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DIAGNOSTIC VALUE COMBINATION COPEPTIN ULTRASENSITIVE WITH HIGH SENSITIVE CARDIAC TROPONIN T (HS-CTNT) IN NON ST SEGMENT ELEVATION SUSPECT ACUTE CORONARY SYNDROME

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Abstract – Early and proper acute coronary syndrome diagnosis needed for rapid and proper the theurapeutic. The purpose of this study was to determine the diagnostic value combination copeptin ultrasensitive and hs-cTnT in suspected of acute coronary syndromes patients with ECG images showing non ST elevation. Between October until november 2015, we included 91 consecutive patients suspect acute coronary syndrome patients from emergency department (ED). We measured copeptin ultrasensitive and hs-cTnT on admission and hs-cTnT after 3 hours later. Mean value copeptin-us for NSTEMI was 151.80 ± 130.03 pmol/L, median copeptin-us for unstable angina was 7.12 [1.145 – 62.23] pmol/L and mean copeptin-us for non ACS was 7.36 ± 4.17 pmol/L. Area under curve (AUC) combination copeptin-us with hs-cTnT was 0.941 (0.82 – 1.00). We obtained diagnostic value combination copeptin-us e" 13.97 pmol / L with hs-cTnT e" 14 pg / mL on admission to distinguish NSTEMI with unstable angina/no ACS for sensitivity 100%, specificity 90.78%, positive predictive value 68.18%,and negative predictive value 100%. Diagnostic value combinationcopeptin-us with hs-cTnT on admission better than hs-cTnT on admission only and it can use to rule out acute myocardinfark.

INTRODUCTION

Acute coronary syndrome (ACS) is clinical manifestations caused by myocardial ischemia due to coronary artery occlusion. The degree of occlusion correlates with clinical manifestations, electrocardiogram features, and cardiac markers (Overbaugh, 2009 and Braunwald, 2000). Acute coronary syndrome consists of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) (Anderson et al., 2007). In an emergency department (ED), triage is needed to determine whether the patient needs to be treated (rule in) or rule out. Mistakes in making decisions can result in increased mortality and morbidity. Sensitive and specific laboratory diagnostics are needed in addition to history, physical examination, and ECG to distinguish and ensure a diagnosis (Panthegini, 2002; Achar, 2005, Stone, 2004; and Tunstall-Pedoe, 1994).

Cardiac troponin (cTn) is the most specific cardiac biochemical marker for diagnosing myocardial infarction but is less sensitive because cTn increases within 4-10 hours after an acute myocard infark (AMI) attack, reaches peak levels at 12-24 hours and will return to normal after 4-10 days. It is become a limitation of cTn in diagnosing AMI quickly (Tunstall-Pedoe, 1994).

Copeptin is a C-terminal provasopressin (CT-proAVP) which is synthesized in the hypothalamus and secreted by the pituitary as an endogenous stress response. Copeptin in the AMI will increase rapidly after symptoms of chest pain and return to normal within 5-10 hours, so copeptin is used to rule out of the diagnosis of AMI (Keller et al., 2010).

MATERIALS AND METHODS

Design and research subject

Design of this study is cross-sectional. The subjects were suspect acute coronary syndromes from emergency department at National Cardiovascular Center Harapan Kita patients from October to November 2015 with onset less than 6 hours, non ST elevation ECG features, and ages 18-85 years. Exclusion criteria of this study were patients with trauma or major surgery in the previous 4 weeks, pregnant women, patients with anemia (Hb<10 g / dL), and terminal renal failure requiring dialysis (CKD stage V). The study was approved by the local ethics committee. Written informed consent was obtained from all participating patients.Patients will be examined hs-cTnT and copeptin-us on admission at ED and 3 hours later for hs-cTnT only. The diagnosis was made by the clinician at ED.

Blood Sampling and Assays

Six mililiters blood from cubiti vein used a tube with heparin anticoagulant on admission and 3 hours later were taken, then centrifuged at 1000-2000g in 10 minutes for hs-cTnT assay. The remaining samples on admission were stored at -20°C until assayed copeptin-us simultaneously. Copeptin-us assayed with immunoluminometric assay principle and using BRAHMS compact kryptor plus system. hS-cTnT assayed using Cobas e411 analyzer with electrochemiluminescence immunoassay (ECLIA) assay principle. Coefficient of variation (CV) within run for normal and high copeptin-us were 3% and 0.9%.

Statistical analysis

The normality of data distribution by Kolmogorov Smirnov test. Data are expressed as mean ± standard deviation or median (with interquartile range) for numeric data and as number and percentage for categorical variable. For the diagnostic test, the calculation of the sensitivity and specificity of the copeptin-us in establishing the NSTEMI diagnosis from UA and non-ACS were determined by the cut-off value with receiver operating curve (ROC) and area under curve (AUC) analysis. Diagnostic test uses a 2 x 2 table to get sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Statistical analysis were performed using SPSS ver.20

Table 1. Laboratory results for hemoglobin, creatinine, and eGFR.

Variable	Result (n=91)
Hemoglobin	13.63 ± 1.64*
Creatinine	1.06 [0.63 – 2.66]**
eGFR	67.91 ± 22.623*

*Normal data distribution
**Abnormal data distribution

RESULTS AND DISCUSSION

Characteristics of patients

From the 91 patients included in this study, mean age of the study subjects was 56.96 ± 11.82 years and 63 (69.2%) was male. The diagnosis was NSTEMI in 15 patients (16.5%), UA in 43 patients (47.3%), and non ACS in 33 patients (36.3%).

