Degree of agreement among sepsis diagnosis criteria in adult emergency room patients with infection

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Abstract. The study on the degree of agreement among three established sepsis diagnosis criteria become the necessity to investigate the best sepsis diagnosis criteria in Indonesia further. A cross-sectional study of adult Emergency Room patients hospitalized with a diagnosis of infection in CiptoMangunkusumo Hospital, Indonesia was conducted during March and April 2017. We recorded diagnosis, gender, age, comorbidities, infection source, and origin. Every subject was classified into sepsis and non-sepsis based on 1991, 2001 and sepsis-3 criteria. Raw % and Kappa agreement coefficients ($\kappa$) were calculated according to previously established formula to measure the degree of agreement among three diagnostic criteria. As many as 278 subjects were included in this study. The raw % agreement and $\kappa$ between 1991 and 2001 criteria is 69.07% and 0.34 respectively. The raw % agreement and $\kappa$ between 2001 and sepsis-3 criteria is 56.12% and 0.15 respectively. The raw % agreement and $\kappa$ between 1991 and sepsis-3 criteria is 48.19% and -0.02. In conclusions, there is unfair agreement between 1991 and 2001 criteria, poor agreement between 2001 and sepsis-3 criteria, and poor disagreement between 1991 and sepsis-3 criteria. This necessitates further Indonesian study of the best diagnosis criteria to diagnose an infected patient with sepsis.

1. Introduction
It is considered to be a problematic task to classify a group of infected patient with high risk of mortality into a sepsis group, although the first diagnosis criteria of sepsis have been published for more than twenty years.[1-4] The first diagnosis criteria for 1991 were constructed with systemic inflammatory response syndrome (SIRS) components, which are considered too sensitive and less specific.[5,6] Sepsis Occurrence in Acutely ill Patients (SOAP) study revealed that 93% patients in intensive care unit (ICU) would fulfill SIRS criteria once during their hospitalization in ICU.[7] The second diagnosis criteria were established as a consensus based on a revision of the first criteria, by adding altered mental status, edema, and hyperglycemia in the general variables.[8] However, this second diagnosis criterion has not been used widely in researchers. In 2016, the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) revised the sepsis diagnosis criteria by using the presence of organ dysfunction to define a group of infected patient with sepsis.[9,10]

The three options for diagnostic criteria could be used by clinicians to diagnose sepsis since there were pro and cons regarding which criteria should be used. However, there is no study on the degree of diagnosis agreement among these three criteria. We investigated the degree of diagnosis agreement
among these three criteria as a basis of necessity to further studied the best diagnosis criteria to diagnose an infected patient with sepsis in Indonesia.

2. Methods
The study was a cross-sectional study of adult Emergency Room patients hospitalized with a diagnosis of infection in Cipto Mangunkusumo Hospital, Indonesia during March and April 2017. Diagnosis, gender, age, comorbidities, infection source, and origin, were recorded. Each subject was classified into sepsis and non-sepsis based on 1991, 2001 and sepsis-3 criteria. Based on 1991 criteria, sepsis was diagnosed in the presence of two from four SIRS, i.e., body temperature above than 38°C or less than 36°C; heart rate more than 90 rate in a minute; respiratory rate more than 20 rate in a minute or hyperventilation with PaCO₂ less than 32 mmHg; and leukocyte count above than 12,000/mm³ or less than 4,000/mm³, or more than 10% immature neutrophil.[5] Based on 2001 criteria by SCCM, the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS), in addition to the previous SIRS criteria, sepsis was diagnosed with additional three general variables, i.e., altered mental status, edema, and hyperglycemia.[8] According to the sepsis-3 criteria, sepsis was diagnosed with an acute change of two or more Sequential Organ Failure Assessment (SOFA) score in a patient with infection.[9,10]

The sample size of the study was based on an estimated probability difference of 0.3. Assuming the relative error was 20%, the required total sample size was calculated to be 278 patients.[11] Raw % and Kappa agreement coefficients (κ) were calculated according to the previously established formula to measure the degree of agreement between 1991 and 2001 criteria, 1991 and sepsis-3 criteria, 2001 and sepsis-3 criteria respectively.[12] Quantitative variables were presented with a mean±standard deviation since the value result was normally distributed; while qualitative data were presented with number and percentage. 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
During March and April 2017, 278 patients with infection who were admitted to Emergency Room were included. The characteristics of subjects were provided in table 1.

