# Mid-regional pro-atrial natriuretic peptide (MR-proANP) testing for the diagnostic and prognostic evaluation of patients with acute dyspnea due to heart failure and pneumonia

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**ABSTRACT**

*Purposes: The purpose of this study was to evaluate the diagnostic and prognostic value of mid-regional pro-atrial natriuretic peptide (MR-proANP) for the evaluation of patients presenting to the emergency department with acute dyspnea. Methods: We prospectively evaluated MR-proANP in consecutive patients presenting with acute dyspnea in a medical emergency unit during a 30-day period. This biomarker was tested for its potential to predict diagnoses and survival. Results: Overall, n = 230 patients were included. Of these, 67.4% had acute heart failure, 32.6% had pneumonia, and 4.7% died. The level of MR-proANP was the highest in patients with acute heart failure. NYHA scores and levels of MR-proANP correlated positively. MR-proANP achieved an AUC of 0.93 for the diagnosis of acute heart failure. Using a cut-off of 153 pmol/L, sensitivity was 93% and specificity 85%. PPV was 93% and NPV 86.5%. In time-dependent analyses, MR-proANP had a high AUC for death during the first month. Just only mid-regional peptide was independently prognostic and reclassified risk at one month [MR-proANP, hazard ratio (HR) =10.87]. Conclusion: Among patients with acute dysponea, MR-proANP is not only accurate for diagnosis of acute heart failure, but also independently prognostic to 1 month of the follow-up.*

***Keywords:*** *diagnosis, prognosis, MR-proANP, heart failure, pneumonia*

## 1. INTRODUCTION

Making the correct diagnosis in dyspneic patients with suspected acute heart failure (AHF) is challenging, and confirmatory in only 40 - 50% of cases, especially in cases accompanied by pneumonia. Several studies have shown that when added to routine history, clinical examination, and conventional investigations (for example, chest radiography), measurement of plasma natriuretic peptide levels improves diagnostic accuracy, and has led to these markers being recommended in international guidelines for the diagnosis and management of heart failure [1, 2]. Pneumonia is one of the most common triggers of acute decompensated heart failure. The differential diagnosis among heart failure and pneumonia or worsening heart failure due to pneumonia is still challenging.

Recently, a novel immunoassay was developed for the detection of the stable prohormone fragment of atrial natriuretic peptide (ANP) [2]. The prohormone fragment is stoichiometrically related to the synthesis of the

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biologically active, but unstable, fragment, and can serve as a surrogate of the mature hormone. Mid-regional epitopes of pro-hormones may be more stable to degradation by exoproteases than epitopes in the N- or C-terminus. Recently, the BACH (Biomarkers in Acute Heart Failure) multinational study showed that mid-region proANP (MR-proANP) is as useful as BNP for establishing a diagnosis of acute heart failure in dyspnoeic patients presenting to the Emergency Department (ED) with shortness of breath and may provide additional clinical utility in situations where BNP is difficult to interpret [3].

Until now, in Viet Nam, however, the values of this kind of pro hormone in dyspneic patients due to heart failure and pneumonia were unknown. The purposes of this study were to determine the thresholds of MR-proANP in diagnostic acute heart failure and prognostic short term (30 days) on patients admitted to the emergency department (ED) at Cho Ray hospital.

## 2. METHODS

### 2.1. Patient population

This research was a prospective, 230 patients presenting to the ED with acute dyspnea, from May of 2014 to May of 2015 at Cho Ray hospital. Patients were excluded if they were < 18 years of age, had acute dyspnea due to myocardial infarction, had severe renal failure (eGFR < 30mL/minutes/1.73m$^2$) or were receiving hemodialysis.

For each the patient enrolled in this study, ED physicians, blinded to the marker results, assessed the probability that patient had AHF or pneumonia.

### 2.2. Confirmation of diagnosis: from Cardiologist and pulmonologist

Patients were classified according to two groups: heart failure and pneumonia. The diagnosis of heart failure was based on ESC 2012, when a patient had typical symptoms and specific signs, had abnormalities in cardiac ultrasonography: left ventricular systole and/or diastole dysfunction [3]. The later was confirmed when patients had clinical symptoms (fever, dullness to percussion, egophony, tachycardia and tachypnea, decreased breath sounds, rales) and abnormal chest X-ray (pulmonary infiltrates) [4].

