Uniwersytet Jagielloński
Collegium Medicum

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# Myocardial infarction with non-obstructive coronary arteries. The selected aspects of pathogenesis, diagnosis, treatment and the impact on long-term prognosis.

Zawał mięśnia sercowego bez istotnych zmian w tętnicach wieńcowych. Wybrane aspekty dotyczące patogenezy, diagnostyki, leczenia oraz wpływu na rokowanie odległe.

*Praca doktorska*

Promotor:
Dr hab. n. med. Jarosław Zalewski

Pracę wykonano w Klinice Choroby Wieńcowej i Niewydolności Serca
Uniwersytetu Jagiellońskiego Collegium Medicum
Kierownik jednostki: Prof. dr hab. n. med. Jadwiga Nessler

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Dziękuję mojemu Promotorowi dr hab. Jarosławowi Zalewskiemu
za poświęcony czas oraz cenne rady, a także za wsparcie i wyrozumiałość
okazane od samego początku mojej drogi naukowej i zawodowej.
Bez tego praca ta nie mogłaby powstać.

*Pracę dedykuję moim Rodzicom*

# Spis treści

# 1. Wprowadzenie

Niniejsza praca doktorska pt.: *„Myocardial infarction with non-obstructive coronary arteries. The selected aspects of pathogenesis, diagnosis, treatment and the impact on long-term prognosis.” („Zawał mięśnia sercowego bez istotnych zmian w tętnicach wieńcowych. Wybrane aspekty dotyczące patogenezy, diagnostyki, leczenia oraz wpływu na rokowanie odległe.”)* powstała w oparciu o monotematyczny cykl trzech artykułów opublikowanych w międzynarodowych czasopismach naukowych indeksowanych w bazie PubMed oraz znajdujących się na liście Journal Citation Reports (Thomson Reuters, Clarivate Analytics).

**Wykaz publikacji stanowiących pracę doktorską:**

| | **Tytuł publikacji** | **Punkty MNiSW** | **Impact factor (IF)** |
|---|---|---|---|
| 1. | ***“High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: Comparison with cryptogenic stroke.”*** **Stepien K**, Nowak K, Wypasek E, Zalewski J, Undas A. Int J Cardiol. 2019; 290: 1-6. doi:10.1016/j.ijcard.2019.05.037. | 100 | 3.229 |
| 2. | ***“Worse long-term prognosis in myocardial infarction occurring at weekends or public holidays with insight into myocardial*** | 140 | 3.277 |

| | | | |
|---|---|---|---|
| | ***infarction with nonobstructive coronary arteries."***<br>**Stepien K**, Nowak K, Nessler J, Zalewski J. Pol Arch Intern Med. 2020; 130: 942-952. doi:10.20452/pamw.15615. | | |
| 3. | ***"Clinical Characteristics and Long-Term Outcomes of MINOCA Accompanied by Active Cancer: A Retrospective Insight Into a Cardio-Oncology Center Registry."***<br>**Stepien K**, Nowak K, Szlosarczyk B, Nessler J, Zalewski J. Front Cardiovasc Med. 2022; 9: 785246. doi:10.3389/fcvm.2022.785246. | 40 | 5.846 |
| | **Podsumowanie punktacji** | **280** | **12.352** |

**Pozostały dorobek naukowy:**

| | **Liczba publikacji** | **Punkty MNiSW** | **Impact factor (IF)** |
|---|---|---|---|
| Prace włączone do pracy doktorskiej | 3 | 280 | 12.352 |
| Prace niewłączone do pracy doktorskiej | 29 | 1659 | 62.961 |
| **Razem** | **32** | **1939** | **75.313** |

# 2. Wykaz skrótów

APS, zespół antyfosfolipidowy

BMI, indeks masy ciała

CI, przedział ufności

CK, kinaza kreatynowa

CK-MB, izoenzym MB kinazy kreatynowej

CS, udar kryptogenny

ESC, Europejskie Towarzystwo Kardiologiczne

HR, ryzyko względne

IQR, rozstęp międzykwartylowy

IRA, tętnica dozawałowa

IRR, współczynnik zapadalności

LVEF, frakcja wyrzutowa lewej komory

MI, zawał mięśnia sercowego

MI-CAD, zawał mięśnia sercowego ze zmianami w tętnicach wieńcowych

MINOCA, zawał mięśnia sercowego bez istotnych zmian w tętnicach wieńcowych

NOAC, doustne leki przeciwkrzepliwe niebędące antagonistami witaminy K

NSTEMI, zawał mięśnia sercowego bez uniesienia odcinka ST

NWD, dni nierobocze

OR, iloraz szans

PCI, przezskórna angioplastyka wieńcowa

RVSP, ciśnienie skurczowe w prawej komorze

STEMI, zawał mięśnia sercowego z uniesieniem odcinka ST

TIMI, skala Thrombolysis In Myocardial Infarction

TTS, zespół takotsubo

VKA, antagonista witaminy K

WD, dni robocze

# 3. Wstęp

Zawał mięśnia sercowego bez istotnych zmian w tętnicach wieńcowych (MINOCA, ang. *myocardial infarction with non-obstructive coronary arteries*), definiowany aktualnie przez brak stwierdzanych zwężeń ≥ 50% w wykonanej koronarografii, jest nierzadkim obrazem angiograficznym wśród pacjentów przyjmowanych z rozpoznaniem zawału mięśnia sercowego (MI, ang. *myocardial infarction*) [1, 2]. Wyniki dużych badań rejestrowych wskazują, że angiograficzne kryteria MINOCA spełnia 1-13% wszystkich pacjentów z MI [3-5]. W dotychczasowej literaturze istnieją sprzeczne dane dotyczące ich rokowania długoterminowego. Pasupathy i wsp. w przeglądzie systematycznym wskazują, że pacjenci z MINOCA charakteryzują się niższą roczną śmiertelnością ogólną w porównaniu do pacjentów z zawałem mięśnia sercowego ze zmianami w tętnicach wieńcowych (MI-CAD, ang. *myocardial infarction and obstructive coronary artery disease*) (4.7 vs 6.7%) [6]. Odmienne, bardziej niekorzystne sygnały płyną z rejestru SWEDEHEART, do którego włączono 9 092 pacjentów z MINOCA. W obserwacji 4.5-letniej istotne zdarzenia sercowo-naczyniowe wystąpiły u 24% pacjentów, a 14% z nich zmarło [7].

Szczegółowe badania wskazują, iż za rozpoznaniem MINOCA kryje się heterogenna grupa jednostek chorobowych o niejednokrotnie złożonej etiopatogenezie. Aktualnie potencjalne przyczyny prowadzące do MINOCA dzielimy na wieńcowe i pozawieńcowe. Z kolei w grupie tych ostatnich przyczyn wyodrębniamy nieprawidłowości mięśnia sercowego oraz przyczyny pozasercowe [1, 2]. Heterogenność etiologiczną MINOCA potwierdzają ostatnie badania z wykorzystaniem rezonansu magnetycznego serca. Sörensson i wsp. udowodnili, że wykorzystanie nowoczesnych technik rezonansu magnetycznego serca umożliwia ustalenie przyczyny MINOCA aż u prawie 80% pacjentów [8]. Z tego powodu aktualne wytyczne poświęcone MINOCA zalecają traktowanie tego rozpoznania jako

'diagnozy roboczej' wymagającej dalszej specjalistycznej diagnostyki w oparciu o proponowane algorytmy [1, 2]. Wartość prognostyczna postępowania opartego na szczegółowych badaniach dodatkowych i w efekcie umożliwiającego personalizację farmakoterapii zostanie sprawdzona w rozpoczynanym badaniu PROMISE [9].

*Rola trombofilii w etiopatogenezie MINOCA*

Jednym z proponowanych mechanizmów rozwoju MINOCA jest spontaniczne formowanie się zakrzepu w tętnicy wieńcowej z jego następową lizą na podłożu niezmienionej intimy wieńcowej lub na niewidocznych angiograficznie dyskretnych zmianach [10]. Taką sekwencję zdarzeń może zainicjować nierozpoznana uprzednio trombofilia, czyli stan nadkrzepliwości wrodzonej lub nabytej. W największym dotychczas przeglądzie systematycznym dotyczącym tego zagadnienia, przeprowadzonym w oparciu o 8 badań obserwacyjnych obejmujących niepełny panel obejmujących 378 pacjentów z MINOCA, ustalono, że trombofilie występują u 14% z nich, a najczęstszą nieprawidłowością jest mutacja czynnika V Leiden [6]. Co istotne, wykrywanie trombofilii u pacjentów z MINOCA może mieć istotne znaczenie we wspomnianej już personalizacji leczenia i włączeniu leczenia przeciwzakrzepowego, zwłaszcza u pacjentów z zespołem antyfosfolipidowym (APS, ang. *antiphospholipid syndrome*). Przyczyniło się to do umieszczenia badania przesiewowego w kierunku trombofilii w aktualnych algorytmach diagnostycznych dla pacjentów z MINOCA rekomendowanych przez Europejskie Towarzystwo Kardiologiczne (ESC, ang. *European Society of Cardiology*) [1]. W dotychczasowej literaturze nie było jednak opisywane zastosowanie pełnego panelu diagnostycznego trombofilii w tej grupie pacjentów.

*Chronobiologia i efekt weekendu a występowanie MINOCA*

Termin *efekt weekendu*, w odniesieniu do zagadnień kardiologicznych, wiąże się z pogorszeniem rokowania pacjentów z MI przyjmowanych do szpitala w dni nierobocze (NWD, ang. *nonworking day*). Po raz pierwszy zjawisko zostało opisane w 2001 roku przez Bell i Redelmeier [11]. Do tej pory powstały jedynie pojedyncze badania dotyczące tego zagadnienia w populacji polskiej [12, 13]. Co więcej, nie ma danych opisujących występowanie i znaczenie *efektu weekendu* w warunkach dobrze rozwiniętej sieci pracowni hemodynamicznych pracujących całodobowo. W literaturze proponowanych jest kilka potencjalnych przyczyn prowadzących do występowania *efektu weekendu*, takich jak mniejszy odsetek skutecznych przezskórnych angioplastyk wieńcowych (PCI, ang. *percutaneous coronary intervention*), mniejsze doświadczenie operatorów dyżurujących w NWD, a także większe opóźnienie przedszpitalne i związany z tym gorszy stan kliniczny pacjentów przyjmowanych w NWD. Żadna jednak z tych hipotez nie została ostatecznie potwierdzona w dotychczasowych badaniach.

Ze względu na swoją specyfikę występowanie MINOCA może być związane ze stresem okołodobowym. Dotyczy to zwłaszcza przyczyn wieńcowych oraz diagnozowanego u dużego odsetka pacjentów z MINOCA zespołu takotsubo (TTS, ang. *takotsubo syndrome*). Wyniki rejestru SWEDEHEART wskazują, że MINOCA występuje najczęściej rano (IRR, ang. *incidence rate ratio*, 1.70; 95% CI 1.63-1.84) oraz w poniedziałki (IRR, 1.28; 95% CI, 1.18-1.38), a rzadziej w weekendy [14]. Te zmienności w czasie nie miały jednak istotnej wartości prognostycznej [14].

*MINOCA u pacjentów z aktywną chorobą nowotworową*

Pacjenci z MI i aktywną chorobą nowotworową stanowią wyjątkowo wymagającą diagnostycznie i terapeutycznie grupę chorych. Co więcej, ze względu na współistnienie

nierzadko zaawansowanego aktywnego procesu nowotworowego charakteryzują się niekorzystnym rokowaniem.

Własne obserwacje kliniczne oraz dane pochodzące z literatury wskazują także, że jest to również grupa, w której pacjenci z MI mają nierzadko stawiane rozpoznanie MINOCA. W metaanalizie autorstwa Pelliccia i wsp. choroba nowotworowa występowała u 2.5% pacjentów z MINOCA i była niezależnym niekorzystnym czynnikiem rokowniczym [15]. Z kolei inna metaanaliza, opracowana przez ten sam zespół autorów, oparta na większej grupie pacjentów, nie potwierdziła tego związku prognostycznego [16]. Biorąc pod uwagę fakt, iż zauważono zwiększone ryzyko tętniczych zdarzeń zakrzepowo-zatorowych w grupie pacjentów onkologicznych [17], a także kumulację czynników predysponujących do MINOCA, takich jak niedokrwistość (wzrost ryzyka zawału typu 2), stosowane leczenie onkologiczne (wzrost ryzyka skurczu nasierdziowych odcinków tętnic wieńcowych), duży ładunek stresu psychicznego i fizycznego (wzrost ryzyka TTS), a także sygnalizowaną już wcześniej zwiększoną gotowość prozakrzepową, chorzy z nowotworem mogą być zaliczani do grupy podwyższonego ryzyka MINOCA [18]. Niemniej jednak wciąż brakuje danych, zwłaszcza opartych na rejestrach kardioonkologicznych, dotyczących charakterystyki onkologicznej tej grupy pacjentów oraz przedstawiających ich rokowanie długoterminowe.

# 4. Hipotezy badawcze i cele pracy

***Hipotezy badawcze:***

1) w grupie pacjentów z MINOCA stany nadkrzepliwości wrodzonej lub nabytej są częste
2) populacja pacjentów z MI leczonych w wolne od pracy lub pracujące dni tygodnia różni się i ma to wpływ na bezpośrednie i odległe efekty leczenia
3) MINOCA wiąże się z częstszym występowaniem aktywnej choroby nowotworowej, a to ma związek z rokowaniem długoterminowym

***Cele pracy:***

1) ocena częstości występowania trombofilii u pacjentów z MINOCA w porównaniu do pacjentów z udarem kryptogennym i analiza ich znaczenia klinicznego
2) określenie chronobiologii MINOCA i analiza wpływu *efektu weekendu* na rokowanie odległe
3) określenie charakterystyki klinicznej oraz rokowania długoterminowego u pacjentów onkologicznych z MINOCA

# 5. Materiał i metody

## Publikacja 1

***Typ badania:***

Prospektywne badanie przekrojowe

***Grupa badana:***

84 pacjentów z MINOCA skierowanych do naszego Ośrodka pomiędzy marcem 2014 a październikiem 2018.

***Grupa kontrolna:***

84 pacjentów z udarem kryptogennym (CS, ang. *cryptogenic stroke*) potwierdzonym w badaniu obrazowym i udokumentowanym brakiem innej przyczyny.

***Kryteria włączenia:***

MINOCA, która została rozpoznana przynajmniej 3 miesiące przed przyjęciem do Ośrodka (maksymalnie 18 miesięcy wcześniej)

***Kryteria wyłączenia:***

Objawy ostrej infekcji w dniu pobrania krwi, rozpoznany aktywny proces nowotworowy, prowadzona dializoterapia, włączone leczenie przeciwkrzepliwe, inny udokumentowany epizod zakrzepowo-zatorowy w okresie poprzedzających 3 miesięcy

***Przyjęte definicje:***

MINOCA: MI (dodatnie markery martwicy mięśnia sercowego, z typową dynamiką w kolejnych oznaczeniach, z przynajmniej jedną wartością powyżej 99 percentyla górnej granicy normy oraz przynajmniej jednym dowodem klinicznym na niedokrwienie) przy braku istotnych zwężeń (≥50%) w tętnicach wieńcowych w wykonanej koronarografii

Zawał mięśnia sercowego z uniesieniem odcinka ST (STEMI, ang. *ST-segment elevation myocardial infarction*): MI z towarzyszącymi uniesieniami odcinka ST w zapisie elektrokardiograficznym spełniającymi wymagane kryteria

Zawał mięśnia sercowego bez uniesienia odcinka ST (NSTEMI, ang. *non-ST-segment elevation myocardial infarction*): MI bez uniesień odcinka ST w zapisie elektrokardiograficznym

Otyłość: wskaźnik masy ciała (BMI, ang. *body mass index*) powyżej 30 kg/m$^2$

Hiperlipidemia: stężenie cholesterolu całkowitego >5.0 mmol/l (190.0 mg/dl), cholesterolu LDL > 2.6 mmol/l (100.0 mg/dl) lub triglicerydów >1.7 mmol/l (150 mg/dl), lub włączone leczenie hipolipemizujące

Cukrzyca: cukrzyca w wywiadzie, włączone leczenie hipoglikemizujące lub glikemia na czczo ≥126 mg/dl (7 mmol/l) w dwóch oddzielnych pomiarach

Nadciśnienie tętnicze: ciśnienie tętnicze krwi stwierdzone na wizycie lekarskiej, skurczowe ≥140 mmHg, rozkurczowe ≥90 mmHg lub włączone leczenie hipotensyjne

Niewydolność nerek: klirens kreatyniny <60ml/min obliczony ze wzoru Cockcroft-Gault

Dodatni wywiad rodzinny w kierunku MI: wystąpienie MI u krewnych pierwszego stopnia bez punktu odcięcia dla wieku

Wcześniejsza żylna choroba zakrzepowo-zatorowa: objawowa zakrzepica żył głębokich i/lub zatorowość płucna potwierdzona z wykorzystaniem badań obrazowych

***Pobieranie próbek:***

Pacjenci leczeni antagonistami witaminy V (VKA, ang. *vitamin K antagonists*) przerwali antykoagulację na 7-14 dni i zostali przestawieni na heparynę drobnocząsteczkową w dawkach terapeutycznych. Pobranie krwi zostało wykonane >12h od ostatniej iniekcji (monitorowana aktywność anty-Xa <0.1 IU/ml).

U pacjentów leczonych doustnymi antykoagulantami niebędącymi VKA (NOAC, ang. *non-VKA oral anticoagulants*) krew została pobrana >24h od ostatniej dawki (stężenie leku <30 ng/ml dla dabigatranu - Hemoclot Thrombin Inhibitor, oraz rywaroksabanu - Biophen DiXaI).

Próbki krwi pobrano z żyły odłokciowej do probówek zawierających antykoagulant cytrynianowy, odwirowano w 2500g w temperaturze 18-22°C przez 20 min i wykonano analizy natychmiast lub przechowywano w temperaturze -80 °C.

Próbki krwi do izolacji DNA pobrano do probówki z EDTA-K3 i przechowywano w temperaturze -80 °C do czasu analizy.

***Metodyka wykonania panelu trombofilii:***

Analiza genetyczna mutacji czynnika V Leiden (dbSNP ID: rs6025) oraz protrombiny G20210A (dbSNP ID: rs1799963) została wykonana z wykorzystaniem testów TaqMan Genotyping (odpowiednio C_11975250_10 oraz C_8726802_20; ThermoFisher Scientific, Waltham, Massachusetts, USA) z zastosowaniem aparatu QuantStudio Dx Real-Time PCT (ThermoFisher Scientific).

Osoczowa aktywność białka C została określona ilościowo za pomocą testu chromogennego (HemosIL Protein C Instrumentation Laboratory, Milan, Italy albo Berichrom Protein C, Siemens Healthcare Diagnostics). Wyniki <70% wskazują na niedobór białka C.

Poziom wolnego białka S był oceniany metodą immunoturbidymetryczną (INNOVANCE® Free PS Ag, Siemens Healthcare Diagnostic). Niedobór białka S był diagnozowany przy poziomie <60%.

Aktywność antytrombiny była oceniana z wykorzystaniem testu opartego na hamowaniu FXa (INNOVANCE™ ATIII, Siemens Healthcare Diagnostics, Marburg, Germany). Niedobór antytrombiny był diagnozowany przy poziomie <75%.

APS był diagnozowany zgodnie z obowiązującymi zaleceniami [19]. Poziomy przeciwciał antykardiolipinowych IgG/IgM oraz przeciw β-2 glikoproteinie I zostały oznaczone metodą ELISA (INOVA Diagnostic, San Diego, CA, USA). Antykoagulant toczniowy również został oceniony zgodnie z rekomendacjami [19]. APS został sklasyfikowany jako jedno-, dwu- i potrójnie dodatni na podstawie liczby wykrytych przeciwciał antyfosfolipidowych.

Osoczowa aktywność FVIII została określona za pomocą testu koagulometrycznego (Siemens Healthcare Diagnostics) a poziomy >150% uznano za podwyższone.

Poziom homocysteiny w osoczu na czczo został oznaczony z wykorzystaniem testu enzymatycznego (Roche Diagnostics, Mannheim, Germany). Hiperhomocysteinemia została zdefiniowana jako stężenie ≥15 μmol/l.

Lipoproteina (a) została oceniona w surowicy za pomocą testu immunoenzymatycznego (DRG Diagnostics, Marburg, Germany). Podwyższony poziom lipoproteiny (a) stwierdzano przy >30 mg/dl.

Współczynniki zmienności wewnątrz- i pomiędzytestowe dla wszystkich wykorzystywanych testów wynosiły <7%.

## Publikacja 2

***Grupa badana:***

865 kolejnych pacjentów przyjętych do naszego Ośrodka z rozpoznaniem MI w latach 2012 – 2017, u których została wykonana koronarografia. 642 (74.2%) pacjentów zostało przyjętych w WD, a 223 (25.8%) w NWD.

Spośród tej grupy 67 (7.7%) spełniało kryteria rozpoznania MINOCA.

***Analizowane dane:***

Wiek, dane antropometryczne, historia medyczna pacjenta, stan kliniczny oraz badania laboratoryjne przy przyjęciu, a także dane dotyczące przebiegu hospitalizacji.

Pomiędzy 2 do 4 dobą od przyjęcia do szpitala została oceniona frakcja wyrzutowa lewej komory (LVEF, ang. *left ventricular ejection fraction*) w dwuwymiarowym przezklatkowym badaniu echokardiograficznym wykonanym w spoczynku.

Przepływ krwi w tętnicach wieńcowych został sklasyfikowany na podstawie skali TIMI (ang. *Thrombolysis In Myocardial Infarction*). Ponadto nieistotne hemodynamicznie zwężenia w tętnicach wieńcowych w MINOCA zostały podzielone na dwie grupy: i) prawidłowe tętnice wieńcowe lub minimalne przyścienne zmiany miażdżycowe - zwężenie <30%; ii) zmiany miażdżycowe łagodne do umiarkowanych - zwężenie 30-50%.

Doświadczenie zabiegowe kardiologów interwencyjnych zostało podzielone zgodnie z powszechnie przyjętymi kryteriami: i) <50 PCI/rok - niskie; ii) 50-100 PCI/rok - umiarkowane; iii) >100 PCI/rok – wysokie [20].

***Główny punkt końcowy:***

Śmiertelność ogólna w obserwacji odległej

***Przyjęte definicje:***

MI, MINOCA, STEMI, NSTEMI, niewydolność nerek: jak w Publikacji 1

NWD: weekendy oraz dni ustawowo wolne od pracy

Dni robocze (WD, ang. *working day*): pozostałe dni roku

TTS: rozpoznanie według kryteriów InterTAK [21]

## Publikacja 3

***Grupa badana:***

1011 kolejnych pacjentów przyjętych do naszego Ośrodka o profilu kardioonkologicznym z rozpoznaniem MI w latach 2012-2017, u których została wykonana koronarografia. Spośród nich 72 (7.1%) spełniało kryteria rozpoznania MINOCA. U 134 pacjentów (13.3%) zidentyfikowano aktywny proces nowotworowy.

