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Association between endostatin and mortality in patients with acute dyspnoea, with or without congestive heart failure: a single-centre, prospective, observational study

Alexander Yaghoubi ,[1] Caroline Heijl ,[2,3] Ardavan M Khoshnood ,[4] Per Erik Wändell ,[5] Axel C Carlsson ,[5] Torgny Wessman [1,3]

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[1]Emergency Department, Skåne University Hospital, Malmo, Skåne, Sweden
[2]Department of Cardiology, Skåne University Hospital, Malmö, Skåne, Sweden
[3]Department of Clinical Sciences Malmö, Lund University, Malmö, Skåne, Sweden
[4]Lund University, Malmö, Sweden
[5]Karolinska Institute, Stockholm, Stockholm, Sweden

Correspondence to
Dr Torgny Wessman;
torgny.wessman@med.lu.se

ABSTRACT

Objective The aim of this study was to assess associations between endostatin levels and short-term mortality in unsorted acute hospitalised dyspnoea patients with or without congestive heart failure (CHF), adjusted for common cardiovascular risk factors.

Design, setting and participants In this prospective observational study, 723 hospitalised patients who visited the emergency department at Skåne University Hospital, Sweden, between 2013 and 2018 were included. Of these, 276 had a history of CHF. The association between endostatin levels and 1 month and 3-month mortality was evaluated, stratified by whether patients had a history of CHF or not.

Results Patients with prior CHF had higher endostatin levels, higher short-term mortality and were more likely to have CHF as discharge diagnosis. In a fully adjusted model, endostatin was independently associated with 3-month mortality (HR=1.01 per 1 ng/mL increment of endostatin; 95% CI 1.00 to 1.02; p=0.016). No evidence of association was identified with 1-month mortality.

Conclusions Endostatins are potential biomarkers for 3 months' mortality in patients hospitalised with CHF seeking emergency care with acute dyspnoea. Further studies are needed in different settings to assess the predictive value of endostatins in patients with CHF.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ It is a strength that the study was conducted in a large cohort of patients.
⇒ The study used validated diagnoses and information on mortality and discharge diagnoses from national data registers, which confirm the correctness of these data.
⇒ The presence of prevalent diseases and comorbidities was asked for and double-checked in the medical records by the research nurses.
⇒ It is a limitation that patients were included only during daytime on working days.
⇒ Critically ill patients went directly to the intensive care unit and were therefore not included.

INTRODUCTION

Background and rationale

Dyspnoea refers to a patient's subjective experience of shortness of breath. It is typically ranked as the third most common single cause for visits to emergency departments (ED) worldwide.[1 2] Dyspnoea causes about 7% of all visits at the ED at Skåne University Hospital (SUS) in Malmö, Sweden. Acute dyspnoea can be caused by several different diseases; the most common causes are cardiovascular diseases such as congestive heart failure (CHF), but chronic obstructive pulmonary disease or pneumonia[3–5] is also prevalent. The prevalence of CHF is 2% in the Swedish population, and dyspnoea is one of its cardinal symptoms. The prevalence as well as the risk of morbidity and mortality increase with age, with a prevalence of over 19% and mortality rate of over 30% at the age of 80.[6] It is more common that patients arrive at an ED with an acute decompensation of a previously known heart failure,[7] but an acute episode of dyspnoea can also be the first symptom or manifestation of a previously unknown heart failure. The prognosis in patients with CHF varies. There are studies that report a survival rate of 81% and 75% at 1 and 3 months, respectively.[8] The literature often describes a poor long-term prognosis with a survival rate of 62% at 12 months and 57% at 18 months. Furthermore, the survival rate drastically decreases to 24.5% and 12.7% at 10 and 15 years, respectively.[8 9] There are currently many studies examining larger cohorts of patients with CHF over a long period of time and simultaneously investigating different prognostic factors for survival, as for example ejection fraction (EF), N-terminal probrain natriuretic peptide (NT-pro-BNP) and

blood pressure.[10–13] Endostatin is a potent endogenous angiogenesis inhibitor[14] but is not yet as evaluated and established as NT-pro-BNP. Circulating endostatin has primarily been associated with the growth and spreading of malignant diseases.[15] Recent studies suggest additional associations with cardiovascular mortality and cardiovascular comorbidities,[16] as well as declining kidney function both in the acute and chronic setting, and decreased glomerular filtration rate (GFR).[17 18] Endostatin has been associated with all-cause death at 3 months in unsorted patients with dyspnoea from the Swedish Acute Dyspnea Study (ADYS) cohort.[19] There are some studies that have examined endostatin with regard to long-term mortality in patients with CHF, but the ones available have shown contradictive results.[20 21] Furthermore, at present and to our knowledge, there are no available studies in the literature that have examined endostatin with regard to short-term mortality in patients with CHF. Even so, it seems that endostatin might be a valuable marker regarding the risk of developing heart failure as well as a marker for the prognosis in patients with heart failure.[17 21–25]

OBJECTIVES

The aim of this study was to study the association between endostatin and short-term mortality in a cohort of unselected acute patients presenting at the ED with dyspnoea with and without CHF, adjusting for known cardiovascular risk factors.

