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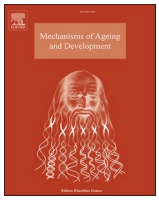

Circulating miR-483–5p predicts long term all-cause mortality in hospitalized older adults

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ABSTRACT

Accurately predicting long-term mortality in older adults remains challenging, as chronological age and conventional clinical indices incompletely capture biological vulnerability. Circulating microRNAs (miRNAs) have emerged as potential biomarkers of aging-related pathophysiology, but their long-term prognostic value remains poorly defined. In this prospective observational study nested within the Report-AGE cohort, we evaluated whether selected circulating miRNAs predict 10-year all-cause mortality in hospitalized adults aged ≥ 65 years. Baseline circulating levels of miR-483–5p, miR-320b, miR-21–5p, and miR-146a-5p were measured in 648 participants and categorized into tertiles. During follow-up, 525 deaths occurred. Among the four miRNAs examined, higher circulating levels of miR-483–5p were associated with increased mortality. In fully adjusted Cox models accounting for demographic characteristics, comorbidity burden, polypharmacy, renal function, hematological indices, inflammatory parameters, albumin, and calcium, participants in the highest miR-483–5p tertile had significantly higher mortality risk than those in the lowest tertile. This association remained robust after exclusion of individuals with chronic kidney disease. In exploratory analyses, miR-483–5p and miR-320b showed stronger associations with Phenotypic Age acceleration than with chronological age. Addition of miR-483–5p modestly improved mortality discrimination at early and intermediate follow-up. These findings suggest that circulating miR-483–5p is associated with mortality and may reflect biological vulnerability in late life.

1. Introduction

Aging is associated with progressive accumulation of multimorbidity and frailty, while the clinical management of multiple chronic conditions frequently leads to polypharmacy, together contributing to disproportionate mortality risk in older adults (Vetrano et al., 2019). However, accurately predicting long-term outcomes in this population remains challenging, as standard clinical indices only partially capture the biological decline underlying aging trajectories (Provost et al., 2025). Identifying biomarkers able to quantify the biological dimension of aging and refine prognostic stratification is therefore a major research priority in geriatric medicine (Moqri et al., 2024).

MicroRNAs (miRNAs, miRs) are small non-coding RNAs that regulate post-transcriptional gene expression and participate in a wide range of cellular pathways. Altered miRNA expression has been consistently reported in major chronic diseases of late life, suggesting that miRNA dysregulation reflects the biological burden of disease (Mensa et al., 2019; Sbriscia et al., 2025; Turko et al., 2025). In particular, circulating

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microRNAs may serve as minimally invasive biomarkers of pathological states that ultimately influence mortality risk (Fehlmann et al., 2020). Large population-based analyses such as in the Framingham Heart Study, composite measures of whole-blood miRNA expression predictive of 'miRNA age' were associated with all-cause mortality independent of chronological age, underscoring the potential utility of miRNA profiles for mortality prediction in human populations (Huan et al., 2018).

In previous work, we tested whether selected circulating microRNAs could predict short-term in-hospital mortality in the context of acute COVID-19. In that setting, two miRNAs - i.e. miR-483–5p and miR-320b - exhibited prognostic value during the acute phase of infection, suggesting that miRNA dysregulation may capture clinically relevant host responses associated with mortality risk in the short term (Giuliani et al., 2022). Consistently, in a separate cohort of hospitalized COVID-19 patients, we showed that reduced circulating levels of the inflammaging-associated microRNA miR-146a-5p were associated with worse clinical outcomes, identifying patients with poor response to IL-6 receptor blockade and higher short-term mortality risk (Sabbatinelli et al., 2021). Based on this prior evidence, miR-483–5p, miR-320b, and miR-146a-5p were selected for the present study to investigate whether their prognostic relevance extends beyond acute systemic illness to long-term mortality in older adults. MiR-21–5p was additionally included as a canonical inflammaging-related microRNA and biologically relevant comparator (Olivieri et al., 2021).

Despite this emerging evidence, whether circulating miRNAs can also predict long-term mortality in older adults, a population in which chronic pathology, multimorbidity and frailty shape survival trajectories, remains largely unexplored. In particular, no studies to date have assessed the long-term prognostic value of circulating miR-483–5p and miR-320b in community-dwelling older individuals, nor clarified whether it can complement classical clinical predictors of mortality over extended time horizons.

To address these gaps, we prospectively investigated whether a prespecified panel of circulating miRNAs, i.e. miR-483–5p, miR-320b, miR-21–5p, and miR-146a-5p, predict 10-year all-cause mortality in a well-characterized geriatric cohort. We further evaluated whether the prognostic contribution of miR-483–5p was independent of demographic, biochemical and functional covariates traditionally associated with mortality risk, and assessed its incremental discriminative value over a clinical model using time-dependent ROC curves.

2. Methods

2.1. Study design and participants

This prospective observational study was conducted within the framework of the Report-AGE project (ClinicalTrials.gov identifier: NCT01397682), an ongoing epidemiological cohort investigating clinical and biological determinants of outcomes in hospitalized older adults (Bustacchini et al., 2015). Patients aged 65 years or older admitted to acute care wards (including geriatric medicine, cardiology, urology, surgery, and neurology) at three Italian IRCCS INRCA hospitals were consecutively enrolled between September 2011 and October 2021. Over the enrolment period, more than 5000 patients were recruited, with written informed consent obtained from over 90% of eligible individuals. The present investigation was designed as a predefined substudy and included approximately 650 patients with available biological samples collected and stored according to standardized procedures. This subset was selected to be representative of the overall cohort with respect to key demographic and clinical characteristics, including mean age, sex distribution, and vital status at follow-up.

