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High long-term mortality in ischaemic heart disease accentuated among ethnic minorities in Eastern Europe: findings from a prospective all-comers percutaneous coronary intervention registry in Romania

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ABSTRACT

Background Long-term outcomes in cardiovascular diseases are historically under-reported in Eastern Europe. Our aim was to report long-term survival and to identify survival predictors in a prospective Romanian percutaneous coronary intervention (PCI) registry, with an emphasis on important under-resourced minorities, such as Hungarian and Roma ethnicities.

Methods An all-comers patient population treated by PCI in a tertiary cardiovascular centre that has been included prospectively in the local registry since January 2016 was analysed. Cardiovascular cause and all-cause mortality data were available as of December 2023.

Results A total of 6867 patients with 8442 PCI procedures were included. Romanian group consisted of 5095 (74.2%) patients, the Hungarian group consisted of 1417 (20.6%) patients and the Roma group consisted of 355 (5.1%) patients. During a median follow-up of 3.60 (1.35–5.75) years, a total of 1064 cardiovascular-cause and 1374 all-cause events occurred. Romanian, Hungarian and Roma patients suffered 5.12, 5.89 and 7.71 all-cause deaths per 100 patient-years, respectively. Romanian, Hungarian and Roma patients suffered 3.94, 4.63 and 6.22 cardiovascular-cause deaths per 100 patient-years, respectively. Both Hungarian and Roma patients presented significantly higher all-cause mortality than Romanian patients (adjusted HR (aHR)=1.20 (1.05–1.36), p=0.005 and aHR=1.51 (1.21–1.88), p=0.0001). Similarly, Hungarian and Roma patients presented significantly higher cardiovascular cause mortality than Romanian patients (aHR=1.22 (1.05–1.41), p=0.006 and aHR=1.51 (1.18–1.92), p=0.0008).

Conclusions High long-term cardiovascular and all-cause mortality was observed for the entire included population. Long-term survival was significantly lower in ethnic minorities, such as the Hungarian and Roma minority than in the Romanian population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long-term mortality in ischaemic heart disease in Eastern Europe is estimated to be high, however, reports rely on aggregated country-specific data and not individual patient-level data.

WHAT THIS STUDY ADDS

⇒ In an all-comers prospective percutaneous coronary interventions registry from Romania, all-cause deaths occurred in 5.40 cases per 100 patient-years, while cardiovascular-cause deaths occurred in 4.19 cases per 100 patient-years. The crude incidence rate is more than double that reported in Western registries.

⇒ Mortality was higher in ethnic minorities such as Roma or Hungarian minority and ethnicity was an independent predictor of events, even after adjusting for potential confounders.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results should encourage clinical practice and policymakers to increase primary prevention efforts since such minorities had a higher burden of risk factors.

INTRODUCTION

Ischaemic heart disease is the leading cause of death and premature mortality, both worldwide and in Europe.[1] However, data regarding long-term outcomes of not only ischaemic heart disease, but of any cardiovascular disease is typically scarce in Eastern Europe. Reports on morbidity and mortality in cardiovascular diseases from Eastern Europe usually rely on aggregated country-specific data and not individual patient-level data.[1 2] Moreover, individual patient-level reports regarding sex-based, race-based and ethnicity-based differences or long-term outcomes in cardiovascular disease are practically absent in Eastern Europe.

Regarding social and economic differences, there are important disparities between Eastern Europe and Western countries. Romania, one of the main Eastern European countries, had 34% of the population at risk of poverty or social exclusion, which is the highest in the European Union (EU) and approximately 70% higher than in Western Europe.[3] According to the 2021 census, the population of Romania consists of 9.3% minorities, of

which 6.6% is the Hungarian minority and 2.46% is the Roma minority.[4] While data on the Roma minority in Romania and across the EU is scarce, the Fundamental Rights Report 2019 revealed an increase in segregation and persistence of anti-gypsyism in the EU.[5] Similarly, data related to health disparities in such minorities is lacking. The county where our tertiary hospital is located had the highest percentage of Roma minority in Romania as reported by the 2021 census.[4] Moreover, the affiliated counties for the acute coronary syndrome (ACS) treating network that our tertiary hospital is responsible for have the highest percentage of Hungarian minorities in Romania.[4] Thus, a minority-focused individual patient report would be of interest, given our location in the most ethnically heterogenous region of Romania.

The aim of this study was to report long-term survival outcomes in an all-comers prospective percutaneous coronary intervention (PCI) population in Romania. Differences among ethnic minorities, in terms of comorbidities, clinical presentation, coronary artery disease (CAD) complexity, PCI procedural characteristics and survival rates were also investigated.

MATERIALS AND METHODS

Patient inclusion

The present all-comers prospective PCI registry was previously described.[6] Briefly, all patients older than 18 years and treated by PCI in the Emergency Institute for Cardiovascular Diseases and Transplantation of Targu Mures have been included prospectively at hospital discharge in the local PCI registry of the institute since January 2016. The registry is accessible online at the website http://pci.cardio.ro/ and is based on the criteria of Cardiology Audit and Registration Data Standards developed by the Department of Health and Children, European Society of Cardiology, Irish Cardiac Society and the European Commission.[7] All the information available regarding all the variables proposed in that document was collected for each included patient, at every PCI. All patients available in the registry as of December 2023 were included in the present analysis.

