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# OH&RM ONE HEALTH & RISK MANAGEMENT

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The Moldovan Association for Biosafety and Biosecurity (MDBBA) is a scientific and practical, instructive and educational, non-governmental, apolitical and non-profit professional organization, founded in 2017.

The main objective of the association is the development of good practices and culture in the field of biosafety and biosecurity and the promotion of knowledge within professional and research-innovation groups.

**BIOSAFETY** includes security principles, technologies and rules to be followed to prevent unintended exposure to pathogens and toxins or their accidental release/ leakage.

*"Protection of personnel, population from unintended exposure to pathogens/ biohazardous material".*

**BIOSECURITY** includes a wide spectrum of measures (biosecurity policies, regulatory regime, scientific and technical measures) applied in an organized framework, necessary to minimize risks (prevention of actions, terrorist attacks by the intentional release of pathogens or toxins as well as loss, their theft or misuse).

*"Protection and prevention of theft, intentional misuse of pathologies/biohazardous material".*

**RISK MANAGEMENT** is a decision-making process in which the results of risk assessment (the process of estimating workplace hazards) are integrated with economic, technical, social and political principles to generate strategies for risk reduction.

One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems.

It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent.

While health, food, water, energy and environment are all wider topics with sector-specific concerns, the collaboration across sectors and disciplines contributes to protect health, address health challenges such as the emergence of infectious diseases, antimicrobial resistance, and food safety and promote the health and integrity of our ecosystems.

By linking humans, animals and the environment, One Health can help to address the full spectrum of disease control – from prevention to detection, preparedness, response and management – and contribute to global health security.

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# Strengthening Viral Hepatitis Prevention and Control Through a One Health Approach

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*Viral hepatitis remains a major global health challenge. The WHO Global Hepatitis Report 2024 estimates that 254 million people are living with hepatitis B, and 50 million people have hepatitis C worldwide. Hepatitis B and hepatitis C are deadly communicable diseases, with 2.2 million new infections recorded in 2022.*

*Global prevalence of hepatitis A, hepatitis D, and hepatitis E varies by region and risk factors. Hepatitis A and hepatitis E are transmitted through contaminated food and water, while hepatitis D occurs only in individuals already infected with hepatitis B or newly infected with hepatitis B and hepatitis D concurrently. The zoonotic nature of hepatitis E has been observed in industrialized and middle-income countries, and the One Health approach, recognizing the interdependence of human, animal, and environmental health, provides a valuable framework for tackling this infection.*

*Laboratory diagnostics play a central role in early detection, prevention, control, and elimination through timely vaccination and treatment. Leveraging One Health infrastructure catalyzes the laboratory potential. New serodiagnostic platforms and Point-of-Care (POC) testing facilitate more efficient decentralized screening, enhancing public health efforts in prevention, control, and elimination. Advanced molecular characterization and surveillance improve viral identification and resistance profiling.*

*The One Health and Risk Management framework fosters informed decision-making through multidisciplinary research, case studies, and surveillance strategies.*

*I commend the editorial team and contributors, and urge continued collaboration between laboratories, academia, clinicians, and public health authorities. Only through joint, evidence-based efforts can we advance the fight against viral hepatitis.*

**Disclaimer:** The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

*Dr. Jan Drobeniuc*

## SYNTHESIS ARTICLE – ARTICLES DE SYNTHÈSE

MEDICAL SCIENCES

OPEN ACCESS

# LONG COVID: CHALLENGES AND COMPLICATIONS – A SYSTEMATIC REVIEW

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## ABSTRACT

**Introduction** Long COVID, a condition that follows the acute phase of COVID-19, presents diverse clinical, psychological, and socioeconomic challenges, with complications such as fatigue, cognitive impairment, musculoskeletal issues, and mental health conditions. Despite its impact, the burden of long COVID symptoms on public health remains underexplored. This systematic review synthesizes current evidence on the complications and challenges of long COVID to inform healthcare providers and policymakers.

**Material and methods** A systematic literature search was conducted using PubMed and Scopus databases for studies published between January 2020 and August 2024. Articles were selected based on inclusion criteria, including both qualitative and quantitative studies. The review adhered to PRISMA guidelines, and the risk of bias was assessed using the NIHR risk-of-bias tool.

**Results** A total of 23 studies from 17 countries were included. Findings presented a multifaceted burden, with physical symptoms such as fatigue (5.5%–84.4%), brain fog (67%), headaches (5%–76.6%) and sleep disturbances (22%–60.9%). Psychological impacts were also prominent, with anxiety and depression frequently reported. Socioeconomic consequences were substantial, with up to 42.3% of individuals unable to return to work.

**Conclusions** Long COVID poses significant challenges to individuals and public health systems. Despite emerging insights, there are substantial gaps in understanding and managing long COVID, underscoring the need for further research and comprehensive healthcare strategies.

**Keywords** Long COVID, Post COVID-19 Syndrome, Post SARS-CoV2, COVID-19.

## SINDROMUL POST-COVID: PROVOCĂRI ȘI COMPLICAȚII – O REVIZUIRE SISTEMATICĂ

**Introducere** Sindromul post-COVID, o afecțiune care survine după faza acută a COVID-19, presupune diverse provocări clinice, psihologice și socioeconomice, incluzând complicații precum oboseala, tulburările cognitive, problemele musculo-scheletale și afecțiunile de sănătate mintală. În pofida impactului său, manifestarea simptomelor asociate sindromului post-COVID asupra sănătății publice rămâne insuficient investigată. Această revizuire sistematică sintetizează dovezile actuale privind complicațiile și provocările sindromului post-COVID și a fost realizată cu scopul de a informa cadrele medicale și factorii de decizie.

**Material și metode** A fost realizată o cercetare sistematică a literaturii în bazele de date PubMed și Scopus pentru studii publicate între ianuarie 2020 și august 2024. Articolele au fost selectate pe baza unor criterii de includere, fiind luate în considerare atât studii calitative, cât și cantitative. Revizuirea a respectat ghidul PRISMA, iar riscul de biais a fost evaluat utilizând instrumentul de estimare a riscului de biais al NIHR.

**Rezultate** Cercetarea a inclus 23 de studii din 17 țări. Rezultatele au relevat un profil simptomatic complex: oboseală (5,5%–84,4%), disfuncții cognitive (67%), cefalee (5%–76,6%) și tulburările de somn (22%–60,9%). Impactul psihologic a fost de asemenea semnificativ, anxietatea și depresia fiind raportate frecvent. Consecințele socioeconomice au fost considerabile, până la 42,3% dintre persoane neputând să revină la muncă.

**Concluzii** Sindromul post-COVID reprezintă o provocare serioasă atât pentru un individ luat în parte, cât și pentru întreg sistemul de sănătate publică. În pofida progreselor înregistrate, ne confruntăm încă cu lacune semnificative în domeniul conștientizării și gestionării acestei afecțiuni. Acest fapt evedențiază necesitatea desfășurării unor cercetări suplimentare și a elaborării unor strategii de îngrijire complexe.

**Cuvinte-cheie** Long COVID, Sindrom post-COVID-19, Post SARS-CoV-2, COVID-19.

## INTRODUCTION

The world faced an unprecedented challenge due to the emergence of the COVID-19 pandemic, which led to increased morbidity and mortality. The COVID-19 disease was caused by the novel severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-Cov-2) (1). COVID-19 presented with a wide array of manifestations, with most cases being a mild infection (80%). However, 20% of infected patients could develop severe disease, and 5% may become critically ill and develop pneumonia or acute respiratory distress syndrome, thus necessitating mechanical ventilation and intensive care unit hospitalization (2). COVID-19 patients with accompanying comorbid ailments (hypertension, diabetes mellitus, cardiac/renal disorders, etc.) were most vulnerable to developing life-threatening complications (septic shock, acute respiratory distress syndrome, etc.), finally resulting in the patient's death (3). Long COVID posed a new problem as the globe struggled to deal with the fallout from this unprecedented public health emergency. It was in the Spring of 2020 that the term Long COVID was described by patients who were not recovering from the acute COVID-19 infection (4). After the initial acute infection, like many other viral disorders, a multitude of long-lasting symptoms had been described. A provisional definition would be persistent symptoms and potential sequelae beyond four weeks from onset, of which the main features are breathlessness, cognitive impairment, fatigue, anxiety and depression (5). The often mentioned "brain fog" is characterized by difficulties with concentration, memory and executive function (6). Post-viral syndrome is more common in depressed patients but can occur after a number of viral infections, for example EBV, HSV and HTLV (7). Globally, these manifestations have had a substantial influence on people's everyday functioning and quality of life. The World Health Organization has defined long COVID as the emergence or persistence of new symptoms three months following the original SARS-Cov-2 infection, and these symptoms must last for at least two months with the absence of an alternate diagnosis (8). As per existing research, the total anticipated cost in the United States alone by autumn of 2021 from direct economic losses combined with COVID-19-related mortality, morbidity, and relative mental health effects was $16 trillion (9).
Within two years of the pandemic's onset, extensive information was gathered on the effects of long COVID, its treatment, and prevention strategies (10). However, the exact nature and its burden of long COVID symptoms on public health is not investigated widely. With the increasing number of patients across the world witnessing prolonged symptoms and complications due to Coronavirus disease, we conducted this systematic review to provide a thorough overview of the disease by synthesizing the available data on the challenges and complications associated with long-COVID. This review aims to identify the most common clinical complications and challenges associated with long COVID across global populations.

## MATERIAL AND METHODS

### SEARCH STRATEGY

The systematic review of literature was conducted using the 2020 Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) guidelines and was registered with the Prospective Register of Systematic Reviews (PROSPERO). The registration ID of this review is CRD42024578106, and it can be accessed at https://www.crd.york.ac.uk/prospero/#myprospero. The PRISMA guidelines includes a 27-item checklist which attests to transparency, iteration and complete reporting for systematic reviews. The literature search was conducted on PubMed and Scopus databases. We used the following Medical Subject Headings (Mesh) terms for

our literature search – "challenges" OR "complications" (Subheading) AND "Post-Acute COVID-19 Syndrome"(Mesh). We also assessed the references of the selected articles to ensure that no study is missed while doing the initial searches.

## ELIGIBILITY CRITERIA:

This systematic review considered as inclusion and exclusion criteria the following items:

**Inclusion Criteria**

- Studies published in English language;
- Studies discussing the challenges and complications of long COVID/post COVID-19 syndrome;
- Qualitative and Quantitative studies;
- Studies published since January 2020 to August 2024.

**Exclusion Criteria**

- Studies focusing on acute COVID-19;
- Studies published in languages other than English;
- Review articles, Systematic reviews, Case series/reports, commentaries not reporting primary findings were excluded;
- Studies discussing only about a particular challenge or complication of long-COVID with a disease condition;
- Studies that hypothesize post-COVID-19 sequelae.

## STUDY SELECTION

Two independent researchers conducted the literature search in August 2024 using specified inclusion and exclusion criteria. In the initial stage, literature studies were screened on the basis of title and abstracts. Further, an in-depth review of the selected studies was performed to assess their eligibility for this review based on the inclusion criteria. The studies which had discussed about challenges and complications of long COVID were included in this review and independently analyzed by two researchers. Any disagreements among the researchers were settled by careful deliberation; if agreement could not be reached, the principal investigator, a third researcher, was consulted to make the final decision.

## DATA EXTRACTION

The findings from each of the selected studies were compiled into Microsoft Excel. We assessed the findings under the following sub-headings: title of the study, authors, year in which study was conducted, sample size, country, type of study, result, and outcomes (challenges and complications of long COVID) to present a summary of our findings.

## RISK OF BIAS ASSESSMENT

The risk of publication bias was performed using the R package and Shiny web app for visualizing risk-of-bias assessments which has been introduced by the National Institute of Health Research (NIHR) (11). The 2020 version of the software was used for the analysis. A total of 23 studies met the inclusion criteria and were included in our systematic review. The tool assessed the studies under the following domains 1. Bias arising from the randomization process 2. Bias due to deviations from intended interventions 3. Bias due to missing outcome data 4. Bias in measurement of the outcome 5. Bias in selection of the reported result and 6. Overall Bias.

## RESULTS

A total of 23 articles meeting the inclusion criteria were selected in this review. Our initial search revealed 5083 articles, and after exclusion of articles based on title, abstract, study design, and duplicate records, we included 23 studies in our review. The selection process adheres to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA); (fig. 1) depicts the selection process.

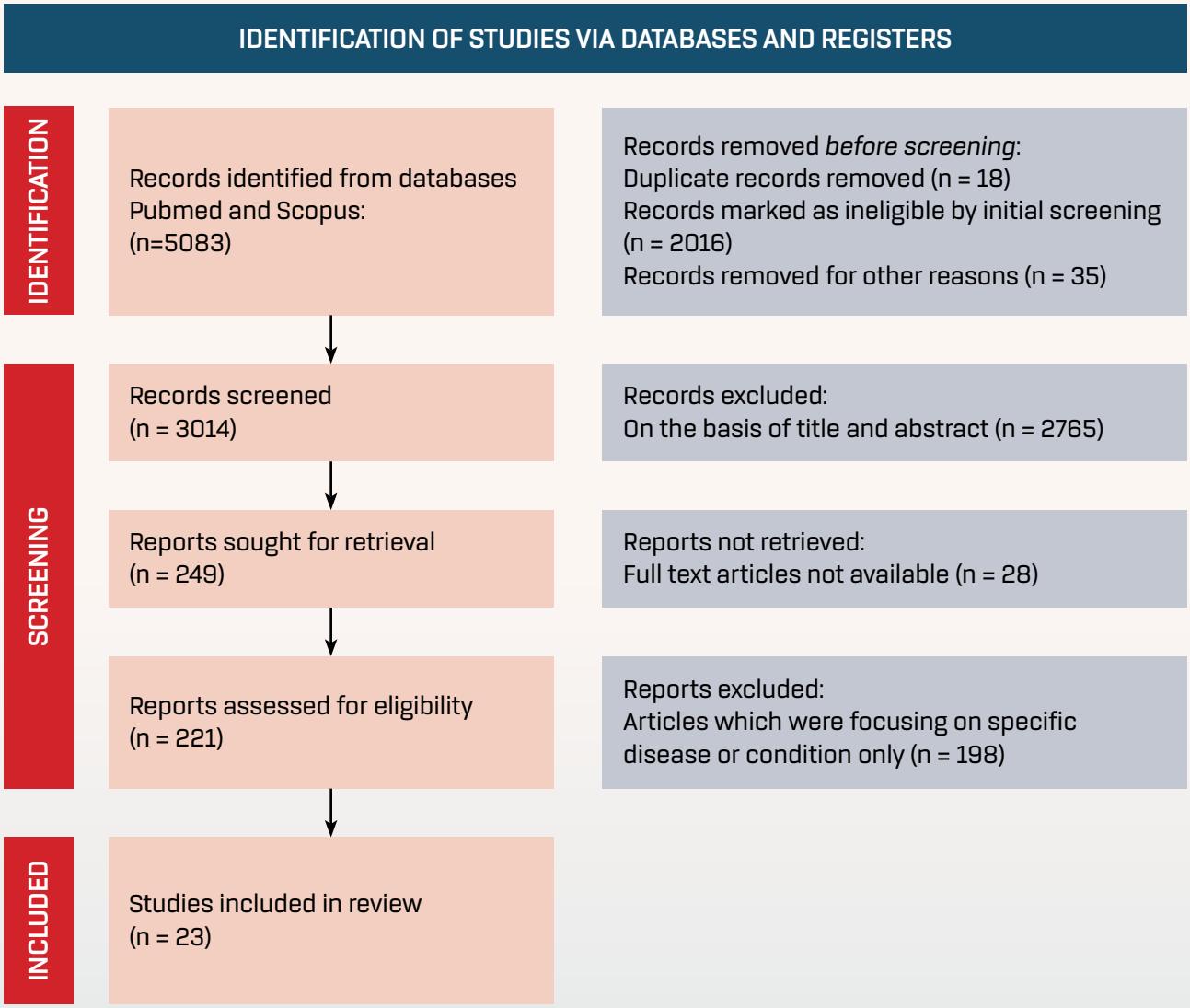


Figure 1. Prisma flowchart.

### STUDY CHARACTERISTICS

The selected studies included were cross-sectional studies, cohort studies, and observational studies published from January 2020 to August 2024. A detailed representation of the included studies is depicted in (tab. 1).

Table 1. Table of study characteristics.

| Author | Year | Sample Size | Country | Study Type | Findings |
|---|---|---|---|---|---|
| Tabacof et al. (12) | 2022 | 156 | US | Cross-sectional study | Fatigue – 82%, brain Fog – 67%, headache – 60%, sleep disturbances – 59%, reduction in patients in full – time work (pre – COVID: 76%, post – COVID: 41%), anxiety disorder – 19%, major depressive disorder – 28% |
| Twomey et al. (13) | 2022 | 213 | UK US Canada | Cross-sectional | Persistent symptoms for more than 6 months – 72.3%, lacking healthcare support – 33%, not able to work – 42.3%, reduced working hours – 41.8%, Chronic fatigue – 71.4%, breathing discomfort – 55.2% |
| Naik et al. (14) | 2021 | 1234 | India | Observational study | Persistent symptoms – 40.11%, long COVID symptoms reported beyond 12 weeks – 9.9%, myalgia – 10.9%, Fatigue – 5.5%. |
| Gerard et al. (15) | 2021 | 549 | France | Prospective Cohort Study | 6 months follow – up – reduced muscle strength – 14.3%, malnutrition and weakness – 91%, impairment – 18.5%, Asthenia – 16%, Mood disorder & anxiety – 10%, Dyspnea – 7.6% |
| Walker et al. (16) | 2023 | 3754 | UK | Cross-sectional study | Pain/Discomfort – 96.2%, Anxiety/Depression – 95%, Lost ≥1 day from work in the previous 4 weeks – 51%, Unable to work at all – 20%, Functional impairment (moderate to severe) – 53% |
| Mutiawati et al. (17) | 2022 | 215 | Indonesia | Cross-sectional study | Persistent Fatigue – 17.7%, prolonged headache – 72%, poor quality of life – 21.4% |
| Imoto et al. (18) | 2022 | 285 | Japan | Cross-sectional study | In 50% patients: persistent fatigue, alopecia, concentration & memory problems, sleeplessness, joint pain, and headache – >50% |
| Gutierre Canales et al. (19) | 2022 | 206 | Mexico | Observational study | Persistence of 1 or more symptoms – 73.3%, fatigue – 36.9%, anxiety – 26.2%, headache – 24.8%, alopecia – 22.8%, inability to walk – 5.8% |
| Badinlou et al. (20) | 2022 | 507 | Sweden | Cross-sectional study | Depression – 55%, anxiety – 20.5%, insomnia – 60.9%, post-COVID impairments and severe fatigue linked to poor mental health outcomes |
| Tsuzuki et al. (21) | 2022 | 457 | Japan | Cross-sectional | Persistence of at least 1 symptom longer than 4 weeks after COVID-19 symptom onset – 44%, persistent Fatigue – 12.7%, Alopecia – 12% |
| Titzede - Almeida et al. (22) | 2022 | 236 | Brazil | Cohort study | Persistent fatigue – 21.2%, headache – 19.1%, myalgia – 16.1%, memory complaints – 39.8%, anxiety >33%, depression – 45%, declined sleep quality – 45.8%, sleepiness – 41.5% |
| Kim et al. (23) | 2022 | 678 | Korea | Prospective study | Concentration Difficulty – 22.4%, cognitive dysfunction – 21.2%, amnesia – 19.9%, depression – 17.8%, fatigue and anxiety – 16.2%, mobility problems – 7.9%, problems with daily activities – 15.4%, pain/discomfort – 22%, anxiety/depression – 40.7% |
| MacEwan et al. (24) | 2022 | 21 | US | Qualitative study | Patients faced care barriers from providers' disbelief, struggled to communicate symptoms, felt helpless, and worried about long-term health impacts. |

| Author | Year | Sample Size | Country | Study Type | Findings |
|---|---|---|---|---|---|
| Balderas et al. (25) | 2023 | 215 | Mexico | Prospective study | Children with Persistent Symptoms at 2 Months – 32.6%, patients with comorbidities – 67.4%, long-term sequelae – anxiety, alopecia |
| Reuschke et al. (26) | 2022 | 1.4 M | UK | Observational study | Left employment – 11.4%, employment exits in elementary occupations – 43% |
| Sykes et al. (27) | 2021 | 134 | England | Observational study | Breathlessness (compared to pre – COVID-19 state) 60%, myalgia – 51.5%, anxiety – 47.8%, extreme fatigue – 39.6%, low mood – 37.3%, sleep disturbance – 35.1% |
| Delbressine et al. (28) | 2021 | 239 | Belgium, Netherlands | Longitudinal study | Participants unable to be physically active or perform sports at 6 months – 12%, weekly walking time at 6 months follow up:90 (30-150) min./week (lower than pre – COVID-19;) |
| Asadi-Pooya et al. (29) | 2021 | 58 | Iran | Observational study | Fatigue – 21%, shortness of breath – 12%, exercise intolerance – 12%, walking intolerance – 9%, sleep difficulty – 5%, muscle pain – 5%, joint pain – 5%, headache – 5% |
| Karaarslan et al. (30) | 2021 | 118 | Turkey | cohort study | Rheumatic and musculoskeletal symptom at 6 months – 43.2%, fatigue 31.6%, joint pain – 18.6%, myalgia – 15.1%, dyspnea – 25.3%, hair loss – 20.0% |
| Rass et al. (31) | 2022 | 76 | Austria | Observational cohort study | New and persistent neurological disorders – 12%, fatigue – 38%, concentration difficulties – 25%, forgetfulness – 25%, sleep disturbances – 22%, myalgia – 17%, limb weakness – 17%, headache – 16%, impaired sensation – 16%, hyposmia – 15%, cognitive deficits – 18%, depression – 6%, anxiety – 29%, post – traumatic stress disorder – 10% |
| Shah et al. (32) | 2022 | 300 | Nepal | Prospective study | Fatigue – 28.3%, shortness of breath – 6.7%, alopecia – 18.3%, anosmia – 4.3%, ageusia – 4.3% |
| Degaldo-Alonso et al. (33) | 2022 | 77 | Spain | Cross sectional study | Patients reported symptoms influencing work capacity – 97.4%, cognitive issues – 92.2%, fatigue – 84.4%, headache – 76.6%, sleep disorders – 70.1%, weakness – 66.2%, anxiety/depression – 5%, dizziness – 55.8%, dyspnea – 59.7%, cognitive complaints – 46.8% |
| Bungenberg et al. (34) | 2022 | 49 | Germany | Longitudinal observational study | Fatigue – 74%, cognitive complaints – 70%, difficulties in attention and concentration – 56%, memory complaints – 38%, smell and/or taste disturbances – 52%, sleep problems – 44%, headache – 22% |

Our selected studies were conducted in multiple geographic locations, which included 17 countries. The majority of the selected studies were conducted amongst adults aged 18 years or more, while 2 (25, 29) studies were conducted in children. The minimum sample size in 1 of the studies was 21 (24), which was a qualitative study conducted in the US, while the largest sample size was 3754 (16) in a cross-sectional study design conducted in the UK.