Eligibility criteria for the Report-AGE cohort included age $\geq$ 65 years, a hospital stay of at least 24 h, and the ability to provide informed consent. Patients with hematological malignancies or active COVID-19 were excluded. For the purposes of the present analysis, patients who died during the index hospitalization were excluded in order to reduce potential bias related to acute conditions. Mortality data were obtained through hospital discharge records and linkage with national registries, ensuring complete ascertainment of vital status without the need for active follow-up. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committees of the IRCCS INRCA network. All participants provided written informed consent prior to enrolment; as a consequence, individuals with severe cognitive impairment or impaired consciousness may be underrepresented.

2.2. microRNA assessment

Selected miRNAs were reverse transcribed using the TaqMan miRNA Reverse Transcription Kit (Life Technologies, Carlsbad, CA, United States) as recommended by the manufacturer and quantified by a miRNA assay (Applied Biosystems, Foster City, CA, USA).

Synthetic cel-miR-39–3p was spiked-in before RNA isolation for normalization in subsequent qRT-PCR. Relative quantification was performed using the $2^{-\Delta C_t}$ method ($\Delta C_t = C_t$microRNA – $C_t$cel-miR-39–3p). Relative expression (RE) of each miRNA was expressed as arbitrary units.

2.3. Covariates

Comorbidities were recorded and coded according to the International Classification of Diseases, Ninth Revision (ICD-9), as follows: AMI: 410–414, CHF: 428; CeVD: 430–438; Dementia: 290; 331; 294; Depression: 296; COPD: 491; 492; 494; 496; Parkinson: 332; Hypertension: 401–405; CKD: 585; 586; 587; Anemia: 280–285; 790; 6842; Diabetes: 2500–2507; Cancer: 140–172; 174–195; 200–208. The category 'Dementia' referred to patients with mild to moderate cognitive impairment, with preserved decisional capacity and ability to provide informed consent. Multimorbidity was assessed using the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). Polypharmacy was defined as the simultaneous use of five or more medications.

Complete blood count with differential, and serum concentrations C-reactive protein (CRP), D-dimer, sodium, potassium, procalcitonin, were measured by standard procedures. Serum IL-6 was determined by using the high-sensitivity ProQuantum qPCR immunoassay (Thermo Fisher) measured on the Aria Mix real-time PCR system (Agilent) following the manufacturer's protocol. Each sample was assayed in duplicate. GFR was estimated according to the Berlin Initiative Study (BIS1) equation (Schaeffner et al., 2012).

Phenotypic Age (PhenoAge) was calculated according to the clinical biomarker-based algorithm proposed by Levine et al. (2018). The algorithm combines chronological age with nine routinely available laboratory parameters: albumin, creatinine, glucose, C-reactive protein, lymphocyte percentage, mean corpuscular volume, red cell distribution width, alkaline phosphatase, and white blood cell count. Laboratory values were harmonized to the units required by the original algorithm before calculation. PhenoAge acceleration was defined as the difference between PhenoAge and chronological age, with positive values indicating an older biological age relative to chronological age.

2.4. Statistical analysis

Continuous variables are reported as medians and interquartile ranges (IQRs), while categorical variables are presented as absolute counts and percentages. Distributional assumptions were evaluated using the Shapiro–Wilk test. Comparisons between survivors and non-survivors were performed using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. Differences in circulating microRNA levels according to sex and major comorbid conditions were assessed using Dunn's post hoc test with Benjamini–Hochberg correction for multiple comparisons. Associations between age and circulating microRNA levels were assessed using

Spearman rank correlation coefficients. For subsequent survival analyses, microRNA levels were categorized into tertiles based on their distribution.

The association between circulating microRNAs and 10-year all-cause mortality was investigated using Kaplan–Meier survival estimates with log-rank tests and Cox proportional hazards regression models. Multivariable Cox proportional hazards models were adjusted for demographic characteristics, overall comorbidity burden, medication use, and laboratory parameters selected on the basis of their significant differences between survivors and non-survivors. Results are reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Potential multicollinearity among covariates included in multivariable Cox models was evaluated by calculating variance inflation factors (VIFs) from auxiliary linear regression models. All VIF values were below 2, indicating no relevant collinearity. Restricted cubic spline functions were applied within multivariable Cox proportional hazards models to explore potential non-linear associations between circulating microRNA levels and all-cause mortality. Predicted hazard ratios were estimated while holding all other covariates constant at their median values for continuous variables and at reference categories for categorical variables.

Model discrimination for mortality was assessed using time-dependent area under the curve (AUC) analyses derived from Cox models. AUCs and corresponding 95% CIs were estimated using the timeROC R package, and pairwise comparisons were performed using a DeLong-type test for correlated AUCs. All statistical analyses were conducted using R version 4.4.3, and a two-sided p value < 0.05 was considered statistically significant.

Table 1
Baseline characteristics of the study population.

