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Cystatin C in a composite risk score for mortality in patients with infective endocarditis: a cohort study

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All presented authors thus fulfil the criteria for authorship.
No else fulfilled the criteria for authorship.
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ABSTRACT

Objective: To develop a multimarker prognostic score for infective endocarditis (IE).

Design: Retrospective case–control.

Setting: Secondary care. Single centre.

Participants: 125 patients with definite IE.

Primary outcome measures: 90-day and 5-year mortality.

Results: Mean age was 62.7±17 years. The 90-day and 5-year mortality was 10.4% and 33.6%, respectively. CysC levels at admission and over 20% increases in CysC levels during 2 weeks of treatment were prognostic for 90-day and 5-year mortality independent of creatinine estimated glomerular filtration rate. In multivariate analyses, CysC (OR 5.42, 95% CI 1.90 to 15.5, p=0.002) and age (OR 1.06, 95% CI 1.02 to 1.10, p=0.002) remained prognostic for 5-year mortality. NT-proBNP, TnT, C reactive protein and interleukin 6 were also linked to prognosis. A composite risk scoring system using levels of CysC, NT-proBNP, age and presence of mitral valve insufficiency was able to separate a high-risk and a low-risk group.

Conclusions: CysC levels at admission and increase in CysC after 2 weeks of treatment were independent prognostic markers for both 90-day and 5-year mortality in patients with IE. A multimarker composite risk scoring system including CysC identified a high-risk group.

ARTICLE SUMMARY

Article focus

- Our aim was to develop a multimarker prognostic score for IE.

Key messages

- CysC levels at admission and increase in CysC after 2 weeks of treatment were independent prognostic markers for both 90-day and 5-year mortality in patients with IE.
- A prognostic score including CysC over 1.2 mg/l, NT-ProBNP over 2000 ng/l, presence of any grade of mitral valve insufficiency (MI) and aged 70 years or older could identify a high-risk and low-risk group in IE.
- The prognostic score might be used to improve patient monitoring and assist treatment choices in IE.

Strengths and limitations of this study

- We were able to monitor changes in levels of biomarkers during treatment in a large cohort of IE patients since blood samples were collected at admission and after 2 weeks of treatment.
- One potential weakness was that 36.2% of patients treated for IE during the study period (71/196) were unavailable for biomarker studies since they lacked stored blood samples. The mortality was lower in the study group (125) compared with all IE patients treated for IE (196) during the study period.

INTRODUCTION

Infective endocarditis (IE) is an infection localised to the endocardial surface of the heart. IE mostly involves the heart valves, resulting in local valve destruction and abscess formation as well as development of vegetations with the ability to embolise to various organs. Despite major advances in both diagnostic and therapeutic procedures, neither the incidence[1] nor the mortality of the disease have decreased in the past 30 years, with a current in-hospital mortality of 15%–20% and 1-year mortality reaching 40% in developed countries.[2] Several epidemiological studies have identified a number of prognostic factors related to higher mortality including advanced age, *Staphylococcus aureus* aetiology,[2 3] cerebral complications[4] and female sex.[5] In addition, biomarkers of inflammation like erythrocyte sedimentation rate,[2] hypoalbuminemia,[6] leucocytosis,[6] C reactive protein (CRP)[7] and procalcitonin[8] can predict poor prognosis but are too non-specific to guide therapy in individual patients. Identification of novel prognostic biomarkers and development of a prognostic score could help to identify IE patients who might benefit from more aggressive therapeutic procedures.

