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Usefulness of cardiac biomarkers for prognosis of better outcomes in chronic heart failure

Retrospective 18-year follow-up study

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Abstract

Brain natriuretic peptide is an established, surrogate follow-up marker, strongly correlated with heart failure severity. Several other biomarkers and tests are useful for assessing the prognosis of patients with HF, such as oxidized low-density lipoprotein antibodies and C-reactive protein. Some inflammatory cells, including monocytes, lymphocytes, and neutrophils, are involved in coronary heart disease and may be useful for prognosis also. This study assessed the potential usefulness of various laboratory biomarkers in predicting long-term outcomes and hospitalization among a cohort of outpatients with chronic, advanced HF.

This retrospective, 18-year follow-up study included all patients admitted to the Heart Failure Outpatient Unit in our tertiary care medical center from 2000 through 2001 due to chronic HF. Excluded were patients with malignant disease, severe stroke, active inflammatory disease, or infection. At the first visit, blood was sampled for routine analysis and biomarkers NT-proBNP, C-reactive protein, myeloperoxidase, heat shock protein, and antibodies to oxidized low density lipoprotein. left ventricular ejection fraction and New York Heart Association class class were also established. Patients were followed every 3 months. Study endpoints were mortality or first hospitalization.

Among 305 study patients, HF duration ranged from 2 months to 18 years. Mean follow-up was 9.1 ± 6 years. Mean time to first hospitalization was 60 ± 58.1 months, median = 38 (range 0–179). Mortality rate was 41%. Regression analysis showed New York Heart Association class, lymphocyte count and alkaline phosphatase were independent predictors of survival, with hazard ratios of 1.0, 0.973, and 1.006, respectively ($P < .05$).

N-terminal pro-B-type natriuretic peptide, alkaline phosphatase, and lymphocyte count are important prognostic predictors for very long-term follow-up among patients with chronic HF.

Abbreviations: CRP = C-reactive protein, HF = heart failure, HR = hazard ratio, HSP = heat shock protein, LVEF = left ventricular ejection fraction, MPO = myeloperoxidase, NT pro-BNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association class, OxLDL Ab = antibodies to oxidized low density lipoprotein.

Keywords: alkaline phosphatase, biomarkers, heart failure, lymphocytes, N-terminal pro-B-type natriuretic peptide

1. Introduction

Heart failure (HF) is the leading cause of morbidity and hospitalization worldwide. Over 5.8 million people in the United States have HF.[1] Continuous clinical follow-up and prognostic predictors are needed to improve management of patients with HF.[2]

Several biomarkers and tests have been established as useful for assessing the prognosis of patients with acute heart HF[1–5] and several types of inflammatory cells, including monocytes, lymphocytes, eosinophils, and neutrophils, have been associated with coronary heart disease.[2–6] Experimental data showed that increased lymphocyte count may be a useful, predictive

Editor: Ovidiu Constantin Baltatu.

**GC and IG contributed equally to this work.*

This study was funded by internal departmental resources.

The study was approved by the Ethics Committee of the Tel Aviv Medical Center (0338-10TLV).

All participants provided written informed consent prior to data collection.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Charach G, Grosskopf I, Galin L, Robinson E, Hershenson R, Charach L. Usefulness of cardiac biomarkers for prognosis of better outcomes in chronic heart failure: retrospective 18-year follow-up study. Medicine 2021;100:5(e23464).

Received: 7 July 2020 / Received in final form: 29 October 2020 / Accepted: 2 November 2020

http://dx.doi.org/10.1097/MD.0000000000023464

biomarker and indicator of favorable outcomes among patients with acute coronary syndromes, post-infarction, HF, coronary artery disease, and atherosclerosis. It is also associated with increased in-hospital mortality.[3–14] White blood cell count and monocytes have an important role in inflammatory, vasculogenetic processes, as well as in regeneration of the vascular wall and in the development of HF.[3–5,8,9,13] C-reactive protein (CRP), heat shock protein (HSP), and myeloperoxidase (MPO) were found to be prognostic predictors of HF.[15–17]

Several studies suggested that oxidative stress might be involved in the pathogenesis of HF. Reactive free radicals have a pathogenetic role in the progressive deterioration of the decompensating myocardium.[18,19] Previously, we reported that oxidized LDL (OxLDL) antibodies and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) have high prognostic value for hospitalization and mortality.[19–22] It was found that OxLDL antibody levels were better predictors than NT pro-BNP for long-term follow-up because antibodies remain in the circulation for 3 to 4 months, as compared to proBNP which is present for several days.[19–21] BNP is widely used in clinics and was found to be a better prognostic factor for exacerbations.[21]

It has still not been established which of 1 or several biomarkers are considered reliable for HF and whether they can be good prognostic predictors of mortality and morbidity.

