UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Katedra Medycyny Sądowej

Rozprawa doktorska

ANALIZA WYBRANYCH PARAMETRÓW KLINICZNYCH I LABORATORYJNYCH WPŁYWAJĄCYCH NA CIĘŻKOŚĆ PRZEBIEGU COVID-19

Aleksander Zińczuk

Katedra Medycyny Sądowej

Promotor: dr hab. n. med. Tomasz Jurek, prof. Uczelni

Promotor pomocniczy: dr hab. n. med. Marta Rorat

Wrocław 2023

Dziękuję ***dr hab. n. med. Tomaszowi Jurkowi, prof. Uczelni****, mojemu promotorowi,*
za okazane zaufanie, bezcenne wskazówki i wsparcie w przygotowaniu pracy doktorskiej.
Dziękuję ***dr. hab. n. med. Marcie Rorat****, mojej promotor pomocniczej,*
za cierpliwość, trafne uwagi oraz możliwość konsultacji na każdym etapie realizacji doktoratu.

Panu ***prof. dr hab. n. med. Krzysztofowi Simonowi*** *dziękuję za opiekę w pracy naukowej*
i zawodowej.
Mojej najbliższej ***Rodzinie*** *i* ***Przyjaciołom*** *dziękuję za zrozumienie, wiarę we mnie*
i w powodzenie realizacji tej pracy.

Wykaz skrótów użytych w pracy

CAC – ang. COVID-19-Associated Coagulopathy, koagulopatia związana z COVID-19

CAR-T – ang. Chimeric Antigen Receptor T-cell therapy, terapia chimerycznymi limfocytami T

COVID-19 – ang. Coronavirus Disease 2019

CRP – ang. C-reactive protein, białko C-reaktywne

CRS – ang. Cytokine Release Syndrome, zespół uwalniania cytokin

CXCL-8/IL-8 – interleukina 8

EASIX – ang. Endothelial Activation and Stress Index

GISAID – ang. Global Initiative on Sharing All Influenza Data

HAIs – ang. Healthcare-Associated Infections, zakażenia związane z opieką zdrowotną

HFNOT – ang. High-Flow Nasal Oxygen Therapy, wysokoprzepływowa tlenoterapia donosowa

IL-18 – interleukina 18

LDH – ang. Lactate Dehydrogenase, dehydrogenaza mleczanowa

LMIC – ang. Low- and Middle-Income Countries, kraje o niskich i średnich przychodach

mEASIX – ang. Modified Endothelial Activation and Stress Index

MERS-CoV – ang. Middle East Respiratory Syndrome Coronavirus, koronawirus bliskowschodniego zespołu oddechowego

NIV – ang. Non-Invasive Ventilation, nieinwazyjna wentylacja

NLR - ang. neutrophil-to-lymphocyte ratio, wskaźnik neutrofilowo - limfocytowy

NPV – ang. Negative Predictive Value, ujemna wartość predykcyjna

OIT – oddział intensywnej terapii

PHEIC – ang. Public Health Emergency of International Concern, stan zagrożenia zdrowia publicznego o zasięgu międzynarodowym

PLT – ang. Platelets, płytki krwi

PPV – ang. Positive Predictive Value, dodatnia wartość predykcyjna

qCSI – ang. Quick COVID-19 Severity Index

ROC – ang. Receiver Operating Characteristic, krzywa charakterystyki operacyjnej odbiornika

RT-PCR – ang. Reverse Transcription – Polymerase Chain Reaction, reakcja łańcuchowa polimerazy z odwrotną transkrypcją

SARS-CoV-1 - ang. Severe Acute Respiratory Syndrome Coronavirus – 1, pierwszy koronawirus ciężkiego ostrego zespołu oddechowego

SARS-CoV-2 - ang. Severe Acute Respiratory Syndrome Coronavirus – 2, drugi koronawirus ciężkiego ostrego zespołu oddechowego

sEASIX – ang. Simplified Endothelial Activation and Stress Index

TK – tomografia komputerowa

VOCs – ang. Variants Of Concern, warianty budzące obawę

VUMs – ang. Variants Under Monitoring, warianty objęte monitorowaniem

WHO – ang. World Health Organization, Światowa Organizacja Zdrowia

Spis treści

Wykaz skrótów użytych w pracy 3

Spis treści 5

I. Nota informacyjna – wykaz publikacji wchodzących w skład cyklu 6

II. Streszczenie 7

III. Summary 9

IV. Wstęp 11

V. Cele rozprawy doktorskiej 14

VI. Materiał i metody 15

VII. Podsumowanie wyników 17

VIII. Dyskusja 20

IX. Wnioski 25

X. Piśmiennictwo 26

XI. Publikacje stanowiące podstawę rozprawy doktorskiej 31

XII. Załączniki 74

a. Oświadczenia współautorów publikacji 74
b. Nota biograficzna autora 85
c. Wykaz publikacji autora 86

I. Nota informacyjna – wykaz publikacji wchodzących w skład cyklu

Rozprawa doktorska lekarza Aleksandra Zińczuka: „Analiza wybranych parametrów klinicznych i laboratoryjnych wpływających na ciężkość przebiegu COVID-19" stanowi zbiór trzech powiązanych tematycznie artykułów: dwóch prac oryginalnych oraz jednej przeglądowej. Badania będące podstawą prac oryginalnych zrealizowano po uzyskaniu pozytywnej opinii Komisji Bioetycznej przy Uniwersytecie Medycznym we Wrocławiu (uchwała nr KB – 826/2020 z dnia 17 grudnia 2020 r.). Każdy z artykułów został opublikowany w anglojęzycznych czasopismach naukowych o zasięgu międzynarodowym. Łączna wartość współczynnika wpływu impact factor (IF) zbioru prac wynosi 8.1, liczba punktów Ministerstwa Edukacji i Nauki (MEiN) 240.

Publikacje wchodzące w skład zbioru:

1. **Zińczuk A.**, Rorat M., Simon K., Jurek T. (2022). EASIX, modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients. *Journal of Personalized Medicine*, 2022, 12 (7), 1022. IF: 3.4; pkt. MEiN: 70.
2. **Zińczuk A.**, Rorat M., Simon K., Jurek T. (2023). Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors – a single-center, retrospective analysis of the first two years of the pandemic. *Viruses*, 2023, 15 (7), 1430. IF: 4.7; pkt. MEiN: 100.
3. **Zińczuk A.**, Rorat M., Jurek T. (2023). COVID-19 - related excess mortality - an overview of the current evidence. *Archiwum Medycyny Sądowej i Kryminologii*, 2023, 73 (1), 33-44, pkt. MEiN: 70.

Oświadczenia współautorów prac, określające wkład każdego z nich, zawarte są w załącznikach w części XII a.

II. Streszczenie

Wstęp: Zakażenia spowodowane przez nowy czynnik etiologiczny jakim jest koronawirus SARS-CoV-2 (ang. Severe Acute Respiratory Syndrome Coronavirus - 2) szybko spowodowały globalne zagrożenie dla zdrowia publicznego ze względu na objawy niewydolności oddechowej i powikłania naczyniowe dominujące w obrazie klinicznym choroby. Łatwość transmisji oraz ciężki przebieg COVID-19 (ang. Coronavirus disease 2019) doprowadziły do przeciążenia systemów opieki zdrowotnej na całym świecie i ograniczenia dostępu do świadczeń medycznych dla innych pacjentów, co było jedną z wiodących przyczyn wystąpienia zgonów nadmiarowych w trakcie pandemii, czyli różnicy w całkowitej liczbie zgonów w sytuacji kryzysowej w porównaniu do liczby zgonów oczekiwanych w normalnych warunkach. Wykazano szereg czynników ryzyka ciężkiego przebiegu choroby, do których należą: wiek powyżej 65 lat, płeć męska, obecność chorób towarzyszących (przede wszystkim chorób układu sercowo – naczyniowego, oddechowego i nerek, nowotworów złośliwych i otyłości), stosowanie leków immunosupresyjnych. Obok intensywnych działań zmierzających do znalezienia skutecznej terapii oraz profilaktyki, od początku poszukiwano markerów służących szybkiej identyfikacji pacjentów zagrożonych ciężkim przebiegiem i zgonem w związku z COVID-19. Do tego celu wykorzystywano między innymi współczynniki powstałe z kalkulacji parametrów laboratoryjnych, np. NLR (ang. neutrophil-to-lymphocyte ratio), skale oceny radiogramów klatki piersiowej oraz korelację czynników demograficznych, klinicznych i laboratoryjnych, np. qCSI (ang. Quick COVID-19 Severity Index).

Cele:

1. Ocena możliwości wykorzystania współczynników opartych na korelacji parametrów laboratoryjnych – aktywności dehydrogenazy mleczanowej (LDH), stężenia kreatyniny, białka C-reaktywnego (CRP) oraz liczby płytek krwi (PLT) pod postacią współczynników EASIX (ang. Endothelial Activation and Stress Index), mEASIX (ang. modified-EASIX), sEASIX (ang. simplified-EASIX) - jako czynników prognostycznych przebiegu COVID-19.

2. Analiza śmiertelnych przypadków COVID-19, tj. ustalenie przyczyny śmierci i czynników ryzyka jej wystąpienia, z uwzględnieniem zdarzeń niepożądanych, które wpłynęły na zgon pacjentów.

3. Określenie zjawiska oraz wskazanie przyczyn występowania nadmiarowych zgonów w trakcie pandemii COVID-19.

Materiał i metody: Analiza retrospektywna, jednoośrodkowa danych medycznych odpowiednio 370 i 477 pacjentów hospitalizowanych w Wojewódzkim Szpitalu Specjalistycznym we Wrocławiu od 6 marca 2020 r. do 30 czerwca 2022 r. z rozpoznanym klinicznie COVID-19. Ocena statystyczna obejmująca parametry charakteryzujące pacjentów, w tym czas trwania i wariant zakażenia SARS-CoV-2 oraz przebieg hospitalizacji. Przegląd i analiza literatury dostępnej w bazie Pubmed w dniu 11 maja 2023 r. dotyczącej zagadnienia zgonów nadmiarowych w okresie pandemii COVID-19.

Wyniki: Współczynniki EASIX, mEASIX, sEASIX wykazują istotną statystycznie korelację z koniecznością hospitalizacji w OIT (oddział intensywnej terapii) (odpowiednio *p=0.026*, *p=0.019*, *p=0.001*) oraz ryzykiem zgonu (*p<0.001*). Wysokie wartości ocenianych współczynników (EASIX ≥2.36, mEASIX ≥704.03, sEASIX ≥3.81) charakteryzuje niska czułość (≤40%) przy wysokiej swoistości (ok. 90%) oraz niskie wartości NPV (ang. negative predictive value – ujemna wartość predykcyjna) (ok. 40%) przy wysokich PPV (ang. positive predictive value – dodatnia wartość predykcyjna) (ok. 80%) w odniesieniu do predykcji zgonu. W analizie zgonów w przebiegu COVID-19 wykazano dominację chorych powyżej 60 roku życia (54.3%), z przewagą płci męskiej (59.3%) oraz pacjentów obciążonych chorobami współistniejącymi (91.4%). Niewydolność oddechowa jako dominująca przyczyna zgonu w przebiegu zakażenia SARS-CoV-2 dotyczyła 88.7% pacjentów. Powikłania związane z procesem hospitalizacji (46.1%) i zdarzenia niepożądane z udziałem personelu medycznego stwierdzono w prawie połowie ocenianych przypadków (49.7%).

Wnioski: Współczynniki EASIX, mEASIX, sEASIX mogą służyć identyfikacji pacjentów zagrożonych ciężkim przebiegiem COVID-19. Hospitalizacja pacjentów z SARS-CoV-2 wiąże się z licznymi zdarzeniami niepożądanymi, takimi jak wystąpienie infekcji szpitalnych, powikłań wentylacji oraz nieprawidłowościami w postępowaniu personelu medycznego, które należy rozpatrywać jako dodatkowy czynnik ryzyka zgonu. Analiza zgonów nadmiarowych obrazuje rzeczywisty wpływ pandemii COVID-19 na zdrowie publiczne, wskazując na dodatkowe czynniki, poza samym zakażeniem, które związane są z przeciążeniem systemów opieki zdrowotnej.

III. Summary

Background: Infections caused by the novel aetiological agent Severe Acute Respiratory Syndrome Coronavirus - 2 (SARS-CoV-2) have rapidly created a global public health threat due to the symptoms of respiratory failure and vascular complications dominating the clinical picture of the disease. The ease of transmission and the severity of COVID-19 (Coronavirus disease 2019) led to overloaded healthcare systems worldwide and reduced access to medical services for other patients, which was one of the leading causes of excess deaths during the pandemic, i.e. the difference in the total number of deaths in an emergency compared to the number of deaths expected under normal conditions. A number of risk factors for severe disease have been demonstrated, which include age over 65 years, male gender, presence of concomitant diseases (primarily cardiovascular, respiratory and renal diseases, malignancies and obesity), use of immunosuppressive drugs. In addition to intensive efforts to find effective therapy and prophylaxis, markers for the rapid identification of patients at risk of a severe course and death due to COVID-19 have been sought from the outset, including coefficients derived from the calculation of laboratory parameters, e.g. NLR (neutrophil-to-lymphocyte ratio), scales for the evaluation of chest radiographs, and the correlation of demographic, clinical and laboratory factors, e.g. qCSI (Quick COVID-19 Severity Index).

Objectives:

1. To assess the feasibility of using coefficients based on the correlation of laboratory parameters - lactate dehydrogenase (LDH) activity, creatinine concentration, C-reactive protein (CRP) and platelet count (PLT) in the form of EASIX (Endothelial Activation and Stress Index), mEASIX (modified-EASIX), sEASIX (simplified-EASIX) - as prognostic factors for the course of COVID-19.

2. Analysis of fatal COVID-19 cases, i.e. determining the cause of death and risk factors for death, including adverse events that influenced the death of patients.

3. Define the phenomenon and identify the causes of excess deaths during the COVID-19 pandemic.

Material and methods: Retrospective, single-centre analysis of medical data of 370 and 477 patients hospitalized at the Wrocław Regional Specialist Hospital from 6 March 2020 to

30 June 2022 with clinically diagnosed COVID-19. Statistical evaluation including parameters characterizing patients, with duration and variant of SARS-CoV-2 infection and course of hospitalization. Review and analysis of the literature available in the Pubmed database on 11 May 2023 on the issue of excess deaths during the COVID-19 pandemic.

Results: EASIX, mEASIX, sEASIX coefficients show a statistically significant correlation with the need for ICU (intensive care unit) hospitalization (*p=0.026*, p=0.*019*, p=0.*001*, respectively) and risk of death (*p<0.001*). The high values of the assessed coefficients (EASIX ≥2.36, mEASIX ≥704.03, sEASIX ≥3.81) are characterized by low sensitivity (≤40%) with high specificity (approximately 90%) and low NPV (negative predictive value) (approximately 40%) with high PPV (positive predictive value) (approximately 80%) for the prediction of death. The analysis of COVID-19 deaths showed a predominance of patients over 60 years of age (54.3%), with a male predominance (59.3%) and patients with comorbidities (91.4%). Respiratory failure as the leading cause of death in SARS-CoV-2 infection affected 88.7% of patients. Complications related to the hospitalization process (46.1%) and adverse events involving staff were found in almost half of the cases assessed (49.7%).

Conclusions: The EASIX, mEASIX, sEASIX coefficients can be used to identify patients at risk of severe COVID-19. Hospitalization of patients with SARS-CoV-2 is associated with numerous adverse events, such as the occurrence of nosocomial infections, ventilation complications and medical staff malpractice, which should be considered as an additional risk factor for death. The analysis of excess deaths illustrates the real impact of the COVID-19 pandemic on public health, pointing to additional factors, beyond the infection itself, that are related to overburdened healthcare systems.

IV. Wstęp

Pierwsze zakażenia nowym wirusem SARS-CoV-2, początkowo określane jako „pneumonia of unknown cause", były raportowane w chińskiej prowincji Wuhan 31 grudnia 2019 r. Już 5 stycznia 2020 r. WHO (ang. World Health Organization) ogłosiło wykrycie ogniska zakażeń nieznanym dotychczas czynnikiem biologicznym [1]. Wzrastająca liczba przypadków nowej choroby w kolejnych tygodniach stycznia, potwierdzenie transmisji zakażenia między ludźmi oraz pojawienie się przypadków zachorowań poza Chinami skłoniło WHO do ogłoszenia 30 stycznia 2020 r. stanu zagrożenia epidemiologicznego o zasięgu międzynarodowym (ang. Public Health Emergency of International Concern [PHEIC]), natomiast 11 marca 2020 r., w związku z brakiem kontroli nad zachorowaniami, sytuację epidemiologiczną związaną z COVID-19 zaklasyfikowano jako pandemię [2], [3]. Jej przebieg wiąże się z występowaniem fal zakażeń, co w największym stopniu zależy od dominacji określonego wariantu wirusa, który wypiera poprzednie w efekcie nabywania nowych cech (np. większej zaraźliwości, nowych manifestacji klinicznych, przełamywania odporności nabytej naturalnie lub sztucznie) [4]. Od stycznia 2020 r. WHO prowadzi monitoring dotyczący krążących wariantów SARS-CoV-2. Dotychczas zidentyfikowano 5 VOCs (ang. Variants of Concern) - Alpha, Beta, Gamma, Delta, Omicron, odpowiedzialnych za fale pandemii [5]. W związku z dominacją VOC-Omicron od lutego 2022 r. zaktualizowane 15 marca 2023 r. wytyczne WHO obejmują nową grupę VUMs (ang. Variants under Monitoring) – będącą w rzeczywistości podwariantami Omicron [6].

Choroba wywołana przez SARS-CoV-2 wiąże się z wysoką śmiertelnością wśród pacjentów hospitalizowanych. Już pierwsze chińskie dane epidemiologiczne z początku pandemii wskazywały na fakt, że ciężki przebieg zakażenia SARS-CoV-2 dotyczył około 16% chorych, z czego 3.2% stanowili pacjenci w stanie krytycznym, u których doszło do rozwoju zaburzeń zakrzepowo-zatorowych, sepsy/wstrząsu septycznego, niewydolności wielonarządowej i zgonu [7], [8]. Analiza danych pochodzących z pierwszych trzech miesięcy pandemii potwierdziła duży odsetek ciężkich przypadków choroby (22.9%) i śmiertelności (5.6%) w grupie 281 461 pacjentów z całego świata [9]. Aktualne dane epidemiologiczne z całego okresu zachorowań (na dzień 31 maja 2023 r.) wskazują, że śmiertelność w przebiegu COVID-19 u wszystkich zakażonych pacjentów nie przekracza 1% [10]. Choroba może manifestować się symptomami z każdego układu i narządu, jednak dominujące w obrazie klinicznym są

objawy zajęcia układu oddechowego i naczyniowego [9]. Patofizjologia ciężkiego przebiegu COVID-19 związana jest między innymi z uszkodzeniem śródbłonka naczyniowego, niekontrolowanym uwalnianiem cytokin i czynników prozapalnych oraz zaburzeniami w składzie i funkcji komórek układu odpornościowego, co ostatecznie doprowadza do niewydolności wielonarządowej [11], [12]. SARS-CoV-2, wiążąc się z komórkami śródbłonka, uaktywnia kaskadę cytokinową, która prowadzi do uwalniania czynników prozapalnych wyzwalających proces krzepnięcia. W efekcie rozwija się charakterystyczny dla COVID-19 stan określany jako „thromboinflammation", który jest podłożem powikłań zakrzepowo – zatorowych, składających się na CAC (ang. COVID-19 associated coagulopathy) [13]. Ciężkość zakażenia SARS-CoV-2 i ryzyko zgonu w jego przebiegu zależy od wielu czynników, spośród których za najważniejsze uznaje się płeć męską, wiek >65 lat, występowanie chorób towarzyszących, przede wszystkim przewlekłych chorób układu krążenia, oddechowego i nerek, nowotworów złośliwych, otyłości, cukrzycy i schorzeń autoimmunizacyjnych; a także wariant wirusa wywołującego chorobę [14–16]. Szczególnie ciężki przebieg zakażenia charakteryzował wariant Delta [17], [18]. Populacją, która jest najbardziej wrażliwa na zakażenie jest grupa osób starszych z wielochorobowością, dlatego wskazuje się, że pandemię COVID-19 powinno określać się mianem syndemii, czyli synergistycznej epidemii, w trakcie której wirus powoduje zgony szczególnie w populacjach kluczowych [19].

Wiedza na temat czynników ryzyka oraz możliwości przewidywania ciężkości przebiegu zakażenia na podstawie rutynowo wykonywanych badań laboratoryjnych i obrazowych stale się rozwija. Dotychczas wykazano, że nieprawidłowe wartości wykładników stanu zapalnego (białko C-reaktywne, liczba limfocytów i neutrofili), a także parametrów związanych z uszkodzeniem komórek śródbłonka naczyniowego (kreatynina, dehydrogenaza mleczanowa, liczba płytek krwi), oznaczone przy przyjęciu, korelują z ciężkością zakażenia i ryzykiem jego niepomyślnego przebiegu [20], [21]. Sugeruje to, że o ciężkości zakażenia decyduje przede wszystkim nasilenie procesu zapalnego. Globalny charakter pandemii spowodował, że poszukiwano narzędzi uniwersalnych i łatwych do zastosowania w warunkach dużej liczby zakażeń, służących do wczesnej oceny rokowania co do przeżycia i ryzyka progresji stanu pacjenta już na podstawie wyjściowych parametrów. Do tego celu wykorzystywano między innymi współczynniki powstałe z kalkulacji parametrów laboratoryjnych: NLR (ang. neutrophil-to-lymphocyte ratio), PLR (ang. platelet-to-lymphocyte

ratio) i EASIX (ang. Endothelial Activation and Stress Index); skale pięcio- i dwunastopunktowe oceny radiogramów klatki piersiowej oraz korelację czynników demograficznych, klinicznych i laboratoryjnych – np. qCSI (ang. Quick COVID-19 Severity Index) lub 4C Mortality Score [22]–[26].

Do dnia 31 maja 2023 r. odnotowano 767 364 883 przypadków zakażenia oraz 6 938 353 zgonów w przebiegu COVID-19 [10]. Rzeczywisty globalny rachunek pandemii jest jednak większy niż wynika to z bezpośredniej liczby zgonów pacjentów z SARS-CoV-2. Narastająca w szybkim czasie duża liczba przypadków niewydolności oddechowej w przebiegu zakażenia, które wymagają hospitalizacji i leczenia specjalistycznego, w istotnym stopniu ogranicza zdolność systemu opieki zdrowotnej do wypełniania swoich dotychczasowych obowiązków, co przekłada się na występowanie zgonów nadmiarowych [27]. WHO na podstawie przeprowadzonych analiz podaje, że liczba wszystkich ofiar pandemii w 2020 r. wyniosła co najmniej 3 miliony, co o ponad 1,2 mln przekracza raportowaną w tym okresie liczbę zgonów COVID-19 [28]. Z kolei w najnowszym dostępnym raporcie obejmującym całe dwa lata pandemii (1 stycznia 2020 r. do 31 grudnia 2021 r.) stwierdzono, że liczba nadmiarowych zgonów wyniosła 14.9 milionów (95% CI: 13.3-16.6) [29]. Przyczyny takiego stanu są złożone. Obejmują przede wszystkim ograniczenie dostępu do opieki zdrowotnej dla pacjentów z chorobami przewlekłymi i ostrymi w związku z przeciążeniem systemu, dodatkowy wpływ innych zagrożeń biologicznych i katastrof naturalnych, a także niedostatki w zakresie diagnostyki.

Pojawienie się nowego zagrożenia biologicznego, które szybko stało się globalnym problemem wpływającym na systemy zdrowotne i gospodarki na całym świecie, wskazuje na konieczność dogłębnej analizy każdego aspektu związanego z zakażeniem SARS-CoV-2. Uzyskane wyniki badań, które stanowią między innymi podstawę niniejszej rozprawy doktorskiej, mogą przysłużyć się w przyszłości poprawie bezpieczeństwa pacjentów z zakażeniami nowymi czynnikami biologicznymi lub znanymi już patogenami, które nabywają czynników zjadliwości.

V. Cele rozprawy doktorskiej

1. Ocena możliwości wykorzystania współczynników opartych na korelacji parametrów laboratoryjnych (liczba PLT, stężenie kreatyniny, stężenie CRP oraz aktywność LDH) pod postacią klasycznego współczynnika EASIX (ang. Endothelial Activation and Stress Index) oraz jego dwóch modyfikacji: simplified - EASIX (sEASIX) i modified - EASIX (mEASIX) jako czynników prognostycznych hospitalizacji w oddziale intensywnej terapii, zastosowania wentylacji inwazyjne oraz zgonu wśród pacjentów z COVID-19 w ciężkim stanie klinicznym.
2. Analiza śmiertelnych przypadków COVID-19, tj. ustalenie przyczyny śmierci i czynników ryzyka jej wystąpienia, z uwzględnieniem zdarzeń niepożądanych, które wpłynęły na zgon pacjentów.
3. Określenie zjawiska związanego z nadmiarowymi zgonami w trakcie pandemii COVID-19 – omówienie przyczyn występowania, ustalenie wspólnych punktów pozwalające na utworzenie spójnej strategii reagowania na przyszłe zagrożenia biologiczne o charakterze pandemicznym.

VI. Materiał i metody

Zbiór publikacji stanowią dwie prace oryginalne oraz jedna przeglądowa. Prace oryginalne to retrospektywna analiza zanonimizowanych danych medycznych pacjentów hospitalizowanych z powodu COVID-19 w oddziałach Wojewódzkiego Szpitala Specjalistycznego im. J. Gromkowskiego we Wrocławiu od 6 marca 2020 r. W pierwszej pracy uwzględniono dane 370 pacjentów o ciężkim przebiegu zakażenia, hospitalizowanych do 30 czerwca 2021 r. Druga praca obejmuje 477 przypadków choroby zakończonej zgonem w okresie do 30 czerwca 2022 r. W obu publikacjach z analizy wykluczono pacjentów, których przeniesiono do innych szpitali oraz tych, u których nie było dostępu do pełnej dokumentacji medycznej.

U wszystkich hospitalizowanych osób zakażenie potwierdzano początkowo testem molekularnym real-time RT-PCR (ang. reverse transcription – polymerase chain reaction), następnie, w związku z pozyskaniem nowych zwalidowanych metod diagnostycznych, testem molekularnym real-time RT-PCR lub antygenowym (PanBio COVID-19 Ag Rapid Test Device by Abbott).

W obu pracach oryginalnych ocenie poddano szereg parametrów charakteryzujących pacjentów - demografię (wiek, płeć), obecność chorób towarzyszących, dane dotyczące zakażenia SARS-CoV-2 (czas trwania objawów przed przyjęciem, wartość saturacji krwi kapilarnej bez tlenoterapii dodatkowej, wyjściowy stan zdrowia pacjenta według 4-stopniowej skali WHO) [30], wyniki badań laboratoryjnych oznaczone przy przyjęciu do szpitala, rodzaj zastosowanych metod tlenoterapii w trakcie pobytu. W obu pracach wykorzystano także współczynnik EASIX, według standardowej formuły podanej przez Luft et al. (LDH [U/L] x kreatynina [mg/dL] / PLT [G/L]) [31]. Pierwsza praca oryginalna zawiera dodatkowo zmodyfikowane współczynniki sEASIX (LDH [U/L] / PLT [G/L]) i mEASIX (LDH [U/L] x CRP [mg/dL] / PLT[G/L]) według Pennisi et al. [32].

Ocena przebiegu procesu hospitalizacji jest zasadniczą częścią drugiej publikacji wchodzącej w skład cyklu. W pracy tej zastosowano podział fali pandemii na 3 okresy: pre-Delta (01.03.2020 – 30.06.2021, Delta (01.07.2021 – 31.12.2021) oraz Omicron (01.01.2022 – 30.06.2022), na podstawie dominujących na terenie Polski sekwencji wirusa SARS-CoV-2, analizowanych w ramach GISAID (ang. Global Initiative on Sharing All Influenza Data [33].

Uwzględniono zastosowane leczenie ukierunkowane na SARS-CoV-2 (przeciwwirusowe, immunomodulujące), leki przeciwkrzepliwe i antybiotyki z oceną zasadności ich włączenia. W kolejnym etapie analizie poddano określone zdarzenia niepożądane: powikłania COVID-19; zakażenia towarzyszące, pozaszpitalne i szpitalne - HAIs (ang. healthcare-associated infections) oraz inne zdarzenia medyczne w trakcie hospitalizacji, dla których przyjęto kryteria zgodne z aktualnym raportem WHO, dotyczącym bezpieczeństwa pacjenta [34]. Opisano także przyczyny zgonu pacjentów, wyróżniając przyczynę główną oraz towarzyszące.

Trzecia publikacja oparta jest na przeglądzie literatury wykonanym 11 maja 2023 roku na podstawie bazy Pubmed przy użyciu słów kluczowych COVID-19, SARS-CoV-2, excess deaths (zgony nadmiarowe), excess mortality (nadmiarowa umieralność).

Analizy statystyczne w pierwszej publikacji przeprowadzono przy użyciu Statistica (wersja 13.3, TIBCO Software Inc.), z kolei w drugiej wykorzystano program R (wersja 4.3) dla systemu Windows. Statystyki opisowe przedstawiono przy użyciu średnich, odchyleń standardowych, median i kwartyli dla zmiennych ilościowych oraz liczby przypadków z wartościami procentowymi dla zmiennych jakościowych. Normalność danych oceniono za pomocą testu Shapiro-Wilka. Zmienne ilościowe analizowano za pomocą testu chi^2, testu Fishera i korelacji rang Spearmana; zmienne jakościowe za pomocą testu Manna-Whitneya, korelacji tau-Kendalla lub testu Kruskala-Wallisa. W razie potrzeby zastosowano analizę post-hoc z wykorzystaniem porównania parami skorygowanego metodą Holma. Optymalne wartości odcięcia log^2-EASIX, log^2-mEASIX i log^2-sEASIX dla zgonu określono za pomocą wskaźnika Youdena z oceną krzywych ROC (ang. Receiver Operating Characteristic). Wszystkie testy statystyczne uznano za istotne przy wartości $p<0.05$.

VII. Podsumowanie wyników

Część pierwsza: *Zińczuk A., Rorat M., Simon K., Jurek T. (2022). EASIX, modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients. Journal of Personalized Medicine, 2022, 12 (7), 1022. IF: 3.4; pkt. MEiN: 70.*

Ocena współczynników opartych na korelacji podstawowych parametrów laboratoryjnych, tj. aktywności LDH, stężenia kreatyniny, stężenia CRP oraz liczby PLT w grupie 370 pacjentów przyjmowanych w ciężkim stanie klinicznym WHO 3 i 4 przyniosła następujące wyniki:

- wartości EASIX, mEASIX i sEASIX istotnie statystycznie (*p<0.001*) korelują ze zgonem pacjentów;
- wszystkie trzy współczynniki, ocenianie w tej populacji pacjentów, cechują się niską czułością (≤40%) przy wysokiej swoistości (ok. 90%) w ocenie ryzyka zgonu;
- wysokie wartości EASIX, mEASIX i sEASIX (powyżej punktów odcięcia) są bardziej wiarygodne w ocenie ryzyka zgonu niż przeżycia, o czym świadczą wyższe dodatnie wartości predykcyjne PPV (ang. positive predictive value) w porównaniu do ujemnych wartości predykcyjnych NPV (ang. negative predictive value);
- jedynie EASIX jest predyktorem konieczności zastosowania wentylacji inwazyjnej, ale nie HFNOT (ang. High-Flow Nasal Oxygenation Therapy) i NIV (ang. Non-Invasive Ventilation), natomiast wartości wszystkich trzech współczynników istotnie statystycznie korelują z koniecznością hospitalizacji w OIT (EASIX *p=0.026*, mEASIX *p=0.019*, sEASIX *p=0.001*).

Część druga: *Zińczuk A., Rorat M., Simon K., Jurek T. (2023). Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors – a single-center, retrospective analysis of the first two years of the pandemic. Viruses, 2023, 15 (7), 1430. IF: 4.7; pkt. MEiN: 100.*

W retrospektywnej analizie 477 śmiertelnych przypadków COVID-19 wykazano szereg kluczowych cech charakteryzujących pacjentów oraz przebieg hospitalizacji:

- w grupie dominowali chorzy powyżej 60 roku życia (259 – 54.3%), z przewagą płci męskiej (283 – 59.3%), obciążeni chorobami współistniejącymi (436 - 91.4%);
- parametry laboratoryjne, oznaczone przy przyjęciu, wykazały podwyższone wykładniki stanu zapalnego oraz wysoką wartość EASIX (średnia 6.22; mediana 3.14);
- pacjenci w grupie wiekowej powyżej 80 roku życia byli znacznie częściej hospitalizowani i częściej umierali na oddziałach chorób zakaźnych ($p<0.001$) z powodu niewydolności oddechowej ($p=0.012$), ich pobyty w szpitalu były krótsze ($p<0.001$) i najczęściej nie otrzymywali wysokospecjalistycznego leczenia ($p=0.006$) w porównaniu do młodszych pacjentów;
- najczęstsze powikłania COVID-19 obejmowały ostre uszkodzenie nerek u 31.2% (149) pacjentów i powikłania zakrzepowo-zatorowe u 23.5% (112);
- przebieg hospitalizacji był powikłany zakażeniami związanymi z opieką zdrowotną (HAIs) w 33.3% (159) przypadków, istotnie częściej u leczonych barycytynibem ($p<0.001$);
- początkowe zastosowanie antybiotyku, choć częste (452 - 94.8%), było nieuzasadnione w prawie połowie przypadków (215 - 47.6%); ich użycie istotnie ($p<0.001$) spadało wraz z postępem pandemii, z początkowych 97.6% - w okresie pre-Delta, do 83.5% - w okresie Omikron;
- powikłania hospitalizacji (220 - 46.1%) i zdarzenia niepożądane z udziałem personelu (237 - 49.7%) stwierdzono u prawie połowy pacjentów;
- w 88.7% (423) przypadków zgon był spowodowany niewydolnością oddechową w przebiegu zakażenia SARS-CoV-2.

