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Original Article

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ABSTRACT

Objectives: This study evaluated the potential of Cystatin-C (Cys-C) and uric acid (UA) to predict the diagnosis of heart failure (HF) in patients with acute dyspnea compared with BNP and echocardiographic (ECHO) findings.

Design: This was a methodological prospective study.

Setting: The study was conducted in the emergency department (ED) of a tertiary care university hospital.

Subjects: Patients presenting through the ED with dyspnea.

Interventions: ED physicians assessed the probability of HF in subjects and if they thought that complaints are due to HF, enrolled patients to the study prospectively. BNP, UA and Cys-C levels were measured and all patients were evaluated with ECHO by the same cardiologist.

Main Outcome Measures: Diagnosing HF in undifferentiated dyspnea patients.

Results: The mean age of the enrolled 94 patients was 70.7±10.4 years 49 of them (52.1%) were male. ED physicians assessed HF in 67 (70%) patients and the cardiologist confirmed in 69 patients (73.4%). BNP levels (p=0.00) and UA levels (p=0.04) were significantly different; however, Cys-C levels was not (p=0.79). On the multivariate analysis, only UA levels and clinical gestalt of the ED physician were strong independent predictors of HF.

Conclusions: Since BNP is an expensive laboratory test and there are some conflicting arguments about its diagnostic performance in ED, UA seems as a cheap and easily accessible 'old' marker for diagnosing acute HF. The physician's gestalt for HF diagnosis is quite important and combining this gestalt with biomarkers in a model would be more useful.

KEYWORDS: diagnosis, dyspnea, emergency department, heart failure

INTRODUCTION

Heart failure (HF) often referred to as congestive heart failure (CHF), occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body demands [1]. 80% of acute HF patients present through the emergency department (ED), and dyspnea is their predominant chief complaint [2]. Delays in diagnosing HF result in increased mortality, hospital stays, and treatment costs [3].

History and physical examination alone are often insufficient to rule in or rule out CHF. Patients often have comorbidities that contribute to their symptoms, thereby making the diagnosis difficult. Therefore, physicians in acute care settings require an accurate diagnostic test that will allow them to rapidly determine whether or not HF is the cause of the shortness of breath and dyspnea.

B-type natriuretic peptide (BNP) was proposed as a potentially valuable diagnostic test to augment the clinical diagnosis of HF. BNP levels are significantly higher in patients with dyspnea due to HF than from another cause. The American College of Emergency Physician (ACEP) clinical policy provides Level B recommendations that "the addition of a single BNP or NT-proBNP measurement can improve the diagnostic accuracy compared to standard clinical judgment alone in ED patients to rule out HF [4].

Previous studies have shown that elevated levels of serum uric acid (UA) are associated with adverse clinical outcomes in patients with chronic HF [5-7]. Some recent studies also showed that the serum UA level was an independent predictor in acute HF [8, 9].

Cystatin-C (Cys-C), a low molecular weight protein, is a known biomarker reflecting renal function and is considered a cardiac prognostic factor, particularly in ischemic heart disease and chronic HF [10, 11]. Since the relationship between Cys-C and cardiac prognosis appears to be either directly or indirectly due to hemodynamic effects, this marker is well suited for acute HF in the ED and has been widely investigated [12 - 15].

The current study evaluated the potential of Cys-C and UA to predict the diagnosis of HF in patients with acute dyspnea compared with BNP and echocardiographic findings.

SUBJECTS AND METHODS

Study design and setting

This methodological prospective study was conducted in the emergency department of a tertiary care university hospital. Our study was approved by the review board of the local Ethics Committee and financial support for the laboratory tests was provided by The Scientific Research Projects Coordination Unit. All study patients enrolled were given information and signed informed consent forms.

Selection of the participants

Eligible patients were enrolled in the study by the ED staff at presentation. To be eligible for the study, a patient had to have shortness of breath as the most prominent symptom. All patients underwent routine clinical examination by an ED physician (ED resident supervised by an ED attending physician). Physicians assessed the probability that the patient had HF as the cause of his/her symptoms and if they thought that complaints are due to HF, enrolled patients to the study. No specific criteria for the diagnosis of HF were determined and inclusion was left to the physician's judgment.

