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Colonization of *Staphylococcus aureus* in nasal cavities of food handlers in a military setting[a]

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ABSTRACT

Aims: The anterior nares constitute the primary ecological reservoir for *Staphylococcus aureus* (*S. aureus*) in healthy individuals, with hands serving as the principal vectors for transmission. This study aimed to determine the prevalence of nasal *S. aureus* carriage and evaluate occupational risk factors among military personnel employed in food handling, personal care, and service delivery roles.

Methods: A retrospective analytical cross-sectional study was conducted on 1,036 healthy male service personnel who presented to family medicine outpatient clinics in Ankara. Nasal swabs were cultured for *S. aureus*, and isolates were classified as methicillin-susceptible (MSSA) or methicillin-resistant (MRSA). Demographic variables and occupational sectors (service personnel, food preparation, and personal care) were recorded. Positive carriers received targeted topical antimicrobial treatment. Statistical analyses were performed using IBM SPSS v25.0, with significance defined as $p<0.05$. Chi-square tests were utilized to assess associations, and 95% confidence intervals (CI) were provided for prevalence rates and odds ratios.

Results: The cohort median age was 21 years (IQR=4.0). Overall nasal colonization with *S. aureus* was 15.1% (n=156). MSSA prevalence was 14.1% (n=146) while MRSA was identified in 1.0% (n=10) of the sample, exclusively among catering personnel. Occupational sector was a significant predictor of nasal carriage ($\chi^2=22.635$, $p<0.001$), with service delivery staff exhibiting increased odds of colonization (OR=3.307, 95% CI: 2.152-5.081).

Conclusion: In this military cohort, moderate *S. aureus* colonization contrasted with infrequent MRSA carriage. However, the elevated risk in specific sectors necessitates targeted infection control. Despite debates over universal screening, these findings justify continued surveillance and decolonization for specialized military food service personnel to mitigate transmission and safeguard public health.

Keywords: *Staphylococcus aureus,* carrier state, military personnel, food handling, methicillin-resistant *Staphylococcus aureus,* MSSA

[a]This paper was presented as an oral presentation at the 18th National Family Medicine Congress, October 31–November 2, 2019, Ankara, Turkiye

INTRODUCTION

Staphylococcus aureus (S. aureus) is the most common potentially pathogenic bacterium that may asymptomatically colonize and lead to carriage in many sites of healthy individuals. While several factors contributing to nasal carriage of *S. aureus* have been identified, it is clear that host-related determinants alone are insufficient to explain the observed inter-individual variations.[1] The nasal cavity is the primary ecological niche for *S. aureus*, thus positioning it as a key site for potential transmission. A number of risk factors have been identified in relation to nasal carriage of *S. aureus*, including male gender, advanced age, alcohol consumption, diabetes mellitus, atopic dermatitis, HIV seropositivity, hospitalization, surgery, antibiotic use, and certain occupations, such as healthcare workers and veterinarians.[1-3] Collective living environments (e.g. military institutions, kindergartens, dormitories) are considered risk factors for nasal carriage and human-to-human transmission.[1-3] Durupt et al.[4] also state that skin conditions like furuncles and impetigo are significant risk factors for recurrent nasal colonization, affecting approximately 60% of those affected.

S. aureus is a cause for concern due to its virulence factors, which cause uncomplicated skin infections and more severe pathologies, such as osteomyelitis and endocarditis.[5-7] Approximately 30% of the population has *S. aureus* in

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their nose, which can lead to more serious infections.[8] There is also a higher rate of *Staphylococcus* in adults, particularly among hospitalized adults.[9] It is important to note that nasal decolonization of *S. aureus* is recognised as an effective strategy for preventing invasive infections, particularly when performed prior to surgery.[10,11] While detection and eradication of the bacterium can be beneficial for persistent carriers this approach may not be suitable for healthy populations. MRSA can lead to food contamination and poisoning, so food handlers should be screened before employment and regularly during their tenure.[12] Anterior nasal swab sampling is considered practical and cost-effective for detecting *S. aureus* colonization. However, while real-time polymerase chain reaction (PCR) for MRSA in nasal swabs is considered a reliable diagnostic tool, the WHO has concluded that preemployment medical examinations and periodic screenings are often unnecessary in general civilian settings.[13,14] Studies suggest that health status influences *S. aureus* nasal bacterium composition.[15,16] However, data on *S. aureus* nasal colonization in healthy workers is limited.[17,18] A baseline is crucial for studying community colonization. This analytical cross-sectional study assessed *S. aureus* carriage in the nares of healthy food handlers in a military setting, focusing specifically on occupational sectors and age as potential determinants.

METHODS

Ethics

This study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Researches Hospital, University of Health Sciences (Date: 10.09.2018, Decision No: 54/21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

This retrospective analytical cross-sectional study was performed to isolate and characterize *S. aureus* isolates. The population consisted of military personnel who presented at the Family Medicine Outpatient Clinic of Dışkapı Yıldırım Beyazıt Training and Researches Hospital, University of Health Sciences for bacterium carrier screening. Of the 1,656 participants who were examined over a period of six months, 1,036 individuals were included in the study as they met the following inclusion criteria: the absence of any known chronic disease, no history of hospitalization within the past month, and no current upper respiratory tract infection at the time of swab collection. All participants were employed in the food, personal care, or service delivery sectors within military units in Ankara, and some were employment applicants.

Isolation and Characterization of *S. aureus*

S. aureus carriage was assessed by swabs taken from the anterior nares. The medical records of all participants were included in the national carrier examination procedure: physical examination, X-ray findings, stool culture, and nasal swab screening. Only the nasal isolate results were evaluated in the present study. The bacterium samples were collected from the participants' anterior nasal mucosa using sterile cotton-tipped swabs with transport media. The blood agar was inoculated using the laboratory reduction method. The samples were incubated at 35-37°C for 16 to 24 hours, after which colony growth was assessed by microbiologists.

In this study, *S. aureus* strain ATCC 33862 was used as the reference strain. The isolates were identified based on colony morphology, Gram stain appearance, and positivity for catalase and coagulase tests. Creamy-yellow, beta-hemolytic colonies were considered "suspect *S. aureus*." Gram-positive colonies with positive catalase and coagulase tests were identified as *S. aureus*. Methicillin resistance was tested using Mueller-Hinton agar (bioMérieux, Marcy-l'Étoile, France) with a cefoxitin disk. A 30 µg cefoxitin disk (Oxoid, Basingstoke, UK) was placed on the medium and incubated at 35°C for 24 hours. Colonies with a zone diameter ≤21 mm were considered methicillin-resistant. Antibiotics tested included erythromycin, clindamycin, gentamicin, vancomycin, teicoplanin, and trimethoprim-sulfamethoxazole (Oxoid). All results were analyzed according to EUCAST guidelines.

A retrospective review of the culture results of nasal isolates obtained by this method was conducted over a six-month period. The results were categorized into normal and pathogenic (MRSA and MSSA) groups. The normal bacterium flora included *Streptococcus*, *Corynebacterium*, *Propionibacterium*, *Acinetobacter*, and others. Participants (n=156) with pathogenic bacterium growth on the initial nasal culture were treated topically with mupirocin, and a follow-up nasal culture was performed after 10 days.

Statistical Analysis

The nasal isolates of the staff sector were evaluated using frequency and percentage values. As the data did not follow a normal distribution, the descriptive statistics of the age variable were presented as median (interquartile range). The differences between the categorical variables were examined using the Chi-square test and Fisher's exact test when indicated. The 95% confidence intervals (CI) for prevalence rates and ratios were calculated. A p-value<0.05 was deemed significant, and values below 0.001 were reported as p<0.001. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

RESULTS

The study cohort comprised 1,036 healthy male participants, with a mean (±SD) age of 24.1 (±6.8) years and a median age of 21 years (range: 19–55). The vast majority (n=948, 91.5%) consisted of service delivery personnel stationed within military dining facilities, including restaurants, cafés, and canteens. Microbiological analysis revealed that 880 participants (84.9%, 95% CI: 82.7-87.1) exhibited only commensal nasal microflora and were consequently classified as uncolonized. Regarding pathogenic isolates, methicillin-sensitive *S. aureus* (MSSA) was identified in 146 individuals (14.1%, 95% CI: 12.0-16.2), whereas methicillin-resistant *S. aureus* (MRSA) was detected in a small proportion of the sample (n=10, 1.0%, 95% CI: 0.4-1.6) (**Figure**). MSSA prevalence was notably higher among food preparation staff (16.7%) and catering personnel (14.1%), groups identified as having more direct contact with food (**Table 1**). Statistical evaluation across four age-defined subgroups demonstrated no significant discrepancy in colonization rates (Kruskal-Wallis: 1.561, p=0.458) (**Table 2**). Participants harboring pathogenic nasal isolates underwent a five-day therapeutic regimen of topical mupirocin. Subsequent follow-up cultures yielded negative results for all pathogens, confirming the successful eradication of carriage.

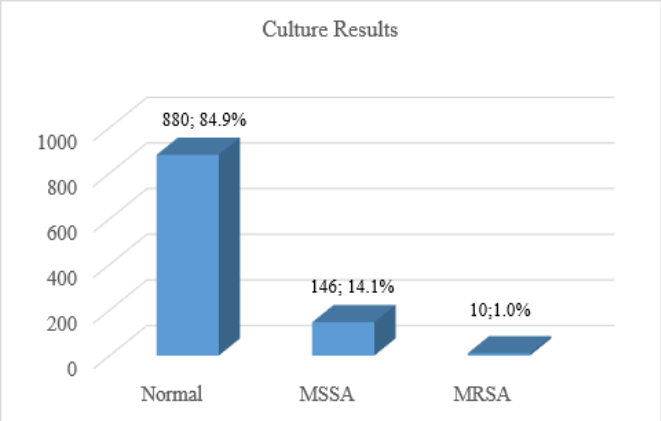


Figure. Number of cases with nasal carriage
MSSA: Methicillin-susceptible *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*

Table 1. Prevalence of nasal methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) carriage among healthy males in military units

Characteristics	Normal n (%)	MSSA n (%)	MRSA n (%)	Total (n)	χ2, p*
Age groups					
≤20	256 (85.6)	39 (13.0)	4 (1.3)	299	
21-30	534 (84.6)	92 (14.6)	5 (0.8)	631	3.149; 0.790
31-40	39 (90.7)	4 (9.3)	0 (0.0)	43	
41-55	51 (81.0)	11 (17.5)	1 (1.6)	63	
Sector					
Food preparation	55 (83.3)	11 (16.7)	0 (0.0)	66	
Hairdresser	21 (95.5)	1 (4.5)	0 (0.0)	22	2.971; 0.563
Catering personnel	804 (84.8)	134 (14.1)	10 (1.1)	948	
Total	880 (84.9)	146 (14.1)	10 (1.0)	1036	

MSSA: Methicillin-susceptible *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*, χ^2: Chi-square, *Pearson Chi-square

Table 2. Distribution of S. aureus growth in culture

Culture result	Mean (SD)	Median (IQR 25-75)	χ2, p*
Normal	24.0 (7.0)	21.0 (20.0-25.0)	
MSSA	25.0 (8.0)	21.0 (20.0-25.0)	1.561; 0.458
MRSA	24.0 (9.0)	21.0 (20.0-21.0)	

SD: Standard deviation, IQR: Interquartile range, χ^2: Chi-square, p*: Kruskal-Wallis, MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*

DISCUSSION

The main result of this study delineates a significant microbiological landscape within the military food-service sector, characterized by a substantial reservoir of MSSA colonization (14.1%) alongside a conspicuously low prevalence of MRSA (1.0%). Our results provide evidence of an MSSA burden among food preparation cohorts, while demonstrating that targeted topical intervention can effectively achieve total eradication of pathogenic carriage. The prevalence of *S. aureus* isolation among workers in military units was found to be 14.1%, a result comparable to those reported in Eastern Ethiopia (15.6%), Nepal (15.7%), and the Democratic Republic of Congo (16.5%).[19-21] However, a multicentre study across nine European countries reported a global prevalence of *S. aureus* nasopharyngeal colonization at 21.6% and in healthy males in Pakistan at 20.5%.[17,22] In addition, the prevalence of *S. aureus* nasal carriage among the community individuals was on average 16.78% in China.[18] In this study, it was determined that the carrier rate was lower than in studies conducted on comparable sample groups. This discrepancy can be attributed to the implementation of pre-employment carrier screening of food handlers in our country, followed by the continuation of regular annual screening. Additionally, the tightly controlled nature of military environments may have contributed to a lower prevalence compared to other community dwellings.

A study conducted in Beijing reported that the prevalence of *S. aureus* nasal carriage among military personnel ranged from 16.1% to 24.6%. Consistent with our findings, MSSA was the predominant isolate.[23] MRSA bacteremia is associated with significantly higher rates of severe and potentially fatal infections compared to MSSA bacteremia.[24] In this study, MRSA prevalence was reported at 1.0%, exclusively among individuals working in catering-related professions. This aligns with research from Peru and China documenting low or zero MRSA carriage among military personnel.[23,25] In contrast, higher MRSA prevalence rates (11.2% to 21.9%) have been reported among healthcare workers. The highest nasal carriage rate was reported among nurses (7.8%).[19-21] These variations in prevalence may be attributable to differences in geographic regions, sample sizes, study periods, and characteristics of the populations studied. It is worthy of note that studies reporting elevated prevalence frequently focus on individuals with heightened occupational exposure to bacterium colonization, a factor that may account for these results.