***Analizowane dane:***

Dane demograficzne, parametry antropometryczne, czynniki ryzyka sercowo-naczyniowego, historia schorzeń sercowo-naczyniowych, choroby współistniejące oraz szczegółowa charakterystyka onkologiczna.
Badania laboratoryjne wykonane przy przyjęciu ze szczególnym uwzględnieniem markerów martwicy mięśnia sercowego.

Dwuwymiarowe badanie echokardiograficzne przezklatkowe zostało wykonane pomiędzy 2-4 dobą hospitalizacji. Wykonywano je w spoczynku w pozycji leżącej na lewym boku za pomocą aparatu Vivid S5 (GE, Solingen, Germany). Wszystkie pomiary zostały przeprowadzone zgodnie z zaleceniami Amerykańskiego Towarzystwa Echokardiograficznego oraz Europejskiej Asocjacji Echokardiografii [22]. Zmierzono standardowe parametry w celu opisu anatomicznego poszczególnych struktur serca oraz przeprowadzenia ich oceny funkcjonalnej.

Analiza angiograficzna – jak w Publikacji 2

***Główny punkt końcowy:***

Czas trwania hospitalizacji oraz śmiertelność ogólna w obserwacji odległej

Przyczyny zgonów zostały pogrupowane na nowotworowe, sercowo-naczyniowe, inne (w większości dotyczące układu oddechowego oraz wypadki) oraz nieznane.

***Przyjęte definicje:***

MI, MINOCA, STEMI, NSTEMI, TTS, niewydolność nerek: jak w Publikacji 1

Aktywna choroba nowotworowa: rozpoznana w ciągu ostatnich 6 miesięcy, z włączonym leczeniem antymitotycznym, nawrotowa, rozsiana, miejscowo zaawansowana lub nieoperacyjna.

Anemia: stężenie hemoglobiny <13 g/dl dla mężczyzn oraz <12 g/dl dla kobiet

Małopłytkowość: liczba płytek krwi $<100 \times 10^3/\mu l$

Ciężka niewydolność nerek: klirens kreatyniny <30ml/min zgodnie ze wzorem Cockcroft-Gault

# 6. Podsumowanie wyników i wnioski

## Publikacja 1

Pacjenci w porównywanych grupach MINOCA i CS mieli podobną charakterystykę kliniczną oraz stosowane leczenie. Pacjenci z MINOCA byli częściej mężczyznami (60.7 vs 33.3%, P<0.001), częściej diagnozowano u nich otyłość (34.5 vs 17.9%, P=0.014), częściej byli aktywnymi palaczami tytoniu (51.2 vs 35.7%, P=0.043) oraz charakteryzowali się dodatnim wywiadem rodzinnym w kierunku MI (27.4 vs 6.0%, P<0.001) w porównaniu z CS. Ponadto istotnie częściej byli leczeni inhibitorem P2Y12 (81.0 vs 0.0%, P<0.001) czy beta-blokerem (31.0 vs 8.3%, P<0.001).

Mediana czasu, który upłynął od analizowanego zdarzenia niedokrwiennego do pobrania próbki krwi była podobna dla MINOCA (8 [IQR, ang. *interquartile range* 6-10 miesięcy) oraz CS (9 [6-11] miesięcy, P=0.56). Na podstawie wykonanego panelu trombofilie zostały rozpoznane u 23.8% pacjentów z MINOCA oraz u 15.5% z CS (P=0.17). W obu grupach obserwowano zbliżony rozkład poszczególnych trombofilii, z wyjątkiem niższej częstości podwyższonego poziomu lipoproteiny (a) w grupie MINOCA (21.4 vs 39.3%, P=0.012). Najczęstszą wrodzoną trombofilią diagnozowaną u pacjentów z MINOCA była mutacja czynnika V Leiden (14.3%). We wszystkich przypadkach pacjenci ci byli heterozygotami. Z kolei, APS został rozpoznany u 15.5% i w większości była to postać jednododatnia. Zestawiając uzyskane wyniki z danymi pochodzącymi z literatury dla populacji ogólnej stwierdzono nadreprezentację wszystkich oznaczanych trombofilii w grupie MINOCA.

MINOCA u pacjentów z trombofilią wrodzoną lub APS rzadziej przebiegała jako zawał STEMI (32.1 vs 55.4%, P=0.04). Co więcej, pacjenci ci częściej byli leczeni VKA po MI

(42.9 vs 8.9%, P<0.001), przy braku istotnej różnicy w częstości występowania wcześniejszych VTE (21.4 vs 8.9%, P=0.11). W kolejnych analizach wykazano rzadsze występowanie APS u pacjentów ≤50 roku życia (5.7 vs 32.3%, P=0.003) oraz leczonych z powodu STEMI (2.5 vs 27.3%, P=0.002). W analizie jednoczynnikowej wiek >50 roku życia, NSTEMI oraz dodatni wywiad rodzinny w kierunku MI były powiązane z diagnozą APS. Jednakże w analizie wieloczynnikowej wyłącznie wiek >50 roku życia był niezależnym czynnikiem związanym z wystąpieniem APS (OR, ang. *odds ratio* 6.5; 95% CI, ang. *confidence interval* 1.6–27.0, P=0.002).

**Wnioski**: Pacjenci z MINOCA charakteryzują się wysoką częstością występowania trombofilii, w tym APS, porównywalną do obserwowanej w populacji z CS, który jest uznanym wskazaniem do diagnostyki w kierunku stanów nadkrzepliwości. To pionierskie badanie poświęcone oznaczeniu kompleksowego panelu trombofilii w MINOCA potwierdza jego znaczenie kliniczne i miejsce w aktualnych rekomendacjach, jak również wskazuje na potrzebę rozważenia wdrożenia długoterminowej antykoagulacji w niektórych nieprawidłowościach, zwłaszcza APS.

## Publikacja 2

Pacjenci przyjęci w WD i NWD nie różnili się pod względem ogólnej charakterystyki klinicznej. U pacjentów z grupy NWD istotnie częściej diagnozowano STEMI (41.3 vs 30.8%, P=0.005), stwierdzono również wyższe wyjściowe wartości kinazy kreatynowej (CK, ang. *creatine kinase*) (202 [112–527] vs 169 [105–335] IU/l, P=0.02) oraz jej izoenzymu MB (CK-MB, ang. *isoenzyme MB of creatine kinase*) (24 [16–61] vs 21 [14–39] IU/l, P=0.003). W analizie angiograficznej stwierdzono istotne różnice w rozkładzie tętnic dozawałowych (IRA, ang. *infarct-related artery*) (P=0.003). U pacjentów NWD częściej było to dorzecze gałęzi międzykomorowej przedniej (38.1 vs 30.2%) oraz prawej tętnicy wieńcowej (38.6 vs 32.6%) a u WD gałęzi okalającej (22.4 vs 15.7%). U pacjentów poddanych PCI istotnie częściej stwierdzano niekompletną reperfuzję w grupie NWD (6.8 vs 1.6%; P<0.001) przy braku różnic w doświadczeniu operatorów w obu grupach (P=0.15).

Nie obserwowano różnic w czasie trwania hospitalizacji (5 [4–8] vs 6 [3–8] dni, P=0.66) oraz śmiertelności wewnątrzszpitalnej (2.7 vs 3%; P=0.84) w porównywanych grupach. Mediana czasu trwania obserwacji długoterminowej wyniosła odpowiednio 68.7 i 68.4 miesięcy w grupach NWD i WD. W pierwszym roku po wypisie nie stwierdzono istotnych różnic w śmiertelności ogólnej (13.5% dla NWD, 11.5% dla WD, P=0.46). Wyższa śmiertelność w grupie NWD została zaobserwowana po upływie pierwszego roku od wypisu (26.8 vs 19%, P=0.027) oraz w całym analizowanym okresie (36.3 vs 28.4%, P=0.037). Nie stwierdzono również różnic w śmiertelności długoterminowej w zakresie poszczególnych typów MI. Jak ustalono w przeprowadzonej analizie wieloczynnikowej, MI w NWD był jedną z niezależnych determinant śmiertelności ogólnej (HR, ang. *hazard ratio* 1.027; 95% CI 1.022–1.032, P<0.001), a jego wpływ był szczególnie zaznaczony w 2 i 3 roku obserwacji.

Rozpoznanie MINOCA, zgodnie z przyjętą definicją, było stawiane istotnie częściej w WD (9 vs 4%, P=0.019). Pacjenci z MINOCA przyjmowani w NWD oraz WD nie różnili się pod względem charakterystyki klinicznej, angiograficznej i laboratoryjnej. W obu grupach wyraźnie dominowało rozpoznanie NSTEMI (100 vs 84.5%, P=0.25). Grupy NWD i WD nie różniły się również długością trwania hospitalizacji (4 [3–5] vs 4 [3–7] dni, P=0.85). W obu grupach nie odnotowano zgonów wewnątrzszpitalnych. W obserwacji odległej nie obserwowano różnic w śmiertelności ogólnej pomiędzy pacjentami z MINOCA przyjętymi w NWD lub w WD (22.2 vs 31%, P=0.35). Różnic nie stwierdzono również w bezpośrednim porównaniu całych grup z MINOCA i MI-CAD (29.9 vs 30.5%, P=0.28), a także odpowiednio przyjętych w WD (31 vs 28.1%, P=0.74) oraz NWD (22.2 vs 36.9%, P=0.12). Rozpoznanie MINOCA nie było również niezależnym czynnikiem prognostycznym śmiertelności ogólnej.

**Wnioski**: Pomimo obserwowanego w ostatnich latach dynamicznego rozwoju sieci pracowni hemodynamicznych, pacjenci hospitalizowani w NWD charakteryzują się gorszym rokowaniem długoterminowym. Zaprezentowane wyniki po raz pierwszy wskazują, że zawał MINOCA był istotnie częściej diagnozowany w WD. Samo rozpoznanie MINOCA, w przeciwieństwie do faktu wystąpienia MI w NWD, nie było czynnikiem w sposób niezależny powiązanym ze śmiertelnością odległą.

## Publikacja 3

Rozpoznanie zawału MINOCA było stawiane istotnie częściej u pacjentów z aktywną chorobą nowotworową (15.7 vs. 5.8%, P<0.001). W obu grupach MINOCA, częściej aniżeli w odpowiednich grupach MI-CAD, były reprezentowane kobiety, a w grupie pacjentów onkologicznych z MINOCA częściej odnotowano niedokrwistość (47.6 vs 21.6%, P<0.05). W obu grupach MINOCA przeważało rozpoznanie NSTEMI (71.4 oraz 88.2%). Przy wypisie zastosowano również podobne leczenie w tych podgrupach. Aspiryna została włączona u 9 na 10 pacjentów, a inhibitor P2Y12 u około połowy pacjentów. W wykonanych badaniach echokardiograficznych, w porównaniu do pacjentów z MINOCA bez choroby nowotworowej, stwierdzono częstsze występowanie TTS (19.1 vs 2.0%, P=0.010), wyższe wartości ciśnienia skurczowego w prawej komorze (RVSP, ang. *right ventricular systolic pressure*) (P=0.03) oraz mniejsze wymiary lewego przedsionka (P=0.05) w grupie onkologicznej. Jednocześnie nie stwierdzono istotnych różnic w LVEF.

Wśród pacjentów z MINOCA i MI-CAD aktywna choroba nowotworowa była diagnozowana istotnie częściej u tych pierwszych (29.2 vs 12.0%, P<0.001). Ograniczając analizę jedynie do chorych z choroba nowotworową zauważono, że wśród pacjentów z MI-CAD w porównaniu do MINOCA częściej byli to mężczyźni (77.9 vs 38.1%, P<0.05). W grupie z MINOCA blisko dwa razy rzadziej włączano inhibitory P2Y12 (47.6 vs 92.9%, P<0.001) i inhibitory pompy protonowej (38.1 vs 74.3%, P=0.001) a także statyny (66.7 vs 87.6%, P<0.05) niż w grupie MI-CAD. U około połowy pacjentów z chorobą nowotworową rozpoznaną podczas analizowanej hospitalizacji diagnoza nastąpiła z powodu krwawienia po włączeniu leczenia przeciwpłytkowego lub przeciwkrzepliwego. W obu grupach dominowały nowotwory układu moczowo-płciowego (38.1 oraz 31.9%). Rak piersi występował częściej w grupie MINOCA (23.8 vs 5.3%, P=0.02) niż w MI-CAD. Nie stwierdzono różnic w stopniu

zaawansowania choroby nowotworowej, a także w rodzaju stosowanego przed wystąpieniem MI leczenia przeciwnowotworowego. TTS był diagnozowany wyłącznie w grupie z MINOCA (19.1 vs 0.0%, P<0.05). W porównywanych grupach nie stwierdzono różnic w wartości RVSP oraz LVEF, natomiast odnotowano większe końcoworozkurczowe i końcowoskurczowe wymiary lewej komory w grupie MI-CAD, jednak bez istotnego związku ze stosowanym wcześniej leczeniem przeciwnowotworowym.

W obu grupach onkologicznych zarówno z MINOCA jak i MI-CAD stwierdzono wyjściowo niższe wartości hemoglobiny oraz wyższe wysokoczułej troponiny T w porównaniu do odpowiednich chorych bez nowotworu. Po wzięciu poprawki na funkcję nerek najsilniejsza odwrotna korelacja hemoglobina-troponina T została stwierdzona dla onkologicznej grupy MINOCA. Dla każdej z czterech analizowanych podgrup obliczono także wskaźnik troponina T/hemoglobina, który był znamiennie większy w obu grupach onkologicznych w porównaniu z odpowiednimi grupami bez choroby nowotworowej.

Mediana czasu trwania obserwacji długoterminowej nieonkologicznych MINOCA i MI-CAD oraz onkologicznych MINOCA i MI-CAD wynosiła odpowiednio 73.4 [33.7–81.7], 41.9 [28.1–73.5], 35.0 [6.2–77.2] oraz 17.3 [4.9–43.9] miesięcy (P<0.001). Jak przewidywano w obu grupach z aktywną chorobą nowotworową stwierdzano częstsze zgony z przyczyn nowotworowych. Z kolei w pozostałych grupach dominowały przyczyny sercowo-naczyniowe. Rokowanie długoterminowe było istotnie lepsze odpowiednio w MINOCA nienowotworowej niż nowotworowej (HR 4.07, 95% CI 1.72–9.64, P=0.002) oraz w MI-CAD nienowotworowym niż nowotworowym (HR 7.62, 95% CI 5.13–11.31, P<0.001). Nie zaobserwowano jednak różnic pomiędzy wyróżnionymi grupami onkologicznymi i nieonkologicznymi. Mediana przeżycia dla nowotworów piersi, układu moczowo-płciowego, przewodu pokarmowego oraz płuca wyniosła odpowiednio 56, 39, 12 oraz 10 miesięcy. Pacjenci z nowotworem układu moczowo-płciowego (HR 0.34, 95% CI 0.18–0.65, P=0.001)

oraz piersi (HR 0.39, 95% CI 0.18–0.85, P=0.02) rokowali istotnie lepiej niż z rakiem płuca. W przeprowadzonej na całej grupie analizie wieloczynnikowej wykazano, że aktywna choroba nowotworowa, niższe wartości hemoglobiny oraz brak rozpoznania MINOCA były niezależnymi czynnikami pozwalającymi prognozować śmiertelność w obserwacji długoterminowej. Z kolei, analiza wieloczynnikowa ograniczona jedynie do pacjentów z MINOCA wskazała wiek, aktywną chorobę nowotworową oraz LVEF jako zmienne niezależnie powiązane ze śmiertelnością długoterminową.

**Wnioski**: Przedstawione wyniki oparte o dane z rejestru kardioonkologicznego wskazują, że aktywny proces nowotworowy występuje istotnie częściej u pacjentów z MINOCA niż z MI-CAD. Po raz pierwszy zaprezentowano szczegółową charakterystykę onkologiczną pacjentów z MINOCA. W obu grupach MINOCA i MI-CAD występowanie aktywnej choroby nowotworowej wiązało się z bardzo wysoką śmiertelnością ogólną w obserwacji 5-letniej i było silnym, niezależnym czynnikiem pogarszającym rokowanie długoterminowe.

# 7. Dyskusja

Artykuły stanowiące rozprawę doktorską poruszają różne aspekty dotyczące złożonej jednostki chorobowej jaką jest MINOCA. Dedykowana dyskusja związana z tematyką każdej z włączonych do rozprawy prac została szczegółowo w nich omówiona. Poniższa dyskusja ma charakter podsumowujący znaczenie już opublikowanych prac, ich rozpoznawalność, walory, ale też słabe punkty oraz prezentuje potencjalne dalsze perspektywy badawcze.

Większość uzyskanych wyników oraz wyciągniętych na ich podstawie wniosków w sposób istotny poszerza dotychczasową wiedzę. Opracowane artykuły zostały opublikowane w ciągu ostatnich 3 lat, począwszy od 2019 roku. Na podstawie bazy danych Web of Science aktualna na dzień złożenia rozprawy doktorskiej liczba cytowań w pracach pełnotekstowych wynosiła odpowiednio 19 dla Publikacji 1 i 3 dla Publikacji 2. Analizując aktualne piśmiennictwo można zauważyć, że wiedza dotycząca poruszanych w prezentowanych pracach aspektów MINOCA od momentu ich publikacji w sposób istotny nie poszerzyła się. W podobnej do Publikacji 1 analizie zaprezentowanej podczas kongresu ESC w 2020 przez Kruchinova i wsp., opartej na podobnej liczbie pacjentów, powtórzono nasze wnioski dotyczące częstości występowania trombofilii w MINOCA [23]. Publikacja 1 została zacytowana w przeglądach literatury poświęconych przedwczesnemu MI opublikowanym w *Journal of the American College of Cardiology* [24] oraz MINOCA w *Current Atherosclerosis Reports* [25]. W doniesieniu z *Thrombosis Research* wykazano wysoką częstość APS u pacjentów z MI <40 roku życia i na tej podstawie zasugerowano konieczność regularnego testowania w kierunku APS w tej grupie chorych [26]. Zgodnie z naszą wiedzą do tej pory nie opublikowano nowych istotnych danych dotyczących chronobiologii oraz *efektu weekendu* w MINOCA. W dalszym ciągu oczekujemy również na kolejne doniesienia dotyczące MINOCA u pacjentów onkologicznych.

Bez wątpienia wyciągnięte przez nas wnioski w omawianych trzech publikacjach wymagają weryfikacji w większych kohortach, aby mogły stanowić solidną podstawę do wpływu na codzienną praktykę kliniczną. Są one również dobrym punktem wyjścia do nowych i ukierunkowanych badań nad zagadnieniem MINOCA. Wartość prognostyczna zaproponowanego przez nas testowania w kierunku trombofilii oraz włączania przewlekłej terapii przeciwzakrzepowej w starannie wyselekcjonowanej grupie pacjentów wymaga zweryfikowania w dobrze zaprojektowanych badaniach klinicznych. Jak wspomniano wcześniej duże nadzieje w tym aspekcie są wiązane z rozpoczynanym badaniem PROMISE [9]. Istotność wpływu chronobiologii oraz okołodobowego stresu na wystąpienie MINOCA może wymagać przeprowadzenia podobnych badań do tych w TTS związanych z oceną poziomu poszczególnych hormonów stresu [27]. Biorąc pod uwagę najnowsze doniesienia, wydaje się, że kluczowe mogą być szczegółowe badania neurobiologiczne. W zaprezentowanym podczas kongresu ESC 2020 przez Williams i wsp. badaniu przeprowadzonym na grupie 39 pacjentów z MINOCA wykazano, że charakteryzują się oni wyższą częstością zaburzeń psychicznych oraz wyższym poziomem lęku przy przyjęciu w porównaniu do klasycznego STEMI [28]. Ponadto, w obrazowaniu mózgowia z wykorzystaniem rezonansu magnetycznego pacjenci z MINOCA mieli istotnie mniejszą objętość istoty szarej w korze oczodołowo-czołowej, a więc w obszarze odpowiedzialnym za przetwarzanie emocji i ściśle związanym z lękiem i depresją [28]. Proponowana przez nas w Publikacji 3 hipoteza zwiększonej krzepliwości krwi u pacjentów onkologicznych z MINOCA wymaga przeprowadzenia szczegółowych badań z wykorzystaniem zaawansowanych metod, takich jak np. analiza skrzepu fibrynowego oraz kalibrowany automatyczny trombogram, wykorzystywanych już przez nas zespół we wcześniejszych projektach [29, 30].

Wchodzące w skład rozprawy doktorskiej prace mają szereg ograniczeń. We wszystkich analizowana grupa pacjentów z MINOCA była stosunkowo niewielka. Dane pochodziły tylko z jednego ośrodka, co prawda o dużej liczbie pacjentów hospitalizowanych w ciągu roku, niemniej reprezentatywność naszych wyników dla szerszych populacji wymaga weryfikacji. Jednak największym ograniczeniem był brak wykorzystania zalecanych obecnie metod obrazowych w tej grupie pacjentów, takich jak rezonans magnetyczny serca czy obrazowanie wewnątrzwieńcowe [1, 2, 8]. Wynikało to przede wszystkim z retrospektywnego charakteru prac oraz ograniczonego dostępu do tych badań w warunkach polskich w analizowanym okresie. Niewątpliwie powinny one być wykorzystywane w kolejnych badaniach dotyczących pacjentów z MINOCA.

# 8. Streszczenie pracy doktorskiej w języku polskim

***Wstęp***

Zawał mięśnia sercowego bez istotnych zmian w tętnicach wieńcowych (MINOCA), definiowany aktualnie przez brak stwierdzanych zwężeń ≥50% w koronarografii, stanowi istotny odsetek pacjentów z zawałem mięśnia sercowego (MI). W istniejącej literaturze istnieją sprzeczne dane dotyczące rokowania długoterminowego w grupie chorych z MINOCA. Nie ulega natomiast wątpliwości, że chorzy z MINOCA stanowi heterogenną jednostkę chorobową o złożonej etiologii. Zgodnie z aktualnymi wytycznymi rozpoznanie MINOCA powinno być traktowane jako diagnoza robocza wymagająca szczegółowego doprecyzowania. Jednym z zalecanych badań jest testowanie w kierunku trombofilii. W literaturze brakuje jednak danych dotyczących wykorzystania ich pełnego panelu w tej grupie pacjentów. Do tej pory nie została odpowiednio zbadana kwestia chronobiologii MINOCA i wpływu *efektu weekendu*. Potencjalnie, grupą szczególnie narażoną na wystąpienie MINOCA są chorzy onkologiczni. Brakuje jednak danych dotyczących rzeczywistej skali tego zjawiska i jego znaczenia prognostycznego.