METHODS

Study population and outline

The original total ADYS cohort consists of 1745 adult patients who visited the ED due to unsorted acute dyspnoea at SUS in Malmö during daytime and weekdays between March 2013 and January 2019. The inclusion criteria were patients over 18 years of age with dyspnoea as the underlying cause of visit. Critically ill patients were excluded as well as patients with reduced consciousness, as these patients were either transferred directly to an intensive care unit or too ill to provide consent to participate. The patients were interviewed following standardised questionnaires and examined following an examination chart (online supplemental tables 1 and 2). When preparing our report, we used the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines.[26]

Register data

The ADYS data register has later been supplemented with data from Statistics Sweden (Statistiska Centralbyrån) regarding date of death, with 13 patients excluded because of missing data. Only the patients hospitalised were included, why 775 patients were excluded because of discharge directly from the ED. Endostatin analyses were only performed on 850 of the patients. Furthermore, the data register has also been supplemented with data from the Swedish National Board of Health (Socialstyrelsen) regarding dates for registrations in the Swedish in-hospital register and concerning discharge diagnoses from hospitalisation according to International Classification of Diseases 10th revision (ICD-10), with 127 patients excluded because of missing data on discharge diagnoses. This prospective observational study thus comprises a cohort of the initial 723 hospitalised patients with endostatin data, death data and discharge diagnoses from the ADYS (figure 1).

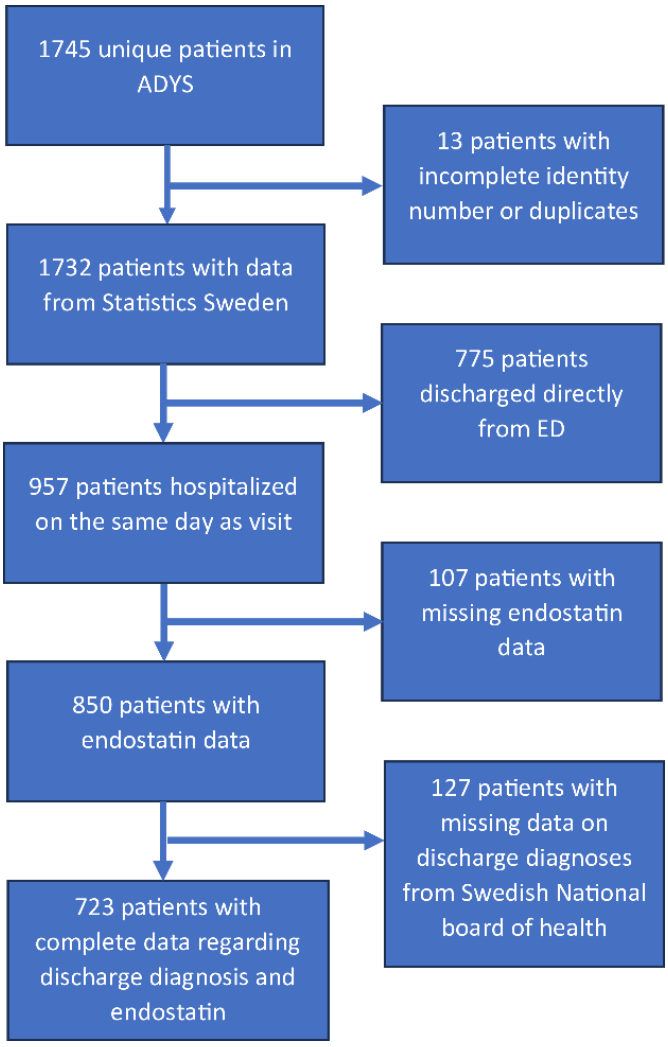

Figure 1 Participant flowchart. ADYS, Swedish Acute Dyspnea Study; ED, emergency department.

Exposure

The exposure in this study was endostatin levels. At inclusion, blood samples were drawn within 1 hour from the visit. The patients' blood samples were frozen and stored at minus 60–80° in Lund University's biobank. The samples were later analysed at the central laboratory of Uppsala University/department of clinical chemistry, Uppsala University using commercial ELISA kits. The results are reported in picograms per millilitre. By shifting the decimal points, the values were converted to more manageable nanograms per millilitre.

Outcomes

The outcomes of this study were mortality rates at 1 and 3 months, based on data from the Swedish Death Register as describes above.