The study found that MSSA prevalence was highest in the food preparation department, whereas MRSA was exclusively identified among a small number of individuals employed in catering roles. This suggests a potential role for service departments in military environments regarding food contamination.

While some literature suggests that routine screening of healthy populations may not always yield clinically significant outcomes that are commensurate with the associated economic burden,[14,26] the specific context of congregate living and food service in military institutions warrants a different approach. Although universal active surveillance in all at-risk groups is debated, the findings of this study support the utility of targeted screening within high-risk occupational sectors like military food service to prevent potential outbreaks.[27] A prospective cohort study involving military personnel indicated that although nasal colonization resulted in a relatively low incidence of self-reported soft-tissue infections (3%), the role of healthy carriers—whether persistent or intermittent—in the horizontal transmission of pathogens to susceptible individuals is well-established.[28] Based on these findings, it is rational to include military food service personnel in routine screening and follow-up programs.

Various therapeutic modalities have been employed to prevent permanent colonization, most notably the application of intranasal mupirocin ointment (2%) b.i.d. for a duration of 5–10 days, augmented by daily chlorhexidine body washes. These aim to prevent recurrent skin and soft tissue

infections, as well as nosocomial MRSA infections.[14,29] In the present study, 156 participants with *S. aureus* colonization in nasal culture received local treatment with mupirocin and nasal isolates were repeated after 10 days. Furthermore, as observed by Hirabayashi et al.[30] The prevalence of MRSA in clinical isolates experienced a significant decline during the SARS-CoV-2 pandemic. The observed decline likely reflects the efficacy of the robust prophylactic measures instituted to halt viral spread. This underscores the notion that, even during pandemics, infection control and self-hygiene are key protection methods against *S. aureus*, as with other communicable diseases. These strategies are crucial for reducing infections and strengthening public health within organized institutions.

Limitations

This study assessed *S. aureus* colonization among military food handlers. However, the reliance on a single nasal culture represents a significant methodological constraint, potentially obscuring the true prevalence of both MRSA and MSSA. Furthermore, the retrospective analytical cross-sectional design and the exclusively military sample may limit the generalizability of the results to broader civilian populations. Although the objective of the study was to assess risk factors, only occupational group and age were analyzed, the omission of other potential risk factors has been formally acknowledged as a study limitation. A notable limitation of the present study is that, since it was conducted exclusively among military personnel, it was only feasible to report the rates of MRSA and MSSA nasal carriage in men. Consequently, it is not possible to generalise the results to the general population.

CONCLUSION

Consequently, the continuation of screening for personnel assigned to provide services in specialized settings, such as military institutions, is deemed appropriate to maintain low colonization rates and prevent transmission. While universal screening in all healthy populations is debated, a targeted and effective surveillance protocol in food-handling sectors provides a rational approach. This strategy optimizes resource management while ensuring effective control measures and optimal health outcomes in high-density living environments.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Researches Hospital (Date: 10.09.2018, Decision No: 54/21).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The author declare no conflicts of interest related to this study.

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Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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Relationship between caregiver burden and levels of depression, anxiety, and stress among palliative care caregivers

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ABSTRACT

Aims: To assess the relationship between caregiver burden and levels of depression, anxiety, and stress among primary caregivers of patients hospitalized in a palliative care unit.

Methods: In this descriptive cross-sectional study, 96 primary caregivers were enrolled. Data were obtained through face-to-face interviews using a sociodemographic data form, the 19-item Zarit Caregiver Burden Interview (ZBI-19), and the Depression Anxiety Stress Scale-21 (DASS-21). Nonparametric group comparisons were conducted with the Mann–Whitney U test and the Kruskal–Wallis test, followed by appropriate post-hoc pairwise analyses when needed. Relationships between variables were assessed using Spearman's rank correlation. Factors independently associated with caregiver burden were examined using multiple linear regression models.

Results: Participants were predominantly female (72.9%), married (72.9%), and unemployed (58.3%), with a mean age of 52.2±11.7 years. Moderate-to-extremely severe symptoms were observed in 29.2% for depression, 39.6% for anxiety, and 18.8% for stress. Moderate-to-severe and severe caregiver burden was present in 33.3%. Female gender was associated with higher depression and anxiety scores, whereas unemployment, lower education, and lower income level were associated with higher psychological distress and higher caregiver burden ($p<0.05$). In multivariable analysis, higher depression scores ($p<0.001$) and longer caregiving duration ($p=0.050$) were independently associated with increased caregiver burden, explaining nearly half of the variance in burden scores.

Conclusion: Primary caregivers in palliative care experience substantial psychological distress and caregiver burden, particularly those with socioeconomic vulnerabilities. Depression severity and caregiving duration are key factors associated with caregiver burden, highlighting the need for routine screening and targeted psychosocial support in clinical practice.

Keywords: Palliative care, caregivers, caregiver burden, depression, anxiety, stress; psychologica

INTRODUCTION

Palliative care is a holistic model of care that focuses on the early recognition, comprehensive assessment, and effective management of physical, psychological, social, and spiritual problems arising in the course of life-threatening illness.[1] The World Health Organization (WHO) defines palliative care as a multidisciplinary approach intended to improve quality of life for patients and their families through the prevention and relief of pain and other distressing symptoms.[1] Core principles include affirming life, acknowledging dying as a natural process, and neither hastening nor postponing death, while supporting patients to live as actively and comfortably as possible.[2] As the burden of chronic and advanced illnesses increases, palliative care has become an essential component of contemporary health services.[3]

Progressive chronic disease is often accompanied by functional decline and challenges in cognitive and psychological adjustment, which can increase the need for sustained and structured care.[4] In many settings, this care is largely provided by family members—most commonly spouses, adult children, or close relatives—within an informal caregiving role.[5] Although caregiving is frequently framed as a natural family responsibility, it may substantially reshape daily routines and social roles, and it can also create financial strain, particularly when care is prolonged or intensive.[6,7]

A key concept in this context is caregiver burden, commonly understood as the multidimensional strain experienced while providing ongoing care to a dependent or chronically

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ill person, affecting the caregiver's physical capacity, emotional balance, social relationships, and economic resources.[8,9] Caregiver burden is therefore not limited to physical fatigue; it may include emotional exhaustion, social isolation, role conflict, and economic pressure.[9] Evidence syntheses consistently indicate that higher caregiver burden is associated with greater symptoms of depression and anxiety among informal caregivers.[10] Findings from studies conducted in palliative care and other high-dependency conditions also suggest that psychological distress among caregivers is common and may persist over time.[11]

Although caregiver burden and psychological distress have been widely studied in oncology and dementia settings, data from inpatient palliative care units—particularly in middle-income countries—remain limited. Moreover, few studies have simultaneously examined depression, anxiety, stress, and caregiving duration within a multivariable framework to identify factors independently associated with caregiver burden. Against this background, the present study aimed to examine the relationship between caregiver burden and levels of depression, anxiety, and stress among primary caregivers of patients hospitalized in a tertiary palliative care unit. The results are expected to support the early identification of caregivers at higher risk and to inform the development of targeted psychosocial support strategies within palliative care teams.

METHODS

This study was approved by the Clinical Researches Ethics Committee of the University of Health Sciences, İzmir Bozyaka Training and Research Hospital (Date: 06.02.2025, Decision No: 2025/12). All procedures were conducted in accordance with ethical guidelines and the principles of the Declaration of Helsinki.

A descriptive cross-sectional design was implemented at the Palliative Care Center, University of Health Sciences İzmir Bozyaka Training and Research Hospital (İzmir, Turkiye), between February and May 2025.

The study population comprised primary caregivers—both informal (family) caregivers and paid caregivers—who were primarily responsible for the care of patients hospitalized in the palliative care unit during the study period. The sample included caregivers who met the eligibility criteria and agreed to participate voluntarily.

An a priori power analysis was conducted in G*Power (version 3.1.9.7) to estimate the sample needed to detect a correlation between Zarit caregiver burden and Depression–Anxiety–Stress scores. Based on an anticipated effect size of r=0.35, a two-sided α=0.05, and power of 0.90, at least 78 participants were required. Allowing for potential attrition and incomplete questionnaires, 96 primary caregivers were enrolled, and the study was finalized with this cohort.[12]

Adults (≥18 years) who could read and understand Turkish, had sufficient cognitive capacity to complete the questionnaires, and had no severe psychiatric condition that would preclude participation were eligible. Participants were required to be the patient's primary caregiver during hospitalization and to provide written informed consent. Individuals were excluded if they were <18 years old, were unable to read/write Turkish, had marked cognitive impairment or communication/behavioral problems that interfered with data collection, or declined consent.

Dependent variables were: total and subscale scores of the Zarit Caregiver Burden Interview (ZBI-19) and the mean subscale scores of the Depression Anxiety Stress Scale–21 (DASS-21) (depression, anxiety, stress). Independent variables included caregiver age, gender, marital status, education, employment, income level, relationship to the patient, caregiving duration (months), sharing caregiving responsibilities and presence of caregiver health problems.

Data were collected through face-to-face interviews conducted by the researcher at the palliative care unit. Each participant completed (i) a descriptive information form, (ii) ZBI-19, and (iii) DASS-21. The descriptive information form was developed based on relevant caregiving literature and included sociodemographic characteristics and caregiving-related variables.[13,14]

The form captured caregiver sociodemographic features (age, gender, marital status, education, income, employment), caregiving characteristics (duration of caregiving, relationship to the patient, receiving support in caregiving, caregiver comorbidity), and selected patient-related information (indication for admission and dependency level), consistent with prior caregiver research.[13,14]

Caregiver burden was assessed using the 19-item Turkish short form of the ZBI-19. Items are rated on a 0 ("never") to 4 ("nearly always") scale, summed to yield a total score (0–76), with higher scores indicating greater burden. Burden severity was categorized as 0–17 (none/very mild), 18–35 (mild), 36–52 (moderate), and ≥53 (severe). In addition to the total score, we examined burden across the validated five-factor structure: psychological strain/disruption of private life (items 2, 3, 10, 11, 12, 17, 19), irritability/restriction (items 5, 9, 22), deterioration in social relations (items 6, 13, 18), economic burden (items 7, 15, 20, 21), and dependency (items 8, 14). Three items from the original pool (1, 4, 16) were not assigned to any subscale in the Turkish validation; therefore, subscale analyses were based on the 19-item structure.[15,16] In the present sample, internal consistency of the ZBI-19 total scale was good (Cronbach's α=0.862).

Psychological symptom severity was assessed with the Depression Anxiety Stress Scale-21 (DASS-21), Scores were calculated for three symptom dimensions (depression, anxiety, and stress), each derived from seven items answered on a four-point response format (0–3). To align scoring with the full-length DASS (42-item) framework, each subscale total was rescaled by a factor of two, and standard severity cut-offs from the original scoring scheme were applied.[17,18] In the present sample, internal consistency was acceptable to good across the three subscales (Cronbach's α: depression=0.851, anxiety=0.812, stress=0.856).

Statistical Analysis

The data procedures were performed using IBM SPSS Statistics for Windows, version 27.0. Descriptive statistics are reported as mean and standard deviation for variables showing an approximately normal distribution, and as median with interquartile range [Q1–Q3] for non-normally distributed variables. Categorical data are summarized as

counts and percentages. Normality was evaluated by visual inspection of histograms and by examining skewness and kurtosis values.

For comparisons between two independent groups, the independent-samples t test was applied when distributional assumptions were satisfied; otherwise, the Mann–Whitney U test was used. For comparisons involving three or more groups, one-way ANOVA was used under normality and the Kruskal–Wallis test otherwise. When the Kruskal–Wallis test indicated a significant difference, Bonferroni-adjusted pairwise comparisons were conducted to determine which groups accounted for the overall effect.

Associations between categorical variables were assessed using the Chi-square test; Fisher's exact test or the Fisher–Freeman–Halton exact test was used when expected cell counts were low. Relationships between continuous/ordinal variables were examined using Spearman's rank-order correlation (ρ). To identify factors independently associated with caregiver burden, a multiple linear regression model was constructed with the ZBI total score as the dependent variable. Given the modest sample size (n=96), we restricted the number of independent variables to minimize model overfitting. Therefore, only variables showing statistically significant associations with caregiver burden in univariate analyses ($p<0.05$ in group comparisons and/or correlation analyses) were selected as candidate variables and entered into the multivariable model. The final model included depression, anxiety, stress (DASS-21 subscale scores), caregiving duration (months), caregiver relationship (0=first-degree family member, 1=paid caregiver), prior caregiving experience (0=no, 1=yes), and income status (1=income<expenses, 2=income=expenses, 3=income>expenses). All selected variables were entered simultaneously using the Enter (forced-entry) method to obtain fully adjusted estimates. Regression results are reported as unstandardized coefficients (B) and standardized coefficients (β) with 95% confidence intervals, along with R^2/adjusted R^2 and p values. Multicollinearity was evaluated using variance inflation factors (VIF). Model assumptions were checked by inspecting residual histograms, normal probability plots, and standardized residuals versus standardized predicted values. A two-sided p value <0.05 was considered statistically significant.