Variables	All patients (n = 648)	Survivors (n = 123)	Deceased (n = 525)	P-value
Age (years), median (IQR)	84.0 (79.0–88.0)	78.0 (73.0–83.0)	85.0 (81.0–88.0)	< 0.001
PhenoAge acceleration (years), median (IQR)	7.20 (-2.26 – 16.31)	-1.53 (-7.17 – 9.52)	9.01 (-0.08 – 17.17)	< 0.001
Sex, n (%)				
Male	307 (47.4%)	51 (41.5%)	256 (48.8%)	0.174
Female	341 (52.6%)	72 (58.5%)	269 (51.2%)	-
Blood parameters				
Albumin (g/dL), median (IQR)	3.70 (3.20–4.10)	4.00 (3.60–4.30)	3.60 (3.20–4.00)	< 0.001
eGFR (BIS1, mL/min), median (IQR)	61.00 (42.00–78.00)	72.00 (62.00–84.00)	57.00 (39.00–75.00)	< 0.001
NLR, median (IQR)	3.62 (2.23–6.15)	2.53 (1.94–4.54)	3.87 (2.37–6.36)	< 0.001
AST (U/L), median (IQR)	17.00 (14.00–23.00)	17.00 (15.00–22.00)	17.00 (14.00–24.00)	0.097
ALT (U/L), median (IQR)	13.00 (10.00–21.00)	14.00 (11.00–22.00)	13.00 (10.00–20.00)	0.016
GGT	23.50 (15.00–46.25)	20.00 (14.00–42.00)	25.00 (15.00–48.00)	0.265
Haemoglobin (g/dL), median (IQR)	12.20 (10.70–13.50)	13.20 (11.85–14.10)	11.90 (10.50–13.20)	< 0.001
RBC ($x10^6/mm^3$)	4.14 (3.68–4.50)	4.34 (3.98–4.66)	4.05 (3.61–4.47)	< 0.001
Platelets ($x10^3/mm^3$), median (IQR)	208.00 (164.00–263.25)	202.00 (170.00–248.00)	211.00 (162.00–267.00)	0.454
WBC (10^3 μL / μL), median (IQR)	7.24 (5.73–9.47)	6.64 (5.35–8.80)	7.40 (5.78–9.66)	0.023
Urea (mg/dL)	45.00 (34.00–64.00)	37.00 (30.00–47.00)	46.00 (35.25–71.75)	< 0.001
Creatinine (mg/ dL)	1.00 (0.80–1.30)	0.80 (0.80–1.00)	1.05 (0.80–1.40)	< 0.001
LDH (U/L)	199.00 (156.50–261.00)	170.50 (138.50–214.50)	210.00 (160.00–263.00)	0.091
Sodium (mEq/L)	139.00 (136.00–141.00)	139.00 (137.00–141.00)	139.00 (136.00–141.00)	0.124
Potassium (mEq/L)	4.10 (3.80–4.50)	4.10 (3.80–4.43)	4.10 (3.80–4.50)	0.695
Chloride (mEq/L)	101.00 (98.00–104.00)	101.00 (99.00–103.48)	101.00 (98.00–104.00)	0.897
Calcium (mg/dL)	8.90 (8.50–9.30)	9.20 (8.70–9.40)	8.90 (8.40–9.30)	< 0.001
Phosphorus (mg/dL)	3.30 (3.00–3.70)	3.30 (2.90–3.70)	3.30 (3.00–3.70)	0.355
Magnesium (mg/dL)	2.00 (1.90–2.20)	2.00 (1.90–2.10)	2.00 (1.90–2.20)	0.75
Glucose (mg/dL), median (IQR)	102.00 (89.00–125.00)	103.00 (93.50–119.50)	102.00 (89.00–126.00)	0.659
Polypharmacy				
Yes	408 (63.0%)	52 (42.3%)	356 (67.8%)	< 0.001
No	240 (37.0%)	240 (37.0%)	169 (32.2%)	
Charlson Index				
0	126 (19.4%)	42 (34.1%)	84 (16.0%)	< 0.001
1	174 (26.9%)	36 (29.3%)	138 (26.3%)	
≥1mir	348 (53.7%)	45 (36.6%)	303 (57.7%)	
Comorbidities				
CHD, n (%)	81 (12%)	7 (5.7%)	74 (14.1%)	0.011
CHF, n (%)	38 (5.9%)	2 (1.6%)	36 (6.9%)	0.026
CeVD, n (%)	213 (32.9%)	42 (34.1%)	171 (32.6%)	0.738
Anemia, n (%)	139 (19.9%)	17 (13.8%)	112 (21.3%)	0.060
Dementia, n (%)	168 (25.9%)	28 (22.8%)	140 (26.7%)	0.374
Depression, n (%)	13 (2%)	6 (4.9%)	7 (1.3%)	0.012
COPD, n (%)	103 (15.9%)	10 (8.1%)	93 (17.7%)	0.009
Diabetes, n (%)		24 (19.5%)	118 (22.5%)	0.474
Parkinson, n (%)	63 (9.7%)	10 (8.1%)	53 (10.1%)	0.508
Hypertension, n (%)	388 (59.9%)	74 (60.2%)	314 (59.8%)	0.943
CKD, n (%)	129 (19.9%)	5 (4.1%)	124 (23.6%)	< 0.001
Cancer, n (%)	88 (13.6%)	11 (8.9%)	77 (14.7%)	0.095
miR-21–5p (RE)	0.0308 (0.0166–0.0610)	0.0274 (0.0166–0.0542)	0.0318 (0.0166–0.0621)	0.453
miR-146a-5p (RE)	0.0029 (0.0015–0.0059)	0.0030 (0.0019–0.0059)	0.0029 (0.0014–0.0059)	0.220
miR-320b (RE)	0.0016 (0.0008–0.0034)	0.0014 (0.0008–0.0026)	0.0017 (0.0008–0.0037)	0.062
miR-483–5p (RE)	0.0007 (0.0002–0.0020)	0.0005 (0.0002–0.0011)	0.0008 (0.0003–0.0025)	< 0.001

