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INTERSECTIONS OF HEALTH, PSYCHOLOGY, AND OCCUPATIONAL CHALLENGES

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Intersections of Health, Psychology, and Occupational Challenges ⎯⎯⎯⎯

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Physical health, mental health, and professional roles are deeply interconnected and influence one another. According to the biopsychosocial model it is important to understand and address human well-being holistically. Understanding this interconnectedness enhances professional competence, the overall well-being of health care professionals and empathy in practice.

In this issue of the journal, there are mainly included the following topics of occupational challenges such as mental health in the workplace, professional development, personality and work-related strength and weaknesses.

- _Mental health in the workplace:_ Stress, anxiety, and depression are common occupational issues that affect employee well-being and performance. Chronic stress at work can lead to burnout. Burnout is a psychological syndrome caused by chronic workplace stress leading to exhaustion, cynicism, and reduced professional efficacy. Psychological resilience, social support, and adaptive strategies can mitigate occupational stress impacts. Two of the following articles are related to this issue: "Occupational Health and Safety among Nurses: Assessing the Level of Stress in Nurses in Infectious Resuscitation during COVID-19" and "Burnout Among Nursing Staff: An overview of Causes, Consequences, and Management Strategies".
- _Professional development:_ Clinical practice plays a crucial role in shaping the professional development of students. One of the articles titled "The Impact of Clinical Practices on the Professional Approach of Imaging Students" shows that the transition from theoretical learning to hands-on experience in clinical environments helps students to acquire technical skills, as well as to cultivate professional attitudes, ethical standards, and effective

communication abilities. This practical exposure strongly influences how students perceive their roles, how to interact with patients and colleagues, and adaptation to the demands of healthcare setting.

- *Personality and work-related challenges*: One of the articles "The Application of the Personality Inventory in the Recruitment of Police Officers" point out that understanding personality can improve tailored recruitment. It is known that personality affects coping mechanisms for both health issues and work challenges, influencing coping strategies at work, communication styles, and conflict resolution. Certain traits can predict how well a person handles workplace stress, job demands, and interpersonal challenges. High conscientiousness often relates to better job performance and persistence. High neuroticism may lead to higher perceived stress and burnout risk. Extraversion can help with social roles but might struggle in isolated or highly structured environments. Another article assesses the challenges of the triad doctor-pharmacist-patient in preventing medical errors.

The other articles of this issue include health topics such as herbal medicine, the cell cycle in cancer and the influence of lifestyle factors on a chronic illness.

The Impact of Clinical Practices on the Professional Approach of Imaging Students: From the Classroom to the Cabinet

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Abstract

Introduction: Bridging the gap from lectures in the classroom to clinical practices is one of the most crucial moments in the life of a radiology student, and it impacts their career development and satisfaction level with their work, especially for the desired career. This research aims to assess how clinical practice influences the career choices of radiology students, looking at their practical exposure to the profession and perceptions.

Objective: The study investigates whether practical radiology experiences support or contradict students' initial career motivations by contrasting their attitudes and expectations before and after clinical exposure.

Methodology: The study includes interviews and surveys with radiology students at various educational stages, as well as the analysis of both qualitative and quantitative data. Two interviews were conducted with the students: one prior to and one subsequent to their clinical exposure.

Results: According to the findings, clinical exposure is essential for fostering students' enthusiasm for the field, for 79% of first-year students and 94% of third-year students. Important elements like patient interaction, innovation in technology, and workplace culture affect their long-term job satisfaction.

Conclusion: Given that radiology is one of the most popular field among high school graduates and that approximately 200 imaging technicians graduate annually only from the Faculty of Medical Technical Sciences Tirana, this study also offers insightful information for new educational strategies and program development aimed at improving curriculum design, to better support students during clinical training, and ultimately to help them make informed decisions about their future in radiology.

Keywords: Clinical practice, students, professional development, imaging.

Introduction

Technical Medical Imaging field in Albania

In 1948, the "First Medical Technical School" was opened, which in 1996 was named the "Higher School of Nursing". During the period of modernization of higher education, new opportunities were created for the opening of new branches that were related to the latest developments in the field of medicine and technology.

In the 1990s, the Faculty of Medicine at "University of Tirana" began offering specializations and study programs in radiology, including the use of modern imaging technology, as well as training young professionals to work with equipment such as radiography, ultrasound, tomography and magnetic resonance imaging (MRI) initially offered at the School of Nursing, which was later expanded and renamed as the Faculty of Medical and Technical Sciences (Faculty of Medicine brochure, 2004).

Considering the significant growth that this branch experienced after the year 2000, due to technological advances and the increasing demand for qualified professionals in this field, the Imaging Technician Program was widely expanded to the private university system as well.

Imaging students at both state and private universities are offered professional internships ranging from two weeks to three months at University Hospital Centers and beyond. Among large centers in which students can practice their theoretical knowledge, we mention: "Mother Teresa University Hospital", Shefqet Ndroqi University Hospital, and the University Trauma Hospital. In addition to them, small private clinics have been an added help for students by giving them the opportunity to witness their job positions requirements across both state and private establishments.

Challenges and opportunities

Facing the reality of their professional choice during hospital internships, is considered by students as the best way to find themselves in the field of radiology. Thanks to the large number of modalities, each student has the opportunity to choose to specialize in one or several of them during the study years, resulting in a easier choice when entering the labor market.

In addition to choosing the modality where the student best finds himself, due to the possibility of being exposed to different departments such as: the noisy emergencies, chaotic Intensive Care Unit Department, oncology service with its social and psychological challenges, or private offices, each personality can easily perceive in which environment their abilities reach its full potential.

Although this type of approach is one of the most important components of medical education, it is full of barriers to its effective implementation.

Clinical teaching faces challenges such as a lack of time for teaching, multiple responsibilities, limitations due to the number of students, lack of structure, heavy workload, among others. In order to achieve high-quality teaching, there is a need of identifying not only the present challenges but also the solutions that would provide better services by increasing teaching effectiveness triggering student's satisfaction, also something reflected in a study conducted in Albania for the challenges and opportunities of Medical Education in our country that states that comprehensive curricula evaluation is needed both in undergraduate and postgraduate training, as well as application of best evidence-based educational strategies that will enable students to develop the competencies identified as appropriate for healthcare professionals in Albania (Rrrumbullaku et al, 2002).

Juggling tasks on a daily basis has mentors feeling worn out, however, when the students part of our study were asked about whether they felt welcomed in the cabinets, the tones were nothing but positive.

One of the proposals offered by mentors was to have students focus on one modality at a time. The first-year students can direct their energy toward X-ray and its many varieties (Trauma, Emergency, Oncology, Pediatrics, Operating room). As years go by, attention can shift to more advanced modalities such as CT-scan, Magnetic Resonance (MRI), Radiotherapy. In their final year, students can prioritize PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography), and Interventional Radiology.

However, considering these types of modalities are hard to grasp for the students, but also tough to navigate for mentors, a well-thought-out program should be the next big step.

TABLE 1. Summary table of the clinical education system

Clinical education system			
STRUCTURAL CHALLENGES	Infrastructure defects	Lack of educational space	Lack of educational and treatment facilities
TIME PRESSURE	Information overload under time pressure	High-demand shifts	
ORGANIZATIONAL PROBLEMS	Multiple students scheduled together		
MULTIPLE RESPONSIBILITIES	Supervisors juggle several tasks concurrently		

Method

Sample

The study included 119 Imaging students, whose participation was voluntary after they were well-informed about the purpose of the study.

Instrument

The questionnaire used in this study is structured, self-reported, and anonymous, while fully preserving the confidentiality of the participants. The questionnaire consists of two parts.

1. The first part includes socio-demographic data of the population studied (gender, age, year of study).
2. The second part of the questionnaire aims to assess the impact of clinical exposures on first-year and third-year students before and after teaching practices.

The distribution of the questionnaire was carried out through Google Forms combined with one-on-one interviews with students in the auditoriums and during practice in the cabinets. The format of the questionnaire used was similar to the one used in a study conducted in 2009 by Emma-Jane Berridge, Della Freeth, Judi Sharpe, C. Michael Roberts (Berridge Emma et al, 2007).

Results

Demographic data

Among 119 students included in the study, it resulted that in the first academic year (n=56) 69% of them belong to the female gender and 31% to the male gender. The same dominance of values is also observed among third-year students (n=63), where female students account for 66% while male students 34%. This trend has been echoed in previous studies on related topics. (Berridge Emma et al, 2007, Walaa M Alsharif et al, 2022, Mazaheri F. et al, 2024).

The age of participants in the first-year student group varies from 18 to 23 years old, with a mean (±SD) of 19.43 (±1) years old. The majority of students are 19, specifically 84% (48 of them). In this group, we do not have any students who belong to the age group 24-26 years old, part of the questionnaire alternatives.

The age of the participants in the group of third-year students ranges from 21 to 26 years old, with a mean (±SD) of 22.1 (±1) years old. The majority of students correspond to the age group 21-23 years old, specifically 93% (59 of them).

Based on the academic profile, all participants are found to be students of the first cycle of Bachelor studies, in the field of radiologic imaging, among whom 56 students (47.1%) are in the first year of studies, while 63 students (52.9%) are in the third year.

The above-mentioned data are summarized.

TABLE 2. Summary of demographic data

FIRST YEAR   **THIRD YEAR**

01.GENDER
- 39 female **students** (69%)
- 17 male **students** (31%)

01. GENDER
- 42 female **students** (66%)
- 21 male **students** (34%)

02.AGE
- **Age group 18-20 years old**: 48 students
- **Age group 21-23 years old**: 8 students
- **Age group 24-26 years old**: 0 student

02. AGE
- **Age group 18-20 years old**: 0 student
- **Age group 21-23 years old**: 59 students
- **Age group 24-26 years old**: 4 students

03. ACADEMIC YEAR
56 **students** (47.1% of sample)

03. ACADEMIC YEAR
63 **students** (52.9% of sample)

Study Findings

Through a combination of surveys and interviews, the research captures the attitudes and expectations of students before and after facing the reality of their professional choice.

Asked about their interest in the field of study, it results that 70.9% (83) of them have a high interest, 25.2% (28) have an average interest, 2.3% (4) have a low interest. Comparable studies have similarly highlighted this trend (Berridge Emma et al, 2007, Walaa M Alsharif et al, 2022, Hizzett K et Snaith B, 2022, Mazaheri F. et al, 2024). Only 1.6% of them have said that they have no interest in the field of study. From later information it was discovered that 2 of the first-year students had dropped off and had decided to perceive another field of study before finishing the first semester.

TABLE 3. Summary of students' interest data.

Student interest in the field of study
expressed as a percentage

- HIGH INTEREST
- AVERAGE INTEREST
- LOW INTEREST
- NO INTEREST

2.3%
25.1%
71%
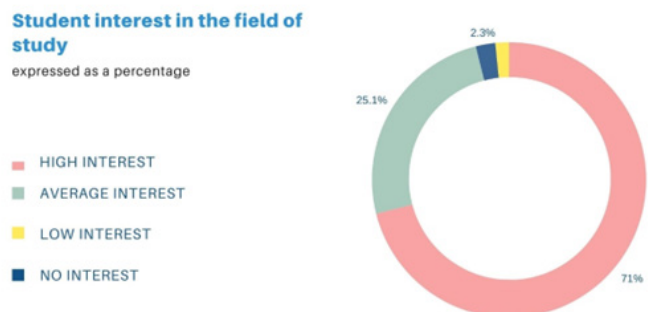
Following the course of the interviews, in addition to the results of the questionnaire, several points of convergence were noted in their attitudes between first year and third-year students, as well as many challenges that were encountered by new students had later disappeared over the years in students on the verge of graduation.

Preclinical Exposure

Students, after graduating High School, are full of perceptions and expectations about the field of study they will join. The main perceptions regarding the profession of imaging technician before clinical exposure and after having completed the first cycle of practice often bring clashes of opinions to students.

First-year students stated that among factors such as: Working with the latest medical technology, direct but minimal interaction with the patient, high

earning potential, job stability and career opportunities or working in a Team-work environment with healthcare professionals, by being under the influence of relatives and family members, they joined Radiology with the concept of a profession with career growth opportunities and high earning potential.

None of the students in this group chose the factor of direct but minimal interaction with the patient as a significant element of their choice. Previous studies in the literature (Walaa M Alsharif et al, 2022) showed that the top-ranked motivational factors for the majority of students to choose a profession are social status and security factors. This indicates that the desire to help and serve the public is not the most important motivational factor for choosing imaging as profession, stating a meeting point with our findings.

Job stability and career opportunities were the most chosen aspects among third-year students, with 62% of the questionnaire results, and the least chosen aspect continued to be that of direct but minimal interaction with the patient.

TABLE 4. Summary of students' perceptions before clinical exposure.
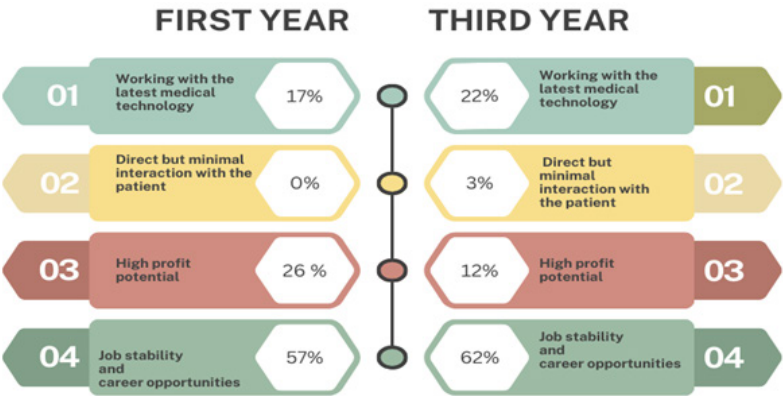
In the curriculum, clinical practices always accompany subjects in which the knowledge acquired in the classroom is applied in practice. Trying to keep theory and practice in parallel, each year follows practices dedicated to the subjects developed up to that point.

Since, in addition to the reality of their professional choice as Imaging Technicians, our students also encounter the risk of radiation both during clinical hours and throughout their careers, a contributor to the study questionnaire was related to the safety of students in the cabinets (Nur Nişancı Bengüsu & Çakına Suat., 2024).

82% of them responded that they felt very safe, and 18% somewhat safe.

The first-year students stated that they had not yet taken a subject based on radiation protection, but their mentors made sure to introduce them to the risks of the imaging cabinets they participated for practice.

This early exposure not only raises awareness but also reinforces the importance of safety protocols from the very beginning of their training. As students progress through the program, their understanding of radiation protection is expected to deepen, enhancing both their confidence and competence in clinical environments. The study listed below affirms the importance of extensive awareness when it comes to radiation safety (Nur Nişancı Bengüsu & Çakına Suat., 2024).

During clinical exposure

TABLE 5. Summary of students' perceptions during clinical exposure.

First year
- The reality gap between learning and doing
- Anxiety regarding potential errors during equipment operation(**34%**)
- High levels of stress induced by demanding clinical settings·(**8%**)
- Lack of clarity regarding career progression(**21%**)

Limited hands-on experience

Third year
- Lack of preparation for independent decision–making(**67%**)
- Monotonous clinical routines(**24%**)
- Lack of clarity regarding career progression(**9%**)

With their expectations in mind, Imaging students from both study groups stated that the welcome they received in the cabinets was describes as truly gratifying for the majority of them (82%) and acceptable for the rest (18%).

The challenges that first-year students faced during clinical practices that influenced their perception of radiology were mostly stress and pressure in fast-paced clinical environments, in addition to uncertainty about career advancement.

In the third-year group, the option of uncertainty about career advancement was selected significantly less by the students, showing once again the positive effect of the combination of theoretical and practical knowledge on the students' self-confidence as they advance in their studies. On the other hand, they did not feel quite adequate for independent decision-making.

Both years have expressed that they would like to complete professional internships during their years of study for a longer period than previously available.

Studies have shown that clinical rotations have the most considerate impact on medical students' attitudes and abilities. A study by Tegel et al. (2016) found that radiology students reported a marked improvement in their self-confidence after completing clinical rotations, particularly in their ability to use imaging

technologies effectively (Watson, S. et al., 2018). In a similar study of Gjergji and bp. (Gjergji V., Kola V. and Roshi E., 2011) clinical rotations in psychiatry impacted positively on medical students' attitudes.

Post-clinical Exposure (Current Perceptions)

The findings suggest that all students who participated in the study had a positive attitude before and after clinical exposure in terms of their self-confidence as future professionals. The opportunity to face the work environment during their academic studies facilitates their advancement in the labor market for what lies ahead.

TABLE 6. Summary of students' perceptions after clinical exposure.

Among the factors that would make one more confident in its decision to pursue radiology as a career, students brought attention to the possibility of being exposed to a greater diversity of radiology modalities during their studies to avoid repetition of the same experiences over and over again, and that they would like to be mentored and guided by professionals for a longer period of time. Conversely, challenges such as stress, workload, and complexity of the profession often result in a lack of adequate attention and time from clinical supervisors to students.

Jackson et al. (2019) found that students experienced a shift in their perceptions of radiology as a "technical" profession to a more " patient-centered " profession after engaging in direct patient interactions during clinical placements (Jackson, L. et al., 2019). However, this alteration was not seen among our students.

Discussions

The overall response rate for the study was reasonably high, although there was lower engagement from the first-year students, perhaps reflecting their limited knowledge of the profession at that stage of their studies.

Secondly, as universities are focusing their work in developing the best programs not only to attract students to join their classes but also making sure they are offering top - notch experiences that will result in qualified specialist in the long run, the core of a well-trained imaging technician lays in the hands of their mentors. Part of the discussion had with both groups of students, the need for a longer and deeper connection between students and their practice coach was heavily mentioned. If the universities do not invest more time and funds into creating a team of technicians that plays both roles, that of the lecturer in class and the mentor in the hospital, the end result of these practice hours will perhaps not be the one they aim for.

Conclusions

Both first year and third-year students' feedback reveals important patterns about their mentor relationships, self-confidence, clarity of career goals, and difficulties encountered while studying. Notably, 63% of third-year students reported feeling a close bond with their mentors; many even grew close to them while they progressed in their studies since 2 of the mentors were also part of the academic staff of the university. Nevertheless, only a shocking 13% of first – year students shared the same opinion.

38% of first-year students reported having no difficulties during their practice hours, 11% reported having fewer difficulties, and 7% reported having significant difficulties. Third-year students, on the other hand, were more confident, with 70% reporting feeling confident in completing their tasks assigned to them during practice hours, compared to 28% who faced some difficulties and 2% even weeks away from graduating lacked confidence.

While 17% of the first year students were unsure if they had made the right choice, the majority, 69%, believed they had clear ideas about their future careers. Values that were even more positive among third year students , where more than 82% of them said they saw themselves succeeding professionally in the field they had chosen three years ago.

As radiology is among the most popular areas of study for recent high school grads, and seeing that with every year more and more students are enrolling in

our university, a more well detailed and thought through scheme between the academical and practical aspects of Radiology should be put in motion. This study brings valuable insights into new educational strategies and programs of how to better shape the curriculum to enable better student support during clinical training and consequently improve the tools students need to make an informed decision when it comes to their future in radiology.

Limitations and recommendations

A limitation of this study relates to the fact that it involved only radiology students who study at "Aldent University" in Tirana. Therefore, the results may not be confidently generalized to the radiology students who study at other universities across the country. An additional potential limitation is the lack of published research that focuses on the radiography profession, and this caused difficulties in comparing the study's findings; however, some of the more relevant studies for other professions, such as nursing and medicine, were identified. Therefore, further research in these areas is recommended. Such research could focus on the role of career counsellors in High School and/or universities in assisting students to identify appropriate professional options. A number of significant changes are suggested in order to improve the clinical experience of radiology students. First, by exposing students to a range of modalities over the course of their academic careers, they will be able to acquire a well-rounded skill set as they progressively become proficient in various imaging techniques.

Additionally, it is essential to monitor occupational exposure during clinical hours in order to protect students. Regular evaluations are conducted to track radiation exposure and ensure that safety procedures are being followed.

By exposing them to a variety of working hours and clinical settings, the use of intermediate shifts in the clinical training schedule would enhance their experience and better prepare them for practice in the real world. Lastly, the inclusion of technician staff to assist students both in the faculty and hospital would help streamline operations, provide necessary technical support, and ensure that students receive hands-on guidance throughout their clinical rotations.

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Occupational Health and Safety among Nurses: Assessing the Level of Stress in Nurses in Infectious Resuscitation during the Period of COVID-19

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Abstract

Background: Nurses working in infectious disease units during the COVID-19 pandemic experienced increased occupational hazards, emotional strain, and physical exhaustion. Understanding the level and sources of stress is essential for developing targeted interventions and fostering a safer working environment.

Objective: This study investigates stress levels among nurses working in infectious resuscitation during the COVID-19 pandemic in Albania. It aims to identify contributing factors such as workload, infection exposure, and demographic variables, and assess their impact on nurses' mental health and care quality.

Methods: A descriptive study was conducted at the Infectious Hospital in Tirana between September and December 2021. Twenty nurses who had provided care for COVID-19 patients completed a structured survey and participated in open-ended discussions. Multiple linear regression analysis was used to evaluate the relationship between stress levels and variables including age, workload, and infection frequency.

Results: Fifty percent of nurses reported high levels of stress, while 40% reported very high stress during the pandemic. Infection rates and increased workload were positively associated with higher stress levels. Age did not significantly impact stress. Frequent infections and demanding work conditions were key stressors affecting both physical and psychological health.

