Original Article

Biomarkers and their combination in a prediction of decompensation after an index hospitalization for acute heart failure

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Abstract

Introduction: Heart failure (HF) still remains as one of the most common causes of hospital admission with a high mortality rate. **Aim:** To investigate the possible prognostic role of brain natriuretic peptide (BNP), high-sensitivity (hs) cardiac troponin (cTn) I, cystatin C, and cancer antigen 125 (CA125) in the prediction of decompensation after an index hospitalization and to investigate their possible additive prognostic value. **Patients and Methods:** Two hundred twenty-two patients hospitalized with acute HF were monitored and followed for 18 months. **Results:** BNP at discharge has the highest sensitivity and specificity in the prediction of decompensation. For a cutoff value of 423.3 pg/ml, sensitivity was 64.3% and specificity was 64.5%, with a positive predictive value of 71.6% and an area under the curve (AUC) of 0.69 ($P < 0.001$). The hazard risk (HR) for decompensation when the discharge BNP was above the cutoff value was 2.18. Cystatin C, at a cutoff value of 1.46 mg/L, had a sensitivity of 57% and specificity of 57.8%, with a positive predictive value of 65.8% and an AUC of 0.59 ($P = 0.028$). CA125, in the prediction of decompensation in patients with acute heart failure (AHF) and at a cutoff value of 80.5 IU/L, had a sensitivity of 60.5% and specificity of 53.3%, with a positive predictive value of 64.5% and an AUC of 0.59 ($P = 0.022$). The time till onset of decompensation was significantly shorter in patients with four versus three elevated biomarkers ($P = 0.047$), with five versus three elevated biomarkers ($P = 0.026$), and in patients with four versus two elevated biomarkers ($P = 0.026$). The HR for decompensation in patients with five positive biomarkers was 3.7 ($P = 0.001$) and in patients with four positive biomarkers was 2.5 ($P = 0.014$), compared to patients who had fewer positive biomarkers. **Conclusion:** BNP, cystatin C, and CA125 are predictors of decompensation, and their combined usage leads to better prediction of new decompensation.

Keywords: Biomarkers, heart failure, prediction

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Introduction

Heart failure (HF) is a complex clinical syndrome and still has a very high rate of hospitalization due to repeated

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decompensation.[1,2] Acute heart failure (AHF) presents as the new onset of HF.[2] In the USA, almost 25% of patients with AHF were re-hospitalized within 30 days of index hospitalization, and in Europe about 44%–50% were re-hospitalized within one year of an acute episode of HF.[3] The number of hospitalizations due to AHF is constantly increasing every day; for example, in Germany there was an increase of 40% between 2000 and 2007 while in England the number of hospitalizations due to decompensation has risen by 57% since 2006.[4-10]

Aim

The aim of this study was to investigate the possible prognostic role of brain natriuretic peptide (BNP) measured at different time points (admission, discharge, percentual changes of BNP during hospitalization) and that of high-sensitivity (hs) cardiac troponin (cTn) I, cystatin C, and cancer antigen 125 (CA125). We also wanted to investigate their possible additive prognostic value, that is, whether their combined use led to a better prediction of decompensation in an 18-month period after an index hospitalization for AHF.

Patients and Methods

Two hundred twenty-two patients were hospitalized at clinic for heart, blood vessels and rheumatism, Clinical Center University of Sarajevo due to AHF, and they were followed for the next 18 months for the occurrence of new AHF. Next 18 months, and occurrence new AHF has been noted. In all patients, an echocardiography exam was performed. Patients were followed for the next 18 months for the occurrence of HF decompensation. Informed consent was obtained from all patients. Ethical approval was obtained from the Ethical Committee of Clinical Center University of Sarajevo.

Statistical analysis

Statistical analysis of data was performed using IBM SPSS Statistics version 13.0 (IBM Corp., Armonk, NY, USA). The specificity and sensitivity of biomarkers in the prediction of decompensation were examined using the receiver operating characteristic (ROC) curve. Independent predictors of decompensation were examined using logistic regression analysis. The Kaplan–Meier survival curve, with respect to the examined variables, was used. We used the logrank test to compare the average survival of the patient in relation to the examined parameters. Accepted statistical significance was at the level of $P < 0.05$.