***Cele pracy***

1) ocena częstości występowania trombofilii u pacjentów z MINOCA w porównaniu do pacjentów z udarem kryptogennym i analiza jej znaczenia klinicznego
2) określenie chronobiologii MINOCA i analiza wpływu *efektu weekendu* na rokowanie odległe
3) określenie charakterystyki klinicznej oraz rokowania długoterminowego u pacjentów onkologicznych z MINOCA

*Materiały i metody*

Pełny panel trombofilii został oceniony prospektywnie u 84 pacjentów z MINOCA. Jako grupę kontrolną wybrano 84 pacjentów z udarem kryptogennym (CS). U wszystkich pacjentów wykonano pełny panel najczęstszych trombofilii zgodnie z aktualną metodyką i zaleceniami.

Ocenę występowania *efektu weekendu* przeprowadzano na grupie 865 kolejnych pacjentów z rozpoznaniem MI, u których została wykonana koronarografia. 642 (74.2%) zostało przyjętych w dni robocze (WD), a 223 (25.8%) w dni nierobocze (NWD). Spośród tej grupy 67 (7.7%) spełniało kryteria rozpoznania MINOCA. Punktem końcowym była śmiertelność ogólna oceniana w obserwacji odległej.

Grupę pacjentów z MINOCA i aktywną chorobą nowotworową wyodrębniono z rejestru kardioonkologicznego opartego na 1011 kolejnych pacjentach przyjętych z rozpoznaniem MI zweryfikowanym koronarografią. Spośród nich 72 (7.1%) spełniało kryteria rozpoznania MINOCA. U 134 pacjentów (13.3%) zidentyfikowano aktywny proces nowotworowy i szczegółowo określono ich charakterystykę onkologiczną. Punktem końcowym była śmiertelność ogólna oceniana w obserwacji odległej.

*Wyniki*

Trombofilie zostały znalezione u 23.8% pacjentów z MINOCA oraz 15.5% z CS (P=0.17). W obu grupach obserwowano zbliżony rozkład poszczególnych trombofilii, z wyjątkiem niższej częstości podwyższonego poziomu lipoproteiny (a) w grupie MINOCA (21.4 vs 39.3%, P=0.012). Najczęstszą wrodzoną trombofilią diagnozowaną u pacjentów z MINOCA była mutacja czynnika V Leiden (14.3%). Z kolei, APS został rozpoznany u 15.5%. Zestawiając uzyskane wyniki z danymi pochodzącymi z literatury dla populacji

ogólnej stwierdzono nadreprezentację wszystkich oznaczanych trombofilii w grupie MINOCA.

Rozpoznanie MINOCA było stawiane istotnie częściej w WD (9 vs 4%, P=0.019). Pacjenci z MINOCA przyjmowani w NWD oraz WD nie różnili się pod względem charakterystyki klinicznej, angiograficznej i laboratoryjnej. Wśród tych chorych nie odnotowano zgonów wewnątrzszpitalnych. W obserwacji odległej nie odnotowano różnic w śmiertelności ogólnej pomiędzy pacjentami z MINOCA przyjętymi w NWD oraz WD (22.2 vs 31%, P=0.35). Rozpoznanie MINOCA nie było również niezależnym czynnikiem pozwalającym prognozować długoterminową śmiertelność ogólną.

Występowanie aktywnej choroby nowotworowej było istotnie częstsze w MINOCA niż w MI ze zmianami w tętnicach wieńcowych (MI-CAD) (29.2 vs 12.0%, P<0.001). Rokowanie długoterminowe było istotnie lepsze odpowiednio w MINOCA nienowotworowej niż nowotworowej (HR 4.07, 95% CI 1.72–9.64, P=0.002) oraz w MI-CAD nienowotworowym niż nowotworowym (HR 7.62, 95% CI 5.13–11.31, P<0.001). W przeprowadzonej na całej grupie analizie wieloczynnikowej wykazano, że aktywna choroba nowotworowa, niższe wartości hemoglobiny oraz brak rozpoznania MINOCA były niezależnymi czynnikami umożliwiającymi prognozowanie śmiertelności długoterminowej. Z kolei, analiza wieloczynnikowa ograniczona tylko do pacjentów z MINOCA wskazała wiek, aktywną chorobę nowotworową oraz LVEF jako zmienne niezależnie powiązane ze śmiertelnością długoterminową.

***Wnioski***

1) Pacjenci z MINOCA charakteryzują się wysoką częstością występowania trombofilii, porównywalną z CS.

2) Pacjenci z MINOCA są częściej diagnozowani i leczeni w WD a samo rozpoznanie MINOCA w przeciwieństwie do faktu wystąpienia MI w NWD nie jest w sposób niezależny powiązane ze śmiertelnością długoterminową.
3) Aktywny proces nowotworowy występuje istotnie częściej w zawale MINOCA niż u pacjentów z MI-CAD. Jego występowanie wiąże się z bardzo wysoką śmiertelnością ogólną w obserwacji długoterminowej.

# 9. Streszczenie pracy doktorskiej w języku angielskim

***Introduction***

Myocardial infarction with non-obstructive coronary arteries (MINOCA), currently defined by the lack of ≥50% stenosis in the coronary angiography, constitutes a significant percentage of patients with myocardial infarction (MI). There are conflicting data concerning long-term prognosis in MINOCA patients. Undoubtedly, MINOCA is a heterogeneous group of disease entities with often complex etiopathogenesis. According to the current guidelines, MINOCA should be considered as a working diagnosis that requires a subsequent diagnostic process. Testing for thrombophilia is one of the recommended steps. However, in the literature there is the lack of data of their full panel use in this group of patients. The issue of MINOCA chronobiology and the impact of the *weekend effect* has not been adequately explored yet. Oncological patients are potentially the group particularly at risk of MINOCA occurrence. However, there is a lack of data on the actual scale of this phenomenon and its prognostic significance.

***Objectives***

1) to assess the frequency of individual thrombophilia in patients with MINOCA compared to patients with cryptogenic stroke and to analyze its clinical significance
2) to determine the MINOCA chronobiology and to analyze the impact of the *weekend effect* on long-term prognosis
3) to determine the clinical characteristics and long-term prognosis in oncological patients with MINOCA

***Materials and methods***

The full thrombophilia panel was evaluated in a prospective cross-sectional study of 84 patients with MINOCA. As controls served 84 patients with cryptogenic stroke (CS). A full panel of the most common thrombophilia was performed in all patients in accordance with the current methodology and recommendations.

The assessment of the occurrence of the *weekend effect* was carried out in a group of 865 consecutive MI patients diagnosed who underwent coronary angiography. 642 (74.2%) were admitted on working days (WD), while 223 (25.8%) on non-working days (NWD). Of this group, 67 (7.7%) met the criteria for MINOCA diagnosis. The study endpoint was the overall long-term mortality .

The group of patients with MINOCA and active cancer was selected from the cardiooncology registry of 1011 consecutive MI patients who underwent coronary angiography. Of these, 72 (7.1%) met the criteria for MINOCA diagnosis. Active cancer was identified in 134 patients (13.3%) and their oncological characteristics were determined in detail. The study endpoint was the overall long-term mortality.

***Results***

Thrombophilia was found in 23.8% of MINOCA patients and 15.5% of CS patients (P=0.17). A similar distribution of individual thrombophilia was observed in both compared groups, except for a lower frequency of elevated lipoprotein (a) levels in MINOCA (21.4 vs 39.3%, P=0.012). The most common inherited thrombophilia diagnosed in MINOCA patients was the factor V Leiden mutation (14.3%). In turn, APS was diagnosed in 15.5%. By comparing the obtained results with the data from the literature for the general population, it was found that all the determined thrombophilia were overrepresented in the MINOCA group.

The MINOCA diagnosis was significantly more frequent in WD (9 vs 4%, P=0.019). Patients admitted on NWD and WD did not differ in terms of clinical, angiographic and laboratory characteristics. There were no in-hospital deaths in both MINOCA subgroups. In long-term follow-up, there was no difference in the overall mortality in MINOCA patients admitted on NWD and WD (22.2 vs 31%, P=0.35). The MINOCA diagnosis was also not an independent predictor of all-cause mortality in the multivariate analysis.

An active cancer was significantly more frequent in patients with MINOCA than with MI and obstructive coronary artery disease (MI-CAD) (29.2 vs 12.0%, P<0.001). The long-term prognosis was significantly better in non-cancer than cancer MINOCA (HR 4.07, 95% CI 1.72–9.64, P=0.002) and in non-cancer than cancer MI-CAD (HR 7.62, 95% CI 5.13–11.31, P<0.001), respectively. A multivariate analysis showed that active cancer, lower hemoglobin values, and no MINOCA diagnosis were independent predictors of long-term mortality. In turn, multivariate analysis limited to MINOCA patients identified age, active cancer and left ventricular ejection fraction as variables independently associated with long-term mortality.

***Conclusions***

1) Patients with MINOCA are characterized by a high incidence of thrombophilia, similar to CS.
2) MINOCA is significantly more often diagnosed in WD. The diagnosis of MINOCA itself, in contrast to the MI admitted on NWD, is not independently associated with long-term overall mortality.
3) An active cancer is significantly more frequent in MINOCA than in MI-CAD patients. Its occurrence is associated with extremely high overall long-term mortality.

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# 11. Artykuły stanowiące monotematyczny cykl publikacji

## *Publikacja 1*

***"High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: Comparison with cryptogenic stroke."***

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# High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: Comparison with cryptogenic stroke☆,☆☆

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ABSTRACT

*Background:* A role of thrombophilia in myocardial infarction with non-obstructive coronary arteries (MINOCA) is unclear. We investigated thrombophilic factors in MINOCA patients versus those following cryptogenic stroke (CS), a well-established indication for thrombophilia screening.

*Methods:* In a prospective cross-sectional study, we assessed 84 consecutive patients (median age: 45.5 years) at least 3 months after MINOCA. Age-matched CS patients (n = 84) and published data on general population served as controls. Thrombophilia screening involved inherited thrombophilia (factor V Leiden, prothrombin G20210A mutation, deficiency of protein C, protein S or antithrombin), antiphospholipid syndrome (APS), along with factor VIII >150%, homocysteine ≥15 μM and lipoprotein (a) >30 mg/dl.

*Results:* Compared to CS, MINOCA were more often males (60.7 vs 33.3%, P < 0.001), obese (34.5 vs 17.9%, P = 0.014), smokers (51.2 vs 35.7%, P = 0.043) and had family history of myocardial infarction (27.4 vs 6.0%, P < 0.001). Inherited thrombophilia occurred in 20 (23.8%) MINOCA patients and in 13 (15.5%) with CS (P = 0.17), without any difference in the parameters except for elevated lipoprotein (a) that was less common in MINOCA (21.4 vs 39.3%, P = 0.012). APS was found in 13 (15.5%) of MINOCA patients, mostly in a single-positive form. APS was diagnosed less frequently in STEMI (2.5 vs 27.3% for NSTEMI, P = 0.002) and MINOCA patients aged ≤50 years (5.7 vs 32.3% for older subjects, P = 0.003).

*Conclusions:* MINOCA patients exhibit high prevalence of thrombophilia including APS, similar to that in CS. Our first comprehensive thrombophilia testing in MINOCA supports its clinical relevance and the need for long-term anticoagulation for some abnormalities, especially APS.



## 1. Introduction

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is clinically defined by general criteria for MI with the absence of obstructive coronary artery disease [1]. Large registries showed that MINOCA represents 1–13% of patients with MI [2–4]. A systematic review involving 28 publications showed that compared with obstructive MI patients, those with MINOCA were more likely to be younger and female but less often had hyperlipidemia [5]. Moreover, the prognosis of patients with MINOCA is likely to be more favourable as suggested by in-hospital all-cause mortality (0.9 vs 3.2%; odds ratio (OR) 0.37; 95% confidence interval (CI) 0.2–0.67) compared with obstructive MI [5].

The etiology of MINOCA remains unclear. Several potential mechanisms, such as vasospasm, spontaneous coronary dissection, microcirculation dysfunction, takotsubo cardiomyopathy or myocarditis have been proposed so far [6]. It has been also postulated that MINOCA

*Abbreviations:* MINOCA, myocardial infarction with non-obstructive coronary arteries; MI, myocardial infarction; FVL, factor V Leiden; APS, antiphospholipid syndrome; PC, protein C deficiency; PS, protein S deficiency; AT, antithrombin deficiency; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; VTE, venous thromboembolism; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant.

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results from in situ thrombus formation with the subsequent lysis, thereby resulting in a morphologically normal angiogram [6]. A prothrombotic state, both inherited or acquired, may lead to such a sequence of pathological events [7]. In the latest MINOCA position paper of the European Society of Cardiology (ESC), a diagnostic flow chart includes imaging methods with a key role of cardiac magnetic resonance, invasive investigations (intravascular ultrasound (IVUS), optical coherence tomography (OCT), provocative spasm testing) and laboratory assays, including thrombophilia screening [1,8] as previously suggested [7]. Individual thrombophilic disorders differ in their prevalence in the general population and their effect on prothrombotic potential – from a 50–100 fold higher thrombosis risk in homozygous factor V Leiden (FVL) to only a mild impact of protein S deficiency (PS) in terms of venous thromboembolism (VTE), the most common indication for such testing [9]. To our knowledge, there has been no single study exploring all known thrombophilias of established clinical relevance in patients with MINOCA. A few small studies yielded inconsistent results [10–13]. In the largest systemic review including 8 available reports involving 378 MINOCA patients who underwent partial thrombophilia screening, thrombophilia disorders were found in 14% and as expected the most common thrombophilia was FVL detected in 12% [5].

A common indication for thrombophilia screening is cryptogenic stroke, defined as symptomatic cerebral infarcts for which no probable cause is identified after adequate diagnostic evaluation [14]. Despite the relatively small groups of cryptogenic stroke patients, significantly higher frequencies of antiphospholipid syndrome (APS) [15] as well as similar trend in case of FVL [16] in comparison to healthy controls were described. Thrombophilic disorders can be detected among 44% of patients with cryptogenic stroke based on extended thrombophilia panel [17]. APS is a well-known independent prothrombotic risk factor for the first and recurrent ischemic stroke especially in young adults [18]. No consistent association between ischemic stroke and FVL, prothrombin G20210A mutation as well as rare deficiencies of protein C (PC), PS or antithrombin (AT) has been demonstrated so far [19–23]. Taken together, solely APS is a well-established risk factor for ischemic stroke at a younger age, which is routinely assessed.

We hypothesized that patients with MINOCA have a significant prevalence of thrombophilia including APS which is similar to that observed for cryptogenic stroke. Therefore, we sought to investigate thrombophilia in MINOCA as compared to that detected in cryptogenic stroke.

## 2. Material and methods

In this prospective cross-sectional study, we enrolled consecutive ambulatory patients with MINOCA and cryptogenic stroke who were referred for further clinical and laboratory work-up between March 2014 and October 2018. Patients were eligible if 3 months or more (up to 18 months) elapsed from the event. Exclusion criteria were as follows: signs of acute infection on the day of blood collection, known malignancy, hemodialysis, current anticoagulant therapy, other documented thromboembolic event within the three preceding months. MINOCA was defined as MI (positive cardiac biomarkers - rising and/or falling in serial levels, with at least one value above 99th percentile upper reference limit and at least one clinical evidence of infarction) without angiographic obstructive coronary artery disease (no lesions ≥50% in coronary angiography) [1]. Patients with ST-segment elevation in at least two contiguous leads were classified as ST-segment elevation MI (STEMI). In contrast, patients without ST-segment elevation at presentation are designated as non-ST-segment elevation MI (NSTEMI) [8]. The age-matched control group represented patients who experienced ischemic stroke confirmed by brain imaging that was not referred to definite cardioembolism, large artery atherosclerosis or small artery disease despite a standard vascular, cardiac and serologic (international normalized ratio (INR), activated partial thromboplastin time (APTT), complete blood count, platelet count) evaluation as described previously [14,24,25].

Comorbidities and cardiovascular risk factors were analyzed. The diagnosis of obesity was established based on body mass index (BMI) over 30 kg/m$^2$. Hyperlipidemia was defined as total cholesterol (TC) >5.0 mmol/l (190.0 mg/dl), low-density lipoprotein (LDL) cholesterol >2.6 mmol/l (100.0 mg/dl), and triglycerides (TG) >1.7 mmol/l (150 mg/dl) or ongoing lipid-lowering treatment. Diabetes mellitus was stated as a history of diabetes, need for antidiabetic agents, or fasting plasma glucose ≥126 mg/dl (7 mmol/l) on two separate occasions. Hypertension was defined as office systolic blood pressure values ≥140 mmHg and/or diastolic blood pressure values ≥90 mmHg or current antihypertensive treatment [26]. Renal failure was diagnosed when creatinine clearance calculated using the Cockcroft-Gault formula was lower than 60 ml/min. A positive family history of MI in first degree relatives (parents, offspring and siblings) without an age cut-off for premature MI was ascertained by interviewing the patients. Prior VTE was recognized in patients with history of symptomatic deep-vein thrombosis and/or pulmonary embolism that were confirmed by colour duplex sonography or computed tomography pulmonary angiography, respectively. Patients who had experienced VTE in the past and stopped therapy, respectively, received vitamin K antagonists (VKA) following MINOCA and CS on the physician's discretion. VKA treatment due to suspected thrombophilia was also allowed.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Jagiellonian University. All included patients gave informed consent.

### 2.1. Sample collection

Patients on VKA discontinued anticoagulation up to 7–14 days and were switched to a low-molecular-weight heparin at therapeutic doses with blood collection >12 h since the last injection (the anti-Xa activity below 0.1 IU/ml). In patients on non-VKA oral anticoagulants (NOACs) blood was taken >24 h since the last dose (drug concentrations below 30 ng/ml when measured using the Hemoclot Thrombin Inhibitor assay for dabigatran and the anti-Xa chromogenic assay, Biophen DiXal for rivaroxaban; both, Hyphen BioMed, Neuville-sur-Oise, France).

Blood samples were drawn from an antecubital vein into tubes containing citrate anticoagulant (9:1 of 0.106 M sodium citrate), centrifuged at 2.500g at a temperature of 18 °C to 22 °C for 20 min and processed immediately or stored in aliquots at −80 °C until analysis. Whole blood samples for DNA isolation were drawn into EDTA-K3 collection tubes and stored in aliquots at −80 °C until processing.

### 2.2. Thrombophilia testing

Genetic analysis of FVL (dbSNP ID: rs6025) and prothrombin G20210A (dbSNP ID: rs1799963) mutations were determined using TaqMan Genotyping Assays (Assay ID: C_11975250_10 and C_8726802_20, respectively; ThermoFisher Scientific, Waltham, Massachusetts, USA) on QuantStudio Dx Real-Time PCT Instrument (ThermoFisher Scientific). Plasma PC activity was quantified using a chromogenic assay (HemosIL Protein C Instrumentation Laboratory, Milan, Italy or Berichrom Protein C, Siemens Healthcare Diagnostics). Results below 70% were recognized as suggestive of PC deficiency. Free PS levels were measured using an immunoturbidimetric assay (INNOVANCE® Free PS Ag, Siemens Healthcare Diagnostic). PS deficiency was diagnosed at the level of 60% or less. AT activity was assessed using an assay based on FXa inhibition (INNOVANCE™ ATIII, Siemens Healthcare Diagnostics, Marburg, Germany) with AT deficiency diagnosed when the level was below 75%. Two positive results were required to confirm the anticoagulant deficiency [27].

APS was diagnosed according to the current recommendations [28]. The levels of IgG/IgM anticardiolipin and anti-β-2 glycoprotein I

antibodies were determined by enzyme-linked immunosorbent immunoassays (INOVA Diagnostic, San Diego, CA, USA). The anticardiolipin antibodies IgG ≥15 GPL and IgM ≥12.5 MPL were assumed as positive. Positive values for anti-β-2 glycoprotein I antibodies were ≥20 Standard IgG and IgM (SGU and SMU) [29]. Lupus anticoagulant was determined as recommended [30]. The APS was categorized as a single-, double- and triple-positive syndrome based on the number of detected antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β-2 glycoprotein I antibodies). As was documented, thromboembolic risk increases with each additional antiphospholipid antibody detected. The number of detected antibodies also influences on the decision about appropriate anticoagulant therapy [31].

Plasma FVIII activity was determined by the coagulometric assay using a deficient plasma (Siemens Healthcare Diagnostics) and levels of 150% or more were considered elevated. Fasting total plasma homocysteine (tHcy) was determined in plasma by the enzymatic assay (Roche Diagnostics, Mannheim, Germany). Hyperhomocysteinemia was defined as tHcy ≥15 μmol/l. Lipoprotein (a) was assessed in serum by an immunoenzymatic assay (DRG Diagnostics, Marburg, Germany) with a lower detection limit of 1.2 mg/dl. Elevated lipoprotein (a) was diagnosed >30 mg/dl. Intra-assay and inter-assay coefficients of variation for all commercially available assays were <7%.

### 2.3. Statistical methods

Statistical analyses were performed with Statistica 13.1 software (StatSoft, Tulsa, OK). Continuous variables are expressed as mean ± standard deviation or median and IQR, whereas categorical variables as number (percentage). Continuous variables were first checked for normal distribution by the Shapiro-Wilk test and then were compared by Student's *t*-test or U-Mann Whitney test if distribution was normal or different than normal, respectively. Categorical variables were analyzed by chi-square test or Fisher exact test. All clinical and laboratory parameters associated ($P < 0.2$) with APS, hyperhomocysteinemia, factor VIII > 150% and lipoprotein (a) >30 mg/dl and not correlated with another independent variable were identified and then included in the multivariate logistic regression models to identify predictors of above-mentioned disorders. Two-sided P-value of <0.05 was considered statistically significant.

## 3. Results

As shown in Table 1, the MINOCA and cryptogenic stroke patients were similar in terms of most cardiovascular risk factors, the history of VTE and the medications used at the time of blood collection. However, MINOCA patients were more often males (60.7 vs 33.3%, $P < 0.001$), obese (34.5 vs 17.9%, $P = 0.014$), current smokers (51.2 vs 35.7%, $P = 0.043$) and were more likely to have a family history of MI (27.4 vs 6.0%, $P < 0.001$). As expected, patients with MINOCA were frequently treated with P2Y12 inhibitors (81.0 vs 0.0%, $P < 0.001$) and beta-blockers (31.0 vs 8.3%, $P < 0.001$) as compared with patients with cryptogenic stroke.