Covariates

Adjustments were made for the following nine cardiovascular risk factors: age, gender, smoking, prior diabetes, prior hypertension, prior coronary artery disease (CAD), prior atrial fibrillation/flutter, estimated GFR (eGFR) and NT-pro-BNP. We chose to limit the number of variables to a total of 10, including endostatin, to avoid random correlations. The variables used in the models were all well established. Age is a significant risk factor for CHF and death[27] as the heart's pumping ability declines with age. Older patients also often have multiple comorbidities, worsening their prognosis. There are sex differences in CHF with regard to phenotype, aetiology and outcomes, with congestive heart failure with preserved ejection fraction (HFpEF) being more common in women and congestive heart failure with reduced ejection fraction (HFrEF) more common in men. Furthermore, ischaemia appears to be a more common aetiology in men, whereas diabetes and hypertension contribute more to the development of CHF in women. Finally, women with CHF in general have a higher survival rate than men.[28] More recent data support a relatively equal incidence of CHF in men and women overall; however, HFrEF and HFpEF are sex neutral despite evidence showing sex-specific differences in the EF and left ventricular (LV) volumes.[29] Smoking is a well-known risk factor for heart diseases, including CHF,[30 31] as it contributes to atherosclerosis, hypertension and reduced oxygen supply to the heart. Diabetes is a significant risk factor for the development of CHF[32] and cardiovascular mortality.[33 34] Hypertension is a common cause of heart failure.[35] High blood pressure increases strain on the heart, leading to hypertrophy and eventually heart failure. Controlling blood pressure is essential for preventing heart failure and reducing mortality. CAD is a common cause of CHF.[36] Damage to heart muscle from reduced blood supply can lead to CHF. Treating CAD is essential for improving survival in these patients. Atrial fibrillation is common in heart failure patients and is associated with increased morbidity and mortality.[37] An irregular heartbeat decreases the heart's pumping efficiency. Treatment can improve prognosis and reduce complications. eGFR measures kidney function. To calculate eGFR, the Revised Lund-Malmö Study equation was used.[38–40] Reduced kidney function and chronic kidney disease is common in CHF patients and increases the risk of death and hospitalisations.[41] Since the kidneys and heart are interconnected, impaired kidney function can worsen CHF. NT-pro-BNP is a biomarker released in CHF when the heart is overloaded. Elevated levels are associated with higher mortality and increased risk of cardiovascular complications.[42] NT-pro-BNP levels are commonly used in the clinical settings of patients with CHF, both as a diagnostic tool and as a means of monitoring treatment response. NT-pro-BNP was analysed with Cobas e411, from Roche laboratories. Both biomarker results were given in picograms per millilitre. By shifting the decimal points, the values were converted to more manageable nanogramsper millilitre and to illustrate the hazard rations in a more comprehensible manner in the Cox regressions.

Patient and public involvement

Patients or the public were not involved in the design, recruitment, conduct reporting or dissemination plans of our research, distinct from patients being participants in the research, of neither this study nor the original ADYS. However, the patients in the original ADYS were informed about the research questions before consent and inclusion.

Statistics

Background characteristics are presented as mean±SD or as median value with IQR if the variables were not normally distributed (table 1). Skewness and kurtosis as well as histograms were used to determine if the variables were normally distributed or not. Endostatin levels in patients with or without prior CHF were used as the exposure with mortality within 1 and 3 months as outcome measures. For survival statistics, Cox proportional hazard models were used to calculate the relative risk associated with higher circulating endostatin levels at 1 month and 3 months. The following models were used:

Model A (endostatin ng/mL, age, gender).
Model B (model A+smoking).
Model C (model B+diabetes).
Model D (model C+hypertension+CAD+atrial fibrillation/flutter).
Model E (model D+eGFR mL/min).
Model F (model E+NT-pro-BNP ng/mL).
P values of <0.05 were considered significant. All analyses were performed using IBM SPSS V.28.0.

RESULTS

Background associations

Of the patients included in this study, 276 (38.2%) had a history of CHF (table 1). Out of these, 42.0% had CHF as their primary diagnosis at discharge from the hospitalisation associated with inclusion in the study, as compared with 6.7% in the group of patients without previous CHF. Patients with a previous CHF diagnosis had higher mortality rates, increased median age and higher median body mass index (kg/m^2) (table 1). They also exhibited lower mean systolic blood pressure (mm Hg), heart rate (beats per minute), oxygen saturation (%) and mean haemoglobin (g/L) levels but higher mean respiratory rate (breaths per minute), elevated median creatinine (µmol/L), NT-pro-BNP (ng/mL) levels and higher mean endostatin (ng/mL) levels. They also had higher incidences of prior presence of CAD, atrial fibrillation/flutter, diabetes mellitus, hypertension and stroke/Transient

Table 1 Background characteristics between patients with a prior congestive heart failure (CHF) diagnosis and no prior CHF diagnosis (n=723)

Variable	CHF, n=276	No CHF, n=447	Missing values (% of total)
Age (year); median (IQR)	81.6 (73.4–87.8)	72.5 (60.6–82.0)	0 (0%)
Gender (male), N (%)	135 (48.9%)	190 (42.5%)	0 (0%)
BMI (kg/m^2); median (IQR)	26.8 (23.7–30.8)	25.0 (22.0–28.7)	18 (2.5%)
Systolic blood pressure (mm Hg); mean (±SD)	143±31	148±27	6 (0.8%)
Heart rate (beats per minute) mean (±SD);	92±24	97±23	7 (1.0%)
Oxygen saturation (%), median (IQR)	93 (89–96)	94 (90–97)	8 (1.1%)
Respiratory rate (breaths per minute); mean (±SD)	26±7	24±7	11 (1.5%)
Haemoglobin (g/L); mean (±SD)	129±19	134±20	12 (1.7%)
Creatinine (µmol/L), median (IQR)	99 (77–139)	75 (62–92)	8 (1.1%)
Estimated GFR (mL/min), median (IQR)	46 (29–62)	68 (54–84)	13 (1.8%)
NT-pro-BNP (ng/mL), median (IQR)	4.2 (2.0–9.1)	0.5 (0.1–2.2)	76 (10.9%)
Endostatin (ng/mL); median (IQR)	79.0 (60.6–110.6)	56.9 (41.0–74.9)	0 (0%)
METTS, N (%)			3 (0.4%)
Prio green	4 (1.4%)	34 (7.6%)	
Prio yellow	121 (43.8%)	194 (43.4%)	
Prio orange	102 (37.0%)	154 (34.5%)	
Prio red	48 (17.4%)	63 (14.1%)	
Dyspnoea level, N (%)			9 (1.2%)
NYHA 1 unaffected	39 (14.1%)	106 (23.7%)	
NYHA 2 mild symptoms, N	104 (37.7%)	153 (34.2%)	
NYHA 3 marked symptoms	55 (19.9%)	76 (17.0%)	
NYHA 4 severe symptoms	75 (27.2%)	106 (23.7%)	
Ever smoker	181 (65.6%)	313 (70.0%)	0 (0%)
Cardiovascular comorbidities			
CAD	157 (56.9%)	77 (17.2%)	4 (0.6%)
Atrial fibrillation/flutter	165 (59.8%)	84 (18.8%)	2 (0.3%)
Diabetes Mellitus	80 (29.0%)	63 (14.1%)	3 (0.4%)
Hypertension	165 (59.8%)	174 (38.9%)	3 (0.4%)
Stroke/TIA	54 (19.6%)	33 (7.4%)	0 (0%)
Number of drugs (on demand included); mean (±SD)	9.2±4.1	5.6±4.1	61 (8.4%)
Discharge diagnosis CHF, N (%)	116 (42.0%)	30 (6.7%)	0 (0%)
Dead within 1 month, N (%)	29 (10.5%)	27 (6.0%)	0 (0%)
Dead within 3 months, N (%)	60 (21.7%)	53 (11.9%)	0 (0%)