Conclusion: Workload and repeated infections were major contributors to elevated stress levels among infectious disease nurses during the COVID-19 pandemic. These findings underline the need for targeted occupational health interventions and mental health support for frontline healthcare workers.

Keywords: *occupational health, nursing, COVID-19, stress, infectious resuscitation, workplace safety*

Introduction

Safety and health at work has to do with guaranteeing safety and protecting the health of employees through the prevention of occupational hazards, the elimination of factors that constitute danger and accidents, as well as the information, consultation and proper training of employees in accordance with the relevant legislation. [1-2].

Nursing is a demanding and high-stress profession. Beyond monitoring vital signs and administering medications, nurses take on a wide range of responsibilities. These include providing direct patient care, supporting medical procedures, maintaining accurate documentation, and often serving in leadership positions within hospitals, healthcare systems, and other organizations [3-4].

Safety and health at work in the nursing service is very important. It is very important that all health workers have the necessary protective equipment and respect safety protocols. There are many factors that affect this aspect, such as protective equipment, security protocols and risk management. Effective nurse leaders embrace safety protocols that ensure their organization provides a safe, protective environment that prioritizes patients and nursing care. An important aspect is the use of protective measures such as masks, gloves and appropriate

clothing. Security protocols also play a key role in minimizing risks and acting effectively in emergencies. However, challenges arising at the organizational, state, and national levels have significantly hindered nurses' ability to perform their duties effectively. To address these issues successfully, it is crucial to first identify and comprehend the full range of obstacles nurses encounter, enabling the development of effective strategies to overcome them. [5, 6].

Clear communication between the healthcare teams is essential. When nurses, physicians, and support staff work together in delivering patient care, they can establish clear roles and responsibilities, reducing the risk of errors or miscommunication. Effective teamwork and communication are particularly vital during shift handovers. Ultimately, fostering a culture of safety within healthcare settings is crucial to ensuring the well-being of patients, staff, and the organization [7,8].

Hospitals and clinics can be dangerous places for nurses. Learn how to minimize risks and stay safe at work. Understand the risks associated with exposure to chemicals, including cleaning products and pharmaceuticals. Proper ergonomics and postural awareness can reduce strain, musculoskeletal pain and injury. Nurses are exposed to various occupational hazards in their work environment. These risks can lead to a range of injuries and illnesses that not only impact on their physical and emotional well-being but also have the potential to compromise the quality of patient care. [9-11].

Risks faced by the nursing staff in the workplace

Physical Injury

Nurses frequently suffer from musculoskeletal disorders due to patient lifting, transferring, or repositioning. These tasks increase the risk of back and joint injuries, especially in hospital and home care settings.

Stress and Mental Well-Being

Irregular hours and demanding work environments contribute to chronic stress among nurses, affecting both their mental and physical health, and impairing concentration and resilience on the job [12].

Infections

Nurses are routinely exposed to infectious agents like influenza, hepatitis, and tuberculosis. Personal protective equipment and vaccinations are essential to reduce infection risks and related absenteeism [13].

Chemical Hazards

Contact with sterilizing agents such as formaldehyde and ethylene oxide can cause nausea, reproductive issues, or cancer. Safe handling practices are critical to minimizing exposure [14].

Radiation Exposure

Nurses in emergency or radiology departments face increased radiation exposure during imaging procedures. Adherence to safety protocols is essential [15].

Burnout

Long shifts, emotional labor, and terminal care duties can lead to burnout—causing exhaustion, absenteeism, and higher error rates in clinical practice [16].

Impact of workplace hazards on patient care

Workplace hazards can greatly affect the quality of patient care. When nurses suffer from injuries or illness, their ability to deliver care is compromised. In settings already facing nursing shortages, this can lead to difficulties in maintaining timely and adequate patient care. Moreover, remaining staff may experience heightened stress due to increased workloads and responsibilities, placing them at greater risk of burnout. Addressing and minimizing workplace hazards is essential to safeguarding nurses' physical and emotional well-being, which in turn supports the delivery of safe and effective patient care. [17]

Nurses play a critical role in ensuring patient safety and preventing harm across both short-term and long-term care settings. Their responsibilities include following organizational protocols to identify potential risks and harms through comprehensive patient assessment, care planning, monitoring and surveillance, double-checking procedures, providing support, and maintaining effective communication with the healthcare team. To successfully prevent practice-related errors and build safer, more sustainable healthcare systems, it is essential not only to have clear policies, leadership, evidence-based safety initiatives, staff training, and patient involvement, but also strong nurse commitment to patient safety principles. [17-18]

The role of the nursing staff in preventing these risks

Nurses can lower their risk of workplace injuries or illnesses by adhering to safety protocols established by the Occupational Safety and Health Administration (OSHA). These guidelines include measures to prevent exposure to infectious pathogens, safe patient handling practices to avoid physical injuries, and the careful management of hazardous chemicals. Additionally, nursing departments can implement strategies to reduce burnout among staff. On a personal level, nurses can also manage stress by engaging in relaxation techniques and self-care practices to support their overall well-being [17-18].

Covid-19 was a disease that was caused by SARS-CoV-2 and was associated with acute respiratory syndrome, becoming a global pandemic at a high speed. Being a known infectious disease not only in humans but also in animals, it made it possible for scientists to understand more quickly the pathogenesis of the virus and this consequently helped in the rapid development of SARS-CoV-2 vaccines, which enabled immunization of all the people who were infected and prevented in this way the high number of deaths that could have occurred if people had not been immunized.

A very high and humanitarian responsibility for providing medical aid was that of the medical and nursing staff. Doctors and nurses, as well as all the rest of the staff, being on the front line of the fight against the pandemic that involved the whole world in 2019-2021, proved to be quite capable of managing stress to enable the preservation of their physical well-being and psychological in the face of many stressful factors that they faced during the pandemic. The study conducted aims to explore the challenges, strategies and outcomes of stress management in nurses who face and contribute to the care of patients with COVID-19. Also, the pandemic not only had negative impacts on the lives of people and the medical and nursing staff, but also served as a big plus for every health profession, as it gave them great experience in treating patients, thus helping not only patients, pores and the professional life of every health professional (doctor, nurse, physiotherapist, imager, etc.) [19-21].

Aims

The purpose of the study is to investigate and analyze the impact of the COVID-19 disease on infectious resuscitation nurses during the pandemic to identify the factors that can increase the level of stress and anxiety in the workplace and to develop effective strategies for the management the stress.

Hypothesis

Being on the front line of the fight against the virus, at risk of getting an infection, and increasing the workload has caused infectious resuscitation nurses to experience a higher level of stress during the pandemic.

Research question

How did age, high volume of work and getting an infection affect the increase in the level of stress among infectious resuscitation nurses during the pandemic?

Methods

The study is based on a descriptive work that was carried out in the Infectious Resuscitation (Infectious Hospital) in the period September-December 2021. Twenty nurses, who take care of patients with Covid-19, were selected as a sample. One of the methods used for the study was the survey to assess the level of stress that they had during the pandemic period. Another method that has been used for this study was the observations made through open conversations with infectious resuscitation nurses. To carry out the survey, the nurses had to fulfill these criteria, which were: have a bachelor's degree in nursing, have at least six months of full-time work experience as a clinical nurse have at least 2 months of professional experience in caring for COVID-19 patients and willingness to share experiences with others.

Results

Among the 20 nurses surveyed in the Infectious Resuscitation Unit, 9 (45%) reported experiencing a high workload, while 10 (55%) described their workload as very heavy during the COVID-19 pandemic. Regarding infection frequency, 8 nurses (40%) indicated they were infected three times during the pandemic, 7 nurses (35%) reported four infections, 4 nurses (20%) experienced five infections, and 1 nurse (5%) reported being infected twice.

Stress levels were notably elevated: 10 nurses (50%) reported a high level of stress, 8 (40%) described it as very high, and 2 (10%) stated they experienced a moderate level of stress during the pandemic.

Multiple linear regression analysis was conducted to examine the relationship between stress level (dependent variable) and three independent variables: age, workload, and infection rate. The analysis revealed no significant association between age and stress level. However, a positive and statistically meaningful relationship was observed between both workload and infection frequency with the reported levels of stress. Nurses who reported heavier workloads and more frequent infections also exhibited higher stress levels, indicating that these factors had a compounding impact on their psychological well-being during the pandemic.

TABLE 1. Infection Frequency Among Nurses During the COVID-19 Pandemic

Infection Frequency	Number of Nurses	Percentage (%)
2 times	1	5
3 times	8	40
4 times	7	35
5 times	4	20

FIGURE 1. Workload among Nurses during the COVID-19 Pandemic
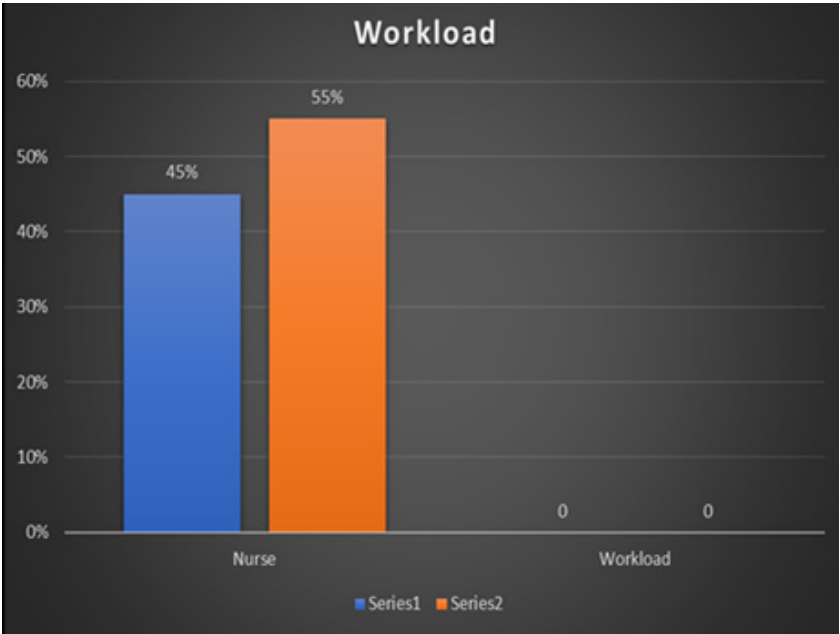
FIGURE 2. Infections among Nurses during the COVID-19 Pandemic
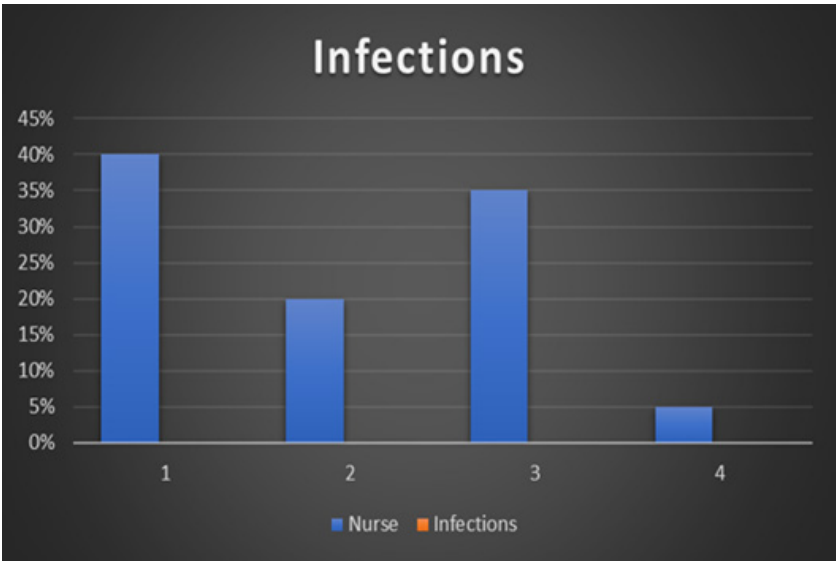
FIGURE 3. Stress level among Nurses during the COVID-19 Pandemic
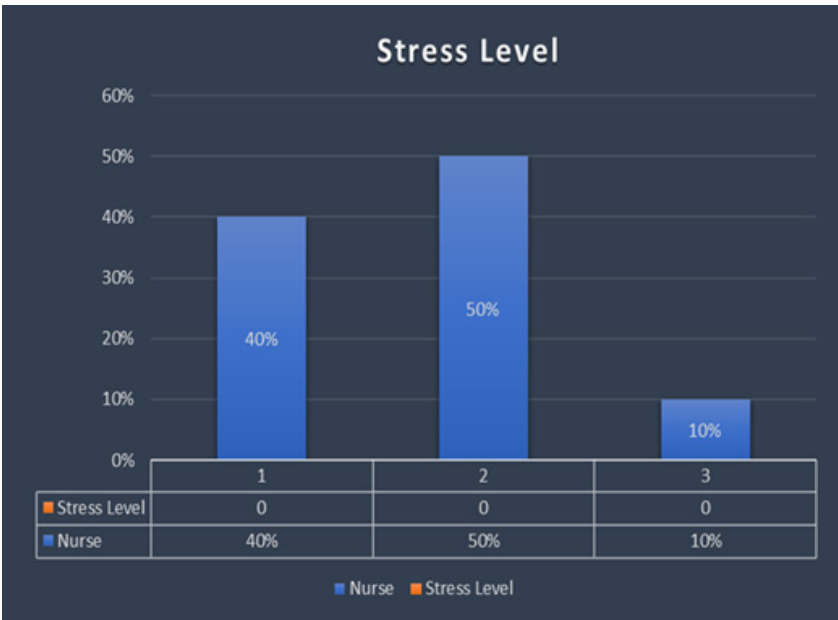
Discussion

This study highlights the critical occupational health challenges faced by nurses in infectious resuscitation during the COVID-19 pandemic. A significant majority reported high or very high workloads, frequent SARS-CoV-2 infections, and elevated stress levels, illustrating the heavy physical and psychological burden borne by frontline healthcare workers.

The observed stress levels align with previous research showing that nurses globally reported severe psychological strain during the pandemic. Dall'Ora et al. (2020) identified excessive workload and prolonged exposure to crisis conditions as key contributors to emotional exhaustion and burnout among nurses [16]. Similarly, a systematic review by Labrague and De Los Santos (2020) confirmed that nurses experienced high levels of stress, burnout, and anxiety due to increased work demands, infection fear, and lack of rest [19].

Frequent infection among respondents—some up to five times—mirrors the findings of Al Maqbali et al. (2021), who noted a correlation between high infection exposure and worsening mental health outcomes among healthcare staff [20]. In our study, infection frequency was also positively correlated with increased stress levels, reinforcing this link.

Our regression analysis confirmed that while age did not significantly influence stress levels, workload and infection frequency had a strong and direct association. This is consistent with studies by Sagherian et al. (2020), which found that job demands and physical exhaustion were major predictors of mental distress among nurses [21-22].

In light of these findings, there is an urgent need for targeted interventions. Evidence-based strategies include maintaining optimal nurse-to-patient ratios, enforcing infection prevention protocols, and promoting mental health services in hospitals (Lai et al., 2020) [23-24].

Limitations of this study include the small sample size and single-site design, which may limit generalizability. Future research should incorporate larger, multi-institutional samples and explore protective factors such as resilience and coping strategies.

Conclusions

This study provides important insights into the occupational health challenges faced by nurses working in infectious resuscitation during the COVID-19 pandemic. The findings demonstrate that excessive workloads and repeated

COVID-19 infections significantly contributed to elevated stress levels among frontline nurses, while age had no substantial influence on stress outcomes.

The strong correlation between infection frequency, workload intensity, and psychological distress underscores the urgent need for structural and organizational interventions to protect the well-being of healthcare workers. Measures such as improved staffing ratios, regular mental health support, access to personal protective equipment, and infection prevention protocols are essential for safeguarding nurses' physical and emotional health—particularly in high-risk care settings.

While limited in scope due to its small sample size and single-institution design, this study reinforces global research on occupational hazards in healthcare during pandemics. Future investigations should aim for broader, multi-center approaches and explore factors that enhance resilience and reduce burnout among nurses in crisis conditions.

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The Application of the Personality Inventory (NEO-PI) in the Recruitment of Police Officers: A Perspective Study for Albania

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Abstarct

One of the main focuses of police psychology is the psychological assessment of potential officers. The main purpose of the study is to evaluate how useful the NEO-PI inventory and its variants are in the recruitment of police officers.

A systematic review of the literature using Google Scholar, PsycNet and ScienceDirect databases was conducted. Key phrases such as "Big Five" and "police officer" or "NEO-PI" and "public safety officer" were identified and analyzed to filter the material.

Based on the studies using the application of the NEO-PI test in the recruitment of police officers, they provide significant data for psychological well-being, adaptability to work, and professional integrity.

The use of the NEO-PI in the selection process of police candidates provides meaningful data to police structures and other law enforcement agencies about mental health, skills, work performance, and professional ethics. Based on applied studies and international practices, the use of personality tests such as NEO-PI in our country would be effective for candidates, the police organization, the Security Academy, and for research purposes.

Keywords: *Public safety officer, police officer, test, Big Five, NEO-PI.*

Introduction

The application of psychological tests in predicting future performance has been documented as far back as 1300 B.C. The Israeli army operating under Gideon used military aptitude tests to select suitable soldiers. The Greek army, as noted by Plato, also implemented military skill testing to screen potential soldiers (Guion, 1976). More recently, some of the earliest published psychological tests were mental ability tests, which were developed by Cattell (1890) to examine which mental abilities are associated with success in school. Blau (1994) noted that psychological testing was used during World War I to select military personnel. At the beginning of 1919 until the end of the war, the Alpha and Beta tests were used in the recruitment of new soldiers (Larson, 1994; McGuire, 1994). These tests served as a model for their other testing and the Army General Classification Test (AGCT), which was designed and implemented during World War II, was created. studies have highlighted a link between individual traits of police officers and their job performance, highlighting that a potential officer's dispositions relate to their effectiveness at work (Stewart, 2008). In recent years, in Albania, several psychological instruments have been applied in the form of interviews in the recruitment process of applicants for police officers at the Security Academy. Currently, no standardized and unified instrument has been implemented, both in the recruitment process of competitors and for police officers..

Methods of systematic literature review

The purpose and objectives of the research

The study examined the usefulness of the NEO-PI inventory and its versions in the recruitment of police officers. The systematic literature review aims to identify and analyze the effectiveness of NEO-PI targeting in the recruitment of applicants for police work.

Search terms for literature and research techniques

The ScienceDirect, PsycNet, and Google Scholar databases were consulted, depending on the study's objectives. "Big Five" and "police officer," or "NEO-PI" and "public safety officer," were the precise search keywords.

Results

Ten publications were deemed appropriate for usage based on the selection criteria (Fig. 1). The study was created and according to the PRISMA process's report for systematic review standards for scientific articles (PRISMA, 2021).

FIG 1: Flow chart of the research strategy
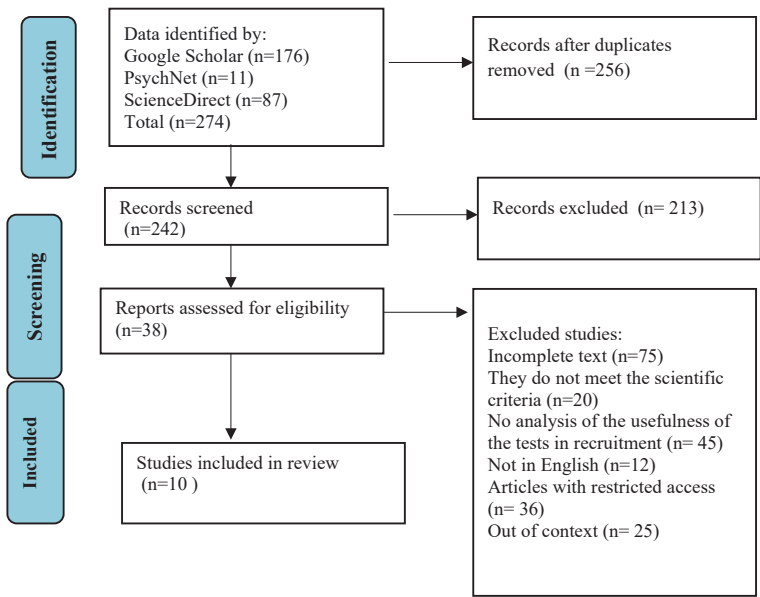
Types of psychological tests used in the recruitment process of police officers

The use of psychological tests in the selection of applicants for police officers is a useful strategy in identifying individuals suitable to be successful employees in police structures. Certain characteristics are said to combine in law enforcement personnel to create a unique "police personality." For law enforcement personnel,

this personality type has been described as a particular value orientation. Bravery, loyalty, authoritarianism, cynicism, skepticism, physical courage, self-confidence, aggression, mistrust, secretiveness, conservatism, dogmatism, and alienation are among its interconnected personality traits. Skolnick (1966) argued that the work personality of the police officer consists of cynicism, suspicion, external isolation, internal solidarity, and conservatism (Zakaria et al., 2023). During the late 1970s, the most popular personality tests in police structures were the Minnesota Multiphase Personality Inventory (MMPI), California Psychological Inventory (CPI), Inwald Personality Inventory (IPI), 16 Personality Factors (16 PF), the Edwards Personal Preference Schedule (EPPS), and various projective tests (Fabricatore et al., 1978; Fabricatore, 1979; Inwald, 1982; Ostrov, 1986). The personality inventory (NEO-PI) was also used, which, in addition to being used in police institutions, has also been applied in other disciplines (Jonathan et al., 2013). In recent years, another set of psychological instruments has been implemented in the selection of police officers, such as the Personality Assessment Inventory (PAI), which is essentially a psychopathology test and has many similarities with the MMPI (Super, 2006). The M-PULSE is an instrument first introduced in 2008 that assesses a range of attitudes and beliefs specifically related to police work duties (Davis, 2008).