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Because IE often influences haemodynamics, biomarkers linked to cardiovascular mortality could have prognostic power in IE. Among these are factors released during cardiovascular stress like NT-proBNP, MR-proANP, copeptin and troponin T (TnT), which are linked to poor prognosis in heart failure,[9] coronary syndromes[10] and sepsis.[11] Markers of renal function like creatinine,[12] estimated glomerular filtration rate (eGFR)[13] and cystatin C (CysC)[14] might also be able to predict prognosis in patients with IE similar to their ability to predict cardiovascular mortality. In this study, we analysed clinical factors and cardiovascular biomarkers in blood samples collected at admission and after 2 weeks of therapy among patients with definite IE and examined their ability to predict 90-day and 5-year mortality. Our primary goal was to develop a prognostic score in IE.

METHODS

In this single-centre retrospective cohort study, patients with IE treated between 1999 and 2005 at the Department of Infectious Diseases, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden, were registered between 1 February 1999 and 3 December 2005. During this time, 196 patients were diagnosed with definite IE according to the modified Duke criteria[15] and 125 patients had a blood sample drawn at diagnosis and stored and were therefore included in the study. After 2 weeks of treatment, 120 of the 125 patients had a second blood sample drawn. Of all 196 IE patients recorded from 1999 to 2005, 13 patients died (6.6%) within 90 days and 43 patients died within 5 years (20.9%). Among the 125 patients with an available admission blood sample, the 90-day mortality was 10.4% and the 5-year mortality was 33.6%. Information regarding mortality was collected from the hospital's registry of administrative data. The study was approved by the Ethical Committee at the University of Gothenburg. All patients were followed for up to 5 years or until death occurred (mean 1449.1±636.8 days).

Clinical data

Demographic and clinical information regarding age, sex, bacterial aetiology, native and prosthetic valve IE, left ventricular ejection fraction (LVEF), comorbidities and surgery during active IE were obtained from the endocarditis database. The study design included analysis of blood samples at admission and after 2 weeks of treatment. The indications for surgery in Sweden are presented elsewhere.[16]

Laboratory analyses

Serial blood samples were obtained during the hospital stay and stored at −70°C until analysis. The first sample was taken at admission and the second sample 2 weeks later. NT-proBNP was analysed by Elecsys proBNP assay (Roche Diagnostics, Rotkreuz, Switzerland). CysC was analysed in serum using reagents from Dako and the Modular P 2551. Creatinine-based eGFR was calculated using 'The Modification of Diet in Renal Disease' (MDRD) formula. TnT was analysed by using The Elecsys Troponin T high-sensitivity assay (Roche Diagnostics). All biomarkers were analysed on frozen serum samples in a single run. All other laboratory parameters examined were part of the routine laboratory services provided by the Clinical Chemistry Laboratory, Sahlgrenska University Hospital.

Echocardiography

All patients were examined by transthoracic and transesophageal echocardiography at least once during the study period. Echocardiographic criteria for IE and degrees of valve insufficiency were evaluated. LVEF was calculated from long-axis planes (two-, three- and four-chamber views) of the heart.

Statistical analysis

Multiple logistic regression models were used to evaluate possible associations between serum levels of biomarkers (NT-proBNP, TnT, creatinine and CysC) and clinical variables including age, sex, echocardiographic parameters and infectious agents and underlying diseases. Univariate comparisons between groups were calculated using conventional t tests. Mann−Whitney U tests were used for non-parametric comparisons of medians. Dichotomous variables were analysed using the χ^2 test. Receiver operating characteristic curves were used to assess the prognostic properties of biomarkers. The log-rank test was used to compare different strata in Kaplan−Meier analyses of survival. Statistical analyses were performed with SPSS V.19. All probabilities were two tailed, and p values <0.05 were regarded as significant. ORs with CIs were collected from outputs from logistic regression analyses. The coefficient of determination (R^2) was calculated in Microsoft Excel 2007 using Spearman's correlation to assess the strength of the correlation between CysC change and mortality. The add-in Analyse-it was used to compare AUCs between receiver operating characteristic curves. The study population was chosen to get a power of over 90% for detecting clinically relevant associations between CysC, NT-proBNP and mortality (expected OR for mortality of at least 2 for each SD increase in the independent variable at a study population of 125 in logistic regression). No missing data existed for the variables included in the prognostic score, but for other tested variables, cases sometimes were excluded if data were missing, although no more than two cases in each analysis had to be excluded due to a high degree of data availability.