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; GFR, glomerular filtration rate; METTS, Medical Emergency Treatment and Triage System; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TIA, Transient Ischemic Attack.

Ischemic Attack (TIA). Finally, patients with CHF had on average a higher total number of medications.

Survival

1-month mortality

In the subcohort of patients with a previous CHF diagnosis (n=276), 10.5% died within 1 month, compared with 6.0% of patients without CHF (n=447). For patients with a prior diagnosis of CHF, in a multivariate cox regression for endostatin and 1-month mortality, with the last step adjusted for all variables, endostatin was not significantly associated with mortality (HR=1.01; 95% CI 0.999 to 1.018; p value 0.078) (table 2). As a comparison for patients without prior CHF diagnosis, in the same multivariate Cox regression for endostatin and 1-month mortality, endostatin remained significantly associated with mortality (HR=1.02; 95% CI 1.01 to 1.03; p value<0.001, online supplemental table 3).

3-month mortality

When 3-month mortality was studied, 21.7% of the patients with CHF died within 3 months, compared with 11.9% in patients without CHF. When patients with a prior diagnosis of CHF were studied in a multivariate

Table 2 Cox regression, multivariate models for endostatin (ng/mL) and 1-month mortality, patients with prior congestive heart failure (n=276)

Variables	HR	95% CI	P value
Endostatin, model A	1.010	1.005 to 1.016	<0.001
Endostatin, model B	1.010	1.005 to 1.016	<0.001
Endostatin, model C	1.012	1.005 to 1.018	<0.001
Endostatin, model D	1.012	1.005 to 1.018	<0.001
Endostatin, model E	1.009	1.000 to 1.019	0.046
Endostatin, model F	1.009	0.999 to 1.018	0.078

Model A (endostatin ng/mL, age, gender;) model B (model A+smoking); model C (model B+diabetes); model D (model C+HT+coronary artery disease+atrial fibrillation/flutter); model E (model D+estimated glomerular filtration rate mL/min); model F (model E+N-terminal pro-brain natriuretic peptide ng/mL).
HT, Hypertension.

Cox regression, endostatin was associated with 3-month mortality, even after adjustments for all variables (HR=1.01; 95% CI 1.00 to 1.02; p value=0.016, table 3). As a comparison for patients without prior CHF diagnosis, in the same multivariate Cox regression, endostatin was significantly associated with mortality (HR=1.02; 95% CI 1.01 to 1.03; p value<0.001, (online supplemental table 4).

DISCUSSION

The main result of this study was that higher levels of endostatin were associated with increased mortality within 3 months after hospital admission for acute dyspnoea in patients with a prior CHF diagnosis, in a fully adjusted model for established risk factors. In the adjusted multivariate regression model for 1-month mortality, endostatin had a significant association with mortality only until the last model but was attenuated and nonsignificant, when adjustments were added for NT-pro-BNP. A possible explanation to the lacking association of endostatin on 1-month mortality is that the information regarding 1-month mortality is better reflected in acutely elevated NT-pro-BNP levels rather than high endostatin levels. It could also be that other acute and serious causes of acute dyspnoea rather than CHF caused death within 30 days. Already in the background variables, patients with prior CHF had significantly higher levels of endostatin and significantly higher mortality at 1 and 3 months. The 1-month and 3-month mortalities are both indicators of short-term prognosis. Endostatin as well as the cardiovascular variables we adjusted for are obviously risk factors with the extension of time. CHF is a chronic disease where the patient often has been exposed to cardiovascular risk factors for many years, as shown previously with the association with hypertension duration.[17] If we had studied endostatin adjusted for cardiovascular risk factors as a prognostic risk factor for long-term mortality, the results might have been completely different. However, the focus of this study was primarily to identify and assess a potential patient-centred prognostic biomarker for patients presenting to the ED with acute dyspnoea. When a patient with CHF seeks emergency care, there is a need to quickly evaluate both the patient's chronic CHF status and the acute decompensation during the short time the patient is at the ED. The intention of the study was primarily to serve as a future aid in an emergency setting for assessing the sum of the chronic and acute CHF situation.

