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Circulating levels of miR-20b-5p are associated with survival in cardiogenic shock

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ABSTRACT

Cardiogenic shock (CS) is a medical emergency with high in-hospital mortality. New biomarkers are needed to identify patients at a greater risk of adverse outcomes. This study aimed to investigate the prognostic potential of microRNAs (miRNAs) in assessment of the outcome of cardiogenic shock.

Circulating miRNA levels were measured by quantitative PCR in plasma samples collected at baseline from 165 patients of the multicenter, prospective, observational CardShock study and compared between in-hospital and 90-day survivors and non-survivors. Of the 10 studied miRNAs, median levels of miR-20b-5p at baseline were significantly higher in in-hospital and 90-day survivors compared to non-survivors [median 0.014 arbitrary units (AU) (interquartile range (IQR) 0.003–0.024) *vs.* 0.008 AU (IQR 0.001–0.015), $p = 0.013$] and [0.015 AU (IQR 0.003–0.025) *vs.* 0.010 AU (IQR 0.001–0.015), $p = 0.012$], respectively. In Cox regression analysis, miR-20b-5p levels in the highest quartile were significantly associated with 90-day survival (adjusted hazard ratio 2.47 (95 % confidence interval 1.16–5.28), $p = 0.019$) when adjusted for CardShock Risk Score variables (age, confusion at presentation, previous myocardial infarction or coronary artery bypass grafting, acute coronary syndrome (ACS) etiology, left ventricular ejection fraction, lactate, and estimated glomerular filtration rate). A similar association of highest quartile miR-20b-5p levels with 90-day survival was also confirmed in ACS patient subcohort (79 % of CS patients).

The results of this study indicate that circulating levels of miR-20b-5p at baseline could help in assessing in-hospital and 90-day survival in CS patients.

1. Introduction

Cardiogenic shock (CS) is a life-threatening condition characterized by decreased cardiac output, leading to inadequate tissue perfusion and end-organ failure [1]. The most common cause of CS is acute coronary syndrome, such as acute myocardial infarction. Other etiologies of CS include *e.g.*, acute decompensated heart failure, valvular diseases, and myocarditis [1,2]. Despite modern technologies and pharmacological therapies, in-hospital and short-term mortality remains high (up to 50 %) [1,3,4]. Different risk-stratification protocols and staging systems have been developed to improve the treatment and prognosis of CS patients [3,5–7]. However, there is still a need for improvements in the current protocols and staging systems.

Circulating microRNAs (miRNAs) have emerged as potential diagnostic and prognostic biomarkers of cardiovascular diseases and their complications [8,9]. miRNAs are short (~ 22 nucleotides) non-coding RNA molecules that regulate gene expression and consequently contribute to the regulation of normal physiological and pathological

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processes [8]. miRNAs can be found in the circulation, and can be isolated and measured from plasma, serum as well as other body fluids. Previously, the circulating levels of miR-423-5p [10], miR-21-5p and miR-320a-3p [11] at baseline have been shown to associate with 90-day all-cause mortality in CS. However, the number of studies regarding miRNAs in CS is still limited.

The complex pathophysiology of CS involves microcirculatory dysfunction, resulting in cell death and multi-organ injury, and a systemic inflammatory response [12,13]. Cytokines have been widely studied as biomarkers of CS, and elevated levels of inflammatory cytokines have been reported to associate with mortality in CS [12–15]. miRNAs are important regulators of inflammation and cell death pathways [16,17], and they could provide new insights into the complex biological processes activated in CS. Thus, we aimed to investigate the prognostic potential of miRNAs targeting inflammation and cell death-associated pathways in a CS patient cohort.

2. Methods

2.1. Patients

This study was part of a predefined biomarker substudy of the CardShock study. The CardShock study (www.clinicaltrials.gov identifier: NCT01374867) was a multicenter, prospective, and observational study on CS. Consecutive patients with varied etiologies of cardiogenic shock (SCAI SHOCK Stage Classification [6] C, D and E) were recruited from nine tertiary care hospitals in eight European countries between October 2010 and December 2012 [7]. The study was approved by the local ethics committees of each participating study center and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients or their next of kin. Echocardiography was performed per protocol, and clinical characteristics were evaluated upon study enrolment. Alanine aminotransferase (ALT), albumin, alkaline phosphatase (AFOS), bilirubin, C-reactive protein (CRP), creatinine, gamma glutamyl transferase (GGT), high-sensitivity troponin T (hsTnT), N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP), total bilirubin, and growth differentiation factor-15 (GDF-15) were analyzed at an accredited laboratory (ISLAB, Kuopio, Finland) using routine clinical chemistry methods (Roche Diagnostics, Basel, Switzerland). Arterial blood lactate was analyzed locally. The estimated glomerular filtration rate (eGFR) of patients was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. [18]. The primary endpoints of the current study were in-hospital and 90-day all-cause mortality. For further details regarding the study population and the main findings of the CardShock study, see Harjola et al. [7].

EDTA plasma samples were collected within 6 h from identification of CS at baseline (0 h). Plasma was immediately separated, aliquoted, and stored frozen at −80 °C. Of the 219 patients recruited for the CardShock study, frozen plasma samples were available at baseline for 178 patients (2 centers did not participate in the biomarker substudy). Patient samples that were visually clearly hemolytic ($n = 10$) or had a sample volume < 400 µl upon RNA extraction ($n = 3$) were excluded. Consequently, the study population of the current study comprised a total of 165 patient samples.