We categorized the severity of heart failure based on NYHA: group 1: NYHA II, III; group 2: NYHA IV.

### 2.3. Measurement of biomarkers

All blood samples were collected in plastic tubes containing ethylenediaminetetraacetic acid, and plasma was stored at -70°C in plastic freezer vials. MR-proANP was measured with an automated sandwich chemiluminescence immunoassay on the KRYPTOR System (BRAHMS AG, Hennigsdorf/Berlin, Germany) in the core laboratory at the biochemistry laboratory in Cho Ray hospital. This automated assay is based on the sandwich chemiluminescence assays. Performance of MR-proANP in this laboratory included a limit of quantitation of 4.5 pmol/L, within-run imprecision coefficient of variation (CV) of 1.2% and total imprecision (CV) of 5.4% [5].

### 2.4. Statistical analysis

Values are expressed as means and standard deviations, medians and interquartile ranges (IQRs), or counts and percentages as appropriate. Diagnostic groups were compared with independent-samples t-tests and chi-square tests as appropriate. All other analyses are exploratory and utilized a p value of 0.05 for significance. The secondary analyses utilized logistic and Cox regressions, and survival curves plotted by the Kaplan-Meier method. Additional methods included receiver-operating characteristic (ROC) curves and Spearman rank-order correlation.

### 2.5. Prognostic value of mid-regional pro-atrial natriuretic peptide in prognosis in acute dysponea

Time-dependent AUC analyses were performed to assess the ability of MR-proANP to discriminate mortality at 30 days after admission. From the ROC curves, optimal cut-points for prognosis were identified, and used to examine the prognostic value of MR-proANP at 30 days. This biomarker was added to multivariate Cox proportional hazards models containing covariates already known to predict death. Hazard ratio (HR) and 95% CI were generated. In these analyses, MR-proANP was entered as dichotomous variables, using the ROC-optimal value for each; in order to evaluate the individual value of the novel marker for prognosis. Kaplan-Meier curves for survival at 30 days was constructed and compared using the log-ranktest.

All p-value are two-sided, with a value < 0.05 considered significant.

## 3. RESULTS

### 3.1. Patients general characteristics

The baseline characteristics of age, gender between the heart failure and pneumonia groups are demonstrated in Table 1.

There are no statistically significant differences between the two groups for age, human sex ratio (p>0.05).

### 3.2. MR-proANP in acutely decompensated heart failure (ADHF) diagnosis

For the diagnosis of ADHF, MR-proANP had an AUC of 0.93 (95% CI = 0.895-0.969; p<0.001).

**Table 1.** The distribution of age, gender between AHF and pneumonia groups

| | **AHF** (n = 155) | **Pneumonia** (n = 75) | **p** |
|---|---|---|---|
| **Age** | 64.1 ± 16 | 66.7 ± 16 | 0.166 |
| **Sex** | Female (55.5%) | Female (46.7%) | 0.052 |
| | Male (44.6%) | Male (53.3%) | |

**Table 2.** The cut-points of MR-proANP in diagnosis heart failure and pneumonia

| **MR-proANP (pmol/L)** | **Sensitivity** | **Specificity** | **Jouden index** |
|---|---|---|---|
| 149 | 93% | 83.8% | 0.768 |
| 150 | 93% | 84.2% | 0.77 |
| 153 | 93% | 85% | 0.78 |
| 156 | 92.3% | 85% | 0.773 |
| 157.5 | 91.7% | 85% | 0.767 |