Table 3 Cox regression, multivariate models for endostatin (ng/mL) and 3-month mortality, patients with prior congestive heart failure (n=276)

Variables	HR	95% CI	P value
Endostatin, model A	1.008	1.004 to 1.013	<0.001
Endostatin, model B	1.008	1.004 to 1.013	<0.001
Endostatin, model C	1.009	1.004 to 1.014	<0.001
Endostatin, model D	1.009	1.004 to 1.013	<0.001
Endostatin, model E	1.008	1.002 to 1.015	0.014
Endostatin, model F	1.008	1.002 to 1.015	0.016

Model A (endostatin ng/mL, age, gender;) model B (model A+smoking); model C (model B+diabetes); model D (model C+HT+coronary artery disease+atrial fibrillation/flutter); model E (model D+estimated glomerular filtration rate mL/min); model F (model E+N-terminal pro-brain natriuretic peptide ng/mL).
HT, Hypertension.

In the literature, there are contradictory data concerning the association between endostatin and CHF. There are data that suggest acute haemodynamic effects of endostatin, and recombinant infused endostatin has been shown to induce heart failure.[43 44] High endostatin levels are associated with LV dysfunction and an increased heart failure risk, as well as in patients with kidney and heart failure, and may also contribute to disease progression.[22 25] In observational studies, increased levels of circulating endostatin were associated with higher levels of NT-pro-BNP[20] as well as increased mortality in patients with CHF.[21] Increased levels of endostatin were observed in patients with pulmonary atrial hypertension and were linked to CHF severity and increased NT-pro-BNP.[45] There are also studies that contradict endostatin's harmful effect on the heart. Endostatin is shown to improve cardiac dysfunction and hemodynamics and attenuated cardiac fibrosis and hypertrophy via inhibiting oxidative stress in myocardial infarction induced heart failure rats.[46] Recombinant endostatin has also been shown to induce vasorelaxation and to acutely lower blood pressure.[47] There are also studies where no association between endostatin and signs of CHF was seen.[48] There is also a study on patients with chronic CHF of ischaemic aetiology were endostatin did not add information regarding negative outcomes.[49]

Regarding the association between endostatin and short-term mortality in patients with heart failure as in our study, beyond what has been stated above, there are several potential biological and pathophysiological casual links between endostatin and mortality. One of the more

important and established influential mechanisms of endostatin is its antiangiogenic effect, as a potent inhibitor of angiogenesis, which has been shown in many studies.[50–56] Endostatin selectively inhibits endothelial cell proliferation. High levels of endostatin may thus influence and exacerbate vascular dysfunction and reduce the capacity for repairing damaged vessels, thereby contributing to further microvascular damage in the cardiac muscle of patients with heart failure. This may be an important causal mechanism for the worsening of CHF with increased mortality as a result. Endostatin has been linked to chronic inflammation, and chronic inflammation has been linked to various heart diseases, including CHF. Elevated levels of endostatin in heart failure patients can be both a consequence of and a contributing factor to chronic inflammation. Chronic inflammation damages endothelium, creating endothelial dysfunction. This might increase vascular resistance and promote the development of conditions like hypertension, which in turn can lead to heart failure. In a study on tumour-bearing mice, endostatin treatment significantly reduced the levels of anti-inflammatory and proangiogenic cytokines, via the reduction of anti-inflammatory cytokines.[57] High endostatin levels have been linked to increased release of inflammatory cytokines (eg, Tumor Necrosis Factor-alpha (TNF-α) and interleukin 6) as well as enhanced oxidative stress in blood vessels and cardiac tissue. In a study regarding the role of endostatin in chronic inflammation in COVID-19 patients, it was observed that endostatin enhanced the activity of neutrophils and platelets as well as disrupted the thrombin-induced microvascular barrier.[58] Inflammation also plays a key role in the development of atherosclerosis[59] in the coronary arteries which can damage the heart muscle and thereby contribute to heart failure. Endostatin also has an important association with chronic kidney disease.[22 24 49 60–62] High levels of endostatin via its antiangiogenic effect are associated with the loss of microcirculation in the renal parenchyma. It is linked to an altered extracellular matrix as well as changes in the basement membrane, which impairs glomerular filtration, leading to impaired kidney function. Kidney failure, in turn, can drive heart failure through the cardiorenal syndrome which encompasses the bidirectional effects of cardiac and renal dysfunction.[63 64] Even if endostatin is mostly known for its antiangiogenic properties, besides being associated with chronic inflammation, endostatin also has effects on organ fibrosis and antitumour effects. The role of endostatin in fibrosis is however complex. Human endostatin shows biological activity by binding to multiple interacting receptors on the cell membrane.[22] Microvascular structure and function are critically dependent on a balance of angiogenesis-regulating factors. If this balance is severely disturbed, the result is in an inadequate response to ischaemia and hypoxia. Inadequate response to hypoxia plays a crucial role in the progression of cardiovascular disease, which is associated with fibrosis, inflammation and oxidative injury.[65] There is also evidence that endostatin can drive the progression of fibrosis by promoting myofibroblast activity, thus exacerbating tissue stiffness and impairing cardiac function. There are however also conflicting, at least theoretical arguments suggesting that endostatin could conversely have positive antifibrotic properties, suggesting a significant antifibrotic potential of endostatin, expressing a homeostatic function, among others by regulating Transforming Growth Factor-beta 1 (TGF-β1), the Ras homolog family member A/Rho-associated coiled-coil containing protein kinase (RhoA/ROCK) pathway, cell proliferation and apoptosis, thus possibly highlighting its antifibrotic activity.[66] Endostatin's antitumoural effect is likely due to its antiangiogenic properties, as it inhibits the formation of new blood vessels within tumours.[67] In summary, there is evidence for negative influential mechanisms of endostatin on cardiac tissues, including its antiangiogenic effects, the induction of chronic inflammation in the coronary vessels, indirect worsening of cardiac function through renal parenchymal damage and possibly even the promotion of cardiac fibrosis.