2.2. RNA isolation and miRNA quantification

Total RNA was isolated from 400 µl of plasma using a mirVana PARIS Kit (Ambion, Applied Biosystems, Lennik, Belgium) according to the manufacturer's instructions as described previously [11]. Spike-in synthetic *Caenorhabditis elegans* miRNA (Cel-miR-39) (Qiagen, Venlo, The Netherlands) was added as an extraction control during RNA isolation. On-column DNase treatment was used to remove potential genomic DNA contamination. RNA was eluted into 50 µl of nuclease-free water and stored frozen at −80 °C.

Reverse transcription (RT) was performed using the miRCURY LNA RT Kit (Qiagen). Spike-in UniSp6 (Qiagen) was added to control the RT reaction. As CardShock patients might have been treated with heparin, a known inhibitor of miRNA quantification, a heparinase treatment with 12 U *Bacteroides* heparinase I (New England BioLabs, Ipswich, Massachusetts, USA) was performed during the RT reaction as described previously [19]. The RT reaction was incubated at 42 °C for 1 h, after which the reverse transcriptase was inactivated for 5 min at 95 °C.

Based on the literature search, a panel of 10 miRNAs associating with ischemia and/or myocardial infarction and implicated in the regulation of inflammation and cell death pathways was selected along with 10 miRNA candidates for normalization (Table S1). The quantification of miRNAs was performed by qPCR using the miRCURY LNA miRNA SYBR Green PCR kit (Qiagen) and miRNA-specific miRCURY LNA miRNA PCR Assay sets (Qiagen) on a LightCycler 480 (Roche Diagnostics). cDNA products were amplified for 45 cycles, with 10 s denaturation at 95 °C and 1 min annealing at 56 °C. Melting curve acquisition was carried out immediately after amplification. Each sample was analyzed in duplicate.

Raw qPCR data of all miRNAs were processed according to the data handling pipeline described by de Ronde et al. [20]. In brief, after performing melting and amplification curve analysis, the consistency of duplicate qPCR results of each sample was checked (see Fig. S1 for representative qPCR amplification and melting curves). The mean Cq values were calculated for each sample. Results were then categorized as valid (mean Cq ≤ 35 and the difference between duplicates was below the maximal acceptable Cq difference, ranging from 0.5 at Cq 25 to 1.9 at Cq 35), undetectable (qPCR reactions with Cq values above 35 were considered too low to be quantitatively measured), or invalid (mean Cq of duplicates ≤ 35, but the difference between duplicates exceeded the maximal acceptable Cq value) (number and percentages of valid, undetectable and invalid results; see Table S2). The maximal acceptable Cq difference in replicates is dependent on the PCR efficiency value and the mean of the Cq values of the replicates [20]. Invalid results, which can be a consequence of *e.g.* pipetting or other technical error, were replaced with imputed values pooled from five imputed data sets generated using the multiple imputation method in SPSS statistical software version 28 (IBM Corp., Armonk, NY, USA) as described by de Ronde et al. [20]. Before the multiple imputation step, the mean Cq of miR-20b-5p of the invalid samples was 33.02 and after the step, it was 34.65. Finally, the mean Cq of each sample was log-transformed and normalized to the geometric mean of miR-16-5p, −19a-3p, −20a-5p, −23a-3p, −93-5p, −106b-5p, −425-5p, and -let-7i-5p from the same sample (sample-specific geometric means between 90-day survivors and non-survivors; $p = 0.8$; Fig. S2). The miRNAs used in normalization were selected from the 10 normalization miRNA candidates by GeNorm in qbase+ software (CellCarta, Quebec, Canada). GeNorm employs an algorithm [21] to determine the most stable and optimal number reference miRNAs from the normalization candidates required for normalization. The normalization miRNAs selected by GeNorm had a reference target stability value (M value) ≤ 1 and GeNorm V < 0.15. Endogenous miRNAs are preferred for normalization because spike-ins, such as Cel-miR-39 and UniSP6, are susceptible to pipetting errors.

2.3. Statistical analysis

Results are presented as numbers (n) and percentages (%), as means and standard deviations (SD) for normally distributed variables, or as medians and interquartile ranges (IQR) for variables with skewed distribution. The results of the regression analyses are presented as hazard ratios (HR) with 95 % confidence intervals (CI).

Patients were dichotomized based on the baseline circulating level of miR-20b-5p. Comparisons between groups were performed with χ^2-test or Fischer's exact test for categorial variables and Student's *t*-test or Mann-Whitney *U* test for continuous variables, as appropriate. Associations between continuous variables with non-normal distributions were assessed using Spearman correlations. Differences in survival

between the groups were assessed using Kaplan-Meier survival plots and log-rank tests. Univariate and multivariate Cox regression analyses were used to determine associations between variables and 90-day all-cause mortality.

All statistical analyses were performed using SPSS statistical software version 28 (IBM Corp., Armonk, NY, USA). A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics and association with outcome

Patient baseline characteristics along with the outcome during the 90-day follow-up are summarized in Table 1. The mean age of the study participants ($n = 165$; the whole study patient cohort) was 67 ± 12 years, and the patients were predominantly (74 %) men. The main etiology of CS in the whole study cohort was acute coronary syndrome ($n = 131$; 79 % of all patients) consisting of patients who presented with ST-elevation myocardial infarction ($n = 108$; 82 % of acute coronary syndrome (ACS) patients), non-ST-elevation infarction ($n = 22$; 17 %), or unstable angina pectoris (n = 1; 1 %). The non-ACS causes of CS ($n = 34$; 21 % of the whole study cohort) comprised mainly worsening of chronic heart failure (11 % of all patients) and valvular causes (7 %).

Out of the whole study cohort, 95 patients (58 %) were alive at the end of the 90-day follow-up. Survivors were significantly younger than non-survivors and had a significantly lower prevalence of ischemic heart disease, diabetes, renal insufficiency, and previous myocardial infarction (MI) or coronary artery bypass grafting (CABG) in their medical history. Interestingly, a higher number of survivors were smokers compared to the non-survivors. There was no significant difference between survivors and non-survivors in the etiology of CS.