RESULTS

A total of 96 primary caregivers were included in the study. The mean age of the participants was 52.2±11.7 years, and the median caregiving duration was 2.5 months [Q1–Q3: 1.0–10.5]. The majority of caregivers were female (72.9%), married (72.9%), and unemployed (58.3%). Regarding the relationship to the patient, 56.3% were adult children, whereas 22.9% were paid caregivers. Two-thirds of the participants reported receiving support in caregiving (66.7%), and 52.1% were providing care for the first time (Table 1).

Based on the DASS-21 severity categories, most caregivers were within the normal range for depression (66.7%), anxiety (54.2%), and stress (70.8%). Nevertheless, moderate-to-extremely severe symptom levels were prevalent, observed in 29.2% of the participants for depression, 39.6% for anxiety, and 18.8% for stress. Regarding caregiver burden (ZBI-19), 18.8% reported little to no burden, 47.9% had mild-to-moderate burden, 25.0% experienced moderate-to-severe burden, and 8.3% indicated severe burden (Table 2).

Table 1. Sociodemographic and caregiving characteristics of the participants (n=96)

Variable	Category	n (%)
Age (years)	Mean±SD	52.2±11.7
Caregiving duration (months)	Median (Q1-Q3)	2.5 (1.0-10.5)
Gender	Female	70 (72.9)
	Male	26 (27.1)
Education level	Literate	8 (8.3)
	Primary school	24 (25.0)
	Middle school	10 (10.4)
	High school	24 (25.0)
	Bachelor's degree	26 (27.1)
	Postgraduate (master's/PhD)	4 (4.2)
Marital status	Married	70 (72.9)
	Single	26 (27.1)
Employment status	Employed	40 (41.7)
	Unemployed	56 (58.3)
Income perception	Income less than expenses	22 (22.9)
	Income equal to expenses	62 (64.6)
	Income more than expenses	12 (12.5)
Relationship to patient	Spouse	14 (14.6)
	Child	54 (56.3)
	Sibling	6 (6.3)
	Paid caregiver	22 (22.9)
Support in caregiving	Yes	64 (66.7)
	No	32 (33.3)
Caregiving experience	Previous experience	46 (47.9)
	First-time caregiver	50 (52.1)

Values are presented as mean±standard deviation (SD) for age and as median [Q1–Q3] for caregiving duration; all other variables are shown as n (%). Percentages may not total 100% due to rounding.

Comparisons of psychological distress and caregiver burden according to caregiver characteristics are detailed in Table 3. Female caregivers exhibited significantly higher depression and anxiety scores compared to males (p=0.041 and p=0.012, respectively), whereas stress and ZBI-19 total scores did not differ significantly by gender.

Education level was significantly associated with depression (p=0.017) and anxiety (p=0.006), but not with stress (p=0.483) or caregiver burden (p=0.092). Bonferroni-adjusted pairwise comparisons revealed that caregivers with primary school education or below had significantly higher depression scores than those with secondary–high school education (adjusted p=0.014), and higher anxiety scores than both secondary–high school (adjusted p=0.027) and university or above groups (adjusted p=0.011).

Unemployed caregivers reported significantly higher depression (p<0.001), anxiety (p=0.001), and stress scores (p=0.003) than employed caregivers, whereas caregiver burden did not differ significantly by employment status (p=0.182).

Income perception was significantly associated with all three DASS-21 subscales and caregiver burden (depression: p=0.005, anxiety: p=0.003, stress: p=0.002, ZBI-19: p=0.033). Bonferroni-adjusted pairwise comparisons indicated that caregivers reporting income less than expenses had

Table 2. Severity levels of depression, anxiety, stress, and caregiver burden (n=96)

Scale/domain	Category	n (%)
Depression (DASS-21)	Normal (0–9)	64 (66.7)
	Mild (10–13)	4 (4.2)
	Moderate (14–20)	18 (18.8)
	Severe (21–27)	2 (2.1)
	Extremely severe (≥28)	8 (8.3)
Anxiety (DASS-21)	Normal (0–7)	52 (54.2)
	Mild (8–9)	6 (6.3)
	Moderate (10–14)	18 (18.8)
	Severe (15–19)	8 (8.3)
	Extremely severe (≥20)	12 (12.5)
Stress (DASS-21)	Normal (0–14)	68 (70.8)
	Mild (15–18)	10 (10.4)
	Moderate (19–25)	6 (6.3)
	Severe (26–33)	6 (6.3)
	Extremely severe (≥34)	6 (6.3)
Caregiver Burden (ZBI)	Little or no burden (0–17)	18 (18.8)
	Mild to moderate burden (18–35)	46 (47.9)
	Moderate to severe burden (36–52)	24 (25.0)
	Severe burden (53–76)	8 (8.3)

Severity cut-offs were adapted from conventional ZBI-22 thresholds by proportional rescaling to the ZBI-19 total score range (0–76). DASS-21: Depression Anxiety Stress Scale 21, ZBI: Zarit Caregiver Burden Interview

significantly higher depression (adjusted p=0.004) and anxiety scores (adjusted p=0.006) than those reporting income equal to expenses, and higher caregiver burden than the income-equal-to-expenses group (adjusted p=0.032). For stress, caregivers reporting income greater than expenses had significantly higher scores than those reporting income equal to expenses (adjusted p=0.004).

Family caregivers reported significantly higher depression (p<0.001), anxiety (p=0.008), stress (p=0.003), and caregiver burden (p=0.001) than paid caregivers. First-time caregivers experienced significantly higher stress (p=0.027) and caregiver burden (p=0.039) than those with prior caregiving experience (Table 3).

Overall, total ZBI was positively associated with psychological distress, showing a moderate correlation with total DASS-21 (ρ=0.64, p<0.001) and the strongest correlation with depression (ρ=0.71, p<0.001); correlations with anxiety (ρ=0.51, p<0.001) and stress (ρ=0.56, p<0.001) were also significant. At the subscale level, F1 was most strongly related to depression (ρ=0.66, p<0.001), F4 showed the strongest link with anxiety (ρ=0.59, p<0.001), and F5 was modestly associated with DASS total (ρ=0.36, p<0.01) and stress (ρ=0.43, p<0.001); weaker but significant correlations were observed for F3–stress (ρ=0.22, p<0.05), F5–anxiety (ρ=0.23, p<0.05), and F5–F3 (ρ=0.26, p<0.05) (Table 4).

Table 3. Comparison of depression, anxiety, stress, and total caregiver burden by caregivers' characteristics

Variable	Group	n	Depression	Anxiety	Stress	ZBI-19
Gender	Female	70	6 (2–14)	10 (2–16)	10 (2–18)	32.3±14.6
	Male	26	2 (1.5–9)	4 (2–6)	6 (1.5–16)	27.5±13.4
p			0.041†	0.012†	0.233†	0.140‡
Education	Primary school or below[a]	32	10 (4–19.5)	12 (6.5–16)	14 (2–21)	34.9±16.3
	Secondary–high school[b]	34	2 (2–11)	4 (2–10)	8 (3.5–16.5)	27.2±13.9
	University or above[c]	30	4 (2–8)	4 (0–14)	6 (2–14)	31.3±14.4
p			0.017§	0.006§	0.483§	0.092¶
Between-group differences			a>b	a>b,c	—	—
Marital status	Married	70	4 (2–14)	6 (2–14)	8 (2–15)	32.0±13.2
	Single	26	4 (2–15)	6 (2–9)	12 (2–18)	28.5±17.1
p			0.653†	0.702†	0.921†	0.290‡
Employment	Employed	40	2 (0–7.5)	3 (0–9)	4 (2–12.5)	28.7±12.8
	Unemployed	56	8 (2–18)	9 (2.5–15.5)	12 (5–18)	32.7±15.3
p			<0.001†	0.001†	0.003†	0.182‡
Income level	Income<expenses[a]	22	12 (6–18)	10 (6–14)	14 (4–16)	40 (25–49)
	Income=expenses[b]	62	4 (2–8)	4 (2–12)	6 (2–12)	28 (18–43)
	Income>expenses[c]	12	11 (2–20)	15 (2–26)	16 (14–28)	26 (23–33)
p			0.005§	0.003§	0.002§	0.033§
Between-group differences			a>b	a>b	c>b	a>b
Caregiver type	Family caregiver	74	8 (3–15)	8 (2–14.5)	12 (3.5–18)	33.5±14.4
	Paid caregiver	22	2 (0–4)	2 (0–6)	4 (0–8)	22.6±10.9
p			<0.001†	0.008†	0.003†	0.001‡
Support in caregiving	Has support	64	4 (2–13)	6 (2–15.5)	7 (2–18)	29.2±13.8
	No support	32	8 (4–14)	7 (2–13.5)	10 (5–15.5)	34.7±15.0
p			0.060†	0.888†	0.261†	0.092‡
Prior caregiving experience	Yes	46	4 (2–14)	4 (2–10)	8 (0–14)	27.8±16.5
	First-time caregiver	50	8 (3.5–14)	8 (2–14.5)	12 (3.5–19)	34.0±11.5
p			0.051†	0.249†	0.027†	0.039‡

Values are median [Q1–Q3] for DASS-21 and mean±SD for ZBI-19 [income: median [Q1–Q3]]. DASS-21: Depression Anxiety Stress Scale 21, ZBI: Zarit Caregiver Burden Interview, SD: Standard deviation, †: Mann–Whitney U, ‡: t test, §: Kruskal–Wallis, ¶: one-way ANOVA. Bonferroni adjustment was applied for pairwise comparisons when applicable. p<0.05 was considered significant

Table 4. Spearman correlations between DASS-21 and the Zarit Caregiver Burden Scale (ZBI) and its subscales

Variable	DASS-21	D	A	S	ZBI-19	F1	F2	F3	F4	F5
DASS-21	1.00									
D	**0.87**	1.00								
A	**0.87**	**0.67**	1.00							
S	**0.91**	**0.74**	**0.66**	1.00						
ZBI-19	**0.64**	**0.71**	**0.51**	**0.56**	1.00					
F1	**0.52**	**0.66**	0.33	**0.48**	**0.88**	1.00				
F2	**0.38**	**0.49**	0.30	0.31	**0.81**	**0.74**	1.00			
F3	**0.33**	**0.43**	**0.32**	0.22	**0.75**	**0.60**	**0.57**	1.00		
F4	**0.55**	**0.43**	**0.59**	**0.45**	**0.46**	0.13	0.17	0.33	1.00	
F5	**0.36**	0.37	0.23	**0.43**	**0.61**	**0.54**	**0.55**	0.26	0.02	1.00

Note: Cells present Spearman's ρ coefficients. Bold values are significant at p<0.01, italic values are significant at p<0.05, remaining coefficients are not statistically significant. Abbreviations: DASS-21: Depression Anxiety Stress Scale-21 Total Score, ZBI-19: Zarit Caregiver Burden Interview Total Score, D: Depression, A : Anxiety, S: Stress. ZBI subscales: F1: Psychological strain/private life, F2: Irritability/restriction, F3: Impairment in social relationships, F4: Economic burden, F5: Dependency.

In the multiple linear regression model predicting the ZBI-19 total score (n=96), higher depression scores remained independently associated with greater caregiver burden (B=0.84, β=0.53, p<0.001). Caregiving duration showed a borderline positive association with caregiver burden (B=0.04, β=0.16, p=0.050). In addition, better income status was independently associated with lower caregiver burden (B=−4.88, β=−0.20, p=0.020). Anxiety, stress, caregiver relationship (first-degree family member vs paid caregiver), and prior caregiving experience were not significantly associated with caregiver burden after adjustment (all p>0.05). Overall model performance was acceptable (R^2=0.502, adjusted R^2=0.462, F(7, 88)=12.65, p<0.001), and multicollinearity was not a concern (VIF range: 1.19–3.91). Although the three DASS-21 subscales are theoretically and empirically correlated—a potential source of multicollinearity—VIF values remained well below the conventional threshold of 5.0 for all predictors, indicating that collinearity did not substantially inflate standard errors or compromise the stability of the regression estimates (Table 5).

