Original Article

Diagnostic and Prognostic Utility of a Multiple Metabolic Biomarkers Panel in Critically ILL Patients with Acute/Chronic Decompensated Heart Failure: BILLIARD Study.

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Abstract:

Introduction: The progression of heart failure is complex and is driven by multiple biological processes. As such, a single biomarker is unlikely to be sufficient for risk stratifying patients with HF. We studied the additive diagnostic and prognostic value of a panel of multiple new biomarkers implicated in the different pathophysiological aspects of the development of the disease; B-type natriuretic peptide (BNP) (Myocyte Stress/Stretch), high sensitivity troponin (hsTnT) (Myocyte Injury), soluble ST2 (sST2) (Myocyte stretch / inflammation) and Galectin-3 (Gal-3) (Inflammation & Extracellular Matrix Modeling), Parathormone hormone (PTH 1-84) (neurohormonal activation). **Methods:** The study was conducted on 60 patients with ADHF, as well as 20 healthy volunteers. The primary endpoints were the improved specificity and sensitivity for the diagnosis of ADHF, and the prediction of short term mortality combining the panel of biomarkers to the ADHERE and EFFECT clinical short term mortality risk scores. The secondary endpoint was the prediction of a composite of major adverse cardiac events (MACEs) in the ADHF group. **Results:** BNP had the best accuracy for the diagnosis 98.75% and the largest ROC derived AUC=0.998 at 100 pg/ml, followed by ST2 91.25% (AUC=0.948) at 2917 pg/ml. Gal-3 and hsTnT have shown similar diagnostic accuracy of 83.75%, (AUC= 0.895, 0,894, respectively) at a cutoff point of 4.9 ng/ml for Gal-3 and 0.015 ng/ml for hsTnT. PTH1-84 accuracy for the diagnosis was 56.67%, AUC=0.733. The levels of BNP, hsTnT, ST2 and Gal-3 were significantly higher in non-survivors compared to survivors. While there were no significant difference in the level of PTH 1.84. The use of the proposed panel of multiple biomarkers (BNP+sST2+hsTnT+Gal-3) significantly improved the prediction of short term mortality in the ADHF patients group compared to the clinical scores alone; improving the AUC for the ADHERE in-hospital mortality score from 0.697 to 0.962 (p=0.006) and for the EFFECT 30 days mortality risk score from 0.734 to 0.954, p=0.027 and for the EFFECT 1 year mortality score from 0.643 to 0.931, p=0.005. **Conclusion:** There is a synergistic value of combining a panel of multiple biomarkers (BNP, hsTnT, ST2, Gal-3) to existing clinical score for the prediction of short term mortality and MACEs in severe ADHF patients. While the additive diagnostic value of this multiple biomarkers study was much less valuable, with little effect on the accuracy of the diagnosis of ADHF compared to BNP.

Keywords: Acute decompensated heart failure – multiple biomarkers strategy – BNP – sST2 – Galectin 3 – hsTnT – Parathormone PTH – Diagnosis – Prognosis.

Introduction:

Heart failure is becoming a major public health problem worldwide. Despite improvements in medical therapy, outcome remains poor, with a 5-year mortality approaching 50% in symptomatic patients and a reported in-hospital mortality up to 19%.[6]

Although HF is increasingly encountered in medical practice, its prompt diagnosis can be challenging, even for experienced clinicians. Furthermore, when the diagnosis of HF is made, it often remains challenging to risk stratify patients.

The progression of heart failure is complex and is driven by multiple biological processes[1] As such, a single biomarker is unlikely to be sufficient for risk stratifying patients with HF and with the development of new assays there has been growing interest in the measurement of a diverse biomarker profiles and panels, reflective of the underlying

biology of heart failure, as a means to improve the accuracy of diagnosis and the precision of risk stratification.[7–9]

The proposed panel in our study included multiple new biomarkers implicated in the different pathophysiological aspects of the development of the disease; B-type natriuretic peptide (BNP) (Myocyte Stress/Stretch), high sensitivity troponin (hsTnT) (Myocyte Injury), soluble ST2 (sST2) (Myocyte stretch / inflammation) and Galectin-3 (Gal-3) (Inflammation & Extracellular Matrix Modeling), Parathormone hormone (PTH 1-84) (neurohormonal activation).