*Comment: Highest Jouden index 0.78 at the level MR-proANP 153 pmol/L.*

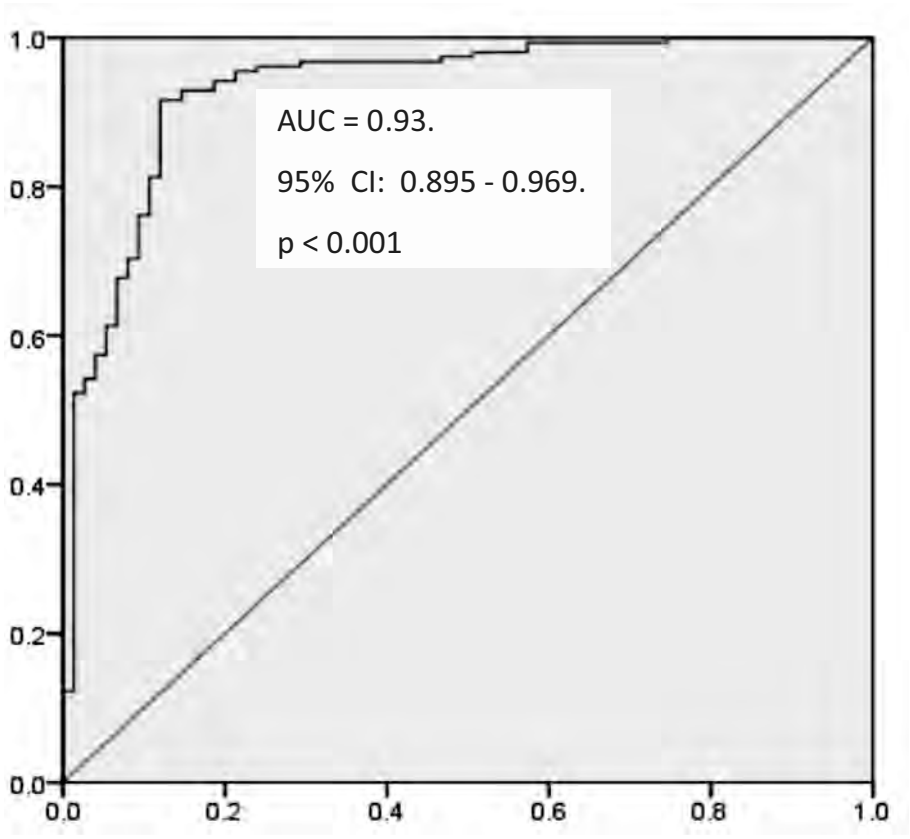


**Figure 1.** The ROC curve of MR-proANP in diagnosis ADHF

*Comment: MR-proANP could differentiate acute dyspnea between heart failure and pneumonia, with high AUC 0.93, significantly.*

**Table 3.** The level of MR-proANP according to ejection fraction in the heart failure group

| EF (%) | The level of MR-proANP (pmol/L) | | | | |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Min** | **Max** | **Median** |
| **< 35 (n = 67)** | 519 | 325 | 65 | 1833 | 407 |
| **35 - 49 (n = 53)** | 401 | 332 | 86 | 2477 | 388 |
| **≥ 50 (n = 35)** | 264 | 140 | 53 | 594 | 235 |
| **R** | - 0.4 | | | | |
| **P** | < 0.001 | | | | |

*Comment: The concentration of MR-proANP was associated with lower EF, significantly.*

Patients with a final diagnosis of ADHF had significantly higher MR-proANP concentrations, compared with those without [median 377 (235 - 493) vs 80 (48 - 111) pmol/L; p < 0.001]. Additionally, worse NYHA symptom severity was associated with higher median MR-proANP concentrations: class II = 240 (53 - 544) pmol/L, class III = 319 (65 - 938) pmol/L, and class IV = 504 (166 - 2477) pmol/L (p < 0.001 across categories).

**Table 4.** The level of MR-proANP according to NYHA class

| NYHA | The level of MR-proANP (pmol/L) | | | | |
|---|---|---|---|---|---|
| | Mean | SD | Min | Max | Median |
| II (n = 15) | 260.5 | 140.4 | 52.7 | 544.2 | 240.1 |
| III (n = 94) | 339.9 | 156.3 | 65.4 | 937.8 | 319.1 |
| IV (n = 46) | 639.7 | 451.2 | 165.6 | 2477 | 504.2 |
| R | 0.42 | | | | |
| P | < 0.001 | | | | |

*Comment: Mid-regional pro-atrial natriuretic peptide (MR-proANP) as prognostic markers at 30 days for patients presenting with acute dyspnea.*