Research ethics

All patients (or their legal representatives) signed the informed consent regarding the PCI procedure and their participation in the study. The protocol was carried out in accordance with the ethical principles for medical research involving human subjects established by the Declaration of Helsinki, protecting the confidentiality of personal information of the patients.

Follow-up and clinical outcomes

The clinical endpoint of this study was the incidence of cardiovascular cause and all-cause mortality. In-hospital mortality data was available from the PCI registry. Romanian National Health Insurance Service (NHIS) database supplied mortality rates as of 31 December 2023 for all the patients. For patients who had died during follow-up, Regional Statistics Office of the Romanian National Institute of Statistics supplied the exact date and cause of death according to the 10th revision of the International Classification of Diseases. If the cause of death belonged to diseases of the circulatory system, then death was considered to be of cardiovascular cause.

Ethnicity background

Included patients were categorised according to the three most common and important ethnic groups that comprise over 97% of Romania's population—Romanian, Hungarian and Roma (colloquially referred to as Gypsy) ethnicities.[4] Categorisation was performed by an algorithmic analysis of the origin of the last name, since ethnic background can be particularly saliently derived from anthroponyms in Romania.[8]

Statistical analysis

A significance level α of 0.05 and a 95% CI were considered. All tests were two-sided. Continuous variables were evaluated for normal distribution using the Shapiro-Wilk test. Continuous variables with parametric distributions were reported as mean±SD and compared using non-paired Student's t-test, while continuous variables with non-parametric distributions and discrete variables were reported as median (IQR) and compared using Mann-Whitney U test. Categorical variables were reported as absolute and relative frequencies and were compared using the χ^2 or Fisher's exact test as appropriate. The cumulative hazard of all-cause and cardiovascular cause mortality was assessed using the Kaplan-Meier method and compared using the log-rank test. To examine the impact of different predictors on survival, univariable and multivariable Cox proportional hazard models were used to predict the association in the form of HR between observed survival and single or multiple independent variables, respectively. The number of predictors in the multivariable models was chosen so that there would be at least 15 events per covariate.[9] Multicollinearity among independent variables in multivariable models was assessed and a strong correlation between variables was considered present if the variance inflation factor was above 2.5. Multivariable models were constructed in a stepwise fashion and overfitting was evaluated using Akaike's information criterion (AIC). AIC was calculated at each step to assess if an overfitting problem was incurred by adding more variables to the model. Given that the final prediction model and model performance were assessed using the same data set, the model performance statistics might be optimistic. To correct this optimism, all 95% CI were bootstrapped with 1000 samples and then reported in order to ensure internal validation. Statistical analysis was performed using R V.4.1.1 (Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/) and RStudio V.1.4.17 (PBC, Boston, Massachusetts, USA, http://www.rstudio.com/). The geographical origin of the treated patients was plotted using GeoPandas and matplotlib libraries implemented in Python V.3.9.13 (Python Software Foundation, https://www.python.org/).

RESULTS

A total of 6867 patients with 8442 PCI procedures were included in the present study. Romanian group consisted of 5095 (74.2%) patients with 6238 (73.9%) PCI procedures, the Hungarian group consisted of 1417 (20.6%) patients with 1780 (21.1%) PCI procedures and the Roma group consisted of 355 (5.1%) patients with 424 (5.0%) PCI procedures. Clinical characteristics of the included population in a per-patient and per-PCI analysis are reported in table 1. The geographical distribution of the included patients is illustrated in figure 1.

During a median follow-up of 3.60 (1.35–5.75) years, a total of 1064 cardiovascular-cause and 1374 all-cause events occurred. All-cause deaths occurred in 5.40 cases per 100 patient-years, while cardiovascular-cause deaths occurred in 4.19 cases per 100 patient-years. In patients with ACS, all-cause and cardiovascular-cause deaths occurred in 6.56 cases and 5.26 cases per 100 patient-years, respectively. In patients with chronic coronary syndrome (CCS), all-cause and cardiovascular-cause deaths occurred in 4.01 cases and 2.92 cases per 100