At baseline, the survivors had significantly lower levels of hsTnT, NT-proBNP, lactate, and GDF-15 and higher eGFR, mean arterial pressure, and left ventricular ejection fraction than the non-survivors. Also, upon study recruitment, the survivors had a significantly lower prevalence of confusion at presentation compared with the non-survivors.

3.2. Plasma miRNA levels in in-hospital and 90-day survivors and non-survivors

The median circulating levels of miR-20b-5p at baseline were significantly ($p < 0.05$) higher in the in-hospital survivors compared to non-survivors [0.014 arbitrary units (AU) (interquartile range (IQR) 0.003–0.024) *vs.* 0.008 AU (IQR 0.001–0.015), $p = 0.013$] (Fig. 1). Similarly, significantly higher circulating levels of miR-20b-5p were observed in the 90-day survivors compared to non-survivors [median 0.015 AU (IQR 0.003–0.025) *vs.* 0.010 AU (IQR 0.001–0.015), $p = 0.012$] (Table 1 and Fig. 1). Similar significant differences in median circulating levels of miR-20b-5p were observed between survivors and non-survivors in the ACS subcohort (Fig. 1): 0.015 AU (IQR 0.005–0.025) *vs.* 0.009 AU (IQR 0.001–0.015), $p = 0.005$ and 0.018 AU (IQR 0.007–0.025) *vs.* 0.009 AU (IQR 0.001–0.014), $p = 0.002$, respectively. When the Bonferoni correction ($p < 0.005$) was applied to account for multiple testing, the median circulating levels of miR-20b-5p in the 90-day survivors of ACS subcohort were found to be significantly higher compared to non-survivors (Fig. 1D). The other median

Table 1
Baseline patient characteristics of all patients (n = 165) of the CardShock cohort in relation to outcome at the end of 90-day follow-up (n = 163, two patients lost during follow-up).

		Outcome‡		
	All patients†	Non-survivors	Survivors	
Variable	(n = 165)	(n = 68)	(n = 95)	P-value
Demographics				
Age, years	67 ± 12	71 ± 11	63 ± 12	<0.001*
Women, n (%)	43 (26)	22 (32)	21 (22)	0.143^
BMI, kg/m2	27.0 ± 4.2	26.9 ± 4.3	27.1 ± 4.1	0.717*
Smoking, n (%)	69 (42)	21 (31)	46 (48)	0.030^
Medical history				
Ischemic heart disease, n (%)	55 (33)	33 (49)	22 (23)	<0.001^
Diabetes mellitus, n (%)	51 (31)	29 (43)	21 (22)	0.005^
Renal insufficiency, n (%)	21 (13)	15 (22)	6 (6)	0.003^
Previous MI or CABG, n (%)	43 (26)	27 (40)	16 (17)	<0.001^
Previous HF (chronic HF), n (%)	29 (18)	15 (22)	14 (15)	0.228^
Hypertension, n (%)	101 (61)	46 (68)	54 (57)	0.162^
Clinical and biochemical findings at baseline				
ACS etiology, n (%)	131 (79)	58 (85)	71 (75)	0.102^
Confusion at presentation, n (%)	107 (66)	55 (81)	50 (54)	<0.001^
Mean arterial pressure, mmHg	64 ± 13	60 ± 14	67 ± 13	0.007*
LVEF, %	33 ± 14	29 ± 12	35 ± 15	0.006*
eGFR, mL/min/1,73 m^2	63 ± 29	50 ± 25	71 ± 28	<0.001*
Lactate, mmol/L	2.7 (1.8–5.9)	4.6 (2.4–8.3)	2.2 (1.4–3.5)	<0.001#
ALT, U/L	46 (21–93)	56 (26–122)	41 (17–84)	0.042#
hsTnT, ng/L	2275 (365–5336)	2829 (976–6587)	1600 (208–4191)	0.035#
NT-proBNP, ng/L	2771 (671–9583)	6432 (1447–16,551)	2109 (481–7066)	0.002#
CRP, mg/L	18 (5–59)	25 (4–60)	14 (5–48)	0.612#
AFOS, U/L	70 (49–82)	64 (50–83)	61 (48–81)	0.809#
GGT, U/L	85 (31–105)	47 (29–82)	57 (34–106)	0.367#
Bilirubin, μmol/L	10 (6–16)	10 (6–16)	10 (6–17)	0.985#
Albumin, g/L	29 ± 6	28 ± 7	31 ± 6	<0.001*
GDF-15, ng/L	9506 (4438–18,596)	12,027 (8759–29,315)	6846 (3248–14,881)	<0.001#
miR-20b-5p, AU	0.012 (0.002–0.021)	0.010 (0.001–0.015)	0.015 (0.003–0.025)	0.012#

Results are presented as numbers (n) and percentages (%), mean ± standard deviation (SD) for normally distributed variables and median with inter quartile range (IQR) for non-normally distributed variables. BMI, body mass index; MI, myocardial infraction; CABG, coronary artery bypass grafting; HF, heart failure; ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; CRP, C-reactive protein; AFOS, alkaline phosphatase; GGT, gamma glutamyl transferase; GDF-15, Growth differentiation factor 15; AU, arbitrary units; † All patients ($n = 165$) of the CardShock study cohort; ‡ 90-day outcome from 163 patients (2 patients were lost during follow-up); * Student t-test; # Mann-Whitney U test; ^ χ2-test.

