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Analiza trendów hospitalizacji u pacjentów z reumatoidalnym zapaleniem stawów i zespołem Sjögrena

Analysis of Hospitalization Trends in Patients with Rheumatoid Arthritis and Sjögren's Disease

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1. Wykaz stosowanych skrótów

bDMARDs – biologiczne leki modyfikujące przebieg choroby (biologic Disease-Modifying Anti-Rheumatic Drugs)

CICU – kardiologiczny oddział intensywnej terapii (Cardiac Intensive Care Unit)

csDMARDs – klasyczne syntetyczne leki modyfikujące przebieg choroby (conventional synthetic Disease-Modifying Anti-Rheumatic Drugs)

DMARDs – leki modyfikujące przebieg choroby (Disease-Modifying Anti-Rheumatic Drugs)

ICU – oddział intensywnej terapii (Intensive Care Unit)

IL-6 – interleukina 6 (Interleukin-6)

FM – fibromialgia

OIOK – oddział intensywnej opieki kardiologicznej

OIT – oddział intensywnej terapii

RA – reumatoidalne zapalenie stawów (Rheumatoid Arthritis)

RZS – reumatoidalne zapalenie stawów

SjD – zespół Sjögrena (Sjögren's Disease)

TNF – czynnik martwicy nowotworów (Tumor Necrosis Factor)

tsDMARDs – celowane syntetyczne leki modyfikujące przebieg choroby (targeted synthetic Disease-Modifying Anti-Rheumatic Drugs)

2. Streszczenie w języku polskim

Choroby autoimmunologiczne tkanki łącznej, takie jak reumatoidalne zapalenie stawów (RZS) i zespół Sjögrena (SjD), stanowią istotne wyzwanie dla współczesnej medycyny ze względu na ich przewlekły przebieg, wielonarządowe powikłania oraz konieczność długotrwałego leczenia. Postępy w terapii tych schorzeń na przestrzeni dekad przyczyniły się do znacznej poprawy rokowania, jednak nie wyeliminowały poważnych konsekwencji wynikających z ich przebiegu oraz współistniejących chorób. Celem niniejszej rozprawy jest kompleksowa analiza tych zagadnień poprzez trzy powiązane tematycznie prace obejmujące historię leczenia RZS, hospitalizacje pacjentów z RZS w oddziałach intensywnej terapii oraz trendy hospitalizacji chorych na SjD w Polsce.

Pierwsza praca, ***" Evolving strategies in the treatment of rheumatoid arthritis: a historical perspective"***, przedstawia ewolucję terapii reumatoidalnego zapalenia stawów od starożytnych metod leczenia po nowoczesne terapie celowane. Na przestrzeni wieków podejście do leczenia RZS ulegało istotnym zmianom – od niezweryfikowanych praktyk medycznych po strategię ukierunkowaną na hamowanie procesów zapalnych i modulację układu odpornościowego. W XX wieku wprowadzono konwencjonalne syntetyczne leki modyfikujące przebieg choroby (csDMARDs), w tym metotreksat, który stał się złotym standardem leczenia. Kolejne przełomy nastąpiły w XXI wieku wraz z rozwojem biologicznych leków modyfikujących przebieg choroby (bDMARDs) oraz celowanych syntetycznych leków modyfikujących przebieg choroby (tsDMARDs). Współczesne badania koncentrują się na medycynie precyzyjnej, wykorzystującej biomarkery i nowe strategie immunomodulacyjne, co daje nadzieję na dalszą poprawę skuteczności terapii RZS.

Druga praca, ***"Hospitalizations of Patients with Rheumatoid Arthritis in Polish Intensive Care Units or Cardiac Intensive Care Units in 2011-2021 - Population Study"***, podejmuje temat hospitalizacji pacjentów z RZS wymagających leczenia w Oddziałach Intensywnej Terapii (OIT) i Oddziałach Intensywnej Opieki Kardiologicznej (OIOK). Analiza 3066 hospitalizacji wykazała rosnącą liczbę przyjęć, ze szczególnym wzrostem w 2021 roku, co mogło być związane z pandemią COVID-19. Istotną obserwacją były wysokie wskaźniki śmiertelności w OIT/OIOK(39,1%), szczególnie wśród pacjentów z chorobami układu

pokarmowego (58,5%) oraz zaburzeniami endokrynologicznymi/metabolicznymi (61,5%). Kluczowymi czynnikami ryzyka zgonu były: starszy wiek oraz nagły tryb przyjęcia, co podkreśla znaczenie wczesnej interwencji i optymalizacji leczenia pacjentów z RZS. Wyniki tej analizy wskazują na konieczność lepszego monitorowania chorych na RZS w celu zapobiegania ciężkim powikłaniom wymagającym intensywnej terapii.

Trzecia praca, "***Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjögren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis***", rozszerza analizę hospitalizacji na pacjentów z zespołem Sjögrena. Choroba ta, podobnie jak RZS, ma podłoże autoimmunologiczne, jednak jej dominującą manifestacją jest przewlekłe zapalenie gruczołów egzokrynnych, prowadzące do suchości błon śluzowych. Badanie obejmujące 13 999 hospitalizacji ujawniło, że kobiety stanowiły 90,3% hospitalizowanych, a średni wiek wynosił 57 lat. Odnotowano zmienność liczby hospitalizacji na przestrzeni lat, ze spadkiem w 2020 roku (prawdopodobnie w związku z pandemią COVID-19) oraz ponownym wzrostem w latach 2021-2023. Najczęstszymi współistniejącymi schorzeniami były choroby układu mięśniowo-szkieletowego (17,8%), sercowo-naczyniowego (16,6%) oraz endokrynologiczne (13,6%). Podobnie jak w przypadku RZS pacjenci hospitalizowani w trybie nagłym oraz osoby starsze wykazywały istotnie dłuższy czas hospitalizacji. Badanie to podkreśla konieczność poprawy diagnostyki i leczenia SjD w warunkach ambulatoryjnych, aby ograniczyć potrzebę hospitalizacji i poprawić jakość życia pacjentów.

Łącząc te trzy prace, można wyciągnąć wnioski dotyczące chorób autoimmunologicznych o różnym stopniu układowej manifestacji. Historia leczenia RZS pokazuje dynamiczny rozwój strategii terapeutycznych, które wpływają nie tylko na kontrolę samej choroby, ale także na zmniejszenie ryzyka powikłań mogących prowadzić do hospitalizacji i intensywnej terapii. Jednocześnie analiza hospitalizacji pacjentów z RZS i SjD ukazuje, że mimo postępu medycznego pacjenci z chorobami autoimmunologicznymi pozostają grupą szczególnie narażoną na poważne powikłania i wielochorobowość. Wyniki tych badań wskazują na konieczność wdrażania strategii prewencyjnych, wczesnej diagnostyki, ścisłego monitorowania pacjentów oraz interdyscyplinarnego podejścia w leczeniu schorzeń reumatycznych.

Zintegrowane podejście do leczenia i monitorowania pacjentów z chorobami autoimmunologicznymi jest kluczowe dla dalszej poprawy wyników leczenia i ograniczenia

potrzeby hospitalizacji. Dalsze badania powinny skupić się na ocenie skuteczności nowych strategii terapeutycznych, ich wpływu na częstość hospitalizacji oraz opracowaniu narzędzi predykcyjnych pozwalających na wczesną identyfikację pacjentów wysokiego ryzyka.

3. Streszczenie w języku angielskim

Analysis of Hospitalization Trends in Patients with Rheumatoid Arthritis and Sjögren's Disease

Autoimmune connective tissue diseases, such as rheumatoid arthritis (RA) and Sjögren's Disease (SjD), pose significant challenges to modern medicine due to their chronic nature, multi-organ complications, and the need for long-term treatment. Advances in the therapy of these conditions over the decades have led to substantial improvements in prognosis; however, they have not eliminated the severe consequences associated with disease progression and comorbidities. The objective of this dissertation is to provide a comprehensive analysis of these issues through three thematically related studies, covering the history of RA treatment, hospitalizations of RA patients in intensive care units, and hospitalization trends among SjD patients in Poland.

The first study, "Evolving Strategies in the Treatment of Rheumatoid Arthritis: A Historical Perspective," presents the evolution of rheumatoid arthritis therapy from ancient treatments to modern targeted therapies. Over the centuries, RA treatment approaches have undergone significant transformations—from unverified medical practices to strategies aimed at suppressing inflammation and modulating the immune system. The 20th century saw the introduction of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, which became the gold standard of treatment. Further breakthroughs occurred in the 21st century with the development of biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Contemporary research focuses on precision medicine, utilizing biomarkers and novel immunomodulatory strategies, offering hope for further improvements in RA therapy effectiveness.

The second study, "Hospitalizations of Patients with Rheumatoid Arthritis in Polish Intensive Care Units or Cardiac Intensive Care Units in 2011-2021 – Population Study," examines hospitalizations of RA patients requiring treatment in Intensive Care Units (ICUs) and Cardiac Intensive Care Units (CICUs). The analysis of 3,066 hospitalizations revealed an increasing number of admissions, with a marked rise in 2021, potentially linked to the COVID-19 pandemic. A significant observation was the high mortality rate in ICU/CICU settings

(39.1%), particularly among patients with gastrointestinal diseases (58.5%) and endocrine/metabolic disorders (61.5%). Key risk factors for mortality included older age and emergency admissions, highlighting the importance of early intervention and optimal management of RA patients. The findings underscore the necessity for improved monitoring of RA patients to prevent severe complications requiring intensive care.

The third study, "Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjögren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis," expands the hospitalization analysis to patients with Sjögren's disease. Similar to RA, SjD has an autoimmune basis, but its dominant manifestation is chronic inflammation of exocrine glands, leading to mucosal dryness. The study, encompassing 13,999 hospitalizations, revealed that women accounted for 90.3% of hospital admissions, with an average age of 57 years. Variability in hospitalization rates was noted over the years, with a decline in 2020 (likely due to the COVID-19 pandemic) followed by a resurgence in 2021-2023. The most common comorbid conditions included musculoskeletal diseases (17.8%), cardiovascular diseases (16.6%), and endocrine disorders (13.6%). As with RA, emergency hospitalizations and older age were associated with significantly longer hospital stays. This study highlights the need for improved outpatient diagnosis and management of SjD to reduce hospitalizations and enhance patients' quality of life.

By integrating these three studies, conclusions can be drawn regarding autoimmune diseases with varying degrees of systemic manifestation. The history of RA treatment demonstrates the dynamic development of therapeutic strategies, impacting not only disease control but also reducing the risk of complications leading to hospitalization and intensive care. Simultaneously, the analysis of RA and SjD hospitalizations reveals that despite medical advancements, patients with autoimmune diseases remain particularly vulnerable to severe complications and multimorbidity. These findings emphasize the need for preventive strategies, early diagnosis, close patient monitoring, and an interdisciplinary approach to rheumatic disease management.

A comprehensive approach to the treatment and monitoring of patients with autoimmune diseases is crucial for further improving treatment outcomes and reducing hospitalization needs. Future research should focus on evaluating the effectiveness of new

therapeutic strategies, their impact on hospitalization rates, and the development of predictive tools for early identification of high-risk patients.

4. WSTĘP

4.1. Reumatoidalne zapalenie stawów – wprowadzenie

Reumatoidalne zapalenie stawów to przewlekła, układowa choroba autoimmunologiczna charakteryzująca się zapaleniem błony maziowej stawów prowadzącym do ich stopniowego uszkodzenia. Choroba dotyczy głównie stawów, jednak może mieć także manifestacje pozastawowe obejmujące skórę, płuca, serce czy naczynia krwionośne. Najczęściej choroba zaczyna się symetrycznie w małych stawach rąk i stóp, a w miarę postępu może obejmować większe stawy oraz inne narządy.

Nieleczone RZS prowadzi do postępującego niszczenia stawów, nadżerek kostnych, a w konsekwencji do niepełnosprawności. Współczesne metody leczenia, w tym leki modyfikujące przebieg choroby (DMARDs), pozwalają na zahamowanie procesu zapalnego, poprawę jakości życia i ograniczenie powikłań. DMARDs obejmują trzy główne grupy: konwencjonalne syntetyczne (csDMARDs), biologiczne (bDMARDs) oraz celowane syntetyczne (tsDMARDs), co umożliwia indywidualizację terapii w zależności od przebiegu i zaawansowania choroby. Wczesna diagnostyka oraz kompleksowa opieka reumatologiczna mają kluczowe znaczenie dla spowolnienia progresji choroby i minimalizacji jej skutków.

4.2. Epidemiologia reumatoidalnego zapalenia stawów

Przegląd systematyczny badań populacyjnych, obejmujący 60 badań, wykazał, że globalna okresowa częstość występowania reumatoidalnego zapalenia stawów wynosiła 0,51% w latach 1955–2015 [1]. RZS występuje częściej w Europie Zachodniej i Północnej, natomiast niższe wskaźniki rozpowszechnienia zaobserwowano w Ameryce Środkowej i Południowej, a jeszcze niższe w Azji Wschodniej i Afryce [2]. W krajach Europy Północnej roczna zapadalność na RZS wynosi około 40 przypadków na 100 000 osób [3]. Częstość występowania RZS jest wyższa na obszarach miejskich (0,69%) w porównaniu z terenami wiejskimi (0,54%) [4].

Ponadto metaanaliza obejmująca 67 badań wykazała wzrost globalnej okresowej częstości występowania RZS o 9,75% w latach 1980–2019 [4]. Dane epidemiologiczne wskazują, że RZS jest częściej diagnozowane u kobiet niż u mężczyzn, a ryzyko zachorowania

w ciągu życia wynosi 3,6% u kobiet w porównaniu z 1,7% u mężczyzn [5]. Prawdopodobieństwo rozwoju RZS wzrasta również wraz z wiekiem, osiągając najwyższą zapadalność między 65. a 80. rokiem życia [6-7].

Istotną rolę w rozwoju RZS odgrywa predyspozycja genetyczna [8] — u osób posiadających krewnego pierwszego stopnia chorego na RZS ryzyko zachorowania jest trzykrotnie wyższe, natomiast w przypadku krewnych drugiego stopnia wzrasta dwukrotnie [9]. Dodatkowo czynniki takie jak dieta oraz wskaźnik masy ciała (BMI) mają wpływ na częstość występowania RZS – szczególnie ryzyko zwiększa się u osób z nadwagą lub otyłością (BMI ≥ 25 kg/m^2) oraz u osób stosujących dietę typu zachodniego, bogatą w tłuszcze nasycone, cukry proste i przetworzoną żywność. [10-11].

4.3. Przebieg reumatoidalnego zapalenia stawów i jego powikłania

RZS powoduje zapalenie błony maziowej stawów, prowadząc do ich obrzęku, bólu, sztywności porannej i ograniczenia ruchomości. Choroba najczęściej rozpoczyna się od zapalenia drobnych stawów rąk i stóp, zwłaszcza międzypaliczkowych bliższych i śródręczno-paliczkowych. W miarę postępu choroby mogą zostać zajęte duże stawy – kolanowe, barkowe, łokciowe czy biodrowe. Synovitis może powodować niszczenie struktur okołostawowych (ścięgien, więzadeł, kaletek maziowych), co prowadzi do deformacji i w konsekwencji upośledzenia ich funkcji. Do charakterystycznych deformacji należą: odchylenie łokciowe palców (ulnar deviation), deformacja typu butonierki, deformacja typu "szyi łabędziej", deformacja kciuka typu „Z” ("Z-thumb"), deformacja palców stóp typu "młotkowatego" (hammer toe). Szacuje się, że u około 40% pacjentów z RZS w ciągu dziesięciu lat od postawienia rozpoznania, wystąpi niepełnosprawność utrudniająca wykonywanie pracy oraz codziennych czynności [12].

Reumatoidalne zapalenie stawów to choroba układowa, której skutki u 15-25% pacjentów wykraczają poza układ mięśniowo-szkieletowy [13]. W zaawansowanych stadiach może prowadzić do zajęcia różnych narządów, przyczyniając się do poważnych powikłań i zwiększonej śmiertelności. Szczególnie istotne są powikłania sercowo-naczyniowe, płucne, hematologiczne, skórne, neurologiczne, nefrologiczne oraz okulistyczne, które mogą istotnie pogorszyć jakość życia pacjentów [14].

Jednym z najpoważniejszych powikłań RZS jest zwiększone ryzyko chorób sercowo-naczyniowych. Przewlekły stan zapalny sprzyja miażdżycy, co znacząco podnosi ryzyko zawału serca i udaru mózgu [15-17]. Dodatkowo mogą występować zapalenie osierdzia, wsierdzia oraz niewydolność serca [18]. Innym istotnym zagrożeniem jest podwyższone ryzyko zakrzepicy żylnej i zatorowości płucnej, które pozostaje wyższe nawet po skorygowaniu innych czynników ryzyka [19]. Zmiany płucne w RZS mogą prowadzić do śródmiąższowego włóknienia płuc, które może skutkować niewydolnością oddechową [20]. Wysięki opłucnowe są kolejnym częstym powikłaniem, które może prowadzić do przewlekłych dolegliwości oddechowych [21]. Co istotne, niektóre leki stosowane w leczeniu RZS, w tym metotreksat i leflunomid, mogą powodować uszkodzenie płuc [22-23]. Wśród manifestacji skórnych najbardziej charakterystycznym objawem są guzki reumatoidalne występujące u około 30% pacjentów [24]. Ponadto pacjenci z RZS częściej cierpią na paradontozę i przedwczesną utratę zębów [25]. Nieleczone RZS może również prowadzić do zapalenia naczyń powodującego owrzodzenia skóry i martwicę nerwów obwodowych [26]. Zaburzenia hematologiczne obejmują przede wszystkim niedokrwistość chorób przewlekłych [27]. U pacjentów z zespołem Felty'ego dochodzi do neutropenii, powiększenia śledziony i zwiększonej podatności na infekcje [28]. Istnieją doniesienia, że RZS wiąże się również z podwyższonym ryzykiem chłoniaków [29]. Choroba może również prowadzić do powikłań neurologicznych. Jednym z częstszych i tych stosunkowo łagodnych jest zespół cieśni nadgarstka [30] . W bardziej zaawansowanych przypadkach może dochodzić do neuropatii obwodowej [30]. Szczególnie niebezpieczne jest podwichnięcie stawu szczytowo-obrotowego, które w skrajnych sytuacjach może skutkować porażeniem, a nawet śmiercią [31]. Powikłania oczne obejmują zapalenie nadtwardówki i twardówki, które w ciężkich przypadkach może prowadzić do perforacji gałki ocznej . Często obserwuje się także suchość oczu spowodowaną limfocytarnym naciekiem w gruczołach łzowych, co może prowadzić do keratopatii i utraty wzroku [32]. RZS przyczynia się również do osteoporozy, która rozwija się w wyniku przewlekłego stanu zapalnego, zmniejszonej aktywności fizycznej oraz długotrwałego stosowania kortykosteroidów. W porównaniu do populacji ogólnej pacjenci z RZS mają o 60% do 100% większe ryzyko złamań [33]. Zwiększone ryzyko złamań stanowi istotne zagrożenie dla pacjentów zwłaszcza w starszym wieku. Nie można pominąć także wpływu RZS na układ nerkowy. Przewlekły stan zapalny może prowadzić do amyloidozy nerek, nazywanej inaczej skrobiawicą nerek [34].

Warto ponadto zauważyć, że pacjenci z RZS są również bardziej podatni na poważne infekcje, co jest efektem zarówno samej choroby jak i stosowania leków immunosupresyjnych, takich jak glikokortykosteroidy czy DMARDs. Osłabiona odpowiedź immunologiczna zwiększa ryzyko infekcji bakteryjnych, wirusowych oraz grzybiczych, które mogą prowadzić do ciężkich powikłań, a nawet sepsy [35].

Nie można również pominąć wpływu RZS na zdrowie psychiczne. Choroba ta znacząco obniża jakość życia, co prowadzi do częstego występowania depresji, zwłaszcza u pacjentów z długotrwałą, aktywną chorobą i ograniczeniami funkcjonalnymi. Metaanaliza z 2013 roku wykazała, że depresja dotyka od 17% do 39% osób z RZS, co dodatkowo komplikuje proces leczenia i prowadzi do gorszych wyników terapeutycznych [36].

Szacuje się, że nawet od 10% do 20% pacjentów z RZS spełnia kryteria rozpoznania fibromialgii (FM). FM może współistnieć z RZS jako tzw. wtórna fibromialgia. Przewlekły ból i stres związany z chorobą zapalną mogą prowadzić do centralnej sensytyzacji, czyli zwiększonej wrażliwości ośrodkowego układu nerwowego na bodźce bólowe – co jest kluczowym mechanizmem fibromialgii. Obecność FM u pacjenta z RZS może prowadzić do przeszacowania aktywności choroby (np. w DAS28), ponieważ skala oceniająca ból i tkliwość będzie zawyżona. Może to prowadzić do niepotrzebnej intensyfikacji leczenia immunosupresyjnego [37].

Narządowe manifestacje RZS mogą prowadzić do poważnych powikłań, które znacząco obniżają jakość życia pacjentów i zwiększają śmiertelność. Wczesne rozpoznanie i kompleksowe leczenie ukierunkowane na redukcję stanu zapalnego oraz kontrolę czynników ryzyka mają kluczowe znaczenie dla minimalizacji powikłań i poprawy rokowania w tej chorobie.