Exclusion criteria

Patients under 18 years of age and those whose dyspnea was clearly not secondary to CHF (for example, those with pulmonary disease) were excluded. Patients with acute myocardial infarction, unstable angina or cardiogenic shock, renal failure and dialysis therapy, trauma, malignancy, gout or digoksin overdose were also excluded.

Data collection

Once the patient was identified as having dyspnea due to HF, written informed consent was obtained, and 5cc blood sample was collected for measurement of B-type natriuretic peptide (BNP), uric acid (UA) and Cystatin-C (Cys-C). Blood samples were taken without tourniquet and centrifuged at 4000 rpm for 5 minutes, and then the separated plasma was transferred to eppendorf tubes. Eppendorf tubes were first collected at -20°C, then transferred to -80°C and stored there until all samples were collected.

The ED physicians collected other data, including information from the medical history, the vital signs, and the physical examination findings. The treatment modalities for the patient did not change during the study period and maintained by the ED physician's according to usual protocols.

Laboratory test measurements

BNP measurements were determined using an Electro-chemiluminescence immunoassay (ECLIA) method on Elecys 2010 immunassay (Roche®Diagnostics, Mannheim, Germany) analyzer and results were given as pg/ml. Cys-C measurements were determined using the nephelometric technology on The BN™ II System (Siemens Healthcare Diagnostics Ltd, USA) and results were given as mg/l. UA measurements were determined using enzymatic and colorimetric technique on Roche Modular PPP chemistry analyzer (Roche Diagnostics, Mannheim, Germany) and results were given as mg/dl. All measurements were done at the same time after the completion of all study patients.

Echocardiograms

Echocardiography (ECHO) was used as a 'gold standard' for diagnosing heart failure and was performed to evaluate cardiac function after stabilization of the patient's hemodynamic status.

All echocardiograms were done by the same cardiologist with Vivid 7 ultrasonography machine (General Electric, Milwaukee, Wisconsin, USA) by using a 1.5 - 4.0 MHz transducer. Echocardiograms were done during the ED evaluation at daytime (08.00-17.00). Patients admitted at night and weekends were gone to ECHO within 6-8 hours with the same cardiologist and the same machine.

Left atrium diameter (LA), left ventricle end diastolic diameter (LVEDD), left ventricle end systolic diameter (LVESD), interventricular septum diastolic diameter (IVS) and posterior wall diastolic diameter (PW) were measured with two-dimensional (2D) imaging. Ejection fraction (EF) was calculated with bi-plane Simpson method. Mitral inflow patterns and velocities (mitral E/mitralA), tricuspid jet velocity (TY jet), systolic pulmonary artery pressure (sPAP) were measured. On tissue Doppler, mitral annulus and lateral annulus velocities, peak early and late diastolic transmitral flow velocities (E' and A', respectively) and systolic velocity (S') were measured.

ECHO parameters and clinical findings of the patient were evaluated by the cardiologist to determine if the patient's dyspnea was due to HF. This was accepted as final diagnosis for the patient.

Statistical analysis

The data analyses were performed using SPSS for Windows, version 15.0.0 (SPSS, Chicago, IL, USA) and Medcalc 11.0.4. All values are presented as the mean standard deviation for continuous variables and as frequencies and percentiles for discrete variables. Univariate comparisons were made with Student's t –test and Mann-Whitney U test as appropriate. The selected variables were derived from the univariate analysis, and multivariate logistic regression analyses were performed. To evaluate and compare the prognostic incremental values of UA, BNP, and Cys-C, individual parameters were added to the predictive model, which was constructed based on clinical and significant multivariate parameters.

Receiver-operating characteristic (ROC) curves and the area under the curves (AUC) were obtained. P -values were two-sided, and a p-value 0.05 was considered statistically significant.

RESULTS

During the study time, approximately 45.000 patients were admitted to the ED. 180 patients were enrolled to the study. 86 of them were excluded from the study. The exclusion criteria for these patients were given at figure 1. Statistical analysis was done with the remaining 94 patients.