Results

Admission, discharge, and percentual reduction of BNP as a predictor of decompensation

Sensitivity, specificity and area under the curve (AUC) for level of admission BNP, discharge BNP and percentual reduction of BNP in a prediction of new AHF was tested. The time from index hospitalization till the occurrence of decompensation was found to be significantly longer in patients with a discharge BNP level > 423.3 pg/ml and the aforementioned time was 8.5 (95% CI = 7.1–9.9) months, whereas the time till decompensation in patients with BNP levels below the cutoff value was 12.3 (95% CI = 11.0–13.7) months ($P < 0.001$) [Table 1]. The hazard risk (HR) for the decompensation when discharge BNP was above the cut-off value was 2.18 (95% CI = 1.5–3.1), compared to patients with BNP levels lower than the cutoff value [Figure 1].

Sensitivity, specificity and AUC for hs cTn I, cystatin C, and CA125 in a prediction of new onset of AHF was investigated. The AUC for hs cTn I was 0.57 ($P = 0.095$) [Figure 2], and it could not be used in the prediction of decompensation. The sensitivity and specificity of the biomarkers in the prediction of re-compensation in patients with AHF are shown in Figure 3.

Combined use of biomarkers in the prediction of decompensation in patients after acute heart failure

Since we proved that admission BNP, discharge BNP, percentual reduction of BNP during hospitalization, cystatin C, and CA125 could be used as a single predictor of decompensation, we wanted to explore their combined use in the prediction of decompensation. We stratified patients according to the number of biomarkers that were elevated above the cutoff value obtained by the ROC curve.

We divided patients into five groups according to the number of biomarkers that were elevated above the cutoff value (admission BNP >908.6 pg/ml, discharge BNP >423.3 pg/ml; percentual reduction in BNP <42.4%; cystatin C >1.46 mg/L, and CA125 >80.5 U/L) [Table 2]. Groups of patients with one, two, three, four, or five elevated biomarkers were compared in a number of hospitalizations due to decompensation.

We found that the time till decompensation in patients with four elevated biomarkers (7.5, 95% CI = 5.5–9.5 months) and in patients with five elevated biomarkers (5.3, 95%

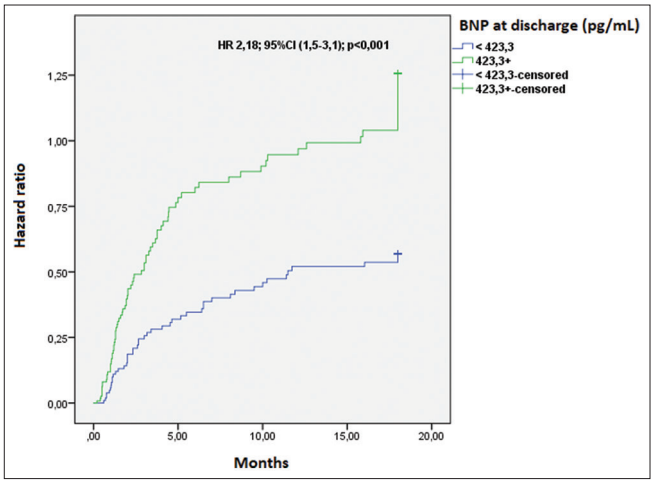

Figure 1: The hazard ratio for decompensation in patients with discharge BNP values above the cutoff value of 423.3 pg/ml

Table 1: Sensitivity and specificity of admission, discharge, and percentual changes in BNP in the prediction of decompensation in patients with acute heart failure