**Table 1**
Patient characteristics.

| | MINOCA N = 84 | Cryptogenic stroke N = 84 | P-value |
|---|---|---|---|
| Age, years | 45.5 (37.0–56.5) | 46.0 (37.5–55.0) | 0.76 |
| Male gender | 51 (60.7%) | 28 (33.3%) | <0.001 |
| Obesity | 29 (34.5%) | 15 (17.9%) | 0.014 |
| Active smoking | 43 (51.2%) | 30 (35.7%) | 0.043 |
| Hyperlipidemia | 36 (42.9%) | 31 (36.9%) | 0.43 |
| Hypertension | 41 (48.8%) | 45 (53.6%) | 0.54 |
| Diabetes mellitus | 11 (13.1%) | 4 (4.8%) | 0.06 |
| Renal failure | 6 (7.1%) | 6 (7.1%) | 1.00 |
| Family MI | 23 (27.4%) | 5 (6.0%) | <0.001 |
| Prior VTE | 11 (13.1%) | 19 (22.6%) | 0.11 |
| Aspirin | 84 (100%) | 84 (100%) | 1.0 |
| P2Y12 inhibitor | 68 (81.0%) | 0 (0.0%) | <0.001 |
| VKA | 17 (20.2%) | 14 (16.7%) | 0.55 |
| ACE-I | 37 (44.1%) | 45 (53.6%) | 0.22 |
| Beta-blocker | 26 (31.0%) | 7 (8.3%) | <0.001 |
| Statin | 55 (65.5%) | 47 (56.0%) | 0.21 |

Abbreviations: ACE-I: angiotensin-converting-enzyme inhibitor, MI: myocardial infarction, MINOCA: myocardial infarction with non-obstructive coronary arteries, VKA: vitamin K antagonist.

### 3.1. Thrombophilia

Median time elapsed since the ischemic event to blood sampling was similar (8.0 [6.0–10.0] months for MINOCA vs 9.0 [6.0–11.0] months for cryptogenic stroke, $P = 0.56$). Thrombophilic factors and additional prothrombotic variables shown in Table 2 indicate their similar distribution in both groups. Inherited thrombophilia occurred in 20 (23.8%) patients with MINOCA and in 13 (15.5%) with cryptogenic stroke ($P = 0.17$). All patients with FVL and prothrombin G20210A mutation were heterozygous. The most common thrombophilia found in both groups was FVL mutation observed in 12 (14.3%) patients with MINOCA and in 5 (6.0%) patients with cryptogenic stroke. Of note, APS was diagnosed frequently in patients with MINOCA at a similar rate compared with those following stroke (15.5 vs 10.7%, $P = 0.36$). The distribution of a single- (8.3 vs 4.8%, $P = 0.27$), double- (6.0 vs 4.8%, $P = 0.50$) and triple- (1.2 vs 1.2%, $P = 1.00$) positive APS were similar in both groups with the highest proportion of patients with the former form.

There was no significant difference between groups regarding the prevalence of prothrombin 20210A mutation, deficiencies of all three natural anticoagulants, as well as elevated FVIII and hyperhomocysteinemia. We found a lower proportion of patients with MINOCA who had elevated lipoprotein (a) compared with those following cryptogenic stroke (21.4 vs 39.3%, $P = 0.012$).

### 3.2. MINOCA patients with inherited thrombophilia or APS

The patients with MINOCA who had inherited thrombophilia or APS ($n = 28$ [33.3%]) did not differ from the remaining subjects in terms of age (48.5 [38.0–60.0] vs 43 [36.5–54.0] years, $P = 0.13$), gender (male: 64.3 vs 58.9%, $P = 0.64$) and cardiovascular risk factors. The significant difference in the patient characteristics was observed only in terms of clinical presentation, i.e. STEMI was diagnosed less frequently in thrombophilic MINOCA patients (32.1 vs 55.4%, $P = 0.04$). Of note, prior VTE tended to be more frequently observed in thrombophilic patients with MINOCA (21.4 vs 8.9%, $P = 0.11$). As expected, patients with inherited thrombophilia or APS were more frequently treated with VKA following MI (42.9 vs 8.9%, $P < 0.001$).

### 3.3. MINOCA patients ≤50 years

In the MINOCA group, 53 (63.1%) patients aged ≤50 years did not differ from the remainder in terms of the prevalence of inherited thrombophilia (24.5 vs 22.6%, $P = 0.84$) as well as in individual thrombophilic disorders. Surprisingly, APS was diagnosed less frequently in patients ≤50 years (5.7 vs 32.3%, $P = 0.003$), without any differences in the distribution of particular APS types. A similar age-dependent analysis of stroke patients demonstrated no differences in the frequency of inherited thrombophilia (13.2 vs 19.4%, $P = 0.54$) and particular thrombophilic factors.

### 3.4. STEMI versus NSTEMI patients

Among MINOCA patients, 40 (47.6%) STEMI patients were diagnosed (Table 3). Median time elapsed since event of MI to blood sampling was similar (8.0 [6.0–10.0] for STEMI vs 8.5 [7.0–10.0] months for NSTEMI, $P = 0.47$). There were no intergroup differences in the prevalence of

**Table 2**
Thrombophilic factors.

| | MINOCA N = 84 | Cryptogenic stroke N = 84 | P-value | General population |
|---|---|---|---|---|
| Inherited thrombophilia | 20 (23.8%)[a] | 13 (15.5%)[b] | 0.17 | – |
| Factor V Leiden | 12 (14.3%) | 5 (6.0%) | 0.07 | 5.0% [34] |
| Prothrombin G20210A mutation | 4 (4.8%) | 3 (3.6%) | 0.70 | 2.0–3.0% [34] |
| Protein C deficiency | 2 (2.4%) | 1 (1.2%) | 0.56 | 0.2–0.3% [27] |
| Protein S deficiency | 2 (2.4%) | 2 (2.4%) | 1.00 | 0.03–0.1% [34] |
| Antithrombin deficiency | 1 (1.2%) | 3 (3.6%) | 0.31 | 0.02–0.2% [27] |
| Antiphospholipid syndrome | 13 (15.5%) | 9 (10.7%) | 0.36 | 1.0–5.0% [38] |
| Single positive | 7 (8.3%) | 4 (4.8%) | 0.27 | |
| Double positive | 5 (6.0%) | 4 (4.8%) | 0.50 | |
| Triple positive | 1 (1.2%) | 1 (1.2%) | 1.00 | |
| Factor VIII >150% | 23 (27.4%) | 22 (26.2%) | 0.86 | 13.0% [49] |
| Hyperhomocysteinemia | 14 (16.7%) | 8 (9.5%) | 0.17 | 5.0–10.0%[c] [50] |
| Lipoprotein (a) >30 mg/dl | 18 (21.4%) | 33 (39.3%) | 0.012 | 33.0% [42] |

Abbreviations: MINOCA: myocardial infarction with non-obstructive coronary arteries, P-value for differences between groups of MINOCA and cryptogenic stroke.
[a] Coexistence of protein S and antithrombin deficiencies in one patient.
[b] Coexistence of prothrombin G20210A mutation and antithrombin deficiency in one patient.
[c] 12 μM as cut-off point.

inherited thrombophilia (20.0 vs 27.3%, P = 0.43, respectively) as well as in the distribution of individual thrombophilic abnormalities. Unexpectedly, APS was diagnosed less frequently in STEMI patients compared with those with NSTEMI (2.5 vs 27.3%, P = 0.002). When 3 types of APS were analyzed, we found that most NSTEMI patients had a single-positive APS, while this form was absent in the former group (0.0 vs 15.9%, P = 0.008).

### 3.5. Multivariable models

Age of >50 years, NSTEMI and family history of MI were identified as associated (P < 0.2) with the diagnosis of APS in univariate model (Table 4). In a final multivariate model only age of above 50 years was independently associated with APS (OR 6.5; 95% CI 1.6–27.0; $R^2$ = 0.13, P = 0.002).

## 4. Discussion

To our knowledge, the current study is the first to present the results of comprehensive thrombophilia screening in patients with MINOCA. We found that inherited thrombophilia occurred in a substantial proportion of patients, including PC, PS or AT deficiency as well as >10% with APS constituting an indication for life-long anticoagulation which has not been reported so far. We also demonstrated a similar prevalence of inherited thrombophilia and APS in patients with MINOCA and those with cryptogenic stroke. Of practical importance is a higher prevalence of APS among MINOCA patients with NSTEMI compared with STEMI.

**Table 3**
Comparison of STEMI versus NSTEMI patients.

| | STEMI N = 40 | NSTEMI N = 44 | P-value |
|---|---|---|---|
| Inherited thrombophilia | 8 (20.0%) | 12 (27.3%)[a] | 0.43 |
| Factor V Leiden | 4 (10.0%) | 8 (18.2%) | 0.28 |
| Prothrombin G20210A mutation | 2 (5.0%) | 2 (4.5%) | 0.92 |
| Protein C deficiency | 1 (2.5%) | 1 (2.3%) | 0.95 |
| Protein S deficiency | 1 (2.5%) | 1 (2.3%) | 0.95 |
| Antithrombin deficiency | 0 (0.0%) | 1 (2.3%) | 0.34 |
| Antiphospholipid syndrome | 1 (2.5%) | 12 (27.3%) | 0.002 |
| Single positive | 0 (0.0%) | 7 (15.9%) | 0.008 |
| Double positive | 1 (2.5%) | 4 (9.1%) | 0.20 |
| Triple positive | 0 (0.0%) | 1 (2.3%) | 0.34 |
| Factor VIII >150% | 10 (25.0%) | 13 (29.5%) | 0.64 |
| Hyperhomocysteinemia | 6 (15.0%) | 8 (18.2%) | 0.70 |
| Lipoprotein (a) >30 mg/dl | 7 (17.5%) | 11 (25.0%) | 0.40 |

Abbreviations: NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction.
[a] Coexistence of protein S and antithrombin deficiencies in one patient.

Our findings provide additional evidence that thrombophilia testing should be routinely performed in MINOCA patients.

The baseline characteristics of the current MINOCA cohort differed from the systematic review of previous observational studies published in 2015 [5]. The sex distributions were similar, however our group was younger (45.5 vs 58.8 years, respectively). In terms of cardiovascular risk factors, we observed similar proportions of patients with hypertension and diabetes mellitus with much higher prevalence of hyperlipidemia (42.9 vs 21%) and a trend towards a higher frequency of active smoking (51.2 vs 42.0%). These differences might be related to a high prevalence of cardiovascular risk factors and adverse health behaviors in the overall Polish population with hyperlipidemia (60%), low physical activity (50%), hypertension (35%), smoking (31%) and obesity (21%) [32,33]. The current data indicate that MINOCA patients should be carefully evaluated for the presence of modifiable risk factors, especially hyperlipidemia and smoking.

Importantly, analysis of inherited thrombophilias and APS in the current MINOCA group showed that their prevalence is higher than in the general European population and patients with MI reported in the literature. The highest heterozygosity rate for FVL of about 5% is found in Caucasians with a positive gradient from Southern to Northern Europe [34]. FVL was associated with an increased risk of premature MI before the age of 45 years in a large Italian cohort [35]. Our data suggest that the prevalence of FVL is substantially greater in MINOCA compared with premature MI patients or in the general population, which is consistent with the 2015 systematic review [5]. The prothrombin G20210A mutation is associated with elevated circulating prothrombin levels, occurs in 2–3% of Caucasians [34] and shows a moderate relationship with MI [36] that is further enhanced among acute coronary syndrome patients who lack the classic cardiovascular risk factors [37]. In our study, this mutation was observed at a similar rate to that in other studies performed in this region of Europe given higher prevalence of this polymorphism in the south of Europe [10,11]. Moreover, the prevalence of PC, PS and AT deficiencies in the general European population ranges

**Table 4**
Independent determinants of antiphospholipid syndrome in MINOCA group.

| | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | OR | 95% CI | P-value |
| Age > 50 years [yes/no] | 7.9 | 2.0–31.8 | 0.003 | 6.5 | 1.6–27.0 | 0.010 |
| NSTEMI [yes/no] | 14.6 | 1.8–118.6 | 0.012 | NA | NA | NA |
| Family MI [yes/no] | 4.0 | 1.2–13.6 | 0.026 | 2.8 | 0.7–10.3 | 0.13 |

Abbreviations: CI: confidence interval, MI: myocardial infarction, MINOCA: myocardial infarction with non-obstructive coronary arteries, NA: not applicable, NSTEMI: non-ST-segment elevation myocardial infarction, OR: odds ratio.

from 0.2–0.3%, 0.03–0.1% and 0.02–0.2%, respectively [27,34], which indicates that the 3 thrombophilias were observed more frequently in our MINOCA cohort like in the 2015 systematic review [5]. Taken together, the present study supports the view that inherited thrombophilia is overrepresented among patients with MINOCA (Table 2).

Of vital importance is the present observation indicating high prevalence of APS among MINOCA patients. It is known that antiphospholipid antibodies can be found in 1–5% of healthy subjects with an increased prevalence in older subjects, while the incidence of APS in MI was determined at 11% [38]. Noteworthy, the dominant forms in our MINOCA cohort were single and double positive APS associated with low and medium thromboembolic risk [31]. To our knowledge, this study is the first to show the prevalence of APS based on the criteria recommended since 2006 [28] in the MINOCA patients.

Additional factors measured in the present study included FVIII. Elevated FVIII above 150% was documented in more than a quarter of the current MINOCA patients. High FVIII has been shown as a risk factor for the first and recurrent VTE [39]. There have been reports suggesting its association with the increased risk of premature MI [40] and cryptogenic stroke [41]. This study is the first to indicate that persistently increased FVIII might characterize patients with MINOCA contributing to a prothrombotic state, however given association of FVIII with inflammatory state, its impact on clinical outcomes in MINOCA patients remains to be established.

We also measured lipoprotein (a), a well-known cardiovascular risk factor related to premature atherosclerosis and VTE though data on this latter issue are inconsistent. The prevalence of hyperlipoproteinemia (a) has not been analyzed in overall Polish population. Surprisingly high prevalence of lipoprotein (a) >30 mg/dl was demonstrated in the Copenhagen City Heart Study [42]. Lipoprotein (a) levels were elevated in young and middle-aged white adults with cryptogenic stroke [43]. As was established previously, MINOCA patients represent more favourable lipid profile than obstructive MI patients with simultaneous similar concentration of lipoprotein (a) [44]. The present study is one of the first to assess a prevalence of this factor in the MINOCA patients, although the rate is much lower compared with subjects with cryptogenic stroke and available data on general population (Table 2).

Regarding hyperhomocysteinemia, a highly controversial risk factor for cardiovascular disease due to the known associated increased thrombogenicity, oxidative stress status and endothelial dysfunction [45], we observed its high prevalence in MINOCA patients. Higher levels of homocysteine and significant prevalence of methylenetetrahydrofolate reductase (MTHFR) mutation were previously reported once in young MINOCA patients [12]. It remains to be established whether folic acid supplementation of hyperhomocysteinemic patients with MINOCA can be beneficial since the data available for typical MI patients yielded negative results providing evidence against routine assessment of this marker [46].

From a practical point of view, most of patients with inherited thrombophilia do not need life-long anticoagulation, however those with previous VTE or severe deficiencies of natural anticoagulants or those homozygous for FVL or prothrombin G20210A are treated with anticoagulant agents. This also applies to APS detected in 15.5% of the current MINOCA patients. The latest Cochrane Library review suggested that contemporary knowledge is not sufficient to determine the proper method of arterial thrombosis treatment in patients with APS [47]. The task force of the 13th International Congress on Antiphospholipid Antibodies recommended high-intensity warfarin or combined moderate-intensity warfarin therapy and an antiplatelet agent for secondary thromboprophylaxis in patients with APS with arterial thrombotic events. However, this recommendation did not reach panel consensus [48]. Based on the current evidence there is a subset of MINOCA patients that following thrombophilia screening should receive anticoagulant therapy and undergo close surveillance to reduce the risk of other thromboembolic manifestations of these abnormalities as well as consider family counseling in selected cases.

Our study has several limitations. First, cardiac magnetic resonance, which is recommended [1], was not performed in MINOCA patients. Second, we did not measure FIX, FX, FXI and FXII since their clinical relevance in thrombophilia screening is uncertain, though they are increasingly tested in many centers [45]. Third, we did not perform comparative measurements in cohorts with obstructive MI or ischemic stroke with determined source. Fourth, follow-up to establish clinical significance of detected thrombophilia was beyond the scope of this study.

## 5. Conclusions

In patients with MINOCA and cryptogenic stroke, the incidence of inherited thrombophilia and most of hypercoagulable states is similar and is higher than in general population. Therefore, we recommend thrombophilia screening in these two groups of patients. In case of a positive result, chronic antithrombotic treatment should be considered in accordance with current recommendations.

## Declaration of Competing Interest

A.U. received lecture honoraria from Bayer, Boehringer Ingelheim, Pfizer and Sanofi-Aventis. The remaining authors have nothing to disclose in relation to this study.

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## *Publikacja 2*

***"Worse long-term prognosis in myocardial infarction occurring at weekends or public holidays with insight into myocardial infarction with nonobstructive coronary arteries."***

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ORIGINAL ARTICLE

# Worse long-term prognosis in myocardial infarction occurring at weekends or public holidays with insight into myocardial infarction with nonobstructive coronary arteries

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**KEY WORDS**

myocardial infarction, myocardial infarction with nonobstructive coronary arteries, prognosis, weekend

**EDITORIALS**

by Lesiak, see p. 930; Mamas and Bharadwaj, see p. 932

**ABSTRACT**

**INTRODUCTION** The weekend effect in Polish patients with myocardial infarction (MI) treated in the current network of catheterization laboratories is poorly understood.

**OBJECTIVES** We sought to investigate long-term prognosis of patients with MI admitted at weekends or public holidays (NWDs) and on working days (WDs).

**PATIENTS AND METHODS** We enrolled 865 patients with MI hospitalized between 2012 and 2017. The long-term mortality within the median (IQR) time of 68.5 (36.7–78.4) months was determined in 223 patients (25.8%) admitted on NWDs and in 642 (74.2%) on WDs.

**RESULTS** Patients admitted on NWDs more often had ST-segment elevation MI (41.3% vs 30.8%; $P = 0.005$), left anterior descending artery as an infarct-related artery (38.1% vs 30.2%; $P = 0.031$) and incomplete reperfusion expressed as Thrombolysis in Myocardial Infarction flow grade 0/1 following primary angioplasty (6.8% vs 1.6%; $P < 0.001$) as compared with those hospitalized on WDs. Myocardial infarction with nonobstructive coronary arteries (MINOCA) occurred less often on NWDs (4% vs 9%, $P = 0.019$). The all-cause long-term mortality was higher in NWD patients as compared with those admitted on WDs (36.3% vs 28.4%; $P = 0.037$). By the Cox proportional hazards model with time-dependent covariates, MI on NWDs (hazard ratio, 1.027; 95% CI, 1.022–1.032; $P < 0.001$) but not MINOCA (hazard ratio, 0.971; 95% CI, 0.595–1.583; $P = 0.91$) was independently associated with long-term mortality.

**CONCLUSIONS** Patients hospitalized on NWDs as compared with those admitted on WDs had a larger ischemic territory and more often had transmural MI with incomplete epicardial reperfusion, which resulted in a higher long-term mortality. The latter outcome was not influenced by MINOCA.

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**INTRODUCTION** The weekend effect and its impact on the outcomes of myocardial infarction (MI) treatment has been intensively studied over the recent years. The first comprehensive report regarding the weekend effect was presented in 2001 by Bell and Redelmeier.[1] Based on their analyses of 3 789 917 broadly defined acute care admissions, they stated a significantly higher in-hospital mortality in various disease entities.[1] Previous findings have been summarized in 2 meta-analyses. Sorita et al[2] ascertained a higher in-hospital (odds ratio [OR], 1.05; 95% CI, 1.03–1.08) and 30-day mortality (OR, 1.05; 95% CI, 1.02–1.09) in patients admitted off-hours. According to their observations, these differences might have eventuated out of the substantially longer door-to-balloon time in ST-segment elevation MI (STEMI). Kwok et al[3] have recently confirmed that with observations regarding a slightly higher early mortality in weekend admissions (OR, 1.06; 95% CI, 1.03–1.09). The hypothesis regarding the impact of the timing of admission on clinical outcomes has not been confirmed based on more recent studies.[3]

There is scarce evidence regarding the weekend effect in Polish patients. Słonka et al[4]

## WHAT'S NEW?

The weekend effect means worse prognosis in patients admitted to hospitals during weekends. Its impact on myocardial infarction has been intensively studied over the recent years. Several hypotheses concerning this phenomenon have been proposed so far, but its etiology has not been fully elucidated. In the current study with over 5-year follow-up, it was shown that patients with myocardial infarction admitted at weekends or public holidays had higher long-term mortality than those hospitalized during working days and this effect was visible after the first year of observation. Patients admitted during nonworking days compared with those admitted during working days had more often ST-segment elevation myocardial infarction accompanied by more frequent myocardial infarctions with larger ischemic territory and incomplete epicardial blood flow not driven by operator experience. Simultaneously, myocardial infarction with nonobstructive coronary arteries was less often diagnosed on nonworking days, but this finding did not influence long-term mortality.

demonstrated similar rates of in-hospital complications as well as 2-year mortality in patients treated with percutaneous coronary intervention (PCI) in the daytime and during off-shift hours in the years 1998 to 2003. Noteworthy, the significantly higher rate of stent implantations was observed in the daytime group.[4] A similar analysis of patients with STEMI collected in the EUROTRANSFER registry showed that thrombolytic therapy was more frequently administered to patients hospitalized off-hours (4.1% vs 2.3%; $P = 0.041$). Surprisingly, the time from chest pain onset to diagnosis of STEMI was shorter in the off-hours group by 10 minutes ($P = 0.007$); nevertheless, 1-year mortality rates were similar in both groups.[5] Despite the above-mentioned observations, there are no available data solely describing the relationship between the current organization of cardiac catheterization laboratories in Poland working for 24 hours, 7 days a week and the long-term prognosis in patients with MI admitted on nonworking days. This problem has been partly raised by Walicka et al.[6] In their recently published study, the authors determined the predictors of in-hospital mortality based on the large number of 2 855 029 nonsurgical hospitalizations.[6] As was shown, vascular diseases were characterized by the highest mortality, whereas weekend admissions (Saturday: OR, 1.40; 95% CI, 1.36–1.43; Sunday: OR, 1.29; 95% CI, 1.26–1.32) and public holidays (OR, 1.25; 95% CI; 1.20–1.30) were independent predictors of in-hospital mortality.

In this study we sought to investigate whether the occurrence of MI at weekends or public holidays influences the long-term prognosis in Polish patients treated in a high-volume university center and to determine the potential causes of these relationships.

