,* Likelihood ratio *untuk hasil tes positif (LR+) (PLR) 14,28, dan* Likelihood ratio *untuk hasil tes negatif (LR-) (NLR) 3,3. Cut off point SAA 54,93 mg/L dengan nilai sensitivitas 60%, spesifisitas 56%, Nilai duga + (PPV) 52%, Nilai duga -(NPV) 64%, Likelihood ratio untuk hasil tes positif (LR+) (PLR) 1,36 dan Likelihood ratio untuk hasil tes negatif (LR-) (NLR) 0,71.*
***Kesimpulan.** DNI mempunyai nilai akurasi diagnostik yang lebih baik sebagai penanda derajat keparahan sepsis dibandingkan nilai SAA.*

***Kata Kunci:** Sepsis, derajat keparahan sepsis, delta neutrophil index (DNI), Serum Amiloid A (SAA)*

Introduction

Sepsis is a heterogenic clinical syndrome in which related to age, etiology, early infection foci location, interval before getting adequate initiation therapy, comorbid condition and organ dysfunction pattern. Sepsis could develop to become organ dysfunction and/or circulation failure. Early diagnosis of infection and sepsis before progressing to become organ dysfunction or circulation failure has significant impact on clinical program and patient outcome.

Systemic inflammatory response against infection provokes released some mediator that used as a marker of sepsis severity level. Among acute phase proteins which have role on inflammatory response are C-reactive protein (CRP) and Serum Amyloid A (SAA). Serum Amyloid A is an Apo lipoprotein reported has a potency to be used to sepsis diagnose.

Serum Amyloid A founded up to 1000 times higher after 8-24 hours from septic onset. Compared to CRP, SAA level was increased faster, higher after septic onset, and stable on relatively high level. Serum Amyloid A has 76.4-98.4% sensitivity, 92.3-100% specificity, 85-100% positive prediction value, 58-99 negative prediction value, and 8-68 mg/L cut off.

Immature granulocyte reported as a marker of infection and sepsis. The disparity on leucocyte sub fraction (Delta Neutrophil Index/DNI) refers to immature granulocyte fraction that circulates on blood. When neutrophil counters stress and infection, its immature shape will enter circulation, known as left shifting, in which the immature granulocyte ratio compared to the total. This granulocyte precursor was more immature than the segment it was used as a better predictor on detecting infection. Immature granulocyte reported as a septic indicator that the proportion measured accurately. Current technology that used to this immature granulocyte was DNI test. In order of that, DNI used as early detection of sepsis (Park *et al.,*[14]), the DNI cut off when infection occurred was >2.8%, non-inflammation is 0, whereas on inflammation was <2.8% with sensitivity of 81.3% and specificity of 91.2%.

Method of Study

This study was a comparative study used cross sectionally design. The study conducted to know the accuracy of DNI compared to SAA as a marker of sepsis severity level. SAA and DNI measured at a time when patients came to the hospital with sepsis diagnose and severe sepsis or shock septic.

Target population was all of patients with clinically sepsis and severe sepsis or septic shock. Achievable population is patients with clinically sepsis and severe sepsis/septic shock taken care in Sardjito's Hospital. Study subjects either were patients with sepsis and severe sepsis /septic shock first known when first came the ER (emergency room) or underwent treatment at the inpatient unit, ICU (Intensive Care Unit) or IMC (Intermediete Care) Sardito's Hospital that fulfilled the inclusion and exclusion criteria. The protocol study approved by local research department and completed with written informed consent. Inclusion criteria are septic patient diagnosed based on clinical appearance and laboratory results, age ≥ years old, and willing to join the study. Patients with clinically sepsis, based on "*The ACCP and SCCM Consensus Conference"* criterias, have two or more of the following symptoms, which proved or clinically suspected that caused by bacteria or microorganism. Temperature >38.3 ºC or < 36ºC, and heart rate >90x/minute, respiratory rate >20x/minute or $PaCO_2$ < 32 mmHg; and/or leucocyte > 12.000/µL or < 4000/µL or band neutrophil > 10%. Exclusion criteria of this study are pregnant woman, hematological malignancy, malignancy of pulmonology and gastrointestinal, suffering of chronic inflammation (arthritis rheumatoid, scleroderma or systemic sclerosis, bronchiectasis, osteomyelitis, liver cirrhosis), congenital disease on liver, renal, lymph node, limp, adrenal and thyroid, on-going or history of GCSF therapy, glucocorticoid, immunosuppressant, or cytostatic given before the study.

