Lek. Szymon Urban

Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca.

Rozprawa doktorska wykonana w Klinice Intensywnej Terapii Kardiologicznej Instytutu Chorób Serca, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

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Spis treści

1. Wykaz stosowanych skrótów

α-AR – receptor alfa adrenergiczny

ACE - enzym konwertujący angiotensynę

ACEI - antagoniści konwertazy angiotensyny

AF – migotanie przedsionków

AHF - ostra niewydolność serca

AI - sztuczna inteligencja

AKI – ostre uszkodzenie nerek

ANG I/II – angiotensyna I/II

ANP – przedsionkowy peptyd natriuretyczny

ARB - antagoniści receptora angiotensyny

ARNI - antagoniści receptora angiotensyny II i inhibitory neprylizyny

AT1/2R – receptor angiotensyny I/II

AUC – pole powierzchni pod krzywą ROC

BMI – wskaźnik masy ciała

CHNS – choroba niedokrwienna serca

CI - indeks sercowy

CMR - rezonans magnetyczny serca

CT - tomografia komputerowa

eGFR - szacowany wskaźnik filtracji kłębuszkowej

GGTP - gamma-glutamylotranspeptydaza

HF - niewydolność serca

HFpEF - niewydolność serca z zachowaną frakcją wyrzutową lewej komory

HFrEF - niewydolność serca z obniżoną frakcją wyrzutową lewej komory

HR - współczynnik ryzyka

HT – nadciśnienie tętnicze

MCV - średnia objętość erytrocytu

MRA - antagoniści receptora mineralokortykoidowego

ML - uczenie maszynowe

NYHA – New York Heart Association

PCWP - ciśnienie zaklinowania w tętnicy płucnej

POCHP – przewlekła obturacyjna choroba płuc

RAA - oś renina-angiotensyna-aldosteron

ROC - krzywa charakterystyki operacyjnej odbiornika

SGLT-2 - inhibitory kotransportera glukozowo-sodowego 2

WRF – pogorszenie funkcji nerek

2. Dorobek naukowy

Na niniejszą rozprawę doktorską składają się 3 publikacje:

1. Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459. (**IF - 4.7, MNiSW 100 pkt)**

2. Błaziak M +, Urban S +, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386. + These authors contributed equally to this work. (**IF - 4.7, MNiSW 100 pkt)**

3. Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716. (**IF - 5.5, MNiSW 100 pkt)**

Łączny Impact Factor publikacji wchodzących w skład rozprawy doktorskiej wynosi 14.9. Całkowita liczba punktów według Ministerstwa Nauki i Szkolnictwa Wyższego wynosi 300 pkt.

Pozostałe publikacje:

1. Kosiorek A, Urban S, Detyna J, Biegus J, Hurkacz M, Zymliński R. The diuretic, natriuretic and chloride-regaining effects of oral acetazolamide as an add-on therapy for acute heart failure with volume overload. A single center, prospective, randomized study. Pol Arch Intern Med. 2023 Jul 6:16526. doi: 10.20452/pamw.16526. Epub ahead of print. PMID: 37415505. **(IF – 4.8, MNiSW – 200 pkt)**
2. Urban S, Fułek M, Błaziak M, Fułek K, Iwanek G, Jura M, Grzesiak M, Szymański O, Stańczykiewicz B, Ptaszkowski K, Zymlinski R, Ponikowski P, Biegus J. Role of dietary sodium restriction in chronic heart failure: systematic review and meta-analysis. Clin Res Cardiol. 2023 Jun 30. doi: 10.1007/s00392-023-02256-7. Epub ahead of print. PMID: 37389661. **(IF - 5, MNiSW – 100 pkt)**
3. Siennicka A, Biegus J, Gajewski P, Młynarska K, Sokolski M, Siwołowski P, Zymliński R, Jedynak K, Ponikowska B, Urban S. A Pilot Study on Standardized In-hospital Education About Heart Failure Conducted During the First Days After Decompensation. Crit Pathw Cardiol. 2023 Mar 1;22(1):13-18. doi: 10.1097/HPC.0000000000000313. Epub 2022 Dec 30. PMID: 36812339. **(IF – 0, MNiSW – 40 pkt)**
4. Łagosz P, Biegus J, Urban S, Zymliński R. Renal Assessment in Acute Cardiorenal Syndrome. Biomolecules. 2023 Jan 27;13(2):239. doi: 10.3390/biom13020239. PMID: 36830608; PMCID: PMC9953721. **(IF – 5.5, MNiSW – 140 pkt)**
5. Jura M, Garus M, Krakowska K, Urban S, Błaziak M, Iwanek G, Zymliński R, Biegus J, Paleczny B. A Methodological Perspective on the Function and Assessment of Peripheral Chemoreceptors in Heart Failure: A Review of Data from Clinical Trials. Biomolecules. 2022 Nov 26;12(12):1758. doi: 10.3390/biom12121758. PMID: 36551186; PMCID: PMC9775522. **(IF – 5.5, MNiSW – 100 pkt)**
6. Siennicka A, Pondel M, Urban S, Jankowska EA, Ponikowska B, Uchmanowicz I. Patterns of Locus of Control in People Suffering from Heart Failure: An Approach by Clustering Method. Medicina (Kaunas). 2022 Oct 27;58(11):1542. doi: 10.3390/medicina58111542. PMID: 36363499; PMCID: PMC9717740. **(IF – 2.6 ,MNiSW- 40 pkt)**
7. Urban S, Fułek M, Błaziak M, Iwanek G, Jura M, Fułek K, Guzik M, Garus M, Gajewski P, Lewandowski Ł, Biegus J, Ponikowski P, Trzeciak P, Tycińska A, Zymliński R. COVID-19 Related Myocarditis in Adults: A Systematic Review of Case

Reports. J Clin Med. 2022 Sep 21;11(19):5519. doi: 10.3390/jcm11195519. PMID: 36233389; PMCID: PMC9573317. **(IF – 3.9 pkt, MNiSW – 140 pkt)**

8. Urban S, Horożaniecka P, Włodarczak S, Błaziak M, Jura M, Zymliński R, Biegus J, Siennicka A. Tablet-Based Assessment of Cognitive Function Among Heart Failure Patients. Crit Pathw Cardiol. 2022 Sep 1;21(3):147-152. doi: 10.1097/HPC.0000000000000291. Epub 2022 Apr 29. PMID: 35880943. **(IF – 0, MNiSW – 40 pkt)**
9. Guzik M, Urban S, Iwanek G, Biegus J, Ponikowski P, Zymliński R. Novel Therapeutic Devices in Heart Failure. J Clin Med. 2022 Jul 25;11(15):4303. doi: 10.3390/jcm11154303. PMID: 35893394; PMCID: PMC9331275. **(IF – 3.9, MNiSW –140 pkt)**
10. Zdanowicz A, Urban S, Ponikowska B, Iwanek G, Zymliński R, Ponikowski P, Biegus J. Novel Biomarkers of Renal Dysfunction and Congestion in Heart Failure. J Pers Med. 2022 May 29;12(6):898. doi: 10.3390/jpm12060898. PMID: 35743683; PMCID: PMC9224642. **(IF - 3.4, MNiSW – 70 pkt)**
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12. Urban S, Błaziak M, Jura M, Biegus J, Kuliczkowski W, Zymliński R. Attitudes of members of the Wroclaw Division of the Polish Cardiac Society to the European Society of Cardiology Guidelines: Survey study. Kardiol Pol. 2022;80(1):76-79. doi: 10.33963/KP.a2021.0150. Epub 2021 Nov 4. PMID: 34734409. **(IF - 3.3, MNiSW – 100 pkt)**
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Łączny Impact Factor publikacji poza cyklem wchodzącym w skład rozprawy doktorskiej wynosi 48.384. Całkowita liczba punktów według Ministerstwa Nauki i Szkolnictwa Wyższego wynosi 1370 pkt.

Łączny Impact Factor całego dorobku wynosi 63.284. Całkowita liczba punktów według Ministerstwa Nauki i Szkolnictwa Wyższego wynosi 1670 pkt.

3. Wstęp

Niewydolność serca

Niewydolność serca (HF), a zwłaszcza ostra niewydolność serca (AHF) to choroba o postępującym przebiegu i złym rokowaniu, która stanowi końcowy etap wielu schorzeń układu krążenia. HF może być spowodowana przez m.in. nadciśnienie tętnicze, chorobę niedokrwienną serca, kardiomiopatie, wady zastawkowe, choroby zapalne w tym infekcje bakteryjne oraz wirusowe, czynniki toksyczne czy też leczenie onkologiczne[1] .

Różnorodność etiologiczna niewydolności serca przekłada się na jej złożoną prezentację kliniczną. Wiele spośród znanych objawów nie ma charakteru w pełni swoistego dla rozpoznania tej jednostki chorobowej. Najczęściej występującymi objawami HF są: duszność wysiłkowa, ze stopniowo pogarszającą się tolerancją wysiłku, aż do duszności spoczynkowej, często pod postacią ortopnoe. Duszności często towarzyszy znużenie, męczliwość oraz wydłużony czas odpoczynku po wysiłku[2]. Ważnym klinicznie objawem niewydolności serca jest zastój, którego pojawienie się ma wyjątkowo istotne znaczenie prognostyczne Najbardziej widocznym objawem zastoju i przewodnienia są obrzęki kończyn dolnych, narastające stopniowo w miarę nasilania się dekompensacji. Pacjenci zazwyczaj prezentują poszerzenie żył szyjnych, hepatomegalię, objaw wątrobowo-szyjny, uczucie pełności i brak apetytu (zastój w ścianie jelita), trzeszczenia u podstawy płuc, wodobrzusze czy płyn w jamach opłucnych.

Szacuje się, że w Polsce na HF choruje ok. 1,24 mln ludzi. Prognozy epidemiologiczne estymują, że jedna na 5 osób rozwinie w którymś momencie swojego życia niewydolność serca. Niesie to ze sobą bardzo realne konsekwencje dla systemu opieki zdrowotnej, wydatki związane z postępowaniem w HF pochłaniają rocznie ok. 1,73 mld złotych[3]. Głównym problemem, niezależnie od wdrażania nowych strategii diagnostycznych i terapeutycznych są częste dekompensacje choroby wiążące się z koniecznością hospitalizacji – HF stanowi najczęstszą przyczynę hospitalizacji po 65 roku życia. Każda dekompensacja wiąże się z pogorszeniem funkcjonowania pacjenta – po wypisie chory nie wraca do poziomu życia sprzed pobytu w szpitalu. Co więcej, 25% pacjentów jest rehospitalizowanych przed upływem miesiąca od wypisu[3].

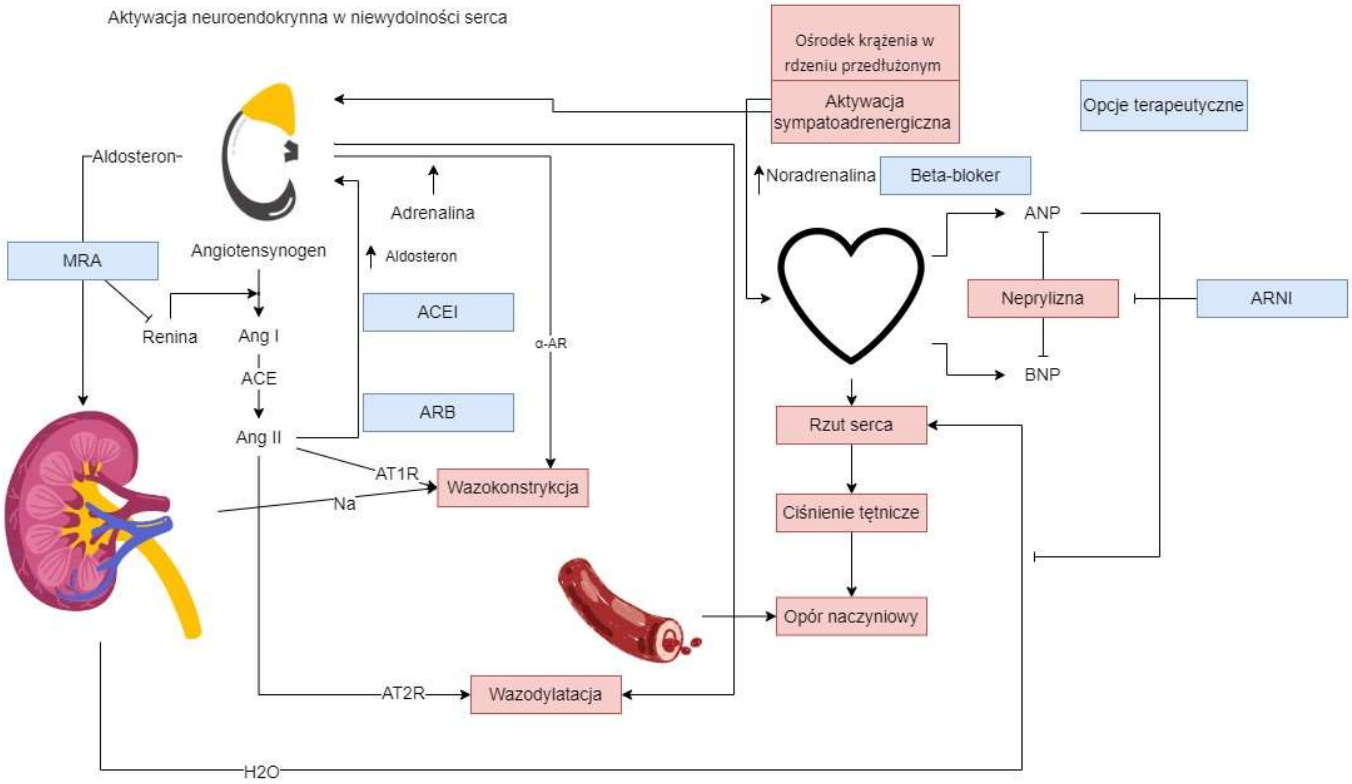
Objawy HF wynikają z pierwotnych zaburzeń w zakresie funkcji skurczowej lub rozkurczowej. Najczęściej stosowaną oraz mająca największe implikacje kliniczne klasyfikacją HF jest podział ze względu na frakcję wyrzutową lewej komory. O ile w niewydolności serca z obniżoną frakcją wyrzutową lewej komory (HFrEF) istnieje leczenie o

udokumentowanym, pozytywnym, wpływie na rokowanie, to w HF z zachowaną frakcją wyrzutową (HFpEF) dowody na skuteczność terapii nie mają oczekiwanej siły. HFpEF częściej dotyczy kobiet, osób starszych z historią źle kontrolowanego nadciśnienia. Pacjenci z HFrEF częściej dotknięci są wielochorobowością w postaci: choroby wieńcowej, w tym ostrego zespołu wieńcowego, wad zastawkowych, źle kontrolowanego nadciśnienia. Skuteczne leczenie powyższych, precyzyjnie zdefiniowanych, chorób, będących również czynnikiem etiologicznym HF, przekłada się na poprawę rokowania tych pacjentów[4].

Główną patomorfologiczną manifestacją HFrEF jest ekscentryczny przerost oraz rozstrzeń lewej komory, z towarzyszącym przeciążeniem objętościowym. Przeciążenie, spowodowane nadmiernym gromadzeniem płynów, jest napędzane przez aktywację osi renina-angiotensyna-aldosteron (RAA). W HFpEF dominują cechy upośledzonej relaksacji i napełniania, sztywność komory i podwyższenie ciśnień napełniania w związku z przeciążeniem ciśnieniowym. Serca chorych na HFpEF prezentują najczęściej cechy koncentrycznego przerostu[5].

Rokowanie pacjentów z HF w ostatnich dekadach uległo poprawie w związku z opublikowaniem szeregu badań klinicznych dotyczących leczenia HF[6–10]. Poprawa rokowania ogranicza się jednak do pacjentów z obniżoną frakcją wyrzutową lewej komory[1].

Podstawę leczenia HF stanowią leki antagonizujące pobudzenie neurohormonalne tj. inhibitory konwertazy angiotensyny (ACEI), w przypadku ich nietolerancji – antagoniści receptora angiotensyny II (ARB)], antagoniści receptora angiotensyny II i inhibitory neprylizyny (ARNI), β-adrenolityki, antagoniści receptora mineralokortykoidowego (MRA) oraz w przypadku suboptymalnej kontroli częstości rytmu iwabradyna. Do leków tych w ostatnim czasie dołączyły inhibitory kotransportera sodowo-glukozowego 2 (SGLT-2), których mechanizm działania pozostaje niejasny[11].

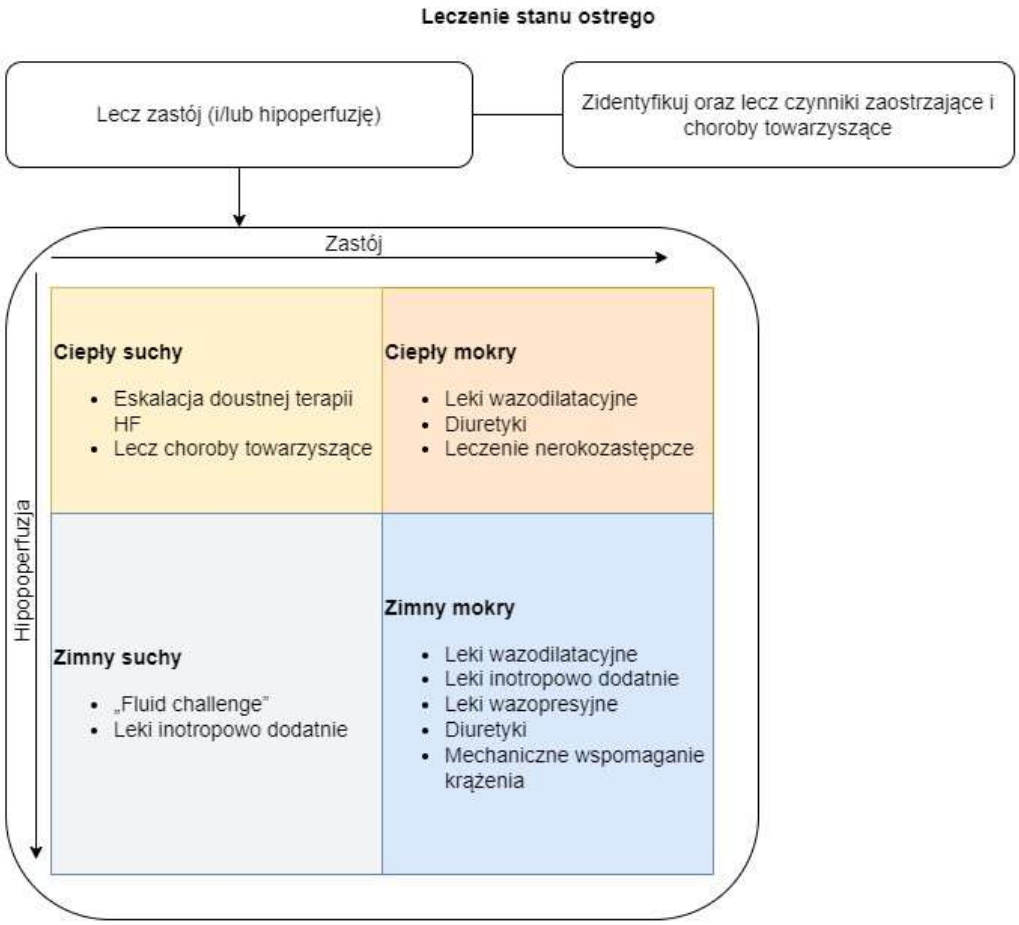


Rycina 1. Podstawowe szlaki biochemiczne zaangażowane w proces aktywacji neuroendokrynnej w niewydolności serca[4]. Skróty na rycinie: α-AR – receptor alfa adrenergiczny, ACE – enzym konwertujący angiotensynę, ACEI – antagoniści konwertazy angiotensyny, ANG I i II - angiotensyna I i II, ANP – przedsionkowy peptyd natriuretyczny, ARB - antagoniści receptora angiotensyny, ARNI - antagoniści receptora angiotensyny II i inhibitory neprylizyny, AT1/2R receptor angiotensyny I/II, BNP – mózgowy peptyd natriuretyczny, MRA - antagoniści receptora mineralokortykoidowego. Grafika na podstawie: - Schwinger, Robert H G. "Pathophysiology of heart failure." Cardiovascular diagnosis and therapy vol. 11,1 (2021): 263-276.

Szczególnym rodzajem HF pozostaje ostra niewydolność serca, której patofizjologia pozostaje nie do końca wyjaśniona. AHF wiąże się z wyjątkowo złym rokowaniem krótko i długoterminowym oraz wysoką śmiertelnością wewnątrzszpitalną. Niestety, postęp w terapii przewlekłej niewydolności serca odnotowany w ostatnich latach nie dotyczy w takim samym stopniu ostrej niewydolności serca[12]. Patofizjologia AHF jest złożona, dodatkowo

zróżnicowana w obrębie HFpEF i HFrEF. W HFrEF na skutek dysfunkcji skurczowej, dochodzi do wzrostu ciśnień wypełniania, narastania zastoju, co w powiązaniu z obniżonym rzutem serca prowadzi do hipoperfuzji obwodowej oraz postępującego uszkodzenia wielonarządowego. W przypadku HFpEF, obraz ten jest bardziej skomplikowany. Uważa się, że ostra niewydolność serca z zachowaną frakcją wyrzutową jest związana z hipertrofią kardiomiocytów, włóknieniem, upośledzoną funkcją rozkurczową, procesem zapalnym w mikrokrążeniu, zaburzoną sygnalizacją adipo-adrenergiczną, sztywnością tętnic obwodowych oraz wazokonstrykcją oddziałującą na afterload[5,13,14].

Ostra niewydolność serca może się różnie manifestować klinicznie. W 1976 Forrester et al., podzielił pacjentów z ostrą niewydolnością serca na 4 grupy, różniące się pod względem parametrów hemodynamicznych[15]. Podgrupy te były oparte na ocenie zastoju, rozumianego jako ciśnienie zaklinowania w tętnicy płucnej PCWP ≥18 mmH oraz adekwatności rzutu serca – wskaźnik sercowy (CI) > 2.2.L/min/m^2. Na podstawie powyższych parametrów wyróżniono następujące profile kliniczne; ciepły-suchy (bez cech zastoju i hipoperfuzji), ciepły-mokry (cechy zastoju bez cech hipoperfuzji), zimny-suchy (cechy hipoperfuzji bez cech zastoju), zimny-mokry (cechy zastoju i hipoperfuzji). Ocena inwazyjna parametrów hemodynamicznych wiąże się z określonymi ograniczeniami oraz ryzykiem powikłań i powinna być zarezerwowana do bardziej skomplikowanych, wymagających przypadków klinicznych[16]. Chorych z AHF można jednak sklasyfikować do powyższych grup na podstawie prezentowanych objawów przedmiotowych i podmiotowych. Klinicznie zastój można ocenić na podstawie m.in.: ortopnoe, poszerzenia żył szyjnych, występowania odruchu wątrobowo-szyjnego, wodobrzusza, obrzęków obwodowych, do oceny perfuzji posłużyć mogą: hipotensja, ochłodzenie kończyn, oliguria oraz pogorszenie statusu mentalnego[17]. Powyższa klasyfikacja ma udowodniony związek z rokowaniem, decyduje również o postępowaniu terapeutycznym.



Rycina 2. Profile hemodynamiczne w AHF. Skróty na rycinie: HF – niewydolność serca. Grafika na podstawie: Arrigo, M., Jessup, M., Mullens, W. et al. Acute heart failure. Nat Rev Dis Primers 6, 16 (2020)[18].

Rokowanie u pacjentów po epizodzie ostrej niewydolności serca pozostaje złe. W okresie od 60 do 90 dni od wypisu śmiertelność oscyluje w granicach 10% i rośnie do około 25-30% w ciągu 1 roku[18]. W rejestrze ADHERE śmiertelność 1-roczna sięgnęła 36%, co można przypisać dużej proporcji pacjentów przyjmowanych we wstrząsie kardiogennym[19,20]. Pacjenci, którzy po wypisie otrzymali pełne, rekomendowane przez wytyczne leczenie przewlekłej niewydolności serca, oraz ci, których włączono do programów opieki nad pacjentami z HF rokowali lepiej, niż odpowiadający im pacjenci bez tych interwencji[21].

Istnieją podejrzenia, że złe rokowanie w niektórych fenotypach niewydolności serca, tj. HFpEF oraz AHF, wynika z dużej różnorodności chorych w obrębie opisywanych grup. Obecnie trwają próby wyodrębnienia nowych, różniących się pod względem rokowania subpopulacji. Mimo gromadzenia na co dzień ogromnych ilości danych obejmujących m.in badanie kliniczne, wywiad, wyniki badań laboratoryjnych, w tym biomarkerowych oraz obrazowych, nie dysponujemy w tym momencie narzędziami, które umożliwiałyby pełną, szybką analizę tych danych i pozwalały na dokładne fenotypowanie pacjentów z AHF. Interesujące jest w tym kontekście poszukiwanie nowych, często nieoczywistych zależności, które mogłyby posłużyć do pełnej charakterystyki chorych. Nadzieję w tym zakresie dają nowoczesne metody analizy danych oparte na technikach sztucznej inteligencji (AI).

Nowe techniki analizy danych i sztuczna inteligencja

Sztuczna inteligencja to rozwijająca się od lat 50 XX wieku dyscyplina informatyki. Jedna z jej wielu definicji, stworzona przez Andreasa Kaplana i Michaela Haenleina określa ją jako zdolność algorytmu do prawidłowego interpretowania danych pochodzących ze źródeł zewnętrznych, nauki na ich podstawie oraz wykorzystywania zdobytej wiedzy do wykonywania określonych zadań i osiągania określonych celów[22]. W pojęciu sztucznej inteligencji mieści się wiele, zróżnicowanych pod względem złożoności wykonywanych zadań oraz zaawansowania technologicznego metod, najważniejsze z nich to: uczenie maszynowe, głębokie uczenie, przetwarzanie języka naturalnego czy cognitive computing. W ostatnich latach, sztuczna inteligencja przeżywa gwałtowny rozwój czego spektakularnymi przykładami mogą być: modele generatywne np. ChatGPT, autonomiczna motoryzacja (Tesla) czy rozpoznawanie twarzy (FaceID) lub głosu (Alexa, Siri).