RESULTS

The mean age among the 125 IE patients was 62.7±16.9 years, 64.8% were men and *S aureus* infection was seen in 28.0% of the patients (supplementary table 1). Vegetations on aorta, mitralis and tricuspidalis were seen in 50.4%, 44.0% and 4.0%, respectively. Prosthetic valve endocarditis was diagnosed in 28

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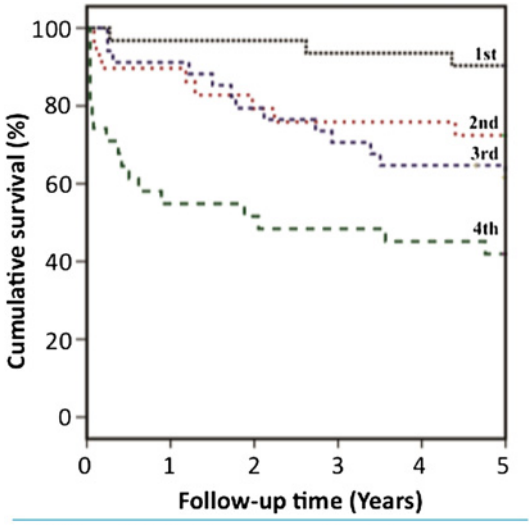
(22.4%) of the patients, and 14 (11.2%) had a pacemaker. Vegetations on pacemaker leads were seen in four of these patients. Most of the patients (91.6%) had LVEF over 40%, and 34.5% underwent heart surgery during antibiotic treatment. Clinical parameters correlating with 5-year mortality included age, history of hypertension and mitral valve insufficiency (MI) but not ejection fraction (supplementary table 1). Aminoglycoside use and duration of aminoglycoside therapy were positively correlated with 5-year survival. No associations were found between the presence of emboli and 5-year survival, biomarker levels or clinical variables examined in the study (data not shown).

In the univariate analysis, CysC levels at admission were associated with both 90-day (OR 5.7, 95% CI 2.2 to 14.7, p≤0.0001) and 5-year mortality (OR 7.11, 95% CI 2.6 to 19.5, p≤0.0001, figure 1). CysC increases over 20% between admission and after 2 weeks of treatment (supplementary figure 1) were also associated with increased 5-year mortality (OR 2.8, 95% CI 1.20 to 6.6, p≤0.017). The relative and absolute changes of all biomarkers were evaluated, but no significant associations with prognosis were found except for CysC.

All eight patients with CysC over 2.1 mg/l died within 5 years. CysC levels and increase over 20% remained significant prognostic indicators for 5-year mortality with similar ORs when alternative multivariate models, including creatinine eGFR or baseline creatinine, were applied (supplementary table 2).

The area under the receiver operator characteristic curve (AUC) for predicting 5-year mortality was 0.70 (95% CI 0.60 to 0.80, p<0.001) for CysC levels at admission and 0.74 (95% CI 0.65 to 0.83, p<0.0001) for CysC levels after 2 weeks of treatment. CysC had a significantly higher AUC compared with creatinine (0.62, 95% CI 0.51 to 0.73, p=0.0042 for difference between AUC for CysC and creatinine after 2 weeks of treatment). Mean creatinine was significantly higher among patients who died within 5 years (table 1). In contrast, median creatinine was not significantly different among patients who died or lived after 5 years.



CysC quartile	CysC level (mg/l)	n	Dead 5 years (n)	p Value
1	<0.98	31	3	Reference
2	0.98–1.17	29	8	0.066
3	1.17–1.52	34	13	0.008
4	>1.52	31	18	<0.0001

Figure 1 Kaplan–Meier survival plot by quartiles of admission levels of CysC.