ADL Activities of Daily Living, *ALT* Alanine Aminotransferase, *AMI* Acute Myocardial Infarction, *AST* Aspartate Aminotransferase, *BIS1* Berlin Initiative Study 1 equation, *CCI* Charlson Comorbidity Index, *CeVD* Cerebrovascular Disease, *CHF* Congestive Heart Failure, *CKD* Chronic Kidney Disease, *COPD* Chronic Obstructive Pulmonary Disease, *eGFR* Estimated Glomerular Filtration Rate, GGT γ-Glutamil Transferase *IADL* Instrumental Activities of Daily Living, *IQR* Interquartile Range, *NLR* Neutrophil-to-Lymphocyte Ratio, *RE* Relative expression, *WBC* White Blood Cell count. Continuous variables were compared between survivors and non-survivors using the Wilcoxon rank-sum test due to non-normal distribution. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics and follow-up

Baseline characteristics of the study population are reported in Table 1. In the study population (n = 648), a total of 525 deaths occurred during follow-up (81.0%), accounting for a total of 37'849 person-months of observation. The median follow-up duration was 52 months (IQR 17–94) when calculated using the conventional approach, and 128 months (IQR 114–135) when estimated using the reverse Kaplan–Meier method.

Non-survivors were significantly older ($p < 0.001$) and showed higher Phenotypic Age (PhenoAge) acceleration ($p < 0.001$), indicating older biological age relative to chronological age. They were also more frequently exposed to polypharmacy ($p < 0.001$), exhibited higher Charlson comorbidity burden ($p < 0.001$), and were more frequently frail ($p < 0.001$). Several biochemical parameters differed between groups, including albumin, hemoglobin, NLR, and eGFR (all $p < 0.001$). Non-survivors also showed a higher prevalence of CHD, CHF, COPD and CKD ($p \leq 0.05$ for all). Among circulating microRNAs, only miR-483–5p differed between groups, with higher values in non-survivors ($p < 0.001$).

Circulating levels of miR-483–5p, miR-320b, miR-146a-5p, and miR-21–5p did not differ significantly between females and males (all $p > 0.15$). In contrast, Spearman correlation analyses revealed weak associations with age, with miR-483–5p and miR-320b showing modest positive correlations (ρ=0.109, p = 0.005 and ρ=0.082, p = 0.036, respectively), miR-146a-5p showing a weak inverse correlation (ρ=−0.083, p = 0.036), and no association observed for miR-21–5p (ρ=0.005, p = 0.90). To further explore whether these age-related associations reflected biological rather than chronological aging, we performed an exploratory analysis using the PhenoAge acceleration biological aging estimate (Levine et al., 2018). In the subset of patients with complete miRNA and PhenoAge data (n = 614), miR-483–5p showed a stronger positive correlation with Phenotypic Age acceleration than with chronological age (ρ=0.246, p = 6.63 $\times 10^{-10}$). A similar pattern was observed for miR-320b (ρ=0.208, p = 2.06 $\times 10^{-7}$), whereas miR-146a-5p showed a weak inverse correlation (ρ=−0.104, p = 0.010). No significant association was observed for miR-21–5p (ρ=0.036, p = 0.37). Overall, the magnitude of these correlations was higher for PhenoAge acceleration than for chronological age

We next examined whether circulating miRNAs differed according to major chronic comorbidities at baseline. Compared with survivors, deceased patients exhibited higher ln(miR-483–5p) and ln(miR-320b) levels, whereas ln(miR-146a) levels were lower. These differences remained statistically significant after adjustment for multiple testing. No significant differences were observed for ln(miR-21–5p) across comorbidity strata (Supplementary Table 1).

3.2. Survival analysis

Given the skewed distribution of circulating microRNAs and the absence of established biological cut-off values in the literature, relative expression levels were categorized into tertiles (T1–T3) based on the empirical distribution of the study cohort. All four circulating microRNAs were first evaluated in univariable Cox proportional hazards models using tertiles of relative expression. Higher levels of miR-483–5p and miR-320b were significantly associated with 10-year all-cause mortality (both $p < 0.05$), whereas miR-21–5p and miR-146a-5p were not significantly associated with mortality ($p > 0.05$ for both). Given the absence of association for miR-21–5p and miR-146a-5p, these two microRNAs were not included in subsequent multivariable models (Table 2).

Because circulating levels of both miR-483–5p and miR-320b were significantly higher in participants with chronic kidney disease (CKD), multivariable analyses were performed both in the overall cohort and after exclusion of subjects with CKD to assess the robustness of the associations. Both microRNAs were then evaluated in multivariable Cox models including covariates that differed significantly between survivors and non-survivors. Among renal function markers, urea, creatinine, and eGFR were all significantly associated with mortality; however, only eGFR was included in the models to minimize collinearity. Similarly, hemoglobin was selected over red blood cell count due to their strong correlation. Individual comorbid conditions were not entered separately, as overall comorbidity burden was already captured by the Charlson Comorbidity Index.

Table 2
Univariable Cox proportional hazards models evaluating the association between circulating microRNA tertiles and all-cause mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported.

miRNA	All subjects (n = 648)	
	HR (95% CI)	p-value
miR-21–5p, Tertile 1	Ref.	-
miR-21–5p, Tertile 2	1.11 (0.90–1.37)	0.319
miR-21–5p, Tertile 3	1.15 (0.93–1.42)	0.187
miR-146a-5p, Tertile 1	Ref.	-
miR-146a-5p, Tertile 2	0.87 (0.70–1.07)	0.176
miR-146a-5p, Tertile 3	0.84 (0.68–1.03)	0.102
miR-320b, Tertile 1	Ref.	-
miR-320b, Tertile 2	1.05 (0.85–1.30)	0.647
miR-320b, Tertile 3	1.36 (1.11–1.68)	0.004
miR-483–5p, Tertile 1	Ref.	-
miR-483–5p, Tertile 2	1.22 (0.98–1.51)	0.076
miR-483–5p, Tertile 3	1.74 (1.41–2.15)	< 0.001

In the fully adjusted models including all participants, higher levels of miR-483–5p remained independently associated with increased mortality risk (Table 3). Specifically, participants in the highest tertile had a 36% higher hazard of death compared with those in the lowest tertile (T3 vs T1: HR 1.37, 95% CI 1.10–1.70, p = 0.0049), whereas no significant difference was observed for the intermediate tertile (T2 vs T1: p = 0.93). In contrast, miR-320b was not independently associated with mortality after multivariable adjustment (T2 vs T1: p = 0.079; T3 vs T1: p = 0.97; Supplementary Table 2).