4.4. Leczenie i rokowanie w reumatoidalnym zapaleniu stawów

Leczenie reumatoidalnego zapalenia stawów (RZS) należy rozpocząć niezwłocznie po postawieniu rozpoznania, najlepiej w ciągu pierwszych sześciu tygodni od wystąpienia objawów. Wczesna interwencja znacząco zwiększa szanse na uzyskanie remisji, spowalnia progresję choroby i poprawia długoterminowe rokowanie. Zgodnie z zasadą „treat-to-target”, leczenie powinno być ukierunkowane na osiągnięcie trwałej remisji lub przynajmniej niskiej aktywności choroby, z częstą oceną skuteczności terapii, zwłaszcza w aktywnej fazie choroby

(co 1–3 miesiące). Jeśli po 3 miesiącach nie obserwuje się poprawy lub po 6 miesiącach nie osiągnięto celu terapeutycznego, leczenie należy zmodyfikować [38]

Podstawę leczenia stanowią leki modyfikujące przebieg choroby (DMARDs), które dzielą się na trzy główne grupy: konwencjonalne syntetyczne (csDMARDs), biologiczne (bDMARDs) oraz celowane syntetyczne (tsDMARDs). Leczenie należy rozpocząć od csDMARDs, z których lekiem pierwszego wyboru jest metotreksat. W przypadku przeciwwskazań lub nietolerancji metotreksatu, jako alternatywę zaleca się sulfasalazynę lub leflunomid [38].

Stosowanie glikokortykosteroidów (GKS) można rozważyć podczas rozpoczęcia lub zmiany terapii csDMARDs – w różnych dawkach i sposobach podawania – jednak ich dawkę należy jak najszybciej zmniejszyć i odstawić (zazwyczaj do 3 miesięcy), ponieważ przewlekłe stosowanie GKS nie jest zalecane. Ich kontynuacja powyżej 3 miesięcy może świadczyć o nieskuteczności leczenia podstawowego i konieczności jego zmiany [38]. Stosowanie glikokortykosteroidów, zwłaszcza długotrwałe, wiąże się z ryzykiem licznych działań niepożądanych, takich jak osteoporoza, cukrzyca, nadciśnienie, zaćma, jaskra, miopatia, zaburzenia psychiczne, zwiększona podatność na infekcje, zaburzenia metaboliczne oraz zmiany skórne i opóźnione gojenie ran [39].

W przypadku braku osiągnięcia celu terapeutycznego po terapii początkowej csDMARDs, dalsze postępowanie zależy od obecności czynników złego rokowania. W ich braku (np. przy umiarkowanej aktywności choroby, niskim mianie przeciwciał, braku nadżerek) można rozważyć zastosowanie innego csDMARD. Gdy natomiast obecne są czynniki niekorzystne (np. wysokie miano ACPA lub RF, wczesne nadżerki, wysoka aktywność choroby), zaleca się dodanie bDMARD lub – po dokładnej analizie ryzyka – rozważenie terapii inhibitorem kinaz JAK (tsDMARD) [38].

Do grupy bDMARDs należą inhibitory TNF-α (adalimumab, etanercept, infliksymab, golimumab, certolizumab pegol), inhibitory interleukiny-6 (tocilizumab, sarilumab), modulator kostymulacji limfocytów T (abatacept) oraz przeciwciało anty-CD20 (rituksymab). Z kolei tsDMARDs obejmują inhibitory JAK: tofacitinib, baricytynib, upadacytynib i filgotynib. Zarówno bDMARDs, jak i tsDMARDs powinny być stosowane w skojarzeniu z csDMARDs (najczęściej

metotreksatem), o ile jest to możliwe. W przypadku nietolerancji csDMARDs, inhibitory szlaku IL-6 (tocilizumab, sarilumab) lub tsDMARDs mogą wykazywać większą skuteczność w monoterapii niż inne bDMARDs [38].

W przypadku nieskuteczności leczenia biologicznym (bDMARD) lub celowanym syntetycznym lekiem (tsDMARD), należy rozważyć zastosowanie innego preparatu – z tej samej klasy (np. inny inhibitor TNF-α) lub o odmiennym mechanizmie działania (np. przejście z inhibitora TNF-α na inhibitor IL-6 lub JAK). Po osiągnięciu trwałej remisji możliwe jest stopniowe zmniejszanie dawek DMARDs, jednak całkowite odstawienie leczenia nie jest zazwyczaj zalecane, ponieważ wiąże się z istotnym ryzykiem nawrotu objawów choroby [38].

Podejmując decyzje terapeutyczne, należy uwzględniać nie tylko aktywność choroby, lecz także obecność chorób współistniejących, preferencje pacjenta, bezpieczeństwo leczenia oraz koszty terapii. Leczenie powinno zawsze być wynikiem wspólnej decyzji lekarza i pacjenta.

Szczegóły dotyczące ewolucji w podejściu do leczenia RZS zostały uwzględnione w pracy przeglądowej *„ Evolving strategies in the treatment of rheumatoid arthritis: a historical perspective”*.

Publikacja “*Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study.”* skupia się na najcięższych powikłaniach reumatoidalnego zapalenia stawów wymagających hospitalizacji na oddziałach OIT/OIOK, obejmujących powikłania infekcyjne, sercowo-naczyniowe i płucne.

4.5. Zespół Sjögrena – wstęp i epidemiologia

Zespół Sjögrena to przewlekła, układowa choroba autoimmunologiczna, w której układ odpornościowy atakuje gruczoły wydzielania zewnętrznego, głównie łzowe i ślinowe. Prowadzi to do ich stopniowego uszkodzenia i upośledzenia funkcji, co skutkuje suchością oczu (kseroftalmią) oraz suchością w jamie ustnej (kserostomią). Może również występować suchość w innych narządach, takich jak skóra, nerki, drogi oddechowe, układ pokarmowy, układ nerwowy. Choroba może mieć postać pierwotną (występującą samodzielnie) lub wtórną (współistniejącą z innymi chorobami autoimmunologicznymi, najczęściej reumatoidalnym zapaleniem stawów) [40].

Częstość występowania zespołu Sjögrena wynosi od trzech do sześciu przypadków na 100 000 osób rocznie [41-42], a choroba dotyka od 0,5% do 1% populacji [43]. Dziewięć na dziesięć osób z SjD stanowią kobiety [43-45]. Choć schorzenie najczęściej pojawia się w wieku średnim, może występować w każdej grupie wiekowej [46]. Podobnie jak w reumatoidalnym zapaleniu stawów ryzyko zachorowania na SjD zwiększa posiadanie krewnego pierwszego stopnia z chorobą autoimmunologiczną [47]. Mimo że mężczyźni rzadziej zapadają na SjD, u nich pierwotna postać choroby często ma cięższy przebieg [48]. Częstość występowania SjD wzrasta wraz z wiekiem, a średni wiek zachorowania wynosi od 40 do 60 lat. Szacuje się, że nawet połowa przypadków może pozostawać niezdiagnozowana lub niezgłoszona [41,49-51].

4.6. Przebieg zespołu Sjögrena, powikłania i rokowanie

Zespół Sjögrena to choroba autoimmunologiczna, w której dochodzi do uszkodzenia gruczołów wydzielania zewnętrznego, co skutkuje uogólnioną suchością błon śluzowych. Niedobór łez wywołuje uczucie „piasku" pod powiekami, światłowstręt oraz nadwrażliwość na bodźce środowiskowe, co może skutkować zakażeniami i uszkodzeniem rogówki [46]. Towarzyszy temu często zaczerwienienie oczu i poszerzenie naczyń spojówki gałkowej. W obrębie jamy ustnej upośledzenie funkcji ślinianek prowadzi do trudności w połykaniu, częstych infekcji i przyspieszonej próchnicy zębów [46,52-53]. Dodatkowo chorzy zgłaszają pieczenie, zaburzenia smaku, problemy z ciągłym mówieniem oraz konieczność nocnego nawadniania. W badaniu fizykalnym stwierdza się suchą, czerwoną i lepką śluzówkę, popękany język oraz charakterystyczne ubytki próchnicowe [46]. Proces chorobowy obejmuje także górne drogi oddechowe – gardło, krtań i oskrzela – co sprzyja występowaniu przewlekłego kaszlu, chrypki i nawracających infekcji [46,54-55]. Zajęcie dodatkowych gruczołów zewnątrzwydzielniczych może objawiać się suchością w nosie, części ustnej gardła, a u kobiet również w obrębie pochwy.

Wśród nieswoistych objawów ogólnych często obserwuje się stan podgorączkowy lub gorączkę, spadek masy ciała oraz przewlekłe zmęczenie, które nierzadko towarzyszą wczesnej fazie choroby. Zespół Sjögrena może prowadzić do uogólnionych powikłań, obejmujących wiele narządów i układów, takich jak skóra, układ ruchu, oddechowy, sercowo-naczyniowy, moczowy, pokarmowy, nerwowy oraz krwiotwórczy [46].

Skóra pacjentów z zespołem Sjögrena staje się wyraźnie odwodniona, podatna na świąd i złuszczanie, a towarzyszące zmiany zapalne w naczyniach włosowatych mogą prowadzić do powstania plamicy i owrzodzeń [41,46]. Powikłaniami ze strony układu ruchu są artralgia oraz niedestrukcyjne zapalenie stawów, które występują łącznie u ok. 41% pacjentów [56]. Zespół Sjögrena może prowadzić do różnych powikłań płucnych (9-20% pacjentów). Powikłania te obejmują choroby śródmiąższowe płuc (ILD), zmiany w drogach oddechowych oraz zaburzenia limfoproliferacyjne. Manifestacje ILD w tej chorobie obejmuje 45% przypadków niespecyficznego śródmiąższowego zapalenia płuc (NSIP), 16% zwykłego śródmiąższowego zapalenia płuc (UIP), 7% organizującego się zapalenia płuc, 15% limfocytarnego śródmiąższowego zapalenia płuc (LIP) oraz 17% innych patologii. Objawami zajęcia układu oddechowego są najczęściej przewlekły kaszl, duszność i świszczący oddech [57]. Manifestacje kardiologiczne w SjD są rzadkie, najszerzej opisaną wydaje się przyspieszony proces miażdżycy w naczyniach [58]. W układzie moczowym mogą pojawić się kwasica cewkowa, białkomocz i kamica nerkowa, manifestacje nerkowe dotykają ok. 5% pacjentów [59]. Suchość błon śluzowych przewodu pokarmowego sprzyja zaburzeniom trawienia, refluksowi i zapaleniu żołądka, natomiast trzustka może wykazywać niewydolność zewnątrzwydzielniczą [60]. Incydentalnie może dochodzić również do autoimmunologicznego zapalenia wątroby [61]. Zespół Sjögrena może prowadzić do zajęcia zarówno obwodowego, jak i ośrodkowego oraz autonomicznego układu nerwowego (8,5–70% pacjentów), przy czym najczęściej występuje przewlekła czuciowa polineuropatia aksonalna. Rzadziej obserwuje się zmiany ośrodkowe przypominające stwardnienie rozsiane, zapalenie rdzenia, uszkodzenia nerwów czaszkowych oraz objawy autonomiczne, takie jak hipotonia ortostatyczna czy zaburzenia motoryki przewodu pokarmowego. [62]. Zmiany w układzie krwiotwórczym obejmują niedokrwistość, leukopenię i trombocytopenię, Chłoniaki rozwijają się u około 5–10% pacjentów z pierwotnym zespołem Sjögrena, co oznacza, że ryzyko ich wystąpienia jest ok. 16–44 razy wyższe niż w populacji ogólnej. Najczęściej występuje chłoniak strefy brzeżnej z komórek B typu MALT (mucosa-associated lymphoid tissue), rzadziej chłoniaki z dużych komórek B (DLBCL). Czynniki ryzyka obejmują m.in. krioglobulinemię, powiększenie ślinianek, limfadenopatię, splenomegalię, neutropenię oraz niskie stężenia dopełniacza C4 [63]. W przebiegu choroby może dochodzić do powiększenia ślinianek, zwłaszcza przyusznych, może być obustronne lub jednostronne. Węzły chłonne u części chorych ulegają powiększeniu, a w przypadku gwałtownego wzrostu ich rozmiarów może to sugerować rozwój chłoniaka [64].

W przebiegu choroby często dochodzi do zapaleń tarczycy, a także do zapaleń naczyń, którym może towarzyszyć objaw Raynauda [65-66]. U kobiet mogą wystąpić zaburzenia cyklu miesiączkowego, suchość pochwy oraz zwiększone ryzyko infekcji i endometriozy, a w przypadku obecności przeciwciał anty-SS-A/Ro istnieje ryzyko bloku serca u płodu [67-68].

Zespół Sjögrena jest chorobą obciążającą, znacznie obniżającą jakość życia pacjentów [69]. Mimo wpływu na zdolność do pracy i podwyższenia wskaźnika niepełnosprawności jest chorobą ze śmiertelnością podobną do populacji ogólnej [70-71]. Obniżenie jakości życia jest podobne do tego obserwowanego w reumatoidalnym zapaleniu stawów, toczniu rumieniowatym układowym czy fibromialgii [72].

4.7. Uzasadnienie połączenia wybranych prac w cykl publikacji

Wskazane trzy publikacje stanowią spójny cykl badawczy dotyczący hospitalizacji pacjentów z reumatoidalnym zapaleniem stawów oraz zespołem Sjögrena, co uzasadnia ich połączenie w jedną rozprawę doktorską pod tytułem " Analiza trendów hospitalizacji u pacjentów z reumatoidalnym zapaleniem stawów i zespołem Sjögrena ".

1. Artykuł dotyczący hospitalizacji pacjentów z zespołem Sjögrena:
    - Obejmuje analizę epidemiologiczną hospitalizacji pacjentów z SjD w Polsce w latach 2012–2023, identyfikując kluczowe trendy, czynniki ryzyka oraz wpływ chorób współistniejących na długość pobytu w szpitalu.
    - Podkreśla systemowe powikłania SjD oraz konieczność optymalizacji strategii leczenia w celu redukcji hospitalizacji.
    - Akcentuje niedostatecznie zbadane aspekty hospitalizacji pacjentów z SjD w porównaniu z innymi chorobami autoimmunologicznymi.
2. Artykuł dotyczący hospitalizacji pacjentów z reumatoidalnym zapaleniem stawów na oddziałach intensywnej terapii:
    - Skupia się na pacjentach z RZS wymagających leczenia w oddziałach intensywnej terapii (ICU/CICU) w latach 2011–2021.
    - Analizuje czynniki ryzyka hospitalizacji na ICU/CICU, długość pobytu oraz śmiertelność pacjentów z RZS, identyfikując krytyczne powikłania, takie jak choroby sercowo-naczyniowe i płucne.

- Podkreśla wzrost liczby hospitalizacji w 2021 r., prawdopodobnie związany z pandemią COVID-19, co ukazuje dodatkowe czynniki wpływające na zdrowie pacjentów z RZS.

3. Przeglądowy artykuł na temat ewolucji leczenia reumatoidalnego zapalenia stawów:
    - Opisuje historyczny rozwój metod leczenia RZS, od terapii empirycznych po nowoczesne terapie celowane.
    - Ukazuje wpływ immunoterapii i inhibitorów JAK na poprawę wyników leczenia pacjentów.
    - Stanowi teoretyczne tło dla analizowanych w dwóch pozostałych artykułach zmian w hospitalizacjach pacjentów z RZS oraz powiązanego z nim SjD.

Spójność i komplementarność cyklu

Połączenie tych trzech artykułów w jeden cykl badawczy jest uzasadnione kilkoma aspektami:

- Wspólna problematyka – wszystkie trzy artykuły dotyczą pacjentów z chorobami reumatycznymi o podłożu autoimmunologicznym - RZS i SjD.
- Kompleksowość analizy – prace obejmują zarówno aspekty kliniczne (hospitalizacje, powikłania, śmiertelność), jak i przegląd strategii terapeutycznych, co pozwala na całościowe spojrzenie na problematykę leczenia i opieki nad tymi pacjentami.
- Nowatorski charakter – brak równie rozległych dotychczasowych badań systematycznie analizujących hospitalizacje pacjentów z SjD oraz ciężkie przypadki RZS wymagające leczenia na OIT w Polsce.
- Zastosowanie praktyczne – wyniki badań mogą wpłynąć na politykę zdrowotną, wskazując na potrzebę lepszego monitorowania pacjentów z RZS i SjD, wcześniejszej interwencji i optymalizacji leczenia.

  Dodatkowym aspektem praktycznym jest wskazanie na istotność skrupulatnego prowadzenia dokumentacji medycznej, jako potencjalnego źródła wiedzy epidemiologicznej.

Komentarz dotyczący osiągnięcia naukowego na tle dotychczasowego stanu wiedzy

Przedstawiony cykl publikacji dostarcza istotnych danych, które poszerzają obecną wiedzę na temat hospitalizacji pacjentów z RZS i SjD. Dotychczasowe badania skupiały się głównie na mechanizmach patogenetycznych oraz skuteczności poszczególnych terapii, podczas gdy analizy epidemiologiczne hospitalizacji były ograniczone.

Najważniejsze osiągnięcia naukowe w kontekście dotychczasowej wiedzy

1. Nowatorska analiza hospitalizacji pacjentów z SjD:
    - Dotychczas badania nad SjD koncentrowały się głównie na patofizjologii i leczeniu, a analiza hospitalizacji była marginalizowana.
    - Przedstawiona praca dostarcza pierwszej tak szerokiej analizy hospitalizacji pacjentów z SjD w Polsce uwzględniającej czynniki ryzyka oraz dynamikę zmian w latach 2012–2023.
2. Pierwsza populacyjna analiza pacjentów z RZS hospitalizowanych na OIT:
    - W literaturze istnieje niewiele badań dotyczących hospitalizacji pacjentów z RZS na OIT.
    - Przedstawiona analiza dostarcza unikalnych danych o śmiertelności i czynnikach ryzyka, co może przyczynić się do lepszego zarządzania pacjentami z ciężkim przebiegiem RZS.
3. Historyczny przegląd ewolucji leczenia RZS jako kontekst dla badań epidemiologicznych:
    - Przeglądowy artykuł pozwala osadzić wyniki badań epidemiologicznych w kontekście postępu w terapii RZS.
    - Wykazuje, jak zmiany w leczeniu wpływały na hospitalizacje i ich wyniki, co jest kluczowe dla dalszego kształtowania strategii terapeutycznych.

Wpływ wyników na przyszłą praktykę kliniczną

- Wyniki badań mogą wpłynąć na optymalizację leczenia ambulatoryjnego pacjentów z SjD i RZS, minimalizując konieczność hospitalizacji.

- Mogą także przyczynić się do poprawy strategii leczenia pacjentów wymagających intensywnej terapii oraz wskazać na potrzebę wczesnej interwencji w grupach wysokiego ryzyka.
- Identyfikacja czynników ryzyka ciężkiego przebiegu choroby może prowadzić do lepszego dostosowania terapii do indywidualnych potrzeb pacjenta.

Podsumowanie

Przedstawiony cykl publikacji tworzy spójne i kompleksowe opracowanie dotyczące hospitalizacji pacjentów z RZS i SjD. Połączenie tych prac w jedną rozprawę doktorską jest w pełni uzasadnione zarówno pod względem naukowym, jak i praktycznym. Badania dostarczają nowych danych epidemiologicznych, które mogą przyczynić się do poprawy opieki nad pacjentami i optymalizacji strategii leczenia. Na tle dotychczasowego stanu wiedzy praca ta wnosi istotne, nowatorskie aspekty, szczególnie w kontekście hospitalizacji pacjentów z chorobami autoimmunologicznymi w Polsce.

5. Cel pracy

Celem pracy doktorskiej jest wieloaspektowa analiza trendów hospitalizacji pacjentów z reumatoidalnym zapaleniem stawów i zespołem Sjögrena w Polsce, z uwzględnieniem dynamiki przyjęć szpitalnych, charakterystyki demograficzno-klinicznej hospitalizowanych pacjentów, czynników ryzyka ciężkich powikłań oraz ich wpływu na długość hospitalizacji i śmiertelność. Istotnym elementem pracy jest także analiza historycznej ewolucji strategii terapeutycznych w RZS, która pozwala osadzić współczesne wyzwania kliniczne i organizacyjne w szerszym kontekście zmian w podejściu do leczenia tej choroby.

Wybór właśnie tych dwóch jednostek chorobowych wynika z faktu, że zarówno reumatoidalne zapalenie stawów, jak i zespół Sjögrena należą do najczęściej występujących autoimmunologicznych chorób reumatycznych. RZS jest najczęstszą układową chorobą zapalną tkanki łącznej, natomiast zespół Sjögrena – zarówno pierwotny, jak i wtórny – zajmuje czołowe miejsce pod względem częstości w tej grupie schorzeń. Obie choroby charakteryzują się nie tylko wysokim rozpowszechnieniem, ale także licznymi powikłaniami narządowymi i znaczącym wpływem na jakość życia oraz rokowanie pacjentów. Dodatkowo, zespół Sjögrena często współwystępuje z RZS, co dodatkowo uzasadnia ich wspólną analizę w ramach jednej pracy doktorskiej.

Połączenie populacyjnej analizy hospitalizacji z przeglądem zmian w leczeniu RZS umożliwia całościowe spojrzenie na obciążenie systemu opieki zdrowotnej, specyfikę współchorobowości, wyznacza kierunek dalszych badań analizujących, jak postęp terapeutyczny może przekładać się na zmniejszenie ryzyka powikłań i hospitalizacji. Wyniki rozprawy mogą przyczynić się do optymalizacji opieki nad pacjentami z RZS i zespołem Sjögrena, zarówno w kontekście wczesnej diagnostyki, monitorowania chorób współistniejących, jak i efektywnego planowania strategii terapeutycznych i organizacyjnych w systemie ochrony zdrowia.

6. Publikacje wchodzące w skład cyklu

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Evolving strategies in the treatment of rheumatoid arthritis: a historical perspective

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Abstract

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by joint inflammation, degradation of cartilage and bone, and potential systemic effects. This paper provides a comprehensive historical overview of RA treatment, tracing the evolution from ancient empirical methods to modern targeted therapies.

Advancements in the understanding of RA's immunopathology have led to the development of conventional, biological, and targeted disease-modifying antirheumatic drugs, including tumor necrosis factor α inhibitors and Janus kinase inhibitors. These innovations have been pivotal in transforming RA management, allowing for more personalized and effective treatment strategies.