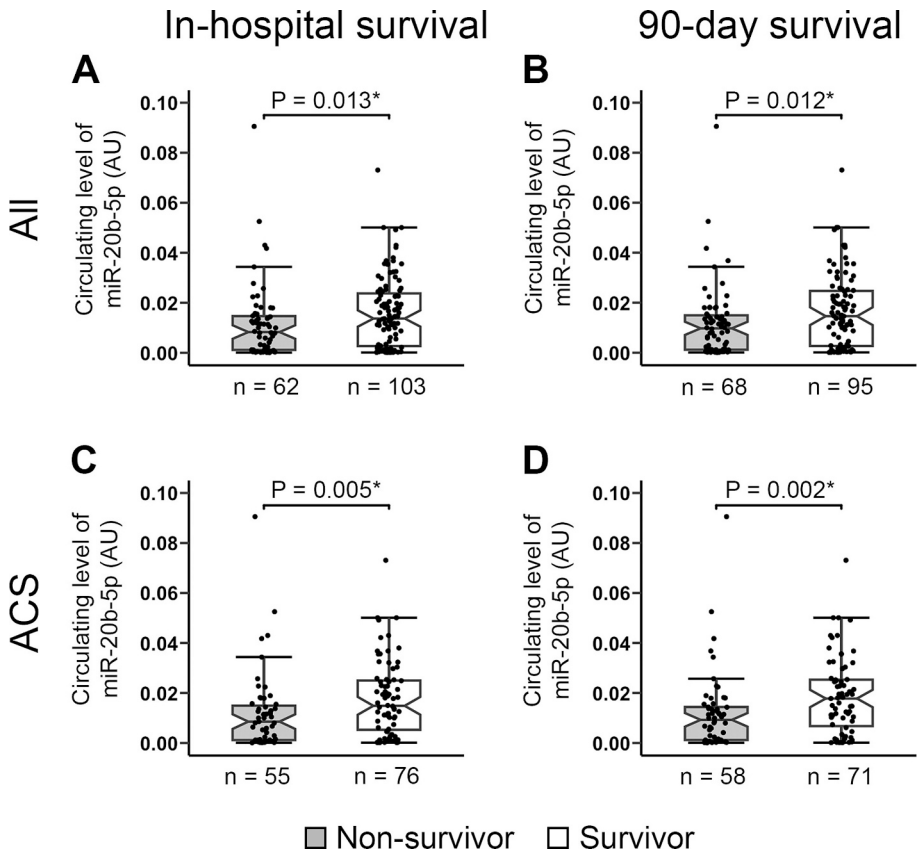

Fig. 1. Circulating levels of miR-20b-5p at baseline. A and C in-hospital non-survivors and survivors; B and D 90-day non-survivors and survivors. All, All patients of the CardShock study cohort (in-hospital survival, $n = 165$; 90-day survival, $n = 163$, 2 patients lost during follow-up); ACS, Patients of the CardShock study cohort with acute coronary syndrome as etiology of cardiogenic shock (in-hospital survival, $n = 131$; 90-day survival, $n = 129$, 2 patients lost during follow-up); AU, arbitrary units; *, Mann-Whitney *U* test; the whiskers in box plots indicate calculated minimum and maximum values, above which value is considered as an outlier.

circulating levels of miR-20b-5p (Fig. 1A-C) in in-hospital and 90-day survivors compared to non-survivors did not surpass the Bonferroni correction. The effect of covariates was tested using logistic regression, adjusting for the CardShock Risk Score variables (age, confusion at presentation, previous myocardial infarction (MI) or coronary artery bypass grafting (CABG), acute coronary syndrome (ACS) etiology, left ventricular ejection fraction (LVEF), lactate, and estimated glomerular filtration rate (eGFR)) at baseline. Although none of the statistically significant associations ($p < 0.05$) surpassed the Bonferroni correction (all *p*-values > 0.005, Table S3), further analyses of circulating levels of miR-20b-5p and its association with in-hospital and 90-day survival were conducted.

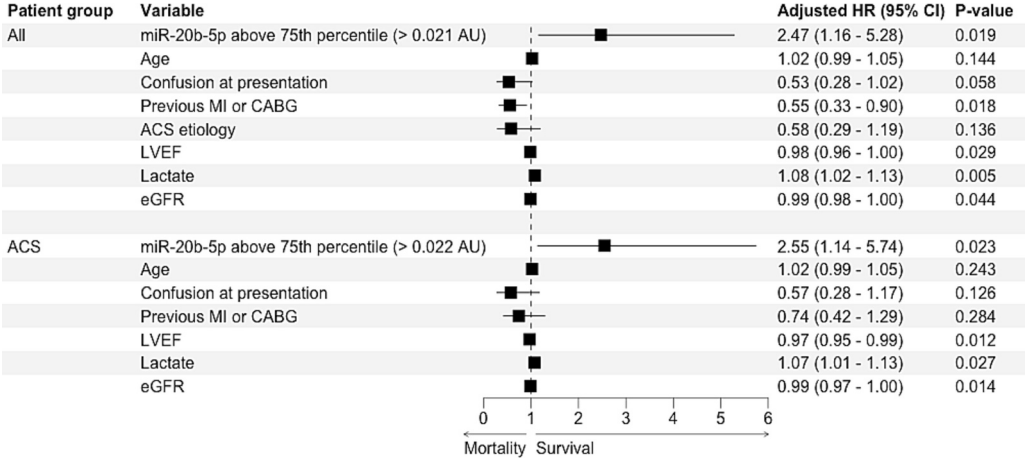

Fig. 2. Adjusted hazard ratios of circulating miR-20b-5p levels above 75th percentile at baseline. The CardShock risk score variables (age, confusion at presentation, previous myocardial infarction or coronary artery bypass grafting, acute coronary syndrome etiology, left ventricular ejection fraction, lactate, and estimated glomerular filtration rate) at baseline were used to adjust the hazard ratios of multivariable Cox regression analysis. All, All patients of the CardShock study cohort (n = 165); ACS, patients of the CardShock study cohort with acute coronary syndrome as etiology of cardiogenic shock (n = 131); AU, arbitrary units; MI, myocardial infarction; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

No significant association with in-hospital or 90-day survival was found for other studied miRNAs in the whole study cohort or in the ACS subcohort (Tables S4 and S5, respectively).