A combined multivariable Cox model including both miR-483–5p and miR-320b yielded consistent results. MiR-483–5p remained significantly associated with mortality (T3 vs T1: HR 1.44, 95% CI 1.14–1.82, p = 0.0023), whereas miR-320b did not reach statistical significance. Comparable estimates were obtained after exclusion of participants with CKD, with miR-483–5p remaining significantly associated with mortality and miR-320b remaining non-significant (Table 4).

Restricted cubic spline analyses indicated significant non-linear associations between circulating levels of miR-483–5p and miR-320b and all-cause mortality (p for non-linearity = 0.005 and p = 0.034, respectively). For miR-483–5p, higher levels above the median of the distribution were associated with increased mortality risk. For miR-320b, the hazard ratio exceeded unity only at higher standardized values, with the lower bound of the 95% confidence interval crossing HR= 1 at approximately 1.2 standard deviations above the mean (Fig. 1).

Kaplan–Meier curves stratified by tertiles of circulating miR-483–5p showed significantly different survival trajectories, with the highest tertile exhibiting markedly reduced survival compared with the lower two tertiles (log-rank $p < 0.0001$) (Fig. 2**A**). Kaplan–Meier curves stratified by tertiles of miR-320b also showed significant separation, with the highest tertile having poorer survival (log-rank $p = 0.0069$), although this association did not persist after multivariable adjustment (Fig. 2**B**).

Time-dependent ROC curves (Fig. 3) were used to assess the incremental discriminative value of miR-483–5p beyond a clinical model including age, sex, comorbidity burden, renal and hematological indices, nutritional status, inflammatory markers and polypharmacy. Addition of miR-483–5p led to a statistically significant, although

Table 3
Multivariable Cox proportional hazards models evaluating the association between circulating miR-483–5p tertiles and all-cause mortality, adjusted for demographic characteristics, overall comorbidity burden, medication use, and laboratory parameters. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported.

Variable	All subjects (n = 648)		CKD excluded (n = 519)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
miR-483–5p, Tertile 1	Ref.	-	Ref.	-
miR-483–5p, Tertile 2	1.01 (0.81–1.26)	0.928	1.05 (0.82–1.34)	0.695
miR-483–5p, Tertile 3	1.37 (1.10–1.70)	0.005	1.51 (1.18–1.93)	**0.001**
Sex, Female	Ref.	-	Ref.	-
Sex, Male	1.43 (1.19–1.71)	< 0.001	1.52 (1.23–1.88)	< 0.001
Charlson index, 0	Ref.	-	Ref.	-
Charlson index, 1	1.22 (0.92–1.62)	0.163	1.21 (0.91–1.61)	0.196
Charlson index, > 1	1.47 (1.14–1.90)	0.003	1.62 (1.23–2.13)	0.001
Polypharmacy	1.36 (1.12–1.65)	0.002	1.35 (1.09–1.67)	0.006
Age	1.05 (1.04–1.07)	< 0.001	1.05 (1.03–1.07)	< 0.001
WBC	1.01 (0.98–1.04)	0.471	1.00 (0.96–1.03)	0.815
NLR	1.00 (0.99–1.02)	0.773	1.02 (1.00–1.04)	0.060
Hgb	0.93 (0.88–0.99)	0.019	0.93 (0.87–1.00)	0.047
Platelets (10^3/mm3)	1.00 (0.99–1.01)	0.543	1.00 (0.99–1.01)	0.96
eGFR (10 mL/min)	0.94 (0.90–0.99)	0.012	0.94 (0.89–1.00)	0.05
Albumin	0.61 (0.48–0.77)	< 0.001	0.55 (0.42–0.72)	< 0.001
ALT	0.99 (0.97–1.01)	0.193	0.99 (0.97–1.01)	0.189
Calcium	1.12 (0.96–1.31)	0.144	1.21 (1.01–1.47)	0.044

Table 4
Multivariable Cox proportional hazards models including both miR-483–5p and miR-320b tertiles, evaluating their independent association with all-cause mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported.