Część trzecia: *Zińczuk A., Rorat M., Jurek T. (2023). COVID-19 - related excess mortality - an overview of the current evidence. Archiwum Medycyny Sądowej i Kryminologii, 2023, 73 (1), 33-44, pkt. MEiN: 70.*

Rzeczywisty wpływ pandemii COVID-19 na zdrowie publiczne jest znacznie szerszy niż rejestrowana liczba zgonów przypisywana COVID-19. Skalę tego zagadnienia oddaje analiza zgonów nadmiarowych, które są definiowane jako różnica w całkowitej liczbie zgonów w sytuacji kryzysowej w porównaniu do liczby zgonów oczekiwanych w normalnych warunkach. Na podstawie przeprowadzonej analizy literatury naukowej za najważniejsze przyczyny występowania zgonów nadmiarowych w czasie pandemii COVID-19 uznano:

- nieprawidłowości w diagnozowaniu i rejestracji zgonów spowodowanych przez COVID-19 z ich niedoszacowaniem na początku i zawyżaniem liczby zgonów związanych z zakażeniem wirusowym wraz z postępem pandemii;
- względy polityczne i przekaz medialny, które to czynniki wpływały na opinię publiczną, między innymi w zakresie akceptacji szczepień i dostosowywania się do zaleceń sanitarnych;
- ograniczenie dostępu do świadczeń medycznych, zarówno szpitalnych jak i ambulatoryjnych, dla pacjentów z innymi schorzeniami i potrzebami medycznymi niż COVID-19;
- przeciążenie systemów opieki zdrowotnej w krajach o niskich i średnich przychodach (ang. LMIC – low- and middle-income countries), w których występowały problemy związane z właściwą opieką zdrowotną jeszcze przed pandemią;
- wprowadzenie zasad dystansu społecznego i innych ograniczeń związanych z tzw. „lockdown", co przełożyło się na zwiększenie liczby zgonów z powodu chorób psychiatrycznych oraz uzależnień;
- wpływ dodatkowych, niezależnych czynników o charakterze klęski żywiołowej (susze, fale upałów, cyklony tropikalne, huragany, powodzie).

VIII. Dyskusja

Pojawienie się nowego zagrożenia biologicznego, jakim jest SARS-CoV-2, skupiło uwagę całego świata. Szybki postęp wiedzy przełożył się na rozwój metod diagnostycznych, terapeutycznych oraz profilaktycznych. Pierwsze terapie opierano na doniesieniach dotyczących mechanizmów działania poprzednich epidemicznych koronawirusów powodujących zakażenia wśród ludzi (SARS-CoV-1 i MERS-CoV), wskazując na konkretne punkty uchwyty dla leków [35], [36]. Następnie stopniowo wprowadzano cząsteczki ukierunkowane na leczenie przyczynowe SARS-CoV-2 (np. molnupiravir, nirmatrelwir) [37]. Po roku od pojawienia się pierwszych zachorowań rozpoczęto szczepienia profilaktyczne, początkowo w populacjach kluczowych, następnie rozszerzając je na kolejne grupy pacjentów. Zbiór publikacji stanowiący niniejszą rozprawę doktorską odnosi się do chorych najciężej chorujących, tym samym stanowiących największe wyzwanie zarówno dla badaczy jak i lekarzy praktyków. Przeprowadzone badania pozwalają na identyfikację, za pomocą podstawowych danych klinicznych oraz prostych narzędzi diagnostycznych, pacjentów obarczonych wysokim ryzykiem ciężkiego przebiegu, a przede wszystkim zgonu w efekcie zakażenia SARS-CoV-2. Badania dostarczają również istotnych informacji na temat okoliczności śmierci pacjentów z COVID-19, a także wskazują przyczyny globalnej nadumieralności w trakcie pandemii.

W pierwszej publikacji z cyklu oceniono współczynniki EASIX, mEASIX, sEASIX, wykorzystujące korelację podstawowych parametrów laboratoryjnych (LDH, kreatynina, PLT, CRP), których odchylenia są składową obrazu klinicznego mikroangiopatii zakrzepowej [31], [32], [38]. Luft et al. pierwotnie zastosował EASIX do oceny rokowania pacjentów poddawanych procedurze przeszczepienia komórek krwiotwórczych oraz wykazał, że współczynnik ten dobrze koreluje ze stężeniem markerów uszkodzenia śródbłonka, przede wszystkim CXCL-8/IL-8 oraz wolnej IL-18 [31], [39]. Podobne obserwacje poczyniono w przypadku COVID-19. W trakcie zakażenia dochodzi do dysfunkcji śródbłonka, którego komórki uwalniają szereg substancji indukujących stres oksydacyjny, co prowadzi do nasilenia stanu zapalnego, wystąpienia powikłań zakrzepowych i niewydolności wielonarządowej [40], [41]. Dysfunkcja śródbłonka wydaje się zatem kluczowym czynnikiem patofizjologicznym ciężkiego przebiegu i powikłań COVID-19, co potwierdzają wczesne analizy z początku pandemii, wykazujące wysokie stężenia cytokin prozapalnych, będących markerami stresu

oksydacyjnego komórek śródbłonka (angiopoetyna-2 oraz CXCL8/IL8) u zakażonych pacjentów [42], [43].

Analiza wybranych parametrów laboratoryjnych, w obu przedłożonych pracach oryginalnych, wskazuje na obecność nasilonego stanu zapalnego oraz zaburzeń ze strony układu naczyniowego już w momencie przyjęcia do szpitala w przypadkach zakażenia SARS-CoV-2 zakończonych zgonem, co potwierdza wstępne doniesienia innych autorów. Modyfikacje EASIX zastosowano po raz pierwszy w pracy Pennisi et al. - zaproponowano wykorzystanie simplified-EASIX (sEASIX), gdzie wykluczono stężenie kreatyniny jako parametru rzadko wykazującego odchylenie u pacjentów z zespołem uwalniania cytokin (ang. CRS – cytokine release syndrome) oraz modified-EASIX (mEASIX), w której to formule kreatyninę zastąpiono stężeniem CRP [32]. Wykazano, że oba zmodyfikowane współczynniki zastosowane przed włączeniem leczenia chimerycznymi limfocytami T (CAR-T) wśród pacjentów z nowotworami hematologicznymi wykazują podobną wartość predykcyjną wystąpienia CRS, natomiast jedynie mEASIX pozwalał na ocenę skuteczności terapii. Pierwsza publikacja z cyklu, oceniająca mEASIX i sEASIX, jest dotychczas jedynym zastosowaniem tych współczynników do oceny pacjentów z COVID-19. Dla każdego z nich (także dla pierwotnego EASIX) wykazano istotność statystyczną ($p<0.001$) w kontekście predykcji zgonu oraz konieczności hospitalizacji w OIT (EASIX $p=0.026$, mEASIX $p=0.019$, sEASIX $p=0.001$). Zastosowanie modyfikacji EASIX nie wpłynęło istotnie na zwiększenie zdolności predykcyjnej współczynnika w odniesieniu do zgonu (osiągnięto porównywalne wyniki analizy PPV, NPV, czułości i swoistości). Podobne wyniki w stosunku do EASIX uzyskano w pracy Kalicińska et al. w porównaniu pacjentów obciążonych nowotworami hematologicznymi w kontekście predykcji hospitalizacji w OIT oraz zgonu. Dodatkowo wykazano związek z wystąpieniem ostrego uszkodzenia nerek i konieczności dializoterapii [44]. Uzyskana w pierwszej publikacji badaniu wartość cut-off, istotna dla predykcji zgonu w przebiegu COVID-19 dla EASIX (2.36), jest wyższa niż w analizach innych badaczy (Kalicińska et al. EASIX ≥1.6, Luft et al. EASIX ≥2.03) [25], [44]. Wpływ na takie rezultaty może mieć charakterystyka analizowanej grupy – wyselekcjonowani pacjenci w ciężkim stanie, z dużym odsetkiem zgonów (65.7%). Kontynuując prowadzone badania współczynnikiem EASIX posłużono się także w drugiej publikacji. Tu z kolei wartość EASIX (średnia 6.22, mediana 3.14) w ocenianej populacji pacjentów, którzy zmarli, była powyżej punktów odcięcia ustalonych w pozostałych

publikacjach, analizujących ten współczynnik. Na uwagę zasługuje fakt, że dane te są porównywalne do analizy z pierwszej pracy. W grupie 243 przypadków zakończonych zgonem spośród wszystkich 370 ocenianych, uzyskano średnią 6.66 oraz medianę 3.11 EASIX. Dodatkowo uzasadnia to jego wykorzystanie do wyjściowej oceny pacjentów z COVID-19.

Ocena przebiegu hospitalizacji pacjentów, którzy zmarli w przebiegu zakażenia SARS-CoV-2, przyniosła szereg istotnych informacji. Na uwagę zasługuje fakt, że publikacja *„Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors - a single-center, retrospective analysis of the first two years of the pandemic."* jest jedną z niewielu, które oceniają zdarzenia niepożądane występujące w tej grupie chorych. Najważniejszym wynikiem analizy jest wykazanie dużego odsetka (prawie 50%) zdarzeń niepożądanych w trakcie opieki nad pacjentami. Ocena nieprawidłowości w aspekcie nowego czynnika etiologicznego, przeciążenia systemu opieki zdrowotnej i braku jednoznacznych wytycznych dotyczących terapii stwarza wiele trudności, w tym także natury etycznej. Nieprawidłowości w postępowaniu personelu medycznego wykazano w 49.7% przypadków. Brak leczenia specjalistycznego (17.0%) u części chorych mógł w istotny sposób przyczynić się do zgonu. Częściej jednak (32.7% przypadków) dochodziło do opóźnienia w zastosowaniu różnych metod terapeutycznych, między innymi w wykonaniu intubacji dotchawiczej oraz włączenia leczenia immunomodulującego, na co wpływ miał ograniczony dostęp do miejsc w OIT oraz brak dostępu do odpowiednich leków. Dużym problemem związanym z leczeniem pacjentów z COVID-19 okazało się nadużywanie antybiotyków. W analizowanej grupie wyjściowo zastosowana antybiotykoterapia dotyczyła aż 94.8% pacjentów, gdzie rzeczywiste wskazania do jej zastosowania występowały jedynie w około połowie przypadków. Już pierwsze wytyczne WHO z 27 maja 2020 r. zwracały uwagę na konieczność zastosowania właściwej polityki antybiotykowej wśród pacjentów z COVID-19: odstąpienie od użycia antybiotyków w przypadkach choroby o lekkim przebiegu oraz kierowaniu się obrazem klinicznymi i parametrami laboratoryjnymi wskazującymi na konieczność zastosowania dodatkowej terapii przeciwdrobnoustrojowej wśród pozostałych pacjentów [30]. W łączności z tymi danymi pozostaje analiza infekcji towarzyszących - jakąkolwiek infekcję stwierdzono u ponad 50% pacjentów (57.4%), którzy zmarli, w tym u 1/3 pacjentów (33.3%) była to infekcja szpitalna, częściej u przyjmowanych do OIT. W badaniach innych autorów częstość występowania infekcji towarzyszących w populacji ogólnej pacjentów hospitalizowanych

z COVID-19 nie przekraczała 7-14%, z dużo większym odsetkiem infekcji nabytych w OIT (nawet ponad 50%) i dużo większą śmiertelnością w OIT wśród pacjentów z koinfekcjami [45]–[48]. Biorąc pod uwagę fakt, że ponad 55% przypadków zgonów w ocenianym materiale dotyczyła OIT, wynik ten jest porównywalny z ww. badaniami.

Najczęstszym powikłaniem związanym z COVID-19, które zostało przez nas zaobserwowane, było ostre uszkodzenie nerek; stwierdzono je u 149 spośród 477 pacjentów (31.2%). Metaanaliza, przeprowadzona przez Yang et al., pozwala stwierdzić, że wynik ten jest porównywalny do danych światowych. W analizie populacji ogólnej pacjentów z COVID-19 ostre uszkodzenie nerek występuje z częstością 12.3% (95%CI 9.5-16.5%) z dużo wyższym odsetkiem wśród przypadków hospitalizowanych w OIT – 39.0% (95%CI 23.2-57.6%) oraz zakończonych zgonem 42.0% (95%CI 30.3-54.7%) [49]. Powikłania zakrzepowo - zatorowe wykazano z kolei wśród blisko ¼ pacjentów (23.5%), najczęściej stwierdzano żylną chorobę zakrzepowo-zatorową – 46 (9.6%), dane te jednak mogą być niedoszacowane, w związku z brakiem technicznej możliwości wykonania badania TK u części pacjentów w ciężkim stanie z dużym zapotrzebowaniem tlenowym i/lub niestabilnych hemodynamicznie. Dane literaturowe podają częstość występowania takich zaburzeń na poziomie 16.5% (95% CI 11.6-22.9) [50].

Szacunkowe dane pochodzące z USA z okresu przedpandemicznego wskazują, że błędy medyczne mogą być trzecią co do częstości przyczyną zgonu w tym kraju [51]. W krajach o wysokich dochodach zdarzenia niepożądane występują średnio u 1 na 10 pacjentów [52]. Szacuje się, że w krajach o niskich i średnich dochodach nawet co czwarty pacjent odnosi szkodę, a rocznie dochodzi do 134 milionów zdarzeń niepożądanych, odpowiadających za 2,6 miliona zgonów możliwych do uniknięcia [53]. Nasze dane, choć orientacyjne, ukazują zdarzenia niepożądane jako istotny czynnik ryzyka niepowodzeń terapeutycznych, który warto zgłębić w kolejnych badaniach.

Podsumowaniem i rozwinięciem analiz danych dotyczących pacjentów hospitalizowanych jest praca przeglądowa,, opisująca zagadnienie zgonów nadmiarowych w skali globalnej. Pojęcie to oddaje rzeczywisty wpływ pandemii COVID-19 na zdrowie publiczne, jest także dobrym wskaźnikiem przygotowania systemów zdrowotnych do nowego zagrożenia [54], [55]. Liczne czynniki organizacyjne, braki kadrowe i rozwiązania tymczasowe zakłóciły funkcjonowanie większości systemów na całym świecie [56]. Wykorzystanie

dotychczasowych środków (personelu i infrastruktury medycznej) do walki z COVID-19 spowodowało ograniczenie w dostępie do właściwej opieki medycznej dla chorych z innymi obciążeniami. Wykazano, że było to przyczyną około 20% nadmiarowych zgonów we Włoszech i Anglii oraz nawet 62% w Grecji w początkowych okresach trwania pandemii [57]–[59]. Głównym powodem był brak dostępu do opieki ambulatoryjnej i procedur chirurgicznych. Podobne przyczyny dużej liczby zgonów w okresie pandemii stwierdzane były w Polsce [60]. Jakość świadczeń spadła z powodu opóźnień we wdrożeniu leczenia zarówno COVID-19 jak i wszystkich pozostałych schorzeń w efekcie braku lub ograniczeń w dostępności do usług. Pacjenci nie otrzymywali standardowej opieki ambulatoryjnej i profilaktycznej między innymi z powodu pierwszeństwa przyjęć pacjentów z COVID-19. Wystąpiły też nowe rodzaje błędów diagnostycznych w różny sposób związane i niezwiązane z samym zakażeniem wirusem SARS-CoV-2 [61]. Podkreśla się, że wpływ pandemii COVID-19 na liczbę nadmiarowych zgonów związanych z mechanizmami zachodzącymi w systemach opieki zdrowotnej może być rozłożony w czasie i występować także w kolejnych latach, nie tylko w okresie rejestracji zgonów, co w oczywisty sposób przełoży się na wyższy rachunek szkód wywołanych pandemią [62]. Znajomość czynników warunkujących ciężki przebieg COVID-19, analiza przebiegu hospitalizacji oraz wykazanie słabych punktów funkcjonowania systemów zdrowotnych, pozwoli poprawić jakość opieki nad pacjentami, którzy w przyszłości mogą doświadczyć nowych zagrożeń biologicznych o zasięgu globalnym.

IX. Wnioski

1. Współczynniki EASIX, mEASIX, sEASIX wykazują dobrą korelację z ryzykiem zgonu oraz koniecznością hospitalizacji w oddziale intensywnej terapii chorych z ciężkim przebiegiem COVID-19 i mogą służyć identyfikacji pacjentów zagrożonych niepomyślnym przebiegiem choroby.
2. Hospitalizacja pacjentów z COVID-19 jest związana z licznymi zdarzeniami niepożądanymi, które, obok samego zakażenia, należy rozpatrywać jako dodatkowy czynnik wpływający na ryzyko zgonu. Zdarzenia te jedynie w części są zależne od personelu medycznego, a w dużej mierze mają związek z przeciążeniem systemu opieki zdrowotnej oraz z pobytem w środowisku szpitalnym.
3. Rzeczywistą miarą wpływu pandemii COVID-19 na zdrowie publiczne są analizy zgonów nadmiarowych, które poza rejestrowanymi zgonami przypisanymi COVID-19 uwzględniają także dodatkowe czynniki związane z przeciążeniem systemów opieki zdrowotnej.

X. Piśmiennictwo

[1] "Pneumonia of unknown cause – China." https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229 (accessed May 11, 2023).

[2] "Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)." https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) (accessed May 11, 2023).

[3] "Archived: WHO Timeline - COVID-19." https://www.who.int/news/item/27-04-2020-who-timeline---covid-19 (accessed May 11, 2023).

[4] "Tracking SARS-CoV-2 variants." https://www.who.int/activities/tracking-SARS-CoV-2-variants (accessed Jun. 16, 2023).

[5] "Tracking SARS-CoV-2 variants." https://www.who.int/en/activities/tracking-SARS-CoV-2-variants (accessed Apr. 01, 2023).

[6] "Statement on the update of WHO's working definitions and tracking system for SARS-CoV-2 variants of concern and variants of interest." https://www.who.int/news/item/16-03-2023-statement-on-the-update-of-who-s-working-definitions-and-tracking-system-for-sars-cov-2-variants-of-concern-and-variants-of-interest (accessed Apr. 01, 2023).

[7] W. H. Liang, W. J. Guan, C. Ch. Li *et al.*, "Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicentre) and outside Hubei (non-epicentre): a nationwide analysis of China," *Eur Respir J*, vol. 55, no. 6, Jun. 2020, doi: 10.1183/13993003.00562-2020.

[8] X. Feng, P. Li, L. Ma *et al.*, "Clinical Characteristics and Short-Term Outcomes of Severe Patients With COVID-19 in Wuhan, China," *Front Med (Lausanne)*, vol. 7, no. August, pp. 1–12, 2020, doi: 10.3389/fmed.2020.00491.

[9] J. Li, D. Q. Huang, B. Zou *et al.*, "Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes," *J Med Virol*, vol. 93, no. 3, pp. 1449–1458, 2021, doi: 10.1002/jmv.26424.

[10] "WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data." https://covid19.who.int/ (accessed Jun. 01, 2023).

[11] T. Iba, J. M. Connors, and J. H. Levy, "The coagulopathy, endotheliopathy, and vasculitis of COVID-19," *Inflammation Research*, vol. 69, no. 12, pp. 1181–1189, 2020, doi: 10.1007/s00011-020-01401-6.

[12] E. Kalicińska, D. Szymczak, A. Zińczuk *et al.*, "Immunosuppression as a hallmark of critical covid-19: Prospective study," *Cells*, vol. 10, no. 6, pp. 1–13, 2021, doi: 10.3390/cells10061293.

[13] J. H. Levy, T. Iba, L. B. Olson *et al.,* "COVID-19: Thrombosis, thromboinflammation, and anticoagulation considerations," *Int J Lab Hematol*, vol. 43, no. S1, pp. 29–35, Jul. 2021, doi: 10.1111/IJLH.13500.

[14] Z. Zheng, F. Peng, B. Xu *et al.*, “Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis,” *J Infect*, vol. 81, no. 2, pp. e16–e25, Aug. 2020, doi: 10.1016/J.JINF.2020.04.021.

[15] J. jin Zhang, X. Dong, G. hui Liu *et al.*, “Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality,” *Clin Rev Allergy Immunol*, vol. 64, no. 1, pp. 90–107, Feb. 2023, doi: 10.1007/S12016-022-08921-5.

[16] A. Rahman and N. J. Sathi, “Risk factors of the severity of COVID-19: A meta-analysis,” *Int J Clin Pract*, vol. 75, no. 7, Jul. 2021, doi: 10.1111/IJCP.13916.

[17] T. Nyberg, N. M. Ferguson, S. G. Nash *et al.*, “Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study,” *Lancet*, vol. 399, no. 10332, pp. 1303–1312, Apr. 2022, doi: 10.1016/S0140-6736(22)00462-7.

[18] M. E. Modes, M. P. Directo, M. Melgar *et al.*, “Clinical Characteristics and Outcomes Among Adults Hospitalized with Laboratory-Confirmed SARS-CoV-2 Infection During Periods of B.1.617.2 (Delta) and B.1.1.529 (Omicron) Variant Predominance — One Hospital, California, July 15–September 23, 2021, and December 21, 2021–January 27, 2022,” *MMWR Recommendations and Reports*, vol. 71, no. 6, pp. 217–223, 2022, doi: 10.15585/mmwr.mm7106e2.

[19] R. Horton, “Offline: COVID-19 is not a pandemic,” *Lancet*, vol. 396, no. 10255, p. 874, Sep. 2020, doi: 10.1016/S0140-6736(20)32000-6.

[20] S. Ghahramani, R. Tabrizi, K. B. Lankarani *et al.*, “Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: A systematic review and meta-analysis,” *Eur J Med Res*, vol. 25, no. 1, pp. 1–10, 2020, doi: 10.1186/s40001-020-00432-3.

[21] Z.-L. Zhang, Y.-L. Hou, D.-T. Li *et al.,* “Laboratory findings of COVID-19: a systematic review and meta-analysis.,” *Scand J Clin Lab Invest*, vol. 0, no. 0, pp. 1–7, 2020, doi: 10.1080/00365513.2020.1768587.

[22] A. S. Chan and A. Rout, “Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19,” *J Clin Med Res*, vol. 12, no. 7, p. 448, 2020, doi: 10.14740/JOCMR4240.

[23] A. D. Haimovich, N. G. Ravindra, S. Stoytchev *et al.*, “Development and Validation of the Quick COVID-19 Severity Index: A Prognostic Tool for Early Clinical Decompensation,” *Ann Emerg Med*, vol. 76, no. 4, pp. 442–453, Oct. 2020, doi: 10.1016/J.ANNEMERGMED.2020.07.022.

[24] S. R. Knight, A. Ho, R. Pius *et al.*, “Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score,” *BMJ*, vol. 370, Sep. 2020, doi: 10.1136/BMJ.M3339.

[25] T. Luft, C.-M. Wendtner, F. Kosely *et al.*, “EASIX for Prediction of Outcome in Hospitalized SARS-CoV-2 Infected Patients,” *Front Immunol*, vol. 12, no. June, pp. 1–9, Jun. 2021, doi: 10.3389/fimmu.2021.634416.

[26] M. Rorat, T. Jurek, K. Simon *et al.,* “The chest radiographic scoring system in initial diagnosis of COVID-19: Is a radiologist needed?,” *Adv Clin Exp Med*, vol. 30, no. 8, Jul. 2021, doi: 10.17219/ACEM/139717.

[27] C. T. Leffler and S. Konda, “The Reasons for Excess Mortality during the COVID-19 Pandemic,” *Am J Trop Med Hyg*, vol. 107, no. 1, p. 218, Jul. 2022, doi: 10.4269/AJTMH.22-0243B.

[28] “The true death toll of COVID-19: estimating global excess mortality.” https://www.who.int/data/stories/the-true-death-toll-of-covid-19-estimating-global-excess-mortality (accessed May 09, 2023).

[29] “14.9 million excess deaths associated with the COVID-19 pandemic in 2020 and 2021.” https://www.who.int/news/item/05-05-2022-14.9-million-excess-deaths-were-associated-with-the-covid-19-pandemic-in-2020-and-2021 (accessed May 12, 2023).

[30] “WHO: Clinical management of COVID-19; interim guidance 27 May 2020”.

[31] T. Luft, A. Benner, S. Jodele *et al.*, “EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis,” *Lancet Haematol*, vol. 4, no. 9, pp. e414–e423, Sep. 2017, doi: 10.1016/S2352-3026(17)30108-4.

[32] M. Pennisi, M. Sanchez-Escamilla, J. R. Flynn *et al.*, “Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells,” *Blood Adv*, vol. 5, no. 17, pp. 3397–3406, Sep. 2021, doi: 10.1182/BLOODADVANCES.2020003885.

[33] J. Hadfield, C. Megill, S. M. Bell *et al.*, “NextStrain: Real-time tracking of pathogen evolution,” *Bioinformatics*, vol. 34, no. 23, pp. 4121–4123, Dec. 2018, doi: 10.1093/BIOINFORMATICS/BTY407.

[34] “Conceptual framework for the international classification for patient safety version 1.1: final technical report January 2009.” https://apps.who.int/iris/handle/10665/70882 (accessed May 23, 2023).

[35] M. Khan, S. F. Adil, H. Z. Alkhathlan *et al.*, “COVID-19: A Global Challenge with Old History, Epidemiology and Progress So Far,” *Molecules*, vol. 26, no. 1, Jan. 2020, doi: 10.3390/MOLECULES26010039.

[36] Y. Yuan, B. Jiao, L. Qu, D. Yang *et al.,* “The development of COVID-19 treatment,” *Front Immunol*, vol. 14, Jan. 2023, doi: 10.3389/FIMMU.2023.1125246.

[37] “Therapeutics and COVID-19: living guideline - NCBI Bookshelf.” https://www.ncbi.nlm.nih.gov/books/NBK582436/ (accessed Apr. 01, 2023).

[38] P. Rajendran, T. Rengarajan, J. Thangavel *et al.*, “The Vascular Endothelium and Human Diseases,” *Int J Biol Sci*, vol. 9, no. 10, p. 1057, Nov. 2013, doi: 10.7150/IJBS.7502.

[39] T. Luft, A. Benner, T. Terzer *et al.*, “EASIX and mortality after allogeneic stem cell transplantation,” *Bone Marrow Transplant*, vol. 55, no. 3, pp. 553–561, Mar. 2020, doi: 10.1038/S41409-019-0703-1.

[40] R. Chang, A. Mamun, A. Dominic *et al*., “SARS-CoV-2 Mediated Endothelial Dysfunction: The Potential Role of Chronic Oxidative Stress,” *Front Physiol*, vol. 11, Jan. 2021, doi: 10.3389/FPHYS.2020.605908.

[41] J. F. Bermejo-Martin, R. Almansa, A. Torres *et al.,* “COVID-19 as a cardiovascular disease: the potential role of chronic endothelial dysfunction,” *Cardiovasc Res*, vol. 116, no. 10, pp. E132–E133, Aug. 2020, doi: 10.1093/CVR/CVAA140.

[42] E. Terpos, I. Ntanasis-Stathopoulos, I. Elalamy *et al.*, "Hematological findings and complications of COVID-19," *Am J Hematol*, vol. 95, no. 7, pp. 834–847, Jul. 2020, doi: 10.1002/AJH.25829.

[43] Z. Varga, A. J. Flammer, P. Steiger *et al.*, "Endothelial cell infection and endotheliitis in COVID-19," *The Lancet*, vol. 395, no. 10234, pp. 1417–1418, May 2020, doi: 10.1016/S0140-6736(20)30937-5.

[44] E. Kalicińska, M. Biernat, J. Rybka *et al.*, "Endothelial Activation and Stress Index (EASIX) as an Early Predictor for Mortality and Overall Survival in Hematological and Non-Hematological Patients with COVID-19: Multicenter Cohort Study," *J Clin Med*, vol. 10, no. 19, p. 4373, Sep. 2021, doi: 10.3390/jcm10194373.

[45] C. Garcia-Vidal, G. Sanjuan, E. Moreno-Garcia *et al.*, "Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study," *Clinical Microbiology and Infection*, vol. 27, no. 1, p. 83, Jan. 2021, doi: 10.1016/J.CMI.2020.07.041.

[46] M. C. Soriano, C. Vaquero, A. Ortiz-Fernández *et al.*, "Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19," *J Infect*, vol. 82, no. 2, p. e20, Feb. 2021, doi: 10.1016/J.JINF.2020.09.010.

[47] L. Lansbury, B. Lim, V. Baskaran *et al.,* "Co-infections in people with COVID-19: a systematic review and meta-analysis," *Journal of Infection*, vol. 81, no. 2, pp. 266–275, Aug. 2020, doi: 10.1016/J.JINF.2020.05.046.

[48] T. M. Rawson, L. S. P. Moore, N. Zhu *et al.*, "Bacterial and Fungal Coinfection in Individuals with Coronavirus: A Rapid Review to Support COVID-19 Antimicrobial Prescribing," *Clinical Infectious Diseases*, vol. 71, no. 9, pp. 2459–2468, Nov. 2020, doi: 10.1093/CID/CIAA530.

[49] X. Yang, S. Tian, and H. Guo, "Acute kidney injury and renal replacement therapy in COVID-19 patients: A systematic review and meta-analysis," *Int Immunopharmacol*, vol. 90, Jan. 2021, doi: 10.1016/J.INTIMP.2020.107159.

[50] Y. J. Suh, H. Hong, M. Ohana *et al.*, "Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis," *Radiology*, vol. 298, no. 2, pp. E70–E80, Feb. 2021, doi: 10.1148/RADIOL.2020203557.

[51] J. G. Anderson and K. Abrahamson, "Your Health Care May Kill You: Medical Errors," *Stud Health Technol Inform*, vol. 234, pp. 13–17, 2017, doi: 10.3233/978-1-61499-742-9-13.

[52] "The economics of patient safety : Strengthening a value-based approach to reducing patient harm at national level | OECD Health Working Papers | OECD iLibrary." https://www.oecd-ilibrary.org/social-issues-migration-health/the-economics-of-patient-safety_5a9858cd-en (accessed May 23, 2023).

[53] "Crossing the Global Quality Chasm: Improving Health Care Worldwide," *Crossing the Global Quality Chasm*, Dec. 2018, doi: 10.17226/25152.

[54] W. Shang, Y. Wang, J. Yuan *et al.,* "Global Excess Mortality during COVID-19 Pandemic: A Systematic Review and Meta-Analysis," *Vaccines (Basel)*, vol. 10, no. 10, Oct. 2022, doi: 10.3390/VACCINES10101702.

[55] N. Islam, "'Excess deaths' is the best metric for tracking the pandemic," *BMJ*, vol. 376, 2022.

[56] P. G. T. Walker, Ch. Whittaker, O. J. Watson *et al.*, "The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries," *Science*, vol. 369, no. 6502, pp. 413–422, Jul. 2020, doi: 10.1126/SCIENCE.ABC0035.

[57] E. Kondilis, F. Tarantilis, and A. Benos, "Essential public healthcare services utilization and excess non-COVID-19 mortality in Greece," *Public Health*, vol. 198, pp. 85–88, Sep. 2021, doi: 10.1016/J.PUHE.2021.06.025.

[58] G. Alicandro, G. Remuzzi, and C. La Vecchia, "Italy's first wave of the COVID-19 pandemic has ended: no excess mortality in May, 2020," *Lancet*, vol. 396, no. 10253, p. e27, Sep. 2020, doi: 10.1016/S0140-6736(20)31865-1.

[59] E. Kontopantelis, M. A. Mamas, J. Deanfield *et al.,* "Excess mortality in England and Wales during the first wave of the COVID-19 pandemic," *J Epidemiol Community Health (1978)*, vol. 75, no. 3, pp. 213–223, Mar. 2021, doi: 10.1136/JECH-2020-214764.

[60] K. Barański, G. Brożek, M. Kowalska *et al.,* "Impact of COVID-19 Pandemic on Total Mortality in Poland," *Int J Environ Res Public Health*, vol. 18, no. 8, Apr. 2021, doi: 10.3390/IJERPH18084388.

[61] "Ensuring a safe environment for patients and staff in COVID-19 health-care facilities: a module from the suite of health service capacity assessments in the context of the COVID-19 pandemic." https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-HCF_assessment-Safe_environment-2020.1 (accessed May 23, 2023).

[62] "Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21," *Lancet*, vol. 399, no. 10334, pp. 1513–1536, Apr. 2022, doi: 10.1016/S0140-6736(21)02796-3.

XI. Publikacje stanowiące podstawę rozprawy doktorskiej

Journal of *Personalized Medicine*

MDPI

Article

EASIX, Modified EASIX and Simplified EASIX as an Early Predictor for Intensive Care Unit Admission and Mortality in Severe COVID-19 Patients

Aleksander Zińczuk [1,2,*], Marta Rorat [1,2], Krzysztof Simon [2,3] and Tomasz Jurek [1]

[1] Department of Forensic Medicine, Wroclaw Medical University, 50-367 Wroclaw, Poland; marta.rorat@umw.edu.pl (M.R.); tomasz.jurek@umw.edu.pl (T.J.)
[2] 1st Department of Infectious Diseases, J. Gromkowski Specialist Regional Hospital, 51-149 Wroclaw, Poland; krzysztof.simon@umw.edu.pl
[3] Department of Infectious Diseases and Hepatology, Wroclaw Medical University, 50-367 Wroclaw, Poland
* Correspondence: aleksander.zinczuk@student.umw.edu.pl; Tel.: +48-883-147-077

Abstract: COVID-19 receives a lot of attention due to its threat to global public health. Research is ongoing to find universal methods to assess the baseline health status of a patient to determine prognosis and management strategies. This study aims to assess the predictive potential of the EASIX (Endothelial Activation and Stress Index) and two of its modifications (mEASIX and sEASIX) in terms of the need for admission to the ICU (intensive care unit), the use of IMV (invasive mechanical ventilation) and death due to COVID-19. The medical data of 370 severely ill patients hospitalised in the COVID-19 departments of the Regional Specialist Hospital in Wroclaw (Poland), including the ICU, were analysed retrospectively. The mortality rate in the group studied was 65.7% (243 cases). In the case of all three indices, EASIX, mEASIX and sEASIX, there was a statistically significant correlation between the need for admission to the ICU ($p = 0.026$, $p = 0.019$, $p = 0.001$, respectively) and the risk of death ($p < 0.001$). In terms of the risk of death, the high values of the assessed indices (EASIX $\geq$ 2.36, mEASIX $\geq$ 704.03, sEASIX $\geq$ 3.81) were characterised by low sensitivity ($\leq$40%), high specificity (approximately 90%) and low NPV (negative predictive value) (approximately 40%) with high PPV (positive predictive value) (approximately 80%). Due to the ease of implementation and the low cost of performing basic laboratory tests, the above-mentioned indices can be used as an additional, but not universal tool for the initial assessment of the health condition of patients admitted to the hospital.