As per the findings from the included studies of our review, we have divided the results into the following categories of physical and neurological symptoms, psychological and social impact, challenges in healthcare delivery services, employment-related issues and impairment of health-related quality of life.

### Physical and Neurological Symptoms

Fatigue was the most commonly reported long COVID symptom, with prevalence ranging from 5.5% to 84.4% across studies (12–23, 27, 29–34). This was followed by brain fog or cognitive impairment, reported in up to 67% of cases (12), and headaches, with a prevalence ranging from 5% to 76.6% (12, 17, 18, 19, 22, 29, 31, 33, 34). Sleep disturbances were observed in 22% to 60.9% of participants (12, 18, 20, 22, 27, 31, 34), while myalgia or reduced muscle strength ranged from 10.9% to 51.5% across studies (14, 22, 27, 30, 31). Studies conducted in Austria and Germany further highlighted the persistence of neurological symptoms, including concentration difficulties, cognitive impairment, and memory complaints in individuals with long COVID (31, 34).

### Psychological and Social Impact

Long COVID is associated with significant psychological and social repercussions, particularly anxiety and depression, with reported prevalence ranging from 5% to 95% across studies (12, 15–16, 19–20, 22–23, 25, 27, 31, 33). Mental health has also been significantly impacted by the social isolation and loss of habits caused by long COVID.

### Challenges in Healthcare Delivery Services

Patients also faced challenges in healthcare delivery services during Long COVID. In a qualitative study conducted in the US, patients reported concerns regarding the lack of comprehension of the healthcare professionals and the lack of addressing long-term COVID symptoms (24). In another study across the UK, US, and Canada, 1/3$^{rd}$ of the long-COVID patients reported not receiving assistance from their medical healthcare team for their chronic symptoms (13).

### Employment-Related Concerns

Long-term COVID has significantly impacted employment. In a study in the US, there was a significant decline in the proportion of patients working full-time from 76% pre-COVID to 41% post-COVID (12). In a study in the UK, the authors reported 20% of post-COVID patients were unable to work at all, and 51% missed at least 1 workday in the past 4 weeks due to long COVID symptoms (16). In another study in the UK, 11.4% of patients with long COVID had left their jobs (26), and 31.6% of patients reduced their working hours post-COVID in a study conducted in Spain (33).

### Health-Related Quality of Life with Physical Inactivity

Physical inactivity and reduced functional ability are common consequences of long COVID. In a study in the US, patients were likely to exercise for 150 minutes less per week after contracting COVID-19 (12). As per a study in Belgium, 44% of patients were unable to do physical activities at 3 months post-infection. Even though this improved to 12% at 6 months, the walking time continued to be less than pre-COVID levels even after 6 months (28).

## ASSESSMENT OF RISK OF BIAS

Risk of bias was assessed using the R-based ROBVIS software package. Of the 23 included studies, 16 (69.6%) were rated as having a low risk of bias, 5 studies (21.7%) had some concerns, and 2 studies (8.7%) showed a high risk of bias (Figures 2 and 3). Each study was evaluated across five key domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results.

| | | RISK OF BIAS DOMAINS | | | | |
|---|---|---|---|---|---|---|
| | | D1 | D2 | D3 | D4 | D5 |
| STUDY | Study 1 | + | + | − | − | + |
| | Study 2 | + | + | − | − | − |
| | Study 3 | + | + | × | − | − |
| | Study 4 | + | + | − | + | + |
| | Study 5 | + | + | − | − | − |
| | Study 6 | + | + | − | − | + |
| | Study 7 | + | + | − | − | − |
| | Study 8 | + | + | − | − | − |
| | Study 9 | + | + | − | − | − |
| | Study 10 | + | + | − | − | − |
| | Study 11 | + | + | − | − | + |
| | Study 12 | + | + | − | − | + |
| | Study 13 | + | + | × | × | + |
| | Study 14 | + | + | − | − | + |
| | Study 15 | + | + | × | − | + |
| | Study 16 | + | + | − | − | + |
| | Study 17 | + | + | − | − | + |
| | Study 18 | + | + | × | − | + |
| | Study 19 | + | + | − | − | + |
| | Study 20 | + | + | × | − | + |
| | Study 21 | + | + | − | − | + |
| | Study 22 | + | + | − | − | + |
| | Study 23 | + | + | × | − | + |

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

× High

− Some concerns

+ Low

Figure 2. Illustration of the Risk-of-Bias Domains.

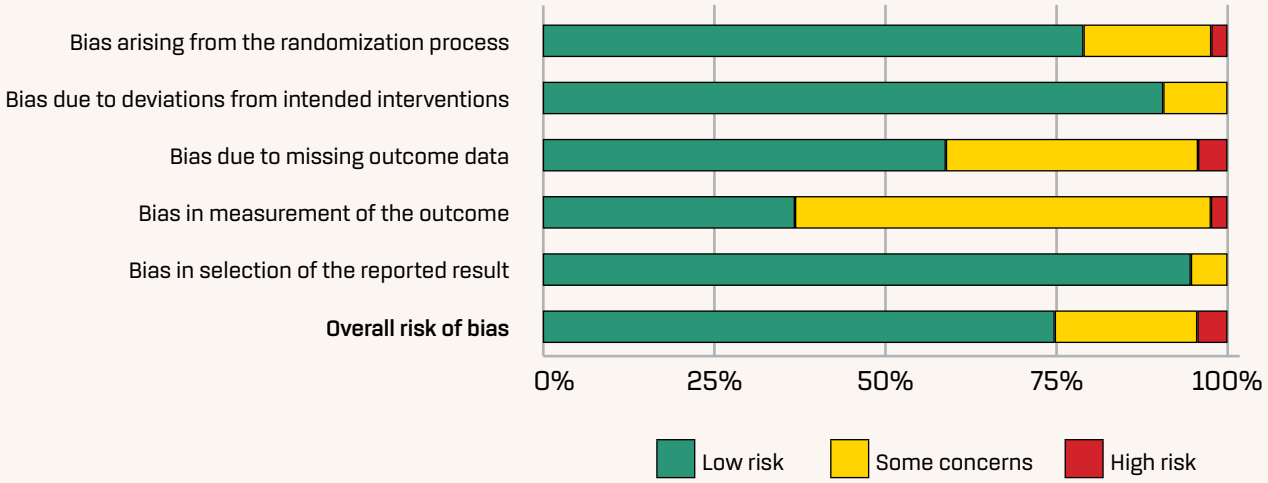


Figure 3. Depiction of the Overall Risk of Bias.

## DISCUSSIONS

Long COVID refers to persistent or newly developed symptoms occurring after the acute phase of SARS-CoV-2 infection, often lasting weeks to many months. In some individuals, new symptoms may emerge after an asymptomatic period following recovery from the acute infection (35). This systematic review highlights the complex and far-reaching impacts of Long COVID on individuals' physical, neurological, and psychological health, as well as on the healthcare system and overall quality of life.

### FATIGUE AND MUSCULOSKELETAL SEQUELAE

Musculoskeletal complications are among the most common and significant outcomes experienced by long COVID survivors, with predominant symptoms including persistent fatigue, muscle pain (myalgia), muscle weakness, joint pain (arthralgia), and skeletal muscle damage (36). The most common symptom that has affected individuals was found to be fatigue, as reported in many studies (37, 38). We observed heterogeneity in the prevalence rates of fatigue, ranging from 5.5% (14) to 84.4% (33) across the included studies. This variation could be attributed to differences in study designs (e.g., cross-sectional vs. cohort vs. qualitative), sample sizes (ranging from 21 to over 1.4 million participants), and timing of post-COVID symptom assessments. Physiological mechanisms underlying these complications may include direct viral infection, systemic inflammation, and lifestyle disruptions. Studies have identified ACE2 receptors and TMPRSS2 proteins in musculoskeletal tissues, suggesting that SARS-CoV-2 may directly infect these areas. (39). Additional pathological findings such as muscle fiber atrophy, necrosis, immune cell infiltration, and neuronal demyelination further contribute to the biological basis of fatigue and weakness (40, 41, 42). Lifestyle changes during the pandemic (e.g., reduced activity, poor sleep) may have compounded these outcomes (43).

### COGNITIVE AND NEUROLOGICAL IMPAIRMENTS

Cognitive dysfunction, including memory loss, impaired concentration, brain fog, and sleep disturbances, was frequently reported (31, 34). A meta-analysis reported significant cognitive impairments in Long COVID patients, including deficits in executive function, memory, attention, and processing speed (44). Another review found persistent neurological symptoms – such as encephalitis, seizures, mood swings, and brain fog – lasting up to 2–3 months post-infection (45). Studies reported significant cognitive and neurological

impairments in Long COVID patients, including deficits in executive function, memory, attention, processing speed, as well as symptoms like encephalitis, seizures, mood swings, and brain fog lasting up to 2–3 months post-infection (44, 45). Additionally, our study reported similar findings, including fatigue, forgetfulness, sleep disturbances, limb weakness, cognitive deficits, and post-traumatic stress disorder even a year after infection (31). Neuropsychiatric symptoms in COVID-19 survivors are linked to the virus entering brain cells via ACE2 receptors and TMPRSS2, while severe cases may trigger cytokine storms causing thrombotic issues like DIC (46, 47).

## PSYCHOLOGICAL AND SOCIAL IMPACT

Long COVID has significant social and psychological impacts. In included studies, it was observed individuals had high rates of anxiety (16.2%–55%), depression (up to 20.5%), and insomnia (up to 60.9%) among post-COVID patients (12, 20). These mental health issues are often linked to job loss, social isolation, poor physical health, and disrupted daily functioning. Patients also expressed concerns about long-term effects on life expectancy and aging, highlighting the ongoing psychological burden of the condition (24). A study reported that nearly half of the patients remained emotionally affected after 8 weeks, with 28 requiring further mental health care (50).

## CHALLENGES IN HEALTHCARE

Long COVID has posed striking challenges for healthcare systems around the world. Patients have reported significant obstacles with regards to access to care, managing long-term symptoms, and receiving an adequate diagnosis. In a qualitative study conducted in the US, many patients felt their symptoms were disregarded or not adequately assessed by health professionals, and they often felt misunderstood by them. The study also reported patients being confused on how to effectively communicate their symptoms and concerns regarding the absence of well-defined treatment guidelines (24). The frustration and concern of patients battling with the long-term impacts of COVID-19 infection may have left them worried about the management of their prolonged symptoms in the future. A study reported that patients living with long COVID shared that they suffered with a range of symptoms and felt ‘abandoned’ and ‘dismissed’ by healthcare providers and got conflicting or limited advice (48). One third of patients in another study reported being ill or in a worse clinical condition than at the onset of infection, even at eight weeks (49).

## IMPACT ON EMPLOYMENT AND DAILY FUNCTIONING

Beyond physical and neurological impacts, long COVID has significantly affected employment levels among patients who have reported a reduced working capacity or being unable to work at all, as reported in our included studies. (12, 13, 16, 26). The main reasons for reduced working hours and capacity to work were found to be fatigue, cognitive problems, and psychosocial variables, as reported in our studies. In another study, the authors reported that amongst 195 patients who were employed prior to hospitalization, 40% of them could not return to work within 8 weeks of discharge due to persistent symptoms or loss of job and of the ones who could resume work in this study, a quarter had to reduce their working hours or alter their responsibilities due to health issues (50) About 70% of previously admitted patients for COVID-19 also could not return to work at 3 months after admission, as reported in another study (51).

Health-related quality of life has also been known to be impacted by long COVID, especially with respect to physical inactivity. In a study in Belgium, 12% of participants post-COVID-19 were unable to be physically active and

perform sports at 6 months (28). In a study in Indonesia, 21.4% of patients reported poor quality of life due to headaches caused by post-COVID infection (17). 5.8% of patients in a study conducted in Mexico reported inability to walk as a frequent complication of long-term COVID (19) and 7.9% of patients had mobility problems, and 15.4% reported challenges with their daily activities in a study in Korea (23). Studies have attributed these impacts to marked deficits in mental health and a lack of social engagement (17, 23). An all-encompassing management of both physical and psychological disturbances can help reduce the impact of post-COVID symptoms on the daily lives of individuals.

Our findings highlight that long COVID follows a prolonged and multifaceted course, with symptoms like fatigue, brain fog, sleep disturbances, and myalgia persisting for months after infection. Studies reported physical, neurological, and psychological complications, with impacts on employment and access to healthcare. The persistence and overlap of these symptoms suggest that long COVID does not follow a uniform trajectory but varies based on individual, clinical, and contextual factors, necessitating long-term multidisciplinary care.

## CONCLUSIONS

1. This systematic review comprehensively evaluates the challenges and complications faced by patients with long COVID. The insights derived from this review can help identify key specific areas for intervention, particularly in addressing clinical, psychological, and socioeconomic complications. Understanding these issues will enable the development of targeted strategies to mitigate the long-term effects of long COVID and improve patient outcomes.
2. The findings of this review are critical for healthcare policymakers and providers as they work to develop protocols that address the gaps in care for long COVID patients. The COVID-19 pandemic has underscored the need for upgraded healthcare systems, particularly in low- and middle-income countries, to adapt to new challenges, with long COVID complications as emerging public health challenge.
3. Our review emphasizes the urgent need for multidisciplinary post-COVID care pathways that seamlessly integrate physical, psychological, and social health services into routine healthcare. Such comprehensive approaches can strengthen clinical guidelines and support evidence-based policymaking, helping health systems become more resilient in managing long COVID and future public health challenges.

## CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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# ENTREPRENEURSHIP AND INNOVATION ECOSYSTEMS IN THE PATIENT EXPERIENCE: A REVIEW OF THE AFRICAN CONTEXT

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## SUMMARY

**Introduction** In the current healthcare context in Africa, numerous challenges remain to be addressed, including limited access to services, disparities in the quality of care, and inequalities in health outcomes. Furthermore, the lack of innovative business models capable of responding to the diverse and evolving needs of patients represents a major obstacle. This situation highlights the need to further integrate the patient's experience into the design of healthcare services, which could transform traditional business models by incorporating a human-centered and experiential dimension.

**Material and methods** A systematic review of the existing literature was conducted to identify and synthesize the main contributions in this field.

**Results** We examined the fundamental principles of a business model that emphasizes patient experience, particularly in the healthcare sector in Africa. We also explored the factors influencing the economic functioning of these experience-based healthcare services. In addition, we analyzed the different ways in which these services are organized and marketed. Finally, we assessed how key performance indicators relate to various components of the experience-driven business model in healthcare.

**Conclusions** A theoretical framework will be developed to clarify the experiential business model and its implications for healthcare stakeholders, particularly regarding its design, promotion, and implementation.

**Keywords** Business models, patient experience, healthcare, Africa.

## ECOSISTEME ANTREPRENORIALE ȘI DE INOVARE ÎN EXPERIENȚA PACIENTULUI DIN AFRICA: REVIU SISTEMATIC

**Introducere** În contextul actual al sistemului de sănătate din Africa, există numeroase provocări care trebuie abordate. Acestea includ accesul limitat la servicii, disparități în calitatea îngrijirii și inegalități în rezultatele de sănătate. În plus, lipsa unor modele de afaceri inovatoare, capabile să răspundă diverselor nevoi în continuă schimbare ale pacienților, reprezintă un obstacol major. Această situație evidențiază necesitatea integrării mai profunde a experienței pacientului în proiectarea serviciilor medicale, ceea ce ar putea duce la transformarea modelelor tradiționale de afaceri prin includerea unei dimensiuni centrate pe om și pe experiență.

**Material și metode** A fost realizată o revizuire sistematică a literaturii existente pentru identificarea și sintetizarea principalelor contribuții în acest domeniu.

**Rezultate** Au fost studiate principiile fundamentale ale unui model de afaceri care pune accent pe experiența pacientului, în special în sectorul sănătății din Africa. De asemenea, au fost analizați factorii care influențează funcționarea economică a acestor servicii medicale bazate pe experiență. În plus, am examinat diferite modalități de organizare și promovare a acestor servicii. În final, am analizat modul în care indicatorii cheie de performanță se raportează la diferite componente ale modelului de afaceri axat pe experiență în domeniul sănătății.

**Concluzii** Va fi elaborat un cadru teoretic pentru a clarifica modelul de afaceri bazat pe experiență și implicațiile acestuia pentru „actorii" din domeniul sănătății, în special în ceea ce privește proiectarea, promovarea și implementarea.

**Cuvinte-cheie** modele de afaceri, experiența pacientului, servicii medicale, Africa.

## INTRODUCTION

Over the past few decades, the concept of *patient experience* has undergone substantial evolution within healthcare systems worldwide. As noted by Wolf, this transformation has progressed from a rudimentary measure of satisfaction to a holistic approach encompassing the emotional, social, and behavioral dimensions of the care journey (1). Giebel *et al.* further emphasize that this shift represents a paradigm change in which patient-centered care has become a foundational element of organizational strategies in healthcare (2).

The Experiential Business Model (EBM) represents a substantial conceptual innovation in the management of healthcare organizations, going beyond conventional approaches by prioritizing value co-creation and emotional engagement at the heart of organizational strategy. In the healthcare sector, Busch et al demonstrate that this model can significantly improve the quality of care while optimizing operational efficiency (3). The integration of Biomedical Engineering Institutes (BIIs) into healthcare facilities, as explained by (4), facilitates the development of personalized experiences that enhance patient engagement and improve clinical outcomes. The African context presents particularities that require specific adaptation of the EAR (Enterprise Application Archive). Maphumulo & Bhengu, highlight the structural and contextual challenges facing African healthcare systems that negatively affect patient experience (5). In South Africa, there is a pronounced gap between the satisfaction levels of private and public providers, as shown by (6). Cultural dynamics also have an impact on interactions, with some people feeling marginalized, fostering mistrust and discouraging them from seeking care (7). Understanding patients' experiences is essential to improving healthcare delivery in Africa. In addition, the public health sector faces inadequate funding, poor infrastructure and a shortage of qualified staff.

The limited adoption of the EBM across the continent raises important questions regarding its contextual adaptation and the mechanisms required to overcome barriers to its implementation. Within this framework, the present study seeks to explore the potential of the experiential business model in African healthcare, based on a systematic review of the existing literature. The analysis aims to identify strategic levers and adjustments necessary for integrating this model into environments as diverse and complex as those found in Africa. This reframing encourages healthcare systems to position themselves as facilitators of holistic care experiences, thereby fostering trust between patients and providers while strengthening the overall healthcare ecosystem.

The main contributions of this article are as follows: first, it examines the conceptual foundations of patient experience, its transformation through innovation, the role of entrepreneurial ecosystems, and the defining features of experiential business models. Second, it details the methodological approach, which involves a systematic literature review. Finally, it presents results and proposes concrete strategies for clarifying the experiential business model and its implications for healthcare stakeholders. The overarching objective is to enrich the body of knowledge on integrating patient experience into healthcare services in Africa, with the aim of fostering patient loyalty. The findings underscore the need for innovative business models that prioritize human-centered approaches and seek to transform conventional practices in the healthcare sector.