Variable	All subjects (n = 648)		CKD excluded (n = 519)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
miR-483–5p, Tertile 1	Ref.		Ref.	
miR-483–5p, Tertile 2	1.06 (0.85–1.32)	0.629	1.08 (0.84–1.38)	0.540
miR-483–5p, Tertile 3	1.44 (1.14–1.82)	0.002	1.56 (1.20–2.03)	0.001
miR-320b, Tertile 1	Ref.		Ref.	
miR-320b, Tertile 2	0.78 (0.63–0.98)	0.031	0.84 (0.66–1.08)	0.174
miR-320b, Tertile 3	0.86 (0.68–1.09)	0.210	0.91 (0.70–1.18)	0.494
Sex, Female	Ref.		Ref.	
Sex, Male	1.44 (1.20–1.74)	< 0.001	1.53 (1.24–1.89)	< 0.001
Charlson index, 0	Ref.		Ref.	
Charlson index, 1	1.25 (0.94–1.65)	0.128	1.22 (0.92–1.63)	0.169
Charlson index, > 1	1.51 (1.16–1.95)	0.002	1.63 (1.23–2.14)	0.001
Polypharmacy	1.37 (1.13–1.66)	0.001	1.36 (1.10–1.68)	0.005
Age	1.05 (1.04–1.07)	< 0.001	1.05 (1.03–1.07)	< 0.001
WBC	1.01 (0.98–1.04)	0.522	0.99 (0.96–1.03)	0.795
NLR	1.00 (0.99–1.02)	0.800	1.02 (1.00–1.04)	0.061
Hgb	0.93 (0.88–0.99)	0.014	0.93 (0.87–1.00)	0.044
Platelets (10^3/mm3)	1.00 (0.98–1.01)	0.536	1.00 (0.99–1.01)	0.960
eGFR (10 mL/min)	0.94 (0.90–0.99)	0.010	0.94 (0.89–1.00)	0.059
Albumin	0.60 (0.48–0.76)	< 0.001	0.55 (0.41–0.72)	< 0.001
ALT	0.99 (0.97–1.01)	0.198	0.99 (0.97–1.01)	0.192
Calcium	1.11 (0.95–1.30)	0.196	1.20 (1.00–1.45)	0.053

modest, improvement in discrimination at 1 year ($p = 0.0484$) and more pronounced improvements at intermediate time horizons, with significant increases in AUC at 3 years ($p \approx 0.03$) and 4 years ($p \approx 0.02$). No significant benefit was observed at later time points, where the accuracy of the two models tended to converge. At 3 years, the clinical model had an AUC of 0.76 compared with 0.77 after inclusion of miR-483–5p; at 4 years, AUC increased from 0.77 to 0.78.

4. Discussion

In this prospective cohort of hospitalized older adults, we found that higher circulating levels of miR-483–5p were associated with increased long-term all-cause mortality over a 10-year follow-up. This association remained significant after adjustment for chronological age, multimorbidity, renal function, nutritional status, inflammatory markers and polypharmacy, and was robust to the exclusion of participants with chronic kidney disease. Among the four candidate microRNAs investigated, miR-483–5p was the only marker independently associated with mortality, whereas miR-320b showed weaker, non-independent associations and miR-21–5p and miR-146a-5p were not associated with long-term survival.

Evidence linking circulating microRNAs to mortality in humans remains limited and heterogeneous. Most available studies focus on short-term outcomes, disease-specific events or composite endpoints rather than long-term all-cause mortality. To our knowledge, no prior study has evaluated the long-term prognostic value of circulating miR-483–5p in older individuals. Previous work has linked miR-483–5p to short-term mortality in acute systemic illness, including COVID-19 (Giuliani et al., 2022), and to pathological phenotypes relevant to aging biology such as fibrosis, endothelial dysfunction (He et al., 2017; Zhu et al., 2023), metabolic dysregulation (Nagaraj et al., 2024; Wlodarski et al., 2020) and oxidative stress (Zhang et al., 2023). Our results extend these observations to a chronic prognostic context and suggest that miR-483–5p may reflect persistent multisystem biological changes that influence survival trajectories beyond acute stress.

These findings are consistent with earlier population-based studies demonstrating that circulating miRNA expression profiles can predict all-cause mortality independently of chronological age. For example, composite miRNA signatures from whole blood were associated with incident mortality and cardiovascular disease in the Framingham Heart Study (Karlin et al., 2024), suggesting that miRNAs constitute molecular correlates of biological aging. Other population cohorts, including those from Rotterdam and Uppsala, have reported miRNA associations with incident chronic disease and mortality, although the specific miRNAs differed across studies, likely due to methodological heterogeneity in specimen type, normalization strategies and age structure. The present study differs in that it focuses exclusively on very old individuals, a population in whom mortality risk is driven by multimorbidity and frailty, and further influenced by treatment complexity, including polypharmacy, and in whom non-invasive biomarkers for prognostication are particularly scarce.

The biological plausibility of miR-483–5p as a marker of long-term vulnerability is supported by mechanistic evidence linking this