Keywords: Endothelial Activation and Stress Index; SARS-CoV-2; endotheliitis; inflammation

check for updates

Citation: Zińczuk, A.; Rorat, M.; Simon, K.; Jurek, T. EASIX, Modified EASIX and Simplified EASIX as an Early Predictor for Intensive Care Unit Admission and Mortality in Severe COVID-19 Patients. *J. Pers. Med.* **2022**, *12*, 1022. https://doi.org/10.3390/jpm12071022

Academic Editor: Eumorfia Kondili

Received: 9 May 2022
Accepted: 20 June 2022
Published: 21 June 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

COVID-19 (coronavirus disease 2019) is a multi-organ disorder that primarily affects the respiratory system [1,2]. The disease, caused by SARS-CoV-2, is associated with high mortality among hospitalised patients. The very first Chinese epidemiological data from the beginning of the pandemic indicated severe SARS-CoV-2 infection in the case of approximately 16% of patients, of whom 3.2% were critically ill patients who developed thromboembolic disorders, sepsis/septic shock, multi-organ failure and death [3,4]. A meta-analysis conducted by Jie Li et al. that involved more than 280,000 patients (based on data up to 6 April 2020), showed that severe disease occurred in 22.9% of cases and mortality reached 5.6% [5]. Current epidemiological data shows that the global COVID-19 mortality rate does not exceed 2% (approximately 1.64%) [6].

Knowledge of risk factors and the ability to predict the severity of an infection is constantly evolving. Data from numerous studies proves the existence of a number of risk factors for a severe course of the disease and death, such as: older age, male gender, smoking, pregnancy, use of immunosuppressants, or comorbidities including chronic heart,

lung, liver and kidney diseases, diabetes, obesity and malignancies [7–11]. The correlation between the severity of the patient's condition and the results of routinely performed laboratory tests (C-reactive protein, lymphocytes, neutrophils, urea, troponin I, bilirubin, ferritin, D-dimer, creatinine kinase and lactate dehydrogenase), or the intensification of inflammatory changes in imaging tests was also demonstrated [4,5,12–14]. However, research is ongoing to find tools that would be universal and easy to use, in the event of a large number of infections, for early assessment of the risk of deterioration of a patient's condition based on baseline parameters.

The pathophysiology of a severe course of COVID-19 is associated with, among other things, damage to the vascular endothelium, uncontrolled release of cytokines and pro-inflammatory factors, and abnormalities in the composition and functioning of immune system cells, which ultimately lead to multiple organ failure [15,16]. By binding to endothelial cells via ACE2 receptors [17], SARS-CoV-2 activates a signalling cascade, which leads to the release of pro-inflammatory cytokines that trigger the coagulation process. Consequently, a condition known as thromboinflammation develops, which is the basis of thromboembolic complications that make up the CAC (COVID-19 associated coagulopathy) [18]. Thus, endothelial dysfunction appears to be the key pathophysiological factor of a severe course and complications due to COVID-19, as confirmed by early analyses, performed at the beginning of the pandemic, of laboratory markers in patients infected with SARS-CoV-2 and the presence of high levels of pro-inflammatory cytokines that are endothelial stress markers (angiopoietin-2 and CXCL8) [19–24].

The above mentioned discovery justified an attempt to use the EASIX index (Endothelial Activation and Stress Index), which is the correlation between popular laboratory markers of endothelial dysfunction: lactate dehydrogenase (LDH) activity, creatinine concentration and thrombocytes count, for the baseline assessment of the condition of patients. Initially, the EASIX index was described by Luft et al. as a predictor of death in patients with acute graft versus host disease (GvHD) after allogeneic haematopoietic marrow cell transplantation it correlated well with the concentration of endothelial stress markers, particularly with CXCL-8/IL-18 and free IL-18 [25,26]. EASIX was also found to be a strong predictor of the severity of COVID-19 and mortality due to the disease. As in the case of haematological diseases, it shows a significant correlation with the concentration of endothelial and inflammatory markers (ANG2, sTM, ST2, CXCL8, CXCL9, IL-18) [27]. To date, there are only three publications on such an assessment and in each of them statistically significant results were achieved justifying further research in that direction [27–29].

The aim of this study is to assess the possibility of using the conventional EASIX index and its two modifications, the simplified EASIX (sEASIX) and the modified EASIX (mEASIX), as predictors of the need for admission to the ICU (intensive care unit), the use of IMV (invasive mechanical ventilation) and death among patients with COVID-19 in a severe clinical condition. To our knowledge, this is the first publication on the use of modified indices (mEASIX, sEASIX) to assess the condition of such patients.

In terms of the management of healthcare systems with limited access to intensive care units, which also applies to Poland, the identification of patients who are at risk of severe illness, in particular those at risk of death from COVID-19, is of key importance. Providing such patients with appropriate specialist monitoring will increase their chances of survival thanks to timely and appropriately targeted treatment. The use of a simple tool, such as the EASIX index, in combination with other popular diagnostic methods to assess the risk of an unfavourable course of the disease is a good opportunity to achieve the above-mentioned goal. The hypothesis of the study is that high values of EASIX and the modified sEASIX and mEASIX coefficients are correlated with the undesirable clinical outcome (death, ICU admission and invasive mechanical ventilation).

2. Materials and Methods

Retrospective analysis of the medical data of patients with severe COVID-19 hospitalised in the period from 6 March 2020 to 30 June 2021 in a specialist hospital dedicated

to the treatment of patients with COVID-19 in Lower Silesia (Poland). The study covered 370 consecutively admitted patients (out of a total of 2407 patients hospitalised during that time) with SARS-CoV-2 infection confirmed by a real-time RT-PCR (reverse transcription-polymerase chain reaction) or rapid antigen test (PanBio COVID-19 Ag Rapid Test Device by Abbott), who developed severe (WHO 3 and 4) disease at different times of hospitalisation, regardless of their condition upon admission, so they could be admitted with WHO 1 or 2 at baseline [30]. Patients with a mild to moderate (WHO 1 and 2) course of the disease, those who were transferred to other hospitals and their survival/non-survival status unknown or those who died before the first basic laboratory tests on admission to the hospital were performed, were excluded from the study.

Demographics (age and gender), presence of comorbidities, the time from onset of symptoms to the time of admission to the hospital, baseline blood saturation measured with the use of room-air pulse oximetry, course of hospitalisation (length, day of admission to the ICU, duration of ICU stay) were taken into account in the study. With regard to the laboratory tests, the values of the parameters on the 1st day of hospitalisation were considered: C-reactive protein (CRP), procalcitonin (PCT) and ferritin concentration, lactate dehydrogenase (LDH) activity, white blood count (WBC), neutrophils count (NEU), lymphocytes count (LYM), haemoglobin (HGB), platelet count (PLT), D-Dimer and creatinine concentration, international normalised ratio (INR), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity. The baseline condition of the patient was assessed using the 4-point WHO scale (1-mild disease, symptomatic COVID-19 patients without evidence of viral pneumonia or hypoxia; 2-moderate disease, clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing), no signs of severe pneumonia, $SpO_2 \geq 90\%$ on room-air; 3-severe disease, clinical signs of pneumonia plus one of the following: respiratory rate > 30/min, severe respiratory distress, $SpO_2 < 90\%$ on room-air; 4-critical disease, ARDS, sepsis or septic shock) [30]. The study also considered the method and duration of individual oxygen therapy (oxygen therapy using a mask with a reservoir at a minimum flow of 10 L/min, HFNO-high flow nasal oxygenation, NIV-non-invasive ventilation, IMV-invasive mechanical ventilation). In the absence of specific recommendations on the application of different types of oxygen therapy in the period assessed, qualification for treatment was performed individually by the attending physician based on the results of blood saturation measurements taken using a pulse oximeter, blood gas tests, imaging studies and general medical condition. The decision to intubate and perform invasive mechanical ventilation was made by an anaesthesiology and ICU specialist. Disease progression was defined as meeting the severe case criteria according to the WHO classification (≥3). If the status of the admitted patient was considered to be 3 according to WHO, progression was assessed as the moment the method of oxygen therapy was changed-the need for escalation. Overall, 369 out of 370 patients had laboratory tests performed on admission, which were necessary for the calculation of: EASIX according to the standard formula by Luft et al. (LDH [U/L] × Creatinine [mg/dL]/platelet count [G/L]) and modified sEASIX (LDH [U/L]/platelet count [G/L]) and mEASIX (LDH [U/L] × CRP [mg/dL]/platelet count [G/L]) according to Pennisi et al. [26,31]. In this study, a different unit of CRP was used, which is commonly used in Poland and worldwide-(mg/L) was used instead of (mg/dL) and the mEASIX index was assessed without conversion to that unit.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bioethics Committee of Wroclaw Medical University (Decision no. KB-826/2020, dated 17 December 2020). The requirement to obtain informed consent from the patients to use their medical data was waived by the bioethics committee. To perform the retrospective study, data was anonymised before being entered into the database and analysed.

3. Statistical Analysis

Descriptive statistics were presented: for quantitative variables as mean values with SD (standard deviation) or/and median with IQR (interquartile range), for qualitative variables as absolute count with percentage. Quantitative variables (including EASIX, mEASIX, sEASIX) were transformed and analysed using $\log_2$. For this, Spearman's rank–order correlation was used. Qualitative variables were compared using the Mann–Whitney test and tau–Kendall correlation. Optimal $\log_2$-EASIX, $\log_2$-mEASIX and $\log_2$-sEASIX cut-off values for death were determined by the Youden Index.

The T-test with Cox-adjustment was used for univariable analysis. The optimal cut-off point for quantitative variables was calculated using the Youden Index. Receiver operating characteristics (ROC) curves analysis was performed to assess the effectiveness of said points (sensitivity, specificity, area under the ROC curve (AUC)).

Analysis was performed using Statistica (version 13.3, TIBCO Software Inc., Palo Alto, CA, USA) for Windows. All statistical tests were considered significant with the p-value < 0.05.

4. Results

The characteristics of the study group divided into subgroups in terms of clinical outcome are presented in Table 1. Overall, 243 patients out of 370 (65.7%) died. The main cause of death among patients was respiratory failure (86.4%), and other disorders predominated in the remaining cases (13.6%), but respiratory failure accompanied them (septic shock in the course of secondary bacterial infection, progression of neoplastic disease, decompensated liver cirrhosis, ischaemic or haemorrhagic stroke, subarachnoid haemorrhage, post-surgery multi-organ failure, sudden circulatory arrest, haemorrhagic stroke and acute renal failure).

Patients who died were older ($p < 0.001$, cut-off $\geq$ 72 years), more frequently burdened with circulatory system diseases ($p = 0.009$), malignant neoplasms ($p = 0.046$), and chronic renal failure ($p = 0.001$). They were also characterised by higher LDH activity ($p = 0.026$), elevated levels of D-dimer ($p = 0.018$) and creatinine ($p = 0.016$) at the time of admission. They required more frequent application of NIV ($p < 0.001$) and IMV ($p < 0.001$), and less frequent application of HFNO ($p < 0.001$) for a shorter period. Furthermore, the disease progression was faster in the group of non-survivors—those patients required earlier admission to the hospital (calculated from the onset of the symptoms) compared to patients from the group of survivors ($p = 0.026$).

Parameters (quantitative variables) determined on admission to the hospital, showing a statistically significant correlation in the context of prediction of mortality, were analysed in terms of the ability to explain the risk of death. None of the parameters achieved AUC > 0.7—the data is presented in Table 2.

The cut-off values relevant for the prediction of mortality (determined by the Youden Index) were specified for the individual factors being assessed: $\log_2$-EASIX 2.36, $\log_2$-mEASIX 704.05, $\log_2$-sEASIX 3.81. Patients were divided into <cut-off and $\geq$cut-off groups, and the p-value was determined for each parameter–the characteristics of the assessed groups are presented in Tables S1–S3 (available in Supplementary Materials). The ability to explain the values of the factors satisfying the $\geq$cut-off criterion (referred to as high EASIX, high mEASIX, high sEASIX) is presented in Table 3 and Figures 1–3.

Table 1. Characteristics of the group—the variables relate to the time of admission to the hospital; quantitative parameters and variables are presented as mean values (standard deviation-SD), median [interquartile range-IQR]; qualitative variables are presented as frequency/number. Standards for laboratory parameters are given in brackets next to each one.

		Clinical Outcome		
Variable	**No. of Patients, *n* = 370**	**Non-Survivors, *n* = 243**	**Survivors, *n* = 127**	***p*-Value**
Male	242 (65.4%)	155 (63.8%)	87 (68.5%)	0.365
Age	66.9 (12.9), 68 [60.8–74.3]	69.7 (11.4), 70 [63–77]	61.6 (14), 65 [52–70]	**<0.001**
Death	243 (65.7%)			
Concomitant diseases				
Cardiovascular diseases	251 (67.8%)	176 (72.4%)	75 (59.1%)	**0.009**
Hypertension Atrial fibrillation Ischemic heart disease	231 (62.4%) 47 (12.7%) 86 (23.2%)	161 (66.3%) 38 (15.6%) 70 (28.8%)	70 (55.1%) 9 (7.1%) 16 (12.6%)	**0.036** **0.019** **<0.001**
Pulmonary diseases	38 (9.7%)	26 (10.7%)	10 (7.9%)	0.384
Asthma COPD Other	19 (5.1%) 11 (3.0%) 8 (2.2%)	13 (5.3%) 8 (3.3%) 7 (2.9%)	6 (4.7%) 3 (2.4%) 1 (0.8%)	0.796 0.617 0.189
Diabetes	134 (36.2%)	97 (39.9%)	37 (29.1%)	0.103
Malignant neoplasm	57 (15.4%)	44 (18.1%)	13 (10.2%)	**0.046**
Chronic kidney disease	33 (8.9%)	30 (12.3%)	3 (2.4%)	**0.001**
Obesity	105 (28.4%)	68 (28.0%)	37 (29.1%)	0.816
SpO_2 without oxygen supply	83.4 (12.1), 86 [80–92]	82.4 (13.6), 86.5 [78–92]	85.4 (7.92), 86 [82–90]	0.442
Severity (according to WHO scale)				0.171
1	5 (1.4%)	3 (1.2%)	2 (1.6%)	
2	103 (27.8%)	69 (28.4%)	34 (26.8%)	
3	222 (60.0%)	136 (56.0%)	86 (67.7%)	
4	40 (10.8%)	35 (14.4%)	5 (3.9%)	
Duration of hospitalisation, days	19.3 (15.2), 16 [10–24]	16.1 (12.6), 14 [8–21]	25.5 (17.7), 21 [13–31.8]	**<0.001**
Duration of symptoms before hospital admission, days	7.1 (4.4), 7 [4–9]	6.7 (4.5), 6 [4–8]	7.8 (4.1), 7 [5–10]	**0.026**
Deterioration, days (from disease onset)	8.5 (5.8), 7 [5–10]	8.4 (6.6), 7 [5–10]	8.8 (4.2), 8 [6–11]	0.564
ICU admission	216 (58.4%)	182 (74.9%)	34 (26.8%)	**<0.001**
Non-rebreather mask 10–15 L/min	352 (95.1%)	229 (94.2%)	123 (96.9%)	0.268
Non-rebreather mask 10–15 L/min duration, days	2.6 (3.3), 2 [1–3]	2.6 (3.6), 2 [1–3]	2.6 (2.6), 2 [1–3]	0.925

Table 1. *Cont.*

		Clinical Outcome		
Variable	**No. of Patients, *n* = 370**	**Non-Survivors, *n* = 243**	**Survivors, *n* = 127**	***p*-Value**
HFNO	253 (68.4%)	147 (60.5%)	106 (83.5%)	**<0.001**
HFNO duration, days	5.6 (5.0), 4 [2–8]	3.6 (3.2), 2 [1–5]	8.3 (5.8), 7 [4–11]	**<0.001**
NIV	69 (18.6%)	60 (24.7%)	9 (7.1%)	**<0.001**
NIV duration, days	4.9 (4.8), 3 [1–6.5]	4.8 (4.9), 3 [1.3–6]	5.1 (5.4), 3 [1–7]	0.829
IMV	220 (59.5%)	186 (76.5%)	34 (26.8%)	**<0.001**
IMV duration, days	13.8 (12.9), 11 [6–17]	12.3 (11.0), 10 [5.5–17]	22.6 (19.3), 17 [11.3–26.3]	**0.001**
Lab test results				
CRP (>6 mg/L)	140.30 (99.23), 123.40 [62–199.2]	142.30 (100.60), 125.00 [63.59–198.30]	136.40 (97.20), 117.6 [59.90–201.10]	0.478
Procalcitonin (>0.05 ng/mL)	1.74 (4.57), 0.26 [0.1–0.86]	2.12 (5.14), 0.35 [0.13–1.14]	1.08 (3.31), 0.15 [0.08–0.39]	0.110
Ferritin (>274.66 ng/mL	1846.93 (2210.77), 1527.24 [593.86–2325.59]	1910.18 (2228.75), 1304.80 [632.49–2489.59]	1763.91 (2212.21), 1138.11 [566.72–2308.85]	0.699
LDH (>220 U/L)	575 (315), 530 [397–671]	602 (368), 550 [388–734]	524 (161), 504 [411–608]	**0.026**
White blood count (4–10 G/L)	9.00 (9.51), 7.56 [5.46–10.49]	9.47 (11.4), 7.99 [5.47–11.02]	8.09 (3.83), 7.39 [5.43–9.77]	0.180
Neutrophils (1.8–7 G/L)	7.10 (4.1), 6.3 [4.1–8.8]	7.22 (4.29), 6.5 [4.1–9.5]	6.75 (3.73), 6.00 [4.28–8.03]	0.362
Lymphocytes (1–4 G/L)	1.00 (0.7), 0.8 [0.6–1.2]	1.00 (0.8), 0.8 [0.6–1.2]	0.90 (0.4), 0.8 [0.6–1.1]	0.188
Haemoglobin (13.5–18.0 g/dL)	13.20 (2.21), 13.4 [12.1–14.7]	12.90 (2.39), 13.1 [11.8–14.5]	13.70 (1.71), 14.10 [12.7–14.9]	0.860
Thrombocytes (150–420 G/L)	222 (106), 197 [152–265]	216 (109), 192 [145–260]	233 (99.9), 206 [167–277]	0.130
D-dimer (>500 ng/mL)	4073.30 (10,041.6), 1409.5 [876.5–2676.75]	5163.78 (12,060), 1797 [976–3327]	2060.79 (3681.20), 1145.00 [728.00–2104.00]	**0.018**
INR (0.8–1.2)	1.17 (0.37), 1.09 [1.02–1.19]	1.20 (0.41), 1.11 [1.03–1.23]	1.12 (0.29), 1.06 [1.00–1.14]	0.073
AST (>34 U/L)	69.34 (57.95), 54.70 [39.00–80.23]	71.07 (61.80), 53 [38.85–82.90]	66.24 (50.73), 57.00 [39.30–73.00]	0.479
ALT (>55 U/L)	52.83 (54.03), 39.35 [25.85–64.40]	51.02 (60.1), 37 [22.85–63.45]	56.27 (40.37), 42.80 [29.20–68.60]	0.386
Creatinine (>1.15 mg/dL)	1.43 (1.57), 1.03 [0.81–1.44]	1.58 (1.78), 1.13 [0.83–1.66]	1.14 (1.03), 0.92 [0.78–1.11]	**0.016**
EASIX	5.39 (11.04), 2.73 [1.68–4.82]	6.66 (13.29), 3.11 [1.89–5.87]	2.94 (2.92), 2.05 [1.59–3.18]	**<0.001**
mEASIX	497.49 (783.11), 303.36 [130.07–598.69]	571.22 (924.56), 315.37 [130.23–740.82]	356.42 (358.55), 264.14 [125.57–468.00]	**<0.001**
sEASIX	3.40 (4.76), 2.49 [1.81–3.79]	3.86 (5.77), 2.60 [1.88–4.25]	2.52 (1.18), 2.36 [1.74–3.23]	**<0.001**

* COPD—Chronic Obstructive Pulmonary Disease; ICU—Intensive Care Unit, HFNO—High Flow Nasal Oxygenation; NIV—Non Invasive Ventilation; IMV—Invasive Mechanical Ventilation; CRP—C-Reactive Protein; LDH—Lactate Dehydrogenase activity; INR—International Normalised Ratio; AST—Aspartate Aminotransferase activity; ALT—Alanine Aminotransferase activity; EASIX—Endothelial Activation and Stress Index, mEASIX—modified-EASIX, sEASIX—simplified-EASIX.

Table 2. AUC, cut-off, sensitivity and specificity for predicting mortality in a patient with COVID-19 according to parameters assessed on admission with $p < 0.05$ (determined by Youden Index).

	p-Value	Cut-Off	AUC	95% CI	Sensitivity	Specificity
Variable Age	<0.001	≥72	0.662	0.603–0.720	0.44	0.80
Duration of symptoms before hospital admission, days	0.026	<7	0.581	0.520–0.642	0.72	0.40
Lab test parameters						
LDH	0.026	≥656	0.540	0.482–0.599	0.34	0.86
D-dimer	0.018	≥1714	0.636	0.576–0.696	0.53	0.68
Creatinine	0.016	≥1.28	0.642	0.585–0.698	0.44	0.85

Table 3. Sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value), AUC for predicting mortality in patients with COVID-19 according to EASIX, mEASIX and sEASIX cut-offs.

	AUC	95% CI	Sensitivity	Specificity	PPV	NPV
High EASIX	0.646	0.589–0.702	0.40	0.87	0.86	0.43
High mEASIX	0.566	0.507–0.626	0.27	0.90	0.83	0.38
High sEASIX	0.586	0.527–0.644	0.32	0.89	0.83	0.41

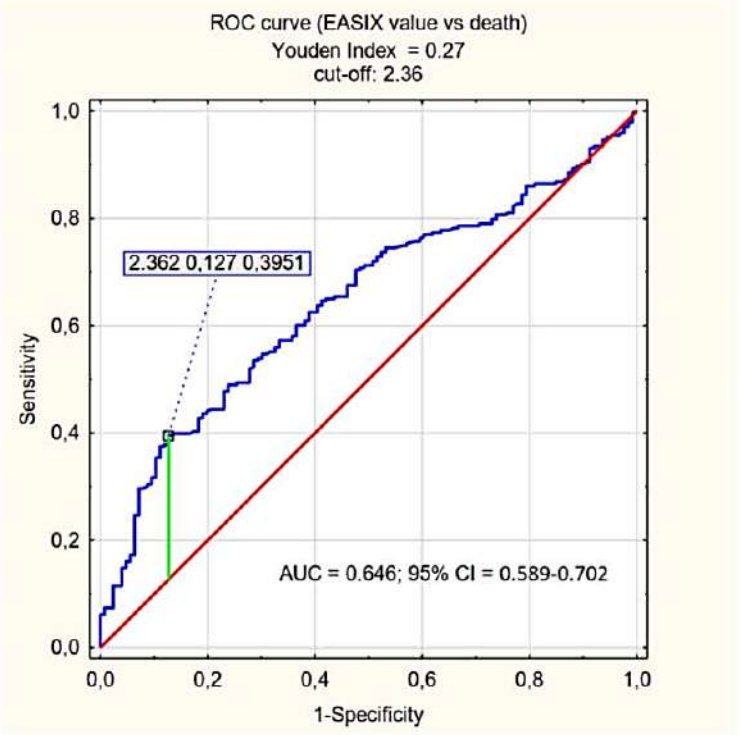


Figure 1. ROC curve (effect of EASIX value on death) = EASIX cut-off.

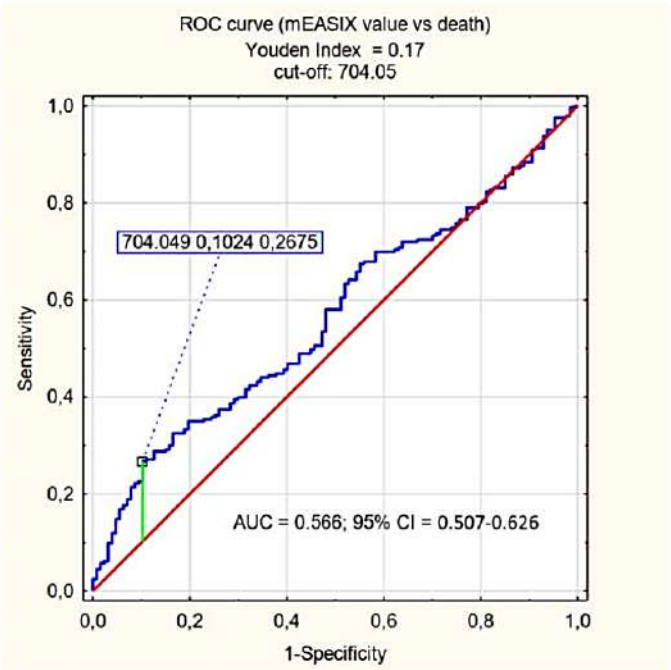


Figure 2. ROC curve (effect of mEASIX value on death) = mEASIX cut-off.

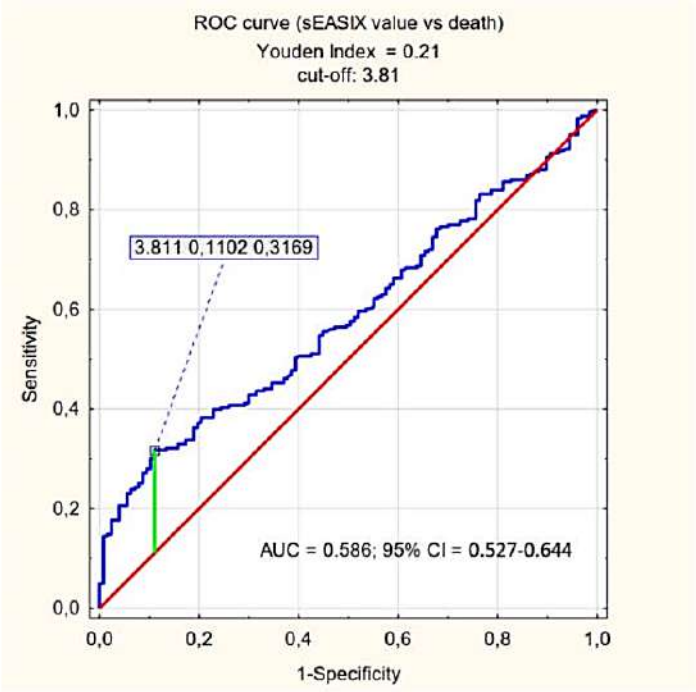


Figure 3. ROC curve (effect of sEASIX value on death) = sEASIX cut-off.

In the group of patients with high EASIX, compared to those with low EASIX values, there were more male patients, more cases of circulatory system diseases and chronic renal failure, a greater frequency and shorter time of application of IMV, and significant differences in CRP, procalcitonin, ferritin, LDH, platelets, D-dimer, INR, AST and creatinine values. The high mEASIX and high sEASIX groups were characterised by a lower frequency and shorter time of application of HFNO, more frequent application of IMV and significant differences in CRP, procalcitonin, ferritin, LDH, lymphocytes, platelets, D-dimer, AST, ALT and creatinine values. Furthermore, higher INR values were observed in the high mEASIX group, which were not observed in the high sEASIX group. In turn, the high sEASIX group was also characterised by significant differences in the neutrophils count. In both modified coefficient groups (high mEASIX and high sEASIX), a shorter period between admission to the hospital and admission to the ICU was observed, while there were no differences with regard to the presence of comorbidities. For all coefficients being assessed, a significantly lower SpO_2 value, shorter period of use of non-rebreather mask 10–15 L/min and a greater frequency of admission to the ICU were observed in the "high" groups. In turn, the patient's age and haemoglobin concentration were not statistically significant in any of the groups, neither was diabetes, obesity and respiratory diseases. Males dominated the high EASIX and high mEASIX groups.

In the subsequent assessments of the course of hospitalisation, the values of the coefficients analysed were determined in the context of forecasting the use of particular methods of oxygen therapy. A significant correlation ($p < 0.001$) was only observed for IMV in the context of EASIX values with a cut-off point of 4.1 (Table 4, Figure 4). For the modified coefficients, the correlation was statistically insignificant.

Table 4. Correlation of EASIX values (cut-off, AUC, sensitivity, specificity) with regard to the need to apply particular methods of oxygen therapy.

		EASIX				
Effect of:	***p***	**Cut-Off**	**AUC**	**95% CI**	**Sensitivity**	**Specificity**
HFNO	0.622					
NIV	0.271					
IMV	**<0.001**	4.10	0.613	0.556–0.671	0.39	0.80

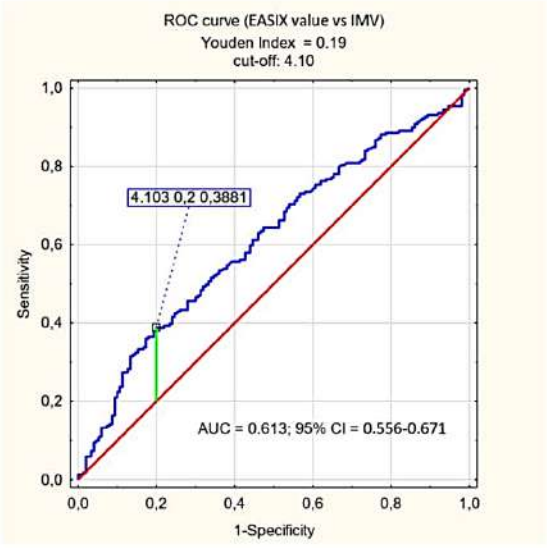


Figure 4. ROC curve (effect of EASIX value on IMV).

5. Discussion

This study proves that all three indices, EASIX, mEASIX and sEASIX, are correlated with SARS-CoV-2 infection clinical outcomes, death and need for admission to the ICU. As they are not strong predictors in the group of severe COVID-19 patients, we do not recommend using them solely, but in addition to other more sensitive factors. Only for EASIX we observed a correlation with a risk of IMV treatment. We are the first to have analysed the above-mentioned indices in a selected group of patients with a severe course of infection. To our knowledge, this work is also the first publication to evaluate the usefulness of the modified coefficients (mEASIX and sEASIX) when it comes to assessing the risk of death in patients with COVID-19. The most important results of our study include: (i) the values of EASIX, mEASIX and sEASIX statistically significantly correlate with patient mortality, (ii) all three indices assessed for the population of patients with severe COVID-19 are characterised by low sensitivity ($\leq$40%) with high specificity (approximately 90%) with regard to the assessment of the risk of death, (iii) high values of EASIX, mEASIX and sEASIX are more reliable in the assessment of the risk of death than survival, as evidenced by greater PPV compared to NPV, (iv) only EASIX is a predictor of the need to use IMV, but not HFNO and NIV; however, all three indices correlate with the need for admission to the ICU.

The high effectiveness of EASIX with regard to the stratification of COVID-19 patients was demonstrated in the study by Garcia et al. where, with the use of a retrospective analysis of more than 3000 patients, it was shown that the age-adjusted coefficient (aEASIX-COVID) has an even higher predictive value for mortality. It was also proved that, based on the values of both indices, EASIX and aEASIX, the chances of patient survival rather than death can be assessed more reliably, as illustrated by the significantly higher NPV (negative predictive value) compared to PPV (positive predictive value) [29]. In other words, with low values of EASIX and aEASIX, there is a greater probability of patient survival than death with high values. An equally significant ($p < 0.001$) correlation between EASIX and mortality in the course of COVID-19 was demonstrated in the study by Kalicinska et al., where two groups of patients were compared—a group of patients with haematological malignancies and patients with no haematological diseases. In addition, according to the study, EASIX is a strong predictor of the occurrence of acute kidney injury and hospitalisation in the ICU and, in the group of haematological patients, also of sepsis [28]. A similar correlation between EASIX and the need for the patient to be admitted to the ICU was determined in our study ($p = 0.026$).

According to the literature on the subject, there are further modifications of the EASIX index which, based on two studies—in groups of haematological patients with LBCL (large B-cell lymphoma) and B-ALL (B-cell acute lymphoblastic leukaemia)—proved to be significant predictors of complications after the application of CAR T-cell therapy (chimeric antigen receptor T-cells) in the form of CRS (cytokine release syndrome) and ICANS (immune effector cell-associated neurotoxicity syndrome). In their publication, Pennisi et al. used simplified EASIX (s-EASIX), where creatinine was excluded as a parameter that rarely showed a deviation in CRS patients, and modified-EASIX (m-EASIX), in which creatinine was replaced with CRP [31]. It turned out that all formulae applied prior to the treatment had a similar predictive value with regard to the occurrence of both complications, while only mEASIX allowed assessment of the effectiveness of the therapy. In the study by Greenbaum et al., EASIX was correlated with the concentration of ferritin (EASIX-F) and, in another case, with the concentration of ferritin and CRP (EASIX-FC) [32]. In this study, the modifications also had a positive effect and there was an increase in the predictive value in terms of the occurrence of complications due to the therapy.