The historical progression in RA treatment reflects a shift from symptomatic management to targeted interventions aimed at the underlying mechanisms of the disease. This shift has not only improved clinical outcomes but also enhanced the quality of life for those affected by RA, underscoring the importance of ongoing research and adaptation of therapeutic strategies.

Key words: rheumatoid arthritis, methotrexate, conventional synthetic DMARD, biologic DMARD, JAK inhibitor.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown origin, primarily characterized by inflammation of the joint's synovial membrane, which leads to the degradation of cartilage and bone, and joint deformities. While RA primarily impacts joints, its effects can extend to other organs and body systems, highlighting its complexity and systemic nature.

Rheumatoid arthritis manifests in various ways, but the most common symptoms include pain, swelling, and stiffness in the joints, particularly worsening after periods of inactivity. Morning stiffness, which can last an hour or more, is often an early indicator of RA [1]. Additionally, RA can cause fatigue, fever, and a loss of appetite, further impacting the general health of patients. This pain and fatigue can hinder basic daily activities, and progressive joint deformities can lead to permanent disability. The disease restricts work ability and significantly reduces quality of life, increasing the risk of depression and social isolation [2].

Managing RA involves a comprehensive approach that includes pharmacological strategies to reduce disease activity and alleviate symptoms, as well as non-pharmacological measures such as physiotherapy and psychological support. The development of modern therapeutic options, particularly biological disease-modifying drugs, Janus kinase (JAK) inhibitors, has significantly improved the management of RA. Despite these advancements, RA remains an incurable condition.

This paper aims to provide a thorough examination of the history of RA treatment. Reviewing the treatment history demonstrates a shift in therapeutic philosophy – from passive and symptom-relieving strategies to proactive and targeted early interventions aimed at achieving remission.

Ancient and medieval treatment strategies

In ancient and medieval times, diseases and their underlying causes were poorly understood and classified, and due to the absence of the scientific method and

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evidence-based medicine, treatment strategies were not adequately verified for effectiveness and safety. Methods such as various herbal therapies, bloodletting (phlebotomy), and the use of laxatives were employed. Although these practices were widely accepted and utilized, they were often ineffective and could even worsen the patients' condition.

The 19th century: beginnings of modern rheumatology

The 19th century marked a pivotal moment in the history of medicine, characterized by significant advances in medical sciences. The first accurate description of RA was provided by the French physician Augustin Jacob Landré-Beauvais in 1800. Landré-Beauvais' work was the first to define RA as a distinct disease, differentiating it from other forms of arthritis that had been known and described earlier [3].

The 20th century: the evolution of pharmacotherapy

Discovery of glucocorticosteroids and their impact on rheumatoid arthritis treatment

Glucocorticosteroids (GCs), discovered in the 1940s, quickly became a crucial tool in the treatment of RA. Philip Hench and his colleagues pioneered the use of cortisone, one of the first GCs, in the treatment of RA, an innovation that earned them the Nobel Prize in Physiology or Medicine in 1950 [4].

Glucocorticosteroids act at the cellular level by binding to cytoplasmic GCs receptors. Once activated, the receptor moves to the cell nucleus, where it regulates the expression of genes responsible for the inflammatory response, inhibiting the production of pro-inflammatory cytokines. This suppresses the inflammatory process, providing relief from symptoms such as pain and joint swelling. Oral and intra-articular administration of cortisone and hydrocortisone began in 1950–1951 [5]. Although GCs are effective in quickly controlling acute RA flare-ups, long-term use is associated with the risk of numerous serious side effects, including osteoporosis, increased susceptibility to infections, and metabolic disorders.

Currently, there is a growing consensus that GCs should be used as a bridging therapy in the treatment of RA, pending the full effect of disease-modifying antirheumatic drugs (DMARDs) [6].

Development and use of disease-modifying antirheumatic drugs

Research on RA has led to a consensus that the primary goal of treating this disease is to achieve remission or low disease activity as quickly as possible. The development of DMARDs has played a crucial role in achieving this goal.

Gold salts

Gold salts, which began to be used in the treatment of RA in 1929, were among the first DMARDs [7]. This group included auranofin, aurothiosulfate, aurothiopropanol sulfonate, aurothiomalate, aurothioglucose, and sodium aurothiomalate, which reduce inflammation and disease progression. Their mechanism of action was not fully understood, but they could inhibit the activity of immune cells and cytokines [8]. With the exception of auranofin, all gold salts were administered via intramuscular injections [9]. Despite initial enthusiasm (approximately 50% of patients achieved remission), the use of gold salts has declined over the years due to potential serious side effects. Common adverse effects included abdominal discomfort, nausea, itching, skin rash, hives, proteinuria, fatal hypersensitivity reactions, kidney dysfunction, and bone marrow suppression [9]. Today, gold salts are rarely used, mainly due to the development of newer, more effective, and safer DMARDs and biological therapies.

Sulfasalazine

Originally used to treat inflammatory bowel diseases, sulfasalazine was first applied in the treatment of RA in the 1940s [10]. The mechanism of action of sulfasalazine in RA is not fully elucidated, but it is believed to have both anti-inflammatory and immunomodulatory effects [11]. This medication is particularly useful in treating milder forms of RA, early RA, and often as part of combination therapies [10, 12, 13]. Sulfasalazine can cause side effects, such as gastrointestinal disturbances and skin reactions [12, 14]. Adverse effects usually manifest within the first 3 months of treatment [10]. Unlike many DMARDs, sulfasalazine may be suitable for pregnant women or those planning pregnancy due to its lower teratogenic risk. Combination therapy with other DMARDs, especially methotrexate (MTX), appears to be more effective than single DMARD therapy [10, 13].

Antimalarial drugs

Antimalarial drugs, such as hydroxychloroquine, were adapted for the treatment of RA in the 1950s. Their mechanism involves blocking the function of lysosomes in the antigen processing pathway, inhibiting the signaling functions of NADPH oxidase and Toll-like receptors (TLRs), reducing levels of pro-inflammatory cytokines, and limiting the activation of T and B lymphocytes [15]. According to European Alliance of Associations

for Rheumatology (EULAR) recommendations from 2022, hydroxychloroquine is regarded as a relatively weak DMARD, appropriate only for patients with early, mild RA when other conventional synthetic DMARDs are unsuitable due to contraindications or intolerance [16]. Hydroxychloroquine is generally safe for long-term use, but it has the potential to cause retinopathy. Consequently, it is recommended that patients without major risk factors undergo annual fundoscopy after five years of taking acceptable doses [17].

Methotrexate

Methotrexate was introduced into the therapy for RA in the 1980s [18]. This drug was synthesized in 1948 and was first tested in the treatment of patients with psoriasis and RA in 1951 [19]. There are many hypotheses explaining the mechanism of MTX efficacy in the treatment of RA. These include folate antagonism, adenosine signaling, polyamine inhibition, generation of reactive oxygen species, and many others. Methotrexate (amethopterin) is a structural analog of folic acid. Found in green vegetables, folic acid is converted by dihydrofolate reductase (DHFR) into tetrahydrofolic acid, essential for purine and thymidine synthesis. Methotrexate binds to and deactivates DHFR, acting as an antimetabolite to prevent purine synthesis. Additionally, it blocks the conversion of glycine to serine and homocysteine to methionine, inhibiting protein synthesis. Methotrexate also inhibits the enzyme responsible for adenosine production and release, increasing adenosine levels in human fibroblast and umbilical endothelial cell cultures. Excess adenosine suppresses immune cell activity and inhibits granulocyte functions and the production of pro-inflammatory cytokines (tumor necrosis factor α [TNF-α], interleukin-6 [IL-6], etc.) by monocytes [18]. Methotrexate has gained the title of the first-choice drug in the treatment of RA worldwide among DMARDs. Methotrexate is not only typically the first-line drug in RA treatment but also enhances the effect of most biological agents used as subsequent lines of treatment in RA [19]. An algorithm for treating RA patients has been developed through observations of treatment efficacy, recommending early and aggressive treatment with doses of MTX therapy (15–25 mg/week) [20]. There is some evidence that subcutaneous administration of the drug is significantly more effective than the oral administration of the same MTX dose – this approach may increase the drug's bioavailability and minimize gastrointestinal side effects [19]. The current treatment goal should be to achieve low disease activity quickly (preferably within 3–6 months) [20]. The use of MTX may be limited due to potential side effects such as liver damage, hematopoietic disorders, and pulmonary toxicity, necessitating regular monitoring of liver and lung functions [21]. Methotrexate remains a standard in RA treatment, offering both efficacy in controlling disease activity and a relatively low side effect profile compared to other medications. Moreover, combining MTX with biologics and JAK inhibitors significantly improves clinical outcomes compared to MTX monotherapy [22].

Advances in molecular profiling, such as RNA sequencing from peripheral blood mononuclear cells, are beginning to elucidate the complex biological responses that underpin individual differences in MTX efficacy.

Leflunomide

Leflunomide (LEF) is a DMARD introduced for the treatment of RA in the 1990s. The active metabolite of LEF inhibits the enzyme dihydroorotate dehydrogenase in the pyrimidine biosynthesis pathway. This inhibition leads to a reduction in T-cell proliferation and other modifications in the immune response [23, 24]. Leflunomide remains a practical choice, particularly in mild to moderate cases. According to the latest EULAR recommendations, LEF should be considered when MTX is not suitable, with a suggested dose of 20 mg per day [16]. This recommendation underscores its established efficacy and safety profile. A systematic review by Alfaro-Lara et al. [23] comparing LEF with MTX showed that LEF is as effective as MTX in achieving ACR20 (American College of Rheumatology 20) response rates, although MTX slightly outperformed LEF in reducing the swollen joint count. Both drugs displayed similar efficacy in reducing tender joint count, physician global assessment, Health Assessment Questionnaire Disability Index (HAQ-DI), and serum CRP levels. Leflunomide, however, was linked to increased liver enzymes, whereas MTX caused more gastrointestinal complaints.

The most commonly reported adverse events in patients treated with LEF included diarrhea, respiratory infections, nausea, headaches, rash, increased serum hepatic aminotransferases, dyspepsia, and alopecia [24].

The role of non-pharmacological treatment and the shift towards comprehensive care

As progress was made in pharmacological treatment, the role of physiotherapy and rehabilitation in the treatment of RA also increased. Physiotherapy, focusing on improving range of motion, muscle strength, and overall functioning, has become an element of comprehensive care for patients with RA. Nonpharmacological therapy includes therapeutic patient education, physical exercises, physical modalities, orthoses, assistive devices, and balneotherapy, as well as dietary interventions [25].

The breakthrough of biologic disease-modifying antirheumatic drugs targeting specific components of the immune system

Biological drugs are preparations produced using advanced biotechnological technologies involving living organisms or their components. Unlike traditional chemically synthesized drugs, biological drugs are usually proteins that mimic natural processes occurring in the body. Their high specificity of action and ability to interact with the immune system make them effective tools in treating autoimmune diseases.

The late 20th century brought a breakthrough in the treatment of RA with the introduction of biological DMARDs (biologic DMARDs, bDMARDs). Biological DMARDs are a group of drugs that specifically target certain components of the immune system responsible for the inflammatory process in RA. Instead of the general suppression of immunity, as is the case with traditional DMARDs, biologic disease-modifying drugs allow for a more targeted and effective approach to treatment.

In the treatment of RA, biological drugs act on various elements of the immune system by blocking key cytokines such as TNF-α or IL-1, IL-6 and modulating the activity of B and T lymphocytes. Monoclonal antibodies and fusion proteins are the most commonly used classes of biological drugs in RA therapy. The first bDMARDs were TNF-α inhibitors, introduced in the 1990s. Drugs such as infliximab (INF), etanercept (ETA), adalimumab (ADA), certolizumab pegol, and golimumab (GOL) revolutionized the treatment of RA, offering patients the possibility of significantly reducing symptoms and slowing disease progression. A summary of clinical trial findings on the efficacy and safety of bDMARDs for treating RA is presented in Table I.

Biological drugs in the treatment of RA offer a new quality of therapy, enabling more effective symptom control, slowing disease progression, and improving patients' quality of life. Their introduction into clinical practice represents a breakthrough in RA management; however, challenges related to costs, availability, and potential side effects remain significant research areas.

Tumor necrosis factor α inhibitors

Tumor necrosis factor α is a crucial pro-inflammatory cytokine central to the pathogenesis of RA. It is primarily produced by macrophages and T lymphocytes and promotes the secretion of other pro-inflammatory cytokines and chemokines, attracting inflammatory cells to the joints. Additionally, TNF-α activates fibroblasts and osteoclasts. Activated fibroblasts overexpress cathepsins and matrix metalloproteinases, leading to cartilage and bone destruction. Activated osteoclasts contribute to synovial hyperplasia and angiogenesis [26].

Biologic DMARDs from the TNF-α inhibitor group, such as ADA, INF, ETA, GOL, and certolizumab pegol, are designed to neutralize the action of TNF-α. These drugs bind directly to TNF-α molecules, preventing them from interacting with receptors on the surface of cells, thereby blocking further pro-inflammatory signaling. As a result, the activation and recruitment of inflammatory cells are reduced, leading to a decrease in the production of other pro-inflammatory cytokines and chemokines, thereby limiting the overall inflammatory response [26].

Consequently, TNF-α inhibitors reduce the activity of osteoclasts and the production of extracellular matrix-degrading enzymes by fibroblasts and chondrocytes, inhibiting the destructive processes in cartilage and bone. Clinical studies have shown that these drugs can significantly reduce RA symptoms such as pain, swelling, and joint stiffness, as well as improving patients' physical function. Additionally, they can slow the radiological progression of joint damage, leading to long-term improvements in patients' quality of life [27].

The use of TNF-α inhibitors is associated with a range of adverse effects and potential dangers. One of the most serious risks is the increased likelihood of infections, as TNF-α plays a crucial role in the body's defense against infections. Blocking TNF-α can weaken the immune response, making patients more susceptible to bacterial, viral, and fungal infections, including severe infections such as tuberculosis. Tumor necrosis factor α inhibitors may also increase the risk of developing cancers, particularly lymphomas and other hematologic malignancies. Additionally, the use of these drugs can lead to new autoimmune diseases or exacerbate existing ones, such as systemic lupus erythematosus and autoimmune inflammatory liver disease. Some patients may experience allergic reactions such as diffuse drug rash. There are also reports of worsening heart failure and the occurrence of demyelinating neurological diseases such as multiple sclerosis [28]. Therefore, the use of TNF-α inhibitors requires a careful assessment of benefits and risks and regular monitoring of patients during therapy.

21st century: advances in understanding the immunopathogenesis of rheumatoid arthritis leading to targeted therapies

Increasing understanding of the immunopathogenesis mechanisms of RA has been crucial in the development of biological therapies. Studies have revealed the complexity of interactions between immune cells, cytokines, and other molecular factors contributing to inflammation and joint destruction. These discoveries

Table I. Summary of clinical trial findings on the efficacy and safety of bDMARDs in RA treatment

bDMARD	First author, year of publication, trial name, reference	Conclusions
INF	Maini et al. 1999, ATTRACT [57]	In a 30-week period, treatment combining INF and MTX proved to be more effective than MTX alone for patients with active RA who had not responded to MTX previously
	Smolen et al. 2006, ASPIRE [58]	Elevated C-reactive protein levels, high erythrocyte sedimentation rate, or ongoing disease activity was linked to increased radiographic progression in patients treated with MTX alone. In contrast, patients receiving both MTX and INF showed minimal radiographic progression, regardless of the presence of these traditional predictors
ETA	Genovese et al. 2002, ERA [59]	As a monotherapy, ETA was safe and more effective than MTX in reducing disease activity, preventing structural damage, and decreasing disability over a 2-year period in patients with early, aggressive RA
	van der Heijde et al. 2006, TEMPO [60]	Over a 2-year period, combining ETA with MTX reduced disease activity, slowed radiographic progression, and improved function more effectively than either treatment alone. The combination therapy did not result in increased toxicity
	Emery et al. 2008, COME [61]	In patients with early severe RA, achieving both clinical remission and radiographic non-progression within 1 year is possible with combined treatment of ETA and MTX
ADA	Weinblatt et al. 2003, ARMADA [62]	Adding ADA at doses of 20 mg, 40 mg, or 80 mg administered subcutaneously every other week to long-term MTX therapy in patients with active RA resulted in significant, rapid, and sustained improvement in disease activity over 24 weeks compared to MTX with placebo
	Breedveld et al. 2006, PREMIER [63]	For patients with early, aggressive RA, combination therapy with ADA and MTX was significantly more effective than either MTX alone or ADA alone in improving disease signs and symptoms, inhibiting radiographic progression, and achieving clinical remission
	Furst et al. 2003, START [64]	Adding 40 mg of ADA, administered subcutaneously every other week, to standard antirheumatic therapy is well tolerated and significantly improves signs and symptoms of RA; ADA is a safe and effective option for patients with active RA who have not adequately responded to standard antirheumatic treatments, including one or more traditional DMARDs, GCs, NSAIDs, and analgesics
Certolizumab pegol	Keystone et al. 2009, RAPID 1 [65]	Treatment with certolizumab pegol at doses of 200 or 400 mg combined with MTX led to rapid and sustained reductions in RA signs and symptoms, inhibited structural joint damage progression, and improved physical function compared to placebo plus MTX in patients with an incomplete response to MTX
	Smolen et al. 2009, RAPID 2 [66]	Certolizumab pegol combined with MTX was more effective than placebo plus MTX, rapidly and significantly improving RA signs and symptoms, enhancing physical function, and inhibiting radiographic progression
	Smolen et al. 2015, CERTAIN [67]	Adding certolizumab pegol to non-biologic DMARDs is an effective treatment for RA patients with predominantly moderate disease activity, enabling the majority to achieve low disease activity or remission. However, the data suggest that certolizumab pegol cannot be withdrawn in patients who achieve remission
	Atsumi et al. 2016, C-OPERA [68]	In MTX-naive early RA patients with poor prognostic factors, certolizumab pegol combined with MTX significantly inhibited structural damage and reduced RA signs and symptoms
	Emery et al. 2017, C-EARLY [69]	Treatment with certolizumab pegol and dose-optimized MTX in DMARD-naive early RA patients resulted in significantly more patients achieving sustained remission and low disease activity, improved physical function, and inhibited structural damage compared to placebo with dose-optimized MTX

Table I. Cont.

bDMARD	First author, year of publication, trial name, reference	Conclusions
GOL	Smolen et al. 2009, GO-AFTER [70]	GOL alleviated the signs and symptoms of RA in patients with active disease who had previously been treated with one or more TNF-α inhibitors
	Emery et al. 2010, GO-BEFORE [71]	GOL alone is comparable to MTX alone in reducing RA signs and symptoms in MTX-naive patients, with no unexpected safety concerns
	Keystone et al. 2011, GO-FORWARD [72]	The response rates achieved by patients receiving GOL at 24 weeks were sustained through 52 weeks. The safety profile was consistent with that of other TNF-α inhibitors
ABA	Genovese et al. 2005, ATTAIN [73]	ABA provided significant clinical and functional benefits for patients who had an inadequate response to anti-TNF-α therapy
	Kremer et al. 2006, AIM [74]	ABA significantly reduced disease activity in RA patients who had an inadequate response to MTX
	Emery et al. 2015, AVERT [75]	ABA combined with MTX showed strong efficacy compared to MTX alone in early RA and maintained a good safety profile. The ability to achieve sustained remission after withdrawing all RA therapy suggests that ABA's mechanism may impact underlying autoimmune processes
	Rech et al. 2024, ARIAA [76]	6 months of ABA treatment reduces MRI-assessed inflammation, clinical symptoms, and the risk of developing RA in high-risk individuals. These benefits persist through a 1-year drug-free observation period
TOC	Smolen et al. 2008, OPTION [77]	TOC may be an effective treatment option for patients with moderate to severe active RA
	Nishimoto et al. 2009, STREAM [78]	TOC demonstrated sustained long-term efficacy and maintained a generally good safety profile
	Jones et al. 2010, AMBITION [79]	TOC monotherapy outperforms MTX monotherapy, providing rapid improvement in RA signs and symptoms and offering a favorable benefit-risk profile for patients who have not previously failed treatment with MTX or biological agents
	Kremer et al. 2011, LITHE [80]	TOC combined with MTX results in greater inhibition of joint damage and improvement in physical function compared to MTX alone; TOC also has a well-established safety profile
	Burmester et al. 2016, FUNCTION [81]	TOC is effective both in combination with MTX and as monotherapy for treating patients with early RA
RTX	Cohen et al. 2006, REFLEX [82]	A single course of RTX combined with MTX significantly and meaningfully improved disease activity in patients with active, longstanding RA who had an inadequate response to one or more anti-TNF therapies
	Mease et al. 2008, DANCER [83]	RTX, when combined with MTX, effectively improved all health-related quality of life outcomes in patients with active RA, consistent with clinical efficacy
	Tak et al. 2011, IMAGE [84]	Treatment with RTX combined with MTX is an effective therapy for patients with MTX-naive RA
SARI	Tanaka et al. 2019, KAKEHASI [85]	In Japanese RA patients with an inadequate response to MTX, treatment with SARI in combination with MTX demonstrated sustained clinical efficacy, evidenced by significant improvements in signs, symptoms, and physical function
	Fleischmann et al. 2017, TARGE [86]	SARI combined with conventional synthetic DMARDs improved the signs and symptoms of RA and enhanced physical function in patients who had an inadequate response or intolerance to anti-TNF agents
	Burmester et al. 2017, MONARCH [87]	SARI monotherapy proved superior to ADA monotherapy in improving signs, symptoms, and physical function in RA patients who could not continue MTX treatment. The safety profiles of both therapies were consistent with expected class effects

ABA – abatacept, ADA – adalimumab, bDMARDs – biological disease-modifying antirheumatic drugs, ETA – etanercept, GCS – glucocorticosteroids, GOL – golimumab, INF – infliximab, MTX – methotrexate, NSAIDS – non-steroidal anti-inflammatory drugs, RA – rheumatoid arthritis, RTX – rituximab, SARI – sarilumab, TOC – tocilizumab.

have enabled the development of targeted therapies that can focus on specific pathological pathways and components of the immune system responsible for the disease.