Parameter	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	95% CI	*P*
Admission BNP							
Cutoff 908.6 pg/ml	0.59	57.4	58.1	65.5	49.5	0.51-0.66	0.031
Discharge BNP							
Cutoff 423.3 pg/ml	0.69	64.3	64.5	71.6	56.6	0.62-0.76	<0.001
% BNP reduction							
Cutoff reduction 42.2%	0.66	64.3	64.5	71.6	56.6	0.58-0.73	<0.001

Cutoff: Limit value, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

Table 2: Sensitivity and specificity of cystatin C and CA125 in the prediction of decompensation in AHF

Variable	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	95% CI	*P*
Cystatin C							
Cutoff 1.46 mg/L	0.59	57	57.8	65.8	48.6	0.51-0.67	0.028
CA125							
Cutoff 80.5 UI/L	0.59	60.5	53.3	64.5	49.0	0.51-0.67	0.023

Cutoff: Limit value, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

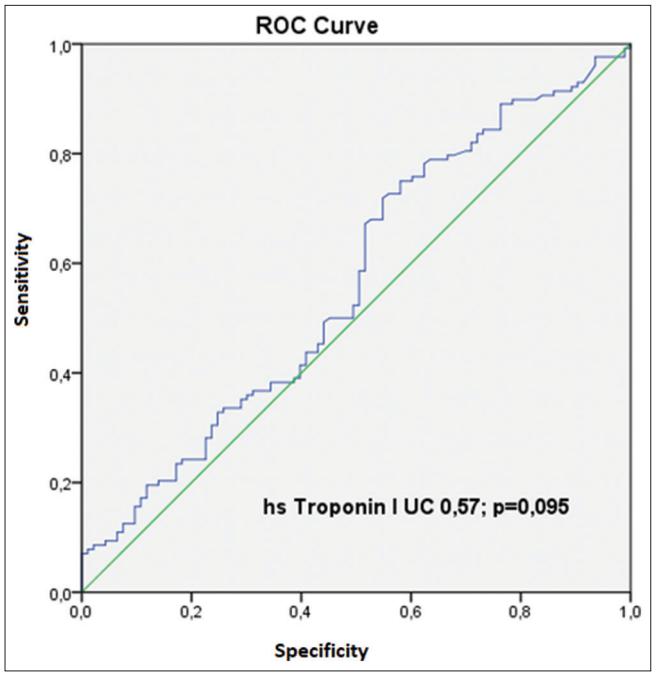

Figure 2: ROC curve for hs troponin I in the prediction of re-compensation in patients with heart failure (ROC: Receiver operating characteristic, AUC: Area under the curve)

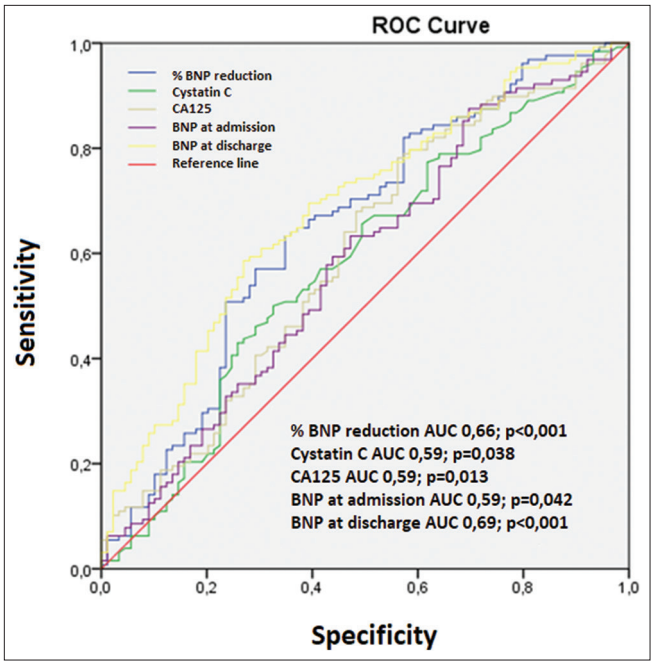

Figure 3: ROC curve in the prediction of re-compensation in patients with AHF (ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval)