In our study, we focused on the population of patients with severe COVID-19 and, also for this specific group of patients, we demonstrated predictive ability of EASIX, mEASIX and sEASIX in the context of mortality. Statistical significance was demonstrated for each parameter ($p < 0.001$). It should be noted, however, that for the established cut-offs (EASIX 2.36, mEASIX 704.05; sEASIX 3.81) the AUC are below 0.7, the sensitivity of the coefficients

did not exceed 40% and they were characterised by high specificity (87%, 90%, and 89%, respectively). The values of PPV were also significantly greater than those of NPV, which should be understood as a greater probability of death with high values of the indices than the probability of survival with their low values. This is a somewhat surprising statistic, especially in the context of the publication by Garcia et al., in the case of which the obtained results are completely opposite (NPV higher than PPV) [29]. The cut-off value obtained in our study, which is significant for the prediction of death in the course of COVID-19 for EASIX (2.36), is greater than the one in the studies conducted by other researchers (Kalicińska et al. EASIX $\geq$ 1.6, Luft et al. EASIX $\geq$ 2.03) [27,28]. Such results may be influenced by the characteristics of the group of patients being assessed-patients in a critical condition, with a high probability of death (65.7%).

All three indices, EASIX, mEASIX and sEASIX, are not only predictors of mortality but also of the need for admission to the ICU ($p = 0.026$, $p = 0.019$, $p = 0.001$, respectively). Similar results with respect to EASIX were obtained in the research by Kalicińska et al. [28]. As part of our research, we also assessed the oxygen therapy methods applied, and only for EASIX was a statistically significant predictive value obtained for the use of IMV (cut off > 4.1, $p < 0.001$). Some of the patients being assessed who received IMV were hospitalised outside the ICU, which may have affected the statistical results. As for the mortality prediction, also in the context of that method of treatment, the sensitivity of that parameter was low (39%) with rather high specificity (80%). No similar correlation was observed for the other methods of oxygen therapy and for the modified indices.

Patients in the high EASIX ($\geq$2.36), high mEASIX ($\geq$704.05) and high sEASIX ($\geq$3.81) groups compared to the "low" groups had significantly lower SpO_2 values, shorter time of use of a non-rebreather mask 10–15 L/min, which resulted from disease progression and the need to intensify the treatment as well as the differences in the values of inflammatory parameters. The results of our analysis, in terms of laboratory parameters, are consistent with the results of studies by other researchers—they correspond to the pathology of the endothelium, which is associated with an intense inflammatory and thrombotic process in patients with severe COVID-19 [27–29,33–35]. Significantly, the modified indices (mEASIX and sEASIX) showed no differences when the "high" and "low" groups were compared with respect to comorbidities, and sEASIX also with respect to gender. The abovementioned results are very promising, although they need to be confirmed with further studies. They indicate the universality of the analysed coefficients and, above all, their independence from the gender of patients (sEASIX) and comorbidities (mEASIX, sEASIX).

The use of EASIX modification did not significantly increase the predictive capacity of the coefficient with respect to mortality (comparable results of the PPV, NPV, sensitivity and specificity analyses were achieved). Therefore, it seems that EASIX, mEASIX and sEASIX can be complementary used to assess patients with COVID-19 or other conditions with similar pathophysiology related to endothelial damage. Referring to the results of the study, EASIX in terms of patients death has an AUC that is closest to 0.7 (0.646) of all three indices and is the only one that relates to the necessity of an IMV, so it should be preferred to use, but even for this one his power is not sufficient. Due to the ease of implementation and the low cost of performing basic laboratory tests, those indices can be one of the tool for the initial assessment of patients admitted to the hospital, and thus facilitate and speed up the decision-making process with regard to the treatment of the patient, which may be crucial for prognosis. It is advisable to assess different variants of EASIX in a wider population of patients to find the most optimal one, that is to say the one with high specificity and sensitivity with regard to predicting mortality due to COVID-19.

This publication also has some limitations. The analysis is a retrospective one and it applies only to severely ill patients from the same institution; there is no control group and reference of the results to the group of patients with a mild course of the infection, which is the result of missing and impossible to obtain data. Therefore, the cut-off value achieved for EASIX is higher than the one reported in the previous publications and higher in relation to the expected values in the general population of patients infected with SARS-CoV-2.

In the case of mEASIX and sEASIX, this is the first publication to assess those indices in the context of COVID-19, so the cut-off value cannot be compared to the previous results. Furthermore, this publication does not attempt to assess vaccination status and the course of hospitalisation, including methods of pharmacological treatment.

6. Conclusions

The EASIX, mEASIX, and sEASIX indices show a correlation with the risk of death and the need for admission to the ICU in patients with severe COVID-19. In the group of patients studied, in terms of the prediction of death, the high values of the three indices (EASIX $\geq$ 2.36, mEASIX $\geq$ 704.03, sEASIX $\geq$ 3.81) are characterised by low sensitivity ($\leq$40%) and high specificity (approximately 90%). The highest AUC value (0.646) was achieved for EASIX. The research revealed that all three indices are not optimal diagnostic tools in to severely ill patients, but they might be used additionally to other more sensitive predictors. High values of EASIX, mEASIX and sEASIX are more reliable in assessing the risk of death than the probability of survival and, additionally, EASIX is a predictor of the need to apply IMV (invasive mechanical ventilation).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jpm12071022/s1, Table S1: Correlation of EASIX with variables being assessed and characteristics of patients with high EASIX ($\geq$2.36) and low EASIX (<2.36); Table S2: Correlation of mEASIX with the variables being assessed and characteristics of patients with high mEASIX ($\geq$704.05) and low mEASIX (<704.05); Table S3: Correlation of sEASIX with variables being assessed and characteristics of patients with high sEASIX ($\geq$3.81) and low sEASIX (<3.81).

Author Contributions: Conceptualisation, A.Z. and M.R.; methodology, M.R. and T.J.; resources, A.Z.; writing—original draft preparation, A.Z.; writing—review and editing, M.R., K.S. and T.J.; supervision, M.R. and T.J. All authors have read and agreed to the published version of the manuscript.

Funding: This work was carried out according to the subject register in Simple System SUBZ.A120.22.077 and supported by a statutory subsidy granted by the Ministry of Science and Higher Education in Poland.

Institutional Review Board Statement: Ethical review and approval were waived for this study due to the retrospective nature of this work.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of this work.

Data Availability Statement: Not applicable.

Acknowledgments: We would like to thank Krzysztof Kujawa (Head of Wroclaw Medical University Statistical Analysis Centre) for his work.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bermejo-Martin, J.F.; Almansa, R.; Torres, A.; Gonzalez-Rivera, M.; Kelvin, D.J. COVID-19 as a Cardiovascular Disease: The Potential Role of Chronic Endothelial Dysfunction. *Cardiovasc. Res.* **2020**, *116*, E132–E133. Available online: https://pubmed.ncbi.nlm.nih.gov/32420587/ (accessed on 18 January 2020). [CrossRef]
2. Yazan Abou-Ismail, M.; Diamond, A.; Kapoor, S.; Arafah, Y.; Nayak, L. The Hypercoagulable State in COVID-19: Incidence, Pathophysiology, and Management. *Thromb. Res.* **2020**, *194*, 101–115. [CrossRef]
3. Liang, W.H.; Guan, W.J.; Li, C.C.; Li, Y.M.; Liang, H.R.; Zhao, Y.; Liu, X.Q.; Sang, L.; Chen, R.C.; Tang, C.L.; et al. Clinical Characteristics and Outcomes of Hospitalised Patients with COVID-19 Treated in Hubei (Epicentre) and Outside Hubei (non-epicentre): A Nationwide Analysis of China. *Eur. Respir. J.* **2020**, *55*, 6. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7144336/ (accessed on 7 February 2020). [CrossRef]
4. Feng, X.; Li, P.; Ma, L.; Liang, H.; Lei, J.; Li, W.; Wang, K.; Song, Y.; Li, S.; Yang, W.; et al. Clinical Characteristics and Short-Term Outcomes of Severe Patients with COVID-19 in Wuhan, China. *Front. Med.* **2020**, *7*, 491. [CrossRef]
5. Li, J.; Huang, D.Q.; Zou, B.; Yang, H.; Hui, W.Z.; Rui, F.; Yee, N.T.S.; Liu, C.; Nerurkar, S.N.; Kai, J.C.Y.; et al. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J. Med. Virol.* **2021**, *93*, 1449–1458. [CrossRef]

6. Dong, E.; Du, H.; Gardner, L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect. Dis.* **2020**, *20*, 533–534. [CrossRef]
7. Li, Y.; Ashcroft, T.; Chung, A.; Dighero, I.; Dozier, M.; Horne, M.; McSwiggan, E.; Shamsuddin, A.; Nair, H. Risk factors for poor outcomes in hospitalised COVID-19 patients: A systematic review and meta-analysis. *J. Glob. Health* **2021**, *11*, 10001. [CrossRef]
8. Alqahtani, J.S.; Oyelade, T.; Aldhahir, A.M.; Alghamdi, S.M.; Almehmadi, M.; Alqahtani, A.S.; Quaderi, S.; Mandal, S.; Hurst, J.R. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis. *PLoS ONE* **2020**, *15*, e0233147. [CrossRef]
9. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. Available online: https://pubmed.ncbi.nlm.nih.gov/31986264/ (accessed on 17 January 2022). [CrossRef]
10. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **2020**, *395*, 1054–1062. Available online: https://pubmed.ncbi.nlm.nih.gov/32171076/ (accessed on 17 January 2022). [CrossRef]
11. Kompaniyets, L.; Pennington, A.F.; Goodman, A.B.; Rosenblum, H.G.; Belay, B.; Ko, J.Y.; Chevinsky, J.R.; Schieber, L.Z.; Summers, A.D.; Lavery, A.M.; et al. Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized with COVID-19, March 2020–March 2021. *Prev. Chronic Dis.* **2021**, *18*, E66. [CrossRef]
12. Rorat, M.; Zińczuk, A.; Szymański, W.; Simon, K.; Guziński, M. Usefulness of a portable chest radiograph in the initial diagnosis of coronavirus disease 2019. *Pol. Arch. Int. Med.* **2020**, *130*, 906–909. Available online: https://pubmed.ncbi.nlm.nih.gov/32666780/ (accessed on 7 February 2022).
13. Rorat, M.; Jurek, T.; Simon, K.; Guzinski, M. Value of quantitative analysis in lung computed tomography in patients severely ill with COVID-19. *PLoS ONE* **2021**, *16*, e0251946. Available online: https://pubmed.ncbi.nlm.nih.gov/34015025/ (accessed on 7 February 2022). [CrossRef]
14. Salvatore, C.; Roberta, F.; Angela, D.L.; Cesare, P.; Alfredo, C.; Giuliano, G.; Giulio, L.; Giuliana, G.; Maria, R.G.; Paola, B.M.; et al. Clinical and laboratory data, radiological structured report findings and quantitative evaluation of lung involvement on baseline chest CT in COVID-19 patients to predict prognosis. *Radiol. Med.* **2021**, *126*, 29–39. Available online: https://pubmed.ncbi.nlm.nih.gov/33047295/ (accessed on 7 February 2022). [CrossRef]
15. Iba, T.; Connors, J.M.; Levy, J.H. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. *Inflamm. Res.* **2020**, *69*, 1181–1189. [CrossRef]
16. Kalicińska, E.; Szymczak, D.; Zińczuk, A.; Adamik, B.; Smiechowicz, J.; Skalec, T.; Nowicka-Suszko, D.; Biernat, M.; Bogucka-Fedorczuk, A.; Rybka, J.; et al. Immunosuppression as a hallmark of critical covid-19: Prospective study. *Cells* **2021**, *10*, 1293. [CrossRef]
17. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271–280.e8. [CrossRef]
18. Levy, J.H.; Iba, T.; Olson, L.B.; Corey, K.M.; Ghadimi, K.; Connors, J.M. COVID-19: Thrombosis, thromboinflammation, and anticoagulation considerations. *Int. J. Lab. Hematol.* **2021**, *43*, 29–35. [CrossRef]
19. Ghahramani, S.; Tabrizi, R.; Lankarani, K.B.; Kashani, S.M.A.; Rezaei, S.; Zeidi, N.; Akbari, M.; Heydari, S.T.; Akbari, H.; Nowrouzi-Sohrabi, P.; et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: A systematic review and meta-analysis. *Eur. J. Med. Res.* **2020**, *25*, 30. [CrossRef]
20. Garcia PD, W.; Fumeaux, T.; Guerci, P.; Heuberger, D.M.; Montomoli, J.; Roche-Campo, F.; Wong, J. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort. *EClin. Med.* **2020**, *25*, 100449.
21. Smadja, D.M.; Guerin, C.L.; Chocron, R.; Yatim, N.; Boussier, J.; Gendron, N.; Khider, L.; Hadjadj, J.; Goudot, G.; Debuc, B.; et al. Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. *Angiogenesis* **2020**, *23*, 611–620. [CrossRef]
22. Terpos, E.; Ntanasis-Stathopoulos, I.; Elalamy, I.; Kastritis, E.; Sergentanis, T.N.; Politou, M.; Psaltopoulou, T.; Gerotziafas, G.; Dimopoulos, M.A. Hematological findings and complications of COVID-19. *Am. J. Hematol.* **2020**, *95*, 834–847. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262337/ (accessed on 18 January 2022). [CrossRef]
23. Gavriilaki, E.; Anyfanti, P.; Gavriilaki, M.; Lazaridis, A.; Douma, S.; Gkaliagkousi, E. Endothelial Dysfunction in COVID-19: Lessons Learned from Coronaviruses. *Curr. Hypertens. Rep.* **2020**, *22*, 63. Available online: https://pubmed.ncbi.nlm.nih.gov/32852642/ (accessed on 18 January 2022). [CrossRef]
24. Varga, Z.; Flammer, A.J.; Steiger, P.; Haberecker, M.; Andermatt, R.; Zinkernagel, A.S.; Mehra, M.R.; Schuepbach, R.A.; Ruschitzka, F.; Moch, H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **2020**, *395*, 1417–1418. [CrossRef]
25. Luft, T.; Benner, A.; Terzer, T.; Jodele, S.; Dandoy, C.E.; Storb, R.; Kordelas, L.; Beelen, D.; Gooley, T.; Sandmaier, B.M.; et al. EASIX and mortality after allogeneic stem cell transplantation. *Bone Marrow Transpl.* **2020**, *55*, 553–561. Available online: https://pubmed.ncbi.nlm.nih.gov/31558788/ (accessed on 17 January 2022). [CrossRef]
26. Luft, T.; Benner, A.; Jodele, S.; Dandoy, C.E.; Storb, R.; Gooley, T.; Sandmaier, B.M.; Becker, N.; Radujkovic, A.; Dreger, P.; et al. EASIX in patients with acute graft-versus-host disease: A retrospective cohort analysis. *Lancet Haematol.* **2017**, *4*, e414–e423.

Available online: https://pubmed-1ncbi-1nlm-1nih-1gov-1yxc2mlpl150f.han.bg.umed.wroc.pl/28733186/ (accessed on 17 January 2022). [CrossRef]
27. Luft, T.; Wendtner, C.M.; Kosely, F.; Radujkovic, A.; Benner, A.; Korell, F.; Kihm, L.; Bauer, M.F.; Dreger, P.; Merle, U. EASIX for Prediction of Outcome in Hospitalized SARS-CoV-2 Infected Patients. *Front. Immunol.* **2021**, *12*, 2425. [CrossRef]
28. Kalicińska, E.; Biernat, M.; Rybka, J.; Zińczuk, A.; Janocha-Litwin, J.; Rosiek-Biegus, M.; Morawska, M.; Waszczuk-Gajda, A.; Drozd-Sokołowska, J.; Szukalski, Ł.; et al. Endothelial Activation and Stress Index (EASIX) as an Early Predictor for Mortality and Overall Survival in Hematological and Non-Hematological Patients with COVID-19: Multicenter Cohort Study. *J. Clin. Med.* **2021**, *10*, 4373. [CrossRef]
29. Pérez-García, F.; Bailén, R.; Torres-Macho, J.; Fernández-Rodríguez, A.; Jiménez-Sousa, M.Á.; Jiménez, E.; Pérez-Butragueño, M.; Cuadros-González, J.; Cadiñanos, J.; García-García, I.; et al. Age-Adjusted Endothelial Activation and Stress Index for Coronavirus Disease 2019 at Admission Is a Reliable Predictor for 28-Day Mortality in Hospitalized Patients with Coronavirus Disease 2019. *Front. Med.* **2021**, *8*, 1445. [CrossRef]
30. WHO: Clinical management of COVID-19; Interim Guidance 27 May 2020, Geneva, World Health Organization. Technical Documents. Available online: https://apps.who.int/iris/handle/10665/332196 (accessed on 11 November 2021).
31. Pennisi, M.; Sanchez-Escamilla, M.; Flynn, J.R.; Shouval, R.; Alarcon Tomas, A.; Silverberg, M.L.; Batlevi, C.; Brentjens, R.J.; Dahi, P.B.; Devlin, S.M.; et al. Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells. *Blood Adv.* **2021**, *5*, 3397–3406. Available online: https://pubmed.ncbi.nlm.nih.gov/34432870/ (accessed on 18 January 2022). [CrossRef]
32. Greenbaum, U.; Strati, P.; Saliba, R.M.; Torres, J.; Rondon, G.; Nieto, Y.; Hosing, C.; Srour, S.A.; Westin, J.; Fayad, L.E.; et al. CRP and ferritin in addition to the EASIX score predict CAR-T-related toxicity. *Blood Adv.* **2021**, *5*, 2799–2806. Available online: https://pubmed.ncbi.nlm.nih.gov/34264268/ (accessed on 18 January 2022). [CrossRef]
33. Zhang, Z.L.; Hou, Y.L.; Li, D.T.; Li, F.Z. Laboratory findings of COVID-19: A systematic review and meta-analysis. *Scand. J. Clin. Lab. Investig.* **2020**, *80*, 441–447. Available online: http://www.ncbi.nlm.nih.gov/pubmed/32449374 (accessed on 18 January 2022). [CrossRef]
34. Verma, S.K.; Molitoris, B.A. Renal endothelial injury and microvascular dysfunction in acute kidney injury. *Semin. Nephrol.* **2015**, *35*, 96–107. Available online: https://pubmed.ncbi.nlm.nih.gov/25795503/ (accessed on 18 January 2022). [CrossRef]
35. Rajendran, P.; Rengarajan, T.; Thangavel, J.; Nishigaki, Y.; Sakthisekaran, D.; Sethi, G.; Nishigaki, I. The Vascular Endothelium and Human Diseases. *Int. J. Biol. Sci.* **2013**, *9*, 1057. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3831119/ (accessed on 18 January 2022). [CrossRef]

viruses

MDPI

Article

Unpacking the Complexity of COVID-19 Fatalities: Adverse Events as Contributing Factors—A Single-Center, Retrospective Analysis of the First Two Years of the Pandemic

Aleksander Zińczuk [1,*], Marta Rorat [1], Krzysztof Simon [2] and Tomasz Jurek [1]

[1] Department of Forensic Medicine, Wroclaw Medical University, 50-369 Wroclaw, Poland; marta.rorat@umw.edu.pl (M.R.); tomasz.jurek@umw.edu.pl (T.J.)
[2] Department of Infectious Diseases and Hepatology, Wroclaw Medical University, 50-369 Wroclaw, Poland; krzysztof.simon@umw.edu.pl
* Correspondence: aleksander.zinczuk@student.umw.edu.pl; Tel.: +48-883-147-077

Abstract: In a retrospective analysis of 477 fatal COVID-19 cases hospitalised at a single medical centre during the period from 6 March 2020 to 30 June 2022, several factors defining those patients at admission were assessed, as well as the course of the hospitalisation and factors contributing to death. There was a predominance of men (59.3% (283)) burdened by comorbidities, with increased inflammation at admission. Patients aged ≥ 81 years were significantly more likely to be admitted to and die in infectious diseases units (IDU) due to respiratory failure, their hospital stays were shorter, and they were most likely not to receive specialist treatment. The most common COVID-19 complications included acute kidney injury in 31.2% (149) patients and thromboembolic complications in 23.5% (112). The course of hospitalisation was complicated by healthcare-associated infections (HAI) in 33.3% (159) of cases, more often in those treated with baricitinib ($p < 0.001$). The initial use of an antibiotic, although common (94.8% (452)), was unwarranted in almost half of the cases (47.6% (215)). Complications of hospitalisation (46.1% (220)) and adverse events involving staff (49.7% (237)) were found in almost half of the patients. In 88.7% (423) of the cases, death was due to respiratory failure in the course of SARS-CoV-2 infection. Adverse events during hospitalisation should be considered as an additional factor that, in addition to the infection itself, may have influenced the death of patients.

Keywords: SARS-CoV-2; death; mortality; treatment; ARDS

check for updates

Citation: Zińczuk, A.; Rorat, M.; Simon, K.; Jurek, T. Unpacking the Complexity of COVID-19 Fatalities: Adverse Events as Contributing Factors—A Single-Center, Retrospective Analysis of the First Two Years of the Pandemic. *Viruses* **2023**, *15*, 1430. https://doi.org/10.3390/v15071430

Academic Editor: Luis Martinez-Sobrido

Received: 5 June 2023
Revised: 16 June 2023
Accepted: 22 June 2023
Published: 24 June 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

SARS-CoV-2 infection has become a global public health threat within a short time of the appearance of the first cases. The pandemic, which has lasted more than three years, resulted in more than 676 million confirmed cases of COVID-19, including more than 6.8 million deaths from the disease—data from 2 May 2023 [1]. The sudden emergence of a large number of patients with severe disease caused by the new coronavirus variant, which was associated with its high infectiousness and ability to cause severe respiratory failure and other complications, led to the overloading of healthcare systems and the occurrence of many excess deaths worldwide as also caused by reduced access to healthcare for patients with other medical conditions [2]. The severity of SARS-CoV-2 infection and the risk of death in its course depends on many factors, the most important of which are considered to be male sex, age > 65 years, the presence of comorbidities, primarily with chronic cardiovascular, respiratory and renal diseases, malignancies, obesity, diabetes and autoimmune conditions, and the variant of the virus causing COVID-19 disease [3–6]. The World Health Organization (WHO) has been monitoring circulating SARS-CoV-2 variants since January 2020, and so far, five VOCs have been identified—variants of concern (Alpha, Beta, Gamma, Delta and Omicron)—that are responsible for the pandemic waves [7].

The severity of the infection and mortality varies according to the VOCs that cause the infection, with particularly significant differences found between the Delta and Omicron variants [8,9].

The onset of the COVID-19 pandemic was particularly difficult for healthcare personnel, and the risk of adverse events during the provision of healthcare services, including those resulting in death, was particularly high [10]. The rapidly spreading infection quickly exposed the inadequacies of healthcare systems worldwide, including shortages of staff, equipment and funding. An urgent search began for the therapeutic and preventive measures necessary to stop the avalanche of infections. Initially, in a haphazard manner and without adequate scientific research, the treatment used included existing antiviral therapies, antibiotics and drugs used for rheumatic conditions (e.g., azithromycin, lopinavir, ritonavir, oseltamivir, amantadine and chloroquine). Such interventions not only failed to provide benefits but proved to be detrimental to patients in some cases [11]. Subsequently, the efficacy of the following drugs and substances were evaluated: convalescent plasma; remdesivir, a drug designed to treat EBOV (Ebola virus) infection; and drugs with immunomodulatory effects (e.g., dexamethasone, tocilizumab) [12,13]. As the pandemic continued, subsequent recommendations from scientific societies were based on reports containing increasingly better scientific data. The next step in the fight against infection was the introduction of vaccines and new therapies targeted directly against SARS-CoV-2 (monlupiravir, nirmatrelvir/ritonavir) [14–16]. Knowledge of the course of COVID-19, the mechanisms of action of the virus and the complications associated with it has evolved rapidly due to the very high number of new publications; from the beginning of the pandemic until 1 April 2023, more than 350,000 publications appeared in the PubMed database under the keyword "COVID-19". Epidemiological data from the entire pandemic period show that severe infection can affect approximately 20% of patients, and mortality does not exceed 2% [1,17]. Patients with a severe course of the disease are most often hospitalised and are the first at risk of dying from COVID-19, encouraging the conduct of research in this group to reduce mortality. On the other hand, a detailed assessment of the course of hospitalisation makes it possible to detect factors that are not directly related to the virus itself but significantly increase the risk of death.

This retrospective study's main objective is to analyse fatal COVID-19 cases to determine the risk factors and causes of death, including adverse events.

2. Materials and Methods

The retrospective analysis included the medical data of 477 fatal COVID-19 cases out of a total of 2671 patients hospitalised from 6 March 2020 to 30 June 2022 in the infectious diseases units (IDU) and intensive care unit (ICU) of the J. Gromkowski Specialist Regional Hospital in Wrocław (Poland). From the beginning of the pandemic, this hospital was dedicated to patients with suspected and confirmed SARS-CoV-2 infection. In all patients, infection was initially confirmed by a real-time molecular RT-PCR (reverse transcription–polymerase chain reaction) test. Then, due to the acquisition of new validated diagnostic methods, the infection was confirmed by a molecular test or antigen test (PanBio COVID-19 Ag Rapid Test Device by Abbott). Patients admitted from or transferred to other hospitals were excluded from the analysis when their full medical records were not available. A division of the pandemic wave into three periods was used: pre-Delta (1 March 2020–30 June 2021), Delta (1 July–31 December 2021) and Omicron (1 January–30 June 2022), which was based on the dominant SARS-CoV-2 virus sequences in Poland as analysed by GISAID (Global Initiative on Sharing All Influenza Data) [8,18].

The baseline assessment of patients included the following demographic data: age, sex and comorbidities (cardiovascular diseases, respiratory diseases, diabetes, obesity, kidney diseases, malignancies). During SARS-CoV-2 infection, the following data were assessed: duration of symptoms before admission (days) and capillary saturation [19]. An evaluation of the following laboratory parameters were included in the baseline characteristics: C-reactive protein (CRP), procalcitonin (PCT), D-dimer, creatinine and ferritin

levels, white blood count (WBC), platelet count (PLT), lactate dehydrogenase (LDH) activity and endothelial activation and stress index (EASIX). The formula proposed by Luft et al. (LDH [U/L] × creatinine [mg/dL]/platelet count [G/L]) was used for the calculation of EASIX [20].

The course of hospitalisation was extensively analysed as follows: length of hospitalisation, oxygen therapy used (oxygen therapy, high-flow nasal oxygenation therapy (HFNOT), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV)); treatment administered, such as antivirals (RDV, remdesivir; MPV, molnupiravir), immunomodulatory (dexamethasone, tocilizumab, baricitinib), convalescent plasma, the type of combination therapy used at the beginning of the pandemic (chloroquine and LPV/r—lopinavir boosted with ritonavir) and the use of low-molecular-weight heparin (LMWH) (enoxaparin or nadroparin) in a prophylactic or therapeutic dose. In the next step, events that occurred during hospitalisation were assessed: coinfections, such as community-acquired infections and healthcare-associated infections (HAIs), which were divided into bloodstream infections (BSIs), urinary tract infections (UTIs) and ventilator-associated pneumonia (VAP). HAIs were diagnosed as defined—an infection that occurred during the provision of medical services and was not present during hospital admission [21]. Questionable culture results that bore the hallmarks of sample contamination (numerous cultured bacteria, organisms that are a component of human microbiota and are detected in only one sample) were excluded from the analysis. The appropriateness (clinical signs, laboratory parameters, microbiological results) of the antibiotic therapy used was analysed in detail. Adverse events were assessed using criteria in line with the current WHO Patient Safety Report, where an adverse event is an event that results in avoidable harm to the patient [22]. The adverse event included both COVID-19 complications (the occurrence of thrombotic complications, such as venous thromboembolism, ischaemic stroke, myocardial infarction and limb ischaemia; bleeding and other complications, such as acute kidney injury (AKI), exacerbation of chronic heart disease and decompensation of liver function) and complications unrelated to the infection but resulting from hospitalisation (HAIs, emphysema and other ventilator-associated complications, trauma or falls; personnel malpractice, such as a lack of or delay in specialist treatment as assessed on an individual basis in accordance with the national or global recommendations for the treatment of COVID-19 patients) [23–25]. Finally, the causes of death of the patients were assessed by distinguishing between the main cause of death and other concomitant causes of death.

The study was positively approved by the Bioethics Committee of the Wroclaw Medical University (Decision no. KB-826/2020 dated 17 December 2020). The retrospective nature of anonymised medical data meant that informed consent from patients was not required.

3. Statistical Analysis

Descriptive statistics were presented using means, standard deviations, medians and quartiles for quantitative variables and counts with percentages for qualitative variables. The normality of the data was assessed using the Shapiro–Wilk test. Due to the non-normality of the data, non-parametric tests were used. The relationship between qualitative and quantitative variables was assessed using the Mann–Whitney U test or the Kruskal–Wallis test for two or three groups, respectively. The qualitative analysis was performed using Fisher's exact test. When necessary, the post hoc analysis using Holm-corrected pairwise comparison was applied. The correlation between two continuous variables was calculated using Spearman's correlation coefficient.

All analyses were performed in R for Windows, version 4.3 [26]. The $p < 0.05$ was selected as the threshold of significance.

4. Results

The analysed group of patients who died of COVID-19 comprised 477 patients aged 27–99 years. The group was predominantly male (283—59.3%). The full age structure is

shown in Figure 1. Detailed data on the characteristics of the overall group are included in Table 1.

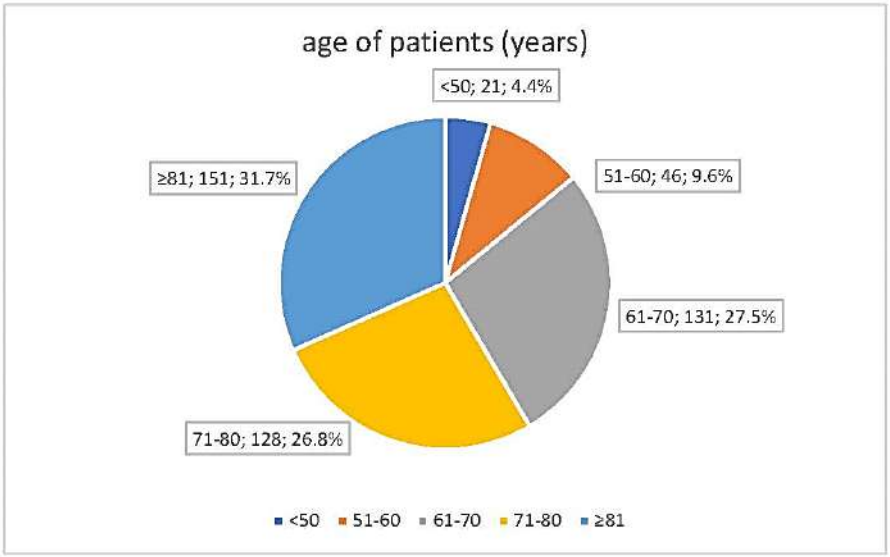


Figure 1. Age of patients (years).

Table 1. Group characteristics. Quantitative parameters and variables are presented as mean values (standard deviation—SD) and median [interquartile range—IQR], while qualitative variables are presented as frequency/number. Normal laboratory parameters are given in brackets next to each value.

Variable	*N* = 477
Age (years)	73.43 (12.43), 74 [6–83]
Sex	female 194 (40.7%)
	male 283 (59.3%)
Ward of admission	ICU 56 (11.7%)
	IDU 421 (88.3%)
Ward where the patient died	ICU 264 (55.3%)
	IDU 213 (44.7%)
Length of hospitalisation (days)	13.87 (10.97), 11 [6–19]
Duration of symptoms before admission (days)	7.3 (4.62), 7 [5–9]
SpO_2 at admission (%)	81.33 (13.5), 85 [74.75–91]
Severity of illness at admission acc. to WHO	1—14 (2.9%) 2—115 (24.1%) 3—236 (49.5%) 4—112 (23.5%)
Comorbidities: Cardiovascular diseases Respiratory diseases Diabetes Malignant neoplasm Chronic kidney disease Obesity	436 (91.4%) 367 (76.9%) 68 (14.3%) 160 (33.5%) 90 (18.9%) 58 (12.2%) 92 (19.3%)

Table 1. *Cont.*

Variable	*N* = 477
Laboratory results at admission	
CRP (>6 mg/L)	128.2 (95.76), 105.44 [54.07–180.67]
D-dimer (>500 ng/mL)	4221.07 (9138), 1766 [1055–3278]
Ferritin (>274.66 ng/mL)	2279.94 (3887.55), 1292.69 [613.75–2690.47]
Creatinine (>1.15 mg/dL)	1.58 (1.63), 1.10 [0.82–1.67]
WBC (4–10 G/L)	9.58 (10.78), 7.64 [5.25–10.92]
PLT (150–420 G/L)	206 (100), 188 [136–248]
PCT (>0.05 ng/mL)	2.33 (10.18), 0.32 [0.12–0.97]
LDH (>220 U/L)	578.78 (304.16), 510 [368–703]
EASIX	6.22 (11.19), 3.14 [1.89–6.07]
Treatment during the entire hospitalisation	
Low-dose oxygen therapy > 10 L/min	431 (90.4%)
HFNOT	265 (55.6%)
NIV	132 (27.7%)
IMV	273 (57.2%)
Antiviral treatment (RDV, MPV)	94 (19.7%)
Chloroquine + LPV/r	29 (6.1%)
COVID-19 convalescent plasma	81 (17%)
Dexamethasone	381 (79.9%)
Tocilizumab	95 (19.9%)
Baricitinib	49 (10.3%)
Low-molecular-weight heparin	none—21 (4.4%) prophylactic dose—353 (74%), therapeutic dose—103 (21.6%)
Coinfections	274 (57.4%)
Healthcare-associated infections	159 (33.3%)
Predominant cause of death—COVID-19 respiratory failure	423 (88.7%)

All patients required supplemental oxygen therapy, while 46 (9.6%) patients received baseline HFNOT or IMV. Twenty-one (4.4%) patients did not receive LMWH during the entire hospitalisation, five patients (1%) did not receive any anticoagulant treatment, while the remaining patients took oral medication (dabigatran, rivaroxaban, acenocumarol or warfarin). For those patients who received the therapeutic dose, the dosage change was mostly due to an increase in D-dimer levels (66 patients, 64.1%) or confirmed thromboembolic disease (24 patients, 23.3%). In the remaining patients (13, 12.6%), the reason for the dosage change was unknown.