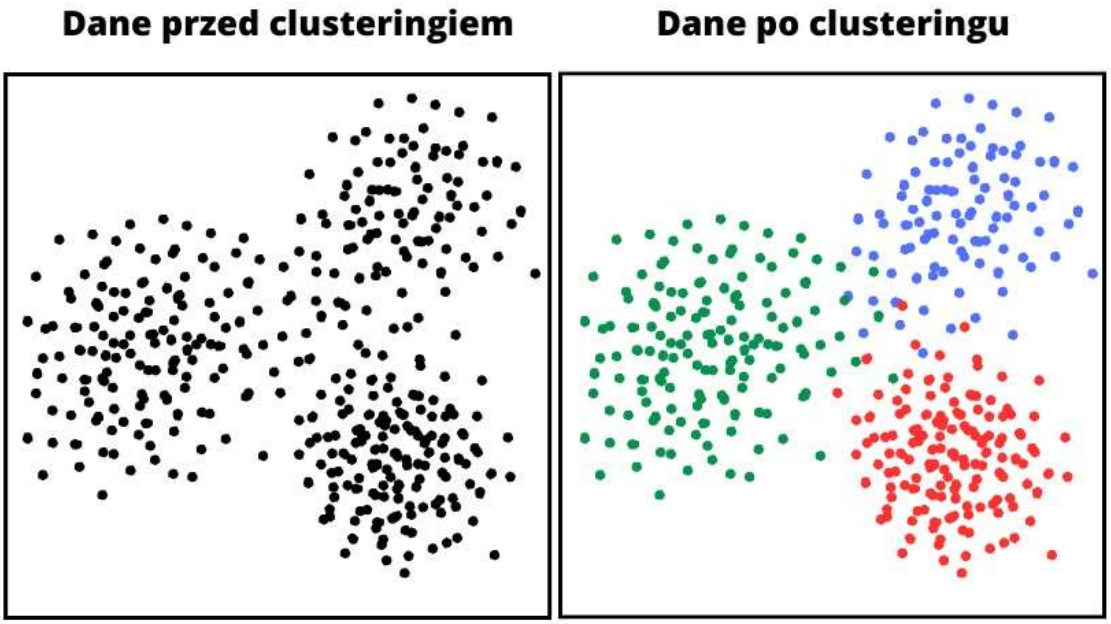
Największe nadzieje w zakresie wykorzystania AI w medycynie budzi wykorzystanie modeli predykcyjnych, opartych najczęściej na technikach uczenia maszynowego. Uczenie maszynowe jest obszarem sztucznej inteligencji poświęconym budowaniu modeli samodoskonalących się wraz ze zdobywanym doświadczeniem[23]. Algorytmy uczenia maszynowego (ML) na podstawie wprowadzonych danych (zbiór uczący) tworzą model matematyczny umożliwiający prognozowanie lub podejmowanie decyzji. Wyróżnia się wiele rodzajów uczenia maszynowego, wszystkie można podzielić na algorytmy uczenia nadzorowanego oraz nienadzorowanego. Uczenie nadzorowane wykorzystuje zbiór, opisanych, zetykietowanych danych. Model na etapie trenowania otrzymuje zestaw danych wejściowych oraz dopasowanych do nich, prawidłowych danych wyjściowych. Na tej

podstawie kalibrowane są parametry, tak, żeby model, na podstawie nowych, niezetykietowanych danych, generował prawidłowe odpowiedzi. Przykładem tego typu narzędzi mogą być narzędzia wykorzystywane do filtrowania spamu czy prognozowania dochodów ze sprzedaży.

Potencjalne narzędzia, które mogą błyskawicznie analizować ogromne zbiory danych, z precyzją i szybkością niedostępną ludzkiemu umysłowi, i na tej podstawie szacować ryzyko lub podejmować decyzje kliniczne, stały się obszarem zainteresowania wielu badaczy na całym świecie. Specjalnie powołane w tym celu konsorcjum Artificial Intelligence for Aortic Stenosis at Risk International Consortium stworzyło model umożliwiający skuteczniejszą walidację ciężkości stenozy aortalnej na podstawie wyłącznie przezklatkowego badania echokardiograficznego ze skutecznością zbliżoną do badania wspartego o dodatkowe techniki obrazowania tj. CT lub CMR[24]. Modele oparte na algorytmach uczenia maszynowego wypadały lepiej niż skala HAS-BLED, w szacowaniu ryzyka krwawienia z przewodu pokarmowego u pacjentów poddawanych leczeniu przeciwkrzepliwemu lub przeciwpłytkowemu[25]. Badacze z Karolinska Institute stworzyli algorytm umożliwiający klasyfikację pacjentów do grupy HFpEF i HFrEF, na podstawie danych rejestrowych. Takie narzędzie może być przydatne do szacowania funkcji lewej komory w sytuacji, w której badanie echokardiograficzne nie jest natychmiastowo dostępne[26]. Stworzono też model predykcyjny umożliwiający w pełni zautomatyzowaną detekcję amyloidozy serca na podstawie echokardiografii oraz EKG[27]. Ciekawym rozwiązaniem zaproponowanym przez badaczy z Mayo Clinic jest algorytm umożliwiający identyfikację pacjentów z migotaniem przedsionków na podstawie EKG wykonanego w trakcie rytmu zatokowego. Do uzyskania satysfakcjonujących parametrów w trakcie trenowania modelu wykorzystano 649 931 elektrokardiogramów[28]. Pierwszym randomizowanym badaniem klinicznym w którym zweryfikowano rozwiązanie oparte na AI było EchoNet-RCT. W powyższym projekcie stworzono model AI, który w zaślepionej próbie osiągnął większą dokładność w szacowaniu frakcji skurczowej lewej komory niż doświadczony echokardiografista[29].

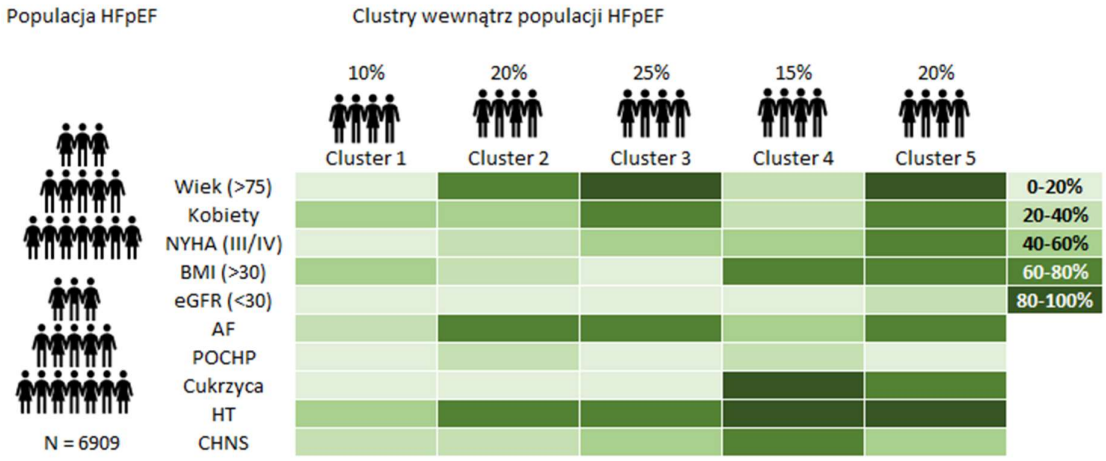
Drugim rodzajem uczenia maszynowego, jest uczenie nienadzorowane. W takim przypadku, algorytmy analizują, surowe, nieopisane dane celem wykrycia wzorów, zależności oraz podobieństw i różnic. W przeciwieństwie do uczenia nadzorowanego, celem modelu nie jest wygenerowanie konkretnych danych wyjściowych[30]. Najczęściej stosowanym w kardiologii rozwiązaniem z zakresu nienadzorowanego ML jest analiza skupień (clustering). Clusterig jest techniką która grupuje przypadki we względnie jednorodne klasy. Celem clusteringu może być

m.in. wyodrębnienie jednorodnych przedmiotów dalszych analiz, wykrycie anomalii, czy też odkrycie niepoznanej dotychczas struktury analizowanych danych[31].



Rycina 3. Przykład clusteringu w macierzy dwuwymiarowej. Grafika na podstawie: https://www.linedata.com/what-unsupervised-machine-learning[32].

Clustering jest z powodzeniem stosowany w kardiologii szczególnie w analizie heterogennych grup pacjentów. Powstał szereg prac, w których wyodrębniono nowe fenotypy pacjentów z HFpEF. Podgrupy pacjentów różniły się między sobą m.in. współchorobowością, parametrami laboratoryjnymi i echokardiograficznymi oraz rokowaniem[33,34]. Clustering znalazł też zastosowanie w analizie różnorodności transkrytpomu pacjentów z kardiomiopatią rozstrzeniową[35]. Możliwe było zidentyfikowanie nowych, fenotypów pacjentów ze stenozą aortalną. Co ciekawe, mimo jednorodności grup pod względem ciężkości wady, stworzone clustry różniły się pod względem rokowania, w tym również, pod względem przyczyny zgonu[36]. Wszystkie wyodrębnione fenotypy, dają nadzieję na możliwość prowadzenia bardziej spersonalizowanego leczenia.



Rycina 4. Przykładowy clustering populacji z HFpEF. Skróty na rycinie: AF – migotanie przedsionków, BMI - wskaźnik masy ciała, CHNS – choroba niedokrwienna serca, eGFR – szacowany wskaźnik filtracji kłębuszkowej, HT – nadciśnienie tętnicze, NYHA – New York Heart Association, POCHP – przewlekła obturacyjna choroba płuc. Grafika na podstawie: Uijl, Alicia et al. "Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction." European journal of heart failure vol. 23,6 (2021): 973-982[33].

4. Uzasadnienie i cele pracy

Uzasadnienie pracy

Ostra niewydolność serca jest stanem o złym rokowaniu zarówno krótko – jak i długoterminowym, o wyjątkowo różnorodnej prezentacji klinicznej oraz złożonej etiologii. Istnieją odmienne fenotypy chorych, zróżnicowane pod względem objawów czynników wyzwalających dekompensację, modyfikujących przebieg choroby oraz warunkujących odpowiedź na leczenie. Wydaje się, że identyfikacja odpowiednich podtypów może pozwolić na skuteczniejsze leczenie pacjentów z AHF zarówno podczas hospitalizacji jak i po wypisie. Może to posłużyć indywidualizacji terapii, wpisując się w postulowaną w ostatnich latach strategię leczenia ukierunkowanego na cele. Wyjątkowa heterogenność chorych z HF a, szczególnie z AHF, utrudnia ten proces w przypadku wykorzystywania klasycznej oceny objawów i wyników badań.

Techniki sztucznej inteligencji, szczególnie clusteringu, dają nowe możliwości analizy różnorodności populacji. Metody te pokazały już swoją skuteczność w badaniach medycznych, dotychczas nie weryfikowano jednakże takiego postępowania na szeroką skalę w populacji pacjentów z ostrą niewydolnością serca.

Niniejsza praca stanowi próbę weryfikacji przydatności wyodrębnienia nowych fenotypów pacjentów z ostrą niewydolnością serca przy użyciu technik sztucznej inteligencji w oparciu o powszechnie zbierane dane . Dodatkowym aspektem pracy jest ewaluacja możliwości technik sztucznej inteligencji w analizie różnorodności pacjentów kardiologicznych oraz ocenie ich rokowania.

Cele pracy

1. Identyfikacja nowych fenotypów klinicznych pacjentów hospitalizowanych z powodu AHF.
2. Ocena rokowania pacjentów z AHF w zależności od przynależności do konkretnego fenotypu.
3. Ocena przydatności modeli AI w analizie danych klinicznych z zakresu HF.

5. Publikacje wchodzące w skład rozprawy doktorskiej

biomedicines

MDPI

Article

Novel Phenotyping for Acute Heart Failure—Unsupervised Machine Learning-Based Approach

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Abstract: Acute heart failure (AHF) is a life-threatening, heterogeneous disease requiring urgent diagnosis and treatment. The clinical severity and medical procedures differ according to a complex interplay between the deterioration cause, underlying cardiac substrate, and comorbidities. This study aimed to analyze the natural phenotypic heterogeneity of the AHF population and evaluate the possibilities offered by clustering (unsupervised machine-learning technique) in a medical data assessment. We evaluated data from 381 AHF patients. Sixty-three clinical and biochemical features were assessed at the admission of the patients and were included in the analysis after the preprocessing. The K-medoids algorithm was implemented to create the clusters, and optimization, based on the Davies-Bouldin index, was used. The clustering was performed while blinded to the outcome. The outcome associations were evaluated using the Kaplan-Meier curves and Cox proportional-hazards regressions. The algorithm distinguished six clusters that differed significantly in 58 variables concerning i.e., etiology, clinical status, comorbidities, laboratory parameters and lifestyle factors. The clusters differed in terms of the one-year mortality ($p = 0.002$) . Using the clustering techniques, we extracted six phenotypes from AHF patients with distinct clinical characteristics and outcomes. Our results can be valuable for future trial constructions and customized treatment.

Keywords: acute heart failure; machine learning; clustering

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1. Introduction

Acute heart failure (AHF) is a life-threatening challenge in a clinical approach, causing a growing number of hospitalizations and a high in-hospital as well as post-discharge mortality range [1]. The present epidemiological situation (e.g., aging population, improved myocardial infarction survival) tends to increase the prevalence of chronic HF, resulting in hospitalization in the near future [2]. Over the years, the approach to the clinical manifestation of AHF has changed; however, it was always crucial for phenotype patients to provide them with a better individual treatment. The AHF diagnostic process starts with the first medical contact and is aimed at identifying the clinical presentation [1]. The clinical severity and medical procedures differ according to a complex interplay between the deterioration cause, underlying cardiac substrate, and comorbidities. It is recommended

to stratify AHF patients based on the presence of signs of congestion and/or peripheral hypoperfusion at admission. According to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, we can distinguish four clinical presentations of AHF: acute decompensated heart failure, acute pulmonary oedema, isolated right ventricular failure and cardiogenic shock, for which phenotyping may bring therapeutic and prognostic value [3]. It could be, nevertheless, questionable if a physical examination and simple dichotomous subgroups sufficiently reflect the complexity of the pathophysiology of AHF and the heterogeneity of AHF patients. These shortcomings in understanding the underlying correlations may be the reason for poor survivability [4].

Machine learning, especially statistical clustering, which is an unsupervised technique that attempts to learn the internal structure of data, might be a feasible tool for elucidating the hidden phenotypic characteristics for a better understanding of the vital differences between clinically important subpopulations [5–8]. Machine learning approaches have been successfully used in analyzing molecular data for many years. Recently, used with clinical variables, cluster analysis proved itself to be effective in the study of the phenotype characteristics of diseases in chronic heart failure with reduced ejection fraction [9] (HFrEF) as well as a preserved ejection fraction (HFpEF) [5].

According to the aforementioned studies, we implemented machine-learning algorithms for AHF patients and their clinical variables obtained at admission alone. We blinded them to the outcomes to detect novel patterns by subgrouping the patients at the first medical contact. By identifying them in such a manner, we hypothesized that subpopulations of patients would have different pathophysiological characteristics and varying outcomes.

2. Materials and Methods

2.1. Study Population

We retrospectively analyzed 381 patients hospitalized due to AHF based on two AHF registries that ran at our institution in 2010–2012 and 2016–2017. Patients were treated and heart failure diagnosis was stated following current ESC guidelines. The inclusion and exclusion criteria were elaborated in our previous references [10]. There were no differences in the collected patients' demographic data or the design of the evaluated registries, except for the criteria of acute heart failure diagnosis, which were slightly varied in the subsequent (2013 and 2016) ESC guidelines.

2.2. Machine Learning and Statistical Analysis

As we aimed to evaluate the baseline heterogeneity of AHF patients, only the variables evaluated at admission were included. The analysis was performed blinded to the outcome; therefore, the follow-up variables were excluded (Figure 1). Initially, 88 variables were divided into domains and selected for the study (Table 1). Then, the automatic preprocessing was performed. The low-quality variables were defined as those with over 90% stability and 10% missing values, and 25 such variables were deleted. Furthermore, remove, which correlated with r = 0.6, was implemented, but 0 variables were found and removed. Sixty-three variables were eventually included in the cluster analysis (Table 1). Due to clustering algorithms' inability to cope with the missing values, they were replaced by mean values. Range transformation normalization (range: 0 to 1) was performed. The nominal parameters were transformed into numerical parameters.

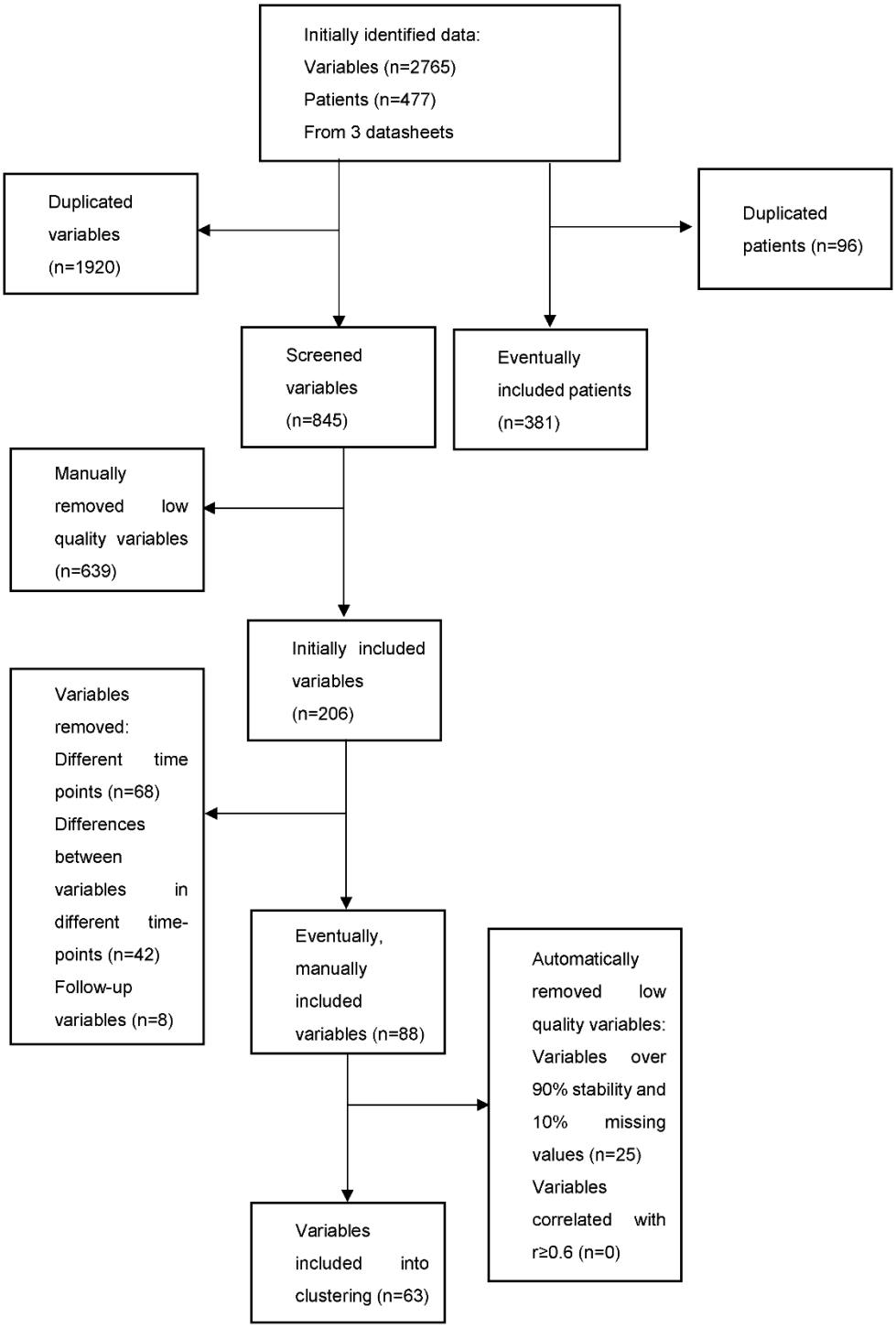

Figure 1. Flowchart of the analyzed variables and patients. The analysis was conducted based on the previously prepared data, therefore, some of the information was duplicated or inadequate for the machine-learning analysis.

Table 1. Variables initially included in the analysis. All parameters were assessed at admission. Bolded variables are variables which were included in the cluster analysis after the automatic preprocessing.

Demographics	**Age, Sex**
HF characteristics	**De novo or chronic HF, Etiology**
Comorbidities	**Coronary artery disease (0 or 1), myocardial infarction (0 or 1), PCI/CABG (0 or 1)**, **hypertension (0 or 1), valvular heart disease (0 or 1), diabetes (0 or 1), diabetes treated with: insulin = 1 Oral drugs = 2, diet = 3, stroke (0 or 1),COPD (0 or 1)**
Clinical status	**Dyspnoea at rest (0 or 1),** Dyspnoea at rest lasts since (number) days, **NYHA at admission, swelling of the lower limbs (lack = 0, 1 + (10–15 s) = 1, 2 + (15–30 s) = 2, 3 + (>30 s) = 3),** Decrease in exercise tolerance (0 or 1), decrease in exercise tolerance (for how many days), body weight, **systolic pressure, diastolic pressure, heart rate, jugular veins pressure (<6 cm = 1, 6–10 cm = 2, >10 cm = 3, not to be assessed = 4)**, **pulmonary congestion (no—0; up to 1/3 of lungs—1; up to 2/3—2; >2/3—3)**, **pulmonary congestion (0 or 1)**, **ascites (0 or 1), hepatomegaly (0 or 1), implantable device, none = 0, 1-PM, 2-ICD, 3-CRT2**
Lifestyle factors	**Smoking status (0 = never, 1 = now, 2 = in the past)**. If smoking in the past, how many cigarettes did the patient smoke? **Alcohol (0 or 1)**, How many cigarettes do the patients smoke daily, How many years did the patient smoke/does the patient smoke cigarettes?
Laboratory parameters	**HGB, HCT, RBC, MCV, MCH, MCHC, RDW, WBC, LYMPH, MONO, NEUTR, PLT,** serum PH, pCO_2, pO_2, ctO_2, BO_2, HCO_3, HCO_3std, $ctCO_2$, BE, sO_2, FO_2Hb, FHHb, ctHb, Lac, mOsm, **Na in serum, K in serum, Creatinine in serum, Urea in serum, Glucose in serum, Ast, Alt**, **CRP,** GGTP, **NTproBNP, Total_bilirubin, INR, Albumin in serum, Troponin in serum, Urine Na, Urine K, Urine Urea, Urine Creatinine, Fe, TIBC, Tsat, sTfR,** Ferritin, **IL-6, eGFR**
Echocardiography	**Reduced ejection fraction (0 or 1);** ejection fraction

Abbreviations: HGB—hemoglobin, HCT—hematocrit, RBC—red blood count, MCV—mean corpuscular volume, MCH—mean corpuscular hemoglobin, MCHC—mean corpuscular hemoglobin concentration, RDW—red cell distribution width, WBC—white blood count, LYMPH—lymphocytes percentage, MONO—monocytes, NEUTR—neutrophiles, PLT—platelets count, pCO_2—partial pressure of CO_2, pO_2—partial pressure of O_2, ctO_2—concentration of O_2, BO_2 -, HCO_3- bicarbonate, HCO_3std—bicarbonate standardized, $ctCO_2$—CO_2 concentration, BE—base excess, sO_2—O_2 saturation, FO2Hb—fraction of oxygenated haemoglobin, FHHb—fraction of deoxyhemoglobin in total hemoglobin, ctHb—total hemoglobin, Lac—lactates, mOsm -milliosmoles, Ast—aspartate aminotransferase, Alt—alanine transaminase, CRP—C-reactive protein, GGTP—gamma-glutamyl transpeptidase, NTproBNP—N-terminal prohormone of brain natriuretic peptide, INR—international normalized ratio, Fe—total iron amount in blood, TIBC—total iron-binding capacity, Tsat—transferrin saturation, sTfR—Soluble Transferrin Receptor, IL-6—interleukin 6th, eGFR—estimated glomerular filtration rate.

Cluster analysis is an unsupervised machine-learning method which divides the set of variables into smaller groups (clusters) based on their similarity. The clusters are composed of cases which are consistent with each other, but not with other collections. Several clustering algorithms have been described. This analysis uses the k-medoids algorithm to obtain clusters (k-medoids operator in RapidMiner). The number of groups has not been assumed in advance. The optimize parameters operator was used to reveal the most accurate cluster quantity and characteristics. The clustering.k and clustering.numerical_measure parameters were used to optimize the clustering, and the Davies-Bouldin index was chosen as the main criterion. The number of clusters was set between 3 and 6 to avoid excessive dataset fragmentation.

K-medoids is a clustering algorithm that requires that the number of resulting clusters (value of parameter K) is specified in advance. Unlike k-means clustering, where the centroids are computed as the average values of data points (examples) within a cluster, the

centroids in the k-medoids algorithm corresponds to the existing data points. This makes the centroids better interpreted. The clustering is based on measuring the distance between the examples; examples in a cluster are similar to each other. The clustering algorithm repeatedly re-assigns the examples into a given number of clusters by minimizing their distance to a centroid and recomputes the centroids. Thus, the concrete distance measure is another important parameter of the method.

Thanks to the option of the automated parameter tuning implemented in RapidMiner, we allowed the system to change the number of clusters K in the range of 3 to 6 and the numeric distance/similarity measure to take any value from the list:

- EuclideanDistance;
- CamberraDistance;
- ChebychevDistance;
- CorrelationSimilarity;
- CosineSimilarity;
- DiceSimilarity;
- DynamicTimeWarpingDistance;
- InnerProductSimilarity;
- JaccardSimilarity;
- KernelEuclideanDistance;
- ManhattanDistance;
- MaxProductSimilarity;
- OverlapSimilarity.

This results in more than 50 particular runs of the clustering algorithm. It seems that the parameter which primarily affects the quality of clustering is the number of clusters. The clustering quality (in terms of the Davies–Bouldin index) improves with an increasing number of clusters. We achieved the best results (lowest Davies–Bouldin index) for clustering into six clusters by using the correlation similarity measure.

The associations between the clusters and clinical features were assessed. The variables which presented a normal distribution were described as a mean ± standard deviation, and the non-normal variables were presented as medians and interquartile ranges. The categorical variables were shown as numbers and percentages (Table 2). The normality of the distribution was checked using the K–S, Lilliefors and Shapiro–Wilk tests. The statistical significance of differences between groups was assessed using analysis of variance, chi-square and ANOVA. The outcome associations were evaluated using the Kaplan–Meier curves and Cox proportional-hazards regressions (Figure 1). A p-value below 0.05 was considered statistically significant. Clustering and preprocessing were performed using RapidMiner 9.1 (RapidMiner GmbH, Dortmund, Germany) , and the statistical analysis was performed using STATISTICA 12 ((StatSoft Polska Sp. z o.o., Krakow, Poland)).

Table 2. Characteristics stratified by clusters and in the whole group. The highest values of the variables are marked red, lowest ones are green.