Table 1 Clinical characteristics of the studied population

	Per-patient analysis			Per-PCI analysis		
Parameter	**All patients (n=6867)**	**HR (95% CI)***	**P value**	**All PCIs (n=8442)**	**HR (95% CI)***	**P value**
Male sex	4762 (69.35%)	0.9 (0.8 to 1.0)	0.05	5895 (85.85%)	0.89 (0.8 to 0.99)	0.02
Age (years)	64.56±10.79	1.06 (1.05 to 1.07)	<0.0001	64.56±10.79	1.06 (1.06 to 1.07)	<0.0001
BMI (kg/m^2)	28.88±4.74	1 (0.98 to 1.01)	0.56	28.88±4.74	1 (0.99 to 1.01)	0.92
Romanian ethnicity	5095 (74.20%)	0.82 (0.73 to 0.93)	0.001	6238 (73.89%)	0.8 (0.72 to 0.89)	0.0001
Hungarian ethnicity	1417 (20.63%)	1.12 (0.99 to 1.27)	0.08	1780 (21.09%)	1.13 (1.01 to 1.27)	0.03
Roma ethnicity	355 (5.17%)	1.43 (1.16 to 1.77)	0.0008	424 (5.02%)	1.53 (1.26 to 1.85)	<0.0001
Hypertension	3346 (48.73%)	1.03 (0.92 to 1.14)	0.66	4392 (63.96%)	1.02 (0.92 to 1.12)	0.77
Hypercholesterolaemia	2603 (37.91%)	0.84 (0.76 to 0.94)	0.002	3431 (49.96%)	0.85 (0.77 to 0.94)	0.001
Smoking status	2981 (43.41%)	1.26 (1.1 to 1.45)	0.0009	3694 (53.79%)	1.25 (1.32 to 1.17)	<0.0001
Diabetes mellitus	1256 (18.29%)	1.44 (1.28 to 1.62)	<0.0001	1778 (25.89%)	1.37 (1.23 to 1.53)	<0.0001
Prior MI	1278 (18.61%)	1.03 (0.91 to 1.18)	0.61	1785 (25.99%)	1.05 (0.93 to 1.17)	0.43
Prior CABG	179 (2.61%)	0.99 (0.73 to 1.36)	0.97	222 (3.23%)	0.92 (0.69 to 1.23)	0.59
Prior PCI	1391 (20.26%)	0.83 (0.73 to 0.95)	0.007	2158 (31.43%)	0.82 (0.73 to 0.91)	0.0004
COPD	627 (9.13%)	2.1 (1.82 to 2.43)	<0.0001	709 (10.32%)	2.09 (1.83 to 2.39)	<0.0001
Atrial fibrillation	848 (12.35%)	2.18 (1.92 to 2.48)	<0.0001	961 (13.99%)	2.13 (1.89 to 2.41)	<0.0001
ACS-STE	2146 (31.25%)	1.81 (1.62 to 2.01)	<0.0001	2263 (32.95%)	1.86 (1.68 to 2.06)	<0.0001
ACS-NSTEMI	638 (9.29%)	1.45 (1.23 to 1.71)	<0.0001	716 (10.43%)	1.65 (1.42 to 1.92)	<0.0001
ACS-UA	1213 (17.66%)	0.72 (0.62 to 0.84)	<0.0001	1538 (22.4%)	0.78 (0.69 to 0.89)	0.0003
CCS	2870 (41.79%)	0.62 (0.55 to 0.69)	<0.0001	3925 (57.16%)	0.59 (0.53 to 0.65)	<0.0001
Creatinine (mg/dL)	1.07±0.72	1.31 (1.27 to 1.35)	<0.0001	1.07±0.72	1.3 (1.26 to 1.34)	<0.0001
CrCl<45 mL/min	235 (3.42%)	3.74 (3.1 to 4.51)	<0.0001	294 (4.28%)	3.78 (3.19 to 4.48)	<0.0001
Haemoglobin (g/L)	136.7±17.3	0.8 (0.77 to 0.82)	<0.0001	136.7±17.3	0.79 (0.77 to 0.81)	<0.0001
Platelets (×10^9/L)	237.05±74.46	1 (1.0 to 1.0)	0.4	237.05±74.46	1 (1.0 to 1.0)	0.09
WBC (×10^9/L)	9.31±3.77	1.09 (1.08 to 1.1)	<0.0001	9.31±3.77	1.09 (1.08 to 1.1)	<0.0001