Previously, we described 3.7 years follow-up of patients with chronic HF regarding biomarkers OxLDL and NT pro-BNP.[21] NT pro-BNP emerged as potential biomarkers of clinical interest in HF management. NT pro-BNP (and BNP) are related to HF severity and to clinical status. NT pro-BNP and BNP are strongly associated with prognosis across the entire spectrum of HF patients.[21]

The aim of this longitudinal 18-year study was to assess the potential usefulness of various laboratory biomarkers in predicting long-term outcomes and hospitalization, which are expressed as morbidity and mortality, among a cohort of outpatients with chronic, advanced HF.

2. Methods

Medical records of all patients who were admitted to the Outpatient HF Unit at our tertiary care medical center from January 2000 through July 2001 because of chronic HF were reviewed. Data retrieved from the electronic medical records included medical history, current and past medications, resting blood pressure, heart rate, weight, New York Heart Association class (NYHA) class, and (based on available information, echocardiography or isotopic ventriculography). Systolic HF was defined as left ventricular ejection fraction (LVEF) $\leq$40% by echocardiography or by Tc^{99} ventriculography.

2.1. Exclusion criteria

Patients who had malignant disease, cerebral vascular disease, inflammatory disorder, rheumatologic disease, or infections, as well as those who were permanently bedridden or those who lacked sufficient follow-up information were excluded.

At the first visit, blood was sampled for routine biochemistry values and for NT pro-BNP, CRP, MPO, HSP, OxLDL-Ab. Patients were examined at least every 3 months throughout the follow-up period.

Study endpoints were morbidity (expressed as time to first hospitalization due to exacerbation of HF), all-cause mortality and a combination of the 2 (referred to as composite outcome).

The study was approved by the Ethics Committee of the Tel Aviv Medical Center (0338-10TLV). All participants provided written informed consent prior to data collection.

2.2. Statistical analysis

Data are presented as numbers and percentages for nominal variables and as means and standard deviations for continuous parameters. Chi-squared test was used to evaluate frequency data and *t* test or Mann–Whitney for metric variables. Multiple Cox regression were used to present variables that influence duration of time to death or hospitalization. ROC curves were used to show area under curve for variables that measure the test's discriminative ability.

3. Results

A total of 345 consecutive outpatients with CHF-related symptoms were eligible for participation in this prospective study. Among them, 40 were excluded for noncompliance or lack of sufficient follow-up information. The remaining 305 patients were entered into the study. HF duration ranged from 2 months to 18 years and mean follow-up was 9.1 $\pm$ 6 years (median 13 years).

Relevant data on the patients' general characteristics are presented in Tables 1 and 2. The mean LVEF was 37% and their mean NYHA was 2.8. The mean number of clinical visits was 15.3. The mean time to first hospitalization was 60 $\pm$ 58.1 months, median 38 (range 0–179). The mortality rate was 41% (125 patients). The mean levels of laboratory values in the cohort were: Hb 12.9 $\pm$ 1.56 g%, creatinine 1.8 $\pm$ 1.2, mean NT proBNP 3675 $\pm$ 5597.1 pg/mL.

The large variety of medications and the frequency of their use are shown in Table 3. The most frequently used medicines were furosemide, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARB), beta blockers, statins, and spironolactone.

Table 4 provides essential laboratory data in cohorts of hospitalized and not hospitalized patients. There were significant differences in age (P=.035), HSP (P=.047), high density lipoprotein (P=.013) and alkaline phosphatase (ALP) (P=.041) between hospitalized and non-hospitalized patients. OxLDL did not differ between the 2 cohorts.

Table 1

General demographic and clinical characteristics.

Characteristic	N = 305	%
Age	70.3 $\pm$ 10.6 yr	
Males	225	73.8
Females	80	26.2
Smoker	93	30.5
Hyperlipidemia	187	61.3
Hypertension	183	60.0
Diabetes mellitus	122	40.0
Ischemic heart disease	231	75.7
Valvular disease	56	18.4
Atrial fibrillation, chronic	73	23.9
Stroke	39	12.8
PCI/CABG	151	49.5

CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention.

Table 2

Laboratory data.