Parameter	Cluster_0	Cluster_1	Cluster_2	Cluster_3	Cluster_4	Cluster_5	Global	*p*
Demographics								
n	86	50	70	71	50	54	381	-
Sex, male (n)	78 (90.698%)	23 (46%)	58 (82.857%)	53 (74.648%)	49 (98%)	24 (44.444%)	285 (74.803%)	<0.001
Age (years)	67.293 [59–79]	76.1 [68–81]	58.821 [51.279–67.003]	72 [63–80]	66 [60.29–74.521]	76.111 [64–82.992]	68 [60–79]	<0.001
aHF charcteristics								
Ejection fraction	34 [28–43]	47.5 [39–55]	28 [20–40]	30 [25–35]	28 [20–35]	50 [30–60]	33 [25–45]	<0.001
Chronic HF (n)	32 (37.209%)	22 (44%)	34 (48.571%)	69 (97.183%)	47 (94%)	38 (70.37%)	242 (63.517%)	<0.001
Reduced EF (n)	67 (77.907%)	16 (32%)	58 (82.857%)	66 (92.958%)	45 (90%)	17 (31.481%)	269 (70.604%)	<0.001
Etiology								<0.001
Coronary artery disease (n)	41 (47.674%)	28 (56%)	3 (4.286%)	61 (85.915%)	43 (86%)	20 (37.037%)	178 (46.719%)	
Valvular (n)	5 (5.814%)	2 (4%)	15 (21.429%)	3 (4.225%)	1 (2%)	2 (3.704%)	46 (12.073%)	
Hypertension (n)	1 (1.163%)	5 (10%)	1 (1.429%)	1 (1.408%)	1 (2%)	4 (7.407%)	13 (3.412%)	
Other (n)	39 (45.349%)	15 (30%)	51 (72.857%)	6 (8.451%)	5 (10%)	28 (51.852%)	144 (37.795%)	
Comorbidites								
Coronary artery disease (n)	56 (65.116%)	38 (76%)	1 (1.429%)	69 (97.183%)	49 (98%)	5 (9.259%)	218 (57.218%)	<0.001
Myocardial infarction in the past (n)	17 (19.767%)	20 (40%)	1 (1.429%)	33 (46.479%)	44 (88%)	3 (5.556%)	118 (30.971%)	<0.001
PCI/CABG in the past (n)	9 (10.465%)	27 (54%)	0 (0%)	50 (70.423%)	37 (74%)	0 (0%)	123 (32.283%)	<0.001
Hypertension (n)	72 (83.721%)	47 (94%)	27 (38.571%)	56 (78.873%)	38 (76%)	47 (87.037%)	286 (75.066%)	<0.001
Valvular disease (n)	52 (60.465%)	16 (32%)	43 (61.429%)	57 (80.282%)	38 (76%)	38 (70.37%)	244 (64.042%)	<0.001
Diabetes mellitus (n)	30 (34.884%)	46 (92%)	13 (18.571%)	22 (30.986%)	27 (54%)	14 (25.926%)	152 (39.895%)	<0.001

Table 2. *Cont.*

Parameter	Cluster_0	Cluster_1	Cluster_2	Cluster_3	Cluster_4	Cluster_5	Global	*p*
Comorbidites								
Diabetes treatment (n)								
Insulin	5 (5.814%)	20 (40%)	1 (1.429%)	7 (9.859%)	9 (18%)	1 (1.852%)	43 (11.286%)	
Oral drugs	11 (12.791%)	17 (34%)	7 (10%)	10 (14.085%)	13 (26%)	11 (20.37%)	69 (18.11%)	
Diet	5 (5.814%)	4 (8%)	0 (0%)	1 (1.408%)	4 (8%)	0 (0%)	14 (3.675%)	
Stroke (n)	7 (8.14%)	11 (22%)	8 (11.429%)	12 (16.901%)	9 (18%)	6 (11.111%)	53 (13.911%)	<0.001
COPD (n)	8 (9.302%)	11 (22%)	4 (5.714%)	12 (16.901%)	8 (16%)	7 (12.963%)	50 (13.123%)	<0.001
Clinical status								
Dyspnoea at rest (n)	76 (88.372%)	42 (84%)	40 (57.143%)	56 (78.873%)	43 (86%)	50 (92.593%)	307 (80.577%)	<0.001
Dyspnoea at rest lasts since (n) days	3 [1–8]	3 [1–7]	3.5 [1–8.5]	3 [2–8.5]	3 [2–7]	3 [2–6]	3 [1–7]	0.8
Decrease in exercise tolerance (n) days	14 [7–21]	7 [6.5–29]	14 [7–29]	14 [7–28]	10 [7–21]	14 [6.5–30]	14 [7–28]	0.6
NYHA (n)								0.243
I	4 (4.651%)	1 (2%)	3 (4.286%)	2 (2.817%)	2 (4%)	1 (1.852%)	13 (3.412%)	
II	11 (12.791%)	8 (16%)	13 (18.571%)	7 (9.859%)	13 (26%)	10 (18.519%)	62 (16.273%)	
III	12 (13.953%)	8 (16%)	23 (32.857%)	26 (36.62%)	9 (18%)	9 (16.667%)	87 (22.835%)	
IV	46 (53.488%)	27 (54%)	23 (32.857%)	36 (50.704%)	26 (52%)	31 (57.407%)	189 (49.606%)	
Swelling of lower limbs (n)								0.006
Swelling of lower limbs 0	18 (20.93%)	16 (32%)	26 (37.143%)	19 (26.761%)	16 (32%)	7 (12.963%)	102 (26.772%)	
Swelling of lower limbs 1	15 (17.442%)	15 (30%)	16 (22.857%)	18 (25.352%)	10 (20%)	16 (29.63%)	90 (23.622%)	
Swelling of lower limbs 2	27 (31.395%)	13 (26%)	17 (24.286%)	23 (32.394%)	11 (22%)	16 (29.63%)	107 (28.084%)	
Swelling of lower limbs 3	26 (30.233%)	6 (12%)	10 (14.286%)	11 (15.493%)	13 (26%)	15 (27.778%)	81 (21.26%)	
Deterioration of Effort Tolerance (n)	79 (91.86%)	47 (94%)	63 (90%)	67 (94.366%)	49 (98%)	53 (98.148%)	358 (93.963%)	0.407

Table 2. *Cont.*

Parameter	Cluster_0	Cluster_1	Cluster_2	Cluster_3	Cluster_4	Cluster_5	Global	*p*
Clinical status								
JVP (n)								<0.001
JVP 1	57 (66.279%)	32 (64%)	42 (60%)	53 (74.648%)	17 (34%)	31 (57.407%)	232 (60.892%)	
JVP 2	24 (27.907%)	17 (34%)	23 (32.857%)	18 (25.352%)	25 (50%)	21 (38.889%)	128 (33.596%)	
JVP 3	5 (5.814%)	0 (0%)	5 (7.143%)	0 (0%)	8 (16%)	2 (3.704%)	20 (5.249%)	
Pulmonary edema (n)								<0.001
no	11 (12.791%)	1 (2%)	12 (17.143%)	2 (2.817%)	7 (14%)	6 (11.111%)	39 (10.236%)	
up to 1/3 of lungs	49 (56.977%)	23 (46%)	45 (64.286%)	50 (70.423%)	31 (62%)	25 (46.296%)	223 (58.53%)	
up to 2/3	20 (23.256%)	14 (28%)	9 (12.857%)	13 (18.31%)	11 (22%)	16 (29.63%)	83 (21.785%)	
>2/3	6 (6.977%)	11 (22%)	4 (5.714%)	6 (8.451%)	1 (2%)	7 (12.963%)	35 (9.186%)	
Pulmonary congestion (n)	75 (87.209%)	48 (96%)	58 (82.857%)	69 (97.183%)	43 (86%)	48 (88.889%)	341 (89.501%)	0.048
Ascites (n)	15 (17.442%)	3 (6%)	9 (12.857%)	2 (2.817%)	13 (26%)	8 (14.815%)	50 (13.123%)	0.003
Hepatomegaly (n)	29 (33.721%)	8 (16%)	11 (15.714%)	1 (1.408%)	27 (54%)	6 (11.111%)	82 (21.522%)	<0.001
Implantable device (n)								<0.001
PM	2 (2.326%)	8 (16%)	2 (2.857%)	8 (11.268%)	2 (4%)	6 (11.111%)	28 (7.349%)	
ICD	3 (3.488%)	1 (2%)	8 (11.429%)	31 (43.662%)	9 (18%)	3 (5.556%)	55 (14.436%)	
CRT	2 (2.326%)	1 (2%)	3 (4.286%)	3 (4.225%)	15 (30%)	2 (3.704%)	26 (6.824%)	
Systolic pressure (mmHg)	140 [120–158]	160 [135–180]	120 [105–131]	126.5 [110–137]	120 [102–145]	120 [107–142]	130 [110–150]	<0.001
Diastolic pressure (mmHg)	80 [70–95.5]	80 [70–95]	77.5 [70–87]	80 [70–85]	70 [62–80]	70 [65–80]	79 [70–90]	<0.001
Heart rate (bpm)	90 [75–110]	80 [70–100]	90.5 [80–105]	80 [70–100]	78 [70–90]	88 [72–110]	82.5 [70–100]	<0.001
Body weight (kg)	85.3 [77–98]	79 [69–90.95]	77.6 [68.5–88.3]	77.4 [70.4–91]	80.5 [71–94]	74.9 [65–82]	79.6 [70–91.5]	<0.001
Lifestyle factors								
Smoking status (n)								<0.001
Never	41 (47.674%)	32 (64%)	35 (50%)	49 (69.014%)	8 (16%)	36 (66.667%)	201 (52.756%)	

Table 2. *Cont.*

Parameter	Cluster_0	Cluster_1	Cluster_2	Cluster_3	Cluster_4	Cluster_5	Global	*p*
Lifestyle factors								
Active	23 (26.744%)	3 (6%)	21 (30%)	7 (9.859%)	4 (8%)	3 (5.556%)	61 (16.01%)	
In the past	22 (25.581%)	15 (30%)	14 (20%)	15 (21.127%)	38 (76%)	15 (27.778%)	119 (31.234%)	
How many cigarettes do patients smoke daily (n)	0.08 [0–15]	1 [0–8]	0 [0–15]	0 [0–9]	15 [4–20]	3 [0–12]	2 [0–15]	0.047
How many years did the patient smoke/does the patient smoke cigarettes (n)	22.5 [0–30]	20 [0–30]	11.5 [0–30]	0 [0–30]	20 [5–30]	0 [0–30]	20 [0–30]	0.36
Active alcohol use (n)	20 (23.256%)	8 (16%)	31 (44.286%)	16 (22.535%)	19 (38%)	12 (22.222%)	106 (27.822%)	0.002
Laboratory parameters								
HGB (g/dL)	13.727 ± 1.881	11.972 ± 1.81	13.975 ± 1.651	13.213 ± 1.817	13.194 ± 2.114	12.391 ± 1.801	13.184 ± 1.953	<0.001
HCT (%)	41.232 ± 5.21	36.686 ± 5.191	41.684 ± 4.665	39.907 ± 5.163	40.066 ± 6.319	37.343 ± 4.854	39.759 ± 5.49	<0.001
RBC ($\times 10^{12}$/L)	4.544 ± 0.662	4.18 ± 0.55	4.595 ± 0.495	4.499 ± 0.65	4.516 ± 0.716	4.226 ± 0.628	4.448 ± 0.636	<0.001
MCH (pg)	30.333 ± 2.325	28.692 ± 2.728	30.457 ± 2.269	29.49 ± 2.261	29.255 ± 2.565	29.479 ± 2.986	29.718 ± 2.552	<0.001
MCV fL	91.188 ± 6.241	87.846 ± 6.236	90.854 ± 5.707	89.057 ± 6.144	89.034 ± 6.797	88.834 ± 6.451	89.668 ± 6.31	0.02
WBC ($\times 10^{9}$/L)	8.6 [6.8–10.68]	9.35 [6.7–12.3]	8.25 [6.3–9.85]	7.8 [6.4–9.52]	8.44 [7.1–10.4]	8.3 [6.1–9.9]	8.3 [6.6–10.35]	0.01
PLT ($\times 10^{9}$/L)	214 [152–252.5]	211 [163–298]	197.5 [164.5–233]	192 [149–234]	195 [159–250]	203 [144–242]	198 [155–245]	0.04
pH	7.44 [7.415–7.47]	7.4 [7.35–7.46]	7.45 [7.42–7.48]	7.45 [7.43–7.47]	7.45 [7.415–7.485]	7.45 [7.385–7.48]	7.44 [7.41–7.47]	<0.001
pCO2 (mmHg)	34.4 [31.55–38.7]	37.3 [32.7–42.9]	34.55 [30.9–36.55]	34.55 [32.2–37.5]	33.6 [31.6–38.25]	36.2 [33.05–39.45]	35.1 [31.8–38.9]	<0.001
HCO3std (mmol/L)	24.016 ± 3.193	22.989 ± 3.657	24.592 ± 2.474	24.676 ± 2.684	24.602 ± 3.376	25.321 ± 3.688	24.367 ± 3.203	0.01
pO2 (mmHg)	64.4 [57.15–73.15]	66.3 [61.2–78.7]	70.2 [62.3–75.5]	65.6 [58.2–74.3]	67.3 [60.05–74.7]	65.15 [57.65–71.8]	66.1 [59–74.6]	0.8
sO2 (%)	92.1 [89.15–95.05]	93.45 [90.6–94.9]	94.45 [91.45–95.95]	92.8 [89.9–94.9]	93.1 [90.4–96]	93.05 [90.2–95.4]	93.1 [90.1–95.4]	0.9
mOsm (Osm/L)	282.5 [274–286]	286.5 [279–291]	283 [274–287]	281 [274–286]	277.5 [272–286]	279.5 [270–287]	282 [274–287]	0.01
K (mmol/L)	4.187 ± 0.577	4.481 ± 0.788	4.197 ± 0.484	4.185 ± 0.521	4.197 ± 0.622	4.063 ± 0.694	4.21 ± 0.614	0.02
Na (mmol/L)	140 [137–142]	140 [137–142]	139 [135.5–141.5]	139 [137–142]	138 [135–140]	138.5 [135–141]	139 [136–142]	0.145
Glucose (mg/dL)	124 [100–162]	144 [121–212]	110 [99.5–131]	113 [101–139]	126.5 [107–150]	117 [105–143]	121 [103–151.5]	<0.001

Table 2. *Cont.*

Parameter	Cluster_0	Cluster_1	Cluster_2	Cluster_3	Cluster_4	Cluster_5	Global	*p*
INR	1.26 [1.08–1.48]	1.31 [1.09–1.99]	1.31 [1.14–1.77]	1.54 [1.18–2.24]	1.42 [1.17–2.08]	1.46 [1.2–2.21]	1.35 [1.12–1.97]	0.06
Total bilirubin (mg/dL)	0.96 [0.72–1.46]	0.785 [0.505–1.275]	1.25 [0.765–1.755]	1.145 [0.775–1.945]	1.225 [0.855–1.705]	1.03 [0.79–1.9]	1.07 [0.73–1.7]	0.09
Albumin (g/dL)	3.675 ± 0.402	3.775 ± 0.342	3.755 ± 0.406	3.831 ± 0.328	3.766 ± 0.386	3.648 ± 0.466	3.739 ± 0.394	0.1
Ast (IU/L)	29 [21.5–44.5]	26 [17–37]	30 [22–40]	26 [20–37]	26.5 [18–34.5]	27 [20.5–38.5]	27 [20–40]	0.5
Alt (IU/L)	28 [21.5–58]	28 [17–41]	34.5 [21.5–55]	30.5 [21–53]	27.5 [16.5–40.5]	24.5 [15.5–32]	29 [19–48]	0.7
GGTP (IU/L)	70 [40–127]	54.5 [39.5–102.5]	82 [48–166]	72 [48–133]	104 [45–183]	60.5 [28–113.5]	71 [41–128]	0.8
TIBC (µg/dL)	331.45 ± 63.813	336.5 ± 84.925	362.968 ± 66.412	364.09 ± 68.448	366.302 ± 60.677	338.765 ± 72.717	349.457 ± 70.214	0.007
Fe (µg/dL)	48 [36–66.5]	47.5 [31.5–65.5]	60 [47–84]	55 [43–79]	62 [43–83]	50 [37–61]	54 [40–71]	0.009
Ferritin (ng/mL)	162.5 [85.325–252]	147.5 [57–249]	124 [52–224]	92 [54–156]	94.985 [53.68–146]	119.6 [67.36–200]	109.3 [61–224]	0.02
Tsat (%)	15.25 [10.113–20.1]	15.05 [9.263–19.057]	16.958 [13.2–25.455]	14.8 [11.4–21.4]	17 [12.429–23.4]	15.9 [12.4–18.3]	15.654 [11.609–21.05]	0.46
sTfR (mg/L)	1.72 [1.42–2.72]	2.02 [1.445–2.635]	1.73 [1.41–2.08]	1.97 [1.69–2.51]	1.905 [1.59–2.46]	1.79 [1.3–2.73]	1.87 [1.46–2.51]	0.66
NTproBNP (pg/mL)	5218 [2674–12496]	4191 [2025–6048]	7189 [5023–12849]	5437 [3612–10572]	5712.5 [3452.5–11170.5]	5337 [2398–8775]	5580 [3169–10421]	0.03
Troponin (ng/mL)	0.042 [0.022–0.12]	0.049 [0.025–0.156]	0.032 [0.017–0.094]	0.058 [0.03–0.156]	0.05 [0.029–0.13]	0.05 [0.02–0.14]	0.05 [0.022–0.127]	0.03
CRP (mg/L)	8.6 [4.4–19.3]	6.8 [3.05–27.25]	6.15 [3.2–14.05]	7.425 [3.8–14.5]	6.95 [3.25–16.05]	8.18 [3.86–19.4]	7.395 [3.5–18]	0.18
IL6 (pg/mL)	12.108 [4.428–26.822]	10.999 [0.633–27.125]	7.979 [0.5–19.923]	8.315 [0.5–14.6]	8 [4.851–16.927]	13.82 [3.785–38.5]	9.989 [2.528–22.89]	0.29
Lactates (mmol/L)	2 [1.4–2.4]	1.95 [1.5–2.7]	2 [1.6–2.7]	1.8 [1.5–2.4]	2.1 [1.45–2.7]	2 [1.5–2.75]	2 [1.5–2.6]	0.64
Urea (mmol/L)	47 [37–73]	55 [39–78]	49.5 [38–68]	53.5 [43–74]	64 [44–86]	44 [35–65]	51 [38–73]	0.3
Creatinine (mg/dL)	1.16 [1.03–1.5]	1.32 [0.93–1.7]	1.1 [0.935–1.295]	1.23 [1.03–1.49]	1.355 [1.09–1.8]	1.2 [0.95–1.44]	1.225 [1–1.505]	0.003
eGFR (mL/min/1.73m^2)	84.463 ± 26.383	68.036 ± 29.564	94.693 ± 31.385	76.697 ± 22.711	77.859 ± 34.792	79.116 ± 43.668	81.074 ± 32.041	<0.001
Urine Urea (mmol/L)	1131 [555.5–1585]	512 [369–905]	886 [484–1674]	730 [442–1330]	887 [487–1509]	514 [339.5–981]	780 [442–1403]	<0.001
Urine Creatinine (mg/dL)	80.55 [41.75–147.6]	33.5 [21.7–79.2]	73.2 [34.7–129.1]	61.5 [28.9–105]	52.9 [38.9–136.8]	42 [23.55–80.65]	59.1 [30.1–110]	<0.001
Urine K (mmol/L)	35.765 [20–49.04]	22.75 [15–32]	28.73 [20–41]	27 [17.14–37]	31.5 [27–50.44]	29.5 [17–41.5]	29.77 [19–42.59]	<0.001
Urine Na(mmol/L)	87.286 ± 39.226	95.432 ± 32.757	90.87 ± 42.771	87.594 ± 37.329	84.533 ± 34.78	96.269 ± 36.412	89.959 ± 37.886	0.55

3. Results

3.1. Patients Characteristics

The study population consisted of 381 patients (all Caucasian), predominantly male 285 (75%), mean age 68 (60–79), with a median EF of 33% (25–45) and a median NTproBNP of 5580 (3169–10421) pg/mL (Table 2). The analyzed cohort presented as median: systolic blood pressure: 130 (110–150) mmHg, serum Na+: 139 (136–142) mmol/L and serum creatinine 1.23 (1–1.51) mg/dL. Table 3 shows the patient characteristics, including the key clinical features of each cluster. The principal clinical, biochemical and echocardiographic features of each cluster are presented in Figure 2.

Table 3. Key clinical features of each cluster.

Cluster	Key Clinical Feature
Cluster 0	Lowest % of chronic HF, most massive lower limbs oedema, highest urine urea, k, creatinine, highest ferritin, highest % of NYHA I, lowest % stroke history, better prognosis—**highest % of de novo HF, with preserved renal function.**
Cluster 1	Higher % of women than in the rest of the population, highest systolic pressure, highest hypertension, diabetes, chronic obstructive pulmonary disease and stroke history (lowest GFR, lowest urine creatinine, urea and K, lowest NTproBNP), most massive pulmonary congestion and least massive peripheral oedema, highest hypertension etiology, better prognosis—**hypertensive, diabetic patients with advanced atherosclerosis and comorbidities, diminished renal function, elderly population with a significant part of de novo HF.**
Cluster 2	Youngest patients, low NYHA and ejection fraction, lowest blood pressure, troponin, CRP and IL-6, lowest % diabetes history, lowest % of CAD history and etiology, lowest hypertension etiology, highest "other" etiology, highest GFR, NTproBNP, bilirubin, Alt, Ast, highest % of active smokers, least massive pulmonary congestion, better prognosis—**young "healthy", early-stage HF, presumed toxic etiology.**
Cluster 3	Lowest WBC, ferritin, urine Na, Tsat, lactates, highest troponin, INR, albumin, highest % of HFrEF and chronic HF, highest % of valvular disease history, highest % of pulmonary congestion (97%), mean prognosis—**HFrEF with reduced iron resources.**
Cluster 4	Predominantly man, highest pH, creatinine, urea, lactates, lowest ejection fraction and pCO_2, highest % of ascites and hepatomegaly, most massive JVP, highest CAD etiology, worse prognosis—**men, HFrEF, with cardiorenal syndrome, hyperventilation, right ventricular failure.**
Cluster 5	Highest EF, no CAD history (0%), oldest population, highest % of women, highest CRP, IL6, lowest body weight, low % of MI/PCI/CABG, worst prognosis—**HFpEF phenotype with increased inflammatory markers.**

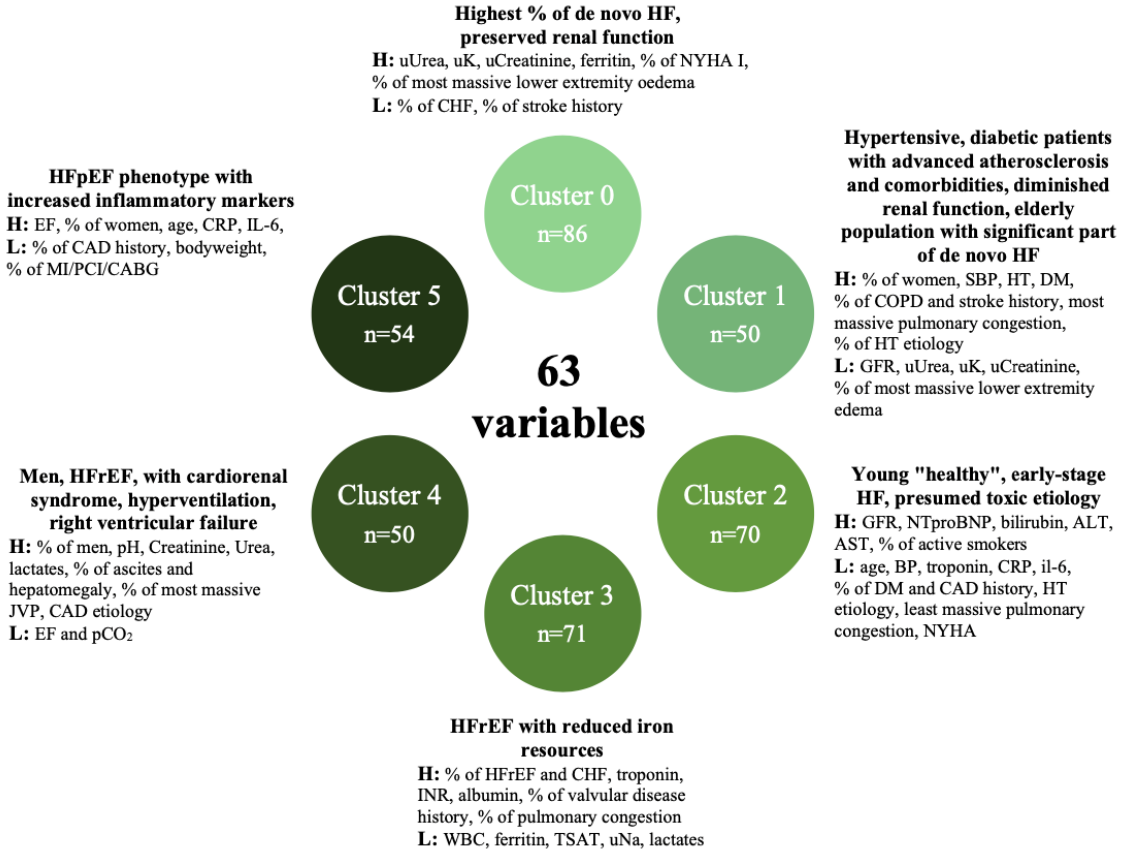

Figure 2. Principal clinical, laboratory and echocardiographic features for each cluster. ALT—Alanine Aminotransferase, AST—Aspartate Aminotransferase, BP—blood pressure, CABG—coronary artery bypass grafting, CAD—coronary artery disease, CHF—chronic heart failure, COPD—chronic obstructive pulmonary disease, CRP—C-reactive protein, DM—diabetes mellitus, EF—ejection fraction, GFR—glomerular filtration ratio, HF—heart failure, HFrEF—heart failure with reduced ejection fraction, HT—hypertension, IL-6—interleukin 6, JVP—jugular venous pulsation, MI—myocardial infarction, NTproBNP—N-terminal-pro B-type natriuretic peptide, NYHA—New York Heart Association class, PCI—percutaneous cardiac intervention, SBP—systolic blood pressure, TSAT—Transferrin saturated with iron, u—urine concentration, WBC—white blood cell count.

3.2. Clustering

The population was divided into six cluster groups by analysis of 63 variables. Clusters have been enumerated from 0 to 5. The variables that were included in the analyses are presented in Table 1.

Cluster 0 (n = 86)

This was the largest cluster and included the highest percentage of patients with HF de novo, qualified as NYHA I, presenting with severe lower extremity edema on admission, and the highest urine K+, creatinine and urea levels. Moreover, this cluster had the highest ferritin levels and the lowest percentage of patients with a history of stroke.

Cluster 1 (n = 50)

Among the other clusters, this cluster was mostly represented by women with the highest prevalence of hypertension, diabetes, COPD and stroke history. On admission, this cluster presented with the highest systolic blood pressure, the highest percentage of patients with severe pulmonary congestion and the least severe signs of peripheral congestion. The NTproBNP, GFR, urine K+, urea and creatinine levels were the lowest in this cluster.

Cluster 2 (n = 70)

On average, this cluster was represented by the youngest patients, the highest percentage of active smokers, and qualified as NYHA IV and HF etiology was classified as

other. Additionally, this cluster presented the lowest percentage of ischemic HF etiology, hypertension, diabetes and pulmonary congestion. On admission, they presented with the highest GFR, NTproBNP, AST, ALT and bilirubin serum levels and the lowest levels of troponin, CRP, and IL-6 serum levels.

Cluster 3 (n = 71)

This cluster consisted of the highest percentage of patients who qualified as HFrEF, the highest percentage of patients who decompensated in CHF, and the highest ratio of patients with valvular heart disease. On admission, this cluster was represented by the highest proportion of patients presenting with the most severe pulmonary congestion and lowest WBC, ferritin, TSAT, urine Na+, lactates and highest troponin, INR and albumin in the laboratory measurements.

Cluster 4 (n = 50)

This cluster was mostly represented by men, smokers with a CAD HF etiology and the lowest EF. On admission, they presented with the highest ratio of hepatomegaly, ascites, the highest JVP and the least frequent severe pulmonary congestion. They also had the highest creatinine and urea serum levels. For the arterial blood gases, this cluster presented with the lowest pCO_2 and the highest pH.

Cluster 5 (n = 54)

The characteristics of these patients appeared to be the oldest population, with the highest percentage of women and the highest EF, lowest body mass, and no CAD history. Moreover, the highest level of CRP and Il-6 serum levels was in this group of patients.

3.3. Prognostic Significance of Clusters

The one-year mortality was 27% (104 events). The mean hospital stay was 8.6 ± 6.7 days.

The one-year mortality from cluster 0 to cluster 5 was: 26% vs 22% vs 17% vs 21% vs 40% vs 43%, $p = 0.002$, respectively (Table 4).

Table 4. Outcomes by Clusters.