**PATIENTS AND METHODS** We enrolled 865 consecutive patients hospitalized between 2012 and 2017 in our hospital with a MI diagnosis and in whom coronary angiography was performed. A total of 223 (25.8%) were admitted on a nonworking day (NWD) including weekends (Saturdays or Sundays) (200 [23.1%]) or public holidays (23 [2.7%]). In turn, 642 (74.2%) patients were admitted on a working day (WD) (FIGURE 1). Patient age, anthropometric data, medical history, clinical presentation, baseline laboratory measurements, and data regarding the course of hospitalization were collected.[7] Patients were classified as STEMI or NSTEMI in accordance with current guidelines.[8,9] Renal failure was diagnosed when the creatinine clearance calculated by means of the Cockcroft–Gault formula was lower than 60 ml/min.[10] Between 2 and 4 days after admission, left ventricular ejection fraction (LVEF) was assessed by 2-dimensional transthoracic echocardiography at rest.[11]

A detailed evaluation of both the infarct-related artery (IRA) as well as the result of the primary PCI procedure were performed based on angiography done for each artery in 2 contralateral projections.[12] Two experienced and blinded physicians reviewed each coronary angiogram. In case of disagreement between the 2 physicians, a third opinion was sought, and a conclusion was drawn.[13,14] Myocardial infarction with nonobstructive coronary arteries (MINOCA) has been defined by the universal criteria of MI and no lesion of 50% or greater on coronary angiography.[15] Moreover, patients with MINOCA were analyzed for the presence of insignificant stenosis in epicardial arteries and were divided into 2 groups with 1) normal coronary arteries or minimal intracoronary irregularities with stenosis of less than 30% or with 2) mild to moderate lesions of at least 30% and less than 50%.[16] Epicardial blood flow was evaluated by means of the Thrombolysis In Myocardial Infarction (TIMI) scale in all patients.[17] TIMI epicardial blood flow grade 2 or 3 without flow limiting dissection not covered by the stent was recognized as the optimal PCI result, whereas TIMI flow grade 0 or 1 was the equivalent of incomplete epicardial reperfusion.[17–19] According to the commonly accepted American College of Cardiology Foundation / American Heart Association / American College of Physicians clinical competence statement, operators performing less than 50 PCIs per year, 50 to 100 PCIs per year, or more than 100 PCIs per year were defined as low, intermediate-, or high-volume, respectively.[20,21]

Long-term follow-up of all-cause mortality was obtained from the Polish National Death Registry. The study protocol was complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients included in the study gave their informed consent.

**Statistical analysis** Statistical analyses were performed with the SPSS Statistics software (version 25.0.0.2, IBM, Armonk, New York, United States). Continuous variables were first checked for normal distribution and expressed as median (interquartile range) or mean (SD), whereas

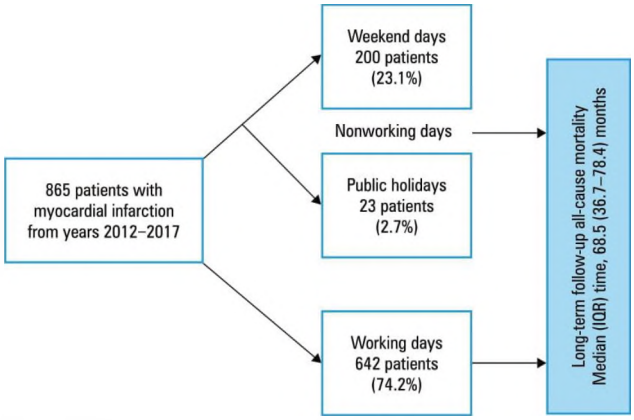


**FIGURE 1** The study flow-chart
Abbreviations: IQR, interquartile range

categorical variables as number (percentage). Continuous variables were compared by the *t* test or the Mann–Whitney test if the distribution was normal or different than normal, respectively. Categorical variables were analyzed by means of the $\chi^2$ test or the Fisher exact test. Kaplan-Meier curves of all-cause mortality in the study groups were performed and compared with the log-rank test. Finally, the proportional hazard assumption was verified with the model interaction of the covariate of interest with time. If such a variable turned out to be significant, the proportional hazard assumption would be violated.[22] Afterwards, the Cox proportional hazards model with time-dependent covariates was performed to find the independent determinants of all-cause mortality. A 2-tailed *P* value of less than 0.05 was considered statistically significant.

**RESULTS** **Clinical characteristics** The baseline characteristics of the enrolled patients are shown in TABLE 1. Patients in NWD and WD groups were similar in terms of demographic data, cardiovascular risk factors, history of MI, stroke, prior percutaneous and / or surgical coronary revascularization, and the distribution of Killip class on admission. The significant differences were observed in the clinical presentation of MI. STEMI was more frequent on NWDs (41.3% vs 30.8%; *P* = 0.005) accompanied by higher values of baseline creatine kinase (median [IQR], 202 [112–527] IU/l vs 169 [105–335] IU/l; *P* = 0.02) and isoenzyme MB of creatine kinase (median [IQR], 24 [16–61] vs 21 [14–39] IU/l, *P* = 0.003) as compared with those admitted on WDs. There were no differences in the remaining laboratory parameters on admission (TABLE 1).

**Angiographic features** The angiographic analysis showed significant differences in the distribution of the IRA in compared groups (*P* = 0.003) (TABLE 2). The left anterior descending artery (LAD) or the diagonal branch (38.1% vs 30.2%) as well as the right coronary artery (38.6% vs 32.6%) were more often identified as IRA in patients admitted during NWDs as compared with WDs. In contrast, patients with IRA of the left circumflex artery or marginal branch were treated more frequently on WDs as compared with NWDs (22.4% vs 15.7%). Interestingly, IRA remained more often undetermined in those admitted on WDs (10.6% vs 4.5%; *P* = 0.006). There were no differences in terms of applied revascularization in both groups. In patients treated with primary PCI, incomplete epicardial reperfusion expressed as TIMI blood flow grade 0/1 was found more frequently in the NWD group as compared with the WD group (6.8% vs 1.6%; *P* <0.001) (TABLE 2). Among patients treated with PCI, there were no significant differences in operators volume (*P* = 0.15). The majority of patients were revascularized by high-volume operators: on NWDs, it was 66.3% of PCIs and on WDs, 71.9%.

**In-hospital and long-term mortality and its determinants** There were no differences between patients admitted on NWDs as compared with WDs in terms of length of hospitalization (median [IQR], 5 [4–8] days vs 6 [3–8] days; *P* = 0.66) and in-hospital mortality (2.7% vs 3%; *P* = 0.84).

The median (IQR) time of follow-up was similar in patients hospitalized on NWDs and WDs (68.7 [37.4–79.2] months vs 68.4 [36.4–78.2] months; *P* = 0.40). At 1 year, mortality rate was 13.5% in those admitted on NWDs and 11.5% on WDs (log-rank *P* = 0.46, FIGURE 2A), whereas after the first year of follow-up mortality rate was 26.8% versus 19%, respectively (log-rank *P* = 0.027, FIGURE 2A). Finally, all-cause long-term mortality was higher in patients who were treated on NWDs as compared with WDs (36.3% vs 28.4%, log-rank *P* = 0.037) (FIGURE 2A). There were no differences in the subgroup analysis regarding the type of MI (FIGURE 2B and 2C), with only nonsignificant trend towards a higher long-term mortality in patients with STEMI hospitalized on NWDs

**TABLE 1** Characteristics of the study patients

| Characteristic | | Nonworking days (n = 223) | Working days (n = 642) | *P* value |
|---|---|---|---|---|
| Demographic data | | | | |
| Male gender | | 161 (72.2) | 437 (68.1) | 0.25 |
| Age, y | | 68 (58–78) | 69 (61–78) | 0.35 |
| Body mass index, kg/m$^2$ | | 27.5 (25–31.6) | 27.7 (24.8–30.8) | 0.57 |
| Cardiovascular risk factors and history | | | | |
| Diabetes mellitus | | 85 (38.3) | 240 (37.5) | 0.83 |
| Hypertension | | 190 (85.6) | 567 (88.6) | 0.24 |
| Dyslipidemia | | 182 (82) | 543 (84.8) | 0.31 |
| Renal failure | | 33 (14.8) | 106 (16.5) | 0.54 |
| Active smoking | | 55 (24.8) | 149 (23.3) | 0.66 |
| Chronic heart failure | | 78 (35.1) | 209 (32.7) | 0.51 |
| Prior stroke | | 15 (6.8) | 42 (6.6) | 0.92 |
| Prior myocardial infarction | | 68 (30.6) | 179 (28) | 0.45 |
| Prior revascularization | Percutaneous coronary intervention | 39 (17.6) | 119 (18.6) | 0.93 |
| | Coronary artery bypass surgery | 8 (3.6) | 26 (4.1) | |
| | Both percutaneous coronary intervention and coronary artery bypass surgery | 6 (2.7) | 21 (3.3) | |
| Killip class on admission | I | 173 (77.9) | 514 (80.1) | 0.71 |
| | II | 32 (14.4) | 74 (11.5) | |
| | III | 6 (2.7) | 24 (3.7) | |
| | IV | 11 (5) | 29 (4.5) | |
| Left ventricular ejection fraction, % | | 50 (40–55) | 50 (40–55) | 0.33 |
| Clinical presentation | NSTEMI | 131 (58.7) | 444 (69.2) | 0.005 |
| | STEMI | 92 (41.3) | 198 (30.8) | |
| Laboratory tests on admission | | | | |
| Troponin, ng/ml | | 0.109 (0.035–0.487) | 0.110 (0.029–0.379) | 0.14 |
| Creatine kinase, IU/l | | 202 (112–527) | 169 (105–335) | 0.02 |
| Isoenzyme MB of creatine kinase, IU/l | | 24 (16–61) | 21 (14–39) | 0.003 |
| Sodium, mEq/l | | 140 (138–142) | 140 (138–142) | 0.91 |
| Potassium, mEq/l | | 4.1 (3.8–4.4) | 4.1 (3.9–4.5) | 0.09 |
| Hemoglobin, g/dl | | 14.2 (13.1–15.1) | 14 (12.7–15) | 0.16 |
| Hematocrit, % | | 41.9 (39–44.7) | 41.6 (38.2–44.4) | 0.25 |
| MCV, fl | | 89.7 (86.6–93.3) | 89.4 (86.4–92.5) | 0.19 |
| White blood cells, × 10$^3$/µl | | 9.3 (7.4–11.6) | 9.2 (7.4–11.8) | 0.90 |
| Platelet count, × 10$^3$/µl | | 222 (190–261) | 220 (182–278) | 0.98 |
| Glucose, mmol/l | | 7.1 (5.9–9.4) | 6.8 (5.7–8.9) | 0.08 |
| Creatinine, µmol/l | | 88 (76–104) | 89 (77–105) | 0.72 |
| Glomerular filtration rate, ml/min | | 71 (58.8–86.5) | 70.3 (56–86) | 0.49 |
| Total cholesterol, mmol/l | | 4.6 (3.7–5.4) | 4.4 (3.6–5.2) | 0.13 |
| LDL cholesterol, mmol/l | | 2.7 (1.7–3.5) | 2.5 (1.6–3.4) | 0.09 |
| HDL cholesterol, mmol/l | | 1.2 (1–1.7) | 1.3 (1–1.7) | 0.73 |
| Triglycerides, mmol/l | | 1.2 (0.9–1.7) | 1.3 (0.9–1.7) | 0.91 |

Data are presented as median (interquartile range) or number (percentage).

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCV, mean corpuscular volume; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction

as compared with those admitted on WDs (log-rank $P = 0.067$).

In the study population, age, gender, admission day, creatinine level, type of MI, IRA, TIMI epicardial flow after PCI, and LVEF were identified as potentially associated with long-term mortality. Moreover, covariates of NWDs as compared with WDs and LAD as compared with non-LAD have been verified as time-dependent variables. By the Cox proportional hazards model with time-dependent covariates, apart from age, higher creatinine level, lower LVEF, also MI admissions at NWD (hazard ratio [HR], 1.027; 95% CI, 1.022–1.032; $P < 0.001$) remained independently

**TABLE 2** Angiography and revascularization in the study groups

| Characteristic | | Nonworking days (n = 223) | Working days (n = 642) | *P* value |
|---|---|---|---|---|
| Infarct-related artery | Left main | 7 (3.1) | 27 (4.2) | 0.003 |
| | Left anterior descending/diagonal branch | 85 (38.1) | 194 (30.2) | |
| | Left circumflex/marginal branch | 35 (15.7) | 144 (22.4) | |
| | Right coronary artery | 86 (38.6) | 209 (32.6) | |
| | Undetermined | 10 (4.5) | 68 (10.6) | |
| Diagnosis of MINOCA | | 9 (4) | 58 (9) | 0.02 |
| Treatment | Percutaneous coronary intervention | 190 (85.2) | 513 (79.9) | 0.21 |
| | Coronary artery bypass surgery | 4 (1.8) | 18 (2.8) | |
| | Conservative | 29 (13) | 111 (17.3) | |
| TIMI flow after percutaneous coronary intervention | 2/3 | 177 (93.2) | 505 (98.4) | <0.001 |
| | 0/1 | 13 (6.8) | 8 (1.6) | |
| Operator volume | >100 percutaneous coronary interventions/year | 126 (66.3) | 369 (71.9) | 0.15 |
| | 50–100 percutaneous coronary interventions/year | 64 (33.7) | 144 (28.1) | |

Data are presented as number (percentage) of patients.

Abbreviations: MINOCA, myocardial infarction with nonobstructive coronary arteries; TIMI, thrombolysis in myocardial infarction

**TABLE 3** Determinants of long-term mortality

| Independent variable | Univariable model | | | Multivariable model | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value | HR | 95% CI | *P* value |
| Age, per 1 year | 1.057 | 1.045–1.071 | <0.001 | 1.046 | 1.033–1.058 | <0.001 |
| Male vs female | 0.989 | 0.762–1.283 | 0.93 | 0.816 | 0.616–1.08 | 0.16 |
| MINOCA, yes vs no | 0.793 | 0.502–1.254 | 0.32 | 0.971 | 0.595–1.583 | 0.91 |
| NWD vs WD[a] | 1.323 | 1.018–1.791 | 0.04 | 1.027 | 1.022–1.032 | <0.001 |
| Creatinine, per 1 µmol/l | 1.003 | 1.002–1.005 | <0.001 | 1.01 | 1.007–1.014 | <0.001 |
| LAD vs non-LAD[a] | 1.01 | 0.86–1.187 | 0.9 | 1.005 | 0.809–1.372 | 0.70 |
| TIMI 2/3 vs 0/1 | 0.368 | 0.207–0.655 | <0.001 | 0.629 | 0.348–1.136 | 0.12 |
| LVEF, per 1% | 0.95 | 0.942–0.959 | <0.001 | 0.962 | 0.953–0.972 | <0.001 |

a Time-dependent covariate

Abbreviations: HR, hazard ratio; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; NWD, nonworking day; WD, working day; others, see TABLE 2

associated with mortality rate (TABLE 3). Admissions on NWDs as compared with WDs were associated with increased mortality rate within the second (HR, 1.96; 95% CI, 1.10–3.45; *P* = 0.023) and the third (HR, 2.08; 95% CI, 1.01–4.35; *P* = 0.047) year following MI, whereas LAD IRA was associated with an increased mortality rate in the first year following MI (HR, 1.65; 95% CI, 1.12–2.44; *P* = 0.012).

### Insight into the population of patients with MINOCA

A subanalysis of all studied patients revealed that MINOCA was diagnosed more frequently on WDs than on NWDs (9% vs 4%; *P* = 0.019). Direct comparison of patients with MINOCA treated on NWDs and WDs showed no significant differences in demographic data, cardiovascular risk factors, prior MI, stroke or PCI, and the distribution of Killip class on admission (TABLE 4). None of the MINOCA patients had prior coronary artery bypass surgery. In the MINOCA population, clinical presentation of NSTEMI dominated in both NWD as well as WD admissions (100% vs 84.5%; *P* = 0.25). Interestingly, Takotsubo cardiomyopathy as a mechanism of MINOCA occurrence was diagnosed only in 2 patients admitted on WDs. In both groups, no differences were found in baseline cardiac necrotic markers and in the distribution of insignificant lesions in coronary arteries on angiography (TABLE 4). The length of hospitalization in both MINOCA groups hospitalized on NWDs and on WDs was similar (median [IQR], 4 [3–5] days vs 4 [3–7] days; *P* = 0.85). There were no in-hospital deaths in the compared groups.

The median (IQR) time of long-term follow-up was similar in both MINOCA subgroups (83.3 [72.9–85.5] months vs 77.3 [70.8–84] months, *P* = 0.38). There was no significant difference in all-cause mortality between NWD versus WD population (22.2% vs 31%; *P* = 0.35; FIGURE 3A). There

**TABLE 4** Characteristics of the study patients with myocardial infarction and nonobstructive coronary arteries

| Characteristic | | Nonworking days (n = 9) | Working days (n = 58) | *P* value |
|---|---|---|---|---|
| Male gender | | 3 (33.3) | 29 (50) | 0.29 |
| Age, y | | 70 (59–74) | 72.5 (66–78) | 0.81 |
| Body mass index, kg/m$^2$ | | 29.1 (26–31.3) | 26.8 (23.8–30.1) | 0.41 |
| Diabetes mellitus | | 5 (55.6) | 15 (25.9) | 0.08 |
| Hypertension | | 9 (100) | 54 (93.1) | 0.55 |
| Dyslipidemia | | 6 (66.6) | 45 (77.6) | 0.37 |
| Renal failure | | 2 (22.2) | 13 (22.4) | 0.68 |
| Glomerular filtration rate, ml/min | | 68.2 (11.7) | 64.5 (21.6) | 0.62 |
| Active smoking | | 3 (33.3) | 6 (10.3) | 0.09 |
| Chronic heart failure | | 3 (33.3) | 19 (32.8) | 0.62 |
| Left ventricular ejection fraction, % | | 52.5 (43.5–60) | 55.0 (42.5–60) | 0.79 |
| Prior stroke | | 1 (11.1) | 3 (5.2) | 0.44 |
| Prior myocardial infarction | | 2 (22.2) | 13 (22.4) | 0.68 |
| Prior PCI | | 1 (11.1) | 11 (19) | 0.49 |
| Killip class on admission | I | 8 (88.9) | 46 (79.3) | 0.67 |
| | II | 1 (11.1) | 7 (12.1) | |
| | III | 0 | 3 (5.2) | |
| | IV | 0 | 2 (3.5) | |
| Clinical presentation | NSTEMI | 9 (100) | 49 (84.5) | 0.25 |
| | STEMI | 0 | 9 (15.5) | |
| Takotsubo cardiomyopathy | | 0 | 2 (3.5) | 0.75 |
| Baseline cardiac necrotic markers | Troponin, ng/ml | 0.055 (0.03–0.24) | 0.064 (0.023–0.245) | 0.75 |
| | Creatine kinase, IU/l | 175 (126–183) | 131 (89–266) | 0.39 |
| | Creatine kinase MB fraction, IU/l | 21 (20–26) | 19 (14–28) | 0.33 |
| Coronary angiography | <30% stenosis | 6 (66.7) | 31 (53.5) | 0.36 |
| | 30%–50% stenosis | 3 (33.3) | 27 (46.5) | |

Data are presented as median (interquartile range) or number (percentage).

Abbreviations: PCI, percutaneous coronary intervention; others, see FIGURE 1 and TABLES 1 and 2

were also no differences in long-term mortality between patients with MINOCA and MI with obstructive coronary artery in the whole analyzed groups (29.9% vs 30.5%; $P = 0.28$; FIGURE 3B) as well as in patients admitted on WDs (31% vs 28.1%; $P = 0.74$; FIGURE 3C) and on NWDs (22.2% vs 36.9%; $P = 0.12$; FIGURE 3D). Finally, MINOCA proved not to be an independent predictor of long-term mortality (TABLE 3).

**DISCUSSION** As shown in this study, the admission of patients with MI to a high-volume university center on NWDs was independently associated with a higher long-term mortality and this effect was visible after the first year since MI. Patients hospitalized during NWDs as compared with those admitted on WDs had a larger ischemic territory and more often transmural MI. As a consequence, the complete epicardial reperfusion was significantly less common in patients admitted on NWDs despite similar experience of PCI operators. Moreover, a diagnosis of MINOCA was more likely on WDs but the latter finding did not influence long-term mortality.