Laboratory results

Copeptin levels compared hs-cTnT

Based on Table 2, the level of copeptin-us on admission in NSTEMI patients (151.80 ± 130.03 pmol/L) was higher than hs-cTnT level (114 pg / mL (29 - 1102 pg / mL). In UA and non-ACS patients, copeptin-us level on admission was in normal range. The level of copeptin-us in NSTEMI patients was higher than hs-cTnT on admission level. hs-cTnT reached the highest level in NSTEMI after 3 hours later.

Table 2. Characteristics of copeptin-us and hs-cTnT levels based on diagnosis

Variable	Result (n=91)
hs-cTnT (on admission)	
▪ NSTEMI	114 pg/mL (29 – 1102 pg/mL)**
▪ UA	16 pg/mL (3 – 3352 pg/mL)**
▪ Non ACS	6 pg/mL (3 – 366 pg/mL)**
Copeptin-us (on admission)	
▪ NSTEMI	151.80 ± 130.03 pmol/L*
▪ UA	7.12 pmol/L (1.145 – 62.23 pmol/L)**
▪ Non ACS	7.36 ± 4.17 pmol/L*
hs-cTnT (3 hours later)	
▪ NSTEMI	488 pg/mL (81 – 18437 pg/mL)**
▪ UA	14 pg/mL (3 – 2224 pg/mL)**
▪ Non ACS	3 pg/mL (3 – 679 pg/mL)**

*Normal data distribution
**Abnormal data distribution

Copeptin is an endogenous stress marker, so the presence of stress in the body will rapidly increase copeptin levels. According to Youlan et al study, copeptin reaches peak levels in the first hours of onset and falls to normal values in 10 hours (Gu et al., 2011).

Area under curve (AUC) to differentiate NSTEMI from UA or non ACS

Based on Table 3, area under curve (AUC) copeptin-us on admission to differentiate NSTEMI from UA / non ACS was higher (0.946 [0.89 - 1.00]) (p <0.001) than hs-cTnT on admission (0.885 [0.79 - 0.98]) (p <0.001) and hs-cTnT 3 hours later (0.925 [0.82 - 1.00]) (p <0.001). Area under curve combination copeptin-us with hs-cTnT on admission was 0.941 [0.88 - 1.00] (p <0.001).

Table 3. Area under curve hs-cTnT on admission, copeptin-us, hs-cTnT 3 hours later, and combination copeptin-us with hs-cTnT on admission.

Variable	AUC (%)	95%CI (%)
hs-cTnT on admission	0.885	0.79 –0.98
Copeptin-us	0.946	0.89 –1.00
hs-cTnT 3 hours later	0.925	0.82 – 1.00
Combination hs-cTnT on admission with copeptin-us	0.941	0.88– 1.00

The combination of copeptin-us with hs-cTnT has a higher accuracy in the diagnosis of AMI than hs-cTnT only. Not much different from Sebbane et al who obtained an AUC combination of hs-cTnT on admission with copeptin-us was 0.928 [0.89 - 0.967] (Folli et al., 2013). Meune et al. and Gianitsis et al also obtained AUC of combination hs-cTnT with copeptin was 0,.94 [0.88 – 1.00] and 0.917 [0.889 –
0.940] (Meune et al., 2011 and Gianitsis, 2011). Keller et al. obtained an AUC of combination cTnT with copeptin was 0.93 [0.92 – 0.95] (Keller et al., 2010).

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)

Based on Table 4, the diagnostic value of a combination hs-cTnT on admission and copeptin-us has a higher sensitivity, specificity, PPV, and NPV compared to hs-cTnT orcopeptin-us only..

Diagnostic value of combination copeptin-us with hs-cTnT on admission was higher than hs-cTnT on admission only and hs-cTnT 3 hours later. In this study, it was not different from the Sebbane et al study, which obtained a sensitivity value of 96% and NPV of 98.9% (Folli et al., 2013). Meune et al obtained a sensitivity value of 86.7%, specificity of 70.4%, PPV of 76.5%, and NPV of 82.6 % (Meune et al., 2011). Gianitsis et al study obtained a sensitivity value of 97.7%, specificity of 55.9%, PPV of 34.4%, and NPV of 99.3% (Gianitsis et al., 2011). Keller et al. study obtained a sensitivity value of 90.9%, specificity 68, 3%, PPV of 48.8%, and NPV of 95.8% (Keller et al., 2010).

Cardiac troponin is a single marker in AMI when it is accompanied by symptoms of ischemia and ECG changes, but has limitation,troponin will increase in circulation 4-10 hours after the onset, so that it requires 6-12 hours of serial examination. Based on European Society of Cardiology in 2011, examination of cardiac biochemical markers was performed at the time of admission to hospital and 3 hours later (Hamm et al., 2011).

CONCLUSION

Diagnostic value of combination copeptin-us withhs-cTnT on admission was better than the hs-cTnT on admission only. Rapid and accurate diagnosis can reduce the waiting period of 3 hours for serial hs-cTnT assay and increase the efficiency of time and energy of medical personnel in emergency rooms.

Table 4. Diagnostic value of hs-cTnT on admission, combination hs-cTnT on admission with copeptin-us, and hs-cTnT 3 hours later to differentiate NSTEMI from UA or non ACS.

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
hs-cTnT on admission > 14 pg/mL	100	55.26	30.61	100
Copeptin-us > 13.97 pmol/L	100	82.89	53.57	100
hs-cTnT 3 hours later > 14 pg/mL	100	59.21	32.60	100
Combination hs-cTnT on admission ≤ 14 pg/mL with copeptin-us ≥ 13.97 pmol/L	100	90.78	68.18	100

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