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RESEARCH ARTICLE

New cardiovascular biomarkers in patients with advanced cancer – A prospective study comparing MR-proADM, MR-proANP, copeptin, high-sensitivity troponin T and NT-proBNP

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Aims Traditional cardiovascular (CV) biomarkers (high-sensitivity troponinT [hsTnT] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) are important to monitor cancer patients' cardiac function and to assess prognosis. Newer CV biomarkers (mid-regional pro-adrenomedullin [MR-proADM], C-terminal pro-arginine vasopressin [copeptin], and mid-regional pro-atrial natriuretic peptide [MR-proANP]) might outperform traditional biomarkers.

Methods and results Overall, 442 hospitalized cancer patients without significant CV disease or current infection were enrolled (61 ± 15 years, 52% male, advanced cancer stage: 85%) and concentrations of CV biomarkers were analysed. Differences in echocardiographic, clinical, laboratory parameters were assessed. Patients were followed for up to 69 months for all-cause mortality. In univariable analyses, MR-proADM, hsTnT, copeptin, MR-proANP, and NT-proBNP predicted all-cause mortality. In multivariable analyses (adjusted for sex, age, Eastern Cooperative Oncology Group performance status, estimated glomerular filtration rate [eGFR], C-reactive protein, anti-cancer

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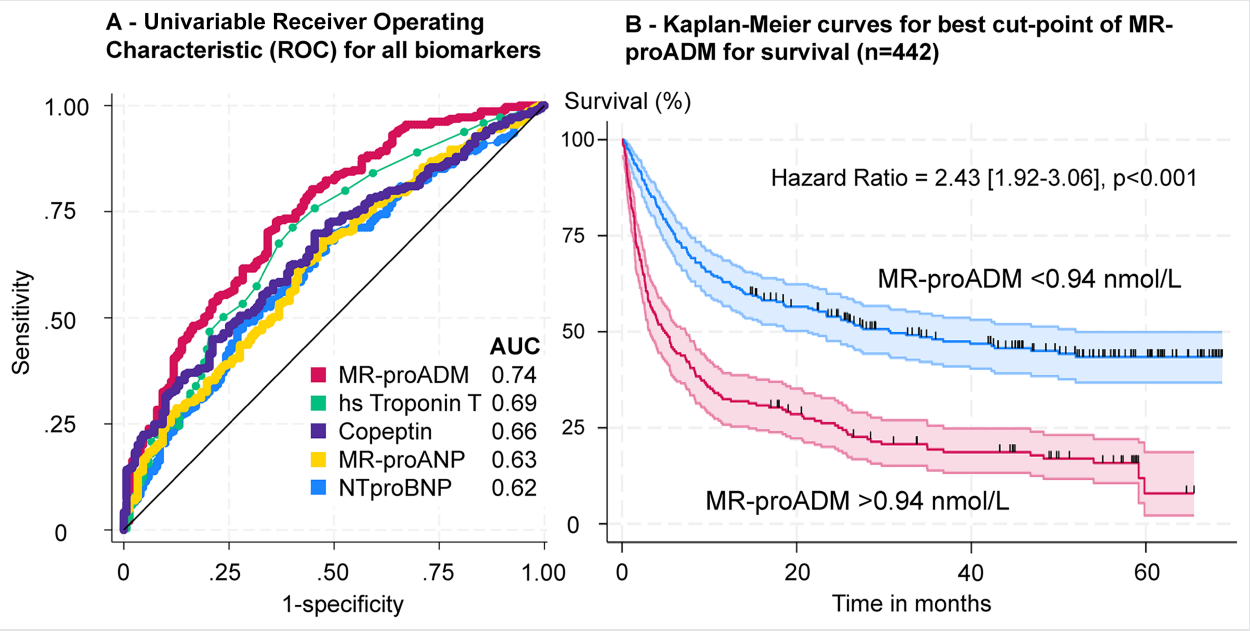
therapy, reason for hospitalization, cancer stage and type), only MR-proADM remained an independent predictor of mortality (MR-proADM per 1 ln: hazard ratio [HR] 2.27, 95% confidence interval [CI] 1.47–3.50], $p < 0.001$). MR-proADM had the highest area under the curve (AUC) using receiver operating characteristic analysis (AUC [95% CI] 0.74 [0.69–0.79]; hsTnT: AUC 0.69; copeptin: AUC 0.66; MR-proANP: AUC 0.63; NT-proBNP: AUC 0.62). Optimal cut-point for mortality prediction with MR-proADM was 0.94 nmol/L (HR 2.43 [95% CI 1.92–3.06], $p < 0.001$). Patients with MR-proADM >0.94 nmol/L were older, more often had cancer stage IV, showed reduced performance status, eGFR, haemoglobin, diastolic left ventricular function, and elevated systolic pulmonary artery pressure.