Our study provides several observations that may allow better understanding of the potential mechanism behind the weekend effect in patients with MI. Undoubtedly, one of the most important issues is the higher frequency of incomplete epicardial reperfusion expressed as TIMI flow grade 0 or 1 on NWDs; nevertheless, a suboptimal recanalization of the IRA was not an independent predictor of death during long-term follow-up most likely due to an interaction with the type of IRA. As has been shown by Henriques et al,[23] the PCI failure occurred more often in patients hospitalized during off-hours (6.9% vs 3.8%; $P < 0.01$). Glaser et al[24] performed a meticulous analysis of angiographies conducted which showed a higher incidence of major dissection and less frequent use of stents, coronary imaging techniques, and mechanical thrombectomy in patients treated off-hours.[24] In the research devoted to the weekend effect, TIMI flow grade 3 has been consequently indicated as an independent predictor of favorable prognosis.[4,25,26] Previous studies indisputably proved that complete post-PCI TIMI flow was an accurate predictor of

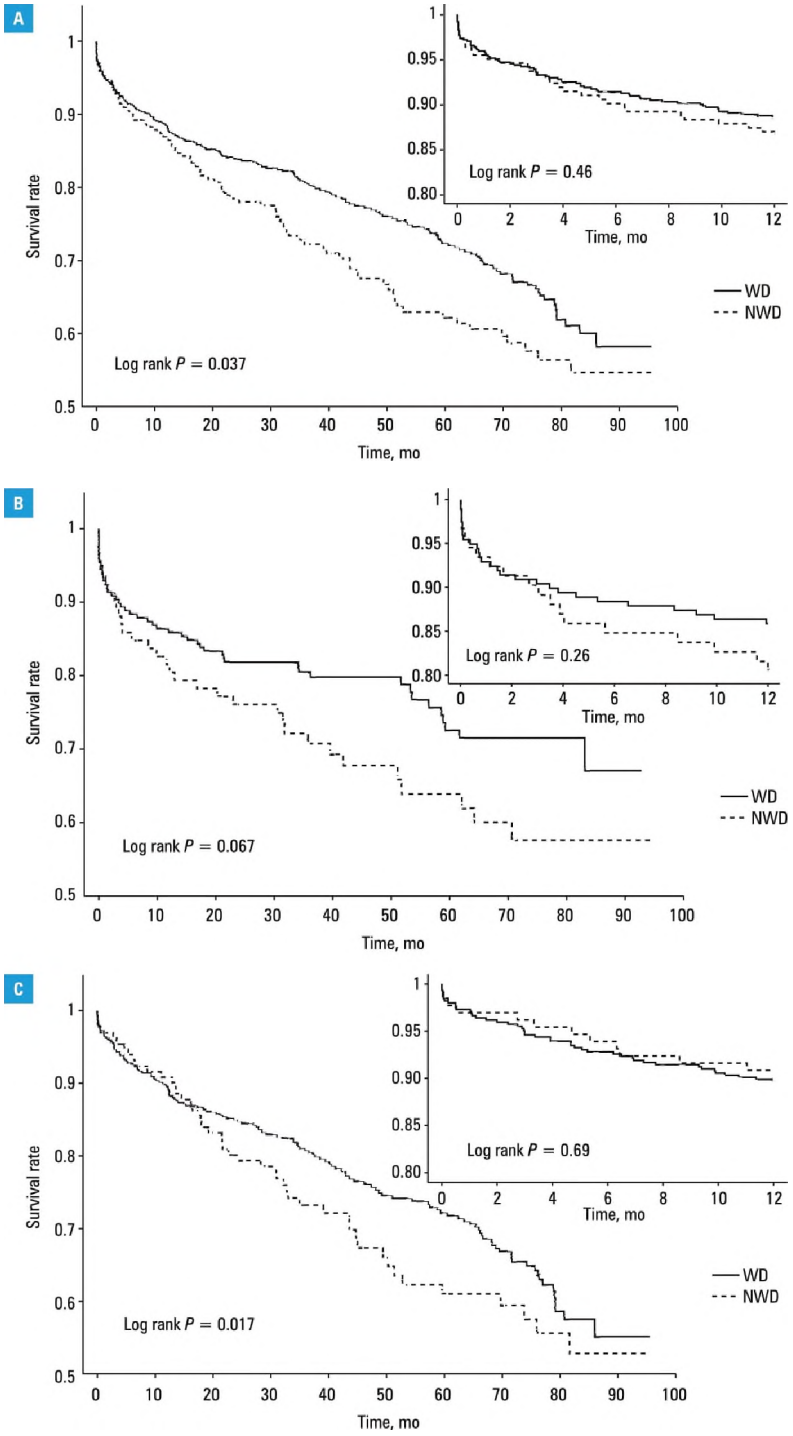


**FIGURE 2** Survival rates on working and nonworking days. The whole study population (A), patients with ST-segment elevation myocardial infarction (B), and patients with non–ST-segment elevation myocardial infarction (C) with 1-year and the whole long-term follow-up.
Abbreviations: see TABLE 3

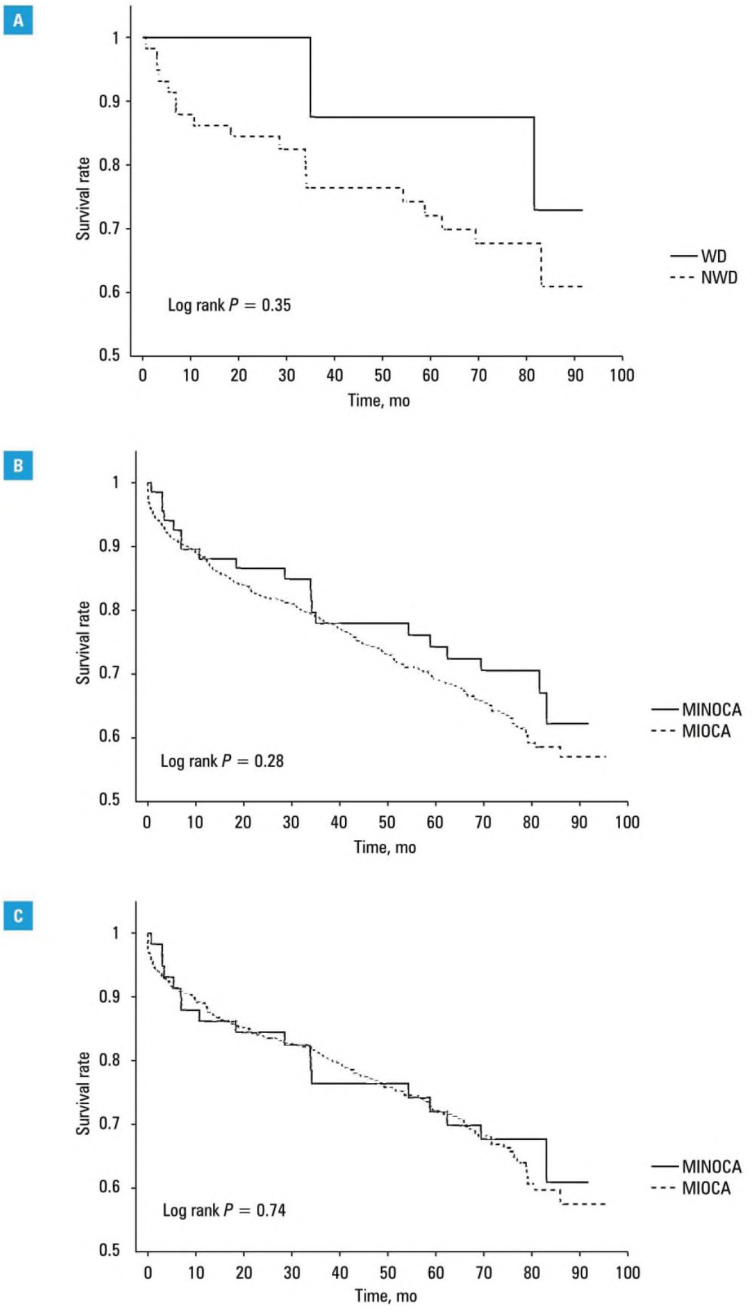


**FIGURE 3** The long-term survival rates in the population of patients with myocardial infarction with nonobstructive coronary arteries: **A** – patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) on working and nonworking days; **B** – patients with MINOCA as compared with those with myocardial infarction with obstructive coronary arteries (MIOCA), **C** – patients with MINOCA as compared with those MIOCA on working days
Abbreviations: see TABLE 3

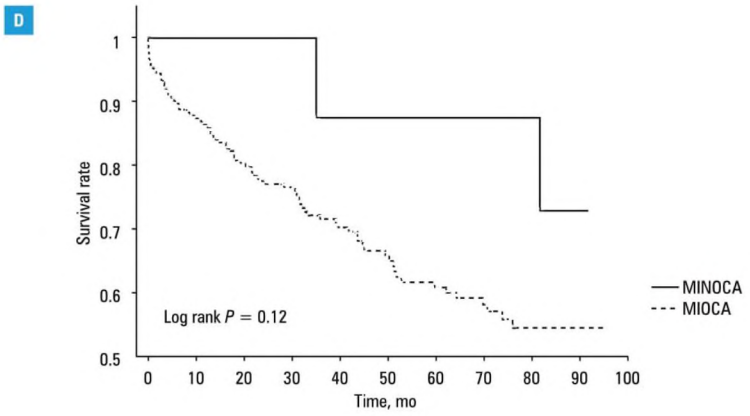


**FIGURE 3** The long-term survival rates in the population of patients with myocardial infarction with nonobstructive coronary arteries: D – patients MINOCA versus MIOCA on nonworking days
Abbreviations: see TABLE 3

better long-term outcomes in patients with MI, especially in STEMI.[27]

The poor general clinical condition of admitted patients was also indicated as potentially associated with the weekend effect. That issue has been explored by Isogai et al[28] who found that the weekend effect was noticeable in Killip class II–IV, but not in Killip class I. We did not find a similar relationship and the baseline clinical condition expressed as Killip class was similar in both compared groups. Moreover, almost an identical distribution of cardiovascular risk factors and comorbidities was noted in the study groups. On the other hand, the percentage of patients with STEMI admitted during NWDs was higher by 10% and associated with higher baseline enzymatic injury suggesting longer time of effective ischemia as compared with WDs. Khoshchehreh et al[29] found that STEMI on WDs and NWDs constituted 13.1% and 17.9% of patients with acute coronary syndromes, respectively, and Martin et al[30] reported 50.7% and 58.7%, respectively. Also myocardial infarctions with larger area at risk expressed as the left anterior descending artery territory were presented more frequently on NWDs than WDs. These findings are probably the consequence of the fact that STEMI and high-risk NSTEMI are immediately treated invasively according to the current guidelines whereas lower-risk patients might be postponed to a post-weekend WD. Thus, larger infarcts treated invasively on NWDs have created higher long-term risk associated with potential stent thrombosis, restenosis, or reintervention as compared with WD admissions.

Previous studies also suggested that the difference in patient prognosis might be associated with a reduced in-hospital staff service and weekend duties which are performed by less experienced operators.[31,32] The experience of PCI operator is a well-recognized prognostic factor in patients treated invasively.[33-35] On the other hand, it is a difficult issue to measure the quality of performed medical procedures. In our study, to evaluate the experience of PCI operators, we chose the most commonly used parameter of annual PCI volume that was counted for each of the PCI operators working in our center. As was shown by Ahmed et al[36] this parameter, but not years of experience, determines the important prognostic factor which is the needle-to-balloon time. Nevertheless, our study did not show any differences in the competence of individual operators performing procedures on NWDs and WDs. Noteworthy, our study covers the years 2012 to 2017 during which the catheterization laboratories network in Poland provided a high-quality service for patients with MI.[37] Our center is also classified as one of the highest-volume institutions, and in the analyzed group, primary angioplasty was performed in over 80% of cases.[37]

It is unclear why the survival curves associated with the weekend effect diverge after the first year since MI but not from the beginning (FIGURE 2A). It is difficult to explain this phenomenon directly on the basis of the study results. One may speculate that after the first year following MI, when dual antiplatelet therapy was stopped and the risk of recurrent ischemic events increased, in the group of patients admitted on NWDs with larger, non-optimally reperfused infarcts, it was much more pronounced. Also, the multivariable model confirmed time-dependence of the weekend effect. Therefore, further research is required to explain this observation.

Interestingly, in this study, also a higher prevalence of undetermined IRA and diagnosis of MINOCA was documented during WDs. Difficulties in determination of IRA are often associated with its spontaneous recanalization without visible residual stenosis, which is a proven favorable

prognostic factor.[17,19] Although MINOCA was less often diagnosed on NWDs, it was not associated with higher long-term mortality. As has been shown in the SWEDEHEART registry, MINOCA occurred most frequently in the morning (incidence rate ratio [IRR], 1.70; 95% CI, 1.63–1.84) and on Mondays (IRR, 1.28; 95% CI, 1.18–1.38) and also less often at weekends.[38] Comparably to our study, the time of MINOCA occurrence did not affect the long-term prognosis.[38] That circadian onset is probably associated with the pathophysiology of MINOCA.[39] It is a complex disease entity and circadian stress might constitute its direct trigger. However, we did not observe differences in the incidence of Takotsubo cardiomyopathy being a common MINOCA etiology and an entity extremely close to the stress factor.[40,41] Nevertheless, this observation was based on a relatively small group of MINOCA patients, therefore this and previous findings require conformational studies on the role of chronobiology in the pathophysiology of MINOCA.

Our study has several limitations. First, we have included a relatively small group of patients, limited to a single high-volume university center, which may misrepresent the results of the Polish population. This applies especially to the tertiary centers in which the operators have a significantly lower annual operator volume.[33,34,42] Second, due to lack of access to complete data, we did not analyze the door-to-balloon or ischemic times as well as the influence of nighttime admissions on outcomes.[2,43] However, the higher baseline cardiac necrotic markers suggest expected longer delay during NWDs. Third, we did not analyze the cause of death in long-term follow-up because of the registry data limitations.[44-46]

**Conclusions** Patients with MI admitted on NWDs, as compared with those hospitalized during WDs, had a larger ischemic territory and more often had transmural MI with incomplete epicardial reperfusion, which was associated with a higher long-term mortality. Although MINOCA was less often diagnosed on NWDs, this finding did not influence long-term mortality. The continuous efforts should be undertaken to ensure the comparable outcomes for all patients with MI regardless of the time of presentation also in high-volume centers.

## ARTICLE INFORMATION

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**CONTRIBUTION STATEMENT** KS conceived the concept of the study. KS, KN, and JZ contributed to the design of the research. KS and KN performed the review of literature and were involved in data acquisition. All authors analyzed and interpreted the data. JN and JZ supervised data processing. JZ coordinated funding for the project. All authors edited and approved the final version of the manuscript.

**CONFLICT OF INTEREST** None declared.



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## *Publikacja 3*

***"Clinical Characteristics and Long-Term Outcomes of MINOCA Accompanied by Active Cancer: A Retrospective Insight Into a Cardio-Oncology Center Registry."***

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# Clinical Characteristics and Long-Term Outcomes of MINOCA Accompanied by Active Cancer: A Retrospective Insight Into a Cardio-Oncology Center Registry

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**Background:** Clinical characteristics and long-term outcomes of patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) and cancer are insufficiently elucidated.

**Objectives:** We sought to characterize these patients hospitalized in a tertiary cardio-oncology center and to find the potential determinants affecting their long-term mortality.

**Methods:** MINOCA was diagnosed in 72 of the 1,011 patients with consecutive myocardial infarction who underwent coronary angiography. Mortality rates and their determinants were analyzed within a median follow-up of 69.2 (37.8–79.9) months.

**Results:** Active cancer was identified in 21 (29.2%) of patients with MINOCA and in 113 (12.0%) patients with myocardial infarction and obstructive coronary artery disease (MI-CAD) ($p < 0.001$). MINOCA patients with cancer were characterized by a higher incidence of anemia (47.6 vs. 21.6%, $p = 0.03$) and more frequently Takotsubo syndrome (19.1 vs. 2.0%, $p = 0.01$) than in non-cancer MINOCA. The troponin T/hemoglobin ratio was higher in both cancer MINOCA and MI-CAD groups when compared with their respective non-cancer patients (both $p < 0.05$). The age and sex-standardized mortality rates were significantly higher in cancer MINOCA (26.7%/year) when compared with non-cancer MINOCA (2.3%/year, $p = 0.002$) and in cancer MI-CAD (25.0%/year) vs. non-cancer MI-CAD (3.7%/year, $p < 0.001$). Active cancer (HR 3.12, 95% CI 2.41–4.04) was independently associated with higher long-term mortality, while higher hemoglobin levels (HR 0.93, 95% CI 0.88–0.99, per g/dl) and a MINOCA diagnosis (HR 0.69, 95% CI 0.47–0.97) improved long-term survival.

**Conclusion:** Patients with MINOCA were comorbid with cancer more frequently than MI-CAD. In turn, an active malignancy was associated with an unfavorable long-term survival both in MI-CAD population and in patients with MINOCA.

**Keywords: MINOCA, MI-CAD, cancer, anemia, cardio-oncology**

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## INTRODUCTION

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is recognized if it meets the general criteria of myocardial infarction (MI) together with the absence of significant lesions in epicardial arteries in angiography (1). As shown in large MI registries, MINOCA concerns 1–13% of all patients with MI (2, 3). Recent reports indicate an unexpectedly unfavorable long-term prognosis in this group of patients. The SWEDEHEART registry included 9,092 patients with MINOCA, of whom 24% experienced a major cardiovascular event, and where 14% died within a mean follow-up period of 4.5 years (4).

The potential mechanisms responsible for MINOCA are heterogeneous (1, 5). According to the current knowledge, the underlying pathophysiological causes of MINOCA are grouped as coronary or non-coronary. Moreover, the latter are classified as myocardial disorders or as those that are typically extra-cardiac (6). Both historical (7) as well as current findings (8) indicate that hypercoagulable states, including the inherited thrombophilia, occurred in 15–25% of patients with MINOCA. This includes deficiency of protein C, protein S, or antithrombin. Additionally, the antiphospholipid syndrome was detected in 15.5% of patients. Concurrently, patients with cancer are a group that is at a particularly high prothrombotic risk, traditionally in the venous system (9). An analysis of the Surveillance, Epidemiology, and End Results involving nearly 280,000 patient pairs showed that the rate of arterial thromboembolic events was 4.7% in cancer patients compared with the 2.2% in controls (10). That predisposition for arterial thromboembolism, defined as MI, ischemic stroke, or peripheral arterial occlusion, has been confirmed recently in a large Danish population-based cohort study (1.5 vs. 0.8% in the 6-month observation, hazard ratio [HR]: 2.36, 95% confidence interval [CI]: 2.28–2.44] (11). Moreover, its occurrence among patients with cancer was associated with an increased risk of mortality (HR 3.28, 95% CI: 3.18–3.38) (11). As the arterial thromboembolic events immediately preceded cancer diagnosis and were correlated with the stage of cancer (10, 11), they can be considered paraneoplastic symptoms, which always require subsequent meticulous diagnostics toward a subclinical neoplastic process (12).

Recently, a review of the meta-regression analysis of nine studies including 26,636 patients with MINOCA has shown that 2.5% of them had a diagnosis of malignancy at presentation (13). Similar findings have been reported in the SWEDEHEART registry (14). Despite relatively low prevalence, both Nordenskjöld et al. (4) (HR: 2.40, 95% CI: 1.58–3.61, $p < 0.001$) and Pelliccia et al. (13) (coefficient: 0.001, 95% CI: −0.001 to 0.001, $p = 0.01$) have found cancer as an independent predictor of death in patients with MINOCA. Another meta-analysis including a higher number of patients with MINOCA, i.e., 36,932, did not confirm a similar relationship (15). Therefore, we sought to characterize subjects with MINOCA and cancer hospitalized in a tertiary cardio-oncology center in order to investigate the potential mechanisms affecting their long-term outcomes.

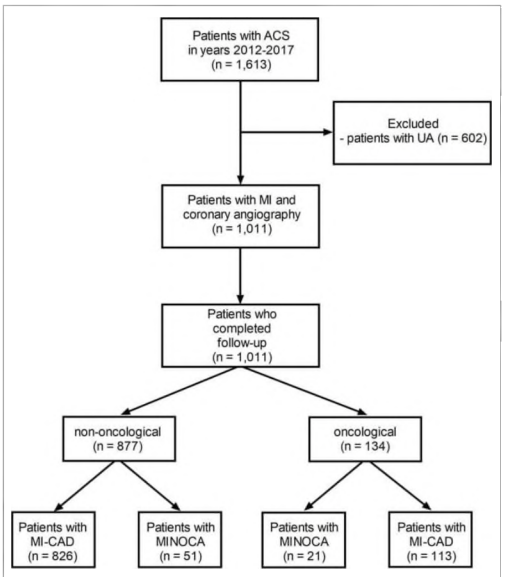


**FIGURE 1 |** The study flow-chart. MINOCA, myocardial infarction with non-obstructive coronary artery; MI-CAD, myocardial infarction and obstructive coronary artery disease.

## MATERIALS AND METHODS

As has been stated retrospectively, in a tertiary cardio-oncology center including closely cooperating departments of cardiology (168 hospital beds), cardiac surgery (80 beds), pulmonology and oncology (74 beds), and thoracic surgery (48 beds), 1,011 consecutive patients underwent coronary angiography between 2012 and 2017 due to the diagnosis of MI based on clinical symptoms, electrocardiographic findings, and the evolution of myocardial necrotic biomarkers (16). MINOCA was recognized in 72 (7.1%) subjects (**Figure 1**) based on the universal criteria of MI (positive cardiac biomarkers rising and/or falling in serial measurements, with at least one value above the 99th percentile as the upper reference limit and at least one clinical sign of infarction). An additional inclusion criterion was a lack of obstructive lesions narrowing epicardial coronary segments by more than 50% in angiography (1, 17). Patients with ST-segment elevation of at least 1 mm in at least two contiguous leads were classified as ST-segment elevation MI (STEMI), whereas patients without ST-segment elevation on admission were diagnosed as non-ST-segment elevation MI (NSTEMI) (18). In addition, 134 (13.3%) patients were identified with active cancer, defined as cancer diagnosed within the past 6 months, receiving antimitotic treatment during the last 6 months, recurrent, metastatic, regionally advanced, or inoperable (19) (**Figure 1**). In the analyzed period of time, five MI patients with advanced cancer did not undergo coronary angiography and

**TABLE 1** | Clinical and angiographic characteristics of the study patients.

| | MINOCA | | MI-CAD | |
|---|---|---|---|---|
| | **Cancer *N* = 21** | **Non-cancer *N* = 51** | **Cancer *N* = 113** | **Non-cancer *N* = 826** |
| Male gender | 8 (38.1) | 27 (52.9) | 88 (77.9) | 591 (71.6) |
| Age, years | 75 (71–79) | 70 (64–78) | 73 (66–79) | 68 (60–78) |
| Body mass index, kg/m$^2$ | 24.2 (22.1–27.4) | 26.7 (23.6–31.5) | 26.0 (23.4–29.1) | 27.7 (25.0–30.9) |
| Diabetes mellitus | 7 (33.3) | 13 (25.5) | 40 (35.4) | 318 (38.6) |
| Hypertension | 16 (76.2) | 47 (92.2) | 96 (85.0) | 717 (87.1) |
| Dyslipidemia | 12 (57.1) | 38 (74.5) | 73 (64.6) | 695 (84.5) |
| Pre-ESRD or ESRD | 1 (4.8) | 2 (3.9) | 2 (1.8) | 20 (2.4) |
| Active smoking | 0 (0.0) | 6 (11.8) | 18 (15.9) | 203 (24.7) |
| Anemia | 10 (47.6) | 11 (21.6) | 52 (46.0) | 169 (20.5) |
| Thrombocytopenia | 3 (14.3) | 2 (3.9) | 3 (2.7) | 9 (1.1) |
| Prior myocardial infarction | 3 (14.3) | 9 (17.7) | 39 (34.5) | 239 (29.0) |
| Prior stroke | 3 (14.3) | 3 (5.9) | 9 (8.0) | 56 (6.8) |
| **Killip class on admission** | | | | |
| I/II | 19 (90.5) | 47 (92.2) | 98 (86.7) | 757 (91.8) |
| III/IV | 2 (9.5) | 4 (7.8) | 15 (13.3) | 68 (8.2) |
| **Clinical presentation** | | | | |
| NSTEMI | 15 (71.4) | 45 (88.2) | 74 (65.5) | 530 (64.2) |
| STEMI | 6 (28.6) | 6 (11.8) | 39 (34.5) | 296 (35.8) |
| Takotsubo syndrome | 4 (19.1) | 1 (2.0) | 0 (0.0) | 8 (1.0) |
| Perioperative myocardial infarction | 1 (4.8) | | 3 (2.7) | |
| **Type of cancer** | | | | |
| Genitourinary | 8 (38.1) | | 36 (31.9) | |
| Breast | 5 (23.8) | | 6 (5.3) | |
| Lung | 3 (14.3) | | 27 (23.9) | |
| Gastrointestinal | 2 (9.5) | | 18 (15.9) | |
| Other | 3 (14.3) | | 26 (23.0) | |
| **Metastatic disease** | | | | |
| Lymph nodes | 0 (0.0) | | 16 (14.1) | |
| Distant | 4 (19.1) | | 24 (21.2) | |
| **Prior oncological treatment** | | | | |
| Surgery | 6 (28.6) | | 24 (21.2) | |
| Surgery with curative intent | 1 (4.8) | | 3 (2.7) | |
| Radiotherapy | 3 (14.3) | | 13 (11.5) | |
| Chemotherapy | 4 (19.1) | | 28 (24.8) | |
| Platinum compounds | 2 (9.5) | | 9 (8.0) | |
| Taxanes | 2 (9.5) | | 2 (1.8) | |
| Fluoropyrimidines | 0 (0.0) | | 10 (8.8) | |
| Anthracyclines | 0 (0.0) | | 3 (2.7) | |
| Other | 0 (0.0) | | 4 (3.5) | |
| Hormonotherapy | 2 (9.5) | | 17 (15.0) | |
| Newly diagnosed cancer during hospitalization | 2 (9.5) | | 21 (18.6) | |
| **Coronary angiography** | | | | |
| <30% stenosis | 13 (61.9) | 34 (66.7) | | |
| 30–50% stenosis | 8 (38.1) | 17 (33.3) | | |
| ≥50% stenosis in one or two coronary arteries | | | 87 (77.0) | 687 (83.2) |
| ≥50% stenosis in three coronary arteries | | | 26 (23.0) | 139 (16.8) |
| ≥50% stenosis in left main | | | 19 (16.8) | 98 (11.9) |
| Epicardial thrombus | 0 (0.0) | 1 (2.0) | 14 (12.4) | 116 (14.0) |
| Distal embolization | 0 (0.0) | 3 (5.9) | 9 (8.0) | 17 (2.1) |

*(Continued)*

**TABLE 1** | Continued

| | MINOCA | | MI-CAD | |
|---|---|---|---|---|
| | **Cancer *N* = 21** | **Non-cancer *N* = 51** | **Cancer *N* = 113** | **Non-cancer *N* = 826** |
| **Treatment strategy** | | | | |
| Percutaneous coronary intervention | | | 101 (89.4) | 724 (87.7) |
| Coronary artery bypass graft surgery | | | 3 (2.7) | 24 (2.9) |
| Conservative | | | 9 (8.0) | 78 (9.4) |
| **Pharmacotherapy** | | | | |
| Aspirin | 19 (90.5) | 44 (86.3) | 108 (95.6) | 810 (98.1) |
| P2Y12 inhibitor | 10 (47.6) | 27 (52.9) | 105 (92.9) | 785 (95.0) |
| Proton pump inhibitor | 8 (38.1) | 35 (68.6) | 84 (74.3) | 618 (75.3) |
| ACEI/ARB | 17 (81.0) | 44 (86.3) | 103 (91.2) | 728 (88.1) |
| β-blocker | 16 (76.2) | 36 (70.6) | 101 (89.4) | 743 (90.5) |
| Statin | 14 (66.7) | 39 (76.5) | 99 (87.6) | 774 (94.3) |

*Data are shown as number (percentage) or median (interquartile range), ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; MINOCA, myocardial infarction with non-obstructive coronary artery; MI-CAD, myocardial infarction and obstructive coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.*

were therefore excluded from further analysis. The study protocol complied with the Declaration of Helsinki and was approved by the Jagiellonian University Medical College Ethics Committee (Consent No. 1072.6120.59.2018). All included patients gave informed consent.