CI = 2.4–8.2 months) was significantly shorter compared to that in patients who had three elevated biomarkers (10.7, 95% CI = 8.3–13.0 months), two elevated biomarkers (11.6, 95% CI = 9.6–13.0 months), one elevated biomarker (13.8, 95% CI = 11.6–16.1 months), and no elevated biomarkers (11.9, 95% CI = 8.8–15.0 months). The time till onset of decompensation was significantly shorter in patients with four versus three elevated biomarkers ($P = 0.047$), with five versus three elevated biomarkers ($P = 0.026$), and in patients with four versus two elevated biomarkers ($P = 0.001$) [Table 3]. We then wanted to explore whether there was an increase in predictive power, that is, whether there was an increase in the AUC in the ROC curve when we used a combination of biomarkers that we found in the ROC curve and whether that could be used as a single biomarker in the prediction of re-compensation (admission BNP, discharge BNP, % reduction of BNP, cystatin C, and CA125).

Increase in predictive strength of CA125 was observed with addition of discharge BNP [Figure 4].

When we combined CA125 (AUC = 0.59) and cystatin C at a level higher than the cutoff value (AUC = 0.59), we obtained an AUC of 0.61 and an increase in predictive power [Figure 5]. HR was calculated for the occurrence of decompensation

Table 3: Time till occurrence of decompensation in the group with different numbers of elevated biomarkers

Number of elevated biomarkers above cutoff	Time till occurrence of decompensation (months)	Comparison of time till occurrence of decompensation	*P*
5	5.3 (95% CI=2.4-8.2)	5+ vs. 4+	0.46
4	7.5 (95% CI=5.5-9.5)	4+ vs. 3+	0.047
3	10.7 (95% CI=8.3-13.0)	5+ vs. 3+	0.026
2	11.6 (95% CI=9.6-13.0)	5+ vs. 2+	0.001
		4+ vs. 2+	0.001
		3+ vs. 2+	0.35
1	13.8 (95% CI=11.6-16.1)	5+ vs. 1+	0.001
		4+ vs. 1+	0.001
0	11.9 (95% CI=8.8-15.0)	5+ vs. 0	0.01
		4+ vs. 0	0.02

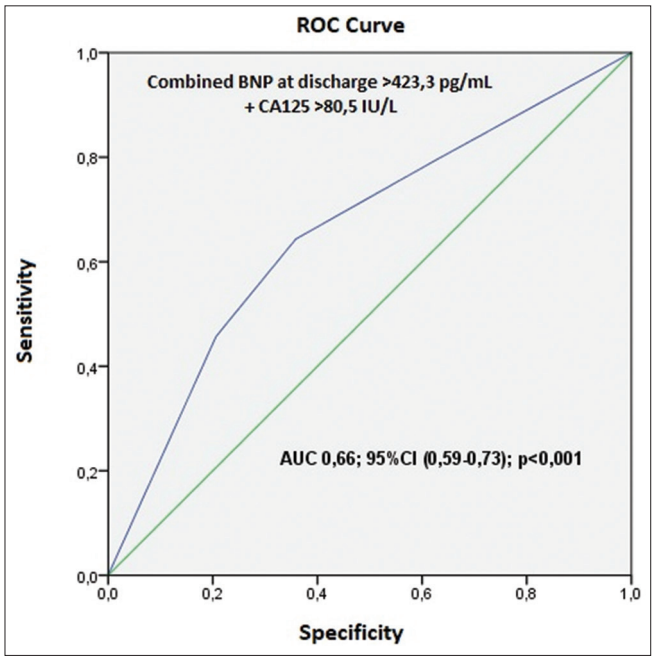

Figure 4: ROC curve in the prediction of re-compensation in combined use of discharge BNP and CA125 above the cutoff values in patients with acute heart failure (ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval)