Blood sample for SAA and DNI analysis, including others laboratory parameter were collected from vein puncture and conducted by skilled nurse in Sardjito's hospital. The samples collected when patients were came to the hospital through ER, or diagnosed as sepsis and severe sepsis/septic shock as patient that taken care in internal ward, ICU, or IMC. The DNI test used *Automated Hematology Analyzer* (ADVIA 2120, *Siemens, Inc.*). The formula to calculate DNI was DNI= (% neutrophil + % eosinophil) in MPO cannal – (% PMN) in core lobular cannal.

SAA tested with ELISA method done by *quantitative sandwich immunoassay* technique. *Micro titer* plate, which had been set together in the kit, were coated with a monoclonal antibody specific for SAA standard or sample, then was added on each *micro titer plate well* and incubated.

Characteristic data of study subject in the form of numeric variable presented as mean and standard deviation, or if assumption of normality rejected then presented as median and interquartile range. Categorical variable presented as frequency number either absolute or relative. Statistical analysis of Kolmogorov-Smirnov test used to determine the distributed data. Here, to deteremine DNI or SAA accuracy used sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio and receiver-operating characteristics (ROC) curve. The results considered significant if $p<0.05$.

This study was non-experimental study, and did not have any particular intervention on subject. Study subject who willing to join

the study signed an informed consent. The ethical clearance issued by Ethical Committee of Medical and Health Research Faculty of Medicine Universitas Gadjah Mada.

Results and Discussion

Characteristic data of study subject demography based on total number and percentage include age and sex. The minimal subjects in this study were 45 subjects. Characteristic data of study subject demography presented in table 1. Mean age of the subjects was 52.98 years, number of patients with age ≤ 52.98 years were 20 patients (44.4%), and number of patients with age >52.98 were 25 patients (55.6%).

Older age was a risk factor for mortality because their relations to comorbid disease, immune response abnormality, malnutrition, increase of pathogen exposure in care, increase use of medical instrument such as urinary catheter and intravenous infusion.

In this study, the subjects who suffered for sepsis was higher in male, 26 patients (57.8%), compare to female, 19 patients (42.2%). In cohort study, patient with severe sepsis was predominantly male patients (58.8%). Male has higher risk to suffer sepsis compared to female with annual relative risk 1.28.

SAA mean was 54.39 ± 45.53 mg/L, DNI mean was 12.47 ± 8.79 % . SAA, and DNI mean from this study result became a cut-off point to determine the level of that SAA and DNI. Study subjects divided into two groups based on severity degree, sepsis group that consisted of 20 patients (44.4%) and severe sepsis/septic shock group that consisted of 25 patients (55.6%). Furthermore, normality test for age and hematologic parameter conducted using Kolmogorov-Smirnov normality test, as the sample amount for each group was more than 30.

Table 1. Demography characteristic of study subjects (n = 45)

Subject characteristic	n (%)	Mean ± SD
SAA		54.39 ± 45.53 mg/L
DNI		12.47 ± 8.79 %
Age (year)		
- >52.98 years	25 (55.6 %)	52.98 ± 16.54
- ≤52.98 years	20 (44.4%)	years
Sex		
- Male	26 (57.8 %)	
- Female	19 (42.2 %)	
Sepsis severity level		
- Sepsis	20 (44.4 %)	
- Severe sepsis/ septic shock	25 (55.6 %)	
Comorbid:		
- Diabetes mellitus (DM)	10 (22.2 %)	
- Renal failure	22 (48.80 %)	
- Heart failure	5 (11.1 %)	
- COPD	4 (8.8 %)	
- Stroke	3 (6.6 %)	
- TBC	1 (2.2 %)	

Table 6. Normality test

Variable	Kolmogorov-Smirnov	Value p	Interpretation
Age	.104	.200	Normal
ANC (/µl)	.088	.200	Normal
WBC (/µl)	.103	.200	Normal
SAA	.117	.149	Normal
DNI	.114	.171	Normal

** p > 0.05, data were normally distributed*

Normality test result displays that all data from variable of age, ANC, WBC, SAA, and DNI were normally distributed (p > 0.05). To see comparison of clinical baseline data of study subject characteristic between sepsis patient and severe sepsis/septic shock patient can refer to table 3.