Research on the role of interleukins in the inflammatory process led to the development and introduction of new bDMARDs – IL-6 inhibitors such as tocilizumab (TOC) and sarilumab (SARI). These drugs are used when standard treatments fail and can be administered intravenously or through subcutaneous injections. Their efficacy includes significant symptom reduction and improvements in overall functioning and quality of life for patients [29].

Interleukin-6 inhibitors

Interleukin-6 is a key pro-inflammatory cytokine playing a crucial role in the pathogenesis of RA. Produced by cells such as macrophages, T lymphocytes, and fibroblasts, IL-6 regulates immune and inflammatory responses. In RA, IL-6 stimulates the differentiation of B lymphocytes into plasma cells, and activates T lymphocytes. Additionally, it affects hepatocytes in the liver, leading to the production of acute-phase proteins such as CRP and amyloid A, and stimulates osteoclasts, causing bone resorption and joint damage. Systemic effects of IL-6 through increased synthesis of acute-phase proteins, hepcidin production, and stimulation of the hypothalamic-pituitary-adrenal axis include anemia and fatigue [30].

Biological drugs from the IL-6 inhibitor group, such as TOC and SARI, block the action of IL-6, leading to reduced inflammation and alleviation of RA symptoms. Tocilizumab and SARI are monoclonal antibodies that bind to the IL-6 receptor (IL-6R), preventing the activation of inflammatory signaling pathways. This results in decreased production of acute-phase proteins in the liver and lower levels of CRP and other inflammatory markers. Interleukin-6 inhibitors also reduce osteoclast activity, protecting bones from resorption. Clinical studies have shown that IL-6 inhibitors can significantly reduce RA symptoms, improve patients' physical function, and slow the progression of joint damage, leading to long-term improvements in patients' quality of life [30, 31].

The use of IL-6 inhibitors is associated with a range of adverse effects. They increase the risk of bacterial, viral, and fungal infections, including severe infections such as pneumonia and sepsis [32, 33]. They can cause elevated liver enzymes and lipids, requiring regular monitoring of liver function and lipid profile [34, 35]. Hematological problems, including neutropenia and thrombocytopenia, increase the risk of infections and bleeding, necessitating regular blood tests [35]. Hypersensitivity reactions, including anaphylaxis, and gastrointestinal issues such as nausea, vomiting, and diarrhea, may also occur [32]. Rarely, serious complications such as intestinal perforation can arise [36]. Local reactions at the injection site, such as pain and redness, are also possible.

T-cell co-stimulation inhibitors

Under normal conditions, the activation of T lymphocytes requires two signals. The first signal comes from the antigen presented by an antigen-presenting cell (APC) on a major histocompatibility complex molecule. The second signal, known as the co-stimulatory signal, is provided by the interaction between CD80/CD86 (cluster of differentiation 80/86) molecules on the surface of the APC and the CD28 (cluster of differentiation 28) molecule on the surface of the T lymphocyte. Both signals are essential for the full activation of T lymphocytes, which then proliferate and secrete pro-inflammatory cytokines, intensifying the inflammatory response [37].

Abatacept (ABA) is a fusion protein consisting of the extracellular domain of CTLA-4 (cytotoxic T-lymphocyte antigen 4) linked to the Fc fragment of human immunoglobulin G1. CTLA-4 naturally occurs on the surface of T lymphocytes and acts as an inhibitor of co-stimulation. Abatacept binds to the CD80/CD86 molecules on APCs, preventing them from interacting with CD28 on T lymphocytes. This way, ABA blocks the second signal necessary for T lymphocyte activation [38, 39].

Blocking co-stimulation with ABA leads to the inhibition of T lymphocyte activation, resulting in decreased proliferation of these cells and reduced secretion of pro-inflammatory cytokines such as interferon γ, IL-2, and TNF-α. Consequently, there is a reduction in the infiltration of inflammatory cells in the joints and the degree of joint tissue damage, leading to alleviation of RA symptoms such as pain, swelling, and joint stiffness [39, 40].

Abatacept is well tolerated and safe for patients with RA. Common side effects include nasopharyngitis, headache, nausea, cough, and fatigue. The rate of serious infections with ABA is similar to other treatments, with no significant issues related to kidney, liver, or blood toxicities. Infusion reactions are rare and usually involve headaches, dizziness, nausea, and vomiting. Additionally, no significant antibody response to the treatment has been detected [40].

B-cell inhibitors

B lymphocytes play a crucial role in the pathogenesis of RA by producing autoantibodies such as anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF), which form immune complexes that trigger inflamma-

tory reactions in the joints. They also act as APCs, activating T lymphocytes and exacerbating inflammation by secreting pro-inflammatory cytokines such as IL-6 and TNF-α [41].

Rituximab (RTX), a biological B cell inhibitor, is a chimeric monoclonal antibody that binds to the CD20 antigen on the surface of B lymphocytes. Upon binding to CD20, RTX induces the destruction of B lymphocytes through antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and the induction of apoptosis. The reduction in B lymphocytes leads to decreased production of autoantibodies, limited antigen presentation, and reduced secretion of pro-inflammatory cytokines, resulting in diminished inflammation and alleviation of RA symptoms [42].

Clinical studies have shown that RTX is effective in reducing disease activity in RA patients, especially those who do not respond to other therapies.

However, the use of RTX in RA patients carries the risk of adverse effects. The main risk is increased susceptibility to infections due to B lymphocyte depletion. Infusion-related reactions, such as fever, chills, rash, itching, shortness of breath, and headache, are common. Rituximab can also cause hypersensitivity reactions, including rare but severe anaphylactic reactions. Hematologic problems, such as neutropenia, thrombocytopenia, and anemia, increase the risk of infections and bleeding, necessitating regular blood tests. There is also a risk of viral reactivation, such as hepatitis B virus, and rare kidney damage, especially in patients with pre-existing kidney conditions [43].

The advent of Janus kinase inhibitors as a new class of oral targeted disease-modifying antirheumatic drugs

Janus kinase inhibitors have significantly advanced the treatment of RA by providing an effective oral therapeutic alternative to bDMARDs. These low-molecular-weight compounds, which include tofacitinib (TOFA), baricitinib (BARI), upadacitinib (UPA), filgotinib (FIL), and peficitinib, block the activation of JAKs – JAK1, JAK2, JAK3 – and Tyk2, which prevents the phosphorylation of the STAT (signal transducer and activator of transcription) proteins, critical regulators of inflammatory and immune responses [44]. This targeted mechanism of action classifies JAK inhibitors as a new class of targeted synthetic DMARDs (tsDMARDS).

The specificity of each inhibitor for different JAK isoforms varies, contributing to their unique efficacy and safety profiles. For instance, UPA and FIL primarily target JAK1, which influences specific cytokines such as interferon, while peficitinib affects a broader range of cytokines.

Janus kinase inhibitors offer convenience with their oral administration and have been shown to be as effective as bDMARDs in inducing remission, controlling disease activity, and improving patient-reported outcomes in RA patients, especially those who have not responded adequately to MTX or bDMARDs [45]. A summary of clinical trial findings on the efficacy and safety of JAK inhibitors in the treatment of RA can be found in Table II.

However, despite these benefits, the use of JAK inhibitors requires careful consideration due to potential adverse effects. These can include serious infections, liver and kidney function impairment, and possible hematological issues. Research indicates that JAK inhibitors are associated with a higher risk of MACE (major adverse cardiovascular events) and malignancy compared to TNF inhibitors, however, this phenomenon is not observed with placebo or MTX. Tumors are rare occurrences in all comparisons [46]. The risk of these events necessitates judicious use and careful monitoring during treatment [44].

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has issued new guidelines for the use of JAK inhibitors aimed at minimizing the risk of serious side effects associated with their use. These guidelines address concerns related to cardiovascular diseases, thrombosis, cancer, and serious infections. They are specifically directed at risk groups, such as individuals over 65 years of age, patients at increased risk of cardiovascular problems, current or former smokers, and those at a higher risk of developing cancer. The committee recommends using JAK inhibitors only when other therapies are not available. The new guidelines are based on study findings, including data from clinical trials on TOFA and observational studies on BARI [47].

Overall, JAK inhibitors have become an integral component of modern RA management strategies, recommended as first-line treatments in cases where traditional therapies fail. Their development and application are poised to continue evolving with ongoing research aiming to optimize their use through precision medicine approaches, potentially enhancing their effectiveness and safety profile for individual patients [45].

A summary of the pharmacological treatment options for RA is presented in Table III.

The role of biomarkers in predicting treatment response and personalizing therapy

The development of biomarkers has been a key step toward the personalization of RA treatment. Biomarkers such as ACPA and RF help in diagnosing the disease and can also be used to predict responses to specific

Table II. Summary of clinical trial findings on the efficacy and safety of JAK inhibitors in RA treatment

JAK inhibitor	Trial name	Conclusions
TOFA	ORAL Solo [88]	In patients with active RA, TOFA monotherapy led to significant reductions in symptoms and improvements in physical function
	ORAL Sync [89]	Patients with active RA who received TOFA along with conventional DMARDs experienced sustained, significant, and meaningful improvements in patient-reported outcomes compared to placebo
	ORAL Standard [90]	For RA patients on background MTX, TOFA was significantly more effective than placebo and had similar efficacy to ADA
	ORAL Step [91]	In a population with an inadequate response to TNF-α inhibitors, TOFA combined with MTX resulted in rapid and meaningful improvements in RA symptoms and physical function over 6 months, with manageable safety
UPA	SELECT-NEXT [92]	Patients with moderately to severely active RA treated with UPA (15 mg or 30 mg) in combination with conventional synthetic DMARDs exhibited significant improvements in clinical signs and symptoms
	SELECT-MONOTHERAPY [93]	UPA monotherapy showed significant improvements in clinical and functional outcomes compared to continued MTX in MTX inadequate-responder patients, with a safety profile similar to earlier studies
	SELECT-BEYOND [94]	UPA (15 mg or 30 mg) significantly improved various aspects of quality of life in patients with inadequate responses to bDMARDs, with a greater number of patients achieving clinically meaningful improvements compared to placebo
BARI	RA-BEGIN [95]	BARI, either alone or combined with MTX, showed better efficacy and acceptable safety compared to MTX alone as initial treatment for active RA
	RA-BEAM [96]	For RA patients with an inadequate response to MTX, BARI significantly improved clinical outcomes compared to both placebo and ADA
	RA-BUILD [97]	In RA patients with an inadequate response or intolerance to conventional synthetic DMARDs, BARI resulted in clinical improvement and slowed progression of radiographic joint damage
FIL	FINCH 1 [98]	FIL significantly improved RA signs and symptoms and physical function, and inhibited radiographic progression in patients with inadequate response to MTX; FIL was non-inferior to ADA and well tolerated
	FINCH 2 [99]	For patients with moderate to severe RA who were refractory to biologic DMARDs, FIL (100 mg or 200 mg) led to a significantly greater clinical response at week 12 compared to placebo. Further research is needed to assess long-term efficacy and safety
	FINCH 3 [100]	FIL in combination with MTX or as monotherapy significantly improved signs, symptoms, and physical function in patients with limited or no prior MTX exposure. However, FIL monotherapy did not achieve a superior ACR20 response rate compared to MTX; FIL was well tolerated and had an acceptable safety profile compared to MTX

ADA – adalimumab, BARI – baricitinib, DMARD – disease-modifying antirheumatic drug, FIL – filgotinib, JAK – Janus kinase, MTX – methotrexate, RA – rheumatoid arthritis, TNF-α – tumor necrosis factor α, TOFA – tofacitinib, UPA – upadacitinib.

Table III. Summary of therapeutic options available for managing RA

Drug category	Examples (with FDA approval years)	Primary function
NSAIDs	Ibuprofen (1974), naproxen (1976)	Pain relief and reduction of inflammation
GCs	Prednisone (1955), methylprednisolone (1961)	Rapid inflammation reduction
Conventional synthetic DMARDs	Gold-based therapies (used since 1929, before FDA criteria development), sulfasalazine (1950), hydroxychloroquine (1955), MTX (1988), LEF (1998)	Slowing disease progression, long-term management
Biologic DMARDs	INF (1998), ETA (1998), anakinra (2001), ADA (2002), ABA (2005), RTX (2006), certolizumab pegol (2009), GOL (2009), TOC (2010), SARI (2017)	Targeting specific immune system components
JAK inhibitors	TOFA (2012), BARI (2018), UPA (2019), FIL (not approved by FDA, approved in Europe in 2020)	Blocking intracellular signaling pathways

ABA – abatacept, ADA – adalimumab, DMARDs – disease-modifying antirheumatic drugs, ETA – etanercept, FDA – Food and Drug Administration, FIL – filgotinib, GCs – glucocorticosteroids, GOL – golimumab, INF – infliximab, JAK – Janus kinase, NSAIDs – nonsteroidal anti-inflammatory drugs, RA – rheumatoid arthritis, RTX – rituximab, SARI – sarilumab, TOC – tocilizumab, TOFA – tofacitinib, UPA – upadacitinib.

therapies. Advances in genetics and genomics pave the way for identifying genetic markers associated with RA, which may enable an even more personalized treatment approach tailored to an individual's risk profile and predicted therapy response. New markers are emerging that may be useful in diagnosing and monitoring the disease, such as anti-pentraxin 3 (anti-PTX3) and anti-dual specificity phosphatase 11 (anti-DUSP11) autoantibodies – biomarkers for the diagnosis of ACPA-negative RA [48]. Anti-carbamylated protein (anti-CarP) antibodies, similarly to ACPA and IgM-RF, can be detected in healthy individuals before developing RA, with anti-CarP antibodies and ACPA appearing years prior to the RA diagnosis, often earlier than IgM-RF [49]. Antibodies against heterogeneous nuclear ribonucleoproteins – anti-hnRNP A2/B1 (RA33) – which interact with pre-mRNA, are another potential biomarker in RA, though further research is needed [50].

Recent advancements in stem cell therapy

Therapies utilizing stem cells have emerged as a promising direction in the treatment of RA. Although research in this area is still in its early stages, preliminary results are promising, suggesting the potential ability of stem cells to promote joint tissue regeneration and modulate the immune response [51].

The impact of digital health technologies on managing rheumatoid arthritis

Digital technologies, including telemedicine, mobile applications, and wearable monitoring devices, have revolutionized the treatment of RA. These technologies enable monitoring of disease progression and treatment effects in real time. Digital self-monitoring tools help patients manage pain, physical activity, and medication adherence, while telemedicine platforms provide easier access to specialist care. Advances in big data and artificial intelligence open new possibilities for analyzing health data, which can lead to a better understanding of RA and more effective treatment strategies [52].

Ongoing research in gene therapy and novel immunomodulatory strategies

New treatment methods are developing, including cellular therapies such as treatments based on mesenchymal stem cells and therapies utilizing tolerogenic dendritic cells, as well as the use of natural substances, e.g. cannabinoid drugs. Research on gene therapy and new immunomodulatory strategies is opening new perspectives for future RA treatments. Gene therapy, aimed at modifying the expression of genes responsible for the inflammatory process, is being investigated as a potential long-term solution for RA [53]. Several modern technologies also offer new possibilities for treating RA. Proteolysis targeting chimera (PROTAC) technology enables targeted degradation of pathogenic proteins, effectively eliminating proteins that cause joint inflammation [54]. Nanoparticles allow for precise delivery of drugs directly to affected joints, minimizing side effects and increasing treatment efficacy [55]. CRISPR-Cas9 technology enables precise gene editing, correcting mutations or silencing pro-inflammatory genes, which can lead to long-term control or even a cure for RA [56]. These methods have the potential to revolutionize RA treatment by offering more personalized and effective therapies.

Current challenges and future directions

Despite significant progress in the treatment of RA, there are still limitations and unmet needs. Current therapies, including DMARDs, bDMARDs, and tsDMARDs are

not effective for all patients, and some may experience unacceptable side effects. Additionally, there is a clear need for better control over the long-term effects of RA, including bone erosion and the risk of comorbidities such as heart disease. In the context of future research, it will also be important to focus on the personalization of therapy, which means tailoring treatment approaches to the individual needs of the patient. The development of precision medicine in RA could lead to more effective and safer therapies, minimizing side effects and improving the quality of life for patients.

Conclusions

The treatment of RA has evolved dramatically, transitioning from ancient, empirical methods to sophisticated, targeted therapies. The 19th century's scientific advancements led to the recognition of RA as a distinct disease. The 20th century introduced GCs, which, despite their efficacy, highlighted the need for more sustainable solutions due to their long-term side effects. The development of DMARDs, particularly MTX, marked significant progress in controlling disease progression.

The introduction of bDMARDs and JAK inhibitors revolutionized RA treatment. The integration of biomarkers for personalized therapy has further refined treatment strategies. Future advancements in gene therapy, and digital health technologies hold promise for further improving RA management. Despite these advances, challenges such as ensuring equitable access to therapies and addressing the needs of patients who do not respond to current treatments persist. The ongoing focus on personalized medicine and the development of safer, more effective therapies will be crucial in overcoming these challenges and enhancing patient outcomes.

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ORIGINAL ARTICLE

Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in the years 2011–2021: a population study

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KEY WORDS

cardiac intensive care unit, intensive care unit, mortality, rheumatoid arthritis

ABSTRACT

INTRODUCTION Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with significant comorbidities, including cardiovascular and respiratory complications, leading to increased hospitalization rates in intensive care units (ICUs) and cardiac intensive care units (CICUs). This study examines factors related to ICU/CICU admissions among Polish patients with RA from 2011 to 2021.

OBJECTIVES We aimed to analyze trends in ICU/CICU admissions, identify key factors influencing outcomes, and assess the impact of comorbidities on RA patient ICU/CICU mortality in critical care settings.

PATIENTS AND METHODS This retrospective population-based study utilized data from the Polish national hospital morbidity registry. Inclusion criteria comprised ICU/CICU admission and an *International Classification of Diseases, Tenth Revision* code for RA. A total of 3066 hospitalization records were analyzed, focusing on demographics, length of stay, primary diagnosis, and ICU/CICU mortality rates. A logistic regression was used to evaluate the predictors of ICU/CICU mortality.

RESULTS The study revealed a rising trend in ICU/CICU admissions, with a significant increase in 2021, potentially due to the COVID-19 pandemic. The overall ICU/CICU mortality rate was 39.1%, with the highest values observed in patients with gastrointestinal (58.5%) and endocrine/metabolic diseases (61.5%). Urgent admissions and older age were strong predictors of ICU/CICU mortality (P <0.001), while sex was not a significant factor.

CONCLUSIONS Our findings emphasize the need for early intervention and comprehensive management strategies to mitigate severe RA complications. Future research should explore long-term outcomes and the impact of RA treatments on ICU/CICU care.

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INTRODUCTION Rheumatoid arthritis (RA) is a chronic systemic connective tissue disease of immunological origin, characterized by nonspecific symmetrical inflammation of the joints, the occurrence of extra-articular changes, and systemic complications, leading to disability, handicap, and premature death. RA affects approximately 0.5%–1% of the global population, with the highest incidence around the age of 80 years.[1,2] Without treatment, RA patients experience numerous exacerbations leading to disability and poor health outcomes. Early treatment can improve performance and reduce disease activity, but mortality remains similar for both early and late treatment.[3]

The patients with RA often develop other chronic conditions that significantly affect their health. Cardiovascular diseases are the most

WHAT'S NEW?

This study uncovers significant trends in hospitalization of patients with rheumatoid arthritis (RA) in Polish intensive care units (ICUs) and cardiac intensive care units (CICUs) from 2011 to 2021, highlighting an increase in admissions and ICU/CICU mortality, particularly in 2021, likely linked to the COVID-19 pandemic. A key finding is a high ICU/CICU mortality rate of 39.1%, especially among older patients and those admitted urgently. This research emphasizes a critical need for early intervention and comprehensive management strategies to improve outcomes for RA patients in critical care, offering new insights into the burden of severe RA complications and their management in clinical practice.

common cause of death in this population. One of the most critical complications of RA is coronary artery disease.[4,5] RA patients have twice the risk of heart attack and up to by 50% higher risk of cardiovascular mortality than the general population.[6] The prevalence of type 2 diabetes is also increased in patients with RA. Glucocorticoids, used to suppress inflammation in RA, adversely affect glycemic control, and diabetes further exacerbates cardiovascular risk.[7]

Respiratory diseases are the second leading cause of death in RA patients, occurring in 30%–40% of cases. RA can affect the lung interstitium, airways, pleura, and less frequently the pulmonary vessels.[8] Conditions such as pleuritis, bronchiolitis, and interstitial lung disease (ILD) are also associated with RA. Reports indicate that ILD develops in 5%–16% of RA patients, and its occurrence is associated with shorter survival.[8,9] Moreover, venous thromboembolic disease is more prevalent in RA patients, especially during therapy with tumor necrosis factor inhibitors and Janus kinase inhibitors.[10]

Chronic anemia and Felty syndrome are common complications in patients with seropositive RA.[11] Secondary Sjögren syndrome, present in about 10% of RA patients, further complicates the disease. Rheumatoid vasculitis, though rare, can have severe consequences, resembling polyarteritis nodosa.[11,12] Furthermore, the patients with RA have a higher likelihood of developing diseases such as Hodgkin and non-Hodgkin lymphoma than the general population.[13]

Premature death is a common outcome of RA complications and their treatment. Serious infections, exacerbated by disease-modifying antirheumatic drugs (DMARDs) and immune system dysfunction, pose significant risks.[14] Osteopenia and osteoporosis, resulting from the disease and drug therapies, increase the risk of fractures, particularly in postmenopausal women and older adults.[15] RA also affects the gastrointestinal system and kidneys, mainly through drug therapies.[6] Depression, a frequent complication, affects patients with long-term active disease and significant physical dysfunction.[16]

RA is one of the most prevalent rheumatological conditions necessitating admission to intensive care units (ICUs).[17-19] The patients with RA have a significantly elevated risk of ICU admission, as compared with the general population, with over 1% of RA individuals experiencing critical illness annually, and a cumulative 10-year risk approaching 8%.[20] This increased risk is often attributed to the disease exacerbation or adverse effects of immunosuppressive therapy.[17,21] The cardiovascular and respiratory systems are the most frequently affected.[18,20]

Mortality in this patient population is associated with several factors, including the severity of illness measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the updated Charlson Comorbidity Index, the Sequential Organ Failure Assessment (SOFA) score, the need for vasopressor support, advanced age, prolonged prothrombin time / international normalized ratio, cytopenia, and extended hospital stays.[17,19,22]

Hospitalization in an ICU or a cardiac intensive care unit (CICU) indicates a severe exacerbation of the illness, often requiring advanced medical interventions and constant monitoring. Understanding the factors related to ICU or CICU admissions among RA patients is crucial for improving clinical outcomes, optimizing resource allocation, and developing preventive strategies to reduce the burden of severe complications.