LDL-cholesterol (mg/dL)	109.2±43.11	1 (1.0 to 1.0)	<0.0001	109.2±43.11	1 (1.0 to 1.0)	<0.0001
HDL-cholesterol (mg/dL)	37.05±10.32	0.98 (0.98 to 0.99)	<0.0001	37.05±10.32	0.98 (0.98 to 0.99)	<0.0001
Triglyceride (mg/dL)	155±111.97	1 (1.0 to 1.0)	0.001	155±111.97	1 (1.0 to 1.0)	0.002
Total cholesterol (mg/dL)	176.47±50.59	1 (0.99 to 1.0)	<0.0001	176.47±50.59	1 (1.0 to 1.0)	<0.0001
LVEF (%)	46.4±9.94	0.94 (0.93 to 0.94)	<0.0001	46.4±9.94	0.93 (0.93 to 0.94)	<0.0001
LVEF≤40%	1135 (16.53)	3.24 (2.89 to 3.63)	<0.0001	1304 (18.99)	3.36 (3.02 to 3.74)	<0.0001
LVEF=41–49%	2946 (42.9)	0.95 (0.85 to 1.07)	0.39	2507 (36.51)	1 (0.9 to 1.11)	0.95
LVEF≥50%	2091 (30.45)	0.38 (0.34 to 0.43)	<0.0001	3847 (56.02)	0.38 (0.34 to 0.42)	<0.0001
Killip class ≥4	111 (1.62%)	8.74 (6.85 to 11.16)	<0.0001	115 (1.67%)	9.35 (7.34 to 11.91)	<0.0001
ICU stay	400 (5.82%)	11.61 (10.05 to 13.42)	<0.0001	422 (5.00%)	12.21 (10.62 to 14.04)	<0.0001
TIMI pre-PCI≤1	1.64±1.37	0.86 (0.83 to 0.9)	<0.0001	1.64±1.37	0.87 (0.83 to 0.9)	<0.0001
Number of diseased vessels	2.03±0.82	1.42 (1.33 to 1.52)	<0.0001	2.03±0.82	1.36 (1.28 to 1.45)	<0.0001
SYNTAX score	17.72±11.53	1.04 (1.03 to 1.05)	<0.0001	18.68±11.52	1.03 (1.02 to 1.04)	<0.0001
SYNTAX II score	14.9±13.0	1.05 (1.03 to 1.07)	<0.0001	15.7±12.5	1.05 (1.03 to 1.07)	<0.0001
LM angioplasty	402 (5.85%)	1.57 (1.29 to 1.92)	<0.0001	475 (6.92%)	1.58 (1.31 to 1.9)	<0.0001
LAD angioplasty	3277 (47.72%)	1.03 (0.91 to 1.17)	0.6	3915 (57.01%)	1.03 (0.93 to 1.13)	0.61
CXA angioplasty	1734 (25.25%)	1.15 (1.01 to 1.3)	0.02	2199 (32.02%)	1.15 (1.03 to 1.28)	0.01
RCA angioplasty	2167 (31.56%)	1.09 (0.97 to 1.23)	0.13	2695 (39.25%)	1.03 (0.93 to 1.15)	0.55
Proximal segment angioplasty	3137 (45.68%)	1.45 (1.3 to 1.61)	<0.0001	3789 (55.18%)	1.49 (1.35 to 1.65)	<0.0001
Complete revascularisation	2676 (38.97%)	0.66 (0.59 to 0.75)	<0.0001	3076 (44.79%)	0.68 (0.61 to 0.77)	<0.0001
Maximum stent diameter	3.78±11.48	1.0 (1.0 to 1.01)	0.38	3.78±11.48	1.0 (1.0 to 1.01)	0.4
Total stent length	31.28±18.84	1.01 (1.01 to 1.01)	<0.0001	31.28±18.84	1.01 (1.0 to 1.01)	<0.0001
Number of stents	1.53±0.87	1.23 (1.16 to 1.3)	<0.0001	1.53±0.87	1.21 (1.15 to 1.28)	<0.0001
Segments treated	1.37±0.72	1.19 (1.11 to 1.27)	<0.0001	1.37±0.72	1.18 (1.11 to 1.26)	<0.0001
TIMI post-PCI≤2	2.9±0.47	0.77 (0.71 to 0.83)	<0.0001	2.9±0.47	0.78 (0.72 to 0.84)	<0.0001
Hospitalisation cost (€)	1943.07±2694.01	0.99 (0.99 to 0.99)	<0.0001	1863.58±2506.17	0.99 (0.99 to 0.99)	<0.0001