4.1. Coinfections

More than half of the patients, 274 (57.4%), suffered from concomitant bacterial or fungal infections. In 159 (58%) of these patients (33.3% of all patients), HAIs were responsible (BSI, VAP, UTI). Fungal pathogens were responsible for 10.2% (28) of the coinfections. In blood cultures, the following were most commonly cultured: CNS—coagulase-negative *Staphylococcus*, including MRCNS, methicillin-resistant coagulase-negative *Staphylococcus* was 23.0% (38); *Klebsiella pneumoniae* ESBL (extended-spectrum beta-lactamases) 15.8% (26);

Acinetobacter baumanii (most commonly, MBL, metallo beta-lactamases), 8.5% (14); and additionally, *Staphylococcus aureus*, including MRSA (methicillin-resistant *Staphylococcus aureus*), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Staphylococcus simulans* and *Staphylococcus capitis*, as well as enterococci, such as *Enterococcus faecalis*, including HLAR (high-level aminoglycoside resistance) and VRE (vancomycin-resistant Enterococcus), *Enterococcus faecium* and *Enterococcus cloacae*; *Pseudomonas aeruginosa*; *Propionibacterium acnes* and the fungi *Candida glabrata* and *Candida krusei*.

In the cultures of bronchial secretions, the following were most commonly cultured: *A. baumanii* (including MER/IMI—meropenem/imipenem resistance and MBL) at 35.3% (61), *K. pneumoniae* ESBL at 10.4% (18), *P. aeruginosa* at 6.9% (12) and, additionally, *S. aureus* (including MRSA), *S. haemolyticus*, *S. simulans*, *Staphylococcus hominis* and CNS (including MRCNS), as well as *Streptococcus agalactiae*, *E. faecalis* (including HLAR and VRE), *E. faecium*, *Escherichia coli* ESBL, *Stenotrophomonas maltophilia*, *Serratia marcenses*, *Kocuria kristinae*, *Pantoea agglomerans*, and the fungi *C. glabrata*, *Candida albicans* and *Candida tropicalis*.

In contrast, the following urine cultures were most commonly cultured: *A. baumanii* (including MER/IMI and MBL)—19.0% (23), *Candida* spp. (*C. albicans*, *C. glabrata*, *C. parapsilosis*)—12.4% (15), *E. faecium*—8.3% (10) and, in addition, *E. faecalis* (including HLAR and VRE), *Str. agalactiae*, *P. aeruginosa*, *E. coli* (including ESBL), *K. pneumoniae* (including ESBL and MBL). An analysis of the structure of coinfections and antibiotic use is shown in Table 2.

Table 2. Characteristics of coinfections.

Variable	*N* = 477
Coinfection	274 (57.4%)
Healthcare-associated infection	159 (33.3%; 58% of all infections)
BSIs (bloodstream infections)	165 (34.6%)
VAP (ventilator-associated pneumonia)	173 (36.3%)
UTIs (urinary tract infections)	121 (25.4%)
Use of antibiotics from the beginning of hospitalisation	452 (94.8%)
Inclusion of an antibiotic without medical indication	215 (47.6%)

Coinfections were more common among patients who were initially admitted to the ICU compared to the IDU ($N = 46$; 82.1% vs. $N = 228$; 54.2%; $p < 0.001$). There was also a higher prevalence of nosocomial infections in that group ($N = 32$; 57.1% vs. $N = 127$; 30.2%; $p < 0.001$). HAI was observed statistically significantly ($p < 0.001$) more often in the youngest patients compared to the ≥81 years group ($N = 15$; 57.1% vs. $N = 24$; 15.9%)—Table S1. The use of an antibiotic at the beginning of hospitalisation did not significantly affect the difference in the incidence of nosocomial infection ($p = 0.7$)—seven (28.0%) patients in the non-antibiotic group and 152 (33.6%) in the group treated with an antibiotic. The analysis of COVID-19 therapies revealed that the use of baricitinib was associated with a higher incidence of nosocomial infections ($p < 0.001$) (Table 3).

Table 3. The relationship between COVID-19 treatment administered and the occurrence of nosocomial infection.

COVID-19 Therapy	Hospital-Acquired Infection [*N* (%), *p*-Value]
Anti-viral treatment (RDV, MPV) ($N = 94$)	27 (28.7%), $p = 0.3$
Chloroquine + LPV/r ($N = 29$)	12 (41.4%), $p = 0.4$
Dexamethasone ($N = 381$)	117 (30.7%), $p = 0.052$
Tocilizumab ($N = 95$)	32 (33.7%), $p > 0.9$
Baricitinib ($N = 49$)	33 (67.3%), $p < 0.001$

4.2. COVID-19 Complications

Table 4 provides data on COVID-19 complications, which are divided into three groups: thrombotic complications, bleeding complications and other complications.

Table 4. COVID-19 complications.

Variable	N = 477
Thrombotic complications:	112 (23.5%)
Venous thromboembolism	46 (9.6%)
Ischaemic stroke	29 (6.1%)
Myocardial infarction	22 (4.6%)
Limb ischaemia	16 (3.4%)
Bleeding complications	71 (14.9%)
Other:	261 (54.7%)
Acute kidney injury (AKI)	149 (31.2%)
Exacerbation of chronic heart disease	100 (21%)
Decompensation of liver function	12 (2.5%)

One patient with saddle pulmonary embolism also had an ischaemic stroke.

4.3. Complications Unrelated to COVID-19

This group assessed events that were related to the patient's hospital stay, including medical personnel malpractice (Table 5). A lack of adequate specialist treatment was highly likely to contribute to patient death, while a delay in specialist treatment was one of the additional factors likely to influence death.

Table 5. Adverse events during hospitalisation of COVID-19 patients.

Variable	N = 477
Complications of hospitalisation	220 (46.1%), including more than one complication in 22 patients (4.6%)
Healthcare-associated infection	159 (33.3%)
Emphysema and other complications of ventilation	36 (7.5%)
Trauma, fall	25 (5.2%)
Personnel malpractice	237 (49.7%)
Lack of specialist treatment	81 (17.0%)
Delay in specialist treatment	156 (32.7%)

Personnel malpractice included the failure or delay in intensifying treatment for respiratory failure, including delayed intubation, transfer of the patient to the ICU, failure to administer immunomodulatory drugs in case of signs of a "cytokine storm", failure to administer antibiotic therapy in the face of a confirmed bacterial infection and inappropriate anticoagulant treatment.

4.4. Causes of Death

Respiratory failure due to SARS-CoV-2 infection was the predominant cause of death in 423 (88.7%) patients, with a significant advantage ($p = 0.003$) in the group admitted in the WHO's stage three and four (318—91.4%) compared to stage one and two (105—81.4%). Out of 54 (11.3%) cases in which the predominant cause of death was not respiratory failure, 47 (87.0%) cases presented with sudden cardiac arrest (SCA) without preceding severe respiratory failure or signs of hypoxaemia. Figure 2 shows the analysis of other concomitant causes of death. The sum of the cases from Figure 2 does not equal 54 (11.3%) because some of the patients who died of COVID-19-associated respiratory failure also had additional relevant factors that influenced this and could not be omitted.

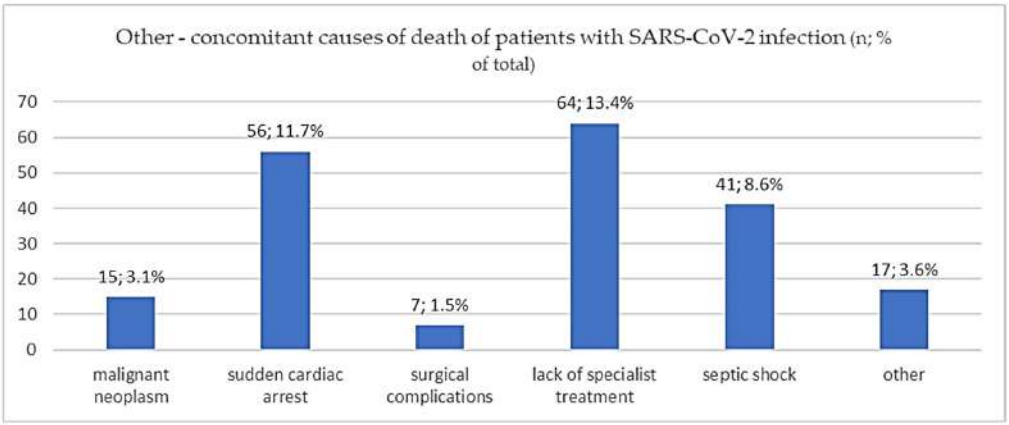


Figure 2. Other—concomitant causes of death of patients with SARS-CoV-2 infection (*N*; % of total).

In terms of the other concomitant causes of death (Figure 2), cases in which the patient's underlying condition (e.g., chronic renal failure on dialysis or malignant neoplasm on systemic therapy) could not be adequately treated due to SARS-CoV-2 infection were included in the "lack of specialist treatment" group. Cases in which ICU treatment was not provided due to the lack of places or low priority for such treatment were also collected under this section. Cases that could not be categorised included: upper gastrointestinal bleeding in a patient with decompensated cirrhosis and hepatocellular carcinoma, pulmonary oedema without an established clear cause, aspiration pneumonia, severe ischaemic and haemorrhagic strokes, subarachnoid haemorrhage, neuroCOVID with myoclonus syndrome and AIDS with pulmonary tuberculosis.

In a further analysis of the collected material, comparisons were made between the different age groups of patients without distinguishing between the sexes (in Table S1) and virus variants in Table 6 and Figure 3. Therapies that were only used in the first pre-Delta pandemic phase (COVID-19 convalescent plasma and chloroquine + LPV/r) were not assessed in the analysis of virus variants.

Table 6. The characteristics of selected parameters according to virus variant quantitative parameters and variables are presented as mean values (standard deviation—SD) and median [interquartile range—IQR], while qualitative variables are presented as frequency/number.

Variable	Pre-Delta (*N* = 288)	Delta (*N* = 110)	Omicron (*N* = 79)	*p*-Value
Age (years)	72.34 (11.9), 72 [65–82]	74.71 (13.23), 76 [66–85.75]	75.63 (12.86), 77 [69–85.5]	0.015
Sex				0.065
Men Women	183 (63.5%) 105 (36.5%)	57 (51.8%) 53 (48.2%)	43 (54.4%) 36 (45.6%)	
Duration of symptoms before admission (days)	6.94 (4.44), 7 [4–8]	7.44 (3.53), 7 [5–9]	8.83 (6.32), 7 [4.25–14]	0.093
Length of hospitalisations (days)	14.01 (11.17), 12 [6–20]	13.99 (9.90), 11.5 [7–19]	13.16 (11.17), 11 [5–16]	0.5
Comorbidities	266 (92.4%)	97 (88.2%)	73 (92.4%)	0.4
Cardiovascular diseases	219 (76.0%)	81 (73.6%)	67 (84.8%)	0.15
Respiratory diseases	42 (14.6%)	9 (8.2%)	17 (21.5%)	0.031
Diabetes	113 (39.2%)	29 (26.4%)	18 (22.8%)	0.004

Table 6. *Cont.*

Variable	Pre-Delta (*N* = 288)	Delta (*N* = 110)	Omicron (*N* = 79)	*p*-Value
Malignant neoplasm	57 (19.8%)	15 (13.6%)	18 (22.8%)	0.2
Chronic kidney disease	41 (14.2%)	9 (8.2%)	8 (10.1%)	0.2
Obesity	71(24.7%)	16 (14.5%)	5 (6.3%)	<0.001
EASIX	6.67 (12.63), 3.17 [1.91–6.23]	5.14 (5.28), 3.28 [2.05–6]	5.64 (9.97), 2.69 [1.66–4.45]	0.3
Treatment				
Antiviral treatment (RDV, MPV)	67 (23.3%)	16 (14.5%)	11(13.9%)	0.054
Dexamethasone	208 (72.2%)	107 (97.3%)	66 (83.5%)	<0.001
Tocilizumab	51 (17.7%)	29 (26.4%)	15 (19.0%)	0.2
Baricitinib	2 (0.7%)	30 (27.3%)	17 (21.5%)	<0.001
Antibiotic use	281 (97.6%)	105 (95.5%)	66 (83.5%)	<0.001
Inclusion of an antibiotic without medical indication	133 (47.0%)	58 (55.2%)	24 (36.4%)	0.051
Coinfection	166 (57.6%)	65 (59.1%)	43 (54.4%)	0.8
COVID-19 complications				
Pulmonary embolism	22 (7.6%)	14 (12.7%)	10 (12.7%)	0.2
Ischaemic stroke	17 (5.9%)	5 (4.5%)	6 (7.6%)	0.7
Myocardial infarction	13 (4.5%)	5 (4.5%)	4 (5.1%)	>0.9
Limb ischaemia	7 (2.4%)	2 (1.8%)	7 (8.9%)	0.028
Bleeding complications	39 (13.5%)	17 (15.5%)	15 (19.0%)	0.5
Acute kidney injury	86 (29.9%)	33 (30.0%)	30 (38.0%)	0.4
Exacerbation of chronic heart disease	60 (20.8%)	29 (26.4%)	11 (13.9%)	0.11
Decompensation of liver function	5 (1.7%)	1 (0.9%)	6 (7.6%)	0.011
Complications of hospitalisation				
Hospital-acquired infection	91 (31.6%)	42 (38.2%)	26 (32.9%)	0.5
Emphysema and other complications of ventilation	21 (7.3%)	12 (10.9%)	3 (3.8%)	0.2
Trauma, fall	8 (2.8%)	9 (8.2%)	8 (10.1%)	0.005
Predominant cause of death—COVID-19 respiratory failure	252 (87.5%)	103 (93.6%)	68 (86.1%)	0.15
Other causes of death				
Malignant neoplasm	10 (3.5%)	2 (1.8%)	3 (3.8%)	0.7
Sudden cardiac arrest	33 (11.5%)	10 (9.1%)	13 (16.5%)	0.3
Surgical complications	5 (1.7%)	2 (1.8%)	0 (0%)	0.7
Lack of specialist treatment	38 (13.2%)	14 (12.7%)	12 (15.2%)	0.9
Septic shock	14 (4.9%)	16 (14.5%)	11 (13.9%)	0.002
other	8 (2.8%)	3 (2.7%)	6 (7.6%)	0.14

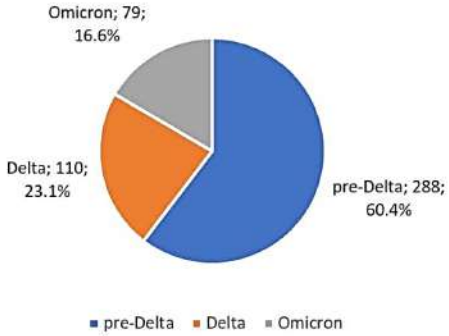


Figure 3. SARS-CoV-2 virus variants in the analysed group.

5. Discussion

The analysis of 477 cases of SARS-CoV-2 infection resulting in death revealed that this group was dominated by elderly men with multimorbidity, who were admitted in a severe or very severe course of the disease according to the WHO classification, with low saturation values (<90%) and laboratory abnormalities indicating the presence of increased inflammation and organ damage. Patients aged ≥ 81 years were significantly more likely to be admitted to and die in infectious diseases units due to respiratory failure, their hospital stays being shorter, and they were most likely not to receive specialist treatment. More than half of the patients suffered from concomitant bacterial and fungal infections, and one-third had HAIs, and the initial use of an antibiotic, although common, was unwarranted in almost half of the cases. The inclusion of baricitinib significantly influenced the occurrence of HAIs, which was not found for the other COVID-19 therapies. The use of dexamethasone was significantly more frequent when the Delta variant was predominant. In terms of COVID-19 complications, AKI and thrombotic complications were the most common. In almost half of the cases, complications of hospitalisation not directly related to COVID-19 were found, and a similar proportion was of medical personnel malpractice. A cause of death other than respiratory failure affected more than 10% of patients.

The currently known risk factors for severe COVID-19 and death from COVID-19 show a clear association with an age > 65 years, male sex, comorbidities and the viral variant being Delta [6,8,9,27–30]. In the analysed group, the results were obtained and are in line with reports by other authors. More than half of the cases were patients aged >70 years. The presence of comorbidities was common (91.4%) and were mostly cardiovascular diseases (76.9%) and diabetes (33.5%). Given the age structure of the patients, such results are not surprising. The male predominance was significant (59.3%) but decreased with age (in the <50-year-old group, the male proportion was 76.2%, while in the ≥80-year-old group, it had already dropped to 51%), which may be influenced by the hormonal differences, ACE2 protein expression and a change in immune function with age. Similar relationships were described in publications on infection with other coronaviruses (SARS—severe acute respiratory syndrome; MERS—Middle East respiratory syndrome) [31–33].

The analyses of selected laboratory parameters indicate the presence of increased inflammation and vascular abnormalities already at the time of hospital admission—this is illustrated by the high mean CRP, PCT, ferritin and D-dimer levels, as well as creatinine and LDH levels, and the high mean and median EASIX that was identified as an independent prognostic factor for a severe course of COVID-19 and risk of COVID-19-related death [34–36]. This factor is derived from the calculation of LDH, creatinine and PLT, whose abnormal values reflect, among other things, vascular endothelial cell damage, which is one of the most significant processes leading to microangiopathy, thrombotic complications and organ failure in severe COVID-19 [37–40]. In the material evaluated, the mean (6.22) and median (3.14) EASIX values were above the cut-off points set in other publications analysing this factor in the light of its predictive ability of ICU hospitalisation and death,

including one of our publications (Luft et al. EASIX ≥ 2.03, Kalicińska et al. EASIX ≥ 1.6 and Zińczuk et al. EASIX ≥ 2.36) [34–36].

Another significant finding of the analysis is the higher prevalence of coinfections and HAIs in younger age groups ($p < 0.001$). Coinfections were found twice as often in the <50-year-old group compared to the ≥81-year-old group (71.4% vs. 35.8%), and HAIs were more than three times as common (57.1% vs. 15.9%). It is possible that such a relationship is related to more frequent hospitalisations in the ICU, where microbiological tests are performed more frequently, and the risk of additional infections is higher than in the IDU [41]. The nearly two-fold shorter duration of hospital stays in the ≥81-year-old group, with a mean of 9.72 days (median 8 days (4–14), compared to the <50-year-old group, is also significant. A study by Contou et al. found that the median survival in critically ill patients with COVID-19 was 14 days after admission to the ICU (9–23) [42]. Our analysis provides data on the overall hospital length of stay of patients, with a median length of stay of 11 days (6–19) over the entire time interval analysed, which is a significantly worse result; however, it is difficult to identify a single reason for this.

A comparison of the course of the pandemic, according to the predominance of a particular viral variant in the Polish setting, is hampered by the lack of capacity to sequence SARS-CoV-2 genetic material in most healthcare institutions. Some publications on the evaluation of individual variants used the GISAID database, which provided reliable data on the dominance of specific viral sequences in a given region at a specific time [18]. In analogy with other publications from the Polish region, there was a division into periods of dominance of the pre-Delta, Delta and Omicron variants [8,9]. The analysis revealed a higher mean age of patients as the pandemic progressed ($p = 0.015$) when comparing the pre-Delta and Omicron variants (Table 6).

The analysis of the infection data produced results confirming the high importance of this problem in COVID-19 patients. A coinfection was found in more than 50% of the patients (57.4%) who died, including one-third of patients (33.3%) who suffered from HAIs, and more often in those who were admitted to the ICU (Table 2). In studies by other authors, the prevalence of coinfections in the general population of COVID-19 patients was less than 7–14%, with a much higher proportion of ICU-acquired infections (even more than 50%) and a much higher ICU mortality rate among patients with coinfections [43–46]. Given that more than 55% of the deaths in our evaluation of the material were in the ICU, this finding may be comparable with those studies. However, the results obtained should be assessed with caution, as each time, the decision to perform cultures of biological material was assessed by an attending physician and thus was not part of the standard management of a SARS-CoV-2 infected patient in IDU; therefore, differences in terms of the number, timing and type of cultures performed are difficult to compare. Importantly, the vast majority of cultures were from patients in the most severe condition—those hospitalised in the ICU. This determines the expected higher frequency (up to five-fold for stays >1 week) of bacterial isolation, including drug-resistant pathogens [43]. The type of pathogens isolated is in agreement with data on the profile of isolated pathogens in ICUs [47–49].

The overuse of antibiotics proved to be a major problem in the treatment of COVID-19 patients. In the analysed group, up to 94.8% of patients were initially treated with antibiotics, while according to our own evaluation of the medical records, indications for the actual use of antibiotics only occurred in approximately half of the cases. A positive aspect of the discussed issue is that as the pandemic progressed and more studies discussing the issue became available, there was a significant ($p < 0.001$) decrease in antibiotic use, from the initial 97.6% for the pre-Delta period to 83.5% during the Omicron period (Table 6). The WHO guidelines (current as of 13 January 2023) indicate the need for an appropriate antibiotic policy among COVID-19 patients: refraining from using antibiotics in cases of mild disease and being guided by the clinical picture and laboratory parameters indicating the need for additional antimicrobial therapy among the remaining patients [25].

From the very beginning of the pandemic, there was a search for therapeutic approaches focused on the causal treatment of SARS-CoV-2 infection. The first therapies

were based on reports concerning the mechanisms of action of previous epidemic coronaviruses causing infections among humans (SARS and MERS), identifying specific targets for drugs [50–52]. In the pre-Delta period, convalescent plasma, chloroquine plus lopinavir/ritonavir and remdesivir were used as part of the clinical trial. With the exception of remdesivir, the other therapies were discontinued in subsequent waves of the pandemic. Immunomodulatory treatments included dexamethasone, tocilizumab and baricitinib. Dexamethasone was the most widely used drug—almost 80% of the patients received it during their hospital stay, with a significant ($p < 0.001$) prevalence during the Delta variant-dominant period (97.3%) (Table 6). Numerous randomised trials, which were also evaluated in meta-analyses, produced results supporting the validity of glucocorticosteroid use among COVID-19 patients [53,54]. The frequency of use of other drugs among the cases evaluated in this study did not depend on the pandemic phase, except for baricitinib ($p < 0.001$). The therapies used against SARS-CoV-2 mostly did not affect the risk of HAIs, with the exception of baricitinib (Table 3), an inhibitor of the enzymatic activity of the JAK1 and JAK2 kinases, which conferred a significantly higher ($p < 0.001$) risk of HAIs. Contradictory to this result, however, is the data from the RECOVERY study and an additional meta-analysis of nine randomised trials on the use of JAK inhibitors in the treatment of COVID-19—no higher infection rate was found in the group of patients receiving these drugs compared to the standard therapy [55]. The differences may be due to the use of baricitinib in our setting in patients with severe respiratory failure who were no longer eligible for RDV therapy or who had completed it.

All patients had supplemental oxygen therapy modalities; however, the oxygen therapy was not, in all cases, the least invasive oxygen therapy at baseline, involving the use of an oxygen mask with an oxygen flow of at least 10 L/min. In approximately 10% of the cases (9.6%), HFNOT was implemented, or endotracheal intubation and mechanical ventilation were performed immediately after the patient was admitted to the emergency room—this concerned the most severely ill patients with profound respiratory failure. This management, dictated by necessity, is also justified by the available literature—patients in whom standard oxygen therapy is ineffective should have HFNOT implemented, resulting in fewer ventilation complications and the need for intubation [25,56–58].

A severe SARS-CoV-2 infection is associated with cytokine abnormalities and overstimulation of the inflammatory response, termed a cytokine storm [59]. Complications that are directly related to this viral infection are thus most often the result of vascular endothelial damage, which results in a higher risk of thromboembolic disorders and, at a later stage, organ damage [60]. In the evaluated group, such complications were confirmed in 112 patients, representing less than 25% of cases. Venous thromboembolism was the most common, found in 46 patients (9.6%). However, these figures may be underestimated due to the lack of technical feasibility of performing a CT in some patients in severe conditions with high oxygen demand. The literature data placed the prevalence of such disorders at 16.5% (95% CI 11.6–22.9) [61]. The most common COVID-19 complication that was observed in this study was AKI, found in 149 patients (31.2%). The meta-analysis by Yang et al. concludes that this result is comparable to global data. In a general population analysis of COVID-19 patients, AKI occurs at a frequency of 12.3% (95% CI 9.5–16.5%), with a much higher rate among cases hospitalised in the ICU being 39.0% (95% CI 23.2–57.6%) and those ending in death being 42.0% (95% CI 30.3–54.7%) [62].

The attempted analysis of adverse events yielded a surprising result—in almost half of the COVID-19 deaths assessed, adverse events in the course of hospitalisation could be identified. The unwarranted use of antibiotics, as discussed above, was one of those adverse events. The assessment of this type of event, in terms of a new aetiological agent, overload of the healthcare system and a lack of clear treatment guidelines, poses many difficulties. Based on the available data, it was not possible for us to establish the root cause of the events that occurred or, in many cases, assess the real impact on survival. An unambiguous analysis of the processes leading up to the incident would require a much larger study using incident reports [63]. Many therapeutic failures are certainly not

described in the medical records. Our data, although indicative, show adverse events as an important risk factor for therapeutic failures, which is worth exploring in further studies. Medical personnel malpractice was found in a total of 49.7% of cases. Lack of specialist treatment (17.0%) in some patients may have contributed significantly to death. However, there was a more frequent (32.7% of cases) delay in the use of various therapeutic modalities, including endotracheal intubation and immunomodulatory treatment, which was influenced by the limited access to places of hospitalisation in the ICU and a lack of medication. The literature data on medical errors and adverse events in the era of the COVID-19 pandemic are limited. Prior to the onset of SARS-CoV-2-related morbidity, estimates from the USA in 2017 indicated that medical errors may be the third predominant cause of death in the country [64]. In high-income countries, adverse events occur, on average, in 1 in 10 patients [65]. Estimates for low- and middle-income countries indicate that up to one in four patients are harmed, and 134 million adverse events occur annually and are responsible for 2.6 million preventable deaths [66]. As many as 60% of deaths in these countries can be attributed to a failure to maintain safety in the delivery of health services and a poor quality of care [67].

Working under the strain of a new, hitherto unprecedented situation faced by the medical staff who were directly involved in the fight against the pandemic may have led to the occurrence of more errors, especially with the scarcity of adequate infrastructure and resources. A large number of severely ill patients requiring mechanical ventilation confronted the physician with the choice of which patient had a higher priority for such treatment [68]. During the COVID-19 pandemic, patient safety became a particular challenge. Numerous organisational factors, staff shortages, redeployment and temporary solutions disrupted the operation of most healthcare systems worldwide. The quality of services declined due to the delays in the implementation of treatment for both COVID-19 and all other conditions due to the lack of or limitations in the availability of services. There were also new types of diagnostic errors that were variously related and unrelated to the SARS-CoV-2 virus infection itself [69].

The WHO, in a document dated 7 June 2020, provided details on defining a COVID-19 death: it is considered to be "a death resulting from a clinically compatible illness, in a probably or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease" [70]. The evaluation of our patient group found that respiratory failure in the course of infection represented the vast majority of deaths (88.7%), while the remaining 11.3% deaths were of other causes representing conditions that resulted directly from infection (mainly SCA without preceding hypoxaemia) but also deaths in patients "with COVID-19 not due to COVID-19". This group included, among others, patients who, due to a positive test for SARS-CoV-2 infection (without symptoms of respiratory failure), could not have continued specialist therapy in the absence of an adequately prepared infrastructure, e.g., dialysis, surgery or the systemic treatment of cancer. In the few available publications evaluating the causes of death, the results were comparable to ours. A retrospective single-centre study by Cobos-Siles et al. found that in 15% out of 128 patients, death was due to another cause with SARS-CoV-2 infection without developing ARDS or other complications directly associated with the viral infection. This group of patients was older (median 88 years) and had a higher multimorbid burden [71]. In contrast, Slater et al., in their report evaluating 162 deaths from one hospital in Leeds, indicated that SARS-CoV-2 infection was the direct cause of death in 93% of patients ("deaths due to COVID-19"); data were based on medical reports without defining a COVID-19 death to the end. It was indicated that 92% of patients had pulmonary infiltrates, and 97% required oxygen therapy [72]. Discrepancies in the correct classification of death during the pandemic may be due to the problem of over-estimation at the start of the pandemic and under-estimation of COVID-19 deaths as the pandemic progressed. It is emphasised that the COVID-19 pandemic is actually a syndemic, where the majority of deaths occur in patients with additional disease burdens, and sometimes determining

which factor actually led to a patient's death can be difficult, especially with the decline in the number of autopsies performed [73–75].

The analysis we performed has several limitations. Firstly, this analysis is retrospective and concerns only COVID-19 cases that ended in death, with no comparison to the group of patients who survived. Secondly, this is not a multicentre study, which means that local conditions, such as the standard of care, access to specific drugs and therapies, and the profile of patients admitted, may differ from the population average (as the standard of care is higher in a centre specialising in infectious diseases than in some hospitals). The analysis only used available medical records, which could also provide an erroneous assessment of the event in question, especially in the case of a delay or lack of specialist treatment, as well as in determining the final cause of death and the type of complications of hospitalisation.

6. Conclusions

COVID-19 is a disease that causes deaths mainly among elderly patients with multiple disease burdens. Respiratory failure due to SARS-CoV-2 infection is the most common mechanism of death, while sudden cardiac arrest and deaths due to thromboembolic complications occur less frequently. The hospitalisation of patients with severe COVID-19 is associated with numerous adverse events, which were only, in part, dependent on medical personnel and were largely related to the shortcomings of the healthcare system or resulted from a stay in a hospital setting. In light of possible future pandemics caused by similar viruses, it should be noted that mechanisms need to be developed for an efficient health system response to the rapidly increasing care needs of critically ill patients, including the elimination of preventable deaths, the implementation of appropriate management standards and an increase in patient safety.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/v15071430/s1, Table S1: Characteristics of selected parameters in different age groups.

Author Contributions: Conceptualisation, A.Z. and M.R.; methodology, M.R. and T.J.; resources, A.Z. and M.R.; writing—original draft preparation, A.Z.; writing—review and editing, M.R., K.S. and T.J.; supervision, M.R. and T.J. All authors have read and agreed to the published version of the manuscript.

Funding: This work was carried out according to the subject register in Simple System SUBZ.A120.23.071 and supported by a statutory subsidy granted by the Ministry of Science and Higher Education in Poland.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Wroclaw Medical University (protocol code No. 826/2020 from 17 December 2020).

Infomed Consent Statement: Patient consent was waived due to the retrospective nature of this work.

Data Availability Statement: Data are available from the authors of the publication.

Conflicts of Interest: The authors declared no conflict of interest within the scope of this work.