Table 5. Multiple linear regression model predicting Zarit Caregiver Burden (ZBI) total score (n=96)

Predictor	B (SE)	Standardized β	p-value	95% CI for B	VIF
Constant	32.79 (4.91)	—	<0.001	23.04 to 42.54	—
Depression	0.84 (0.22)	0.53	<0.001	0.40 to 1.27	3.41
Caregiving duration (months)	0.04 (0.02)	0.16	0.050	0.00 to 0.07	1.19
Anxiety	−0.10 (0.19)	−0.06	0.618	−0.48 to 0.29	2.63
Stress	0.16 (0.21)	0.12	0.432	−0.25 to 0.57	3.91
Caregiver relationship*	−2.66 (3.26)	−0.08	0.417	−9.13 to 3.81	1.62
Prior caregiving experience†	−2.35 (2.90)	−0.08	0.419	−8.11 to 3.40	1.81
Income status‡	−4.88 (2.07)	−0.20	0.020	−8.99 to −0.78	1.27

Model fit: R^2=0.502, Adjusted R^2=0.462, F(7, 88)=12.65, p<0.001. *Caregiver relationship coding: 0=first-degree family member, 1=paid caregiver, † Prior caregiving experience coding: 0=no, 1=yes, ‡ Income status coding: 1=income less than expenses, 2=income equals expenses, 3=income greater than expenses, SE: Standard error, CI: Confidence interval, VIF: Variance inflation factors

DISCUSSION

This cross-sectional study in an inpatient palliative care unit shows that psychological distress and caregiver burden are common among primary caregivers. Moderate-to-extremely severe symptoms were observed in 29.2% of caregivers for depression, 39.6% for anxiety, and 18.8% for stress. At least moderate-to-severe caregiver burden was present in 33.3% of participants. These findings support the view that caregiving in palliative care is not only a practical responsibility but also a sustained psychosocial load that can affect daily functioning and well-being.[1,7]

The prevalence pattern we observed is broadly consistent with the international literature, where depressive and anxiety symptoms in informal caregivers frequently fall in the 25%–50% range, depending on population and measurement thresholds.[19] In Turkiye, studies conducted in similar settings have also reported elevated rates of depression and anxiety among relatives of palliative care patients, reinforcing that this is a recurrent clinical issue rather than a context-specific anomaly.[20,21] Of note, Turkiye's palliative care infrastructure has expanded substantially in recent years, with the number of inpatient units growing rapidly under the Ministry of Health's national palliative care program. Despite this expansion, systematic psychosocial support for caregivers remains inconsistently implemented across units. The present study, conducted in an inpatient tertiary palliative care center, adds locally grounded evidence that caregiver screening and structured psychosocial pathways are needed within the Turkish palliative care context—not only in oncology or home-care settings where most prior Turkish data originate. Taken together, the convergence between our data and prior reports suggests that routine caregiver assessment is clinically justified, particularly in inpatient palliative care where symptom trajectories and uncertainty are often intense.[22]

Caregiver burden is typically conceptualized as multidimensional (emotional strain, restriction of personal time, disruption of social life, and financial concerns), rather than a single construct.[7,8] Our results align with this framework: the burden profile indicates that caregivers are primarily challenged by the loss of personal time, the sense of constant vigilance, and future-related uncertainty—dimensions that often emerge prominently in caregiver studies, especially in progressive or life-limiting conditions.[8,23] In practical terms, these "time-dependent" and "psychological strain" elements may be the most actionable targets for brief interventions (education, structured respite planning, and anticipatory guidance) integrated into inpatient palliative routines.

Females constituted the majority of caregivers and showed higher depression and anxiety scores than men. This pattern is frequently observed across caregiver research and is often interpreted in light of gendered role expectations and unequal distribution of emotional labor.[13,24] While the present study cannot determine mechanisms, the finding underscores a pragmatic implication: caregiver-facing psychosocial interventions should explicitly consider gender-related vulnerabilities and barriers to help-seeking.

Socioeconomic markers mattered in our sample. Unemployment, lower education, and lower income were associated with higher psychological distress, and lower income was also associated with higher caregiver burden. Similar gradients have been documented elsewhere and may reflect reduced access to supportive resources, fewer opportunities for respite, and higher perceived insecurity during prolonged caregiving.[25,26] Importantly, the relationship between income and distress is not always linear in population studies; higher status or higher income can coincide with specific stress exposures (responsibility load, role conflict), which may partly explain why distress does not always decrease monotonically with income.[27,28] For palliative care services, the clinical takeaway is straightforward: screening and supportive pathways should not be "one size fits all." Socioeconomically vulnerable caregivers may require more proactive referral and structured follow-up.

Family caregivers tended to report higher distress and caregiver burden than paid caregivers in univariate analyses, which may reflect greater emotional involvement, anticipatory grief, and role conflict—factors less central in professional caregiving. Similarly, first-time caregivers showed higher stress and burden than those with prior caregiving experience in bivariate comparisons. However, neither caregiver relationship nor prior caregiving experience remained significant in the multivariable model, suggesting that these differences may be partly explained by co-occurring psychological distress and socioeconomic factors. Nevertheless, these findings highlight a modifiable window for practice: early-stage caregiver orientation (what to expect, symptom management basics, communication tips, and how to navigate unit resources) may help reduce distress and prevent escalation of perceived burden, particularly among family caregivers and those new to the caregiving role.

In the multivariable model, higher depression scores remained robustly associated with greater caregiver burden, while better income status was independently associated with lower burden. Caregiving duration showed a borderline positive association with burden, whereas anxiety, stress, caregiver relationship, and prior caregiving experience were not significant after adjustment. Meta-analytic evidence has consistently shown strong associations between subjective burden and depression/anxiety in informal caregivers.[10] Our finding—depression remaining central even when anxiety and stress are modeled together—suggests that depressive symptom severity may be a particularly useful clinical marker of high-burden trajectories in this setting. Clinically, a brief depression screen, repeated over time (especially as caregiving duration extends), may be an efficient way to identify caregivers most likely to benefit from targeted psychosocial support.

Guidelines increasingly emphasize that palliative care should address family/caregiver needs alongside patient symptom control.[22] Evidence-based caregiver interventions (psychoeducation, skills training, structured psychological support) can reduce depressive symptoms and perceived overload, and improve caregiver quality of life.[29,30] In a resource-constrained inpatient unit, stepped support may be realistic: (i) routine screening at admission, (ii) brief targeted counseling for high-risk caregivers (female, unemployed, low-income, family caregivers, first-time caregivers), and (iii) referral pathways for those with clinically significant depressive symptoms or persistent high burden.

Limitations

Several limitations warrant consideration. First, this was a single-center study conducted in one inpatient palliative care unit; therefore, the findings may not fully represent caregiver experiences in other institutions or care models. Second, the cross-sectional design does not allow causal inferences. Psychological distress and caregiver burden may influence each other in both directions, and the temporal sequence cannot be established. Third, all outcomes were assessed using self-report scales, which may introduce reporting bias. In addition, we did not include detailed patient-level indicators (e.g., functional status, symptom burden, or disease severity) that could contribute to caregiver distress and burden and act as unmeasured confounders. Finally, although we aimed to keep the regression model conservative given the sample size, variables were selected based on significant univariate associations; thus, the stability of some coefficients—especially borderline effects—should be interpreted with caution and confirmed in larger, multi-center studies.

Alongside these limitations, several strengths merit acknowledgment. The study employed two validated, psychometrically sound instruments with good internal consistency in the present sample. The multivariable regression approach, with VIF-confirmed model stability, allowed for adjusted estimates beyond simple correlational analysis. Additionally, the inpatient tertiary palliative care setting represents a relatively underrepresented context in the caregiver literature, particularly in middle-income countries, which adds to the generalizability of the findings within similar healthcare systems.

CONCLUSION

Caregivers in inpatient palliative care frequently experience substantial psychological distress and caregiver burden.

Depression severity and longer caregiving duration are key factors associated with caregiver burden, and these findings are consistent across sociodemographic subgroups. Integrating routine caregiver screening and targeted psychosocial support into palliative care workflows—particularly for socioeconomically vulnerable family caregivers—should be considered a clinical priority. This is especially relevant in the Turkish palliative care context, where inpatient units have expanded rapidly but structured caregiver support pathways remain inconsistently implemented. Future research should adopt longitudinal and multi-center designs to confirm these associations and evaluate the effectiveness of tailored interventions for high-risk caregiver subgroups.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of the University of Health Sciences, İzmir Bozyaka Training and Research Hospital (Date: 02.06.2025, Decision No: 2025/12).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

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A bibliometric snapshot of Turkish and international publications on oral dietary supplements

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ABSTRACT

Aims: This study aimed to systematically compare Turkish-origin and international publications indexed in PubMed on oral dietary supplements in terms of temporal distribution, methodological characteristics, and research approaches.

Methods: This descriptive bibliometric study analyzed 40 articles indexed in PubMed. Articles were retrieved on December 2, 2025, using the search query ("dietary supplements" OR "oral supplement") AND ("Turkey" OR "Türkiye"). The first 20 Turkish-origin and 20 international articles, which were sorted by the "best match" option and screened sequentially from the top of the results list and met inclusion criteria were analyzed. Variables including publication year, number of authors, article views, submission-to-acceptance time, study design, and research approach were extracted. Statistical analyses were performed using non-parametric tests and logistic regression, with $p<0.05$ considered significant.

Results: A total of 40 articles were included. Turkish-origin publications were predominantly published in 2024–2025 (70.0%), whereas international publications were mainly concentrated in 2021–2023 (65.0%) ($p=0.018$). Quantitative research approaches were more frequent in Turkish-origin studies (65.0%), while qualitative methods predominated in international publications (70.0%) ($p=0.056$). International articles had significantly higher article views compared to Turkish-origin articles (median: 26.247 vs. 3.272, $p<0.001$). Logistic regression analysis demonstrated that quantitative research approach was independently associated with Turkish-origin publications (OR: 4.28, 95% CI: 1.09–16.80, $p=0.037$).

Conclusion: Publication timing differed significantly between Turkish-origin and international studies. The difference in research approach was not statistically significant in Fisher's exact test ($p=0.056$). However, a quantitative approach was independently associated with Turkish origin in exploratory multivariable logistic regression (OR: 4.28; 95% CI: 1.09-16.80; $p=0.037$). These findings should be interpreted cautiously given the small sample size and warrant confirmation in larger studies.

Keywords: Bibliometrics, administration; oral, dietary supplements, Turkiye

INTRODUCTION

Dietary supplements are defined as concentrated sources of nutrients or other substances with nutritional or physiological effects intended to supplement the normal diet.[1] The prevalence of dietary supplement use varies across populations and age groups.[2] In recent years, dietary supplement use has increased substantially worldwide, reflecting growing interest in preventive health strategies and nutritional support. At the same time, the dietary supplement market and the scientific literature in this field have expanded rapidly, highlighting the rising global interest in nutrition-based health approaches.[3] The relationship between diet and health, including systemic and oral health outcomes, has been increasingly emphasized in the literature, underscoring the importance of nutrition in disease prevention and health promotion.[4] Among dietary supplement components, vitamins have received particular scientific attention because of their roles in biological regulation and disease prevention. Bibliometric evidence has shown a rapid increase in research concerning vitamins and cancer, reflecting broader scientific interest in the clinical relevance of micronutrients.[5] Supplement use is particularly common among older adults, many of whom use these products together with prescription medications, which may increase the risk of potential drug–supplement interactions.[6] This issue is further reinforced by recent longitudinal data showing that dietary supplement use may exceed 80% in older populations and

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contributes substantially to overall medication burden and polypharmacy.[7] Nationally representative data from the United States have also shown that dietary supplement use increased over time among older adults, while the risk of potential major drug–drug interactions rose in parallel, emphasizing the clinical relevance of monitoring supplement use in real-world settings.[8] Recent bibliometric studies have identified evolving research hotspots and emerging trends in the field of dietary supplements, demonstrating that scientific interest in this area is dynamic and continuously developing.[9] In addition, the field has evolved from relatively simple nutrient-focused investigations toward more complex, mechanism-based and interdisciplinary approaches, indicating progressive maturation of the literature.[10] Because of this growing and increasingly diverse body of evidence, reliable biomedical databases are essential for identifying publication trends and comparing research outputs. PubMed is widely recognized as a comprehensive and dependable resource for accessing biomedical literature and supporting evidence-based research.[11] Therefore, this study aimed to systematically compare Turkish-origin and international publications indexed in PubMed on oral dietary supplements, with a focus on publication year, research approach, and methodological characteristics.

METHODS

Ethics

Ethical committee approval was not required for this study, as it did not involve human participants, identifiable personal data, human biological material, or animal experiments. The study was conducted in accordance with the relevant ethical principles and publication ethics standards.

Study Design and Data Source

This study was designed as a descriptive bibliometric analysis. A structured literature search was conducted in the PubMed database to identify articles related to oral dietary supplements. PubMed was selected due to its comprehensive coverage of peer-reviewed biomedical literature and its widespread use in academic research.

Search Strategy

The literature search was performed on December 2, 2025, using the following search query: ("dietary supplements" OR "oral supplement") AND ("Turkey" OR "Türkiye"). No restrictions were applied regarding study design. Articles indexed in PubMed up to the search date were considered. Only articles with accessible abstracts and full texts in English were included.

Study Selection

This study adopted a structured but non-systematic sampling framework to generate a focused and comparative assessment of contemporary research trends. Relevant articles were identified through a predefined search strategy conducted in the PubMed database, and all retrieved records were evaluated in accordance with explicitly determined inclusion criteria. Instead of undertaking a full systematic review, a targeted sampling method was implemented to enhance feasibility while preserving the ability to directly compare Turkish-origin and international publications. Articles were sorted using the "best match" option and screened sequentially from the top of the results list. This approach may introduce ranking bias due to PubMed's relevance algorithm. Following eligibility assessment, a total of 40 studies were included, comprising the first 20 Turkish-origin and the first 20 international articles. A fixed sample size (n=40) was preferred to enable detailed manual data extraction and facilitate methodological comparison. This sample size was deemed sufficient for exploratory comparative analysis but not for generalization.

Although the study ensured a balanced and manageable dataset, it was not designed as a systematic review; therefore, PRISMA guidelines were not applied. Particular emphasis was placed on maintaining transparency and reproducibility by clearly defining the search strategy, eligibility criteria, and data extraction procedures. All records underwent duplicate screening, and no duplicate entries were detected.