| Table 1. Subjects’ characteristics. |
|------------------------------------|
| **Variable** | **Subjects (n=278)** |
| Sex (n, male/female) | 130/148 |
| Age (years) a | 50.33 ± 15.17 |
| Comorbidity (n, %) b | | |
| Chronic heart failure | 29 (10.43) |
| Chronic kidney disease | 83 (29.85) |
| Cerebrovascular disease | 19 (6.83) |
| Hepatic cirrhosis | 39 (14.02) |
| Malignancy | 62 (22.30) |
| Diabetes mellitus | 79 (28.41) |
| Infection source (n, %) b | | |
| Intracranial | 11 (3.95) |
| Respiratory tract | 208 (74.82) |
| Intra-abdominal | 38 (13.66) |
| Genito-urinary tract | 16 (5.75) |
| Skin and soft tissue | 46 (16.54) |
| Infection origin (n, %) | | |
| Community acquired-infection | 218 (78.41) |
| Hospital acquired-infection | 60 (21.58) |

a data presented as mean ± standard deviation; 
b subjects fulfill multiple variables were calculated more than once.
3.2. Degree of agreement among sepsis diagnostic criteria
From 278 subjects, 162 (58.27%), 190 (68.34%), 126 (45.32%) fulfilled sepsis diagnosis based on 1991 criteria, 2001 criteria and sepsis-3 criteria respectively. Table 2-4 showed the agreement between those diagnosis criteria.

Table 2. Agreement on the diagnosis of sepsis between 1991 and 2001 criteria.

|                        | Sepsis based on 1991 criteria | Not sepsis based on 1991 criteria | Total, 2001 criteria |
|------------------------|-------------------------------|-----------------------------------|---------------------|
| Sepsis based on 2001   | 133 (47.84%)                 | 57 (20.5%)                       | 190 (68.34%)        |
| criteria               |                               |                                  |                     |
| Not sepsis based on    | 29 (10.43%)                  | 59 (21.23%)                      | 88 (31.66%)         |
| 2001 criteria          |                               |                                  |                     |
| Total, 1991 criteria   | 162 (58.27%)                 | 116 (41.73%)                     | 278 (100%)          |

Table 3. Agreement on the diagnosis of sepsis between 1991 and sepsis-3 criteria.

|                        | Sepsis based on 1991 criteria | Not sepsis based on 1991 criteria | Total, sepsis-3 criteria |
|------------------------|-------------------------------|-----------------------------------|-------------------------|
| Sepsis based on sepsis-3 criteria | 72 (25.89%)                 | 54 (19.43%)                       | 126 (45.32%)            |
| criteria               |                               |                                  |                         |
| Not sepsis based on    | 90 (32.38%)                  | 62 (22.30%)                       | 152 (54.68%)           |
| sepsis-3 criteria      |                               |                                  |                         |
| Total, 1991 criteria   | 162 (58.27%)                 | 116 (41.73%)                      | 278 (100%)             |

Table 4. Agreement on the diagnosis of sepsis between 2001 and sepsis-3 criteria.

|                        | Sepsis based on 2001 criteria | Not sepsis based on 2001 criteria | Total, sepsis-3 criteria |
|------------------------|-------------------------------|-----------------------------------|-------------------------|
| Sepsis based on sepsis-3 criteria | 97 (34.89%)                 | 29 (10.43%)                       | 126 (45.32%)           |
| criteria               |                               |                                  |                         |
| Not sepsis based on    | 93 (33.45%)                  | 59 (21.23%)                       | 152 (54.68%)           |
| sepsis-3 criteria      |                               |                                  |                         |
| Total, 2001 criteria   | 190 (68.34%)                 | 88 (31.66%)                       | 278 (100%)             |

Based on data in table 2-4, we calculated the degree of agreement between diagnosis criteria and presented with raw % agreement and Kappa agreement coefficients, as can be seen in table 5.