In our study, the group of patients without prior CHF, endostatin was still strongly associated with 1-month mortality as well as for 3-month mortality in the final adjusted multivariable step (online supplemental tables 3 and 4). This is perhaps not surprising as high endostatin levels are found in many other conditions besides CHF. Even if conflicting results have been reported, there are associations between endostatin and malignant diseases, obesity, hypertension, diabetes, kidney disease, cerebral atherosclerosis and stroke.[18 19 49 68 69]

Strengths and limitations

It is a strength that the study was conducted on a fairly large cohort of patients. The study used validated diagnoses and information on mortality and discharge diagnoses from National data registers,[70] which confirm the correctness. Even if the blood samples used for later measurement of endostatin and NT-pro-BNP were drawn at the immediate entry to the ED, it is a strength that the results were not known for the ED physician, thus not biasing the treatment and immediate follow-up of the patients. We acknowledge several limitations. Patients were included only during daytime on working days. Patients with high acuity or deranged consciousness went directly to the intensive care unit and were therefore not included. These could partly have biased the cohort. The presence of prevalent diseases and comorbidities was asked for, and the research nurses checked the medical records at our hospital. However, we did not check for the presence of prevalent comorbidities in the national in-patient and out-patient register, thus possibly missing information of comorbidities from medical records and visits in other regions in Sweden.

Implications

Endostatin was associated with short-term mortality in patients with and without CHF. Because of contradictory overall associations in the study as well as in the literature

between endostatin and mortality in patients with or without prior CHF, it is still too early to recommend the usage of endostatin as a biomarker for mortality in CHF patients in clinical practice. Further studies are needed to better determine the prognostic value of endostatin with regard to mortality in patients with CHF and to determine if endostatin on its own or in a combined risk score together with other biomarkers and risk factors could be a diagnostic or a prognostic marker in patients with cardiovascular diseases or acute dyspnoea in general.

CONCLUSION

Endostatin is elevated in patients hospitalised with acute dyspnoea with prior CHF in this study and associated with 3-month mortality but not with 1-month mortality. Patients with prior CHF have higher mortality and are more often hospitalised with CHF as the discharge diagnosis. Endostatin was also associated with both 1-month and 3-month mortality in patients hospitalised with acute dyspnoea without prior CHF.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Regionala Etikprövningsnämnden EPN, Lund, Sweden (Dnr 2011/537, 2012/762, 2016/138, 2017/301 and 2018/781) and complies with the Declaration of Helsinki (Rickham PP, Experimentation H. Code of Ethics of the World Medical Association. Decl of Helsinki Br Med J 1964;2:177. 10.1136/bmj.2.5402.177). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. Technical appendix, statistical code and datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID iDs
Alexander Yaghoubi http://orcid.org/0009-0004-6817-5832
Caroline Heijl http://orcid.org/0000-0003-4276-3797
Ardavan M Khoshnood http://orcid.org/0000-0002-3142-4119
Per Erik Wändell http://orcid.org/0000-0001-5169-2965
Axel C Carlsson http://orcid.org/0000-0001-6113-0472
Torgny Wessman http://orcid.org/0000-0002-7314-2240