	Cluster 5	Cluster 4	Cluster 3	Cluster 2	Cluster 1	Cluster 0	*p*
One-year mortality	45.3%	40%	21.1%	17.1%	22%	25.6%	0.002
One-year mortality or HF rehospitalization	68.1%	77.3%	55.7%	63.2%	55.3%	53.5%	0.112
In-hospital deterioration	8.5%	16.3%	8.2%	3.1%	15.2%	7.8%	0.1
Duration of hosp. [days]	9.3 ± 5.7	9.4 ± 6.8	6.7 ± 3.4	8.2 ± 7.5	9.7 ± 8.5	9.0 ± 7.3	0.1

The risks for one-year compared with the rest of the population were calculated for each cluster. Clusters 5 and 4 had the highest one-year mortality risks, hazard ratio (95% confidence interval); cluster 5 had a HR (95% CI): 2.095 [1.327–3.306], $p = 0.002$; cluster 4: HR (95% CI): 1.738 [1.067–2.831], $p = 0.026$. Cluster 2 had the lowest one-year mortality risk, HR (95% CI): 0.537 [0.294–0.979], $p = 0.043$. There were no significant differences compared to the rest of the population for clusters 0, 1 and 3 (Table 5).

Table 5. Hazard ratios for one-year mortality; each cluster was compared with the rest of the population.

	One-Year Mortality Risk		
	X^2	Hazard Ratio (95% Confidence Interval)	*p*
Cluster 0	0.194	0.900 [0.562–1.441]	0.662
Cluster 1	0.679	0.776 [0.415–1.449]	0.425
Cluster 2	4.807	0.537 [0.294–0.979]	0.043
Cluster 3	1.964	0.688 [0.397–1.188]	0.179
Cluster 4	4.393	1.738 [1.067–2.831]	0.026
Cluster 5	8.753	2.095 [1.327–3.306]	0.002

Figure 3 shows the Kaplan–Meier curves for the one-year mortality risks by clusters.

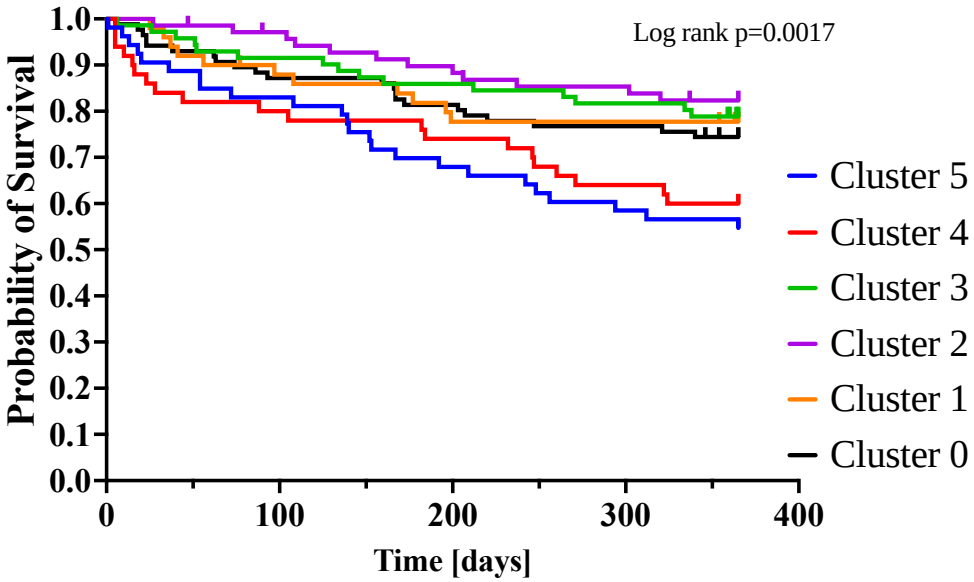

Figure 3. Kaplan–Meier curves for one-year mortality by clusters.

4. Discussion

A cluster analysis was applied to the cohort of 381 AHF patients. Both the clinical and biochemical variables were included and were either continuous or numerical. When writing this article, this was the most numerous analysis of such a type done in a European AHF population. Six clinically and pathophysiological relevant phenotypes were distinguished. The clusters varied in outcomes, including mortality and AHF re-hospitalization rates. Notably, the number of groups has not been prespecified, as in previous papers on the AHF population [1], but mathematically assessed. The quantity of the analyzed population allowed us to distinguish the highest number of virtually equally dense clusters [4,8,11–13], which provide the most thorough insight into an AHF's population heterogeneity. Although during the collection of both registries guidelines for the treatment of heart failure have changed and a variety of new drugs have been implemented in therapy, such as angiotensin receptor neprilysin inhibitor, sodium-glucose co-transporter-2 inhibitors, a new class of beta-blockers and mineralocorticoid receptor antagonists, distinguished clusters seem to be resistant to that changes, because we have not included pre-admission treatment into cluster analysis. The decision above was dictated by practical reasons. According to the characteristics of the studied population and the numerous comorbidities with their special treatment, the quality of the analysis would not have been enhanced by including them. Therefore, the new drugs and guidelines are very unlikely to impact our cluster

analysis, especially in terms of the cluster composition, which was based on the clinical and biochemical profiles at admission. The new guidelines would rather impact the patients' prognosis. Noteworthy, these changes had very little, if any, impact on the outcomes of the population of patients with AHF. The one-year mortality of the studied population was 27%, which is not very distant from the current numbers (25–30%) [1]. Below, we present a detailed description of the clusters grouped according to their distinguishing clinical feature.

4.1. Clusters 1 and 4

Clusters 1 and 4 included patients with a high number of cardiovascular and non-cardiovascular comorbidities. In both these groups, coronary artery disease was the predominant etiology of heart failure.

Although these two clusters demonstrated similarities in terms of etiology, their prognosis and clinical outcome were significantly different. Cluster 1 had a relatively good prognosis, while cluster 4 had a poor clinical outcome. The one-year mortality was equal to 22% in cluster 1 and was almost twice as high in cluster 4 (40%), which can be explained by two factors.

The results of this study indicate that gender has a significant impact on the development of coronary artery disease and the progression of heart failure. It is well known that the male gender is itself a risk factor for cardiovascular events, and the prevalence of cardiovascular disease is higher in men than in women of a similar age [14].

In the case of the male population, the risk of cardiovascular disease increases linearly over time, and the atherosclerotic process develops continuously. On the other hand, due to the protective role of estrogen and its beneficial effects on the cardiovascular system, women of a fertile age may be protected from atherosclerosis [15–18]. This statement is consistent with our observations. Despite many risk factors, only 56% of patients from cluster 1(female-dominated) developed CAD, and only 40% had an MI. These values were significantly higher in the male-dominated population represented by cluster 4.

Additionally, as is commonly known, the incidence of stroke increases significantly in the postmenopausal period [19,20]. This also aligns with our observations, as the highest rate of stroke was reported for cluster 1.

It can, therefore, be inferred that gender plays a significant role in the development of cardiovascular diseases, and we assume that the differences in prognosis and clinical outcomes between these two groups could be partially explained by this fact. However, what determines the differences between these two clusters' prognoses, for the most part, is their renal function.

Importantly, the phenotype of cluster 4 reflects the common problem of cardiorenal syndrome (the highest mean value of creatinine (1.36) and urea (64)) and right ventricular failure with the highest incidence of ascites, JVP and hepatomegaly, which constitute a sign of congestion. Cardiorenal syndrome and volume overload are well-documented predictors of poor outcomes [21] and are strongly associated with each other. Therapy for heart failure patients with cardiorenal syndrome remains a challenge. Its main goal should be reasonable decongestion, which can be achieved by natriuresis-guided diuretic therapy, ultrafiltration, or, in the refractory cases, experimental techniques.

4.2. Cluster 2

Patients included in cluster 2 were the youngest (mean age 58.8) and had the highest NTproBNP (7189), bilirubin (1.25), Ast (30), and Alt (34.5), and had the lowest ejection fraction (28%), serum creatinine concentration (1,1) incidence of diabetes (19%), pulmonary congestion (17%), COPD (5.7%), HT (39%), CAD (1.4%) and MI in the past (1.4%). These patients constituted the highest percentage of active smokers (30%) and alcohol consumers (44%). The underlying cause of HF was mostly valvular (21%) or other (73%). We assume that the presented phenotype, especially the elevated concentration of liver enzymes and frequent tobacco and alcohol use, suggests a significant role in toxic myocardial

damage. Importantly, cluster 2 was associated with the most positive prognosis. It can be explained by the youngest age, low morbidity, and high potential compensatory reserves. Therefore, these patients represent great therapeutic potential, and clinicians should focus on education in the context of eliminating the harmful impact of xenobiotics.

4.3. Cluster 3

The distinguishing features of cluster 3 (n = 71) were the incidence of chronic heart failure (93%) and iron deficiency

The prevalence of iron deficiency (defined as a serum ferritin < 100 ng/mL or TSAT < 20) [22] is common in this population. In comparison to the other groups, cluster 3 represented the lowest mean value of ferritin (92) and TSAT (14.8%).

Iron deficiency is a frequent comorbidity in heart failure, present in approximately 30–50% of patients and is associated with worse long-term outcomes [23–25].

The detrimental effect of imbalanced iron homeostasis on HF progression has been widely studied; however, it remains unclear what the exact mechanism is by which an iron deficit worsens HF. It appears that there is a wide range of factors involved in this process.

First of all, iron deficiency alters mitochondrial function and impairs the already disturbed energetics of the heart with a reduced ejection fraction [26].

Secondly, in the condition of iron deficiency anemia, depleted oxygen delivery to the metabolizing tissues induces a variety of hemodynamic, renal, and neurohormonal alterations [27]. Volume expansion (caused by sympathetic and RAA activation), as well as vasodilatation, leads to an increase in cardiac output. All these mechanisms result in an increased myocardial workload and further hypertrophy/remodeling of LV, which contributes to worsening HF [28].

We assume that the iron deficiency could explain the mean prognoses of patients in this cluster and constitute a relatively easy-achievable therapeutic goal to improve these patients' outcomes.

4.4. Cluster 1 and Cluster 5

Both clusters 1 and 5 include mostly elderly (mean age 76.1 in both clusters) women (46% and 44%, respectively), with the highest ejection fraction (47.5% and 50%) and a high incidence of hypertension (94% and 87%). The presented phenotype corresponds to the well-established HFpEF patient characteristics [29]. The clusters present the most frequent incidence of massive pulmonary congestion (congestion auscultated over two-thirds of the lungs in the 22% and 13%), which is reflected by the highest proportion of the NYHA IV (54% and 57%). The highest mean values of the pCO_2 (37.2 mmHg and 36.2 mmHg) reflect the most massive pulmonary oedema or the relatively high incidence of lung comorbidities, especially COPD in the HFpEF population [30]. Despite the apparently similar phenotypes, the clusters significantly differed in outcomes (Figure 3). Cluster 1 presented a relatively good prognosis, and conversely, cluster 5 was associated with an ominous outcome. The features that especially differ the clusters are the types of HF (chronic/de novo) and the concentration of the inflammatory markers. Cluster 1 consisted mostly of the patients who presented with their first episode of HF (56%), and cluster 5 were the patients suffering from chronic HF (70%). The duration of HF is a well-established prognostic factor. Moreover, cluster 1 presented the highest natriuresis, probably due to the effect of the first presentation of HF and frequent loop-diuretics naiveness and, as a sign of adequate diuretic response, predicted a favorable outcome [31]. Subsequently, cluster 5 presented with the highest mean concentration of inflammatory biomarkers—CRP and Il-6, which, with the lowest mean body weight (74.9), suggests frailty syndrome and explains the poor prognosis [32,33].

4.5. Novelty and Clinical Implications

We presume that our paper has two significant advantages over the currently published clustering-based analysis of acute heart failure populations. Noteworthy, it is, by

now, the most numerous clustering analysis for a European AHF population. Moreover, we have not prespecified the number of the clusters in advance, in order to allow the algorithm to distinguish the optimal, natural number of different subgroups autonomously.

The clustering technology is currently far from being an ideal solution for heart failure phenotyping. Nevertheless, we strongly believe that this technique presents great potential as a tool which can capture the relationships which are too complex to be noticed by a classical statistical analysis but can be visible to the experienced clinician. We believe it will eventually immediately segregate admitted HF patients into previously described groups (clusters). Such a segregation will highlight the therapeutic aspects that clinicians should focus on (e.g., cardiorenal syndrome, iron deficiency, etc.) and initially estimate a prognosis. Further, the patients who would be placed into the group with a worse prognosis could be provided with more careful/insightful treatment from the very beginning of the therapeutic process. For example, clusters 2 and 3 revealed the recognized relationships between HF and, consequently, chronic intoxication and iron deficiency. The precise outpatient care for the cluster 3 patients, with a regular iron level assessment and intravenous supplementation if needed, could reduce the likelihood of HF deterioration [25] Further, proper education and providing cluster 3 patients with specialist psychiatric care regarding their addiction and substance abuse could slow the progress of HF [34]. Noteworthy, the clustering, in that case, does not reveal relationships that are astounding for the experienced cardiologist. The potential value of such algorithms and provided classifications is its ability to immediately categorize the patients into one of the pheno-groups and underline cluster-specific treatment targets which can be accidentally omitted due to, e.g., the doctors' overwork, overfilling the hospitals or the lack of experience of medical professionals.

5. Limitations

Our study is not free from limitations. First, the study included retrospective data. Therefore, the availability of potentially important clinical parameters was restricted. Variables, such as the echocardiographic parameters, invasive hemodynamic measurements or novel experimental markers, were not collected. New cluster-based trials with a broader biochemical and clinical composition would deliver exciting data. Moreover, the gathered data contained missing values. Notwithstanding restricting the data inclusion to 10% of the missing values, some bias could occur. Second, our analysis was based on single-center data from Poland, which included a relatively small sample size and lacked an external validation cohort. Consequently, the evaluated patients were treated following outdated guidelines. The current clinical presentation of AHF patients and their outcomes can differ from the presented results.

The machine-learning techniques can be associated with the overfitting problem, in which the model performs well on the seen population and poor on the new one. In other words, the model is not generalizable. However, in unsupervised learning, to which clustering belongs, there is no such information about a "true" or "correct" assignment of examples to clusters. The clustering only works with the given data, and the possible generalization of the clusters is rather a question of their interpretation by the domain (medical) experts rather than a question of evaluation on another dataset. Thus, overfitting, in the standard sense, is not an issue for clustering.

What is important in clustering is having a "reasonable" number of clusters. The small number of clusters will produce over-general results—the worst case is just one cluster for everything, a large number of clusters will produce over-specific results—the worst case is that each example creates its own cluster. The problem of over-specific results can be, in some sense, considered similar to the problem of overfitting—we tried to avoid it by automatically tuning the range of clusters. We designed the range of the number of possible clusters from three to six to avoid excessive data fragmentation. Such an approach was consistent with prior studies, which usually consisted of three to four groups [4,8,12,13]. We decided to increase the potential number of the clusters due to the bigger included population. Further analyses to highlight more nuanced phenotypes are warranted.

6. Conclusions

We successfully extracted six novel phenotypes of acute heart failure patients, providing a fresh insight into their heterogeneity. The proposed clusters were consistent with the latest understanding of pathophysiology (e.g., de novo HF, HT HFpEF, toxic HF, iron reduced left ventricle HF, cardiorenal, inflammatory HFpEF) and previous clustering-based papers, providing a more distinctive classification of the population. Presented results can be valuable for future AHF trial constructions and more customized treatments.

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Institutional Review Board Statement: This research study was approved by the Ethics Committee of Wroclaw Medical University (387/2015) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available within the article. Further data are available on request from the corresponding author.

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Systematic Review

An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review

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Abstract: Heart failure (HF) is one of the leading causes of mortality and hospitalization worldwide. The accurate prediction of mortality and readmission risk provides crucial information for guiding decision making. Unfortunately, traditional predictive models reached modest accuracy in HF populations. We therefore aimed to present predictive models based on machine learning (ML) techniques in HF patients that were externally validated. We searched four databases and the reference lists of the included papers to identify studies in which HF patient data were used to create a predictive model. Literature screening was conducted in Academic Search Ultimate, ERIC, Health Source Nursing/Academic Edition and MEDLINE. The protocol of the current systematic review was registered in the PROSPERO database with the registration number CRD42022344855. We considered all types of outcomes: mortality, rehospitalization, response to treatment and medication adherence. The area under the receiver operating characteristic curve (AUC) was used as the comparator parameter. The literature search yielded 1649 studies, of which 9 were included in the final analysis. The AUCs for the machine learning models ranged from 0.6494 to 0.913 in independent datasets, whereas the AUCs for statistical predictive scores ranged from 0.622 to 0.806. Our study showed an increasing number of ML predictive models concerning HF populations, although external validation remains infrequent. However, our findings revealed that ML approaches can outperform conventional risk scores and may play important role in HF management.

Keywords: artificial intelligence; machine learning; deep learning; heart failure; predictive model; systematic review

1. Introduction

Heart failure (HF) remains a major clinical and public health problem. HF is associated with substantial morbidity and mortality but also with poor quality of life. HF affects more than 64 million people worldwide [1]; its prevalence is estimated at 1–3% in the general population and is expected to rise due to the ageing of the population and improved survival of treated patients. In consequence, HF represents 1–2% of all hospitalizations and

is still a leading cause of admissions in Europe and the United States [2]. Given that, risk stratification and prognosis prediction in HF populations is significant. Risk assessments play a crucial role in identifying high-risk cases and in guiding clinical decisions. A tailored, patient-level approach improves survival and quality of life and could reduce the rate of readmissions and the burden on the health care system. However, precisely predicting outcomes in heart failure patients remains difficult. There is a great need to develop and validate data-driven predictive models supporting this purpose.

Recently, artificial intelligence (AI) methods are successfully implemented in several medical fields e.g., in radiological images analysis or in prediction of suicide attempts [3–10]. The same applies to heart failure population. The clustering technology enables classification of HF patients with regard to their clinical characteristic [11–14]. Machine learning techniques provides tools to discriminate HF patients from subjects with no HF, where most of current models use heart rate variability to detect heart failure [15–19]. One of the widely known problem in clinical practice is accurate selection of candidates for cardiac resynchronization therapy (CRT). The high percentages of nonresponders for CRT remains an important problem. ML methods showed the possibility of improving decision making in CRT [20–23]. ML approaches can be also used to predict untypical outcomes such as treatment adherence [24] and left ventricular filling pressure among HF patients [25] and can reveal relationships between HF symptom profiles and depressive symptoms [26]. Finally, AI algorithms can predict crucial outcomes in HF management such as mortality and readmission rates. Currently, clinicians have at their disposal several predictive models focusing on heart failure such as Get with the Guide- lines-Heart Failure (GWTG-HF) score and Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score [27,28] (Table 1). These models used conventional statistical approaches, mostly multivariate analysis based on logistic regression. These scores have several limitations such as inability to capture multidimensional correlations between variables in medical records. Moreover, their usefulness can be hampered in specific situations; they were developed on selected cohorts and therefore may achieve only modest accuracy. Furthermore, the clinical implementation of these tools is limited due to the requirement of medical staff involvement in each patient's risk estimation.

Table 1. Predictor variables used in MAGGIC and GWTG-HF scores. COPD—Chronic Obstructive Pulmonary Disease, NYHA—New York Heart Association, ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blockers, BMI—body mass index, BUN—blood urea nitrogen.

No.	Variables	MAGGIC	GWTG-HF
1.	Age	X	X
2.	COPD history	X	X
3.	Systolic blood pressure	X	X
4.	Gender	X	
5.	Diabetes	X	
6.	Heart failure diagnosed within the last 18 months	X	
7.	Current smoker	X	
8.	NYHA class	X	
9.	Receives beta blockers	X	
10.	Receives ACEI/ARB	X	
11.	BMI	X	
12.	Creatinine	X	
13.	Ejection fraction	X	

Table 1. *Cont.*

No.	Variables	MAGGIC	GWTG-HF
14.	BUN		X
15.	Sodium		X
16.	Black race		X
17.	Heart rate		X

Conversely, AI algorithms seem to have certain advantages in these fields. Machine learning (ML) algorithms are able to capture nonlinear, unstructured interactions between the data, including clinical features, and their associations with a patient's prognosis [29]. Thus, this type of approach can achieve superior accuracy compared with the linear models. ML-based predictive models provide an opportunity for more individualised, patient-level management. Of note, a significant increase in the number of studies which included AI-based predictive models in medicine has been reported recently [30]. The role of this novel approach will be increasing in clinical practice in the near future. Hence, this study aims to screen and analyse predictive models based on AI algorithms among HF patients. We took into consideration all types of outcomes: mortality, rehospitalization, response to treatment and medication adherence among patients with already detected HF. To the best of our knowledge, this is the first systematic review concerning ML predictive models with external validation.

2. Methods

2.1. Search Strategy

A systematic literature review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31]. Two independent reviewers (M.B. and S.U.) engaged in online searches, and all disputable issues were solved through discussion with the third reviewer (M.J.). Literature searches were conducted in Academic Search Ultimate, ERIC, Health Source Nursing/Academic Edition and MEDLINE until 31 March 2022. In addition, the references of eligible reports and papers which cited the included studies were screened. The protocol of the current systematic review was registered in the PROSPERO database with the registration number CRD42022344855. In order to find the relevant studies, we used the following combination of keywords: Mortal* OR Death OR Readmi* OR Rehosp* OR Hospital* OR Risk* OR Predict* OR Prognos* OR Admission* OR Outcome*) AND (Machine Learning OR Deep Learning OR artificial intelligence OR artificial neural network* OR Unsupervised OR supervised) AND (Heart Failure OR Heart Failure Systolic OR Heart Failure Diasystolic OR Acute Heart Failure OR AHF OR Chronic Heart Failure OR CHF OR Heart Failure with preserved ejection fraction OR HFpEF OR Heart Failure with mid-range ejection fraction OR HFmrEF OR Heart Failure with reduced ejection fraction OR HFrEF).

2.2. Eligibility Criteria

All records that incorporated machine learning and/or deep learning models among patients with heart failure (risk prediction of readmission after index hospitalization, risk of mortality, prediction of response to treatment and medication adherence) were considered important and included in our systematic review. Other inclusion criteria were: external validation of the model and confirmed heart failure. Analysed records were excluded from the systematic review if they met the following conditions: internal validation only, implemented logistic regression alone, models predicted first incidence of HF, congenital HF was a studied population, unconfirmed heart failure, reviews, commentaries, editorials, not available in English language, did not have full text available and animal model studies.

2.3. Data Extraction and Quality Assessment

The following data were extracted from eligible publications: (1) year of publication, (2) data source, (3) size of training cohort, (4) size of validation cohort, (5) setting, (6) outcomes, (7) predictor variables, (8) algorithm used, (9) AUC, (10) comparator score in the particular dataset and (11) management of missing values. Quality assessment was performed using a checklist for quantitative studies [32]. This checklist contains 14 questions, and evaluation was performed by two reviewers (M.B. and M.J.). The total score of this scale range between 0 and 28. In the first step, the mean of the two assessments was calculated. In the next step, quality scores were expressed as the percentage of maximum quality score which can be assigned to a particular study. A higher percentage indicates a better-quality study (Table 2).

Table 2. Characteristic of included ML predictive models. MIMIC—Medical Information Mart for Intensive Care, UCSD—University of California, San Diego, KorAHF—Korea Acute Heart Failure, EHR—electronic health record, TOPCAT—Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial.

No	Author	Year	Data Source	Population	Setting	Validation Size	Number of Variables	Outcome	Quality
1.	C. Luo et al. [33]	2022	MIMIC-III database	5676	inpatient	1349	24	in-hospital mortality in intensive care unit	87%
2.	E. Adler et al. [34]	2020	UCSD database	5822	inpatient and outpatient	1512 + 888	8	general mortality	80%
3.	J. Kwon et al. [35]	2019	KorAHF	2165	inpatient	4759	23	in-hospital, 12-month and 36-month mortality	87%
4.	L. Jing et al. [36]	2020	Geisinger EHR	26,971	inpatient and outpatient	548	209	1-year all-cause mortality	73%
5.	J. Chirinos [37]	2020	TOPCAT	379	inpatient and outpatient	156	12	composite endpoints of death or heart failure–related hospitalization	87%
6.	J. Kwon et al. [38]	2019	register	20,651	inpatient	1560	65	in-hospital mortality	87%
7.	S. Mahajan [39]	2019	register	27,714	inpatient	8531	Not reported	30-day readmission	66%
8.	S. Mahajan [40]	2019	register	1279	inpatient	340	Not reported	30-day readmission	66%
9.	S. Kakarmath et al. [41]	The protocol for the study							

3. Results

3.1. The Review Process

The initial search identified 1297 publication records through database searching and 352 through other sources (Figure 1). After screening titles and abstracts, only 9 studies met the inclusion criteria and did not meet exclusion criteria. The excluded publications were: 307 duplicates, 578 based on a different model, 159 different studied populations, 73 reviews, 13 systematic reviews, 29 editorials, 4 animal studies, 8 posters, 4 lectures and 7 that were not available in English. What we mean by different model is studies using conventional, statistical methods or an AI analysis other than prediction. In the next step, the full texts of 115 studies were assessed concerning type of validation. External validation was missing in 106 studies, which were excluded. Additionally, we analysed the references of eligible publication records and studies that cited the included papers. None

of the 352 screened records met the inclusion criteria. Finally, nine predictive models were included in the systematic review (Table 2).

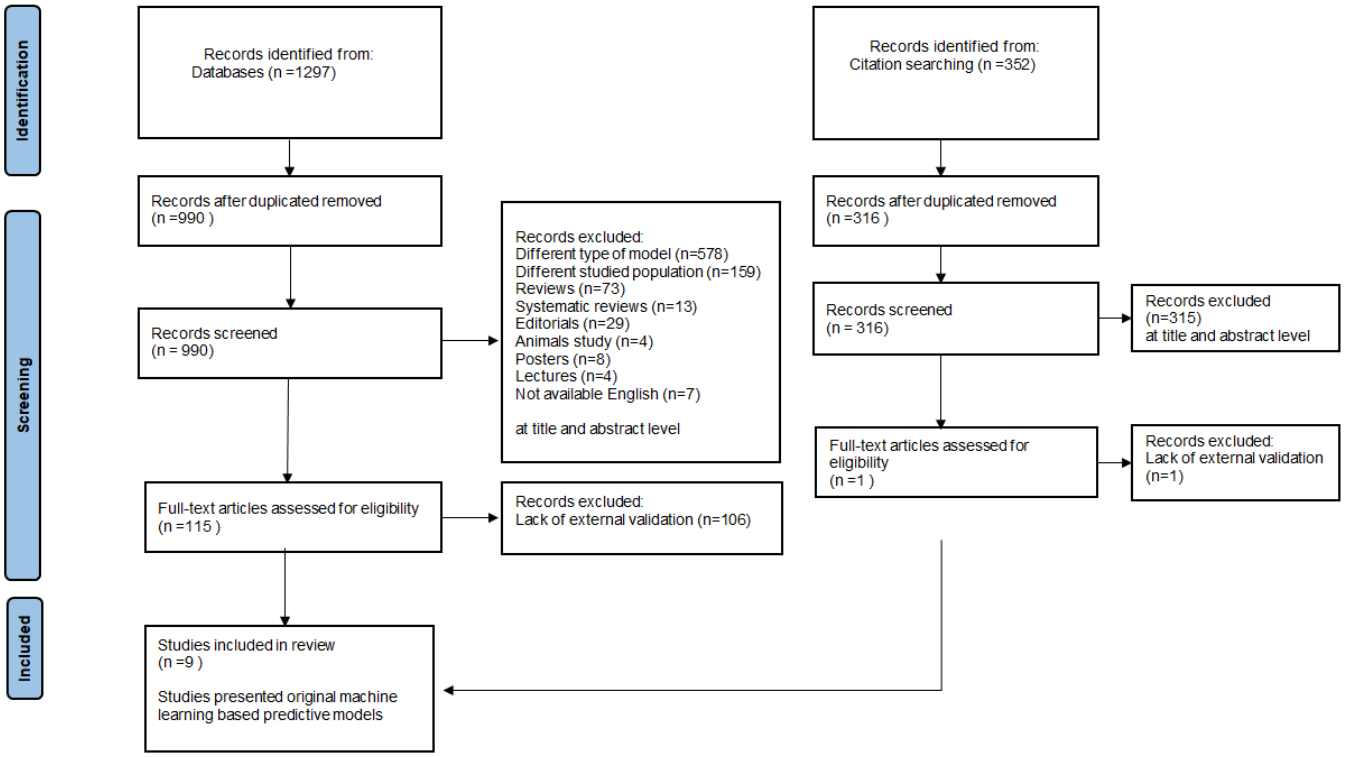

Figure 1. Flow chart of the systematic literature research.