Table 3. Clinical baseline of study subject characteristic (N = 45)

Variable	Sepsis severity level		*p value*
	Sepsis	Severe sepsis/shock septic	
Age	54.70 ± 16.70	51.60 ± 16.63	0.538
Sex: N (%)			
• Male	7 (15.6 %)	12 (26.7 %)	0.284
• Female	13 (28.4 %)	13 (28.9 %)	
Comorbid			
- Diabetes mellitus (DM)	4 (8.9%)	6(13.3%)	
- Renal failure	10 (22.2%)	12 (26.7%)	
- Heart failure	2 (4.4%)	3 (6.7%)	0.763
- COPD	3 (6.7%)	1 (2.2%)	
- Stroke	1 (2.2%)	2 (4.4%)	
- TBC	0	1 (2.2%)	
ANC(/µl)	14.36 ± 7.43	11.93 ± 5.57	0.218
WBC(/µl)	17.03 ± 8.10	14.07 ± 6.06	0.168

Based on independent test *t-test/Mann Whitney U-test* on table 3, it showed that mean age, sex percentage, mean ANC, WBC, and comorbid between sepsis group and severe sepsis/septic shock group were not statistically significant ($p > 0.05$).

Main output

Sensitivity and specificity test conducted to see prediction result of DNI accuracy compared to SAA on diagnosing sepsis severity level.

Table 8. Comparison of Delta Neutrophil Index (DNI) and Amyloid A Serum (SAA) toward sepsis severity level, sepsis-severe sepsis/ septic shock (N=45)

Variable	Sepsis Severity Level		*p value*
	Sepsis (N = 20)	Severe Sepsis/Septic Shock (N = 25)	
DNI	5.56 ± 3.42	18.00 ± 7.78	0.001*
SAA	45.96 ± 39.94	61.14 ± 49.31	0.271

** Value p ≤ 0.05 = statistically significant*

After conducted *independent t-test* study result showed that there's statistically significant between sepsis patient and severe sepsis/septic shock patient on DNI (Delta Neutrophil Index) variable with p value $p < 0.05$, greater significance on severe sepsis/septic shock patient compared to sepsis patient (18.00 % compared to 5.56%). SAA (Serum Amyloid A) variable between sepsis patient and severe sepsis/septic shock patient is not statistically significant ($p > 0.05$). Severe sepsis/septic shock patient has higher level of SAA compared to sepsis one (61.14 mg/L compared to 45.96 mg/L).

Statistically determining the cut-off point

To test the diagnostic value of the DNI and SAA assessment Area Under the Curve (AUC) and the determination of the point of intersection or Cut off Point (COP). After the determination of the COP will be categorized based on that value into two categories (high and low) are then performed cross tabulation to determine the sensitivity, specificity, predictive value and likelihood ratio AUC following determination result, COP and cross-tabulation of the DNI and SAA.

In the picture above, the ROC curve DNI and SAA above, indicates that the value

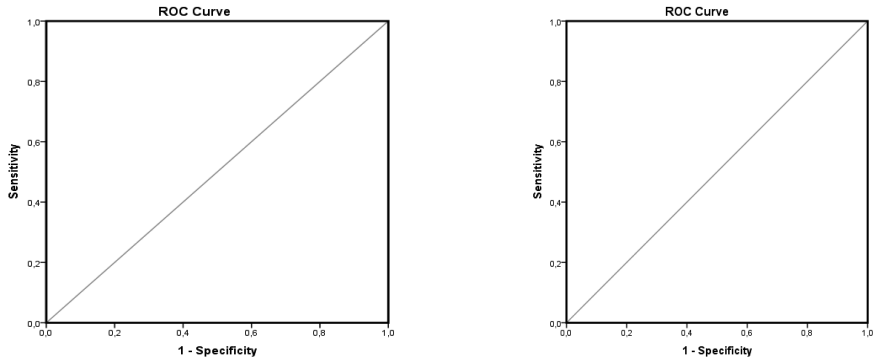


Figure 9. Graph ROC DNI and SAA as a marker the severity of sepsis

Table 9. Area under the Cuvier (AUC) DNI and SAA as a marker of the severity of sepsis is sepsis and severe sepsis / septic shock