*HR are provided for all-cause mortality prediction.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CCS, chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CXA, circumflex artery; HDL, high-density lipoprotein; ICU, intensive care unit; LAD, left anterior descending artery; LDL, low-density lipoprotein; LM, left main artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis In myocardial infarction; UA, unstable angina; WBC, white blood cells.

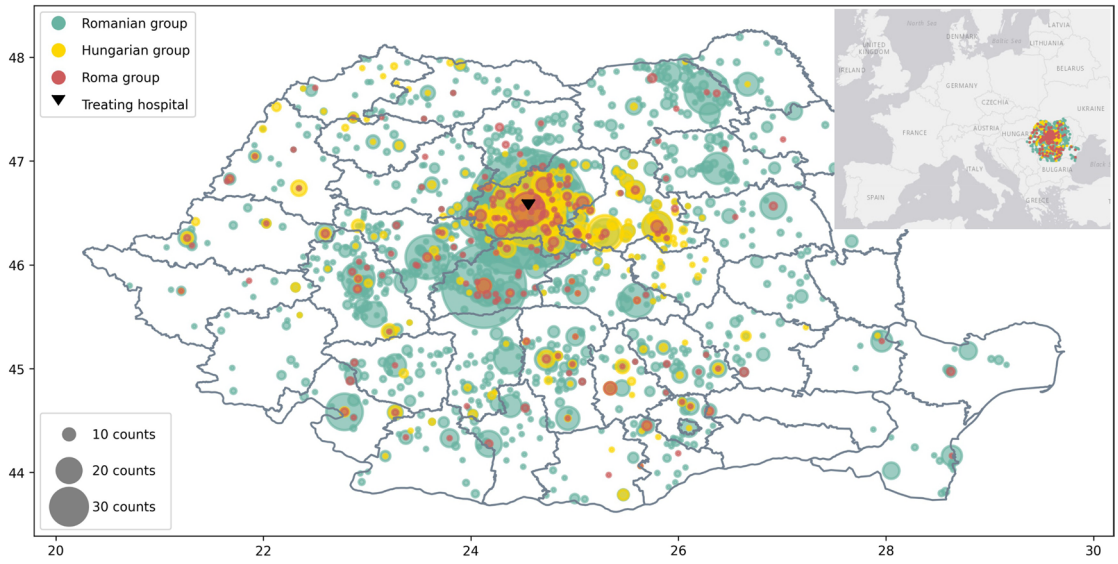
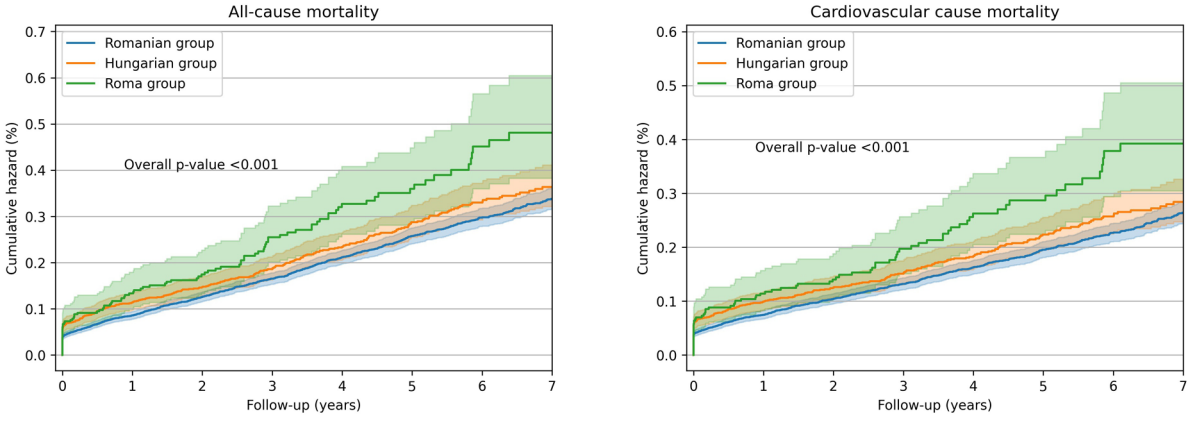


Figure 1 Geographical origin of treated patients in Romania.

patient-years, respectively. Cumulative hazard curves for cardiovascular and all-cause mortality are reported in online supplemental figure 1. In-hospital mortality occurred in 191 (3.75%) patients for the Romanian group, in 77 (5.43%) patients for the Hungarian group and in 20 (5.63%) patients for the Roma group (p=0.007). Cumulative hazard curves for cardiovascular-cause and all-cause mortality in a per-patient analysis are reported in figure 2 and in a per-PCI analysis are reported in online supplemental figure 2. Cumulative hazard curves for acute and chronic coronary syndromes are reported in online supplemental figure 3-5. There was a significant increase of in-hospital, 1-year and 2 years mortality in 2020 and 2021, consistent with the recent coronavirus pandemic (online supplemental figure 6), however hospitalisations for CCS decreased during that time frame and a relative increase in hospitalisations for ACS was observed (online supplemental figure 7). 18 (0.02%) patients had an active coronavirus infection at the time of PCI, with no differences among ethnic groups. Yearly mortality trends are illustrated in online supplemental figure 7.

Roma patients were significantly younger, had higher rates of risk factors and comorbidities and presented more often with ACS and with lower left ventricular ejection fraction (LVEF) when compared with Romanian patients (online supplemental table 1 and online supplemental table 2). While the complexity of the CAD was similar among the treated groups, the PCI procedure was less complex (lower complete revascularisation rates, fewer segments treated and fewer implanted stents) when compared with Romanian patients (online supplemental table 1 and online supplemental table 2). However, thrombolysis in myocardial infarction (TIMI) flow post-PCI did not differ among treated groups. Hungarian patients were less frequently males, and had similar rates of risk factors and comorbidities, but



Romanian group								
At risk	5095	4398	3693	3040	2561	2085	1481	885
Censored	0	280	824	1344	1694	2063	2597	3146
Events	0	417	578	711	840	947	1017	1064
Hungarian group								
At risk	1417	1179	986	830	700	545	367	216
Censored	0	86	243	364	457	579	738	879
Events	0	152	188	223	260	293	312	322
Roma group								
At risk	355	289	242	193	148	111	75	42
Censored	0	22	58	90	123	156	184	215
Events	0	44	55	72	84	88	96	98

Romanian group								
At risk	5095	4398	3693	3040	2561	2085	1481	885
Censored	0	333	918	1478	1871	2271	2820	3373
Events	0	364	484	577	663	739	794	837
Hungarian group								
At risk	1417	1179	986	830	700	545	367	216
Censored	0	105	270	403	508	638	801	944
Events	0	133	161	184	209	234	249	257
Roma group								
At risk	355	289	242	193	148	111	75	42
Censored	0	28	68	105	139	173	201	233
Events	0	38	45	57	68	71	79	80

Figure 2 Cumulative hazard and numbers at risk table for all-cause and cardiovascular cause mortality among investigated groups.

presented more often with ACS when compared with Romanian patients (online supplemental table 1 and online supplemental table 2). Both the complexity of the CAD and that of the PCI procedure were similar in Hungarian patients when compared with Romanian patients (online supplemental table 1 and online supplemental table 2).