## MATERIAL AND METHODS

### SYSTEMATIC LITERATURE REVIEW

The aim of this *Systematic Literature Review* (SLR) is to develop comprehensive and coherent theoretical concepts. This objective is pursued through the synthesis of existing evidence and the identification of methodological gaps in prior research. The study will commence with a descriptive analysis, followed by a qualitative analysis that examines the thematic patterns present in the literature. This approach is intended to identify critical variables rather than merely grouping findings into broad thematic categories, thereby providing a stronger analytical foundation. Furthermore, the review will adopt an integrated perspective on patient experience and the patient journey, while also examining emerging technologies and innovations in the field. Finally, strategies to minimize the risk of bias will be outlined.

### ARTICLE SELECTION PROTOCOL

In this study, primary literature was collected using the Web of Science (WOS) database. The WOS database is widely regarded as one of the most comprehensive and reliable academic databases, incorporating a wide range of renowned publishers and journals. To ensure the relevance of the information collected, emphasis was placed on journal articles, as they are considered to provide more in-depth and impactful research than conference proceedings (10).

The selection process was carried out meticulously in three stages. First, we conducted a search using specific search terms. These search terms included expressions such as:

*("Business model" OR "Commercial strategy" AND "digital transformation" OR "innovation" AND "Healthcare" OR "Medical care" AND "Patient experience" OR "Patient journey" AND "Africa" OR "continent of Africa")*

Only articles published in journals specializing in patient experience were selected. In the subsequent step, the selection was refined by reviewing abstracts, with particular attention to studies addressing strategic issues. This process yielded a total of 60 articles. In the third phase, exclusion criteria were applied following a comprehensive review of the full texts. This phase resulted in the retention of 28 articles (Tab. 1).

Table 1. Results filtering process.

| Step | Action | Results |
|---|---|---|
| Initial search | Keyword search with equation | 80 850 documents identified |
| Filter by domain | Limited to Business, Management, Economics, Social Sciences | 10,901documents |
| Filter by document type | Limited to items | 998 documents |
| Filter by language | Limited to articles in English | 960 documents |
| Filter by access | Limited to open access articles | 775 documents |
| Filter by citations | Selection of the most quoted articles | 28 documents |

### CODING AND ANALYSIS TECHNIQUE

After identifying 28 articles that met the sample selection criteria, the data were processed using NVivo 15. A thematic analysis was performed to identify critical variables related to the business model, the healthcare sector, and the patient experience. These variables were subsequently classified into themes and incorporated into a conceptual framework (3, 10). The results were strengthened by situating them within a clearly defined conceptual framework grounded in well-established theoretical foundations from the existing literature.

The analytical process comprised the following steps:

1. **Idea generation from primary studies.** In this stage, the significant findings from each reviewed article were identified and documented.
2. **Data coding, synthesis, and simplification.** Recurring patterns and themes were identified through systematic analysis of results with similar contexts and concepts. Findings were organized according to a predefined coding system, which facilitated the grouping of results and the subsequent identification of themes. Keywords encapsulating these findings were then extracted.
3. **Development of a contextual framework.** Based on the initial literature, a contextual framework was formulated and organized into three components: the design, promotion, and practices of the experiential healthcare business model.

## RESULTS

### DESCRIPTIVE ANALYSIS

The annual distribution of publications (Fig. 1) reveals a marked upward trend beginning in 2022, peaking at seven publications in 2023 – the highest level of activity in the corpus. Although 2024 recorded a slight decline, publication levels remained relatively high.

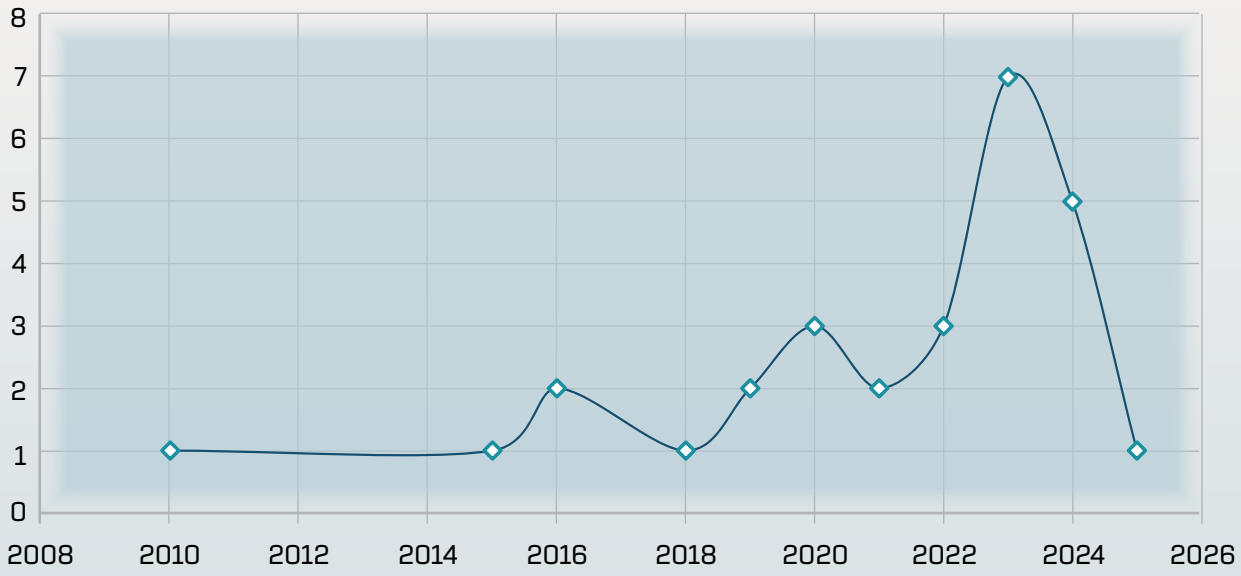


Figure 1. The visualization shows the number of publications published each year.

## TYPES OF REFERENCES

The distribution of the 28 references by type is shown in fig.2. Articles were the main source of information for our literature review, accounting for 71% of the total. The other references were book chapters (11%) and conference papers (17%).

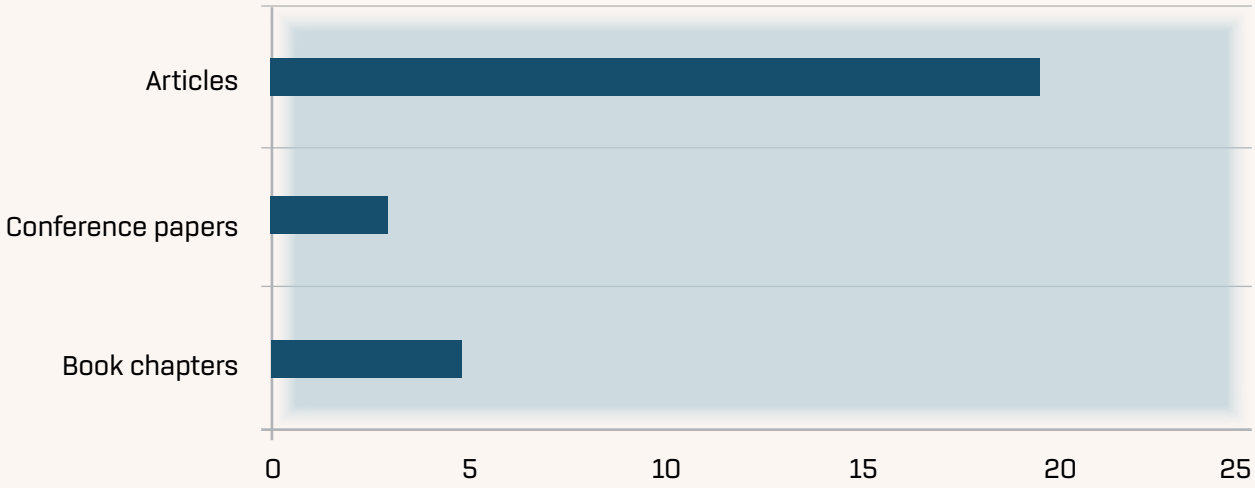


Figure 2. The types of references.

## PUBLICATION SOURCES

The table below presents the main journals in which the selected sources were published. Most articles appeared in management and public health journals, suggesting that these are the preferred venues for research on entrepreneurship and innovation ecosystems in the context of patient experience. According to the data, 60% of studies on experiential business models were published across 17 different journals classified in the "other" category (Tab. 2), indicating that research on this topic is dispersed across a broad range of specialized publications.

Table 2. Distribution of references by journal title.

| Journal Title | Number of corresponding sources | % |
|---|---|---|
| Journal of Contemporary Management Issues | 1 | 3% |
| Technovation | 2 | 7% |
| Journal of best practices in health professions diversity | 1 | 3% |
| Journal of the Division of Health Psychology | 1 | 3% |
| International Journal of Person-Centered Medicine | 1 | 3% |
| Applied Nursing Research | 1 | 3% |
| Revue Management & Avenir | 2 | 7% |
| Journal of Business Venturing Insights | 1 | 3% |
| Journal of Supply Chain Management Science | 1 | 3% |
| Others | 17 | 60% |
| Total | 28 | 100% |

## QUALITATIVE ANALYSIS

### Issues and Challenges in the Healthcare Sector in Africa

Despite notable progress achieved in recent years, the African continent continues to face structural and systemic barriers that hinder the optimal development of its health sector (Tab. 3). A key challenge is the lack of universal access to healthcare, particularly in rural areas where medical infrastructure is often inadequate or under-equipped and the availability of qualified personnel remains critically low (11). Continuity of care for discharged patients is another persistent problem, exacerbated by insufficient follow-up and poor coordination across different levels of the health system (12, 13).

These difficulties are further compounded by widespread socioeconomic constraints (12). Poverty, low levels of education, and geographic isolation – especially in remote areas – limit access to healthcare services and reduce the capacity of individuals to adopt health-promoting behaviors (12). Moreover, healthcare providers, often overworked, operate under chronic shortages of material and human resources, diminishing their ability to meet the increasing needs of patients (14).

The consequences of these challenges are significant, including patient attrition, rising antimicrobial resistance, and dissatisfaction among both patients and providers (12, 15). Addressing these multifaceted issues requires comprehensive and innovative strategies aimed at improving equity, accessibility, and sustainability within African health systems (16). In this context, the development of public–private partnerships and the promotion of inter-institutional collaboration are essential. Table 3 summarizes the main challenges and the corresponding solutions proposed for the healthcare sector across the continent (17).

Table 3. Synthesis of challenges and proposed solutions.

| Identified Challenges | Proposed Solutions | References |
|---|---|---|
| Limited access to healthcare infrastructure | Optimized healthcare infrastructure planning and affordable technologies | (11) |
| Insufficient continuity of care post-hospitalization | Development of personalized treatment plans and active patient engagement | (12, 13). |
| Socio-economic constraints (poverty, isolation) | Cross-subsidy models to ensure equity in healthcare access | (12, 16) |
| Overburdened healthcare providers | Organizational innovation (Entrepre Nursing) and capacity building | (14, 17) |
| Weak interinstitutional collaboration | Public-private partnerships and interinstitutional collaborations | (14, 18) |

### Transforming the Patient Experience through Healthcare Innovation in Africa

Designing innovative, patient-centered solutions for healthcare in Africa requires a holistic approach that emphasizes collaboration and patient engagement (18). A key strategy involves leveraging digital health technologies to broaden patient access to healthcare services. Telemedicine, for instance, has emerged as a transformative solution by enabling remote consultations and overcoming barriers commonly encountered in traditional healthcare delivery systems. This innovation not only enhances accessibility but also appeals to patients who prioritize convenience and efficiency throughout their care journey (19).

Another promising avenue for innovation is the integration of patient feedback mechanisms within healthcare settings. Utilizing patient-reported outcome measures (PROMs) alongside patient-reported experience measures (PREMs) ensures that patients' perspectives are incorporated into care delivery, aligning services more closely with their expectations and preferences (Tab. 4). Such engagement empowers patients to take greater ownership of their care, leading to improved satisfaction and clinical outcomes (20).

Moreover, healthcare organizations should promote co-creation processes involving patients from the initial stages of product and service development. Collaborations with patient advocacy groups and other stakeholders across the healthcare ecosystem help ensure that innovations effectively address patients' real-world challenges. Participatory approaches have demonstrated enhanced relevance and efficacy, thereby reducing the risk of developing solutions that fail to meet actual needs (21).

Finally, embedding innovations within value-based healthcare business models can better align incentives between providers and patients. For example, implementing reimbursement models tied to performance metrics linked to patient satisfaction encourages providers to prioritize high-quality, patient-centered care while optimizing operational efficiency (19, 21).

By adopting these innovative strategies, African healthcare systems can substantially enhance the patient experience while addressing persistent gaps in service delivery.

Table 4. The aspects and implications of patient experience through innovation.

| Authors | Aspect | Description | Implication |
|---|---|---|---|
| (Sodiq Odetunde Babatunde, 2024) | Digital health technologies | Tools to expand patient access to healthcare services | These innovations not only improve accessibility, but also resonate with patients who prioritize convenience and efficiency in their healthcare journey. |
| (Fernandes et al., 2020). | Patient feedback mechanisms | Using patient-reported outcome measures (PROMs) as well as experience measures (PREMs), | This type of commitment allows patients to take ownership of their care pathway. |
| (Glover et al., 2024) | Co-creation between companies in the sector | Partnering with patient advocacy groups and stakeholders across the healthcare ecosystem | Innovators can ensure that the solutions they develop directly address the real challenges faced by patients. |
| (Sodiq Odetunde Babatunde, 2024) | Integrating innovations into business models | A substantial conceptual innovation in the management of healthcare organizations | The implementation of models that incorporate reimbursements based on performance directly linked to patient satisfaction measures. |

## CHARACTERISTICS OF EXPERIENTIAL BUSINESS MODELS

In healthcare, experiential business models seek to create value by comprehensively understanding patients' needs and preferences. These frameworks emphasize patient engagement through systematic feedback mechanisms, which enhance satisfaction and health outcomes. Unlike traditional transaction-based models, experiential models provide holistic experiences that promote overall well-being.

Technology plays a crucial role in enabling personalized care delivery, with services such as telemedicine allowing patients to consult providers remotely, thereby meeting growing demands for convenience and accessibility. These models frequently adopt community-focused strategies tailored to local healthcare needs. For example, Philips' Community Life Centers in Africa demonstrate how experiential models can effectively engage communities to provide essential healthcare services in a cost-efficient manner (22). By focusing on specific contexts and leveraging available resources, such innovations help bridge gaps in healthcare access.

Moreover, experiential business models foster collaboration among diverse stakeholders within the healthcare ecosystem. Partnerships between providers, technology companies, and patients facilitate information exchange and resource sharing, which are vital for driving innovation and enhancing service delivery.

Additionally, these models often incorporate varied payment structures that align incentives among stakeholders, shifting from fee-for-service toward value-based care paradigms. This transition encourages an emphasis on patient outcomes rather than volume of services rendered (19, 22).

## LEVERS OF THE EXPERIENTIAL HEALTHCARE BUSINESS MODEL

The experiential business model centers on creating enriching experiences for all stakeholders, including patients, providers, and healthcare institutions. Its primary objective is to optimize interactions among these groups to enhance satisfaction and improve healthcare outcomes (6, 23). This model emphasizes a patient-centric approach that encompasses engagement, education, and support alongside traditional care delivery (23, 24).

Enhancing the quality of communication between patients and healthcare professionals is essential to strengthening patient-centered care (25–27), improving understanding of patient needs, and encouraging active patient involvement in co-constructing their care pathways (28–30). Developing strategies tailored to specific patient needs, such as personalized treatment plans, is crucial for delivering holistic, customized care that increases patient satisfaction while optimizing clinical outcomes (14, 22, 31).

Integrating people-centered approaches within healthcare systems has been identified as a key strategy to elevate care quality and foster lasting trust between patients and providers. In terms of organizational innovation, fostering innovative behaviors among healthcare professionals – such as Entrepreneur Nursing, which promotes entrepreneurial spirit in nursing – is imperative (17, 31). This approach stimulates creativity and the implementation of novel solutions to address challenges faced by the healthcare sector.

Moreover, the integration of technological tools acts as a strategic catalyst for improving both access to and the quality of healthcare services. As noted by Al-Bader *et al.*, innovation models based on affordable technologies play a pivotal role in transforming healthcare systems, particularly in settings marked by limited organizational efficiency and inequitable healthcare access (18, 32).

Finally, inter-institutional collaborations – especially strategic partnerships among hospitals, community clinics, and private entities – are recognized as crucial mechanisms for optimizing resource utilization and expanding healthcare coverage (14, 32).

## DIMENSIONS OF THE EXPERIENTIAL HEALTHCARE BUSINESS MODEL

### *Design*

This study began with a comprehensive review of existing literature on business models in the healthcare sector, drawing upon seminal works such as those by (19, 24, 32). In addition to the literature review, direct observations and in-depth discussions were conducted with key stakeholders, including local health authorities, administrators, hospital Information Technology (IT) directors, general practitioners, and pharmacists, following the recommendations of (25, 32).

The literature review revealed that much of the existing research either remains at a relatively abstract level – for example, the business model frameworks proposed by (26, 32) – or focuses on very specific aspects, as noted by the European Commission (2011). Notably, there is a scarcity of studies providing in-depth analyses of common business logic models. Similarly, in practice, we observed a lack of robust conceptual approaches to business design.

To address this gap, we broadened our perspective on e-health business models by exploring general business logic derived from e-commerce, which enabled a deeper understanding through field-based discussions. To illustrate the practical application of business design models in e-health, we selected three specific design models for detailed analysis.

### *Promotion*

As noted by Garcia *et al.* (27), health promotion and therapeutic education – rooted in care practices – have reached a significant stage of maturity. Concurrently, over the past two decades, new perspectives from patients, relatives, and users have introduced innovative practices into the field (27, 32). This evolving dynamic warrants further exploration to deepen understanding of its theoretical and practical dimensions.

Health promotion plays a crucial role in both individual and collective development by providing valuable information, delivering appropriate education, and strengthening essential daily life skills (3, 16, 32). Such efforts empower individuals to take control of their health and make informed decisions that promote well-being. Encouraging lifelong learning by supporting patients, their families, and other users is essential to help them navigate various life stages with confidence and peace of mind. Given its rapid expansion, this dynamic area merits continued investigation to enhance comprehension of its foundational theories and practical applications.

### *Practices*

#### Free Healthcare Initiatives and Specialized Service Models in South Africa

Initiatives such as *"Free healthcare for pregnant women and children under six"* and *"Universal access to primary healthcare for all South Africans"* illustrate a shift in health system priorities – from focusing on the construction of physical infrastructure to emphasizing the activities and services delivered within these facilities. Increasingly, patients' perspectives are being incorporated into policy-making processes.

In some cases, a variant of the healthcare business model takes the form of specialist care, where hospitals concentrate on specific services – such as cataract surgery or cardiac care – thereby achieving high levels of efficiency and optimizing staff utilization (3, 16, 32). These facilities play a pivotal role in healthcare development by providing accessible services to large populations (Fig. 3). High staff productivity and the ability to maintain reasonable pricing contribute to the affordability of these services.

However, in sub-Saharan Africa, hospitals employing cross-subsidy models face growth constraints due to the limited number of patients who can afford high-quality care. In response, many healthcare facilities are increasingly adopting cross-subsidy business models as a strategic solution. These models enable hospitals to adjust fees according to patients' financial capacity, distributing operational costs across a larger patient base. Patients with higher incomes may access enhanced services, such as comfortable waiting areas, private rooms, and expedited booking, while lower-income patients benefit from reduced fees that are critical for accessing essential care.

A notable example of innovation in healthcare delivery can be found in Tsilitwa, a rural town in South Africa's Eastern Cape. The Tsilitwa clinic serves approximately 10,000 patients but operates without an on-site physician; the nearest hospital with available doctors is over 15 km away, and the absence of direct transport further limits healthcare access (9, 28, 32). To address this challenge, South Africa's Centre for Scientific and Industrial Research, in collaboration with the University of Cape Town's Department of Informatics, implemented a telemedicine initiative using wireless internet technology. This system enables nurses to transmit medical images to doctors in real time, facilitating remote consultations and significantly improving access to medical expertise.


Figure 3. Synthesis of experiential healthcare business model.

## Indicator clusters

In this section, we present the result of cluster coding similarity in Nvivo 15, using Pearson's correlation coefficient. This is a method for detecting any similarity in indicators between Dimensions of the experiential business model (Tab.5).

Table 5. Top 7 common indicators.

| Indicators | E-ecommerce | Therapeutic education | Health accessible | Costs | Co-creation | Ecosystem | Patient opinion |
|---|---|---|---|---|---|---|---|
| Conception | 21 | 2 | 1 | 9 | 5 | 12 | 14 |
| Promotion | 8 | 24 | 3 | 7 | 1 | 4 | 6 |
| Pratiques | 0 | 1 | 17 | 3 | 2 | 1 | 4 |

In order to gain a better understanding of the indicators used in the literature on the experiential economic model, we attempted, in the third stage of processing the indicators, to classify them into 7 categories, namely e-commerce, therapeutic education, health accessible, costs, co-creation, ecosystem, Patient opinion. (Fig. 4) shows the frequency of these categories in the dimensions included in the sample. In e-commerce, Therapeutic education is the most frequent. In fact, they have a positive impact on business performance (29, 32). And they have a positive effect on the value of patient experiences (30, 32) and on the two main stakeholders: entrepreneurs and patients, improving the environmental management of a healthcare center can be achieved through the appropriate allocation of economic, human and financial resources.

