Lactate clearance cut off for early mortality prediction in adult sepsis and septic shock patients

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Abstract. Previous lactate clearance cut off for early mortality prediction in sepsis and septic shock patient was determined by consensus from small sample size-study. We investigated the best lactate clearance cut off and its ability to predict early mortality in sepsis and septic shock patients. This cohort study was conducted in Intensive Care Unit of CiptoMangunkusumo Hospital in 2013. Patients' lactate clearance and eight other resuscitationendpoints were recorded, and theoutcome was observed during the first 120 hours. The clearance cut off was determined using receiver operating characteristic (ROC) analysis, and its ability was investigated with Cox's proportional hazard regression analysis using other resuscitation endpoints as confounders. Total of 268 subjects was included, of whom 70 (26.11%) subjects died within the first 120 hours. The area under ROC of lactate clearance to predict early mortality was 0.78 (95% % confidence interval [CI] 0.71-0.84) with best cut off was <7.5% (sensitivity and specificity 88.99% and 81.4% respectively). Compared with group achieving lactate clearance target, group not achieving lactate clearance target had to increase early mortality risk (adjusted hazard ratio 13.42; 95%CI 7.19-25.07). In conclusion, the best lactate clearance cut off as anearly mortality predictor in sepsis and septic shock patients is 7.5%.

1. Introduction

An era of the quantitative resuscitative strategy of sepsis and septic shock patients had begun in the early year 2000 when early goal-directed therapy protocol was published.[1] In accordance with the publication, an interest of microcirculation endpoint resuscitation concept has emerged, with the recommendation of central venous oxygen saturation ($ScvO_2$) and lactate measurement in resuscitation process of sepsis and septic shock patients.[2-5] With the limitation of invasive procedure which was needed to be performed in gaining $ScvO_2$, researchers have searched whether less invasive indicators, i.e., lactate and lactate derived-parameter, were a valid option to assess resuscitation response and could be used as a prognostic marker. Lactate derived-parameters reflect a more general whole body metabolic process compared with an indicator of oxygen delivery and consumption that was reflected by $ScvO_2$.[6-8]

Numerous studies on the use of lactate clearance as endpoint resuscitation have been published since Nguyen, et al. published the use of lactate clearance >10% as a marker of survival predictors in sepsis and septic shock patients.[9-12] Although this cut off was used by several types of research afterward, this early study was done on a relatively small sample size, and there was no specific statistical analysis performed to determine the cut off to predict mortality.[10] Moreover, this cut off

has not been accepted as a target of resuscitation in Surviving Sepsis Campaign 2016. The committee suggests normalization of lactate as an endpoint resuscitation.[13] Considering these limitations, we investigated the best lactate clearance cut off for mortality prediction in sepsis and septic shock patients. We then investigated the ability of the cut off for mortality prediction in those population.

2. Methods

The study was a one-year retrospective cohort study from medical record of adult patients hospitalized in Intensive Care Unit (ICU), CiptoMangunkusumo Hospital, Indonesia during 2013 who were based on re-classification met the sepsis and septic shock definition according to the sepsis-3 criteria. Sepsis is defined as infection resulting in an acute change of two or more organ dysfunction score; as well as a septic shock is defined as sepsis patient with persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) $\geq$65mmHg and lactate >2mmol/L despite adequate volume resuscitation.[14-15]

Diagnosis, gender, age, comorbidities, sepsis origin, 6-hour resuscitation endpoints (including central venous pressure (CVP), MAP, urine output, hematocrit (Ht), $ScvO_2$, lactate, lactate clearance, standard base excess (SBE), and a number of organ dysfunction) were recorded. Survival was followed up during 120 hours (early period), based on the early mortality definition used in previous sepsis study. Lactate clearance was defined by an equation: [(pre-resuscitation lactate concentration – post-resuscitation lactate concentration) / pre-resuscitation lactate concentration] x 100%.[10]

Quantitative variables were presented with median (interquartile range [IQR] since the value results were not normally distributed; while qualitative data were presented with number and percentage. Best lactate clearance cut off for early mortality prediction was determined using receiver operating characteristic (ROC) analysis. The result was expressed with 95% confidence interval (CI). We then classified subjects into two groups based on the determined lactate clearance cut off. The lactate clearance cut off theability for early mortality prediction was investigated with Cox's proportional hazard regression analysis using other resuscitation endpoints as confounders. Statistical analysis was performed with SPSS software version 20.0 (IBM Corp., USA). The Faculty of Medicine Universitas Indonesia Ethics Committee approved the study.