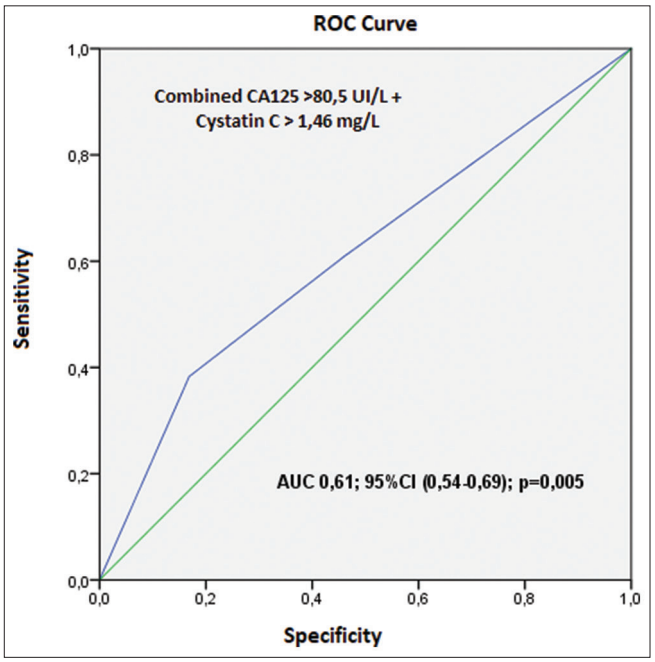

Figure 5: ROC curve in the prediction of re-compensation in CA125 and cystatin C above the cutoff values in patients with acute heart failure (ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval)

in groups with different numbers of elevated biomarkers. The HR for decompensation in patients with five positive biomarkers was 3.7 (95% CI = 1.7–8.2, $P = 0.001$) and in patients with four positive biomarkers was 2.5 (95% CI = 1.2–5.1, $P = 0.014$), compared to patients who had fewer positive biomarkers [Figure 6].

Discussion

There is a need for accurate patient risk stratification in AHF that aims at an early introduction of modern therapy, thereby resulting in better survival. Usage of multiple biomarkers improves risk stratification and determination of prognosis in AHF. In our sample, the highest AUC in the prediction of decompensation belonged to BNP at discharge (cutoff value = 423.3 pg/ml, AUC = 0.69; $P < 0.001$), followed by percentual reduction in BNP (cutoff = 42.4%, AUC = 0.66; $P < 0.001$); the lowest AUC was of admission BNP (cutoff value = 908.6 pg/ml; AUC = 0.59; $P = 0.031$). Omar *et al.*[11] reported that the absolute BN*P* value at discharge was a more accurate predictor of six-month mortality than the magnitude of percentage of in-hospital BNP reduction and baseline BNP. Therefore, we believe that serial determination of BNP is needed: patients with high BNP on discharge or inadequate decline or even increase in BNP are at high risk for new AHF onset.

The following are strategies that can be applied in high-risk patients to prevent early rehospitalization after AHF:

- Consider prolonging the length of hospitalization due to the patient's need for extra intravenous (IV) diuretic therapy.
- After discharge, in the "vulnerable phase," administer IV diuretics at home through the through the HF nurse or at

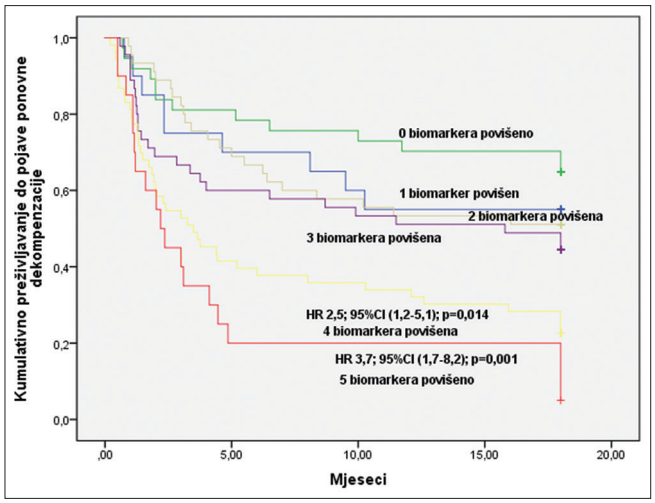

Figure 6: Kaplan–Meier survival curve for occurrence of re-compensation in patients with positive (elevated) biomarkers (above the established limit values obtained by the ROC curve) in relation to the cumulative number of elevated biomarkers

the general physician's office.