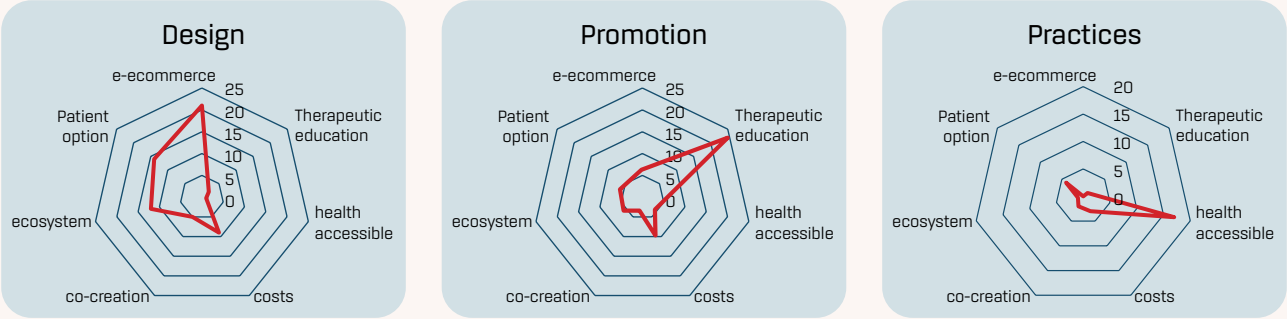


Figure 4. Categories frequency by dimension.

## DISCUSSIONS

Our study underscores the critical role of healthcare innovators in enhancing the patient experience, particularly in resource-constrained regions such as Africa (7, 32). Concrete actions are required to encourage these stakeholders to develop innovative solutions aimed at improving both the quality of care and patient satisfaction. Entrepreneurs are encouraged to leverage technological advances to create platforms that facilitate communication between patients and healthcare professionals. Digital health innovations – such as telemedicine and mobile applications – offer substantial opportunities to expand access to care in underserved communities, enabling remote consultations and follow-up services, thereby overcoming geographical barriers (30, 32).

Incorporating patient feedback into service design is fundamental to developing effective care solutions. Actively involving patients in the development process fosters trust and loyalty, granting them a participatory role throughout their care journey. Collaboration with established healthcare providers can further strengthen service quality. Start-ups should explore strategic partnerships to share best practices, provide team training, and ensure standardized patient management, thereby optimizing the use of available resources.

Investment in data analytics represents another strategic lever for improving the patient experience. The use of big data enables a deeper understanding of patient behavior and treatment outcomes, allowing for more personalized interventions that can enhance both clinical results and patient satisfaction. Addressing systemic inequalities within healthcare systems is equally essential for sustainable progress. Initiatives targeted at marginalized populations – including individuals with disabilities and those in remote areas – are crucial to promoting equitable access to care (22, 32).

However, current research on entrepreneurship and innovation ecosystems in the patient experience reveals several notable gaps. One such gap is the

limited exploration of how innovation can be strategically harnessed within entrepreneurial models. While a substantial body of literature examines the application of innovation to patient experience and customer engagement, there remains a need for further research on tailoring innovation to foster brand loyalty at the territorial level and effectively engage local populations. Moreover, the relationship between entrepreneurship and patient loyalty is insufficiently understood (32).

This study contributes to addressing these gaps by exploring the integration of entrepreneurship and innovation ecosystems into the patient experience within the African healthcare context. It examines the challenges of limited access, disparities in care quality, and the need for innovative business models that prioritize human-centered approaches (6, 32). By focusing on inpatient clinical pathways, it synthesizes evidence from randomized controlled trials to provide actionable insights for improving both patient experience and outcomes in African healthcare settings.

Finally, building networks among innovative actors in the healthcare sector will strengthen the entrepreneurial ecosystem. Collaborative platforms for sharing challenges and successes can foster collective advancement while opening opportunities for mentorship and funding – both essential to supporting the development of sustainable businesses dedicated to improving the patient experience across Africa.

## CONCLUSIONS

1. The potential of the Experiential Business Model (EBM) in the African healthcare sector is significant, particularly in reimagining how organizations can place patient experience and engagement at the core of their practices. However, successful implementation requires overcoming key challenges, including the fragmentation of healthcare systems, limited infrastructure funding, and the absence of governance frameworks that foster innovation.
2. For effective integration, the EBM must be tailored to local African contexts, taking into account the socio-economic, cultural, and technological factors unique to each setting. While community dynamics can serve as important positive levers, disparities in technology access – especially in rural areas – remain critical obstacles to address.
3. A phased approach, beginning with localized pilot projects, appears to be a prudent strategy for testing and refining the EBM to align with field-specific realities. This process necessitates collaborative governance supported by multisectoral partnerships involving public, private, and non-governmental stakeholders, enabling the exchange of best practices and the promotion of innovation.
4. Further applied research is needed to explore how the EBM, along with its technological components such as the Enterprise Application Repository (EAR), can be adapted to diverse environments. It is essential to examine the influence of institutional dynamics, develop reliable indicators for measuring the patient experience, and assess the contribution of digital technologies – such as telemedicine and data analytics – to optimizing the care pathway.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare in relation to the content of this article.

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# RESEARCH ARTICLES – ARTICLES DE RECHERCHE

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## AREAS OF CONTINUING EDUCATION FOR PHARMACISTS ON THE CARE OF HIGH-RISK PATIENTS

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## ABSTRACT

**Introduction** The presence of qualified pharmacists in community pharmacies ensures that high-risk patient groups receive safe and effective pharmaceutical care when using pharmacy services.

**Material and methods** This study employed a descriptive methodology. The research tool is a questionnaire, which includes 16 questions that describe to respondents' characteristics and assess respondents' attitudes toward continuous training in specialized fields. The number of respondents was 406. Data processing were performed using Excel software.

**Results** The majority of respondents (64,06%, $CI_{95}$: 59,37-68,7) believe that there is a frequent need for improving knowledge in the field of geriatrics, and 82.86% ($CI_{95}$: 79,53-85,99) of respondents fully agree that the community pharmacists should be well-informed in pediatrics. Pharmacists are aware of the responsibility they bear towards these categories of patients in community pharmacies and believe it is beneficial (63,01%, $CI_{95}$: 58,35-67,74) for them to periodically update their knowledge in specialized pharmaceutical care, covering a variety of topics.

**Conclusions** Pharmacists' views emphasized the importance of enhancing their professional training in delivering specialized pharmaceutical services. These findings support the development and implementation of the course "Specialized Pharmaceutical Assistance for High-Risk Patients" within pharmacists' continuing education programs.

**Keywords** Pharmacists, specialized pharmaceutical care, high-risk patients, professional development.

## DOMENIILE DE EDUCAȚIE CONTINUĂ A FARMACIȘTILOR PRIVIND ASISTENȚA PACIENȚILOR CU RISC SPORIT

**Introducere** Prezența farmaciștilor calificați în farmaciile comunitare este garanția categoriilor de pacienți cu risc sporit, că vor primi îngrijiri farmaceutice sigure și eficiente atunci când utilizează serviciile farmaciei.

**Material și metode** Cercetarea efectuată este una de tip descriptiv, instrumentul de cercetare este chestionarul,aplicat la 406 respondenți, ce includea 16 itemi care descriu caracteristica respondenților și măsura în care sunt de acord sau nu cu procesul de formare continuă în domenii înguste. Prelucrarea datelor a fost efectuată prin intermediul softului Excel.

**Rezultate** Majoritatea respondenților (64,06%, ÎÎ95: 59,37-68,7) consideră că este necesară perfecționarea frecventă a cunoștințelor în domeniul geriatriei, iar 82,86% (ÎÎ95:79,53-85,99) dintre ei susțin în totalitate că farmacistul din farmacia comunitară să fie informat în domeniul pediatric. Farmaciștii sunt conștienți de responsabilitatea pe care o au față de aceste categorii de pacienți ai farmaciei comunitare și consideră că este în beneficiul (63,01%, ÎÎ95: 58,35-67,74) lor să își actualizeze periodic cunoștințele în domeniul îngrijirilor farmaceutice specializate, pe o diversitate de tematici.

**Concluzii** S-au evidențiat opiniile farmaciștilor privind necesitatea pregătirii lor profesionale în domeniul prestării serviciilor farmaceutice specializate și s-a argumentat elaborarea și implementarea cursului „Asistență farmaceutică specializată la pacienții cu risc sporit", în cadrul ciclurilor de perfecționare a farmaciștilor.

**Cuvinte-cheie** Farmaciști, îngrijiri farmaceutice specializate, pacienți cu risc sporit, perfecționare.

## INTRODUCTION

Continuous professional training in pharmaceutical care is a legal and/or ethical requirement, as outlined in the Code of Ethics for pharmacists, which varies by country. The International Pharmaceutical Federation (FIP) defines continuous professional development as the „individual responsibility of the pharmacist for the systematic maintenance, development, and extension of knowledge, skills, and attitudes, to ensure ongoing competence as professionals throughout their careers" (1, 2). This refers a pharmacist's commitment to continually improving their skills, knowledge, and performance to benefit from career growth and professional satisfaction.

Community pharmacies must adhere to a series of regulations and standards to secure and maintain their position in the pharmaceutical market, and investing in their staff represents a key strategy in this regard.

In the Republic of Moldova, continuous education in the pharmaceutical field is mandatory throughout a pharmacist's entire career and is organized in different training formats regulated by the Ministry of Health (3).

The concept of continuous professional education in medicine and pharmacy is outlined in the Regulation on the organization and implementation of education and continuous professional development activities at the *Nicolae Testemițanu* State University of Medicine and Pharmacy of the Republic of Moldova. It encompasses "a series of planned educational activities aimed at maintaining, updating, and developing the knowledge, behavior, and professional attitudes necessary for doctors and pharmacists to perform their professional activities effectively. Simultaneously, through the continuous development of individual performance, these activities aim to achieve a real improvement in the quality of medical and pharmaceutical services provided" (4).

The presence of qualified pharmacists in community pharmacies guarantees that pharmacy patience will receive safe and effective pharmaceutical care when using pharmacy services.

The target groups of patients to whom pharmaceutical services are directed are high-risk groups, including the elderly, children with their legal representatives, and patients with rare diseases, due to their specific characteristics in medication use. The vulnerability of the elderly and children is determined by various factors that influence medication administration as well as issues related to their irrational use, especially in outpatient settings (5, 6). In addition to the specific biological characteristics of pediatric or geriatric patients, such as metabolism, age, and bioavailability, the proper use of medications for these patients is influenced by several factors. These include the lack of age-appropriate dosage forms, the use of "off-label" medications, the rising use of dietary supplements that have not been studied for these patient groups, and, last but not least, the patient's adherence to and compliance with treatment (7).

Providing specialized pharmaceutical services to elderly individuals, while considering the factors and characteristics mentioned, helps identify, resolve, and prevent medication-related problems (8, 9).

Planning pharmaceutical services that meet the individual health needs of elderly individuals or children requires the implementation of specialized pharmaceutical age specific care. The implementation of these services requires an integrated, multidisciplinary approach and collaboration among healthcare professionals. Specialized pharmaceutical care for these patient groups involves pharmacists' actions or interventions in community phar-

macies focused on evaluating, preventing, and reducing risks associated with irrational medication use while enhancing the benefits of drug therapies. The development and implementation of such pharmaceutical services involve three key steps: identifying the medication-related problems that need to be addressed, selecting effective interventions to resolve these issues, and implementing, monitoring, and evaluating the impact of these interventions in community pharmacies (10, 11).

Therefore, it highlights the necessity for pharmacists to possess comprehensive knowledge in addressing the specific medication-related needs of elderly patients, children, and those with rare diseases, while also improving the delivery of information to ensure that the specific requirements of these patients are adequately considered.

In the Republic of Moldova, there are no specialized programs for pharmacists in specialized areas of training, such as geriatrics, pediatrics, or assistance for patients with rare diseases. For instance, in the United States, the majority of training required to become a specialist in geriatric pharmacy occurs subsequent after completing pharmacy school. A common way to become a specialist is to complete a residency in geriatric pharmacy. Residency experiences are elective in the field of pharmacy, but they serve to provide intensive training experiences. A residency in geriatric pharmacy allows the trainee to be immersed in the field of geriatrics by providing experiences in long-term care, ambulatory care, and acute care settings, all focusing on providing care for elderly individuals. All states require a license to practice pharmacy, and there are some differences from state to state that would require a license transfer. State pharmacy boards use several components in their licensing process, one of which is the NAPLEX exam administered by the National Association of Boards of Pharmacy (12).

After practicing in the field of geriatrics, pharmacists may also wish to become board-certified geriatric specialists. To obtain this certification, pharmacists must pass an exam from the Board of Pharmacy Specialties, which focuses on providing healthcare to elderly adults. In order to maintain their certification, pharmacists may either retake the examination every seven years or engage in continuing education courses specifically focused on geriatrics (12, 13).

Data on the need to prepare students and practitioners to provide pharmaceutical care to the elderly population are highlighted in the work „*Geriatric pharmacy education: a strategic plan for the future*" (14) presented by a group of authors who indicate that the care of elderly individuals is an essential component of the education of all pharmacists. In this regard, in the mid-1980s, the Office of Health Professions developed a model curriculum in geriatric pharmacy.

American College of Clinical Pharmacy which supports practitioners, scientists, educators, and other professionals involved in clinical pharmacy and pharmacotherapy, including in pediatric clinical pharmacy (*ACCP Pediatrics PRN*), emphasizes in its Opinion Paper, recommendations aimed to improve both the quality and quantity of education in pediatric pharmacy, such as: increasing the minimum expectations for pharmacists entering practice to provide pediatric care; standardizing education in pediatric pharmaceutical care; expanding the number of pediatric clinical pharmacists; creating an infrastructure for the development of pediatric clinical pharmacists and clinician scientists (15).

Subsequently, professional organizations, such as the American Association of Colleges of Pharmacy (AACP), in collaboration with the American Society

of Consultant Pharmacists (ASCP), American Geriatrics Society (AGS), American Association of Colleges of Nursing (AACN) and the Institute of Medicine (IOM) have significantly contributed to the development of geriatric pharmaceutical education (14).

Additionally, the guidelines of the Accreditation Council for Pharmacy Education (ACPE) emphasize that every graduate pharmacist must be prepared to provide direct pharmaceutical care to patients across a wide variety of healthcare domains, with the responsibility to ensure optimal and safe therapy outcomes for a wide range of patients. As a result, ACPE asserts that this competency can be attained through the development of a solid training foundation, including understanding specific populations, such as pediatric or geriatric patients, and related prescription and non-prescription pharmacotherapy, population-specific dosage calculations and adjustments, and the monitoring of rational use of medications (15).

Based on the aforementioned, the objective of this study has been defined as follows: to evaluate the attitudes of practicing pharmacists in the Republic of Moldova regarding continuous education in these fields, in order to highlight the importance and necessity of a specialized training course in pharmaceutical care for these patient groups.

## MATERIAL AND METHODS

The present study employed a quantitative and descriptive research design to investigate pharmacists' attitudes toward continuous pharmaceutical education, with a focus on high-risk patient groups such as the elderly, children, and individuals with rare diseases. A case series approach was used as a descriptive methodology aimed at identifying and analyzing trends and characteristics among pharmacists involved in delivering specialized pharmaceutical services. This method allowed for a detailed examination of participants' professional experiences and practices, offering valuable insights into the continuing education needs associated with the care of high-risk patients. Elderly patients were of particular interest due to the numerous risks posed by irrational medication use, especially in outpatient settings.

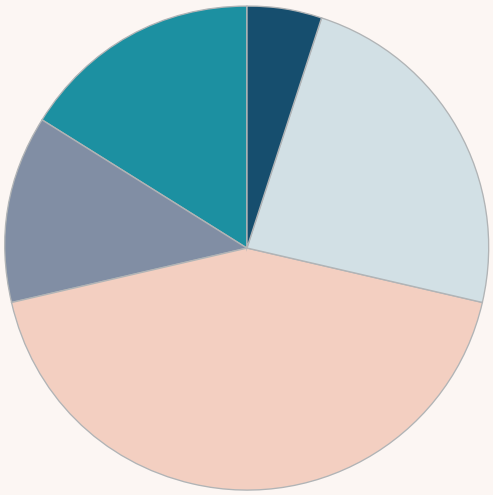
The study was conducted over a two-year period (2022–2024) and involved a sample of 406 specialist pharmacists working in community pharmacies. To determine the minimum representative sample size, Cochran's formula was applied using the following parameters: a total pharmacist population of 1.873 (as reported by the National Bureau of Statistics in 2023), a 95% confidence level (Z = 1.96), a 5% margin of error, and an estimated population proportion of 0.5. The resulting adjusted sample size for this population was approximately 319 pharmacists.

Data were collected using a structured, anonymous questionnaire to ensure objectivity of responses. The questionnaire included 16 closed-ended items: three questions pertained to demographic characteristics, while 13 assessed respondents' levels of agreement or disagreement with statements regarding continuous training in specialized fields.

Microsoft Excel was used for data entry and statistical processing. Descriptive statistics, including frequencies and percentages, were applied to summarize participants' responses and highlight patterns in preferences for continuing education in specialized pharmaceutical care.

## RESULTS

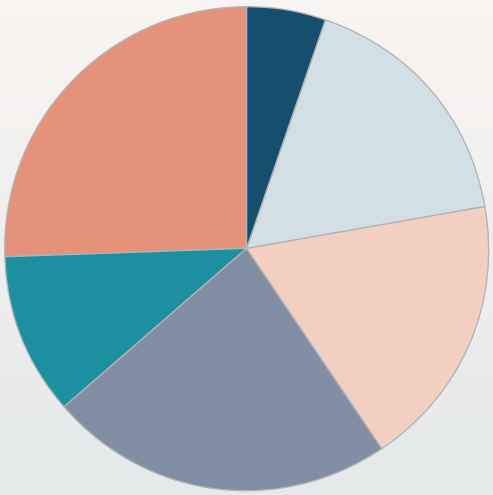
The majority of respondents are specialists aged between 31 and 40 years (42.60%, $CI_{95}$: 37.8-47.4), had over 21 years of professional experience (25.40%, $CI_{95}$: 21.14-29.6) and work in urban environments (86.50%, $CI_{95}$: 83.12-89.78) (see Figures 1-3).



| Color | % | Age category |
|---|---|---|
| | 5.20 | 61-70 years |
| | 23.60 | 20-30 years |
| | 42.60 | 31-40 years |
| | 12.60 | 41-50 years |
| | 16.00 | 51-60 years |

Figure 1. Age category of the respondent pharmacists.

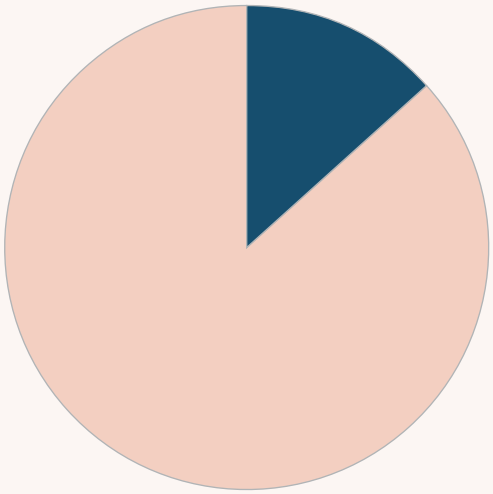
The largest age group among respondent pharmacists is 31-40 years, comprising 42.6% of the total. The second most represented group is 20-30 years, making up 23.6%. Pharmacists aged 51-60 years account for 16%, while those aged 41-50 years represent 12.6%. The smallest category is 61-70 years, with 5.20% of respondents.



| Color | % | Experience |
|---|---|---|
| | 5.40 | Up to one year |
| | 17.00 | 1-5 years |
| | 18.20 | 6-10 years |
| | 23.20 | 11-15 years |
| | 10.80 | 16-20 years |
| | 25.40 | >21 years |

Figure 2. Professional experience of the respondent pharmacists.

The largest group consists of pharmacists with more than 21 years of experience, representing 25.4% of respondents. Those with 11-15 years of experience make up 23.2%, while 6-10 years accounts for 18.2%. Pharmacists with 1-5 years of experience represent 17.0%, and those with 16-20 years make up 10.8%. The smallest category includes pharmacists with less than one year of experience, comprising 5.4% of respondents.