**Table 5.** The cut-point of MR-propANP in prognosis death after 30 days

| MR-proANP (pmol/L) | Sensitivity | Specificity |
|---|---|---|
| 392 | 82% | 72% |

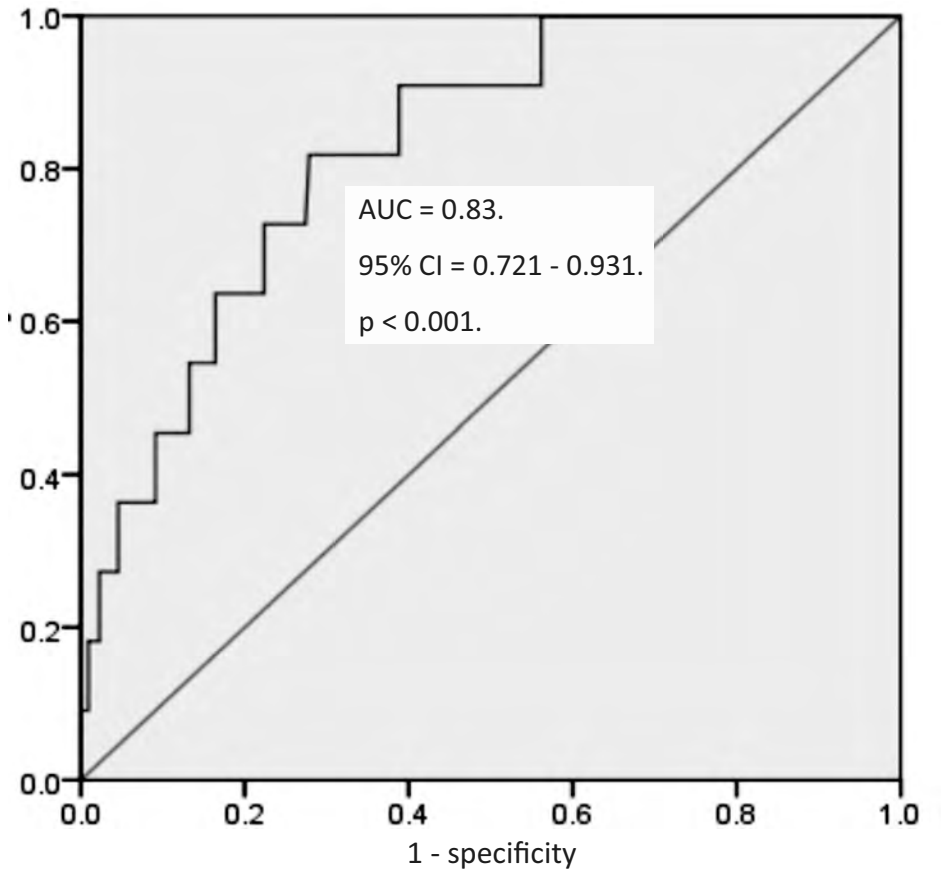


**Figure 2.** The ROC curve of MR-proANP in prognosis death after 30 days

*Comment: At the level of MR-proANP 392 pmol/L, could prognosis survival status within 30 days in hospital, with AUC 0.83.*

**Table 6.** The level of MR-proANP in two groups

| MR-proANP | Survivors (n = 219) | Nonsurvivors (n = 11) | p |
|---|---|---|---|
| | 296 ± 255 | 764 ± 649 | < 0.001 |
| **Ln MR-proANP** | 5.5 | 6.4 | |
| **Median** | 242 | 513 | |
| **Percentile 25 - 75** | 103 - 408 | 392 - 988 | |

*Comment: There were 11 deaths within 30 days (death rate 4.8%). Survivors had a median MR-proANP of 242 pmol/L (IQR 103 to 408 pmol/L) and nonsurvivors, 513 pmol/L (IQR 392 to 988 pmol/L, p < 0.0001).*