Prescription of guidelines recommended treatment was present in 1905 (27.74%) of patients for ticagrelor as a potent P2Y12 receptor inhibitor, in 376 (19.24%) and 229 (11.72%) of patients with LVEF≤40% for angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter-2 inhibitor (SGLT2) inhibitors, respectively, and in 432 (51.67%) of patients with an anticoagulation indication (836 (12.1%)) for direct oral anticoagulant (DOAC), and there was a significant increasing trend in their prescription (online supplemental figure 8). All 836 (12.1%) patients with an anticoagulation indication also received aspirin and clopidogrel as part of the triple antithrombotic therapy. The increase in prescription trends was consistent with nationwide price-volume agreements and NHIS coverage. There was no difference in the prescription of ARNI, SGLT2 inhibitors or DOAC among the treated groups. However, the 32.2% prescription rate of potent P2Y12 receptor inhibitor in Roma patients was higher than the 27.7% prescription rate in the rest of the population (p=0.04; online supplemental figure 8). 30 (9.35%) Roma patients were uninsured, which is significantly higher than Hungarian patients (12 (0.86%)) and Romanian patients (24 (0.47%); p<0.0001). High prescription rates were observed for other treatment classes, such as aspirin (in 6509 (94.8%) patients), beta-blockers (in 6214 (90.5%) patients), ACE inhibitors or angiotensin receptor blockers (in 6269 (91.3%) patients) and statin (in 6674 (97.2%) patients), with no heterogeneity among ethnic groups.

PCI via radial vascular access was performed in 5452 (79.39%) patients and a vascular closure device was used in 439 (6.39%) patients. Drug-eluting and biodegradable stents were implanted in 6373 (92.8%), and 409 (5.96%) patients, respectively. 85 (1.2%) patients received balloon-only angioplasty. Regarding bleeding risk, 15 (0.002%) patients suffered major clinical overt bleeding, 66 (0.1%) patients had a haemoglobin drop ≥50 g/L after PCI and 189 (2.0%) patients had a haemoglobin drop ≥15% after PCI. No periprocedural stroke occurred. No in-hospital death was attributed to bleeding events. Extensive patient characteristics and procedural details are reported in online supplemental table 3.

When adjusting for potential confounders in a Cox multivariable regression, the presence of guidelines recommended treatment (potent P2Y12 receptor inhibitor, ARNI, SGLT2 inhibitor and DOAC), higher pre-PCI TIMI flow, higher post-PCI TIMI flow or higher LVEF were protective against cardiovascular cause and all-cause mortality (figure 3). Advanced age, higher creatinine, higher Killip class, presence of proximal segment culprit or number of diseased coronary arteries were among risk factors for cardiovascular cause and all-cause mortality (figure 3). Both Hungarian and Roma patients presented significantly higher all-cause mortality than Romanian patients (adjusted HR=1.20 (1.05–1.36), p=0.005 and adjusted HR=1.51 (1.21–1.88), p=0.0001, respectively). Similarly, Hungarian and Roma patients presented significantly higher cardiovascular cause mortality than Romanian patients (adjusted HR=1.22 (1.05–1.41), p=0.006 and adjusted HR=1.51 (1.18–1.92), p=0.0008, respectively). Ethnicity was an independent predictor of events, including in subgroups such as ACS, CCS, LVEF or atrial fibrillation (figure 4). As an exception, Hungarian ethnicity in the ACS subgroup did not have a higher adjusted HR when compared with Romanian ethnicity (figure 4).

DISCUSSIONS

Our study findings could be summarised as follows: (1) High long-term cardiovascular and all-cause mortality was observed for the entire included population. Long-term survival was significantly lower in ethnic minorities, such as the Hungarian and Roma minorities. (2) Roma patients were significantly younger, had higher rates of risk factors and comorbidities and presented more often with ACS. While the complexity of the CAD was similar, the PCI procedure was less complex, although TIMI flow post-PCI did not differ in Roma patients when compared with Romanian patients. (3) Hungarian patients