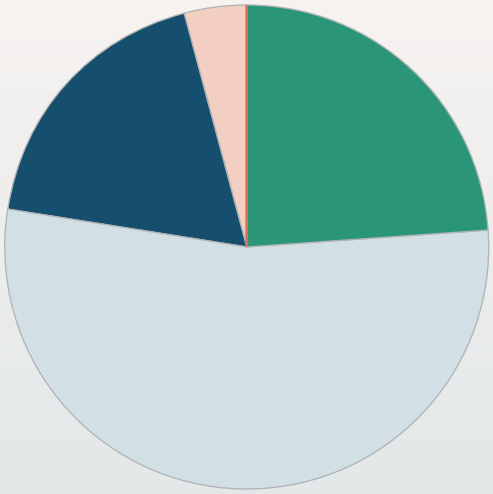


| Color | % | Work areas |
|---|---|---|
| | 13.50 | Rural |
| | 86.50 | Urban |

Figure 3. Work environment of the respondent pharmacists.

The majority of respondent pharmacists work in urban areas, accounting for 86.5% of the total. In contrast, 13.5% of pharmacists work in rural areas.

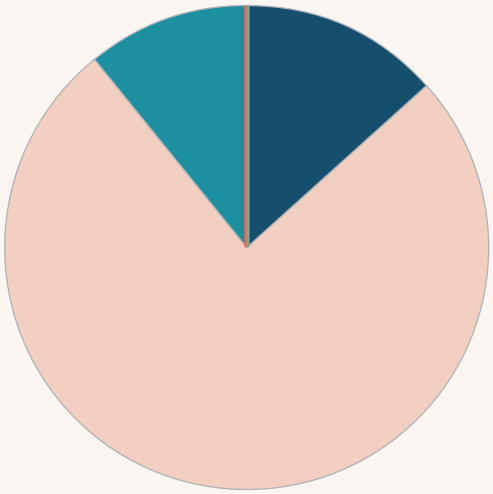
The majority of respondents indicated that they agree that the elderly follow the pharmacist's recommendations regarding the use of medications – total agreement of 23.90% ($CI_{95}$: 19.74-28.04) and partial agreement of 53.70% ($CI_{95}$: 48.84-58.54) (Fig. 4). 75.68% ($CI_{95}$: 71.44-79.79) of the respondents indicated that the elderly often follows their advice regarding medication administration in outpatient settings (Fig. 5). Additionally, more than half of the respondents – total agreement of 21.90% ($CI_{95}$: 17.89-25.94) and partial agreement of 53,20% ($CI_{95}$: 48.34-58.06) claim that they are able to monitor the medication of elderly patients, including OTC, Rx, and potentially dangerous drugs, and can provide specific recommendations when necessary (Fig. 6).



| Color | % | Agree/degree recommendations |
|---|---|---|
| | 0.00 | Total disagreement |
| | 23.90 | Total agreement |
| | 53.70 | Partial agreement |
| | 18.50 | Neutral |
| | 3.90 | Partial disagreement |

Figure 4. To what degree do you agree that elderly patients follow the pharmacist's recommendations regarding medication use?

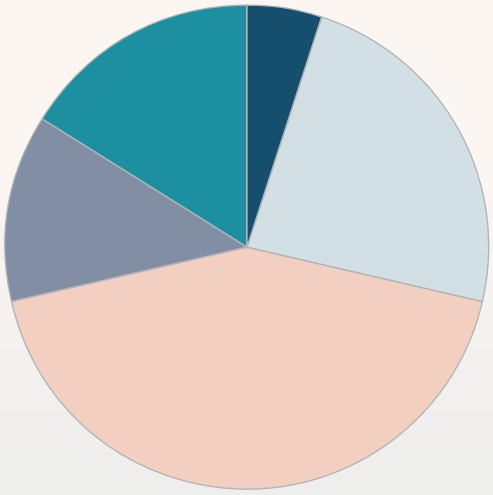
The majority of respondents expressed partial agreement (53.7%), indicating that elderly patients generally follow pharmacists' recommendations regarding medication use. A significant portion (23.9%) reported total agreement, while 18.5% remained neutral. Partial disagreement was noted by 3.9% of respondents, and none (0%) indicated total disagreement.



| Color | % | Follow recommendations |
|---|---|---|
| | 0.00 | Never |
| | 13.51 | Very often |
| | 75.68 | Often |
| | 10.81 | Rarely |
| | 0.00 | Very rarely |

Figure 5. How often does the elderly patient follow your advice regarding medication use?

The majority of respondents indicated that elderly patients often follow pharmacists' advice regarding medication use (75.6%). A smaller portion reported that patients follow recommendations very often (13.5%), while 10.8% noted that adherence occurs rarely. No respondents indicated very rarely or never.



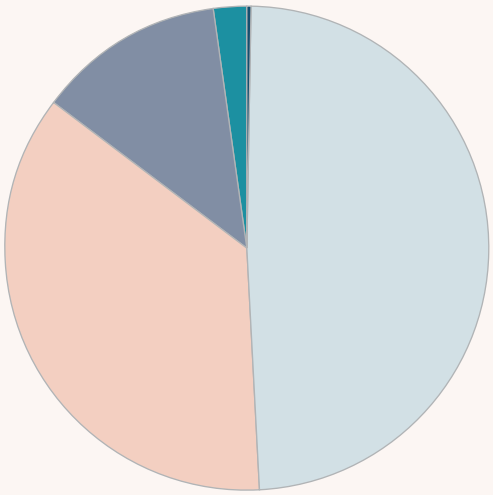
| Color | % | Agree/degree monitoring |
|---|---|---|
| | 2.50 | Total disagreement |
| | 21.90 | Total agreement |
| | 53.20 | Partial agreement |
| | 18.20 | Neutral |
| | 4.20 | Partial disagreement |

Figure 6. To what degree do you agree that the pharmacist is capable of monitoring the elderly patient's medication and intervening, when necessary, with specific recommendation?

The majority of respondents (53.2%) expressed partial agreement, suggesting that pharmacists are generally capable of monitoring elderly patients' medication and providing necessary interventions. 21.9% reported total agreement, indicating strong confidence in pharmacists' ability to manage medication use. 18.2% remained neutral, while 4.2% expressed partial disagreement, and 2.5% indicated total disagreement.

The number of drugs registered in the state drug registry is constantly increasing, along with the variety of dietary supplements used as adjunctive treatments. However, as the range of both drugs and dietary supplements expands, the responsibility of the community pharmacist increases proportionally, because many of these products have not been tested for use in high-risk patient groups, such as children and the elderly. Pharmacists have expressed their total agreement (48.8%, $CI_{95}$: 43.90-53.63) and partial agreement (36.2%, $CI_{95}$: 31.53-40.88) on the relationship between the quality of pharmaceutical

care for the elderly and the effectiveness of pharmacists' ongoing professional education (Fig. 7), that helps pharmacists enhance their skills in managing age-related minor health conditions, recognizing drug interactions, and providing personalized care, minimizing risks associated with polypharmacy and adverse drug reactions etc.

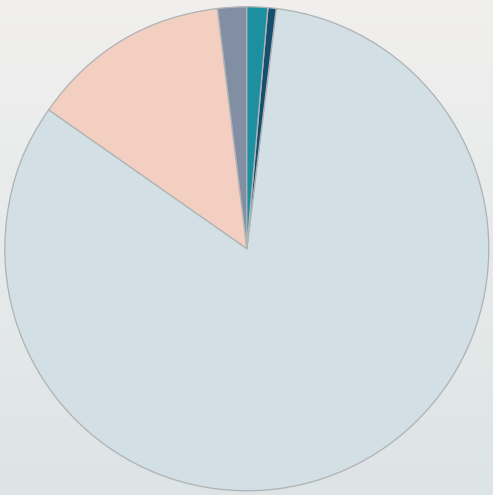


| Color | % | Agree/degree that the quality of care depends on the pharmacists' performance |
|---|---|---|
| | 0.50 | Total disagreement |
| | 48.80 | Total agreement |
| | 36.20 | Partial agreement |
| | 12.60 | Neutral |
| | 2.00 | Partial disagreement |

Figure 7. To what extent do you agree that the quality of geriatric pharmaceutical care depends on the pharmacists' performance obtained through continuous professional training?

The majority of respondents (48.8%) expressed total agreement, indicating strong confidence that the quality of geriatric pharmaceutical care depends on pharmacists' performance gained through continuous professional training. 36.2% reported partial agreement, 12.6% remained neutral, 2.0% expressed partial disagreement and 0.5% indicated total disagreement.

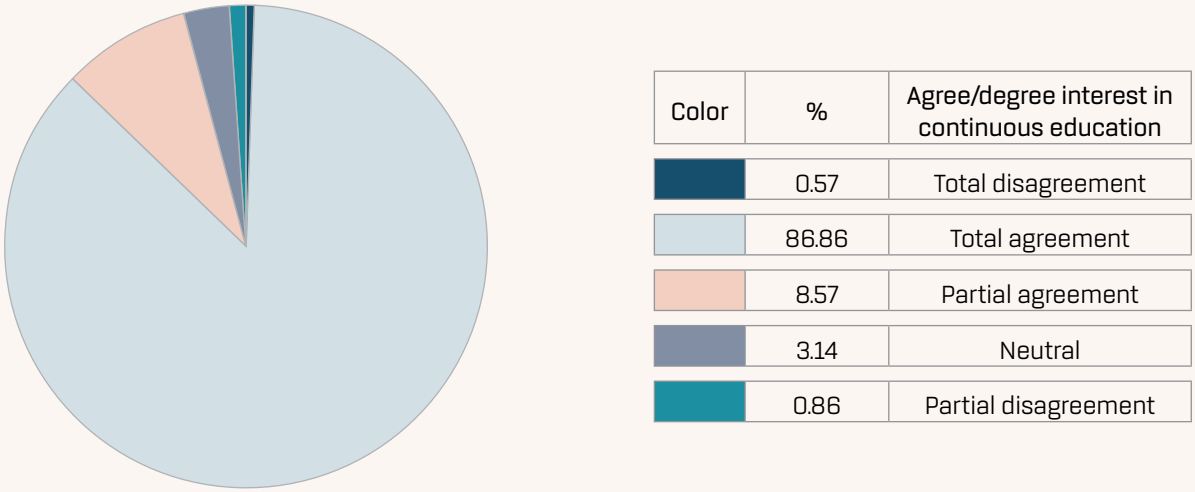
This understanding is reflected in pharmacists' attitudes. Thus, 82.86% ($CI_{95}$: 79.53-85.99) of respondents agree with the statement: „It is important for the community pharmacist to be informed in the field of pediatrics" (Fig. 8). Additionally, 86.86% ($CI_{95}$: 84.04-89.36) of respondents agree with continuous education in the field of pediatric medication (Fig. 9).



| Color | % | Agree/degree informing the community pharmacist about pediatrics |
|---|---|---|
| | 0.57 | Total disagreement |
| | 82.86 | Total agreement |
| | 13.43 | Partial agreement |
| | 1.71 | Neutral |
| | 1.43 | Partial disagreement |

Figure 8. The importance of informing the community pharmacist about pediatrics.

The majority of respondents (82.86%) expressed total agreement, emphasizing the high importance of informing community pharmacists about pediatrics. 13.43% reported partial agreement, 1.71% remained neutral, while 1.43% expressed partial disagreement, and 0.57% indicated total disagreement.



| Color | % | Agree/degree interest in continuous education |
|---|---|---|
| | 0.57 | Total disagreement |
| | 86.86 | Total agreement |
| | 8.57 | Partial agreement |
| | 3.14 | Neutral |
| | 0.86 | Partial disagreement |

Figure 9. Interest in continuous education in the field of pediatric medication.

The majority of respondents (86.86%) expressed total agreement, highlighting strong interest in continuous education in the field of pediatric medication. 8.57% reported partial agreement, 3.14% remained neutral, while 0.86% expressed partial disagreement, and 0.57% indicated total disagreement.

In the context of pediatric medication, several areas for continuous improvement were identified. Specifically, the following areas of interest were highlighted: „Methods of calculating drug dosages for children or for *„off-label"* medications (71.43%, $CI_{95}$: 67.03-75.82); "Evaluating the appropriateness of the prescribed pediatric dose according to the child's age" (60.1%, $CI_{95}$: 55.34-64.86); „Selecting the most appropriate form of administration for pediatric prescriptions" (47.21%, $CI_{95}$: 52.15-42.43); „Counselling parents, guardians, or legal representatives of the child regarding medication administration techniques and potential side effects of medications prescribed to children" (53.44%, $CI_{95}$: 48.60-58.30); "Methods of direct communication with pediatric patients to increase treatment adherence" (52.71%, $CI_{95}$:47.85-57.57). This indicates an increased interest in the topic of training related to high-risk patient care.

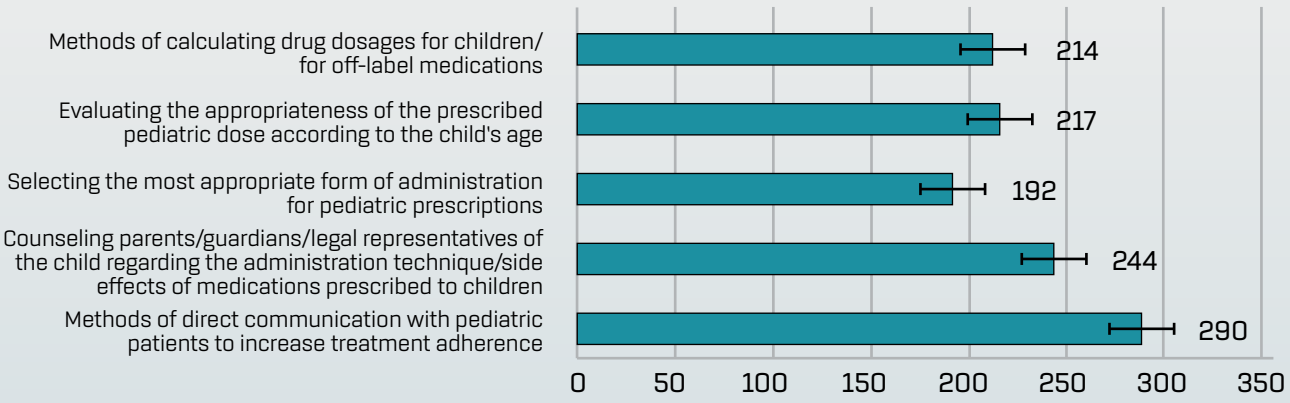



Figure 10. Areas of interest for continuous improvement in the field of pediatric medication.

The most emphasized area of professional interest is the calculation of drug dosages for children, including off-label medications (290 responses). Evaluating the appropriateness of the prescribed pediatric dose according to the child's age is also highly prioritized (244 responses). Additionally, counselling parents, guardians, or legal representatives on administration techniques and potential side effects plays a crucial role (217 responses). There is also considerable interest in methods of direct communication with pediatric patients to improve treatment adherence (214 responses). Lastly, selecting the most appropriate form of administration for pediatric prescriptions remains an area requiring ongoing attention (192 responses).

Since pharmacists are service providers dedicated to supporting the health and well-being of these patient groups, it is essential for them to enhance their values, knowledge, and skills through various avenues of continuous professional development. The rigorous regulation of continuous professional training ensures that pharmacists expand their expertise and knowledge, update their existing skills, and acquire new methods for performing tasks in the community pharmacy, as the profession assumes various roles within health services. The majority of respondents (64.06%, $CI_{95}$: 59.37-68.7) consider that there is often a need for improving knowledge in the field of geriatrics; only 43 respondents indicated that it is rarely needed, one respondent said very rarely, and two said never (Fig. 11). These findings suggest that pharmacists are aware of the responsibility they bear towards the visitors of the community pharmacy. Additionally, they recognize the benefit of periodically updating their knowledge in the field of geriatric pharmaceutical care, with the majority expressing total agreement (63.01%, $CI_{95}$: 58.35-67.74) and 30% ($CI_{95}$: 25.58-34.50) indicating partial agreement. Only 5 respondents disagreed (Fig. 12).

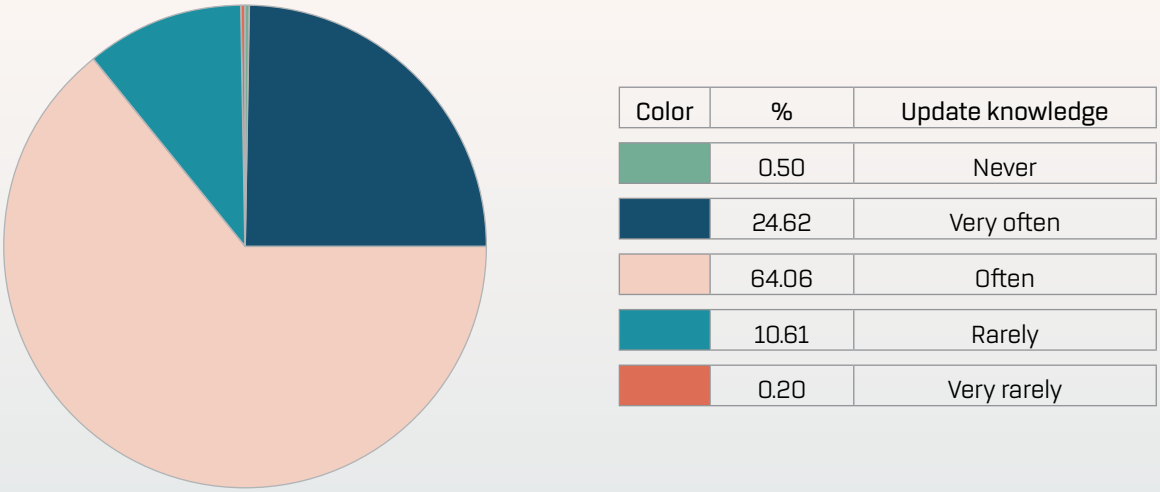



Figure 11. Indicate how often the pharmacist should update their knowledge in the field of geriatrics.

The majority of respondents (64%) believe that pharmacists should update their knowledge in geriatrics often. 24.6% consider it necessary to update knowledge very often, 10.6% think updates should occur rarely, while 0.2% suggest very rarely, and 0.5% believe it is never necessary to update knowledge in this field.

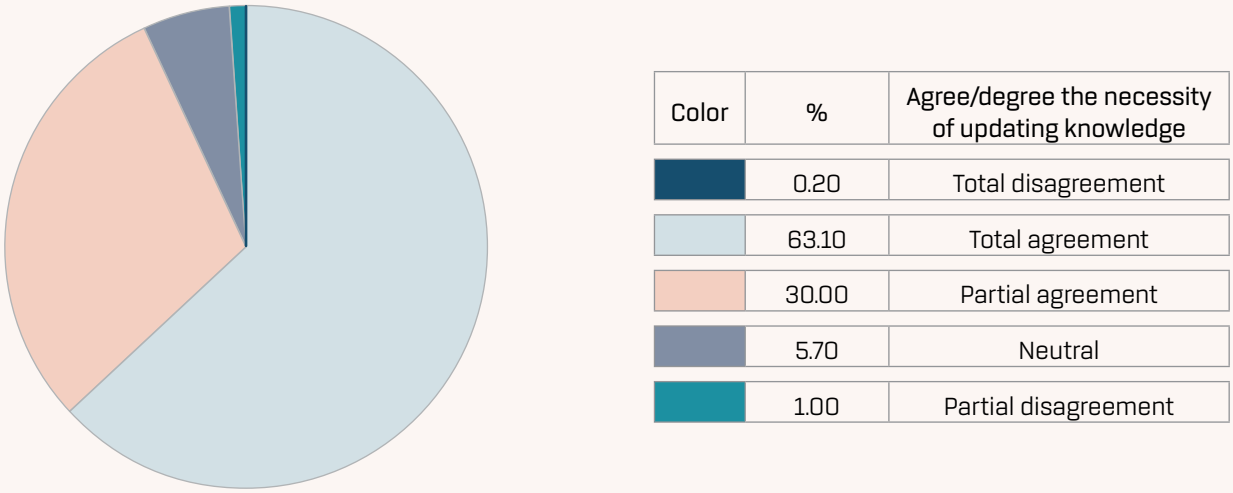



Figure 12. Please state your agreement regarding the necessity of updating knowledge in the field of geriatrics.

The majority of respondents (63.1%) expressed total agreement, emphasizing the necessity of updating knowledge in the field of geriatrics. 30% reported partial agreement, 5.7% remained neutral, while 1% expressed partial disagreement, and 0.2% indicated total disagreement

In response to the question regarding the topics for continuous training in geriatric pharmaceutical care, more than half of the respondents indicated the following: potentially dangerous medications for the elderly, specificities of pharmacotherapy in the elderly, drug interactions, controlled self-medication in the elderly, communication with the elderly patients, polypharmacy, and healthy nutrition for age-related diseases (Tab. 1).