In the univariate analysis, log NT-proBNP, GFR, creatinine, age, MI and hypertension were linked to poor prognosis, whereas copeptin and MR-proANP did not reach statistical significance. CRP, interleukin 6 (IL-6) and TnT at 2 weeks, but not at admission, were also linked to prognosis (tables 1 and 2). No sex-based differences were present. There was no association between surgery and prognosis.

The four risk factors with the highest AUC for death within 5 years that appeared to be independent from each other were used to generate a composite risk score where each factor added 1 point. The factors included in the score were CysC over 1.2 mg/l, NT-ProBNP over 2000 ng/l, presence of any grade of MI and aged 70 years or older. The AUC of the risk score was 0.74 (95% CI 0.70 to 0.87, p<0.001). If substituting CysC for eGFR calculated from creatinine levels, the AUC decreased to 0.67 (95% CI 0.57 to 0.78).

Patients with a risk score of 0–2 had a significantly better prognosis (11% (8/71) died within 5 years) compared with those with a score of 3–4 (63% (34/54) died within 5 years, p<0.0001) (figure 2). No significant difference in prognosis could be found between patients differing by 1 point. The score's ability to separate patient prognosis was improved when the 34.5% of patients that underwent cardiac surgery were excluded (0–2 points 7% (3/41), 3–4 points 66% (22/33) died within 5 years, p<0.0001). The composite risk score also predicted death within 90-days (0–2 points 0% (0/71), 3–4 points 24.1% (13/54) died within 90 days, p<0.0001).

Furthermore, dividing the cohort based on a score of 0–2 or 3–4 predicted 5-year mortality in patients with left-sided IE (OR 14.6, 95% CI 5.55 to 38.2 p<0.001), left-sided IE that did not undergo surgery (OR 25.7, 95% CI 6.35 to 103.7, p<0.001) and *S aureus*-infected left-sided IE that did not undergo surgery (OR 31.5, 95% CI 2.35 to 422.3, p=0.009). Lastly, the score was also able to predict mortality if the MI parameter was excluded (OR 2.30, 95% CI 1.41 to 3.72, p=0.001) indicating that the composite score was not reliant on the MI parameter and was able to predict mortality in important subgroups of IE.

DISCUSSION

CysC levels at admission, CysC levels after 2 weeks and over 20% increases in CysC levels during 2 weeks of treatment were prognostic for mortality in patients with definite IE. The combination of CysC levels and three other risk factors generated a powerful risk score.

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Table 1 Laboratory characteristics of IE patients

Variable	Total	Dead*	Alive*	p Value
CRP (mg/l) (at admission)	58.6±57.9	61.1±54.7	57.3±64.3	0.72
CRP (mg/l) (after 2 weeks)	28.0±49.3	45.0±26.7	20.7±78.2	0.013
CRP (mg/l) (peak level)	139.9±94.1	160.8±86.5	130.5±107.3	0.12
IL-6 (ng/l) (at admission)	45.3±112.1	43.5±134.5	46.3±42.2	0.90
IL-6 (ng/l) (after 2 weeks)	24.1±42.5	39.1±25.4	17.9±65.2	0.011
Hb (g/l)	112.2±17.3	109.8±17.5	113.2±16.9	0.48
Creatinine (μmol/l)	95.3±66.6	123.2±26.7	81.4±104.1	<0.001
eGFR (ml/min/1.73m^2) (MDRD)	81.0±41.2	67.3±44.1	87.0±29.6	0.016
TnT (ng/l) (at admission)	106.9±226.1	156.1±204.7	82.3±259.3	0.083
TnT (ng/l) (after 2 weeks)	75.7±124.2	109.7±104.4	61.1±157.6	0.048
Incremental TnT (%)	40.8%	44.4%	39.3%	0.60
NT-proBNP (ng/l) (at admission)	3874.2±6868.4	8209.8±1962.6	1706.4±10314.3	<0.001
NT-proBNP (ng/l) (after 2 weeks)	2597.2±3363.6	4782.3±2042.7	1660.8±4633.1	<0.001
Incremental NT-proBNP (%)	41.7%	30.6%	46.4%	0.11
CysC (mg/l) (at admission)	1.34±0.67	1.73±0.35	1.15±0.94	<0.001
CysC (mg/l) (after 2 weeks)	1.45±0.81	0.99±0.65	0.66±0.99	<0.001
CysC (>20% increase) (%)	26.7%	41.7%	20.2%	0.015
MR-proANP (pmol/l) (at admission)	327.6±199.3	378.8±227.0	302.0±452.7	0.21
MR-proANP (pmol/l) (after 2 weeks)	290.2±39.6	249.2±219.1	218.8±135.1	0.15
Copeptin (pmol/L) (at admission)	23.3±29.0	30.1±24.3	19.9±59.2	0.17
Copeptin (pmol/L) (after 2 weeks)	24.0±29.0	21.2±31.8	31.7±21.2	0.42