REFERENCES

1 Shrestha AP, Shrestha R, Shrestha SK, *et al*. Prevalence of Dyspnea among Patients Attending the Emergency Department of a Tertiary Care Hospital: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc* 2019;57:302–6.
2 DeVos E, Jacobson L. Approach to Adult Patients with Acute Dyspnea. *Emerg Med Clin North Am* 2016;34:129–49.
3 Renier W, Winckelmann KH, Verbakel JY, *et al*. Signs and symptoms in adult patients with acute dyspnea: a systematic review and meta-analysis. *Eur J Emerg Med* 2018;25:3–11.
4 Martindale JL, Wakai A, Collins SP, *et al*. Diagnosing Acute Heart Failure in the Emergency Department: A Systematic Review and Meta-analysis. *Acad Emerg Med* 2016;23:223–42.
5 Suau SJ, DeBlieux PMC. Management of Acute Exacerbation of Asthma and Chronic Obstructive Pulmonary Disease in the Emergency Department. *Emerg Med Clin North Am* 2016;34:15–37.
6 Zarrinkoub R, Wettermark B, Wändell P, *et al*. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *Eur J Heart Fail* 2013;15:995–1002.
7 Nieminen MS, Brutsaert D, Dickstein K, *et al*. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;27:2725–36.
8 Cowie MR, Wood DA, Coats AJ, *et al*. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000;83:505–10.
9 Taylor CJ, Ordóñez-Mena JM, Roalfe AK, *et al*. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ* 2019;364:l223.
10 Karaye KM, Sani MU. Factors associated with poor prognosis among patients admitted with heart failure in a Nigerian tertiary medical centre: a cross-sectional study. *BMC Cardiovasc Disord* 2008;8:16.
11 Blair JEA, Manuchehry A, Chana A, *et al*. Prognostic markers in heart failure--congestion, neurohormones, and the cardiorenal syndrome. *Acute Card Care* 2007;9:207–13.
12 Valdivia-Marchal M, Zambrana-Luque JL, Girela-López E, *et al*. Prognostic factors on mortality in patients admitted to hospital with heart failure. *An Sist Sanit Navar* 2020;43:57–67.
13 Jan VM, Mushtaq M, Aslam K, *et al*. Risk and prognostic factors in patients of heart failure. *J Indian Coll Cardiol* 2012;2:64–74.
14 O'Reilly MS, Boehm T, Shing Y, *et al*. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell* 1997;88:277–85.
15 Sund M, Kalluri R. Tumor stroma derived biomarkers in cancer. *Cancer Metastasis Rev* 2009;28:177–83.
16 Ruge T, Carlsson AC, Larsson A, *et al*. Endostatin: a promising biomarker in the cardiovascular continuum? *Biomark Med* 2017;11:905–16.
17 Carlsson AC, Ruge T, Sundström J, *et al*. Association between circulating endostatin, hypertension duration, and hypertensive target-organ damage. *Hypertension* 2013;62:1146–51.
18 Ruge T, Carlsson AC, Larsson TE, *et al*. Endostatin level is associated with kidney injury in the elderly: findings from two community-based cohorts. *Am J Nephrol* 2014;40:417–24.
19 Carlsson AC, Wessman T, Larsson A, *et al*. Endostatin predicts mortality in patients with acute dyspnea - A cohort study of patients seeking care in emergency departments. *Clin Biochem* 2020;75:35–9.
20 Jungbauer CG, Riedlinger J, Block D, *et al*. Panel of emerging cardiac biomarkers contributes for prognosis rather than diagnosis in chronic heart failure. *Biomark Med* 2014;8:777–89.
21 Gouya G, Siller-Matula JM, Fritzer-Szekeres M, *et al*. Association of endostatin with mortality in patients with chronic heart failure. *Eur J Clin Invest* 2014;44:125–35.
22 Li M, Popovic Z, Chu C, *et al*. Endostatin in Renal and Cardiovascular Diseases. *Kidney Dis (Basel)* 2021;7:468–81.