Table 1. The continuous training topics for providing geriatric pharmaceutical care.

| Answer options | Respondents (%) | $CI_{95}$ |
|---|---|---|
| Specificities of pharmacotherapy in the elderly | 65.1 | 60.45-69.75 |
| Controlled self-medication in the elderly | 60.1 | 55.37-64.92 |
| Compliance/adherence to treatment in the elderly | 42.3 | 37.51-47.14 |
| Potentially dangerous medications for the elderly | 72.8 | 68.43-77.11 |
| Communication with the elderly | 56.7 | 51.85-61.51 |
| Drug interactions | 61.1 | 56.38-65.89 |
| Healthy nutrition for certain diseases in the elderly | 50.7 | 45.87-55.62 |
| Detection, monitoring, and analysis of adverse reactions | 38.4 | 33.62-43.01 |
| Polypharmacy | 55.4 | 50.59-60.29 |
| Promotion of an active lifestyle | 45.8 | 40.93-50.65 |
| Including family members in ensuring medication therapy | 32.9 | 28.34-37.50 |

## DISCUSSIONS

The results of this study underscore the importance of continuous pharmaceutical education, particularly in the context of providing care for high-risk patient groups such as the elderly, children, and individuals with rare diseases. These populations face significant risks associated with irrational medication use – especially in outpatient settings – which highlights the crucial role of pharmacists in managing drug therapies and preventing complications.

Continuous professional education is perceived as a key factor in optimizing specialized pharmaceutical care for elderly patients, with pharmacists acknowledging its positive impact on the quality of services provided to this group. The findings highlight a need for enhanced training in managing drug interactions, polypharmacy, and adverse drug reactions – critical components for ensuring the safety of older adults.

In the field of pediatric medication, the study indicates a high level of interest among pharmacists in continuous training, particularly in the correct dosing and counselling of parents regarding medication administration and its effects. Parental counselling plays a distinct role in this regard, and training pharmacists to improve this interaction can have a significant impact on treatment adherence.

In conclusion, the findings not only emphasize the importance of continuous pharmaceutical education but also demonstrate pharmacists' active interest in advancing their expertise in caring for high-risk patients. Strengthening knowledge in geriatrics and pediatrics is essential for improving pharmaceutical care, ensuring the safe use of medications, and supporting pharmacists' ongoing professional development as healthcare providers.

## CONCLUSIONS

1. The study highlighted pharmacists' views on the importance and necessity of strengthening their professional training in delivering pharmaceutical care to high-risk patient groups throughout the medication process.
2. The development and implementation of the course *Specialized Pharmaceutical Assistance for High-Risk Patients* within pharmacists' continuous professional training cycles were justified by the findings.
3. Investing in the development of pharmaceutical personnel and involving them in the provision of healthcare services for high-risk individuals would help meet the specific medication needs of these patients and improve the management of their treatment in outpatient settings.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

## ETHICS APPROVAL

This study was conducted within the framework of the following scientific research projects:

1. „Management of pharmaceutical care for the elderly", minutes of the Research Ethics Committee no. 52 at no. 62 dated 18.06.2015;
2. „Peculiarities of pharmaceutical care for children in outpatient and inpatient conditions", minutes of the Research Ethics Committee no. 75 at no. 81 dated 19.06.2018.

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# CLINICAL AND LABORATORY PREDICTORS OF THERAPEUTIC RESPONSE TO TOCILIZUMAB IN RHEUMATOID ARTHRITIS

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## Summary

**Introduction** Biological disease-modifying antirheumatic drugs (bDMARDs), such as tocilizumab (TCZ), are essential for reducing disease activity in moderate to severe rheumatoid arthritis (RA). This study aims to identify clinical and laboratory predictors of a favorable response to TCZ, enabling personalized therapeutic strategies.

**Material and methods** A longitudinal clinical study in dependent samples included 133 bio-naïve patients (121 women, 12 men, mean age 49.87±13.31 years) with seropositive RA (radiological stages I-III) treated with TCZ and csDMARDs at the Timofei Moșneaga Republican Clinical Hospital. Clinical and laboratory parameters were monitored monthly over a six-month period. Statistical analysis was performed using Spearman's correlation and multiple regression. The Wilcoxon signed-rank test was applied to compare parameters before and after TCZ treatment.

**Results** Favorable response predictors included swollen joint counts (ρ=0.59, p<0.01), tender joint counts (ρ=0.40, p<0.01), C-reactive protein (ρ=0.46, p<0.01), ESR (ρ=0.25, p<0.01), platelet count (ρ=0.29, p<0.01), hemoglobin (ρ=-0.26, p<0.01), hematocrit (ρ=-0.23, p<0.01), and age (ρ=-0.49, p<0.01). Regression analysis confirmed the influence of swollen joint counts (ρ=0.30, p<0.001), age (ρ=-0.30, p<0.001), and C-reactive protein (ρ=0.18, p=0.016) on DAS28 reduction.

**Conclusions** Swollen and tender joint counts, C-reactive protein, and age are key independent predictors of therapeutic success with TCZ after six months of treatment.

**Keywords** Rheumatoid arthritis, bio-naïve, tocilizumab, predictors, markers.

## PREDICTORII CLINICI ȘI DE LABORATOR AI RĂSPUNSULUI TERAPEUTIC LA TOCILIZUMAB ÎN ARTRITA REUMATOIDĂ

**Introducere** Medicamentele biologice antireumatice modificatoare de boală (bDMARDs), precum tocilizumab (TCZ), sunt esențiale pentru reducerea activității bolii în artrita reumatoidă (AR) moderată și severă. Studiul urmărește identificarea predictorilor clinici și de laborator ai unui răspuns favorabil la TCZ pentru optimizarea tratamentului personalizat.

**Material și metode** Studiul prospectiv a inclus 133 de pacienți bio-naivi (121 femei, 12 bărbați, vârsta medie 49,87±13,31 ani) cu AR seropozitivă (stadii radiologice I-III), tratați cu TCZ și csDMARDs la Spitalul Clinic Republican „Timofei Moșneaga". Parametrii clinici și de laborator au fost monitorizați lunar timp de 6 luni. Datele au fost analizate statistic prin corelații Spearman și regresie multiplă. Wilcoxon signed-rank test a fost utilizat pentru a compara parametrii înainte și după tratament.

**Rezultate** Parametrii asociați cu răspuns favorabil au inclus numărul articulațiilor tumefiate (ρ=0,59, p<0,01), numărul articulațiilor dureroase (ρ=0,40, p<0,01), proteina C reactivă (ρ=0,46, p<0,01), VSH (ρ=0,25, p<0,01), trombocitele (ρ=0,29, p<0,01), hemoglobina (ρ=-0,26, p<0,01), hematocritul (ρ=-0,23, p<0,01) și vârsta (ρ=-0,49, p<0,01). Regresia multiplă a confirmat influența numărului articulațiilor tumefiate (ρ=0,30, p<0,001), vârstei (ρ=-0,30, p<0,001) și proteinei C reactive (ρ=0,18, p=0,016) asupra reducerii scorului DAS28.

**Concluzii** Numărul articulațiilor tumefiate și dureroase, proteina C reactivă și vârsta sunt predictori esențiali ai succesului terapeutic cu TCZ după 6 luni de tratament.

**Cuvinte-cheie** Artrită reumatoidă, bio-naiv, tocilizumab, predictor, markeri.

## INTRODUCTION

According to the Treat-to-Target (T2T) strategy, the primary objective in managing rheumatoid arthritis (RA) is to achieve and sustain remission or low disease activity (1). Biological disease-modifying antirheumatic drugs (bDMARDs), such as tocilizumab (TCZ), are essential in implementing this strategy in patients with moderate to severe RA. Despite their effectiveness, there is limited guidance on selecting the most appropriate bDMARD for initiating therapy in bio-naïve patients. Given that up to one-third of RA patients receiving tumor necrosis factor-alpha inhibitors (TNF-i) fail to achieve adequate clinical improvement, a personalized approach to bDMARD therapy may be warranted (2). Initiating treatment with the agent most likely to obtain a positive therapeutic response which could shorten the time to disease control, reduce healthcare costs, and prevent patient frustration – factors that may ultimately enhance treatment compliance. Evidence also suggests that bio-naïve patients may exhibit better responses to biologic therapies compared to those previously treated with biologics, although it remains uncertain whether this is attributable solely to their treatment-naïve status (3). To optimize treatment selection, it may be beneficial to identify clinical and laboratory parameters that predict a more favorable response to specific bDMARDs. This study aims to identify such predictive markers for tocilizumab, a humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor, in patients with seropositive RA.

## MATERIAL AND METHODS

A longitudinal clinical study involving dependent samples was conducted on 133 biologic-naïve patients (121 women and 12 men) diagnosed with seropositive rheumatoid arthritis, according to the 2010 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria. All patients were receiving intravenous tocilizumab (TCZ) in accordance with standard treatment protocols, in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Tocilizumab was administered at a dose of 8 mg/kg every 4 weeks in 113 patients (85%), while the remaining 20 patients (15%) received 4 mg/kg at the same interval. In addition to TCZ, 115 patients (86%) were treated with methotrexate at weekly doses ranging from 10 to 12.5 mg, and 18 patients (14%) received leflunomide at a maintenance dose of 10–20 mg daily. Prior to initiating TCZ therapy, 101 patients (76%) were taking daily methylprednisolone at doses of 4–12 mg, while 32 patients (24%) did not require corticosteroids for symptom control. Corticosteroid dosages were individually tapered throughout the course of treatment. The mean age of the patients was 49.87 ± 13.31 years. Before initiating TCZ therapy, the mean disease activity, assessed using the Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP), was 6.12 ± 1.02, and the mean disease duration was 10.08 ± 6.9 years. Most patients had radiologically confirmed signs of disease, classified as Steinbrocker stage II in 64.66%, stage III in 30.83%, and stage I in 4.51%. Data from patients who discontinued or interrupted TCZ therapy – thereby deviating from the standard treatment regimen – as well as those who ceased csDMARD use, were excluded from the final analysis. To evaluate treatment efficacy, the following parameters were assessed prior to each TCZ administration (initially and then approximately once per month): tender joint count (TJC), swollen joint count (SJC), DAS28-CRP score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, hematocrit, red blood cell (RBC) count, absolute neutrophil count, absolute lymphocyte count, and platelet count.

Data were collected from the medical records of patients who received TCZ treatment at the Timofei Moșneaga Republican Clinical Hospital in Chișinău, Moldova, between February 2022 and July 2024, with informed patient consent. The compiled data were used to conduct statistical analyses aimed at identifying baseline clinical and laboratory parameters that could predict a favorable therapeutic response to TCZ. Spearman correlation coefficients were calculated to assess the relationship between individual parameters and the reduction in disease activity. Multiple regression analysis was conducted to determine independent predictors of treatment efficacy. The Wilcoxon signed-rank test was applied to compare clinical parameters before and after TCZ therapy. Disease activity was assessed using the composite score DAS28-CRP. To quantify changes in disease activity, the delta DAS28-CRP was calculated as the difference between the baseline DAS28-CRP score and the score recorded after six months of treatment. The multiple regression model used the following equation for the dependent variable DAS28-CRP: $z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k$ where z – result of the equation, $X_1$-$X_k$ – investigated predictors, $\beta_0$ – intercept, and $\beta_1$-$\beta_k$ – regression coefficients. Probability of the multiple regression ($P = 1/(1 + e^{-z})$; e≈2.71828) and coefficient of multiple determination $R^2$ were calculated. The statistical analysis was performed using Statistica StatSoft 10, 95% CI, $p<0.05$.

This study did not require approval from an Ethics Committee because it adhered strictly to standard clinical protocols and guidelines outlined in the national clinical protocol *"Rheumatoid Arthritis in Adults"* of the Republic of Moldova. All procedures, including the administration of tocilizumab and csDMARDs, were carried out as part of routine medical practice and complied with national healthcare regulations under the mandatory health insurance program. Data were collected from patient records with full respect for anonymity and confidentiality. Informed consent was obtained from all participants for the use of their anonymized medical data for research purposes.

## RESULTS

The EULAR response criteria for assessing treatment effectiveness in rheumatoid arthritis are based on changes in the DAS28 composite score after 3 to 6 months of therapy. A good response is defined as a reduction in DAS28 of more than 1.2, with a final score below 3. A moderate response corresponds to a reduction of 0.6 to 1.2, while a reduction of less than 0.6 indicates a non-response (4). According to these criteria, 49 patients (36.85%) were classified as good responders, 80 (60.15%) as moderate responders, and 4 (3.01%) as non-responders to tocilizumab therapy, which was added to their existing csDMARD and corticosteroid regimen.

Swollen joint count (SJC) showed a moderate positive correlation with the reduction in disease activity ($\rho = 0.59$, $p < 0.01$) (Fig. 1). Similarly, tender joint count (TJC) was positively correlated with disease activity reduction, though to a lesser extent ($\rho = 0.40$, $p < 0.01$) (Fig. 2). Age showed a moderate negative correlation with the reduction in disease activity ($\rho = –0.49$, $p < 0.01$). C-reactive protein (CRP) levels ($\rho = 0.46$, $p < 0.01$) (Fig. 3) and erythrocyte sedimentation rate (ESR) ($\rho = 0.25$, $p < 0.01$) were both positively associated with a reduction in disease activity. While the correlation with CRP was moderate, the correlation with ESR was weak. A moderate positive correlation was also observed between CRP and ESR ($r = 0.52$, $p < 0.01$). Baseline hemoglobin ($\rho = –0.26$, $p < 0.01$) and hematocrit ($\rho = –0.23$, $p < 0.01$) levels before initiating TCZ therapy were inversely correlated with the degree of DAS28 reduction. An increase in hemoglobin levels was noted over the course of treatment (Fig. 4). Platelet counts, although within normal ranges, showed a weak but statisti-

cally significant positive correlation with the reduction in disease activity ($\rho = 0.29$, $p < 0.01$) (Fig. 5). In contrast, red blood cell counts, absolute neutrophil and lymphocyte counts, and disease duration did not demonstrate any significant correlation with changes in disease activity.

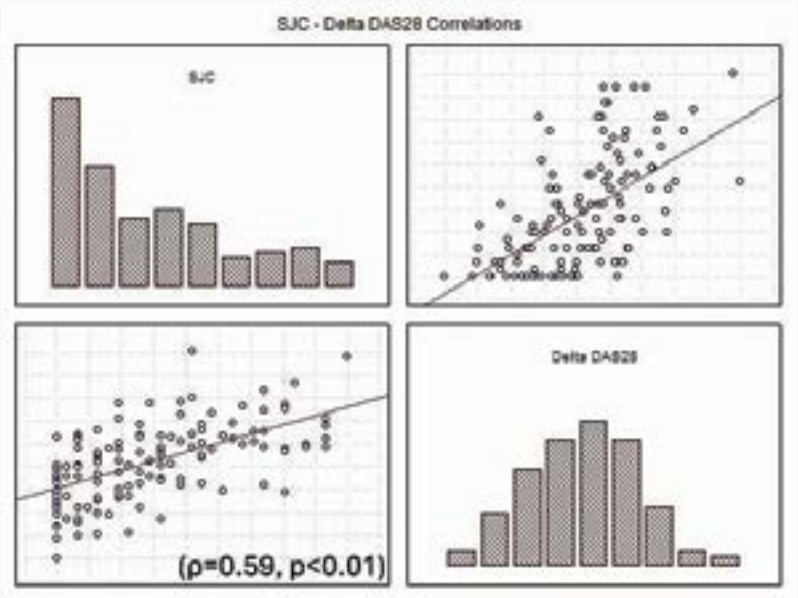


Figure 1. Swollen joint count (SJC) upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after a 6-month treatment (scatterplot).

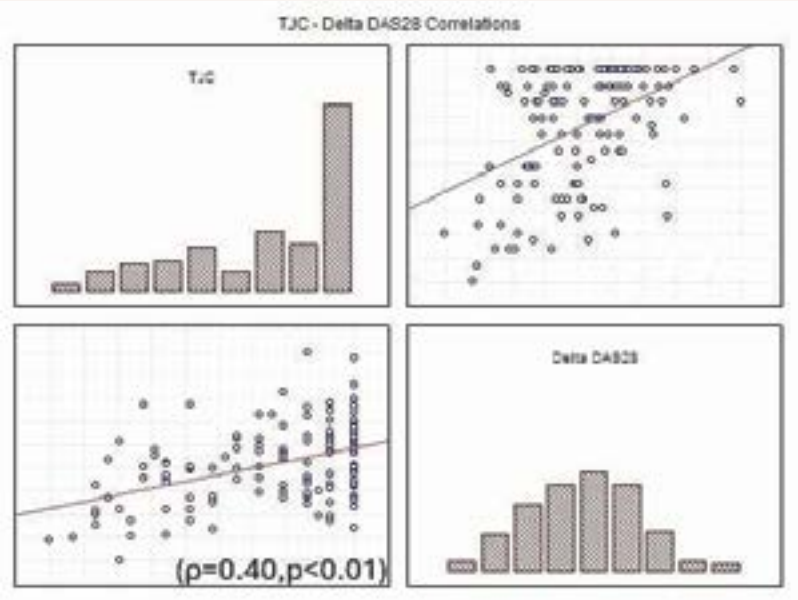


Figure 2. Tender joint count (TJC) upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after 6-month treatment (scatterplot).

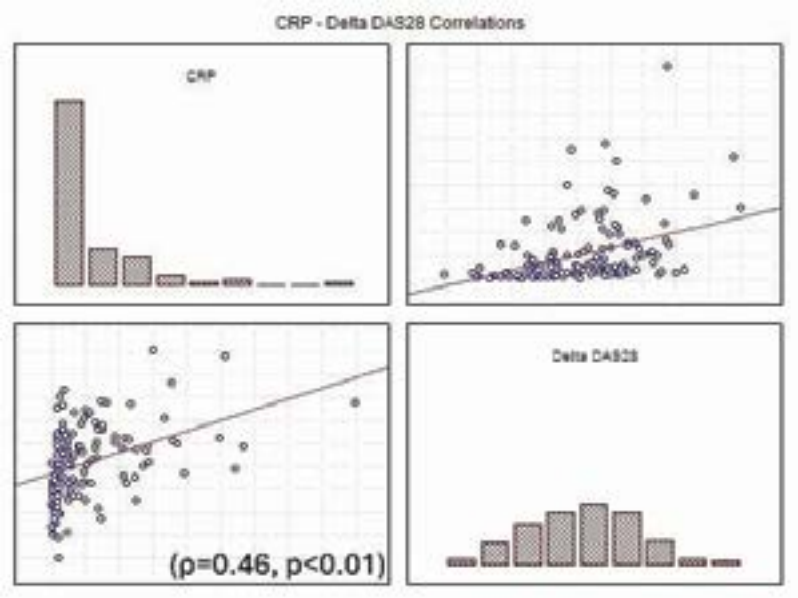


Figure 3. C-reactive protein levels upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after 6-month treatment (scatterplot).

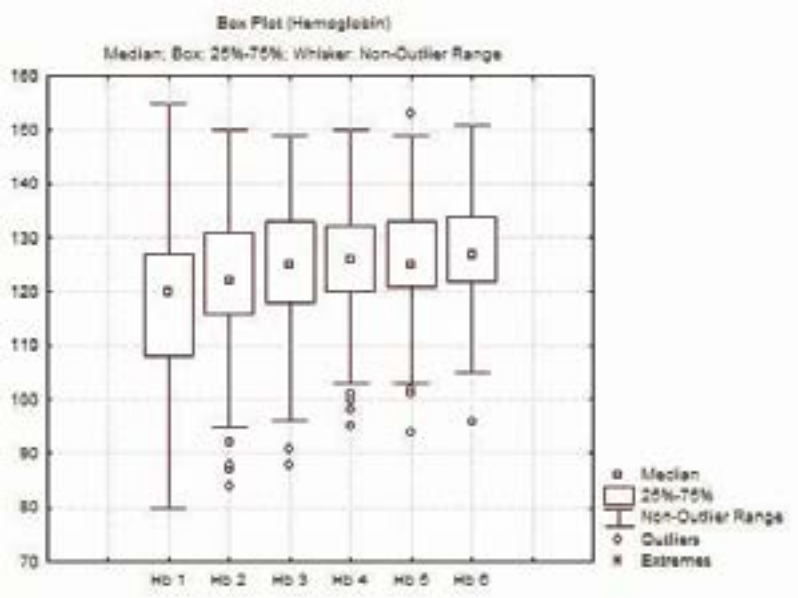


Figure 4. Hemoglobin levels assessed monthly over the 6-month treatment period (box and whisker plot).

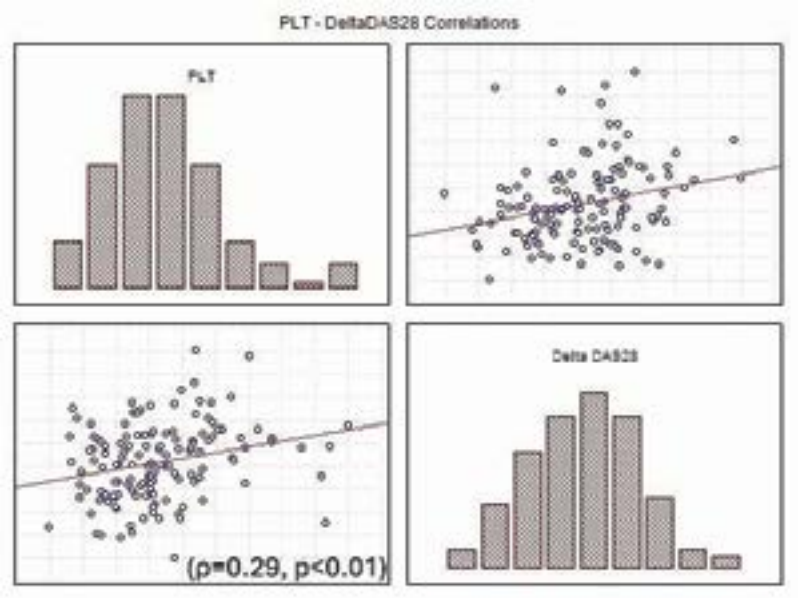


Figure 5. Platelet count upon the start of tocilizumab therapy correlated with reduction in DAS28-CRP score after 6-month treatment (scatterplot).