Table 5. Raw % agreement and Kappa agreement coefficients of sepsis diagnosis criteria.

|                        | 1991 criteria                  | 2001 criteria                  | Sepsis-3 criteria      |
|------------------------|--------------------------------|--------------------------------|------------------------|
|                        | Raw=100%; \( \kappa=1 \)     | Raw=69.07%; \( \kappa=0.34 \) | Raw=48.19%; \( \kappa=-0.02 \) |
| 1991 criteria          |                                |                                |                        |
| 2001 criteria          | Raw=69.07%; \( \kappa=0.34 \) | Raw=100%; \( \kappa=1 \)      | Raw=56.12%; \( \kappa=0.15 \) |
| Sepsis-3 criteria      | Raw=48.19%; \( \kappa=-0.02 \) | Raw=56.12%; \( \kappa=0.15 \) | Raw=100%; \( \kappa=1 \) |

4. Discussion
An under-diagnosis of sepsis will potentially put a high risk of mortality patient in less observation and treatment.\[13,14\] On the other hand, the over-diagnosis of sepsis will results in over-treatment, including abuse of broad-spectrum antibiotics as a risk factor for antimicrobial resistance.\[15\] Failure to classify uniform patient in the sepsis group will also impact on global sepsis epidemiology report problem. Gattinoni et al. reported a mortality rate in France Sepsis pan study reached 60-62%, while the mortality...
rate of sepsis in the Australia and New Zealand study was 22.9-25.6%. [3,16] An Indonesian data from CiptoMangunkusumo Hospital, a top referral hospital in Indonesia, showed the mortality rate of severe sepsis and septic shock patients in ICU in 2012 was 47.8%. [17] The big discrepancy of mortality rate reported in several studies could be caused by the different severity of disease of patients included in the studies. Thus it is important to define the best criteria to diagnose an infected patient with sepsis if there is no agreement among those diagnosis criteria. [18-20] This is not only the first Indonesian study investigated the degree of agreement among 3 sepsis diagnosis criteria, but also the first reported study concerning the use of sepsis-3 diagnosis criteria done in the developing country.

The simplest measurement of agreement between two methods is by using raw % agreement or concordance rate. However, this raw % agreement can be misleading when the observations are unevenly distributed among the categories. In the uncommon diagnosis, the 2 diagnosis criteria can have nearly perfect agreement just by rarely stating that the diagnosis is present. On the other hand, in the very common diagnosis, the 2 diagnosis criteria can have a nearly perfect agreement by almost always stating that the diagnosis is present. Thus, in this study, we calculated the degree of agreement in those two measurement methods. [11,12]

The degree of agreement between 1991 and 2001 criteria is fair (raw % agreement=69.07%; κ=0.34); while the degree of agreement between 2001 and sepsis-3 criteria is poor (raw % agreement =56.12%; κ=0.15). The worst degree of agreement is shown by 1991 and sepsis-3 criteria (raw % agreement =48.19%; κ=0.02). Among three calculation of agreement degree, the best agreement is shown by 1991 and 2001 criteria. It can be explained by four similar components criteria to define infected patients with sepsis (body temperature, heart rate, respiratory rate, leukocyte count). [5,8]

However, the fair degree of the agreement reflects altered mental status, edema, and hyperglycemia as common manifestations found in infected patients with severe degree severity. The worst agreement between 1991 and sepsis-3 criteria can be explained by only slightly similarity of those 2 sepsis diagnosis criteria, i.e., respiratory rate in 1991 criteria and arterial O2 pressure divided by an inspiratory O2 fraction in 1991 and sepsis-3 criteria respectively. [5,10] This is in accordance with the opinion of many experts that while 1991 criteria are considered too sensitive and less specific, the sepsis-3 criteria is too specific and less specific. [14,21] The fair to the poor agreement of the three sepsis diagnosis criteria necessitates further Indonesian study of the best diagnosis criteria to diagnose an infected patient with sepsis.

5. Conclusion
There is a fair agreement between 1991 and 2001 criteria, poor agreement between 2001 and sepsis-3 criteria, and poor disagreement between 1991 and sepsis-3 criteria.

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