23 Barroso MC, *et al*. *Endostatin a Potential Biomarker for Heart Failure with Preserved Ejection Fraction*. . Arq Bras Cardiol, 2017:109. 448–56.
24 Carlsson AC, Östgren CJ, Länne T, *et al*. The association between endostatin and kidney disease and mortality in patients with type 2 diabetes. *Diabetes Metab* 2016;42:351–7.
25 Ruge T, Carlsson AC, Ingelsson E, *et al*. Circulating endostatin and the incidence of heart failure. *Scand Cardiovasc J* 2018;52:244–9.
26 von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *Int J Surg* 2014;12:1495–9.
27 Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016;13:368–78.
28 Regitz-Zagrosek V. Sex and Gender Differences in Heart Failure. *Int J Heart Fail* 2020;2:157–81.
29 Lala A, Tayal U, Hamo CE, *et al*. Sex Differences in Heart Failure. *J Card Fail* 2022;28:477–98.
30 Lu Y, *et al*. *Smoking and Heart Failure: A Mendelian Randomization and Mediation Analysis*. . ESC Heart Fail, 2021:8. 1954–65.
31 Aune D, Schlesinger S, Norat T, *et al*. Tobacco smoking and the risk of heart failure: A systematic review and meta-analysis of prospective studies. *Eur J Prev Cardiol* 2019;26:279–88.
32 Jankauskas SS, Kansakar U, Varzideh F, *et al*. Heart failure in diabetes. *Metab Clin Exp* 2021;125:154910.
33 Bertoni AG, Hundley WG, Massing MW, *et al*. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699–703.
34 Dunlay SM, Givertz MM, Aguilar D, *et al*. Type 2 Diabetes Mellitus and Heart Failure, A Scientific Statement From the American Heart Association and Heart Failure Society of America. *J Card Fail* 2019;25:584–619.
35 Slivnick J, Lampert BC. Hypertension and Heart Failure. *Heart Fail Clin* 2019;15:531–41.
36 Lala A, Desai AS. The role of coronary artery disease in heart failure. *Heart Fail Clin* 2014;10:353–65.
37 Reddy YNV, Borlaug BA, Gersh BJ. Management of Atrial Fibrillation Across the Spectrum of Heart Failure With Preserved and Reduced Ejection Fraction. *Circulation* 2022;146:339–57.
38 Nyman U, Grubb A, Larsson A, *et al*. The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. *Clin Chem Lab Med* 2014;52:815–24.
39 Fu EL, Levey AS, Coresh J, *et al*. Accuracy of GFR estimating equations based on creatinine, cystatin C or both in routine care. *Nephrol Dial Transplant* 2024;39:694–706.
40 Zhang D, Fu L, Jiang S, *et al*. Relative superiority of the revised Lund-Malmö equation over 22 other equations used for glomerular filtration rate estimation in undialyzed patients with end-stage renal disease. *Pol Arch Intern Med* 2022;132:16321:11:.
41 Banerjee D, Rosano G, Herzog CA. Management of Heart Failure Patient with CKD. *Clin J Am Soc Nephrol* 2021;16:1131–9.
42 Januzzi JL, van Kimmenade R, Lainchbury J, *et al*. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J* 2006;27:330–7.
43 Jing Q, Xinyu Q, Rougcheng L. Recombinant human endostatin-associated acute left heart failure. *Clin Oncol (R Coll Radiol)* 2008;20:268.
44 Qin J, Zhang P-H, Qian X-Y, *et al*. Assessment of the cardiotoxicity of recombinant human endostatin using myocardial biochemical markers in cancer patients. *Nan Fang Yi Ke Da Xue Xue Bao* 2008;28:930–2.
45 Damico R, Kolb TM, Valera L, *et al*. Serum endostatin is a genetically determined predictor of survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2015;191:208–18.
46 Xu X, Jiang T, Li Y, *et al*. Endostatin attenuates heart failure via inhibiting reactive oxygen species in myocardial infarction rats. *Biosci Rep* 2021;41.
47 Sunshine SB, Dallabrida SM, Durand E, *et al*. Endostatin lowers blood pressure via nitric oxide and prevents hypertension associated with VEGF inhibition. *Proc Natl Acad Sci U S A* 2012;109:11306–11.
48 Eleuteri E, Di Stefano A, Giordano A, *et al*. Prognostic value of angiopoietin-2 in patients with chronic heart failure. *Int J Cardiol* 2016;212:364–8.
49 Ueland T, Aukrust P, Nymo SH, *et al*. Predictive value of endostatin in chronic heart failure patients with poor kidney function. *Cardiology* 2015;130:17–22.
50 O'Reilly MS. Angiostatin: an endogenous inhibitor of angiogenesis and of tumor growth. *EXS* 1997;79:273–94.
51 Wickström SA, Alitalo K, Keski-Oja J. An endostatin-derived peptide interacts with integrins and regulates actin cytoskeleton and migration of endothelial cells. *J Biol Chem* 2004;279:20178–85.
52 Cattaneo MG, Pola S, Francescato P, *et al*. Human endostatin-derived synthetic peptides possess potent antiangiogenic properties in vitro and in vivo. *Exp Cell Res* 2003;283:230–6.
53 Chillemi F, Francescato P, Ragg E, *et al*. Studies on the structure-activity relationship of endostatin: synthesis of human endostatin peptides exhibiting potent antiangiogenic activities. *J Med Chem* 2003;46:4165–72.
54 Morbidelli L, Donnini S, Chillemi F, *et al*. Angiosuppressive and angiostimulatory effects exerted by synthetic partial sequences of endostatin. *Clin Cancer Res* 2003;9:5358–69.
55 Cho H, Kim WJ, Lee YM, *et al*. N-/C-terminal deleted mutant of human endostatin efficiently acts as an anti-angiogenic and anti-tumorigenic agent. *Oncol Rep* 2004;11:191–5.
56 Gu J-W, Shparago M, Tan W, *et al*. Tissue endostatin correlates inversely with capillary network in rat heart and skeletal muscles. *Angiogenesis* 2006;9:93–9.
57 Foguer K, Braga M de S, Peron JPS, *et al*. Endostatin gene therapy inhibits intratumoral macrophage M2 polarization. *Biomed Pharmacother* 2016;79:102–11.
58 Jandl K, Berg JL, Birnhuber A, *et al*. Basement membrane product, endostatin, as a link between inflammation, coagulation and vascular permeability in COVID-19 and non-COVID-19 acute respiratory distress syndrome. *Front Immunol* 2023;14:1188079.
59 Spagnoli LG, Bonanno E, Sangiorgi G, *et al*. Role of inflammation in atherosclerosis. *J Nucl Med* 2007;48:1800–15.
60 Futrakul N, Butthep P, Laohareungpanya N, *et al*. A defective angiogenesis in chronic kidney disease. *Ren Fail* 2008;30:215–7.
61 Wątorek E, Paprocka M, Duś D, *et al*. Endostatin and vascular endothelial growth factor: potential regulators of endothelial progenitor cell number in chronic kidney disease. *Pol Arch Med Wewn* 2011;121:AOP17:296–301:.
62 Chen J, Hamm LL, Kleinpeter MA, *et al*. Elevated plasma levels of endostatin are associated with chronic kidney disease. *Am J Nephrol* 2012;35:335–40.
63 Rangaswami J, Bhalla V, Blair JEA, *et al*. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation* 2019;139:e840–78.
64 Pliquett RU. Cardiorenal Syndrome: An Updated Classification Based on Clinical Hallmarks. *J Clin Med* 2022;11:2896:10:.
65 Uchida L, Tanaka T, Saito H, *et al*. Effects of a prolyl hydroxylase inhibitor on kidney and cardiovascular complications in a rat model of chronic kidney disease. *Am J Physiol Renal Physiol* 2020;318:F388–401.
66 Zhang Z, Liu X, Shen Z, *et al*. Endostatin in fibrosis and as a potential candidate of anti-fibrotic therapy. *Drug Deliv* 2021;28:2051–61.
67 Méndez-Valdés G, Gómez-Hevia F, Lillo-Moya J, *et al*. Endostatin and Cancer Therapy: A Novel Potential Alternative to Anti-VEGF Monoclonal Antibodies. *Biomedicines* 2023;11:718.
68 Ärnlöv J, Ruge T, Ingelsson E, *et al*. Serum endostatin and risk of mortality in the elderly: findings from 2 community-based cohorts. *Arterioscler Thromb Vasc Biol* 2013;33:2689–95.
69 Zhang C, Qian S, Zhang R, *et al*. Endostatin as a novel prognostic biomarker in acute ischemic stroke. *Atherosclerosis* 2020;293:42–8.
70 Ludvigsson JF, *et al*. External Review and Validation of the Swedish National Inpatient Register. *BMC Public Health* 2011;11:450.