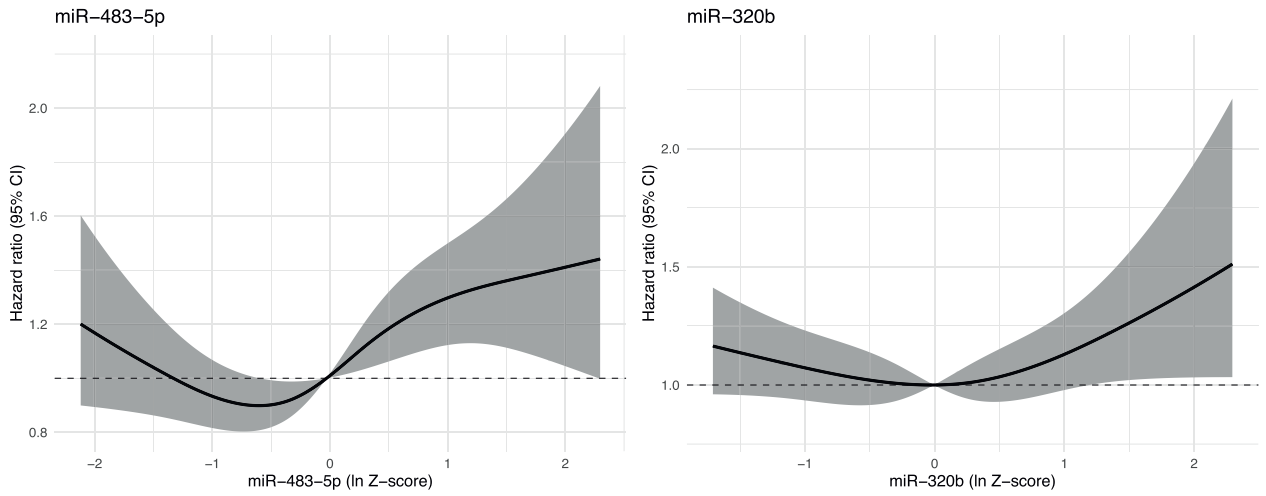

Fig. 1. Restricted cubic spline curves showing the association between circulating levels of miR-483–5p (left panel) and miR-320b (right panel) and all-cause mortality. Hazard ratios (solid lines) and 95% confidence intervals (shaded areas) were estimated from multivariable Cox proportional hazards models and are shown relative to the reference value (HR = 1).

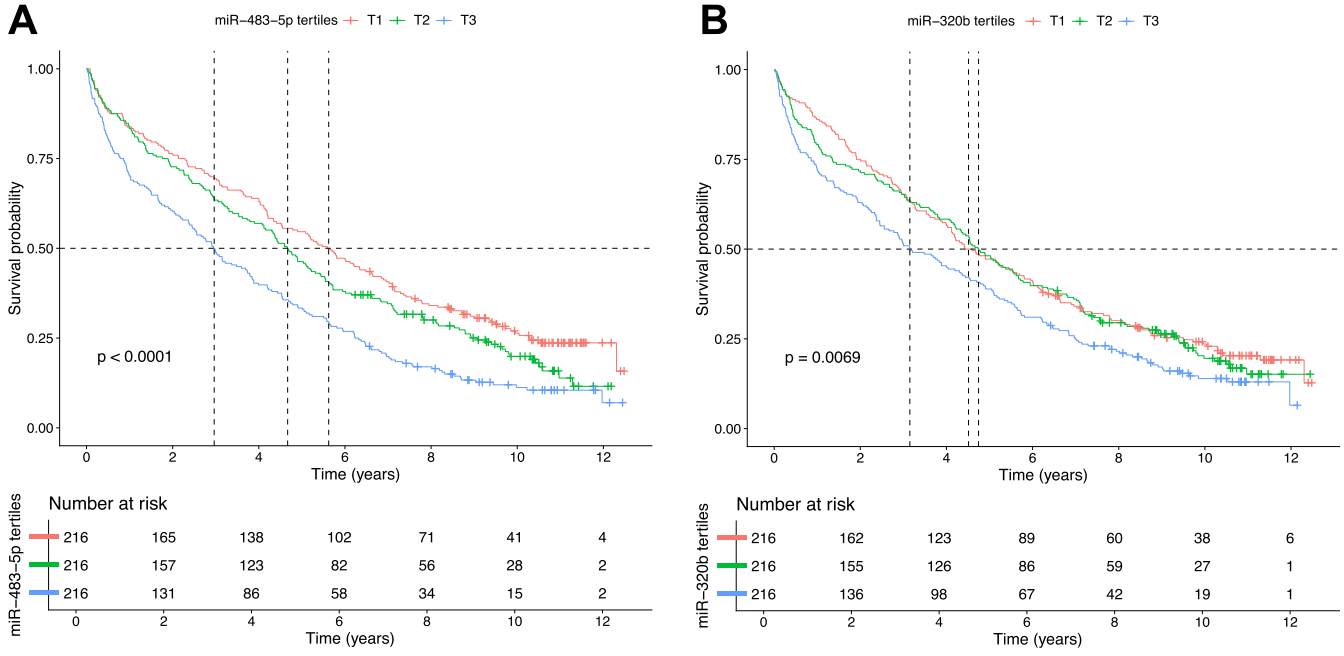

Fig. 2. Kaplan-Meier survival curves stratified by tertiles of circulating **(A)** miR-483–5p and **(B)** miR-320b. Differences in survival across tertiles were assessed using the log-rank test. Numbers at risk are shown below each plot. Dashed lines indicate the 50% survival probability and the median survival time for each tertile when reached.

microRNA to pathways involved in metabolic regulation, fibrosis, vascular dysfunction and tissue remodeling. MiR-483–5p is encoded within an intronic region of the IGF2 gene and has been implicated in the modulation of IGF and TGF-β signaling, insulin sensitivity, extracellular matrix dynamics and endothelial homeostasis (Matson et al., 2023). Dysregulation of these pathways has been consistently associated with aging-related conditions, including diabetes, cardiovascular disease, chronic kidney disease and frailty. In line with this framework, circulating miR-483–5p levels have been reported to be elevated in metabolic and cardiovascular disorders and to correlate with disease severity rather than with isolated clinical events (Matson et al., 2023; Zhao et al., 2023).

Renal function deserves particular consideration, as circulating levels of miR-483–5p were higher in participants with chronic kidney disease. Given the strong association between renal dysfunction and mortality in older adults, this raised the possibility of confounding. However, the association between miR-483–5p and mortality persisted after adjustment for eGFR and remained significant after exclusion of participants with chronic kidney disease, suggesting that impaired renal clearance alone does not fully explain the observed relationship. Rather, kidney disease may represent one of several clinical contexts in which miR-483–5p reflects broader biological vulnerability.