The aim of this study was to characterize selected factors related to ICU/CICU hospitalizations of Polish patients diagnosed with RA over a long-term perspective, covering the years 2011–2021. This study sought to identify the patterns and trends in hospital admissions, evaluate the impact of comorbidities, and explore the outcomes of RA patients requiring intensive care. By gaining insights into these aspects, the research aimed to contribute to better management strategies and enhanced care for the individuals suffering from this debilitating condition.

PATIENTS AND METHODS This retrospective study utilized anonymized data derived from the Polish national hospital morbidity registry. The research was conducted in collaboration with the Department of Social Medicine and Public Health of Medical University of Warsaw, and institutions such as the National Institute of Public Health NIH – National Research Institute and the National Institute of Geriatrics, Rheumatology, and Rehabilitation. The study was approved by the ethics committee of the National Institute of Geriatrics, Rheumatology, and Rehabilitation in Warsaw (KBT-4/4/2024). The ethics committee did not require an informed consent from the patients analyzed in this retrospective study and approved publication of its results. Each study procedure complied with the Declaration of Helsinki or similar standard of ethics.

High completeness of the hospital morbidity data is due to the legal obligation imposed on inpatient health care units to periodically report hospitalization data to the National Institute of Public Health – National Institute of Hygiene.

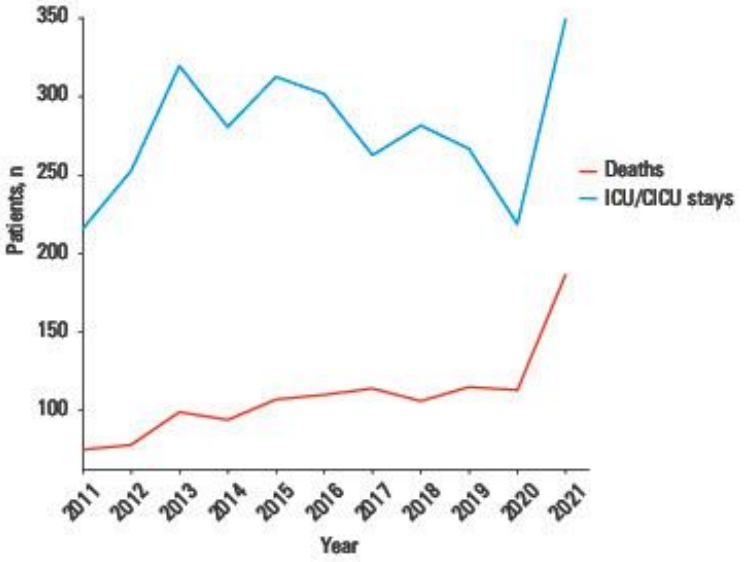

FIGURE 1 Intensive care unit (ICU)/cardiac intensive care unit (CICU) admissions and deaths of patients with rheumatoid arthritis from 2011 to 2021

The information is reported by the hospitals using the General Hospital Statistical Card Mz/Szp-11, covering all hospitalizations within the analyzed period. The accuracy and reliability of the data result from the efficiency and precision of reporting by individual entities. The study population, encompassing nearly 100% of hospitalizations in Poland, ensures the accuracy and reliability of the utilized data.

The study inclusion criteria comprised an ICU or CICU stay code in the hospitalization record and an *International Classification of Diseases, Tenth Revision* (ICD-10) code for RA (M05, M05.x, or M06, M06.x) in the reported hospital morbidity data.

Both criteria had to be met simultaneously for patient inclusion in the study. There were no exclusion criteria.

The study involved 3066 hospitalization records. Of these, 2815 hospitalizations (91.8% of all records) were in the ICUs, and 251 (8.2%) in the CICUs. The majority of hospitalizations concerned women (n = 2270; 74%). Women accounted for 74.3% of the ICU and 71.3% of the CICU hospitalizations. The age of patients ranged from 19 to 96 years (mean [SD], 65.2 [11.5] years; median, 66 [range, 19–96] years).

Statistical analysis Descriptive statistics were computed for the patient population. Frequencies were calculated for categorical variables, while means (SD) were computed for continuous variables. Trend lines for ICU/CICU admissions and patient deaths per year were plotted to examine temporal trends. Cross-tabulation analyses were performed to investigate the distribution of primary diagnosis groups based on ICD-10 codes, including their length of stay (LOS) and ICU/CICU mortality rates. The term "ICU/CICU mortality" used throughout the study refers to deaths recorded during the stay in the ICU/CICU.

A cross-tabulation table was also created to display the primary wards to which the patients were admitted, including the frequency of emergency admissions.

A logistic regression model was used to identify the predictors of patient mortality during ICU/CICU stay. The dependent variable was ICU/CICU mortality (0 = survived, 1 = died), and the predictors included sex, age, and hospital admission mode. The predictors were introduced into the model in blocks to assess the incremental value of each block of predictors. The logistic regression results provided odds ratios with 95% CIs for each predictor. The model's fit was evaluated using Nagelkerke pseudo R^2. The significance level was set at a P value below 0.05.

All analyses and figures were prepared using R (version 4.3.3; R Core Team, Vienna, Austria) with the ggplot2, MASS, broom, and rcompanion packages.

RESULTS The analysis demonstrated that 1198 patients out of the studied population (39.1%) died during their stay in the ICU/CICU. FIGURE 1 shows the trend lines for the number of ICU/CICU admissions and the number of deaths per year.

The chart indicates an increase in the ICU/CICU admissions and deaths in 2021, possibly related to the COVID-19 pandemic.

In the next section, the factors related to the hospital admission were analyzed. As many as 1885 patients (63.9% of the study population) were urgently admitted to the hospital. The LOS ranged from 0 to 248 days (median [interquartile range {IQR}], 14 [7–23.75] days).

Mortality rates among the ICU patients were compared with those in the CICU, with the value of 42% in the former and 6.4% in the latter. The χ^2 test showed a notable relationship between the type of ICU and the occurrence of death ($\chi^2 = 123$; $P < 0.001$; $\phi = 0.2$).

TABLE 1 presents the frequency of disease groups based on ICD-10 codes for the primary diagnosis upon admission to the first ward. It shows that the largest group consisted of patients with diseases of the circulatory system (22% of the study population), musculoskeletal system and connective tissue (19.5% of the study population), and respiratory system (16.2% of the study population). Conversely, out of specific system diseases, the notably high ICU/CICU mortality rates were observed in patients with gastrointestinal (58.5% ICU/CICU mortality), endocrine, nutritional, and metabolic diseases (61.5% ICU/CICU mortality). The longest median (IQR) LOS was associated with the diseases of the skin and subcutaneous tissue (26 [19–39] days), while the shortest with pregnancy, childbirth, and puerperium (8 [5–14.5] days), where none of the 23 patients died. This lower ICU/CICU mortality rate and shorter LOS in the pregnancy, childbirth, and puerperium group could be attributed to the generally healthier and younger population and the nature of the hospital

TABLE 1 Frequency of the *International Classification of Diseases, Tenth Revision* codes for the primary diagnosis in the studied population of rheumatoid arthritis patients admitted to the intensive care unit/cardiac intensive care unit

Disease group (ICD-10 code)	Study population, n (%)	LOS, median (IQR)	ICU/CICU mortality rate, %
Diseases of the circulatory system (I00–I99)	674 (22)	10 (5–21)	34.9
Diseases of the musculoskeletal system and connective tissue (M00–M99)	599 (19.5)	15 (10–22)	19
Diseases of the respiratory system (J00–J99)	498 (16.2)	15 (7–28)	47.6
Diseases of the digestive system (K00–K95)	234 (7.6)	15 (7–28)	58.5
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	160 (5.2)	12 (4–26.5)	52.5
Certain infectious and parasitic diseases (A00–B99)	143 (4.7)	14 (5–27)	57.3
Neoplasms (C00–D49)	226 (7.4)	12 (6–20)	31.4
Codes for special purposes (U00–U85)	136 (4.4)	15 (9.75–24)	71.3
Diseases of the genitourinary system (N00–N99)	96 (3.1)	12.5 (5–25.2)	51
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89)	87 (2.8)	12 (5.5–20.5)	46
Injury, poisoning, and certain other consequences of external causes (S00–T88)	140 (4.5)	15 (11.2–21)	27.1
Diseases of the nervous system (G00–G99)	44 (1.4)	16 (9–31.5)	38.6
Factors influencing health status and contact with health services (Z00–Z99)	39 (1.3)	13 (9–21.5)	15.4
Endocrine, nutritional, and metabolic diseases (E00–E89)	26 (0.8)	10 (6–18.8)	61.5
Diseases of the skin and subcutaneous tissue (L00–L99)	25 (0.8)	26 (19–39)	56
Pregnancy, childbirth, and puerperium (O00–O9A)	23 (0.8)	8 (5–14.5)	0
Congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99)	2 (0.1)	11.5[a]	50
Mental, behavioral and neurodevelopmental disorders (F01–F99)	1 (0.05)	16.4[a]	0

a Due to a low number of individuals, calculating quartiles was impossible

Abbreviations: CICU, cardiac intensive care unit; ICD-10, *International Classification of Diseases, Tenth Revision*; ICU, intensive care unit; LOS, length of stay

TABLE 2 Primary ward of admission for patients included in the study

Ward	Total admissions		Emergency admissions	
	N_1	Percent of the study population	N_2	N_2/N_1, %
Department of trauma and orthopedic surgery	563	18.4	72	12.8
Intensive care unit	553	18	447	80.8
Internal medicine ward	330	10.8	298	90.3
Hospital emergency ward	290	9.5	284	97.9
General surgery department	221	7.2	173	78.3
Cardiac intensive care unit	179	5.8	141	78.8

admission related to childbirth rather than acute or severe illness.

TABLE 2 lists the primary wards to which the patients were admitted. The wards not shown in the table had individual frequencies below 5%. In the analyzed population of patients with RA, the most common initial admission was to a department of trauma and orthopedic surgery, which accounted for 18.4% of all patients, primarily for elective procedures. Other common initial departments included ICU (18%), internal medicine (10.8%), hospital emergency (9.5%), general surgery (7.2%), and CICU (5.8%). In these cases, the admissions were predominantly emergencies.

FIGURE 2 shows the percentage of deaths among patients admitted to a hospital on an urgent vs elective basis. The data indicate a significantly higher ICU/CICU mortality rate among the patients admitted urgently, as compared with those admitted electively. Specifically, the urgent admissions accounted for a ICU/CICU mortality rate of 52.8%, whereas the elective admissions had a substantially lower ICU/CICU mortality rate of 16.1%. This disparity can be attributed to a critical nature of conditions requiring the urgent admission, where patients often present with severe, life-threatening complications necessitating immediate medical intervention. In contrast,

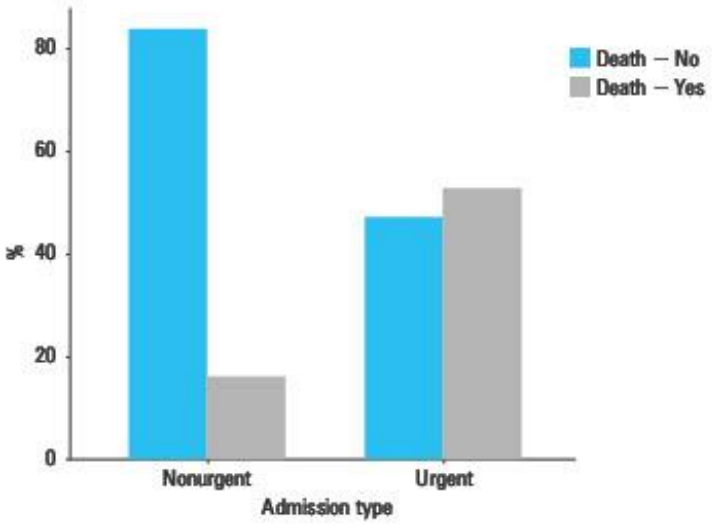

FIGURE 2 Intensive care unit/cardiac intensive care unit mortality rate by hospital admission mode

TABLE 3 Results of the logistic regression analysis predicting intensive care unit/cardiac intensive care unit mortality

Independent variable	Estimate	SE	Z	*P* value	Odds ratio (95% CI)
Intercept	–3.313	0.297	11.137	<0.001	–
Sex (0 – men; 1 – women)	0.048	0.092	0.521	0.6	1.049 (0.875–1.259)
Age	0.024	0.003	6.567	<0.001	1.025 (1.018–1.033)
Admission type (0 – nonurgent; 1 – urgent)	1.701	0.096	17.721	<0.001	5.483 (4.543–6.619)
Nagelkerke $R^2 = 0.195$					

elective admissions typically involve preplanned procedures for managing chronic conditions or routine surgeries, allowing for better preparation and stabilization of the patient's health status prior to admission. The literature points out that surgical patients generally have better ICU prognoses than nonsurgical ones, who may present with complex, multisystem conditions requiring intensive, multifaceted management.[23] Our findings highlight the importance of timely and effective acute care management for reducing ICU/CICU mortality rates in emergency situations.

In the logistic regression analysis, the dependent variable was death. The predictors included sex, age, and hospital admission mode. The results are presented in TABLE 3.

The data included in TABLE 3 indicate that sex was not a predictor of ICU/CICU mortality in the studied population ($P = 0.6$). However, the results suggest that the older the patient is during their ICU/CICU stay, the higher the risk of death ($P < 0.001$). There is also a higher risk of death among patients admitted to the hospital on an urgent basis ($P < 0.001$).

DISCUSSION This study provides a comprehensive analysis of hospitalizations of patients with RA in Polish ICUs and CICUs over a decade of 2011–2021. The findings highlight significant trends and outcomes that are crucial for understanding the burden of severe RA complications and improving patient management strategies.

Trends in intensive care unit/cardiac intensive care unit admissions The study demonstrated an upward trend in ICU/CICU admissions and associated ICU/CICU mortality over the observed period, particularly in 2021, which could be attributed to the COVID-19 pandemic. The pandemic likely exacerbated existing health issues in RA patients, who are already at an increased risk for severe infections and complications due to their immunocompromised status and the use of immunosuppressive therapies. Of the analyzed patients, 165 were diagnosed with COVID-19 during their hospital stay between 2020 and 2021, and 125 individuals died.

Intensive care unit/cardiac intensive care unit mortality and comorbidities The ICU/CICU mortality rate among RA patients was notably high at 39.1%. This finding underscores the severe nature of RA and its associated complications. Cardiovascular and respiratory diseases were the most common primary diagnoses upon admission, consistent with existing literature that highlights these conditions as leading causes of ICU/CICU mortality in RA patients.[17,19] Interestingly, the highest mortality rates were observed in the patients with gastrointestinal and endocrine, nutritional, and metabolic diseases, which points to the complexity and severity of comorbid conditions in this population. Patients with RA are particularly susceptible to infections, as evidenced by the fact that sepsis was identified in 351 of ICU/CICU hospitalized individuals.

Admission patterns and outcomes A significant proportion of RA patients (63.9%) was admitted urgently, and they had higher ICU/CICU mortality rates than those admitted electively. This finding is critical, as it emphasizes the urgent need for timely and effective acute care management. The logistic regression analysis confirmed that urgent admissions and older age were significant predictors of ICU/CICU mortality. This aligns with previous studies suggesting that advanced age and the acute nature of hospital admissions are key factors influencing outcomes in critically ill RA patients.[3-5,9,11]

Sex disparities While the majority of hospitalizations concerned women, reflecting the higher prevalence of RA among them, sex did not significantly predict ICU/CICU mortality. This finding suggests that while RA more often affects women, the severity of outcomes in ICU/CICU settings is influenced more by age and the urgency of admission rather than sex.

Length of stay and disease groups The length of hospital stay varied significantly, with the longest

average stay associated with diseases of the skin and subcutaneous tissue and the shortest with pregnancy, childbirth, and puerperium. This variation reflects the different nature and severity of the conditions leading to the ICU/CICU admissions. The notably lower ICU/CICU mortality and shorter hospitalizations in the pregnancy-related group highlight the generally healthier status of these patients, as compared with those admitted for acute or severe RA complications.

Implications for clinical practice The findings of this study have several implications for clinical practice, as described below.

Early intervention and monitoring Given the high ICU/CICU mortality associated with urgent admissions, there is a need for proactive monitoring and early intervention strategies for RA patients, particularly those with known cardiovascular or respiratory comorbidities. Studies indicate that prompt detection and management of critical conditions, such as fluid overload, may help reduce mortality in acutely ill patients.[24] Noninvasive monitoring techniques, including chest X-rays enhanced with deep-learning models, could be instrumental in identifying early signs of patient deterioration and facilitating timely interventions, especially when invasive approaches are not feasible.

Comprehensive management plans Health care providers should develop comprehensive management plans that address both RA and its associated comorbidities to mitigate the risk of severe complications requiring ICU/CICU admissions. For end-of-life patients, maintaining an appropriate balance between essential interventions and nonbeneficial treatments is paramount. A focus on patient-centered care and minimizing unnecessary interventions can offer greater benefit, particularly through palliative and supportive methods.[25] This approach aligns with guidelines that advocate for respectful, dignified care plans and a balanced application of intensive treatments.

Resource allocation Understanding the factors leading to ICU/CICU admissions can help optimize resource allocation and improve the preparedness of health care facilities to manage severe RA cases effectively. Furthermore, circumstances such as the recent, rapidly progressive streptococcal toxic shock syndrome epidemic in Kraków underscore the importance of response capability for diverse emerging threats.[26]

The above implications are confirmed by a large European study examining ICU mortality in patients over 80 years old,[27] which found that delayed access to critical care, particularly in countries with lower health care expenditures, can exacerbate severity of the illness and boost mortality rates. This suggests that organizational factors and early access to ICU care for urgent RA admissions play a critical role in outcomes.

Limitations and future research While this study provides valuable insights, it has several limitations. Its retrospective design and reliance on hospital records may introduce bias due to inaccuracies in coding and reporting. Another limitation is a lack of data on the illness severity on admission, such as APACHE or SOFA scores, which restricts the ability to assess the impact of patient condition on outcomes. Similarly, the absence of information on baseline RA treatment (eg, conventional, targeted, and biological DMARDs) and ICU interventions (eg, mechanical ventilation, continuous renal replacement therapy, vasopressors) limits the understanding of how organ support may have influenced mortality. Furthermore, the study did not explore the impact of specific RA treatments on ICU/CICU outcomes, which could be an area for future research.

While urgent admissions and older age are well-established predictors of mortality in most ICU populations, our study highlights that patients with RA present additional complexities due to the burden of specific comorbidities, such as cardiovascular and respiratory diseases. These factors compound the already increased risk, making early intervention and comprehensive management strategies particularly important for this vulnerable group. No data on patient frailty on admission were available, despite frailty being a known predictor of mortality in critically ill patients, particularly among the elderly. This further constrains the analysis of baseline risk factors.

The analyzed data indicate that a notable portion of nonemergent admissions took place at the orthopedics and traumatology departments, raising the possibility that the ward of admission, rather than the urgency status alone, may play a role in influencing the prognosis. The fact that an admission was not classified as urgent does not necessarily mean it was elective. A substantial portion of such cases included, for example, transfers from other hospitals or compulsory admissions. These facts may represent a significant limitation of the above analysis and should be considered by the reader.

Future studies should aim to address these gaps by incorporating severity scores, treatment data, frailty assessments, and cause-specific mortality to provide a more comprehensive analysis. Further investigations could also examine the long-term outcomes of RA patients post-ICU/CICU discharge to provide a better understanding of their recovery and quality of life.

Conclusions This study highlights the significant burden of hospitalizations among patients with RA in Polish ICUs/CICUs from 2011 to 2021. The rising trend in the ICU/CICU admissions and associated mortality, particularly visible in 2021, underscores the heightened vulnerability of RA

patients to severe complications, exacerbated by the COVID-19 pandemic.

Key findings indicate a high overall ICU/CICU mortality rate of 39.1% among the RA patients in critical care, with cardiovascular and respiratory diseases being the most common primary diagnoses. The study also found that urgent admissions and older age were significant predictors of ICU/CICU mortality, emphasizing the need for timely and effective acute care management.

Sex did not significantly predict ICU/CICU mortality, despite the higher prevalence of hospitalizations among women. The length of hospital stay varied significantly across different disease groups, reflecting the diverse nature of the conditions leading to ICU/CICU admissions.

The findings underscore the need for proactive monitoring, early intervention, and comprehensive management plans that address both RA and its comorbidities to reduce severe complications and improve patient outcomes. Future research should focus on the long-term recovery and quality of life of RA patients post-ICU/CICU discharge and the impact of specific RA treatments on critical care outcomes.