Laboratory Parameter	Mean		SD
Heat shock protein, u/L	0.029	±	0.030
Cholesterol, mg/dL	185.3	±	42.2
Low density lipoprotein, mg/dL	330.3	±	116.2
High density lipoprotein, mg/dL	44.6	±	11.2
Oxidized LDL antibodies, units/mL	0.004	±	0.021
C-reactive protein mg/dL	7.9	±	12.4
Creatinine mg/dL	1.8	±	1.1
Myeloperoxidase, ng/m	207.6	±	267.3
Monocytes%	7.7	±	5.5
White blood cells*1000	7.5	±	2.3
Hemoglobin, g%	13.1	±	2.6
Triglyceride, mg/dL	157.2	±	89.2
NT-proBNP, pg/mL	3675.9	±	5597.1
Polymorphonuclear cells%	63.7	±	15.0
Lymphocytes %	24.6	±	24.6

LDL = Low density lipoproteins, NT pro-BNP = N-terminal pro-B-type natriuretic peptide.

Table 3

Patients' medications (N = 305).

Medications	N	%
Coumadin	60	19.7
Aspirin	218	71.5
Statins	167	54.8
ACE Inhibitors	148	48.5
Candesartan	67	22.0
Clopidogrel	26	8.5
Nitrates	109	35.7
Ca blockers	49	16.1
Beta blockers	185	60.7
Insulin	21	6.9
Oral hypoglycemic drugs	71	23.3
Alpha blockers	53	17.4
Bezafibrates	53	17.4
Anti-arrhythmic drugs	52	17.0
Digoxin	68	22.3
Spironolactone	177	58.0
Diuretics	245	80.3

ACE = angiotensin converting enzyme.

Table 5 shows main laboratory data according to mortality. Age, creatinine and NT-proBNP, were significantly lower, whereas lymphocyte count, polymorphonuclear cell count, and ALP were higher among survivors. Age was the best predictor of longevity in HF patients but this was excluded during analysis to find other prognostic factors.

A Cox multivariate regression analysis was used to predict mortality (Table 6). The adjusted hazard ratios (HR) of the general, clinical and laboratory parameters that were examined as predictors of survival are shown. The results were adjusted for age and weight. NT pro-BNP, lymphocyte count and ALP had HR of 1.0, 0.973, and 1.006, respectively and were independent predictors of survival. Ejection fraction, OxLDL AB, CRP, MPO, HSP, NYHA, and other laboratory parameters had no significant effects on mortality outcome.

Table 7 shows the HRs of the main laboratory parameters that had an impact on time to first hospitalization (morbidity). Only lymphocyte count and ALP were significant.

Figure 1 shows Kaplan–Meier survival curve of all patients during 18 years of follow-up. A total of 41% of patients died during follow-up. Figure 2 displays Kaplan–Meier survival curves according to a NT-proBNP statistical mean cut point of 1429 pg/mL, where lower levels indicate better outcomes.

Figure 3 shows Kaplan–Meier survival curves according to Alkaline phosphatase. Statistical mean cut point -52 mg/dL. Lower levels indicate better outcomes. Figure 4 shows ROC curves of 4 predictors for outcomes: NT-proBNP, uric acid, ALP, and polymorphonuclear cells. NT-proBNP had the highest specificity and sensitivity. Figure 4. shows ROC curve of 4 predictors for outcome: NT pro-BNP, uric acid, alkaline

Table 4

Impact of laboratory parameters on time to first hospitalization (morbidity).

	Hospitalization						
	No = 129			Yes = 176			
Parameter	Mean	±	SD	Mean	±	SD	*P*
Age, yr	71.8	±	10.0	69.2	±	10.9	.035
Heat shock protein, u/L	0.025	±	0.025	0.032	±	0.033	.047
Cholesterol, mg/dL	185.3	±	41.3	185.3	±	42.9	.992
Low density lipoproteins, mg/dL	325.2	±	90.2	333.9	±	131.9	.527
High density lipoproteins, mg/dL	46.4	±	12.0	43.2	±	10.4	.013
Oxidized LDL antibodies, units/mL	0.003	±	0.022	0.005	±	0.020	.395
C-reactive protein, mg/dL	7.4	±	12.0	8.2	±	12.8	.562
Creatinine, mg/dL	1.8	±	1.2	1.8	±	1.0	.888
Myeloperoxidase, ng/m	174.9	±	149.8	231.5	±	326.0	.068
Monocytes %	7.1	±	5.0	8.2	±	5.8	.076
White blood cells*1000	7.4	±	2.5	7.6	±	2.2	.547
Hemoglobin, g%	13.0	±	1.6	13.1	±	3.2	.679
Triglycerides, mg/dL	157.1	±	90.5	157.2	±	88.6	.997
NT-proBNP, pg/mL	4094.6	±	6241.7	3374.0	±	5079.6	.275
Polymorphonuclear cells, %	62.2	±	12.2	64.8	±	16.6	.158
Alkaline phosphatase	60.2	±	33.8	70	±	45.2	.041
Lymphocytes%	25.3	±	8.4	24.1	±	8.0	.242

NT pro-BNP = N-terminal pro-B-type natriuretic peptide.