3. Results

3.1. Subjects' characteristics and resuscitationendpoints

In 2013, 268 ICU sepsis and septic shock patients meeting the sepsis-3 criteria were included and eligible for further analysis. The characteristics of subjects were provided in table 1 while achievement of resuscitation endpoints was provided in table 2.

Table 1. Comparison of characteristics of subjects based on the early outcome.

Variable	Early period survivors (n=198)	Early period non-survivors (n=70)
Sex (*n*, male/female)	110/80	37/33
Age (years) [a]	48 (25)	50 (24)
Septic shock (*n*, %)	95 (47.97)	57 (81.42)
Comorbidity (*n*, %)		
Chronic heart failure	25 (12.62)	15 (21.42)
Chronic kidney disease, dialysis	10 (5.05)	10 (14.28)
Cerebrovascular disease	24 (12.12)	10 (14.28)
Hepatic cirrhosis	6 (3.03)	2 (2.85)
Malignancy	72 (36.36)	28 (40)
Diabetes mellitus	52 (26.26)	29 (41.42)
Sepsis origin (*n*, %)[b]		
Intracranial	9 (4.54)	3 (4.28)

Respiratory tract	130 (65.65)	51 (72.85)
Intra-abdominal	58 (29.29)	26 (37.14)
Genito-urinary tract	16 (8.08)	6 (8.57)
Skin and soft tissue	34 (17.17)	10 (14.28)

[a]data presented as median (interquartile range).
[b]subjects fulfill multiple variables were calculated more than once.

Table 2. Comparison of resuscitation endpoints achievement of subjects based on the early outcome.

Variable	Early period survivors (n=198)	Early period non-survivors (n=70)
Central venous pressure (*n*, %)		
8-12 mmHg	62 (31.32)	28 (40)
<8 mmHg	127 (64.14)	35 (50)
>12 mmHg	9 (4.54)	7 (10)
Mean arterial pressure (*n*, %)		
≥65 mmHg	178 (89.89)	48 (68.57)
<65 mmHg	20 (10.11)	22 (31.43)
Urine output (*n*, %)		
≥0,5 mL/kg/hour	181 (91.42)	42 (60)
<0,5 mL/kg/hour	17 (8.58)	28 (40)
Hematocrit (*n*, %)		
≥30 %	108 (54.55)	26 (37.14)
<30%	90 (45.45)	44 (62.86)
Central venous oxygensaturation ($ScvO_2$) (*n*, %)	144 (72.73)	54 (77.15)
≥70%	54 (27.27)	16 (22.85)
<70%		
Lactate (*n*, %)		
<2 mmol/L	109 (55.06)	10 (14.29)
2-3.9 mmol/L	63 (31.81)	26 (37.14)
≥4 mmol/L	26 (13.13)	34 (48.57)
Standard base excess (*n*, %)		
>-2 mmol/L	106 (53.55)	15 (21.44)
-2 to -5,9 mmol/L	48 (24.24)	17 (24.28)
-6 to -14,9 mmol/L	39 (19.69)	32 (45.71)
≤-15 mmol/L	5 (2.52)	6 (8.57)
Number of organ dysfunction based on Sequential Organ Failure Assessment (SOFA) (*n*, %)		
1 organ dysfunction	87 (43.93)	7 (10)
2 organ dysfunctions	64 (32.32)	14 (20)
More than two organ dysfunctions	47 (23.75)	49 (70)

3.2. Determination of lactate clearance cut off

Best lactate clearance cut off for early mortality prediction was ≤7.5%, with AUROC was 0.78 (95% CI 0.71-0.84) (figure 1), sensitivity and specificity were 88.99% and 81.4% respectively.