Conclusion MR-proADM is an independent predictor of mortality in advanced stage, hospitalized cancer patients without significant CV disease or current infection. The optimal MR-proADM cut-point for mortality prediction was 0.94 nmol/L with hazards for mortality being approximately 2.5 times higher. There was a continuous increase in mortality risk with stepwise increase of MR-proADM concentrations. Elevated concentrations of MR-proADM were also associated with reduced performance status and mildly reduced left ventricular diastolic function as well as higher age and more often cancer stage IV.

Graphical Abstract



(*A*) Univariable receiver operating characteristic (ROC) curves for all biomarkers. (*B*) Kaplan–Meier curves for best cut-point of mid-regional pro-adrenomedullin (MR-proADM) for survival ($n = 442$). AUC, area under the curve; CI, confidence interval; HR, hazard ratio; hsTnT, high-sensitivity troponin T; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Cardio-oncology • MR-proADM • Cardiovascular biomarkers • Mortality • Diastolic dysfunction

Introduction

In 2020, about 20 million cancer diagnoses and 10 million cancer deaths occurred worldwide.[1] By 2040, the incidence of new cancer diagnoses will increase by 40–50%.[1] Moreover, cancer patients are at significant risk of cardiovascular (CV) mortality.[2,3] Both heart failure (HF) and cancer are known to be associated with cachexia, reduced muscle strength, and poor quality of life.[4]

Recent studies show that cardiac wasting develops in advanced stage cancer,[5,6] which can change myocardial structure leading to a HF-like syndrome.[7,8] This could explain why non-sustained ventricular tachycardias were detected in 8% of advanced stage cancer patients without significant CV disease and in one-third cancer patients with CV disease.[9]

Cardiovascular biomarkers like troponin and natriuretic peptides aid in screening and classification of heart diseases, and are most commonly used biomarkers in cardio-oncology.[10–13] These biomarkers prognosticate risk for all-cause mortality in cancer patients before, during, and after chemotherapy.[14,15] Recently, novel biomarkers have emerged for predicting mortality risk including mid-regional pro-adrenomedullin (MR-proADM), mid-regional pro-atrial natriuretic peptide (MR-proANP), and C-terminal pro-arginine vasopressin (copeptin). Markers like MR-proADM and copeptin are influenced by various disease states and critical conditions, beyond just CV diseases, and have shown promising results in predicting outcomes in cancer patients.[16,17] Pavo *et al.*[18] assessed high-sensitivity troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), MR-proADM, MR-proANP, and copeptin in chemotherapy naïve cancer patients (with or without CV disease) and found that all biomarkers predicted mortality to some extent. These novel biomarkers also independently predict mortality in patients with CV diseases.[19–21] However, the significance of these biomarkers in chemotherapy recipients without significant CV disease remains uncertain. Therefore, our study aimed to explore their relevance in a distinct cohort primarily comprising advanced stage cancer patients without significant CV disease or antibiotic-treated infections at baseline. We sought to determine which biomarker exhibited the strongest predictive capacity for all-cause mortality and its association with physical performance and cardiac function, as evaluated by echocardiography.