3.3. Survival and prognostic value of miR-20b-5p at baseline

The overall survival during the 90-day follow-up was 58 % ($n = 95$) in the whole study cohort and 55 % ($n = 71$) in the ACS subcohort (Table 1 and Fig. 1). Higher survival was observed in in-hospital patients who had circulating levels of miR-20b-5p above the median at baseline compared with patients with miR-20b-5p levels below the median (Table S6). Similar findings were detected in the ACS subcohort.

In Cox regression analysis miR-20b-5p levels above the median [0.012 AU (IQR 0.002–0.021)] were associated with 90-day survival with an unadjusted hazard ratio (HR) of 2.69 (95 % CI 1.33–5.42, $p = 0.006$) in the whole patient cohort and 2.98 (95 % CI 1.41–6.29, $p = 0.004$) in the ACS subcohort. After adjusting the model with CardShock Risk Score variables (age, confusion at presentation, previous MI or CABG, ACS etiology, LVEF, lactate, and eGFR) at baseline, we found that miR-20b-5p levels in the highest quartile were independently associated with 90-day survival [adjusted HR 2.47 (95 % CI 1.16–5.28), $p = 0.019$] (Fig. 2 and Fig. S3). Similar results were obtained for the ACS subcohort (Fig. 2 and Fig. S3). In Kaplan-Meier survival analysis, circulating levels of miR-20b-5p above the median were associated with higher 90-day survival (Fig. 3).

3.4. Association of miR-20b-5p with baseline characteristics

Spearman correlation analysis revealed a weak positive correlation between circulating levels of miR-20b-5p and albumin and a weak negative correlation with lactate and GDF-15 (Table 2).

Patient characteristics, medical history, and clinical and biochemical findings stratified by the circulating miR-20b-5p quartiles at baseline are summarized in Table 3. While no differences were observed in patient characteristics or medical history in relation to miR-20b-5p levels, above 75th percentile level of miR-20b-5p was significantly associated with lower lactate, NT-proBNP, and GDF-15 levels ($p < 0.05$) in the whole study patient cohort.

There was no difference in the median circulating levels of miR-20b-5p between women and men in the whole study cohort [0.012 AU (IQR 0.001–0.020) *vs.* 0.012 AU (IQR 0.002–0.023), $p = 0.764$] or in the ACS subcohort [0.014 AU (IQR 0.001–0.021) *vs.* 0.012 AU (IQR 0.002–0.023), $p = 0.948$]. In addition, there was no difference in the median circulating levels miR-20b-5p between ACS *vs.* non-ACS etiology of CS [0.012 AU (IQR 0.002–0.022) *vs.* 0.010 AU (IQR 0.001–0.017), $p = 0.249$]. No correlation between age and circulating level of miR-20b-5p (spearman correlation coefficient −0.105, $p = 0.181$) or difference in the circulating level of miR-20b-5p between smokers and non-smokers was observed in the whole study cohort or in the ACS subcohort (Table S7).

4. Discussion

In the current study, we demonstrate that the median circulating level of miR-20b-5p at baseline was significantly higher in in-hospital and 90-day survivors compared to non-survivors of the CardShock study patient cohort. In addition, we show that the circulating level of miR-20b-5p is associated with 90-day survival: Survival of patients with above median circulating levels of miR-20b-5p was improved compared to patients with lower levels of miR-20b-5p. To the best of our knowledge, this is the first study to investigate plasma miR-20b-5p levels in CS. Furthermore, the association of higher miR-20b-5p levels with better survival suggests that miR-20b-5p may have an important and possibly protective role in the pathophysiology of CS. This is a unique finding, as in previous studies, higher levels of miR-21-5p, −320a-3p, −423-5p and −619-5p were associated with mortality [10,11,22]. The other studied miRNAs did not associate with mortality in this cohort comprising only CS patients. An interesting question remains whether they could predict the development of cardiogenic shock in ACS patients.

Many previous studies on miR-20b-5p have focused on its role in cancer [23,24], where miR-20b-5p has been shown to have both tumor suppressor and oncogenic properties depending on the target cells and expression level of the miRNA. In addition, there is increasing evidence that miR-20b-5p also plays an important role in other biological and disease processes, including normal cardiac physiology and cardiac disorders [23,24].