The mean age of the enrolled patients was 70.7 ± 10.4 years median 71 years (min. 48, max. 95), and 49 of them (52.1%) were male. The mean of breath per minute was 28.0 ± 6.8 breath/min, median 28 (min-max: 14-50), and the mean of artery pressure was 102 ± 17.8 mmHg, median 100.5 (min-max: 61-150). The other vital signs and mean and median values were shown at Table 1.

ED physicians assessed CHF as the cause of dyspnea in 67 (70%) patients, and the remaining 27 (30%) were assessed as combined heart and respiratory failure. The cardiologist confirmed HF in 69 patients (73.4%) after evaluating the ECO parameters and clinical findings of the patient. Historical physical examination findings suggesting HF were evaluated in the study population. Distention of the jugular vein was found in 35 (37.2%) patients, hepatojugular reflux in 30 (31.9%) patients, pretibial edema in 56 (59.6%) patients and rales heard over the lung bases in 93 (98.9%) patients.

When we compared the patients without and with HF, BNP levels were different between groups (median: 1550 pg/ml vs 4737 pg/ml, respectively, p = 0.00) and the difference was statistically significant. Statistically significant difference was also found for UA levels (median: 6.20 mg/dl vs 7.30 mg/dl, respectively, p=0.04). However, the difference between groups for Cys-C levels was not statistically significant (1.32 mg/L vs 1.25 mg/L, respectively, p = 0.79) (Table 2).

We also used a multiple logistic-regression model combining clinical findings and the laboratory test values to predict the final diagnosis. The predictors in the model included historical clinical examination findings (hepatojugular reflux, pretibial edema, rales heard over the lung bases), BNP, UA and Cys-C levels, and the clinical gestalt of the ED physician for predicting HF. On the multivariate analysis, the model showed that only UA levels and clinical gestalt of the ED physician were strong independent predictors of congestive heart failure (Table 3).

The ROC analysis revealed that the sensitivity was 92.7% (95% CI, 83.9-97.6) for UA levels under 4.4 mg/dl, and the spesifity was 92% (95% CI, 74-99) for UA levels over 10.4 mg/dl. (Figure 2)

Limitations

Since our study was supported financially by The Scientific Research Projects Coordination Unit of our university, we had a limited budget for laboratory kits. As it could be seen in the patient flowchart, we had to exclude many patients unexpectedly because of missing data. This unexpected condition resulted with a relatively small patient population for the study and the confidence intervals were found less wide. Although we believe that there is no selection bias risk, this is also weakness of our study.

DISCUSSION

Dyspnea is one of the most common presenting symptoms to the EDs which can be life threatening for patients. Since diagnostic modalities and treatment choices can significantly differ according to various causes of dyspnea, the differential diagnosis is important for emergency evaluation and for patient survival and disease prognosis. Acute HF is one of the most frequent diagnoses in emergency medicine, with 1-year mortality rates exceeding 25–30% [15]. We designated a good and reliable 'gold standard' for acute congestive heart failure diagnosis, by evaluating all patients with echocardiogram using new and old measuring techniques done by a single cardiologist. When we compared with this gold standard, BNP levels were found to be high in cardiac dyspnea patients however; it was not an independent predictive factor in multivariate analysis model. Cys-C levels were not found significant for diagnosing acute heart failure in ED patients. UA levels were found significant both in univariate and multivariate analysis for predicting HF diagnosis in dyspnea patients, especially in selected level thresholds.

HF could be exacerbated or triggered by multifactorial potential factors such as the cardio-renal relationship. Renal insufficiency and worsening renal function are prevalent in acute HF, and they often coincide with diuretic unresponsiveness and inability to relieve congestion. Hence, preservation of renal function is an important therapeutic goal in the treatment of acute heart failure [16]. Cys-C could play a key role as a useful renal marker, could be observed at increased levels in acute HF and it is related to cardiac prognosis even in elderly patients [17]. The prognostic effect seems to be independent of other renal function markers, and even in patients with normal creatinine values, elevated Cys- C levels have a powerful impact on prognosis [15]. Cys-C seems not to be affected by gender, age, body mass index (BMI), or diet, leading to the suggestion that it be the preferred endogenous marker of renal function. Although the exact mechanism that causes Cys-C to be linked with the cardiovascular system was not identified clearly, cardiorenal hemodynamic interaction is primarily responsible for the relationship between Cys-C and the adverse outcomes. Recent studies showed that higher Cys-C levels were associated with increased risk of death both in short- and long-term follow-up [12-17]. We studied Cys-C as a diagnostic test for HF in dyspneic patients in our study; however, we could not found any statistical significance both at univariate and multivariate analysis. The previous reports exploring Cys-C in acute HF looked for its prognostic properties and prediction of adverse events. In light of these reports and our results, it is possible to say that Cys-C in acute HF could be a useful marker for predicting increased risk; however, it is not useful as a diagnostic test.