Methods

Study population

We enrolled 442 hospitalized cancer patients (302 with solid cancers and 140 with haematological cancers) at the Department of Haematology and Oncology at Charité-Universitätsmedizin Berlin (online supplementary *Table Appendix S1*). Most patients had an advanced cancer stage at baseline (Union Internationale Contre le Cancer stage I/II/III/IV – 23/45/59/315). A detailed medical history was recorded for every patient and a standard transthoracic echocardiogram was performed with a Vivid E90 machine (GE Healthcare) and Tomtec software for image analysis at baseline. We included only patients with a histologically confirmed diagnosis of cancer and active disease. Exclusion criteria were: (i) age <18 years, (ii) current infection with fever or antibiotic treatment, (iii) another cancer diagnosis in the past 5 years, (iv) left ventricular ejection fraction <50%), (v) ischaemic heart disease or severe valvular disease or prior myocardial infarction, (vi) pre-existing treatment-related cardio-toxicity, (vii) other significant CV disease, (viii) chronic obstructive pulmonary disease defined as GOLD (Global Initiative for Chronic Obstructive Lung Disease) status >II. Patients with uncomplicated arterial hypertension or type 2 diabetes mellitus were included. All patients were followed for mortality by monitoring electronic hospital records and by telephone contact with patients, relatives, or caregivers for up to 60 months. The study was conducted according to the Declaration of Helsinki and was approved by the Charité Ethics Committee. All patients signed an informed consent form to participate in the study.

Laboratory analyses

At baseline examination, standard venous blood samples were drawn from all patients. High-sensitivity troponin T and NT-proBNP were measured using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Measurement of MR-proADM, MR-proANP, and copeptin was done with an automated sandwich chemiluminescence immunoassay using a Kryptor test platform (BRAHMS, Hennigsdorf/Berlin, Germany).

Statistical analyses

Materials and methods

The Kolmogorov–Smirnov test was used to test for normal distribution. Student's unpaired two-sample *t*-test was used, and mean values ± standard deviation are displayed. In case of non-normally distributed values, Mann–Whitney U test was used, and the median with interquartile range is shown.

Multivariable survival model building

Baseline and clinical characteristics of patients such as age, sex, cancer type (solid vs. haematological), anti-cancer therapy-naïve (yes vs. no), hsTnT, NT-proBNP, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), and all other parameters that were univariable predictors of survival with a p-value <0.2 were included in the multivariable survival model-building process (online supplementary *Table S2*). We performed a Cox regression of the baseline model with backward and forward selection. Subsequently, a multivariable fractional polynomial procedure was done to find transformations for variables that do not meet the proportional hazard assumption. The assumption of proportional hazard was verified using the Schoenfeld test and the visual evaluation of the Schoenfeldt residuals. Since sex and anti-cancer therapy-naïve status are also important co-factors, these variables were additionally included in the model, even if they were not univariably significant. The variables cancer stage, and cancer type (solid vs. haematological) did not meet the proportional hazard assumption and showed a significant correlation with each other. Therefore, these two variables were included as a multiplicative interaction term. The metric variable age satisfied the proportional hazard assumption after a transformation using $(age/100)^{-2}$. Univariable and multivariable hazard ratios (HRs), 95% confidence intervals (CIs), and p-values are given. Prediction accuracy for the Cox proportional hazards models was assessed by time-dependent adjusted receiver operating characteristic (ROC) curves, as well as Harrell's C-index. The best cut-off for the biomarker MR-proADM with the most significant split was chosen based on the standardized log-rank test. In this exploratory study, significance tests have a descriptive character and therefore were not corrected for multiplicity. Kaplan–Meier cumulative survival curves for the entire analysis time and a multivariable-adjusted contour plot, which show the relation of baseline MR-proADM values to survival, were constructed for illustrative purposes. A p-value of <0.05 was considered statistically significant in all analyses. Data analysis was generated using SAS/STAT software version 9.4 (SAS Institute, Inc., Cary, NC, USA) and SPSS software version 26.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline characteristics

Baseline and clinical characteristics of all 442 cancer patients are shown in *Table 1*. The mean age was 61 ± 15 years, 52% were male, and advanced cancer stage was present in 85% of patients. Reasons for admission to the hospital were: receiving anti-cancer therapy (42%), staging/diagnostics (28%), or due to worsening of the clinical state of patients (31%) (*Table 1*). Two traditional CV biomarkers (hsTnT and NTproBNP) and three newer CV biomarkers (MR-proADM, MR-proANP and copeptin) were measured.