ARTICLE INFORMATION

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Article

Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjogren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis

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Abstract: Background/Objectives: Sjögren's disease (SjD) is a chronic autoimmune disease primarily affecting exocrine glands, often leading to systemic complications and comorbidities. While SjD is known to impact quality of life, research on hospitalization trends, demographic characteristics, and factors influencing hospital stay duration remains limited. This study aims to analyze hospitalizations due to SjD in Poland between 2012 and 2023, identifying key trends, risk factors, and healthcare implications. **Methods**: A retrospective analysis was conducted using data from the National General Hospital Morbidity Study, covering 13,999 first-time hospitalizations with an SjD diagnosis (ICD-10: M35.0). Descriptive statistics were applied to evaluate patient demographics, hospitalization trends, and comorbidities. The Mann–Whitney U test and chi-square test were used to compare groups, while a linear regression model identified predictors of hospital stay duration. **Results**: Women accounted for 90.3% of hospitalizations, with a median age of 57 years, compared to 53 years for men. The hospitalization rate fluctuated over time, with a decline in 2020, possibly due to the COVID-19 pandemic, followed by an increase in 2021–2023. The most common comorbidities included musculoskeletal disorders (17.8%), cardiovascular diseases (16.6%), and endocrine disorders (13.6%). Women had longer hospital stays than men (median 5 vs. 4 days, $p < 0.001$). Older patients and those admitted in emergency settings had significantly longer hospital stays. The overall mortality rate was low (0.2%), with a slightly higher but statistically insignificant mortality rate among men. **Conclusions**: The study highlighted the increasing burden of SjD-related hospitalizations and the need for improved outpatient management to reduce inpatient admissions. Factors such as older age, female sex, and emergency admissions were associated with prolonged hospitalization. Strengthening early diagnostic strategies, optimizing access to specialist care, and monitoring comorbidities could enhance patient outcomes and reduce hospital resource utilization.

Keywords: Sjögren's disease; Sjögren's syndrome; epidemiology; rheumatology; autoimmune disease

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1. Introduction

Sjögren's disease (SjD, formerly referred to as Sjögren's syndrome or Sjögren syndrome) is a chronic autoimmune disease primarily affecting exocrine glands, leading to sicca symptoms, such as xerophthalmia and xerostomia. However, beyond glandular dysfunction, SjD is a systemic condition with the potential to involve multiple organ systems, increasing the risk of severe complications, comorbidities, and long-term morbidity.

Although numerous studies have explored the immunological and clinical aspects of SjD, research focusing on hospitalization patterns, demographic characteristics, and factors influencing the length of hospital stay remains limited. Given the progressive nature of SjD and its frequent coexistence with other autoimmune and metabolic diseases, understanding these factors is crucial for optimizing healthcare strategies and improving patient outcomes.

This study aims to provide a comprehensive analysis of first-time hospitalizations associated with SjD in Poland between 2012 and 2023. By evaluating hospitalization frequency, patient demographics, comorbidities, and factors affecting the length of hospital stay, we seek to identify key trends that may inform better disease management, early intervention strategies, and healthcare resource allocation. Our findings can contribute to a more integrated approach to SjD care, emphasizing early diagnosis, outpatient management, and targeted interventions to reduce the burden of hospital admissions.

Sjögren's disease is classified as either primary (pSjD) or secondary (sSjD), depending on whether it occurs independently or alongside other systemic autoimmune diseases [1,2]. The term "secondary" is most frequently used to describe SjD associated with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or systemic sclerosis (SS). SjD can also coexist with other autoimmune conditions like celiac disease, autoimmune hepatitis, hypothyroidism, and Grave's disease [3]. The ratio of pSjD to sSjD varies between sources: 1/3 in [4] and 2/5 in [5]. Studies indicate that SjD occurs in 19.5% of patients with rheumatoid arthritis and in 13.96% of patients with systemic lupus erythematosus, with female-to-male ratios of 14.7:1 and 16.82:1, respectively [6].

Sjögren's disease primarily affects middle-aged women, with a female-to-male ratio of 9:1 [1,6,7]. The disease is most commonly diagnosed in the fifth or sixth decade of life [8]. The estimated prevalence of SjD is approximately 0.5%, with an annual incidence rate of 4 cases per 1000 individuals [2,9]. According to a meta-analysis by Qin et al. (2015), the cumulative incidence is 6.92 per 100,000 persons per year, while the prevalence is 60.82 cases per 100,000 inhabitants [8,9]. SjD can also be diagnosed in children, although this is less common [10].

Mortality analyses have shown that the leading causes of death in SjD patients are infections, cardiovascular diseases, and solid organ or hematologic malignancies. Although the overall mortality risk in SjD is not significantly higher than in the general population, it may be increased in patients with a more severe disease course. Factors contributing to a higher mortality risk include older age at diagnosis, male sex, parotid gland enlargement, extraglandular organ involvement, vasculitis, the presence of SS-B antibodies, hypocomplementemia, and cryoglobulinemia [11].

The pathogenesis of SjD is complex, involving genetic, environmental, and immune dysregulation factors. Genetic predispositions, such as specific HLA (human leukocyte antigen) alleles and polymorphisms in IFN (interferon) pathways, along with epigenetic modifications, contribute to disease susceptibility [12]. Environmental factors, like viral infections (e.g., Epstein–Barr virus), may trigger SjD through molecular mimicry and apoptosis [13]. Immune dysregulation occurs with epithelial cells actively presenting antigens and secreting proinflammatory cytokines, while overactivation of the IFN pathway stimulates B-cells and autoantibody production. T-cells (Th1 and Th17) further amplify inflammation [14]. The hallmark histological feature is focal lymphocytic sialadenitis (FLS),

leading to glandular damage and systemic complications, including dry eyes, mouth, and potential involvement of the lungs, kidneys, and nervous system [15]. Severe cases may lead to non-Hodgkin lymphoma [16].

Sjögren's disease manifests through a variety of glandular and systemic symptoms. The most common signs are dryness of the eyes and mouth, affecting nearly all patients. This dryness can cause difficulty swallowing (dysphagia), altered taste (dysgeusia), and discomfort, such as pain and burning sensations. Dryness of the oral mucosa, dental issues like caries, and enlarged salivary glands, particularly the parotid glands, are also frequently observed. Ocular symptoms, including dry eyes, photosensitivity, and foreign body sensations, are common, often exacerbated in dry or windy environments, potentially causing long-term corneal damage. Other glandular manifestations include dryness of the respiratory tract, leading to hoarseness and a dry cough, as well as reduced vaginal secretion and gastrointestinal dysfunction [16–18]. Systemically, fatigue, sleep disorders, anxiety, and chronic pain are prevalent in 70–80% of patients. Musculoskeletal symptoms such as joint pain, muscle pain, and morning stiffness are common, though arthritis is less frequent [19]. Dermatologically, patients may experience dry skin (xerosis), annular erythema, and vasculitic lesions [20]. In up to 20% of cases, pulmonary issues such as dry cough, bronchiolitis, or interstitial lung disease (ILD) are seen, while cardiac involvement is rarer, though it can include cerebrovascular events and myocardial infarction [21,22]. Neurological involvement may include neuropathy, cognitive dysfunction, and sleep disturbances [23]. Renal and gastrointestinal complications like chronic nephritis and motility disorders are also common [24,25]. Furthermore, SjD carries an increased risk of non-Hodgkin lymphoma, particularly in active disease areas like the salivary glands [1]. In pregnancy, women with SjD face an elevated risk of miscarriage, preterm birth, and neonatal lupus, with some babies experiencing congenital heart block [26].

Sjögren's disease is diagnosed using the 2016 ACR/EULAR (American College of Rheumatology/European Alliance of Associations for Rheumatology) classification criteria, which combine elements of previous systems to improve patient selection for clinical trials. These criteria focus on primary SjD and require a score of $\geq$4 based on objective markers, such as anti-SSA/Ro (anti-Sjögren's syndrome-related antigen A) antibody positivity, ocular staining scores, Schirmer's test results, and salivary gland function [27].

Autoantibodies, including ANA (antinuclear antibodies), RF (rheumatoid factor), anti-Ro/SSA, and anti-La/SSB (anti-Sjögren's syndrome-related antigen B), are key immunological markers for SjD, though isolated anti-La/SSB positivity is excluded [27,28]. Labial salivary gland biopsy remains crucial, especially in seronegative patients, as it confirms lymphocytic infiltration and assesses lymphoma risk [15,29]. Other diagnostic tests include Schirmer's test for tear production, ocular staining to evaluate eye surface damage, and sialometry to measure unstimulated saliva flow [27]. SjD diagnosis requires comprehensive clinical evaluation to rule out other conditions. Classification criteria help guide diagnosis but should be used alongside clinical judgment.

To assess disease severity, EULAR developed two indices: ESSPRI (EULAR Sjögren's Syndrome Patient Reported Index) and ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index). A newer version, ClinESSDAI, omits immunological parameters to better assess clinical manifestations. These tools help monitor disease progression and evaluate treatment effectiveness [30,31].

The treatment of Sjögren's disease requires an interdisciplinary approach, encompassing both symptomatic therapy for sicca symptoms and immunosuppressive treatment in cases of organ involvement. Due to the lack of a curative method, treatment focuses on symptom relief and improving patients' quality of life, necessitating collaboration among

various specialists, including general practitioners, immunologists, rheumatologists, ophthalmologists, otolaryngologists, and dentists.

For the management of dry mouth (xerostomia), fluoride, artificial saliva, and saliva-stimulating medications, such as pilocarpine and cevimeline, are used. Patients are advised to avoid factors that exacerbate dryness, such as xerogenic medications, caffeine, alcohol, and smoking. For dry eyes (xerophthalmia), tear substitutes, eye drops, ointments, and, in more severe cases, cyclosporine are employed. In some instances, procedures such as punctal occlusion or corneal transplantation may be necessary. The treatment of dry skin (xeroderma) and nasal dryness involves the use of emollients and moisturizing agents [32,33].

Systemic symptoms, such as fatigue and arthritis, are managed with anti-inflammatory medications, including hydroxychloroquine, methotrexate, azathioprine, and mycophenolate. In more advanced cases, when symptoms are refractory to conventional treatment, immunosuppressive drugs such as rituximab, cyclophosphamide, or belimumab are used. Fatigue management may also involve regular physical exercise [32,33].

The use of immunosuppressive drugs in the treatment of Sjögren's disease, particularly in cases with systemic involvement, carries a risk of infectious complications, including opportunistic infections and viral reactivations [34]. Prolonged therapy may also lead to hematologic abnormalities, organ toxicity, metabolic disturbances, and bone loss. Regular monitoring and careful risk assessment are essential to minimize these complications [35–38].

2. Materials and Methods

2.1. Data Sources

This retrospective study aimed to characterize selected factors related to the hospitalization of patients with a first-time diagnosis of Sjögren's syndrome over the years 2012–2023. The study was based on anonymized hospital morbidity data obtained from the National General Hospital Morbidity Study, conducted by the National Institute of Public Health NIH—National Research Institute.

The dataset included anonymized patient records. The data were systematically reported by hospitals using the General Hospital Statistical Card (Mz/Szp-11), ensuring high completeness and accuracy due to the legal obligation for inpatient healthcare facilities to report hospitalizations.

2.2. Study Population

The study population consisted of all hospitalizations in Poland between 1 January 2012 and 31 December 2023, during which the ICD-10 code M35.0 (Sjögren's disease) appeared for the first time. The inclusion criteria for this analysis were:

1. The presence of ICD-10 code M35.0 as either the principal or additional diagnosis.
2. Hospital admission recorded within the study period (2012–2023).
3. The ICD-10 code M35.0 appearing for the first time during the hospitalization.

Hospitalizations that did not meet these criteria were excluded from the study. Based on these criteria, and with the caveat of potential coding inaccuracies, the study can be considered to include all initial hospitalizations of patients with a newly diagnosed Sjögren's disease. The final dataset comprised 13,999 hospitalization records, with a female predominance (12,642 cases; 90.3%) and a smaller proportion of male patients (1357 cases; 9.7%). This study covered nearly 100% of hospitalizations for SjD in Poland, ensuring a robust and representative sample for epidemiological assessment.

2.3. Statistical Methodology

The statistical analysis comprised descriptive statistics, including frequency distributions, as well as the calculation of mean and median for quantitative variables. The Mann–Whitney U test and the chi-square test were applied. A significance threshold of $p < 0.05$ was established, and given the large sample size, effect size measures were also reported. Additionally, a linear regression model was employed to analyze the data. Predictor multicollinearity was evaluated using the variance inflation factor (VIF). Variables were introduced into the model in sequential blocks to assess changes in the R-squared value with each added predictor. All statistical analyses were performed using the R software package (version 4.3.3).

2.4. Use of GenAI in Writing

During the preparation of this work, the authors used ChatGPT (Model GPT-4o) for language correction. After using these tools/services, the authors reviewed and edited the content as needed and therefore take full responsibility for the content of the publication.

3. Results

3.1. General Findings

A total of 13,999 hospitalizations related to Sjögren's disease were analyzed. The majority of hospitalized patients were women (90.3%; n = 12,642), while men accounted for 9.7% (n = 1357). The age of patients ranged from 1 to 95 years, with a median age of 56 years (IQR = 22). The data suggest that Sjögren's disease is primarily diagnosed in middle-aged and older adults, with a peak prevalence observed in patients aged 50–60 years.

3.2. Trends in Hospitalization

Between 2012 and 2023, the hospitalization rate for patients with Sjögren's disease showed significant fluctuations. Figure 1 presents the number of hospitalizations in the respective years covered by the analysis. From 2012 to 2014, hospitalizations declined, reaching their lowest point in 2014, likely due to improved disease management, changes in hospitalization criteria, or healthcare system adjustments. However, from 2015 onward, hospitalizations increased, possibly reflecting a higher diagnostic rate or changes in treatment and admission practices.

A period of relative stability between 2016 and 2019 suggests the healthcare system adapted to these trends. In 2020, a sharp decline occurred, likely due to the COVID-19 pandemic limiting hospital access for non-COVID cases. From 2021, a steady increase in hospitalizations was observed, potentially due to delayed admissions from the pandemic and the return to normal hospital operations. By 2023, hospitalizations reached their highest level in the analyzed period, possibly indicating a growing need for hospital treatment in Sjögren's disease or increased diagnostic awareness among physicians.

3.3. Demographic Characteristics

The patients' ages ranged from 1 to 95 years, with a median age of 56 years (IQR: 22). Females had a slightly higher median age (57 years) compared to males (53 years), and this difference was statistically significant ($p < 0.001$). The mean age for all participants was 54.2 years, with females having a similar mean age (54.8 years) and males being significantly younger (48.8 years). These findings align with the well-documented higher prevalence of Sjögren's disease among middle-aged and older women. Figure 2 shows the age distribution of the patients.

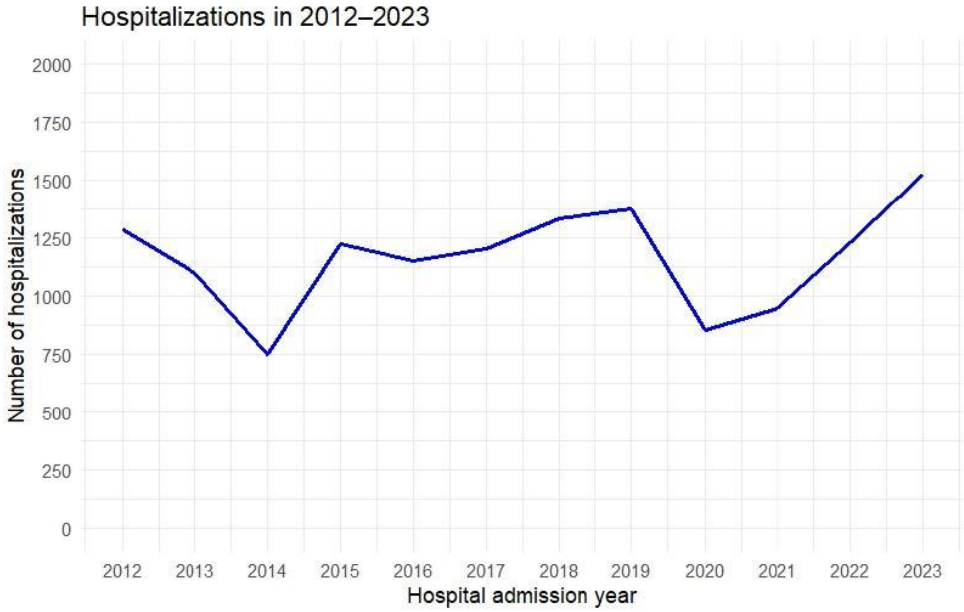

Figure 1. Number of hospitalizations by year.

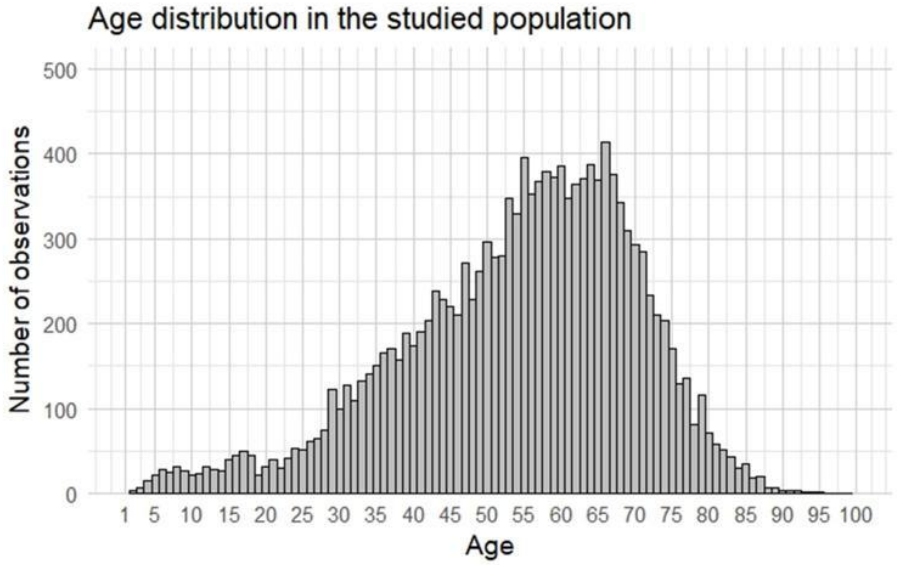

Figure 2. Age distribution of the patients.

There were significantly more rural inhabitants than urban dwellers (N = 4439, 31.7% vs. N = 9507, 67.9%; $p < 0.001$; 53 missing data points regarding the size of the place of residence were recorded). The distribution of residence also differed between genders, with a slightly higher proportion of men living in urban areas (36.0%) compared to women (31.3%) ($p < 0.001$). This suggests a potential disparity in healthcare access or disease recognition between urban and rural populations. Table 1 provides an overview of demographic characteristics.

Table 1. Demographic and clinical data for the comparison of male and female groups.

Variable		All Participants	Females	Males	*p*	Effect Size
Age					<0.001 [a]	0.150 [c]
	Min–Max	1–95	1–95	2–90		
	Me (IQR)	56 (22)	57 (21)	53 (28)		
	M (SD)	54.2 (15.9)	54.8 (15.3)	48.8 (19.8)		
Place of residence					<0.001 [b]	0.031 [d]
City	N (%)	4439 (31.8%)	3951 (31.3%)	488 (36.0%)		
Village	N (%)	9507 (68.2%)	8659 (68.5%)	858 (63.4%)		
Lengths of stay (LOS)					<0.001 [a]	0.097 [c]
	Min–Max	0–373	0–373	0–53		
	Me (IQR)	5 (6)	5 (6)	4 (6)		
	M (SD)	6.40 (6.85)	6.48 (6.97)	5.71 (5.55)		
Number of deaths					0.411 [b]	0.007 [d]
	N (%)	28 (0.2%)	24 (0.1%)	4 (0.3%)		

[a] Mann–Whitney U test; [b] chi-square test; [c] Glass's rank correlation coefficient; [d] Cramér's V coefficient.

3.4. Length of Hospital Stay and Mortality

The length of stay varied widely, ranging from 0 to 373 days, with a median of 5 days for all participants. Males had a shorter median hospital stay (4 days) compared to females (5 days), and this difference was statistically significant ($p < 0.001$). The mean hospital stay was also slightly longer for females (6.48 days) than for males (5.71 days), suggesting that women with Sjögren's disease might require more extended inpatient care.

The overall mortality rate among hospitalized patients was very low (0.2%, with 28 recorded deaths). Mortality was slightly higher in males (0.3%) compared to females (0.1%), but the difference was not statistically significant ($p = 0.411$). This indicates that while Sjögren's disease itself is not directly associated with high mortality, comorbidities and complications might contribute to rare cases of fatal outcomes.

3.5. Admission Type and Hospital Departments

The majority of hospitalizations were planned admissions (80.7%; n = 11,294; among females: 80.7%; n = 10,203; among males: 80.4%; n = 1901), while emergency admissions constituted 19.2% (n = 2686) ($p < 0.001$). Most patients were admitted to the department of rheumatology (69.7%), followed by the department of internal medicine (7.9%). This distribution suggests that SS patients are primarily managed in specialized hospital units rather than general medical wards.

3.6. Comorbid Conditions

A total of 9837 patients (70.3%; among females: 70.1%; n = 8856; among males: 72.4%; n = 981) had the ICD-10 code M35.0 as their primary diagnosis, while the remaining patients had M35.0 as a comorbid condition. Table 2 outlines the most common comorbidities among hospitalized patients. The most prevalent coexisting conditions are listed below.

- Diseases of the musculoskeletal system and connective tissue (M00–M99) were the most frequent comorbid conditions, affecting 17.8% of hospitalizations. This aligns with the known autoimmune nature of Sjögren's disease, which frequently coexists with other rheumatologic conditions. When stratified by sex, musculoskeletal and connective tissue diseases were similarly common in both females (17.9%) and males (16.9%).