Personality Inventory (NEO-PI)

The Big Five are five fundamental personality qualities that are the focus of numerous contemporary and conventional psychological investigations. D.W. Fiske created the notion of five basic personality traits in 1949, and additional scholars including Norman, Smith (1967), and Goldberg (1990) have since added to it. The first version of the NEO was developed in 1978 by McCrae and Costa, which included only three personality domains: neuroticism, extraversion, and openness to experience, giving the instrument the name NEO. The NEO inventory was developed to assess stable personality characteristics in normal populations (Groth & Wright, 2016). It was later revised in 1985 and included the five traits, being renamed the Personality Inventory (NEO-PI). The inventory assesses individual traits in five dimensions, which are extraversion, neuroticism, openness to experience, conscientiousness, and agreeableness. In later periods, researchers updated it to other versions, such as the (NEO-PI-R) in 1992 and the (NEO-PI-3) in 2005. The NEO inventory is still widely used as the basis of personality studies. on a global scale. Another version was created based on the NEO-PI inventory by the Oregon Research Institute in collaboration with the International Personality Item Pool (IPIP-NEO) (Goldberg et al., 2006; Johnson, 2014).

The validity of NEO-PI and its versions
in the recruitment of police officers

In evaluating psychological tests, two important components are predictive validity and concurrent validity. Predictive validity is the degree to which an inventory or test predicts a person's performance on the dimensions or attributes the instrument is designed to measure. An instrument has predictive validity if it is able to identify which candidates will or will not succeed in the job position for which they are competing. Concurrent validity is the degree to which a test or inventory identifies a person's actual performance on the dimensions and tasks it is supposed to assess (Bartol & Bartol, 2019). As an inventory that operationalizes the five-factor model, the (NEO PI-R) is often used in personnel selection. The California Commission on Peace Officer Standards and Training has identified ten dimensions that increasingly serve as a model for screening police officer applicants. According to them, (NEO PI-R) seems suitable to be used as an instrument in the process of screening applicants for police work (Detrick & Chibnall, 2019). The personality traits of the five-factor model have demonstrated significant validity in predicting job performance (Hurtz & Donovan, 2000). A meta-analysis identified positive associations between some of the Big-Five domains and police officer performance. According to the authors, the strongest predictor of police work performance was the dimension of conscientiousness (Black, 2000). Also, the "Big-Five" approach has given positive results in predicting teamwork performance. Regarding this, in a review article, the "Big-Five" model was studied in the selection process of police personnel, the data reflected a positive correlation between extroversion and behavior related to teamwork (Rothstein & Goffin (2006). Also the findings of a another study presented significant data of (NEO) regarding group interaction style, verbal communication, leadership in emergency situations and leadership task behavior (Bowles & Bartone, 2017).Inventory (NEO-PI-3), u applied to 257 applicants for police officers, the results showed usefulness which can be used as a comparison group and reference point for future samples of recruits Chibnall et al., 2024). In another study (NEO-FFI) was applied to college students where the data showed a positive relationship between extraversion and conscientiousness, and a negative relationship between neuroticism and mental health (Yuan et al., 2011). The results of a study that explored the relationship between personality and job satisfaction among police officers showed that individuals with high conscientiousness and low neuroticism had better psychological well-being scores (Anum, 2023).

Despite its widespread use, the test (NEO-PI) presents several disadvantages that must be considered, especially when used in the context of police officer recruitment. Schmit and Ryan (1993) in their findings pointed out that the five

factor model is suitable for students and not for competitors for employment effect (Schmit & Ryan, 1993). An individual's emotional state at the time of testing can affect the results. If a candidate is under temporary stress or fatigue, this can negatively affect the assessment of their emotional stability or extraversion, giving an inaccurate result about their overall personality. The inventory (NEO-PI-R) is a standard test and does not have much flexibility to adapt to specific situations or special criteria that may be important in the recruitment of police officers. Some special structures or agencies have specific needs for their employees and may require more adapted instruments to evaluate potential candidates.

The role of the psychologist in the State Police in Albania

Psychological services in police structures in Albania started about a decade and a half ago. The work of the psychologist in the State Police is focused on the assessment, testing and psychological counseling of police officers. In 2021, the "Police Psychologist's Manual" was drafted. In cooperation with the Directorate of Human Resources and the Training Sector, under the General Directorate of the State Police. In 2022, a commission was created for the drafting of the standard procedure of assessment and psychological counseling, and trainings with international psychologists related to the recruitment procedures of applicants for police officers were also developed. For many years, psychologists from different structures of the State Police have been engaged in the selection of candidates for police officers at the Security Academy. Currently, the level of professional training of psychologists in the police organization in Albania is at satisfactory levels, based on qualifications, training, being licensed and involvement in scientific research.

Discussions

Based on the studies used, the primary purpose of the (NEO-PI) is the detailed description of the five personality dimensions and subscales. A significant part of the studies emphasize that the inventory (NEO PI-R) is suitable for use in the recruitment process of police officers (Detrick & Chibnall, 2017). Also, a limited number of researches have identified some limitations of the instrument. According to them the test (NEO-PI-R) focuses only on personality and does not measure other important skills such as cognitive skills, reaction in dangerous situations and the ability to make quick decisions. The test (NEO-PI-R) is more applied in European countries mainly in Scandinavian countries, unlike the Inventories (MMPI) and (CPI), which are widely used in English-speaking countries. Based on the widespread use of the NEO-PI inventory in countries similar to Albania, it

would be effective to standardize and apply the instrument in our country as well, in the police organization and in law enforcement agencies.

Conclusions

Five personality factors are thoroughly analyzed by the Personality Inventories (NEO-PI), which aids in behavior and performance prediction on certain tasks. In law enforcement agencies, the "Big-Five" model has proven to be a reliable predictor of both individual and group work success. Additionally, the exam is frequently utilized in academic research and the social sciences. Despite its broad application, some researchers have pointed out certain drawbacks and restrictions regarding its psychometric qualities. Researchers recommend the use of extra data, including clinical interviews, demographics, education, and employment information, when choosing candidates for police officer positions. Based on the Albanian context within the framework of the reformation of the police organization and alignment with contemporary standards, it is necessary to standardize and apply (NEO-PI) in the police structures and in the relevant law enforcement agencies. Knowing that the inventory (NEO-PI) is widely used in European countries, its application in Albania would be useful based on cultural similarities and some demographic aspects.

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Burnout Among Nursing Staff: An Overview of Causes, Consequences, and Management Strategies

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Abstract

Introduction: Burnout is a significant problem among nurses, who face constant challenges in their work environment, including heavy workloads, emotional pressure and lack of sufficient support. This study aims to provide a review of the literature to identify the factors that contribute to the development of burnout and the consequences it causes on the health of nurses and the quality of patient care, as well as the most effective strategies for its management and prevention.

Purpose: This review aims to analyze the existing literature to better understand the prevalence and impact of burnout among nurses, proposing more effective measures to reduce it in healthcare settings.

Methodology: To carry out this review, scientific articles published during the last decade were used and analyzed from databases of good academic reputation. The review included evidence-based studies addressing risk factors, their effects, and proposed interventions for the management of burnout in nursing. The literature was selected based on clear criteria of relevance, methodological quality and scientific content.

Results: Findings from the existing literature show that the main factors leading to burnout include workplace overload, long shifts, lack of autonomy and emotional support, and the psychological pressure of patient care. Burnout negatively affects not only the physical and emotional well-being of nurses, but also the quality of the healthcare system, leading to a decrease in efficiency and an increase in errors during treatment. Proposed management strategies include institutional interventions, such as improving working conditions, rescheduling and psychological support, as well as individual approaches, such as stress management techniques and mental well-being programs.

Conclusions: In conclusion, this review highlights the need for an integrated approach involving both organizational and individual interventions to reduce the impact of work burnout and promote a healthier work environment for nurses.

Keywords*: Burnout, nurses, work stress, health care quality, organizational interventions, emotional well-being.*

Introduction

Burnout is a multidimensional professional syndrome characterized by emotional exhaustion, depersonalization and a diminished sense of personal accomplishment. Although it was first described by Freudenberger in the 1970s, its importance has received increased attention during the last decades due to the severe impact on health care professionals, especially nurses (Zhang et al., 2018; Shah et al., 2021). Recognized by the World Health Organization (2019) as an occupational phenomenon in ICD-11, Burnout is now not only seen as an individual psychological issue, but as a complex challenge to the system formed by organizational structures, work environments and broader health care policies. The prevalence of burnout among healthcare professionals is high, because the work environment in hospitals is characterized by activities that are demanding and strenuous both physically and mentally (Gjergji V., 2024). Nurses, as essential components of providing care in a close relationship with the patient, are particularly sensitive to physical fatigue due to constant exposure

to the physical and emotional demands that patients have. The large ratio that a nurse has with a certain number of nurses, the lack of staff, insufficient resources and prolonged exposure to the suffering that patients have - especially in high-intensity units such as emergency, intensive care and palliative settings - form a perfect ground for chronic work stress (Galanis et al., 2021; Membrive-Jiménez et al., 2020; Wang et al., 2024). The COVID-19 pandemic further increased these pressures, exacerbating existing gaps in staffing, mental health support and institutional responsiveness (Buchan et al., 2022; WHO, 2024).

The consequences of Burn-out are far-reaching. At an individual level, it is associated with chronic fatigue, depression, anxiety and reduced job satisfaction, often culminating in leaving the workforce or even early retirement (Prémusz et al., 2022; Woo et al., 2020). At the organizational level, burn-out in the nursing team contributes to increased absenteeism, reduced productivity, higher costs of job switching and reduced quality of patient care (Jun et al., 2021; Li et al., 2024). Furthermore, patient safety and satisfaction are negatively affected by nurse fatigue through increased rates of medical errors and incorrect communication (Quesada-Puga et al., 2024).

While various strategies have been proposed to address Burn-out, many of them focus narrowly on individual resilience and stress management techniques, such as mindfulness and emotional management (Lee & Cha, 2023; Todaro-Franceschi, 2019). Although these interventions can be helpful, they often fail to address the root causes embedded in health care systems. Evidence increasingly supports the implementation of organizational-wide strategies, including improved staffing models, supportive leadership, and policies that promote work-life balance (Maslach & Leiter, 2022; National Academies of Sciences, 2019; OECD, 2024).

Methodology

The methodology of this literature review was carried out through several structured phases, using a systematic approach to identify, analyze and synthesize studies on burnout among nursing staff, focusing on its causes, consequences and strategies in its management. Inclusion and exclusion criteria were defined to include studies published between 2018 and 2025, in the English language and in peer-reviewed journals with recognized scientific impact. Eligible studies addressed the risk factors, outcomes, and management strategies associated with burnout in nursing staff. The selection process involved comprehensive searches in databases such as PubMed, Scopus and Web of Science, using keywords such as burnout syndrome, nurses, work stress, job satisfaction and coping strategies. After an initial review of articles based on titles and abstracts, information was extracted and categorized into three main areas: causes of burnout, its consequences and management strategies.

Results and Discussion

Burnout has emerged as a critical issue in the nursing profession, attracting increasing scientific and institutional attention due to its significant impact on the well-being of nurses and the quality of health care provided by them. This review analyzes the main causes, consequences and evidence-based strategies for the prevention and management of burnout, synthesizing findings from a wide range of peer-reviewed studies, international organizational reports and published academic sources.

Current evidence indicates that burnout in nursing staff results from a complex interaction of organizational, professional, and personal factors. Studies from various health care systems around the world consistently identify that excessive workloads, long working hours, insufficient staff and lack of managerial support are major contributors to burnout (Galanis et al., 2021; Shah et al., 2021; Wang et al., 2024). For example, data from European and American health institutions show that more than 60% of nurses report symptoms of burnout, mainly driven by long staff absences and high patient demands (Quesada-Puga et al., 2024; Lee & Cha, 2023).

Emotional overload and the constant lack of various resources contribute to feelings of powerlessness and lack of autonomy among nurses, especially in intensive care units and environments with a high level of concentration (Monsalve-Reyes et al., 2022; Souza-Veloso et al., 2024). These environments require constant clinical vigilance and rapid decision-making and high-risk for the vital quality of patients, which, when they do not receive the appropriate institutional care, can lead to a rapid decrease in emotional and physical reserves. The added burden of balancing difficult professional responsibilities with personal responsibilities further exacerbates stress, accelerating the onset of Burn-out (WHO, 2024; OECD, 2024).

The consequences of burn-out are multidimensional. On a personal level, it is strongly associated with anxiety, depression, sleep disorders and chronic fatigue, which impair their professional judgment and performance (Prémusz et al., 2022; Woo et al., 2020). A meta-analysis found that a significant proportion of nurses experiencing burn-out also exhibited clinical signs of depression, directly affecting patient care outcomes (Chen & Meier, 2021).

In the patient relationship, burn-out among nursing staff is associated with an increased risk of medical errors, reduced service standards, and decreased patient satisfaction (Li et al., 2024; Jun et al., 2021). A retrospective study in US hospitals reported that nursing units with high levels of Burn-out had a 32% higher incidence of reported errors compared to those with lower levels of Burn-out (CDC, 2022).

On the organizational side, burnout contributes to workplace absenteeism, high turnover of nursing staff, and increased costs associated with recruiting and retraining new staff (ICN, 2021; WHO, 2019). Healthcare systems facing workforce shortages have difficulty maintaining service quality and patient safety, especially after the pandemic (Buchan et al., 2022). Furthermore, the financial burden of nurses leaving the workplace, coupled with the loss of experienced staff, compromises institutional efficiency and continuity of care (OECD, 2023; Stewart & Moore, 2025).

To combat these challenges, a number of strategies have been implemented, targeting both individual and institutional aspects. Interventions focusing on stress management and social support showed significant improvements in employee well-being. (Merkuri L, Paja E., 2024). At the individual level, interventions such as mindfulness-based stress reduction (MBSR), psychological resilience training, and cognitive-behavioral techniques have been shown to be effective in improving emotional regulation and reducing symptoms of burnout (Todaro-Franceschi, 2019; Gaffney & Foster, 2023). For example, a hospital-based mindfulness program was found to significantly reduce emotional exhaustion within six weeks (Lee & Cha, 2023). However, these personal strategies need to be reinforced by systemic changes in health systems.

The literature highlights the need for organizational reforms, including improved nurse-patient ratios, flexible schedules, equitable workload distribution, and supportive leadership (Maslach & Leiter, 2022; National Academies of Sciences, 2019). Transformational leadership approaches that prioritize empowerment and psychological safety have been associated with lower levels of burnout and higher staff motivation (Shah et al., 2021; WHO, 2024).

The evidence reviewed confirms that burnout in nursing staff is a structural and multidimensional phenomenon. It cannot be fully addressed without addressing the systemic deficits that perpetuate stressful working conditions. The lack of clear institutional policies to support staff, coupled with insufficient investment in mental health infrastructure, only exacerbates the problem (OECD, 2024; WHO, 2024).

Therefore, a comprehensive approach to alleviating burnout must encompass all levels – from fostering individual coping mechanisms for stress and workload to creating an institutional culture that prioritizes psychological well-being. Healthcare organizations are encouraged to establish monitoring systems that regularly assess the overall well-being of staff and track the effectiveness of interventions over time (Galanis et al., 2021; Shah et al., 2021).

Finally, prioritizing the humanization of care environments and promoting a culture based on compassion, respect, and teamwork is essential in managing burnout among nursing staff. As global demands for higher quality healthcare increase, investing in the well-being of nurses should be considered a strategic

investment and a commitment that ensures not only the sustainability of the workforce, but also safe, equitable, and high-quality healthcare for patients (WHO, 2024; ICN, 2021; Stewart & Moore, 2025).

Conclusions

Burn-out is a growing problem in the nursing profession, driven by heavy workloads, long work shifts and inadequate institutional support. It leads to anxiety, depression, fatigue and reduced clinical performance. Institutionally, it increases absenteeism or absenteeism, strains staff, reduces the quality of care, and increases costs to the system. Addressing burn-out requires both personal and organizational interventions, including stress management training and mental resilience building strategies. Long-term improvement depends on coordinated efforts among nurses, leaders, and policymakers to implement supportive and evidence-based solutions for a stronger health care system.

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Bastar Ointment: A Promising Herbal Medicine in Dermatology

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Abstract

Introduction and Aim: Bastar ointment is a widely used medicinal product in the Tirana Highlands and beyond. It is composed of a blend of several herbs known for their medicinal properties, along with meat by-products. This precise combination results in an ointment that effectively treats various types of wounds, including burns, infected wounds, deep lacerations, and scratches.

The aim of this study is to investigate how this popular medicine influences the treatment of various wounds, referencing the research conducted by the respective authors for each plant.

Materials and Methods: A total of 513 cases were included in the study. Participants who responded to the questionnaire varied in age and had different types of wounds. Additionally, they were not exclusively from the Tirana highlands. The responses included information on the care provided, the duration of treatment, any combinations with other herbs, as well as any side effects or allergies experienced.

Results: The average time for wound healing is approximately 12 days, with burns accounting for 32% of the cases. Fortunately, no allergic reactions were observed, and the medication was administered twice daily in 63% of cases.

Conclusions: Bastar Ointment has demonstrated positive effects on wound healing, thereby confirming the pharmacological properties of this traditional folk

medicine. The findings indicate its anti-inflammatory, antimicrobial, antinociceptive, antioxidant, and anticarcinogenic effects, as well as its content of essential vitamins and beneficial fats. Given its diverse range of biological activities, Bastar Ointment can be regarded as a medicine with valuable and intriguing properties.

*   **Key words:** *Bastar Ointment, folk traditional medicine, various wounds, medicinal plants.*

Introduction

Traditional medicine encompasses "the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, used in maintaining health and in preventing, diagnosing, curing, or treating physical and mental illnesses" (World Health Organization, 2005). In addition to conventional wound care options, traditional medicine can also be utilized (Azimi et al., 2020).

Bastari Ointment is a traditional folk medicine that has been utilized in the Tirana Highlands since World War I. It is composed of a blend of several medicinal plants and meat by-products, which gives us medicine in the form of an effective ointment. The beneficial effects of these medicinal plants from the Balkan region for wound healing, as per traditional practices, have been substantiated by numerous scientific studies. The unique geographical and ecological characteristics of the Balkan Peninsula have fostered a remarkable diversity of medicinal plants. In the traditional culture of the Balkan peoples, including Albania, the diverse flora has demonstrated significant medical, economic, and anthropological/cultural importance. This is reflected in the extensive knowledge of their diversity and applications (Jarić et al., 2018). This folk medicine comprises a combination of several medicinal plants, with their therapeutic value stemming from various chemical compounds that exert physiological effects on the human body, leading to positive health outcomes and enhanced wound healing (Džamić & Matejić, 2017). Bastari ointment is utilized for the treatment and healing of wounds, particularly infected wounds, as well as burns and deep tissue injuries, facilitating the regeneration of these wounds. Compounds derived from natural products can serve as direct medications for wound healing or as drug carriers for the delivery of other therapeutic agents (Sharifi-Rad et al., 2018). Traditional wound healing therapies have been explored both experimentally and clinically, with numerous studies providing extensive information about the role of these therapies in addressing the underlying causes of wounds. Medicinal plants are regarded as potent and promising therapeutics for enhancing wound healing processes, owing to the diverse array of active and effective ingredients they contain. Traditional medicines may be favored over modern therapies due to

their low cost, minimal adverse effects, bioavailability, and efficacy (Hajialyani et al., 2018). Bastari ointment, along with various medicinal herbs, is rooted in the rich experiences of countless healers over the centuries, passed down through generations or developed through personal experiences over time. Modernity and cultural revolutions have not diminished the profound wisdom inherent in this natural medical paradigm (Khan, 2014). The awareness of medicinal plant usage is the result of many years of efforts to combat diseases, leading humanity to learn how to utilize drugs derived from barks, seeds, fruiting bodies, and other plant parts (Petrovska, 2012).

The purpose of this paper is to investigate how this folk remedy, which comprises a combination of several medicinal herbs and meat by-products, influences the healing of various wounds by examining the effects of each component.

Materials and Methods

This is a descriptive study that focuses on the development of a questionnaire consisting of eight questions regarding "Bastar Ointment". The theoretical framework is grounded in a review of literature and various studies that have been conducted by relevant authors, where the data conducted by other authors have confirmed the effects of each of the medicinal plants. The data collected in this study pertains to the period from January 2024 to April 2024.

In total, 513 participants (241 men and 272 women) completed the questionnaire. The age groups of the participants were categorized as follows: 0-20 years, 21-40 years, 41-60 years, and participants over the age of 60 years. The participants who responded to the questionnaire were mainly from the Tirana Highlands and surrounding villages; however, there were also participants from other cities in the country and from outside the region of Albania.

TABLE 1 presents the age distribution and the number of participants.

Participants' age	Number of participants'
0 - 20	136
21 - 40	123
41 - 60	141
>61	113

The Properties and Composition of Bastar Ointment

The effects of the ointment are numerous; it aids in skin regeneration and ensures the formation and strengthening of cell membrane structures. The Bastar ointment is composed of a blend of herbs, including sage, which contributes beneficial compounds that combat infections due to its high antibacterial and antifungal properties. Additionally, it has calming effects, preventing the aggravation of infections, and, importantly, it has no side effects (Ghorbani & Esmaeilizadeh, 2017). A medicinal plant is defined as any plant that contains substances in one or more of its organs that can be used for therapeutic purposes or that serve as precursors for the synthesis of useful drugs (Sofowora et al., 2013).