Survival analyses

All five CV biomarkers predicted all-cause mortality in univariable Cox proportional hazard analyses (*Table 2*). MR-proADM had the highest AUC (0.74, 95% CI 0.69–0.79) (*Figure 1A*) in comparison with hsTnT (0.69, 95% CI 0.64–0.74), copeptin (0.66, 95% CI 0.60–0.71), MR-proANP (0.63, 95% CI 0.57–0.68) and NT-proBNP (0.62, 95% 0.56–0.67). An identical AUC pattern over time was observed for the individual sections of the observation period (*Figure 1B*). Additionally, other clinical characteristics of cancer patients were tested for survival prediction (online supplementary *Table S2*). Each of the five CV biomarkers was adjusted for those parameters that remained significant predictors of mortality after forward and backward selection and including clinically relevant parameters (*Table 2* and online supplementary *Table S2*). Only MR-proADM remained a significant predictor of mortality in multivariable analyses. The optimal cut-point for MR-proADM for mortality prediction was 0.94 nmol/L (95% CI 0.92–0.96 nmol/L), providing an HR of 2.43 [95% CI 1.92–3.06] ($p < 0.001$) (*Figure 2A*). There was a continuous increase in mortality risk with stepwise increase of MR-proADM values as shown in *Figure 2B*.

Clinical characteristics according to MR-proADM cut-off

Patients were divided into two groups according to the optimal MR-proADM cut-point (0.94 nmol/L) for mortality prediction (*Table 1*). Patients with higher MR-proADM concentrations were more likely to be older, had advanced cancer (tumor stage IV: 82% vs. 64%), arterial hypertension, type 2 diabetes mellitus, and had a reduced Eastern Cooperative Oncology Group performance status. These patients also had lower levels of haemoglobin and eGFR, and were more often prescribed beta-blockers, opioids, and diuretics. Patients with higher MR-proADM concentrations also had higher levels of hsTnT, NT-proBNP, MR-proANP, copeptin, and CRP. There was no different distribution of patients with solid or haematological cancers above or below the cutpoint of MR-proADM ($p = 0.53$).

Echocardiographic function according to MR-proADM cut-off

Patients with elevated MR-proADM concentrations (>0.94 nmol/L) showed a tendency towards reduced diastolic function (higher mitral E/E' mean and lower mitral E/A ratio), a tendency towards increased systolic pulmonary artery pressure, and a tendency towards reduced right ventricular function (right ventricular S' reduced while tricuspid annular plane systolic excursion was similar between both groups; online supplementary *Table S3*) compared to patients who had MR-proADM concentrations below the optimal cut-off. Systolic function as assessed by left ventricular ejection fraction was similar between groups.

Discussion

In this study of 442 advanced stage, hospitalized cancer patients without significant CV disease or current infection, we found several noteworthy findings. First, whilst hsTnT, NT-proBNP MR-proADM, MR-proANP, and copeptin all predict mortality, only MR-proADM remained an independent predictor of mortality after multivariable adjustment. Second, elevated concentrations of MR-proADM are associated with reduced performance status and mildly reduced diastolic function as well as higher age and more often cancer stage IV. Lastly, the optimal cut-point for MR-proADM for mortality prediction is 0.94 nmol/L with hazards for mortality being approximately 2.4 times higher above versus below this cut-point (*Graphical Abstract*). Moreover, there was a continuous increase in mortality risk with stepwise increase in MR-proADM concentrations. These findings can have important implications for future management of cardio-oncology patients.

This is the first study in which only cancer patients without CV disease or infection were included and different CV biomarkers were compared to assess the impact on mortality. Monitoring serum biomarkers in cancer patients is routinely done to screen for cardio-toxicity, especially while patients are on anti-cancer treatment.[13] Multiple studies have focused on the relationship between elevated CV biomarkers, anti-cancer treatment and mortality; however most of the studies have only been based on high-sensitivity troponin and NT-proBNP.[22,23] Pavo *et al.*[18] have previously shown in cancer patients with possible baseline CV disease but before start of cardiotoxic chemotherapy, that elevated baseline levels of hsTnT, NT-proBNP, MR-proADM, MR-proANP, and copeptin independently predicted mortality. On the contrary, in our study with mostly advanced stage cancer patients without significant CV disease but largely undergoing anti-cancer therapy, only MR-proADM remained an independent predictor of mortality in multivariable analyses.