Methods:

The study was conducted on 60 patients admitted the Alexandria University Main Hospital (AUMH) ICUs presented with acute decompensated heart failure (ADHF), as well as 20 healthy volunteers, selected to match the patients group's age and gender after exclusion of heart failure.

The primary endpoints were the improved specificity and sensitivity for the diagnosis of ADHF, and the prediction of short term (in-hospital / 30 days) and 1 year mortalities. A second endpoint was determined including a composite of major adverse cardiac events (MACEs): in-hospital hemodynamic instability (cardiogenic shock) with subsequent need for vasopressor and inotropic IV drugs, in-hospital life threatening arrhythmias – defined as new onset arrhythmia during hospitalization responsible of instability or worsening of hemodynamic status –, need for mechanical ventilation (for severe pulmonary congestion or cardiogenic shock – Killip class III/IV) and re-hospitalization for decompensation of heart failure during a 1 year follow up period.

On ICU admission, serum levels of BNP have been measured using the Dxl® BNP (Beckman Coulter, Alere reagents). R&D Systems® (Abingdon, United Kingdom) ELISA kits were used for the measurement of sST2 and Gal-3. hsTnT serum level has been measured using Roche Diagnostics® (Indianapolis, Indiana) reagents, while serum PTH 1-84 has been measured using the LIAISON® PTH 1-84 assay (DiaSorin).

Clinical risk score were calculated for each patient in the ADHF group; ADHERE tree algorithm for in-hospital mortality and the EFFECT 30 days and 1 year mortality risk score.

Results:

Patients' characteristics and outcome are fully illustrated in table 1. The levels of the studied biomarkers were significantly higher in the ADHF patients group in comparison with the control group. For each marker a ROC curve derived cut off point was calculated for achieving the best sensitivity, specificity and accuracy for the diagnosis of ADHF. BNP had the best accuracy for the diagnosis 98.75% and the largest ROC derived AUC=0.998 at 100 pg/ml, followed by ST2 with an accuracy for the diagnosis with 91.25% (AUC=0.948) at 2917 pg/ml. Gal-3 and hsTnT have shown similar diagnostic accuracy of 83.75%, (AUC= 0.895, 0,894, respectively) at a cutoff point of 4.9 ng/ml for Gal-3 and 0.015 ng/ml for hsTnT. While PTH1-84 showed the least accuracy for the diagnosis with 56.67%, AUC=0.733.

The levels of BNP, hsTnT, ST2 and Gal-3 were significantly higher in non-survivors compared to survivors. While there were no significant difference in the level of PTH 1.84. The optimal cut-off points for the prediction of mortality were 1278 pg/mL for BNP, 0.04 ng/mL for hsTnT, 3788 pg/mL for sST2 and 11.16 pg/mL for Gal-3.

The use of the proposed panel of multiple biomarkers (BNP+sST2+hsTnT+Gal-3) significantly improved the prediction of 1 year mortality in the ADHF patients group compared to the routinely used BNP alone, with a larger ROC derived AUC of 0.924 versus 0.822, p=0.03.

Patients with higher ADHERE risk tree score showed a higher -but not statistically significant - trend for in-hospital mortality (p=0.063), while patients with higher EFFECT risk score showed a statistically significant higher 30 days mortality (p=0.028). Adding the proposed panel of multiple new biomarkers (BNP+hsTnT+ST2+Gal3) to these clinical scores, improved their performance for the prediction of short term mortality, significantly improving the ROC derived AUC for the ADHERE score from 0.697 to 0.962 (p=0.006) and for the EFFECT 30 days risk score from 0.734 to 0.954, p=0.027. The same results were reproduced for the EFFECT 1 year mortality risk score that showed a modest performance in our study, which significantly

improved when combined to the proposed panel of biomarkers, (AUC 0.643, 0.931 respectively, p=0.005).