- Plan frequent post-discharge controls, say, after seven days instead of after one month.
- Carry out more intensive monitoring: for example, contact by HF nurse for identification of possible weight gain, intensifying of diuretic treatment, etc.

On the other hand, in patients with low BNP at discharge, especially if there has been a significant reduction in levels during hospitalization, the physician can be sure that it is the right time for discharge and that less intensive monitoring is required. If we consider CA125 as a surrogate for congestion, that is, volume overload, it is clear why increased levels were associated with readmission. In our study, CA125 was a predictor of decompensation (cutoff value = 80.5 UI/L, AUC = 0.59, 95% CI 0.51–0.67, $P = 0.023$). In a recent multicenter study by Núñez *et al.*,[12] elevated CA125 in patients with worsening HF showed an association with mortality and risk of HF hospitalization at one year. Kaya *et al.*[13] found that CA125 was associated with longer hospital stays and an increased risk of re-readmission in HF; in patients hospitalized for more than four days, CA125 values were higher (114 [9–298] U/ml) compared to patients who were hospitalized for less than four days (19 [3–68] U/ml, $P < 0.001$). Hung *et al.*[14] demonstrated that in Heart failure with preserved ejection fraction (HFpEF), CA125 was associated with an increased incidence of HF hospitalizations and remained an independent prognosticator in the multivariate Cox model. In the ROC analysis, both CA125 and NT-proBNP were predictors of decompensation, with an AUC of 0.70 (95% CI = 0.54–0.86) and 0.72 (95% CI = 0.59–0.85), respectively, and when CA125 joined NT-ProBNP there was a significant increase in AUC from 0.72 to 0.82 (95% CI 0.71–0.94, C statistic = 0.0049). In our sample, we analyzed the AUC in the prediction of decompensation when CA125 was added to discharge BNP; there was an increase in the predictive power of CA125 (cutoff value = 80.5 IU/L, AUC = 0.59) when BNP was added (cutoff value = 423.3 pg/ml, AUC = 0.69), and the AUC when both markers were elevated was 0.66. In 2016, Núñez *et al.*[15] reported the results of a CHANCE-HF study (Carbohydrate Antigen-125–Guided Therapy in Acute Heart Failure) that evaluated the effect of HF therapy through the serial determination of CA125 in the plasma of 380 patients diagnosed with AHF. Patients in whom CA125 was determined showed a reduction in the incidence of HF hospitalizations and overall mortality. The decrease in the frequency of hospitalizations was certainly due to the timely increase in the diuretic dose or the introduction of IV diuretic therapy in case of an increase in CA125 as a reflection of congestion, thereby preventing hospitalization. Also, elevated CA125 values could unmask congestion in a patient with HF when rales and edema were absent. We did not prove troponin as a predictor of decompensation, and maybe we should determine troponin a few times to see a possible rise or drop. Xue *et al.*[16] analyzed hs cTn I (hscTnI) in AHF; almost every patient had troponin levels higher than the detection level. Patients with hscTnI levels >23.25 ng/L showed an increased risk of readmission and mortality. In our sample, cystatin C was proven as a predictor of decompensation (cutoff value = 1.46 mg/L, AUC = 0.50, $P = 0.028$). Contributing mechanisms that are responsible for the prognostic role of cystatin C are the association between cystatin C and inflammation, the direct role of cystatin C in the vascular wall remodeling in atherosclerosis, and the role of cystatin C in the remodeling of the cardiac extracellular matrix.[17] Carrasco-Sanchez *et al.*[18] reported that cystatin C in patients with HFPEF was an independent predictor of overall mortality and/or readmission in patients with AHF, regardless of renal function. Several studies demonstrated that the multimarker approach, which reflected different pathophysiology processes in HF pathogenesis, significantly improved risk prediction.[18] Subsequent measurements in addition to those on admission are needed for most biomarkers to maximize their prognostic values over time, especially in the long run. We wanted to investigate the predictive role of a combination of biomarkersfor which we prove to be in relation with AHF onset. ACC/AHA guidelines suggest that a combination of biomarkers (in particular NPs, soluble suppression of tumorigenesis 2 [sST2], galectin-3, and hs cTnI/T) may be more informative than individual biomarkers for risk stratification.[19] In our sample, when we combined an increase in CA125 levels >80.5 IU/L (AUC = 0.59) and cystatin C levels >1.46 mg/L (AUC = 0.59) we obtained an AUC of 0.61 and obtained an increase in the predictive strength of these two biomarkers. In the end, we combined five biomarkers, through which we proved that each one could be used individually in prediction in a multimarker panel, and we examined whether their simultaneous determination improved risk prediction. This is logical if we know that multiple risk factors coexist in the same patient.