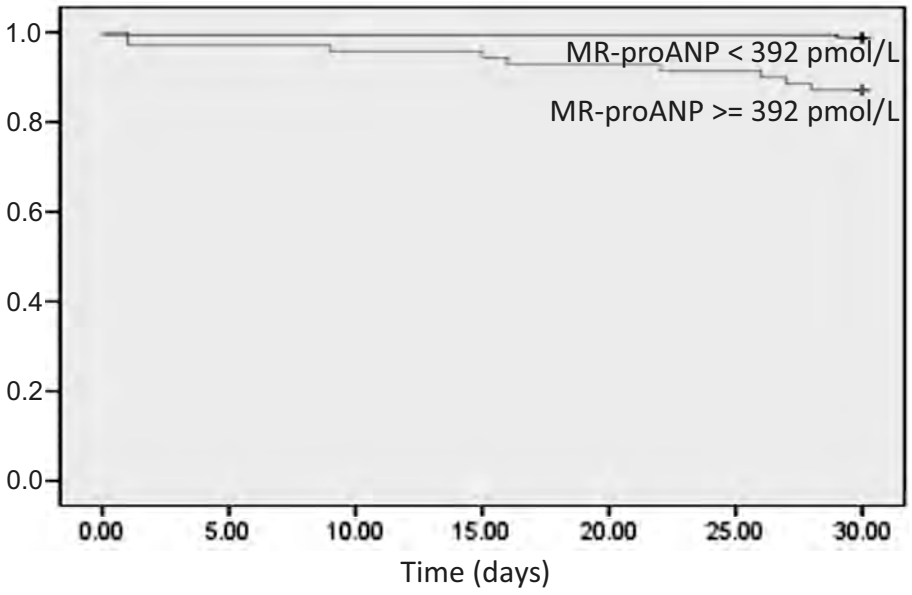


**Figure 3.** Kaplan-Meier survival curves by level of MR-proANP

**Table 7.** Univariable and multivariable Cox proportional hazards analysis for 30 days survival for several factors

| Variable | Chi square | HR (90% CI) | p (univariable) | p (multivariable) |
|---|---|---|---|---|
| **Age > 60** | 4.2 | 3.35 (0.98 - 11.5) | 0.054 | # |
| **Female** | 1.2 | 1.97 (0.58 - 6.73) | 0.279 | # |
| **EF < 30%** | 6.35 | 2.47 (1.15 - 5.3) | 0.021 | 0.372 |
| **MR-proANP > 392 pmol/L** | 14.6 | 10.87 (2.35 - 50.3) | < 0.001 | 0.019 |
| **NYHA IV** | 4,632 | 1.5 (1.01 - 2.23) | 0.043 | 0.796 |

## 4. DISCUSSION

In the present study, we found MR-proANP to be accurate for the identification or exclusion of acute heart failure in dyspneic patients, had an AUC 0.93. MR-proANP at the level of 153 pmol/L showed high sensitivity (93%), but lower specificity.

The cut-point in this study is higher than the BACH trial because of the following reasons: first of all, we just chose two groups of common dyspneic patients in ED, namely acute heart failure and pneumonia; secondly, the inflammatory factors had also up-regulated on MR-proANP concentration. In addition, we revealed that the concentration of MR-proANP had positive correlation with the severity of heart failure. This means the more significant heart failure is, the higher level of MR-proANP is.

All-cause mortality was the best predictable end point for some variables (MR-proANP, NYHA, sex, age). Cut points for MR-proANP was determined from ROC analysis for 30-day survival. The optimal cut point was 392 pmol/L for MR-proANP. Using this cut point, the specificity and sensitivity were 82%, 72%, irrespectively.

The 230 dyspneic patients with MR-proANP results were studied in a similar fashion as the entire cohort, with comparable prognostic importance as in the cohort as a whole. In the largest published study of MR-proANP in undifferentiated dysponea (the Biomarkers in Acute Heart Failure (BACH) study) [6], an MR-proANP was inde-pendently predictive of events. From the Kaplan Meier, it was seen that two curves separated clearly at the end of the second week. This means that, the patients with MR-proANP above-cut point have a high risk of death, especially on the fifteenth day after admission with dyspneic symptoms.