3.2. Comparison of the Predictive Value

We aimed to thoroughly describe and compare the predictive value of the different models, and thus, we decided to use the area under the receiver operating characteristic curve (AUC) as a standard parameter. The AUC is commonly used to compare the performance of models with each other and with conventional prediction scores. The AUC represents the sensitivity against 1-specificity (Figure 2). The AUC of a classifier means the probability that the classifier model will rank a randomly chosen positive instance higher than a randomly chosen negative instance. The AUC is always between 0 and 1.0, where an AUC of 0.5 means no better accuracy than chance and an AUC of 1.0 means perfect accuracy [42]. To compare the certain AUC scores, we can refer to the following rule: AUC = 0.5 means no discrimination, AUC = 0.5–0.7 means poor discrimination, AUC = 0.7–0.8 means acceptable discrimination, AUC = 0.8–0.9 means excellent discrimination, AUC > 0.9 means outstanding discrimination [43].

3.3. Relevant Studies

The first study conducted by Luo et al. aimed to create a risk stratification tool assessing the all-cause in-hospital mortality in intensive care unit (ICU) patients with HF [33]. The model was developed based on records from the Medical Information Mart for Intensive Care MIMIC-III database and externally validated with the use of eICU database. The study included patients admitted to the ICU due to their first manifestation of HF. The demographic data and comorbidities were collected at admission, and then vital signs and laboratory records were collected hourly during the first 24 h after admission. In this way, physicians took the minimum, maximum, mean and range of the values over a period. After records extraction, the variables with missing data of more than 40% and patients with more than 20% missing parameters were excluded to avoid bias. The XGBoost algorithm was used to develop the machine learning model. The derivation data (5676 patients)

were randomly divided into a training cohort (90%), and then the rest of the cohort (10%) was used to validate the performance. Finally, 24 features were selected as the most important from the predictive model as follows: mean anion gap, mean Glasgow Coma Scale, urine output, mean blood urea nitrogen (BUN), maximum Pappenheimer O2 (pO2), age, mean plasma calcium, minimum plasma glucose, mean plasma magnesium, mean respiratory rate (RR), mean arterial base excess, mean creatinine, body mass index (BMI), mean temperature, maximum temperature, maximum platelet, minimum prothrombin time (PT), mean systolic blood pressure (SBP), mean partial thromboplastin time (PTT), mean oxyhaemoglobin saturation (spO2), mean PT, mean diastolic blood pressure (DBP) and minimum PTT. In internal validation (10% of the derivation data), the AUC reached 0.831. In the next stage, records from the eICU database were used to conduct external validation; the AUC was 0.809. In effect, the current classifier had only a slight deterioration in performance in the external cohort. Anion gap, blood coagulation status and volume of urine output were found to be the three most important predictors in this model.

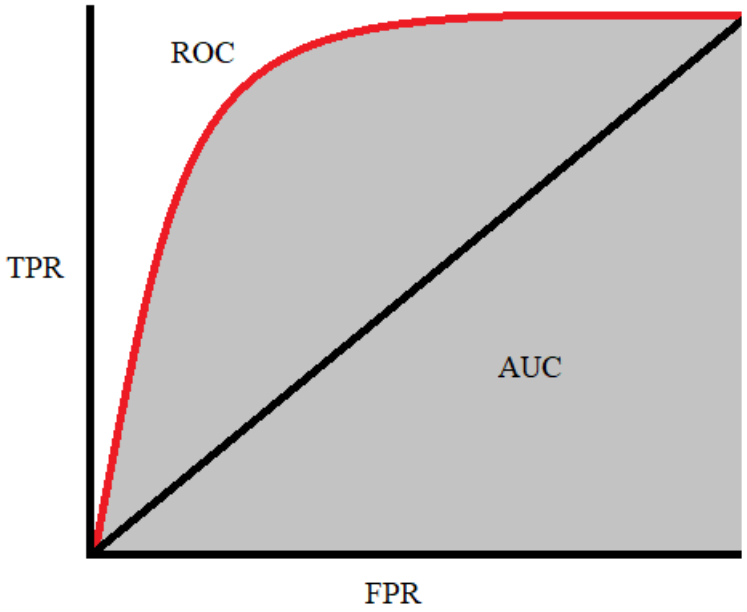

Figure 2. The receiver operating characteristic curve is plotted with the true positive rate (TPR) against the false positive rate (FPR), where FPR is on the *x*-axis and TPR is on the *y*-axis [44].

Kwon et al. described a deep-learning-based artificial intelligence algorithm for predicting mortality of patients with acute heart failure (DAHF) [35]. The endpoints were in-hospital, 12-month and 36-month mortality. The patients' electronic health records (demographic information, treatment therapy, laboratory results, electrocardiography (ECG) and echocardiography results, final diagnosis and clinical outcomes during their hospital stay) were collected from two hospitals during their admission and used to train the algorithm (2165 patients). The deep neural network was used to develop a prediction model. Further, separate data from the independent Korea Acute Heart Failure register (KorAHF) with 4759 patients were implemented as an external validation cohort. The age, sex, body mass index, SBP, DBP, heart rate (HR), present atrial fibrillation, QRS duration, corrected QT interval, left atrial dimension, left ventricular dimension end-diastole, left ventricular dimension end-systole, ejection fraction (EF), white blood cell (WBC), haemoglobin, platelet, albumin, sodium, potassium, blood urea nitrogen, creatinine and glucose were assessed as the predictor variables. These data were obtained during each ECG assessment, and in consequence, complete datasets for each patient were created. The AUCs for DAHF were 0.880 for predicting in-hospital mortality and 0.782 and 0.813 for predicting 12- and 36-month mortality, respectively, in the KorAHF register. The well-established scores

revealed poorer AUCs: 0.782 (GWTG-HF) for in-hospital mortality, 0.718 for 12-month mortality and 0.789 for 36-month mortality (MAGGIC).

Another study by Kwon et al. aimed to develop a machine learning predictive model for mortality among heart disease patients based only on the results of echocardiography [38]. The data from the first hospital (20,651 patients) were used as the derivation data and for internal validation (by splitting), and data from the second hospital (1560 patients) were used for external validation. The derivation data consists of patients with atrial fibrillation/flutter (AF/AFL), HF and coronary artery diseases (CAD). The internal validation group contained 3840 subjects from the first hospital. The external validation group consisted of 604 subjects with CAD and 760 subjects with HF. Patients with missing values were excluded. The primary outcome was in-hospital mortality. Only echocardiography features were used as predictor variables: 11 continuous (age, weight, height, HR, left ventricular diastolic diameter (LVDD), left ventricular systolic dysfunction (LVSD), septum thickness, posterior wall thickness (PWT), aorta dimension, left atrium dimension and EF) and 54 categorical (rhythm, mitral valve description (10 features), aortic valve description (9 features), mitral valve description (9 features), left ventricle regional description (12 features), left ventricle functional description (2 features), pericardium description (2 features), inferior vena cava (2 features) and right ventricle description (2 features)). The deep neural network (DNN) was used to develop a prediction model. In internal validation, the model yielded AUC = 0.912 for predicting in-hospital mortality for heart diseases. In external validation, the model achieved AUC = 0.898 for heart diseases and 0.958 for CAD. In the HF group, the created model produced AUC = 0.913 in external validation in comparison with the MAGGIC score (0.806) and GWTG-HF (0.783). The ML model outperformed the existing predictive models regardless of the underlying disease.

The machine learning assessment of risk and early mortality in HF (MARKER-HF) risk scale was developed based on a cohort of 5822 patients from out- and inpatient care. They were identified from medical history by their first episode of HF [34]. The boosted decision tree algorithm was used to build the model. During the training process, eight variables were identified as the predictor features: DBP, creatinine, BUN, haemoglobin (Hb), WBC count, platelets, albumin and red blood cell distribution width (RDW). The external validation was performed with the use of two, independent registers containing 1512 and 888 subjects. The model was designed to distinguish patients with high and low risk of death. The patients who died before 90 days since the index hospitalization were considered the high-risk group, and patients with a last-known follow-up 800 or more days after the index hospitalization were classified as the low-risk group. In internal validation, AUC = 0.88, while external validation in two independent cohorts gave AUCs of 0.84 (888 patients) and 0.81 (1516 patients). Moreover, the authors compared the performance of the model with the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), which were available in the derivation database. NT-proBNP is a well-established biomarker associated with mortality amongst HF patients [45,46]. A higher MARKER-HF score is associated with high NT-proBNP, but in the comparison of predictive power, MARKER-HF reached superior AUC to that of natriuretic peptide (0.88 vs. 0.69). In comparison with the GWTG-HF (AUC = 0.74), the created model presented superior discriminatory power in all three populations.

Another study conducted by Chirinos et al. concerns associations between plasma biomarkers of patients with heart failure with preserved ejection fraction and the composite endpoint of all-cause death or heart failure-related hospital admission [37]. The authors selected 379 patients from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) database for creating their predictive model, and they validated it externally (156 subjects) with the use of data from the Penn Heart Failure Study (PHFS). Only patients with fully available variables from TOPCAT were included in the study. The tree-based pipeline optimizer platform was utilized to build a predictive model, and the following biomarkers were found to be relevant for predicting death or HF-related rehospitalization: 2 biomarkers related to mineral

metabolism/calcification (fibroblast growth factor 23 (FGF-23) and osteoprotegerin (OPG)), 3 inflammatory biomarkers (tumour necrosis factor-alpha (TNF-alpha), soluble tumour necrosis factor receptor I (sTNFRI) and interleukin 6 (IL-6)), YKL-40 (related to liver injury and inflammation), 2 biomarkers related to intermediary metabolism and adipocyte biology (fatty acid-binding protein 4 (FABP-4) and growth differentiation factor 15 (GDF-15)), angiopoietin-2 (related to angiogenesis), matrix metallopeptidase 7 (MMP-7, related to extracellular matrix turnover), ST-2 cardiac biomarker and NT-proBNP. In this project, test performance was assessed with the C-index (concordance index), which is analogous to the receiver operator characteristic curve. In the internal validation, the C-index was 0.743, whereas in the external validation was 0.717. Moreover, the authors combined their ML model with the MAGGIC score. As a result, the C-index for this combination was 0.73 in internal and external validations. There was a slight deterioration in the C-index in the external validation of the machine learning (ML) model alone, but the model containing ML and the MAGGIC score revealed the same C-index in both cohorts. This shows the very similar predictive power between the ML model alone and the model containing ML and the MAGGIC score. The FGF-23, YKL-40 and sTNFRI were found to be the three biomarkers most associated with the endpoint.

Jing et al. created a ML model for predicting 1-year all-cause mortality among HF patients [36]. The data from 26,971 subjects (with 276,819 clinical episodes) were used to train the model, and data from 548 patients/episodes were used to perform external validation. All clinical visits since 6 months before HF detection date including outpatient visits, hospitalizations, emergency department admissions, laboratory tests and cardiac diagnostic measurements were identified and grouped into episodes. All clinical visits since 6 months before the HF diagnosis date, which includes outpatient visits, hospitalizations, emergency department admissions, laboratory tests and cardiac diagnostic measurements were identified, grouped into episodes and used as independent sets. The predictive model was based on the XGBoost algorithm. The following features were incorporated from the electronic health records: 26 clinical variables (age, sex, height, weight, smoking status, HR, SBP, DBP, use of loop diuretics, antihypertensive and antidiabetic medications and laboratory test values (haemoglobin, estimated glomerular filtration rate, creatine kinase-muscle/brain, lymphocytes, high-density lipoprotein, low-density lipoprotein, uric acid, sodium, potassium, NT-proBNP, troponin T (cTnT), haemoglobin A1c (HbA1c), troponin I (cTnI), creatinine, and total cholesterol), 90 cardiovascular diagnostic codes (International Classification of Diseases-10th—ICD10), 41 ECG assessments and patterns, 44 echocardiographic measurements and 8 evidence-based "care gaps": flu vaccine, blood pressure of < 130/80 mm Hg, HbA1c of < 8%, cardiac resynchronization therapy, and active medications (active angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker/angiotensin receptor-neprilysin inhibitor, aldosterone receptor antagonist, hydralazine, and evidence-based beta-blocker). The authors selected these care gaps as the important evidence-based interventions in HF treatment for which associations with risk reduction were assessed. To measure the predicted effect of closing care gaps on reducing rate of endpoint, the authors closed artificial care gaps according to the following formula: for binary gap variables, changing the value from 1 (open/untreated) to 0 (closed/treated); for continuous variables, changing the value to goal. After that, the influence of this simulation on the risk score was calculated. Only complete sets of variables were included. The model achieved discriminatory power in assessing mortality risk with an AUC of 0.77 in cross-validation and 0.78 in the external validation. This showed that the model tended to slightly overestimate the risk of mortality. Moreover, the simulation of closing the 8 care gaps resulted in a 1.7% reduction of mortality.

Mahajan et al. developed two predictive models using different ML methods. The first of them combined structured and unstructured data, and the second one used ensemble ML methods for predicting the risk of readmissions for HF. All dependent variables were available, and there were up to 5% missing values of independent variables; thus, in order to maintain consistency, the authors used multiple imputation by chained equations resam-

pled over five imputed datasets for the missing values assuming missingness at random. Both models aimed to predict 30-day readmissions, and both studies used the same structured data predictors: sodium, potassium, BUN, creatinine, Hb, haematocrit (Ht), glucose, albumin, B-natriuretic peptide, SBP, DBP, pulse, RR, demographics (age, sex, race, marital status, insurance type, residential area), pre-index admission factors (appointments in past year, no show to appointment in past year, emergency department visits in past year, prior diagnoses, admissions in previous year, telemetry monitor during index admission, index admission via emergency length of stay concurrent procedures), comorbidities (alcohol abuse, cardiac arrhythmia, CAD, cancer, cardiomyopathy, cerebrovascular accident, depression, diabetes mellitus, drug abuse, functional disability, liver disease, lung disease, protein caloric malnutrition, psychiatric disorder, rheumatic disease group, renal disease group, vascular disease group, aortic valve disorder), and concurrent procedure (cancer related, cardiac devices, cardiac surgery, coronary angioplasty, history of mechanical ventilation devices). In the first instance, the authors used the parametric statistical method and statistical natural language processing (NLP) to create three models: one using structured, one using unstructured data and one that combined these two approaches [40]. The structured dataset contained 1619 patients, where 1279 patients enrolled from 2011 to 2014 were the derivation cohort, and 340 patients from 2015 were the external validation subgroup. Then, 136,963 clinical notes were extracted (as unstructured records) such as history and physician notes at admission, progress notes, social workers' notes and discharge summaries. Of these, 102,055 notes were for the derivation cohort, and 34,908 were for the validation cohort. The combined dataset had over 4900 predictors, although the authors showed only 10 with relative importance: creatinine, BUN, haematocrit and other not listed administrative predictors. The AUC for the structured model was 0.6494, for the unstructured model, 0.5219 and for the combined model, 0.6447. As a result, the performance of the structured and combined models was very similar, but the unstructured data model showed very poor discrimination. In the second instance, the authors selected 27,714 admissions (from 2011 to 2014) that represented a derivation cohort, and 8531 admissions from 2015 were used as the external validation subgroup [39]. The authors used 10 different base learning models and two ensemble schemes to combine base learner outputs (Super learner and Subsemble scheme). Further, the AUCs for each base learner and ensemble schemes were calculated. The best single base learner achieved AUC = 0.6993 (Extratrees); for Super Learner, it was 0.6987 and for Subsemble, 0.6914. This showed that ensemble techniques can ensure performance at least as good as the best-performing single-base algorithm.

The protocol of the study conducted by Kakarmath et al. presents a promising design for investigations [41]. This project aimed to build a ML model predicting 30-day readmissions in HF patients. The study concerns all types of heart failure: left; systolic, diastolic, combined; acute, chronic, acute on chronic and unspecified with the expected population of 1228 index admissions.

4. Discussion

Our systematic review revealed several factors with significant impacts on the utility of AI-based tools in heart failure patient management. First, this study showed an increasing number of studies concerning artificial intelligence methods incorporated in heart failure population (Figure 3). Particularly during the last four years, we can observe a significant increase of interest in this field.

Second, this analysis has shown that tens of predictive models are being generated, but only a small part of them were externally tested. External validation means the assessment of predictive performance (discrimination and calibration) with the use of an independent, individual dataset different from the one used to generate the model [47]. The external validation can be performed in different cohorts including race, geographical region, period, social-economic settings or type of care (outpatient/inpatient) [48]. This approach determines objective discriminating ability in different settings from those of the derivation data, thus revealing the utility of the model in the real world. The evaluation

of the model based only on the derivation data can lead to misleading performance, for example, mortality probability models (MPM II) predicting mortality among intensive care unit patients achieved AUC = 0.836 [49], whereas the external validation performed 16 years later revealed only a modest AUC of 0.66, demonstrating very low discriminating ability [50]. In the case of HF, it is worth mentioning that this disease is characterized by different causes, comorbidities and demographic profiles around the world [51,52]. Given that, the lack of test performance in different circumstances is the first barrier to applying prediction calculators in clinical practice.

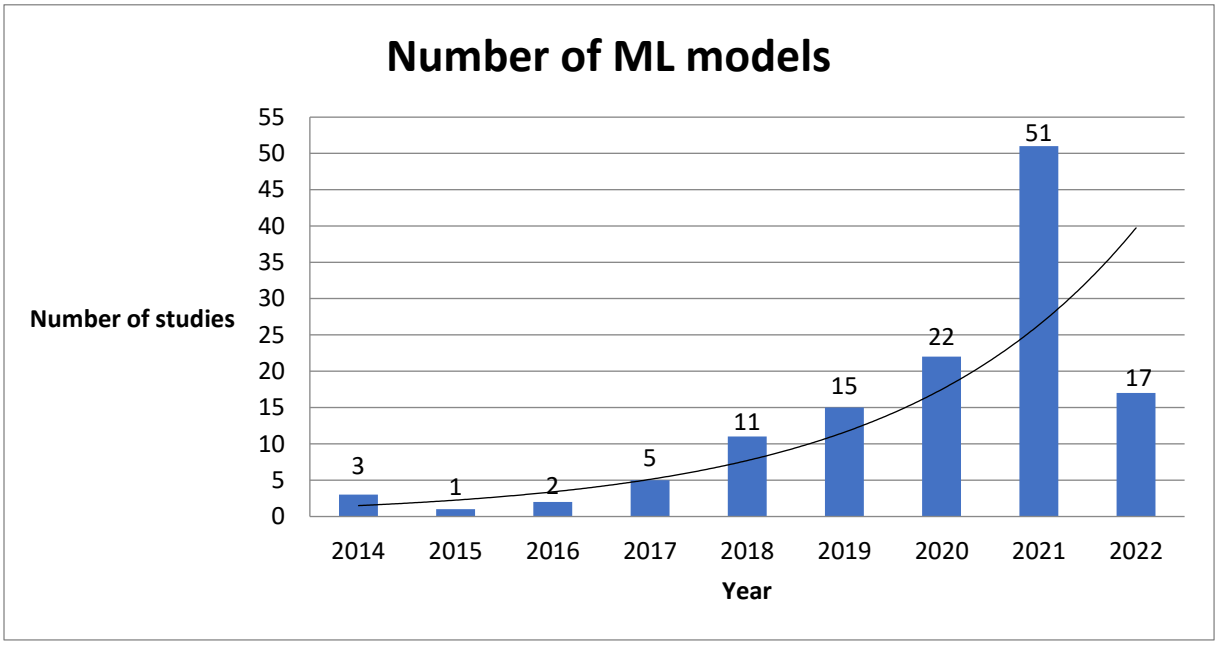

Figure 3. Number of ML predictive models created during last 9 years.

Third, our analysis revealed that machine learning predictive models can accurately predict different types of outcomes among HF populations. This is particularly important when we compare the performance of AI-based models with conventional statistical predictive models [53]. Most of the selected studies in our review showed satisfactory accuracies in external validation. The AUCs range from 0.6494 to 0.913 in independent datasets, whereas AUCs for statistical predictive scores range from 0.622 to 0.806 (Table 3). What is more, the majority of included studies used either tree-based or neural network-based methods to generate their models. The early assessment of a patient's clinical risk is crucial for tailored treatment and improving the patient's prognosis. Furthermore, we revealed that these models can use various types of data to predict the outcomes. This indicates that all types of clinical data such as demographic, laboratory, clinical examination, medication and echocardiographic and electrocardiographic metrics contain predictive information and are suitable for building an effective model. Our study showed the potential of the incorporation of features into predictive models that were not previously considered predictor parameters. It is especially important to use commonly available features in order to provide real-time evaluation and to ensure inclusiveness by avoiding subjects with missing data.

However, ML-based approaches are not free from limitations. First, predictive models are associated with the overfitting problem. Overfitting can lead to the over-training of the training data and in consequence limit discriminatory ability in other populations. One of the solutions is to evaluate the model in an independent cohort. That is why we established external validation as an inclusion criterium. Second, the interpretability or explainability of the created models has become a significant topic in the area of machine learning. The end users are interested not only in the quality of the models but also in

understanding the classification processes. Some models are easy to understand by their nature (typical examples are decision trees), but some models, typically neural networks, work as black-box models. To provide some insights into a particular model's decisions, several approaches have been proposed. Local interpretable model-agnostic explanations (LIME) is an interpretability surrogate model which can be used on any black-box model to provide local interpretability for the prediction or classification of a single instance [54]. SHapley Additive exPlanations (SHAP) is a game theory-based method of interpreting any machine learning model's output [55]. It uses the traditional Shapley values from game theory and their related extensions to correlate optimal credit allocation with local explanations. As the explainability issue was not discussed in the reviewed papers, we cannot assess them from this point of view.

Table 3. Performance metrics for machine learning algorithms and conventional risk scores. IV—internal validation, EV—external validation, ML—machine learning, NLP—natural language processing, HF—heart failure, HFrEF—heart failure with reduced ejection fraction, HFmrEF—heart failure with mid-range ejection fraction, HFpEF—heart failure with preserved ejection fraction HD—heart disease, CAD—coronary artery disease.

No.	Author	Algorithm	AUC for ML in IV	AUC for MAGGIC in IV	AUC for GWTG-HF in IV	AUC for ML in EV	AUC for MAGGIC in EV	AUC for GWTG-HF in EV
1.	C. Luo et al. [33]	XGBoost	0.831	-	0.667	0.809	-	-
2.	E. Adler et al. [34]	boosted decision tree	0.88	-	0.74	0.81–0.84	-	0.758
3.	J. Kwon et al. [35]	deep neural network	-	-	-	0.88—in-hospital mortality 0.782—12-month mortality 0.813—36-month mortality	0.718—12-month mortality 0.729—36-month mortality	0.728—in-hospital mortality
4.	L. Jing et al. [36]	XGBoost	0.77	-	-	0.78	-	-
5.	J. Chirinos [37]	created by the tree-based pipeline optimizer platform	0.743 (C-index)	0.621 (C-Index)	-	0.717 (C-index)	0.622 (C-index)	-
6.	J. Kwon et al. [38]	deep neural network	0.912—(HD)	-	-	0.913 (HF) 0.898 (HD) 0.958 (CAD)	0.806 (HF)	0.783 (HF)
7.	S. Mahajan [39]	ensemble ML	-	-	-	0.6987	-	-
8.	S. Mahajan [40]	created by NLP process	-	-	-	0.6494	-	-
9.	S. Kakarmath et al. [41]	The protocol for the study						

Third, the described models used only variables that were collected in datasets used as derivation cohorts. Three of all the included studies used a well-established prognostic marker such as NT-proBNP as a predictive feature, but only one model used troponin to predict outcomes [56,57]. There exist other, not included parameters that can be also important prognostic factors for cardiovascular diseases and can potentially improve model performance [58,59].

There is space for applying complex ML techniques in HF management. In the first step, during hospitalization, low-cost and non-invasive ML calculators can be used for patient risk assessments. In the second step, ML models can be used in outpatient care as

everyday support tools for patients. The absence of sufficient education, inadequate self-care and lack of medication adherence are well-studied reasons why patients do not reach clinical goals, leading to readmissions, and all these issues can be addressed using ML-based solutions [60]. Personal health plans using sensing devices and artificial intelligence methods can support patients during routine care [61]. The combined approach using ML tools during hospitalization and in outpatient care may result in clinical benefits.

The perspective of AI-based techniques holds great promise for cardiovascular research and clinical practice. Some fields seem especially attractive. Well-trained models can perform real-time, automatized patient risk stratification undertaken at the beginning of the diagnostic path. We can imagine a case when the admitted patient is classified into one of the pre-established clusters. Affiliation with one of the clusters initially suggests diagnostics, treatment and risk groups. Basing patients' management on models trained on large cohorts could help physicians not to overlook some important issues, especially in conditions of overwork and lack of personnel. Further, AI tools can provide more information about the patient from the same amount of data. Sengupta et al. created a model which can provide the same amount of information about aortic stenosis severity as if both echocardiography and cardiac CT/MR were performed using only echocardiography and the model. Such solutions can be widely implemented in less-developed areas where sophisticated diagnostic methods are not available [62]. Another field that represents great potential is predicting pathology from seemingly physiological findings; for instance, there are successful attempts to identify patients with a history of atrial fibrillation from the ECG performed during the sinus rhythm [63]. The earlier detection of atrial fibrillation can lead to vast reductions in vascular changes in the brain and thereby improve patients' quality of life.

5. Limitations

Our systematic literature review has several limitations. Our selected inclusion and exclusion criteria resulted in a low number of analysed studies. All of the eligible records were markedly heterogeneous in terms of outcomes but did use ML methods and predictor variables. As a consequence, we did not perform meta-analysis, which could have been challenging and unrepresentative. However, meta-analysis would have enabled better insight into the models' performance, and this issue should be addressed in the next research investigating this field. Finally, our review focuses mainly on the medical issues of predictive models in HF. We aimed to show state-of-art achievements in this area, current solutions and level of advancement. We did not consider technical nuances of modelling processes such as hyperparameter optimization or the tuning of algorithms. There is an increasing need for a pragmatic framework for evaluating clinical utility and validity in ML studies [64]. The development of guidelines for ML implementations in medical research is a clear field for further investigations.

6. Conclusions

The implementation of artificial intelligence methods in heart failure management is still in the very early stage. There is a great necessity to evaluate new predictive algorithms, train models in different populations and try to combine various types of predictor variables. Our study showed that artificial intelligence techniques may play an imminent role in heart failure management. Data-driven predictive models showed promise in handling large volumes of medical data. Machine learning techniques may also enable patient-level management, allowing for possibly reducing adverse outcomes in this population.

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Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure

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Abstract: Acute heart failure (AHF) is a common and severe condition with a poor prognosis. Its course is often complicated by worsening renal function (WRF), exacerbating the outcome. The population of AHF patients experiencing WRF is heterogenous, and some novel possibilities for its analysis have recently emerged. Clustering is a machine learning (ML) technique that divides the population into distinct subgroups based on the similarity of cases (patients). Given that, we decided to use clustering to find subgroups inside the AHF population that differ in terms of WRF occurrence. We evaluated data from the three hundred and twelve AHF patients hospitalized in our institution who had creatinine assessed four times during hospitalization. Eighty-six variables evaluated at admission were included in the analysis. The k-medoids algorithm was used for clustering, and the quality of the procedure was judged by the Davies–Bouldin index. Three clinically and prognostically different clusters were distinguished. The groups had significantly ($p = 0.004$) different incidences of WRF. Inside the AHF population, we successfully discovered that three groups varied in renal prognosis. Our results provide novel insight into the AHF and WRF interplay and can be valuable for future trial construction and more tailored treatment.