*After 5 years follow-up.
CRP, C reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin 6.

CysC is a small 13 kDa cysteine protease inhibitor produced at a constant rate by all nucleated human cells tested. CysC is cleared predominantly by renal filtration and is most often used as a replacement for creatinine as a marker of GFR. CysC is regarded as a more accurate marker of kidney function than creatinine (reviewed in Lassus and Harjola[14]). CysC also offers superior ability to diagnose acute kidney injury[17] and declining GFR[18] compared with creatinine. Furthermore, several studies have shown that elevated CysC is a strong risk factor for adverse cardiovascular prognosis in older people even when creatinine levels are normal.[19] Increased CysC levels indicate a future risk of developing heart failure,[20] as well as a poor prognosis among patients with already established heart failure,[21] independent of creatinine levels. Therefore, CysC is a marker of kidney function and prognosis that outperforms creatinine in most studies.

The associations between CysC levels and prognosis in our study might reflect that IE itself or nephrotoxic agents used during treatment of IE impairs kidney function. The ability of CysC to more correctly predict

Table 2 ORs* for mortality among IE patients

Variable†	OR (all patients)	p Value	OR (no surgery‡)	p Value
Age	1.06 (1.03–1.10)	<0.001	1.09 (1.03–1.14)	0.001
MI (all degrees)	2.94 (1.30–6.67)	0.010	5.45 (1.84–16.2)	0.002
Hypertension	3.12 (1.37–7.10)	0.007	2.81 (1.03–7.62)	0.043
CRP (mg/l) (after 2 weeks)	1.01 (1.00–1.03)	0.040	1.00 (0.99–1.01)	0.75
Creatinine (μmol/l)	1.02 (1.00–1.02)	0.006	1.02 (1.00–1.04)	0.025
GFR (MDRD)	0.98 (0.97–1.00)	0.012	0.98 (0.96–1.00)	0.041
logNT-proBNP (ng/l) (at admission)	12.2 (4.28–34.9)	<0.001	23.2 (4.68–115.0)	<0.001
logNT-proBNP (ng/l) (after 2 weeks)	5.91 (2.43–14.4)	<0.001	9.44 (2.83–31.5)	<0.001
CysC (mg/l) (at admission)	7.11 (2.59–19.5)	<0.001	37.5 (4.58–308.1)	0.001
CysC (mg/l) (after 2 weeks)	2.55 (1.37–4.76)	0.003	41.7 (5.43–320.6)	<0.001
CysC (mg/l) (>20% increase)	2.82 (1.20–6.59)	0.017	2.60 (0.90–7.50)	0.080
TnT (ng/l) (after 2 weeks)	1.00 (1.00–1.01)	0.059	1.03 (1.01–1.05)	0.008
IL-6 (ng/l) (after 2 weeks)	1.02 (1.00–1.03)	0.044	1.10 (1.04–1.17)	0.002

*From multiple logistic regression.
†Insignificant predictors excluded from the table.
‡Subgroup analysis of patients who did not undergo surgery.
CRP, C reactive protein; GFR, glomerular filtration rate; IL-6, interleukin 6; MI, mitral valve insufficiency.