Table 5

Impact of Laboratory parameters on mortality.

	Mortality						
	No = 180			Yes = 125			
Variable	Mean	±	SD	Mean	±	SD	*P*
Age, yr	65.8	±	9.3	76.7	±	8.9	.000
Heat shock protein, u/L	0.027	±	0.029	0.032	±	0.032	.202
Cholesterol, mg/dL	189.8	±	41.5	178.8	±	42.5	.025
LDL, mg/dL	333.6	±	129.5	325.6	±	94.9	.561
HDL, mg/dL	44.1	±	11.0	45.3	±	11.5	.374
Oxidized LDL antibodies, units/mL	0.003	±	0.022	0.006	±	0.019	.317
CRP, mg/dL	7.2	±	13.5	8.8	±	10.7	.279
Creatinine, mg/dL	1.60	±	0.86	2.10	±	1.29	.000
Myeloperoxidase, ng/m	191.5	±	180.4	230.7	±	356.6	.208
Monocytes, %	7.6	±	6.4	7.9	±	3.8	.687
White blood cell*1000	7.4	±	2.1	7.7	±	2.7	.243
Hemoglobin, g%	13.3	±	3.2	12.8	±	1.5	.121
Triglycerides, mg/dL	159.4	±	86.2	154.0	±	93.6	.606
NT-proBNP, pg/mL	2221.3	±	3339.2	5750.5	±	7283.8	.000
Polymorphonuclear cells, %	61.9	±	11.3	66.4	±	19.0	.016
Alkaline phosphatase	61.7	±	34.6	71.8	±	48.3	.035
Lymphocytes, %	26.8	±	7.0	21.4	±	8.7	.000

CRP = C-reactive protein, HDL = high density lipoprotein, LDL = Low density lipoproteins, NT pro-BNP = N-terminal pro-B-type natriuretic peptide.

phosphatase, and polymorphonuclear cells and shows area under the curve as a criterion to measure the test's discriminative ability in HF disease (i.e., the probability that in 2 randomly sampled objects 1 from each class, the first will be greater than the second).

4. Discussion

The pathogenesis of HF is multifactorial, with enhanced oxidative stress playing a major role in its development.[23,24] In the current study, we examined which biomarkers might predict long-term outcomes in a large cohort of patients with HF. The endpoints of the study were time to first hospitalization (which reflects morbidity) and all-cause mortality. We showed that plasma levels of NT-proBNP, lymphocytes and ALP were the best, significant, independent predictors of morbidity and mortality among patients with HF.[25] Unexpectedly, the HR for OxLDL-Ab was not significant, in contrast to our previous report in an elderly population.[21]

The findings of this study extend the information from several reports that showed that more severe HF is related to higher NT pro- BNP.[19–21] It was also reported that lymphocytes can be a good prognostic predictor for outcome in HF.[20,21] Both of these biomarkers: low levels of NT pro-BNP and high levels of lymphocytes were shown to be independent predictors of very long-term survival. This has not been reported previously, and is novel.[18,19,20–22,26] Our data take previous reports 1 step further by underscoring the predictive value of NT pro-BNP and lymphocytes for prognosis of long-term survival.[22,26] In the current study, ALP levels were shown to be good predictors for long-term outcomes, which has not been reported in the literature. This can be explained by congestive liver. Patients with HF who were asymptomatic had normal or slightly elevated ALP levels. In contrast, those who were less balanced had hepatomegaly because of congestive liver.

We previously reported that while NT pro-BNP had HR less than 1 for hospitalization, both OxLDL-Ab and NT pro-BNP had significant HRs for the composite outcome.[20,21] Compared to the survivors, the increased HR for OxLDL-Ab level exceeded that of NT pro-BNP level by more than 2-fold.[21]

Table 6

Hazard ratios of clinical and laboratory parameters, adjusted for age and weight, on survival in heart failure patients.