While hsTnT, ST2 and Gal-3 were significantly higher in patients who showed at least one of the MACEs (p<0.001), BNP levels were not significantly higher (p=0.07). The ROC curve analysis showed an AUC for the prediction of all events of 0.636 for the BNP, which significantly improved when combining all biomarkers proposed in our panel (BNP+hsTnT+ST2+Gal-3) into 0.958, with a strong statistical significance between both AUCs (p<0.001).

Discussion:

Our findings demonstrate the powerful diagnostic value of BNP for the diagnosis of ADHF, as previously demonstrated in many previous studies. [10] In a systematic review of 20 studies, using a cutoff value of 52 pg/ml for BNP achieved a high diagnostic sensitivity; values below this cutoff point were able to exclude the diagnosis of heart failure.[11] These findings led to a Class I LoE A recommendation for the use of this marker in the diagnosis of heart failure, especially in case of diagnosis uncertainty.[1]

Interestingly, analysis from Breathing Not Properly (BNP) Multinational Study,[12] showed an add on benefit of the measurement of BNP levels for the diagnosis of congested heart failure (CNF), even in patients with clinical certainty for the diagnosis; at an 80% cutoff level of certainty for the diagnosis of CHF, adding BNP to the clinical judgment would have enhanced diagnostic accuracy from 74% to 81%.

The use of the proposed panel of multiple biomarkers BNP+ST2+Gal-3+hsTnT had a modest additive diagnostic value, with a non-significant improvement of the ROC derived AUC for the diagnosis of ADHF compared to the routinely used BNP alone (p=0.498), accordingly we dis-recommend their sole use for the diagnosis of ADHF.

Yet, in special situation, their combined use may be useful for the diagnosis of ADHF, in case of uncertainty, especially in the presence of any of the known confounding factors for the natriuretic peptides are present; female sex, old age, absence of sinus rhythm & high BMI.

In our study, only one patient had an admission BNP level below the calculated cutoff point of ≤100 pg/ml**,** but had the levels of ST2, Gal3 and hsTnT above the calculated cutoff point for the diagnosis of ADHF. Further studies with larger number of patients are needed to show the utility of the combined biomarker strategy for the diagnosis of ADHF in cases where BNP levels are low. The answer for this question is important because a prompt diagnosis of ADHF and consequently the early management has been shown in many studies to be associated with better outcome and to be cost effective; decreasing the length of hospital stay and the rate of re-hospitalization. [13] [14] [15]

After establishing the diagnosis of ADHF, assessing the patient's risk is, at times, a challenging proposal. Early risk stratification may help identify patients who are likely to receive the greatest benefit from early resources-intensive strategies. There are few data on short-term risk stratification for ADHF patients.[3,4,16–20] Most of these scores has been derived and validated before the era of the recently described new HF biomarkers, even before the widespread routine use of natriuretic peptide measurement for patients hospitalized with ADHF. For example, the derivation cohort of the ADHERE model - using the CART statistical method that tends to prioritize available data over missing data - only 25% of the patients had BNP levels available in their records. This limitation may suggest that more sensitive and specific variables have been rejected just for their unavailability according to the retrospective design of the study.

In our opinion, with the availability of the new HF biomarkers reflect the different pathophysiological processes of HF and the current data about their ability to predict worsened outcome, as demonstrated in our study and other pilot studies,[21][22][23][24][25][26][27][28,29][30] new prediction models will be developed associating multiple biomarkers with the existing clinical risk scores, to improve the accuracy for the prediction of mortality in ADHF. Choosing the panel of biomarkers to deploy in clinical practice is yet to be defined

depending on its significant predictive ability cost and ease of assay.

In the present work, the use of the proposed panel of multiple biomarkers (BNP+sST2+hsTnT+Gal-3) significantly improved the prediction of 1 year mortality in the ADHF patients group compared to the routinely used BNP alone, with a larger ROC derived AUC of 0.924 versus 0.822, p=0.03.