Adrenomedullin is a peptide hormone with natriuretic, vasodilatory and hypotensive effects, and its expression occurs in many tissues and organ systems.[24] The prognostic potential of MR-proADM has been shown in several studies across various patient populations including patients with sepsis, COVID-19, and acute respiratory distress syndrome.[25] In the BACH (Biomarkers in Acute Heart Failure) trial, MR-proADM was superior to both B-type natriuretic peptide and NT-proBNP in predicting mortality at 14 and 90 days.[26–28] MR-proADM has also been shown to predict CV events in patients with coronary artery disease in the AtheroGene Study.[19] Gezelius *et al.*[29] studied MR-proADM plasma levels in 252 patients with small cell lung

Table 1 Baseline characteristics according to MR-proADM in all cancer patients

	All cancer patients ($n = 442$)	Patients with cancer and MR-proADM <0.94 nmol/L ($n = 257$)	Patients with cancer and MR-proADM >0.94 nmol/L ($n = 185$)	*p*-value
Clinical characteristics				
Age, years	61 ± 15	58 ± 15	66 ± 12	**<0.001**
Male sex, *n* (%)	232 (52)	135 (53)	97 (52)	0.984
BMI, kg/m^2	24 ± 5	24 ± 5	24 ± 5	0.921
Cancer stage, *n* (%)				
I	23 (5)	21 (8)	2 (1)	**<0.001**
II	45 (10)	38 (15)	7 (4)	**<0.001**
III	59 (13)	34 (13)	25 (14)	0.999
IV	315 (71)	164 (64)	151 (82)	**<0.001**
Cancer type: solid, *n* (%)	302 (68)	170 (66)	132 (71)	0.530
Anti-cancer therapy-naïve, *n* (%)	72 (16)	49 (19)	23 (12)	0.058
Reason for hospital admission, *n* (%)				
Staging/diagnostics	123 (28)	80 (31)	43 (23)	**<0.001**
Anti-cancer therapy	184 (42)	125 (49)	59 (32)	**<0.001**
Worsening of the clinical condition	135 (31)	52 (20)	83 (45)	**<0.001**
Current smoker, *n* (%)	86 (20)	47 (18)	39 (21)	0.599
ECOG, *n* (%)				
0	66 (15)	60 (23)	6 (3)	**<0.001**
1	133 (30)	96 (37)	37 (20)	**<0.001**
2	113 (26)	60 (23)	53 (29)	0.225
3	104 (24)	33 (13)	71 (38)	**<0.001**
4	26 (6)	8 (3)	18 (10)	**0.007**
Cardiovascular parameters				
Systolic blood pressure, mmHg	127 ± 19	127 ± 18	126 ± 20	0.596
Diastolic blood pressure, mmHg	78 ± 12	80 ± 11	76 ± 12	**<0.001**
Laboratory parameters				
Haemoglobin, g/dl	11.1 ± 2.1	11.8 ± 2.0	10.1 ± 1.96	**<0.001**
eGFR, ml/min/1.73 m^2	88 ± 23	95 ± 20	77 ± 24	**<0.001**
Creatinine mg/dl	0.83 ± 0.35	0.75 ± 0.20	0.96 ± 0.47	**<0.001**
hsTnT, ng/L	11 [7–21]	8 [5–13]	18 [11–29]	**<0.001**
NT-proBNP, ng/L	254 [103–592]	154 [80–308]	554 [259–1142]	**<0.001**
MR-proADM, nmol/L	0.83 [0.63–1.15]	0.66 [0.55–0.78]	1.22 [1.06–1.70]	**<0.001**
MR-proANP, pmol/L	137 ± 90	97 ± 48	193 ± 104	**<0.001**
Copeptin, pmol/L	8 [5–17]	6 [4–10]	13 [7–27]	**<0.001**
CRP, mg/L	10.6 [2.8–37.9]	5.5 [1.55–17.3]	27.6 [7.2–66.0]	**<0.001**
Secondary diagnoses, *n* (%)				
Arterial hypertension	186 (42)	90 (35)	96 (52)	**<0.001**
Diabetes mellitus type 2	57 (13)	18 (7)	39 (21)	**<0.001**
Hypercholesterolaemia	127 (29)	71 (28)	56 (30)	0.542
Previous stroke	12 (3)	4 (2)	8 (4)	0.134
Medications on examination day, *n* (%)				
ACE-I/ARBs	110 (25)	55 (21)	55 (30)	0.058
Beta-blockers	78 (18)	34 (13)	44 (24)	**0.005**
Diuretics	77 (17)	24 (9)	53 (29)	**<0.001**
Opioids	109 (25)	50 (19)	59 (32)	**0.004**
Antidepressants	56 (13)	33 (13)	23 (12)	0.899
Steroids	137 (31)	80 (31)	57 (31)	0.943