			95.0% CI for HR	
Parameter	Sig.	HR	Lower limit	Upper limit
Age	0.411	6.507	0.075	568.006
Weight	0.609	0.995	0.976	1.015
Alkaline phosphatase	0.188	1.003	0.998	1.008
AO stenosis	0.426	0.163	0.002	14.202
BUN	0.142	1.009	0.997	1.021
Creatinine clearance test	0.856	0.998	0.979	1.018
Cholesterol	0.192	1.005	0.998	1.012
Creatinine	0.482	0.906	0.689	1.192
Low density lipoproteins	0.115	0.994	0.986	1.002
Lymphocytes	0.046	0.973	0.947	0.999
NT-proBNP	0.005	1.000	1.000	1.000
Red blood cells	0.685	0.929	0.650	1.327
Statin	0.458	1.172	0.771	1.781
TIA/CVA	0.086	0.650	0.397	1.063
Aspirin	0.338	1.246	0.795	1.955
Alkaline phosphatase	0.007	1.006	1.002	1.011

CVA = cerebrovascular accident, HR = hazard ratio, NT pro-BNP = N-terminal pro-B-type natriuretic peptide, TIA = transient ischemic attack.

Table 7

Cox regression- hazard ratio of the main variables on time to hospitalization.

			95% CI for HR	
Parameter	Sig.	HR	Lower limit	Upper limit
Polymorphonuclear cells	0.229	1.007	0.996	1.018
Lymphocyte count	0.007	0.970	0.948	0.992
Alkaline phosphatase	0.000	1.006	1.003	1.009

HR = hazard ratio.

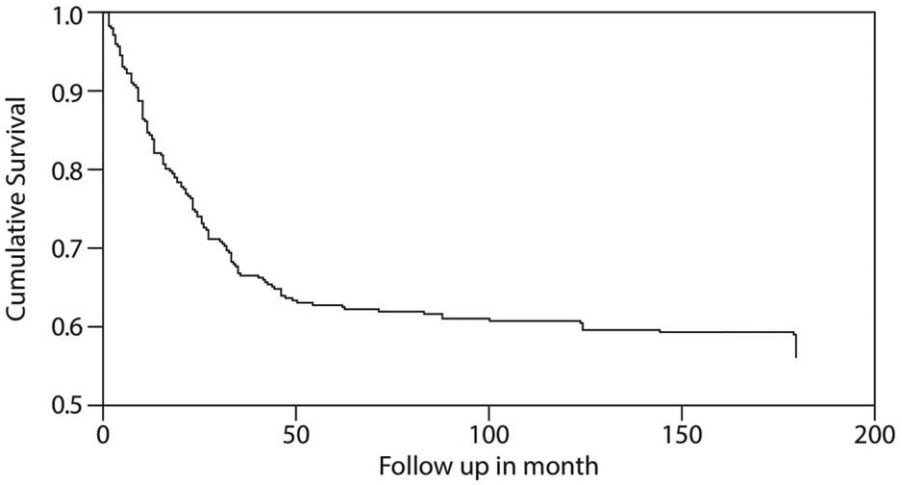

Figure 1. Kaplan–Meier survival curve of all patients over 18-year follow-up.

The current, very long-term study did not find any predictive value of OxLDL antibodies as a biomarker for better outcome. CRP was reported to bind to OxLDL[15] as part of the innate immune response to oxidized phosphorylcholine-bearing phospholipids in this modified lipoprotein. Interestingly, as reported previously, in the current study, the HR for CRP did not reach a level of significance, suggesting that while CRP may be related to myocardial injury, it is not a good predictor for long-time outcomes of HF. This agrees with previous reports.[20,21,26]

Creatinine level did not emerge as a significant prognostic factor, either. This can be because the study patients were monitored in a specialized HF clinic with very strict attention to renal function

In previous reports, HSP and MPO showed some prognostic value.[16,17] In the current investigation, they were not related to the prognosis of HF; however, HSP was higher among hospitalized patients. NT-proBNP and PMN were higher, whereas lymphocyte count was lower among the patients who died.

Unsurprisingly, age was the best predictor for longevity in HF patients. Surprisingly, LVEF (< 40% versus ≥40%) did not emerge as a prognostic marker for HF. The NYHA class was significant only for predicting morbidity but not for the composite outcome. Medication did not add to the prediction of long-term survival, either.

The current results demonstrate that high levels of NT pro-BNP, low lymphocyte count, and elevated ALP levels were predictors for unfavorable outcomes among patients with HF. In an earlier study, we found OxLDL-Ab levels were better predictors of the combined endpoint (mortality and hospitalization).[20,21]

NT pro-BNP reflects the activation of the neurohormonal axis. The short lifespan of the hormones (catecholamines) cannot explain why NT pro-BNP has better prediction for long-time follow-up, Unfortunately, logically NT pro-BNP is more suitable for estimating short-term outcomes during acute events.[20,21,27–29] The mechanism is still unknown.