Serum uric acid (UA) is a byproduct of the terminal steps of purine catabolism. In HF, UA levels may rise due to increased purine catabolism resulting from tissue hypoxia, apoptosis, and/or enhanced or upregulated enzymatic activity. Therefore, UA could be used as a prognostic marker in HF progression [6]. Many studies have indicated that higher UA is a predictor of cardiovascular mortality in acute HF [18-20]. In two recent investigations, the authors assessed the role of UA in the prediction of early post-discharge event in patients with acute HF, and admission hyperuricemia was shown to be associated with higher risk of death or HF rehospitalization [8, 9]. High UA levels increase all-cause mortality in patients with both acute and chronic HF, and that this increase in risk seems to start at an SUA level of 7 mg/dL [6]. Also, a meta-

analysis of published prospective studies suggests that elevated UA levels are associated with an increased risk of cardiovascular and all-cause mortality. However, high SUA appears to increase the risk of all-cause mortality for men but not for women [21]. Our study findings showed that high UA levels revealed favorable sensitivity and specificity rates for diagnosing HF in dyspneic patients, besides predicting mortality and risk groups. Additionally, UA was found as an independent factor in the multivariate analysis.

BNP is a cardiac neuro-hormone specifically secreted from the ventricles in response to volume expansion and pressure overload and has been studied widely as a potential tool to enhance the accuracy of HF diagnosis [22]. Although observational trials have shown promise to improve clinicians' diagnostic accuracy for HF in the ED, the role of these biomarkers in the acute management of dyspnea remains undefined. It can also paradoxically increase diagnostic uncertainty on low-risk populations [23]. Serum levels can be elevated by non-HF conditions like pulmonary hypertension, left ventricular hypertrophy, renal failure, acute coronary syndrome, atrial dysrhythmia, sepsis, and lung cancer [23]. Mueller *et al* showed that patients who had BNP testing in the ED had earlier initiation of appropriate treatment, decreased hospital and intensive care unit admission rates, earlier discharge, and decreased cost of treatment [24]. In contrast, the randomized controlled trial BNP in Shortness of Breath (SOB) study conducted by Schneider *et al* showed that BNP testing in dyspneic patients presenting to the ED did not improve hospital admission rates, length of hospital stay, or management in the ED [25]. A recent randomized controlled study conducted in Australia, found that, although BNP values were significantly higher in patients with a final diagnosis of HF, in the real-life setting, adding the BNP test to clinical judgment did not significantly add to the accuracy of the disposition diagnosis of HF [26]. We found BNP levels higher in the HF patients in our study. The difference was statistically significant in the univariate analysis, however when we created a multivariate model, BNP was not an independent predictor for HF diagnosis. These findings are not contrary to previous reports, and also support the theory that, in real emergency setting using BNP testing not for differentiating all dyspneic patients but combining test with the ED physicians' assessment of the probability of HF, will improve the diagnostic accuracy. ED physicians' gestalt of probability of HF was also high in our study. ED physicians assessed HF as the cause of dyspnea at 70% of patients, and the cardiologist confirmed HF in 73.4% after evaluating the ECHO parameters and clinical findings of the patient.