A multiple regression analysis was performed to evaluate the combined effect of various factors on the dependent variable ΔDAS28. The resulting equation was as follows:

$$z = 2.346 - 0.3X_1 + 0.085X_2 + 0.145X_3 + 0.240X_4 + 0.30X_5 - 0.25X_6 + 0.246X_7 - 0.08X_8 - 0.01X_9 + 0.020X_{10} + 0.038X_{11} + 0.001X_{12}$$

where $X_1$ – patient age; $X_2$ – erythrocyte sedimentation rate; $X_3$ – C-reactive protein levels; $X_4$ – tender joint count; $X_5$ – swollen joint count; $X_6$-hemoglobin level; $X_7$ – hematocrit; $X_8$ – red blood cell count; $X_9$ – neutrophil count; $X_{10}$- lymphocyte count; $X_{11}$ – duration of disease; $X_{12}$ – platelet count.

The multiple regression model was statistically significant, adjusted $R^2$ = 0.4863 ($p<0.001$). The calculated probability of multiple regression was high (P=94%).

Regression analysis determined SJC ($\beta=0.30$, $p<0.001$), TJC ($\beta=0.24$, $p=0.0012$) and age ($\beta=-0.30$, $p<0.001$) as significant predictors. Neither CRP nor ESR showed statistically significant beta coefficients in the model when both were included ($p > 0.05$). However, when CRP was excluded, ESR became a significant predictor ($\beta = 0.16$, $p = 0.028$), and when ESR was excluded, CRP showed a significant effect ($\beta = 0.18$, $p = 0.016$). Hemoglobin level, hematocrit, platelet count, red blood cell count, and absolute neutrophil and lymphocyte counts were not statistically significant predictors ($p > 0.05$).

The tables below present the pre- and post-treatment values of the analyzed clinical (Tab. 1) and laboratory (Tab. 2) parameters, along with the median change in each parameter following tocilizumab treatment and the statistical significance of these changes, as determined by the Wilcoxon signed-rank test.

Table 1. Clinical features assessed at the initiation of tocilizumab therapy.

| Clinical parameters | Mean before TCZ | Mean after 6 months of treatment | Median of change after 6 months of treatment | Significance level calculated by Wilcoxon signed-rank test (p) |
|---|---|---|---|---|
| TJC | 21.1±7.3 | 8.1±5.3 | - 13.0 | <0.001 |
| SJC | 8.8±7.6 | 1.4±2.4 | - 6.0 | <0.001 |
| DAS28-CRP | 6.1±1.02 | 3.5±0.8 | - 2.64 | <0.001 |
| *Note*: TJC, tender joint count; SJC, swollen joint count. DAS28-CRP, Disease Activity Score in 28 joints with C-reactive protein. | | | | |

Table 2. Laboratory findings assessed at the initiation of tocilizumab therapy.

| Laboratory parameters | Mean before TCZ | Mean after 6 months of treatment | Median of change after 6 months of treatment | Significance level calculated by Wilcoxon signed-rank test (p) |
|---|---|---|---|---|
| ESR (mm/hour) | 25.7±14.9 | 6.9±6.6 | - 15.0 | <0.001 |
| CRP (mg/L) | 19.1±25.0 | 2.2±2.9 | - 7.1 | <0.001 |
| Hb (g/L) | 118.2±14.5 | 127.8±9.8 | 9.0 | <0.001 |
| Hct (%) | 36.43±4.22 | 38.36±2.86 | 1.5 | <0.001 |
| RBC ($\times 10^6/\mu L$) | 4.16±0.42 | 4.17±0.29 | -0.16 | 0.524 |
| NEU ($10^3/\mu l$) | 4.25±2.1 | 4.4±1.3 | 0.67 | 0.106 |
| LYM ($10^3/\mu l$) | 2.1±0.8 | 5.5±5.0 | 3.85 | <0.001 |
| PLT ($10^3/\mu l$) | 311.8±91.5 | 208.5±53.0 | -97.0 | <0.001 |
| *Note*: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, Hemoglobin; Hct, hematocrit; RBC, red blood cell count; NEU, absolute neutrophil count; LYM, absolute lymphocyte count; PLT, platelet count. | | | | |

## DISCUSSIONS

In previous studies, rheumatoid factor, platelet count, hemoglobin levels, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) have been identified as potential predictors of a more favorable response to tocilizumab compared to other bDMARDs (5, 6). In the present sample, factors associated with a greater reduction in disease activity included elevated CRP and ESR, higher platelet counts, lower hemoglobin and hematocrit levels, younger age, and increased swollen and tender joint counts.

C-reactive protein is an acute-phase reactant produced by hepatocytes in response to stimulation by pro-inflammatory cytokines, particularly interleukin-6 (IL-6), whose activity is inhibited by TCZ (7). Previous studies suggest that in certain cases of RA, specific cytokines may play a more dominant role, rendering bDMARDs targeting less involved pathways less effective (2). It has been proposed that CRP could serve as a readily accessible, indirect marker of IL-6-driven disease, with higher baseline CRP levels potentially indicating greater responsiveness to IL-6 blockade. However, CRP appears to be an

unreliable standalone predictor of therapeutic efficacy, as reductions in CRP levels do not consistently correspond with clinical improvement (8, 9).

In contrast to CRP, ESR is also likely influenced by RF and other immunoglobulins (10). A 2022 study further suggests that ESR may serve as a predictor of tocilizumab efficacy in slowing the radiological progression of RA (11). However, due to its low specificity, ESR should be considered a supportive indicator of disease activity – and by extension, a potential predictor of treatment response – only when interpreted alongside more specific biomarkers and clinical findings.

Platelet counts are elevated by IL-6 through increased megakaryocyte differentiation and high thrombopoietin expression (12). It has been hypothesized that elevated platelet counts may characterize RA cases in which IL-6-driven inflammation predominates. A 2017 study used platelet counts, along with hemoglobin, AST, and ALT levels, to develop a scoring system for comparing the efficacy of TCZ and TNF-i therapies (6). The present findings align with the notion that higher platelet counts may be associated with a more favorable response to TCZ.

In this patient cohort, pre-treatment hemoglobin levels showed an inverse correlation with treatment efficacy. The gradual increase in hemoglobin observed during therapy (Figure 4) suggests that systemic inflammation was likely a major contributing factor to anemia at the tocilizumab treatment initiation. Prior to therapy, 62 patients (46%), all of whom were women, were found to be anemic – 34 with moderate and 28 with mild anemia based on hemoglobin levels. As inflammation subsided, hemoglobin levels rose, and by six months, anemia was identified in only 17 patients (13%) – 4 with moderate and 13 with mild anemia.

Although the literature supports the beneficial effect of TCZ on hemoglobin levels in patients with RA (13), this study lacks data on baseline iron status. It remains unclear whether any patients received concurrent treatment for iron deficiency anemia, making it difficult to determine the relative impact of iron deficiency versus RA-associated chronic inflammation on hemoglobin levels. Nevertheless, a 2013 study also reported that tocilizumab was more effective in improving anemia than TNF-α inhibitors, attributing this effect to reduced hepcidin production following IL-6 inhibition (14).

In the present study sample, younger patients tended to show a greater reduction in disease activity, a finding consistent with previous research (15). This may be partly due to a shorter disease duration, as biological therapy was initiated sooner after diagnosis in younger patients compared to older ones. Consequently, younger individuals often exhibit fewer morphological changes, and the associated cyto-molecular processes may be less established. A similar rationale has been proposed in discussions regarding whether bio-naïve patients respond more favorably to biologics, as they are typically younger, have a shorter disease course, and exhibit less advanced pathological changes. However, in this sample, disease duration was not a significant predictor of TCZ treatment efficacy.

In the study sample, both tender and swollen joint counts showed a correlation with tocilizumab efficacy. Among them, the swollen joint count was the more significant and specific predictor of therapeutic success, a finding supported by previous studies as well (16). One possible explanation for the superior predictive value of SJC is that tenderness may be reported in joints affected by other conditions, such as osteoarthritis, making it a less specific marker for RA activity. In contrast, joint swelling can be more objectively assessed by the clinician, thereby offering greater diagnostic specificity.

Multiple recent studies contributed to the individualization of treatment by comparing the efficacy of various biologic agents and exploring cyto-molecular characteristics of RA that may serve as predictors of therapeutic response (17). Notably, elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) have been associated with a poor response to tocilizumab (18). At the same time, the combination of histopathological classification and genetic analysis appears to offer promising results in identifying RA subtypes more likely to respond to specific therapies, thus guiding the choice of therapies (19).

This study has several limitations. Firstly, the relatively small sample size limited the ability to thoroughly analyze less typical presentations of RA (e.g., age <30, disease duration >25 years). Secondly, the medical charts lacked detailed information on investigations and treatments unrelated to RA management, which prevented conclusions regarding certain findings – such as potential causes of the observed changes in hemoglobin levels. Thirdly, the data reflected outcomes only at the end of a limited follow-up period, making it uncertain whether the identified predictors remain valid for maintaining low disease activity beyond the 6-month period.

## CONCLUSIONS

1. A greater reduction in disease activity following tocilizumab treatment added to background therapy was positively associated with higher swollen and tender joint counts, elevated C-reactive protein (CRP) levels, increased erythrocyte sedimentation rate (ESR), and elevated platelet counts.
2. Hemoglobin and hematocrit levels were negatively correlated with the reduction in disease activity.
3. Swollen and tender joint counts, as well as age, were identified as independent predictors of improved therapeutic response to tocilizumab.
4. These findings indicate that bio-naïve, seropositive rheumatoid arthritis patients who are younger, exhibit high disease activity, and have a greater number of affected joints are more likely to achieve a favorable response to tocilizumab after six months of treatment.

## CONFLICT OF INTEREST

The authors of the article deny the existence of any conflict of interest in the publication of this research.

## ETHICS APPROVAL

The study was approved by the Research Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy (Decision no. 21 of 21.12.2019).

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BIOLOGICAL SCIENCES

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# SYNTHESIS, ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION AND ANTIOXIDANT ASSAY OF SOME N4 – SUBSTITUTED THIOSEMICARBAZONES OF CINNAMALDEHYDE

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## ABSTRACT

**Introduction** The increasing number of cancer diagnoses is a pressing issue in modern medicine. One contributing factor to cancer development is oxidative stress caused by free radicals, which can damage proteins, lipids, and DNA. Antioxidants are commonly used to mitigate these effects by neutralizing free radicals and reducing their harmful impact. Recent studies have shown that thiosemicarbazones may have antioxidant properties. These compounds are also known for their potential as anticancer, antibiotic, and antifungal agents. In this research, a series of thiosemicarbazones were synthesized and their antioxidant capacity was evaluated. Additionally, the ADME (Absorption, Distribution, Metabolism, Excretion) parameters of the synthesized compounds were evaluated to determine their potential as pharmaceutical candidates.

**Material and methods** All starting reagents were purchased from Sigma Aldrich or Alfa Aesar. The synthesis of the compounds was carried out using classical methods, adopted for this study. ADME analysis was performed using ADMETLabs 3.0 platform. Antioxidative properties were investigated using the standard assay method.

**Results** Five thiosemicarbazones were synthesized. The presence of characteristic functional groups was confirmed by FTIR spectroscopy. Synthesized compounds have a good ADME profile, characteristic of biologically active compounds. It was found that compounds 1 and 5 exhibit antioxidative activity in 6 times and 3 times higher than Trolox.

**Conclusions** Obtaining new thiosemicarbazones based on cinnamaldehyde with the study of antioxidant properties and ADME screening would allow in the future that these products can be tested in the clinical and preclinical stages with rigorous evaluations. The synthesized products represent an increased antioxidant potential for the biopharmaceutical field.

**Keywords** N4-substituted thiosemicarbazones; cinnamaldehyde; antioxidant activity; ADME analysis.

## SINTEZA, STUDIUL ADME ȘI ACTIVITATEA ANTIOXIDANTĂ A UNOR TIOSEMICARBAZONE N4 SUBSTITUITE ALE ALDEHIDEI CINAMICE

**Introducere** Una dintre problemele actuale ale medicinei moderne o constituie creșterea permanentă a cazurilor de cancer. Deseori, cancerul reprezintă consecința stresului oxidativ, cauzat de radicalii liberi. Acesta conduce la deteriorarea ADN-ului și a proteinelor. Pentru combaterea stresului oxidativ sunt folosite substanțe cu efect antioxidant. Ele captează radicalii liberi, reducând efectele nocive ale acestora. Mulți cercetători raportează că tiosemicarbazonele pot manifesta efecte antioxidante. Pe lângă aceasta, compușii respectivi sunt cunoscuți și pentru efectele lor anticancerigene, antibiotice și antifungice. În cadrul cercetării a fost sintetizată o serie de tiosemicarbazone și a fost examinată proprietatea lor antioxidantă. De asemenea au fost evaluați parametrii ADME, în scopul determinării potențialului farmaceutic al compușilor sintetizați.

**Material și metode** Toți reagenții au fost achiziționați de la Sigma Aldrich sau Alfa Aesar. Sinteza compușilor 1-5 a fost realizată conform procedurilor de sinteză clasică, cu unele adaptări de rigoare, în cazul nostru. Analiza ADME a fost efectuată utilizând ADMET Labs 3.0. Analiza antioxidantă a fost realizată prin intermediul metodei standard.

**Rezultate** Au fost sintetizate cinci tiosemicarbazone noi. Prezența grupelor funcționale caracteristice a fost confirmată prin intermediul spectroscopiei FTIR. Compușii sintetizați au un profil ADME bun, caracteristic substanțelor biologic active. S-a observat, în cazul compușilor 1 și 5, o activitate antioxidantă de 6 și de 3 ori mai mare decât în cazul Trolox, substanță de referință.

**Concluzii** Obținerea de noi tiosemicarbazone pe bază de cinamaldehidă, prin studiul proprietăților antioxidante și screening ADME, ar permite în viitor testarea acestor produse în stadiile clinice și preclinice cu evaluări riguroase. Produsele sintetizate reprezintă un potențial antioxidant sporit pentru domeniul biofarmaceutic.

**Cuvinte-cheie** Tiosemicarbazone N4-substituite, cinamaldehidă, activitate antioxidantă, analiza ADME.

## INTRODUCTION

Medicinal chemistry, like many scientific disciplines, is continually evolving to meet emerging health challenges. The recent SARS-CoV-2 pandemic has underscored humanity's vulnerability to global health crises and emphasized the urgent need for the development of novel therapeutic agents. The rising incidence of cancer remains a major concern. As shown in Figure 1, the annual incidence is expected to nearly double by 2050 (1). One contributing factor to cancer development is the presence of free radicals – highly reactive species capable of inducing oxidative stress (2). These species can damage cellular proteins, impairing their function, and disrupt lipid membranes, thereby compromising membrane integrity (3). Additionally, free radicals can induce DNA damage and genetic mutations (4). For example, mutations in the gene encoding phosphoinositide 3-kinase (PI3K), a key enzyme in the PI3K/AKT/mTOR signaling pathway, can result in permanent activation of PI3K, leading to uncontrolled cell growth (5). Antioxidants are commonly used to combat free radicals. These compounds have the ability to trap and bind free radicals, neutralizing their harmful effects. This process can reduce or even prevent oxidative damage and mutations.

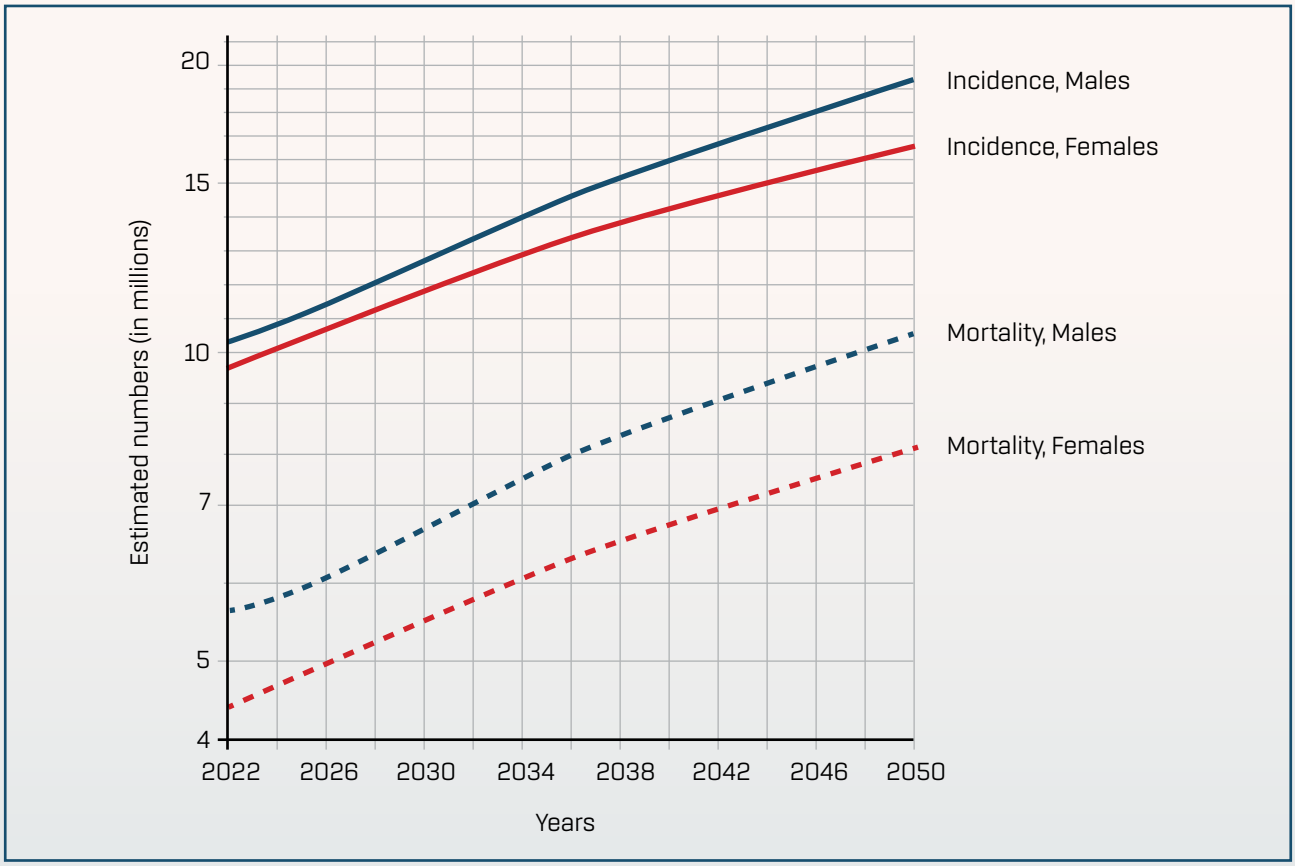


Figure 1. Estimated numbers of cancer incidence and mortality for 2022-2050 period, for males and females (1).

In this context, the development of novel compounds with antioxidant properties represents a highly promising area of research. Thiosemicarbazones, which can be considered derivatives of Schiff bases, have attracted considerable attention due to their diverse biological activities. Several studies (6, 7) have reported the antioxidant properties of specific thiosemicarbazones and their metal complexes, some of which have demonstrated greater activity than reference antioxidants such as Trolox and Rutin. Additionally, other

studies (8, 9) have described the antiproliferative activity of thiosemicarbazones against HL-60 leukemia cells. These compounds have also exhibited antimicrobial (10–12), antifungal (12, 13), and antitumor (14, 15) properties. Despite their promising biological effects, it is crucial for thiosemicarbazones to exhibit low toxicity levels for practical use. One potential solution to this issue is the introduction of natural compounds in their synthesis. In this study, thiosemicarbazones were synthesized using cinnamaldehyde, a compound naturally found in the bark of cinnamon trees (16). Previous research has shown that cinnamaldehyde itself possesses antimicrobial activity (17) and it is safe for human consumption, as it is commonly used in the food industry. This article reports the synthesis of five cinnamaldehyde-based thiosemicarbazones and evaluates their antioxidant activity and ADME (Absorption, Distribution, Metabolism, and Excretion) profiles. The aim of this study was to obtain thiosemicarbazone derivatives with antioxidant properties and favorable pharmacokinetic parameters, supporting their potential for future pharmaceutical development.

## MATERIAL AND METHODS

All starting reagents were purchased from Sigma Aldrich or Alfa Aesar and used without any further purification. FTIR spectroscopy was performed using a Brucker Alpha spectrometer at room temperature. ADME analysis was performed using ADMETLab3.0 (18). Antioxidant activity assay was performed using the procedure described in source (19). General procedures for compounds synthesis have been taken and adapted from sources (20, 21, 22).