The study by Pascual-Figal, on 136 ADHF patients showed the same significant association of elevated levels of ST2, hsTnT and NT-proBNP with short term mortality. The combination of the three biomarkers had an additive value for the prediction of short term mortality.[28]

The latest study describing the utility of a combined biomarkers strategy for the risk stratification of patients with HF was The Barcelona Bio-Heart Failure Risk Study (BCN Bio-HF Calculator) that was derived and validated on 864 patients with chronic ambulatory heart failure. The stratification for 1, 2, and 3 years mortality was better in the models containing more than one biomarker; with the highest found using the combination of ST2 and hs-cTnT.[31]

We tested the performance of two of the most widely validated clinical scores for the prediction of short term mortality in patients hospitalized with ADHF, the ADHERE risk tree for the prediction of in-hospital mortality [3] and the EFFECT risk score for the prediction of 30 days. [4] Surprisingly, the performance of these clinical scores in our study cohort was modest. ROC derived AUC of 0.697 for the ADHERE score, p=0.075, while the AUC for the EFFECT risk score was 0.734, p=0.034.

When comparing the performance of the two clinical scores, they showed matching, yet weak, AUC for the prediction of short term mortality risk with no statistically significant difference between both AUCs, p=0.639. This is in concordance with data published by Auble et. al, on over 30,000 patients hospitalized with ADHF, that showed similar AUCs for the ADHERE and the EFFECT for the prediction of in-hospital and 30-days mortality, (0.72, 0.74, respectively). The two models had equal ability to stratify patients at high risk, while the EFFECT score was superior to identify patients at low risk for short term mortality.[32]

The modest performance of these scores, observed in our study, may be explained by many factors concerning the study design, the characteristics of our cohort of patients as well as the process of implementation and calculation of these scores.

Our study has been concerned with the risk stratification of critically ill patients admitted to the ICU presenting with severe forms of ADHF, the mean SBP on admission was 107 mmHg, 40% needed resources-intensive support strategies including support with mechanical ventilation (25%) and/or use of vaso-active drugs for hemodynamic instability (31.67%). In reviewing the patients' characteristics deriving and validating the ADHERE and EFFECT clinical scores for the risk stratification of patients with ADHF, we found that most of the patients cohorts are lacking or under-presenting critically ill ADHF patients with such severe forms of heart failure.

In the ADHERE study, only 30% of the 65 thousands studied patients had severe heart failure at presentation, only 23.4 % received vaso-active drug therapy – 60% of these drugs were vasodilators, the mean SBP on admission was 144.7 mmHg and 47% of the patients had an LVEF above 40%. As for the EFFECT study cohort including 4031 patients, only 47.7% had an LVEF below 40%, the mean systolic blood SBP was 148 mmHg, clearly a less sick cohort of patients than our group of interest.

Similarly critically ill patients with severe ADHF were under presented in derivation cohorts for other available clinical scores. The PROTECT 7 days in-hospital outcome score [33], derived and validated on a cohort of 2033 patients, while 77% of these patients had NYHA class III-IV, those on inotropic therapy or mechanical ventilation support were excluded from the derivation model, as well as those with co-morbidities including severe pulmonary disease, recent ischemia or cerebrovascular stroke, and significant arrhythmias.

An interesting risk model, where severe form of ADHF was well represented is the

ESCAPE risk model, derived out of 423 full data patients, mean LVEF was 20%, mean SBP was 106 mmHg and a mean hospital stay of 8.5 days, with 5% in-hospital and 18.7% six months' mortality rates. Yet the derived risk prediction model was only validated at patients' hospital discharge and not for in-hospital risk stratification.

Another point that may explain the modest performance of these clinical scores for critically ill ADHF patients may be the process of their calculation. In our experience, we found the implementation of the ADHERE score to be easy and simple through its easily retained tree algorithm design including only admission BUN, SBP and creatinine values, yet in this cohort of critically ill patients, the measure of SBP could rapidly vary during the first hours of admission, as well as the values of BUN and creatinine that could largely vary during the first days from admission, as previously demonstrated in previous studies; showing worsening of renal function especially during the first 3 days post-admission, a small increase in serum creatinine of 0.1 mg/dl or in BUN levels were linked with worsen patients outcome.[34] [35] [36] [37]This, in our opinion can be confusing; whether to include for the risk score calculation the worst SBP or renal function values early after ICU admission rather than the first measured values on admission.