Inclusion and Exclusion Criteria

Articles were included if they focused on oral dietary supplements or had accessible bibliographic and methodological data; articles were excluded if they were not directly related to oral supplements or lacked sufficient methodological or bibliometric data or were conference abstracts, editorials without data, or non-scientific content.

Data Extraction

The following variables, which were extracted from each article, are publication year, number of authors, article views, submission-to-acceptance time, study design (review vs. original research), research approach (quantitative vs. qualitative), country of origin. Data extraction was performed independently and systematically using a standardized data collection form. Article view data were obtained from the respective publisher platforms.

Classification of Variables

Publication years were categorized into three periods: ≤2020, 2021–2023, and 2024–2025. Study designs were grouped as review articles (including narrative and systematic reviews) and original research (including cohort, cross-sectional, retrospective, and randomized/prospective studies). Research approaches were classified as quantitative or qualitative.

Statistical Analysis

All data analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p<0.05$. Continuous variables were assessed for normality and, as they did not follow a normal distribution, were analyzed using non-parametric methods. Continuous variables are presented as median (minimum–maximum), and comparisons between groups were performed using the Mann–Whitney U test. Categorical variables are presented as frequencies (n) and percentages (%), and comparisons were conducted using Fisher's exact test. Binary logistic regression analysis was performed to identify factors independently associated with Turkish-origin publications (dependent variable: Turkish=1, international=0). Variables with clinical and methodological relevance were included in univariate models. A parsimonious multivariable model was constructed including selected covariates to minimize overfitting, given the limited sample size. Logistic regression was performed as an exploratory analysis and results should be interpreted cautiously due to the small sample size. Given the limited number of observations, model stability may be constrained.

RESULTS

A total of 40 articles were included in the analysis, comprising 20 Turkish-origin and 20 international publications. The general characteristics of the included articles by group are presented in Table 1. International articles had significantly higher article views compared to Turkish-origin articles (median: 26.247 vs. 3.272, p<0.001). Submission-to-acceptance time was also significantly longer in Turkish-origin articles (median: 112 vs. 52 days, p=0.028). No statistically significant differences were observed between the two groups in terms of number of authors (p=0.142).

Table 1. General characteristics of the included articles by origin

Variable	Turkish (n=20)	International (n=20)	Total (n=40)	p
Number of authors median (min–max)	5 (1–10)	6 (1–27)	6 (1–27)	0.142
Article views median (min–max)	3,272 (1,078–40,000)	26,247 (11,363–110,334)	13,685 (1,078–110,334)	<0.001*
Submission-to-acceptance time (days) median (min–max)	112 (20–753)	52 (11–239)	61 (11–753)	0.028*

*p<0.05. Mann-Whitney U test applied for all continuous variables. Min: Minimum, Max: Maximum

The distribution of articles across publication periods is shown in Table 2. Articles were classified into three periods: ≤2020, 2021–2023, and 2024–2025. Turkish-origin articles were predominantly published in 2024–2025 (70.0%), whereas international articles were more evenly distributed across 2021–2023 (65.0%). None of the international articles were published in or before 2020, in contrast to 15.0% of Turkish-origin articles.

Table 2. Distribution of articles by publication period

Publication period	Turkish n (%)	International n (%)	Total n (%)	p
≤2020	3 (15.0)	0 (0.0)	3 (7.5)	
2021–2023	3 (15.0)	13 (65.0)	16 (40.0)	0.018*
2024–2025	14 (70.0)	7 (35.0)	21 (52.5)	

Fisher's exact test. *p<0.05 considered statistically significant

Regarding study design, review articles constituted the most common design overall (70.0%) but were notably more prevalent among international publications (85.0%) than Turkish-origin publications (55.0%). Original research designs—including cohort, cross-sectional, active, and randomized/prospective studies—accounted for 45.0% of Turkish-origin articles compared to 15.0% of international articles (p=0.082). In terms of research approach, quantitative methods were more frequently employed in Turkish-origin articles (65.0%) compared to international articles (30.0%), without statistical significance (Fisher's exact test, p=0.056). The distribution of study designs and research approaches is presented in Table 3.

Table 3. Distribution of articles by study design and research approach

Category	Turkish n (%)	International n (%)	Total n (%)	p
Study design				0.082†
Review	11 (55.0)	17 (85.0)	28 (70.0)	
Original research	9 (45.0)	3 (15.0)	12 (30.0)	
Research approach				**0.056†**
Quantitative	13 (65.0)	6 (30.0)	19 (47.5)	
Qualitative	7 (35.0)	14 (70.0)	21 (52.5)	

†Fisher's exact test. p<0.05 considered statistically significant. Original Research encompasses cohort, cross-sectional, retrospective, and randomized/prospective study designs

To identify factors independently associated with Turkish-origin publications, binary logistic regression analysis was performed (outcome: Turkish origin=1, international=0). In univariate analysis, a quantitative research approach (OR: 4.33, 95% CI: 1.15–16.32, p=0.030) and an original research design (OR: 4.64, 95% CI: 1.02–21.00, p=0.047) were each significantly associated with Turkish origin. Article views were inversely associated with Turkish origin (OR: 0.85 per 1,000 views, 95% CI: 0.78–0.94, p<0.001), consistent with the descriptive findings. Number of authors showed a non-significant inverse trend (OR: 0.84, 95% CI: 0.69–1.03, p=0.092). Publication period was not independently associated with Turkish origin in univariate analysis (p=0.117). In the parsimonious multivariable model including publication period and research approach, a quantitative research approach remained independently associated with Turkish origin (OR: 4.28, 95% CI: 1.09–16.80, p=0.037), while publication period did not reach significance (p=0.148). The regression analysis results are presented in Table 4.

Table 4. Binary logistic regression analysis of factors associated with Turkish-origin publications

Variable	OR	95% CI	p	Model
Univariate analysis				
Recent publication period (2024–2025 vs. others)	2.79	0.77–10.04	0.117	Univariate
Quantitative research approach (vs. qualitative)	4.33	1.15–16.32	0.030*	Univariate
Original research design (vs. review)	4.64	1.02–21.00	0.047*	Univariate
Number of authors (per 1 author increase)	0.84	0.69–1.03	0.092	Univariate
Article views (per 1,000 views increase)	0.85	0.78–0.94	<0.001*	Univariate
Multivariable analysis — model 1 (parsimonious)				
Recent publication period (2024–2025 vs. others)	2.74	0.70–10.74	0.148	Multivariable
Quantitative research approach (vs. qualitative)	4.28	1.09–16.80	0.037*	Multivariable

Dependent variable: Turkish-origin article (1=Turkish, 0=International). OR: Odds ratio, CI: Confidence Interval. *p<0.05. Article views entered as continuous variable per 1.000-unit increase; number of authors entered as continuous variable per 1-unit increase. Multivariable model 1 includes publication period and research approach as covariates

DISCUSSION

Consistent with our findings, dietary supplement use has expanded globally in recent years, driven by increasing public interest in health promotion, wellness, and preventive strategies.[1] Because the present study was based on PubMed-indexed publications, the choice of database is also relevant, as PubMed is considered a reliable and widely used source for biomedical literature retrieval.[11] Within this growing

field, recent national data from Turkiye have also shown that dietary supplement use is common in children, indicating that supplement-related behaviors are increasingly relevant across different age groups.[2] In parallel, bibliometric studies in related areas have demonstrated that scientific output on supplements and micronutrients is rising steadily, with research themes diversifying over time.[3-5,9,10,12] Consistent with our findings, Turkish-origin publications were concentrated in more recent years, whereas international studies showed a broader temporal distribution. This pattern may reflect a recent increase in academic interest in Turkiye, potentially driven by evolving academic incentive systems, increased indexing of national journals, and growing awareness of nutrition-related research topics.

In line with our results, another important observation from the literature is that dietary supplement use is particularly common in older adults and often occurs in the context of chronic health concerns and regular medication use.[6-8,13] At the same time, safety considerations have become increasingly important in specific populations such as military personnel, where inappropriate or uninformed supplement use may pose health risks.[14] Similarly, studies conducted in older adults with chronic venous leg ulcers suggest that supplement use is frequent in clinically vulnerable populations, further emphasizing the real-world relevance of this topic.[15] Taken together, these findings support the idea that supplement use is not a marginal behavior, but rather a widespread practice with potential clinical, economic, and public health implications. These findings also support our observations that the clinical value of supplementation remains inconsistent. A major systematic review reported limited and non-uniform evidence for the efficacy and safety of multivitamin and mineral supplementation in the prevention of cancer and chronic disease.[16] This cautious interpretation is important when considering more recent interest in targeted interventions. For example, niacin and NAD^+-related supplementation have been discussed as potentially relevant for age-related disorders through metabolic and inflammatory pathways.[17] Likewise, omega-3 fatty acids have attracted attention in wound-healing research, including trial designs specifically developed for chronic venous ulcers,[18] and randomized evidence has shown that eicosapentaenoic acid and docosahexaenoic acid supplementation can reduce circulating proinflammatory cytokines in aging adults.[19] Nutritional and pharmacological approaches for sarcopenia have also highlighted the possible role of targeted supplementation in preserving function in older adults,[20] while a systematic review and meta-analysis suggested that protein and amino acid supplements may provide benefits in selected acute or chronic conditions, although results remain dependent on patient profile and study context.[21] Mechanistic reviews of fish oil have further supported the plausibility of such effects by describing anti-inflammatory and pro-resolving actions of fatty acids in tissue biology.[22]

Overall, these studies suggest that supplementation may be useful in selected settings, but that benefits are more convincing when interventions are targeted and biologically justified rather than broadly generalized. In line with our findings, population-based research also reinforces the need for caution in interpretation. National US data have shown that dietary supplement use was very high among older adults in 2011–2014,[23] and other large studies have documented frequent concurrent use of prescription drugs, over-the-counter medications, and dietary supplements in older populations.[24] This is clinically relevant because the motivations for supplement use are often not limited to correction of nutritional inadequacy. In nationally representative analyses, adults most reported using supplements to improve or maintain overall health rather than specifically to compensate for poor dietary intake.[25] At the population level, trends in the United States further show that overall and micronutrient-containing dietary supplement use continued to increase over time, although product types changed, with increasing use of some single-nutrient products and declining reliance on traditional multivitamin-mineral formulations.[26] Importantly, those who use multivitamin-multimineral supplements are often individuals with healthier diets, higher physical activity, lower body-mass index, and more favorable lifestyle characteristics.[27] This pattern suggests that observed associations between supplement use and health outcomes may be partly influenced by confounding from underlying health behaviors rather than by supplementation alone.

Consistent with our results, a further issue concerns the actual composition of supplement products. Analyses of multivitamin/mineral products for young children have shown marked heterogeneity in both the number and amount of included micronutrients.[28] Although some products contain nutrients of public health interest such as vitamin D, many provide inadequate amounts of calcium or potassium, while others include excessive levels of nutrients such as folic acid, vitamin A, and zinc.[28] These findings illustrate a broader problem in supplement research and practice: formulations are not always aligned with true nutritional needs, and both under-correction and overexposure may occur simultaneously. In this context, our findings gain additional importance, because differences between Turkish-origin and international publications are not only temporal but may also reflect broader differences in how supplementation is conceptualized, studied, and translated into practice. From a bibliometric perspective, consistent with our findings, the higher number of article views observed in international publications represents another notable finding. Differences in article views may reflect journal visibility, indexing status, international collaboration networks, and open-access policies rather than scientific quality alone. In addition, higher impact factor journals, broader dissemination strategies, and stronger international research collaborations may contribute to increased visibility and citation potential of international studies.

Overall, consistent with our findings, the literature on oral dietary supplements is expanding rapidly but remains methodologically and conceptually heterogeneous. The recent increase in Turkish-origin publications may reflect growing national interest and research activity, whereas the broader methodological diversity observed in international publications may indicate a more mature and differentiated evidence base. Future studies should prioritize clearer methodological standardization, stronger alignment between supplement formulations and actual nutrient gaps, and more clinically meaningful outcome measures. Such improvements would help generate evidence that is not only

more comparable across regions, but also more useful for guiding safe and effective supplement use.

Limitations

Regarding the limitations of this study, it examines only the top 20 articles from the search results in both samples, which may introduce selection bias due to the use of the "best match" ranking algorithm. The study is also limited to a single database (PubMed), which may not fully represent the global literature. Additionally, the relatively small sample size limits statistical power and may affect the generalizability of the findings. The absence of quality appraisal limits interpretation beyond descriptive trends. Furthermore, bibliometric indicators were restricted to a predefined and limited set of variables, which may not comprehensively capture the overall scientific impact of the publications. These limitations suggest that more comprehensive studies with larger datasets, multiple databases, and broader analytical parameters are needed to provide more robust and generalizable conclusions.