## Patients Clinical and Laboratory Characteristics

Information on demographics, anthropometric parameters, cardiovascular risk factors, cardiovascular disease history, and comorbidities of all the study patients was gathered. Anemia was recognized if the hemoglobin level was <13 g/dl for men and <12 g/dl for women. The cut-off value for the thrombocytopenia was $100 \times 10^3/\mu l$ (20). Pre-end-stage renal disease and end-stage renal disease was diagnosed when creatinine clearance calculated using the Cockcroft-Gault formula was lower than 30 ml/min. Finally, creatine kinase serum activity (IU/L, upper limit of normal: 170 IU/L), isoenzyme MB of creatine kinase (IU/L, upper limit of normal: 24 IU/L), and concentration of high-sensitive cardiac troponin T (ng/ml, upper limit of normal: 0.014 ng/ml) were measured on admission and at least one time within the first 24 h.

## Angiography

All coronary angiograms were analyzed off-line, using two contralateral projections for each artery at baseline and after angioplasty if applicable, by a cardiologist unaware of the clinical data. All coronary segments were carefully evaluated for the presence of visible thrombus, distal embolization, and degree of stenosis based on visual inspection (21, 22). In cases of borderline lesions between 40 and 70%, quantitative coronary angiography (QCA Quantcor, Siemens, Germany) was applied for precise assessment. According to the guidelines (1, 5), lesions narrowing the coronary artery by <50% were defined as insignificant. All patients with insignificant stenosis were divided into two groups with either i) normal coronary arteries or minimal intracoronary irregularities with stenosis of <30% or with ii) mild to moderate lesions of at least 30 and <50%.

## Echocardiography

A two-dimensional transthoracic echocardiography was performed by a trained physician between the second and fourth day of hospitalization. It was performed at rest in a left decubitus position, using a Vivid S5 ultrasound (GE, Solingen, Germany) equipped with a multi-frequency harmonic transducer, 3Sc-RS (1.3-4 MHz). All measurements were carried out according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography (23). Standard parameters were collected to describe individual heart structures and enable their functional assessment. Screening for Takotsubo syndrome was also routinely conducted, the diagnosis of which was performed according to the InterTAK criteria (24), irrespective of the severity of coronary artery disease (25).

## Clinical Follow-Up

The length of hospitalization was collected from hospital records, whereas long-term all-cause mortality was obtained from the National Health Registry. The additional data regarding the cause of death were obtained from the Polish Office of Statistics. The causes of death were categorized as cancer, cardiovascular, other (the most common causes included respiratory system disease or accident/trauma), or unknown. Major cardiovascular causes of death included coronary artery disease, cerebrovascular disease, heart failure, or atherosclerosis.

## Statistical Analysis

Statistical analysis was performed with the SPSS Statistics software (Version 25.0.0.2, IBM, USA). Continuous variables were expressed as medians (interquartile range) and categorical variables as numbers (percentage). Continuous variables were

**TABLE 2** | The selected laboratory and echocardiography characteristics.

| | MINOCA | | MI-CAD | |
|---|---|---|---|---|
| | Cancer $N = 21$ | Non-cancer $N = 51$ | Cancer $N = 113$ | Non-cancer $N = 826$ |
| **Laboratory tests** | | | | |
| Hemoglobin, g/dl | 12.9 (10.2–13.9) | 14.1 (12.3–14.7) | 12.8 (11.2–14.1) | 14.0 (12.8–15.1) |
| Hematocrit, % | 38.7 (31.7–41.9) | 41.5 (36.6–42.8) | 38.3 (34.6–41.3) | 41.7 (38.4–44.6) |
| White blood cells, $x10^3/\mu l$ | 8.9 (6.1–11.7) | 8.6 (6.5–11.5) | 10.0 (7.3–13.3) | 9.3 (7.5–12.0) |
| Platelet count, $x10^3/\mu l$ | 226 (166–284) | 223 (163–263) | 238 (182–292) | 221 (184–271) |
| Creatinine, μmol/l | 91 (76–124) | 90 (73–113) | 93 (77–112) | 88 (76–103) |
| Glomerular filtration rate, ml/min | 57.1 (36.7–71.2) | 63.9 (53.0–88.1) | 65.6 (52.7–86.0) | 71.0 (57.2–86.3) |
| Glucose, mmol/l | 7.5 (5.7–9.3) | 6.3 (5.5–7.1) | 7.5 (5.7–8.6) | 6.9 (5.8–9.1) |
| Troponin, ng/ml | 0.306 (0.102–0.680) | 0.076 (0.027–0.265) | 0.141 (0.046–1.070) | 0.113 (0.033–0.429) |
| Troponin peak, ng/ml | 0.489 (0.102–1.190) | 0.145 (0.053–0.344) | 0.952 (0.178–7.160) | 0.897 (0.249–4.300) |
| Creatine kinase, IU/l | 134 (51–163) | 132 (90–266) | 151 (62–376) | 186 (109–381) |
| Creatine kinase peak, IU/l | 137 (77–246) | 150 (99–319) | 313 (140–852) | 553 (192–1,652) |
| Creatine kinase MB isoenzyme, IU/l | 24 (13–35) | 20 (14–29) | 23 (15–61) | 22 (15–45) |
| Creatine kinase MB isoenzyme peak, IU/l | 27 (19–42) | 21 (16–32) | 44 (23–145) | 61 (26–155) |
| **Echocardiography characteristics** | | | | |
| Right ventricular systolic pressure, mmHg | 45 (33–63) | 32 (26–40) | 36 (29–44) | 28 (26–37) |
| TAPSE, mm | 24 (20–28) | 22 (20–25) | 22 (16–24) | 21.8 (19–25) |
| Left atrium, mm | 36 (33–43) | 42 (36–45) | 41 (38–46) | 42 (38–46) |
| E/A ratio | 0.6 (0.5–0.8) | 0.8 (0.6–1) | 0.8 (0.7–1) | 0.7 (0.6–1.1) |
| End-diastolic LV diameter, mm | 45 (41–52) | 50 (45–53) | 51 (46–56) | 51 (48–56) |
| End-systolic LV diameter, mm | 25 (23–33) | 32 (27–37) | 34 (29–42) | 32 (28–37) |
| LV ejection fraction, % | 50 (40–59) | 55 (45–60) | 45 (36–55) | 50 (40–55) |
| Aortic valve peak gradient, mmHg | 8.5 (7–13.5) | 7 (6–10) | 7 (5–9) | 7 (5–8) |
| Ascending aorta diameter, mm | 34 (29–36) | 36 (33–38) | 35 (33–38) | 36 (33–38) |

*Data are shown as median (interquartile range), HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; MINOCA, myocardial infarction with non-obstructive coronary artery; MI-CAD, myocardial infarction and obstructive coronary artery disease; TAPSE, tricuspid annular plane systolic excursion.*

first checked for normal distribution using the Shapiro–Wilk test. Afterward, differences in the four groups were compared with an analysis of variance, followed by a *post-hoc* Bonferroni test if the data distribution was normal. Non-normally distributed data were analyzed *via* the Kruskal–Wallis test, and differences between the groups were identified using a test for multiple comparisons of mean ranks. Categorical variables were analyzed with the chi-square test or Fisher's exact test with a *post-hoc* z-test for comparison of column proportions with the Bonferroni method. The mortality rates were expressed as crude or age and sex-standardized for the European population based on Eurostat data available online (26). The Kaplan–Meier curves for overall mortality were constructed in order to estimate the survival rates, and a log-rank test with a Bonferroni-corrected threshold was performed to assess the differences in survival between the study groups. Finally, all independent variables with the potential to confound both the exposure and the outcome were included in the Cox proportional hazard regression model to determine independent predictors of long-term all-cause mortality. A two-tailed $p$-value of $<0.05$ was considered statistically significant.

## RESULTS

Based on detailed angiographic and oncological characteristics, four groups of patients were created (**Figure 1**). Within 1,011 MI patients, active cancer and MINOCA were identified in 21 (2.1%) patients, whereas MINOCA without cancer was diagnosed in 51 (5.0%) subjects. Of the 939 remainders with type 1 MI with obstructive coronary artery disease (MI-CAD), 113 (11.2%) patients had active cancer and 826 (81.7%) had no evidence of active cancer. In 111 patients, the malignancy process was diagnosed before index MI, whereas new cancer was found during index hospitalization in two patients with MINOCA and in 21 with MI-CAD (**Table 1**).

Among the four groups, there were significant differences in the distribution of gender, anthropometric parameters, dyslipidemia, active smoking status, and initial clinical presentation ($p < 0.01$ for each) (**Table 1**). The angiographic analysis also revealed a different proportion of epicardial thrombus in the compared groups ($p = 0.02$). Hemoglobin levels were lower, whereas baseline high-sensitive troponin T was higher in both cancer groups compared with non-cancer

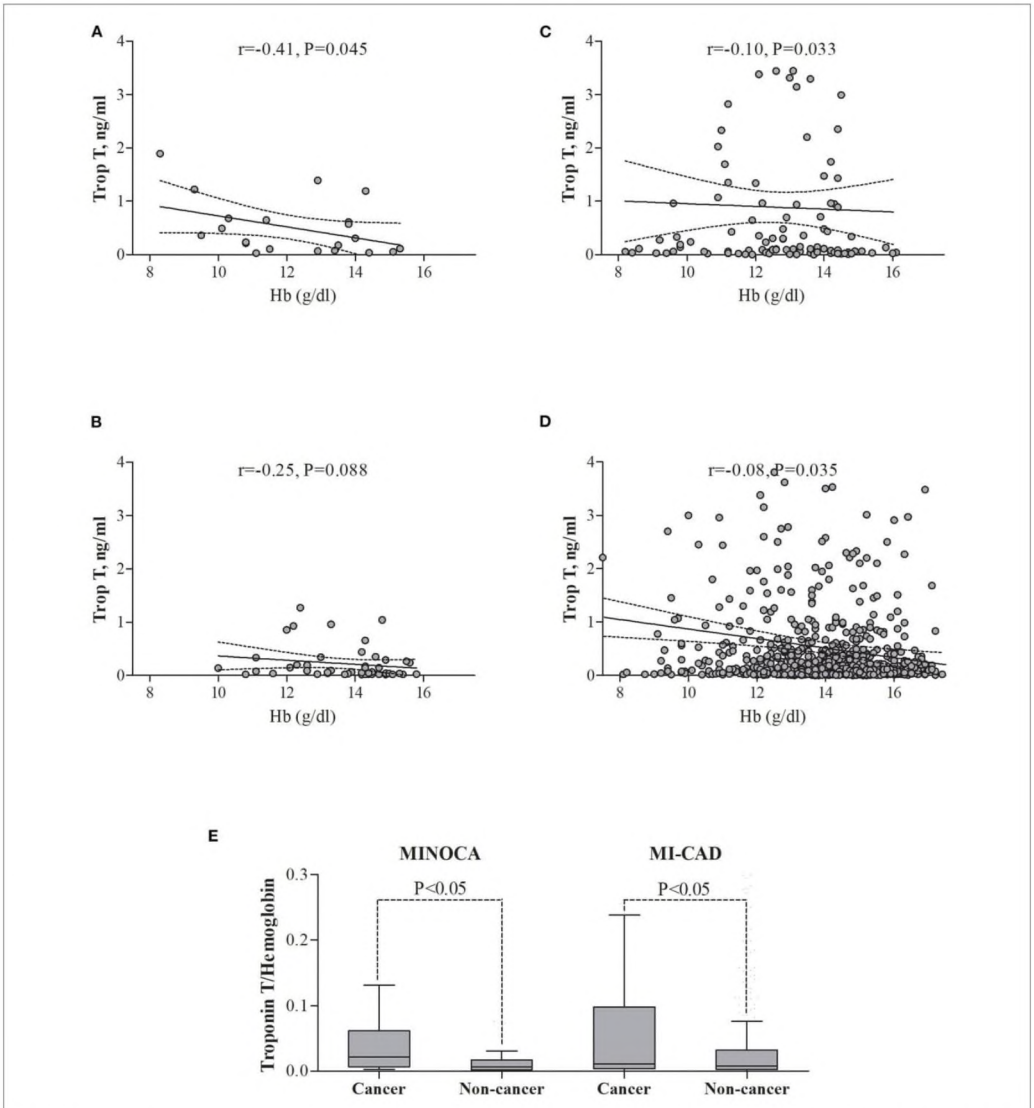


**FIGURE 2 |** The relationships between troponin T and hemoglobin level in the study groups. **(A)** Cancer MINOCA, **(B)** Non-cancer MINOCA, **(C)** Cancer MI-CAD, **(D)** Non-cancer MI-CAD, and **(E)** In both cancer groups, the ratio of troponin T to hemoglobin was higher than in the respective non-cancer groups. MINOCA, myocardial infarction with non-obstructive coronary artery; MI-CAD, myocardial infarction and obstructive coronary artery disease.

MINOCA subjects ($p < 0.05$ for all pairwise comparisons) with the blurring of differences during hospitalization in maximal peak values (**Table 2**). After adjustment for renal function, the highest inverse correlation between hemoglobin level and baseline troponin T concentration was found in the cancer MINOCA ($r = -0.41$, $p = 0.05$) group (**Figures 2A–D**). The

**TABLE 3** | The long-term mortality and its causes.

| | MINOCA | | MI-CAD | | *P*-value |
|---|---|---|---|---|---|
| | Cancer $N = 21$ | Non-cancer $N = 51$ | Cancer $N = 113$ | Non-Cancer $N = 826$ | |
| Patients who died during follow-up | 14 (66.7)#,^ | 15 (29.4) | 82 (72.6) #,^ | 256 (31.0) | <0.001* |
| Crude mortality rate, %/year | 19.2#,^ | 5.9 | 31.7#,^ | 7.9 | <0.001** |
| Age- and sex-standardized mortality rate, %/year | 26.7#,^ | 2.3 | 25.0#,^ | 3.7 | <0.001** |
| **Causes of death, expressed as number (% of patients who died)** | | | | | |
| Cancer | 6 (42.8)#,^ | 3 (20.0) | 46 (56.0)#,^ | 45 (17.6) | <0.001* |
| Unknown | 0 | 1 (6.7) | 3 (3.7) | 8 (3.1) | |
| Other | 2 (14.3) | 3 (20.0) | 9 (11.0) | 54 (21.1) | |
| Cardiovascular: | 6 (42.8) | 8 (53.3) | 24 (29.3)#,^ | 149 (58.2) | |
| Coronary artery disease | 1 (7.1) | 2 (13.3) | 8 (9.8) | 63 (24.6) | NA* |
| Cerebrovascular disease | 1 (7.1) | 2 (13.3) | 4 (4.9) | 22 (8.6) | |
| Heart failure | 2 (14.3) | 3 (20.0) | 6 (7.3) | 28 (10.9) | |
| Atherosclerosis | 2 (14.3) | 1 (6.7) | 6 (7.3) | 36 (14.1) | |

*Data are shown as number (percentage) unless otherwise indicated, MINOCA, myocardial infarction with non-obstructive coronary artery; MI-CAD, myocardial infarction and obstructive coronary artery disease; NA, not applicable; p-value for differences in four groups based on a chi-square test with a post-hoc z-test for comparison of column proportions with the Bonferroni method (*) or a log-rank test for multiple comparisons of survival curves with the Bonferroni-corrected threshold (**), #$p < 0.05$ non-cancer MINOCA, ^$p < 0.05$ non-cancer MI-CAD.*

proposed ratio of troponin T to hemoglobin was higher in cancer patients with MINOCA and MI-CAD when compared with the respective non-cancer groups (**Figure 2E**). The time of hospitalization was insignificantly shorter in non-cancer MINOCA (4 (3–7) days) as compared with cancer MINOCA (6 (3–12) days), cancer MI-CAD (6 (3–9) days), and non-cancer MI-CAD (6 (4–8) days) and ($p = 0.07$).

## Active Cancer Diagnosis Among MINOCA Patients

MINOCA was recognized significantly more often in cancer patients (21 of 134) compared with the non-cancer (51 of 877) cohort (15.7 vs. 5.8%, $p < 0.001$). A higher percentage of women was found in both cancer and non-cancer MINOCA groups than in the respective MI-CAD populations ($p < 0.05$ for both pairwise comparisons). A higher incidence of anemia was observed in cancer vs. non-cancer MINOCA group (47.6 vs. 21.6%, $p < 0.05$), without a significant difference in thrombocytopenia (14.3 and 3.9%). In both groups, the vast majority of MIs were classified as NSTEMI (71.4 and 88.2%, respectively). Similar treatment regimens were found in both MINOCA subgroups (**Table 1**). Aspirin was used in 90.5 and 86.3% of patients, respectively, whereas P2Y12 inhibitor was used in approximately half of the patients in both groups. Only proton pump inhibitors were used less frequently in cancer than in non-cancer MINOCA patients (38.1 vs. 68.6%, $p < 0.05$).

The echocardiographic screening showed more frequent Takotsubo syndrome in the oncological patients (19.1 vs. 2.0%, $p = 0.010$), with almost the same distribution of insignificant lesions in angiography in both groups (**Table 1**). Both epicardial thrombi and distal embolization were not found in cancer MINOCA and were reported only in the single non-cancer patients with MINOCA. Higher right ventricular systolic pressures ($p = 0.03$) and lower left atrium diameters ($p = 0.05$) (**Table 2**) were found in cancer vs. non-cancer patients with MINOCA with no differences in left ventricular ejection fraction (LVEF).

## Active Cancer in Patients With MI With vs. Without Obstructive Coronary Artery Disease

Active cancer was found more often in patients with MINOCA (21 of 72) compared to patients (29.2 vs. 12.0%, $p < 0.001$) with MI-CAD (113 of 939) (**Table 1**). Men were almost two times as represented in the cancer MI-CAD group compared with the MINOCA subgroup (77.9 vs. 38.1%, $p < 0.05$). Almost half of the patients had anemia in both groups, and both cancer groups presented with thrombocytopenia less frequently than anemia (**Table 1**) in a similar proportion when compared with respective non-cancer populations. In-hospital use of P2Y12 inhibitors (47.6 vs. 92.9%, $p < 0.001$), proton pump inhibitors (38.1 vs. 74.3%, $p = 0.001$), and statins (66.7 vs. 87.6%, $p < 0.05$) was less frequent in cancer MINOCA than in cancer MI-CAD.

In half of the newly diagnosed neoplasms, the first symptom was bleeding associated with antiplatelet and/or antithrombotic treatment administered during index MI, including hematuria (26%), hemoptysis (13%), and bleeds from the gastrointestinal tract (13%). Genitourinary neoplasms were predominant in

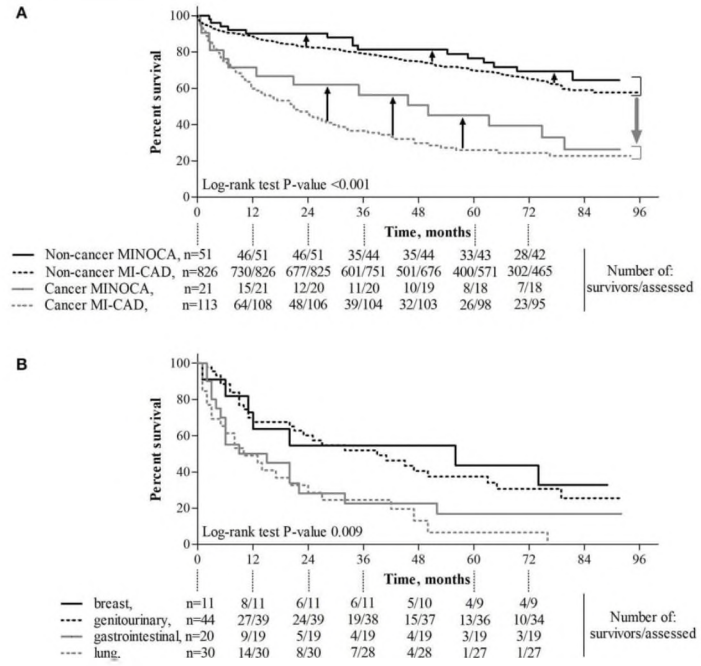


**FIGURE 3 |** The effect of cancer and its type and MINOCA on long-term survival. **(A)** Diagnosis of cancer was associated with significantly reduced long-term survival ($p < 0.001$, gray, wide arrow), whereas MINOCA diagnosis improved ($p = 0.048$, black, narrow arrows) long-term survival. **(B)** Long-term survival in patients with lung cancer was lower than that in those with genitourinary cancer ($p = 0.001$) or breast cancer ($p = 0.018$). MINOCA, myocardial infarction with non-obstructive coronary artery; MI-CAD, myocardial infarction and obstructive coronary artery disease.

both patients with MINOCA and MI-CAD (38.1 and 31.9%, respectively), whereas breast cancer was more frequent in the MINOCA group (23.8 vs. 5.3%, $p = 0.02$). There were significant differences neither in the locoregional and distant advancement of the neoplastic process nor in the anticancer treatment applied before the index MI (**Table 1**). The most commonly used chemotherapeutic agents in the MINOCA group were platinum compounds and taxanes. In turn, platinum compounds and fluoropyrimidines dominated in MI-CAD (**Table 1**).