Keywords: acute heart failure; machine learning; clustering; artificial intelligence; cardiorenal syndrome

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1. Introduction

Acute heart failure (AHF) remains a significant problem with a high mortality and a massive financial burden for healthcare providers [1,2]. AHF is a multidimensional state with a complex interplay between the cardiovascular and other systems, including the renal. The pathological condition of simultaneous dysfunction of the kidneys and heart, in which the disorder of one organ induces the damage of the second one, is called cardiorenal syndrome [3]. One of the clinical manifestations of cardiorenal syndrome is the worsening renal function (WRF), which can be defined as, e.g., an increase in serum creatinine or/and a decrease in urine output in a specified period [4]. WRF is a frequent complication overlapping the AHF, especially in conditions of intensive cardiac care units [5], and is associated with prolonged hospitalization and diminished survival [4]. The population of AHF patients endangered by the WRF is heterogenous, and so is the postulated WRF's impact on prognosis. Some authors showed contrary evidence that WRF has a negative, neutral, or even positive effect [4,6,7]. Considering this uncertainty, we presumed that the current lack of well-established classifications describing the risk of WRF is insufficient and does not reflect significant clinical differences between AHF patients. Thus, we decided

to analyse the heterogeneity of the AHF population by resorting to novel methods of data analysis, aiming to describe different risk groups of WRF and, further, its impact on prognosis. Importantly, we have only included variables, which are the standard-of-care parameters routinely assessed during AHF patient monitoring.

Data science algorithms, especially Machine Learning (ML), enable novel, clinically important insight into existing data and distinguish previously unrecognized patterns [8]. Clustering is an unsupervised ML technique that organizes the set of data into internally similar subgroups. We presumed that this technique, which was successfully leveraged in marketing [9], could as well prove its value in cardiovascular research. Considering these advances, we decided to implement clustering in the AHF population to understand the occurrence and significance of the WRF better.

2. Materials and Methods

2.1. Study Population

We have retrospectively analysed three hundred and twelve acute heart failure (AHF) patients from two registries conducted in our institution between 2010–2012 and 2016–2017. Our previous papers described the eligibility criteria in both registries [10]. Heart failure diagnosis was stated according to the current ESC guidelines by a responsible physician [11,12]. To ensure the creatinine course in every patient and avoid missing values in the analysis, we have only included the patients who had serum creatinine assessed at four points, i.e., at admission, after 24 and 48 h of hospitalization, and at discharge.

2.2. Worsening of the Renal Function Evaluation

As there was a significant lack of data about diuresis and GFR or parameters indispensable for its calculation, we have based the diagnosis of worsening renal function (WRF) and acute kidney injury (AKI) on creatinine assessment only. AKI was defined according to the KDIGO guidelines as the $\geq$0.3 mg/dL increase of serum creatinine in 48 h [13]. WRF was defined as the $\geq$0.3 mg/dL increase of serum creatinine at any point during hospitalization. We decided to analyse both of these phenomena in order to caption as many renal endpoints as possible. Throughout the paper we will stick to using the term WRF, as it is a broader qualification.

2.3. Clustering and Data Analysis

Variables included in the analysis are shown in Table 1. Initially, we chose 86 variables regarding the patient's clinical status, i.e., HF subtype, aetiology, comorbidities, symptomatology, and biochemical presentation. All parameters were assessed at patient admission to the hospital. Variables were manually screened to eliminate potential errors; e.g., anomalies, single values out of range, etc. The dataset was implemented into RapidMiner and autocleaning was performed. Variables with over 90% stability, 10% of missing values, or correlated with at least r = 0.6 were meant to be removed, but none of the variables fulfilled these criteria. Missing values were replaced by average values, as clustering algorithms cannot proceed with missing values. Further, nominal values were converted into numerical, and all the numerical parameters were normalized to range from 0 to 1, so each variable had the same impact on the calculated distance.

Clustering is a widely used descriptive data analysis method on the border between statistical analysis and data mining with a relatively long history. The goal of clustering (also called segmentation) is to identify groups of similar examples. Thus, the critical issue in clustering is a proper definition of similarity or distance. There are several clustering methods and algorithms that can be divided into various types, such as hierarchical versus partitional, exclusive versus overlapping versus fuzzy, and complete versus partial [14].

We used the k-medoids algorithm in our experiments. K-medoids is a partitional method that creates non-overlapping clusters. The number of resulting groups must be specified in advance. The algorithm repeatedly re-assigns the examples into the given number of clusters by minimizing their distance to a centroid and recomputes the centroids. Unlike

k-means clustering, where cluster centroids are computed by averaging values for examples in a given cluster, each cluster in k-medoids clustering is represented using an existing, most representative example. This makes the results of the k-medoids clustering easier to interpret. The implementation in RapidMiner luckily offers the option to tune hyperparameters of the algorithm automatically. In our case, we adjusted the number of clusters and the similarity measure. The process of the clusters' calculation performed in RapidMiner is displayed in Figure 1, and the file is attached in Supplementary Materials File S1.

Table 1. Variables included in the analysis. All parameters were assessed at admission.

Demographics	**Age, Sex**
HF characteristics	De novo or chronic HF, Etiology
Comorbidities	Coronary artery disease, myocardial infarction, PCI/CABG, Hypertension, Valvular heart disease, Diabetes, Diabetes treated with insulin, oral drugs or diet, stroke, COPD
Clinical status	Dyspnoea at rest, Dyspnoea at rest (since number of days), NYHA scale at admission, Swelling of the lower limbs, Decrease in exercise tolerance, Decrease in exercise tolerance (since number of days), Body weight, Systolic pressure, Diastolic pressure, Heart rate, Jugular veins pressure, Pulmonary congestion, Pulmonary congestion, Ascites, Hepatomegaly, Implantable device: none = 0, 1-PM, 2-ICD, 3-CRT2
Lifestyle factors	Smoking status (0 = never, 1 = now, 2 = in the past), how many cigarettes did the patient smoke, Active alcohol use, how many cigarettes patients smoke daily, ow many years did/does the patient smoke
Laboratory parameters	PH serum, pCO_2, pO_2, ctO_2, BO_2, HCO_3, HCO_3std, $ctCO_2$, BE, sO_2, FO_2Hb, FHHb, ctHb, Lac, mOsm, HGB, HCT, RBC, MCV, MCH, MCHC, RDW, WBC, LYMPH, MONO, NEUTR, PLT, Na serum, K serum, Creatinine serum, Urea serum, Glucose serum, Ast, Alt, CRP, GGTP, NTproBNP, Total_bilirubin, INR, Albumins serum, Na urine, K urine, Urea urine, Creatinine urine, Fe, TIBC, Tsat, sTfR, Ferritin, IL-6
Echocardiography	Reduced ejection fraction; ejection fraction

Abbreviations: pCO_2—partial pressure of CO_2, pO_2—partial pressure of O_2, ctO_2—concentration of O_2, BO_2 -, HCO_3—bicarbonate, HCO_3std—bicarbonate standardized, $ctCO_2$—CO_2 concentration, BE—base excess, sO_2—O_2 saturation, FO_2Hb—fraction of oxygenated haemoglobin, FHHb—fraction of deoxyhemoglobin in total hemoglobin, ctHb—total hemoglobin, Lac—lactates, mOsm –milliosmoles, HGB—hemoglobin, HCT—hematocrit, RBC—red blood count, MCV—mean corpuscular volume, MCH—mean corpuscular hemoglobin, MCHC—mean corpuscular hemoglobin concentration, RDW—red cell distribution width, WBC—white blood count, LYMPH—lymphocytes percentage, MONO—monocytes, NEUTR—neutrophiles, PLT—platelets count, Ast—aspartate aminotransferase, Alt—alanine transaminase, CRP—C-reactive protein, GGTP—gamma-glutamyl transpeptidase, NTproBNP—N-terminal prohormone of brain natriuretic peptide, INR—international normalized ratio, Fe—total iron amount in blood, TIBC—total iron-binding capacity, Tsat—transferrin saturation, sTfR—Soluble Transferrin Receptor, IL-6—interleukin 6th, eGFR—estimated glomerular filtration rate.

We assessed the quality of clustering using the Davies–Bouldin index [15]. This index evaluates the quality of clustering considering the intra-cluster distance (that should be low) and inter-cluster distance (that should be high). The lower the value of the Davies–Bouldin index, the better the clustering.

Associations between clusters and clinical variables were evaluated. The normality was checked using K-S, Shapiro–Wilk, and Lilliefors tests. Parameters with normal distributions are shown as means ± standard deviations. The non-normal variables are displayed as the medians and interquartile ranges. Categorical variables are shown as numbers and percentages (Table 2). Statistical significance was evaluated using analysis of variance; the p below 0.05 was considered statistically significant. Clustering was performed in RapidMiner 9.1 (RapidMiner GmbH, Dortmund, Germany), and the statistical assessment was conducted in STATISTICA 12 (StatSoft Polska Sp. z o.o., Krakow, Poland).

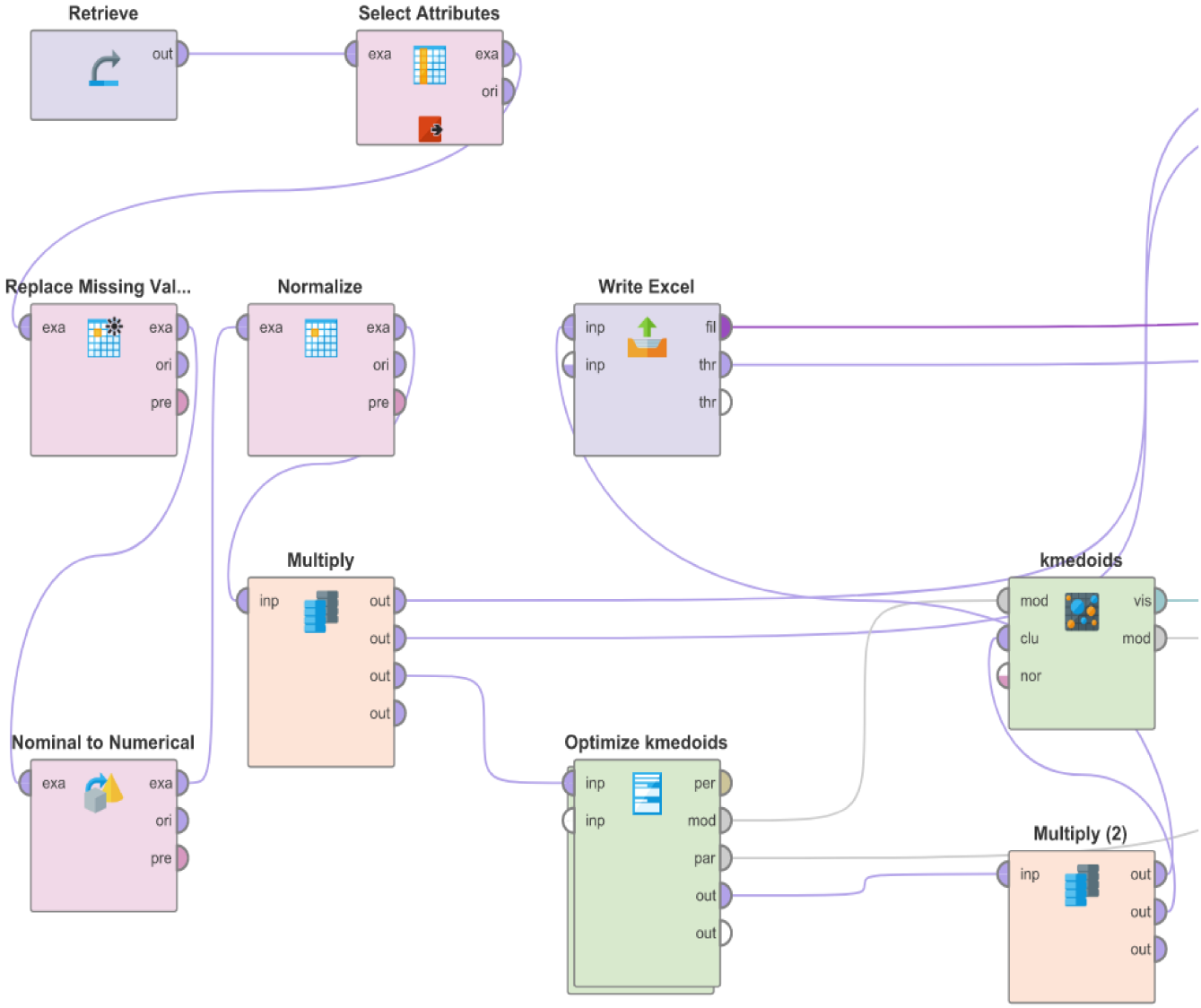

Figure 1. The process of the clusters' calculation was performed in RapidMiner. The file is attached in the Supplementary Materials.

Table 2. Characteristics of patients in each cluster and the whole group. The lowest values are marked green and the highest ones are red.

Parameter	Cluster 0	Cluster 1	Cluster 2	Global	*p*
Demographics					
n	158 (51%)	110 (35%)	44 (14%)	312	
Sex, male (*n*)	138 (87%)	53 (48%)	43 (98%)	234 (75%)	<0.001
Age (years)	69.192 ± 11.826	72.217 ± 11.736	56.015 ± 13.273	68.4 ± 13.054	<0.001
AHF characteristics					
Ejection fraction	30 (25–38.5)	43 (30–53.5)	25 (15–35)	32 (25–45)	<0.001
Chronic HF (*n*)	133 (84%)	29 (26%)	34 (77%)	196 (63%)	<0.001
Reduced EF (*n*)	133 (84%)	59 (54%)	34 (77%)	226 (72%)	<0.001
Aetiology					<0.001
Coronary artery disease (*n*)	120 (76%)	19 (17%)	8 (18%)	147 (47%)	

Table 2. *Cont.*

Parameter	Cluster 0	Cluster 1	Cluster 2	Global	*p*
Valvular (*n*)	12 (8%)	21 (19%)	6 (14%)	39 (13%)	
Hypertension (*n*)	5 (3%)	6 (5%)	0 (0%)	11 (4%)	
Other (*n*)	21 (13%)	64 (58%)	30 (68%)	115 (37%)	
Comorbidities					
Coronary artery disease (*n*)	139 (88%)	37 (34%)	7 (16%)	183 (59%)	<0.001
Myocardial infarction in the past (*n*)	73 (46%)	22 (20%)	4 (9%)	99 (32%)	<0.001
PCI/CABG in the past (*n*)	75 (47%)	19 (17%)	3 (7%)	97 (31%)	<0.001
Hypertension (*n*)	127 (80%)	100 (91%)	10 (23%)	237 (76%)	<0.001
Valvular disease (*n*)	113 (72%)	62 (56%)	29 (66%)	204 (65%)	0.037
Diabetes mellitus (*n*)	63 (40%)	56 (51%)	5 (11%)	124 (40%)	<0.001
Diabetes treatment (*n*)					0.002
Insulin	25 (16%)	11 (10%)	1 (2%)	37 (12%)	
Oral drugs	28 (18%)	25 (23%)	4 (9%)	57 (18%)	
Diet	6 (4%)	4 (4%)	0 (0%)	10 (3%)	
Stroke (*n*)	21 (13%)	14 (13%)	6 (14%)	41 (13%)	0.986
COPD (*n*)	27 (17%)	9 (8%)	4 (9%)	40 (13%)	0.073
Clinical status					
Dyspnoea at rest (*n*)	131 (83%)	84 (76%)	35 (80%)	250 (80%)	0.299
Dyspnoea at rest lasts for (number) days	3 (2–7)	2 (1–7)	5.5 (2.5–8.5)	3 (1–7)	0.370
Deterioration of effort tolerance (*n*)	152 (96%)	103 (94%)	39 (89%)	294 (94%)	0.175
Deterioration of effort tolerance (number) days	14 (7–21)	14 (7–30)	14 (7–30)	14 (7–28)	0.021
NYHA (n)					<0.001
I	5 (3%)	3 (3%)	4 (9%)	12 (4%)	
II	39 (25%)	8 (7%)	9 (20%)	56 (18%)	
III	42 (27%)	19 (17%)	14 (32%)	75 (24%)	
IV	64 (41%)	62 (56%)	14 (32%)	140 (45%)	
Swelling of lower limbs (*n*)					0.050
Swelling of lower limbs 0	43 (27%)	32 (29%)	8 (18%)	83 (27%)	
Swelling of lower limbs 1	37 (23%)	25 (23%)	8 (18%)	70 (22%)	
Swelling of lower limbs 2	50 (32%)	32 (29%)	12 (27%)	94 (30%)	
Swelling of lower limbs 3	28 (18%)	20 (18%)	16 (36%)	64 (21%)	
JVP (n)					0.005
JVP 1	97 (61%)	70 (64%)	17 (39%)	184 (59%)	
JVP 2	51 (32%)	38 (35%)	23 (52%)	112 (36%)	
JVP 3	10 (6%)	1 (1%)	4 (9%)	15 (5%)	
Pulmonary congestion (*n*)	147 (93%)	91 (83%)	40 (91%)	278 (89%)	0.026
Pulmonary oedema (*n*)					0.108
no	11 (7%)	18 (16%)	4 (9%)	33 (11%)	

Table 2. *Cont.*

Parameter	Cluster 0	Cluster 1	Cluster 2	Global	*p*
up to 1/3 of lungs	102 (65%)	48 (44%)	33 (75%)	183 (59%)	
up to 2/3	35 (22%)	24 (22%)	5 (11%)	64 (21%)	
>2/3	10 (6%)	19 (17%)	2 (5%)	31 (10%)	
Ascites (*n*)	19 (12%)	7 (6%)	15 (34%)	41 (13%)	<0.001
Hepatomegaly (*n*)	25 (16%)	14 (13%)	26 (59%)	65 (21%)	<0.001
Implantable device (*n*)					<0.001
PM	16 (10%)	7 (6%)	1 (2%)	24 (8%)	
ICD	43 (27%)	2 (2%)	3 (7%)	48 (15%)	
CRT	15 (9%)	2 (2%)	4 (9%)	21 (7%)	
Systolic pressure (mmHg)	130 (110–150)	145 (124–171)	110 (100–127)	130 (110–150)	<0.001
Diastolic pressure (mmHg)	75.5 (70–87)	83 (70–100)	70 (60–83.5)	80 (70–90)	<0.001
Heart rate (beats per minute)	78 (70–100)	90 (72–110)	100 (80–110)	83 (70–100)	<0.001
Body weight (kg)	80 (72.55–93)	78.25 (68.5–88.6)	76 (67–87.8)	79.2 (70–91)	0.437
Lifestyle factors					
Smoking status (*n*)					<0.001
Never	74 (47%)	74 (67%)	15 (34%)	163 (52%)	
Active	18 (11%)	15 (14%)	15 (34%)	48 (15%)	
In the past	66 (42%)	21 (19%)	14 (32%)	101 (32%)	
How many cigarettes patient smoke daily (*n*)	10 (0–20)	10 (0–20)	10 (0–20)	10 (0–20)	0.797
How many years did the patient smoke/does the patient smoke cigarettes (*n*)	20 (0–30)	10 (0–30)	13 (0–30)	20 (0–30)	0.380
Active alcohol use (*n*)	40 (25%)	18 (16%)	29 (66%)	87 (28%)	<0.001
Laboratory parameters					
HGB (g/dL)	13.232 ± 1.993	12.955 ± 1.892	13.975 ± 1.759	13.239 ± 1.947	0.013
HCT (%)	39.844 ± 5.535	39.145 ± 5.233	41.766 ± 5.173	39.868 ± 5.427	0.025
RBC (× 1012/L)	4.482 ± 0.663	4.389 ± 0.568	4.552 ± 0.586	4.459 ± 0.621	0.274
MCV (fL)	89.195 ± 6	89.31 ± 5.743	92.125 ± 7.124	89.649 ± 6.145	0.015
MCH (pg)	29.597 ± 2.253	29.546 ± 2.466	30.828 ± 2.992	29.749 ± 2.472	0.008
WBC (× 109/L)	8.54 (6.5–10.3)	8.1 (6.5–10.4)	8.45 (7.1–9.85)	8.3 (6.6–10.3)	0.872
PLT (× 109/L)	196 (159–242)	201 (158–248)	207 (174–250)	198 (159–245)	0.777
pH	7.45 (7.42–7.48)	7.425 (7.375–7.465)	7.45 (7.43–7.49)	7.44 (7.41–7.47)	0.003
sO_2 (%)	92.85 (90.1–95.45)	93.55 (91.3–94.9)	93.8 (88.7–96.3)	93.2 (90.4–95.4)	0.946
pO_2 (mmHg)	65.35 (57.9–73.25)	67.4 (62.4–74.45)	66.9 (55.2–80.6)	66.1 (59–74.6)	0.956
pCO_2 (mmHg)	34.65 (32.15–38.8)	35.8 (32.4–39.25)	33.4 (30.4–36.9)	35.2 (32–38.9)	0.517
HCO_3 (mmol/L)	24.025 ± 3.223	22.805 ± 3.416	23.939 ± 4.62	23.578 ± 3.558	0.025
BE mEq/l	0.197 ± 3.42	-1.252 ± 3.712	0.3 ± 4.523	-0.304 ± 3.755	0.007
mOsm (Osm/L)	281 (274–286)	286 (280–290)	274 (264-285)	282 (274–288)	<0.001
Na (mmol/L)	139 (137–142)	140 (138–142)	136.5 (133.5–141)	139 (136–142)	0.007
K (mmol/L)	4.117 ± 0.549	4.296 ± 0.627	4.107 ± 0.537	4.179 ± 0.581	0.031

Table 2. *Cont.*

Parameter	Cluster 0	Cluster 1	Cluster 2	Global	*p*
Lactates (mmol/L)	1.9 (1.5–2.4)	2 (1.5–2.7)	2 (1.6–3)	2 (1.5–2.55)	0.088
Glucose (mg/dL)	120 (102–157)	131 (106–186)	107.5 (94.5–126.5)	120 (102.5–152)	0.001
INR	1.37 (1.12–1.8)	1.32 (1.12–1.93)	1.35 (1.175–1.7)	1.345 (1.12–1.8)	0.102
Albumin (g/dL)	3.775 ± 0.367	3.743 ± 0.402	3.602 ± 0.42	3.738 ± 0.39	0.036
Ast (IU/L)	26 (19–34.5)	29.5 (22–41)	28.5 (20.5–40)	27 (20–38)	0.004
Alt (IU/L)	28 (17.5–47)	31 (20.5–55.5)	28 (18.5–44)	29 (19–48)	0.019
Total bilirubin (mg/dL)	1.06 (0.77–1.6)	0.9 (0.63–1.47)	1.415 (0.905–2.455)	1.04 (0.72–1.67)	<0.001
GGTP (IU/L)	70 (45–135)	54.5 (29–103)	99 (48–206)	69.5 (40–123.5)	0.021
CRP (mg/L)	7.04 (4–15.4)	6.2 (2.6–14)	10.25 (4.35–24.35)	7.1 (3.4–16.2)	0.513
IL6 (pg/mL)	8.346 (1.155–21.1)	11.705 (3.257–26.299)	11.352 (6.338–30.117)	10.056 (2.508–22.9)	0.734
Ferritin (ng/mL)	101.9 (51.94–191)	125.6 (65.5–218.75)	115.15 (51–287.9)	105.7 (57.08–212)	0.372
Tsat (%)	16.1 (12.3–21.9)	15.608 (11.9–18.519)	16.026 (10.7–26.6)	15.84 (11.82–21.1)	0.030
sTfR (mg/L)	1.885 (1.495–2.46)	1.82 (1.46–2.46)	1.755 (1.4–2.53)	1.85 (1.46–2.46)	0.972
TIBC (µg/dL)	352.192 ± 72.92	338.052 ± 62.645	366.357 ± 76.825	349.514 ± 70.639	0.075
Fe (µg/dL)	56 (43–79)	51 (40–64)	60.5 (43–88)	54 (42–73)	0.005
NTproBNP (pg/mL)	5291 (3081–9203)	5525 (2755–13,629)	7106 (5026–11,759)	5659 (3119–10,572)	0.021
Creatinine (mg/dL)	1.21 (1.04–1.47)	1.23 (0.95–1.62)	1.14 (0.925–1.44)	1.21 (1.005–1.49)	0.761
Urine Creatinine (mg/dL)	69.4 (37.1–126.5)	43.5 (27.6–88.7)	73.6 (34.7–125.9)	61.5 (31.6–110.9)	0.026
Urea (mmol/L)	52 (39–73)	48 (38–73)	56 (39–74)	51 (38–73)	0.224
Urine Urea (mmol/L)	841 (506–1413)	581 (384–1232)	1122.5 (482–1663)	813 (433–1437)	0.023
Urine K (mmol/L)	30 (20.53–43.27)	26 (17–39)	28.415 (19.6–45)	29 (19–42.59)	0.249
Urine Na (mmol/L)	88.253 ± 38.623	97.721 ± 32.398	84.786 ± 48.268	91.05 ± 38.333	0.078

3. Results

3.1. Population Characteristics

The population consisted of 312 patients, predominantly men (75%). The mean age was 68.4 ± 13.054. Average values of important clinical parameters were systolic blood pressure-130 mmHg (110–150), ejection fraction–32% (25–45), NT-proBNP–5659 pg/mL (3119–10,572), and serum creatinine −1.21 mg/dL (1.005–1.49). A detailed description of the patient's characteristics, including characteristics by clusters, is displayed in Table 2.

3.2. Clustering

The population was segmented into three clusters, enumerated from 0 to 2. Groups included were, respectively, 158, 110, and 44 patients.

3.2.1. Cluster 0

Cluster 0 was the most numerous one. It comprised the highest proportion of chronic HF with reduced ejection fraction, with the underlying cause of coronary artery disease. Patients usually had a history of PCI/CABG and electrical device implantation. COPD and insulin-dependent diabetes were most frequently reported. Clinical status comprised common pulmonary congestion, moderate limb oedema, and the lowest heart rate. In laboratory parameters, they presented the lowest Ast, Alt, ferritin, IL-6, and NT-proBNP.

3.2.2. Cluster 1

Among other clusters, this group was composed predominantly of older women. They manifested the first manifestation of HF, with preserved ejection fraction and high comorbidity burden, i.a., diabetes and hypertension. Their clinical presentation was reflected by the most frequent NYHA IV, least frequent lower limb oedema and pulmonary congestion, and highest blood pressure. In laboratory measurements, they reached the lowest haemoglobin, HCO3, bilirubin, GGTP, and the highest serum sodium and potassium concentration, serum osmolarity, glucose, Ast, Alt, IL-6, and ferritin.

3.2.3. Cluster 2

The last group was the youngest, with the highest proportion of males and the lowest ejection fraction. They reported the highest stroke history and presented with frequent ascites and hepatomegaly. They achieved the highest HGB, HCT, MCV, bilirubin, GGTP, Fe, NT-proBNP, urine creatinine, and urea and the lowest albumin in laboratory parameters. They were also the most frequent active alcohol users and smokers.

The most important clinical features of each cluster are shown in Table 3 and Figure 2.

Table 3. Key clinical features of each cluster.