CONCLUSION

As a result, publication timing differed significantly between Turkish-origin and international PubMed-indexed articles on oral supplements. Turkish-origin studies were predominantly published in 2024-2025, whereas international studies were concentrated in 2021-2023, suggesting more recent national research activity in this sample. Quantitative approaches were more frequent in Turkish-origin studies, but the between-group difference was not statistically significant in Fisher's exact test (p=0.056). In contrast, a quantitative research approach was independently associated with Turkish origin in the exploratory multivariable logistic regression model (OR: 4.28; 95% CI: 1.09-16.80; p=0.037). Thus, evidence of a statistically significant association for research approach was confined to the logistic regression analyses. Given the small sample size, these exploratory findings should be interpreted cautiously and confirmed in larger datasets. They may inform future research design and international collaboration strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was not required for this study, as it was based exclusively on publicly available data and did not involve human participants or patient-level data.

Informed Consent

As this study is based solely on openly accessible bibliometric data and does not involve any individual patient information, ethical committee approval was not required.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

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Review

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Concerns about vaccines: ingredients and side effects

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ABSTRACT

Vaccines are among the most effective public health interventions; however, concerns regarding their components and potential adverse effects continue to contribute to vaccine hesitancy. This narrative review aims to critically evaluate the current scientific evidence regarding vaccine ingredients and their alleged side effects. A narrative literature review was conducted using PubMed and Scopus databases. Studies published in English and Turkish over the past 15 years were prioritized, with emphasis on systematic reviews, meta-analyses, and reports from international health authorities like World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) and The European Medicines Agency (EMA). High-quality evidence indicates that commonly discussed vaccine components such as thimerosal, aluminum adjuvants, and formaldehyde are present in quantities that are not associated with clinically significant harm. No causal relationship has been demonstrated between vaccines and autism spectrum disorder. Some hypotheses, such as autoimmune/inflammatory syndrome induced by adjuvants (ASIA), remain controversial and lack robust clinical validation. The current body of scientific evidence strongly supports the safety of vaccines. Misinterpretation of low-quality studies and misinformation contribute significantly to public concerns. Strengthening evidence-based communication is essential to reduce vaccine hesitancy.

Keywords: Vaccines, immunization, adverse effects

INTRODUCTION

Vaccination represents one of the most successful and cost-effective interventions in modern medicine, significantly reducing morbidity and mortality associated with infectious diseases.[1,2]

Vaccines undergo a rigorous development and regulatory approval process before being introduced into routine use. Development begins with preclinical studies, including laboratory and animal testing, to evaluate safety, immunogenicity, and appropriate dosage. Following submission of the necessary regulatory documentation, vaccines progress through phase I, II, and III clinical trials, which assess safety, immune response, and efficacy in increasingly larger populations. Because vaccines are administered to healthy individuals, particularly children, regulatory agencies require extensive evidence regarding both efficacy and safety. Following approval, post-marketing surveillance and, when necessary, phase IV studies continue to monitor vaccine safety and effectiveness in real-world settings. These processes ensure that licensed vaccines meet strict standards of quality, safety, and efficacy before and after public use.[3]

Global immunization programs have prevented millions of deaths annually and contributed to the eradication or control of several life-threatening diseases.

Despite the success of vaccination programs, concerns regarding vaccine safety have increased worldwide.[4] These concerns are frequently driven by misinformation, misinterpretation of scientific findings, and the dissemination of low-quality evidence.[5] Vaccine hesitancy has been identified by the World Health Organization (WHO) as one of the top threats to global health.[2]

Understanding the scientific basis of these concerns is essential for clinicians, policymakers, and public health professionals. This review aims to critically evaluate the evidence on vaccine ingredients and their potential adverse effects, distinguishing scientifically supported findings from unsupported claims.

METHODS

A structured narrative review was conducted. Searches were performed between January 2024 and February 2024. Relevant publications from 2025 were also considered to

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ensure that the review reflected the most recent available evidence.

Search Strategy

A comprehensive search was conducted in PubMed and Scopus databases covering publications from 2008 to 2023. The following keywords and Boolean combinations were used: "vaccine safety," "vaccine ingredients," "adjuvant toxicity," "thimerosal," "aluminum vaccines," "formaldehyde vaccines," "autism and vaccines."

Although the literature search period was defined as 2008–2023, publications from 2005, 2024, and 2025 were used solely for general background information and methodological explanations

Selection Criteria

The inclusion and exclusion criteria of the review were:

Inclusion criteria:

- Systematic reviews and meta-analyses
- Large cohort and case-control studies
- Reports and guidelines from WHO, CDC, EMA
- English and Turkish publications

Exclusion criteria:

- Low-quality studies (small sample size, lack of control group)
- Opinion articles or non-peer-reviewed publications
- Studies without clear methodology

Data Evaluation

Priority was given to high-level evidence (systematic reviews, meta-analyses, large cohort studies). Findings were synthesized narratively, focusing on consistency, biological plausibility, and reproducibility.[1,2,4,5]

A total of 324 records were identified. After removal of duplicates (n=68), 256 records were screened by title and abstract. Following full-text assessment, 72 publications met the inclusion and exclusion criteria and were included in the review (Figure). (https://aperta.ulakbim.gov.tr/records/303698)

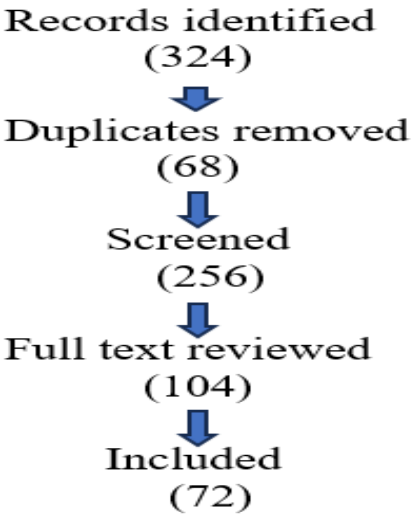


Figure. Literature search and study selection process

RESULTS

Vaccine ingredients and their side effects found as a result of the literature review are stated below:

Mercury (Thimerosal)

Thimerosal contains ethylmercury, which differs significantly from methylmercury in its pharmacokinetics. Ethylmercury is eliminated from the body more rapidly and does not accumulate to toxic levels.[6] Extensive epidemiological studies and meta-analyses have demonstrated no association between thimerosal-containing vaccines and neurodevelopmental disorders, including autism.[7,8] Most currently licensed vaccines do not contain thimerosal. In formulations where it remains present, only trace amounts are used.[1,4] WHO recommends reducing the use of mercury in all areas and promoting the use of mercury-free alternatives.[9]

Aluminum Adjuvants

Aluminum salts are used to enhance immune responses. Exposure to aluminum from water, food and environmental sources exceeds exposure from vaccines. Pharmacokinetic studies indicate low absorption and efficient renal elimination of vaccine-derived aluminum. Available epidemiological and toxicological evidence have not demonstrated an association with neurological or autoimmune disorders.[1,4,10-12] Current evidence supports the safety of aluminum-containing vaccines.

Formaldehyde

Formaldehyde is a naturally occurring compound involved in normal metabolic processes. Vaccine concentrations are substantially lower than endogenous levels. The studies have not shown any association between vaccine-related formaldehyde exposure and adverse health outcomes.[3,13]

Antibiotics, Gelatin, and Polysorbate 80

Residual antibiotics used during vaccine production are present in negligible amounts and are not associated with clinically significant allergic reactions.[3] Antibiotics known to cause severe hypersensitivity (e.g., penicillin,cephalosporins and sulfa drugs) are not used. Gelatin, used as a stabilizer in some vaccines, has been associated with rare allergic reactions; however, these events are extremely uncommon and manageable in clinical settings.[14] Polysorbate 80 is widely used in pharmaceuticals and has not been shown to cause significant adverse effects at doses used in vaccines.[15]

Autoimmune Diseases and ASIA Syndrome

Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) has been proposed as a possible explanation for vaccine-related autoimmune phenomena. However, epidemiological studies have not demonstrated an increased risk of autoimmune disease following vaccination.[1,11,16]

Autism

The proposed association between vaccines and autism has been extensively investigated. Meta-analyses and large population-based studies involving more than one million children have consistently reported no increased risk of autism following vaccination or exposure to vaccine components such as thimerosal.[7,8,17]

Allergic Reactions

Vaccine-associated allergic reactions may include urticaria, angioedema, bronchospasm, gastrointestinal symptoms, and anaphylaxis. Severe allergic reactions are rare, and most events are mild and self-limiting.[13]

Rare Adverse Events and Signal Detection

Although vaccines are generally safe, rare adverse events may occur and are often detected through post-marketing surveillance systems. Examples include Guillain-Barré syndrome following influenza vaccination and rare thrombotic events associated with certain COVID-19 vaccines. These events are extremely rare. Available risk–benefit analyses indicate that the benefits of vaccination substantially outweigh the associated risks.[1,18,19] The ability to detect such rare events highlights the effectiveness of global pharmacovigilance systems.

DISCUSSION

Strength and Consistency of Evidence

Evidence regarding vaccine safety is derived from large cohort studies, case-control studies, and meta-analyses conducted in diverse populations. A Danish nationwide cohort study involving more than 650,000 children found no association between MMR vaccination and autism, including among high-risk groups. Similarly, large meta-analyses have reported no increased risk of neurodevelopmental disorders following vaccination.[7,8,17] Pharmacokinetic and toxicological studies further support these findings by demonstrating that exposure to vaccine ingredients such as aluminum remains well below established safety thresholds.[10]

Biological Plausibility and Mechanistic Evidence

Biological plausibility is an important consideration when evaluating vaccine safety concerns. Proposed associations between vaccines and conditions such as autism, neurotoxicity, or autoimmune diseases have not been supported by established biological mechanisms or epidemiological evidence. In particular, concerns regarding thimerosal and aluminum are inconsistent with known pharmacokinetic and toxicological data.[6,10] Regarding autoimmune diseases, while immune activation is a theoretical concern, large epidemiological studies and systematic reviews have not demonstrated increased incidence following vaccination.[11,20] The ASIA hypothesis, although biologically intriguing, remains unsupported by reproducible clinical evidence and lacks standardized diagnostic criteria.[16]

Risk–Benefit Balance

A key issue in vaccine hesitancy is the discrepancy between perceived and actual risk. Rare adverse events often receive disproportionate attention in traditional and social media. This may contribute to cognitive biases, including the availability heuristic, which can influence public perceptions of vaccine risk.[5,19] For example, the risk of anaphylaxis following vaccination is approximately 1 per million doses.[14] Whereas the risks associated with vaccine-preventable diseases—such as measles-related encephalitis or death—are significantly higher.[1,21] Despite this, public perception often overestimates vaccine risks and underestimates disease risks. This imbalance is further exacerbated by misinformation and anecdotal reports, which are often perceived as more compelling than statistical evidence.[5,19]

Regulatory Oversight and Pharmacovigilance

Vaccines are subject to some of the most rigorous safety monitoring systems in medicine. Pre-licensure evaluation includes multiple phases of clinical trials assessing safety, immunogenicity, and efficacy.[1] Post-marketing surveillance systems such as:

- VAERS (Vaccine Adverse Event Reporting System)
- EudraVigilance (European Union)
- WHO Global Pharmacovigilance Database

enable continuous monitoring of adverse events in real-world settings.[1,18]

Importantly, these systems are designed to detect even rare adverse events. For example, the identification of rare thrombotic events associated with certain COVID-19 vaccines demonstrates the sensitivity and effectiveness of pharmacovigilance systems.[18]

Misinformation and the Role of Digital Media

The rapid spread of misinformation—particularly through social media—has significantly contributed to vaccine hesitancy.[5,22] False claims frequently rely on emotional narratives, selective interpretation of data, or discredited studies.[23] One notable example is the Wakefield study, which falsely linked MMR vaccination to autism. The article was subsequently retracted because of serious ethical and methodological concerns.[24,25] Recent evidence suggests that misinformation disseminated through social media remains one of the strongest predictors of vaccine hesitancy, highlighting the importance of evidence-based risk communication strategies.[26,27] Combating misinformation requires proactive strategies, including digital literacy, fact-checking, and engagement with trusted healthcare professionals.

Clinical and Public Health Implications

Healthcare professionals are central to addressing vaccine hesitancy. Evidence suggests that physician recommendation is one of the strongest predictors of vaccine acceptance.[28] Effective communication strategies include acknowledging patient concerns, providing clear evidence-based explanations, using risk comparisons (e.g., disease risk versus vaccine risk), and avoiding dismissive language. From a public health perspective, maintaining high vaccination coverage is essential for achieving herd immunity and preventing outbreaks. Even small declines in vaccination rates can lead to the re-emergence of previously controlled diseases, as observed in recent measles outbreaks in several countries.[21] Recent reports from WHO and EMA continue to support the favorable benefit–risk profile of licensed vaccines and emphasize the importance of ongoing pharmacovigilance and transparent risk communication.[29,30]

Limitations

Although the overall evidence base is strong, certain limitations exist. Rare adverse events may not be detected during pre-licensure trials because of limited sample sizes. In addition, observational studies remain susceptible to residual confounding. Nevertheless, the consistency of findings across different study designs and populations strengthens confidence in the overall conclusions.

CONCLUSION

Vaccines are among the safest and most effective public health interventions. Combating vaccine-related misinformation and providing clear, evidence-based communication to the public are critical for sustaining confidence in vaccination programs and maintaining adequate vaccination coverage.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The author declares no conflicts of interest.