Epicardial thrombus (12.4%) as well as distal embolization (8.0%) were observed numerically in a high percentage of cancer patients with MI-CAD but were not found in the cancer MINOCA group (**Table 1**). In the majority of cancer patients with MI-CAD, the significant atherosclerotic lesions were limited to one or two coronary arteries (77%). Most of these patients were treated with percutaneous coronary intervention (89.4%). In contrast, Takotsubo syndrome among patients with cancer was diagnosed only in the MINOCA group (19.1 vs. 0.0%, $p < 0.05$) (**Table 1**). There were no significant differences in right ventricular systolic pressure ($p = 0.18$) and LVEF ($p = 0.28$), but significantly larger end-diastolic ($p = 0.02$) and end-systolic ($p = 0.03$) left ventricular (LV) diameters were identified in the cancer MI-CAD group. Chemotherapy and radiotherapy administered before index MI did not affect LVEF ($p = 0.59$), end-diastolic ($p = 0.90$), or end-systolic ($p = 0.86$) LV diameters (**Table 2**).

## Long-Term Mortality, Its Causes, and Predictors

The median follow-up time in patients with non-cancer MINOCA, non-cancer MI-CAD, cancer MINOCA, and cancer MI-CAD was 73.4 [33.7–81.7], 41.9 [28.1–73.5], 35.0 [6.2–77.2], and 17.3 [4.9–43.9] months, respectively ($p < 0.001$). Both crude or age- and sex-standardized mortality rates as well as causes of death differed among the four groups (**Table 3**). As expected, the higher prevalence of cancer deaths was more pronounced in both oncological groups. In turn, cardiovascular causes of death were predominant in both non-cancer MINOCA and MI-CAD groups. Long-term survival was significantly higher in non-cancer MINOCA when compared with cancer MINOCA (HR 4.07, 95% CI 1.72–9.64, $p = 0.002$) and in non-cancer MI-CAD when compared with cancer MI-CAD (HR 7.62, 95% CI 5.13–11.31, $p < 0.001$). Concurrently, there were no significant differences in long-term survival between both cancer groups of MINOCA and MI-CAD (HR 0.76, 95% CI 0.45–1.28, $p =$

**TABLE 4** | The independent predictors of death in the whole group and in patients with MINOCA.

| | Univariable model | | | Multivariable model | | |
|---|---|---|---|---|---|---|
| | *P*-value | HR | 95% CI for HR | *P*-value | HR | 95% CI for HR |
| **The whole group** | | | | | | |
| Age, per year | 0.009 | 1.01 | 1.00–1.02 | 0.24 | 1.01 | 0.99–1.02 |
| Male gender, yes/no | <0.001 | 0.65 | 0.53–0.80 | 0.53 | 0.93 | 0.74–1.17 |
| Active cancer, yes/no | <0.001 | 3.33 | 2.64–4.21 | <0.001 | 3.12 | 2.41–4.04 |
| MINOCA, yes/no | 0.18 | 0.90 | 0.65–1.15 | 0.048 | 0.69 | 0.47–0.97 |
| Anemia, yes/no | <0.001 | 1.76 | 1.40–2.20 | - | - | - |
| Hemoglobin, per 1 g/dl | <0.001 | 0.88 | 0.84–0.93 | 0.018 | 0.93 | 0.88–0.99 |
| LVEF, per 5% | 0.74 | 1.00 | 0.99–1.01 | - | - | - |
| Killip 3/4 vs. 0/1 on admission | 0.61 | 1.10 | 0.77–1.57 | 0.94 | 1.01 | 0.71–1.45 |
| **MINOCA patients** | | | | | | |
| Age, per 1 year | 0.019 | 1.05 | 1.01–1.10 | 0.044 | 1.04 | 1.00–1.08 |
| Female gender, yes/no | 0.73 | 1.14 | 0.55–2.37 | - | - | - |
| Active cancer, yes/no | 0.003 | 3.09 | 1.49–6.41 | 0.040 | 2.24 | 1.04–4.80 |
| LVEF, per 5% | 0.007 | 0.96 | 0.94–0.99 | 0.012 | 0.95 | 0.93–0.97 |

*CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MINOCA, myocardial infarction with non-obstructive coronary artery.*

0.31), as well as both non-cancer groups of MINOCA and MI-CAD (HR 0.80, 95% CI 0.50–1.28, $p = 0.35$) (**Figure 3A**). The median survival time irrespective of the type of MI was 56, 39, 12, and 10 months for breast, genitourinary, gastrointestinal, and lung cancer, respectively (**Figure 3B**). A significantly better survival rate was found in patients with genitourinary cancer vs. lung cancer (HR 0.34, 95% CI 0.18–0.65, $p = 0.001$) and in breast cancer vs. lung cancer (HR 0.39, 95% CI 0.18–0.85, $p = 0.02$).

In the MINOCA group, there were no significant differences in the long-term survival between patients with vs. without Takotsubo syndrome (**Supplementary Figure 1**). There was also a significantly higher long-term mortality rate in cancer vs. non-cancer patients matched for age, gender, body mass index, diabetes, hypertension, and hyperlipidemia (**Supplementary Table 1** and **Figure 2**). A Cox proportional hazard regression limited to patients matched for demographic parameters and cardiovascular risk factors showed that unfavorable prognosis was associated with active cancer, a lower hemoglobin level, and age of older patients. Simultaneously, hypertension, hyperlipidemia, and better LVEF independently improved long-term survival (**Supplementary Table 2**).

In the whole group, age, female gender, cancer, anemia, and lower hemoglobin level were identified as associated with a higher mortality rate in a univariate model (**Table 4**). Using a Cox proportional hazard regression, an active cancer was independently associated with a higher long-term mortality rate, while higher hemoglobin levels and MINOCA diagnosis improved long-term survival (**Table 4**). A Cox proportional hazard regression limited to only patients with MINOCA showed that age, cancer, and LVEF were independently associated with a long-term mortality rate (**Table 4**).

## DISCUSSION

To our knowledge, this study is the first and most comprehensive analysis derived from a tertiary cardio-oncology center concerning the complex relationship between cancer and MINOCA, as well as its influence on long-term clinical outcomes. As shown, neoplasm has been identified more frequently in patients with MINOCA than in those with atherosclerosis and/or thrombus-based type 1 MI (defined as MI-CAD). However, a multivariable analysis showed that an active malignancy was associated with unfavorable long-term outcomes. We have also provided clinical features that characterized cancer patients with MINOCA, which might be useful in their differential diagnosis. It is important to note that the diagnosis of cancer in both MINOCA and MI-CAD groups was associated with an extremely high all-cause mortality in a 5-year observation. Moreover, a multivariable approach limited to only the MINOCA group showed that active cancer irrespective of age and lower left ventricular systolic function affected a higher mortality rate.

Patients with MI-CAD and cancer distinguished in our study were characterized by a highly unfavorable prognosis driven mostly by neoplastic disease. Although treatment of such patients should be strictly individualized, there are still limited data sufficiently addressing the optimal management of MI in patients with cancer (27). Further studies are warranted to establish an optimal antithrombotic regimen, especially in the acute phase, due to the proven high risk of stent thrombosis (9, 28). The results derived from the large Nationwide Inpatient Sample indicate that cancer in patients receiving percutaneous coronary intervention is common, but its prognostic impact depends on detailed oncological characteristics (29). Our results also indicate that, in both cancer and non-cancer MI-CAD patients, the rate of revascularization with the percutaneous coronary

intervention was almost 90% emphasizing current trends in interventional cardiology. While cancer patients with type 1 MI were historically less likely to receive primary percutaneous coronary intervention with first-generation drug-eluting stents mainly due to the need for a shorter course of dual antiplatelet therapy following bare-metal stents, the new drug-eluting stents requiring shorter antiplatelet therapy time have become more effective and as safe as bare-metal stents. According to the current registries, dual antiplatelet therapy was prescribed in only half of the patients with MINOCA, mainly in those with sinus rhythm, prior percutaneous coronary intervention, and active smokers (30).

In contrast, the prognosis in patients with MINOCA remains controversial, with the latest studies suggesting comparable (4, 31) or lower (15) long-term mortality rates in patients with MINOCA vs. MI-CAD. The abovementioned studies indicate that a history of cancer coexisting with 2–2.5% of patients with MINOCA (4, 13) is (13) or is not (15) an independent predictor of their long-term mortality. In our MINOCA and MI-CAD groups, a diagnosis of active cancer made before index MI was more common. This overrepresentation of neoplastic status was independently associated with unfavorable long-term survival. When compared with the available literature, such a high proportion of cancer patients is primarily a result of the structure of our center, as well as that of direct admissions from oncology and thoracic surgery departments to the cardiology ward. Interestingly, there is a visible trend toward more frequent admissions of cardio-oncology patients due to their prolonged survival time.

The etiology of MI in the oncological population is multifactorial. In previous studies, the role of cancer-induced immunological disorders, oxidative stress, prothrombotic state, and oncological treatment was underlined in MI development among cancer patients (32). Moreover, oncological patients are generally high-risk due to the significant prevalence of traditional cardiovascular risk factors, such as older age, hypertension, dyslipidemia, diabetes, obesity, or tobacco addiction (28). This was also corroborated in this current study. Most of the above-indicated factors contribute to the shifted oxidase-reductase balance and endothelial injury. This exacerbates coronary artery disease progression and promotes the rupture of atherosclerotic plaque associated with type I of MI, identified as MI-CAD (28, 32, 33) in our study. On the contrary, the influence of cancer and antitumor treatment is undeniable among MINOCA survivors. The rupture of non-obstructive plaque, distal embolization, hypercoagulable state with thrombus formation, transient artery spasm, microvascular dysfunction often caused by endothelial impairment, and supply-demand mismatch, among others, are all mechanisms responsible for MINOCA (5). It is worth noting that, each of these sequences of events might be triggered by both tumor and antineoplastic treatment (13). The classic chemotherapy drugs have been proven to damage the coronary arteries, mainly in their endothelium. Therefore, they can lead to acute thrombosis and coronary spasms (33). Drugs that particularly increase the risk of MI include fluoropyrimidines (5-fluorouracil, capecitabine, gemcitabine) and platinum compounds (33), which were also often used among the analyzed patients. Moreover, combining chemotherapeutics from different groups, especially those mentioned above, significantly increases the risk of MI (33). However, there is a lack of original reports demonstrating the relationship between chemotherapy and MINOCA. Our study provides detailed angiographic and echocardiographic characteristics of cancer patients with MINOCA, shedding light on their potential relationships. These findings might be helpful in further research dedicated for personalized treatment in this demanding group of patients.

A long-term prognosis is associated with myocardial infarct size. As we have shown, both cancer and non-cancer patients with MINOCA were characterized by a better preserved global LV function and lower peak high-sensitive troponin levels compared with the corresponding MI-CAD groups. This indirectly indicates a lower myocardial injury rate and most likely a smaller infarct size in patients with MINOCA. These findings are in line with previous data showing that, among the MINOCA population, patients with heart failure with preserved LV ejection fraction (34, 35) predominated. Post-infarction myocardial remodeling is also less frequently observed in this group. There are at least a few potential explanations for this relationship. First, the smaller myocardial infarct size is a consequence of a higher prevalence of NSTEMI in MINOCA (8). Second, cardiac magnetic resonance imaging provides evidence that, in patients with MINOCA, only small foci of necrosis are often observed, while myocardial edema is the dominant abnormality (36).

In this study, hemoglobin levels were lower in both cancer groups, compared with respective non-cancer MINOCA and MI-CAD groups. Moreover, as has been shown in our multivariable models, lower hemoglobin levels worsen long-term prognosis in the whole group, but not in the population limited to patients with MINOCA. According to criteria similar to ours, anemia at baseline was found in approximately 40% of patients in the European Cancer Anemia Survey (37). This proportion increased up to 60–70% during either anticancer treatment or cancer progression, affecting the higher overall mortality risk (38). In our cancer patients with MINOCA, lower hemoglobin levels were associated with higher baseline troponin concentrations, suggesting the possibility of anemia-induced myocardial injury (16). As has been shown previously, active cancer should be considered as a secondary cause of troponinosis that is not associated with acute coronary syndrome (39, 40). Moreover, troponin elevation was linked with a higher mortality rate, especially in patients with lung cancer (41). We have also found that the ratio of troponin T to hemoglobin was significantly higher in both cancer populations when compared to the respective non-cancer groups. Our findings are one more argument for the adoption of a higher troponin cut-off value for MI in patients with cancer (39, 40). The relatively high proportion of patients with cancer-induced anemia, also visible in our cohort, may require blood transfusion or other available methods of treatment (erythropoietin or iron supplementation). In a propensity-matched analysis, Salisbury et al. have demonstrated that blood transfusion was associated with a lower risk of in-hospital mortality (42). In turn, a meta

analysis done by Chatterjee et al. indicates that a liberal blood transfusion strategy is associated with higher all-cause mortality when compared to a more restricted strategy, which might be associated with volume overload, increased thrombogenicity, impaired oxygen delivery, and a risk of infection (43).

### Limitations

Our study has several limitations. First, the analyzed cancer MINOCA group is relatively small. However, it represents a unique and comprehensively characterized cohort. Second, despite their obvious heterogeneity and applied various methods of anticancer treatment, due to the small sample size of patients with different types of cancer, a multivariable analysis had to be performed for all patients with cancer. Third, cardiac magnetic resonance and intracoronary imaging were not performed to confirm an alternative diagnosis including myocarditis (44, 45). Fourth, apart from death, we did not analyze other clinical outcomes, such as recurrent MI, ischemic stroke, or heart failure decompensation. Moreover, the fact of quitting smoking after the cancer diagnosis undoubtedly contributed to its underestimated self-reporting. Finally, we also did not perform specific coagulation tests that would determine the role of prothrombotic states involved in the etiology of MINOCA (8, 46, 47).

## CONCLUSIONS

Our findings provide evidence that active cancer in the whole cohort of patients with MI, overrepresented among the MINOCA population, is associated with extremely high long-term mortality. A multivariable approach indicates that an active malignancy was independently associated with unfavorable long-term survival in the whole MI population as well as in patients with MINOCA.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Jagiellonian University Medical College Ethics Committee (Consent No. 1072.6120.59.2018). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

KS conceived the concept of the study. KS, KN, and JZ contributed to the design of the research. KS, KN, and BS reviewed the literature and were involved in data acquisition. All authors analyzed and interpreted the data. JN and JZ supervised data processing. All authors edited and approved the final version of the manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.785246/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# 12. Opinie komisji bioetycznej

UNIWERSYTET JAGIELLOŃSKI W KRAKOWIE

## AKCEPTACJA

dot. opinii nr: **122.6120.61.2016 z dnia 31 marca 2016 roku**

**TYTUŁ BADANIA:**
„Ładunek niestabilnych blaszek miażdżycowych związanych z upośledzonym potencjałem naprawczym sieci fibrynowej determinuje przetrwałe ryzyko prozakrzepowe po zawale serca"

Komisja Bioetyczna
Uniwersytetu
Jagiellońskiego

**WNIOSKODAWCA:**
dr hab. med. Jarosław Zalewski
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31 – 202 Kraków, ul. Prądnicka 80

**PRZEDSTAWIONE DOKUMENTY:**
Zgłoszenie poprawki z dnia 30 listopada 2021 r. dotyczącej wyrażenia zgody Komisji Bioetycznej Uniwersytetu Jagiellońskiego o **przedłużenie badania do dnia 31 grudnia 2022 roku.**

Komisja Bioetyczna Uniwersytetu Jagiellońskiego na posiedzeniu w dniu 15 grudnia 2021 r., po zapoznaniu się z wyżej wymienionym dokumentem pozytywnie zaopiniowała zgłoszoną poprawkę.

Lista członków Komisji Bioetycznej biorących udział w posiedzeniu:

Przewodnicząca: prof. dr hab. n. med. Dominika Dudek – lekarz – psychiatra
Zastępca Przewodniczącej: dr hab. Jacek Jaśtal, prof. PK – filozof

Członkowie:
dr hab. n. med. Ewa Cichocka-Jarosz, prof. UJ – lekarz – pediatra, alergolog
prof. dr hab. n. med. Tomasz Kaczmarzyk – lekarz stomatolog, chirurg stomatolog
dr hab. n. med. Ewa Konduracka, prof. UJ – lekarz – specjalista chorób wewnętrznych, kardiolog
prof. dr hab. n. med. Piotr Major – lekarz – chirurg ogólny, chirurg onkolog
dr hab. n. med. Agnieszka Olszanecka – lekarz – specjalista chorób wewnętrznych, hipertensjolog, kardiolog
dr hab. n. med. Szymon Skoczeń – lekarz – pediatra, onkolog, hematolog dziecięcy, transplantolog kliniczny
dr hab. n. med. Klaudia Stangel-Wójcikiewicz – lekarz – ginekolog-położnik
dr n. med. Stefan Bednarz – lekarz – specjalista chorób wewnętrznych – przedstawiciel Okręgowej Rady Lekarskiej w Krakowie
dr n. farm. Łukasz Hondo – farmaceuta – specjalista farmacji klinicznej
dr Jacek Prusak – duchowny, psycholog
mgr Anna Layer-Janiga – radca prawny
Jolanta Kopeć – położna

**Skład i działanie Komisji zgodne z GCP oraz wymogami lokalnymi**

Kraków, 15 grudnia 2021 r.

OPINIA KOMISJI BIOETYCZNEJ UJ DO WYŁĄCZNEGO WYKORZYSTANIA DLA CELÓW STATUTOWYCH UNIWERSYTETU JAGIELLOŃSKIEGO

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UNIWERSYTET
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Komisja Bioetyczna
Uniwersytetu
Jagiellońskiego

# OPINIA
## nr 1072.6120.59.2018 z dnia 23 marca 2018 roku

Na zebraniu w dniu 23 marca 2018 r. Komisja zapoznała się z wnioskiem z dnia 8 marca 2018 r.
złożonym:
przez kierownika tematu: **dr hab. n. med. Jarosław Zalewski**
zatrudnionego **Klinika Choroby Wieńcowej i Niewydolności Serca UJCM**
**31 – 202 Kraków, ul. Prądnicka 80**

oraz jego merytorycznym uzasadnieniem dotyczącym przeprowadzenia eksperymentu medycznego pt. „Pacjent z chorobą nowotworową i ostrym zespołem wieńcowym. Ocena rokowania odległego".

Do wniosku dołączono:
1. Protokół badania, wersja 1 z dnia 06.03.2018 r.
2. Informacja dla uczestników badania, wersja 1 z dnia 06.03.2018 r.
3. Formularz świadomej zgody uczestnika badania, wersja 1 z dnia 06.03.2018 r.
4. Wzór formularza zgody na przetwarzanie danych osobowych, wersja 1 z dnia 06.03.2018 r
5. Życiorys naukowy Wnioskodawcy.
6. Lista piśmiennictwa.
7. Wzór ankiety używanej w badaniu, wersja1 z dnia 06.03.2018 r.
8. Oświadczenie o realizacji projektu w ramach prac badawczych UJ/UJCM.

Komisja wyraża pozytywną opinię w sprawie przeprowadzenia wnioskowanego badania - na warunkach określonych we wniosku oraz dodatkowo zastrzegając:
1/ obowiązek uzyskania pisemnej zgody każdej osoby wyrażającej wolę (gotowość) udziału w danym eksperymencie, zgodnie z obowiązującym przepisami,
2/ obowiązek przedstawienia Komisji:
- wszystkich zmian w protokole mających wpływ na przebieg oraz ocenę badania,
- zawiadomienia o przyczynach przedwczesnego zakończenia badania,
- sprawozdania w toku przeprowadzanych badań - co sześć miesięcy,
- raportu końcowego,
3/ warunek przedłożenia przed rozpoczęciem badania opinii eksperta o jakości ankiety używanej w badaniu,
4/ warunek zamieszczenia w formularzu „informacja dla uczestników badania" informacji o przewidywanym czasie niezbędnym na wypełnienie kwestionariusza.

**Badanie może być prowadzone do dnia 30 września 2018 roku.**
**Skład i działanie Komisji zgodne z GCP oraz wymogami lokalnymi. Lista członków Komisji biorących udział w podjęciu uchwały stanowi załącznik do niniejszego dokumentu.**

Kraków, dnia 23 marca 2018 r.

Przewodniczący
Komisji Bioetycznej UJ

*prof. dr hab. n. med. Piotr Thor*

OPINIA KOMISJI BIOETYCZNEJ UJ
DO WYŁĄCZNEGO WYKORZYSTANIA
DLA CELÓW STATUTOWYCH
UNIWERSYTETU JAGIELLOŃSKIEGO

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# 13. Oświadczenia współautorów prac

Kraków, 24.06.2022 r.

Lek. Konrad Stępień
/tytuł zawodowy, imię i nazwisko/

**OŚWIADCZENIE**

Jako współautor pracy pt. „**High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: Comparison with cryptogenic stroke"** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:

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Oświadczam, iż moja samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

.....
/podpis współautora/

Kraków, 24.06.2022 r.

Lek. Karol Nowak
/tytuł zawodowy, imię i nazwisko/

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.....
/podpis współautora/

Kraków, 24.06.2022 r.

Dr hab. Ewa Wypasek
/tytuł zawodowy, imię i nazwisko/

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Ewa Wypasek
/podpis współautora/

Kraków, 24.06.2022 r.

Dr hab. Jarosław Zalewski
/tytuł zawodowy, imię i nazwisko/

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Jarosław Zalewski
.....
/podpis współautora/

Kraków, 24.06.2022 r.

Prof. dr hab. Anetta Undas
/tytuł zawodowy, imię i nazwisko/

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.....

/podpis współautora/

Kraków, 24.06.2022 r.

Lek. Konrad Stępień
/tytuł zawodowy, imię i nazwisko/

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Konrad Stępień
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/podpis współautora/

Kraków, 24.06.2022 r.

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/podpis współautora/

Kraków, 24.06.2022 r.

Prof. dr hab. Jadwiga Nessler
/tytuł zawodowy, imię i nazwisko/

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Jadwiga Nessler
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/podpis współautora/

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Jarosław Zalewski
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/podpis współautora/

Kraków, 24.06.2022 r.

Lek. Konrad Stępień
/tytuł zawodowy, imię i nazwisko/

**OŚWIADCZENIE**

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/podpis współautora/

Kraków, 24.06.2022 r.

Lek. Barbara Szlósarczyk
/tytuł zawodowy, imię i nazwisko/

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