The implementation of the EFFECT score model in clinical practice, was also more complex, because of the sometimes encountered difficulties to determine the presence of the co-morbidities at admission (dementia, liver-cirrhosis), required for its calculation. These difficulties have been encountered and described by other studies validating this clinical score. [32]

Lastly, in our study, these clinical scores showed a superior ability to identify less sick patients, who are at low risk for short term mortality, (none of the patient with a score of 1 showed short term or 1 year mortality). This demonstrates the stronger capability of these clinical score to identify patients at low risk, rather than high risk for mortality, emphasizing on their role for especially triaging ADHF patients who might be effectively and safely treated and monitored in intermediate care wards rather than intensive care units.

In our study, we showed that adding the proposed panel of multiple new biomarkers (BNP+hsTnT+ST2+Gal3) to these available clinical scores, improved their performance for the prediction of short term mortality, with a significant improvement of the ADHERE AUC for the prediction of in-hospital mortality (from 0.697 to 0.962, p=0.006). Also, the performance of the EFFECT risk score for the prediction of 30 days mortality has significantly improved when combined to the proposed biomarkers panel, significantly improving the AUC from 0.734 to 0.954, p=0.027. Similarly for the EFFECT 1 year mortality risk score, improving the ROC curve derived AUC from 0.643 to 0.931, p=0.005.

Similarly, Ky et al. have recently showed that adding a more complex biomarker panel consisting of high-sensitivity C-reactive protein, myeloperoxidase, B-type natriuretic peptide, soluble fms-like tyrosine kinase receptor-1, troponin I, sST2, creatinine, and uric acid to the Seattle HF Model improves the predictive accuracy for 1-year all-cause death in chronic heart failure patients. [7]

The use of the combined biomarkers strategy of (BNP+hsTnT+ST2+Gal-3) had also a better performance for the prediction of all MACEs compared to the routinely used BNP levels alone, (AUC 0.958, 0.636, respectively, p<0.001). When analyzing each of the selected events, levels of BNP, hsTnT, ST2 and Gal-3 were significantly higher in patients who showed hemodynamic instability, need for inotropic and vasopressor IV drugs as well as mechanical ventilation (MV).

As expected, BNP as a marker of myocyte stretch, was the only marker in our proposed panel to show significantly higher levels in patients who needed high doses of IV diuretics (p=0.025). While ST2 was the only biomarker in our proposed panel to show significantly higher level and so to identify patients who needed IV vasodilator drugs, p=0.02. This is an interesting finding that could support the recently described link between sST2 and endothelial function. It has recently been described that human venous and arterial endothelial cells secrete sST2 protein.[38] Moreover, it has been proved that increased expression of sST2 is mediated, in part, by endothelin-1, a potent vasoconstrictor[39] and also in response to elevated indexes of diastolic load[40]. All these findings suggest that the vascular endothelium, sensing hemodynamic and inflammatory status, is a potential source of s ST2 levels in hemodynamic overload and heart failure,

hence the need for vasodilator treatment for patients with elevated sST2 levels.

These findings from our study might represent the first step for a biomarker guided therapy for patients with ADHF; this strategy would permit a more tailored individualised management. This hypothesis, if proven, shows that biomarkers are not only markers of severity of the disease and high mortality but also might help for guiding the therapy and the prevention of this mortality.

To our best knowledge, our study is the first to combine the use of sST2 and Gal-3 in a panel for the risk stratification of patients with ADHF. Patients with elevated Gal-3 (levels above the calculated cutoff point of 11.16 ng/ml) and low sST2 (below the calculated cutoff point of 3788 pg/ml) showed a significantly better outcome than patients with high Gal-3 and high sST2 (p=0.001). Galectin-3 is a product of active macrophages, with binding sites on cardiac-resident fibroblasts, leading to an increase in myocardial collagen expression and interstitial fibrosis and subsequent LV dysfunction in response to myocardial injury or inflammation.[41,42]

The response of healthy cardiac tissue to injury or mechanical stress involves the production and binding of IL-33 to membrane bound ST2 (ST2L), which stimulates a cardioprotective signaling cascade that defends against fibrosis and cardiac remodeling.[43][44][45] When sST2 levels are elevated, however, it acts as a as a soluble decoy receptor of IL-33, binding to IL-33, thus reducing the beneficial effect of IL-33 through the ST2L receptor, so that cardiac fibrosis starts to develop.[39] These scenarios suggest an immunoregulatory roles for sST2 and ST2L in heart failure, regulating inflammatory signals in heart failure.[46]

Our results support this hypothesis showing that despite the elevated levels of the Gal3 as a marker of inflammation, the low levels of sST2 permitted the modulation of this inflammation, attenuating the magnitude of its deleterious effect and leaded to a better outcome for these patients.