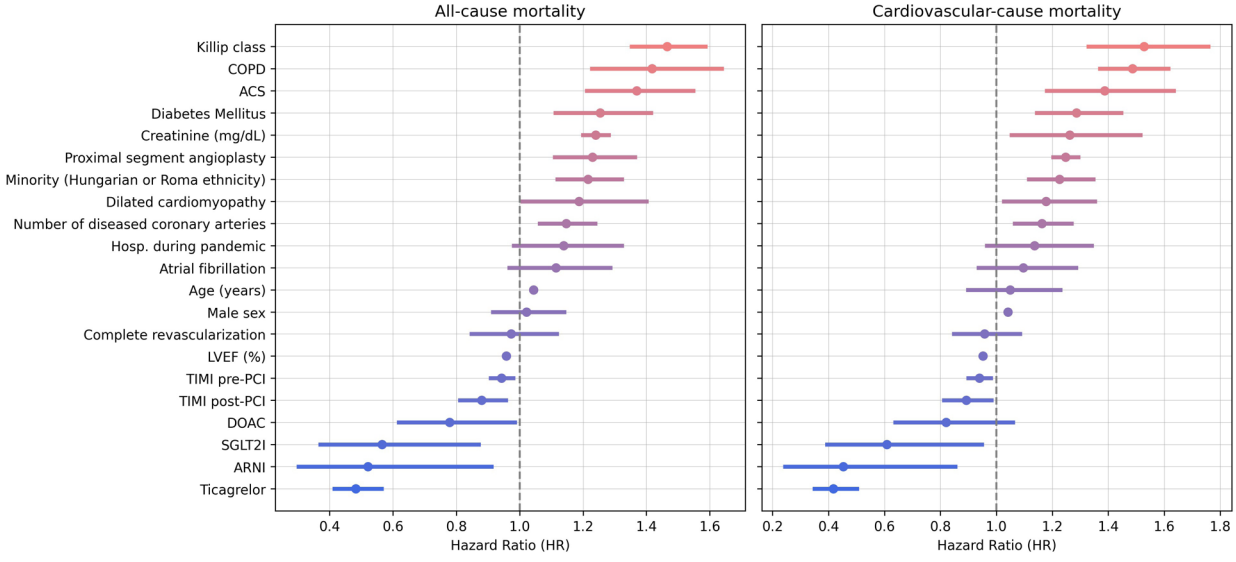


Figure 3 Multivariable Cox proportional hazards for mortality prediction. All variables were one-hot encoded, including DOAC, SGLT2I, ARNI and ticagrelor. ACS, acute coronary syndrome; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; LVEF, left ventricular ejection fraction; SGLT2I, sodium-glucose cotransporter-2 inhibitor; TIMI, thrombolysis in myocardial infarction flow.

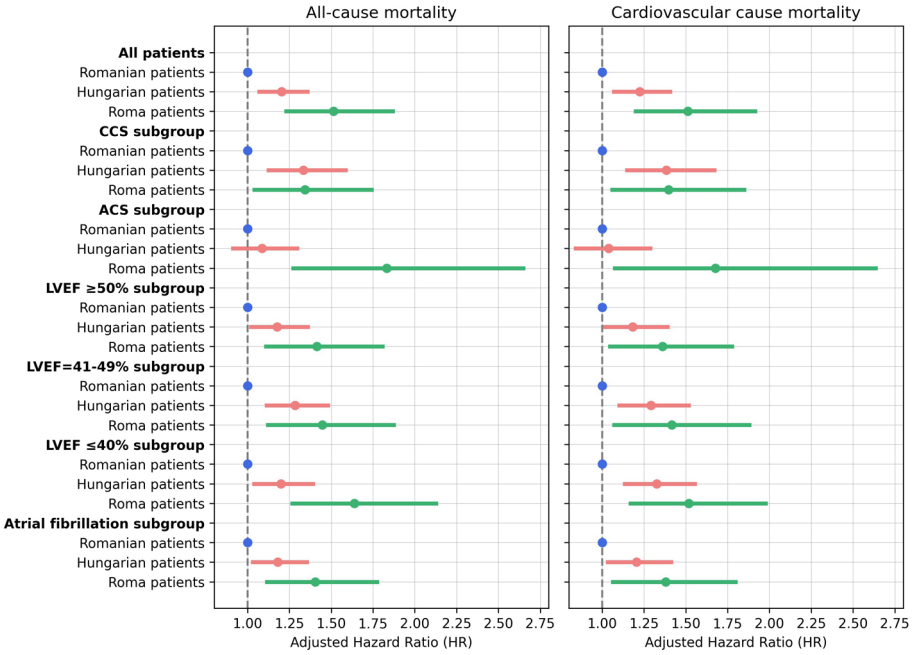


Figure 4 Adjusted HR among entire and subgroup populations. *Adjusted for the following variables: age, sex, atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus, dilated cardiomyopathy, number of diseased vessels, proximal segment angioplasty, Killip class, thrombolysis in myocardial infarction flow pre-PCI and post-PCI, creatinine, left ventricular ejection fraction (LVEF), acute coronary syndrome (ACS), ticagrelor, angiotensin receptor-neprilysin inhibitor, sodium-glucose cotransporter 2 inhibitors and direct oral anticoagulant administration. CCS, chronic coronary syndrome; PCI, percutaneous coronary intervention.

were less frequently males, had similar rates of risk factors and comorbidities, but presented more often with ACS. Both the complexity of the CAD and that of the PCI procedure were similar in Hungarian patients when compared with Romanian patients.