The HR for decompensation in patients with five positive biomarkers was 3.7 (95% CI = 1.7–8.2, $P = 0.001$) and in patients with four positive biomarkers was 2.5

(95% CI = 1.2–5.1, P = 0.014), compared to patients who had fewer positive biomarkers. In patients with one, two, or three elevated biomarkers, HR for decompensation was not significantly elevated.

Simultaneous increase in BNP (pressure or volume overload), CA125 (volume overload, inflammation), and cystatin C (inflammation, extracellular matrix fibrosis) levels indicates that multiple pathophysiological mechanisms are activated and that the prognosis is worse in patients with multiple elevated biomarkers. Demissei *et al.*[20] found in their PROTECT study that multimarker models had a much better prognostic value. The combination of urea, chloride, interleukin (IL)-6, cTnI, sST2, and vascular endothelial growth factor receptor 1A (VEGFR-1A) in the clinical model led to an 11% increase in C statistics (0.84 and 0.78 for 30-day and 180-day overall mortality, respectively) and a cNRI of 0.86 (95% CI = 0.55–1.11) and 0.76 (95% CI = 0.57–0.87). Therefore, risk prediction can be strengthened and improved when risk factors are combined.[20–24] The prognostic value of a biomarker can be increased through a multimarker approach because each biomarker reflects a different active pathophysiological process.