This study is mainly limited by the small sample size with mainly male patients and the single centre design, which increases the risk of a type II error. Also, each of the biomarkers proposed in our panel was a significant predictor of primary and secondary endpoints by univariate analysis, when entered into multivariate analysis including other predictors, none showed statistical significance. Only sST2 showed independent significant relation with ALL MACEs, on the multi-variant logistic regression analysis. This is likely due to the limited power of our study. Larger studies with larger patients' cohort are needed to confirm the findings of our study.

Furthermore, a major limitation of our study is the comparison of the diagnostic value of the proposed biomarkers between ADHF patients and completely healthy asymptomatic volunteers. More interestingly was to study the behavior of this panel of biomarkers in a control group of symptomatic patients admitted to the ICU after the exclusion of the ADHF diagnosis. Yet, as this panel has never been studied in the Egyptian population, and their characteristics have never been described in this population, we found it reasonable to include a group of healthy volunteers as a pilot first step study; especially that this design has previously been adopted in other studies. [30]

Lastly, we hypothesized in our study the ability of the proposed panel of biomarkers to guide therapy but further prospective studies designed specifically for the purpose to study the success of each biomarker guided intervention are needed to prove this hypothesis.

We demonstrated for the first time, the synergistic effect of a panel of multiple biomarkers (BNP, hsTnT, ST2, Gal-3) for the prediction of short term mortality and MACEs in severe ADHF patients compared to the routine use of BNP alone as well as the use of clinical scores alone. While the additive diagnostic value of this multiple biomarkers study was much less valuable, with little effect on the accuracy of the diagnosis of ADHF compared to BNP.

For better understanding of our study design and results, we estimate patient stratification and triaging like a BILLIARD game, where the used score acts like a tool (BILLIARD stick) to sort patients (balls), into different outcomes and risks (pockets). Adding the multiple biomarker score to the clinical scores, not only adjusted the precision of the patients' risk stratification, but also added the number of predictable events (pockets), of interest specially in the cohort of critically ill patients, such as the need for MV, need for inotrope and need for vasopressor drug therapy, which may guide patients' management and consequently improve outcome.

Disclaimer

This study complied with the Declaration of Helsinki and was approved by ethical committee of the Alexandria Faculty of Medicine Main University Hospital. There is no conflict of interest to disclaim.

Table I: ADHF patients group characteristics

	Mean ± SD.	
Age	59.7 ± 12.6	
BMI	26.6 ± 3.1	
NYHA	3.3 ± 0.7	
EF	31.7 ± 7	
ICU stay	5.1 ± 3	
Hospital Stay **Routine laboratory tests**	9.0 ± 3.4	
Hb (g/dl)	12.2 ± 2.2	
WBCs (103c/mm3)	12.0 ± 4.6	
Sodium (Na) (meq/L)	133.4 ± 5.4	
Potassium (K) (meq/L)	4.5 ± 0.74	
Urea (mg/dl)	85.6 ± 55	
Creatinine (Cr) (mg/dl)	1.53 ± 1	
ASAT (Ul/l)	114.2 ±288	
ALAT (Ul/l)	101.02 ± 243	
RBS (mg/dl)	184.1 ± 88	
	n	**%**
Male patients	43	71.7
Primary outcome		
Short term mortality **(In-hospital/30 days)**	8	13.3
1 year mortality	3	5
ALL mortality	11	18.3
Secondary outcome		
ALL MACEs	30	50
HD Instability	19	31.6
Serious in-hospital Arrhythmias	10	16.6
Mechanical Ventilation	12	20
Re-Hospitalization for ADHF	12	20
Initial line of **ICU support treatment**		
Need for IV Vasopressor	14	23.33
Need for IV Inotrope	17	28.33
IV Diuretic Shots	37	61.67
IV Diuretic Infusion	8	13.33
High Dose IV diuretic	16	26.67
Need for IV nitrates	12	20.00
ATB	19	31.67