Bastar Balm/Ointment contains

Sage – Salvia officinalis
Balsam Flower – Hypericum haplophylloides
Poppies – Papaver rhoeas
Spanish Broom – Spartium junceum L.
Olive Oil – Oleum Olivarum
Bee Pollen – Propolis
Honey – Mel
Sheep tail fat

The enhanced efficacy of treatments utilizing natural extracts is attributed to the creation of synergy, which amplifies the effects of products derived from natural sources, as well as contemporary therapeutic approaches. Numerous studies have demonstrated that this synergistic interaction stems from the antibacterial, antioxidant, and anti-inflammatory properties of these substances, which are highly beneficial for wound healing (Azimi et al., 2020).

In folk medicine, S. officinalis has been used to treat various disorders (Ghorbani et al., 2017). Currently, many reports are using S. officinalis (L.) to analyze its pharmacological activity and studies have shown its potential as anti-inflammatory (Rodrigues et al., 2012), antioxidant (Generalic et al., 2012), to prevent neurodegenerative disease (Takano et al., 2011), antimicrobial (Garcia et al., 2016), antitumor activity (Al-Barazanjy et al., 2013; Akaberi et al., 2015), and anti-diabetic activity (Christensen et al., 2010).

The major phytochemicals in the flowers, leaves and stems found in plant S. officinalis have been well identified. A wide range of constituents including alkaloids, carbohydrates, fatty acids, glycoside derivatives (e.g., cardiac glycosides, flavonoid glycosides, saponins), phenolic compounds (e.g., coumarins,

flavonoids, tannins), polyacetylenes, penetrants (monoterpenoids, diterpenoids, triterpenoids, sesquiterpenoids) and waxes have been found in S. officinalis (Ghorbani et al., 2017).

Balsam flower – *(Hypericum perforatum)*, it is a very popular traditional herbal medicine due to its wide range of applications, including the treatment of skin problems such as healing burns, stomach ulcers, gallbladder disorders, inflammation of the bronchi and genitourinary system, colds, migraines, headaches, diabetes mellitus, and obesity. It is also effective in the treatment of mild to moderate depression (Nobakht et al., 2022).

Balsam flowers have long been used both orally and topically for wound and burn healing in folk medicine of various countries. In the clinical study of Özturk et al., it was shown that the oil extract of hypericum perforatum promotes the healing of surgical wounds from cesarean section birth as a result of increased epithelial reconstruction (Özturk et al., 2007).

The plant Papaver Rhoeas L, belonging to the Papaveraceae family, is also used as food and is used to treat inflammation, respiratory problems, diarrhea, cough, insomnia, asthma, and anxiety. Extracts of P. rhoeas have many pharmacological actions, including antioxidant, antimutagenic, cytoprotective, antibacterial, analgesic, and antiulcerogenic properties (Katarzyna et al., 2021).

Several international phytochemical studies show that Papaver rhoeas contains a high concentration of secondary and primary metabolites, including amino acids, carbohydrates, fatty acids, vitamins, phenolic compounds, essential oils, flavonoids, alkaloids, coumarins, organic acids and other compounds, which explains its use in foods and traditional pharmacopoeia (Grauso et al., 2021).

Virgin olive oils have anti-atherosclerotic potential, favoring endothelial function and maintaining blood pressure, preserving lipoprotein function, exerting anti-inflammatory and antioxidant effects, and modifying gene expression in several tissues to maintain proper homeostasis (Visiol et al., 2018). Polyphenols in extra virgin olive oil (EVOO) have also demonstrated beneficial effects on wound healing. EVOO includes triacylglycerols (~98%), fatty acids, and mono- and diacylglycerols (Han et al., 2009).

The healing property of honey is due to the fact that it provides antibacterial activity, maintains a moist wound condition, and its high viscosity helps to provide a protective barrier to prevent infection (Mandal et al., 2011). Honey also contains essential oils, the composition of which includes terpenes (thymol, bisabolol, farnesol and cineol). Other components of honey include water, amino acids and proteins. Proline (50-80%) dominates among amino acids and its increased presence indicates the maturity of honey. Vitamins constitute a small group of components present in honey and they are mainly: thiamine, riboflavin, pyridoxine, p-aminobenzoic acid, folic acid, pantothenic acid and vitamins A, C,

E. Honey also contains minerals: phosphorus, potassium, calcium, magnesium, sulfur, iron, copper, manganese and zinc (Kurek-Górecka et al., 2020).

Propolis has been used for a long time in medicine due to its bactericidal, antiviral, antifungal, anti-inflammatory, antitumor, immunomodulatory and antioxidant activity (El-Sakhawy et al., 2024).

Spartium junceum L, consists of cellulose, a biocompatible and biodegradable polymer, useful in various applications such as scaffolds in tissue repair, wound dressings, artificial tissues/skin, controlled drug delivery, blood purification, and cells (Azimi et al., 2020).

Results

Study Population and Data Collection

The study involved the collection of 513 responses to a questionnaire administered between January 2024 and April 2024. The questionnaire was distributed in both digital and written formats to accommodate participants of varying ages, as not all had access to complete the online version. Participants were entrusted to provide accurate data. Prior to distributing the questionnaire, all participants were informed about the study's purpose and assured that their privacy would be strictly maintained.

The wounds varied in type, including burns, infected wounds, deep lacerations, and scratches.

In addition to using Bastar Ointment, participants were asked whether they had utilized any other medications, such as antibiotics or similar treatments. They also inquired about any allergic reactions experienced while using the ointment, as this folk remedy contains various medicinal plants. Patients were requested to describe their wound care regimen, specifically how many times a day they treated the wound—once, twice, or three times—and the duration it took for the wound to heal. The healing period was categorized into three ranges: 5 to 10 days, 11 to 15 days, and more than 15 days.

Data Analysis

Based on the data extracted from the administered questionnaire, 513 participants reported positive outcomes. Among them, 12% used the treatment for scratches, 28% for deep wounds, another 28% for infected wounds, and 32% for burns. When asked whether they used concomitant medications, such as antibiotics, to evaluate the effects of the treatment—whether it was their own or assisted by another medication, the results indicated that 99% did not use any concomitant

medication, while only 1% did. Additionally, when participants were asked if they experienced any allergic reactions, the results showed that 100% reported no adverse reactions. The Bastar ointment was used by 19% of patients once a day, 63% of patients twice a day, and 18% of patients three times a day.

The data analysis based on the patients' responses indicates that 51% of patients required 10 to 15 days for their wounds to heal, 30% needed 5 to 10 days, and 19% required more than 15 days.

It has been observed that the participants who used Bastari Ointment primarily hail from the Tirana Highlands and Tirana, although a significant number also comes from the city of Burrel. Additionally, there is a notable presence of users from other cities in Albania, as well as from outside the region. This data indicates that Bastari Ointment enjoys widespread use within the community (see table 2). Table three presents' data regarding the types of wounds for which Bastar Ointment was utilized. Patients reported that Bastar Ointment was used for 12% of scratches, 28% of deep wounds, 28% of infected wounds, and 32% of burns. When asked whether they had used any other concomitant medications (such as antibiotics) during wound treatment, the responses indicated that 99% of patients did not use any concomitant medication, while 1% of patients did use any concomitant medication. In response to the question regarding whether patients experienced any allergic reactions while using Bastar Ointment, the data indicated that 100% of patients did not report any allergic reactions. When asked how long it took for their wounds to heal, the data revealed that 30% required 5 to 10 days, 51% needed 10 to 15 days, and 19% took more than 15 days. Regarding the frequency of wound treatment, the results showed that 19% of patients treated their wounds once a day, 63% treated them twice a day, and 18% treated them three times a day (see table 3).

TABLE 2 displays the residences of patients from various cities and regions in Albania, as well as from abroad.

Tirana highlands	270
Tiranë	130
Burrel	55
Durrës	12
Kamëz	6
Krujë	4
Shkodër	5
Elbasan	4
Tetovë	4
Prizren	3
Preshevë	3
Gjilan	2

Dibër	2
Kukës	3
Berat	1
Stamboll	1
Prishtinë	1
Lushnje	1
Lezhë	1
Tepelenë	1
Bulqizë	1
Tropojë	1
Itali	1
Korçë	1

TABLE 3 summarizes participants' answers regarding wounds, whether any concomitant medication was used, whether any allergy was shown during the treatment, healing time and frequency of wound treatment.

Types of wounds reported	Participants
Scratch	63
Deep wound	143
Infected wound	144
Burn	163
Whether any concomitant medications were used	
Yes, they did use	508
No, they didn't	5
Whether participants had any allergies	
Yes	0
No	513
The healing time required for each participant	
5 – 10 days	154
11 – 15 days	260
>16 days	99
The frequency of wound treatments	
Once a day	95
Twice a day	325
Three times per day	93

Discussion

To our knowledge, this study is the first of its kind in Albania. We hope that further research will be conducted to enhance our understanding of this traditional folk medicine.

Based on the pharmacological properties of each ingredient in the popular formulation and the data collected, we can conclude that Bastar Balm ointment positively influences the rapid closure of wounds and the reduction of complications. Previous studies have identified a broad spectrum of pharmacological activities associated with *Salvia officinalis*. These findings include anti-inflammatory, antinociceptive, antioxidant, antimicrobial, antimutagenic, antidementia, hypoglycemic, and hypolipidemic effects (Ghorbani & Esmaeilizadeh, 2017). These results align with our study, as participants reported no side effects and experienced quick healing times. Furthermore, the results indicate that *Hypericum perforatum* extract is highly effective in wound healing, promoting re-epithelialization and collagen accumulation while leaving no scars, due to its anti-inflammatory and antigranulation properties. Additionally, this plant exhibits antibacterial and antifungal effects (Yalcınkaya et al., 2022). According to the results obtained from relevant studies, the extract of *Papaver rhoeas* exhibits antimicrobial properties that are effective even against microbes resistant to antibiotics. Additionally, it possesses anti-aging properties (Shahyad et al., 2023). Previous clinical studies have demonstrated that extra virgin olive oil (EVOO) contains anti-inflammatory, antioxidant, antimicrobial, angiogenic, and antitumor properties, all of which significantly impact wound healing (Rodrigues et al., 2021). Honey also possesses antibacterial properties and promotes fibroblast migration and collagen deposition, playing a crucial role in tissue regeneration (Kurek-Górecka et al., 2020). In studies reviewed by Yang, it was observed that propolis stimulates collagen production and exhibits antimicrobial and anti-inflammatory properties, while also enhancing scarring and reducing pain (Yang et al., 2022). Furthermore, several previous studies have reported beneficial effects on tissue regeneration that align with our data, as all our participants reported positive effects from Bastar Ointment, which is composed of a blend of herbs and honey. It is important to note that Bastar Ointment also contains sheep's tail fat, which has been shown to be rich in vitamins that contribute to cell membrane construction, strengthen the immune system, and positively impact the treatment of sciatic nerve pain (Ahmed, 2023). All of these properties play a vital role in wound healing.

The observed increase in the extractability of the subunits of the substances contained, particularly from wounds treated with the ointment, may explain its beneficial reparative properties. Furthermore, wound healing is characterized by the absence of significant reduction of the inflammatory phase, accompanied

by accelerated re-epithelialization. According to the results, Bastar Ointment can enhance the re-epithelialization process. The increased extractability in wounds treated with this folk remedy may stem from its ability to stimulate the proliferation and survival of monocytes, thereby indirectly increasing cell counts (Volk et al., 2011). Additionally, the presence of vitamins A and C in sheep's tail fat may positively influence the remodeling phase, as vitamin C is essential for collagen biosynthesis, while vitamin A may regulate the preferential expression of TGF-β3, promoting scar-free wound regeneration and repair (Aust et al., 2010). The antimicrobial activity observed in most ointments is attributed to the enzymatic production of hydrogen peroxide (Mandal & Mandal, 2011).

We can attribute the healing properties of Bastar Ointment to its antibacterial activity, which helps maintain a moist wound environment. Additionally, its high viscosity creates a protective barrier that prevents potential infections. The ointment's immunomodulatory properties also play a crucial role in wound repair.

Conclusions

The current study presents therapeutic data on Bastar Ointment, which has been traditionally used in the Tirana Highlands, an area known for its diverse and rich biodiversity. We conclude that our study confirms the therapeutic efficacy of Bastar Ointment, which is associated with the creation of a favorable biochemical environment that supports the wound healing process.

Limitations and Recommendations

We acknowledge that there are limitations to our study, such as the number of participants. Although we have a substantial number of participants, having more data is always advisable. The second limitation is the lack of biochemical analysis of the ointment, which could provide us with a better understanding of its underlying mechanisms. However, to the best of our knowledge, this is the first study conducted on Bastar Ointment in Albania, and we hope that more studies will be carried out in the future.

We believe that integrating advanced pharmacological techniques with traditional knowledge could be a significant step forward in the development of cost-effective, innovative, and effective medications. This combination of traditional and modern approaches may lead to the creation of new wound healing drugs with a marked reduction in undesirable side effects. Our research enhances the understanding of the chemistry and biological potential of Bastar Ointment, which has not been previously studied. This work provides a foundation for

future investigations that may result in the development of herbal-based health-promoting agents for various wound-related issues.

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The challenges of doctor-pharmacist-patient interactions in preventing medical errors: An overview

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Abstract

Introduction: Medication errors remain a major global problem for patient safety. They are often associated with misunderstandings in the prescription, dispensing and administration of medicines. The literature suggests that collaboration between doctors, pharmacists and patients is one of the most effective strategies to prevent them.

Purpose: This paper aims to examine the specific roles of each actor and to analyze effective forms of their collaboration to minimize medication-related medical errors.

Methodology: The review includes 44 international sources published between 2018 and 2024, including scientific articles, institutional guidelines and meta-analyses. Special focus was given to empirical studies on collaborative practices in community and hospital pharmacies.

Results: Evidence shows that pharmacist interventions and patient involvement improve adherence to therapy and reduce errors. Models such as PPMC and CDTM have yielded positive results in different countries. However, obstacles such as the lack of common protocols, legal barriers and insufficient communication continue to limit the impact of collaboration.

Conclusions: Strengthening physician-pharmacist-patient collaboration is crucial for patient safety. This requires systemic reforms, interprofessional training and policies that promote active patient involvement in the decision-making process.

Key words: *medication errors, pharmacist, physician, patient, collaboration, patient safety, medication use*

Introduction

Medication-related errors, those that occur during prescribing, dispensing, or administering drugs remain one of the most persistent and dangerous problems in modern healthcare. The World Health Organization (WHO, 2019) ranks these errors among the leading causes of preventable patient harm worldwide. Each instance not only increases the risk of complications, hospitalizations, or even death, but also imposes a substantial financial burden on health systems globally, with costs estimated in the billions of dollars annually (WHO Collaborating Centre for Patient Safety, 2020).

Addressing such a complex and high-risk issue requires more than the competence of individual professionals. Patient safety today depends on a well-coordinated, multidisciplinary approach, especially in cases involving polypharmacy, chronic illness, or elderly patients contexts where the potential for medication errors is especially high (International Pharmaceutical Federation, 2018; WHO, 2022). Within this collaborative framework, pharmacists play a central role. Their clinical expertise in medication management enables them to evaluate prescriptions, prevent drug interactions, educate patients, and support individualized treatment plans (FIP, 2020; Farr & Bates, 2021). Research consistently shows that when pharmacists are actively engaged in care, treatment adherence improves, adverse effects decrease, and outcomes in conditions like hypertension, diabetes, and asthma are significantly better (Chisholm-Burns et al., 2020; Lee et al., 2019; Alhabib & Alhossan, 2020).

Yet the success of the pharmacist's contribution relies heavily on effective collaboration both with prescribing physicians and with the patients themselves. In practice, such collaboration is often limited. Barriers include poor communication, vague or overlapping professional roles, and institutional limitations such as the

absence of shared health information systems (Mercer et al., 2020; Zheng et al., 2022; Rakvaag et al., 2020). Patients, too, are frequently sidelined left uninformed or excluded from conversations about their own therapy, which can result in misunderstanding and poor adherence (Tobiano et al., 2024; Giles et al., 2020).

Multiple international reports, including from FIP and the CDC, underline the importance of collaborative triads doctors, pharmacist, and patient to ensure a seamless and safe treatment process (CDC, 2020; FIP, 2022). When pharmacists are fully integrated into care teams and have access to patient records, the risk of medication error drops significantly, and clinical results improve (Health Quality Ontario, 2020). Despite these benefits, pharmacists often face systemic obstacles ranging from lack of training in adverse event reporting to time constraints and unsupportive institutional cultures (Abduelkarem & Mustafa, 2021; Alfadl et al., 2023). These barriers can prevent the flow of critical information that is essential for patient safety.

Given these complexities, this paper aims to review and critically analyze recent empirical evidence on the challenges of collaboration among physicians, pharmacists, and patients. It focuses on how the presence or absence of such collaboration affects the rate of medication errors, and what structural, professional, and educational changes are needed to support more effective interprofessional partnerships. Through a thematic analysis of international studies published in the last decade, this review seeks to identify current gaps and offer informed recommendations for improvement.

The aim of this review is to provide a comprehensive and critical synthesis of international empirical research on the dynamics of collaboration among physicians, pharmacists, and patients, with particular attention to how such cooperation contributes to the prevention of medication errors. The key objectives of the review include: identifying the primary obstacles that impede effective communication and coordination between physicians and pharmacists in clinical practice; highlighting the essential role of patient engagement in the safe management and use of medications; evaluating interprofessional collaboration models that have shown proven efficacy in enhancing patient safety; delivering evidence-informed recommendations to improve collaborative healthcare practices and guide policy development that supports structured, tripartite interaction in patient care.

Methodology

This paper follows a narrative literature review approach to examine how collaboration between doctors, pharmacists, and patients helps prevent medical errors. Rather than applying a systematic or meta-analytical method, the review

focuses on a thoughtful selection of recent, peer-reviewed empirical studies that align with the paper's aims. The literature search was carried out between March and May 2025 using databases such as PubMed, Scopus, ScienceDirect, Web of Science, and Google Scholar, included keywords "physician-pharmacist collaboration", "medication errors", "patient safety", and "polypharmacy risks". Filters were applied to limit results to studies published from 2018 to 2025. Studies were included if they presented original empirical data (qualitative, quantitative, or mixed-methods), focused on interprofessional collaboration, and explored its impact on patient safety or medication-related outcomes. A total of 43 studies met these criteria. They covered a range of healthcare settings-hospital, outpatient, and community—and came from diverse regions, including North America, Europe, Asia, and the Middle East. The selected studies were analyzed thematically. Key findings were organized around four main topics: the role of each professional in preventing errors, models of collaboration, institutional and interpersonal barriers, and the involvement of patients in communication and treatment. All sources were documented using APA 7 style, and the review emphasized both the presentation of results and critical evaluation of their relevance and quality.

Results

Preventing medical errors is a complex process that requires precise coordination between healthcare professionals and the patients themselves. At the center of this collaboration are three key actors: the doctor, the pharmacist and the patient. Each actor carries specific responsibilities and functions, which, when combined effectively, significantly reduce the risk of errors in prescribing, dispensing and administering medications.

Our overviwe found that *the pharmacist* represents an indispensable link in the chain of medication care, helping to maintain patient safety through direct education, individual counseling and monitoring of drug side effects (pharmacovigilance). In modern healthcare settings, the role of the pharmacist has gone beyond the dispensing of medicines and has expanded to deeper clinical functions, which are directly related to preventing medical errors and improving treatment outcomes (FIP, 2020; Farr & Bates, 2021).

Patient education is one of the fundamental tasks of the pharmacist. Many patients do not have sufficient knowledge about how to use medicines, the side effects that may occur, or the rules for storing them. The pharmacist, in this context, serves as a reliable source of information, clarifying the most common questions related to dosing, timing of taking medicines, and preventing unwanted interactions (Alhabib & Alhossan, 2020; Sleath & Carpenter, 2018). Personalized advice from the pharmacist has been proven to significantly improve treatment

adherence, a key factor in avoiding complications related to medication misuse (Chisholm-Burns et al., 2020). In addition to education, pharmacists play an active role in monitoring and reporting adverse drug reactions – a process known as pharmacovigilance. Pharmacists are often among the first professionals to encounter adverse drug reactions and can identify risky patterns of use through direct patient observation. This allows them to intervene early, alert the appropriate physician, and help prevent further harm (Gonzalez, Pérez, & Sosa, 2023). However, pharmacists' capacity to perform this role is often limited by institutional barriers, including a lack of clear protocols, high workload, and lack of access to electronic health record systems (Abduelkarem & Mustafa, 2021; Alfadl, Ibrahim, & Hassali, 2023). In addition, continuing professional education of pharmacists is essential to keep them up to date with the latest developments in pharmaceutical therapies and safety reporting practices. Without institutional support, a collaborative structure and appropriate training, pharmacists cannot fully exercise their role, even when they are professionally prepared. According to a systematic review conducted by Yousefi and Ahmadi (2021), interventions that include pharmaceutical education and counseling have had a significant impact on improving clinical outcomes, especially in patients with chronic diseases. In summary, the pharmacist is not simply a dispenser of medicines, but a key figure in the medication safety system, who through education, counseling and clinical supervision helps to significantly reduce errors and improve the patient's experience with their therapy.