References

1. Dong, E.; Du, H.; Gardner, L. An interactive web-based dashboard to track COVID-19 inealime. *Lancet Infect. Dis.* **2020**, *20*, 533–534. [CrossRef]
2. Wang, H.; Paulson, K.R.; Pease, S.A.; Watson, S.; Comfort, H.; Zheng, P.; Murray, C.J. Estimating excess mortality due to the COVID-19 pandemic: A systematic analysis of COVID-19-related mortality, 2020–2021. *Lancet* **2022**, *399*, 1513–1536. [CrossRef]
3. Zheng, Z.; Peng, F.; Xu, B.; Zhao, J.; Liu, H.; Peng, J.; Li, Q.; Jiang, C.; Zhou, Y.; Liu, S.; et al. Risk factors of critical & mortal COVID-19 cases: A systematic literatureeview and meta-analysis. *J. Infect.* **2020**, *81*, 16–25.
4. Rahman, A.; Sathi, N.J. Risk factors ofhe severity of COVID-19: A meta-analysis. *Int. J. Clin. Pract.* **2021**, *75*, e13916. [CrossRef] [PubMed]
5. Ouchetto, O.; Drissi Bourhanbour, A. Risk Factors of COVID-19 Patients. *Disaster Med. Public Health Prep.* **2022**, *16*, 1300–1302. [CrossRef] [PubMed]

6. Zhang, J.; Dong, X.; Liu, G.; Gao, Y. Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality. *Clin. Rev. Allergy Immunol.* **2023**, *64*, 90–107. [CrossRef]
7. Tracking SARS-CoV-2 Variants. 2023. Available online: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants (accessed on 1 April 2023).
8. Flisiak, R.; Rzymski, P.; Zarębska-Michaluk, D.; Ciechanowski, P.; Dobrowolska, K.; Rogalska, M.; Jaroszewicz, J.; Szymanek-Pasternak, A.; Rorat, M.; Kozielewicz, D.; et al. Variability in the Clinical Course of COVID-19 in a Retrospective Analysis of a Large Real-World Database. *Viruses* **2023**, *15*, 149. [CrossRef]
9. Dobrowolska, K.; Brzdęk, M.; Zarębska-Michaluk, D.; Rzymski, P.; Rogalska, M.; Moniuszko-Malinowska, A.; Flisiak, R. Differences between the course of SARS-CoV-2 infections in the periods of the Delta and Omicron variants dominance in Poland. *Pol. Arch. Intern. Med.* **2023**, *2023*, 16403. [CrossRef]
10. Karlinsky, A.; Kobak, D. Tracking excess mortality across countries during the COVID-19 pandemic with the World Mortality Dataset. *Elife* **2021**, *10*, e69336. [CrossRef]
11. Elavarasi, A.; Prasad, M.; Seth, T.; Sahoo, R.K.; Madan, K.; Nischal, N.; Soneja, M.; Sharma, A.; Maulik, S.K.; Shalimar; et al. Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: A Systematic Review and Meta-analysis. *J. Gen. Intern. Med.* **2020**, *35*, 3308–3314. [CrossRef] [PubMed]
12. dos Santos, W.G. Natural History of COVID-19 and Current Knowledge on Treatment Therapeutic Options. *Biomed. Pharmacother.* **2020**, *129*, 110493. [CrossRef] [PubMed]
13. Singh, B.; Ryan, H.; Kredo, T.; Chaplin, M.; Fletcher, T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database Syst. Rev.* **2021**, 2, CD013587. [CrossRef]
14. Panahi, Y.; Gorabi, A.M.; Talaei, S.; Beiraghdar, F.; Akbarzadeh, A.; Tarhriz, V.; Mellatyar, H. An overview on the treatments and prevention against COVID-19. *Virol. J.* **2023**, *20*, 23. [CrossRef] [PubMed]
15. Yuan, Y.; Jiao, B.; Qu, L.; Yang, D.; Liu, R. The development of COVID-19reatment. *Front. Immunol.* **2023**, *14*, 1125246. [CrossRef]
16. Najjar-Debbiny, R.; Gronich, N.; Weber, G.; Khoury, J.; Amar, M.; Stein, N.; Goldstein, L.H.; Saliba, W. Effectiveness of Paxlovid in Reducing Severe Coronavirus Disease 2019 and Mortality in High-Risk Patients. *Clin. Infect. Dis.* **2023**, *76*, 342–349. [CrossRef]
17. Li, J.; Huang, D.Q.; Zou, B.; Yang, H.; Hui, W.Z.; Rui, F.; Yee, N.T.S.; Liu, C.; Nerurkar, S.N.; Kai, J.C.Y.; et al. Epidemiology of COVID-19: A systematiceview and meta-analysis of clinical characteristics, risk factors, and outcomes. *J. Med. Virol.* **2021**, *93*, 1449–1458. [CrossRef]
18. Hadfield, J.; Megill, C.; Bell, S.M.; Huddleston, J.; Potter, B.; Callender, C.; Sagulenko, P.; Bedford, T.; Neher, R.A. NextStrain: Real-time tracking of pathogen evolution. *Bioinformatics* **2018**, *34*, 4121–4123. [CrossRef] [PubMed]
19. *WHO: Clinical Management of COVID-19*; WHO: Geneva, Switzerland, 2020.
20. Luft, T.; Benner, A.; Jodele, S.; Dandoy, C.E.; Storb, R.; Gooley, T.; Penack, O. EASIX in patients with acute graft-versus-host disease: Aetrospective cohort analysis. *Lancet Haematol.* **2017**, *4*, 414–423. [CrossRef]
21. Sikora, A.; Zahra, F. Nosocomial Infections. StatPearls. 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK559312/ (accessed on 10 April 2023).
22. Conceptual Framework for the International Classification for Patient Safety Version 1.1: Final Technical Report January 2009. 2023. Available online: http://apps.who.int/iris/handle/10665/70882 (accessed on 10 April 2023).
23. Flisiak, R.; Horban, A.; Jaroszewicz, J.; Kozielewicz, D.; Pawłowska, M.; Parczewski, M.; Zarębska-Michaluk, D. Management of SARS-CoV-2 Infection: Recommendations of the Polish Association of Epidemiologists and Infectiologists. *Pol. Arch. Intern. Med.* **2020**, *130*, 557–558. [CrossRef]
24. Flisiak, R.; Horban, A.; Jaroszewicz, J.; Kozielewicz, D.; Mastalerz-Migas, A.; Owczuk, R.; Zarębska-Michaluk, D. Management of SARS-CoV-2 infection: Recommendations of the Polish Association of Epidemiologists and Infectiologists as of February 23, 2022. *Pol. Arch. Intern. Med.* **2022**, *132*, 16230. Available online: https://pubmed.ncbi.nlm.nih.gov/35352546/ (accessed on 2 May 2023). [CrossRef]
25. Living Guidance for Clinical Management of COVID-19. 2023. Available online: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2 (accessed on 2 May 2023).
26. R Core Team. European Environment Agency. 2020. Available online: https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006 (accessed on 12 May 2023).
27. Pijls, B.G.; Jolani, S.; Atherley, A.; Derckx, R.T.; Dijkstra, J.I.; Franssen, G.H.; Zeegers, M.P. Original research: Demographic risk factors for COVID-19 infection, severity, ICU admission and death: A meta-analysis of 59 studies. *BMJ Open* **2021**, *11*, e044640. [CrossRef] [PubMed]
28. Li, Y.; Ashcroft, T.; Chung, A.; Dighero, I.; Dozier, M.; Horne, M.; Mc Swiggan, E.; Shamsuddin, A.; Nair, H. Risk factors for poor outcomes in hospitalised COVID-19 patients: A systematic review and meta-analysis. *J. Glob. Health* **2021**, *11*, 10001. [CrossRef] [PubMed]
29. Modes, M.E.; Directo, M.P.; Melgar, M.; Johnson, L.R.; Yang, H.; Chaudhary, P.; Chen, P. Clinical Characteristics and Outcomes Among Adults Hospitalized with Laboratory-Confirmed SARS-CoV-2nfection During Periods of B.1.617.2 (Delta) and B.1.1.529 (Omicron) Variant Predominance—One Hospital, California, July 15–September 23, 2021, and December 21, 2021–January 27, 2022. *MMWR Recomm. Rep.* **2022**, *71*, 217–223.

30. Nyberg, T.; Ferguson, N.M.; Nash, S.G.; Webster, H.H.; Flaxman, S.; Andrews, N.; Thelwall, S. Comparative analysis ofheisks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: A cohort study. *Lancet* **2022**, *399*, 1303–1312. [CrossRef] [PubMed]
31. Alwani, M.; Yassin, A.; Al-Zoubi, R.M.; Aboumarzouk, O.M.; Nettleship, J.; Kelly, D.; Shabsigh, R. Sex-based differences in severity and mortality in COVID-19. *Rev. Med. Virol.* **2021**, *31*, 31. [CrossRef] [PubMed]
32. Karlberg, J.; Chong, D.S.Y.; Lai, W.Y.Y. Do Men Have a Higher Case Fatality Rate of Severe Acute Respiratory Syndrome than Women Do? *Am. J. Epidemiol.* **2004**, *159*, 229. [CrossRef]
33. Jansen, A.; Chiew, M.; Konings, F.; Lee, C.-K.; Li, A. Sex matters–a preliminary analysis of Middle East respiratory syndrome in the Republic of Korea, 2015. *Western. Pac. Surveill. Response J.* **2015**, *6*, 68. [CrossRef]
34. Kalicińska, E.; Biernat, M.; Rybka, J.; Zińczuk, A.; Janocha-Litwin, J.; Rosiek-Biegus, M.; Morawska, M.; Waszczuk-Gajda, A.; Drozd-Sokołowska, J.; Szukalski; et al. Endothelial Activation and Stressndex (EASIX) as an Early Predictor for Mortality and Overall Survival in Hematological and Non-Hematological Patients with COVID-19: Multicenter Cohort Study. *J. Clin. Med.* **2021**, *10*, 4373. [CrossRef]
35. Zińczuk, A.; Rorat, M.; Simon, K.; Jurek, T. EASIX, Modified EASIX and Simplified EASIX as an Early Predictor for intensive Care Unit Admission and Mortality in Severe COVID-19 Patients. *J. Pers. Med.* **2022**, *12*, 1022. [CrossRef]
36. Luft, T.; Wendtner, C.M.; Kosely, F.; Radujkovic, A.; Benner, A.; Korell, F.; Merle, U. EASIX for Prediction of Outcome in Hospitalized SARS-CoV-2nfected Patients. *Front. Immunol.* **2021**, *12*, 1–9. [CrossRef]
37. Chang, R.; Mamun, A.; Dominic, A.; Le, N.T. SARS-CoV-2 Mediated Endothelial Dysfunction: The Potential Role of Chronic Oxidative Stress. *Front. Physiol.* **2021**, *11*, 605908. [CrossRef]
38. Smadja, D.M.; Guerin, C.L.; Chocron, R.; Yatim, N.; Boussier, J.; Gendron, N.; Khider, L.; Hadjadj, J.; Goudot, G.; Debuc, B.; et al. Angiopoietin-2 as a marker ofndothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. *Angiogenesis* **2020**, *23*, 611–620. [CrossRef] [PubMed]
39. Gavriilaki, E.; Anyfanti, P.; Gavriilaki, M.; Lazaridis, A.; Douma, S.; Gkaliagkousi, E. Endothelial Dysfunction in COVID-19: Lessons Learned from Coronaviruses. *Curr. Hypertens. Rep.* **2020**, *22*, 1–12. [CrossRef]
40. Koh, G.; Varga, Z.; Flammer, A.J.; Steiger, P.; Haberecker, M.; Zinkernagel, R.A.A.S.; Mehra, M.R.; Schuepbach, R.A.; Ruschitzka, F.; Moch, H. Faculty Opinions recommendation of Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **2020**, *395*, 1417–1418.
41. Vincent, J.L.; Rello, J.; Marshall, J.; Silva, E.; Anzueto, A.; Martin, C.D.; Epic II Group of Investigators. International study ofhe prevalence and outcomes of infection in intensive care units. *JAMA* **2009**, *302*, 2323–2329. [CrossRef] [PubMed]
42. Contou, D.; Cally, R.; Sarfati, F.; Desaint, P.; Fraissé, M.; Plantefève, G. Causes and timing of death in critically ill COVID-19 patients. *Crit. Care* **2021**, *25*, 1–4. [CrossRef]
43. Garcia-Vidal, C.; Sanjuan, G.; Moreno-García, E.; Puerta-Alcalde, P.; Garcia-Pouton, N.; Chumbita, M.; Fernandez-Pittol, M.; Pitart, C.; Inciarte, A.; Bodro, M.; et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: Retrospective Cohort Study. *Clin. Microbiol. Infect.* **2021**, *27*, 83. [CrossRef]
44. Soriano, M.C.; Vaquero, C.; Ortiz-Fernández, A.; Caballero, A.; Blandino-Ortiz, A.; de Pablo, R. Low incidence of co-infection, but high incidence of CU-acquired infections in critically ill patients with COVID-19. *J. Infect.* **2021**, *82*, 20. [CrossRef] [PubMed]
45. Lansbury, L.; Lim, B.; Baskaran, V.; Lim, W.S. Co-infections in people with COVID-19: A systematic review and meta-analysis. *J. Infect.* **2020**, *81*, 266–275. [CrossRef]
46. Rawson, T.; Moore, L.; Zhu, N.; Ranganathan, N.; Skolimowska, K.; Gilchrist, M.; Satta, G.; Cooke, G.; Holmes, A. Clinical Infectious Diseases Bacterial and Fungal Coinfection in Individuals with Coronavirus: A Rapid Review to Support COVID-19 Antimicrobial Prescribing. 2023. Available online: https://academic.oup.com/cid/article/71/9/2459/5828058 (accessed on 2 May 2023).
47. Litwin, A.; Fedorowicz, O.; Duszynska, W. Characteristics of Microbial Factors of Healthcare-Associated Infections Including Multidrug-Resistant Pathogens and Antibiotic Consumption at the University Intensive Care Unit in Poland in the Years 2011–2018. *Int. J. Environ. Res. Public Health* **2020**, *17*, 6943. [CrossRef]
48. Bogossian, E.G.; Taccone, F.S.; Izzi, A.; Yin, N.; Garufi, A.; Hublet, S.; Njimi, H.; Ego, A.; Gorham, J.; Byl, B.; et al. The Acquisition of Multidrug-Resistant Bacteria in Patients Admitted to COVID-19 Intensive Care Units: A Monocentric Retrospective Case Control Study. *Microorganisms* **2020**, *8*, 1821. [CrossRef] [PubMed]
49. Patel, A.; Emerick, M.; Cabunoc, M.K.; Williams, M.H.; Preas, M.A.; Schrank, G.; Rabinowitz, R.; Luethy, P.; Johnson, J.K.; Leekha, S. Rapid Spread and Control of Multidrug-Resistant Gram-Negative Bacteria in COVID-19 Patient Care Units. *Emerg. Infect. Dis.* **2021**, *27*, 1234–1237. [CrossRef]
50. Khan, M.; Adil, S.F.; Alkhathlan, H.Z.; Tahir, M.N.; Saif, S.; Khan, M.; Khan, S.T. COVID-19: A Global Challenge with Old History, Epidemiology and Progress So Far. *Molecules* **2020**, *26*, 39. [CrossRef] [PubMed]
51. Shaffer, L. 15 drugs being tested to treat COVID-19 and how they would work. *Nat. Med.* 2020; *ahead of print*.
52. Gavriatopoulou, M.; Ntanasis-Stathopoulos, I.; Korompoki, E.; Fotiou, D.; Migkou, M.; Tzanninis, I.-G.; Psaltopoulou, T.; Kastritis, E.; Terpos, E.; Dimopoulos, M.A. Emerging treatment strategies for COVID-19 infection. *Clin. Exp. Med.* **2020**, *21*, 167–179. [CrossRef] [PubMed]

53. Chaudhuri, D.; Sasaki, K.; Karkar, A.; Sharif, S.; Lewis, K.; Mammen, M.J.; Alexander, P.; Ye, Z.; Lozano, L.E.C.; Munch, M.W.; et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: A systematic review and meta-analysis. *Intensive Care Med.* **2021**, *47*, 521–537. [CrossRef]
54. Cochrane Haematology Group; Wagner, C.; Griesel, M.; Mikolajewska, A.; Mueller, A.; Nothacker, M.; Fichtner, F. Systemic corticosteroids for the treatment of COVID-19. *Cochrane Database Syst. Rev.* **2021**, *8*, CD014963.
55. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet* **2022**, *400*, 359–368. [CrossRef] [PubMed]
56. Alhazzani, W.; Evans, L.; Alshamsi, F.; Møller, M.H.; Ostermann, M.; Prescott, H.C.; Arabi, Y.M.; Loeb, M.; Gong, M.N.; Fan, E.; et al. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. *Crit. Care Med.* **2021**, *49*, e219–e234. [CrossRef]
57. Rochwerg, B.; Einav, S.; Chaudhuri, D.; Mancebo, J.; Mauri, T.; Helviz, Y.; Goligher, E.C.; Jaber, S.; Ricard, J.-D.; Rittayamai, N.; et al. The role for high flow nasal cannula as a respiratory support strategy in adults: A clinical practice guideline. *Intensive Care Med.* **2020**, *46*, 2226–2237. [CrossRef]
58. Rorat, M.; Szymański, W.; Jurek, T.; Karczewski, M.; Zelig, J.; Simon, K. When Conventional Oxygen Therapy Fails-The Effectiveness of High-Flow Nasal Oxygen Therapy in Patients with Respiratory Failure in the Course of COVID-19. *J. Clin. Med.* **2021**, *10*, 4751. [CrossRef]
59. Ye, Q.; Wang, B.; Mao, J. The pathogenesis andreatment of the 'Cytokine Storm' in COVID-19. *J. Infect.* **2020**, *80*, 607–613. [CrossRef]
60. Conway, E.M.; Mackman, N.; Warren, R.Q.; Wolberg, A.S.; Mosnier, L.O.; Campbell, R.A.; Gralinski, L.E.; Rondina, M.T.; van de Veerdonk, F.L.; Hoffmeister, K.M.; et al. Understanding COVID-19-associated coagulopathy. *Nat. Rev. Immunol.* **2022**, *22*, 639–649. [CrossRef] [PubMed]
61. Suh, Y.J.; Hong, H.; Ohana, M.; Bompard, F.; Revel, M.-P.; Valle, C.; Gervaise, A.; Poissy, J.; Susen, S.; Hékimian, G.; et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. *Radiology* **2021**, *298*, E70–E80. [CrossRef] [PubMed]
62. Yang, X.; Tian, S.; Guo, H. Acute kidney injury and renal replacement therapy in COVID-19 patients: A systematic review and meta-analysis. *Int. Immunopharmacol.* **2021**, *90*, 107159. [CrossRef]
63. World Health Organization. Patient Safety Incident Reporting and Learning Systems. In *Technical Report and Guidance*; WHO: Geneva, Switzerland, 2020; pp. 1–51.
64. Anderson, J.G.; Abrahamson, K. Your Health Care May Kill You: Medical Errors. *Stud. Health Technol. Inform.* **2017**, *234*, 13–17. [PubMed]
65. The Economics of Patient Safety: Strengthening a Value-Based Approach to Reducing Patient Harm at National Level | OECD Health Working Papers | OECD iLibrary. 2023. Available online: https://www.oecd-ilibrary.org/social-issues-migration-health/the-economics-of-patient-safety_5a9858cd-en (accessed on 23 May 2023).
66. Crossing the Global Quality Chasm: Improving Health Care Worldwide. Crossing the Global Quality Chasm. 2018. Available online: https://pubmed.ncbi.nlm.nih.gov/30605296/ (accessed on 23 May 2023).
67. E Kruk, M.; Gage, A.D.; Arsenault, C.; Jordan, K.; Leslie, H.H.; Roder-DeWan, S.; Adeyi, O.; Barker, P.; Daelmans, B.; Doubova, S.V.; et al. High-quality health systems in the Sustainable Development Goals era: Time for a revolution. *Lancet Glob. Health* **2018**, *6*, e1196–e1252. [CrossRef]
68. Cohen, G.; Crespo, A.M.; White, D.B. Potential Legal Liability for Withdrawing or Withholding Ventilators During COVID-19: Assessing The Risks and Identifying Needed Reforms. *JAMA* **2020**, *323*, 1901–1902. [CrossRef] [PubMed]
69. Ensuring a Safe Environment for Patients and Staff in COVID-19 Health-Care Facilities: A Module from the Suite of Health Service Capacity Assessments in the Context of the COVID-19 Pandemic. 2023. Available online: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-HCF_assessment-Safe_environment-2020.1 (accessed on 23 May 2023).
70. Medical Certification, CD Mortality Coding, and Reporting Mortality Associated with COVID-19. 2023. Available online: https://www.who.int/publications/i/item/WHO-2019-nCoV-mortality-reporting-2020-1 (accessed on 29 April 2023).
71. Cobos-Siles, M.; Cubero-Morais, P.; Arroyo-Jimenez, I.; Rey-Hernandez, M.; Hernandez-Gomez, L.; Vargas-Parra, D.J.; Corral-Gudino, L. Cause-specific death in hospitalized individuals infected with SARS-CoV-2: More than just acute respiratory failure or thromboembolic events. *Intern. Emerg. Med.* **2020**, *15*, 1533. [CrossRef]
72. Slater, T.A.; Straw, S.; Drozd, M.; Kamalathasan, S.; Cowley, A.; Witte, K.K. Dying 'dueo' or 'with' COVID-19: A cause of death analysis in hospitalised patients. *Clin. Med.* **2020**, *20*, 189. [CrossRef]
73. Salerno, M.; Sessa, F.; Piscopo, A.; Montana, A.; Torrisi, M.; Patanè, F.; Murabito, P.; Volti, G.L.; Pomara, C. No Autopsies on COVID-19 Deaths: A Missed Opportunity and the Lockdown of Science. *J. Clin. Med.* **2020**, *9*, 1472. [CrossRef]
74. Ioannidis, J.P.A. Over- and under-estimation of COVID-19 deaths. *Eur. J. Epidemiol.* **2021**, *36*, 581. [CrossRef] [PubMed]
75. Horton, R. Offline: COVID-19 is not a pandemic. *Lancet* **2020**, *396*, 874. Available online: http://pmc/articles/PMC7515561/ (accessed on 29 April 2023). [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

Archiwum Medycyny Sadowej i Kryminologii
Archives of Forensic Medicine and Criminology

COVID-19-related excess mortality – an overview of the current evidence

Nadmierna śmiertelność związana z COVID-19 – przegląd aktualnych informacji

Aleksander Zińczuk, Marta Rorat, Tomasz Jurek

Department of Forensic Medicine, Wroclaw Medical University

Abstract

Analysis of excess deaths, defined as the difference in the total number of deaths in an emergency compared to the number of deaths expected under normal conditions, allows a more reliable assessment of the impact on health systems caused by the global threat of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). So far, data for the two years of the pandemic (2020-2021) indicates the occurrence of 14.9 million excess deaths according to WHO (World Health Organization) estimates. The purpose of the analysis conducted was to define the concept and identify the causes of excess mortality during the COVID-19 pandemic. Inconsistent and unreliable death registration systems; overburdened health systems in low- and middle-income countries; reduced access to medical services for patients with health problems other than COVID-19; the introduction of social distancing and lockdown rules, which translated into increased deaths from psychiatric illnesses and addictions; political considerations and media messages that interfered with vaccination acceptance and adherence; and the additional impact of other natural disasters (hurricanes, floods, drought) were identified as the most important reasons for excess deaths occurrence. The correct identification of country-specific factors and the correct response and countermeasures taken appear crucial in terms of limiting the negative impact of the current pandemic, but also of future threats of a similar nature, in order to reduce excess deaths.

Keywords

SARS-CoV-2, death, global mortality, pandemic

AMSiK 2023 | vol. 73 (1), 33-44 DOI: 10.4467/16891716AMSIK.22.004.18214

Streszczenie

Analiza zgonów nadmiarowych definiowanych jako różnica w całkowitej liczbie zgonów w sytuacji kryzysowej w porównaniu do liczby zgonów oczekiwanych w normalnych warunkach, pozwala bardziej wiarygodnie ocenić wpływ globalnego zagrożenia jakim okazał się nowy koronawirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronaviruse-2) na systemy opieki zdrowotnej. Dotychczasowe dane dotyczące dwóch lat pandemii (2020-2021) wskazują na wystąpienie 14.9 miliona zgonów nadmiarowych według szacunków WHO (World Health Organization). Celem przeprowadzonej analizy było zdefiniowanie pojęcia oraz wskazanie przyczyn występowania nadmiarowych zgonów w trakcie pandemii COVID-19. Jako najważniejsze przyczyny ich pojawienia się należy uznać: niespójne i mało wiarygodne systemy rejestracji zgonów; przeciążenie systemów opieki zdrowotnej w krajach o niskich i średnich dochodach; ograniczenie dostępu do świadczeń medycznych dla pacjentów z innymi niż COVID-19 problemami zdrowotnymi; wprowadzenie zasad dystansu społecznego oraz lockdownu, co przełożyło się na zwiększenie liczby zgonów z powodu chorób psychiatrycznych i uzależnień; względy polityczne i przekaz medialny, które ingerowały w akceptację szczepień i stosowanie się do zaleceń; dodatkowy wpływ innych klęsk żywiołowych (huraganów, powodzi, suszy). Właściwa identyfikacja czynników występujących w danym kraju oraz prawidłowa reakcja i podjęte środki zaradcze wydają się kluczowe w aspekcie ograniczenia negatywnych skutków aktualnej pandemii, ale także przyszłych zagrożeń o podobnym charakterze, w celu ograniczenia liczby nadmiarowych zgonów.

Słowa kluczowe

SARS-CoV-2, zgon, globalna śmiertelność, pandemia

Introduction

Infections with the new Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), initially referred to as pneumonia of unknown cause, were first reported on 31 December 2019 by the China Country WHO Office. As early as on 5 January 2020, WHO officially announced the detection of a cluster of infections with an unknown biological agent [1]. Initial observations of the mechanism of spread of the infection and the clinical picture of the disease it causes indicated similarities with SARS-CoV-1 (Severe Acute Respiratory Syndrome Coronavirus-1) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus). The increasing number of infections, confirmation of human-to-human transmission and emergence of new cases in other countries prompted WHO to declare a Public Health Emergency of International Concern (PHEIC) on 30 January 2020, while on 11 March 2020, due to the lack of control of the disease, COVID-19 (Coronavirus disease 2019) was classified as a pandemic [2], [3].

Analyzing the impact of a pandemic on public health is crucial for any national health system to identify links that are not functioning properly. Proper evaluation of the causes of death and their circumstances in the context of preventable deaths is a task that unites epidemiologists, clinicians and pathologists (including forensic pathologists) who determine the pathogenesis of death. All over the world, the first cases of COVID-19 deaths were subjected to post-mortem diagnosis [4], and further studies allowed rapid understanding of the etiopathogenesis and course of the disease, refining ways to diagnose and treat it [5], [6].

During the pandemic, there was a tendency for COVID-19 deaths to be diagnosed in almost every case of positive antigen or PCR (Polymerase Chain Reaction) test, significantly affecting epidemiology and mortality statistics. Inferring the cause of death is based on establishing causation. Not every abnormality is necessarily important in the pathogenesis of death, not every positive test result means active infection, much less disease. Lack of diagnostic insight leads to a false assessment of the mortality structure with omission of its important elements not directly related to coronavirus disease incidence. This could be very important for learning from the effects of the pandemic and, in the event of further global threats, for increasing the number of deaths that could have been avoided. For this reason, in the authors' opinion, it is necessary to present many different aspects of mortality during the COVID-19 pandemic.

The rapidly increasing number of cases of respiratory failure in the course of SARS-CoV-2 infection, which required hospitalization and specialized treatment, significantly limited the capacity of the health care system to provide services to other patients in need. Initially, only selected centers, particularly infectious diseases wards/hospitals, provided care for patients with COVID-19. Lack of knowledge about the mechanisms of virus transmission and action; organizational chaos due to lack of recommendations, limited access to personal protective equipment, and unpreparedness of medical entities for an epidemiological disaster; coupled with fear of the medical personnel, resulted in greatly impaired access to

many procedures and specialists. All this had an obvious impact on the number of deaths, because in addition to the cases caused by SARS-CoV-2, there were also deaths that were an indirect effect of the pandemic (so-called non-COVID victims of the pandemic). This is an issue that is difficult to assess, as it also involves a critical assessment of the correctness of medical personnel's conduct and systemic errors made by health care managers.

The analysis of the available data on excess mortality related to the COVID-19 pandemic aims to define the issue, identify the causes of their occurrence, and establish common areas to create a coherent strategy for responding to future pandemic biological threats. The literature review was performed on 11 May 2023 in the Pubmed database using the keywords: COVID-19, SARS-CoV-2, excess deaths, excess mortality.

Excess Deaths

Excess deaths are considered to be "the difference in the total number of deaths in a crisis compared to those expected under normal conditions" [7], [8]. This is a concept used to assess the impact of a threat on the number of deaths during a crisis, taking into account intermediate elements such as the restrictions implemented or the overloading of the health care system, which more reliably reflects the true scale of the problem [9], [10]. Assessing excess deaths is also an indicator to show how prepared a country's health system is for a mass event, and to indicate social inequalities, such as those related to gender, age, wealth, ethnicity [11]. It should be noted that excess death rates report aggregate numbers of deaths due to various causes, such as an increase as a result of lack of access to health care, but also a decrease due to a reduction in traffic accidents after the introduction of movement restrictions due to the pandemic [10]. The COVID-19 pandemic is not the first global event to use this parameter. The impact of the so-called "Spanish flu" pandemic in 1918 and other mass disaster-type events (Hurricane Maria in Puerto Rico) was previously evaluated in this way [12], [13]. In practice, excess deaths are the difference between observed deaths and those expected based on the averages from previous years.

Excess Mortality

Excess mortality is the ratio of the number of observed deaths to expected mortality in percentage terms. The higher it is, the higher the number of all additional deaths above the expected ones, a negative value means mortality lower than average. Rates of excess mortality caused by COVID-19, in addition to the infection itself, are related to overall mortality rates in a country and to the age structure of the population - especially the number of >65 year olds, the group most at risk of death [14], [15]. For this reason, the COVID-19 pandemic is referred to as a syndemic, or synergistic epidemic, during which the virus causes deaths primarily in key populations (the elderly and people with concomitant diseases) [16]. It is emphasized that the impact of COVID-19 on the number of excess deaths related to the mechanisms of health systems under the impact of the pandemic may be spread over time and also occur in subsequent years, not only during the period of death registration [17].

In order to comprehensively assess deaths during the pandemic, a WHO Technical Advisory Group on COVID-19 Mortality Assessment was established in February 2021. Based on its analysis, WHO states the number of victims of the 2020 pandemic to be at least 3 million, about 1.2 million more than the reported number of COVID-19-related deaths in that period. However, the data came from only two areas - European and American, while the others lacked sufficient data for calculations [7]. In contrast, the latest available report covering the period from 1 January 2020 to 31 December 2021 found that the number of excess deaths was 14.9 million (13.3-16.6), 84% of which occurred in middle-income countries [18]. A higher figure for this time frame was reported by the authors of an analysis published in The Lancet, according to which the number of excess deaths by 31 December 2021 reached 18.2 million globally [95% uncertainty interval (UI) 17.1-19.6], and the excess mortality rate reached 120.30 [95% UI 113.1-129.3] per 100,000, with the highest rates per 100,000 population in Andean Latin America (511.9), Central (315.7) and Eastern (345.2) Europe, Southern Sub-Saharan Africa (308.6) and Central America (274.4)[17]. The country that accounted for 22.3% of the globally analyzed excess deaths is India with 4.07 million (95% UI 3.71-4.36) [17]. In contrast, a meta-analysis by Shang et al. covering data available from 1 January 2020 to 21 May 2022 indicates 104.84 [95% confidence interval (CI) 85.56-124.13] excess deaths per 100,000 globally. The highest rates were achieved in South America (134.02) and North America (124.63), and in Europe (122.16), as well as among people over 60 (781.74) and among men (130.10) [9]. More recent data is available for the European area. According to the information provided by Eurostat, February 2023 was the first month since the start of the pandemic in which there were no excess deaths for the entire European Union (EU) area - the excess mortality rate dropped to -2.3%. In contrast, analysis of the entire EU pandemic period to date indicates that there have been 4 peaks of excess mortality - the highest one in November 2020 (40.0%, in Eastern European countries reaching over 90.0%), in November 2021 (26.5%), in April 2020 (25.2%) and in April 2021 (20.9%) [19].

Causes

The gap between the recorded number of COVID-19 deaths and the actual number of pandemic victims is filled by excess deaths, the number of which reflects the actual impact of the pandemic on public health. When discussing the causes of the occurrence of these deaths, it is important to note the strongly varying background of this issue.

Diagnosis and Registration of Deaths

Since their inception, COVID-19 death registration systems have been based on a positive test result for SARS-CoV-2. Later on, with the possibility of diagnosis based on symptoms and results of additional laboratory and imaging tests, but labora-

tory confirmation was usually required anyway [10]. It should also be noted that testing policies varied from country to country and from pandemic stage to pandemic stage [10]. This has obvious implications. Where access to diagnostics is limited and the number of symptomatic patients is high, there is a significant overload on the system and an underestimation of the number of COVID-19 cases identified, which translates into underestimating deaths from this cause and showing more excess deaths [20]. Such a relationship was described especially at the beginning of the pandemic in China. Based on a mathematical model, the authors of one publication showed that up to 86% of COVID-19 cases were unrecognized prior to the implementation of travel restrictions within Wuhan on 23 January 2020, translating into a rapid global spread of the infection [21]. Similar observations have been found in other countries around the world, while emphasizing the importance of early isolation in the absence of access to widespread and efficient diagnostics [22]–[25].

An additional diagnostic concern is the sensitivity and specificity of PCR tests, which depends, among others, on the type of test, the timing of the test, and where and how the biological material is collected for testing [26]. False-negative PCR test results were obtained at the beginning of the pandemic in up to 29% of cases [27]. It is emphasized that a single negative result of such a test in a situation of high probability of disease (e.g., based on the clinical picture) is not sufficient to exclude the disease, especially when the test was developed in a population with a large number of cases, and is used in conditions where there are fewer cases, which translates into a higher number of false-negative results [10], [14], [28]. Incorrect test results affect death registries based on the need for a positive result, especially if a negative test result was obtained before the patient died [29].

Overburdening the health system may have led to COVID-19 deaths being attributed to iatrogenic causes - such as the use of harmful pharmacotherapy, as in the case of hydroxychloroquine, or inappropriate oxygen therapy [30]–[33]. The issue of iatrogenic harm associated with the use of therapies with no proven efficacy in the treatment of COVID-19 was addressed in the course of establishing the respective WHO recommendations. The current guidelines, dated 13 January 2023, include summaries of studies arguing against the use of hydroxychloroquine (30 randomized clinical trials), lopinavir-ritonavir (7 randomized clinical trials) and ivermectin (16 randomized clinical trials), detailing the adverse effects caused by these therapies [34]. However, there was no clear effect on increased mortality in the groups taking the drugs analyzed.

It should be emphasized that the difference between the actual and laboratory-confirmed number of COVID-19 deaths is only a fraction of the total number of excess deaths, although the difference indicates the quality of national health systems' preparation for the pandemic [35]. Post-mortem diagnosis of COVID-19-related deaths has not been routinely conducted on a large scale. The time of the COVID-19 pandemic, especially its beginning, was a period when the number of autopsies performed dropped dramatically. In April 2020, when some 150,000 deaths from SARS-CoV-2 were reported, only 16 autopsy descriptions were published in the literature, with more than half of the autopsies incomplete [36]. This is a disadvantageous situation due, among others, to uncertainty about the proper classification of the cause of death, as well as the lack of key information about the pathological changes caused by the virus [37]. As a rule, a full post-mortem diagnosis includes not only an autopsy with histopathological, toxicological or microbiological examinations, but also a detailed analysis of the patient's medical history, medical data or history from witnesses to the last days of the patient's life - which often allows verification of the causes of death assumed by clinicians. In the case of COVID-19, patient autopsies were limited to single or serial case studies to clarify the etiopathogenesis and nature of the pathologies caused by the disease, with occasional indications for forensic medical autopsies [38]–[40]. For this reason, the most thorough investigations into the causes and circumstances of death by pathologists and forensic pathologists have little impact on epidemiological determinations of the causes of excess mortality.

Looking at the issue from the other side - during successive periods of pandemics, further effective methods of fighting the infection, such as targeted therapies and vaccines, were acquired, which are particularly important in protecting key populations [14]. Access to reliable, rapid diagnostic tests has improved, with most patients having tests performed in primary care, which has significantly improved the detection of infections, including those asymptomatic or with few symptoms. Deaths of people with a history of positive results, often due to lack of proper case analysis, were routinely classified as caused by infection, which translated into overestimation of the total number of COVID-19 deaths [14], [41].