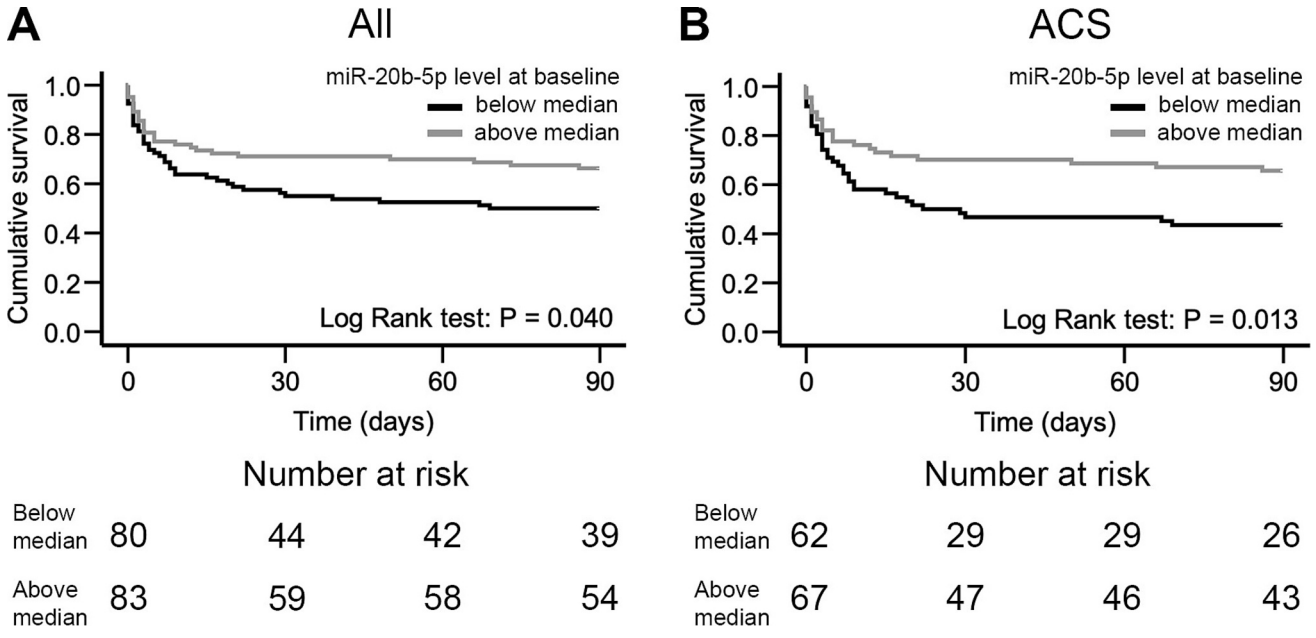

Fig. 3. Kaplan-Meier survival curves of patients with circulating level of miR-20p-5p at baseline below and above median. (A) All patients of the CardShock cohort (n = 163) and (B) patients of the CardShock cohort with acute coronary syndrome (ACS) as an etiology of cardiogenic shock (n = 129). The differences in outcomes between patients with circulating level of miR-20p-5p at baseline below *versus* above median were compared using log rank test.

Table 2
Spearman correlation coefficients of miR-20b-5p and biochemical values at baseline of all patients of the CardShock cohort ($n = 165$) and patients of the CardShock cohort with acute coronary syndrome as an etiology of cardiogenic shock (n = 131).

		Lactate	hsTnT	NT-proBNP	eGFR	CRP	ALT	AFOS	GGT	Bilirubin	Albumin	GDF-15
All	ρ	−0.182*	0.096	−0.120	0.079	0.009	−0.043	−0.106	−0.087	0.082	0.162*	−0.168*
	n	165	164	164	165	164	165	165	165	165	165	165
ACS	ρ	−0.210*	0.060	−0.109	0.111	0.022	−0.066	−0.086	−0.062	0.077	0.199*	−0.166
	n	131	130	130	131	130	131	131	131	131	131	131

All, all patients of the CardShock cohort; ACS, patients of the CardShock cohort with acute coronary syndrome as an etiology of cardiogenic shock; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AFOS, alkaline phosphatase; GGT, gamma glutamyl transferase; GDF-15, growth differentiation factor-15; ρ, Spearman correlation coefficient; *, p-value < 0.05.

Recently, miR-20b-5p was proposed as a cardiac-specific biomarker for atrial remodeling progression and arrhythmia recurrence after catheter ablation in patients with atrial fibrillation [25]. Harada et al. confirmed cardiospecificity using a specific blood sampling from the coronary sinus and femoral vein, both of which are not routinely used for venous blood sampling. Dysregulation of miR-20b-5p has been detected in myocardial ischemia, and *in vitro* studies have suggested that miR-20b-5p plays a role in mediating cardiomyocyte apoptosis under hypoxic conditions [23,26,27].

Autophagy and apoptosis are crucial for the maintenance of myocardial homeostasis. miR-20b-5p has been shown to directly interact with the 3'UTR of ATG7, an essential autophagy effector enzyme that works in concert with other autophagy-related proteins [28]. CircHIPK3 promotes cardiomyocyte autophagy and apoptosis during myocardial hypoxia/reoxygenation (H/R) injury by acting as an endogenous sponge to sequester and inhibit miR-20b-5p activity, leading to increased ATG7 expression. However, transfection of miR-20b-5p mimics and inhibitors had no effect on the autophagy and apoptosis of normal cultured cardiomyocytes [27]. Furthermore, using human umbilical vein endothelial cell cultures, Lu et al. showed that miR-20b regulates H/R-induced autophagy by directly targeting ULK1, which is a core component of the autophagy initiation complex [29]. Specific binding sites in ULK1 mRNA for miR-20b-5p have been identified, and re-expression of ULK1 restores autophagy inhibited by miR-20b [29]. miR-20b-5p serves as a significant regulator of both autophagy and apoptosis through its interaction with various downstream targets. Further studies into the underlying mechanisms could provide insights into the strategies aiming at regulation of autophagy and apoptosis by miR-20b-5p in diseases associated with oxidative stress.