Normal distributed variables are presented as mean ± standard deviation, non-normal distributed variables as median [interquartile range], and nominal variables as *n* (%). Bold *p*-values if $p < 0.05$.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group performance status scale; eGFR, estimated glomerular filtration rate; hsTnT, high-sensitivity troponin T; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2 Cox regression survival analysis in all cancer patients

	Univariable model				Multivariable model*		
	HR	95% CI	*p*-value	Schoenfeld residual test	HR	95% CI	*p*-value
MR-proADM (per 1 ln [MR-proADM in nmol/L] increase)	2.74	2.22–3.39	**<0.001**	0.737	2.27	1.47–3.50	**<0.001**
hsTnT (per 1 ln [hsTnT in ng/L] increase)	1.59	1.39–1.82	**<0.001**	0.813	1.01	0.84–1.21	0.905
Copeptin (per 1 ln [copeptin in pmol/L increase])	1.56	1.37–1.77	**<0.001**	0.716	1.17	1.00–1.37	0.055
MR-proANP (per 1 ln [MR-proANP in pmol/L] increase)	1.61	1.32–1.96	**<0.001**	0.233	0.74	0.53–1.03	0.074
NT-proBNP (per 1 ln [NT-proBNP in ng/L] increase)	1.20	1.09–1.31	**<0.001**	0.078	0.97	0.84–1.11	0.626

CI, confidence interval; HR, hazard ratio; hsTnT, high-sensitivity troponin T; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*Multivariable model with all biomarkers in the model and adjusted for sex, age, Eastern Cooperative Oncology Group performance status scale, estimated glomerular filtration rate, C-reactive protein, cancer stage (I–IV), anti-cancer therapy-naïve (yes vs. no), reason for hospital admission (staging/diagnostics vs. anti-cancer therapy vs. worsening of the clinical condition) and solid cancer vs. haematological cancer. For the multivariable model, the Schoenfeld residual test is $p = 0.252$, Harrell's C = 0.751, Akaike's information criterion = 2997.87; Bayesian information criterion = 3050.91.