High mortality was observed in our study when compared with contemporary PCI cohorts. Overall, the 7-year all-cause mortality in the CCS subgroup in our study was 32%, which is higher than the 7-year all-cause mortality of 12.4% in the PCI-treated arm of the ISCHEMIA trial.[10] Similarly, the 7-year cardiovascular-cause mortality in the CCS subgroup in our study was 23%, which is higher than the 7-year cardiovascular-cause mortality of 6.4% in the ISCHEMIA trial.[10] The incidence rate of all-cause mortality in patients with ACS in our study was 6.56 cases per 100 patient-years, more than twice that of 2.4 cases per 100 patient-years reported in a large PCI-treated ACS Western population.[11] Higher Killip class, hospitalisation for ACS, lower pre-PCI TIMI flow, diabetes mellitus and advanced age were among the independent predictors of mortality (figure 3). Our findings are in line with previous studies that revealed higher mortality when cardiogenic shock is associated with diabetes mellitus or low pre-PCI TIMI flow.[12] Moreover, bioresorbable stents were associated with improved survival (online supplemental table 3), similar to other reports.[13] Regarding periprocedural safety, no stroke (ischaemic or haemorrhagic) occurred in our study. A previous large PCI registry reported a periprocedural stroke rate of approximately 0.02%.[14]

Significantly higher mortality rates were observed in our study for Roma and Hungarian minorities. A relatively small study from Central Europe, in which 75% of patients had angiographically significant CAD, reported higher mortality among the Roma minority when compared with the general population.[15] That difference was significant even after adjusting for socioeconomic factors. However, the fact that belonging to an ethnic minority is an independent risk factor for higher all-cause and cardiovascular cause mortality needs attention. Possible explanations could be genetic, socioeconomic and even cultural differences in the studied populations.

Our study confirms a higher prevalence of cardiovascular risk factors among Roma patients. Even though the complexity of CAD as reflected by the SYNTAX score and the number of diseased coronary arteries was similar among ethnic groups, Roma patients were younger, had more risk factors and had more comorbidities than their counterparts. A higher risk for a 10-year development of cardiovascular diseases as quantified by Framingham score and a reduction in specific high-density lipoprotein cholesterol subfraction in Roma patients than the general population were also previously reported.[16 17] Interestingly, genetic polymorphisms of apolipoprotein E, such as the ε2 allele, are associated with obesity phenotype in Roma patients.[18] Moreover, certain cardiovascular risk factors, such as smoking which is a strong part of Roma culture, can reach extremely high rates. While in our study 60% of Roma patients were smokers, other studies report smoking rates of up to 72%.[19] Certain attempts towards smoking cessation in Roma patients have ultimately proven to be ineffective.[20] While there is a paucity of reliable data regarding the Roma population, it is clear that comprehensive lifestyle modification interventions along with maximising guidelines recommended treatment should be pursued.

Although prescription trends were increasing, average prescription numbers for guidelines-directed pharmacological treatment were relatively low, especially for drug classes whose benefit was established in randomised trials before our PCI registry such as ticagrelor, ARNI or DOAC. Ticagrelor prescription rate was 19% in our study, much lower than that of a recent registry where ticagrelor usage was 63%.[21] While other registries reported that ticagrelor was not superior to clopidogrel in reducing adverse events,[22] in our population ticagrelor was

among the most important clinical parameters that improved patient survival. Low ARNI prescription rates, in 19% of patients with LVEF≤40% in our study, were also observed in previous studies, where despite the strong evidence, prescription rates only rose to 26%.[23 24] Similarly, an SGLT2 inhibitor was used in 11% of patients with LVEF≤40% which is less than 37% of SGLT2 inhibitor use in other Western registries.[25] DOAC usage instead of vitamin K antagonists for patients with an anticoagulation indication was 51% in our study, while in other PCI registries rose up to 87%.[26] Prescription rate was also observed to increase following the introduction of price-volume agreements in other studies. For instance, affordability and cost-sharing are major factors in increasing prescription rates of quadruple therapy for heart failure.[27] Not surprisingly, lower affordability of cardiovascular drugs was associated with a higher rate of adverse events and mortality.[28] Interestingly, in our study Roma patients had a higher prescription rate of ticagrelor, which may be due to the fact that clopidogrel price is not fully covered in Romania, while ticagrelor price is fully covered and, thus, cheaper. Moreover, prasugrel was not prescribed since it lacks a national cost-volume agreement and is commercially unavailable, emphasising the relationship between affordability and prescription.

An increased mortality was observed during the recent coronavirus pandemic, although the pandemic did not have a significant impact on mortality per se in multivariable analysis, it was due to a decrease in CCS hospitalisations and a relative increase in ACS hospitalisations. A recent registry-based meta-analysis reported higher mortality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive patients.[29] However, in the present study, a small number of SARS-CoV-2-positive patients were included, which may explain why hospitalisation during the coronavirus pandemic did not impact mortality in the multivariate analysis.

Study limitations

Although our tertiary centre is located in the most ethnically heterogeneous region of Romania and the percentages of minorities in the present study were higher than nationwide percentages, the included patients in each minority were still relatively few (20% for Hungarian patients and 5% for Roma patients). Although ethnical background can be easily found by anthroponomic analysis in Romania,[8] a self-affirmed and phenotypic-derived ethnical background or genetic ancestry could have led to more precise results and should constitute further research directions.

CONCLUSIONS

High long-term cardiovascular and all-cause mortality was observed for the entire included population and mortality was higher among ethnic minorities than Romanian population. Roma minority had a significantly higher incidence of associated comorbidities, and it had significantly lower survival than the Romanian population, even after adjusting for potential confounders. Moreover, the Hungarian minority had significantly lower survival, even though it shared the same clinical characteristics as the Romanian population.

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