The term "death with SARS-CoV-2 infection" has appeared in the literature [10], [42]. This described, inter alia, situations in which the death was a result of a crime, suicide or road traffic accident, and a post-mortem test positive for SARS-CoV-2 was obtained [43]. In 2020, WHO issued a document with instructions for recognizing COVID-19 as a direct cause of death. According to the proposed definition, it is "a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease" [44]. Currently, in the dominant phase of the Omicron variant, this issue is particularly relevant, due to the decidedly milder nature of the infection [45], [46]. This requires a meticulous analysis of the case before classifying it as a COVID-19 death [10], [47].

An additional motive for improper reporting of the cause of death may have been the funding of benefits depending on

Table 1. Summary of factors affecting the reliability of COVID-19 death rate data
Tabela 1. Podsumowanie czynników wpływających na wiarygodność danych dotyczących współczynnika zgonów z powodu Covid-19

Underestimation of the number of deaths	Overestimation of the number of deaths
Lack of testing at the start of the pandemic.	Attribution of death due to COVID-19 in those with a positive test result and no signs of infection or respiratory failure.
The use of low-sensitivity tests.	Iatrogenic deaths (use of incorrect therapy) attributed to COVID-19.
Lack of adequate technical facilities and infrastructure for diagnostics.	Lack of post-mortem diagnosis and verification of causes of death.
Lack of reliable death registers.	Better funding of COVID-19 diagnosis by healthcare funding authorities.

the diagnosis code. In some health systems, temporarily including Poland, making a COVID-19 diagnosis according to the ICD-10 (International Classification of Diseases, Tenth Revision) classification has been associated with better valuation of services, in others - even with compensation payments to families, including India [48].

Reliability and consistent maintenance of medical records is a very important factor in determining the reliability of statistical data. The shortcomings of electronic medical records were highlighted - an analysis of electronic data, and data in paper form, of 516 patients of a London hospital, showed differences of 40% of cases. This also translates into the veracity of the conclusions drawn from the interpretation of these documents [49]. WHO notes that the reliability of the data is influenced by a well-functioning statistical system that allows for efficient recording and evaluation of population demographics. For the African region, the lowest death registration rates in the world are found (about 10%), resulting in underestimation of deaths and lack of reliable epidemiological data from the area [7], [50]. In contrast, an analysis of death certificates from the US shows a high correspondence between the actual number of deaths and the reports according to the ICD-10 classification [51].
In sum, with successive periods of the pandemic, diagnostic advances and changes in the dominant variants, there was a downward trend in the number of underestimated deaths and an increase in the overdiagnosis of COVID-19 as the cause of death, which obviously translated into a global assessment of excess mortality – these factors are summarized in Table 1.

Political Considerations Affecting Reporting

Pandemic in some countries has also proven to be a tool of political gamesmanship to keep voters with a particular party. The applied narrative of the authorities, in which there was no clear message about the positive effects of vaccination or the actual number of deaths, and the failure to admit their own mistakes in preparing and organizing the health system to deal with the pandemic, caused a false sense of security among the public, which resulted, among others, in challenging vaccinations and translated into a large number of excess deaths in the subsequent waves of the pandemic in Poland [52]. In the US and South Korea, political views were related to perceptions of the risk of viral infection being significantly higher, which the US researchers found to be reflected in the use of masks, frequency of vaccinations, number of COVID-19 cases and SARS-CoV-2 deaths [53]–[56]. The use of political disinformation, the undermining of the authority of the health ministry, and the promotion of pseudoscience by the Brazilian president at the beginning of the COVID-19 pandemic, were important underpinnings of the country's subsequent health crisis, as highlighted in various studies [57]–[59]. A study from Italy revealed a significant influence of politics and the media on the perception of scientific messages and scientific authorities during the pandemic [60]. This shows the importance of properly conducted political leadership based on clear principles and in cooperation with authorities, in order to make sound decisions that will translate into later success in the fight against the pandemic. The effectiveness of such measures has been confirmed in Asian countries [61].

Impact of Lockdown and Other Restrictions on the Occurrence of Certain Medical Events

From the very beginning of the pandemic, non-pharmaceutical interventions (NPIs), such as social distance, lockdown and movement restrictions, were undertaken to reduce the number of COVID-19 cases and deaths [62], [63]. However, it transpired that these restrictions also had a direct impact on the number of excess deaths, as a result of the occurrence of (mostly incorrect) non-COVID-19 events related to the provision of medical services. The impact on the number of excess deaths was greater the longer and more intensive the restrictions applied, as found in an analysis of countermeasures taken in 22 European countries [64]. As a consequence of lockdown, the number of hospital emergency department admissions and patient hospitalizations for general causes and cardiovascular events decreased, as studies from Germany, England and Greece have shown [65]–[69]. In the US, it has been estimated that the pandemic affected a 12% decrease in emergency care reporting for adult patients and more than 30% for elective reasons [70]. There has also been a catastrophic decline in the number of detected and treated cases

of tuberculosis, which had been previously the most common infectious cause of death worldwide [71]. According to WHO reports, this has translated into an increase in tuberculosis-related deaths and an increase in cases of drug-resistant tuberculosis [72]. A significant decline in cancer diagnoses has been found in numerous countries as a result of a decrease in the number of screening tests performed and restrictions on cancer treatment, such as the choice of systemic treatment regimens that are less effective but carry a lower risk of patient hospitalization [73]–[76]. In particular, there was a significant decrease in the number of surgical procedures performed compared to other therapies (-33.9% vs. -12.6%) [77]. A reduction in vaccination rates has also been shown globally for the number of vaccinations with the third dose of DTP (diphtheria-tetanus-pertussis) and the first MCV (measles-containing vaccine) [78]. In India and Namibia, a decline in hospital births of about 50% has been reported [79], [80]. The use of existing resources (personnel and medical infrastructure) to combat COVID-19 has resulted in restrictions on access to medical assistance for patients with other disorders. This has been shown to have been responsible for about 20% of excess deaths in Italy and England and up to 62% in Greece during the early stages of the pandemic [9], [69], [81], [82]. The main reason was lack of access to outpatient care and surgical procedures [69]. Similar reasons for the high number of deaths during the pandemic were found in Poland [83].

Isolation and restrictions on movement have also translated into mental health problems - an increase in depressive disorders, suicide and drug overdose deaths [84], [85]. According to the data published by the Centers for Disease Control and Prevention (CDC), by the end of May 2020 alone, there were more than 80,000 drug overdose deaths in the US, the highest recorded so far in analyzed 12-month periods [86]. In addition to social distancing requirements, the factors underlying suicides were financial stressors related to reduced or no income, more frequent alcohol abuse and lack of access to existing psychiatric care [87]. This is a phenomenon also observed during other pandemics, including the Spanish flu in 1918 in the US and SARS in Hong Kong in 2003 [88]–[90].

One of the positive effects of the reduction in population movement, the global use of personal protective equipment and hand hygiene, has proven to be a decrease in the number of deaths caused by exposure to certain risk factors, such as a reduction in traffic accidents [91]–[93]. Another effect of the pandemic was a significant reduction of up to 80% in cases of influenza or RSV infection, including deaths caused by these viruses [94]–[100].

Other Natural Disasters During the Period of the COVID-19 Pandemic

The vast majority of excess deaths during the pandemic were related to COVID-19. The co-occurrence of other natural disaster events affecting higher death rates added to the catastrophic nature of the pandemic [17]. Of particular importance were events that occurred before the peaks of COVID-19 incidence, which translated into an accumulation of negative factors, such as the need to evacuate the population, the inability to maintain a safe distance and isolate sick people, limited access to medical infrastructure and pharmaceuticals [101], [102]. Such events have occurred in many areas of the world, including: tropical cyclone Yasa in Fiji, Vanuatu, Tonga and the Solomon Islands; Hurricane Laura in the southern US; floods in South Africa; Cyclone Amphan in Bangladesh and West Bengal; heat waves and droughts in Zimbabwe, the US and Europe [101], [103]. According to the data reported by Eurostat, excess mortality in August 2022 reached 13.9%, almost double that of the same period in 2020 (7.6%). A heat wave that covered Europe at the time is believed to be the cause of that condition [19]. The authors of a theoretical mathematical model showed that the eruption of Vesuvius in Campania, Italy, during the COVID-19 outbreak, would cause up to 8-fold higher mortality in the area compared to the situation without such an event [101]. These results show that there are also numerous independent factors occurring during a pandemic that can dynamically affect the overall number of deaths.

Systems with Poor Health Care Quality

Even before the pandemic, low- and middle-income countries (LMICs) showed some 15.6 million excess deaths, 5 million of which were related to access to a low-quality health system [104]. The COVID-19 pandemic highlighted gaps in access to Intensive Care Units (ICUs), shortages of trained medical personnel, insufficient diagnostic facilities, and limited access to pharmaceuticals, personal protective equipment and vaccines in developing countries [105], [106]. The authors of an analysis of the impact of the pandemic on excess mortality published in The Lancet emphasize that the high death rates for such countries can probably be attributed at least in part to diagnostic deficiencies, limited access to certain medical practices, and ambiguous guidelines for recording COVID-19 deaths [17]. Analyses from the respective countries confirm these reports. In Peru, the total number of deaths during the pandemic period consisted, among others, of those related to the limited availability of ICU beds and qualified personnel to work in such units, oxygen shortages, lack of testing, and lack of clear guidelines and support from medical authorities [93]. The data from Mexico indicates an increased exposure to COVID-19-related adverse events, but also an underestimation of the number of deaths due to it and a higher rate of excess deaths in socially marginalized populations, which additionally have poorer access to medical care as a result of transport restrictions [107], [108]. In comparison, the number of excess deaths due to the COVID-19 pandemic in some high-income countries (Belgium, Sweden), which conduct meticulous death reporting, was little related to the impact of COVID-19 on deaths from other causes, such as chronic diseases [17]. Oceania was the least affected area in Shang et al.'s meta-analysis in terms of the magnitude of excess deaths, as it had a lower-than-ex-

pected number of deaths from any cause (a rate of -32.15 per 100,000) [9]. Among the reasons cited for this in Australia and New Zealand are a well-functioning medical surveillance system and strict rules for detecting and monitoring COVID-19 cases, as well as the substantial support provided to at-risk groups [109], [110].

Analysis of the location of deaths (home, hospital, long-term care center) also provides important data. It has been noted that more deaths attributed to COVID-19 were found in high-income countries, where hospital and elderly care is provided at a higher level, mainly among patients in terminal conditions residing in long-term care facilities [14]. This has been influenced by a number of factors, primarily better diagnostics, but also a higher number of infections in clusters of susceptible people [111]–[113]. It is also known that the elderly population (aged >60) is particularly susceptible to the occurrence of excess deaths, as shown in the meta-analysis by Shang et al. and reports from various countries [9], [10], [114], [115]. In contrast, an analysis of causes of death in one hospital in Spain at the start of the pandemic found that 15% of 128 patients with a positive test for SARS-CoV-2 died from causes other than Acute Respiratory Distress Syndrome (ARDS) or complications of infection ("death with SARS-CoV-2 infection"). Among the reasons for this are the susceptibility of an older group of patients to decompensation of their chronic conditions and the inability to use supportive therapies (such as systemic rehabilitation) during hospitalization in isolation [116]. In this group, more deaths are attributed to COVID-19, although the recognition of SARS-CoV-2 infection as a cause of death among the elderly, and especially those in the terminal condition, without a thorough analysis of each case, is a matter of debate, as partially discussed above. Hence, the high number of excess deaths in this group, especially in low-income countries. Inferior diagnostic capabilities, marginalization of their health problems and reduced access to existing medical services during a pandemic particularly hit populations burdened by other health problems that come with age [9].

Summary

The full impact of the COVID-19 pandemic on the world population cannot be measured by the incidence and deaths from the infection alone. One additional parameter, which depends on many different factors, is excess mortality. Proactively searching for the causes of excess mortality is extremely important for any country to detect weaknesses in the organization of the health care system and, at the same time, implement adequate safety mechanisms. Without knowing, analyzing and significantly eliminating risk factors for excess mortality during the current pandemic, we will not avoid increased mortality during other emergencies. Currently, after three years of COVID-19, despite a decrease in the severity of the infection and countries adapting to the new situation, some of them are still recording excess mortality. This may indicate a delayed effect of the pandemic in these countries.

Analysis of excess mortality carries certain limitations, including those related to the quality of the data used to assess them. Death registration systems that function in a limited way do not allow to obtain certain data. In addition to epidemiological data derived from collections of death certificates or statistical codes of disease entities, post-mortem investigations based on analysis of baseline medical data, circumstances of death and post-mortem diagnostic results should be considered on a larger scale. The assessment of excess mortality in the context of the global impact of the COVID-19 pandemic is only an estimate, but nonetheless, the lack of a coherent and consistent epidemiological and clinical strategy; limitations in access to health care and organizational errors; as well as lack of intensive support for groups at high risk of death, can be considered as the main reasons for its occurrence.

date of submission | data nadesłania: **02.07.2023**
acceptance date | data akceptacji: **11.07.2023**

Corresponding author:
Aleksander Zinczuk
Department of Forensic Medicine, Wroclaw Medical University
ul. J. Mikulicza-Radeckiego 4, 50-372 Wrocław, Poland
e-mail: aleksander.zinczuk@student.umw.edu.pl

References

[1] "Pneumonia of unknown cause – China." https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229 (accessed May 11, 2023).

[2] "Archived: WHO Timeline – COVID-19." https://www.who.int/news/item/27-04-2020-who-timeline---covid-19 (accessed May 11, 2023).

[3] "Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)." https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) (accessed May 11, 2023).

[4] X. W. Bian, "Autopsy of COVID-19 patients in China," *Natl Sci Rev*, vol. 7, no. 9, pp. 1414–1418, Sep. 2020, doi: 10.1093/NSR/NWAA123.

[5] R. G. Menezes, T. Rizwan, S. S. Ali, W.Hassan et al., "Postmortem findings in COVID-19 fatalities: A systematic review of current evidence," *Leg Med (Tokyo)*, vol. 54, p. 102001, Feb. 2022, doi: 10.1016/J.LEGALMED.2021.102001.

[6] D. Wichmann, J. P. Sperhake, M. Lutgehetmann, S. Steurer et al., "Autopsy Findings and Venous Thromboembolism in Patients With COVID-19," *https://doi.org/10.7326/M20-2003*, vol. 173, no. 4, pp. 268–277, May 2020, doi: 10.7326/M20-2003.

[7] "The true death toll of COVID-19: estimating global excess mortality." https://www.who.int/data/stories/the-true-death-toll-of-covid-19-estimating-global-excess-mortality (accessed May 09, 2023).

[8] F. Checchi and L. Roberts, "Interpreting and Using Humanitarian Mortality Data in Humanitarian Emergencies. A primer for non-epidemiologists," 2005, Accessed: May 11, 2023. [Online]. Available: www.ennonline.net/mortalitydataprimer

[9] W. Shang, Y. Wang, J. Yuan, Z. Guo et al., "Global Excess Mortality during COVID-19 Pandemic: A Systematic Review and Meta-Analysis," *Vaccines (Basel)*, vol. 10, no. 10, Oct. 2022, doi: 10.3390/VACCINES10101702.

[10] M. Karanikolos and M. Mckee, "HOW COMPARABLE IS COVID-19 MORTALITY ACROSS COUNTRIES?," *Eurohealth (Lond)*, vol. 26, no. 2, 2020.

[11] N. Islam, "'Excess deaths' is the best metric for tracking the pandemic," *BMJ*, vol. 376, 2022.

[12] R. Cruz-Cano and E. L. Mead, "Excess Deaths After Hurricane Maria in Puerto Rico," *JAMA*, vol. 321, no. 10, p. 1005, Mar. 2019, doi: 10.1001/JAMA.2018.20861.

[13] S. Dahal, M. Jenner, L. Dinh, K. Mizumoto et al., "Excess mortality patterns during 1918-1921 influenza pandemic in the state of Arizona, USA," *Ann Epidemiol*, vol. 28, no. 5, pp. 273–280, May 2018, doi: 10.1016/J.ANNEPIDEM.2017.12.005.

[14] J. P. A. Ioannidis, "Over- and under-estimation of COVID-19 deaths," *Eur J Epidemiol*, vol. 36, no. 6, p. 581, Jun. 2021, doi: 10.1007/S10654-021-00787-9.

[15] M. O'Driscoll, G. R. dos Santos, L. Wang, D. A. T. Cummings *et al.*, "Age-specific mortality and immunity patterns of SARS-CoV-2," *Nature*, vol. 590, no. 7844, pp. 140–145, Feb. 2021, doi: 10.1038/S41586-020-2918-0.

[16] R. Horton, "Offline: COVID-19 is not a pandemic," *Lancet*, vol. 396, no. 10255, p. 874, Sep. 2020, doi: 10.1016/S0140-6736(20)32000-6.

[17] "Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21," *Lancet*, vol. 399, no. 10334, pp. 1513–1536, Apr. 2022, doi: 10.1016/S0140-6736(21)02796-3.

[18] "14.9 million excess deaths associated with the COVID-19 pandemic in 2020 and 2021." https://www.who.int/news/item/05-05-2022-14.9-million-excess-deaths-were-associated-with-the-covid-19-pandemic-in-2020-and-2021 (accessed May 12, 2023).

[19] "Excess mortality – statistics – Statistics Explained." https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Excess_mortality_-_statistics#Excess_mortality_in_the_EU_between_January_2020_and_February_2023 (accessed May 12, 2023).

[20] S. Achilleos, A. Quattrocchi, J. Gabel, A. Heraclides *et al.*, "Excess all-cause mortality and COVID-19-related mortality: a temporal analysis in 22 countries, from January until August 2020," *Int J Epidemiol*, vol. 51, no. 1, pp. 35–53, 2022, doi: 10.1093/IJE/DYAB123.

[21] R. Li, S. Pei, B. Chen, Y. Song *et al.*, "Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2)," *Science*, vol. 368, no. 6490, p. 489, May 2020, doi: 10.1126/SCIENCE.ABB3221.

[22] C. Rothe, M. Schunk, P. Sothmann, G. Bretzel *et al.*, "Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany," *New England Journal of Medicine*, vol. 382, no. 10, pp. 970–971, Mar. 2020, doi: 10.1056/NEJMC2001468.

[23] I. C. Álvarez, L. Orea, and A. Wall, "Estimating the propagation of both reported and undocumented COVID-19 cases in Spain: a panel data frontier approximation of epidemiological models," *Journal of Productivity Analysis*, vol. 59, no. 3, p. 259, Jun. 2023, doi: 10.1007/S11123-023-00664-5.

[24] R. K. Biswas, A. Afiaz, and S. Huq, "Underreporting COVID-19: the curious case of the Indian subcontinent," *Epidemiol Infect*, vol. 148, 2020, doi: 10.1017/S0950268820002095.

[25] E. Kupek, "How many more? Under-reporting of the COVID-19 deaths in Brazil in 2020," *Trop Med Int Health*, vol. 26, no. 9, pp. 1019–1028, Sep. 2021, doi: 10.1111/TMI.13628.

[26] N. N. Y. Tsang, H. C. So, K. Y. Ng, B. J. Cowling et al., "Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis," *Lancet Infect Dis*, vol. 21, no. 9, pp. 1233–1245, Sep. 2021, doi: 10.1016/S1473-3099(21)00146-8.

[27] I. Arevalo-Rodriguez, D. Buitrago-Garcia, D. Simancas-Racines, P. Zambrano-Achig *et al.*, "False-negative results of initial RT-PCR assays for COVID-19: A systematic review," *PLoS One*, vol. 15, no. 12, p. e0242958, Dec. 2020, doi: 10.1371/JOURNAL.PONE.0242958.

[28] J. Watson, P. F. Whiting, and J. E. Brush, "Interpreting a covid-19 test result," *BMJ*, vol. 369, May 2020, doi: 10.1136/BMJ.M1808.

[29] J. R. Gill and M. E. Dejoseph, "The Importance of Proper Death Certification during the COVID-19 Pandemic," *JAMA – Journal of the American Medical Association*, vol. 324, no. 1, pp. 27–28, Jul. 2020, doi: 10.1001/jama.2020.9536.

[30] Y. Prkachin, "The Reign of the Ventilator: Acute Respiratory Distress Syndrome, COVID-19, and Technological Imperatives in Intensive Care," *Ann Intern Med*, vol. 174, no. 8, pp. 1145–1150, Aug. 2021, doi: 10.7326/M21-0270.

[31] L. Gattinoni, D. Chiumello, P. Caironi, M. Bussana *et al.*, "COVID-19 pneumonia: different respiratory treatments for different phenotypes?," *Intensive Care Med*, vol. 46, no. 6, pp. 1099–1102, Jun. 2020, doi: 10.1007/s00134-020-06033-2.

[32] C. Axfors, A. M. SchmitT, P. Janiaud, J. van't Hooft *et al.*, "Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials," *Nat Commun*, vol. 12, no. 1, Dec. 2021, doi: 10.1038/S41467-021-22446-Z.

[33] N. Maggialetti, S. Piemonte, E. Sperti, F. Inchingolo *et al.*, "Iatrogenic Barotrauma in COVID-19-Positive Patients: Is It Related to the Pneumonia Severity? Prevalence and Trends of This Complication Over Time," *Biomedicines*, vol. 10, no. 10, Oct. 2022, doi: 10.3390/BIOMEDICINES10102493.

[34] "Therapeutics and COVID-19: Living guideline, 13 January 2023." https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1 (accessed Jul. 02, 2023).

[35] F. Sanmarchi, D. Golinelli, J. Lenzi, F. Esposito *et al.*, "Exploring the Gap Between Excess Mortality and COVID-19 Deaths in 67 Countries," *JAMA Netw Open*, vol. 4, no. 7, pp. e2117359–e2117359, Jul. 2021, doi: 10.1001/JAMANETWORKOPEN.2021.17359.

[36] A. Tzankov and D. Jonigk, "Unlocking the lockdown of science and demystifying COVID-19: how autopsies contribute to our understanding of a deadly pandemic," *Virchows Archiv*, vol. 477, no. 3, p. 331, Sep. 2020, doi: 10.1007/S00428-020-02887-5.

[37] M. Salerno, F. Sessa, A. Piscopo, A. Montana *et al.*, "No Autopsies on COVID-19 Deaths: A Missed Opportunity and the Lockdown of Science," *J Clin Med*, vol. 9, no. 5, May 2020, doi: 10.3390/JCM9051472.

[38] L. A. Mucheleng'anga, V. Telendiy, A. Hamukale, A. L. Shibemba, et al., "COVID-19 and Sudden Unexpected Community Deaths in Lusaka, Zambia, Africa – A Medico-Legal Whole-Body Autopsy Case Series," *Int J Infect Dis*, vol. 109, pp. 160–167, Aug. 2021, doi: 10.1016/J.IJID.2021.07.001.

[39] R. L. Geller, J. N. Aungst, A. Newtion-Levinson, G. P. Smith *et al.*, "Is it COVID-19? The value of medicolegal autopsies during the first year of the COVID-19 pandemic," *Forensic Sci Int*, vol. 330, Jan. 2022, doi: 10.1016/J.FORSCIINT.2021.111106.

[40] C. V. Siserman, I. I. Jeican, D. Gheban, V. Anton *et al.*, "Fatal Form of COVID-19 in a Young Male Bodybuilder Anabolic Steroid Using: The First Autopsied Case," *Medicina (B Aires)*, vol. 58, no. 10, Oct. 2022, doi: 10.3390/MEDICINA58101373.

[41] B. I. B. Lindahl, "COVID-19 and the selection problem in national cause-of-death statistics," *Hist Philos Life Sci*, vol. 43, no. 2, Jun. 2021, doi: 10.1007/S40656-021-00420-8.

[42] T. A. Slater, S. Straw, M. Drozd, S. Kamalathasan et al., "Dying 'due to' or 'with' COVID-19: a cause of death analysis in hospitalised patients," *Clinical Medicine*, vol. 20, no. 5, p. e189, 2020, doi: 10.7861/CLINMED.2020-0440.

[43] M. Bogdanović, T. Atanasijević, V. Popović, Z.Mihailović *et al.*, "Proper death certification in the time of the COVID-19 pandemic: Forensic perspective," *J Infect Dev Ctries*, vol. 16, no. 6, pp. 966–968, Jun. 2022, doi: 10.3855/jidc.16556.

[44] C. Rao, "Medical certification of cause of death for COVID-19," *Bull World Health Organ*, vol. 98, no. 5, May 2020, doi: 10.2471/BLT.20.257600.

[45] T. Nyberg, N. M. Ferguson, S. G. Nash, H. H. Webster *et al.*, "Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study," *Lancet*, vol. 399, no. 10332, pp. 1303–1312, Apr. 2022, doi: 10.1016/S0140-6736(22)00462-7.

[46] L. A. Post and R. Lorenzo-Redondo, "Omicron: fewer adverse outcomes come with new dangers," *The Lancet*, vol. 399, no. 10332, pp. 1280–1281, Apr. 2022, doi: 10.1016/S0140-6736(22)00514-1.

[47] C. Yek, S. Warner, A. Mancera, and S. S. Kadri, "Misclassification bias in estimating clinical severity of SARS-CoV-2 variants," *The Lancet*, vol. 400, no. 10355, p. 809, Sep. 2022, doi: 10.1016/S0140-6736(22)01469-6.

[48] D. Juyal, A. Kumar, S. Pal, S. Thaledi et al., "Medical certification of cause of death during COVID-19 pandemic – a challenging scenario," *J Family Med Prim Care*, vol. 9, no. 12, p. 5896, 2020, doi: 10.4103/JFMPC.JFMPC_1435_20.

[49] J. Poulos, L. Zhu, and A. D. Shah, "Data gaps in electronic health record (EHR) systems: An audit of problem list completeness during the COVID-19 pandemic," *Int J Med Inform*, vol. 150, p. 104452, Jun. 2021, doi: 10.1016/J.IJMEDINF.2021.104452.

[50] L. Mwananyanda, C. J. Gill, W. MacLeod, G. Kwenda *et al.*, "Covid-19 deaths in Africa: prospective systematic postmortem surveillance study," *BMJ*, vol. 372, Feb. 2021, doi: 10.1136/BMJ.N334.

[51] A. V. Gundlapalli, A. M. Lavery, T. G. Boehmer, M.J. Beach *et al.*, "Death Certificate–Based ICD-10 Diagnosis Codes for COVID-19 Mortality Surveillance — United States, January–December 2020," *MMWR Morb Mortal Wkly Rep*, vol. 70, no. 14, pp. 523–527, 2021, doi: 10.15585/MMWR.MM7014E2.

[52] M. P. Walkowiak and D. Walkowiak, "Underestimation in Reporting Excess COVID-19 Death Data in Poland during the First Three Pandemic Waves," *Int J Environ Res Public Health*, vol. 19, no. 6, Mar. 2022, doi: 10.3390/IJERPH19063692.

[53] Y. Ju and M. You, "It's Politics, Isn't It? Investigating Direct and Indirect Influences of Political Orientation on Risk Perception of COVID-19," *Risk Anal*, vol. 42, no. 1, pp. 56–68, Jan. 2022, doi: 10.1111/RISA.13801.

[54] K. T. Paul, J. M. Eberl, and J. Partheymüller, "Policy-Relevant Attitudes Toward COVID-19 Vaccination: Associations With Demography, Health Risk, and Social and Political Factors," *Front Public Health*, vol. 9, Jul. 2021, doi: 10.3389/fpubh.2021.671896.

[55] D. Albrecht, "Vaccination, politics and COVID-19 impacts," *BMC Public Health*, vol. 22, no. 1, Dec. 2022, doi: 10.1186/S12889-021-12432-X.

[56] J. Kerr, C. Panagopoulos, and S. van der Linden, "Political polarization on COVID-19 pandemic response in the United States," *Pers Individ Dif*, vol. 179, Sep. 2021, doi: 10.1016/J.PAID.2021.110892.

[57] R. Parker and D. Ferraz, "Politics and pandemics," *https://doi.org/10.1080/17441692.2021.1947601*, vol. 16, no. 8–9, pp. 1131–1140, 2021, doi: 10.1080/17441692.2021.1947601.

[58] E. M. da Fonseca, N. Nattrass, L. L. B. Lazaro, and F. I. Bastos, "Political discourse, denialism and leadership failure in Brazil's response to COVID-19," *https://doi.org/10.1080/17441692.2021.1945123*, vol. 16, no. 8–9, pp. 1251–1266, 2021, doi: 10.1080/17441692.2021.1945123.

[59] F. Ortega and M. Orsini, "Governing COVID-19 without government in Brazil: Ignorance, neoliberal authoritarianism, and the collapse of public health leadership," *Glob Public Health*, pp. 1257–1277, 2020, doi: 10.1080/17441692.2020.1795223.

[60] S. Crabu, P. Giardullo, A. Sciandra, and F. Neresini, "Politics overwhelms science in the Covid-19 pandemic: Evidence from the whole coverage of the Italian quality newspapers," *PLoS One*, vol. 16, no. 5, May 2021, doi: 10.1371/JOURNAL.PONE.0252034.

[61] F. Sazzad, V. P. Rajan, and M. A. Demircioglu, "The Role of Leadership in Public Sector Innovation: A Systematic Review and Meta-Analysis of the Management of COVID-19 in Asian Countries," *Front Public Health*, vol. 9, p. 743748, Dec. 2021, doi: 10.3389/FPUBH.2021.743748.

[62] S. Talic, S. Shah, H. Wild, D.Gasevic *et al.*, "Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: Systematic review and meta-analysis," *The BMJ*, vol. 375, Nov. 2021, doi: 10.1136/BMJ-2021-068302.

[63] S. Flaxman, S. Mishra, A. Gandy, H. J. T. Unwin *et al.*, "Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe," *Nature*, vol. 584, no. 7820, pp. 257–261, Aug. 2020, doi: 10.1038/S41586-020-2405-7.

[64] F. Zhou, T. J. Hu, X. Y. Zhang, K. Lai et al., "The association of intensity and duration of non-pharmacological interventions and implementation of vaccination with COVID-19 infection, death, and excess mortality: Natural experiment in 22 European countries," *J Infect Public Health*, vol. 15, no. 5, pp. 499–507, May 2022, doi: 10.1016/J.JIPH.2022.03.011.

[65] V. Schwarz, F. Mahfoud, L. Lauder, W. Reith *et al.*, "Decline of emergency admissions for cardiovascular and cerebrovascular events after the outbreak of COVID-19," *Clin Res Cardiol*, vol. 109, no. 12, pp. 1500–1506, Dec. 2020, doi: 10.1007/S00392-020-01688-9.

[66] M. Seiffert, F. J. Brunner, M. Remmel, G. Thomalla *et al.*, "Temporal trends in the presentation of cardiovascular and cerebrovascular emergencies during the COVID-19 pandemic in Germany: an analysis of health insurance claims," *Clinical Research in Cardiology*, vol. 109, no. 12, pp. 1540–1548, Dec. 2020, doi: 10.1007/s00392-020-01723-9.

[67] A. K. Gitt, A. K. Karcher, R. Zahn, and U. Zeymer, "Collateral damage of COVID-19-lockdown in Germany: decline of NSTE-ACS admissions," *Clinical Research in Cardiology*, vol. 109, no. 12, pp. 1585–1587, Dec. 2020, doi: 10.1007/s00392-020-01705-x.

[68] J. Thornton, "Covid-19: A&E visits in England fall by 25% in week after lockdown," *BMJ*, vol. 369, p. m1401, Apr. 2020, doi: 10.1136/BMJ.M1401.

[69] E. Kondilis, F. Tarantilis, and A. Benos, "Essential public healthcare services utilization and excess non-COVID-19 mortality in Greece," *Public Health*, vol. 198, pp. 85–88, Sep. 2021, doi: 10.1016/J.PUHE.2021.06.025.

[70] M. É. Czeisler, K. Marynak, K. E.N. Clarke, Z.Salah *et al.*, "Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns – United States, June 2020," *MMWR Morb Mortal Wkly Rep*, vol. 69, no. 36, pp. 1250–1257, Sep. 2020, doi: 10.15585/MMWR.MM6936A4.

[71] A. Zumla, J. Chakaya, M. Khan, R.Fatima *et al.*, "World Tuberculosis Day 2021 Theme – 'The Clock is Ticking' – and the world is running out of time to deliver the United Nations General Assembly commitments to End TB due to the COVID-19 pandemic," *International Journal of Infectious Diseases*, vol. 113, pp. S1–S6, Dec. 2021, doi: 10.1016/j.ijid.2021.03.046.

[72] World Health Organization, "Annual Report of Tuberculosis," *Annual Global TB Report of WHO*, vol. 8, no. 1, pp. 1–68, 2022, Accessed: May 15, 2023. [Online]. Available: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-re-

port-2022%0Ahttps://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022#:~:text=-context of global...-,Download,-Read More%0Ahtt

[73] A. G. Dinmohamed, O. Visser, R. H. A. Verhoeven, M. V. J. Louwman *et al.*, "Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands," *Lancet Oncol*, vol. 21, no. 6, pp. 750–751, Jun. 2020, doi: 10.1016/S1470-2045(20)30265-5.

[74] D. Schrag, D. L. Hershman, and E. Basch, "Oncology Practice during the COVID-19 Pandemic," *JAMA – Journal of the American Medical Association*, vol. 323, no. 20, pp. 2005–2006, May 2020, doi: 10.1001/JAMA.2020.6236.

[75] D. Bu, "The impact of COVID-19 on Australian cancer screening and strategies to mitigate ongoing disruption of screening services," *Aust J Gen Pract*, vol. 50, pp. 1–2, 2021, doi: 10.31128/AJGP-COVID-50.

[76] F. Teglia, M. Angelini, L. Astolfi, G. Casolari et al., "Global Association of COVID-19 Pandemic Measures With Cancer Screening: A Systematic Review and Meta-analysis," *JAMA Oncol*, vol. 8, no. 9, pp. 1287–1293, Sep. 2022, doi: 10.1001/JAMAONCOL.2022.2617.