- Diseases of the circulatory system (I00–I99) were the second most common comorbidity with Sjögren's disease, which has been previously reported in autoimmune diseases. Circulatory system diseases affected 16.8% of females and 15.3% of males, indicating a slightly higher cardiovascular burden among women.
- Endocrine, nutritional, and metabolic diseases (E00–E90) accounted for 13.6% of hospitalizations, indicating a possible association with metabolic disorders such as diabetes or thyroid dysfunction, which are known to co-occur with autoimmune diseases. These conditions were more prevalent among females (14.2%) compared to males (8.7%). Notably, a significant proportion of patients also had autoimmune comorbidities, including rheumatoid arthritis and systemic lupus erythematosus, which may indicate a broader spectrum of systemic autoimmune involvement.

Table 2. The frequencies of comorbid conditions in the analyzed period.

	N (Percentage of Hospitalizations)		
ICD-10 Code	**All Participants**	**Females**	**Males**
Certain infectious and parasitic diseases A00–B99	141 (1.0%)	115 (0.9%)	26 (1.9%)
Neoplasms C00–D49	353 (2.5%)	311 (2.5%)	42 (3.1%)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism D50–D89	422 (3.0%)	391 (3.1%)	31 (2.3%)
Endocrine, nutritional, and metabolic diseases E00–E90	1907 (13.6%)	1789 (14.2%)	118 (8.7%)
Mental and behavioral disorders F00–F99	105 (0.7%)	99 (0.8%)	6 (0.4%)
Diseases of the nervous system G00–G99	324 (2.3%)	297 (2.4%)	27 (2.0%)
Diseases of the eye and its adnexa, ear, and mastoid process H00–H95	205 (1.5%)	189 (1.5%)	16 (1.2%)
Diseases of the circulatory system I00–I99	2328 (16.6%)	2120 (16.8%)	208 (15.3%)
Diseases of the respiratory system J00–J99	773 (5.5%)	657 (5.2%)	116 (8.5%)
Diseases of the digestive system K00–K93	770 (5.5%)	686 (5.4%)	84 (6.2%)
Diseases of the skin and subcutaneous tissue L00–L99	326 (2.3%)	295 (2.3%)	31 (2.3%)
Diseases of the musculoskeletal system and connective tissue other than ankylosing spondylitis M00–M99 without M35	2494 (17.8%)	2265 (17.9%)	229 (16.9%)
Diseases of the genitourinary system N00–N99	560 (4.0%)	493 (3.9%)	67 (4.9%)
Pregnancy, childbirth, and the puerperium O00–O99	65 (0.5%)	65 (0.5%)	0
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified R00–R99	248 (1.8%)	220 (1.7%)	28 (2.0%)
Injury, poisoning, and certain other consequences of external cause S00–T98	57 (0.4%)	49 (3.9%)	8 (0.6%)

The low proportion of infection-related codes among patients hospitalized for the first time with a diagnosis of Sjögren's disease may stem from the absence of immunosuppressive treatment at the time of diagnosis, which would otherwise increase susceptibility to infections.

3.7. Predictors of Length of Stay (LOS)

Table 3 presents the results of the linear regression analysis predicting LOS in the analyzed group. The results presented in the table indicate that women had a significantly longer LOS (M = 6.48; Me = 5.00) than men (M = 5.71; Me = 4.00), although the relationship was not strong. It was also found that the older the patient, the longer the LOS. Rural

residents had a longer LOS than urban residents (M = 6.70; Me = 6 vs. M = 6.28; Me = 5). An important predictor of LOS was also the emergency mode of admission (M = 8.57; Me = 8 compared to M = 5.86; Me = 5 for the planned mode of admission).

Table 3. Results of the linear regression analysis predicting LOS.

Predictor	B (SE)	β	*p*	$R^2_{adj.}$	Model Comparison	
					ΔR^2	*p*
Intercept	2.53 (0.23)		<0.001			
Gender (0—Males, 1—Females)	0.39 (0.17)	0.02	0.023	0.002		
Age	0.04 (0.003)	0.17	<0.001	0.03	0.03	<0.001
Size of the place of residence (0—village, 1—city)	−0.66 (0.11)	−0.05	<0.001	0.03	0.003	<0.001
Mode of admission (0—planned, 1—emergency)	2.57 (0.13)	0.17	<0.001	0.06	0.03	<0.001

B—unstandardized coefficient; SE—standard error; β—standardized coefficient.

4. Discussion

This study analyzed hospitalization data for patients diagnosed with Sjögren's disease in Poland between 2012 and 2023, providing a comprehensive overview of hospitalization frequency, demographic characteristics, and clinical factors influencing the length of hospital stay.

The analysis of 13,999 hospitalizations revealed a significant predominance of women (90.3%), which aligns with the commonly reported female-to-male ratio in SjD (9:1) [1,6,7]. The median age of female patients was 57 years, while for male patients, it was 53 years, consistent with epidemiological data indicating the most frequent diagnosis occurring in the fifth or sixth decade of life [8]. However, it is noteworthy that the median age among hospitalized men was slightly lower, which may suggest either an earlier onset of symptoms requiring hospitalization or a different disease progression pattern in men.

Demographic differences between rural and urban patients, including longer hospital stays among rural residents, may indicate disparities in access to medical care, delayed specialist consultations, or a different disease burden profile in the rural population.

During the study period, fluctuations in the number of hospitalizations were observed: a decline from 2012 to 2014, followed by an increase starting in 2015, a period of relative stabilization between 2016 and 2019, and then a sharp drop in 2020, likely related to the COVID-19 pandemic. There are reports, based on an analysis of 53 articles published between December 2019 and September 2021, indicating that the COVID-19 pandemic and the measures adopted significantly affected access to healthcare for patients with non-COVID-19 conditions. A generalized reduction in the use of health services was observed, particularly in the early stages of the pandemic. The most frequently identified barriers to accessing care for non-COVID-19 patients were related to both the healthcare system and the population. On the system side, the primary issue was a lack of resources, while on the population side, predisposing factors, such as fear of contagion, stigma, and anticipation of access difficulties, were common. Enabling factors, including lower socioeconomic status and increased technological barriers, further limited access. Overall, the pandemic not only introduced new obstacles but also exacerbated pre-existing inequalities in access to care [39,40].

The increases observed after 2021 may indicate a "catch-up" effect in diagnostic and therapeutic backlogs and a return to the standard hospital admission process. Additionally, 2023 recorded the highest hospitalization rate, which may reflect both improved disease detection (increased diagnostic vigilance among physicians of various specialties) and a genuine rise in the demand for hospital treatment due to the development of complications and comorbidities.

Women remained in the hospital longer than men (median 5 vs. 4 days), which may be related to differences in disease progression, a higher prevalence of coexisting autoimmune disorders among female patients [1,2], or differing therapeutic needs. A correlation was also observed between age and hospitalization duration: older patients required longer hospital stays, potentially due to more frequent complications, a greater number of comorbidities, or the need for more complex diagnostics [11,41,42]. Similarly, emergency admissions were significantly associated with longer hospital treatment—patients admitted with acute deterioration, symptom exacerbation, or with complications typically require comprehensive care and in-depth diagnostics.

According to previous reports, the low mortality rate in the studied group (0.2%) suggests that Sjögren's disease itself is not, in most cases, a direct cause of high mortality [11]. However, the slightly higher mortality among men (though statistically insignificant) may indicate a more severe course of the disease in this group, warranting further research into immunological mechanisms and hormonal differences.

Additionally, pSjD is a chronic, slowly progressing disease that does not pose a direct life threat to most patients, as evidenced by a 10-year cumulative survival rate exceeding 90%. Subgroup analyses and sensitivity tests have not demonstrated a significant increase in mortality among pSjD patients.

The slightly higher mortality among men (though statistically insignificant) may suggest a more severe course of the disease in this group, requiring further research into immunological mechanisms and hormonal differences.

The most common coexisting conditions were musculoskeletal disorders (17.8%), cardiovascular diseases (16.6%), and endocrine disorders (13.6%). This can be attributed, on one hand, to the frequent coexistence of SjD with other rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus [2,6], and on the other hand, to the widespread prevalence of cardiovascular and metabolic diseases, particularly among older individuals. The presence of various coexisting endocrine disorders (e.g., thyroid diseases) is also consistent with previous observations that patients with autoimmune diseases are at higher risk of developing multi-organ autoimmune disorders [1,2].

The study results confirmed that SjD poses a significant challenge to the healthcare system, as evidenced by the increasing number of hospitalizations in recent years. The obtained data suggest the need for:

- Strengthening outpatient care and early diagnosis, particularly in high-risk populations (middle-aged women and patients suspected of having other autoimmune diseases), which could help reduce the necessity for planned hospitalizations.
- Improving access to specialists (rheumatologists, ophthalmologists, dentists, and endocrinologists) in outpatient care, especially in smaller towns, to prevent exacerbations and complications requiring hospital treatment.
- Addressing the mode of patient admissions—emergency hospitalizations are associated with a significant increase in hospital stay duration, indicating that optimizing the diagnostic and therapeutic process in outpatient consultations could reduce the number of acute admissions.
- Monitoring coexisting diseases, particularly endocrine and cardiovascular conditions, which may improve patient prognosis and quality of life.

The study has several limitations that should be taken into account when interpreting the results. Most of these limitations stem from the nature of the data source, which relied on administrative hospital discharge records containing only ICD-10 diagnostic codes, along with basic demographic and hospitalization information. These records do not provide a complete clinical picture of patients, as they lack detailed medical histories, outpatient care data, and follow-up information. Consequently, it was not possible to track patient outcomes after discharge, preventing the assessment of long-term disease progression, readmission rates, or treatment effectiveness. Furthermore, the dataset did not include clinical severity indicators, laboratory results, or standardized disease activity measures such as ESSDAI or ESSPRI, precluding the stratification of patients by disease activity and limiting insights into the relationship between disease severity and hospitalization. The absence of such data restricts the ability to fully assess the clinical conditions of hospitalized patients and their longer-term outcomes. Additionally, the influence of specific pharmacological treatments, such as hydroxychloroquine, rituximab, or other immunosuppressive therapies, on hospitalization rates could not be assessed due to the lack of detailed treatment data within the administrative records. Therefore, while the study offers valuable insights into the epidemiology and hospitalization patterns of Sjögren's disease in Poland, it does not capture the full clinical spectrum, long-term burden, or post-hospitalization disease course. Future research based on clinical registries or prospective cohort studies, incorporating detailed clinical data and follow-up information, will be essential to better understand the long-term outcomes, the specific treatment effectiveness, and the impact of disease severity on hospitalization patterns and overall patient prognosis.

Another important limitation is the reliance on ICD-10 codes for identifying cases of Sjögren's disease. Although the ICD-10 system is a widely used classification tool, its accuracy depends on correct coding practices by healthcare providers, which may be influenced by differences in clinical experience, institutional policies, and coding conventions. Misclassification, undercoding, or overcoding of Sjögren's disease cannot be entirely excluded and may have impacted the completeness and accuracy of case identification. This inherent limitation should be considered when interpreting the findings and highlights the need for future studies using clinical registries or validated diagnostic criteria applied directly at the point of care.

Furthermore, retrospective studies are subject to confounding factors that cannot always be accounted for, such as differences in hospital admission criteria, regional disparities in healthcare access, and variations in clinical management strategies over time. Additionally, missing values in the dataset necessitated exclusions, which may introduce selection bias. These factors may influence hospitalization trends and patient outcomes.

Despite these limitations, our study provides valuable epidemiological insights due to the large sample size and the nationwide coverage of the database, which captures nearly 100% of hospitalizations in Poland. This extensive dataset enhances the reliability of our findings and allows for meaningful observations on hospitalization trends in Sjögren's disease. Future prospective studies incorporating clinical, biochemical, and pharmacological data would help address the limitations of this analysis and provide a more comprehensive understanding of the disease course and treatment outcomes.

5. Conclusions

The conducted study confirms that Sjögren's disease is most frequently diagnosed in middle-aged and older women, with them being the most frequently hospitalized, and the dynamics of hospitalization between 2012 and 2023 reflect both changes in the availability of hospital services and increasing clinical vigilance. Longer hospitalizations in women, older individuals, and in emergency settings highlight the importance of early diagnosis

and effective conservative treatment, which can reduce the number of flare-ups requiring hospital intervention. The low mortality rate in the analyzed group suggests that although SjD often causes a significant decrease in quality of life and requires frequent healthcare interactions, it rarely directly leads to death. However, the growing awareness of the role of comorbidities (endocrine, cardiological, and others) in the course of SjD emphasizes the need for further research and the development of integrated care models for patients.

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Informed Consent Statement: Patient consent was waived due to the study being a retrospective analysis of anonymized hospitalization data, which did not require patient identification or involvement.

Data Availability Statement: Data are available upon reasonable request according to ICMJE requirements. Data shared: All the individual participant data were collected during the trial, after deidentification. Available documents: study protocol, statistical analysis, analytic code. When will data be available: beginning three months and ending two years following the article's publication. With whom: researchers who provide a methodologically sound proposal. For what type of analyses: to achieve the aim of the approved proposal. By what mechanism will data be made available: The proposal should be directed to julia-domanska03@wp.pl.

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7. Podsumowanie

Praca przeglądowa przedstawia ewolucję strategii leczenia reumatoidalnego zapalenia stawów na przestrzeni wieków – od historycznych, empirycznych metod po nowoczesne, celowane terapie biologiczne i syntetyczne. Przeanalizowano kluczowe etapy rozwoju strategii terapeutycznych RZS, począwszy od prymitywnych metod leczenia w starożytności, poprzez wprowadzenie glikokortykosteroidów, klasycznych syntetycznych leków modyfikujących przebieg choroby, aż po przełomowe wprowadzenie biologicznych leków modyfikujących przebieg choroby i inhibitorów kinaz Janusowych (JAK).

Historia leczenia RZS ukazuje stopniowe odchodzenie od leczenia objawowego na rzecz strategii ukierunkowanych na mechanizmy immunopatologiczne leżące u podłoża choroby. Kluczową rolę w tej ewolucji odegrało lepsze poznanie patogenezy choroby, co umożliwiło opracowanie celowanych terapii ograniczających proces zapalny i destrukcję stawów. Istotnym elementem współczesnego leczenia jest wczesne wdrażanie agresywnych terapii, monitorowanie skuteczności leczenia, dążenie do remisji oraz personalizacja terapii w oparciu o biomarkery i profil pacjenta.

Współczesne leczenie RZS opiera się na złożonym, wielokierunkowym podejściu, co pozwala nie tylko kontrolować objawy, ale także spowalniać postęp choroby i ograniczać jej skutki systemowe. Postęp w zakresie terapii celowanych i leków biologicznych znacząco poprawił rokowanie i jakość życia pacjentów z RZS, jednak nadal kluczowe pozostaje monitorowanie bezpieczeństwa długoterminowego, zwłaszcza w kontekście infekcji, chorób sercowo-naczyniowych oraz ryzyka nowotworów.

Przeprowadzona analiza populacyjna obejmująca hospitalizacje pacjentów z reumatoidalnym zapaleniem stawów w polskich oddziałach intensywnej terapii oraz kardiologicznych oddziałach intensywnej terapii w latach 2011-2021 ukazuje narastające obciążenie systemu ochrony zdrowia w tej grupie chorych. Zidentyfikowano istotny wzrost liczby przyjęć do oddziałów intensywnej terapii w 2021 roku, co prawdopodobnie jest związane z pandemią COVID-19 i jej wpływem na populację pacjentów z RZS.

Spośród 3066 analizowanych hospitalizacji, odnotowano wysoką śmiertelność wynoszącą 39,1%. Najczęstsze przyczyny przyjęć do ICU/CICU w tej grupie pacjentów to choroby układu krążenia, choroby układu oddechowego oraz powikłania narządowe samego RZS. Szczególnie wysoka śmiertelność występowała u pacjentów z chorobami układu pokarmowego (58,5%) oraz chorobami endokrynologicznymi i metabolicznymi (61,5%), co podkreśla znaczenie współistniejących chorób ogólnoustrojowych dla rokowania pacjentów z RZS.

Analiza wykazała, że nagły tryb przyjęcia oraz starszy wiek pacjentów istotnie zwiększały ryzyko zgonu podczas hospitalizacji w oddziałach intensywnej terapii. Z kolei płeć pacjentów nie była istotnym predyktorem śmiertelności w tej grupie. Wyniki te potwierdzają, że stan ogólny pacjenta, współchorobowość oraz charakter przyjęcia do szpitala (planowe vs nagłe) mają kluczowe znaczenie dla rokowania.

Przeprowadzona analiza populacyjna obejmująca hospitalizacje pacjentów z nowo rozpoznanym zespołem Sjögrena w Polsce w latach 2012-2023 pozwoliła na ocenę trendów hospitalizacji, charakterystyki demograficznej oraz czynników wpływających na długość pobytu w szpitalu. Zidentyfikowano zmienną dynamikę liczby hospitalizacji — po spadku w latach 2012-2014, od 2015 roku odnotowano wzrost liczby przyjęć, z wyraźnym załamaniem w 2020 roku, prawdopodobnie wynikającym z pandemii COVID-19, a następnie ponownym wzrostem w latach 2021-2023.

Większość pacjentów stanowili mieszkańcy terenów wiejskich, a dominującą grupą były kobiety (90,3%), co jest zgodne z epidemiologią zespołu Sjögrena. Mediana wieku kobiet wynosiła 57 lat, natomiast mężczyzn 53 lata. Hospitalizacje kobiet były istotnie dłuższe niż mężczyzn (mediana 5 vs. 4 dni), co może wynikać z większej współchorobowości lub bardziej złożonego przebiegu choroby.

Najczęstsze współistniejące choroby to choroby układu mięśniowo-szkieletowego (17,8%), choroby układu krążenia (16,6%) oraz choroby endokrynologiczne (13,6%). Zdecydowana większość hospitalizacji miała charakter planowy (80,7%), a przyjęcia nagłe były istotnym czynnikiem wydłużającym pobyt w szpitalu. Całkowita śmiertelność była bardzo niska

(0,2%), co sugeruje, że zespół Sjögrena rzadko prowadzi do bezpośredniego zagrożenia życia podczas pierwszej hospitalizacji.

8. Wnioski

1. Ewolucja leczenia RZS odzwierciedla postęp wiedzy o immunopatogenezie choroby, który umożliwił odejście od leczenia wyłącznie objawowego na rzecz strategii celowanych, ukierunkowanych na kluczowe mechanizmy zapalne.
2. Wczesna diagnostyka i szybkie wdrożenie skutecznego leczenia, szczególnie opartego na metotreksacie oraz terapiach biologicznych oraz celowanych syntetycznych istotnie poprawia rokowanie pacjentów, zwiększa szanse na osiągnięcie remisji i zmniejsza ryzyko niepełnosprawności.
3. Terapie biologiczne i inhibitory JAK zrewolucjonizowały leczenie RZS, umożliwiając personalizację terapii i wybór leków dostosowanych do indywidualnych cech pacjenta, w tym jego odpowiedzi immunologicznej, chorób współistniejących oraz profilu bezpieczeństwa.
4. Pomimo znacznych postępów terapeutycznych RZS nadal pozostaje chorobą nieuleczalną, wymagającą dożywotniego monitorowania i dostosowywania leczenia, co podkreśla potrzebę dalszych badań nad nowymi metodami terapeutycznymi oraz biomarkerami predykcyjnymi odpowiedzi na leczenie.
5. Dalsze doskonalenie strategii terapeutycznych w RZS powinno obejmować nie tylko rozwój nowych leków, ale także tworzenie narzędzi do precyzyjnego monitorowania skuteczności i bezpieczeństwa terapii oraz wdrażanie kompleksowej opieki obejmującej wsparcie fizjoterapeutyczne, psychologiczne i edukacyjne.
6. Długoterminowe bezpieczeństwo stosowania nowych terapii, zwłaszcza inhibitorów JAK, wymaga dalszych badań epidemiologicznych i rejestrowych, szczególnie w grupach pacjentów wysokiego ryzyka (osoby starsze, pacjenci z chorobami sercowo-naczyniowymi, aktywni i byli palacze).
7. Pacjenci z reumatoidalnym zapaleniem stawów stanowią istotną grupę chorych hospitalizowanych w oddziałach intensywnej terapii, a ich liczba rosła w analizowanym okresie, zwłaszcza w 2021 roku, co mogło być związane z pandemią COVID-19.
8. Wysoka śmiertelność pacjentów z RZS w ICU/CICU (39,1%) może wskazywać na poważny charakter powikłań wymagających intensywnego leczenia oraz na konieczność ścisłego monitorowania tej grupy chorych.