Exploratory analyses further suggested that miR-483–5p may be linked to biological rather than chronological aging. Indeed, miR-483–5p correlated more strongly with PhenoAge acceleration than with age itself, supporting its potential role as a marker of systemic vulnerability rather than of a specific disease phenotype. This interpretation is consistent with recent population-based evidence showing that plasma miRNA signatures are associated with PhenoAge, frailty, and mortality, and that miRNA-based aging biomarkers trained on health-related

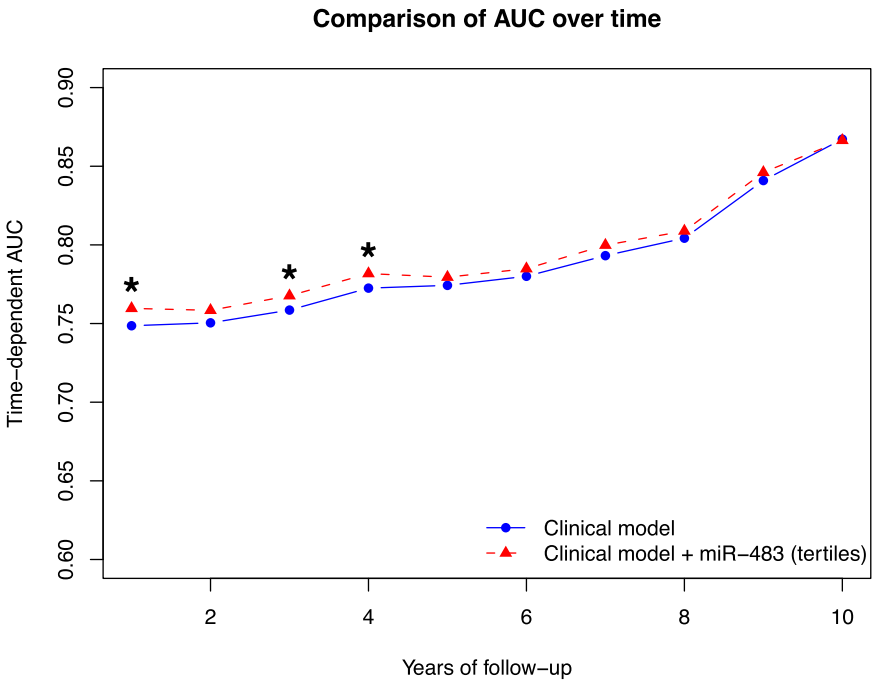

Fig. 3. Time-dependent AUC for all-cause mortality comparing a clinical model including age, sex, polypharmacy, Charlson Comorbidity Index, and laboratory parameters, and the same model with the addition of miR-483–5p tertiles. Asterisks denote time points with statistically significant differences between models.

outcomes may better capture adverse aging phenotypes than those trained on chronological age alone (Kuiper et al., 2025). This finding should be considered hypothesis-generating and requires validation in independent cohorts, ideally including methylation-based aging clocks.

Interestingly, canonical inflammation-related microRNAs did not predict long-term mortality in this cohort. MiR-146a-5p and miR-21–5p have been extensively linked to inflammaging, immune regulation and age-related diseases, and have shown prognostic relevance in acute inflammatory and cardiovascular settings (Olivieri et al., 2021; Xiao et al., 2021). However, their lack of association with long-term mortality in the present study suggests that chronic mortality risk in late life is not simply the cumulative result of inflammatory burden, but rather reflects the integration of metabolic, structural and functional decline across multiple systems.

From a prognostic point of view, the incremental discriminative value of miR-483–5p beyond a comprehensive clinical model was statistically significant and mainly confined to early and intermediate follow-up horizons. This pattern is consistent with the multifactorial nature of mortality in advanced age, where the contribution of any single biomarker is necessarily limited and progressively diluted by competing risks, intercurrent events and care-related factors. Importantly, these findings do not support the use of miR-483–5p as a standalone prognostic tool or as a biomarker ready for clinical implementation. Instead, miR-483–5p should be viewed as a biological signal capturing dimensions of vulnerability that are incompletely reflected by traditional clinical and laboratory measures.

Several limitations should be acknowledged. The observational design precludes causal inference, and mechanistic data linking circulating miR-483–5p levels to tissue-specific aging processes were not available. The microRNA panel was limited to four candidates selected a priori, and broader profiling may identify multimarker signatures with greater predictive value. In addition, the cohort consisted of hospitalized older adults who were able to provide informed consent, potentially limiting generalizability to more severely impaired populations. Finally, external validation in independent cohorts is required before firm conclusions can be drawn.

In conclusion, this study identifies circulating miR-483–5p as an independent correlate of long-term mortality in older adults, extending previous observations from acute illness to a chronic aging context. While the prognostic impact is modest, the findings support the concept that specific circulating microRNAs may reflect cumulative biological vulnerability in late life. Future studies should focus on replication, longitudinal assessment and integration of miRNAs with functional, clinical and molecular aging phenotypes, rather than on premature clinical translation.

CRediT authorship contribution statement

Chiara Giordani: Data curation. **Angelica Giuliani:** Writing – original draft, Visualization, Supervision. **Dalila Colombaretti:** Investigation. **Jacopo Sabbatinelli:** Writing – original draft, Visualization. **Mirko Di Rosa:** Data curation. **Fabiola Olivieri:** Supervision, Conceptualization. **Matilde Sbriscia:** Investigation. **Fabrizia Lattanzio:** Writing – review & editing, Project administration. **Deborah Ramini:** Investigation, Conceptualization. **Iryna Rusanova:** Writing – review & editing. **Silvia Di Valerio:** Investigation. **Rina Recchioni:** Writing – review & editing, Supervision. **Francesca Marchegiani:** Writing – review & editing. **Sonia Fantone:** Data curation. **Giulia Matacchione:** Investigation, Data curation. **Francesco Piacenza:** Writing – review & editing, Data curation.

Consent for publication

Not applicable.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mad.2026.112190.

Data availability

Data will be made available on request.

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