Cluster	Key Clinical Features
Cluster 0	Most numerous cluster. Highest: % of chronic and reduced EF HF, CAD, Valvular heart disease, COPD, implanted electric devices, pulmonary congestion, albumins, HCO_3, Tsat, insulin-dependent, and diet-treated diabetes. Lowest: deterioration of effort tolerance (number) of days, HR, MCV, Ast, Alt, NT-proBNP. Non-significant: highest % of dyspnea at rest, deterioration of effort tolerance, swelling of the lower limbs 1, 2, body weight, past smokers. Lowest: limbs oedema III, JVP II, active smokers—**elderly chronic HFrEF male, with mild congestion, moderate WRF and AKI, and one-year mortality occurrence**
Cluster 1	Highest: % of females, age, ejection fraction, % of de novo HF and preserved EF, valvular and hypertension aetiology, hypertension, diabetes, RR, mOsm, Na, K, glucose, Ast, Alt, lowest: ascites, hepatomegaly, HGB, HCT, MCH, pH HCO_3, urine creatinine and urea, Non-significant: highest: NYHA IV, limbs oedema I, JVP I, no pulmonary oedema, pCO_2, IL-6, ferritin, creatinine, urine Na—**first manifestation of HFpEF older woman, with high inflammatory markers, creatinine and osmolarity, highest AKI and WRF occurrence, and moderate one-year mortality**
Cluster 2	Highest: % of males, other aetiology, stroke history, ascites, hepatomegaly, HR, active alcohol users, HGB, HCT, MCV, bilirubin, GGTP, Fe, NT-proBNP, and urine creatinine and urea. Lowest: age, ejection fraction, CAD history, RR, mOsm, Na, K, glucose, and albumin Non-significant: highest: active smokers, limbs oedema III, pulmonary oedema I. Lowest: body weight, CO_2, creatinine, urine Na—**young men, with massive oedema and substance abuse involvement, low AKI and WRF occurrence, and highest one-year mortality**

Abbreviations: EF—ejection fraction, HF—heart failure, CAD—coronary artery disease, COPD—chronic obstructive pulmonary disease, Tsat—transferrin saturation, HR—heart rate, MCV—mean corpuscular volume, Ast—aspartate aminotransferase, Alt—alanine transaminase, NT-proBNP—N-terminal brain natriuretic peptide, JVP—jugular venous pressure, HFrEF—heart failure with reduced ejection fraction, WRF—worsening of renal function, AKI—acute kidney injury, RR—blood pressure, mOsm—osmolarity, N—sodium, K—potassium, HGB—haemoglobin, HCT—haematocrit, MCH—mean corpuscular haemoglobin, NYHA—New York Heart Association scale, IL-6—interleukin 6, GGTP—gamma-glutamyl transferase, and Fe—iron.

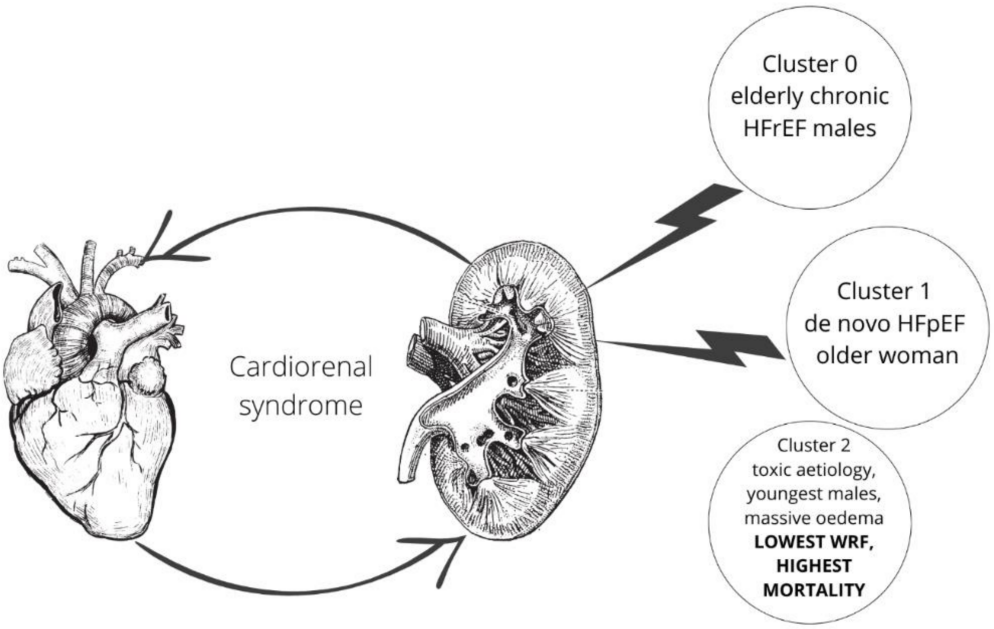

Figure 2. Summary of the most important cluster characteristics and association with renal function.

3.3. Outcome

The global one-year mortality in the studied group was 24% (74 events occurred). The mortality did not significantly differ between the clusters ($p = 0.2$), from cluster 0 to cluster 2: 22% vs. 22% vs. 34%. The Cox regression was performed, but none of the cluster's hazard ratios reached statistical significance ($p = 0.35$, $p = 0.75$, $p = 0.0.09$), and neither did the Kaplan–Meier estimation ($p = 0.21$).

Clusters differed in terms of the time of hospitalization, AKI, and WRF occurrence. Patients in cluster 2 were the least likely to develop AKI or WRF and were hospitalized for the longest time.

The outcomes and findings are summarised in Table 4.

Table 4. Outcome by cluster and in the whole group.

Parameter	Cluster 0	Cluster 1	Cluster 2	Global	*p*
WRF, *n*	24 (15%)	26 (24%)	1 (2%)	51 (16%)	0.004
AKI, *n*	12 (8%)	17 (15%)	0 (0%)	29 (9%)	0.007
Time of hospitalization (days)	6 (5–9)	7 (5–9)	8 (6–14)	7 (5–9.5)	0.006
In hospital deterioration of HF, *n*	9 (6%)	7 (6%)	3 (7%)	19 (6%)	0.856
One year mortality, *n*	35 (22%)	24 (22%)	15 (34%)	74 (24%)	0.200

Abbreviations: WRF—worsening of the renal function, AKI—acute kidney injury, HF—heart failure.

4. Discussion

The WRF and AKI in AHF are common complications associated with ominous outcomes [4]. The occurrence of AKI has been estimated at 9–13% of AHF patients [16,17]. The underlying causes of the WRF in AHF are complex and not fully understood; the most prominent hypotheses include the impact of, i.a., congestion [18]. Given this lack of specific evidence, we decided to analyse the heterogeneity of the AHF population in the context of WRF occurrence and possible clinical phenotypes which determine it.

The ML-based analysis is gaining popularity in cardiovascular research [19]. There were some magnificent attempts to implement ML in the HF population [20–26]. Yagi tried to identify distinct phenotypes among AHF patients who experienced WRF [27]. Nevertheless, our study is the first to incorporate clustering into the analysis of the HF population,

aiming to distinguish subgroups varied in terms of the WRF. The clustering techniques were able to distinguish three interesting clinical subtypes with different pathophysiology and implications for the outcome.

4.1. Cluster 0

This cluster represents the population of older men with chronic HF. We can assume that these patients represent the population with a relatively long history of cardiovascular treatment as they are frequently secured with the electric device and have undergone coronary intervention. They have also been saddled with comorbidities, i.e., end-stage insulin-dependent diabetes and COPD. As these patients represent the group of the chronic and fragile population, therapeutic interventions should be targeted at stable heart failure and comorbidities management [28–30].

4.2. Cluster 1

Cluster 1 is mainly composed of females. It is the oldest population with the first manifestation of HF, non-ischaemic aetiology, and preserved ejection fraction. They present signs of minimal congestion. In the biochemical assessment, patients in cluster 1 reached the highest serum creatinine, sodium potassium, and osmolarity. This phenotype corresponds with the described HFpEF phenotype [31]. Cluster 1 achieved the highest concentration of selected inflammatory biomarkers (IL-6, ferritin), and high activation of inflammatory pathways was reported to be unique for the HFpEF [32]. Recent studies showed that higher osmolarity correlates with the incidence of WRF in AHF [33]. Importantly, this group reached the highest incidence of AKI and WRF but moderate mortality; our consideration of its explanation is presented in the next paragraph. As the HFpEF population currently suffers from the lack of evidence-based treatment, therapeutic interventions should focus on comorbidities management and lifestyle changes [2]. Some hope for efficient pharmacotherapy is provided by the recent trials on SGLT-2 inhibitors [34–36].

4.3. Cluster 2

Cluster 2 seems to be the most interesting. It consists almost exclusively of men. They represent the youngest population with chronic HF with the lowest ejection fraction, developed on aetiology described as "other". Patients suffered from the least burden of comorbidities, which can be explained by their youngest age and probable underdiagnosis due to low commitment to their health management. These patients can be described as having toxic aetiology. They represent the highest frequency of active smokers and alcohol users and have the highest values of GGTP and bilirubin, which reflect the afflicted liver function [37]. Moreover, they reached the highest mean value of MCV, which might be associated with alcohol abuse [38]. In the clinical assessment, they manifest frequent and massive peripheral oedema, i.e., the highest incidence of lime oedema III, hepatomegaly, and ascites, but somewhat limited pulmonary congestion. This discrepancy between the aggravation of oedema in different vascular areas should be further evaluated. Laboratory signs of congestion, e.g., NT-proBNP, are also the highest among the clusters. Notably, patients in cluster 2 achieved the lowest pCO2, which can be a sign of heightened chemosensitivity—the predictor of an a unfavourable outcome [39].

Notably, the cluster with the lowest incidence of AKI and WRF (cluster 2) was the one with the highest one-year mortality (non-significant). In our opinion, that can be explained by two intertwined hypotheses. First, creatinine is the late marker of kidney function [40] and has limited value in assessing renal damage [41]. Some authors distinguish true and pseudo-WRF based on the concentration of so-called new renal biomarkers, i.e., NGAL, KIM-1, and cystatin-c [42]. Considering this, the isolated increase in serum creatinine can be insufficient for an accurate kidney assessment. Secondly, creatinine can rise during decongestive therapy [43,44]. It was reported that the transient rise of creatinine during decongestive treatment could even be a promising sign, as it reflects the exhaustiveness of the decongestion [45]. Thus, increased creatinine during diuretic treatment does not

necessarily indicate genuine kidney injury, which would worsen the outcome, but it can be a sign of diminishing volume overload. The incompleteness of the decongestion was shown to be an important prognostic factor of mortality in AHF [46], which, in our case, could explain why the cluster with the lowest WRF incidence reaches the highest mortality.

The proposed novel classification may complement the classical ways of AHF patient profiling and has significant clinical implications. Each of the extracted clusters has a different suggested pathophysiology and, therefore, another therapeutic pathway that can be therapeutically addressed; e.g., cluster 0-uptitration of the evidence-based HFrEF medical therapy, cluster 1-comorbidities management, and cluster 2-substance abuse counselling and harm reduction. Focusing on these aspects should lead to more accurate treatment tailoring and eventually optimization of therapy. The efficiency of the proposed cluster-based approach to the therapy adjustments should be evaluated in the prospective studies. Notably, clustering does not reveal baffling relationships. The uncovered connections are clear for the experienced cardiologist. The value of the presented analyses is that it provides tangible evidence for the existence of such phenogroups. Potentially, clustering could immediately categorize a patient into one of the groups and suggest to a physician a relevant proceeding, which can sometimes be omitted due to overworking or lack of experience.

4.4. Limitations

Our study is not free from limitations. Our data comes from the single-centre registries gathered between 2010–2012 and 2016–2017. Patients in these registries were treated with the current ESC criteria, which did not mention the modern drugs, i.a., a SGLT-2 inhibitor. This influences the potential extrapolation of our results to the present AHF population. Further, we did not assess the novel kidney markers, which would increase the thoroughness of the renal status evaluation. However, the presented assessment model mirrors the commonly used, well-understood variables. Importantly, we have only included the patients who had their creatinine evaluated at four time points, including discharge. Thus, we only included patients who survived the hospitalization. We have also prespecified the number of clusters, as we wanted to avoid the over-fragmentation of the data; however, pre-specification of the number of clusters to three follows the previous papers about clustering in HF [27,47,48]. All the issues mentioned above should be addressed in further trials.

5. Conclusions

Machine learning techniques provided fresh insights into the existing medical datasets. We were able to distinguish three clinically and prognostically different phenotypes. Importantly, these phenotypes are different in terms of the AKI or WRF occurrence. These groups constitute valuable insight into AHF and WRF interplay and may be leveraged for future trial construction and more tailored treatments. Our data provides further evidence for the hypothesis that the serum creatinine concentration should be analysed in the broader context in the population of decongested patients and that its increase is not necessarily prognostically worrying.

Noteworthy, we used the k-medoids algorithm instead of the more popular k-means algorithm because k-medoids represent centroids of clusters as existing data points (patients in our case). This makes the results better interpretable. The k-medoids algorithm is also more robust to outliers than the k-means algorithm [49], which is meaningful in medical data.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biom12111616/s1, File S1: RapidMiner procces.

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Institutional Review Board Statement: This research study was approved by the Ethics Committee of Wroclaw Medical University (387/2015) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available within the article. Further data are available on request from the corresponding author.

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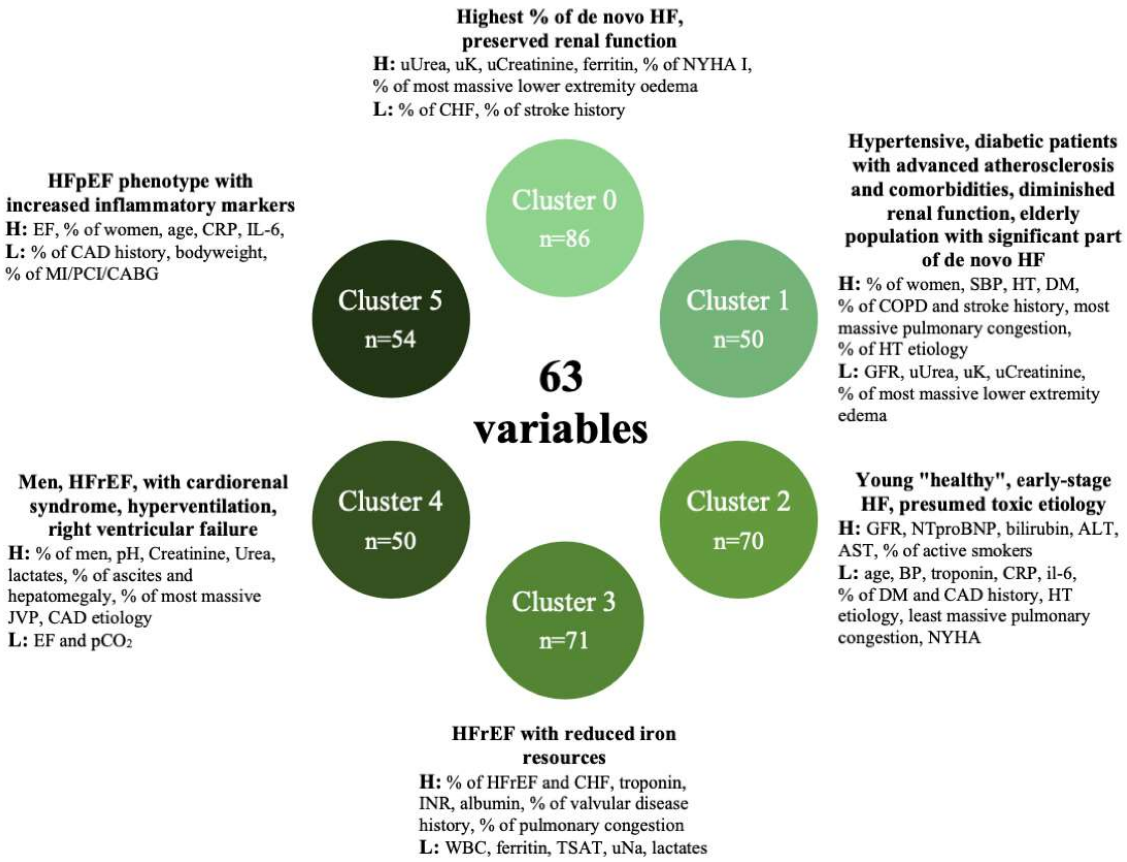
6. Podsumowanie i wnioski

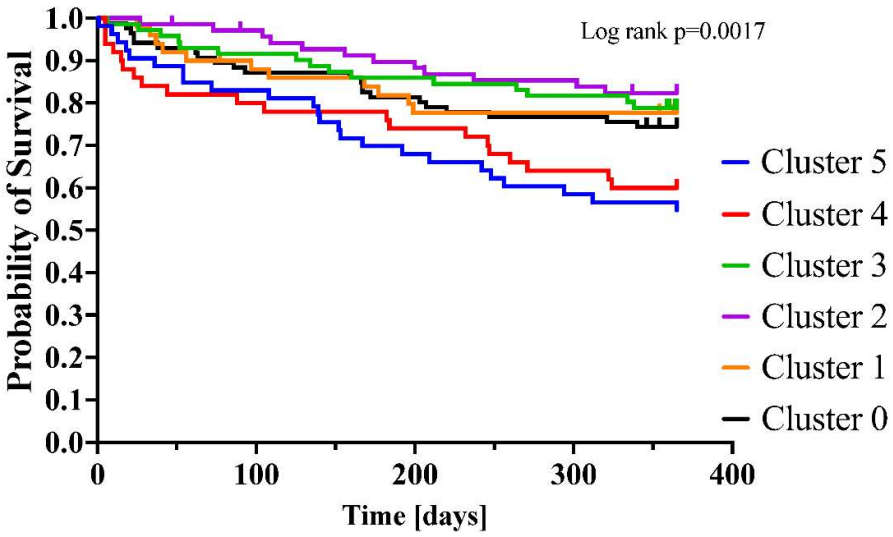
Niniejsza praca stanowi próbę charakterystyki i opisu populacji chorych z ostrą niewydolnością serca. W poniższych pracach zaproponowano nowe fenotypy chorych z AHF, różniące się zarówno pod względem prezentacji klinicznej jak i rokowania. Zaprezentowano również przegląd dostępnych na dany moment modeli predykcyjnych opartych na technikach AI możliwych do stosowania w analizie populacji chorych na HF.

1. publikacja

W pierwszej pracy wchodzącej w skład rozprawy doktorskiej pt. "Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach" przeanalizowano 381 pacjentów zgromadzonych w rejestrze pacjentów hospitalizowanych z powodu AHF w 4 Wojskowym Szpitalu Kliniczny we Wrocławiu a następnie w Uniwersyteckim Szpitalu Klinicznym we Wrocławiu w latach 2010-2012 oraz 2016-2017. Celem analizy było znalezienie różnych profili klinicznych pacjentów. W tym celu wyselekcjonowano 88 zmiennych - parametrów z wywiadu, badania fizykalnego, badań laboratoryjnych oraz obrazowych – wszystkie dane pochodziły z dnia przyjęcia chorego na oddział. Po wstępnym przygotowaniu danych, usunięto zmienne niskiej jakości, tj. na przykład ze zbyt dużą ilością brakujących wartości, zmienne skorelowane ze sobą, czy ze zbyt małą różnorodnością zmiennych. Następnie, zaimplementowano model ML oparty na clusteringu, Wybrano algorytm k-medoids, w którym, w przeciwieństwie do najpopularniejszego algorytmu k-means, gdzie centroidy obliczane są jako średnie wartości punktów danych (przykładów) w klastrze, centroidy w algorytmie k-medoids odpowiadają istniejącym punktom danych – w tym przypadku konkretnym pacjentom. To sprawia, że centroidy są lepiej interpretowalne. Dzięki opcji automatycznego dostosowywania parametrów pozwoliliśmy systemowi ustalić liczbę klastrów w zakresie od 3 do 6. Najlepsze pod względem jakości, rozumianej jako najniższy Davies-Bouldin index, clustry uzyskano przy 6 podgrupach. Otrzymane grupy różniły się od siebie pod względem charakterystyki klinicznej oraz rokowania.



Rycina 5. Charakterystyka kliniczna każdego z wyodrębnionych clustrów.



Rycina 6. Różnice w śmiertelności 1-rocznej pomiędzy badanymi clustrami.

Wykonano analizę różnic pomiędzy clustrami oraz stworzono ich krótkie, opisowe charakterystyki:

Cluster 0 (n=86) - wysoka proporcja chorych z HF de novo, najczęściej w klasie NYHA I, z masywnymi obrzękami kończyn dolnych

Cluster 1 (n = 50) i cluster 4 (n = 50) - Clustry 1 i 4 obejmowały pacjentów z dużą liczbą chorób współistniejących. W obu tych grupach dominującą przyczyną niewydolności serca była choroba wieńcowa. Mimo że te dwa klastry wykazywały podobieństwa pod względem etiologii, ich rokowanie było znacząco różne. Cluster 1 miał stosunkowo dobre rokowanie, podczas gdy w clustrze 4 było złe. Śmiertelność w ciągu jednego roku wynosiła 22% w clustrze 1 i była prawie dwukrotnie wyższa w clustrze 4 (40%), co można potencjalnie wyjaśnić dwoma czynnikami. Pierwszym z nich są różnice w strukturze płci danego clustra - mężczyźni stanowili 46% clustra 1 i 98% clustra 4. Drugim natomiast, różnice w zakresie funkcji nerek w obu opisywanych clustrach – cluster 4 obrazuje powszechny problem zespołu sercowo-nerkowego.

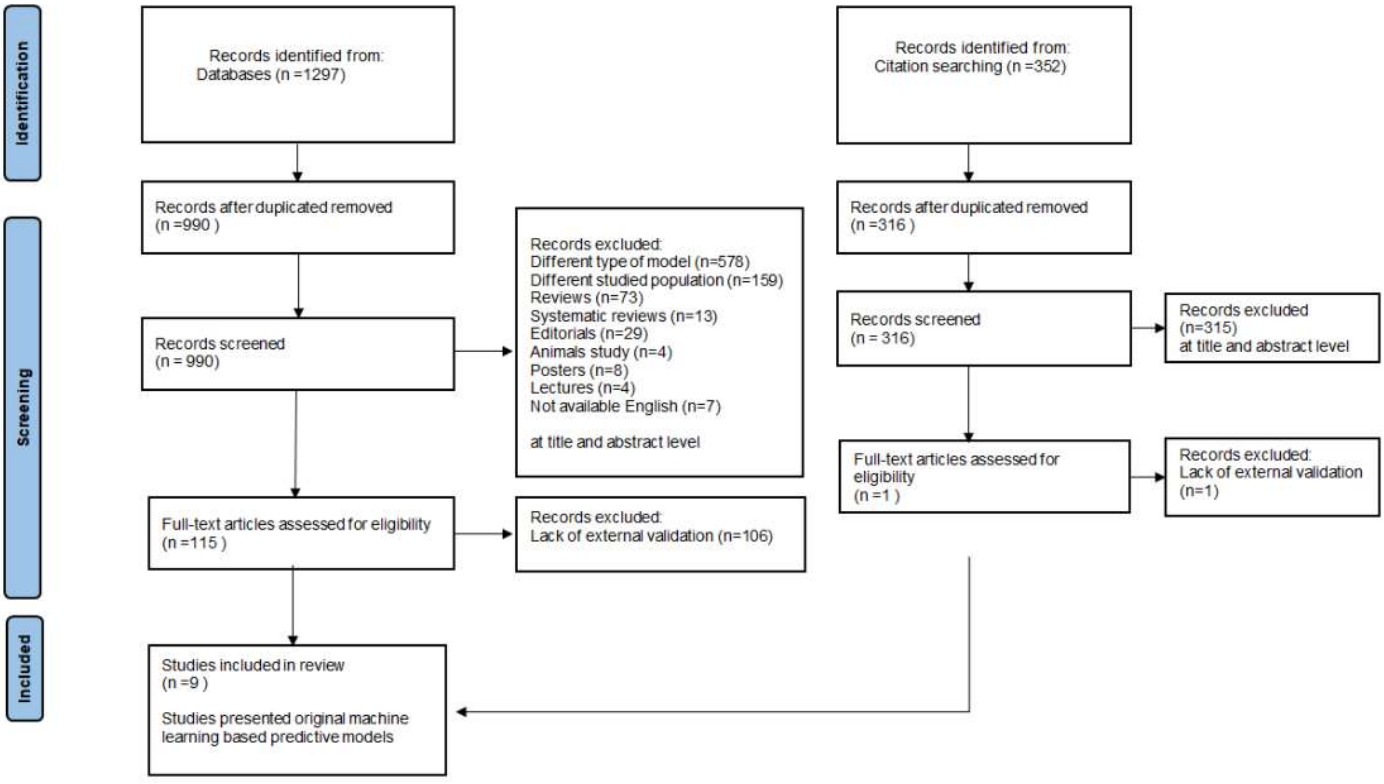
Cluster 2 (n = 70) - Pacjenci zaklasyfikowani do clustra 2 byli najmłodsi i mieli najwyższe wartości NTproBNP, bilirubiny, AST i ALT a także najniższą frakcję wyrzutową (28%) oraz stężenie kreatyniny w surowicy. Pacjenci w clustrze 2 stanowili najwyższy odsetek aktywnych palaczy tytoniu oraz konsumentów alkoholu. Cluster 2 został określony jako grupa z dominującą etiologią toksyczną HF. Prezentował on najlepsze rokowanie, co można prawdopodobnie wytłumaczyć najmłodszym wiekiem, niską liczbą współistniejących chorób, wysokimi rezerwami kompensacyjnymi oraz częstą odwracalnością toksycznego uszkodzenia serca w przypadku odstawienia ksenobiotyków.

Cluster 3 (n = 71) - W clustrze 3 dominowali chorzy prezentujący kolejny epizod dekompensacji przewlekłej niewydolności serca, częsty był także niedobór żelaza. Uznano, że zaburzenia gospodarki żelazowej mogą tłumaczyć umiarkowane rokowanie pacjentów w tym clustrze i stanowić stosunkowo łatwy do osiągnięcia cel terapeutyczny, mający na celu poprawę wyników tych pacjentów.

Cluster 5 (n = 54) - Cluster 5 i Cluster 1 zawierają dużą proporcję starszych pacjentów oraz kobiet, z najwyższą spośród wszystkich clustrów średnią frakcją wyrzutową. Oba te clustry reprezentują chorych z HFpEF. Clustry różniły się jednak rokowaniem, pacjenci w clustrze 2 rokowali dobrze, natomiast w clustrze 5 źle. Wynika to prawdopodobnie m.in z różnic w czasie trwania choroby, cluster 5 to głównie chorzy z kolejną dekompensacją przewlekłej HF, oraz możliwej dużej reprezentacji zespołu kruchości w tym clustrze.