3.3. Early mortality risk prediction

Compared with group achieving those lactate clearance target, group which did not achieved those lactate clearance target had increase early mortality risk (hazard ratio [HR] 17.65; 95%CI 9.60-32.45). After adjustment with 8 other resuscitation endpoints as potential predictors, early lactate clearance ≤7.5% was still significantly associated with early mortality (adjusted HR 13.42; 95%CI 7.19-25.07).

4. Discussion

In the era of quantitative resuscitation in sepsis, two issues that need to be addressed are endpoint resuscitation option and target needed to be reached, that can be used in guiding and determining theadequacy of resuscitation.[5,6] Lactate clearance has been regarded as apredictor of sepsis mortality based on its consistent link with higher mortality risk. Although numerous studies have cited the lactate clearance cut off that was firstly used by Nguyenet al. in their study; there is no valid statistical analysis used to determine those cutoff, i.e., 10%.[7,9,10,12] Without valid statistical analysis, one could assume lower, and higher cut off probably show better prediction ability. This is the first Indonesian study assessing best lactate clearance cut off for early mortality prediction using valid statistical analysis. Compared with previous similar studies, this study has a larger sample size (i.e.111 and 166 subjects in Nguyenet al. and Arnold, et al. studies respectively) and address more specific time frame of early period outcome in sepsis as was used in Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis trial.[9,10,12,16]

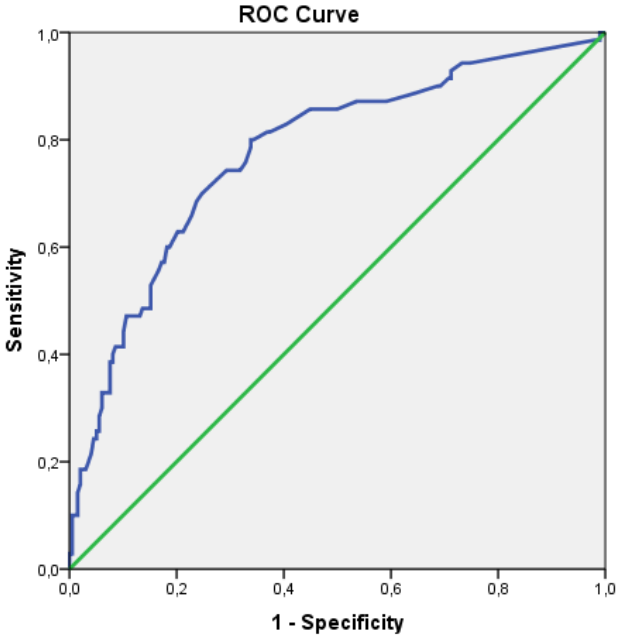

Figure 1. The area under ROC of lactate clearance for early mortality prediction.

Compared with the cut off that widely used in previous studies, our study proves a lower lactate clearance target (i.e.,≥7.5%) is the best cut off with good AUROC (figure 1), positive and negative predictive value. This cut off further showed a powerful determinant of sepsis mortality predictors after it was tested in multivariate analysis using other resuscitation endpoints as a covariate. Thus, this analysis showed a potential use of lactate clearance ≥7.5% as asingle predictor of resuscitation adequacy in sepsis and septic shock patients. With 10% cut off, our data showed a lesser sensitivity (86.9% versus 88.9% with 7.5% cut off) with no difference in sensitivity. Witha little difference in sensitivity, this study supports the consideration of using the previous cut off since it has been extensively investigated and cited in resuscitation protocols.

There is an important limitation of our study. This is an observational retrospective cohort study that bears limitations of retrospective study with theinability to directly establish cause and effect relationships. However indirect cause and effect relationships could be concluded based on fulfillment of Bradford Hill criteria on the causality of lactate clearance and mortality.[17] Further clinical trials are needed to prove the impact use of this cut off as endpoint resuscitation in decreasing early mortality of sepsis and septic shock patients.

5. Conclusion

The best lactate clearance cut off for early mortality prediction in sepsis and septic shock patients is 7.5%. Lactate clearance is an independent predictor of mortality in sepsis and septic shock patients.

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