Physicians play a central role in the patient treatment process, as they are responsible for clinical decision-making, including establishing the diagnosis and prescribing pharmacological treatment. The decisions that physicians make about the type, dosage, and combination of medications have a direct impact on the safety and health of the patient. For this reason, safe prescribing of medications is a fundamental component in preventing medical errors. One of the most common sources of errors is the failure to assess the patient's medication history, the prescription of medications that interact negatively with existing therapies, or the duplication of prescriptions for the same substance. At this point, collaboration with the pharmacist is essential, as he can provide a second perspective on the prescription and help identify potential risks that the physician, due to workload or lack of information, may not be aware of (Smith & Bates, 2019; WHO, 2019). Safe prescribing is not an isolated act, but a collaborative process. The integration of the pharmacist into medical decision-making, particularly in hospital settings and structured primary care, has resulted in significant reductions in medication errors. In a classic study, Leape et al. (1999) reported that pharmacist participation during medical visits in intensive care units reduced the number of medication errors by more than 60%. In addition to accurate prescribing, physicians have an important function in coordinating care between different professionals,

including pharmacists and nurses. In systems where this coordination is missing or fragmented, the risk that treatment information will not be transmitted correctly increases significantly, leading to double prescribing, interruption of therapy, or patient confusion (Mercer et al., 2018; Zheng, Wang, & Zhang, 2022). An additional challenge is related to the use of integrated health data systems. Doctors often do not share the same IT system with pharmacists, limiting the possibility of immediate exchange of information on prescriptions, reported effects or changes made to therapy. As a result, pharmacists do not have access to complete patient data and are forced to operate in a fragmented manner. Furthermore, the role of the doctor is not only technical, but also educational and communicative. The patient often refers to the doctor as the main figure of health authority and, if he does not receive clear and complete information about the therapy, he risks not following the treatment properly. Therefore, the doctor's communication with the patient and with the pharmacist is essential for building a sustainable and effective collaboration model (Tobiano et al., 2024; Briesacher et al., 2019).

In summary, the doctor has a decisive influence on the safety of pharmacological treatment. Through accurate prescribing, interprofessional communication and coordination of care, he directly contributes to the prevention of medical errors. However, this role cannot be fully fulfilled without a clear collaboration structure with the pharmacist and without the active involvement of the patient in decision-making.

In recent decades, the approach to *the patient* in health systems has evolved from a paternalistic model, where the patient was simply a passive recipient of care, to a collaborative model, where the patient is treated as an active partner in decision-making. This is particularly important in pharmacological treatment, where the success and safety of therapy depend not only on the correct prescription, but also on the correct and conscious adherence to medical and pharmaceutical instructions by the patient. Studies show that a significant percentage of medication errors occur at the level of use by the patient, as a result of misunderstanding the instructions, taking the wrong dose, stopping treatment prematurely, or self-medicating with unnecessary or inappropriate drugs (Briesacher, Gurwitz, & Soumerai, 2019). In this context, patient education and empowerment become essential for the prevention of errors. Direct advice from the pharmacist, clear communication from the doctor, and the opportunity to ask questions and express their concerns are elements that increase patient involvement in treatment and help build a lasting partnership (Alhabib & Alhossan, 2020; Sleath & Carpenter, 2018). Patients who feel involved are more likely to follow treatment properly, report side effects, and not change therapy without consultation. Furthermore, patients can help identify and correct errors that may go unnoticed by professionals. In a study conducted by Giles et al. (2020), it was evidenced that patients who had actively participated in discussions about the medications they were taking had a greater sensitivity to

potential risks, raising valid concerns that were later verified as real errors. Even in the discharge process or transitions of care, patient involvement is key to avoiding interruptions in therapy or taking the wrong medication. A recent pilot study by Tobiano et al. (2024) showed that interventions aimed at involving the patient in therapy discussions during discharge significantly improved communication and reduced uncertainty in medication administration at home. However, taking an active role by the patient requires education, time, and a supportive culture on the part of professionals. Not all patients feel empowered to raise questions, and they are often reluctant to challenge medical decisions, even when they have doubts. Therefore, creating an open and collaborative environment, where the patient is seen as a collaborator, not a passive subject, is the foundation of therapeutic safety. The patient is not a secondary figure in treatment – on the contrary, he is an active and essential actor in medication safety. Empowering it through information, involvement, and building trusting relationships with professionals is among the most effective strategies to reduce errors and increase the quality of healthcare.

Collaboration between doctors, pharmacists and patients does not happen by itself; it requires structures, processes and organizational cultures that enable and support it. Depending on the health system, level of care and local practices, this collaboration takes different forms – from informal information exchange to integrated models of multidisciplinary teamwork. Forms of collaboration directly affect the effectiveness of treatment, patient safety and the prevention of medication errors.

Clinical collaboration between doctors and pharmacists has taken different forms depending on the organizational context, health legislation and institutional culture of different countries. In some systems, pharmacists are directly involved in clinical decision-making, while in others they function more independently, with a mainly advisory role. These models, when operating in an integrated and well-coordinated manner, have shown tangible results in preventing medication errors, improving the quality of care and increasing therapeutic efficacy.

One of the most successful forms of this collaboration is the participation of clinical pharmacists in daily medical visits in hospital settings, especially in intensive care units. In a classic study by Leape et al. (1999), it was reported that the involvement of the pharmacist in the clinical team led to a reduction in medication errors by over 60%. This involvement enabled the identification of unwanted interactions, the correction of incorrect dosages and the provision of immediate recommendations for improving therapy.

Another advanced model is Collaborative Drug Therapy Management (CDTM), which is widely practiced in the USA, Canada and some countries of Northern Europe. This model gives clinically trained pharmacists the authority to modify or adapt a patient's therapy in accordance with protocols agreed upon with the prescribing physician. This formal collaboration is based on legal and

professional agreements, and has proven effective in improving the control of chronic diseases, such as hypertension and diabetes (Chisholm-Burns et al., 2020; Alhossan & Alazba, 2019).

According to the International Pharmaceutical Federation (2020), effective clinical collaboration relies on four key elements: clearly defined roles and responsibilities, mutual trust among professionals, open and well-documented communication, and strong institutional support through shared systems and standardized guidelines. These factors create a structured, reliable foundation for teamwork in healthcare.

In everyday clinical practice, these models do not always function ideally. In many cases, pharmacists face barriers such as lack of access to patients' medical records, high workload, or non-acceptance of their interventions by physicians, especially in systems where there are no well-defined protocols for collaboration (Mercer et al., 2020; Gonzalez et al., 2023). This situation is more pronounced in countries with more fragmented health structures, where interprofessional coordination is lacking and collaboration is based on individual relationships rather than on stable institutional mechanisms. However, where these models are successfully implemented, the results are clear and measurable: reduced prescribing errors, improved treatment efficacy, increased patient satisfaction, and reduced overall costs for the health system (WHO, 2022; CDC, 2020; Health Quality Ontario, 2020).

Interprofessional communication is the foundation on which every functional and effective relationship in healthcare is built. In the context of doctor–pharmacist–patient collaboration, clear, regular and reciprocal communication is not a luxury – it is a necessity to ensure that clinical decisions, therapy information and patient instructions are coordinated and without inconsistencies. Lack or fragmentation of communication is one of the most common causes of preventable medication errors, especially in situations where the prescription, distribution and use of medicines occur at different points in the healthcare system (WHO, 2019; Farr & Bates, 2021).

At a practical level, communication between a doctor and a pharmacist can take different forms: face-to-face discussions, telephone consultations, information exchange through shared information systems, or through written documentation. Successful collaboration models are closely linked to pharmacist access to patient medical information, which allows for more accurate therapy assessments and more informed interventions (Mercer et al., 2018; Zheng, Wang, & Zhang, 2022).

However, the reality is that in many settings, especially in community pharmacies, pharmacists do not have direct access to clinical data, limiting their role to a reactive level, based on partial information. This situation not only exposes patients to risks, but also forces pharmacists to work in a fragmented environment, where errors become more difficult to prevent and easier to go unnoticed (Mercer et al., 2020).

On the other hand, when communication is two-way, respectful, and based on professional trust, it creates opportunities for correcting misprescriptions, clarifying doubts about medications, and coordinating shared decisions. According to Gonzalez et al. (2023), pharmacists who are integrated into pharmacovigilance programs and have direct contact with doctors are more successful in identifying side effects and in interventions that improve patient safety.

Another important aspect is communication between professionals and patients. When this communication is fragmented – where the patient receives one piece of information from the doctor and another from the pharmacist, often in an incomplete or contradictory form – confusion increases and treatment adherence decreases (Briesacher et al., 2019; Giles et al., 2020). For this reason, it is essential that information is harmonized and that the patient is actively involved in treatment conversations, building a stable line of communication with both professionals.

Effective interprofessional communication is not only an auxiliary tool, but a guarantee of patient safety. It must be supported not only through a culture of collaboration, but also through technology, clear institutional guidelines, and ongoing training for both parties. Only in this way can physician-pharmacist collaboration function as a protective mechanism against preventable errors.

In recent years, the approach to health care has shifted from a model based on unilateral professional authority to a collaborative and patient-centered model, where the patient is no longer treated as a passive recipient of the service, but as an equal part of the care team. In this context, the involvement of the patient as an active partner in the doctor-pharmacist-patient collaboration has proven essential for the safety of medication use and the avoidance of medication errors (WHO, 2022; Giles et al., 2020).

Contemporary pharmaceutical care models, especially those applied in community pharmacies, have begun to develop specific programs aimed at patient engagement in the decision-making process for therapy, education on the use of medicines and self-monitoring for side effects. A clear example of this approach is the New Medicine Service in the United Kingdom, a pharmaceutical service based on personal counseling of patients who have just started new therapies. This service has been shown to be effective in increasing adherence to treatment and reducing misunderstandings about the use of medicines (NHS England, 2021).

Active patient involvement also helps in the early identification of prescription or dispensing errors, as a patient who is informed and aware of the treatment they are following is more likely to notice discrepancies and seek clarification. In a study conducted by Giles et al. (2020), it was found that patients who were educated about their therapy contributed to the detection of errors that had not been identified by professionals.

On the other hand, patient involvement requires doctors and pharmacists to adopt an open and non-dominant communication style, where space is given to questions, concerns and the active involvement of the individual in the choices about their health. This approach, known as shared decision-making, has been shown to improve not only the quality of medical decisions, but also the patient's sense of control and safety (Sleath & Carpenter, 2018; Briesacher et al., 2019).

However, the implementation of these models faces several challenges. Not all patients have the appropriate level of health literacy, the knowledge necessary to understand their therapies, or feel empowered to discuss openly with professionals. For this reason, ongoing pharmaceutical and medical education, as well as the development of simple and understandable materials for patients, are necessary to build a sustainable collaborative relationship (Alhabib & Alhossan, 2020; Tobiano et al., 2024).

In summary, models that include the patient as an active partner do not diminish the role of professionals, but rather strengthen the therapeutic relationship by making it more open, transparent, and safe. This collaboration is not only an ethical ideal, but a proven practical strategy to reduce medical errors and increase the quality of care at all levels of the health system.

Community pharmacies represent a direct and frequent point of contact between patients and the health system, especially in countries where access to primary or hospital care is limited. Due to their proximity to the population and their daily role in the distribution of medicines, community pharmacists have a great potential to positively influence medication safety. However, this potential often remains untapped due to structural constraints, lack of integration with other health professionals and unclear role in the interprofessional care network.

One of the main challenges faced by community pharmacies is the lack of systematic communication with prescribing physicians. In most cases, the pharmacist does not have direct access to the patient's clinical history and is not regularly involved in the therapeutic decision-making process. This forces the pharmacist to operate on the basis of partial information, often with only the prescription in hand, without knowing the patient's clinical context or possible interactions with other treatments (Mercer et al., 2020; Zheng et al., 2022).

Despite these limitations, studies conducted in countries as diverse as Poland, Peru, and the Middle East have shown that community pharmacists are willing to contribute more, but require clarity of competencies, more specialized training, and formal channels for communication with physicians (Wrześniewska-Wal et al., 2023; Gonzalez et al., 2023; Alfadl et al., 2023). Sustainable collaboration requires more than professional will – it requires institutional support, shared accountability protocols, and shared IT systems.

In some countries, initiatives have been developed to involve community pharmacists in enhanced services, such as periodic medication reviews for

patients with multiple medications, monitoring of side effects, or follow-up of patients who have recently been discharged from hospital. These services require direct collaboration with physicians and have shown positive results in reducing medication errors and improving patient adherence (Health Quality Ontario, 2020; FIP, 2022).

A concrete example is the involvement of pharmacists in the implementation of educational services for chronic patients (such as in the case of hypertension, asthma, and diabetes), where the pharmacist monitors medication use and provides additional instructions on how to administer it. These interventions, when implemented in collaboration with the prescribing physician and with patient involvement, increase the effectiveness of therapy and reduce the burden on the hospital system (Lee et al., 2019; Chisholm-Burns et al., 2020).

However, to have a real and sustainable impact, community pharmacies must be treated as an integrated part of the health network, not as an isolated structure oriented only towards the sale of medicines. This requires changes in public policies, dedicated funding for collaborative services, as well as greater recognition of the professional role of the pharmacist at the community level. Community pharmacies have an extraordinary potential to contribute to patient safety, but to realize this function effectively, it is necessary to build sustainable bridges of collaboration with doctors and the active involvement of patients. Only through this sustainable collaboration can the role of the community pharmacist evolve from a distributor of medicines to a guardian of therapeutic safety.

Despite the clear benefits that collaboration between doctors, pharmacists and patients brings in increasing medication safety, the effective implementation of this collaboration faces a number of challenges. These challenges are of an institutional, professional and cultural nature and directly affect the quality of care and the risk of medical errors. Below are five of the most important obstacles identified in the international literature.

Communication between healthcare professionals is the basis of any safe and effective patient care. However, in daily practice, communication between doctors and pharmacists is often fragmented, infrequent or reactive, creating a fertile ground for misunderstandings, medication errors and inadequate treatment of patients.

One of the most common obstacles is the lack of formal and structured channels for the exchange of clinical information. In many health systems, community pharmacists do not have access to patients' medical records, including diagnoses, laboratory tests, or past medication lists. As a result, any recommendations or corrections that the pharmacist may suggest regarding a drug prescription are based on partial information, limiting the impact of their intervention (Mercer et al., 2018; Zheng, Wang, & Zhang, 2022).

Furthermore, many pharmacists report feeling unappreciated when they contact physicians to discuss prescription uncertainties, and often receive

lukewarm responses or are ignored altogether (Rakvaag et al., 2020; Mohammed & Marouf, 2022). This creates a cold collaborative environment, where professionals feel hesitant to intervene, even when potential errors that compromise patient safety are apparent.

Another important problem is related to the lack of a culture of shared clinical responsibilities. In many countries, the role of the pharmacist is still traditionally seen as a dispenser of medicines, without being considered an active partner in the therapeutic process. This perspective reduces the incentive for collaboration and inhibits shared decision-making (Kelly et al., 2013; Alhossan & Alazba, 2019).

Even when there are efforts to build integrated communication platforms (such as shared electronic files), these are often not implemented in practice or are limited to certain users. As a result, valuable information is not always accessible in real time, making it difficult to respond to urgent situations or correct errors before they affect the patient.

On the other hand, lack of time and heavy workload also have a negative impact. Both doctors and pharmacists are often overwhelmed, not having the time to have full conversations about clinical cases. This leads them to focus more on fulfilling immediate tasks than on building professional relationships that support long-term patient safety (Gemmechu & Eticha, 2021; Tan et al., 2024). In summary, barriers to physician-pharmacist communication are fundamentally structural and cultural. Building sustainable bridges of collaboration requires not only improvements in technological infrastructure and institutional protocols, but also a paradigm shift that recognizes both professions as equal parts of the healthcare team.

A prominent obstacle to physician-pharmacist collaboration is the lack of clarity and consensus regarding professional roles and responsibilities, which often leads to silent conflicts, lack of coordination, and obstacles to interventions that are beneficial to patient safety.

In many countries and clinical practices, physicians still view pharmacists as support professionals, not as equal members of the healthcare team. This perspective is rooted in undergraduate education and subsequent professional experience, where a clear hierarchical division dominates instead of a collaborative model (Kelly et al., 2013; Rakvaag et al., 2020).

On the other hand, pharmacists often face difficulties in asserting professional authority, even when they identify problems with the prescribed therapy. They are reluctant to challenge the physician's decision-making, especially in settings where there is no genuine culture of interdisciplinary collaboration (Mohammed & Marouf, 2022). This role imbalance is not only a matter of perception, but also translates into a lack of responsiveness to potential errors and avoidance of shared responsibilities.

A study by Mercer et al. (2020) found that even in settings where some formal collaboration exists, physicians tend to adopt a leadership role and limit the pharmacist's role to verifying prescriptions and dispensing medications, without involving them in therapeutic decision-making. This also occurs in advanced health systems, where clear protocols that define boundaries and professional interaction are still lacking.

The challenges are further exacerbated when there is no shared approach to patient care. Physicians may follow more traditional or diagnosis-focused approaches, while pharmacists focus on optimizing drug use. In the absence of a collaborative platform, these two perspectives do not converge but remain separate, missing the opportunity for synergy that could prevent errors (Wrześniewska-Wal et al., 2023; Alhossan & Alazba, 2019).

In some cases, legal and regulatory structures are vague regarding pharmacists' responsibilities, making it more difficult for them to intervene in a safe and supported manner when they detect inaccuracies or potential for errors in prescriptions (FIP, 2020; WHO, 2022).

In conclusion, the lack of clear boundaries and mutual recognition of professional competencies creates a difficult terrain for healthy collaboration. Resolving this problem requires reforms in interprofessional education, clarification of roles in health policies, and cultivating an environment where the pharmacist profession is valued as an essential part of the safety chain in patient care.

In the context of medical errors and patient safety, an often underestimated aspect is the lack of active involvement of the patient in treatment decision-making. Although theoretically the patient is at the center of healthcare, in practice, he or she is often excluded from the decision-making process, especially when there is a lack of strong collaboration between doctors and pharmacists.

This exclusion occurs in several forms. First, patients rarely receive complete and clear information about the purpose, side effects and duration of the prescribed therapy. When information is provided, it is often technical, non-personalized and does not encourage discussion or questions from the patient. According to Giles et al. (2020), many patients feel hesitant to seek clarification because they fear appearing to challenge medical authority.

Second, the lack of patient involvement reduces the effectiveness of pharmaceutical interventions, as the pharmacist often has neither the opportunity nor the permission to discuss alternatives with the patient or to correct deviations in medication use without the involvement of the physician. This limits the pharmacist to a technical role and places the patient in a passive position, completely dependent on formal instructions.

A study by Tobiano et al. (2024) found that patients often do not fully understand changes in their therapies upon discharge from the hospital, and are rarely involved

in discussions about those changes. This increases the risk of medication errors after discharge from hospital care, especially in cases of polypharmacy.

On the other hand, the active involvement of the patient in the therapeutic discussion not only increases trust and adherence to therapy, but is a powerful preventive tool against medical errors. When patients feel empowered to ask questions, report concerns, or express disagreement, they can help catch errors before they happen—a form of "last-minute check" in the health safety system (Briesacher, Gurwitz, & Soumerai, 2019; Sleath & Carpenter, 2018).

Patient disengagement is also associated with other factors, such as: lack of time in consultations, lack of simple educational materials, inability to understand medical terminology, or previous negative experiences with the health system. This leaves many patients feeling unempowered to actively contribute to the choice and monitoring of their treatment (WHO, 2020; FIP, 2022).

To bridge this gap, it is recommended to build a shared decision-making model where doctors, pharmacists, and patients discuss together alternatives, risks, and therapeutic goals, giving the patient an equal voice in the decision. This model requires training for professionals, but also promoting health education for patients – to turn them from passive recipients of care, into active participants in their own safety.

In the last decade, many health systems have developed and tested concrete forms of collaboration between doctors, pharmacists and patients, with the aim of improving the use of medicines and reducing medical errors. These models provide practical examples of how successful collaboration can be structured and institutionalized.

One of the most documented models of doctor-pharmacist collaboration in preventing medical errors is Partnered Pharmacist Medication Charting (PPMC), widely applied in several hospitals in Australia and supported by safety care policies in the United Kingdom. This model consists of the active involvement of the pharmacist in the initial phase of prescribing medicines for hospitalized patients. Instead of the pharmacist intervening only after the prescription has been given, he becomes part of the process of compiling the therapy chart, together with the doctor.

This approach is fundamentally different from traditional practices where the pharmacist was simply a post-prescription controller. In the PPMC model, pharmacists participate in the medical community, assess the patient's medication history, contribute to the choice of medications, and monitor for potential errors from the outset (Tong et al., 2020). This proactive involvement increases the quality of decision-making and significantly reduces the risk of duplication, incorrect dosages, or harmful interactions.

Key benefits of this model are: significant reduction in prescribing errors, especially in elderly patients or those on multiple medications (polypharmacy);

increased efficiency in the transfer of information from the ambulance to the hospital or from one unit to another and improved doctor-pharmacist communication in real time, creating a culture of shared responsibility.

A study conducted in four Australian hospitals (Tong et al., 2020) reported a 78% reduction in serious medication errors when PPMC was used compared to the traditional model. Physicians also valued the presence of the pharmacist as a practical aid in decision-making, especially in complex clinical situations.

This model requires several prerequisites for successful implementation: formal training of pharmacists to make clinical decisions, equal access to patient data, and institutional support for the collaborative role. Changing the role alone is not enough; it is necessary to build an interprofessional culture, where the pharmacist's competencies are not perceived as an intervention, but as an added value to patient safety.

Partnership in prescribing is not only a means to reduce errors; it represents a fundamental change in the way healthcare is conceived – not as a fragmented process, but as a coordinated practice where each professional contributes their knowledge at the right time.