For patients who present to emergency departments or urgent care settings with signs and symptoms suggestive of HF, BNP and NT-proBNP have good diagnostic performance to rule out, but lesser performance to rule in [27]. For good diagnostic performance to rule in, it is better to use BNP in a clinical model combining tests, as well as clinical findings and physician's gestalt. There are a few studies combining BNP and other biomarkers. Park *et al* found that the combination of UA and NT-ProBNP levels appears to be more useful than either marker alone as an independent predictor for short-term outcomes in patients with acute HF [28]. FINN-AKVA Study group concluded that, combining Cys-C and NT-proBNP gives a new possibility to categorize patients into a wider spectrum of risk profiles with patients at very low risk of death at one end and cumulatively high risk at the other [15]. In the RELAX-AHF trial, seven circulating biomarkers [NT-proBNP, high sensitivity cardiac troponin T (hs-cTnT), soluble ST2 (sST2), growth differentiation factor 15 (GDF-15), cystatin-C, galectin-3, and high sensitivity C-reactive protein (hs-

CRP)] were measured at baseline and on days 2, 5, 14, and 60. A multimarker approach based on a panel of serially evaluated biomarkers provides the greatest prognostic improvement unmatched by a single time point-based single marker strategy [29]. Kim TH *et al* evaluated whether Cys-C could be a useful prognostic indicator in acute HF and compared with UA and proBNP [16]. In their retrospective, observational analysis, the patients with cardiac events showed higher concentrations of Cys-C, UA, and NT-proBNP and Adding Cys-C, NT-proBNP, and UA improved the prognostic ability of the model constructed based on the general risk factors. However, on the multivariate analysis, only Cys-C, but not NT-proBNP and UA, was related to the recurrence of cardiac events. This study evaluated the same biomarkers as our study; however, there are some major differences. First of all, they conducted a retrospective analysis and looked for the predictability of the biomarkers for cardiac events. We conducted a prospective trial, created a good and reliable 'gold standart' with ECHO done by single cardiologist, and evaluated the diagnostic performance of the studied biomarkers rather than their prognostic values. To our knowledge, our work is the unique prospective study conducted in an ED and evaluated diagnostic performance of these markers in a multivariate model.

CONCLUSION

In conclusion, UA reveals promising results for diagnosing HF in undifferentiated dyspnea patients in the ED. Since BNP is an expensive laboratory test and there are some conflicting arguments about its diagnostic performance in ED, UA seems as a cheap and easily accessible 'old' marker for diagnosing acute HF. The second outcome is that the physician's gestalt for HF diagnosis is quite important and combining this gestalt with biomarkers in a model would be more useful for differentiating patients.

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Table 1: The demographics and median and mean values of the vital signs of patients

Vital signs	**Mean±SD** **N=94**	**Median (min-max)** **N=94**
Age	70.7±10.5	71.0 (48-95)
Pulse	93.5±22.2	92.0 (41-150)
Breathing	28.0±6.8	28.0 (14-50)
Mean arterial pressure	102.0±17.8	100.5 (61-150)
Saturation	90.9±8.1	93.0 (60-100)
Fever	36.7±0.5	36.6 (36-38)

SD: Standard Deviation, Min: Minimum, Max: Maximum

Table 2: The statistical differences and p values for B-type natriuretic peptide (BNP), uric acid (UA) and Cystatin-C (Cys-C) levels between the groups without and with heart failure (HF)

Laboratory Tests	Patients with HF, N=69 Median (min-max) Mean±SD	Patients without HF, N=25 Median (min-max) Mean±SD	P
BNP	4737 (423 – 35000) 7975 ± 8160	1550 (65 – 35000) 5244 ± 9895	0.00
UA	7.3 (2.2 – 12.7) 7.36 ± 2.17	6.2 (1.9 – 12.8) 6.34 ± 2.72	0.04
Cys-C	1.25 (0.46 – 3.03) 1.41 ± 0.58	1.32 (0.62 – 2.85) 1.42 ± 0.57	0.79

BNP: B-type natriuretic peptide, UA: Uric Acid, Cys-C: Cystatin-C, HF: Heart Failure, SD: Standard Deviation, Min: Minimum, Max: Maximum

Table 3: Factors predicting heart failure

Laboratory Tests	Odds ratio	%95 Confidence Interval	P
BNP	1.00	1.00 – 1.00	0.10
UA	1.43	1.06 – 1.92	0.01
Cys-C	0.18	0.04 – 0.74	0.01
Physician's gestalt	1.74	1.16 – 2.60	0.01