Variable	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
DNI	1.000	.000	.000	1.000	1.000
SAA	1.000	.000	.000	1.000	1.000

of the DNI and SAA have a good diagnostic value for the curve away from the line of 50% and even up to 100% with ap value of 0.001. In Table 9 above are statistically AUC values of 99.6% (95% CI 98.6% -100%) the relatively strong. To determine the exact value of the DNI and the SAA in order to gain sensitivity and specificity, and predictive value was good then continued determination of the point of intersection curves of sensitivity and specificity.

Based on data in the image above, a score cut of point DNI contained in the value of 16. At that point, there cut off sensitivity and specificity. At the cut-off point value of 6.85 DNI. The following diagnostic tests are to determine the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio.

Cut Off Point DNI

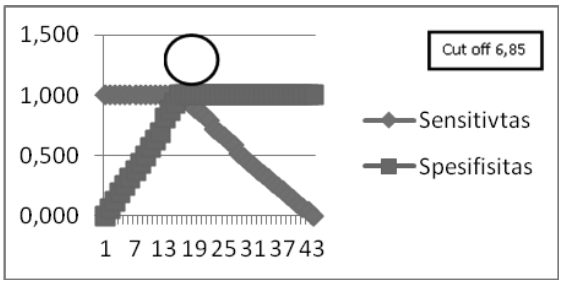


Figure 10. Cut of Point DNI

Table 10. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio prediction accuracy of the DNI as a marker of the severity of sepsis is sepsis and severe sepsis / septic shock

		Severity of Sepsis		
	Cut off point	Severe sepsis/ Septic shock	Sepsis	Total
DNI	≥6.85	23	6	29
	<6.85	2	14	16
	Total	25	20	45

Sensitivity (Sn) : 93 %
Specificity (Sp) : 70 %
Diagnostic accuracy (DA) : 82.2 %
+ Predictive value (PPV) : 79.31 %
- Predictive value (NPV) : 87.5 %
Likelihood ratio for positive test result (LR+) (PLR): 14.28
Likelihood ratio for negative test result (LR-) (NLR): 3.3

Cut Off Point SAA

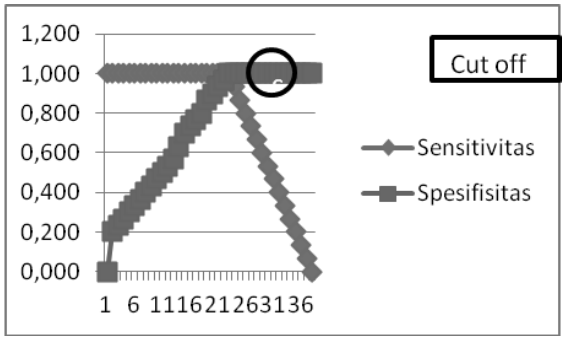


Figure 11. *Cut of Point* **SAA**

Based on data in the image above, a score cut of point SAA contained in the value of 13. At that cut off point, the sensitivity and specificity value SAA 66.185. The following diagnostic tests are to determine the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio.

In the above data showed that the value of the DNI was statistically better than the SAA with sensitivity 93% and specificity of 70%. While SAA values were statistically, lower than the DNI with a sensitivity of 40% and a specificity of 75%.

Determination of clinical cut-off point

On the data above, the calculation of the cutoff point based on statistics, obtained SAA values were lower than the DNI. Therefore, researchers perform calculations clinical cut-off point is to use the average DNI and the existing SAA on 45 research subjects. Cut-off point used to determine low and high DNI using the average is 12.47%. Results of statistical test sensitivity and specificity of the DNI of the severity of sepsis are sepsis and severe sepsis or septic shock seen in table 13 below.

Table 11. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio prediction accuracy of SAA as a marker of the severity of sepsis is sepsis and severe sepsis / septic shock

	Severity of Sepsis			
	Cut off point	Severe sepsis/ Septic shock	Sepsis	Total
SAA	≥ 66.185	10	5	15
	<661185	15	15	30
	Total	25	20	45

*Sensitivity (Sn) : 40 %, Specificity (Sp): 75 %, Diagnostic accuracy (DA): 55.5 %
+ Predictive value (PPV): 66.67 %, - Predictive value (NPV): 50 %, Likelihood ratio for positive test result (LR+) (PLR): 1.67, Likelihood ratio for negative test result (LR-) (NLR):4

Each prediction of DNI accuracy compared to SAA as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, measured based on diagnostic test.