In the United States of America, one of the most advanced forms of collaboration between physicians and pharmacists is the model known as Collaborative Drug Therapy Management (CDTM). This model allows pharmacists, through an agreement signed with a physician (collaborative practice agreement), to take a broader role in the management of patients' drug treatment. Their involvement may include: reviewing medication history, changing dosage, stopping or starting new therapy, interpreting laboratory tests, and providing therapeutic advice, without the need for immediate physician approval for each action.

The implementation of CDTM models has been most successful in the management of chronic diseases, such as hypertension, diabetes, dyslipidemia, and asthma, where close monitoring and continuous adaptation of therapy are essential for sustainable results. Studies in this field show that pharmacists involved in CDTM have significantly improved patients' clinical parameters, such as blood pressure control or HbA1c levels (Chisholm-Burns et al., 2020).

A direct benefit of this model is the reduction of the burden on doctors, who can focus on more complex cases, while pharmacists are responsible for regulating and following up on routine and chronic treatments. At the same time, this collaboration also brings about better patient involvement in decision-making, as the pharmacist plays an important educational and supportive role.

However, the CDTM model requires several essential components to function properly: clear institutional and legal discourse on the pharmacist's role in treatment; advanced clinical training for participating pharmacists; mutual access to patient medical information (through shared systems) and financial

support and recognition for clinical pharmacy services, to ensure that this work is economically sustainable.

Difficulties in implementing CDTM include the lack of uniformity in legislation across US states, initial resistance from some healthcare professionals, and challenges in financial compensation for pharmacists (Alhossan & Alazba, 2019).

However, CDTM models are a key reference for systems that aim to increase physician-pharmacist collaboration. They demonstrate that when pharmacists are actively involved in a structured and structured manner, the impact on patient safety and treatment effectiveness is direct and measurable.

In the health systems of Canada and the Scandinavian countries (Sweden, Norway, Denmark, Finland), the approach to medical care is based on integrated care models, where interprofessional collaboration is an essential part of the institutional structure and not simply an individual initiative. In these countries, pharmacists are involved from the primary care level, working alongside family doctors, nurses and social workers as part of a unified team that follows the patient continuously.

This model aims not only to treat the disease, but also to prevent medication errors through continuous information exchange, joint consultations and multidisciplinary team meetings. Pharmacists not only advise on medications and monitor therapy, but are also involved in patient education, assessing the need for interventions, and improving treatment compliance.

A study by Mercer et al. (2020) on the relationship between doctors and pharmacists in primary care centers in Canada showed that the key to success is building a stable and reciprocal relationship, where the pharmacist is perceived as a clinical partner and not as a technical assistant. When trust is established and communication is open, the positive impact on patient safety and treatment effectiveness increases.

Also, in these models, the pharmacist has full access to the patient's clinical data through integrated electronic systems, which facilitates real-time analysis and decision-making. This practice is very different from traditional models in which the pharmacist operates in isolation from the rest of the system.

In Scandinavian countries, such as Sweden, pharmacists are regular participants in hospital meetings to review patient records, where potential risks of therapies are identified and concrete recommendations for change are made. This has significantly reduced the rate of serious side effects and reduced the need for readmissions to hospital (Rakvaag et al., 2020).

Essentially, the scandinavian and canadian model of integrated care operates on three main pillars: clearly and transparently divided responsibility among health professionals; structured and regular communication between clinical actors and involving the patient as an active participant in decision-making, in line with the

principles of patient-centered care. This model proves that a strong institutional cooperation structure is more efficient than fragmented or temporary solutions, making cooperation the standard rather than the exception.

In low- and middle-income countries (LMICs), the inclusion of pharmacists in healthcare teams faces a number of structural, cultural and legal challenges. However, even in these contexts, efforts have been made to develop adapted forms of doctor-pharmacist-patient collaboration, which aim to improve patient safety and reduce medication errors. A major challenge in these countries is the lack of sufficient human and technological resources, which limits access to electronic health information systems and divides professionals into fragmented groups. As a result, communication often occurs in an unplanned and unstructured manner. Pharmacists are often not integrated into clinical decision-making and are perceived more as drug suppliers than as therapeutic partners.

However, studies conducted in countries such as Peru, Ethiopia, India, and Iraq show that when pharmacists are actively involved, clinical outcomes and patient safety improve significantly. For example, the integration of clinical pharmacists into pharmacovigilance programs in public hospitals in Peru has led to increased reporting of adverse events and preventive interventions for potential errors (Gonzalez et al., 2023).

In Ethiopia, a study by Gemmechu and Eticha (2021) showed that the level of collaboration depends significantly on factors such as the pharmacist's professional experience, mutual trust, and support from hospital administration. If these elements are missing, pharmacists have difficulty gaining their place in the therapeutic process. In India, educational interventions and joint training programs for doctors and pharmacists have proven effective in improving collaboration and communication, especially in rural or high-patient-load settings. Although a strong legal infrastructure for CDTM-type models is lacking, local adaptations based on simple collaborative protocols have yielded positive effects in reducing polypharmacy and improving treatment compliance.

Another key challenge is the informality of role allocation. In some cases, pharmacists are forced to intervene without legal support or clear protocols, taking on responsibilities that may not be institutionally recognized.

However, the challenges shouldn't overshadow the potential for progress. In low- and middle-income countries (LMICs), interprofessional collaboration can be significantly improved through a few targeted strategies. First, the clinical training of pharmacists needs to move beyond theory and focus more on hands-on, practical skills. Many pharmacists are well-versed in drug knowledge but lack real-world clinical exposure. Second, collaboration doesn't require complex systems it starts with clear, simple protocols that fit the local context and resources. These guidelines should be easy to implement and support daily cooperation

among healthcare workers. Third, promoting mutual respect among professionals and increasing institutional recognition of the pharmacist's role are key. Without this cultural shift, even the best systems can fall short.

Finally, interdisciplinary training that brings doctors, pharmacists, and nurses together as a team can help break silos and foster a shared understanding of each role. With these steps, LMICs can unlock the benefits of genuine, practical teamwork in healthcare.Examples from low- and middle-income countries show that even in challenging conditions, effective collaboration is possible if supported by will, training, and inclusive health sector policies.

Although the importance of collaboration between physicians, pharmacists, and patients is widely recognized in the international literature, the implementation of this approach in practice faces a number of challenges that directly affect the quality of care and patient safety. These barriers can be divided into several main categories:

One of the most documented barriers in the international literature is related to the lack of effective communication channels between physicians and pharmacists, as well as limited access to patient clinical information. In many health systems, pharmacists do not have direct access to clinical data such as diagnoses, medical history, or treatment plans, which limits them to the role of drug dispensers and impairs their potential to prevent medical errors (Wrześniewska-Wal et al., 2023; Mercer et al., 2020). In some settings, information is considered the "property" of the physician and is not shared equally with other team members, excluding the pharmacist from clinical decision-making. The lack of integration of information systems between physicians, pharmacists, and nurses further exacerbates this situation, leaving room for misunderstandings and errors in the use of medicines.

On the other hand, in cases where shared information management systems have been developed, such as in the UK or Scandinavia, a significant improvement in the reporting of side effects, medication management, and compliance with therapy has been observed (Mercer et al., 2020; Tong et al., 2020). This shows that pharmacists' access to clinical information is a key element in ensuring patient safety and reducing medication errors.

Another strong obstacle to building a functional collaboration is the existence of professional stereotypes and the lack of mutual trust between physicians and pharmacists. In many professional cultures, pharmacists are viewed as mere drug logistics experts, rather than active contributors to clinical decision-making. This perception reduces motivation for collaboration and excludes pharmacists from therapeutic discussions (Mohammed & Marouf, 2022; Rakvaag et al., 2020).

On the other hand, pharmacists often face difficulties in establishing their professional authority, especially in settings where physicians have a dominant position. They may feel unvalued and hesitate to intervene even when they have

doubts about patient safety, to avoid conflicts or due to a lack of institutional support. This unbalanced dynamic negatively affects the flow of information and the rapid response to medical errors.

The literature emphasizes that building interprofessional trust requires shared experiences, interdisciplinary training, and collaborative protocols that clarify the roles of each professional (Kelly et al., 2013; Mercer et al., 2020). When pharmacists and physicians see each other as equal partners and recognize respective competencies, collaboration is not only enhanced but also brings direct benefits in reducing errors and improving clinical outcomes

Conclusions

Medical errors, especially those related to the use of medicines, represent a continuing challenge in health systems worldwide, affecting not only the quality of treatment, but also the safety and well-being of patients. This literature review has made it clear that structured and effective collaboration between doctors, pharmacists and patients is a key element in preventing these errors.

The role of pharmacists, supported by international organizations such as WHO and FIP, has expanded significantly in the last decade, including not only the distribution of medicines, but also clinical advice, therapeutic education, therapy monitoring and pharmacovigilance. In this context, evidence shows that pharmacist-led interventions have a direct impact on improving treatment adherence, reducing adverse effects and better managing chronic diseases.

However, to realize the full potential of this collaboration, a number of structural and cultural barriers need to be addressed. The lack of common protocols, legal restrictions, ineffective sharing of clinical data and insufficient communication are some of the factors that reduce the effectiveness of this collaboration. On the other hand, patient involvement in decision-making still remains weak and often underestimated, although the literature qualifies it as an important factor in increasing the safety of therapy. To improve the situation, this paper has identified a series of recommendations that range from restructuring health policies and developing interprofessional training, to promoting the active role of the pharmacist and empowering the patient as a co-decision maker. If these recommendations are addressed by the relevant institutions, the potential to significantly reduce medical errors and build a safer and more coordinated health system is real and achievable.

Recommendations

Based on the analysis of scientific literature and international sources, it is clear that to address the challenges of collaboration between doctors, pharmacists and patients, multifaceted interventions are required at systemic, institutional and professional levels.

Below are some key recommendations to improve interprofessional collaboration and reduce the risk of medical errors:

Formalization of collaboration protocols between doctors and pharmacists: In most health systems, the relationship between doctors and pharmacists is not supported by formal structures that define roles, responsibilities and boundaries of professional interaction. This lack of clarity makes collaboration fragmented, often haphazard, and dependent on personal relationships or the local culture of the institution. As a result, many opportunities to prevent medication errors remain unexploited.

Addressing this issue requires formalizing collaborative protocols, where pharmacists are given a clear and legally recognized role in medication management – for example through Collaborative Drug Therapy Management (CDTM) agreements. These models have been successfully implemented in the US, where pharmacists, in coordination with physicians, have the right to monitor, adjust, or renew the medication treatment of chronic patients (Alhossan & Alazba, 2019).

The establishment of such protocols not only strengthens the professional role of pharmacists, but also helps build trust and mutual respect between the professions. Furthermore, these structures help patients better understand who to turn to for various treatment and medication safety issues.

Integrating shared IT platforms for clinical data sharing. One of the biggest obstacles to effective collaboration between doctors and pharmacists is the lack of shared access to a patient's clinical data. In many countries, pharmacists do not have access to diagnoses, the full list of prescribed medications, laboratory results or side effect history. This limits them from making informed decisions and identifying potential errors in prescribing or using medications.

Addressing this challenge requires the development and integration of shared data platforms- IT systems that enable real-time sharing of clinical information between healthcare professionals involved in a patient's care. A good example is the use of shared electronic health records (EHRs), which have been implemented in several countries such as Finland, Australia and Canada (Tong et al., 2020).

When pharmacists have access to complete treatment information, they can play a greater role in controlling potential interactions, unnecessary duplications

or incorrect doses. Furthermore, data sharing strengthens transparency and promotes a culture of collaboration based on facts and not just perceptions.

Strengthening interprofessional training. One of the roots of the lack of effective collaboration between doctors and pharmacists is the lack of mutual exposure during the professional training process. Often, health professionals are trained in separate "silos", with little or no practical interaction with other professions. This directly affects how they understand each other's roles and in building professional trust.

Interprofessional training, which takes place in both undergraduate and postgraduate training, is an approach that has shown significant improvement in communication, understanding of responsibilities and willingness to share decision-making (WHO, 2022). Learning together, through clinical simulations, joint projects or integrated modules, helps to shape a collaborative culture that continues into real practice.

International health organizations such as WHO and FIP have strongly recommended the introduction of interprofessional education into the curricula of all health professions. Implementing this approach requires not only pedagogical changes, but also institutional and policy commitments that support it as a development priority.

Promoting the pharmacist's role as a patient educator and counselor. For many patients, the pharmacist is still seen as a technical professional who dispenses medicines, rather than as an advisor or active partner in healthcare. This affects not only the way patients interact with pharmacists, but also the way they are involved in decision-making about their therapy.

Promoting the pharmacist's advisory and educational role is key to improving compliance with treatment and reducing the risk of errors caused by misunderstanding, incorrect following of instructions or careless use of medicines (Sleath & Carpenter, 2018; Alhabib & Alhossan, 2020).

When the pharmacist is present and active in every step of the drug use process – from prescription to monitoring – he becomes a guarantor of patient safety.

Drafting national policies that promote patient involvement in decision-making. At the heart of drug safety is the patient himself. However, patient involvement in decision-making often remains limited, especially in systems where their role is perceived as passive. Lack of understandable information, fear of the authority of professionals and lack of self-confidence are some of the reasons that prevent patients from being co-responsible for their therapy.

Patient involvement should be institutionalized through national policies that: oblige professionals to provide clear and understandable information about treatment; guarantee the patient the right to ask questions and refuse therapy without penalty; support public health education initiatives that empower citizens to actively participate in their own care (Giles et al., 2020; Tobiano et al., 2024).

In countries where this approach has been successfully implemented, a significant reduction in medication errors has been observed, as well as an improvement in patients' experience with the health system as a whole.

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Lifestyle Factors and Their Impact on Rheumatoid Arthritis: A Literature Review

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation and systemic manifestations. Increasing attention has been directed towards the role of modifiable lifestyle factors in influencing RA susceptibility, disease progression, and therapeutic response.

Objective: This review aims to systematically evaluate the associations between lifestyle factor including tobacco use, dietary patterns, obesity, physical activity, educational attainment, and socioeconomic status and the risk, clinical course, and treatment outcomes of RA.

Methods: A comprehensive search of the PubMed database was conducted to identify epidemiological and prospective studies examining the impact of lifestyle behaviors on RA onset and management. Studies were selected based on relevance, methodological rigor, and focus on both disease incidence and treatment efficacy.

Results: Consistent evidence implicates smoking, poor dietary quality, excess adiposity, lower educational levels, and socioeconomic deprivation as significant contributors to increased RA incidence. Furthermore, smoking, obesity, and physical inactivity are associated with attenuated responses to disease-modifying antirheumatic therapies.

However, heterogeneity in study designs and residual confounding limit definitive causal conclusions.

Conclusions: Despite inherent methodological challenges, current data underscore the importance of lifestyle modification—specifically smoking cessation, adherence to a nutritious diet, maintenance of healthy body weight, and regular exercise—as critical strategies to mitigate RA risk and enhance therapeutic outcomes. Future longitudinal and mechanistic studies are warranted to further elucidate these relationships and inform personalized interventions.

Keywords: Mediterranean diet, cigarette smoking, socioeconomic status, physical activity, obesity, disease progression, rheumatoid arthritis, lifestyle factors

Introduction

Individuals afflicted with inflammatory rheumatic diseases (IRDs) often seek to enhance therapeutic efficacy or reduce pharmacologic dependency through lifestyle modifications. This interest is partly driven by widespread media narratives emphasizing the role of nutrition, body mass regulation, physical activity, and psychosocial stressors in health outcomes and longevity. Meanwhile, commercial entities target this population with dietary supplements and wellness products claiming to offer prophylactic or therapeutic benefits for rheumatic diseases.

Despite these claims, evidence-based medicine identifies a limited set of lifestyle factors that clearly influence disease risk or progression in IRDs. Most research focuses on rheumatoid arthritis (RA), where epidemiological and mechanistic studies have highlighted lifestyle determinants as key modulators of disease susceptibility. Notably, longitudinal analyses within large cohorts have examined modifiable behavior including smoking, obesity, sedentary lifestyle, diet quality, and alcohol consumption and their relationship to RA risk. Researchers developed composite indices, such as the Healthy Lifestyle Index Score (HLIS), to quantify these factors, finding that adherence to healthier lifestyle practices correlates with a significantly reduced risk of RA, particularly among women and in seropositive subtypes.

This review aims to synthesize the current evidence on lifestyle influences in RA, critically evaluating the literature and addressing its limitations.

Nutritional Determinants in the Etiology and Progression of Rheumatoid Arthritis (RA)

Understanding the role of nutrition in the onset and progression of rheumatoid arthritis (RA) is complex due to the diverse nature of diet and its interactions with systemic inflammation. Diet significantly influences the gut microbiome, which is a key factor in inflammatory rheumatic diseases. For instance, high-fiber diets are linked to lower levels of inflammatory cytokines, while omega-3 polyunsaturated fatty acids demonstrate anti-inflammatory effects and are associated with reduced autoantibody levels in individuals at risk of RA [5, 6, 8].

Large cohort studies such as the Nurses' Health Study (NHS) have shown that healthier dietary patterns, reflected by scores like the Alternative Healthy Eating Index (AHEI), correlate with a decreased risk of RA. Diets rich in fruits, vegetables, nuts, unsaturated fats, and whole grains tend to be protective, whereas high consumption of sugar-sweetened beverages is associated with increased RA risk. Moderate alcohol intake and lower red meat consumption also appear beneficial .

The Empirical Dietary Inflammatory Index (EDII) further identifies pro-inflammatory diets, characterized by high intake of red and processed meats and refined grains, which correspond with elevated inflammatory markers and increased RA risk. Conversely, components like wine, coffee, and leafy greens are linked to anti-inflammatory effects [11, 12].

While evidence on the Mediterranean diet (MD) is mixed, some studies report a protective effect against seropositive RA, particularly among men, although other large cohorts have not found a definitive association [14, 15].

Fish and Polyunsaturated Fatty Acids (PUFAs) in Rheumatoid Arthritis (RA)

Polyunsaturated fatty acids (PUFAs), including fish oil and plant-derived oils, are well-recognized for their anti-inflammatory properties. Several studies suggest a protective effect of oily fish consumption on RA development, although the statistical strength varies [16,19]. Data from the UK Biobank (n > 500,000) reported an inverse relationship between RA risk and intake of oily fish, breakfast cereals, and moderate alcohol consumption . Moreover, a cohort of over 30,000 elderly women showed a dose-response effect, where PUFA intake above 0.21 grams/day was associated with a 52% reduction in RA incidence . Higher erythrocyte levels of n-6 PUFAs were linked to lower RA risk (OR 0.29, highest vs. lowest tertile) . Similarly, n-3 PUFA concentrations negatively correlated with rheumatoid factor and anti-CCP antibodies in genetically susceptible individuals .

Adiposity and Rheumatoid Arthritis Risk

The association between a pro-inflammatory diet (high EDII) and RA risk diminished after adjusting for body mass index (BMI) [1]. Obesity stands out as a major modifiable risk factor for RA, as highlighted in the Nurses' Health Study (NHS) cohort . After BMI adjustment, dietary quality (AHEI score) showed no independent effect on RA risk . Longitudinal data from approximately 108,000 women (1989–2017) indicated that weight gain over 20 kg was linked to a significantly higher risk of seropositive RA (RR 3.8) [2]. These results align with previous findings showing a positive relationship between BMI and RA risk, despite some variability among studies . Notably, combined obesity and smoking synergistically increase RA risk beyond their individual effects [3]. Central adiposity, often measured by waist circumference, has been implicated as a significant RA risk factor in some cohorts , although other studies found no independent effect beyond overall adiposity [4].

Alcohol Consumption and Rheumatoid Arthritis

Moderate alcohol intake appears to reduce the risk of rheumatoid arthritis (RA). The Malmö Diet and Cancer Study (n=30,447) reported that consuming 3.5 to 15.2 grams of alcohol per day was associated with a 52% lower odds of RA compared to lower intake, even after adjusting for smoking and education . A meta-analysis of eight prospective cohorts (over 195,000 participants) confirmed this protective effect, showing a relative risk (RR) of 0.86 for low-to-moderate drinkers versus abstainers, with a non-linear dose-response peaking at around 9 grams daily. Higher intake (~30 grams) may negate this benefit . Beverage type did not significantly influence RA risk.

Nutritional Interventions in the Management of Rheumatoid Arthritis

The efficacy of dietary interventions as adjunctive treatments for rheumatoid arthritis (RA) remains a subject of considerable debate, with existing evidence characterized by heterogeneity and limited conclusiveness. A Cochrane systematic review published in 2009, encompassing 14 clinical trials with a cumulative sample of 837 patients, concluded that the impact of dietary modifications on RA outcomes was uncertain, primarily due to methodological limitations including small sample sizes and a high risk of bias . Subsequent systematic reviews have reinforced this uncertainty, underscoring the current lack of robust evidence to definitively support dietary interventions as effective modalities in RA management .

Although certain studies have observed trends suggesting amelioration of pain and inflammatory markers following specific dietary regimens, the extant data are insufficient to endorse any dietary protocol as a viable substitute for conventional disease-modifying antirheumatic drugs (DMARDs). Diets such as the Mediterranean diet (MD) and other anti-inflammatory dietary patterns have demonstrated potential in attenuating systemic inflammation and improving cardiovascular risk profiles among RA patients, yet consistent evidence demonstrating a reduction in disease activity remains elusive [35,37–39].

Notably, nutritional interventions incorporating the Mediterranean diet have been associated with modest improvements in disease activity indices, including reductions in the Disease Activity Score in 28 joints (DAS28), which are partially attributed to enhanced intake of omega-3 polyunsaturated fatty acids (PUFAs). Nonetheless, such interventions are unlikely to supplant DMARD therapy or forestall the progression of joint damage in the long term . Furthermore, dietary approaches involving vegan or Mediterranean patterns may yield improvements in patient-reported outcomes such as pain; however, these benefits do not extend to the prevention of structural joint damage or the control of highly active disease states.