A limitation of this study was the relatively small sample size of 305 patients with HF, for prognostic value of NT pro-BNP level for mortality and hospitalization. EF did not have long term predictive value. A larger group of patients is needed for further

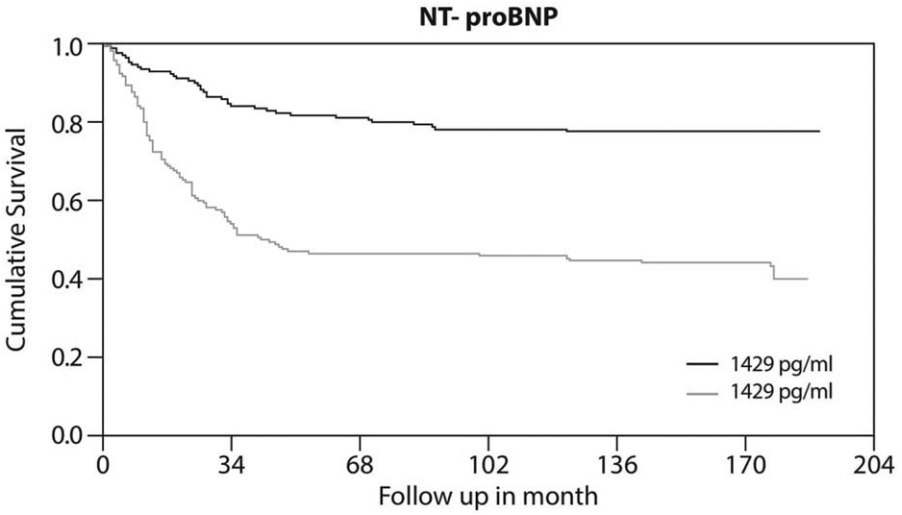

Figure 2. Kaplan–Meier survival curves according to N-terminal pro-B-type natriuretic peptide; cut point 1429 pg/mL.