9. Najczęstsze przyczyny przyjęć do oddziałów intensywnej terapii obejmują choroby układu krążenia i oddechowego, co potwierdza istotny wpływ chorób współistniejących na przebieg kliniczny pacjentów z RZS.
10. Najwyższe ryzyko zgonu pacjentów z RZS w ICU/CICU dotyczy pacjentów z chorobami układu pokarmowego oraz chorobami endokrynologicznymi i metabolicznymi, co wskazuje na potrzebę kompleksowej oceny internistycznej i wczesnej interwencji u pacjentów z wielochorobowością.
11. Starszy wiek oraz nagły tryb przyjęcia istotnie zwiększają ryzyko śmiertelności w ICU/CICU, co podkreśla konieczność optymalizacji opieki nad pacjentami z RZS w warunkach ambulatoryjnych i szpitalnych, z naciskiem na wczesne wykrywanie pogorszenia stanu ogólnego.
12. Płeć pacjentów nie była istotnym czynnikiem prognostycznym, co sugeruje, że ostateczne rokowanie w ICU/CICU u pacjentów z RZS jest bardziej związane ze stanem klinicznym i obecnością powikłań niż z różnicami biologicznymi między płciami.
13. Przyszłe badania powinny skupić się na ocenie długoterminowych wyników leczenia pacjentów z RZS po hospitalizacji w ICU/CICU oraz na analizie wpływu stosowanych terapii reumatologicznych na przebieg krytycznych powikłań.
14. Zespół Sjögrena w Polsce najczęściej diagnozowany jest u kobiet w wieku średnim i starszym, co potwierdza dobrze znaną przewagę kobiet w tej jednostce chorobowej.
15. Dynamika hospitalizacji pacjentów z nowo rozpoznanym zespołem Sjögrena może odzwierciedlać zmiany w dostępności opieki szpitalnej, zwiększoną czujność diagnostyczną lekarzy oraz możliwy wzrost liczby pacjentów wymagających hospitalizacji z powodu powikłań.
16. Pandemia COVID-19 spowodowała gwałtowny spadek liczby hospitalizacji pacjentów z zespołem Sjögrena w 2020 roku, co może wynikać z ograniczonego dostępu do opieki szpitalnej oraz obaw pacjentów przed zakażeniem.
17. Czynniki istotnie wydłużające czas hospitalizacji pacjentów z rozpoznaniem zespołu Sjögrena to: starszy wiek, płeć żeńska, przyjęcia w trybie nagłym oraz zamieszkiwanie na terenach wiejskich, co wskazuje na potencjalnie cięższy przebieg choroby w tej populacji.
18. Chociaż śmiertelność w badanej grupie była niska, współistnienie licznych chorób układu krążenia, endokrynologicznych i innych schorzeń autoimmunologicznych

podkreśla potrzebę kompleksowej opieki i monitorowania pacjentów z chorobą Sjögrena, zarówno w warunkach szpitalnych, jak i ambulatoryjnych.

19. Wyniki badania wskazują na potrzebę wzmocnienia opieki ambulatoryjnej nad pacjentami z podejrzeniem lub rozpoznanym zespołem Sjögrena, co mogłoby ograniczyć liczbę hospitalizacji planowych i nagłych oraz poprawić jakość opieki.
20. Istotne różnice w długości hospitalizacji i profilu współchorobowości w zależności od płci, wieku i miejsca zamieszkania sugerują konieczność dalszych badań nad czynnikami społeczno-demograficznymi i klinicznymi wpływającymi na przebieg zespołu Sjögrena w Polsce.

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10. Opinia Komisji Bioetycznej

Komisja Bioetyczna
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e-mail: komisja.bioetyczna@spartanska.pl

UCHWAŁA nr KBT-8/1/2024
Komisji Bioetycznej
działającej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji
im. prof. dr hab. med. Eleonory Reicher
z dnia 03.10.2024 r.
w sprawie przyjęcia opinii o projekcie badania naukowego
pt. „Identyfikacja czynników ryzyka niepowodzenia leczenia reumatoidalnego zapalenia stawów (RZS) klasycznymi syntetycznymi lekami modyfikującymi przebieg choroby (ksLMPCh) u pacjentów kwalifikowanych do leczenia biologicznego – retrospektywne badanie kliniczno-kontrolne"

Na podstawie § 20 ust. 1 w zw. z § 15 Regulaminu Komisji Bioetycznej działającej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji im. prof. dr hab. med. Eleonory Reicher uchwala się, co następuje:

§ 1.

Komisja Bioetyczna działająca przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji im. prof. dr hab. med. Eleonory Reicher wyraża pozytywną opinię o projekcie badania naukowego pod tytułem „Identyfikacja czynników ryzyka niepowodzenia leczenia reumatoidalnego zapalenia stawów (RZS) klasycznymi syntetycznymi lekami modyfikującymi przebieg choroby (ksLMPCh) u pacjentów kwalifikowanych do leczenia biologicznego – retrospektywne badanie kliniczno-kontrolne" realizowanego przez badacz lek. Julię Domańską-Pobożą pod kierunkiem prof. dr hab. n. med. Małgorzaty Wisłowskiej – kierownik Kliniki i Polikliniki Reumatologii NIGRiR.

§ 2.

Uchwała została sporządzona w dwóch egzemplarzach, po jednym dla Wnioskodawcy i dla Komisji.

§ 3.

Uchwała wchodzi w życie z dniem podjęcia.

Uprawnionych do głosowania: 10 osób
Głosowało: 10 osób
Opiniowało pozytywnie: 10 osób
Opiniowało negatywnie: 0

UZASADNIENIE

Badacz złożył wniosek do Komisji Bioetycznej działającej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji im. prof. dr hab. med. Eleonory Reicher (dalej: „**Komisja**") o wydanie opinii w sprawie badania retrospektywnego pod tytułem „Identyfikacja czynników ryzyka niepowodzenia leczenia reumatoidalnego zapalenia stawów (RZS) klasycznymi syntetycznymi lekami modyfikującymi przebieg choroby (ksLMPCh) u pacjentów kwalifikowanych do leczenia biologicznego – retrospektywne badanie kliniczno-kontrolne".

Wniosek wpłynął w dniu 02.10.2024 r.

Przedmiotem badania retrospektywnego będzie analiza danych klinicznych pacjentów hospitalizowanych w Klinice i Poliklinice Reumatologii NIGRiR z rozpoznaniem reumatoidalnego zapalenia stawów w latach 01.01.2015 – 30.09.2024 r. Celem projektu jest identyfikacja kluczowych czynników ryzyka wpływających na niepowodzenie leczenia klasycznymi lekami modyfikującymi przebieg choroby oraz analiza czynników demograficznych, diagnostycznych i terapeutycznych istotnych dla skuteczności leczenia oraz konieczności wdrożenia leków biologicznych. Dane pacjentów wykorzystywane w badaniu będą przetwarzane po ich spseudonimizowaniu. Wniosek został złożony do Komisji Bioetycznej w związku z planami opublikowania wyników w czasopismach naukowych.

Członkowie Komisji nie wnieśli dodatkowych uwag do wniosku. Projekt ma charakter retrospektywny. Wniosek został rozpatrzony pozytywnie.

POUCZENIE

Od uchwały wyrażającej negatywną opinię o projekcie badania naukowego odwołanie nie przysługuje. Wnioskodawca jest uprawniony do wniesienia ponownego wniosku o wydanie opinii o projekcie badania naukowego po wprowadzeniu zmian wynikających z uzasadnienia uchwały. W przypadku wniesienia ponownego wniosku o wydanie opinii o projekcie badania naukowego, gdy projekt ten jest tożsamy z projektem badania naukowego, co do którego została wydana uchwała wyrażająca negatywną opinię, wniosek pozostawia się bez rozpatrzenia, o czym informuje się Wnioskodawcę.

PRZEWODNICZĄCA
KOMISJI BIOETYCZNEJ
przy Narodowym Instytucie Geriatrii,
Reumatologii i Rehabilitacji w Warszawie

prof. dr hab. n. med. Lidia Rutkowska-Sak

KIEROWNIK
KLINIKI I POLIKLINIKI GERIATRII
Narodowy Instytut Geriatrii, Reumatologii
i Rehabilitacji w Warszawie ul. Spartańska 1

prof. dr hab. n. med. Tomasz Targowski

Komisja Bioetyczna
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UCHWAŁA nr KBT-1/4/2025
Komisji Bioetycznej
działającej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji
im. prof. dr hab. med. Eleonory Reicher
z dnia 30.01.2025 r.
w sprawie przyjęcia opinii o projekcie badania naukowego
pt. „Analiza trendów w hospitalizacjach pacjentów z pierwotnym lub wtórnym zespołem Sjögrena w Polsce w latach 2012-2023"

Na podstawie § 20 ust. 1 w zw. z § 15 Regulaminu Komisji Bioetycznej działającej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji im. prof. dr hab. med. Eleonory Reicher uchwala się, co następuje:

§ 1.

Komisja Bioetyczna działająca przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji im. prof. dr hab. med. Eleonory Reicher wyraża pozytywną opinię o projekcie badania naukowego pod tytułem „Analiza trendów w hospitalizacjach pacjentów z pierwotnym lub wtórnym zespołem Sjögrena w Polsce w latach 2012-2023" realizowanego przez badacz lek. Julię Domańską-Pobożą pod kierunkiem prof. dr hab. n. med. Małgorzaty Wisłowskiej – kierownik Kliniki i Polikliniki Reumatologii NIGRiR.

§ 2.

Uchwała została sporządzona w dwóch egzemplarzach, po jednym dla Wnioskodawcy i dla Komisji.

§ 3.

Uchwała wchodzi w życie z dniem podjęcia.

Uprawnionych do głosowania: 11 osób
Głosowało: 11 osób
Opiniowało pozytywnie: 11 osób
Opiniowało negatywnie: 0

UZASADNIENIE

Badacz złożył wniosek do Komisji Bioetycznej działającej przy Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji im. prof. dr hab. med. Eleonory Reicher (dalej: „**Komisja**") o wydanie opinii w sprawie badania retrospektywnego pod tytułem „Analiza trendów w hospitalizacjach pacjentów z pierwotnym lub wtórnym zespołem Sjögrena w Polsce w latach 2012-2023".

Wniosek wpłynął w dniu 20.01.2025 r.

Badanie retrospektywne oparte o analizę danych klinicznych i demograficznych dotyczących hospitalizacji pacjentów z zespołem Sjögrena będzie prowadzone z wykorzystaniem baz danych udostępnionych przez Narodowy Instytut Zdrowia Publicznego PZH – Państwowy Instytut Badawczy w ramach nawiązanej współpracy naukowej. Kierownik projektu załączył do wniosku pisma potwierdzające uzyskanie zgód w NIZP-PZH na korzystanie z danych medycznych pozostających w dyspozycji ww. Instytutu. Wniosek został złożony do Komisji Bioetycznej w związku z wymogami publikacyjnymi czasopisma naukowego.

Członkowie Komisji nie wnieśli dodatkowych uwag do wniosku. Projekt ma charakter retrospektywny. Wniosek został rozpatrzony pozytywnie.

POUCZENIE

Od uchwały wyrażającej negatywną opinię o projekcie badania naukowego odwołanie nie przysługuje. Wnioskodawca jest uprawniony do wniesienia ponownego wniosku o wydanie opinii o projekcie badania naukowego po wprowadzeniu zmian wynikających z uzasadnienia uchwały. W przypadku wniesienia ponownego wniosku o wydanie opinii o projekcie badania naukowego, gdy projekt ten jest tożsamy z projektem badania naukowego, co do którego została wydana uchwała wyrażająca negatywną opinię, wniosek pozostawia się bez rozpatrzenia, o czym informuje się Wnioskodawcę.

PRZEWODNICZĄCA
KOMISJI BIOETYCZNEJ
przy Narodowym Instytucie Geriatrii,
Reumatologii i Rehabilitacji w Warszawie

prof. dr hab. n. med. Lidia Rutkowska-Sak

z. up.
KIEROWNIK
KLINIKI i POLIKLINIKI GERIATRII
Narodowy Instytut Geriatrii, Reumatologii
i Rehabilitacji w Warszawie ul. Spartańska 1

prof. dr hab. n. med. Tomasz Targowski

11. Oświadczenia współautorów publikacji

Oświadczenia wszystkich współautorów publikacji stanowiących rozprawę doktorską

Lek. Julia Domańska-Poboża, Klinika i Poliklinika Reumatologii, Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji – opracowanie koncepcji projektu, zaplanowanie metodologii, przygotowanie manuskryptów – pisanie; przegląd; redakcja, interpretacja danych, zatwierdzenie, zarządzanie projektem

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Nitsch-Osuch, A., Goryński, P., & Wisłowska, M. (2025). Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study.

Opublikowane w czasopiśmie: Polish archives of internal medicine

Szacowany wkład w publikację: 70%

Domańska-Poboża, J., Wisłowska, M. (2025). Evolving strategies in the treatment of rheumatoid arthritis: a historical perspective.

Opublikowane w czasopiśmie: Reumatologia

Szacowany wkład w publikację: 90%

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Lewtak, K., Gorycki, P., Wisłowska, M. (2025).

Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjogren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis

Opublikowane w czasopiśmie: *Journal of Clinical Medicine*

Szacowany wkład w publikację: 75%

Julia Domańska-Poboża

(Podpis współautora)

Oświadczenia wszystkich współautorów publikacji stanowiących rozprawę doktorską

Prof. dr hab. n. med. Małgorzata Wisłowska (Klinika i Poliklinika Reumatologii, Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji) – walidacja, przegląd i redakcja, nadzór merytoryczny i formalny

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Nitsch-Osuch, A., Goryński, P., & Wisłowska, M. (2025). Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study.

Opublikowane w czasopiśmie: Polish archives of internal medicine

Szacowany wkład w publikację: 10%

Domańska-Poboża, J., Wisłowska, M. (2025). Evolving strategies in the treatment of rheumatoid arthritis: a historical perspective.

Opublikowane w czasopiśmie: Reumatologia

Szacowany wkład w publikację: 10%

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Lewtak, K., Gorycki, P., Wisłowska, M. (2025).

Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjogren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis

Opublikowane w czasopiśmie: *Journal of Clinical Medicine*

Szacowany wkład w publikację: 5%

Jednocześnie wyrażam zgodę na wykorzystanie w/w prac jako rozprawy doktorskiej lek. Julii Domańskiej-Pobożej

Małgorzata Wisłowska

(Podpis współautora)

Oświadczenia wszystkich współautorów publikacji stanowiących rozprawę doktorską

Dr hab. n. med. Krzysztof Kanecki (Zakład Medycyny Społecznej i Zdrowia Publicznego Warszawski Uniwersytet Medyczny) – koncepcja i założenia, zasoby, wstępne opracowanie danych

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Nitsch-Osuch, A., Goryński, P., & Wisłowska, M. (2025). Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study.

Opublikowane w czasopiśmie: Polish archives of internal medicine

Szacowany wkład w publikację: 5%

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Lewtak, K., Gorycki, P., Wisłowska, M. (2025).

Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjogren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis

Opublikowane w czasopiśmie: *Journal of Clinical Medicine*

Szacowany wkład w publikację: 5%

Jednocześnie wyrażam zgodę na wykorzystanie w/w prac jako rozprawy doktorskiej lek. Julii Domańskiej-Pobożej

Krzysztof Kanecki

(Podpis współautora)

Oświadczenia wszystkich współautorów publikacji stanowiących rozprawę doktorską

Mgr Łukasz Kapica – Zakład Ergonomii, Centralny Instytut Ochrony Pracy – Państwowy Instytut Badawczy – metodologia, oprogramowanie, opracowanie danych, wizualizacja

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Nitsch-Osuch, A., Goryński, P., & Wisłowska, M. (2025). Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study.

Opublikowane w czasopiśmie: Polish archives of internal medicine

Szacowany wkład w publikację: 5%

Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Lewtak, K., Gorycki, P., Wisłowska, M. (2025).

Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjogren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis

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Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Nitsch-Osuch, A., Goryński, P., & Wisłowska, M. (2025). Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study.

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Domańska-Poboża, J., Kapica, Ł., Kanecki, K., Lewtak, K., Gorycki, P., Wisłowska, M. (2025).

Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjogren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis

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Profesor dr hab. n. med. i n. o zdrowiu Aneta Nitsch-Osuch (Zakład Medycyny Społecznej i Zdrowia Publicznego Warszawski Uniwersytet Medyczny) – koncepcja i założenia, zasoby, wstępne opracowanie danych

Domańska-Pobóża, J., Kapica, Ł., Kanecki, K., Nitsch-Osuch, A., Goryński, P., & Wisłowska, M. (2025). Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study.

Opublikowane w czasopiśmie: Polish archives of internal medicine

Szacowany wkład w publikację: 5%

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ANALIZA BIBLIOMETRYCZNA CAŁOKSZTAŁTU DOROBKU PUBLIKACYJNEGO
PANI JULII DOMAŃSKIEJ-POBOŻEJ,
W POSTĘPOWANIU O NADANIE STOPNIA NAUKOWEGO DOKTORA

Lp.	Opis bibliograficzny	Impact Factor	MNiSW
I. Artykuły opublikowane w czasopismach naukowych lub w recenzowanych materiałach z konferencji międzynarodowych ujętych w aktualnym wykazie MNiSW[1]			
1.	**Domańska J**, Poboży K, Kuryłek M, Fudalej M, Sobiborowicz A, Deptała A, Badowska-Kozakiewicz A. ELF3 as an important factor in carcinogenesis – a brief review of the recent studies. OncoReview, 2020;10(2)77-81 [Rodzaj publikacji: praca poglądowa]	-	20
2.	Konarski W, Poboży T, Hordowicz M, Poboży K, **Domańska J**. Current concepts of natural course and in management of frozen shoulder: A clinical overview. Orthopedic Reviews. 2020;12(4):8832 [Rodzaj publikacji: praca poglądowa]	-	70
3.	Poboży T, Konarski W, Piotrowska-Lis K, **Domańska J**, Poboży K, Kielar M. Basic Differences and Most Common Findings in Ultrasound Examinations of Musculoskeletal System in Children: A Narrative Literature Review. Healthcare. 2022;10(10):2010 [Rodzaj publikacji: praca poglądowa]	2,800	40
4.	Poboży K, **Domańska J**, Domański P. The current state of knowledge on small cell and non-small cell lung cancer and the position of durvalumab immunotherapy in lung cancer treatment. A review. OncoReview. 2023;12(4):75-82 [Rodzaj publikacji: praca poglądowa]	-	20

[1] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. b Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz stanowi załącznik do komunikatu MNiSW z 5 stycznia 2024 r. w sprawie wykazu czasopism naukowych i recenzowanych materiałów z konferencji międzynarodowych.

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5.	**Domańska J**, Poboży K, Domański P, Fudalej M, Deptała A, Badowska-Kozakiewicz A. The role of E2F2 in signaling pathways associated with cancer pathogenesis and potential treatment: A review of current studies. OncoReview, 2023;13(2):58-66 [Rodzaj publikacji: praca poglądowa]	-	20
6.	Poboży K, **Domańska J** [aut. koresp.], Domański P. Poly(ADP-ribose) Polymerase Inhibitor Olaparib in the Treatment of Ovarian Cancer: A Comprehensive Review of Current Literature. OncoReview. 2023;13(2):39-47 [Rodzaj publikacji: praca poglądowa]	-	20
7.	Poboży T, Konarski W, Poboży K, **Domańska J**. Ultrasonography as a diagnostic tool for posteromedial corner pathologies: a pictorial essay. Medical Ultrasonography. 2023;25(3):340-346 [Rodzaj publikacji: praca poglądowa]	1,800	40
8.	Konarski W, Poboży T, Poboży K, **Domańska J**, Konarska K. Current concepts of natural course and in management of medial epicondylitis: a clinical overview. Orthopedic Reviews. 2023;15:84275 [Rodzaj publikacji: praca poglądowa]	1,400	70
9.	Poboży K, Domański P, **Domańska J** [aut. koresp.], Konarski, W, Poboży T. Advances in immunotherapy for osteosarcoma: a review of emerging treatment strategies. OncoReview. 2023;13(3):75-84 [Rodzaj publikacji: praca poglądowa]	-	20
10.	Poboży, K, **Domańska J** [aut. koresp.], Domański, P. Neoantigen therapeutic cancer vaccines: a promising approach to personalized immunotherapy. OncoReview. 2023;13(4):93-98 [Rodzaj publikacji: praca poglądowa]	-	20
11.	Rzemieniewski B, Kasztelan A, Poboży K, **Domańska-Poboża J**. Growth differentiation factor 15 – a review of current literature on biological roles and clinical significance. European Journal of Clinical and Experimental Medicine. 2024;22(4):921-933 [Rodzaj publikacji: praca poglądowa]	-	20
12.	Poboży T, Konarski W, Poboży K, **Domańska J**, Konarska K. Evaluation of Remodeling and Extrusion of Polyurethane Meniscal Implants after Meniscus Reconstruction using Ultrasonography. Current Medical Imaging. 2024;20:e15734056281005 [Rodzaj publikacji: praca oryginalna]	1,100	20
13.	**Domańska-Poboża J**, Wisłowska, M. Evolving strategies in the treatment of rheumatoid arthritis: a historical perspective. Reumatologia. 2025;63(1):1–15 [Rodzaj publikacji: praca poglądowa]	1,400	70
14.	**Domańska-Poboża J**, Kapica Ł, Kanecki K, Nitsch-Osuch A, Goryński P, Wisłowska M. Hospitalizations of patients with rheumatoid arthritis in Polish intensive care units or cardiac intensive care units in 2011-2021: population study. Polskie Archiwum Medycyny Wewnętrznej. 2025:16913 (ahead of print) [Rodzaj publikacji: praca oryginalna]	3,800	200
15.	Domańska-Poboża J [aut. koresp.], Kapica Ł, Kanecki K, Lewtak, K, Goryński P, Wisłowska M. Trends in Initial Hospitalizations of Patients with Newly Diagnosed Sjogren's Disease in Poland Between 2012 and 2023: A Retrospective Data Analysis. Journal of Clinical Medicine. 2025;14(6):1999 [Rodzaj publikacji: praca oryginalna]	3,000	140

16.	Poboży K, Poboży T, Domański P, Derczyński M, Konarski W, **Domańska-Poboża J.** Evolution of Light-Sensitive Proteins in Optogenetic Approaches for Vision Restoration: A Comprehensive Review. Biomedicines. 2025;13(2):429 [Rodzaj publikacji: praca poglądowa]	3,900	100
	Łącznie:	19,200	890
II. Artykuły opublikowane przed 1.01.2019 r. w czasopismach ujętych w wykazie czasopism MNiSW z dnia 25.01.2017 r., o ile czasopismo uzyskało co najmniej 10 pkt.			
	Łącznie:	-	-
III. Pozostałe artykuły			
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[2] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. a Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz ogłoszony komunikatem MEiN z dnia 22 lipca 2021 r. w sprawie wykazu wydawnictw publikujących recenzowane monografie naukowe.

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