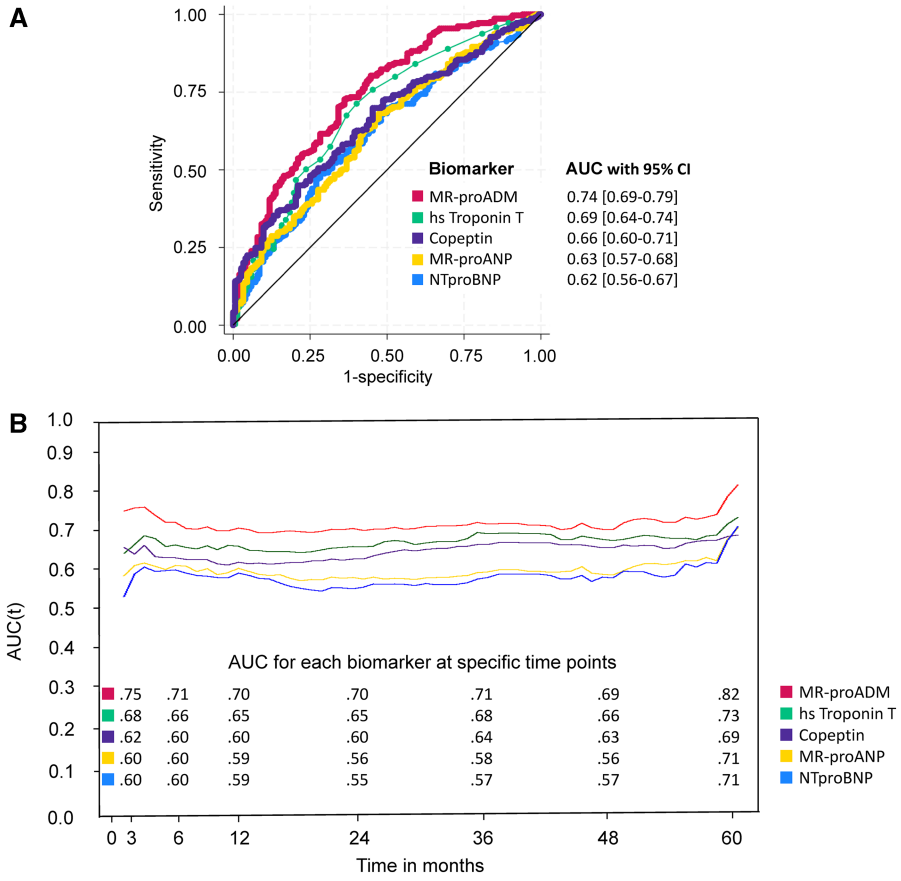


Figure 1 (*A*) Univariable receiver operating characteristic (ROC) curves. (*B*) Time-dependent area under the curve (AUC) from 0 to 69 months. CI, confidence interval; HR, hazard ratio; hsTnT, high-sensitivity troponin T; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