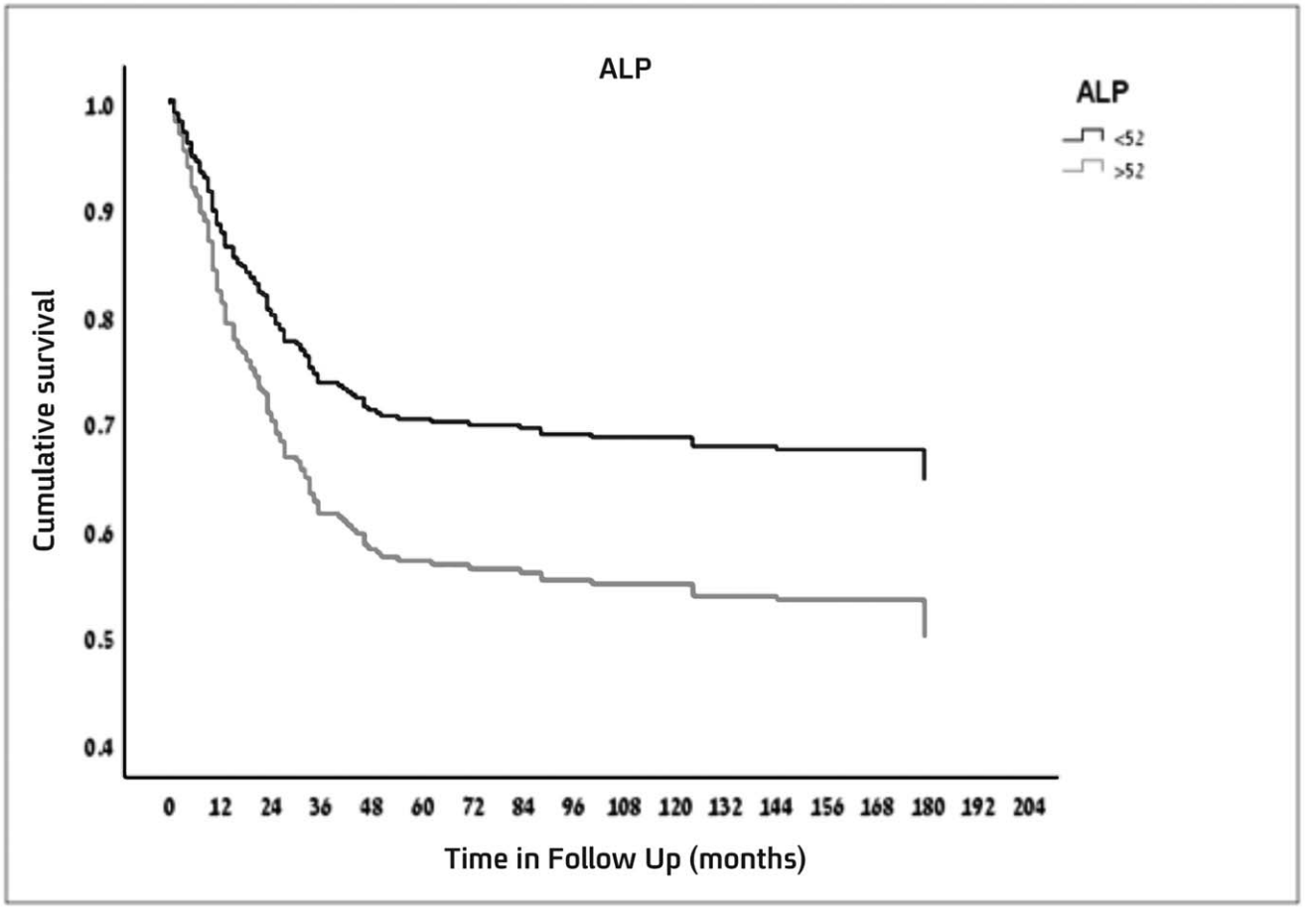

Figure 3. Kaplan–Meier survival curves according to alkaline phosphatase; cut point 52 mg/dL.

evaluation of this important outcome. In this historical cohort study, we did not evaluate biomarkers such as vascular cell adhesion protein 1, also known as vascular cell adhesion molecule 1 (VCAM-1 and ICAM-1 (intercellular adhesion molecule 1) also known as CD54, because the information was not available at the study onset.

In conclusion, the present study demonstrated that NT pro-BNP, ALP, and lymphocyte count are important long-term

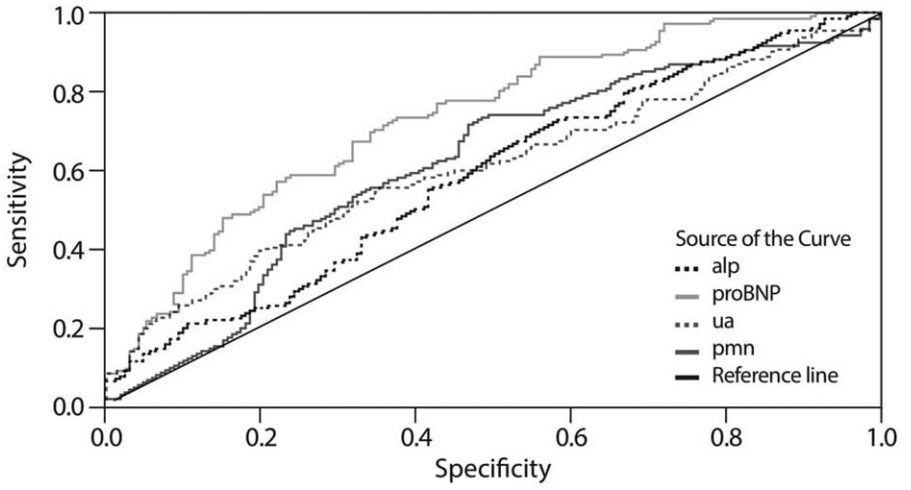

Figure 4. ROC curve of 4 predictors for outcome: N-terminal pro-B-type natriuretic peptide, uric acid, alkaline phosphatase, and polymorphonuclear cells.

prognostic markers for approximately 18 years, in patients with chronic HF.

Acknowledgments

Faye Schreiber, the institutional medical, and scientific editor, are thanked for editorial assistance.

Author contributions

Gideon Charach, Itamar Grosskopf conception, design and analysis, interpretation of data, major revision, and final approval of the manuscript submitted.
Lior Charach, Leonid Galin, Roy Hershenson, and Gideon Charach performed the experiments and treatment of the patients.
Eyal Robinson performed drafting of the manuscript and revision.
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Investigation: Roy Hershenson.
Methodology: Gideon Charach, Itamar Grosskopf.
Project administration: Gideon Charach, Lior Charach.
Supervision: Gideon Charach.