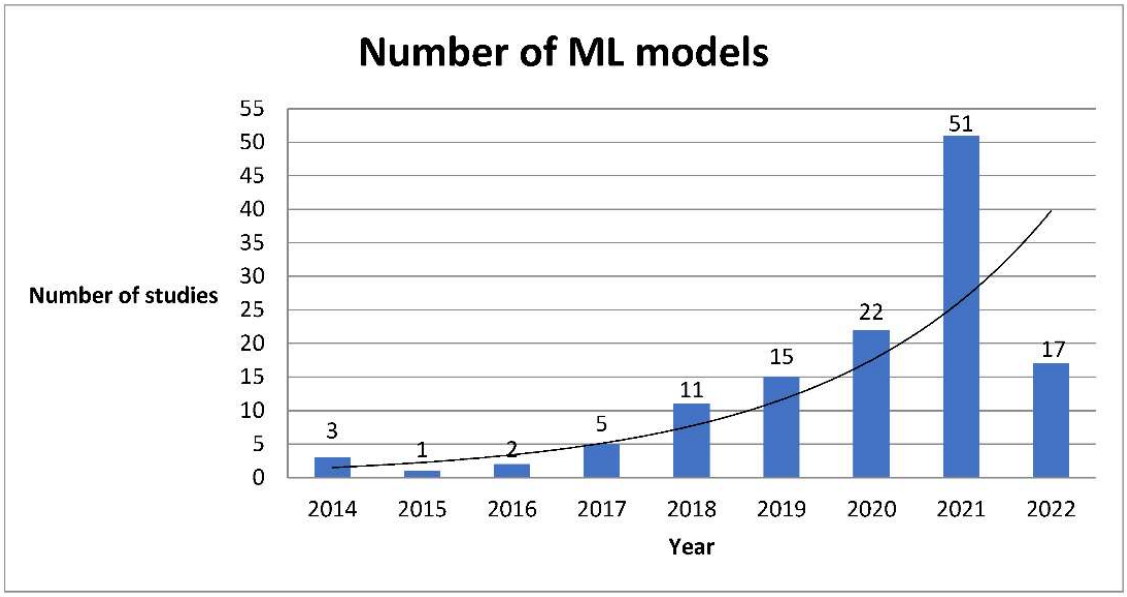
2. publikacja

Druga publikacja pt: "An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review" to przegląd systematyczny podsumowujący obecnie istniejące modele predykcyjne AI stosowane w populacji chorych z HF. Przegląd został zarejestrowany w PROSPERO i wykonany zgodnie z wytycznymi PRISMA. Kryteria włączenia obejmowały publikacje pełnotekstowe, wykorzystujące modele stworzone w oparciu o AI do predykcji określonych punktów końcowych w populacji chorych z HF. Wykluczono prace, w których nie wykonano walidacji stworzonego modelu w zewnętrznej kohorcie. Używając słów kluczowych przeszukano wybrane bazy danych, zidentyfikowano 9 artykułów które włączono do przeglądu. Z prac wyekstrahowano m.in. następujące parametry: rok publikacji, źródło danych, wielkość kohorty treningowej, wielkość kohorty walidacyjnej, środowisko w jakim gromadzone był dane pacjentów (wewnątrz/zewnątrzszpitalne), analizowane punkty końcowe, wybrane zmienne predykcyjne, wykorzystany algorytm, AUC, sposób zarządzania brakującymi danymi.



Rycina 7. Flowchart przeglądu systematycznego.

Wnioski z powyższej analizy były następujące: po pierwsze, zauważono rosnącą ilość prac wykorzystujących techniki AI w analizie populacji chorych z HF w okresie ostatniej dekady. Po drugie, pokazano skuteczność tworzonych modeli; zweryfikowane w zewnętrznych populacjach modele uzyskiwały AUC na poziomie 0.649-0.913, co jest satysfakcjonującym wynikiem. Użycie AI wiąże się jednak z szeregiem problemów. Większość tworzonych modeli nie jest testowanych w odrębnych kohortach. Powoduje to powszechny w dziedzinie AI problem overfittingu – model uzyskuje świetne parametry w kohorcie na której został wytrenowany, natomiast jest mało efektywny w zewnętrznych zbiorach danych. W sytuacji, w której, pacjenci z HF prezentują ogromną różnorodność, zarówno jeśli chodzi o obraz kliniczny, jak i ich pochodzenie, zaplecze socjoekonomiczne, uwarunkowania społeczne regionu, w którym żyją etc. rodzi to duże zastrzeżenia co do uniwersalności tworzonych algorytmów. Co więcej, modele trenowane są na konkretnym zestawie zmiennych, co w przypadku próby wykorzystania danego modelu w innym środowisku rodzi konieczność unifikacji gromadzonych danych o pacjentach. Różnice mogą wynikać z m.in. odrębnych technik laboratoryjnych oznaczania tych samych parametrów, czy aparatów na których wykonuje się badania obrazowe. Ostatnim ograniczeniem, jest przejrzystość tworzonych modeli i możliwość wytłumaczenia wydawanych przez nie predykcji. Modele AI w większości stanowią tzw. black box – algorytm generuje odpowiedź natomiast nie jest w stanie wytłumaczyć w jaki sposób do niej doszedł.



Rycina 8. Ilość prac opisujących wykorzystanie modeli ML w predykcji wybranych aspektów klinicznych w HF na przestrzeni lat.

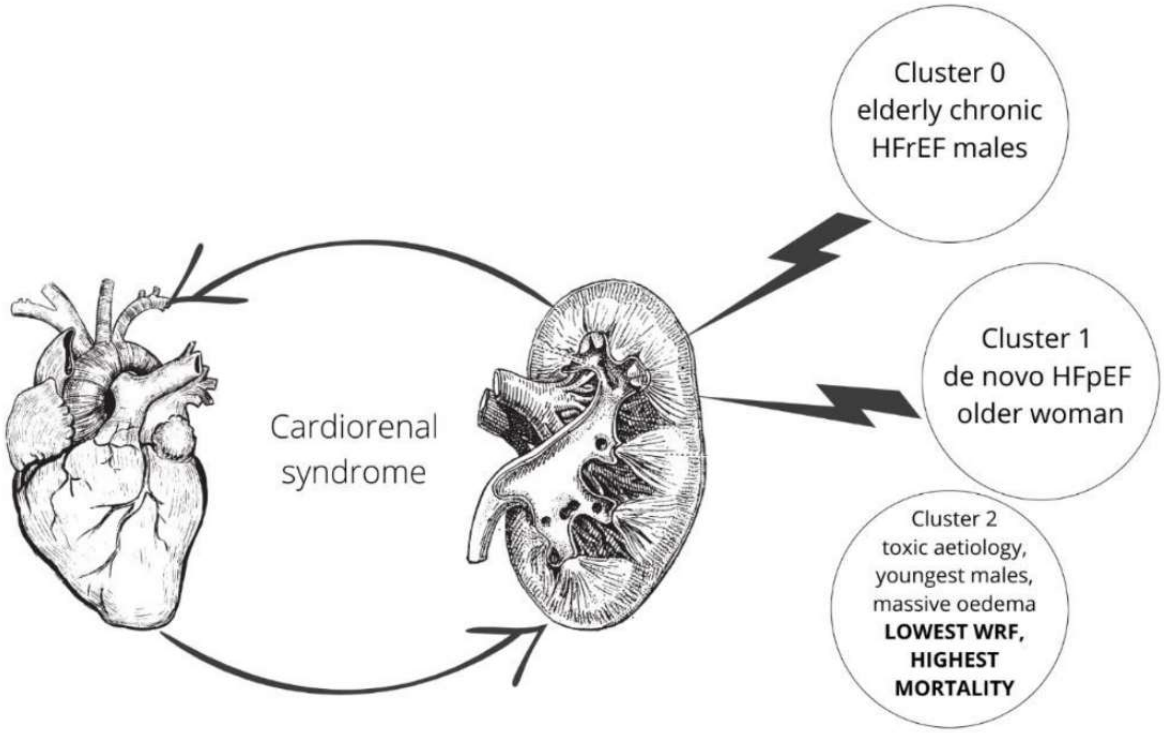
3. publikacja

Trzecia praca pt: "Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure" to próba zastosowania technik ML do analizy ryzyka wystąpienia pogorszenia funkcji nerek (WRF) lub ostrego uszkodzenia nerek (AKI) w populacji chorych z AHF. Do analizy ponownie wykorzystano istniejący rejestr pacjentów z AHF prowadzony w naszym ośrodku. Z całej populacji wyodrębniono chorych (312 pacjentów) którzy mieli ocenione stężenie kreatyniny w każdym z 4. punktów czasowych i.e. przy przyjęciu, w 24. i 48. godzinie oraz przy wypisie. Pogorszenie funkcji nerek zostało zdefiniowane jako wzrost stężenia kreatyniny w osoczu o 0.3 mg/dL pomiędzy dowolnymi punktami czasowymi w trakcie hospitalizacji, jako AKI kwalifikowano identyczny wzrost, jednak musiał on wystąpić w ciągu maksymalnie 48 godzin zgodnie z kryteriami KDIGO[37]. Do clusteringu początkowo wybrano zmienne dotyczące statusu klinicznego pacjenta – wszystkie były oznaczone przy przyjęciu na oddział. Przystosowano dane do algorytmów clusteringu, usunięto zmienne niskiej jakości. Do grupowania pacjentów wykorzystano wyżej opisywany algorytm k-medoids, uzyskano 3 clustry.

Cluster 0 – to grupa składająca się w większości ze starszych mężczyzn z kolejnym epizodem dekompensacji przewlekłej HF. Pacjenci w tym clustrze prezentowali pośrednie ryzyko zarówno WRF/AKI jak i śmiertelności 1-rocznej. Cluster 1 to głównie starsze kobiety, z pierwszą manifestacją HFpEF. U tych chorych obserwowaliśmy istotnie podniesiony poziom parametrów zapalnych, kreatyniny oraz osmolarności osocza, jak również najwyższe ryzyko AKI/WRF oraz umiarkowane ryzyko zgonu w ciągu 1 roku. Cluster 2 to podgrupa składająca się prawie wyłącznie z mężczyzn. Jest to najmłodsza populacja, z silnie upośledzoną frakcją wyrzutową oraz mocno wyrażonymi objawami zastoju. Chorzy w tym clustrze często aktywnie palili tytoń oraz spożywali alkohol, co znalazło odzwierciedlanie w wynikach laboratoryjnych. W tym clustrze chorzy osiągali najwyższe wyniki w zakresie bilirubiny, GGTP oraz MCV.

Co ciekawe, cluster który najrzadziej rozwijał WRF/AKI (cluster 2) rokował najgorzej w kontekście śmiertelności 1-rocznej. Wynika to prawdopodobnie z tego, że wzrost kreatyniny w trakcie odwadniania pacjenta z HF może być związany z efektywnością prowadzonej terapii, a niekoniecznie z prawdziwym uszkodzeniem funkcji nerek. Wzrost ten wynika wówczas, ze zmniejszającego się przewodnienia, a tym samym przejściowo zmniejszającej się objętości wewnątrznaczyniowej. W pracach, w których na podstawie wzrostu kreatyniny rozpoznawano WRF, a następnie różnicowano prawdziwe i rzekome WRF bazując na zaostrzeniu lub braku

poprawy w zakresie objawów AHF, pokazano, że jedynie prawdziwe WRF – rozumiane jako wzrost kreatyniny oraz pogorszenie objawów HF związane jest z gorszym rokowaniem[38]. Niekompletność odwodnienia w AHF, opisywana była jako niekorzystny czynnik rokowniczy[39], co po części wyjaśnia opisywane zjawisko.



Rycina 9. Najważniejsze cechy wyodrębnionych clustrów.

Każdy z wyodrębnionych clustrów, różni się pod względem patofizjologii. Różnice te mogą i powinny być adresowane w terapii. Warto zaznaczyć, że powyższe analizy nie ujawniają zaskakujących relacji. Odkryte powiązania są jasne dla doświadczonego kardiologa. Wartość prezentowanych analiz polega na dostarczeniu namacalnych dowodów na istnienie takich fenogrup. Teoretycznie, techniki clusteringu, mogłyby natychmiastowo przyporządkować pacjenta do jednej z grup i sugerować lekarzowi odpowiednie postępowanie, które czasem może być pominięte z powodu przepracowania lub braku doświadczenia.

Wnioski

1. Techniki AI są w stanie skutecznie wyodrębniać różniące się pod względem prezentacji klinicznej oraz patofizjologii podgrupy wewnątrz populacji chorych z AHF.
2. Wyodrębnione grupy wykraczają poza dotychczas istniejące klasyfikacje chorych z AHF. Subpopulacje różnią się pod względem rokowania tj. śmiertelności z dowolnej przyczyny oraz częstości hospitalizacji.
3. Ilość tworzonych modeli AI mających zastosowanie w kardiologii gwałtownie rośnie. Zwiększają się również możliwości potencjalnych zastosowań AI – od modeli predykcyjnych przez analizę różnorodności populacji.
4. Wiele powstających modeli AI jest niedoskonałych metodologicznie. Najczęstszym problemem jest brak zewnętrznej walidacji wytrenowanych modeli. Rodzi to szereg problemów które stoją na drodze do szerszej implementacji AI w ochronie zdrowia.
5. Techniki clusteringu są w stanie wyodrębnić podgrupy chorych z AHF zróżnicowane pod względem ryzyka wystąpienia niepożądanych zdarzeń nerkowych.
6. Podgrupa najczęściej rozwijająca pogorszenie funkcji nerek w trakcie leczenia AHF, prezentuje najlepsze rokowanie, jeśli chodzi o śmiertelność ogólną. Wynika to prawdopodobnie ze zmian stężenia kreatyniny w trakcie odwadniania pacjentów, które świadczą o zmniejszaniu zastoju, bardziej niż o uszkodzeniu funkcji nerek.

7. Streszczenie rozprawy doktorskiej

Wstęp

Niewydolność serca (HF) jest globalnym problemem zdrowotnym dotykającym w pewnym momencie życia do 10 % populacji. Jednym z rodzajów HF jest ostra niewydolność serca (AHF) – stan zagrożenia życia, wciąż wiążący się ze złym rokowaniem. Mimo postępów w terapii HF, wyniki w AHF pozostają niezadowalające. Techniki sztucznej inteligencji (AI), w tym nienadzorowanego uczenia maszynowego – clusteringu, dostarczają nowych możliwości analizy różnorodności populacji. Clustering to technika, która dzieli zbiór na mniejsze grupy (clustry) na podstawie ich podobieństwa. Clustry składają się z przypadków, które są spójne ze sobą, ale nie z innymi zbiorami. Wyodrębnienie przy pomocy algorytmów AI nowych fenotypów chorych z AHF rodzi nadzieję na bardziej spersonalizowane podejście oraz poprawę skuteczności leczenia.

Cel pracy

Celem pracy była ocena przydatności technik AI w analizie danych medycznych, jak również próba wyodrębnienia nowych klinicznych fenotypów AHF. Kolejnym celem pracy była analiza istniejącego piśmiennictwa dotyczącego zastosowania AI w ocenie pacjentów z HF.

Materiał i metody

W pierwszej pracy przeanalizowano 381 pacjentów z AHF zgromadzonych w prowadzonym w naszym ośrodku rejestrze. W kolejnym kroku, korzystając z ocenionych przy przyjęciu pacjenta na oddział zmiennych wykonano clustering. Następnie oceniono otrzymane clustry pod względem różnic w obrazie klinicznym jak również rokowania tj. śmiertelności 1-rocznej oraz częstości hospitalizacji. Kolejna praca stanowi przegląd systematyczny dotyczący modeli predykcyjnych AI wykorzystywanych w HF. Do analizy włączono wyłącznie badania oparte na modelach z walidacją zewnętrzną. W trzeciej pracy przeanalizowano pacjentów z wyżej wspomnianego rejestru pod względem ryzyka wystąpienia niepożądanych zdarzeń nerkowych. Wykluczono pacjentów, którzy nie mieli oznaczonego stężenia kreatyniny w osoczu w każdym z 4. punktów czasowych tj. przy przyjęciu po 24 i 48 godzinach oraz przy wypisie ze szpitala. Pogorszenie funkcji nerek zdefiniowano jako wzrost kreatyniny o 0.3 mg/dL. Następnie wykonano clustering i porównano podgrupy pod względem charakterystyki klinicznej i rokowania nerkowego.

Wyniki

W pierwszej pracy zidentyfikowano 5 podgrup chorych pacjentów z AHF. Grupy różniły się pod względem śmiertelności 1- rocznej (HR 0.9 vs 0.776 vs 0.537 vs 0.688 vs 1.738 vs 2.095, cluster 0 vs 1 vs 2 vs 3 vs 4 vs 5). Grupy różniły się od siebie prezentacją kliniczną, wśród fenotypów można było wyróżnić m.in. podgrupę pacjentów z HFpEF czy pacjentów z HF o etiologii toksycznej. Przegląd systematyczny zidentyfikował 9 modeli AI wykorzystywanych w ocenie pacjentów z HF. Modele były zróżnicowane pod względem technicznym, jak również rodzajem przewidywanych zdarzeń. W ostatniej pracy zidentyfikowano 3 clustry, zróżnicowane pod względem rokowania nerkowego (pogorszenie funkcji nerek wystąpiło w 15% vs 24% vs 2%, p = 0.004, w clustrze 0 vs 1 vs 2).

Wnioski

Techniki AI dostarczają skutecznych narzędzi do analizy różnorodności istniejących zbiorów danych. Dzięki AI udało się wyodrębnić zróżnicowane podgrupy pacjentów z AHF. Analiza naturalnej różnorodności chorych może potencjalnie umożliwiać personalizację leczenia, a co za tym idzie, przekładać się na jego wyniki.

8. Summary

Introduction

Heart failure (HF) is a global health issue affecting up to 10% of the population at some point in their lives. One type of HF is acute heart failure (AHF) – a life-threatening condition that remains associated with poor prognosis. Despite advances in HF therapy, outcomes in AHF remain unsatisfactory. Artificial intelligence (AI) techniques, including unsupervised machine learning such as clustering, provide novel opportunities for analyzing population heterogeneity. Clustering is a technique that divides a dataset into smaller groups (clusters) based on their similarities. Clusters consist of cases that are coherent within themselves but not with other groups. The extraction of new phenotypes of AHF patients using AI algorithms holds the promise of a more personalized approach and improved treatment efficacy.

Aim

The aim of this study was to assess the utility of AI techniques in the analysis of medical data, as well as to attempt the identification of novel clinical phenotypes in AHF. Another objective

of the study was to analyze the existing literature concerning the application of AI in the evaluation of HF patients.

Methods

In the first study, a cohort of 381 AHF patients registered at our institution was analyzed. In the subsequent step, utilizing variables assessed upon patient admission, clustering was performed. The resulting clusters were then assessed based on differences in clinical presentation as well as outcomes, including one-year mortality and hospitalization frequency. The second study comprised a systematic review of predictive AI models employed in HF. Only studies utilizing externally validated models were included in the analysis. In the third study, patients from the aforementioned registry were analyzed in terms of their risk for adverse renal events. Patients lacking serum creatinine measurements at all four time points—admission, 24 and 48 hours, and discharge—were excluded. Renal deterioration was defined as a 0.3 mg/dL increase in creatinine. Subsequently, clustering was conducted, and subgroups were compared with regard to clinical characteristics and renal prognosis.

Results

In the first study, five distinct subgroups of AHF patients were identified. These groups exhibited variations in terms of one-year mortality (HR 0.9 vs 0.776 vs 0.537 vs 0.688 vs 1.738 vs 2.095, cluster 0 vs 1 vs 2 vs 3 vs 4 vs 5). The groups also differed in clinical presentation, with identified phenotypes including i.a. subsets of patients with HFpEF and those with toxin-induced HF. The systematic review identified a total of 9 AI models used for assessing HF patients. These models exhibited technical diversity as well as variation in the types of predicted events. In the final study, three distinct clusters were identified. These clusters exhibited variations in renal prognosis (renal function deterioration occurred in 15% vs 24% vs 2%, $p = 0.004$, in cluster 0 vs 1 vs 2).

Conclusions

AI techniques provide effective tools for analyzing the diversity within existing datasets. Through the use of AI, it has become possible to discern diverse subgroups of AHF patients. The analysis of inherent patient diversity has the potential to enable treatment personalization, ultimately translating into improved treatment outcomes.

9. Oświadczenia współautorów

Prof. Petr Berka
Department of Information and Knowledge Engineering,
Prague University of Economics and Business

Prague, 23.08.2023

Declaration

I hereby declare that: in the paper: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure - Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459**, my contribution consisted of: study conceptualization, establishment of interdisciplinary collaboration, substantive supervision, and machine learning tools application;

In the paper: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386**, my contribution consisted of: study conceptualization, establishment of interdisciplinary collaboration, substantive supervision;

In the paper: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716**, my contribution consisted of: study conceptualization, establishment of interdisciplinary collaboration, substantive supervision, and machine learning tools application.

I hereby consent to the utilization of the aforementioned publications, of which I am a co-author, in the doctoral dissertation of Dr. Szymon Urban, entitled "Application of Artificial Intelligence Methods in the Assessment of Selected Clinical Aspects in Heart Failure."

Signature

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Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: konceptualizacji badania, nawiązaniu współpracy międzyośrodkowej, nadzorze merytorycznym, organizacji finansowania projektu;

w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: weryfikacji merytorycznej stworzonego artykułu, nawiązaniu współpracy międzyośrodkowej, organizacji finansowania projektu;

w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: konceptualizacji badania, nawiązaniu współpracy międzyośrodkowej, nadzorze merytorycznym, organizacji finansowania projektu.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

Podpis

Dr hab. n. med. Robert Zymliński
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Lek. Mikołaj Błaziak
Instytut Chorób Serca,
Uniwersytet Medyczny we Wrocławiu

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: pisaniu manuskryptu, uczestniczeniu w procesie analizy danych, nawiązaniu współpracy międzyośrodkowej oraz pomocy przy procesie submisyjnym;

w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: gromadzeniu danych, pisaniu manuskryptu, uczestniczeniu w procesie analizy danych;

w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: pisaniu manuskryptu, tworzeniu grafik, poprawkach edytorskich.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Podpis

Lek. Artur Borkowski
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Oddział w Gliwicach

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: przygotowaniu danych do analizy, analizie statystycznej, tworzeniu graficznej prezentacji wyników.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Artur Borkowski

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Instytut Immunologii i Terapii Doświadczalnej im. Ludwika Hirszfelda,
Polska Akademia Nauk

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: współpracy merytorycznej, zorganizowaniu finansowania projektu i współpracy międzyośrodkowej.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Lek. Piotr Gajewski
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Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: analizie piśmiennictwa, przygotowania koncepcji badania, przygotowaniu submisji artykułu.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Lek. Mateusz Guzik
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Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: konceptualizacji badania, przygotowaniu oryginalnego draftu, odpowiedzi na recenzje.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Mgr. Inż. Jolanta Horudko

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: analizę zgromadzonych danych, przygotowaniu grafik i tabel.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: analizie danych, pisaniu manuskryptu, odpowiedzi na recenzje.

w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: gromadzeniu danych, przygotowaniu grafik.

w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: opracowaniu i interpretacji wyników.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

Dr hab n. med. Robert Zymliński
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Podpis

Lek. Maksym Jura
Katedra Fizjologii i Patofizjologii,
Uniwersytet Medyczny we Wrocławiu

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: pisaniu manuskryptu, uczestniczeniu w procesie analizy danych, interpretacji wyników, nawiązaniu współpracy międzyośrodkowej oraz korekcie powstającego draftu;

w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: analizie piśmiennictwa, pisaniu manuskryptu, analizie danych;

w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: syntezie istniejących danych, pre-processingu, pisaniu manuskryptu, tworzeniu tabel, poprawkach edytorskich.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Podpis
Maksym Jura

Dr hab. Wiktor Kuliczkowski, prof. UMW
Instytut Chorób Serca,
Uniwersytet Medyczny we Wrocławiu

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: nadzorze merytorycznym, nawiązaniu współpracy międzyośrodkowej, wsparciu w odpowiedzi na recenzje.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

Podpis

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Dr Maciej Pondel, prof. UEW
Katedra Inteligencji Biznesowej w Zarządzaniu,
Uniwersytet Ekonomiczny we Wrocławiu

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Blaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: nawiązaniu współpracy międzyośrodkowej, nadzorze merytorycznym nad operacjami Machine Learning przygotowaniu manuskryptu;

w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: nadzorze merytorycznym pod względem data science, przygotowaniu manuskryptu, modyfikacji manuskryptu zgodnie z zaleceniami recenzentów.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

Podpis

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Inteligencji Biznesowej w Zarządzaniu
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dr inż. Maciej Pondel, prof. UEW

Lek. Barbara Ponikowska
Uniwersytecki Szpital Kliniczny we Wrocławiu,

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: pisaniu manuskryptu, analizie danych, poprawkach edytorskich, przygotowaniu manuskryptu pod submisję.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

Podpis

Barbara Ponikowska

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Prof. Piotr Ponikowski
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Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: konceptualizacji badania, nawiązaniu współpracy międzyośrodkowej, nadzorze merytorycznym, organizacji finansowania projektu;

w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: konceptualizacji badania, nawiązaniu współpracy międzyośrodkowej, nadzorze merytorycznym, wsparciu w odpowiedzi na recenzje, organizacji finansowania projektu.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

Podpis

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Wydział Lekarski
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Katedra Fizjologii i Patofizjologii,
Uniwersytet Medyczny we Wrocławiu

Wrocław, 23.08.2023

OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: nawiązaniu współpracy międzyośrodkowej, analizie zgromadzonych danych, pisaniu manuskryptu, odpowiedzi na recenzje;

w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: nawiązaniu współpracy międzyośrodkowej, analizie zgromadzonych danych, pisaniu manuskryptu, odpowiedzi na recenzje;

w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: nawiązaniu współpracy międzyośrodkowej, analizie zgromadzonych danych, pisaniu manuskryptu, odpowiedzi na recenzje.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Podpis

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OŚWIADCZENIE

Oświadczam, że: w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: nadzorze merytorycznym nad metodologią przeglądu systematycznego, pisaniu artykułu, wsparciu w odpowiedzi na recenzje.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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OŚWIADCZENIE

Oświadczam, że: w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: gromadzeniu danych, pisaniu manuskryptu, uczestniczeniu w procesie analizy danych, przygotowaniu artykułu pod względem wymogów formalnych.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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Lek. Agata Zdanowicz-Ratajczyk
Katedra Radiologii,
Uniwersytet Medyczny we Wrocławiu

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OŚWIADCZENIE

Oświadczam, że: w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Zdanowicz A, Guzik M, Borkowski A, Gajewski P, Biegus J, Siennicka A, Pondel M, Berka P, Ponikowski P, Zymliński R. Novel Phenotyping for Acute Heart Failure-Unsupervised Machine Learning-Based Approach. Biomedicines. 2022 Jun 27;10(7):1514. doi: 10.3390/biomedicines10071514. PMID: 35884819; PMCID: PMC9313459** mój udział polegał na: pisaniu manuskryptu, uczestniczeniu w procesie analizy danych, przygotowaniu formy prezentacji wyników, przygotowaniu manuskryptu wedle wymogów wydawnictwa.

Wyrażam zgodę na wykorzystanie powyższych publikacji, których jestem współautorem, w rozprawie doktorskiej lekarza Szymona Urbana pt. "Zastosowanie metod sztucznej inteligencji w ocenie wybranych aspektów klinicznych w niewydolności serca."

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OŚWIADCZENIE

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w pracy: **Błaziak M, Urban S, Wietrzyk W, Jura M, Iwanek G, Stańczykiewicz B, Kuliczkowski W, Zymliński R, Pondel M, Berka P, Danel D, Biegus J, Siennicka A. An Artificial Intelligence Approach to Guiding the Management of Heart Failure Patients Using Predictive Models: A Systematic Review. Biomedicines. 2022 Sep 5;10(9):2188. doi: 10.3390/biomedicines10092188. PMID: 36140289; PMCID: PMC9496386.** mój udział polegał na: weryfikacji merytorycznej stworzonego artykułu, modyfikacji artykułu zgodnie z zaleceniami recenzentów;

w pracy: **Urban S, Błaziak M, Jura M, Iwanek G, Ponikowska B, Horudko J, Siennicka A, Berka P, Biegus J, Ponikowski P, Zymliński R. Machine Learning Approach to Understand Worsening Renal Function in Acute Heart Failure. Biomolecules. 2022 Nov 2;12(11):1616. doi: 10.3390/biom12111616. PMID: 36358966; PMCID: PMC9687716.** mój udział polegał na: konceptualizacji badania, nadzorze merytorycznym, modyfikacji artykułu zgodnie z zaleceniami recenzentów.

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10. Piśmiennictwo

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