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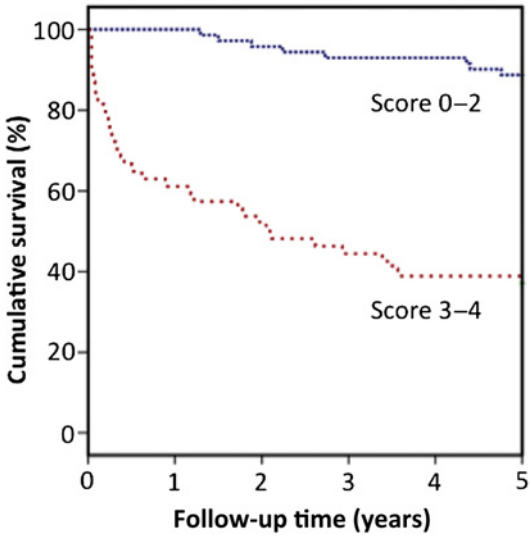

Figure 2 Kaplan–Meier survival plot by risk score for death within 5 years among patients with IE. Patients with 0–2 points were compared with patients with 3–4 points ($p<0.001$). The presence of these risk factors adds 1 point each: any grade of MI, CysC >1. 2 mg/l, NT-proBNP >2000 ng/l, aged >70 years.

GFR among older people and to respond to rapid changes in GFR compared with creatinine could explain the stronger association between CysC levels and IE prognosis compared with creatinine levels.

There are different conceivable explanations for decreased kidney function in IE. One factor could be decreased cardiac output during the acute phase of IE. Although there was no correlation between LVEF and prognosis (supplementary table 1), levels of the heart failure biomarker, NT-proBNP and prevalence of MI were significantly higher among patients with poor prognosis. In addition, levels of TnT after 2 weeks of treatment were associated with prognosis. TnT levels are affected by cardiac stress found among patients with heart failure[22 23] and correlate with prognosis in a number of heart-related conditions.[24] Therefore, the link between CysC levels and poor prognosis among IE patients could be decreased cardiac output resulting in low kidney perfusion and low GFR.

It is also possible that factors that increase production of CysC, such as increased glucocorticoid levels,[25] and possibly inflammation,[26–28] could explain the correlation between CysC levels and IE prognosis. CysC levels show a stronger association with cardiovascular risk factors compared with creatinine, independent of iohexol clearance.[29] Among patients with chronic renal failure followed for 10 years, CysC levels correlated better with cardiovascular disease mortality compared with creatinine or iothalamate clearance[30] indicating that CysC levels predict prognosis partly independent from GFR. In line with this possibility, we found that CysC levels and change in CysC levels during 2 weeks of treatment remained prognostic even after multivariate analysis correcting for creatinine levels and creatinine eGFR (supplementary table 2), suggesting that conditions that increase production of CysC may correlate with IE prognosis. One such factor could be persistent inflammation because high CRP or IL-6 levels after 2 weeks of treatment were also linked to poor prognosis in our study. Moreover, it is also possible that increased glucocorticoid levels due to a general stress response among IE patients could be the link between poor prognosis and CysC levels.

One important aspect of this study was that we could monitor changes in biomarkers during treatment in a large group of IE patients. We found that levels of CRP, IL-6 and TnT after 2 weeks of treatment, but not admission levels, were significantly associated with 5-year survival. This association likely reflects the fact that a rapid response to initial treatment is of great importance for the prognosis. In contrast, levels of the otherwise promising cardiac stress markers MR-proANP and copeptin failed to predict prognosis, even when levels were assessed after 2 weeks of treatment, indicating that these biomarkers are less valuable among IE patients.