### GENERAL PROCEDURE FOR ISOTHIOCYANATES SYNTHESIS

The primary amine (1.0 equiv.) was dissolved in a biphasic mixture of hexane and water, followed by the addition of sodium bicarbonate ($NaHCO_3$, 2.0 equiv.). The reaction mixture was cooled to approximately 0 °C, and a solution of thiophosgene (1.0 equiv.) in hexane was added dropwise under stirring. The mixture was then stirred at room temperature until the red-orange color disappeared. The organic (hexane) layer was separated, washed three times with saturated $NaHCO_3$ solution, and dried over anhydrous $Na_2SO_4$. After removal of the solvent under reduced pressure, the resulting pale yellow oils were obtained, affording hexyl isothiocyanate in 76% yield and octyl isothiocyanate in 83% yield.

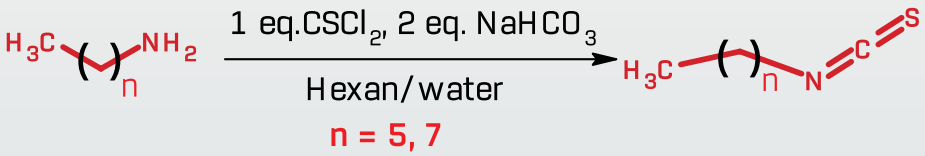


Figure 2. Scheme of isothiocyanates synthesis.

### GENERAL PROCEDURE FOR THIOSEMICARBAZIDES SYNTHESIS

The reaction for the formation of thiosemicarbazides was carried out according to the following synthesis protocol: the appropiate isothiocyanate dissolved in tetrahydrofuran is added dropwise to the solution of hydrazine monohydrate in THF while the reaction mixture was cooled in an ice and salt bath during the mixing of the initial reagents. After the addition was complete, the mixture was stirred at room temperature for 30 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC).

The resulting precipitate was filtered, washed with cold ethanol, and then washed three times with diethyl ether. The reaction afforded white solids: $N^4$-hexylthiosemicarbazide (85% yield), $N^4$-octylthiosemicarbazide (92% yield), and $N^4$-norbornylthiosemicarbazide (91% yield). The melting points and IR spectra of the products were consistent with those reported in the literature.

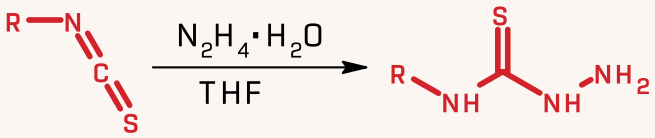


Figure 3. Scheme of thiosemicarbazides synthesis, R = *exo*-norborn-2-yl, hex-1-yl and oct-1-yl.

## MORPHOLINE-THIOSEMICARBAZIDE SYNTHESIS

Thiophosgene (1.0 equiv.) was dissolved in chloroform and, with constant stirring, added to a chloroform solution of morpholine (1.0 equiv.) and triethylamine (1.0 equiv.), which had been cooled in an ice–salt bath. The reaction mixture was then stirred at room temperature for 3 hours. Diethyl ether was subsequently added until triethylamine hydrochloride fully precipitated. The precipitate was removed by filtration, and the resulting solution was concentrated using a rotary evaporator. Cold hexane was added to the concentrated solution to induce crystallization. The crystalline solid was collected by filtration and air-dried to afford morpholine-4-carbothioyl chloride as a pale yellow solid in 55% yield.

To a solution of hydrazine monohydrate (1.0 equiv.) in absolute 1,4-dioxane, a solution of morpholine-4-carbothioyl chloride (1.0 equiv.) was added dropwise. The reaction mixture was stirred for 30 minutes at room temperature, leading to the formation of a light pink precipitate. The product was filtered, washed with diethyl ether, and dried to yield morpholine-thiosemicarbazide (IUPAC name: morpholine-4-carbothiohydrazide) as a white solid in 67% yield.

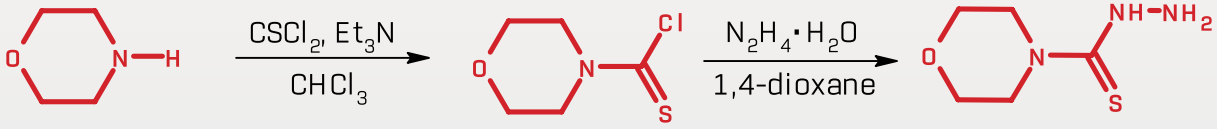


Figure 4. Scheme of morpholine-4-carbothiohydrazide synthesis.

## GENERAL PROCEDURE FOR THIOSEMICARBAZONES SYNTHESIS

In a round-bottomed flask, 1 equivalent of the corresponding thiosemicarbazide and 1 equivalent of cinnamaldehyde were added, using ethanol as a solvent. A small amount of glacial acetic acid (3-5 drops) was then added as a catalyst. The mixture was refluxed for 2-4 hours, with the consumption of the initial compounds monitored using chromatography. After cooling, the reaction mixture was filtered and the solid product was washed with ethanol and dried.

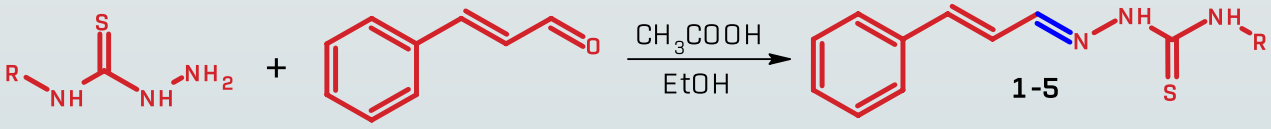


Figure 5. Scheme of thiosemicarbazones synthesis R= H, norborn-2-yl, hex-1-yl and oct-1-yl, *morpholin-1*-yl.

## RESULTS

### COMPOUNDS SYNTHESIS

The thiosemicarbazones were synthesized using a general synthetic procedure, resulting in good yields of 79-93% with the exception of compound 5, which was obtained in 66% yield. The presence of functional groups was confirmed using FTIR spectroscopy, indirectly confirming the structure of the synthesized compounds. The structures of the synthesized compounds are shown in Figure 6.

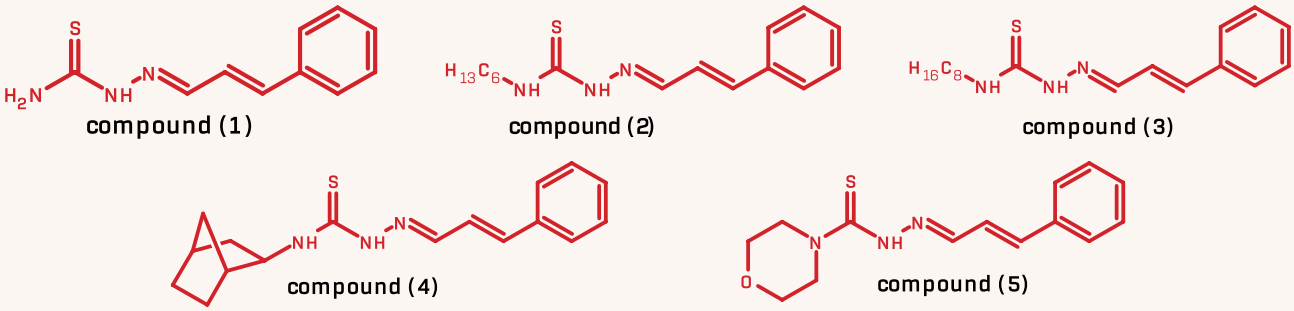


Figure 6. Structure of synthesised compounds **1-5**.

Compound (**1**) *(2E)-2-[(2E)-3-phenylprop-2-en-1-ylidene]hydrazine-1-carbothioamide*

It was synthesized according to the general procedure. Yellow solid, reflux time – 2.5 hours. Yield: 93%. FTIR ($cm^{-1}$): 3340 ν (N-H, secondary amine); 3058 ν (C-H, Alkene); 1545 ν (C=N, imine); 765, 696 ν (C-H, monosubstituted benzene ring), 1245 ν (C=S).

Compound (**2**) *(2E)-N-hexyl-2-[(2E)-3-phenylprop-2-en-1-ylidene]hydrazine-1-carbothioamide*

It was synthesized according to the general procedure. Yellow solid, reflux time – 3.5 hours. Yield: 85%. FTIR ($cm^{-1}$): 3344 ν (N-H, secondary amine); 3132, 3004, 2924, 2853 ν (C-H, Alkane); 3056 ν (C-H, Alkene); 1540 ν (C=N, imine); 750, 691 ν (C-H, monosubstituted benzene ring), 1258 ν (C=S).

Compound (**3**) *(2E)-N-octyl-2-[(2E)-3-phenylprop-2-en-1-ylidene]hydrazine-1-carbothioamide*

It was synthesized according to the general procedure. Yellow solid, reflux time – 4.5 hours. Yield: 88%. FTIR ($cm^{-1}$): 3347 ν (N-H, secondary amine); 3139, 3008, 2921, 2861 ν (C-H, Alkane); 3060 ν (C-H, Alkene); 1553 ν (C=N, imine); 751, 689 ν (C-H, monosubstituted benzene ring), 1246 ν (C=S).

Compound (**4**) *(E)-N-((1R,2S,4S)-bicyclo[2.2.1]heptan-2-yl)-2-((E)-3-phenylallylidene) hydrazinecarbo-thioamide*

It was synthesized according to the general procedure. Yellow solid, reflux time – 5 hours. Yield: 79%. FTIR ($cm^{-1}$): 3313 ν (N-H, secondary amine); 3123, 2983, 2945, 2866 ν (C-H, Alkane); 3037 ν (C-H, Alkene); 1533 ν (C=N, imine); 745, 689 ν (C-H, monosubstituted benzene ring), 1231 ν (C=S).

Compound (**5**) *N'-[(1E,2E)-3-phenylprop-2-en-1-ylidene]morpholine-4-carbothiohydrazide (**5**)*

It was synthesized according to the general procedure. Yellow solid, reflux time – 6 hours. Yield: 66%. FTIR ($cm^{-1}$): 2965, 2859 ν (C-H, Alkane); 3026 ν (C-H, Alkene); 1450 ν (C=N, imine); 754, 693 ν (C-H, monosubstituted benzene ring), 1240 ν (C=S).

## ADME analysis

ADME analysis is an essential initial screening tool for assessing the potential biological activity of compounds. Additionally, analyzing the data obtained from this assay provides some valuable insights into key parameters for the compound's future use. Table 1 presents the calculated physicochemical properties, including the logarithm of the octanol-water partition coefficient (Log $P_{o/w}$), which indicates the ratio of a compounds solubility in lipophilic (octanol) and hydrophilic (water) phases. Ideally, Log P value should not exceed 5, as it indicates that the compound will primarily remain in the cell membrane. Conversely, values below 1 suggests that the compound will not penetrate the membrane at all. It is worth noting that all synthesized compounds, except for 3, have acceptable partition coefficient values. Furthermore, the $pK_a$ values for the synthesized compounds fall within the range of 8.3-9.9, indicating that they are more likely to be absorbed in the intestine rather than the stomach.

Table 1. Some physicochemical properties calculated for compounds 1-5.

| Physicochemical properties | | | | | |
|---|---|---|---|---|---|
| Compound | Number of H-bond acceptors | Number of H-bond donors | Molecular weight | Log $P_{o/w}$ | $pK_a$ |
| 1 | 1 | 2 | 205.28 | 2.81 | 8.36 |
| 2 | 1 | 2 | 289.44 | 4.82 | 9.48 |
| 3 | 1 | 2 | 317.49 | 5.55 | 9.87 |
| 4 | 1 | 2 | 299.43 | 4.56 | 9.26 |
| 5 | 2 | 1 | 275.37 | 3.01 | 8.83 |

*Log$P_{o/w}$ – logarithm of the octanol-water partition index value, $pK_a$ – acidity constant*

In general, the descriptors in Table 1-namely, the number of H-bond acceptors, number of H-bond donors, molecular weight, and Log $P_{o/w}$) can be evaluated using drug likeness rules to identify potential drug-like compounds with promising biological activity. As shown in Table 2, all compounds, with the exception of compound 3, meet all commonly used rules, indicating a high likelihood of biological activity. However, compound 3 does not meet the Veber and Muegge rule due to its high Log $P_{o/w}$ value.

Table 2. Correspondence to drug-likeness rules of synthesized compounds.

| Drug-likeness rules correspondence | | | | | |
|---|---|---|---|---|---|
| Compound | Lipinski | Ghose | Veber | Egan | Muegge |
| 1 | +* | + | + | + | + |
| 2 | + | + | + | + | + |
| 3 | + | + | -** | + | - |
| 4 | + | + | + | + | + |
| 5 | + | + | + | + | + |

**+ correspond; **- not correspond*

Table 3 presents calculated ADME data, which shows that all compounds, except for 5, are not inhibitors or substrates for permeability glycoprotein (Pgp), also known as MDR1 – multidrug resistance protein 1.

These findings suggest that compounds 1–4 are unlikely to exhibit drug resistance effects mediated by this protein. The calculated plasma clearance val-

ues indicate a relatively slow clearance rate, which may result in prolonged retention in the body and potentially lower dosing requirements. However, this could also increase the risk of accumulation and associated toxicity. Additionally, all compounds – except for compound 5 – are predicted to have oral bioavailability (F% > 20%), indicating favorable systemic exposure following oral administration.

None of the synthesized compounds are predicted to cross the blood–brain barrier, suggesting a low likelihood of central nervous system–related side effects. Furthermore, all compounds are expected to exhibit good intestinal absorption, with predicted absorption rates of at least 30%.

Table 3. Calculated ADME parameters for compounds 1-5.

| ADME parameters | | | | | | |
|---|---|---|---|---|---|---|
| Compound | Plasma clearance, mL/min/kg | Pgp inhibitor | Pgp substrate | HIA | BBB | F20% |
| 1 | 3.36 | - | - | >30% | -** | +* |
| 2 | 5.46 | - | - | >30% | - | + |
| 3 | 5.23 | - | - | >30% | - | + |
| 4 | 3.10 | - | - | >30% | - | + |
| 5 | 6.79 | - | + | >30% | - | - |

*HIA – human intestinal absorption, BBB – crossing of blood-brain barrier, F20% – bioavailability >20%; Pgp – permeability glycoprotein*
**+Yes; **-No*

## ANTIOXIDANT ACTIVITY ASSAY

The antioxidant activity of the synthesized compounds was also assessed, following the procedure described in (19). The results are shown in Figure 7. The data reveals that compounds 2, 3, and 4 do not possess significant antioxidant activity. However, compound 5 exhibits three times the antioxidant activity of Trolox, and compound 1 has six times the activity.

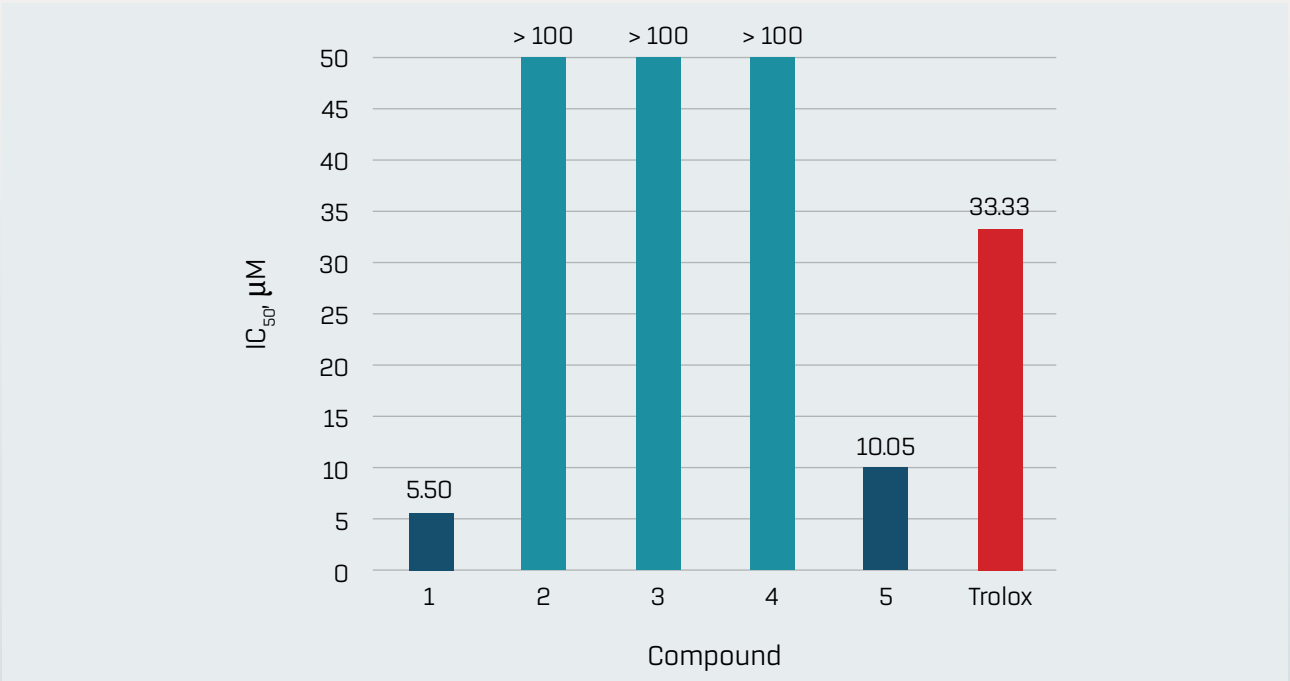


Figure 7. Antioxidant activity $IC_{50}$ of tested compounds compared with Trolox.

## DISSCUSIONS

The compounds were synthesized using to the procedures outlined in our previous work. The final yields of the compounds 1-5 can be considered good. All compounds, with the exception of compound 3, correspond to all the most widespread used drug likeness rules. The activity of the synthesized compounds, with the exception of compound 5, is not expected to be affected by MDR1- mediated drug resistance. Furthermore, the ADME profile obtained from the results indicates that the synthesized compounds possess drug likeness indices characteristic of medicinal compounds. Antioxidant analysis revealed that compound 1 and 5 exhibit stronger antioxidant properties than Trolox. Based on these findings and the ADME analysis, it can be assumed that compound 1 has the highest potential for reducing oxidative stress in biochemical systems.

## CONCLUSIONS

1. Five thiosemicarbazone derivatives based on cinnamaldehyde were successfully synthesized, and their structures were confirmed through infrared spectroscopy.
2. The synthesized compounds exhibited favorable pharmacokinetic properties, including absorption, distribution, metabolism, and excretion, with the exception of compound 5, which deviates from commonly accepted drug-likeness criteria.
3. These compounds are not expected to cross the blood-brain barrier, thereby reducing the risk of adverse effects related to central nervous system interactions.
4. With the exception of compound 5, the compounds are unlikely to act as substrates or inhibitors of permeability glycoprotein, suggesting their bioavailability and activity are not significantly influenced by this efflux transporter.
5. Antioxidant assays revealed that compounds 1 and 5 exhibit significantly enhanced activity compared to Trolox, being approximately 6-fold and 3-fold more potent, respectively.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## AUTHOR CONTRIBUTIONS

Conceptualization, A.G.; methodology and compounds synthesis, R.R. and A.C.; validation, R.R., A.C., and A.G.; Antioxidant activity, A.C.; investigation, A.C., R.R.; writing – original draft preparation, A.C.; writing – review and editing, R.R., A.C., and A.G.; visualization, A.G, R.R., A.C; supervision, A.C., R.R., A.G.; project administration, A.G.; All authors have read and agreed to the published version of the manuscript.

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- **MATERIAL AND METHODS**
- **RESULTS**
- **DISCUSSIONS**
- **CONCLUSIONS**
- **CONFLICT OF INTERESTS**
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- **METHODES**
- **RESULTATS**
- **DISCUSSIONS**
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## The *One Health* concept

Globally, the One Health concept is a worldwide strategy to expand interdisciplinary collaborations and communications in all aspects related to the health care of humans, domestic animals or wildlife, which can no longer be approached separately, but only jointly.

One Health addresses not only human and animal disease concerns, but also issues related to lifestyle, diet, exercise, the impact of different types of human-animal relationships, and environmental exposures that can affect both populations. In order to achieve the expected effects, it is also necessary to educate the population to make them aware of the risk factors and benefits of prevention, as well as communication and understanding between patients and healthcare providers.

### HUMAN HEALTH

The WHO defined health in 1946 as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”, with the later addition of “the capacity to lead a socially and economically productive life”.

### ANIMAL HEALTH

The OIE defines animal welfare in 2008: an animal is in good condition if it is healthy, enjoys comfort, is well fed, is safe, is able to display its innate (natural) behavior and does not suffer from unpleasant conditions such as pain, fear and stress.

### PLANT AND ENVIROMENTAL HEALTH

Environmental health refers to those aspects of human health that include the quality of life determined by physical, biological, socio-economic and psycho-social factors in the environment. The interrelationships of people with the environment concern medicine, when an ecological system is in a state of equilibrium, the health of the population prevails.


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