Fasting and Rheumatoid Arthritis Disease Activity

Short-term fasting interventions have demonstrated potential benefits in alleviating symptoms associated with rheumatoid arthritis (RA), although evidence supporting their sustained efficacy, particularly in the context of structural joint preservation, remains lacking. A meta-analysis synthesizing available clinical trials on fasting in RA patients concluded that controlled fasting protocols, typically not exceeding 12 weeks in duration, may result in transient reductions in pain and inflammatory symptoms [5]. Nevertheless, these symptomatic improvements appear to be temporary, and current data are insufficient to endorse fasting as a viable long-term therapeutic strategy for RA management.

Exclusion Diets in Rheumatoid Arthritis

Various exclusion diets have been investigated for their potential therapeutic effects in rheumatoid arthritis (RA), primarily targeting the removal of suspected dietary allergens such as gluten and dairy. One study evaluating the elimination of milk allergens and azo dyes failed to demonstrate any definitive clinical benefit among RA patients, although it remains plausible that specific food allergies may influence disease activity in certain subpopulations. A 2001 investigation employing a vegan, gluten-free diet reported modest

improvements in inflammatory markers, including reductions in C-reactive protein (CRP) levels; however, adherence was notably poor, with over 40% of participants discontinuing the regimen due to its restrictive nature . Despite some encouraging outcomes in limited studies, exclusion diets are generally not recommended for RA management owing to challenges related to tolerability, potential nutritional deficiencies, and inconsistent evidence regarding their efficacy.

Weight Reduction Interventions in Rheumatoid Arthritis

Weight management constitutes a critical component of rheumatoid arthritis (RA) care, given the contributory role of excess adiposity in amplifying systemic inflammation and disease activity. Multiple studies have evaluated the efficacy of weight reduction interventions among RA patients, with bariatric surgery and hypocaloric dietary regimens demonstrating favorable outcomes. A retrospective cohort analysis of RA patients undergoing bariatric surgery revealed significant decreases in inflammatory biomarkers alongside notable improvements in clinical disease activity following the surgical intervention [7]. Correspondingly, a randomized controlled trial investigating a 12-week hypocaloric diet (ranging from 1000 to 1500 kcal/day) in RA patients reported an average weight loss of 9.5 kilograms, which was concomitant with statistically significant reductions in disease activity scores (DAS28) and enhancements in functional status, as assessed by the Health Assessment Questionnaire (HAQ) Disability Index [8].

Nutritional Supplements in the Management of Rheumatoid Arthritis

Nutritional supplementation has been investigated as a potential adjunctive strategy in the management of rheumatoid arthritis (RA), with varying degrees of efficacy and quality of evidence. Among the most extensively studied are omega-3 polyunsaturated fatty acids (PUFAs), which have demonstrated beneficial effects in reducing joint pain intensity, morning stiffness, and the requirement for nonsteroidal anti-inflammatory drugs (NSAIDs) in several clinical trials [12].

Other supplements, including curcumin, garlic, and saffron, have shown anti-inflammatory and antioxidative properties in preclinical models; however, the clinical literature supporting their use in RA remains limited and is frequently characterized by small sample sizes, methodological weaknesses, and substantial risk of bias . Similarly, probiotic supplementation has been explored for its potential to modulate immune and inflammatory responses, yet existing studies are heterogeneous and underpowered, providing insufficient evidence to support their routine use in RA management [23-24-25].

Although omega-3 PUFA supplementation appears to offer modest clinical benefits, there is no robust evidence to support the efficacy of trace element supplementation such as zinc, copper, magnesium, or selenium in altering disease activity or progression in RA patients [27-28-29-30-31-32-33]. Furthermore, while vitamin E was initially proposed as a therapeutic antioxidant, subsequent studies have failed to demonstrate significant clinical benefit, and excessive intake has been associated with increased all-cause mortality, raising concerns about its safety in long-term use .

Consequently, supplementation with vitamins, trace elements, and other micronutrients should be approached with caution. Nutritional interventions in RA should be guided by laboratory-confirmed deficiencies particularly of vitamin D and iron which may warrant correction within the broader framework of disease management.

Nutrition and Rheumatoid Arthritis: Current Recommendations

Current clinical guidelines acknowledge the role of nutrition as a supportive element in the comprehensive management of rheumatoid arthritis (RA). The European League Against Rheumatism (EULAR) recommends the adoption of a balanced diet and the maintenance of a healthy body weight for individuals with rheumatic and musculoskeletal diseases, including RA, as part of a broader strategy to improve health outcomes and reduce comorbid risk factors .

The French Society for Rheumatology has issued more specific dietary guidance, advocating for adherence to a Mediterranean diet rich in fruits, vegetables, legumes, whole grains, and healthy fats, alongside supplementation with polyunsaturated fatty acids. Importantly, the society discourages restrictive dietary patterns such as vegan or gluten-free diets and the unnecessary elimination of dairy products, citing a lack of consistent evidence supporting their efficacy in RA management. In addition, these guidelines emphasize the importance of cardiovascular risk reduction, given the well-documented association between RA and increased cardiovascular morbidity and mortality [6].

In summary, while evidence supports the role of balanced nutrition, weight control, and Mediterranean dietary patterns in modulating inflammation and improving comorbid outcomes, dietary interventions should be viewed as adjunctive strategies rather than standalone therapies. Disease-modifying antirheumatic drugs (DMARDs) remain the cornerstone of RA treatment. Continued research is warranted to further elucidate the role of specific nutritional interventions and to inform evidence-based dietary recommendations for RA patients.

Smoking and the Development of Rheumatoid Arthritis (RA)

Tobacco smoke exposure is among the most well-established environmental risk factors for the development of rheumatoid arthritis (RA), particularly in seropositive disease forms. Epidemiological studies estimate that smoking accounts for approximately 20% of all RA cases and up to 35% of anti-citrullinated protein antibody (ACPA)-positive RA cases [70,71]. The causal link between smoking and RA has been substantiated through robust longitudinal and genetic studies. A landmark twin study conducted in 1996, involving 79 monozygotic and 71 dizygotic twin pairs discordant for RA, demonstrated that smoking was associated with a fourfold increase in RA risk among smoking twins, with the odds ratio (OR) rising to 5.5 among monozygotic pairs underscoring a gene environment interaction in RA pathogenesis [16].

Further evidence arises from a large Swedish case-control study involving 858 incident RA cases and 1,048 controls, which investigated the combined effects of smoking and genetic susceptibility conferred by the shared epitope (SE) alleles of the HLA-DRB1 gene. The study revealed a striking synergistic interaction between smoking and SE alleles in promoting seropositive RA. Specifically, individuals with one SE allele who smoked had a relative risk (RR) of 7.5, which increased to 15.7 in those with two SE alleles. Notably, smoking did not elevate the risk of seronegative RA regardless of SE status, highlighting a distinct pathogenic mechanism in ACPA-positive disease .

These findings were further supported by data from the Swedish Epidemiological Investigation of RA (EIRA), which demonstrated a dose-dependent relationship between smoking intensity and the risk of developing ACPA-positive RA. Among individuals with one or two copies of the SE allele, smoking increased the risk by 6.5-fold and 21-fold, respectively. No such association was observed for ACPA-negative RA, reinforcing the specificity of the smoking–genotype interaction in driving seropositive disease .

The biological mechanisms by which smoking contributes to RA pathogenesis are multifaceted. Tobacco smoke promotes systemic inflammation through its impact on pulmonary and periodontal inflammation two conditions frequently linked to RA onset. Nicotine, a key component of tobacco smoke, has been shown to promote autoimmunity through multiple pathways. One of the principal mechanisms involves the activation of peptidyl-arginine deaminase (PAD) enzymes in the lung, leading to protein citrullination. This process generates neoantigens that are central to ACPA formation, particularly in genetically susceptible individuals carrying HLA-DRB1 SE alleles.

Moreover, nicotine has been implicated in the induction of neutrophil extracellular trap (NET) formation, or NETosis, a mechanism through which neutrophils release citrullinated proteins into the extracellular space, thereby enhancing autoantigen exposure and promoting autoreactive B and T cell activation [17]. Experimental models have shown that nicotine administration exacerbates disease activity and NET formation, even in the absence of other tobacco smoke components. This suggests that nicotine alone, such as through e-cigarette use, may contribute to RA pathogenesis in genetically predisposed individuals [17].

A large cohort study involving 6,239 Japanese RA patients corroborated these findings, identifying a positive correlation between nicotine exposure and the presence of both ACPA and rheumatoid factor (RF). Interestingly, nicotine use showed a stronger association with RF formation than with ACPA, though the development of ACPA was confined to individuals carrying the SE allele. Furthermore, elevated ACPA levels were detectable up to 20 years after smoking cessation, indicating the long-term immunological consequences of nicotine exposure .

In conclusion, smoking is a significant and modifiable environmental risk factor for RA, particularly in individuals with genetic susceptibility defined by the presence of shared epitope alleles. The cumulative evidence supports a gene–environment interaction in the pathogenesis of ACPA-positive RA, with mechanisms involving citrullination and NET formation. These insights underscore the critical importance of smoking cessation—both as a primary prevention strategy and as a means of reducing disease risk and severity in predisposed populations.

Smoking and the Outcome of Rheumatoid Arthritis (RA)

Beyond its well-established role in the pathogenesis of rheumatoid arthritis (RA), smoking also significantly influences disease progression, treatment response, and the development of comorbidities. Numerous studies have demonstrated that smoking is associated with a poorer prognosis in RA patients, including reduced responsiveness to both conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic agents, particularly tumor necrosis factor-alpha (TNF-α) inhibitors . Smokers are less likely to achieve sustained remission and are at greater risk for disease flare-ups compared to non-smokers. These adverse outcomes are believed to be mediated by smoking's pro-inflammatory effects, which intensify synovial inflammation and alter immune system dynamics.

Importantly, the negative impact of smoking on disease activity persists even after RA is established. Retrospective cohort analyses have indicated that smoking

cessation following RA diagnosis does not significantly alter the disease course. Patients who discontinued smoking after diagnosis continued to experience similar levels of disease activity and joint damage compared to those who remained active smokers . These findings suggest that the pathogenic effects of smoking may induce irreversible immunologic and structural changes in established RA.

The role of passive smoking has also been investigated. The Swedish BARFOT (Better Anti-Rheumatic PharmacOTherapy) study reported a high prevalence (68%) of secondhand smoke exposure among RA patients who identified as non-smokers—a figure notably higher than in the general population. While passive smoke exposure was not directly associated with increased disease activity, the data imply that environmental tobacco exposure may contribute to RA pathogenesis, particularly in genetically predisposed individuals, by amplifying early immune dysregulation .

Smoking is further linked to an increased risk of comorbid conditions in RA, notably interstitial lung disease (ILD), which affects approximately 10% of RA patients. The risk of developing RA-associated ILD is significantly elevated among smokers, especially in those with high titers of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) . The underlying mechanism involves nicotine-induced citrullination of lung proteins, which promotes ACPA production. These autoantibodies not only play a central role in RA pathogenesis but are also implicated in the development of ILD, indicating a shared immunopathogenic mechanism .

In summary, smoking exerts a multifactorial detrimental influence on RA, compromising treatment efficacy, accelerating disease progression, and increasing the likelihood of comorbid complications such as ILD. Although smoking cessation is universally recommended, current evidence suggests that its benefits may be more pronounced in disease prevention than in modifying established disease. Passive smoking, though less directly associated with disease activity, may still contribute to RA onset and severity in genetically susceptible individuals. These findings underscore the critical importance of early smoking cessation and public health measures aimed at minimizing tobacco exposure to reduce both the incidence and burden of RA.

Fine Particulate Matter and Rheumatoid Arthritis (RA)

Fine particulate matter (PM), especially particles with aerodynamic diameters of 10 micrometers or less (PM_{10}) and 2.5 micrometers or less ($PM_{2.5}$), has garnered increasing attention as a potential environmental contributor to the development of rheumatoid arthritis (RA) and its pulmonary comorbidities, particularly interstitial lung disease (ILD). Among these environmental exposures, silica

dust often encountered in occupational setting has been most robustly linked to increased RA risk.

One of the earliest recognized associations is between silica exposure and the dual manifestation of pulmonary fibrosis and RA, a clinical presentation known as Caplan's syndrome, commonly observed among coal miners . In the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study, occupational exposure to stone dust among men was associated with a twofold increased risk of developing RA . Subsequent analyses reinforced this finding, revealing that silica exposure was significantly associated with an increased risk of ACPA-positive RA (odds ratio [OR]: 1.7), while no corresponding association was observed for ACPA-negative RA. This distinction highlights the relevance of autoimmune mechanisms in the development of RA in the context of particulate exposure.

Moreover, a synergistic effect has been observed between smoking and silica exposure. In individuals who both smoked and were exposed to silica, the risk of developing ACPA-positive RA increased substantially, with an OR of 7.4 compared to unexposed non-smokers . These findings suggest that environmental triggers can interact with one another and with genetic susceptibility to enhance autoimmune responses, potentially through mechanisms involving lung inflammation and citrullination of self-proteins.

While the role of silica exposure is well established, the evidence regarding ambient exposure to fine particulate matter, such as PM_{10} and $PM_{2.5}$, is more nuanced. Early investigations, including those conducted within the EIRA and the Nurses' Health Study (NHS) cohorts, did not demonstrate a statistically significant association between general PM exposure and RA risk . However, more recent evidence has suggested a broader environmental impact. A large Italian retrospective cohort study involving 81,363 individuals reported a dose-dependent relationship between PM exposure and the development of autoimmune diseases, including RA . Specifically, higher concentrations of $PM_{2.5}$ were more strongly associated with increased RA incidence compared to PM_{10}, suggesting that smaller particulate size may facilitate deeper penetration into lung tissue, thereby enhancing immune activation and systemic inflammatory responses.

In summary, while occupational exposure to silica is a well-documented risk factor for ACPA-positive RA, particularly in smokers, the relationship between general fine particulate matter and RA is still evolving. Emerging data suggest that $PM_{2.5}$, in particular, may play a role in triggering autoimmune processes through chronic pulmonary inflammation, potentially leading to ACPA production and RA onset in genetically predisposed individuals. These findings underscore the importance of considering both occupational and environmental air quality in RA risk assessment and prevention strategies.

Socioeconomic Status and Rheumatoid Arthritis (RA)

The relationship between socioeconomic status (SES) and health outcomes is well established, with individuals of higher SES generally experiencing more favorable health outcomes than those of lower SES . In rheumatoid arthritis (RA), SES influences not only disease onset but also progression and prognosis. Several SES-related factors such as smoking behavior, nutritional status, obesity, and marital status contribute to disease activity and functional impairment. Importantly, evidence suggests that SES itself may independently affect the severity and course of RA.

Multiple observational studies have demonstrated that lower SES correlates with more severe disease activity and greater functional limitations in RA patients. A cohort study conducted in England involving 869 RA patients found that lower SES, as measured by educational attainment, was associated with higher disease activity both at baseline and longitudinally. Patients from lower SES backgrounds exhibited worse functional outcomes, including elevated Health Assessment Questionnaire (HAQ) scores, reduced grip strength, and increased joint involvement. However, these disparities were not reflected in radiographic progression or inflammatory markers such as erythrocyte sedimentation rate (ESR) .

Educational level, often employed as a proxy for SES, has also been linked to disease severity. A U.S. study with 385 RA patients reported that individuals with lower educational attainment had higher disease activity, as indicated by ESR, grip strength, and joint counts . Similarly, a prospective study of 814 RA patients in England and Scotland observed that residence in socioeconomically deprived areas was associated with greater functional impairment, evidenced by elevated HAQ scores, although no significant differences were found in inflammatory markers such as ESR or C-reactive protein (CRP) . A recent review of 30 studies examining social status and RA disease activity concluded that 25 studies demonstrated a clear association between lower SES and increased disease severity. However, heterogeneity in the operationalization of SES and disease activity limited cross-study comparability, underscoring the need for standardized measures in future research .

While the impact of SES on RA progression and severity is well documented, its role as a risk factor for RA development is less clear. The Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case-control study, which included 930 incident RA cases and 1,126 controls, assessed the relationship between SES indicators (education and occupation) and RA risk. After adjustment for confounders including age, smoking, and residential area, individuals without a

university degree had a relative risk (RR) of 1.4 for developing RA, with a stronger effect observed for seropositive RA (RR = 1.6). Moreover, individuals employed in high-ranking non-manual occupations had a 20% lower risk of RA compared to those in other non-manual jobs .

In summary, socioeconomic status significantly influences RA disease activity and progression. Lower SES is consistently associated with greater disease severity and functional impairment. Although the evidence is less definitive, lower SES may also increase the risk of developing RA, particularly seropositive RA. Future research employing standardized definitions of SES and disease metrics is essential to clarify these relationships and to guide targeted public health interventions aimed at reducing socioeconomic disparities in RA outcomes.

Psychosocial Stress and Rheumatoid Arthritis (RA)

Chronic psychosocial stress is increasingly recognized as a potential contributor to the development and progression of various chronic diseases, including rheumatoid arthritis (RA). Many RA patients report psychological stress as a possible trigger for disease onset or exacerbation. Psychoneuroendocrinological frameworks propose that chronic psychosocial stress influences immune function via activation of the hypothalamic-pituitary-adrenal (HPA) axis, thereby potentially facilitating autoimmune processes such as those observed in RA .

A recent review examining psychological stress in RA differentiated between types of stress, including role stress, social stress, and work-related stress. The review of 16 studies revealed considerable heterogeneity in stress measurement tools and conceptual definitions. Nonetheless, findings consistently indicated that RA patients experience higher levels of work-related and social stress compared to healthy controls. While the psychological burden of chronic illness and pain on mental health is well documented, research directly addressing the causal role of psychosocial stress in RA development remains sparse.

The Swedish Epidemiological Investigation of RA (EIRA) study provided important insights into work-related psychosocial stress as a risk factor for RA. Using self-reported data and job exposure matrices to assess psychological demand and decision latitude at work, the study found that low decision latitude—reflecting limited control over work tasks—was significantly associated with increased RA risk (odds ratio [OR] = 1.6). Conversely, high psychological job demands showed a nonsignificant trend towards a reduced risk. These associations persisted after adjusting for social class, suggesting an independent role of workplace psychosocial stress in RA pathogenesis .

Furthermore, a Danish population-based survey of 19,890 participants investigated the association between loneliness and RA prevalence. The analysis

revealed a modest positive association (OR = 1.3), although the study design did not allow for causal inference, underscoring the need for further longitudinal research to clarify this relationship .

In summary, although evidence remains limited, current studies suggest that psychosocial stress—particularly in occupational and social contexts—may influence both the onset and course of RA. Future research employing standardized stress measurement and longitudinal designs is essential to elucidate underlying mechanisms and identify effective stress management interventions for RA prevention and treatment.

Psychosocial stress also appears to affect prognosis in established RA. Clinical trial data indicate that psychosocial factors can modulate disease outcomes, particularly in relation to remission maintenance and flare frequency. For instance, the randomized controlled CareRA trial, involving patients with early arthritis, demonstrated that individuals experiencing high psychosocial stress were more likely to relapse from remission, highlighting the negative impact of stress on disease control .

These findings emphasize the complex interplay between psychological and biological factors in RA progression and suggest that integrating psychosocial support and stress management into comprehensive RA care could enhance treatment outcomes. Addressing psychosocial well-being may therefore be vital not only for improving patients' mental health but also for mitigating biological disease activity.

Marital and Family Status in Rheumatoid Arthritis (RA)

While rheumatoid arthritis (RA) does not appear to significantly affect divorce rates compared to the general population, marital status has been shown to influence disease progression and patient well-being. Research indicates that married individuals with RA generally experience slower progression of disability relative to their unmarried counterparts . Moreover, those in stable, non-distressed marriages report lower pain levels and decreased physical disability compared to individuals who are unmarried or in distressed relationships . These observations underscore the potential protective role of social support and emotional security factors commonly associated with stable marital relationships in mitigating both the physical and psychological burdens associated with RA and other inflammatory rheumatic diseases (IRDs).

Sexual dysfunction is notably more prevalent among RA patients than in the general population, although it remains an under-discussed issue in clinical practice . The pathophysiology of sexual dysfunction in RA is multifactorial, involving chronic pain, comorbidities, and psychological factors such as

depression and fatigue . Additionally, disease activity, patient and partner age, and sleep disturbances contribute to the severity and frequency of sexual health problems. Studies report that nearly 50% of female RA patients experience sexual dysfunction, which substantially impairs quality of life .

Regarding parenthood, direct research on the impact of having children on RA disease activity or outcomes is lacking. However, a recent large-scale study investigating parent-child relationships found that offspring born to mothers with RA exhibited an increased incidence of mental health disorders. These included heightened risks of autism spectrum disorders, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, and major depressive disorder . These findings suggest that the effects of RA may extend beyond the affected individual, potentially influencing the mental health and well-being of offspring, particularly in cases of maternal RA.

Physical Activity and Rheumatoid Arthritis (RA)

The beneficial effects of regular physical activity on various health parameters, including quality of life, cardiovascular fitness, and muscle strength, in patients with rheumatoid arthritis (RA) are well-established . Reflecting these benefits, the European League Against Rheumatism (EULAR) recommends regular physical exercise as part of the management strategy for RA patients . However, the impact of physical exercise on inflammatory disease activity in established RA remains unclear. While a meta-analysis encompassing ankylosing spondylitis, systemic lupus erythematosus, and RA reported a reduction in inflammatory activity with exercise across these conditions , other meta-analyses focused specifically on RA found no significant effect of cardiovascular or resistance training on disease activity, as measured by the Disease Activity Score 28 (DAS28) .