Financial Disclosure

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Author Contributions

Author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

Editor Note

Hilal Aksoy is a member of the Editorial Board of this journal. She was not involved in the editor assignment, reviewer selection, peer review process, or editorial decision for this manuscript. The peer review process was managed independently by another editor.

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Impact of radiation on humans

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ABSTRACT

Humans are continuously exposed to radiation from natural sources (notably indoor radon), medical procedures, occupational settings, and occasional nuclear accidents. In this review we discuss the mechanisms of ionizing radiation injury and summarize major clinical syndromes across organ systems. Ionizing radiation deposits energy that directly damages DNA or indirectly generates hydroxyl radicals, producing single- and double-strand breaks and oxidative base lesions; higher linear energy transfer tends to create complex damage that is harder to repair. These lesions activate apoptosis, mitotic catastrophe, and inflammatory cell-death pathways, with tissue responses shaped by dose, irradiated volume, fractionation, oxygenation, and cell-cycle sensitivity. At whole-body doses of roughly 1–8 Gy, hematopoietic acute radiation syndrome (ARS) causes early lymphopenia followed by neutropenia and thrombocytopenia, increasing risks of infection and bleeding. At approximately 6–15 Gy, gastrointestinal ARS results from intestinal crypt stem-cell loss, leading to severe diarrhea, barrier failure, sepsis, and malnutrition; at very high doses, neurovascular collapse and cerebral edema can be fatal. The skin is also a critical target: cutaneous radiation injury has a threshold near 2 Gy and progresses from erythema to desquamation and ulceration with late fibrosis, and pain may be opioid-resistant. Thoracic exposure can cause pneumonitis progressing to fibrosis, while central nervous system (CNS) injury includes acute encephalopathy and delayed radionecrosis/cognitive impairment. Practical preparedness includes early triage (time-to-emesis, serial lymphocyte counts, biodosimetry when available) and prevention through justification, optimization, dose limitation, and radon mitigation.

Keywords: Radiation; ionizing, acute radiation syndrome, DNA damage, radiation injuries, radiobiology.

INTRODUCTION

Radioactive atomic nuclei release energy into their surroundings to reach a more stable structure; this energy is known as radiation**.** In daily life, we are exposed to radiation in many areas without even realizing it. Natural radiation refers to radiation that occurs spontaneously in nature and is encountered by all living beings. Cosmic rays, radon gas, gamma emissions, or internal radiation that occurs when radioactive substances enter the body through inhalation or digestion can be given as examples of natural sources. The most important source of natural radiation is radon gas. It is found abundantly in rocks and soil within the Earth's crust. By leaking into indoor environments through gaps or cracks in building foundations, it can pose risks to human health.[1,2]

Radiation is broadly classified into two main groups: ionizing and non-ionizing radiation. Ionizing radiation produces ions by removing electrons from atoms or molecules. It is divided into two categories: particles (alpha particles, beta particles, neutrons) and electromagnetic waves (X-rays, gamma rays). Non-ionizing radiation does not cause ion formation in the atoms or molecules it interacts with. Because its energy is lower than that of ionizing radiation, its harmful effects are more limited. Visible light, ultraviolet, infrared radiation, radio frequencies, and microwaves are examples of this group.[3,4]

During nuclear decay, alpha (α) particles, beta (β) particles, and frequently gamma (γ) rays are released. Ionizing radiation refers to nuclear radiation that carries sufficient energy to remove electrons from atoms or molecules, resulting in their ionization. Ionizing radiation spans high-energy electromagnetic waves—most notably gamma rays and X-rays—and it also includes the higher-energy end of ultraviolet light. Ionization can also be triggered by particulate radiation such as alpha and beta particles, as well as by neutrons. When primary cosmic rays strike molecules in Earth’s atmosphere, they create cascades of secondary particles, including muons, mesons, and positrons.[1,4] These interactions also lead to the formation of naturally occurring radionuclides (for example, carbon-14), which later release ionizing radiation as they undergo radioactive decay.[5]

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The harmful health effects of ionizing radiation were recognized shortly after the discovery of X-rays in 1895. For instance, hair loss (epilation) was reported in 1896, and skin burns were soon described. Moreover, studies conducted in 1928 demonstrated that X-rays induced germline mutations in fruit flies.[6]

On August 6, 1945, humanity encountered nuclear weapons for the first time when an atomic bomb was dropped on Hiroshima, Japan; a second bomb was dropped on Nagasaki three days later. These explosions generated powerful shock waves, extreme heat, and the release of ionizing radiation. In addition to injuries caused directly by blast pressure and thermal effects, the intense radiation exposure led to acute dose-dependent effects, including deaths resulting from gastrointestinal and bone marrow damage, as well as non-fatal manifestations such as epilation. Among the survivors, the long-term effects of radiation resulted in various health problems in the years that followed.[7]

The Fukushima Daiichi Nuclear Power Plant accident resulted in low-dose internal or external radiation exposure for approximately two million residents of the surrounding region. In contrast, the Chernobyl Nuclear Reactor accident released nearly ten times more radioactive material than Fukushima, dispersing across many European countries. Millions of children in Ukraine, Belarus, and Russia were exposed to the isotopes Cs-137 and I-131. These radioisotopes caused moderate radiation accumulation, particularly in thyroid tissue, with doses exceeding 100 mSv in a subset of affected children. Over the past 25 years, approximately 7,000 cases of thyroid cancer (mostly papillary type) have been reported, and 20 children have died due to metastatic disease.[8,9]

This review aims to provide a comprehensive overview of the biological mechanisms, organ-specific effects, clinical manifestations, and current management of ionizing radiation injury. The literature search was conducted in PubMed, Scopus, and Web of Science, primarily focusing on studies published between 2020 and 2026, while also including relevant earlier landmark studies published since 2005.

ABSORBED DOSE AND EFFECTIVE DOSE

Absorbed dose, expressed in gray (Gy), represents the amount of ionizing radiation energy deposited per unit mass of tissue. Effective dose, expressed in sievert (Sv), accounts for both the type of radiation and the differing sensitivities of exposed organs and tissues, and is mainly used to estimate the overall long-term stochastic health risk, such as cancer.[10]

RADIATION EFFECT AT THE CELLULAR LEVEL

Cell death caused by radiation is commonly divided into two main categories: interphase death and reproductive death. Interphase death describes cells that stop functioning normally after irradiation and die within a few hours rather than continuing to divide. It is thought to result from severe damage to intracellular components after exposure to high radiation doses, along with the activation of nucleases and proteolytic enzymes that cause chromatin breakdown and release of histones. These events are followed by nuclear condensation and destruction, rapid loss of normal nuclear structure, and eventual cell death. In addition, radiation-related membrane damage and impaired cellular energy metabolism are also important contributors to interphase death.[11,12]

The majority of cells die through proliferative death. This form of death usually occurs via mitotic catastrophe, a process triggered by the buildup of chromosomal damage and incorrect repair of DNA double-strand breaks caused by radiation. After completing one or more rounds of cell division, the affected cells eventually lose their capacity to keep proliferating and then die.[12,13] It is widely accepted that cellular responses, including cell death, are influenced not only by the radiation dose but also by the specific type of cell and its stage in the cell cycle (Table 1).

Table 1. Radiation-related cell-death patterns

Radiation-related trigger	Cell-death pattern
Receptor signaling or intracellular stress (DNA/ER stress)	Apoptosis
Severe structural or bioenergetic damage	Necrosis
Widespread subcellular damage and need for turnover	Autophagy (excessive)
Lipid peroxidation overload	Ferroptosis
Inflammasome-driven inflammatory signaling	Pyroptosis
Danger signals and antigen exposure	Immunogenic cell death
Checkpoint, chromosome, or mitotic apparatus damage	Mitotic catastrophe

DNA: Deoxyribonucleic acid, ER: Endoplasmic reticulum

Recent advances show that radiation responses extend beyond direct DNA damage. Ionizing radiation activates the DNA damage response, particularly the ataxia-telangiectasia mutated (ATM) and ATM- and Rad3-related pathways, which regulate DNA repair, cell-cycle arrest, apoptosis and radiosensitivity.[14,15] Unrepaired deoxyribonucleic acid fragments and micronuclei can activate the cyclic GMP–AMP synthase–stimulator of interferon genes pathway, inducing type I interferons, dendritic-cell activation and tumor-specific T-cell responses.[16,17] Radiation may also induce immunogenic cell death through the release of damage-associated molecular patterns, which promote antigen presentation and antitumor immunity.[18] Alternatively, irradiated cells may become senescent and develop a senescence-associated secretory phenotype, contributing to inflammation and tissue injury.[19] Signals released from irradiated cells can damage neighboring non-irradiated cells, producing the bystander effect, whereas systemic immune activation may cause regression of distant, non-irradiated tumors, known as the abscopal effect.[20]

Various types of DNA damage can occur during radiation therapy. The most harmful are double-strand breaks and oxidative base damage. These lesions kill cancer cells and underlie the therapeutic effect of radiotherapy.[3] The fundamental feature of ionizing radiation is that it induces DNA breaks, directly or indirectly, thereby driving the cell toward apoptosis and cell death.[21] Radiation exerts biological effects on the DNA molecule by acting directly on structures that carry genetic information or on components essential for cell survival.[22,23]

The biological impact also depends on radiation quality. High-linear-energy-transfer (LET) radiation (e.g., alpha

particles, some neutrons, and heavy ions) tends to produce clustered, complex DNA damage that is harder to repair, while oxygenation increases fixation of radiation damage (oxygen effect) and can modify radiosensitivity.[3]

Indirect DNA breaks occur when low-energy radiation enters the cell and strikes a water molecule, resulting in the formation of hydroxyl radicals (free radicals derived from water).[24] If these radicals are close to DNA, they can cause a break in one strand of the helix. Depending on the extent of the damage to the helix, the cell may repair this damage or undergo apoptosis.[25]

Radiation primarily affects multiple systems—mainly the hematologic, gastrointestinal, and neurovascular systems—and it can also significantly affect the skin.[26] As illustrated in Figure 1, ionizing radiation causes direct and reactive oxygen species (ROS)-mediated DNA damage, triggering cellular repair or death pathways that lead to tissue and organ injury and ultimately result in acute and chronic clinical manifestations.

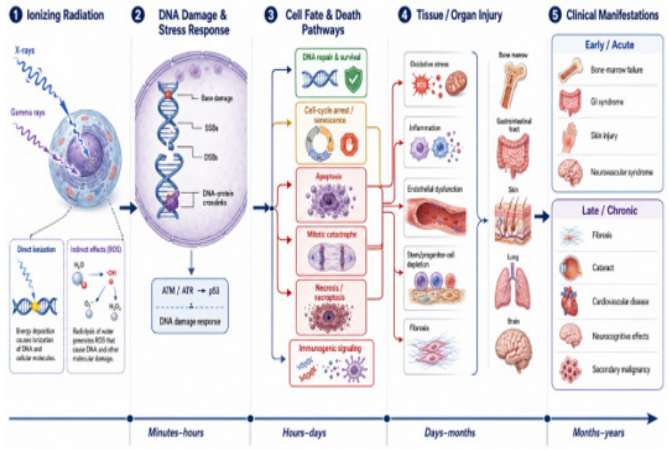


Figure 1. Molecular, cellular, tissue, and clinical consequences of ionizing radiation exposure
DNA: Deoxyribonucleic acid, ATM: Ataxia-telangiectasia mutated

In suspected ARS, early triage is aided by time-to-emesis, serial absolute lymphocyte counts, and, where available, biodosimetry methods such as dicentric chromosome assays or other cytogenetic/biomarker approaches to estimate whole-body dose and guide escalation of supportive care.[27] ARS classically progresses through four phases. The prodromal phase develops within minutes to days after exposure and commonly includes nausea, vomiting, fatigue, and diarrhea. This is followed by a latent phase, during which symptoms temporarily improve despite ongoing cellular and tissue injury. The manifest illness phase subsequently appears with clinical findings determined by the radiation dose and the predominantly affected organ system, particularly the hematopoietic, gastrointestinal, or neurovascular system. Finally, patients enter either the recovery phase, which may last weeks to months, or experience progressive organ failure and death after severe exposure.[26,27]

In mass-casualty scenarios, identifying individuals exposed to ionizing radiation and stratifying them into treatment-relevant groups is a major challenge for medical response teams. For example, individuals with minimal exposure (<2 Gy) may not require emergency care. Those exposed to moderate (2–6 Gy) or high (6–10 Gy) doses are likely to benefit from timely treatment. However, individuals exposed to supralethal doses (>10 Gy), for whom survival is not achievable, should receive only palliative care. Defining these subcategories is crucial for conserving the limited resources expected to be available in any mass-casualty situation.[28]

ORGAN-SPECIFIC EFFECTS OF IONIZING RADIATION

Cutaneous Radiation Injury

Cutaneous radiation injury (CRI) is a deterministic effect that occurs in the skin and subcutaneous tissues after radiation exposure. The skin is radiosensitive due to both rapidly renewing cells (basal keratinocytes) and microvascular structures. The threshold dose is 2 Gy, and the severity increases with higher doses.[29] Cutaneous radiation injury typically results from radioactive fallout, radiotherapy, or medical radiological procedures. The Hiroshima, Nagasaki, and Chernobyl incidents are historical examples of this type of injury.[9,30] The cutaneous manifestations that develop according to increasing severity are shown sequentially in Figure 2. Very high localized doses can cause necrosis/radionecrosis and chronic, non-healing wounds.[31]