The expression of miR-20b-5p has also been shown to be decreased in severe acute pancreatitis models, whereas the inflammatory markers IL-1β, TNF-α, and IL-6 were increased [30]. In our study, miR-20b-5p was not correlated with the inflammatory marker CRP. This may be due to the nonspecific nature of CRP, as we also observed no difference in admission CRP levels between survivors and non-survivors. However, the association between miR-20b-5p and other inflammatory markers, such as cytokines could be worth investigating in future CS studies.

miR-20b-5p has shown significant expression across various tissues, including cardiac tissue (*e.g.* cardiomyocytes and endothelial cells), skeletal muscle, neurons, T cells, and cancer cells [23,24]. Most of the CS patients in the current study comprised patients with ACS as an etiology. However, similar results were observed in the whole study cohort compared with the ACS subcohort. In CS, decreased cardiac output can lead to an inadequate supply of oxygenated blood to vital organs, which can cause local hypoxia and tissue damage and alterations in the expression of miR-20b-5p. Currently the original source of miR-20b-5p in plasma is not known. As there was no difference in the circulating level of miR-20b-5p between CS patients with ACS and non-ACS etiologies, miR-20b-5p detected in the plasma samples of the current study may have originated mainly from tissues and organs other than the heart.

miR-20b-5p belongs to the miR-17 family, and MIR20B gene encoding miR-20b-5p is located in Xq26.2. Due to the X-chromosomal location of the MIR20B gene, we also wanted to evaluate the possible dose effect of miR-20b-5p. However, no difference was observed between women and men in the median circulating level of miR-20b-5p.

Different models and schemas have been proposed to stage the severity of CS. The CardShock risk score for risk prediction of in-hospital mortality in CS patients was published in 2015 by Harjola et al. [7]. Another CS classification model was published by the Society for Cardiovascular Angiography and Interventions (SCAI) in 2019 and has recently been revised [5,6]. A refined version of the SCAI consensus statement has been evaluated for the prediction of in-hospital mortality [3]. There is increasing evidence that miRNAs could be utilized to evaluate the outcomes of CS patients. Previously, Jäntti et al. have shown that miR-423-5p level at baseline associates with markers of hypoperfusion and seems to predict 90-d mortality [10]. In addition, Hänninen et al. have previously shown that above median circulating levels of miR-21-5p and miR-320a-3p at baseline associate with 90-day all-cause mortality in the CardShock cohort [11]. Recently, Escate et al. reported significantly higher plasma level of miR-619-5p in CS patients with fatal outcome compared with those that survived [22]. In this study, we demonstrate that miR-20b-5p is a new candidate miRNA for assessing survival in CS patients. SCAI and other CS classification systems emphasize a variety of physical examination findings and traditional laboratory markers in the stratification of patients into various stages of shock severity. The use of one or more miRNAs as a novel laboratory marker could be used to redefine classifications and further improve the prediction of outcome and guide therapy in the CS population, as proposed by Patenè et al. [31]. miRNAs could also provide insight into the biological processes activated in different phenotypes of patients [32,33]. However, standardization of methodologies and protocols is required before miRNAs can be taken into routine clinical practice [34,35]. Despite challenges, miRNAs remain promising as novel diagnostic and prognostic tools.

Finally, it should be noted that this study has some limitations. First, our study cohort consisted of only CS patients of whom 79 % had ACS as etiology of CS. There were no ACS patients without CS, or healthy controls included in our cohort. The comparisons were made in CS patients that had been dichotomized based on survival or circulating level of miR-20b-5p at baseline. Therefore, we are unable to provide information on the changes in miR-20b-5p expression levels compared to healthy controls. Second, the number of women and the etiologies of cardiogenic shock other than ACS were limited. Since the recruitment of patients for the CardShock study, the proportion of patients with heart failure (HF) etiology has increased, surpassing ACS as a cause of CS in several studies [36]. In the current study, 11 % of the patients had HF-related CS. Third, we used a targeted approach to select studied miRNA candidates instead of unbiased miRNA profiling using microarray or RNA sequencing. It is possible that other miRNAs have prognostic potential in CS. On the other hand, the strength of the current study is the rather homogenous, fair sized, and well documented cohort. Nevertheless, as CS is a heterogenous syndrome with mixed etiologies and phenotypes, further evaluation of miRNAs with larger patient cohorts and

Table 3
Patient characteristics, clinical and biochemical findings in relation to circulating level of miR-20b-5p at baseline of all patients of the CardShock cohort (n = 165).