Our results confirmed that MI is a powerful prognostic indicator in IE irrespective of the infected valve. The reason for the significant association between MI of all degrees, and not with the worst degrees alone (3 and 4), can be explained by the fact that the patients with severe MI often underwent surgery, which is linked to improved survival.[31] This association could, however, not be confirmed in this study (supplementary table 1).

The multitude of biomarkers and clinical factors included in this study allowed us to explore a composite risk score based on the four strongest and apparently independent risk factors. The composite risk score was able to separate a high-risk and a low-risk group with significantly different 90-day and 5-year survival. IE has still a poor prognosis, despite major advances in diagnostic and therapeutic procedures, and we still have limited ability to find the patients that should be considered for more aggressive treatment. In this light, this novel risk score could add decisional information and allow for a multifactorial judgement of patients and consideration for more active intervention like heart valve replacement or surgical removal of vegetations.

A potential problem with the current study was that 36.2% of the patients treated for IE during the study period (71/196) lacked stored blood samples. In addition, there was a bias for patients with a worse prognosis in the study group. On the other hand, the study group of 125 IE patients had a 5-year prognosis (66.4% 5-year survival) closer to the 60% 5-year survival reported in most studies[1 2] compared with the complete cohort (79% 5-year survival) indicating that the prognosis in our study group were comparable with the outcome in previous studies. Furthermore, data on haemodynamic parameters on admission and during the hospital stay were not recorded. As this was a single-centre study, our findings must be validated before the risk score can be included in clinical routine.

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In summary, a prognostic score including CysC over 1.2 mg/l, NT-proBNP over 2000 ng/l, presence of any grade of MI and aged 70 years or older could identify a high-risk and low-risk group in IE.

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Contributors All authors have contributed significantly to the conception and design of the manuscript, interpretation of data, drafting the article and revisions for important intellectual content and final approval of the version to be published. CB, US-M and LO have also worked on the acquisition and analysis of data. All authors have approved the final version of the manuscript submitted.

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Competing interests None.

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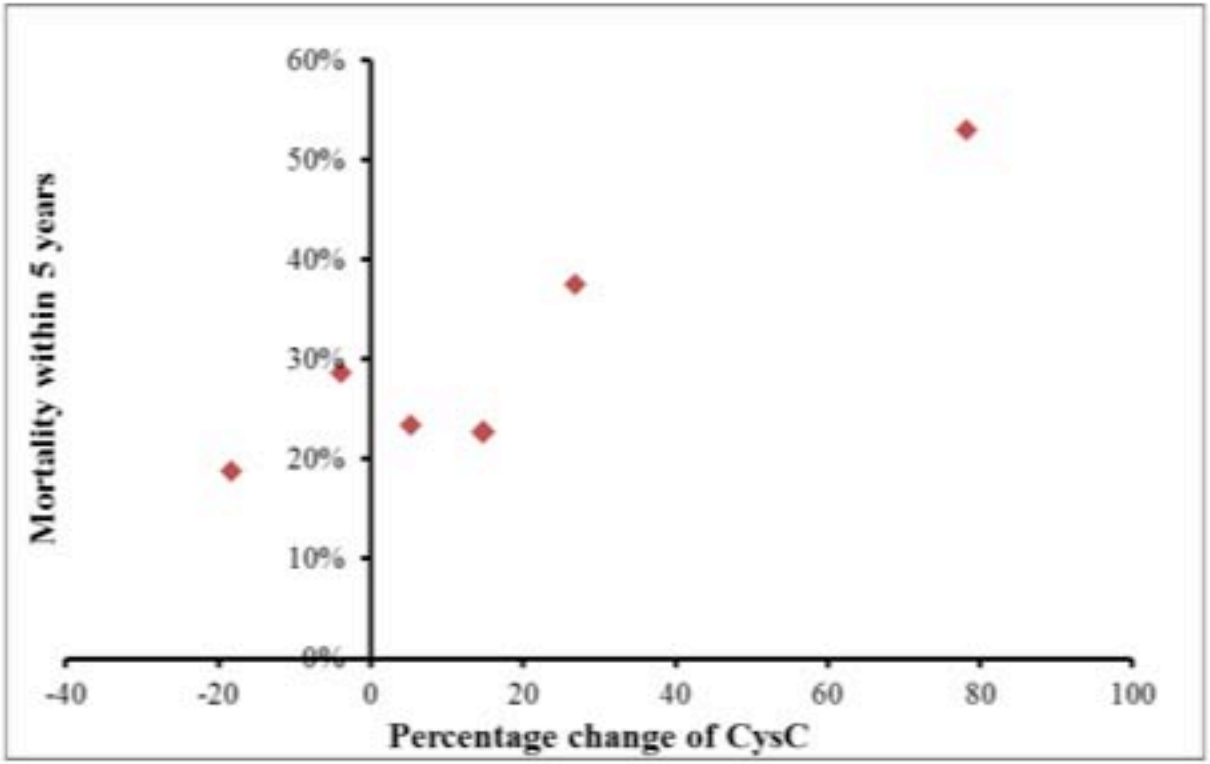
Supplementary Fig. 1 Bjurman et al.