References

[1] Bui A, Horwich T, Fonarow G. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30–41.
[2] Naylor S. Biomarkers: current perspectives and future prospects. Expert Rev Mol Diagn 2003;3:525–9.
[3] Shahid F, Lip GYH, Shantsila E. Role of monocytes in heart failure and atrial fibrillation. J Am Heart Assoc 2018;7:e007849.
[4] Wrigley BJ, Shantsila E, Tapp LD, et al. CD14++CD16+ monocytes in patients with acute ischaemic heart failure. Eur J Clin Invest 2013; 43:121–30.
[5] Gillum RF, Mussolino ME, Madans JH. Counts of neutrophils, lymphocytes, and monocytes, cause-specific mortality and coronary heart disease: the NHANES-I epidemiologic follow-up study. Ann Epidemiol 2005;15:266–71.
[6] Prentice RL, Szatrowski TP, Fujikura T, et al. Leukocyte counts and coronary heart disease in a Japanese cohort. Am J Epidemiol 1982; 116:496–509.
[7] Umemoto S, Suzuki N, Fujii K, et al. Eosinophil counts and plasma fibrinogen in patients with vasospastic angina pectoris. Am J Cardiol 2000;85:715–9.
[8] Batista M, Santos R, Lopes R, et al. Endurance training modulates lymphocyte function in rats with post-MI CHF. Med Sci Sport Excer 2008;40:549–56.
[9] Avanzas P, Quiles J, Lopez de Sa E, et al. Neutrophil count and infarct size in patients with acute myocardial infarction. Int J Cardiol 2004; 97:155–6.
[10] Madjid M, Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease: in-depth review and update. Tex Heart Inst J 2013;40:17–29.
[11] Biasucci LM, D'Onofrio G, Liuzzo G, et al. Intracellular neutrophil myeloperoxidase is reduced in unstable angina and acute myocardial infarction, but its reduction is not related to ischemia. J Am Coll Cardiol 1996;27:611–6.
[12] Wheeler JG, Mussolino ME, Gillum RF, et al. Associations between differential leucocyte count and incident coronary heart disease: 1764 incident cases from seven prospective studies of 30,374 individuals. Eur Heart J 2004;25:1287–92.
[13] Nasir K, Guallar E, Navas-Acien A, et al. Relationship of monocyte count and peripheral arterial disease: results from the national health and nutrition examination survey 1999-2002. Arterioscler Thromb Vasc Biol 2005;25:1966–71.
[14] Grau AJ, Boddy AW, Dukovic DA, et al. Leukocyte count as an independent predictor of recurrent ischemic events. Stroke 2004;35: 1147–52.
[15] Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: prognostic value and effect of valsartan. Circulation 2005;112: 1428–34.
[16] Li Z, Song Y, Xing R, et al. Heat shock protein 70 acts as a potential biomarker for early diagnosis of heart failure. PLoS One 2013;8:e67964.
[17] D'Onofrio G, Mancini R, Vallone R, et al. Acquired myeloperoxidase deficiency: an indicator of subclinical activation of blood coagulation? Blood Cells 1983;9:455–64.
[18] Singal PK, Kapur N, Dhillon KS, et al. Role of free radicals in catecholamine-induced cardiomyopathy. Can J Physiol Pharmacol 1982;60:1390–7.
[19] Dhalla AK, Hill MF, Singal PK. Role of oxidative stress in transition of hypertrophy to heart failure. J Am Coll Cardiol 1996; 28:506–14.
[20] George J, Wexler D, Roth A, et al. Usefulness of anti-oxidized LDL antibody determination for assessment of clinical control in patients with heart failure. Eur J Heart Fail 2006;8:58–62.
[21] Charach G, George J, Afek A, et al. Antibodies to oxidized LDL as predictors of morbidity and mortality in patients with chronic heart failure. J Card Fail 2009;15:770–4.
[22] Anand IS, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the valsartan heart failure trial (Val-HeFT). Circulation 2003;107: 1278–83.
[23] Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263–71.
[24] McMurray J, Chopra M, Abdullah I, et al. Evidence of oxidative stress in chronic heart failure in humans. Eur Heart J 1993;14: 1493–8.
[25] Wright SP, Doughty RN, Pearl A, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. J Am Coll Cardiol 2003;42:1793–800.
[26] Charach G, Grosskopf I, Roth A, et al. Usefulness of total lymphocyte count as predictor of outcome in patients with chronic heart failure. Am J Cardiol 2011;107:1353–6.
[27] Holvoet P, Mertens A, Verhamme P, et al. Circulating oxidized LDL is a useful marker for identifying patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2001;21:844–8.
[28] Tsutsui T, Tsutamoto T, Wada A, et al. Plasma oxidized low-density lipoprotein as a prognostic predictor in patients with chronic congestive heart failure. J Am Coll Cardiol 2002;39:957–62.
[29] Steinerova A, Racek J, Stozicky F, et al. Antibodies against oxidized LDL-theory and clinical use. Physiol Res 2001;50:131–41.