[77] F. Teglia, M. Angelini, G. Casolari, L. Astolfi et al., "Global Association of COVID-19 Pandemic Measures with Cancer Treatment: A Systematic Review and Meta-Analysis.," *Cancers (Basel)*, vol. 14, no. 22, Nov. 2022, doi: 10.3390/cancers14225490.

[78] K. Causey, N. Fullman, R. J. D. Sorensen, N. C. Galles *et al.*, "Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study," *The Lancet*, vol. 398, no. 10299, pp. 522–534, Aug. 2021, doi: 10.1016/S0140-6736(21)01337-4.

[79] V. Kumari, K. Mehta, and R. Choudhary, "COVID-19 outbreak and decreased hospitalisation of pregnant women in labour," *Lancet Glob Health*, vol. 8, no. 9, pp. e1116–e1117, Sep. 2020, doi: 10.1016/S2214-109X(20)30319-3.

[80] B. N. Ezenwa, I. B. Fajolu, H. Nabwera, D. Wang, et al., "Impact of COVID-19 lockdown measures on institutional delivery, neonatal admissions and prematurity: a reflection from Lagos, Nigeria," *BMJ Paediatr Open*, vol. 5, no. 1, Apr. 2021, doi: 10.1136/BMJPO-2021-001029.

[81] G. Alicandro, G. Remuzzi, and C. La Vecchia, "Italy's first wave of the COVID-19 pandemic has ended: no excess mortality in May, 2020," *Lancet*, vol. 396, no. 10253, p. e27, Sep. 2020, doi: 10.1016/S0140-6736(20)31865-1.

[82] E. Kontopantelis, M. A. Mamas, J. Deanfield, M. Asaria et al., "Excess mortality in England and Wales during the first wave of the COVID-19 pandemic," *J Epidemiol Community Health (1978)*, vol. 75, no. 3, pp. 213–223, Mar. 2021, doi: 10.1136/JECH-2020-214764.

[83] K. Barański, G. Brożek, M. Kowalska, A. Kaleta-Pilarska et al., "Impact of COVID-19 Pandemic on Total Mortality in Poland," *Int J Environ Res Public Health*, vol. 18, no. 8, Apr. 2021, doi: 10.3390/IJERPH18084388.

[84] A. John, J. Pirkis, D. Gunnell, L. Appleby et al., "Trends in suicide during the covid-19 pandemic," *BMJ*, vol. 371, Nov. 2020, doi: 10.1136/BMJ.M4352.

[85] M. Rezaeiahari and B. J. Fairman, "Impact of COVID-19 on the characteristics of opioid overdose deaths in Arkansas," *Int J Drug Policy*, vol. 109, p. 103836, Nov. 2022, doi: 10.1016/J.DRUGPO.2022.103836.

[86] "Overdose Deaths Accelerating During COVID-19 | CDC Online Newsroom | CDC." https://www.cdc.gov/media/releases/2020/p1218-overdose-deaths-covid-19.html (accessed May 15, 2023).

[87] D. Gunnell, L. Appleby, E. Arensman, K. Hawton *et al.*, "Suicide risk and prevention during the COVID-19 pandemic," *Lancet Psychiatry*, vol. 7, no. 6, pp. 468–471, Jun. 2020, doi: 10.1016/S2215-0366(20)30171-1.

[88] I. M. Wasserman, "The Impact of Epidemic, War, Prohibition and Media on Suicide: United States, 1910–1920," *Suicide Life Threat Behav*, vol. 22, no. 2, pp. 240–254, Jun. 1992, doi: 10.1111/J.1943-278X.1992.TB00231.X.

[89] Y. T. Cheung, P. H. Chau, and P. S. F. Yip, "A revisit on older adults suicides and Severe Acute Respiratory Syndrome (SARS) epidemic in Hong Kong," *Int J Geriatr Psychiatry*, vol. 23, no. 12, pp. 1231–1238, 2008, doi: 10.1002/GPS.2056.

[90] S. M. S. Chan, F. K. H. Chiu, C. W. L. Lam, P. Y. V. Leung et al., "Elderly suicide and the 2003 SARS epidemic in Hong Kong," *Int J Geriatr Psychiatry*, vol. 21, no. 2, pp. 113–118, Feb. 2006, doi: 10.1002/gps.1432.

[91] Y. J. Yasin, M. Grivna, and F. M. Abu-Zidan, "Global impact of COVID-19 pandemic on road traffic collisions," *World Journal of Emergency Surgery*, vol. 16, no. 1, pp. 1–14, Dec. 2021, doi: 10.1186/S13017-021-00395-8/TABLES/2.

[92] S. Parr, B. Wolshon, J. Renne, P. Murray-Tuite, et al., "Traffic impacts of the COVID-19 pandemic: statewide analysis of social separation and activity restriction," *Nat Hazards Rev*, vol. 21, no. 3, p. 04020025, Aug. 2020, doi: 10.1061/(asce)nh.1527-6996.0000409.

[93] M. C. Ramírez-Soto and G. Ortega-Cáceres, "Analysis of Excess All-Cause Mortality and COVID-19 Mortality in Peru: Observational Study," *Trop Med Infect Dis*, vol. 7, no. 3, Mar. 2022, doi: 10.3390/TROPICALMED7030044.

[94] S. Tempia, S. Walaza, J. N. Bhiman, M. L. McMorrow *et al.*, "Decline of influenza and respiratory syncytial virus detection in facility-based surveillance during the COVID-19 pandemic, South Africa, January to October 2020," *Euro Surveill*, vol. 26, no. 29, Jul. 2021, doi: 10.2807/1560-7917.ES.2021.26.29.2001600.

[95] J. H. Kim, Y. H. Roh, J. G. Ahn, M. Y. K. RN *et al.*, "Respiratory syncytial virus and influenza epidemics disappearance in Korea during the 2020-2021 season of COVID-19," *Int J Infect Dis*, vol. 110, pp. 29–35, Sep. 2021, doi: 10.1016/J.IJID.2021.07.005.

[96] N. Spantideas, A. M. Bougea, E. G. Drosou, N. Khanderia et al., "COVID-19 and Seasonal Influenza: No Room for Two," *Cureus*, vol. 13, no. 9, Sep. 2021, doi: 10.7759/CUREUS.18007.

[97] H. Mirza, M. Mirza "Lessons Learned From the COVID-19 Pandemic: Factors Affecting Decreased Incidence of Influenza – PubMed." https://pubmed.ncbi.nlm.nih.gov/36940124/ (accessed May 14, 2023).

[98] V. Rana, M. William, A. Kewalramani, J. Daloya *et al.*, "COVID-19 Mask Mandates in NY and Their Effect on the Incidence of Flu," *J Community Hosp Intern Med Perspect*, vol. 13, no. 1, Jan. 2023, doi: 10.55729/2000-9666.1140.

[99] F. W. S. Ko, L. H. S. Lau, S. S. Ng, T. Ch. F. Yip *et al.*, "Respiratory admissions before and during the COVID-19 pandemic with mediation analysis of air pollutants, mask-wearing and influenza rates," *Respirology*, vol. 28, no. 1, pp. 47–55, Jan. 2023, doi: 10.1111/RESP.14345.

[100] N. Horita and T. Fukumoto, "Two years of the pandemic suppressed deaths from non-COVID-19 respiratory infections: A nationwide surveillance in Japan," *Respirology*, vol. 28, no. 1, pp. 82–83, Jan. 2023, doi: 10.1111/resp.14392.

[101] M. V. W. de Vries and L. Rambabu, "The impact of natural disasters on the spread of COVID-19: a geospatial, agent-based epidemiology model," *Theor Biol Med Model*, vol. 18, no. 1, pp. 1–9, Dec. 2021, doi: 10.1186/S12976-021-00151-0/FIGURES/4.

[102] M. C. Quigley, J. Attanayake, A. King, and F. Prideaux, "A multi-hazards earth science perspective on the COVID-19 pandemic: the potential for concurrent and cascading crises," *Environ Syst Decis*, vol. 40, no. 2, p. 199, Jun. 2020, doi: 10.1007/S10669-020-09772-1.

[103] C. A. Phillips, A. Caldas, R. Cleetus, K. A. Dahl *et al.*, "Compound climate risks in the COVID-19 pandemic," *Nature Climate Change 2020 10:7*, vol. 10, no. 7, pp. 586–588, May 2020, doi: 10.1038/s41558-020-0804-2.

[104] M. E. Kruk, A. D. Gage, N. T. Joseph, G. Danaei et al., "Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries," *The Lancet*, vol. 392, no. 10160, pp. 2203–2212, Nov. 2018, doi: 10.1016/S0140-6736(18)31668-4.

[105] C. R. Wells and A. P. Galvani, "The global impact of disproportionate vaccination coverage on COVID-19 mortality," *Lancet Infect Dis*, vol. 22, no. 9, pp. 1254–1255, Sep. 2022, doi: 10.1016/S1473-3099(22)00417-0.

[106] P. G. T. Walker, Ch. Whittaker, O. J. Watson, M. Baguelin *et al.*, "The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries," *Science*, vol. 369, no. 6502, pp. 413–422, Jul. 2020, doi: 10.1126/SCIENCE.ABC0035.

[107] V. Rios, E. Denova-Gutierrez, and S. Barquera, "Association between living in municipalities with high crowding conditions and poverty and mortality from COVID-19 in Mexico," *PLoS One*, vol. 17, no. 2 Febuary, Feb. 2022, doi: 10.1371/journal.pone.0264137.

[108] N. E. Antonio-Villa, L. Fernandez-Chirino, J. Pisanty-Alatorre, J. Mancilla-Galindo *et al.*, "Comprehensive Evaluation of the Impact of Sociodemographic Inequalities on Adverse Outcomes and Excess Mortality During the Coronavirus Disease 2019 (COVID-19) Pandemic in Mexico City," *Clin Infect Dis*, vol. 74, no. 5, pp. 785–792, Mar. 2022, doi: 10.1093/CID/CIAB577.

[109] S. Jefferies, N. French, Ch. Gilkison, G. Graham *et al.*, "COVID-19 in New Zealand and the impact of the national response: a descriptive epidemiological study," *Lancet Public Health*, vol. 5, no. 11, pp. e612–e623, Nov. 2020, doi: 10.1016/S2468-2667(20)30225-5.

[110] A. Stobart and S. Duckett, "Australia's Response to COVID-19," *Health Econ Policy Law*, vol. 17, no. 1, pp. 95–106, Jan. 2022, doi: 10.1017/S1744133121000244.

[111] T. M. McMichael, S. Clark, S. Pogosjans, M. Kay *et al.*, "COVID-19 in a Long-Term Care Facility — King County, Washington, February 27–March 9, 2020," *Morbidity and Mortality Weekly Report*, vol. 69, no. 12, p. 339, Mar. 2020, doi: 10.15585/MMWR.MM6912E1.

[112] M. He, Y. Li, and F. Fang, "Is There a Link between Nursing Home Reported Quality and COVID-19 Cases? Evidence from California Skilled Nursing Facilities," *J Am Med Dir Assoc*, vol. 21, no. 7, pp. 905–908, Jul. 2020, doi: 10.1016/j.jamda.2020.06.016.

[113] R. T. Konetzka, E. M. White, A. Pralea, D. C. Grabowski et al., "A systematic review of long-term care facility characteristics associated with COVID-19 outcomes," *J Am Geriatr Soc*, vol. 69, no. 10, pp. 2766–2777, Oct. 2021, doi: 10.1111/JGS.17434.

[114] L. Sempé, P. Lloyd-Sherlock, R. Martínez, S. Ebrahim et al., "Estimation of all-cause excess mortality by age-specific mortality patterns for countries with incomplete vital statistics: a population-based study of the case of Peru during the first wave of the COVID-19 pandemic," *The Lancet Regional Health – Americas*, vol. 2, Oct. 2021, doi: 10.1016/j.lana.2021.100039.

[115] M. A. Sinnathamby, H. Whitaker, L. Coughlan, J. L. Bernal et al., "All-cause excess mortality observed by age group and regions in the first wave of the COVID-19 pandemic in England," *Euro Surveill*, vol. 25, no. 28, Jul. 2020, doi: 10.2807/1560-7917.ES.2020.25.28.2001239.

[116] M. Cobos-Siles, P. Cubero-Morais, I. Arroyo-Jimenez, M. Rey-Hernandez *et al.*, "Cause-specific death in hospitalized individuals infected with SARS-CoV-2: more than just acute respiratory failure or thromboembolic events," *Intern Emerg Med*, vol. 15, no. 8, p. 1533, Nov. 2020, doi: 10.1007/S11739-020-02485-Y.

XII. Załączniki

a. Oświadczenia współautorów publikacji

Dr hab. n. med. Tomasz Jurek, prof. UMW
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2022). EASIX, modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients. Journal of Personalized Medicine, 2022, 12 (7), 1022.

mój udział polegał na opracowaniu metodologii, uczestnictwie w stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji; krytycznej ocenie pracy.

Podpis

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
kierownik

dr hab. n. med. Tomasz Jurek, prof. nadzw.

Dr hab. n. med. Tomasz Jurek, prof. UMW
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

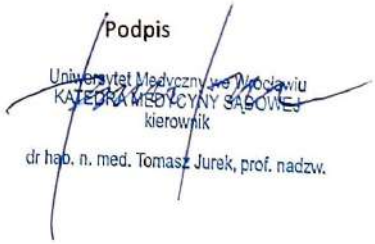
OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2023). Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors – a single-center, retrospective analysis of the first two years of the pandemic. Viruses, 2023, 15 (7), 1430.

mój udział polegał na opracowaniu metodologii, uczestnictwie w stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji; krytycznej ocenie pracy.

Podpis



Dr hab. n. med. Tomasz Jurek, prof. UMW
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Jurek T. (2023). COVID-19 – related excess mortality – an overview of the current evidence. Archiwum Medycyny Sądowej i Kryminologii, 2023, 73 (1), 33-44.

mój udział polegał na stworzeniu koncepcji pracy, opracowaniu metodologii, uczestnictwie w stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji; krytycznej ocenie pracy.

Podpis

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
Kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

Dr hab. n. med. Marta Rorat
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2022). EASIX, modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients. Journal of Personalized Medicine, 2022, 12 (7), 1022.

mój udział polegał na stworzeniu koncepcji pracy, opracowaniu metodologii, uczestnictwie w stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji oraz krytycznej ocenie pracy.

Uniwersytet Medyczny we Wrocławiu
Katedra Medycyny Sądowej
ZAKŁAD PRAWA MEDYCZNEGO
p.o. kierownik
dr hab. n. med., mgr prawa Marta Rorat
Podpis

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

Dr hab. n. med. Marta Rorat
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2023). Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors – a single-center, retrospective analysis of the first two years of the pandemic. Viruses, 2023, 15 (7), 1430.

mój udział polegał na stworzeniu koncepcji pracy, opracowaniu metodologii, stworzeniu bazy danych, opracowaniu wyników, uczestnictwie w stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji oraz krytycznej ocenie pracy.

Uniwersytet Medyczny we Wrocławiu
Katedra Medycyny Sądowej
ZAKŁAD PRAWA MEDYCZNEGO
p.o. kierownik
Podpis
dr hab. n. med., mgr prawa Marta Rorat

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

Dr hab. n. med. Marta Rorat
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Jurek T. (2023). COVID-19 – related excess mortality – an overview of the current evidence. Archiwum Medycyny Sądowej i Kryminologii, 2023, 73 (1), 33-44.

mój udział polegał na nadzorze nad prowadzoną pracą, stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji.

Uniwersytet Medyczny we Wrocławiu
Katedra Medycyny Sądowej
ZAKŁAD PRAWA MEDYCZNEGO
p.o. kierownik
Podpis
dr hab. n. med., mgr prawa Marta Rorat

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

Prof. dr hab. n. med. Krzysztof Simon
Klinika Chorób Zakaźnych i Hepatologii
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2022). EASIX, modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients. Journal of Personalized Medicine, 2022, 12 (7), 1022.

mój udział polegał na uczestnictwie w stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji.

Podpis

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY RODZINNEJ
kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

Uniwersytet Medyczny we Wrocławiu
KLINIKA CHORÓB ZAKAŹNYCH I HEPATOLOGII
kierownik
prof. dr hab. n. med. Krzysztof Simon

Prof. dr hab. n. med. Krzysztof Simon
Klinika Chorób Zakaźnych i Hepatologii
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 29.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2023). Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors – a single-center, retrospective analysis of the first two years of the pandemic. Viruses, 2023, 15 (7), 1430.

mój udział polegał na uczestnictwie w stworzeniu ostatecznej wersji manuskryptu, jego recenzji i edycji.

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

Podpis

Uniwersytet Medyczny we Wrocławiu
KLINIKA CHORÓB ZAKAŹNYCH
I HEPATOLOGII
kierownik
prof. dr hab. n. med. Krzysztof Simon

Lek. Aleksander Zińczuk
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 28.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2022). EASIX, modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients. Journal of Personalized Medicine, 2022, 12 (7), 1022.

mój udział polegał na głównej roli w stworzeniu koncepcji pracy, metodologii, bazy danych oraz opracowaniu wyników, stworzeniu pierwotnej i ostatecznej wersji manuskryptu.

Podpis

Aleksander Zińczuk

Potwierdzam

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
Kierownik

dr hab. n. med. Tomasz Jurek, prof. nadzw.

Lek. Aleksander Zińczuk
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 28.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Simon K., Jurek T. (2023). Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors – a single-center, retrospective analysis of the first two years of the pandemic. Viruses, 2023, 15 (7), 1430.

mój udział polegał na głównej roli w stworzeniu koncepcji pracy, metodologii, bazy danych oraz opracowaniu wyników, stworzeniu pierwotnej i ostatecznej wersji manuskryptu.

Podpis

Aleksander Zińczuk

potwierdzam

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
Kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

Lek. Aleksander Zińczuk
Katedra Medycyny Sądowej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

Wrocław, 28.08.2023 r.

OŚWIADCZENIE

Oświadczam, że w pracy:

Zińczuk A., Rorat M., Jurek T. (2023). COVID-19 – related excess mortality – an overview of the current evidence. Archiwum Medycyny Sądowej i Kryminologii, 2023, 73 (1), 33-44.

mój udział polegał na głównej roli w stworzeniu koncepcji pracy, metodologii oraz opracowaniu wyników, stworzeniu pierwotnej i ostatecznej wersji manuskryptu.

Podpis

Aleksander Zińczuk

Uniwersytet Medyczny we Wrocławiu
KATEDRA MEDYCYNY SĄDOWEJ
kierownik
dr hab. n. med. Tomasz Jurek, prof. nadzw.

b. Nota biograficzna autora

Autor rozprawy doktorskiej – Aleksander Zińczuk, urodził się 24 stycznia 1991 r. we Wrocławiu. W 2016 r. ukończył studia na Wydziale Lekarskim Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu i uzyskał tytuł lekarza. W 2017 r. rozpoczął specjalizację w trybie rezydenckim w dziedzinie chorób zakaźnych, realizowaną w I Oddziale Chorób Zakaźnych Wojewódzkiego Szpitala Specjalistycznego im. J. Gromkowskiego we Wrocławiu. W kwietniu 2022 r. zdał Państwowy Egzamin Specjalizacyjny z najlepszym wynikiem z przedmiotu w sesji. W grudniu 2022 r. uzyskał tytuł specjalisty chorób zakaźnych. Od października 2019 r. jest doktorantem Katedry Medycyny Sądowej - uczestnikiem Szkoły Doktorskiej Uniwersytetu Medycznego we Wrocławiu. Doświadczenie zawodowe zdobywał w ramach licznych konferencji i warsztatów o zasięgu krajowym i międzynarodowym, w tym także jako uczestnik Projektu „Dolnośląscy Liderzy Medycyny" w edycji 2020/2021. Jest członkiem Polskiego Towarzystwa Epidemiologów i Lekarzy Chorób Zakaźnych, Polskiego Towarzystwa Naukowego AIDS, Polskiego Towarzystwa Hepatologicznego, Polskiego Towarzystwa Wakcynologii oraz Polskiego Towarzystwa Medycyny Morskiej, Tropikalnej i Podróży.

c. Wykaz publikacji autora

Aleksander Zińczuk

1. Publikacje w czasopismach naukowych

1.1 Publikacje w czasopiśmie z IF

Lp.	Opis bibliograficzny	IF	Punkty
1	Biernat Monika M., **Zińczuk Aleksander**, Biernat Paweł, Bogucka-Fedorczuk Aleksandra, Kwiatkowski Jacek, Kalicińska Elżbieta, Marciniak Dominik, Simon Krzysztof, Wróbel Tomasz: Nosocomial outbreak of SARS-CoV-2 infection in a haematological unit - High mortality rate in infected patients with haematologic malignancies, Journal of Clinical Virology, 2020, vol. 130, art.104574 [10 s.], DOI:10.1016/j.jcv.2020.104574	3,168	100
2	Pazgan-Simon Monika, Rorat Marta, Buczyńska Iwona, **Zińczuk Aleksander**, Simon Krzysztof: Gastrointestinal symptoms as the first, atypical indication of severe acute respiratory syndrome coronavirus 2 infection, Polskie Archiwum Medycyny Wewnętrznej, 2020, vol. 130, nr 4, s. 338-339, DOI:10.20452/pamw.15278	3,277	140
3	Rorat Marta, **Zińczuk Aleksander**, Szymański Wojciech, Simon Krzysztof, Guziński Maciej: Usefulness of a portable chest radiograph in the initial diagnosis of coronavirus disease 2019, Polskie Archiwum Medycyny Wewnętrznej, 2020, vol. 130, nr 10, s. 906-909, DOI:10.20452/pamw.15512	3,277	140
4	Kalicińska Elżbieta, Szymczak Donata, **Zińczuk Aleksander**, Adamik Barbara, Śmiechowicz Jakub, Skalec Tomasz, Nowicka-Suszko Danuta, Biernat Monika, Bogucka-Fedorczuk Aleksandra, Rybka Justyna, Martuszewski Adrian, Goździk Waldemar, Simon Krzysztof, Wróbel Tomasz: Immunosuppression as a hallmark of critical COVID-19: prospective study, Cells, 2021, vol. 10, nr 6, art.1293 [13 s.], DOI:10.3390/cells10061293	7,666	140
5	Kalicińska Elżbieta, Biernat Monika, Rybka Justyna, **Zińczuk Aleksander**, Janocha-Litwin Justyna, Rosiek-Biegus Marta, Morawska Marta, Waszczuk-Gajda Anna, Drozd-Sokołowska Joanna, Szukalski Łukasz, Rymko Marcin, Jabłonowska Paula, Simon Krzysztof, Wróbel Tomasz: Endothelial activation and stress index (EASIX) as an early predictor for mortality and overall survival in hematological and non-hematological patients with COVID-19: multicenter cohort study, Journal of Clinical Medicine, 2021, vol. 10, nr 19, art.4373 [16 s.], DOI:10.3390/jcm10194373	4,964	140
6	Kalicińska Elżbieta, Szymczak Donata, Andrasiak Iga, Bogucka-Fedorczuk Aleksandra, **Zińczuk Aleksander**, Szymański Wojciech, Biernat Monika, Rymko Marcin, Semeńczuk Grażyna, Jabłonowska Paula, Rybka Justyna, Simon Krzysztof, Wróbel Tomasz: Lymphocyte subsets in haematological patients with COVID-19: multicentre prospective study, Translational Oncology, 2021, vol. 14, nr 1, art.100943 [10 s.], DOI:10.1016/j.tranon.2020.100943	4,803	100
7	**Zińczuk Aleksander**, Rorat Marta, Simon Krzysztof, Jurek Tomasz: EASIX, modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients, Journal of Personalized Medicine, 2022, vol. 12, nr 7, art.1022 [14 s.], DOI:10.3390/jpm12071022	3,4	70
8	Janocha-Litwin Justyna, **Zińczuk Aleksander**, Serafińska Sylwia, Szymanek-Pasternak Anna, Simon Krzysztof: Analysis of deaths among HIV-infected patients hospitalized in 2009-2018 in Main Centre of Infectious Disease in Region of Lower Silesia in Poland, detailing lesions in the central nervous system, Medicina, 2022, vol. 58, nr 2, art.270 [10 s.], DOI:10.3390/medicina58020270	2,6	40

9	**Zińczuk Aleksander**, Rorat Marta, Simon Krzysztof, Jurek Tomasz: Unpacking the complexity of COVID-19 fatalities: adverse events as contributing factors - a single-center, retrospective analysis of the first two years of the pandemic, Viruses-Basel, 2023, vol. 15, nr 7, art.1430 [17 s.], DOI:10.3390/v15071430	4,7	100
	Podsumowanie	37,855	970

1.2 Publikacje w czasopiśmie bez IF

Lp.	Opis bibliograficzny	Punkty
1	**Zińczuk Aleksander**, Janocha-Litwin Justyna, Rostkowska Karolina, Simon Krzysztof: Pozawątrobowe manifestacje zakażenia wirusem zapalenia wątroby typu C - epidemiologia, patofizjologia i leczenie, Medical Science Review -Hepatologia, 2018, vol. 18, s. 28-36, [Publikacja w czasopiśmie spoza listy MNiSW], DOI:10.5114/hepatologia.2018.75977	1
2	Janocha-Litwin Justyna, **Zińczuk Aleksander**, Czarnecki Marcin, Simon Krzysztof: Manifestacje pozawątrobowe zakażenia HBV - patogeneza, epidemiologia i leczenie, Medical Science Review -Hepatologia, 2018, vol. 18, s. 37-46, [Publikacja w czasopiśmie spoza listy MNiSW], DOI:10.5114/hepatologia.2018.75978	1
3	**Zińczuk Aleksander**, Janocha-Litwin Justyna, Simon Krzysztof: Nieinwazyjne metody oceny nadciśnienia wrotnego, Medical Science Review -Hepatologia, 2019, vol. 19, s. 128-132, [Publikacja w czasopiśmie spoza listy MNiSW]	5
	Podsumowanie	7

1.3 Publikacje w czasopiśmie - prace kontrybutorskie -

2. Monografie naukowe

2.1 Książka autorska

2.2 Książka redagowana

2.3 Rozdziały

Lp.	Opis bibliograficzny	Punkty
1	**Zińczuk Aleksander**, Janocha-Litwin Justyna: Tularemia - epidemiologia, obraz kliniczny, diagnostyka, leczenie : opis przypadku, W: Choroby odkleszczowe, (red.) Krzysztof Simon, Sylwia Serafińska, Wrocław 2018, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 79-92, ISBN 978-83-65071-34-7, [Publikacja w wydawnictwie spoza listy MNiSW]	5
2	Janocha-Litwin Justyna, **Zińczuk Aleksander**: Żółta gorączka, W: Medycyna podróży w teorii i praktyce, (red.) Krzysztof Simon, Justyna Janocha-Litwin, Wrocław 2018, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 279-295, ISBN 978-83-65071-37-8, [Publikacja w wydawnictwie spoza listy MNiSW]	5
3	**Zińczuk Aleksander**, Janocha-Litwin Justyna, Simon Krzysztof: Wirus Ebola, W: Medycyna podróży w teorii i praktyce, (red.) Krzysztof Simon, Justyna Janocha-Litwin, Wrocław 2018, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 63-87, ISBN 978-83-65071-37-8, [Publikacja w wydawnictwie spoza listy MNiSW]	5
4	Janocha-Litwin Justyna, Serafińska Sylwia, **Zińczuk Aleksander**, Simon Krzysztof: Nowoczesne terapie przewlekłego wirusowego zapalenia wątroby typu C, W: Postępy i kontrowersje w farmakoterapii, (red.) Dorota Ksiądzyna, Wrocław 2018, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 143-169, ISBN 978-83-65071-36-1, [Publikacja w wydawnictwie spoza listy MNiSW]	5

5	Janocha-Litwin Justyna, **Zińczuk Aleksander**, Simon Krzysztof: Kleszczowe zapalenie mózgu - wstępne dane epidemiologiczne pacjentów hospitalizowanych w latach 1998-2018 w oddziałach zakaźnych we Wrocławiu : opis przypadków, W: Choroby odkleszczowe, (red.) Krzysztof Simon, Sylwia Serafińska, Wyd.2 zaktual., popr. i uzup., Wrocław 2019, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 173-179, ISBN 978-83-65071-40-8	0
6	**Zińczuk Aleksander**, Janocha-Litwin Justyna: Tularemia - epidemiologia, obraz kliniczny, diagnostyka, leczenie : opis przypadku, W: Choroby odkleszczowe, (red.) Krzysztof Simon, Sylwia Serafińska, Wyd.2 zaktual., popr. i uzup., Wrocław 2019, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 79-93, ISBN 978-83-65071-40-8	0
7	Janocha-Litwin Justyna, **Zińczuk Aleksander**: Żółta gorączka, W: Medycyna podróży w teorii i praktyce, (red.) Krzysztof Simon, Justyna Janocha-Litwin, Wyd.2 uzup., popr. i poszerz., Wrocław 2019, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 247-263, ISBN 978-83-65071-44-6	0
8	**Zińczuk Aleksander**, Janocha-Litwin Justyna: Holiday PrEP, W: Medycyna podróży w teorii i praktyce, (red.) Krzysztof Simon, Justyna Janocha-Litwin, Wyd.2 uzup., popr. i poszerz., Wrocław 2019, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 299-308, ISBN 978-83-65071-44-6	0
9	**Zińczuk Aleksander**, Janocha-Litwin Justyna, Simon Krzysztof: Wirus Ebola, W: Medycyna podróży w teorii i praktyce, (red.) Krzysztof Simon, Justyna Janocha-Litwin, Wyd.2 uzup., popr. i poszerz., Wrocław 2019, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 63-81, ISBN 978-83-65071-44-6	0
10	**Zińczuk Aleksander**, Janocha-Litwin Justyna: Hiponatremia w marskości wątroby, W: Zaawansowane choroby wątroby : patofizjologia, obraz kliniczny i leczenie, (red.) Monika Pazgan-Simon, Krzysztof Simon, Wrocław 2019, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 143-154, ISBN 978-83-65071-41-5, [Publikacja w wydawnictwie spoza listy MNiSW]	5
11	Janocha-Litwin Justyna, Szymanek-Pasternak Anna, **Zińczuk Aleksander**, Simon Krzysztof: Zespół wątrobowo-nerkowy, W: Zaawansowane choroby wątroby : patofizjologia, obraz kliniczny i leczenie, (red.) Monika Pazgan-Simon, Krzysztof Simon, Wrocław 2019, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 227-240, ISBN 978-83-65071-41-5, [Publikacja w wydawnictwie spoza listy MNiSW]	5
12	Janocha-Litwin Justyna, **Zińczuk Aleksander**: Żółta gorączka, W: Choroby zakaźne i pasożytnicze. T. 3, (red.) Robert Flisiak, Lublin 2020, Wydawnictwo Czelej, s. 846-853, ISBN 978-83-7563-290-3, [Publikacja w wydawnictwie spoza listy MNiSW]	5
13	**Zińczuk Aleksander**: Zakażenia bakteryjne - bakterie Gram-dodatnie, W: Choroby zakaźne u pacjentów leczonych onkologicznie, (red.) Krzysztof Simon, Marta Kucharska, Poznań 2020, Termedia sp. z o.o., s. 29-45, ISBN 978-83-7988-351-6	20
14	**Zińczuk Aleksander**: Gruźlica i mykobakteriozy, W: Choroby zakaźne u pacjentów leczonych onkologicznie, (red.) Krzysztof Simon, Marta Kucharska, Poznań 2020, Termedia sp. z o.o., s. 72-91, ISBN 978-83-7988-351-6	20
15	**Zińczuk Aleksander**: Szczepienie przeciwko kleszczowemu zapaleniu mózgu (KZM), W: Szczepienia dorosłych w praktyce, (red.) Anna Szymanek-Pasternak, Krzysztof Simon, Wrocław 2020, Wrocławskie Wydawnictwo Naukowe Atla 2, s. 215-221, ISBN 978-83-65071-47-7, [Publikacja w wydawnictwie spoza listy MNiSW]	5
	Podsumowanie	80

3 Abstrakty

Lp.	Opis bibliograficzny
1	**Zińczuk Aleksander**: Co gryzie Polaków - czyli kiedy myśleć o profilaktyce wścieklizny, folklor w chorobach zakaźnych, W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 15-17.11.2019. Księga abstraktów, Wrocław 2019, s. 13
2	Janocha-Litwin Justyna, Szymanek-Pasternak Anna, **Zińczuk Aleksander**, Simon Krzysztof: Liver complication as a cause of death in HIV-infected patients hospitalized in 2009-2018 in main centre of

	infectious disease in region of Lower Silesia in Poland, Reviews in Antiviral Therapy & Infectious Diseases, 2019, nr 9, 32 poz.30, [5th Central and Eastern European Meeting on Viral Hepatitis and HIV. Vilnius, Lithuania, 9-20 September 2019. Abstract book]
3	**Zińczuk Aleksander**, Rorat Marta, Jurek Tomasz: Sepsa w podstawowej opiece zdrowotnej - zgony możliwe do uniknięcia, W: VIII Kongres Polskiego Towarzystwa Medycyny Rodzinnej. Wrocław, 11-13 października 2019 r. Streszczenia prac plakatowych [online] 2019, s. 8

Impact factor: 37,855

Punkty ministerialne: 1057,0

Przyjęte do druku

1. **Aleksander Zińczuk**, Marta Rorat, Tomasz Jurek. COVID-19 - related excess mortality - an overview of current evidence. Archiwum Medycyny Sądowej i Kryminologii [2023, 23 vol.1] DOI: 10.4467/16891716AMSIK.22.004.18214
Punkty ministerialne: 70,0

23.08.23r. Beata Majewska

Uniwersytet Medyczny we Wrocławiu
Biblioteka Główna
DZIAŁ BIBLIOGRAFII I BIBLIOMETRII
ul. Marcinkowskiego 2-6, 50-368 Wrocław
tel. 71 784 19 25