Conclusion

Aside from its individual prognostic role, combined usage of biomarkers is more useful in the prediction of future decompensation. Early recognition of a high-risk population is one possible method for reduction of rehospitalization rate. Multimarker panels or scores represent perspectives for future research studies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Malik A, Brito D, Vaqar S, Chhabra L. Congestive Heart Failure. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
2. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, *et al.* Acute heart failure. Nat Rev Dis Primers 2020;6:16.
3. Maggioni AP, Dahlström U, Filippatos G. EURObservational Research Programme: Regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur Heart J 2013;15:808-17.
4. Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T, *et al.* Improving care for patients with acute heart failure: Before, during and after hospitalization. ESC Heart Fail 2014;1:110-45. doi: 10.1002/ehf2.12021.
5. Castiglione V, Aimo A, Vergaro G, Saccaro L, Passino C, Emdin M. Biomarkers for the diagnosis and management of heart failure. Heart Fail Rev 2022;27:625-43.
6. Seferović P, Farmakis D, Bayes-Genis A, Ben Gal T, Böhm M, Chioncel O, *et al.* Biomarkers for the prediction of heart failure and cardiovascular events in patients with type 2 diabetes: A position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2022;24:1162-70.
7. Aulin J, Hijazi Z, Lindbäck J, Alexander JH, Gersh BJ, Granger CB, *et al.* Biomarkers and heart failure events in patients with atrial fibrillation in the ARISTOTLE trial evaluated by a multi-state model. Am Heart J. 2022;251:13-24. doi: 10.1016/j.ahj. 2022.03.009.
8. Bayes-Genis A, Cediel G, Domingo M, Codina P, Santiago E, Lupón J. Biomarkers in heart failure with preserved ejection fraction. Card Fail Rev 2022;8:e20.
9. Begic E, Hadzidedic S, Kulaglic A, Ramic-Brkic B, Begic Z, Causevic M. SOMAscan-based proteomic measurements of plasma brain natriuretic peptide are decreased in mild cognitive impairment and in Alzheimer's dementia patients. PLoS One 2019;14:e0212261.
10. Naser N, Kulic M, Dilic M, Dzubur A, Durak A, Pepic E, *et al.* The cumulative incidence of stroke, myocardial infarction, heart failure and sudden cardiac death in patients with atrial fibrillation. Med Arch 2017;71:316-9.
11. Omar HR, Guglin M. Discharge BNP is a stronger predictor of 6-month mortality in acute heart failure compared with baseline BNP and admission-to-discharge percentage BNP reduction. Int J Cardiol 2016;221:1116-22.
12. Núñez J, Bayés-Genís A, Revuelta-López E, Ter Maaten JM, Miñana G, Barallat J, *et al.* Clinical role of CA125 in worsening heart failure: A BIOSTAT-CHF study subanalysis. JACC Heart Fail 2020;8:386–97.
13. Kaya H, Kurt R, Beton O, Zorlu A, Yucel H, Gunes H, Ter Maaten JM, Miñana G, Barallat J, *et al.* Cancer antigen 125 is associated with length of stay. Tex Heart Inst J 2017;44:22-8.
14. Hung CL, Hung TC, Liu CC, Wu YJ, Kuo JY, Hou CJ, *et al.* Relation of carbohydrate antigen-125 to left atrial remodeling and its prognostic usefulness in patients with heart failure and preserved left ventricular ejection fraction in women. Am J Cardiol 2012;110:993-1000.
15. Núñez J, Llácer P, Bertomeu-González V, Bosch MJ, Merlos P, García-Blas S, *et al.* Carbohydrate antigen 125-guided therapy in acute heart failure: CHANCE-HF: A randomized study. JACC Heart Fail 2016;4:833-43.
16. Xue Y, Clopton P, Peacock WF, Maisel AS. Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure. Eur J Heart Fail 2011;13:37-42.
17. Diez J. Altered degradation of extracellular matrix in myocardial remodelling: The growing role of cathepsins and cystatins. Cardiovasc Res 2010;87:591–2.
18. Carrasco-Sanchez FJ, Galisteo-Almeda L, Paez-Rubio I, Martinez-Marcos FJ, Camacho-Vazquez C, Ruiz-Frutos C, *et al.* Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Card Fail 2011;17:31-8.
19. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, *et al.* 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-61.
20. Demissei BG, Valente MA, Cleland JG, O'Connor CM, Metra M, Ponikowski P, *et al.* Optimizing clinical use of biomarkers in high-risk acute heart failure patients. Eur J

Heart Fail 2016;18:269-80.

21. Aimo A, Januzzi JL Jr, Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, *et al.* Clinical and prognostic significance of sST2 in heart failure: JACC review topic of the week. J Am Coll Cardiol 2019;74:2193-203.
22. Lotierzo M, Dupuy AM, Kalmanovich E, Roubille F, Cristol JP. sST2 as a value-added biomarker in heart failure. Clin Chim Acta 2020;501:120-30.
23. Erturk I, Saglam K, Elasan S, Aykan MB, Acar R, Yesildal F, *et al.* Evaluation of the effects of different treatment modalities on angiogenesis in heart failure patients with reduced/mid-range ejection fraction via VEGF and sVEGFR-1. Saudi Med J 2018;39:1028-34.
24. Zhao X, Sui Y, Ruan X, Wang X, He K, Dong W, *et al.* A deep learning model for early risk prediction of heart failure with preserved ejection fraction by DNA methylation profiles combined with clinical features. Clin Epigenetics 2022;14:11.