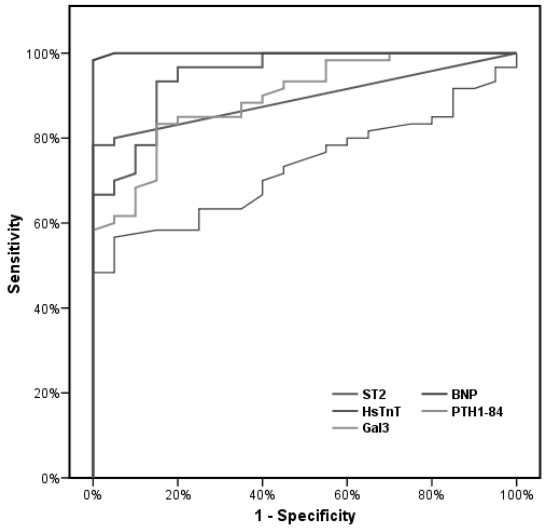

Figure (1): ROC curve for ST2, Gal3, PTH1-84, BNP and hsTnT for the diagnosis of ADHF

Table II: Comparison between AUCs for each mortality score and its biomarkers combination

	AUC	p	Difference between AUCs
ADHERE in-hospital mortality risk score	0.697	0.075	0.006*
ST2,BNP,hsTnT,Gal3 + ADHERE risk	0.962*	<0.001	
EFFECT 30 days mortality risk score	0.734*	0.034	0.027*
ST2,BNP,hsTnT,Gal3 + EFFECT 30d risk	0.954*	<0.001	
EFFECT 1 year mortality risk score	0.643	0.141	0.005*
ST2,BNP,hsTnT,Gal3 + EFFECT 1 year Risk	0.931*	<0.001	

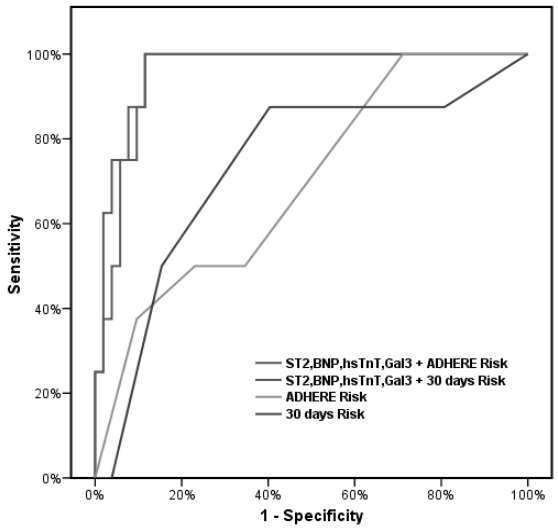

Figure (2):ROC curves for the ADHERE & EFFECT 30 days mortality scores and their combination to the panel of multiple biomarkers

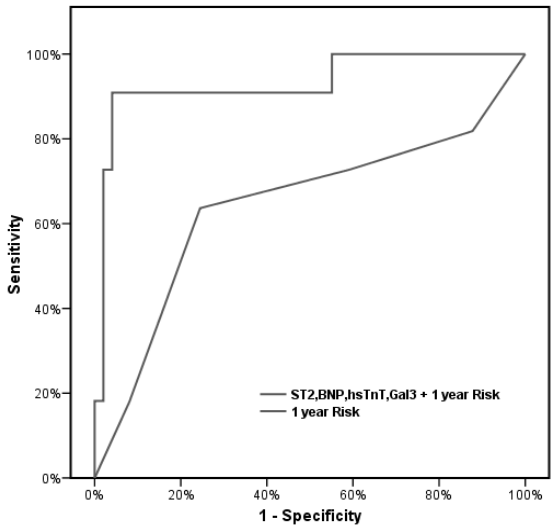

Figure (3):ROC curves for the effect 1 year mortality score and its combination to the panel of multiple biomarkers

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