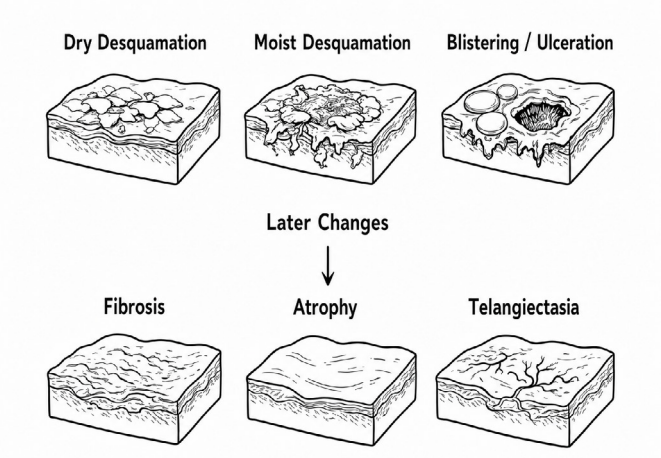


Figure 2. Skin manifestations of cutaneous radiation injury

Radiation-induced skin pain is often resistant to opioid therapy. For diagnosis, a detailed medical history, physical examination, complete blood count, ultrasound, and thermography are useful. Although there is no specific approved treatment, management requires a multidisciplinary approach. First-line treatment includes pain control, infection prevention, and psychological support. Topical corticosteroids and a combination of pentoxifylline and α-tocopherol may be beneficial.[32]

When necessary, surgical interventions such as excision, flap coverage, or amputation may be performed. Hyperbaric oxygen therapy has shown promising results. In addition, mesenchymal stem cell (MSC) applications contribute to healing through anti-inflammatory and regenerative effects.[33]

Effects of Radiation on the Respiratory System

Ionizing radiation to the chest (most often during thoracic radiotherapy, but also after high-dose accidental exposure) can injure the respiratory system through direct cellular damage and an amplified inflammatory cascade. The major toxicity is radiation-induced lung injury, which typically evolves from an early inflammatory phase (radiation pneumonitis) to a later fibrotic remodeling phase (radiation-

induced pulmonary fibrosis).[34] Mechanistically, injury to alveolar epithelium and pulmonary microvascular endothelium promotes capillary leak, disturbed surfactant, and cytokine signaling (including pro-inflammatory and pro-fibrotic mediators such as IL-1, IL-6, TNF-α, and TGF-β), leading to edema and impaired gas exchange.[35] Clinically, pneumonitis often appears weeks to months after exposure with dry cough, dyspnea, low-grade fever, and radiographic ground-glass opacities or consolidation; untreated or severe cases can progress to chronic fibrosis with reduced lung compliance and diffusion capacity.[36] Risk increases with larger irradiated lung volumes and higher dose-volume metrics, as well as patient factors and concurrent systemic therapies. Management focuses on ruling out infection or tumor progression, providing supportive care, and using corticosteroids for symptomatic pneumonitis; prevention relies on modern planning techniques and adherence to lung dose constraints.[37] In extreme exposures, acute respiratory distress and pleural effusions may occur, requiring oxygen and close monitoring.

Effects of Radiation on the Nervous System

Until recently, the nervous system was thought to be relatively insensitive to radiation. However, more recent research has shown that the central nervous system (CNS) can react even to low levels of radiation, and these effects often lead to tissue injury.[38] The harmful effects of radiation on the CNS are particularly important in the contexts of cancer radiotherapy and space research.[39] The brain and spinal cord are late-responding tissues, and low-dose irradiation of large volumes may cause long-term complications.[40] Acute effects include cerebral edema, encephalopathy, and seizures, whereas delayed effects comprise demyelination, white matter loss, and cognitive impairment.[41] In addition, pseudoprogression and brainstem syndrome may develop after radiotherapy.[42] Within minutes to hours, manifestations may include severe headache, dizziness, altered consciousness, ataxia, seizures, and agitation; coma may develop later. Prominent early nausea/vomiting, profound fatigue, and hypotension can accompany the picture. Prognosis is generally poor, with high mortality at very high whole-body doses despite supportive care.[26]

Among late complications, the most important is radionecrosis, which arises from glial and endothelial injury and disruption of the blood–brain barrier.[40] Very high doses can cause endothelial injury, capillary leak, cerebral edema, microvascular failure, and a severe inflammatory response.[43] Secondary CNS tumors such as meningiomas, gliomas, and sarcomas are more frequently observed in individuals exposed to radiation.[44] NASA has identified cancer, CNS performance loss, and ARS as critical risks for astronauts. For long-duration spaceflight, exposure to galactic cosmic rays and sporadic solar particle events involves a mixed field that includes high-energy heavy ions; these components have higher LET and may pose distinct carcinogenic and neurocognitive risks compared with terrestrial low-LET exposures, motivating mission-specific risk modeling.[45]

Hematopoietic Syndrome

Because the hematopoietic system contains rapidly dividing stem and progenitor cells, it is among the most radiosensitive targets. After whole-body exposure to radiation doses of approximately 1–8 Gy, hematopoietic ARS may develop following a latent phase. DNA damage and apoptosis in bone marrow lead to an early drop in lymphocytes (first days), followed by neutropenia and thrombocytopenia (days to weeks).[46]

As a result of radiation-induced damage, bone marrow failure develops and blood cells can no longer be produced. This may lead to aplastic anemia, myelodysplastic syndrome, erythrocyte aplasia, megakaryocytic thrombocytopenia, and chronic neutropenia.[47] Consequently, hematopoietic organs (bone marrow, thymus, spleen) are suppressed, and serious, life-threatening conditions such as anemia, leukemia, secondary infections, and immunodeficiency may occur.[48]

Effects of Radiation on the Gastrointestinal System

Gastrointestinal ARS is characterized by intestinal dysfunction that develops after exposure to high radiation doses of 6–15 Gy. GI injury usually appears at higher doses than the hematopoietic syndrome and is closely related to loss of intestinal crypt stem cells. Shortly after exposure, nausea, vomiting, and diarrhea occur; following a latent phase, bloody diarrhea, sepsis, and risk of death increase. Hematopoietic syndrome often coexists and worsens the prognosis. With modern treatment, the survival rate is around 50%.[48] Radiotherapy damages not only cancer cells but also rapidly dividing tissues such as the intestines.[49] Salivary gland damage can lead to hyposalivation, mucositis, and functional impairment.[50]

High-dose radiation causes complications such as ulcers, malnutrition, and diarrhea.[51] Fractionated treatments, protection of radiosensitive regions, and the use of hydrogels are recommended for radioprotection.[52]

Finally, radiation induces apoptosis, ferroptosis, and inflammation in intestinal cells. Inhibition of these processes and supplementation with tetrahydrobiopterin (BH4) can reduce intestinal ischemia and radiation enteritis.[53] The major organ-specific effects of radiation, including typical dose thresholds, clinical manifestations, diagnostic approaches, and management strategies, are summarized in **Table 2**.

Effects of Radiation on Other Systems: Cardiovascular, Endocrine, and Reproductive Effects

Ionizing radiation can also cause clinically important cardiovascular, endocrine, and reproductive toxicity. Cardiac and vascular exposure promotes endothelial injury, inflammation, oxidative stress, and fibrosis, increasing the long-term risks of coronary artery disease, cardiomyopathy, valvular dysfunction, and pericardial disease.[54] Endocrine effects are generally dose- and site-dependent; irradiation of the hypothalamic–pituitary region may cause growth hormone, thyroid, adrenal, or gonadotropin deficiencies, whereas direct thyroid exposure can result in hypothyroidism.[55] Reproductive tissues are particularly radiosensitive: testicular irradiation may impair spermatogenesis and reduce testosterone production, while ovarian exposure can deplete the follicular reserve, leading to premature ovarian insufficiency, infertility, and early menopause.[56,57] Therefore, long-term cardiovascular, hormonal, and reproductive surveillance should be considered in exposed individuals.

Table 2. Radiation effects, summary

	Cutaneous radiation injury	Effects of radiation on the respiratory system	Effects of radiation on the nervous system	Hematopoietic syndrome	Effects of radiation on the gastrointestinal system
Typical dose/ threshold	Threshold dose>2 Gy Severity increases with higher dose	Risk rises with larger irradiated lung volumes and higher dose-volume metrics	Low-dose large-volume exposure may cause long-term complications Very high whole-body doses cause acute neurovascular picture	Hematopoietic syndrome typically at 1–8 Gy whole-body exposure	GI-ARS typically at 6–15 Gy (often with hematopoietic syndrome)
Clinical features	Dry desquamation → moist desquamation Blistering/ulceration, late fibrosis/atrophy/ telangiectasia	Dry cough, dyspnea, low-grade fever Imaging: ground-glass or consolidation Late: reduced compliance and diffusion	Headache, dizziness, altered consciousness, ataxia, seizures Delayed: demyelination, white matter loss, cognitive impairment, radionecrosis	Early lymphopenia (days) followed by neutropenia and thrombocytopenia (days–weeks) anemia, infections, bleeding	Early nausea/vomiting/ diarrhea, later bloody diarrhea, sepsis, malnutrition, ulcers and radiation enteritis
Diagnosis	Detailed history+physical exam Ultrasound and thermography may help	Differentiate from infection/tumor progression	Neurologic exam+imaging monitor for pseudoprogression and brainstem syndrome after radiotherapy	Serial CBC with differential; consider marrow evaluation if needed	Clinical course+laboratory examination for hydration/ electrolytes Evaluate for sepsis Imaging/endoscopy as indicated
Management	Pain control, infection prevention, psychological support Topical steroids Pentoxifylline+alpha-tocopherol	Supportive care Corticosteroids for symptomatic pneumonitis Prevention via modern planning and lung dose constraints	Supportive care Manage delayed complications (radionecrosis/ cognitive decline) Spaceflight adds high-LET particle risk considerations	Supportive care, antimicrobials as needed, transfusions and hematopoietic growth-factor support when indicated Manage marrow failure complications	Supportive care and radioprotection strategies (fractionation, sparing, hydrogels) Target ROS/RNS-driven injury Inhibition of apoptosis/ ferroptosis and BH4 supplementation mentioned

GI-ARS: Gastrointestinal acute radiation syndrome, CBC: Complete blood count, LET: Linear-energy-transfer, GI: Gastrointestinal, ROS: Reactive oxygen species, RNS: Reactive nitrogen species, BH4: Tetrahydrobiopterin

RADIATION CARCINOGENESIS

Radiation carcinogenesis is a major long-term stochastic effect of ionizing radiation; its probability increases with dose, whereas cancer severity is not dose-dependent. Radiation-induced DNA damage, genomic instability, and mutations may initiate malignancy after a latency ranging from several years to decades.[58] Leukemia generally appears earlier than most solid tumors and shows a clear dose–response relationship.[59] The thyroid is especially radiosensitive during childhood, as demonstrated by the increased incidence of thyroid cancer after exposure to radioactive iodine following the Chernobyl accident.[60] Breast cancer risk is also elevated after irradiation, particularly among females exposed at a young age,[61] while lung cancer risk is influenced by both radiation dose and smoking.[62] In addition, radiotherapy may produce secondary malignancies within or near the irradiated field, including lung, esophageal, thyroid, bone, and soft-tissue cancers, often after a prolonged latency.[63]

The health consequences of low-level radiation exposure remain unclear, largely because existing studies lack sufficient statistical strength. As a result, the linear no-threshold (LNT) model continues to serve more as a cautious framework than a fully validated biological principle. Future research should focus on developing dependable molecular biomarkers to assess radiation exposure. Integrative approaches such as multi-omics combined with machine learning could accelerate and personalize biodosimetry. Although new radioprotective compounds show potential, current findings are predominantly derived from animal experiments. To bring these innovations into clinical practice, large-scale, multicenter studies in humans are essential.[64,65]

CONCLUSION

As a result, this review highlights that radiation exposure is not limited to rare disasters; people encounter it routinely through natural sources such as cosmic rays and especially indoor radon that can enter buildings through cracks and gaps, creating a preventable public-health risk. It also emphasizes why ionizing radiation matters biologically: by damaging cellular components—most critically DNA—it can trigger cell death pathways and, depending on dose and tissue sensitivity, lead to clinically important outcomes. Historical events (e.g., Hiroshima/Nagasaki) and large-scale nuclear accidents illustrate both the acute deterministic injuries seen at high doses and the longer-term health consequences that may appear years later, reinforcing the importance of risk communication and preparedness.

Clinicians must be aware of both the short-term and long-term health consequences of radiation exposure to enable timely diagnosis, effective treatment, and ongoing patient monitoring. To reduce unnecessary risks, strict compliance with radiation protection principles—such as justification of use, dose optimization, and proper shielding—remains vital. Robust emergency preparedness requires coordinated multidisciplinary protocols, rapid dose evaluation, efficient triage systems, and the presence of skilled personnel with adequate medical resources.

ETHICAL DECLARATIONS

Peer Review Process

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Conflict of Interest

The author declare no conflicts of interest.

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Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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