BNP: B-type natriuretic peptide, UA: Uric Acid, Cys-C: Cystatin-C

Figure 1: Patient flow chart of the study

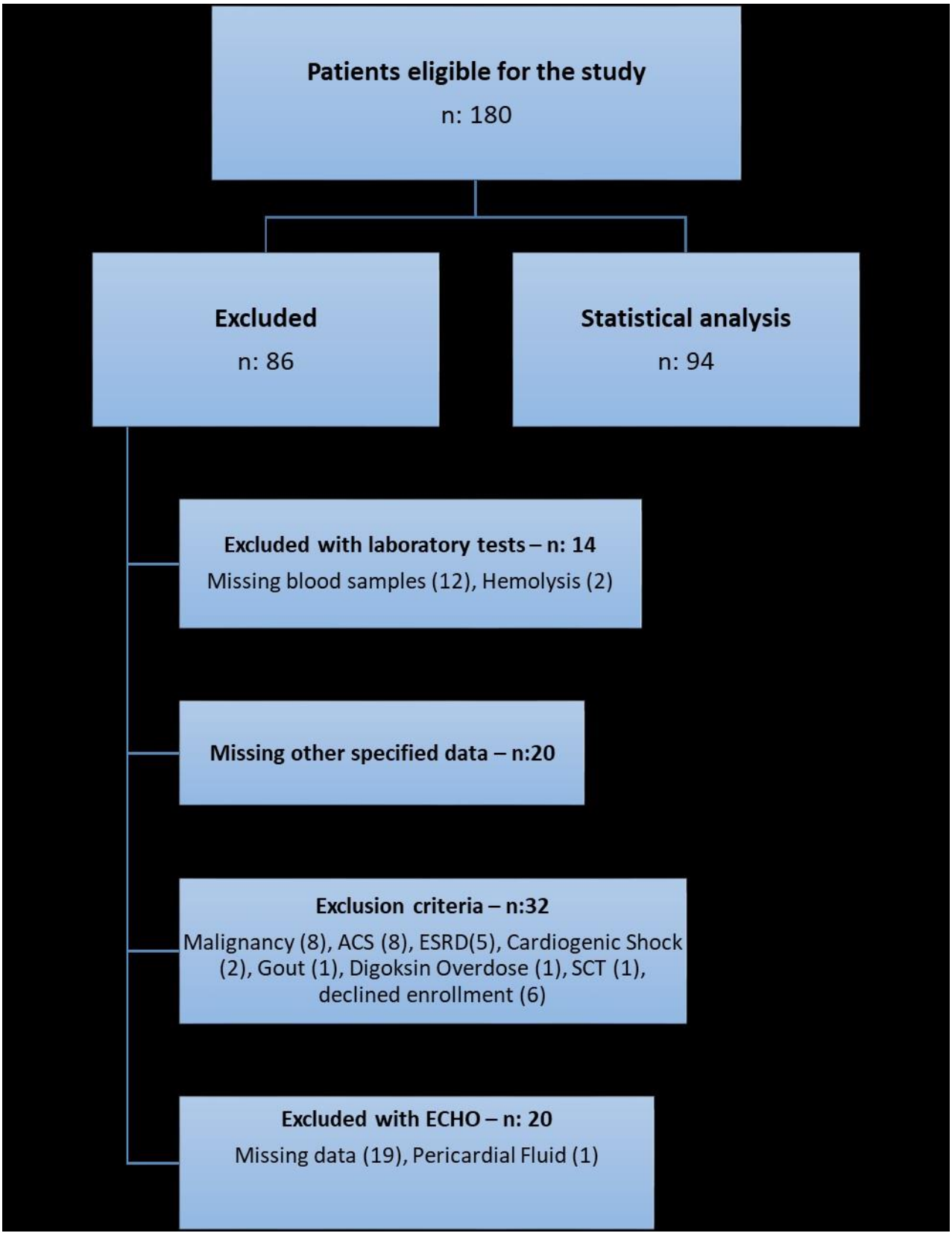

Figure 2: ROC analysis for serum uric asid levels