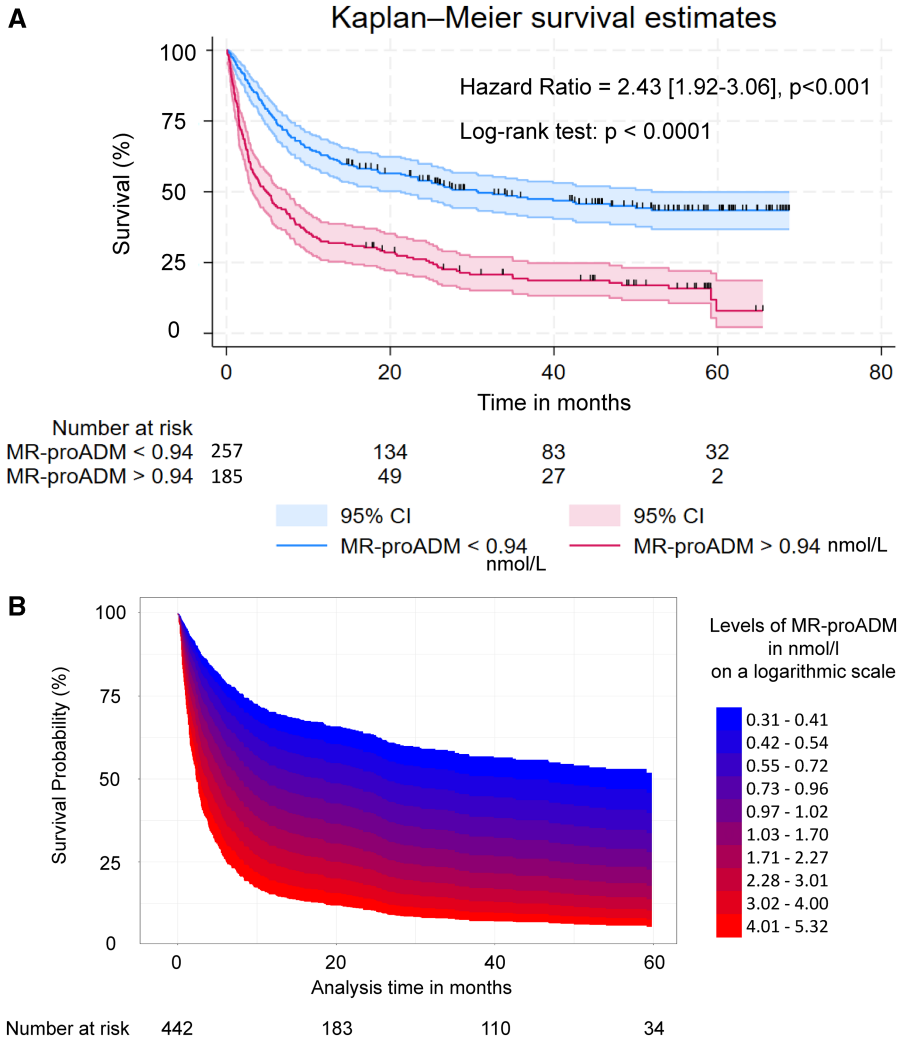


Figure 2 (*A*) Kaplan–Meier curves for the cut-point of mid-regional pro-adrenomedullin (MR-proADM, 0.94 nmol/L). (*B*) Contour plot. Multivariable survival probability in relation to baseline levels of MR-proADM (nmol/L), adjusted for sex, age, performance status, estimated glomerular filtration rate, C-reactive protein, cancer stage (I-IV), anti-cancer therapy-naïve (yes vs. no), reason for hospital admission (staging/diagnostics vs. anti-cancer therapy vs. worsening of the clinical condition) and solid cancer vs. haematological cancer. CI, confidence interval.

cancer recruited into the randomized controlled RASTEN trial that compared standard treatment with or without the addition of the low-molecular-weight heparin enoxaparin. Among the CV biomarkers analysed in this dataset, the authors found that MR-proADM and suppression of tumorigenicity-2 (ST2) best predicted survival.[29] Unfortunately, an optimal cut-off level was not reported for MR-proADM. Interestingly, we did not only find a best-cut off in this study, but there was also a continuous increase in mortality risk with stepwise increase of MR-proADM concentrations. This suggests that assessing MR-proADM may result in better categorization of risk and tailored care among cancer patients.

Adrenomedullin and MR-proADM also have pro-angiogenic and tumorigenic characteristics. Adrenomedullin promotes angiogenesis by endothelial cell proliferation and migration, leading to tumour growth and metastasis.[30] Notably, our study revealed elevated MR-proADM concentrations in advanced cancer patients with a tendency toward reduced diastolic dysfunction, which is concerning due to the association between high MR-proADM levels and cardiac dysfunction.[31] In patients with advanced stage cancer, there has been an emerging concern regarding cardiac wasting associated cardiomyopathy which is characterized by the loss of left ventricular mass.[32,33] Multiple studies have shown that cancer-related clinical wasting can cause various myocardial structural and haemodynamic alterations, which can result in arrhythmias and a HF-like syndrome.[8,34] Findings from our study suggest that MR-proADM may be able to identify cancer patients who are at increased risk for cardiac dysfunction. It is important to note that even without manifest CV disease, elevated CV biomarker levels were frequently detected in our study population of cancer patients.

Limitations

There are several limitations which should be considered. We included patients with several different aetiologies of cancers. While this may be regarded as a limitation, it is important to note that this is reflective of a real-world cohort of hospitalized cancer patients. We only included patients without clinical infections to avoid elevations of all tested biomarkers secondary to infections. Similarly, patients were included independent of their prior anti-cancer therapy or reason for hospitalization, which increases the generalizability of our findings. Of note, we did not find significant differences between patients with elevated or reduced concentrations of MR-proADM according to baseline anti-cancer therapy-naïve status. Future studies should assess these new CV biomarkers in a longitudinal study design and investigate the temporal changes over time. Moreover, we could not adjudicate the specific cause of deaths in cancer patients, and therefore took all-cause mortality as the endpoint which may have reduced the bias in the study. Despite a thorough multivariable adjustment of the mortality analysis, residual confounding could have occurred for factors that we did not record in the study. Lastly, as we excluded patients with significant CV disease at baseline, we did not record CV events during follow-up. Nonetheless, future studies should consider analysing the frequency of CV and non-CV causes of death as well as CV events during follow-up according to these new CV biomarkers.

Conclusion

MR-proADM is an independent predictor of mortality in hospitalized patients with advanced stage cancer without significant CV disease or current infection. The optimal cut-point for MR-proADM for mortality prediction was 0.94 nmol/L with hazards for mortality being approximately 2.5 times higher at this cut-point. There was a continuous increase in mortality risk with stepwise increase of MR-proADM concentrations. Elevated concentrations of MR-proADM were also associated with reduced performance status and mildly impaired diastolic left ventricular function as well as higher age and more often cancer stage IV. More research regarding the role of MR-proADM in cancer patients is needed, especially its value in longitudinal monitoring of cancer patients should be further investigated.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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