Supplementary Table 1: Demographic and clinical characteristics of IE patients

Variable	**Total**	**[a] Dead**	**[a] Alive**	**p value**
N	125	42	84	
Age [years]	62.7±16.9	71.9±13.6	58.6±16.7	0.0001[b]
Male [%]	64.8%	61.9%	66.3%	0.63
LVEF <0.40	8.0%	11.1%	7.2%	0.49
[c] MI [all degrees]	48.7%	66.7%	41.0%	0.01[b]
[c] MI [>2/4]	14.3%	16.7%	13.3%	0.63
[c] AI [all degrees]	34.5%	33.3%	35.0%	0.87
[c] AI [>2/4]	10.1%	11.1%	9.6%	0.81
Hypertension	40.4%	60.0%	31.6%	0.004[b]
Dialysis	1.8%	2.9%	1.3%	0.56
Cardiac surgery	34.5%	28.6%	37.2%	0.37
NVE	76.8%	71.4%	79.5%	0.14
PVE	23.2%	28.6%	20.5%	0.14
Staphylococcus aureus	29.4%	30.6%	28.9%	0.86

[a] within five years, [b] p <0.05, [c] MI: Mitral Insufficiency, [d] AI: Aortic Insufficiency,

[d] NVE: Native valve endocarditis, [e] PVE: Prosthetic valve endocarditis

Supplementary Table 2: Multivariate models for prediction of five-year mortality (with adjustments for possible confounders)

Variables included in the model[a]	**OR (CysC)**	**p value**
CysC (at admission), MI[b], and age	5.42 (1.90–15.5)	0.002[c]
CysC (at admission), creatinine	9.69 (2.29-41.1)	0.002[c]
	OR (CysC increase >20%)	**p value**
CysC (increase >20%), MI[b], hypertension, and age	4.86 (1.62–14.5)	0.005[c]
CysC (increase >20%), MI[b], eGFR (MDRD), and age	4.07 (1.46–11.4)	0.007[c]
CysC (increase >20%), MI[b], creatinine, hypertension, and age	5.19 (1.63–16.5)	0.005[c]
CysC (increase >20%), MI[b], *Staphylococcus aureus*, hypertension, and age	4.86 (1.59–14.9)	0.006[c]

[a] Models created to adjust cystatin C (at admission or increase >20%) for age, eGFR, baseline creatinine, and/or pathogen (Staphylococcus aureus),[b] MI: Mitral Insufficiency, [c] $p < 0.05$.