Analysis on table 12 and 15 showed that DNI has higher accurate prediction as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, compared to SAA. This result of DNI accuracy as a marker of sepsis severity level supported by previous study that had results of sensitivity 81.3% and specificity 91%. Another study reported SAA accuracy as

Table 12. Comparison DNI prediction accuracy compared to the SAA as a marker of the severity of sepsis is sepsis and severe sepsis or septic shock

Variable	AUC	Sn	Sp	PPV	NPV	PLR	NLR
DNI	100%	93%	70%	79.31	87.5%	14.28	3.33
SAA	100%	40%	75%	66.67%	50%	1.67	4

*DNI = *Delta Neutrophil Index*; SAA = *Serum Amyloid A*

Table 13. Calculation of sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio on prediction of DNI accuracy as a marker of sepsis severity level, sepsis-severe sepsis/septic shock

		Sepsis Severity Level		
		Sepsis	Severe Sepsis/Septic Shock	Total
DNI	Low (< 12.47 %)	18 (a)	3 (b)	21 (a+b)
	High (≥ 12.47 %)	2 (c)	22 (d)	24 (c+d)
	Total	20 (a+c)	25 (b+d)	45 (a+b+c+d)

**Sensitivity (Sn): 90 %, Specificity (Sp): 88%, Diagnostic accuracy (DA): 44 %*
+ Predictive value (PPV) : 86%, (-) Predictive value (NPV) : 92%, Likelihood ratio for positive test result (LR+) (PLR):7.50, Likelihood ratio for negative test result (LR-) (NLR):0.11, Cut off point used on determining the level of SAA is SAA mean, which is 54.39 mg/L.

Tabel 14. Calculation of sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio on prediction of SAA accuracy as a marker of sepsis severity level, sepsis-severe sepsis/septic shock

		Sepsis Severity Level		
		Sepsis	Severe Sepsis/Septic Shock	Total
SAA	Low (< 54.39 mg/L)	12 (a)	11 (b)	23 (a+b)
	High (≥ 54.39 mg/L)	8 (c)	14 (d)	22 (c+d)
	Total	20 (a+c)	25 (b+d)	45 (a+b+c+d)

**Sensitivity (Sn) : 60 %, Specificity (Sp): 56%, Diagnostic accuracy (DA): 44 %,*
+ Predictive value (PPV): 52%, - Predictive value (NPV): 64%, Likelihood ratio for positive test result (LR+) (PLR): 1.36, Likelihood ratio for negative test result (LR-) (NLR): 0.71

a marker of sepsis severity level and had results of sensitivity 76.4% and specificity 92.3%.

To see prediction of DNI and SAA accuracy as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, value of area under the curve (AUC) from ROC method used. Statistically, area under the curve value could be interpreted as follows: > 50% - 60% (very weak), > 60%- 70% (weak), >70% - 80% (moderate), > 80%- 90% (strong), and 90% - 100% (very strong). To determine the result of DNI and SAA ROC curve and value of area under the curve as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, could see at the table 12 and figure 9.

Based on study results on table 16 and figure 11, it showed that the prediction level of DNI accuracy as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, have high discrimination value 93% (95% CI: 0.846-1.014; p < 0.001). It means that the prediction power of DNI accuracy as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, interpreted as very strong (90%-100%). ROC graphic shows that diagonal line consisted of point with sensitivity value = 1-specificity. As ROC curve goes closer to diagonal line, the result is getting worse. The best cut off is the farthest point at upper-left side of diagonal line. The study result shows that ROC graphic displays the very good prediction as the cutoff point is far from diagonal line located at upper-left side of diagonal line.