One study noted progression of joint damage in patients with pre-existing severe joint involvement following high-intensity, weight-bearing exercise . Nevertheless, the consensus from most studies and meta-analyses supports the safety and benefits of resistance and aerobic exercises for RA patients . Accordingly, EULAR guidelines endorse not only aerobic activities but also targeted muscle-strengthening exercises for this population .

Regarding the potential protective role of physical activity against the development of RA, findings are inconsistent. The Nurses' Health Study II, including 113,366 women with 506 incident RA cases, demonstrated a dose-dependent association between recreational physical activity and reduced RA risk. Women engaging in 4 to 7 hours or more than 7 hours per week of physical activity exhibited relative risks (RR) of 0.84 and 0.67, respectively, compared to those with less than 1 hour per week . Similarly, the Swedish Mammography

Cohort, tracking 30,112 women aged 54 to 89 years, found that participants in the highest physical activity category had a significantly lower risk of developing RA (RR: 0.7) relative to the least active group .

In contrast, the Iowa Women's Health Study, involving 31,336 women aged 55 to 69 years, did not identify a significant association between leisure-time physical activity and RA risk, as varying exercise levels (low, medium, high) failed to influence disease development . Furthermore, a meta-analysis of four studies with 255,365 women and 4,213 incident RA cases indicated a negative association between physical activity and RA development (highest activity group RR: 0.8 versus lowest). However, Mendelian randomization analysis from the same authors did not support a causal relationship, suggesting potential limitations in observational studies such as insufficient statistical power or inadequate confounder adjustment .

Major limitations of studies assessing physical activity's role in RA onset include challenges in controlling for confounding lifestyle factors such as diet, smoking, and body mass index. Individuals with higher physical activity levels often engage in generally healthier behaviors, complicating efforts to isolate the independent effect of exercise on RA risk. In conclusion, while physical activity clearly benefits RA patients regarding symptoms and functional status post-diagnosis, current evidence is insufficient to establish a causal preventive role in RA development.

Conclusions

Environmental factors play a critical role in the pathogenesis and progression of rheumatoid arthritis (RA), frequently interacting synergistically with genetic predispositions. A prominent example is the interplay between smoking and the shared epitope (SE), which substantially influences the generation of anti-citrullinated protein antibodies (ACPA), a hallmark of seropositive RA . Modifiable environmental exposures, including diet, physical activity, and tobacco use, are subject to individual behavioral modification, offering opportunities for personalized interventions aimed at reducing disease burden.

Accurately quantifying the individual contribution of environmental factors to RA development remains challenging due to the complex, multifactorial interactions involved. Many such factors—such as lifestyle behaviors (diet, smoking, physical activity) and socioeconomic status—often co-occur and are strongly influenced by educational attainment. Disentangling their independent effects necessitates robust methodological designs, including large-scale cohort studies with multivariate stratification. Furthermore, the onset of RA may itself precipitate changes in lifestyle, engendering a bidirectional relationship between disease activity and socioeconomic determinants.

Epidemiological research on environmental exposures has primarily utilized retrospective cohort designs, with some prospective studies contributing additional insights. Although these investigations demonstrate significant associations, establishing causality remains difficult due to potential confounding variables. The relationship between smoking and RA onset and progression is well-established and underpinned by extensive evidence. In contrast, associations between other factors such as diet, physical activity, and socioeconomic status while consistently linked to improved disease outcomes, are yet to be rigorously defined.

Nonetheless, it is widely accepted that healthy dietary patterns, regular physical exercise, and higher socioeconomic status correlate with more favorable outcomes in RA patients. These factors may also confer protective effects against RA development, although the precise mechanisms remain incompletely understood.

Future research should prioritize elucidating the mechanistic pathways through which environmental factors influence RA initiation and progression. Longitudinal studies integrating genetic and epigenetic analyses will be essential for clarifying causal relationships. Advancing understanding in this domain will facilitate the development of evidence-based preventive strategies and enable more personalized therapeutic approaches for individuals at risk of, or living with, RA.

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The Cell Cycle in Cancer: Molecular Pathways, Checkpoint Aberrations, and Therapeutic Opportunities

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Abstract

The eukaryotic cell cycle is a finely orchestrated sequence of events ensuring accurate DNA replication and equal segregation of chromosomes. Dysregulation of this system lies at the heart of malignant transformation and cancer progression. Here, we provide an in-depth synthesis of the genetic, epigenetic, and biochemical alterations that affect cell cycle regulation in cancer, emphasising oncogene activation, tumour suppressor inactivation, and disruption of checkpoint fidelity. We explore the molecular mechanisms by which these perturbations foster replication stress, genomic instability, and aneuploidy. Furthermore, we review emerging therapeutic strategies that target these vulnerabilities, including inhibitors of cell cycle kinases, replication stress response mediators, and chromosomal segregation checkpoints. By integrating foundational discoveries with contemporary insights, this review elucidates the central role of cell cycle dynamics in oncogenesis and its therapeutic exploitation.

Introduction

Cell proliferation is fundamental to organismal development, tissue homeostasis, and regeneration. The eukaryotic cell cycle comprises a series of well-defined phases—G1 (gap 1), S (DNA synthesis), G2 (gap 2), and M (mitosis)—each governed by precise molecular machinery. Progression through these phases depends on the dynamic interaction between cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors (CKIs), transcription factors, and DNA damage response (DDR) proteins. Temporal control of these interactions ensures proper DNA replication, accurate chromosome segregation, and maintenance of genomic integrity (Malumbres & Barbacid, 2009).

Each phase of the cell cycle is stringently regulated. In G1, cells evaluate extracellular signals and intrinsic stressors to decide whether to proceed to DNA replication. The transition from G1 to S phase is orchestrated by CDK4/6-cyclin D and CDK2-cyclin E complexes, which sequentially phosphorylate the retinoblastoma protein (pRB), leading to release of E2F transcription factors and activation of S-phase gene transcription (Sherr & McCormick, 2002). During S phase, origin licensing and helicase activation enable DNA synthesis, while the replication fork machinery must coordinate with histone deposition, transcription, and repair pathways to maintain fidelity. The G2 phase serves as a checkpoint to ensure complete replication and repair of any damage incurred. Finally, mitosis involves highly coordinated structural changes in chromosomes and the mitotic spindle to allow equitable segregation of sister chromatids (Morgan, 2007).

Cancer emerges when this regulation fails. Mutations in cell cycle regulators disrupt the balance between proliferation and quiescence, favoring uncontrolled division and survival of genetically unstable cells. These events are often driven by gain-of-function mutations in oncogenes, such as MYC and RAS, and loss-of-function alterations in tumour suppressors like TP53 and RB1 (Hanahan & Weinberg, 2011). Oncogene-induced signals often override physiological constraints, driving inappropriate proliferation and rendering cells refractory to anti-proliferative cues. Additionally, defects in key checkpoints—G1/S, intra-S, G2/M, and the spindle assembly checkpoint (SAC)—permit the propagation of replication errors and aneuploid progeny (Kastan & Bartek, 2004).

Cell cycle deregulation also fosters additional hallmarks of cancer, including resistance to apoptosis, increased metabolic demands, and immune evasion. As tumors evolve, subclonal populations develop differential reliance on specific cell cycle pathways, creating both complexity and opportunity for targeted intervention. Recent advances in single-cell genomics, functional screening, and synthetic lethality have deepened our understanding of cell cycle dependencies

in cancer and identified novel therapeutic targets (Nijman, 2011; Lawson et al., 2020). Thus, elucidating the disrupted cell cycle machinery in cancer not only provides insight into disease pathogenesis but also reveals critical vulnerabilities that may be exploited therapeutically.

Oncogenic Deregulation of Cell Cycle Control: The Roles of MYC and RAS

MYC: A Central Transcriptional Regulator in Proliferation and Tumorigenesis

The MYC oncogene encodes a basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factor that regulates genes involved in nearly all aspects of cell physiology, including cell cycle progression, metabolism, protein synthesis, and apoptosis. MYC forms heterodimers with MAX and binds to canonical E-box sequences (CACGTG) in the promoter regions of target genes, leading to chromatin remodelling and transcriptional activation (Dang, 2012).

In cancer, MYC is frequently overexpressed due to gene amplification, chromosomal translocations, or dysregulated upstream signalling pathways (e.g., WNT, RAS, or PI3K/AKT). For example, translocations involving the immunoglobulin heavy chain locus and MYC (t(8;14)(q24;q32)) are characteristic of Burkitt lymphoma (Taub et al., 1982). Constitutive MYC expression results in the upregulation of genes encoding cyclins (e.g., CCND1, CCNE1), CDKs, and E2F transcription factors, which collectively accelerate G1/S transition. Additionally, MYC represses CDK inhibitors such as p21 and p27, further dismantling cell cycle checkpoints (Bouchard et al., 2007).

Oncogenic MYC also induces replication stress by driving unscheduled origin firing and nucleotide depletion, contributing to DNA damage and genomic instability (Dominguez-Sola et al., 2007). In normal cells, such stress activates a p53-dependent failsafe mechanism leading to apoptosis or senescence; however, in the context of TP53 mutations, MYC-driven stress supports malignant progression. Targeting MYC directly remains challenging due to its disordered protein structure, but emerging strategies include disruption of MYC-MAX dimerisation, inhibition of MYC transcription or translation, and synthetic lethality approaches (Whitfield et al., 2017).

RAS: A Molecular Switch Governing Proliferative and Survival Pathways

The RAS family of small GTPases (KRAS, NRAS, HRAS) acts as a key signal transduction node downstream of receptor tyrosine kinases (RTKs). Upon growth factor stimulation, guanine nucleotide exchange factors (GEFs) such

as SOS catalyse GDP-GTP exchange, converting RAS to its active GTP-bound state. Activated RAS engages multiple effectors, including the RAF-MEK-ERK and PI3K-AKT-mTOR pathways, which promote cell proliferation, growth, and survival (Cox et al., 2014).

Mutations in RAS genes—particularly KRAS codons 12, 13, and 61—abolish intrinsic GTPase activity or disrupt GAP-mediated inactivation, resulting in constitutive signalling. Oncogenic RAS upregulates cyclin D1 expression and suppresses CDK inhibitors, driving cell cycle progression. Moreover, RAS-induced ERK signalling enhances MYC stability, creating a positive feedback loop that amplifies oncogenic transcriptional programs.

RAS-driven tumours, such as pancreatic ductal adenocarcinoma, colorectal carcinoma, and non-small-cell lung cancer, are notoriously aggressive and refractory to conventional therapies. While direct RAS inhibition has historically been elusive, KRAS G12C inhibitors (e.g., sotorasib) now provide proof-of-concept for allele-specific targeting (Canon et al., 2019). Understanding RAS-driven cell cycle dependencies and co-targeting parallel pathways (e.g., CDK4/6, MEK, or autophagy) represents a promising therapeutic avenue.

Tumour Suppressors in Cell Cycle Control: RB1 and TP53 as Molecular Gatekeepers

RB1: The Retinoblastoma Pathway and G1/S Transition Restriction

The RB1 gene encodes the retinoblastoma protein (pRB), a key regulator of the G1/S checkpoint that functions as a transcriptional repressor by binding to E2F transcription factors. In quiescent and early G1-phase cells, hypophosphorylated pRB forms inhibitory complexes with E2Fs, preventing the transcription of S-phase-promoting genes. Mitogenic stimulation activates CDK4/6-cyclin D complexes, initiating pRB phosphorylation. Hyperphosphorylation by CDK2-cyclin E leads to the dissociation of pRB-E2F complexes, allowing transcriptional activation of genes essential for DNA synthesis and S-phase progression (Burkhart & Sage, 2008).

Loss of RB1 function occurs via diverse mechanisms, including point mutations, deletions, and epigenetic silencing. Biallelic inactivation results in constitutive E2F activity, unchecked S-phase entry, and heightened susceptibility to replication stress. This phenomenon is a hallmark of retinoblastoma, osteosarcoma, and small-cell lung carcinoma. Moreover, RB1 inactivation promotes chromosomal instability by uncoupling cell cycle progression from mitotic fidelity, further exacerbating tumorigenesis (Dick & Rubin, 2013).

Beyond its canonical role in E2F regulation, pRB interacts with chromatin remodels, DNA replication machinery, and apoptotic regulators, underscoring its multifaceted tumour suppressor function. RB-deficient tumours often exhibit compensatory reliance on p53 or CDK2, highlighting potential vulnerabilities for targeted therapy (McClellan & Slack, 2020).

TP53: Guardian of the Genome and Coordinator of Stress Responses

TP53, encoding the p53 protein, is the most frequently mutated tumour suppressor gene in human cancers. p53 integrates signals from DNA damage, hypoxia, and oncogenic stress to regulate transcription of genes involved in cell cycle arrest, apoptosis, senescence, DNA repair, and metabolism. Upon activation, p53 induces CDKN1A (p21), a potent inhibitor of CDK2, which in turn stabilises pRB and enforces G1 arrest (Vousden & Prives, 2009).

In response to genotoxic stress, the ATM/ATR-Chk1/Chk2 signalling cascade phosphorylates p53, stabilising it and preventing MDM2-mediated ubiquitination and degradation. This allows for temporal orchestration of cell cycle arrest, providing a window for DNA repair. If damage is irreparable, p53 promotes apoptosis through transcriptional upregulation of PUMA, NOXA, and BAX, or induction of senescence via p21 and p16 pathways (Horn & Vousden, 2007).

Mutations in TP53 typically result in missense variants within the DNA-binding domain, abolishing transcriptional activity or conferring dominant-negative and gain-of-function properties. These mutant p53 proteins not only fail to induce cell cycle arrest and apoptosis but also promote tumour cell migration, invasion, and metastasis through chromatin remodelling and metabolic reprogramming (Freed-Pastor & Prives, 2012).

Importantly, p53-deficient cancers exhibit synthetic lethality with checkpoint kinase inhibition. Pharmacologic agents targeting WEE1, ATR, and CHK1 pathways are under clinical investigation for selectively eliminating p53-incompetent tumour cells by exacerbating replication stress (Reinhardt & Schumacher, 2012).

Checkpoint Dysregulation and Oncogene-Induced Replication Stress

Disruption of G1/S and Intra-S Phase Checkpoints

In healthy cells, the G1/S checkpoint ensures that damaged or unprepared DNA is not replicated. This restriction is achieved through the coordinated activity of tumour suppressors (e.g., RB1, TP53), checkpoint kinases (ATM/ATR), and CDK inhibitors (e.g., p21, p27). DNA double-strand breaks activate ATM,

whereas replication stress, characterised by stalled replication forks and exposed single-stranded DNA, activates ATR. These kinases phosphorylate and stabilise downstream effectors such as CHK1 and CHK2, resulting in the inhibition of CDC25 phosphatases, suppression of CDK2 activity, and maintenance of RB1 in a hypophosphorylated, growth-suppressive state (Bartek & Lukas, 2007).

In cancer, frequent inactivation of p53, deletion of CDKN2A (encoding p16INK4A and p14ARF), and overexpression of cyclin D1 or CDK4/6 bypass this checkpoint, leading to inappropriate S-phase entry. The consequence is a permissive environment for replication of damaged DNA, enhancing the risk of mutations, chromosomal rearrangements, and genomic instability (Negrini et al., 2010).

Oncogene-Induced Replication Stress: Molecular Drivers and Outcomes

Oncogene activation, particularly of MYC, RAS, and cyclin E, accelerates cell cycle progression and increases replication origin firing. This hyperproliferative state exhausts nucleotide pools, reduces replication fork speed, and leads to frequent fork stalling and collapse. The resulting accumulation of single- and double-stranded DNA breaks triggers chronic activation of the DDR, particularly the ATR-CHK1 pathway, which becomes essential for cell survival under stress (Zeman & Cimprich, 2014).

Replication stress is not merely a byproduct of transformation; it is a driver of genomic instability and tumour heterogeneity. It contributes to chromothripsis, kataegis, and other mutational phenomena frequently observed in cancer genomes. Importantly, while normal cells resolve such stress via transient arrest or apoptosis, cancer cells tolerate replication errors, thus accumulating a mutator phenotype that fuels evolution and therapy resistance (Gaillard et al., 2015).

Checkpoints in G2/M and Mitosis: Balancing Genome Integrity and Survival

The G2/M checkpoint ensures that cells do not enter mitosis with damaged or incompletely replicated DNA. Activation of ATM/ATR and CHK1/CHK2 kinases in G2 leads to inhibition of CDC25C, preventing activation of CDK1-cyclin B and delaying mitotic entry. In TP53-deficient tumours, G2/M checkpoint control is often the last line of defence against propagation of DNA lesions. This reliance creates vulnerability to WEE1 inhibitors, which disrupt CDK1 control and induce mitotic catastrophe (Sloss et al., 2016).

During mitosis, the spindle assembly checkpoint (SAC) monitors the proper attachment of kinetochores to spindle microtubules. Key components—MAD2, BUB1, BUBR1—sequester CDC20 and inhibit the anaphase-promoting complex

(APC/C) until proper alignment is achieved. In cancer, SAC is frequently dysregulated. Either its components are overexpressed (causing mitotic delay and chromosomal instability) or underactive (allowing premature anaphase and aneuploidy) (Kops et al., 2005).

Exploiting Replication Stress and Checkpoint Dependence for Therapy

Cancer cells' dependence on ATR, CHK1, and WEE1 for survival under replicative stress has prompted the development of small-molecule inhibitors targeting these kinases. ATR inhibitors (e.g., berzosertib), CHK1 inhibitors (e.g., prexasertib), and WEE1 inhibitors (e.g., adavosertib) have shown efficacy in preclinical models and early-phase clinical trials, particularly in TP53-deficient or MYC-driven cancers (Lecona & Fernández-Capetillo, 2014). The combination of these inhibitors with DNA-damaging agents or immune checkpoint inhibitors may enhance therapeutic response.

Future strategies will likely involve precision profiling of checkpoint dependencies using functional genomics and real-time imaging of replication dynamics. Understanding how tumours adapt to chronic checkpoint inhibition will also be crucial to overcoming resistance mechanisms.

Chromosomal Instability and Spindle Checkpoint Tolerance in Tumor Evolution

Chromosomal Instability: Mechanisms and Consequences

Chromosomal instability (CIN) refers to an increased rate of chromosomal missegregation and structural alterations during cell division. It is a hallmark of most solid tumours and haematological malignancies and manifests as both numerical changes (aneuploidy) and structural rearrangements (translocations, deletions, duplications). CIN arises from defects in mitotic spindle assembly, kinetochore-microtubule attachments, centrosome amplification, and cohesion fatigue (Bakhoum & Compton, 2012).

Aberrant mitotic progression in CIN-positive cells often stems from weakened or overridden spindle assembly checkpoint (SAC) signals. Incomplete kinetochore attachments, if uncorrected, can lead to lagging chromosomes, chromatin bridges, and micronuclei formation. These structures are prone to nuclear envelope rupture and catastrophic DNA fragmentation, as seen in chronotherapies, a phenomenon where a single mitotic error can result in tens to hundreds of rearrangements in a localised genomic region (Zhang et al., 2015).

Although high levels of CIN are associated with tumour heterogeneity and adaptability, they also pose fitness costs. Excessive CIN can lead to mitotic catastrophe or immune detection via cytosolic DNA sensing pathways like cGAS-STING. Thus, tumours maintain CIN within a tolerable range to balance adaptability with viability (Santaguida & Amon, 2015).

Tolerance of Spindle Assembly Checkpoint Disruption

The SAC ensures temporal fidelity in mitosis by delaying anaphase onset until all kinetochores are bi-oriented on the mitotic spindle. Core SAC components—including MAD1, MAD2, BUB1, BUB3, and BUBR1—form a mitotic checkpoint complex that inhibits CDC20, a co-activator of the APC/C. In cancer, SAC regulators are frequently overexpressed or mutated, leading to prolonged mitosis or premature anaphase, respectively (Ryan et al., 2012).

Paradoxically, SAC overexpression may reflect a compensatory adaptation to other mitotic defects. For instance, increased MAD2 levels correlate with enhanced tolerance to microtubule poisons but also with elevated aneuploidy and poor prognosis in several cancers. Conversely, partial loss of SAC function reduces mitotic duration and increases segregation errors, contributing to the generation of diverse karyotypes from a single progenitor clone (Li & Murray, 2011).

Targeting SAC regulators is an emerging therapeutic strategy. Inhibitors of MPS1 (TTK), a kinase essential for SAC activation, induce premature mitotic exit and chromosome missegregation in cancer cells, pushing CIN beyond sustainable limits. Clinical trials of MPS1 inhibitors are ongoing in tumours with high baseline CIN or TP53 deficiency (Tardif et al., 2021).

CIN as a Driver of Therapy Resistance and Immune Modulation

CIN-driven tumour evolution facilitates adaptation to cytotoxic therapies and targeted agents. Subclonal karyotypic heterogeneity allows for rapid selection of resistant populations. Moreover, CIN influences immune recognition: micronuclei-derived DNA activates the cGAS-STING axis, leading to interferon responses that can either promote immune surveillance or drive immune evasion depending on the context (Mackenzie et al., 2017).

CIN also creates opportunities for synthetic lethality. For example, cells with elevated replication stress and chromosomal missegregation depend heavily on spindle checkpoint proteins and mitotic DNA damage response pathways. Exploiting these dependencies via dual targeting of SAC components and replication stress mediators holds promise in high-CIN tumours.

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