Additionally, our research also revealed that, in univariate Cox proportional hazard analyses, several variables, namely: EF < 30%, MR-proANP > 392 pmol/L, NYHA IV were prognostic of survival at 30 days (Table 7). The hazard ratios increase was 10.87 (95% CI: 2.35 to 50.3, $p < 0.001$) for MR-proANP; 2.47 (95% CI: 1.15 to 5.3, $p = 0.021$) for EF < 30% and 1.5 (95% CI:1.01 to 2.23, $p = 0.043$) for NYHA IV. However, in multivariable model, only MR-proANP carried independent prognostic factor.

The value of natriuretic peptides in the diagnostic and prognostic assessment of patients with congestive heart failure is reflected in their inclusion in guidelines across the world as well as by a recent consensus statement. Mid-regional prohormone markers are very stable in blood samples kept at room temperature, and hence may offer some practical analytical advantages. The test for MR-proANP is now available in a fast-assessment format, making diagnostic and prognostic information available to the acute care physician within 30 to 60 minutes. While it need not replace the other signs for the diagnosis of heart failure, the use of MR-proANP levels are acceptable alternatives, depending on the laboratory platform available, pricing, and so forth, and may add to the other criterions in ambivalent diagnostic cases.

The better prognostic marker helps patients in many ways, as it identifies those patients who should “move to the front of the line” with respect to immediate therapeutic inter-ventions. In the emergency setting, untreated acute heart failure worsens rapidly and can lead to respiratory compromise, intubation with mechanical ventilation, and even death. Thus, interventions based on high MR-proANP levels might include specialist consultation by a cardiologist, intensive care unit admission, noninvasive ventilation, and so forth. Additionally, the astute clinician will more closely follow up patients with a poor prognostic marker after discharge to prevent relapse and readmission. MR-proANP may also help to identify patients who are in need of longer courses of inpatient therapy to relieve congestion. MR-proANP levels may also serve as a surrogate marker in therapeutic heart failure trials, although both of these suggestions require validation.

## 5. CONCLUSION

We found firm evidence of diagnostic and prognostic value for MR-proANP, in patients with acute dyspnea due to heart failure and pneumonia. Accordingly, the level of MR-proANP at 153 pmol/L and 392 pmol/L have significant differentiation etiology of acute dyspnea between heart failure and pneumonia and prognosis these such patients within 30 days after admission.

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# MR-proANP trong chẩn đoán và tiên lượng bệnh nhân khó thở cấp do suy tim và viêm phổi

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**TÓM TẮT**

*Mục tiêu của nghiên cứu này là đánh giá giá trị chẩn đoán và tiên lượng của dấu ấn sinh học MR-proANP trên bệnh nhân khó thở cấp tại khoa cấp cứu. Phương pháp nghiên cứu: tiến cứu, chọn liên tiếp các bệnh nhân khó thở cấp tại khoa cấp cứu và theo dõi 30 ngày. Thực hiện xét nghiệm MR-proANP trên các đối tượng này để đánh giá khả năng chẩn đoán suy tim cấp và tiên lượng sống còn. Kết quả: có 230 bệnh nhân, trong số này suy tim cấp chiếm tỷ lệ 67.4%; viêm phổi 32.6%; với 4.7% bệnh nhân tử vong trong 30 ngày. Nồng độ MR-proANP ở nhóm suy tim cấp cao nhất, MR-proANP có tương quan thuận với mức độ suy tim theo NYHA. MR-proANP có giá trị tốt trong chẩn đoán khó thở do suy tim cấp với AUC = 0.83. Tại điểm cắt 153 pmol/L với độ nhạy, độ đặc hiệu là 93% và 85%, giá trị tiên đoán dương 93%, giá trị tiên đoán âm 86.5%. Ngoài ra, MR-proANP có khả năng dự báo khả năng sống còn của bệnh nhân trong 30 ngày theo dõi. MR-proANP là yếu tố nguy cơ độc lập trong dự báo khả năng tử vong của nhóm bệnh nhân này với HR = 10.87. Kết luận: MR-proANP không chỉ có khả năng chẩn đoán nguyên nhân khó thở cấp do suy tim mà còn có thể tiên lượng được khả năng sống còn trên những đối tượng này.*

***Từ khóa:*** *chẩn đoán, tiên lượng, MR-proANP, suy tim cấp, viêm phổi*

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