		Circulating level of miR-20b-5p								
		25th percentile			Median			75th percentile		
	All patients†	Below	Above		Below	Above		Below	Above	
Variable	(n = 165)	(*n* = 41)	(*n* = 124)	P-value	(*n* = 82)	(*n* = 83)	P-value	(n = 124)	(n = 41)	P-value
Demographics										
Age, years	67 ± 12	70 ± 11	66 ± 13	0.074*	67 ± 12	66 ± 13	0.344*	67 ± 12	64 ± 13	0.186*
Women, n (%)	43 (26)	12 (29)	31 (25)	0.589^	20 (24)	23 (28)	0.627^	33 (27)	10 (24)	0.779^
BMI, kg/m2	27.0 ± 4.2	27.0 ± 4.1	27.0 ± 4.3	0.984*	26.9 ± 4.3	27.1 ± 4.2	0.758*	26.8 ± 4.2	27.9 ± 4.2	0.163*
Smoking, n (%)	69 (42)	13 (33)	56 (45)	0.158^	35 (43)	34 (41)	0.771^	51 (42)	18 (44)	0.784^
Medical history										
Ischemic heart disease, n (%)	55 (33)	13 (32)	42 (34)	0.799^	25 (31)	30 (36)	0.441^	42 (34)	13 (32)	0.799^
Diabetes mellitus, n (%)	51 (31)	14 (34)	37 (30)	0.605^	27 (33)	24 (29)	0.577^	41 (33)	10 (24)	0.297^
Renal insufficiency, n (%)	21 (13)	5 (12)	16 (13)	0.906^	12 (15)	9 (11)	0.465^	17 (14)	4 (10)	0.510^
Previous MI or CABG, n (%)	43 (26)	9 (22)	34 (27)	0.489^	20 (24)	23 (28)	0.627^	33 (27)	10 (24)	0.779^
Previous HF (chronic HF), n (%)	29 (18)	7 (17)	22 (18)	0.922^	16 (20)	13 (16)	0.516^	23 (19)	6 (15)	0.568^
Hypertension, n (%)	101 (61)	27 (66)	74 (60)	0.482^	51 (62)	50 (60)	0.797^	76 (61)	25 (61)	0.971^
Clinical and biochemical findings at baseline										
ACS etiology, n (%)	131 (79)	32 (78)	99 (80)	0.806^	64 (78)	67 (81)	0.671^	96 (77)	35 (85)	0.275^
Confusion at presentation, n (%)	107 (66)	30 (75)	77 (63)	0.151^	55 (68)	52 (63)	0.546^	80 (65)	27 (68)	0.776^
Mean arterial pressure, mmHg	64 ± 13	61 ± 13	65 ± 13	0.094*	62 ± 14	66 ± 13	0.099*	64 ± 14	64 ± 12	0.997*
LVEF, %	33 ± 14	30 ± 16	34 ± 13	0.120*	32 ± 14	33 ± 14	0.623*	32 ± 14	34 ± 14	0.566*
eGFR, mL/min/1,73 m^2	63 ± 29	58 ± 29	64 ± 29	0.276*	60 ± 28	64 ± 30	0.422*	60 ± 29	69 ± 27	0.084*
Lactate, mmol/L	2.7 (1.8–5.9)	3.2 (2.2–5.9)	2.5 (1.7–5.9)	0.172#	3.1 (2.0–6.6)	2.4 (1.6–5.3)	0.073#	3.1 (1.7–6.6)	2.3 (1.6–3.2)	0.027#
ALT, U/L	46 (21–93)	44 (15–86)	47 (21–105)	0.337#	52 (21–109)	41 (20–83)	0.483#	50 (21−111)	33 (20–79)	0.172#
hsTnT, ng/L	2275 (365–5336)	1460 (279–3562)	2473 (386–5784)	0.201#	2205 (314–5211)	2344 (379–5663)	0.709#	2307 (339–5279)	1743 (542–6908)	0.602#
NT-proBNP, ng/L	2771 (671–9583)	3604 (1186–11,206)	2500 (626–9360)	0.552#	3655 (1192–9249)	2068 (555–9715)	0.396#	4564 (1102–12,249)	1086 (286–3686)	0.001#
CRP, mg/L	18 (5–59)	15 (4–80)	21 (5–55)	0.556#	19 (4–56)	14 (5–61)	0.911#	21 (5–73)	8 (4–44)	0.159#
AFOS, U/L	61 (49–82)	61 (51–84)	62 (49–81)	0.695#	65 (52–85)	59 (45–80)	0.110#	63 (51–87)	59 (43–75)	0.048#
GGT, U/L	54 (31–105)	48 (26–107)	54 (33–104)	0.648#	58 (30–115)	46 (32–84)	0.496#	60 (33−113)	42 (28–70)	0.018#
Bilirubin, μmol/L	10 (6–16)	9 (6–14)	10 (6–17)	0.480#	9 (6–13)	11 (7–20)	0.047#	10 (6–15)	10 (6–17)	0.998#
Albumin, g/L	29 ± 6	29 ± 6	30 ± 6	0.472*	29 ± 6	30 ± 7	0.269*	29 ± 6	32 ± 7	0.002*
GDF-15, ng/L	9506 (4438–18,596)	10,659 (3589–31,859)	9112 (4532–17,120)	0.411#	10,342 (5068–23,779)	8860 (4222–15,522)	0.173#	10,723 (5323–22,634)	6607 (2664–13,284)	0.005#

Results are presented as numbers (n) and percentages (%), mean ± standard deviation (SD) for normally distributed variables and median with inter quartile range (IQR) for non-normally distributed variables. BMI, body mass index; MI, myocardial infraction; CABG, coronary artery bypass grafting; HF, heart failure; ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; CRP, C-reactive protein; AFOS, alkaline phosphatase; GGT, gamma glutamyl transferase; GDF-15, Growth differentiation factor 15; † All patients (n = 165) of the CardShock study cohort; * Student t-test; # Mann-Whitney *U* test; ^ χ2-test.

etiologies other than ACS are in place. Another intriguing question is whether miR-20b-5p has therapeutic potential in cardiogenic shock. Further studies using miRNA mimics are therefore warranted.

5. Conclusions

The results of the current study indicate that circulating levels of miR-20b-5p at baseline could help assessment of in-hospital and 90-day survival in CS patients.

CRediT authorship contribution statement

Tuomas Mäntylä: Writing – review & editing, Writing – original draft, Visualization, Investigation, Funding acquisition, Formal analysis. **Chunguang Wang:** Writing – review & editing, Formal analysis. **Mikko Hänninen:** Writing – review & editing, Data curation. **Katariina Immonen:** Writing – review & editing, Investigation, Formal analysis. **Toni Jäntti:** Writing – review & editing, Investigation. **Johan Lassus:** Writing – review & editing, Investigation. **Ilkka Tikkanen:** Writing – review & editing, Funding acquisition. **Kari Pulkki:** Writing – review & editing, Supervision. **Yvan Devaux:** Writing – review & editing, Methodology. **Veli-Pekka Harjola:** Writing – review & editing, Investigation, Conceptualization. **Päivi Lakkisto:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

Yvan Devaux holds patents on RNA biomarkers of cardiovascular disease, is a member of the Scientific Advisory Board of Firalis SA, and is a member of the Editorial Board of The Journal of Molecular and Cellular Cardiology Plus. The other authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmccpl.2025.100284.

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