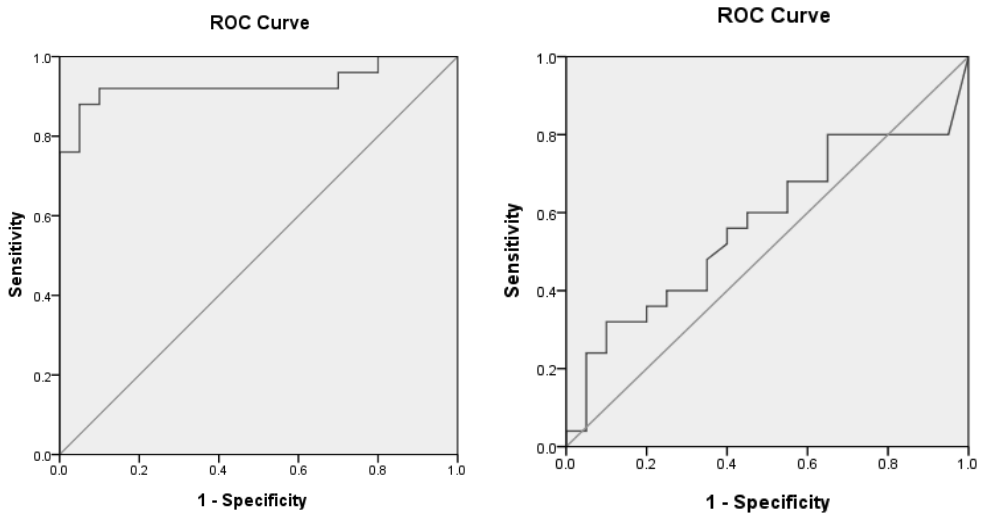
Table 15. Prediction comparison of DNI accuracy compared to SAA as a marker of sepsis severity level, sepsis-severe sepsis/septic shock

Variable	Sn	Sp	DA	PPV	NPV	PLR	NLR
DNI	90 %	88 %	44 %	86 %	92 %	7.50	0.11
SAA	60 %	56 %	44 %	52 %	64%	1.36	0.71

*DNI = Delta Neutrophil Index; SAA = Serum Amyloid A

Table 16. Value of DNI and SAA area under the curve (AUC) as a marker of sepsis severity level, sepsis-severe sepsis/septic shock

Variable	Area	Std. Error (a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
DNI	.930	.043	.000	.846	1,014
SAA	.570	.086	.424	.401	.739



(DNI) (SAA)

Figure 11. DNI and SAA ROC graphics as a marker of sepsis severity level

Based on study results on table 15 and figure 10, it show that the prediction level of SAA accuracy as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, have high discrimination value 57% (95% CI: 0.401-0.739; p < 0.05 = 0.424). It means that the prediction power of SAA accuracy as a marker of sepsis severity level, sepsis-severe sepsis/septic shock, is interpreted as very weak (>50%-60%). ROC graphic shows that diagonal line consisted of point with sensitivity value = 1-specificity. As ROC curve goes closer to diagonal line, the result is getting worse. The best cut off is the farthest point at upper-left side of diagonal line. The study result shows that ROC graphic displays the bad prediction, as the cut-off point is close from diagonal line located at right side of diagonal line.

On table 16, which is table of area under the curve (AUC) value-confidence interval, 95% on DNI shows value of 0.846-1.019. This results shows the value goes across value 1 which means DNI is a strong predictor as a marker of sepsis severity level, whereas area

under the curve (AUC) value-confidence interval 95%on SAA shows value of 0.401-0.739. This results show the value is under value 1 which means SAA is a weak predictor as a marker of sepsis severity level. DNI refers to the number of granulocyte precursor in the blood that correlated to sepsis severity level on critical patient. Increase of DNI level preceding the condition of organ failure so that it can contribute to identify patient with risk of severe sepsis/septic shock. DNI level significantly increase in condition of severe sepsis/septic shock and DIC (disseminated intravascular coagulation). This condition possibly related to relation of DNI, hypercoagulable state, and sepsis condition so that DNI used as a predictor of sepsis severity level. DNI cut-off point >5.2% is an optimal cut off on predicting severe sepsis/septic shock and as a superior marker than lactate test and others. Therefore, did Park *et al.* (2011) stated that DNI with cutoff point >6.5% is a superior marker on severe sepsis/septic shock condition than WBC, ANC, lactate or CRP.

Conclusions

The DNI has better diagnostic accuracy value as a marker of sepsis severity level than SAA value. Periodic DNI may serve as prognostic factor for sepsis.

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